Short running title:

iGlarLixi effective in achieving glycaemic control in two patient subgroups of the LixiLan-O trial

Title:

Glycaemic benefit of iGlarLixi in insulin-naive type 2 diabetes patients with high HbA1c or those with inadequate glycaemic control on two oral antihyperglycaemic drugs in the LixiLan-O randomized trial

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ABSTRACT

In this post hoc analysis of the randomized controlled LixiLan-O trial in insulin-naive type 2 diabetes mellitus (T2DM) patients not controlled on metformin with or without a second oral antihyperglycaemic drug (OAD), the efficacy and safety of the fixed-ratio combination, iGlarLixi (insulin glargine 100 U [iGlar] and lixisenatide [Lixi]), compared to its individual components was assessed in two patient subgroups: (1) a baseline HbA1c ≥9% (*n* = 134); (2) inadequate control (HbA1c ≥7.0% and ≤9.0%) despite administration of two OADs at screening (*n* = 725).

Treatment with iGlarLixi resulted in a significantly greater reduction in least squares mean HbA1c compared with iGlar or Lixi alone in both subgroups (HbA1c ≥9% group: 2.9%, 2.5%, 1.7%; two OADs group: 1.5%, 1.2%, 0.7%, respectively). Target HbA1c <7% was achieved in >70% of patients on iGlarLixi in both subgroups, while mitigating the weight gain observed with iGlar alone. Rates of hypoglycaemic events were low overall.

These results suggest that iGlarLixi achieves superior glycaemic control compared with iGlar or Lixi alone in T2DM patients with HbA1c ≥9% or those inadequately controlled on two OADs.

Trial registration number: NCT02058147 (LixiLan-O)

Keywords (3–10 keywords required)**:**

glycaemic control, iGlarLixi, insulin glargine 100 U, lixisenatide, type 2 diabetes mellitus

1 | INTRODUCTION

The 2018 American Diabetes Association(ADA)/European Association for the Study of Diabetes (EASD) consensus report on the management of hyperglycaemia in type 2 diabetes mellitus (T2DM) recommend that glycaemic targets should be individualized based on patient preferences and goals and the risk of adverse treatment effects, and that combination therapy may be considered in patients presenting with glycated haemoglobin (HbA1c) levels >1.5% above their target.[1] In addition, in patients with an HbA1c >2% above target or >10%, recommendations include combination therapy with both basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1 RA) (or a fixed-ratio combination thereof) or a basal–prandial combination.[1] This consensus report is aligned with the UK National Institute for Health and Care Excellence diabetes management guidelines, which also recommends considering fixed mixed insulin combinations (premixed insulins).[2] For patients uncontrolled on two oral antihyperglycaemic drugs (OADs), both reports recommend treatment intensification with a third OAD, insulin initiation or a GLP-1 RA.[1-3]

In spite of current recommendations, treatment of diabetes worldwide remains suboptimal, with many patients failing to achieve targets despite the approval of over 40 new treatment options worldwide since 2005.[4-8] While reasons for suboptimal glycaemic control are multiple, major contributing factors include, non-adherence to treatment, therapeutic inertia, and resource limitations.[1,6,8,9] Adverse events, including hypoglycaemia, and weight gain may also affect patient adherence and healthcare professionals' confidence in therapy.[1,6,8,9] Moreover, employing a stepwise approach to treatment intensification may prolong the time to reach effective treatment(s)[10] and possibly contributes to treatment non-adherence. Treatment approaches that simplify therapy and accelerate time to reach target HbA1c, such as early treatment with a fixed-ratio combination of basal insulin and a GLP-1 RA,[1,10,11] could help to address therapeutic inertia, improve outcomes and prevent complications.

The once-daily, titratable, fixed-ratio combination of basal insulin glargine 100 U (iGlar) and the GLP-1 RA lixisenatide (Lixi), iGlarLixi, allows for a single, daily injection targeting both fasting and postprandial glucose. The LixiLan-O trial (NCT02058147) enrolled 1170 patients with T2DM inadequately controlled on metformin with or without a second OAD and found greater HbA1c reductions at Week 30 with iGlarLixi versus iGlar or Lixi alone with no increased risk of hypoglycaemia versus iGlar.[12] iGlarLixi also mitigated the weight gain observed with iGlar alone.

In this post hoc, subgroup analysis of patients from the LixiLan-O trial, we assessed whether intensification to iGlarLixi was efficacious in achieving glycaemic targets in patients with HbA1c ≥9% and those with inadequate glycaemic control (HbA1c ≥7.0% and ≤9.0%) on two OADs. These subgroups of patients were selected because they are predicted to be more difficult to treat with a lower likelihood of reaching target HbA1c. These are also patients who, current guidelines recognise, may need an injectable combination therapy to rapidly achieve glycaemic control, or represent a patient population for whom treatment with two OADs is insufficient.

2 | METHODS

2.1 | LixiLan-O study

The LixiLan-O study design and main results have been published previously.[12] Briefly, LixiLan-O was a 30-week, open-label, randomized, multicentre, Phase 3 clinical trial, enrolling insulin-naive T2DM patients, aged ≥18 years, with inadequate glycaemic control despite being treated for at least 3 months with metformin with or without a second OAD. Inadequate glycaemic control was defined as HbA1c ≥7.5% and ≤10.0% for patients treated with metformin alone and ≥7.0% and ≤ 9.0% for those treated with metformin and a second OAD. Eligible patients entered a 4-week run-in phase during which all OADs except metformin were stopped. In the current post hoc study the efficacy and safety of iGlarLixi compared to its individual components was assessed in two patient subgroups: (1) those with a baseline (after run-in) HbA1c ≥9%; (2) those with inadequate control (HbA1c ≥7.0% and ≤9.0%) despite administration of two OADs at screening. The study was designed and monitored in accordance with Good Clinical Practice, the International Conference on Harmonisation, and the Declaration of Helsinki. Institutional review boards or ethics committees at each study site approved the protocol. Each patient gave written informed consent. This manuscript was prepared in line with the Consolidated Standards of Reporting Trials guidelines.

2.2 | Interventions

At the end of run-in, patients were randomized (2:2:1) to receive iGlarLixi, iGlar or Lixi. iGlarLixi was self-administered once daily, in the hour (0–60 minutes) before breakfast, by SoloSTAR® (Sanofi; Paris, France) pen; doses ranged from 10 U/5 µg to 60 U/20 µg of iGlar/Lixi, respectively. iGlar was self-administered once daily, at any time of the day but at about the

same time every day, by disposable prefilled Lantus SoloSTAR® (Sanofi) pen (100 U/mL) with doses starting at 10 U and capped at 60 U. Lixi was self-administered once daily, in the hour (0–60 minutes) before breakfast, (10 µg for 2 weeks and up-titrated to 20 µg maintenance dose) by disposable prefilled pens (Sanofi). The same dose adjustment algorithm was recommended for iGlar and iGlarLixi. After the first week, the dose was titrated once a week based on insulin glargine dose until the patient reached a target fasting self-monitored plasma glucose of 80–100 mg/dL without hypoglycaemia episodes.

2.3 | Post hoc analysis

Efficacy outcomes in the two subgroups included the effect of treatment on HbA1c and body weight, and final iGlar and Lixi doses. Safety outcomes in these subgroup analyses included gastrointestinal treatment-emergent adverse events (TEAEs). In addition, the proportion of patients with clinically important hypoglycaemia (accompanied by plasma glucose <54 mg/dL) was assessed. Severe symptomatic hypoglycaemia was defined as requiring another person's assistance actively to administer carbohydrate, glucagon, or other resuscitative actions.

2.4 | Statistical analyses

Differences between treatments were determined using an analysis of covariance model with treatment groups, randomization strata of HbA1c at screening (<8%, ≥8%), and country as fixed effects, and baseline value as a covariate, unless otherwise stated. Differences in proportion were analysed using the Cochran–Mantel–Haenszel method. Safety analysis was performed descriptively.

The analysis populations were the modified intent-to-treat (mITT) population, comprising all randomized patients with a baseline and at least one post-baseline assessment, and the safety population, comprising all randomized patients who received at least one dose of study drug.

3 | RESULTS

3.1 | Patient disposition and demographics

At the end of the run-in period, 6% (71 out of 1167) of the patients randomized in LixiLan-O were on two OADs at screening and also had an HbA1c ≥9% at baseline (after run-in). These

patients were therefore included in both subgroup analyses. The two subgroup analyses included 134 patients with baseline HbA1c ≥9% (subgroup 1) and 725 patients receiving two OADs at screening (subgroup 2; mITT populations contained 133 and 722 patients, respectively). Demographics and baseline characteristics were well balanced across treatment groups within each subgroup and generally similar to the overall study cohort (Table S1).

3.2 | Efficacy outcomes

In line with the overall cohort, treatment with iGlarLixi achieved statistically significant greater improvements in HbA1c at Week 30 compared with iGlar or Lixi alone in both subgroups (Figure 1).

3.2.1 | Patients with HbA1c ≥9% at baseline

Treatment with iGlarLixi, iGlar and Lixi reduced least squares (LS) mean HbA1c by 2.9%, 2.5% and 1.7%, respectively ($P = 0.0297$ for iGlarLixi versus iGlar; $P < 0.0001$ for iGlarLixi versus Lixi; final mean HbA1c at Week 30: 6.8%, 7.3% and 8.1%, respectively; Figure 1a). Furthermore, 73.5% of patients achieved HbA1c levels <7% by Week 30 with iGlarLixi versus 47.3% with iGlar and no patients with Lixi (Figure 1b).

Patients on iGlarLixi tended to gain less weight compared with iGlar (LS mean weight gain: 1.3 kg versus 2.0 kg; $P = 0.3$; Figure 1c).

3.2.2 | Patients with two OADs at screening

Treatment with iGlarLixi, iGlar and Lixi reduced LS mean HbA1c by 1.5%, 1.2% and 0.7%, respectively ($P < 0.0001$ for both iGlarLixi versus iGlar and iGlarLixi versus Lixi), from a mean baseline value of 8.0%, 8.0% and 8.1%, respectively (final mean HbA1c at Week 30: 6.6%, 6.9% and 7.4%, respectively; Figure 1a). Moreover, 72.4% of patients achieved HbA1c levels <7% by Week 30 with iGlarLixi versus 57.8% with iGlar and 27.6% with Lixi (Figure 1b). Treatment with iGlarLixi resulted in significantly less weight gain than with iGlar (LS mean weight change: –0.1 versus +1.3 kg; $P < 0.0001$; Figure 1c).

3.3 | Final iGlar and Lixi doses

In the overall study population and both subgroups, final iGlar doses were similar in iGlarLixi and iGlar treatment groups (40–45 U; Table S2). For iGlarLixi, final mean doses of the Lixi component were similar (16–17 μg) in the overall study cohort and both subgroups (Table S2).

3.4 | Safety outcomes

Consistent with the entire LixiLan-O population, gastrointestinal TEAE rates in the iGlarLixi arm were lower compared with the Lixi arm, and higher compared with the iGlar arm in both subgroups. The rates of gastrointestinal TEAEs leading to discontinuation were low in both subgroups (Table 1).

Rates of clinically important hypoglycaemia were similar for the iGlarLixi and iGlar arms in the overall population and the two OADs subgroup (Table 1), but numerically higher in the iGlarLixi versus iGlar arm in the HbA1c ≥9% subgroup. As the number of patients with hypoglycaemic events was low, no meaningful statistical testing could be performed. One patient in the iGlar arm in the two OADs subgroup experienced severe symptomatic hypoglycaemia.

4 | CONCLUSIONS

In these post hoc analyses of insulin-naive patients with T2DM on metformin with an HbA1c ≥9% or inadequately controlled on two OADs at screening, treatment with iGlarLixi resulted in a greater reduction in HbA1c compared with iGlar or Lixi alone. In both subgroups, over 70% of patients treated with iGlarLixi achieved an HbA1c <7%. Consequently, the fixed-ratio combination of iGlar and Lixi, delivered via a single daily injection in iGlarLixi, with its complementary mechanism of action targeting both fasting and postprandial hyperglycaemia, is a viable treatment option for patients with T2DM who have HbA1c levels ≥9% or failed to achieve glycaemic control on two OADs.

There are some limitations to this post hoc analysis. The original trial was not designed or powered to detect differences between treatments within these two subgroups. Additionally, the LixiLan-O study did not apply forced titration but allowed the investigator to make clinical judgements on dosing while avoiding hypoglycaemic episodes. Despite reaching a similar fasting plasma glucose at the end of the study,[12] with a similar unit of insulin glargine

(Supplementary Table 2) and a similar titration algorithm, a greater proportion of patients treated with iGlarLixi achieved the HbA1c target compared with those treated with iGlar. In both arms, there was a proportion of patients who did not reach HbA1c <7% and may have benefitted from further up-titration. Finally, sample sizes, particularly for the HbA1c ≥9% subgroup, were rather small. Patient populations with HbA1c ≥9% are often not well represented in randomized clinical trials, and data focusing on this group are limited. The findings presented here would benefit from validation in a prospective, randomized trial in a larger patient cohort or in a real-world setting.

The results of these subgroup analyses, within the context of the limitations of a post hoc analysis, are in line with the recent ADA/EASD consensus statement[1] and NICE guidelines[2] recommending the initiation of a combination of basal insulin and a GLP-1 RA in patients with an HbA1c >2% above target or >10% overall. The achievement of HbA1c <7% by >70% of patients via a single therapeutic intervention may facilitate treatment intensification in this difficult-to-treat patient group.

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CONFLICT OF INTEREST

MJD: Advisory panel: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, Servier; Consultant: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis; Research support (grants in support of investigator and investigator initiated trials): Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi-Aventis; Speakers bureau: AstraZeneca, Boehringer Ingelheim,

Eli Lilly, Janssen, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk, Sanofi-Aventis, Takeda.

DR-J: Advisory panel, board member, consultant, research support: AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi; Speakers bureau: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Takeda.

TMB: Advisory panel: AstraZeneca, Boehringer Ingelheim, Napp Pharmaceuticals, Novo Nordisk, Sanofi; Research support: AstraZeneca, Bayer, Shire.

FJL-G: Advisory panel: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi; Board member: AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi; Speakers bureau: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi.

GRG: Advisory Panel: AbbVie, AstraZeneca, Merck Sharp & Dohme, Novo Nordisk, Pfizer, Sanofi; Speakers bureau: Amgen, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Eli Lilly, LifeScan, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Servier, Takeda.

DZ: Nothing to disclose.

MB: Employee and stock/shareholder: Sanofi; Honorary Associate Professor: University of Swansea; Non-Executive Director of Ashford and St Peter's Hospital NHS Foundation Trust.

CD-B: Employee and stock/shareholder: Sanofi.

RJM: Advisory panel: Eli Lilly, Novo Nordisk, Sanofi; Speakers bureau: Eli Lilly, Sanofi.

AUTHOR CONTRIBUTIONS

CD-B and MB were involved in the concept/design. TMB, MJD, RJM and DR-J were involved in conduct/data acquisition. All authors were involved in data analysis/interpretation. All authors were involved in critically revising the manuscript, have provided final approval and take full accountability for the work.

DATA SHARING

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and

study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

PRIOR PUBLICATIONS

The subgroup analyses data have been presented previously at the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, USA, 9–13 June 2017 (Davies M, et al. *Diabetes.* 2017;66(suppl. 1A):LB36 [Abstract 137-LB]; Russell-Jones D, et al. *Diabetes.* 2017;66(suppl. 1A):LB35 [Abstract 134-LB]).

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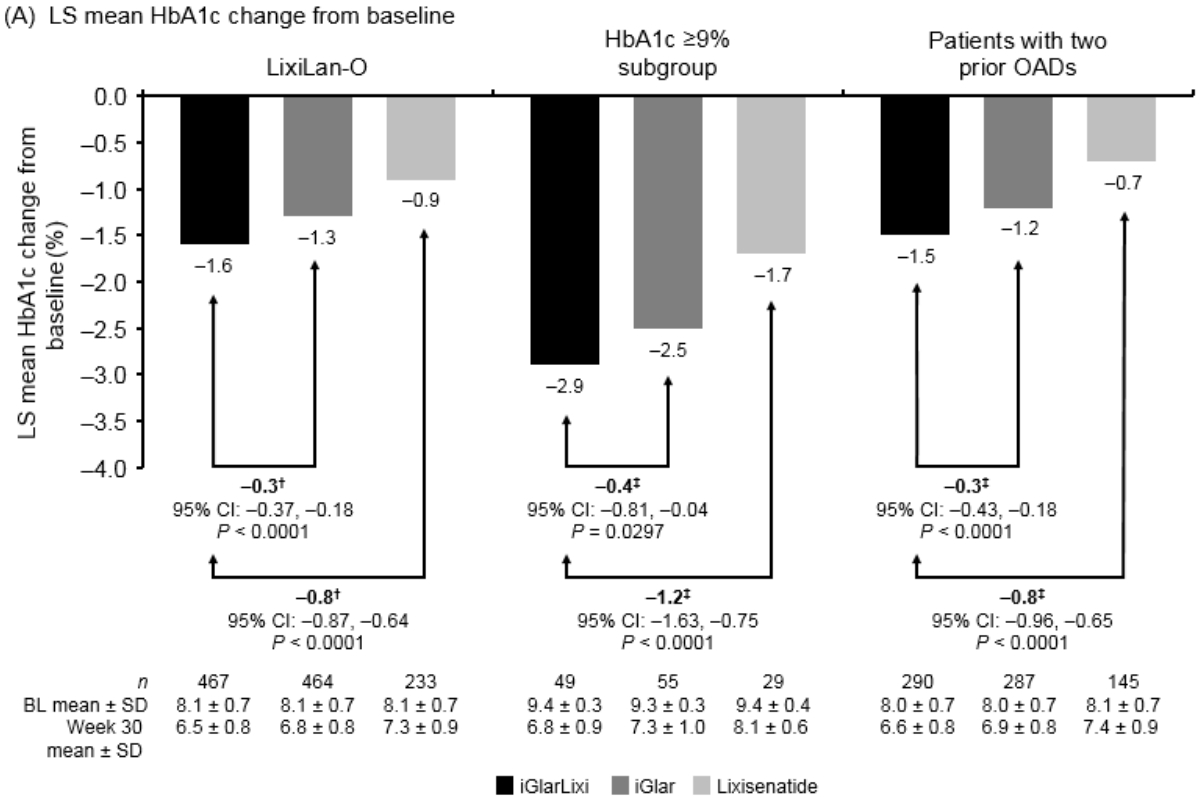
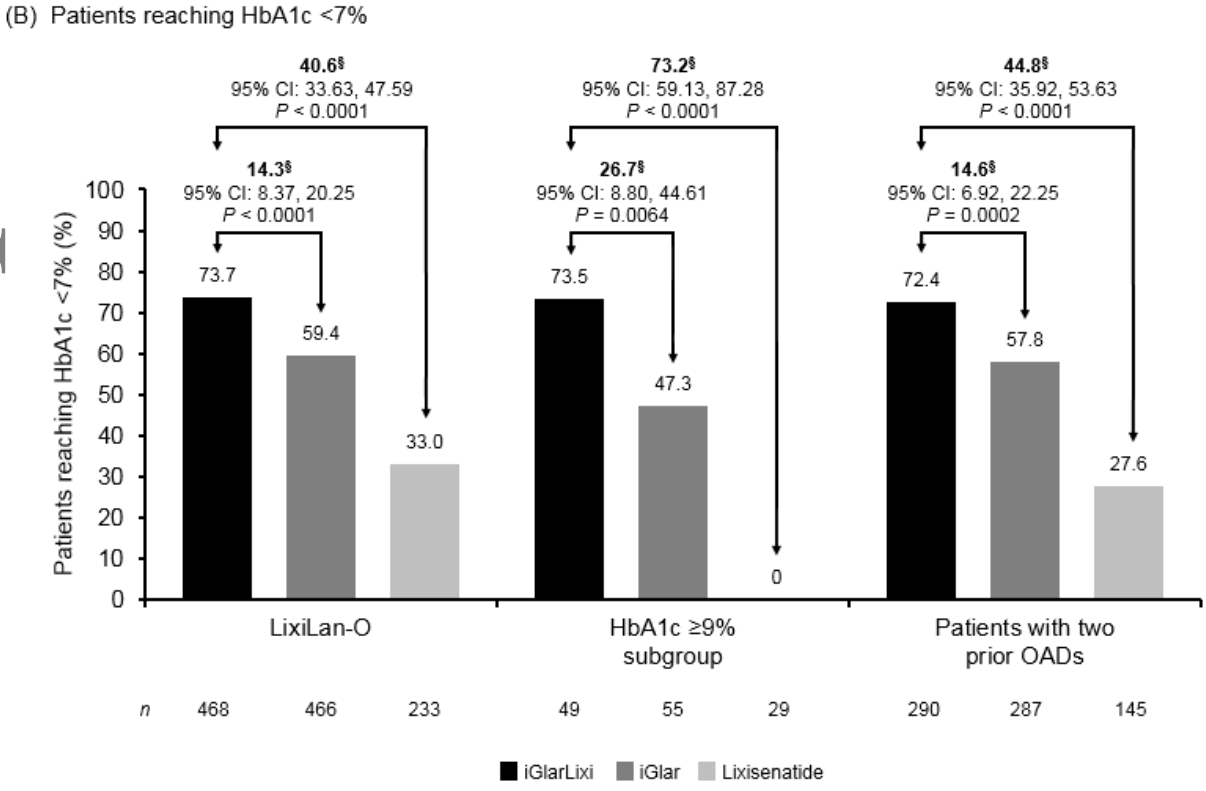
TABLES AND FIGURES





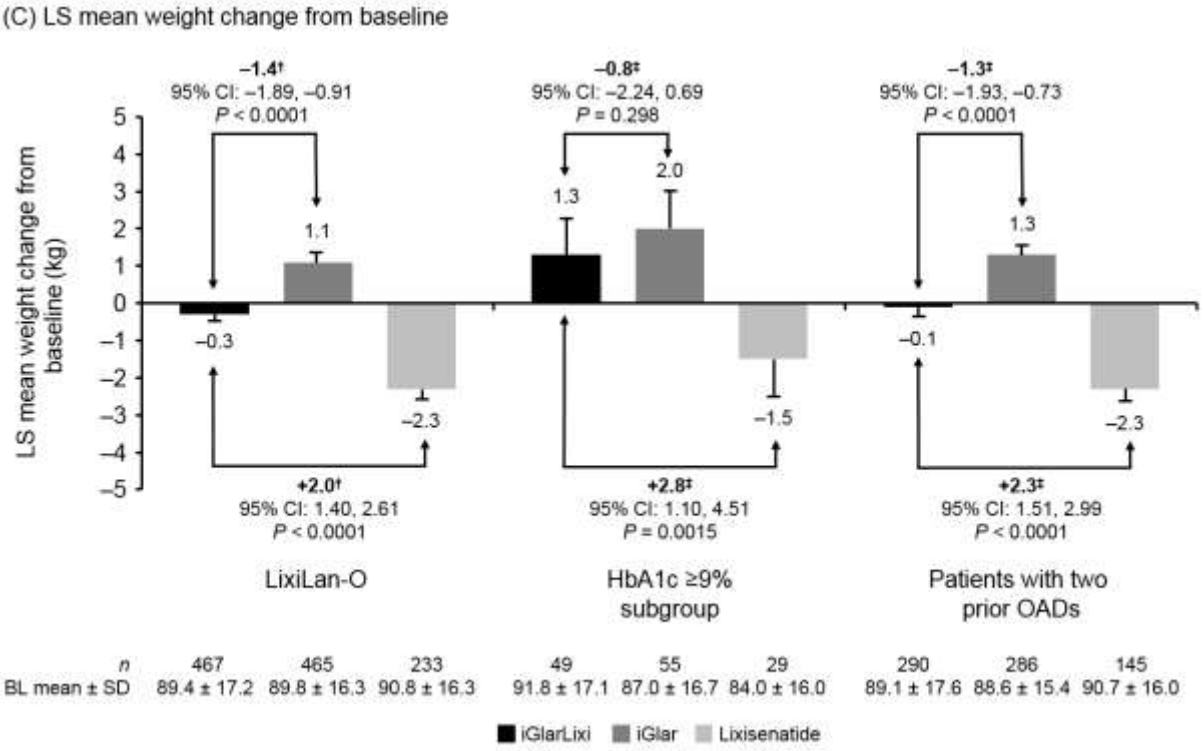


FIGURE 1 HbA1c and body weight outcomes for patients with T2DM from the overall LixiLan-O study population,[12] patients with baseline HbA1c ≥9% and patients with two OADs according to randomization strata at screening (mITT population).
Error bars indicate SE.

Abbreviations: ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; HbA1c, glycated haemoglobin; iGlar, insulin glargine 100 U; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed-effect model with repeated measures; OAD, oral antihyperglycaemic drug; SD, standard deviation; SE, standard error; T2DM, type 2 diabetes mellitus.

†Overall LixiLan-O data based on MMRM analysis.

‡LS mean difference for iGlarLixi versus iGlar or lixisenatide alone, ANCOVA; LOCF was used to handle missing data.

§Differences in the proportions of patients achieving HbA1c <7% were analysed based on weighted average differences between treatment groups from each strata using a Cochran–Mantel–Haenszel method.

TABLE 1 Clinically important hypoglycaemia outcomes and gastrointestinal disorders (safety population)

	All patients (*N* = 1169)			Patients with baseline HbA1c ≥9% (*n* = 134)			Patients with two OADs according to randomization strata at screening (*n* = 724)		
	iGlarLixi (*n* = 469)	iGlar (*n* = 467)	Lixi (*n* = 233)	iGlarLixi (*n* = 50)	iGlar (*n* = 55)	Lixi (*n* = 29)	iGlarLixi (*n* = 291)	iGlar (*n* = 288)	Lixi (*n* = 145)
Clinically important hypoglycaemia[†]									
Patients with events, *n* (%)	38 (8.1)	32 (6.9)	4 (1.7)	6 (12.0)	1 (1.8)	1 (3.4)	24 (8.2)	24 (8.3)	3 (2.1)
Events per patient per year, *n*	0.24	0.14	0.06	0.43	0.07	0.13	0.23	0.17	0.07
Gastrointestinal disorders									
Gastrointestinal disorders, overall	102 (21.7)	59 (12.6)	86 (36.9)	14 (28.0)	8 (14.5)	14 (48.3)	64 (22.0)	36 (12.5)	54 (37.2)
Nausea	45 (9.6)	17 (3.6)	56 (24.0)	6 (12.0)	4 (7.3)	10 (34.5)	31 (10.7)	12 (4.2)	37 (25.5)
Discontinuation due to nausea	2 (0.4)	0	6 (2.6)	1 (2.0)	0	0	1 (0.3)	0	5 (3.4)
Vomiting	15 (3.2)	7 (1.5)	15 (6.4)	0	0	1 (3.4)	13 (4.5)	5 (1.7)	7 (4.8)
Discontinuation due to vomiting	2 (0.4)	0	4 (1.7)	0	0	0	2 (0.7)	0	3 (2.1)
Diarrhoea	42 (9.0)	20 (4.3)	21 (9.0)	8 (16.0)	1 (1.8)	3 (10.3)	26 (8.9)	13 (4.5)	12 (8.3)
Discontinuation due to diarrhoea	1 (0.2)	0	2 (0.9)	0	0	1 (3.4)	0	0	1 (0.7)

Abbreviations: HbA1c, glycated haemoglobin; iGlar, insulin glargine 100 U; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; OAD, oral antihyperglycaemic drug.

Patient-years of exposure was calculated as time from the first to the last injection of study drug plus 1 day. Number of events per patient-year was calculated as number of events divided by total patient-years of exposure.

[†]Clinically important hypoglycaemia: symptoms typical of hypoglycaemia accompanied by plasma glucose <54 mg/dL.