DOI: 10.1111/dme.14094

Research: Treatment

Glycaemic target attainment in people with Type 2 diabetes treated with insulin glargine/lixisenatide fixed-ratio combination: a *post hoc* analysis of the LixiLan-O and LixiLan-L trials

J. A. Davidson[1], C. Desouza[2], V. Fonseca[3], J. P. Frias[4], L. Van Gaal[5], F. Giorgino[6], J. Chao[7], T. A. Dex[8], M. Roberts[8], A. Saremi[8] and L. A. Leiter[9]

[1]Touchstone Diabetes Center, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX, [2]University of Nebraska Medical Center, Omaha, NE, [3]Tulane University Health Sciences Center, New Orleans, LA, [4]National Research Institute, Los Angeles, CA, USA, [5]Antwerp University Hospital, Edegem-Antwerp, Belgium, [6]University of Bari Aldo Moro, Bari, Italy , [7]Xinyi, Inc., [8]Sanofi US, Inc., Bridgewater, NJ, USA and [9]Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

Accepted 29 July 2019

Abstract

Aims Both fasting (FPG) and postprandial plasma glucose (PPG) contribute to HbA_{1c} levels. We investigated the relationship between achievement of American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommended FPG and/or PPG targets and glycaemic efficacy outcomes in two trials.

Methods In this *post hoc* analysis, data from participants with Type 2 diabetes in the phase 3 LixiLan-O (NCT 02058147) and LixiLan-L (NCT 02058160) trials were evaluated to compare the relationship between achievement of society-recommended FPG and/or PPG targets and efficacy (HbA_{1c} change, HbA_{1c} goal attainment, weight change) and safety outcomes in the treatment groups.

Results Across treatment arms, iGlarLixi achieved the highest proportion of participants meeting both ADA- and AACE-recommended FPG and PPG targets at study end in both trials. A higher proportion of participants in the iGlarLixi (fixed-ratio combination of insulin glargine and lixisenatide) vs. insulin glargine alone or lixisenatide alone treatment arms achieved HbA_{1c} goals ($P < 0.001$ for overall comparisons), irrespective of ADA- or AACE-defined targets. Hypoglycaemia rates [any, documented symptomatic (plasma glucose ≤ 3.9 mmol/l), and clinically important (plasma glucose < 3.0 mmol/l)] were low across all groups. Participants treated with iGlarLixi tended to show weight loss or less weight gain compared with participants receiving insulin glargine alone. No differences were observed in average daily basal insulin dose at week 30 between the two treatment arms or across the different FPG and PPG target groups.

Conclusion Insulin glargine and lixisenatide as a fixed-ratio combination resulted in more participants reaching both FPG and PPG targets, leading to better HbA_{1c} target attainment.

Diabet. Med. 37, 256–266 (2020)

Introduction

Attaining and maintaining glycaemic control as safely as possible is fundamental to the management of Type 2 diabetes [1,2]. Control of HbA_{1c} is linked to a reduced risk of microvascular and, to a lesser extent, macrovascular complications [2,3], and serves as a convenient guide of overall glycaemic control. Although HbA_{1c} is a primary consideration and gold standard of glycaemic control measurement in people with diabetes [2], treatment guidelines are increasingly recognizing the need to consider both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG), to select optimal treatment in pursuit of overall glycaemic control [2,4–6]. The American Diabetes Association (ADA) recommends target preprandial capillary plasma glucose of 4.4–7.2 mmol/l (80–130 mg/dl), and peak postprandial capillary plasma glucose levels of < 10.0 mmol/l (<

Correspondence to: Jaime A. Davidson.
E-mail: Jaime.Davidson@UTSouthwestern.edu

What's new?

- Achievement of both fasting (FPG) and postprandial plasma glucose (PPG) targets is important for optimal glycaemic control in Type 2 diabetes.
- This *post hoc* analysis of the LixiLan-O and LixiLan-L trials shows that targeting both FPG and PPG results in improved glycaemic control, with weight neutrality and a low risk of hypoglycaemia.
- It is clinically desirable to achieve control of FPG and PPG. More people treated with iGlarLixi achieved control, and those who did so reached an HbA_{1c} target of < 53 mmol/mol (< 7.0%), had a greater drop in HbA_{1c}, and did not gain weight compared with insulin glargine or lixisenatide alone.

180 mg/dl) [2], whereas the American Association of Clinical Endocrinologists (AACE) recommends more stringent targets of < 5.6 mmol/l (< 110 mg/dl) for FPG and < 7.8 mmol/l (< 140 mg/dl) for PPG for people without serious comorbidities and no known risk of hypoglycaemia [5].

PPG has been shown to be a main contributor to HbA_{1c} levels in people with Type 2 diabetes with HbA_{1c} levels < 56 mmol/mol (< 7.3%), whereas in people with poorly controlled Type 2 diabetes, the importance of FPG increases, becoming the predominant contributing factor at HbA_{1c} levels > 78 mmol/mol (> 9.3%) [7–9]. A meta-analysis of 14 randomized controlled trials (RCT) found that PPG had a stronger correlation with HbA_{1c}, and contributed to a larger reduction in HbA_{1c} than FPG [10]. A study of people with Type 2 diabetes treated with insulin found that FPG correlated significantly with HbA_{1c} only before lunch, whereas PPG levels correlated significantly at all times of the day [11].

Basal insulin analogues are effective anti-diabetes drugs and primarily reduce FPG. Considering that elevated PPG remains untreated and is usually the first glycaemic defect observed in people with diabetes [12], early therapy to target both elevated PPG and FPG levels may be a better approach to achieve glycaemic control in people with hyperglycaemia. Epidemiological studies also have shown that PPG can be associated with increased cardiovascular risk independent of FPG, but not HbA_{1c} [3,13]. Thus, due to the contributions and impact of both FPG and PPG on HbA_{1c} levels in the course of Type 2 diabetes, treating specific glycaemic abnormalities is an important therapeutic goal.

The recently published joint consensus report by the ADA and the European Association for the Study of Diabetes places a higher importance on lifestyle modifications and individual glycaemic targets than previous guidelines, with more consideration given to the concerns of people with diabetes [4]. Metformin remains the preferred initial glucose-lowering monotherapy; however, contrary to previous recommendations, glucagon-like peptide-1 (GLP-1) receptor agonists are now recommended as the first injectable therapy in people with diabetes requiring treatment intensification, particularly in those with existing cardiovascular disease, unless contraindications exist [4]. This recommendation is based upon evidence demonstrating the positive impact of GLP-1 receptor agonists on body weight with little to no risk of hypoglycaemia [14]. Basal insulin is recommended in people with extreme hyperglycaemia (HbA_{1c} > 97 mmol/mol; > 11.0%), symptoms of hyperglycaemia or evidence of ongoing catabolism [4]. The consensus statement also suggests the use of an injectable combination (i.e. GLP-1 receptor agonist + basal insulin) therapy if HbA_{1c} levels are > 86 mmol/mol (> 10.0%) and/or > 22 mmol/mol (> 2.0%) above target [4].

iGlarLixi is a titratable, fixed-ratio combination of insulin glargine 100 units/ml (iGlar) and the GLP-1 receptor agonist lixisenatide, and is indicated for the treatment of adults with Type 2 diabetes inadequately controlled with basal insulin (< 60 units/day) or lixisenatide alone [15,16]. The rationale for the combination lies in the complementary mode of action of the two components [17]. iGlar predominantly targets FPG by reducing hepatic glucose production, and promoting glucose uptake in liver, muscle and adipose tissue. Lixisenatide primarily targets PPG excursions by reducing glucagon secretion and slowing gastric emptying [18]. The safety and efficacy of iGlarLixi in insulin-experienced and -naive participants with Type 2 diabetes has been demonstrated previously in the open-label, phase 3 clinical trials LixiLan-O and LixiLan-L [15,16].

This *post hoc* analysis of the LixiLan-O and LixiLan-L trials aimed to investigate the relationship between achievement of society-recommended FPG and/or PPG targets, other efficacy outcomes such as changes in HbA_{1c} and attainment of HbA_{1c} goals, and safety outcomes in participants uncontrolled on oral anti-diabetes drugs and/or basal insulin.

Participants and methods

Trials

This *post hoc* analysis evaluated data from the LixiLan-O (clinicaltrials.gov NCT 02058147) and LixiLan-L (NCT 02058160) phase 3 clinical trials, details of which have been published previously [15,16]. For details on ethics committee approvals for these clinical trials, see the previously published study results [15,16].

Briefly, LixiLan-O [15] included people with Type 2 diabetes inadequately controlled on metformin with or without a second oral anti-diabetes drug. After a 4-week optimization period, participants were randomized to receive either iGlarLixi (n = 469) or iGlar (n = 467), both titrated to FPG < 5.6 mmol/l (< 100 mg/dl) up to a maximum insulin dose of 60 units/day, or to once-daily lixisenatide (10–20 μg/day up-titration over 2 weeks, and then maintained at 20 μg/day; n = 234) while continuing with metformin for 30 weeks.

LixiLan-L [16] included people with Type 2 diabetes inadequately controlled on basal insulin with or without up to two oral anti-diabetes drugs. After a 6-week optimization period, participants were randomized to either iGlarLixi ($n = 367$) or iGlar ($n = 369$), both titrated to FPG < 5.6 mmol/l (< 100 mg/dl) up to a maximum insulin dose of 60 units/day for 30 weeks.

For the present analysis, participant data from both studies were stratified by glycaemic target achievement at the end of the study period based on recommendations of the ADA guidelines: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (< 130 mg/dl), and 2-h PPG < 10.0 mmol/l (< 180 mg/dl) [2]; or the AACE guidelines: HbA_{1c} ≤ 48 mmol/mol (≤ 6.5%), FPG < 6.1 mmol/l (< 110 mg/dl), and peak PPG < 7.8 mmol/l (< 140 mg/dl) [5]. The 2-h PPG values were assessed using a standardized meal-test at baseline and week 30. Participants were categorized as follows: both FPG and PPG at target; FPG only at target; PPG only at target; neither at target. Efficacy endpoints were: week 30 attainment of either FPG and/or PPG targets or neither and the relationship to HbA_{1c}; week 30 attainment of HbA_{1c} goals; HbA_{1c} mean change from baseline; mean HbA_{1c} levels; change in body weight; and composite endpoint of achieving target HbA_{1c} without hypoglycaemia and without weight gain. Safety endpoints were: documented symptomatic hypoglycaemia [plasma glucose ≤ 3.9 mmol/l (≤ 70 mg/dl)] and clinically important hypoglycaemia [defined as plasma glucose < 3.0 mmol/l (< 54 mg/dl) with or without symptoms]; and gastrointestinal adverse events.

Statistical analysis

Efficacy analyses were evaluated with a modified intent-to-treat population of all randomly assigned participants who had a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variables. Last observation carried forward was used for participants with missing data at week 30. The safety population was defined as all randomized participants who received at least one dose of iGlarLixi, iGlar or lixisenatide. *P*-values for continuous variables were based on one-way analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when adjusted on baseline values. *P*-values for categorical variables were based on Fisher's exact test because of the small number of participants. *P*-values for hypoglycaemia incidence rates and events rates were calculated using a generalized linear model with binomial distribution.

Results

Baseline demographics

For the analysis based on ADA criteria, baseline characteristics were similar across FPG and PPG categories between treatment arms in LixiLan-O (Table 1) and LixiLan-L (Table 2), with the exception of a higher percentage of women overall in the iGlarLixi vs. lixisenatide arm ($P = 0.0164$) and a higher baseline 2-h PPG in the iGlarLixi vs. iGlar arm ($P = 0.0476$) in LixiLan-O.

In the analysis based on AACE criteria, baseline characteristics of participants in the LixiLan-O study showed significant differences in the group of participants reaching both FPG and PPG targets, demonstrating a significantly higher baseline FPG in iGlarLixi- vs. iGlar-treated participants ($P = 0.0007$). Baseline 2-h PPG was higher in the iGlarLixi vs. the iGlar and lixisenatide arms ($P < 0.0001$ and $P = 0.0375$, respectively) (Table S1). In the LixiLan-L study, baseline characteristics were similar across FPG and PPG categories between treatment arms (Table S2).

Glycaemic targets

FPG and PPG

In both LixiLan-O and LixiLan-L, the proportion of participants reaching both FPG and PPG targets according to ADA criteria, or PPG target only, was higher in the iGlarLixi arms compared with the iGlar arms of each trial, whereas a higher proportion of participants reached FPG only or neither target in the iGlar arms (Tables 1 and 2; Fig. S1). Similar trends were seen when AACE recommendations were considered (Tables S1 and S2).

HbA_{1c}

In the analysis following ADA criteria for glycaemic targets, significantly more participants achieved HbA_{1c} < 53 mmol/mol (< 7.0%) when treated with iGlarLixi vs. iGlar or lixisenatide in LixiLan-O (76.3% vs. 60.3% and 33.9%, respectively; $P < 0.001$ for both comparisons) and with iGlarLixi vs. iGlar in LixiLan-L (56.3% vs. 30.4%, respectively; $P < 0.001$). Reductions in HbA_{1c} and proportion of participants achieving HbA_{1c} < 53 mmol/mol (< 7.0%) were highest in those achieving both FPG and PPG targets, and lowest in those not achieving either target (Fig. 1). Notably, in both studies, participants in the iGlarLixi arm achieved a greater reduction in HbA_{1c} across FPG and PPG targets, with the exception of the group at PPG target only, where the reduction in the iGlarLixi vs. iGlar arm was similar (LixiLan-O) or slightly less (LixiLan-L) (Fig. 1a,b). More importantly, across all FPG and PPG targets, more participants in the iGlarLixi vs. iGlar or lixisenatide arms achieved HbA_{1c} targets, with the exception of the group not achieving FPG or PPG targets in LixiLan-O, where the proportion of participants achieving targets between treatment groups was similar and the differences were non-significant (Fig. 1c,d). Similar results were seen in the analysis following AACE criteria, with iGlarLixi also achieving greater reduction in HbA_{1c} across all FPG and PPG targets along with a greater proportion of participants achieving HbA_{1c} targets. The only exception in both trials was the group reaching both FPG and PPG target, where the proportions of participants achieving

Table 1 Participant demographic and baseline characteristics by attainment of fasting plasma glucose and/or postprandial plasma glucose PPG targets (ADA recommendations) in LixiLan-O

	FPG and PPG at target			FPG at target only			PPG at target only			Neither at target			Overall		
Characteristic	iGlarLixi	iGlar	Lixi	iGlarLixi	iGlar	Lixi	iGlarLixi	iGlar	Lixi	iGlarLixi	iGlar	Lixi	iGlarLixi	iGlar	Lixi
Participants achieving ADA targets at week 30, *n* (%)	241 (51)	119 (26)	46 (20)	117 (25)	203 (44)	27 (12)	40 (9)	22 (5)	63 (27)	70 (15)	122 (26)	97 (42)	468	466	233
Age, years	58.4 (8.9)	58.0 (9.4)	59.7 (8.5)	57.6 (10.2)	59.9 (9.7)*	60.1 (8.9)	62.0 (9.0)	57.2 (10.6)	58.3 (8.9)	56.6 (10.2)	56.4 (8.3)	57.9 (8.6)	58.2 (9.5)	58.3 (9.4)	58.6 (8.7)
Women, %	51.0	54.6	43.5	65.8	50.7*	48.1	52.5	45.5	39.7	35.7	42.6	43.3	52.6	49.4	42.9*
Race, %															
White	88.0	88.2	84.8	88.9	92.6	85.2	100	90.9	100	85.7	87.7	92.8	88.9	90.1	92.3
Black	7.1	7.6	10.9	7.7	3.9	14.8	0.0	9.1	0.0	10.0	11.5	3.1	7.1	7.1	5.2
Asian	2.1	2.5	0.0	0.9	2.0	0.0	0.0	0.0	0.0	2.9	0.0	3.1	1.7	1.5	1.3
Other	2.9	1.7	4.3	2.6	1.5	0.0	0.0	0.0	0.0	1.4	0.8	1.0	2.4	1.3	1.3
BMI, kg/m^2	31.3 (4.3)	32.0 (4.1)	31.9 (4.4)	31.5 (4.5)	30.8 (4.4)	32.0 (4.2)	33.1 (4.1)	32.4 (4.7)	33.1 (4.0)	32.3 (4.6)	32.7 (4.7)	31.4 (4.6)	31.7 (4.4)	31.7 (4.5)	32.0 (4.4)
Type 2 diabetes duration, years	9.2 (5.8)	8.5 (5.2)	9.8 (7.7)	8.6 (5.4)	9.4 (6.1)	10.3 (8.3)	9.1 (5.1)	6.2* (3.6)	8.4 (5.5)	8.3 (4.9)	7.9 (5.2)	8.3 (5.2)	8.9 (5.5)	8.6 (5.6)	8.9 (6.2)
Basal insulin dose, units/day	10.1 (0.9)	10.1 (0.5)	n/a	10.1 (0.5)	10.0 (0.8)	n/a	10.2 (0.9)	10 (0.00)	n/a	10.3 (1.0)	10.2 (0.8)	n/a	10.1 (0.81)	10.1 (0.7)	n/a
Baseline HbA_{1c}, mmol/mol	65 (8.1)	63 (7.2)	63 (7.1)	64 (7.1)	65 (7.5)	65 (7.0)	65 (6.3)	67 (8.2)	66 (7.7)	67 (7.9)	66 (7.5)	66 (8.4)	65 (7.7)	65 (7.5)	65 (7.9)
Baseline HbA_{1c}, %	8.0 (0.7)	7.9 (0.7)	7.9 (0.7)	8.0 (0.6)	8.1 (0.7)	8.1 (0.6)	8.1 (0.6)	8.3 (0.7)	8.2 (0.7)	8.3 (0.7)	8.2 (0.7)	8.2 (0.8)	8.1 (0.7)	8.1 (0.7)	8.1 (0.7)
Baseline FPG, mmol/l	9.6 (2.3)	8.7‡ (2.0)	9.1 (2.2)	9.6 (2.3)	10.0 (2.2)	9.1 (2.3)	10.8 (2.1)	9.9 (2.0)	10.3 (2.2)	10.6 (2.5)	10.3 (2.5)	10.0 (2.0)	9.9 (2.3)	9.8 (2.3)	9.8 (2.2)
Baseline 2-h PPG, mmol/l	14.5 (3.6)	12.6‡ (3.1)	13.2* (3.3)	15.6 (3.5)	16.1 (3.5)	14.1 (3.8)	15.6 (3.3)	12.3† (3.1)	14.8 (3.0)	15.8 (3.8)	14.6* (3.2)	15.9 (3.2)	15.1 (3.6)	14.6* (3.6)	14.9 (3.3)

Data are shown as mean (SD), unless indicated otherwise. Corresponding data for AACE targets are shown in Table S1. ADA targets: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (< 130 mg/dl), 2-h PPG < 10.0 mmol/l (< 180 mg/dl). mg/dl = 18 × mmol/l.

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; Lixi, lixisenatide; n/a, not applicable; PPG, postprandial plasma glucose; SD, standard deviation.

*P < 0.05 vs. iGlarLixi; ‡P < 0.001 vs. iGlarLixi; †$P \leq 0.0001$ vs. iGlarLixi.

Table 2 Participant demographic and baseline characteristics by attainment of fasting plasma glucose and/or postprandial plasma glucose targets (ADA recommendations) in LixiLan-L

	FPG and PPG at target		FPG at target only		PPG at target only		Neither at target		Overall	
Characteristic	iGlarLixi	iGlar	iGlarLixi	iGlar	iGlarLixi	iGlar	iGlarLixi	iGlar	iGlarLixi	iGlar
Participants achieving ADA targets at Week 30, *n* (%)	152 (42)	51 (14)	86 (23)	189 (52)	39 (11)	7 (2)	89 (24)	118 (32)	366	365
Age, years	59.1 (9.6)	58.7 (9.5)	59.2 (9.9)	60.4 (8.4)	59.2 (8.9)	62.6 (7.7)	61.1 (8.8)	60.8 (8.7)	59.6 (9.4)	60.3 (8.7)
Women, %	57.9	52.9	54.7	52.9	59.0	71.4	48.3	49.2	54.9	52.1
Race, %										
White	90.8	90.2	86.0	91.5	97.4	85.7	96.6	92.4	91.8	91.5
Black	5.9	9.8	8.1	4.8	2.6	14.3	0.0	5.1	4.6	5.8
Asian	3.3	0	5.8	2.6	0	0	2.2	2.5	3.3	2.2
Other	0	0	0	1.1	0	0	1.1	0	0.3	0.5
BMI, kg/m^2	31.2 (4.1)	31.9 (4.8)	31.1 (4.4)	30.8 (4.1)	32.3 (4.4)	32.3 (3.5)	31.2 (4.3)	30.8 (4.0)	31.3 (4.2)	31.0 (4.1)
Type 2 diabetes duration, years	11.5 (6.9)	11.3 (5.6)	11.7 (5.7)	11.9 (7.2)	12.4 (5.4)	13.7 (4.6)	13.2 (7.4)	12.6 (7.0)	12.0 (6.6)	12.1 (6.9)
Oral anti-diabetes drug at screening, %										
0	5.3	0.0	9.3	4.2	0.0	0.0	2.2	9.3*	4.9	5.2
1	48.7	66.7*	44.2	58.7*	56.4	42.9	60.7	50.0	51.4	56.7
2	46.1	33.3	46.5	37.0	43.6	57.1	37.1	40.7	43.7	38.1
Baseline HbA_{1c}, mmol/mol	63 (6.9)	64 (8.6)	66 (7.6)	65 (8.1)	65 (8.6)	68 (9.2)	66 (7.4)	65 (7.4)	65 (7.5)	65 (8.0)
Baseline HbA_{1c}, %,	7.9 (0.6)	8.0 (0.8)	8.2 (0.7)	8.1 (0.7)	8.0 (0.8)	8.4 (0.8)	8.2 (0.7)	8.1 (0.7)	8.1 (0.7)	8.1 (0.7)
Baseline FPG, mmol/l	6.9 (1.7)	6.8 (1.8)	7.3 (1.9)	7.2 (2.1)	7.6 (1.7)	8.4 (2.2)	8.0 (2.3)	7.7 (2.1)	7.3 (1.9)	7.3 (2.1)
Baseline 2-h PPG, mmol/l	13.7 (3.7)	12.9 (3.2)	15.4 (4.0)	15.3 (3.7)	15.4 (3.6)	16.1 (3.2)	15.7 (3.4)	15.2 (3.8)	14.7 (3.8)	14.9 (3.7)

Data are shown as mean (SD), unless indicated otherwise. Corresponding data for AACE targets are shown in Table S2. ADA targets: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (< 130 mg/dl), 2-h PPG < 10.0 mmol/l (< 180 mg/dl). mg/dl = 18 × mmol/l.

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; PPG, postprandial plasma glucose; SD, standard deviation.

*P < 0.05 vs. iGlarLixi.

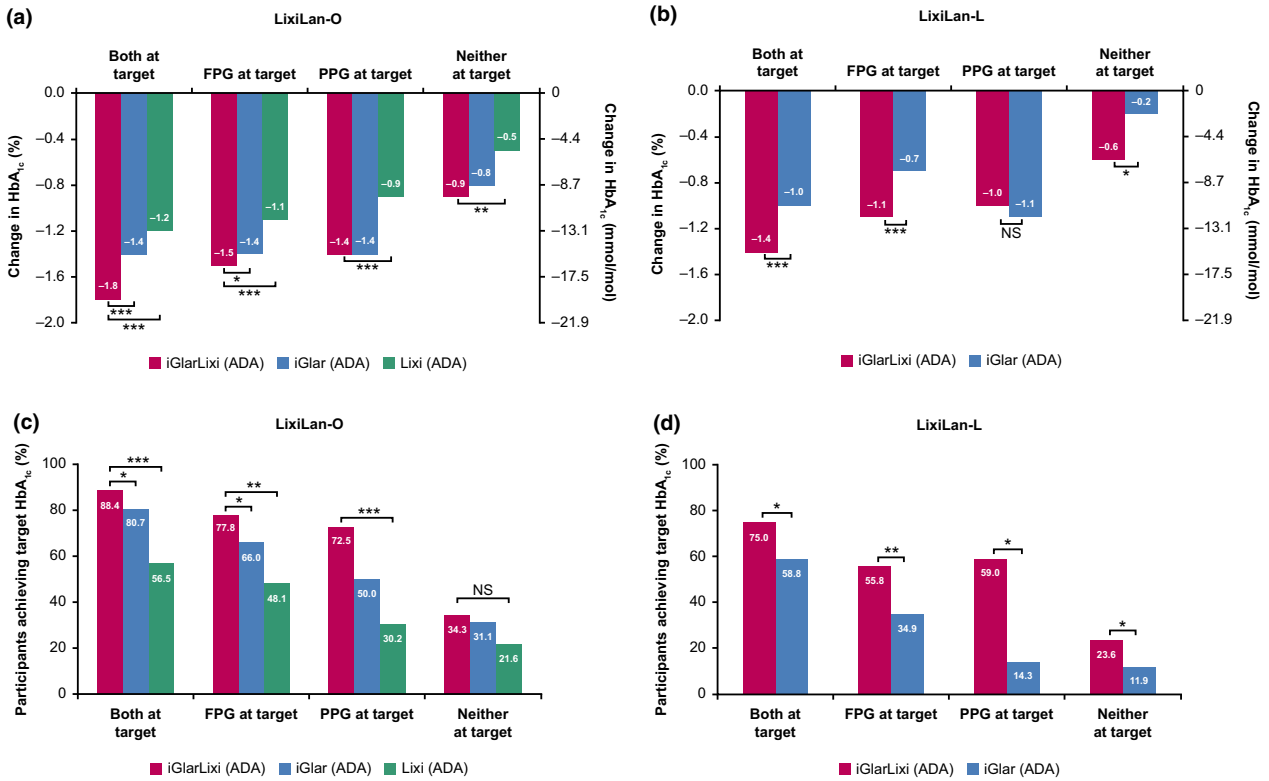

FIGURE 1 (a,b) Mean change in HbA_{1c} and (c,d) proportion of participants achieving HbA_{1c} targets by attainment of fasting plasma glucose (FPG) and/or postprandial plasma glucose (PPG) targets (American Diabetes Association recommendations) at week 30 in (a,c) LixiLan-O and (b,d) LixiLan-L trials. Corresponding data for analysis by American Association of Clinical Endocrinologists targets are shown in Fig. S2. American Diabetes Association targets: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (130 mg/dl), PPG < 10.0 mmol/l (< 180 mg/dl). ADA, American Diabetes Association; iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; Lixi, lixisenatide; NS, not significant.*$P \leq 0.05$; **$P \leq 0.005$; ***$P \leq 0.001$.

HbA_{1c} targets were similar across all treatment groups (Fig. S2). In both studies, mean week 30 HbA_{1c} levels were generally lower in participants treated with iGlarLixi vs. iGlar or lixisenatide, regardless of attainment of FPG or PPG targets or society-recommended glycaemic targets (ADA or AACE recommendations) (Fig. S3).

Hypoglycaemia

Overall hypoglycaemia rates—in the analysis using ADA criteria for glycaemic targets—were low in both LixiLan-O and LixiLan-L (Table 3), and no significant differences between treatment groups across recommended FPG and PPG targets were observed in LixiLan-O or LixiLan-L, except for clinically important hypoglycaemia (plasma glucose < 3.0 mmol/l; < 54 mg/dl) event rates in LixiLan-L, whereas rates were higher in iGlarLixi vs. iGlar among participants reaching both FPG and PPG targets ($P = 0.0415$) or those achieving neither the FPG nor the PPG target ($P = 0.0061$) (Table 3).

Overall, similar results were observed for the analysis using AACE criteria for glycaemic targets, with the only significant differences between iGlarLixi and iGlar seen in participants who did not achieve either target (Table S3).

Insulin dose

There were no differences in average daily basal insulin dose at week 30 between the iGlarLixi and iGlar treatment arms overall or across the different FPG and PPG categories (Fig. S4)

Change in body weight

Participants on iGlarLixi who reached both FPG and PPG targets irrespective of ADA or AACE targets, or trial enrolment achieved weight loss (Fig. 2; Fig. S5). Interestingly, weight change was also less pronounced in participants on iGlar when achieving both ADA and AACE targets. Overall, participants treated with iGlarLixi compared with iGlar tended to experience less weight gain or weight loss across both trials. Although weight change was consistently significant between the two arms in LixiLan-O, the difference in weight change in LixiLan-L between the two arms was significant only in participants achieving FPG targets or neither target (Fig. 2; Figs S5 and S6) Overall, a higher proportion of participants achieved weight loss while on iGlarLixi compared with iGlar. (Fig. S6a,b,e,f).

Table 3 Incidence (%) and event rates of hypoglycaemia (events/participant-year) by attainment of fasting plasma glucose and/or postprandial plasma glucose targets (ADA recommendations) at Week 30 in LixiLan-O and LixiLan-L trials

	FPG and PPG at target			FPG at target only			PPG at target only			Neither at target		
Characteristic	iGlarLixi	iGlar	*P*-value*	iGlarLixi	iGlar	*P*-value*	iGlarLixi	iGlar	*P*-value*	iGlarLixi	iGlar	*P*-value*
LixiLan-O	*N* = 237	*N* = 118		*N* = 108	*N* = 193		*N* = 40	*N* = 23		*N* = 84	*N* = 133	
Any hypoglycaemia												
Incidence, % (SE)	30.8 (3.0)	27.97 (4.13)	0.5825	32.41 (4.5)	33.68 (3.4)	0.8223	32.50 (7.41)	34.78 (9.93)	0.8532	26.19 (4.80)	24.81 (3.75)	0.8201
Event rate, events/participant-year (SE)	1.93 (0.33)	1.79 (0.42)	0.7959	1.64 (0.33)	1.76 (0.32)	0.8852	1.80 (0.60)	1.57 (0.60)	0.8242	2.26 (0.61)	1.71 (0.40)	0.5444
Documented symptomatic hypoglycaemia†												
Incidence, % (SE)	25.32 (2.82)	22.03 (3.82)	0.4968	26.85 (4.26)	27.46 (3.21)	0.9093	32.50 (7.41)	26.09 (9.16)	0.5940	21.43 (4.48)	19.55 (3.44)	0.7374
Event rate, events/participant-year (SE)	1.45 (0.27)	1.10 (0.32)	0.3812	1.20 (0.28)	1.30 (0.29)	0.9098	1.37 (0.42)	0.67 (0.32)	0.3356	1.80 (0.57)	1.34 (0.36)	0.5725
Clinically important hypoglycaemia‡												
Incidence, % (SE)	7.59 (1.72)	4.24 (1.85)	0.2325	8.33 (2.66)	8.29 (1.98)	0.9896	10.0 (4.74)	0.0 (-)	0.9999	8.33 (3.02)	8.27 (2.39)	0.9870
Event rate, events/participant-year (SE)	0.22 (0.06)	0.07 (0.03)	0.0631	0.18 (0.06)	0.15 (0.04)	0.7305	0.21 (0.11)	0.0 (-)	0.9999	0.38 (0.18)	0.20 (0.06)	0.2626
LixiLan-L	*N* = 152	*N* = 51		*N* = 75	*N* = 180		*N* = 39	*N* = 7		*N* = 99	*N* = 127	
Any hypoglycaemia												
Incidence, % (SE)	46.71 (4.05)	35.29 (6.69)	0.1569	44.00 (5.73)	53.33 (3.72)	0.1753	43.59 (7.94)	42.86 (18.70)	0.9713	40.40 (4.93)	43.31 (4.40)	0.6610
Event rate, events/participant-year (SE)	3.49 (0.58)	4.32 (1.27)	0.5260	4.49 (1.12)	6.11 (0.83)	0.2438	3.96 (0.96)	1.23 (0.62)	0.1765	4.83 (1.17)	4.15 (0.74)	0.3687
Documented symptomatic hypoglycaemia†												
Incidence, % (SE)	43.42 (4.02)	31.37 (6.50)	0.1313	41.33 (5.69)	50.00 (3.73)	0.2075	35.90 (7.68)	42.86 (18.70)	0.7260	35.35 (4.80)	36.22 (4.26)	0.8927
Event rate, events/participant-year (SE)	2.82 (0.47)	3.61 (1.23)	0.4811	3.05 (0.68)	5.25 (0.77)	0.0542	2.68 (0.80)	0.98 (0.51)	0.2965	3.59 (1.03)	3.13 (0.67)	0.3887
Clinically important hypoglycaemia‡												
Incidence, % (SE)	18.42 (3.14)	7.84 (3.76)	0.0821	14.67 (4.09)	15.00 (2.66)	0.9457	17.95 (6.15)	14.29 (13.23)	0.8143	19.19 (3.96)	11.02 (2.78)	0.0879
Event rate, events/participant-year (SE)	0.54 (0.13)	0.17 (0.09)	**0.0415**	0.43 (0.15)	0.46 (0.11)	0.8568	0.35 (0.13)	0.49 (0.49)	0.7153	1.04 (0.43)	0.35 (0.13)	**0.0061**

Corresponding data for AACE targets are shown in Table S3. ADA targets: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (< 130 mg/dl), 2-h PPG < 10.0 mmol/l (< 180 mg/dl).
*Compared with iGlarLixi.
†Documented symptomatic hypoglycaemia: PPG ≤ 3.9 mmol/l (≤ 70 mg/dl).
‡Clinically important hypoglycaemia: < 3.0 mmol/l (< 54 mg/dl), regardless if hypoglycaemia was symptomatic or non-symptomatic.
If no assessment was available at Week 30, it was treated as not at goal.
Significant *P*-values shown in bold. *P*-values for hypoglycaemia incidence were from a generalized linear model (PROC GENMOD, Binomial distribution) which included treatment arm as factor. *P*-values for hypoglycaemia event were from a generalized linear model (PROC GENMOD, Negative Binomial distribution) which included treatment arm as factor, and log of exposure as offset term.
Hypoglycaemia events with missing 2-h PPG are excluded.
AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; FPG, fasting plasma glucose; iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; PPG, postprandial plasma glucose; SE, standard error.

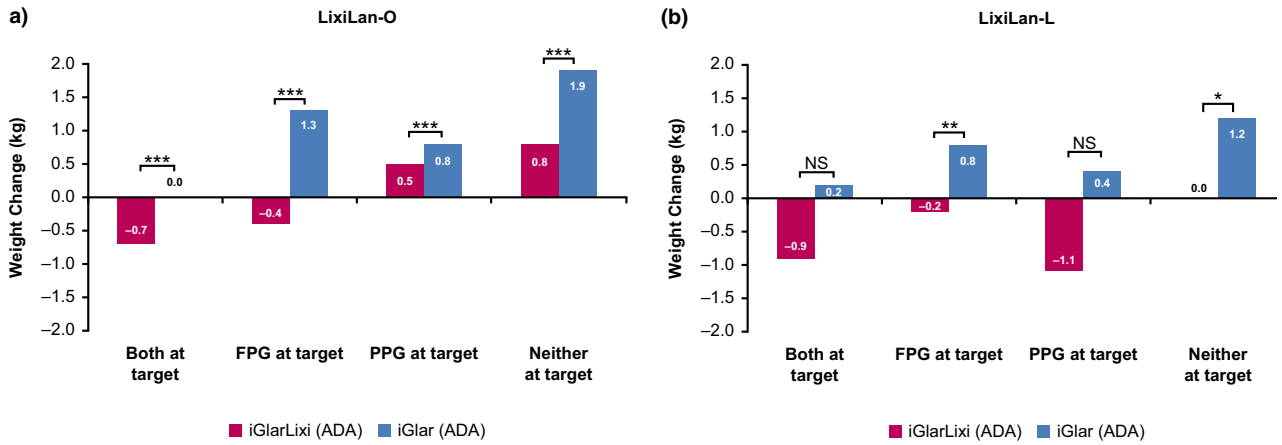

FIGURE 2 Weight change by attainment of fasting plasma glucose (FPG) and/or postprandial plasma glucose (PPG) targets (American Diabetes Association recommendations) at week 30 in (a) LixiLan-O and (b) LixiLan-L trial. Corresponding data for analysis according to American Association of Clinical Endocrinologists targets are shown in Fig. S5. American Diabetes Association targets: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (< 130 mg/dl), PPG < 10.0 mmol/l (< 180 mg/dl). iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; NS, not significant. *$P \leq 0.05$; **$P \leq 0.005$; ***$P \leq 0.001$.

Composite endpoint

In both LixiLan-O and LixiLan-L, a higher proportion of participants who achieved both FPG and PPG goals also achieved HbA_{1c} < 53 mmol/mol (< 7.0%) with no hypoglycaemia and no weight gain compared with those who achieved FPG only or PPG only or neither target (Fig. 3; Fig. S7). Participants who did not achieve either FPG or PPG targets were the least likely to achieve the composite endpoint (Fig. 3; Fig. S7). In LixiLan-O, those treated with iGlarLixi and who achieved the FPG target only according to ADA and AACE criteria, were more likely to achieve the composite endpoint compared with those treated with iGlar (both $P \leq 0.005$) (Fig. 3a; Fig. S7). Conversely, among those who achieved neither the FPG nor the PPG target, those treated with iGlar were more likely to achieve the composite endpoint compared with those treated with iGlarLixi ($P \leq 0.05$) (Fig. 3a). In LixiLan-L, those treated with iGlarLixi who achieved the FPG target (AACE criteria only) or neither the FPG nor the PPG targets (ADA and AACE criteria) were more likely to achieve the composite endpoint than those treated with iGlar ($P \leq 0.05$) (Fig. 3b; Fig. S7). All other comparisons were non-significant.

Gastrointestinal adverse events

In both LixiLan-O and LixiLan-L, the groups with the fewest participants experiencing gastrointestinal adverse events were those reaching the PPG target only, in both the ADA

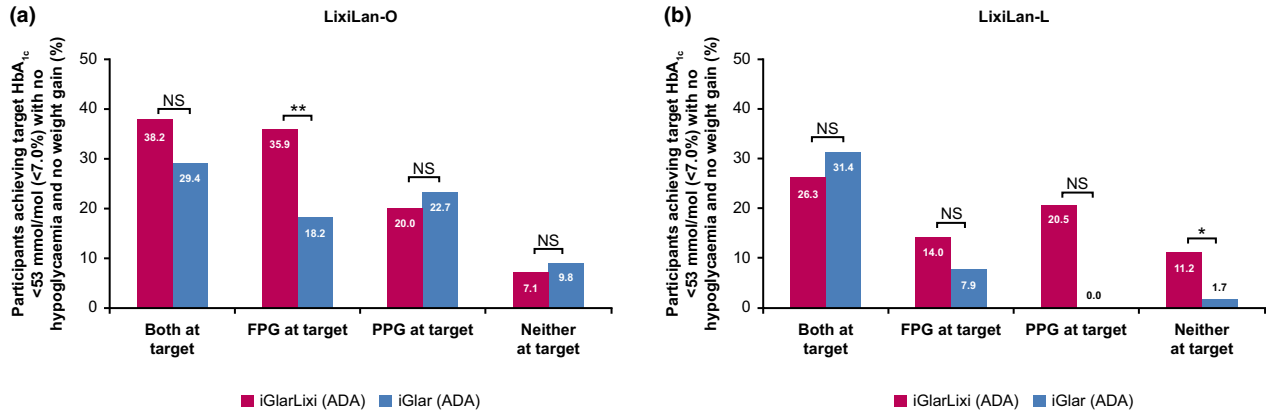

FIGURE 3 Proportion of participants achieving composite endpoint of target HbA_{1c} < 53 mmol/mol (< 7.0%) without hypoglycaemia and without weight gain by attainment of fasting plasma glucose (FPG) and/or postprandial plasma glucose (PPG) targets (American Diabetes Association recommendations) at week 30 in (a) LixiLan-O and (b) LixiLan-L trials. Corresponding data for American Association of Clinical Endocrinologists targets are shown in Fig. S7. American Diabetes Association targets: HbA_{1c} < 53 mmol/mol (< 7.0%), FPG < 7.2 mmol/l (< 130 mg/dl), PPG < 10.0 mmol/l (< 180 mg/dl). iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; NS, not significant. *$P \leq 0.05$; **$P \leq 0.005$.

and AACE criteria analyses (Fig. S8). Regardless of study, FPG or PPG target group or society recommendation (ADA or AACE), more participants treated with iGlarLixi vs. iGlar experienced GI AEs (Fig. S8).

Discussion

Achievement of glycaemic control while minimizing the risk of hypoglycaemia and weight gain are three of the key needs and challenges for physicians and people with Type 2 diabetes. This *post hoc* analysis of data from the LixiLan-O and LixiLan-L trials further corroborates previous studies showing that targeting both FPG and PPG by combining iGlar and lixisenatide can help to address these needs, resulting in improved glycaemic control, together with a low risk of hypoglycaemia and weight gain [19]. In insulin-naive participants with Type 2 diabetes in LixiLan-O, and insulin-experienced participants with Type 2 diabetes in LixiLan-L, a higher proportion of participants achieved HbA_{1c} goals when both FPG and PPG targets were also achieved, regardless of treatment. However, participants were more likely to reach both FPG and PPG targets when they were treated with iGlarLixi compared with iGlar alone, according to both the ADA's recommendations and the more stringent AACE's recommendations at similar doses of insulin. Basal-plus, basal–bolus and premixed regimens are alternative methods to intensify basal insulin regimens by providing additional PPG control. However, these regimens are also associated with increased risk of hypoglycaemia vs. basal insulin alone, as well as the potential for weight gain, and the need for additional daily injections. The use of a single daily injection of iGlarLixi allows for a less complex and more convenient dosing schedule, while mitigating insulin-associated weight gain and without increasing the incidence of hypoglycaemia compared with basal insulin alone. Co-administration of a GLP-1 receptor agonist and basal insulin may also help limit excess use of total insulin, and has the potential to be insulin sparing [20]. In LixiLan-O and LixiLan-L trials, despite the similar final mean basal insulin daily dose between the iGlarLixi and the iGlar groups, significantly more people in the iGlarLixi group achieved the glycaemic targets [15,16]. This apparent lack of insulin-sparing effect may be a reflection of the study design which limited the iGlar dose to a maximum of 60 units to match the capped dose of iGlarLixi [20]. For example, in the DUAL II trial of the combination of insulin degludec and liraglutide (IDegLira), where the dose of degludec was capped, the end of study daily insulin dose was the same for IDegLira and degludec, whereas in the DUAL V trial where the dose of degludec was not capped, the end of study daily insulin dose of IDegLira was significantly lower [21].

Rates of hypoglycaemia were low and generally comparable between iGlarLixi and iGlar within each trial, with higher rates of hypoglycaemia in the participants who had the longest duration of diabetes in LixiLan-L. However, clinically important hypoglycaemia event rates were slightly higher among those reaching both FPG and PPG or reaching neither FPG nor PPG target subcategories in the iGlarLixi group vs. iGlar. The reasons for these differences are not clear, as there were no significant differences in week 30 iGlar doses between treatment arms or across FPG and PPG categories.

In keeping with previous analyses, people in the overall population who received iGlarLixi tended to experience either weight loss or lower weight gain compared with iGlar alone [15,16]. This was not affected by FPG or PPG target achievement, as these findings were consistent in all target achievement groups. Even with participants who did not reach the FPG and PPG targets, those treated with iGlarLixi experienced weight benefits compared with those treated with iGlar. Interestingly, in both trials, among participants treated with iGlar, weight gain was generally lowest in those who reached both FPG and PPG targets. Furthermore, the proportion of people with composite endpoints of HbA_{1c} at target, without weight gain and without hypoglycaemia was highest among those at both FPG and PPG targets in both treatment groups in both trials. This again signifies the importance of addressing both FPG and PPG targets for optimal diabetes treatment.

As expected, iGlarLixi was associated with a greater number of participants experiencing gastrointestinal adverse events compared with iGlar across all FPG and PPG target groups. In general, these gastrointestinal adverse events associated with iGlarLixi are less frequent than those observed with lixisenatide alone [15], likely due to the more gradual titration of lixisenatide that would occur with iGlarLixi. Overall, gastrointestinal adverse events tended to be transient, of mild/moderate severity, and were generally associated with the initial titration period, mostly waning after approximately 8 weeks [22]. Overall, the rate of withdrawal due to adverse events was low, and predominantly occurred in participants who failed to achieve either FPG or PPG goals.

The limitations of this study relate to its *post hoc* nature. In addition, some FPG and PPG categories for some analyses included only a small number of participants, especially in the PPG category. These small numbers may have resulted in the statistical analyses being underpowered to identify differences.

Conclusion

Targeting both FPG and PPG helps to improve attainment of recommended HbA_{1c} goals compared with controlling FPG levels alone [23,24]. In the present *post hoc* analysis, attaining both FPG and PPG targets resulted in better HbA_{1c} control without weight gain and without hypoglycaemia. Because of the complementary mechanism of action of the two components included in iGlarLixi, more participants reached FPG and PPG targets compared with treatment with iGlar alone or lixisenatide alone.

Funding sources

This study was funded by Sanofi US, Inc.

Competing interests

J.A.D. is a consultant or member of advisory board panel for Amgen Inc., Aspire Bariatrics, AstraZeneca, Boston Therapeutics, Eli Lilly & Co., GSK, Janssen Pharmaceuticals, Merck & Co., Inc., Novo Nordisk and Valeritas, and speaker's bureau member for AstraZeneca, Janssen, Merck-Serono, Novo Nordisk and Takeda; and is in receipt of a research grant from AstraZeneca. C.D. is a consultant for Takeda and NovoNordisk. V.F. is in receipt of research support from Bayer and Boehringer Ingelheim and consulting honoraria from Asahi, Astra-Zeneca, Eli Lilly, Intarcia, NovoNordisk, Sanofi and Takeda. J.P.F. is a member of the advisory panel of AstraZeneca and Sanofi; a consultant for AstraZeneca, BMS and Sanofi; in receipt of research support from AbbVie, AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Ionis, Janssen Pharmaceuticals, Inc., Johnson and Johnson, Lexicon, Ligand, Merck & Co., Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, Theracos and vTv; and is on the speakers' bureau of Sanofi. L.V.G. is in receipt of research support from the European Union (HEPADIP and Resolve consortium) and National Research Funds, Belgium; and is on the advisory board and speakers' bureaus of AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck MSD, Novo Nordisk, Sanofi and Servier. F.G. is in receipt of research support from Eli Lilly, Lifescan and Takeda; and is a consultant and author for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Merck Sharp and Dohme, NovoNordisk, Roche Diabetes Care and Takeda. J.C., T.A.D., M.R. and A.S. are employees of Sanofi US, Inc. L.A.L. is in receipt of research support from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Novo Nordisk, Sanofi; is on the advisory boards of Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi and Servier; and is in receipt of honoraria for providing CME from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi.

Acknowledgements

The authors received writing/editorial support provided by Luke Shelton PhD and Martina Fuchsberger PhD of Excerpta Medica, funded by Sanofi US, Inc. For details on ethics compliance and participants' informed consent, see the previously published study results [15,16].

References

1 Blevins T. Control of postprandial glucose levels with insulin in type 2 diabetes. *Postgrad Med* 2011; **123**: 135–147.
2 American Diabetes Association. 6. Glycemic targets. Standards of medical care in diabetes–2018. *Diabetes Care* 2018; **41**(Suppl 1): S55–S64.
3 Båvenholm PN, Efendic S. Postprandial hyperglycaemia and vascular damage – the benefits of acarbose. *Diab Vasc Dis Res* 2006; **3**: 72–79.
4 Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G *et al*. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2018; **61**: 2461–2498.
5 Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA *et al*. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. *Endocr Pract* 2018; **24**: 91–120.
6 International Diabetes Federation. Global Guidelines for Type 2 Diabetes. 2012. Available at https://www.idf.org/e-library/guidelines/79-global-guideline-for-type-2-diabetes Last accessed 16 August 2018.
7 Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 2003; **26**: 881–885.
8 Monnier L, Colette C. Contributions of fasting and postprandial glucose to hemoglobin A1c. *Endocr Pract* 2006; **12**(Suppl 1): 42–46.
9 Monnier L, Colette C. Postprandial and basal hyperglycaemia in type 2 diabetes: contributions to overall glucose exposure and diabetic complications. *Diabetes Metab* 2015; **41**(Suppl 1): 6S9–6S15.
10 Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Arch Public Health* 2015; **73**: 43.
11 Shimizu H, Uehara Y, Okada S, Mori M. Contribution of fasting and postprandial hyperglycemia to hemoglobin A1c in insulin-treated Japanese diabetic patients. *Endocr J* 2008; **55**: 753–756.
12 Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care* 2007; **30**: 263–269.
13 Ceriello A, Hanefeld M, Leiter L, Monnier L, Moses A, Owens D *et al*. Postprandial glucose regulation and diabetic complications. *Arch Intern Med* 2004; **164**: 2090–2095.
14 Scheen AJ, Van Gaal LF. Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes. *Lancet Diabetes Endocrinol* 2014; **2**: 911–922.
15 Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P *et al*.; LixiLan-O Trial Investigators. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care* 2016; **39**: 2026–2035.
16 Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G *et al*.; LixiLan-L Trial Investigators. 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.
17 Valentine V, Goldman J, Shubrook JH. Rationale for, initiation and titration of the basal insulin/GLP-1RA fixed-ratio combination products, IDegLira and iGlarLixi, for the management of type 2 diabetes. *Diabetes Ther* 2017; **8**: 739–752.
18 Horowitz M, Rayner CK, Jones KL. Mechanisms and clinical efficacy of lixisenatide for the management of type 2 diabetes. *Adv Ther* 2013; **30**: 81–101.

19 Anderson SL, Trujillo JM. Basal insulin use with GLP-1 receptor agonists. *Diabetes Spectr* 2016; **29**: 152–160.
20 Aroda VR, Arulandu JR, Cannon AJ. Insulin/glucagon-like peptide-1 receptor agonist combination therapy for the treatment of type 2 diabetes: are two agents better than one? *Clin Diabetes* 2018; **36**: 138–147.
21 Lingvay I, Pérez Manghi F, García-Hernández P, Norwood P, Lehmann L, Tarp-Johansen MJ *et al*. Effect of insulin glargine uptitration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. *JAMA* 2016; **315**: 898–907.
22 Trujillo JM, Roberts M, Dex T, Chao J, White J, LaSalle J. Low incidence of gastrointestinal adverse events over time with a fixed-ratio combination of insulin glargine and lixisenatide versus lixisenatide alone. *Diabetes Obes Metab* 2018; **20**: 2690–2694.
23 Woerle HJ, Neumann C, Zschau S, Tenner S, Irsigler A, Schirra J *et al*. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes: importance of postprandial glycemia to achieve target HbA1c levels. *Diabetes Res Clin Pract* 2007; **77**: 280–285.
24 Riddle M, Umpierrez G, DiGenio A, Zhou R, Rosenstock J. Contributions of basal and postprandial hyperglycemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. *Diabetes Care* 2011; **34**: 2508–2514.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Proportions of participants achieving ADA targets by attainment of FPG and PPG targets at week 30 in LixiLan-O and LixiLan-L trials.
Figure S2 Mean change in HbA_{1c} and proportion of participants achieving HbA_{1c} targets by attainment of FPG and PPG targets (AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials.
Figure S3 Mean HbA_{1c} by attainment of FPG and PPG targets (ADA and AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials, respectively.
Figure S4 Mean basal insulin dose at week 30 by attainment of FPG and PPG targets (ADA and AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials.
Figure S5 Weight change by attainment of FPG and PPG targets (AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials.
Figure S6 Proportions of participants achieving weight loss and mean weight by attainment of FPG and PPG targets (ADA and AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials.
Figure S7 Proportion of participants achieving composite endpoint of target HbA_{1c} < 53mmol/mol (< 7.0%) without hypoglycaemia and without weight gain by attainment of FPG and PPG targets (AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials.
Figure S8 Number of people with Type 2 diabetes experiencing GI AEs by attainment of FPG and PPG targets (ADA and AACE recommendations, respectively) at week 30 in LixiLan-O and LixiLan-L trials.
Table S1 Participant demographic and baseline characteristics by attainment of FPG and PPG targets (AACE recommendations) in LixiLan-O.
Table S2 Participant demographic and baseline characteristics by attainment of FPG and PPG targets (AACE recommendations) in LixiLan-L.
Table S3 Incidence (%) and event rates of hypoglycaemia (events/pt-year) by attainment of FPG and PPG targets (AACE recommendations) at week 30 in LixiLan-O and LixiLan-L trials.