diabetesresearchandclinicalpractice 209 (2024) 111604

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Consistent glycaemic efficacy and safety of concomitant use of iGlarLixi and sodium-glucose co-transporter-2 inhibitor therapy for type 2 diabetes: A patient-level pooled analysis of three randomised clinical trials

Francesco Giorgino [a,*], Cristian Guja [b], Hasan Aydın [c], Felipe Lauand [d], Lydie Melas-Melt [e], Julio Rosenstock [f]

[a] Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari 70124, Italy
[b] Department of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest 030167, Romania
[c] Department of Endocrinology, Yeditepe University School of Medicine, Istanbul 34724, Turkey
[d] Sanofi, Paris 75017, France
[e] Ividata Life Sciences, Levallois-Perret 92300, France
[f] Velocity Clinical Research at Medical City, 75230 Dallas, TX, USA

ARTICLE INFO

Keywords:
Type 2 diabetes
Glycaemic control
GLP-1 RA
SGLT2 inhibitor
Hypoglycaemia

ABSTRACT

Aims: Sodium glucose co-transporter 2 inhibitors (SGLT2is) and/or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with proven cardio- and reno-protective benefits are recommended in people with type 2 diabetes (T2D) at high risk of cardiovascular disease, chronic kidney disease, and/or heart failure. This pooled analysis compared efficacy and safety outcomes of iGlarLixi with or without SGLT2is in people with T2D.

Methods: This post hoc analysis evaluated outcomes in participants who were receiving an SGLT2i when initiating iGlarLixi (SGLT2i users) and those who were not (SGLT2i non-users) in a pooled dataset from three trials: LixiLan-G (advancing from a GLP-1 RA), SoliMix and LixiLan ONE CAN (advancing from basal insulin).

Results: Baseline characteristics were generally similar between 219 users and 746 non-users. Least squares mean changes in HbA_{1c} from baseline to Week 26 were similar for users (−1.2 % [95 % confidence intervals: −1.4 %, −1.1 %]) and non-users (−1.2 % [−1.2 %, −1.1 %]). Changes in body weight, fasting glucose and post-prandial glucose were similar between groups, as were hypoglycaemic events.

Conclusions: Pooled results from three studies of adults with T2D demonstrated that iGlarLixi provided similar clinically meaningful improvements in glycaemic control without increased hypoglycaemia risk, regardless of concomitant use of SGLT2is.

1. Introduction

Type 2 diabetes (T2D) is a complex, heterogeneous disease affecting a high proportion of people with a spectrum of comorbidities that may influence the optimal treatment pathway for each individual [1–3]. Cardiovascular and renal comorbidities, alongside other factors such as disease duration and patient preference, affect both the setting of glycaemic targets and choice of specific glucose-lowering medications, as advised by current American Diabetes Association (ADA) clinical guidelines [4]. Achieving sustained glycaemic control can be challenging and often requires multiple concomitant medications for its maintenance. Guidance supports advancing therapy for individuals not meeting their treatment goals, with the addition of oral anti-hyperglycaemic drugs (OADs) or an injectable therapy such as a glucagon-like peptide 1 receptor agonist (GLP-1 RA), which may also be used in combination with insulin [5].

For people with T2D who live with, or are at risk of, cardiovascular disease, chronic kidney disease, and/or heart failure, current recommendations indicate treatments that not only lower HbA_{1c} levels but also provide cardio- and reno-protective benefits [6]. Among people with T2D with established cardiovascular or kidney disease, the preferred approach is to use a therapy such as a sodium-glucose co-

* Corresponding author.
E-mail addresses: francesco.giorgino@uniba.it (F. Giorgino), cristian.guja@hotmail.com (C. Guja), hsnydn@yahoo.com (H. Aydın), felipe.lauand@sanofi.com (F. Lauand), lydie.melas-melt-ext@sanofi.com (L. Melas-Melt), jrosenstock@velocityclinical.com (J. Rosenstock).

https://doi.org/10.1016/j.diabres.2024.111604
Received 17 January 2024; Received in revised form 29 February 2024; Accepted 1 March 2024
Available online 5 March 2024

transporter 2 inhibitor (SGLT2i) or a GLP-1 RA with proven cardiovascular/renal benefits; in certain cases, a combination of the two may be considered for additive reduction in HbA_{1c} levels and cardio-renal protection [7,8]. A meta-analysis found that the use of SGLT2is or GLP-1 RAs in people with T2D was associated with lower mortality than no treatment or placebo [9], and many clinical trials have shown cardiovascular and renal benefits in people with T2D [10,11]. A further meta-analysis reported that the SGLT2i/GLP-1 RA combination was associated with improved glycaemic control and greater body weight loss versus SGLT2i alone [12]. Consequently, clinical practice guidelines for T2D are changing and the individual risk of cardiovascular or kidney disease may inform treatment decisions [13,14].

The ADA/EASD (European Association for the Study of Diabetes) 2022 Consensus reports that greater glycaemic control can be achieved with concomitant use of a basal insulin and a GLP-1 RA as a fixed-ratio combination than with either monotherapy, with less weight gain and lower rates of hypoglycaemia than with intensified insulin regimens [6]. Furthermore, better gastrointestinal tolerability is seen for the fixed-ratio combination than with GLP-1 RA alone [15]. iGlarLixi is a titratable fixed-ratio combination of basal insulin glargine 100 units/mL (iGlar) and the short-acting GLP-1 RA lixisenatide (Lixi) delivered via a once-daily injection. Phase 3 studies have shown that iGlarLixi is well tolerated and more efficacious in reducing HbA_{1c}, with provided weight benefit and no increased risk of hypoglycaemia, than either basal or biphasic insulin therapy [16,17]. Treatment with iGlarLixi is also more efficacious in lowering HbA_{1c} than continuing on GLP-1 RAs alone [18]. These results have been further validated by real-world evidence studies [19–22].

Concomitant use of iGlarLixi and SGLT2is has not been well characterised, with only limited evaluation in a small number of patients from a clinical randomised study and from a real-world evidence database [19]. The available results showed that iGlarLixi provided glycaemic control with comparably low rates of hypoglycaemia regardless of the use of SGLT2is [19].

The current analysis aims to further assess efficacy and safety outcomes in participants with T2D receiving iGlarLixi, with or without concomitant use of SGLT2i therapy. For this purpose, we used pooled data from three large randomised clinical studies, LixiLan-G [18], SoliMix [16] and LixiLan ONE CAN [23].

2. Materials and Methods

2.1. Study design and population

This post hoc exploratory analysis examined outcomes in people with T2D who were (SGLT2i users) or were not (SGLT2i non-users) receiving an SGLT2i when initiating iGlarLixi in a pooled dataset of three previously published iGlarLixi randomised clinical trials: LixiLan-G [18], SoliMix [16] and LixiLan ONE CAN [23]. All trials were conducted in accordance with Good Clinical Practice guidelines, the International Conference on Harmonisation, and the Declaration of Helsinki. As this post hoc analysis used data from previously published studies, no additional approval was required; all trial participants provided informed consent.

In brief, LixiLan-G (NCT02787551) was a randomised open-label, parallel-group, Phase 3 trial that compared participants switching to iGlarLixi with those continuing on prior GLP-1 RA therapy [18]. Eligible participants had T2D diagnosed ≥ 1 year prior to screening with HbA_{1c} 7.0–9.0 % (53–75 mmol/mol) treated with the maximum tolerated dose of a GLP-1 RA, taken in combination with OADs (metformin/pioglitazone/SGLT2is). Participants self-administered iGlarLixi subcutaneously once daily before breakfast using one of two pen injectors administering either a 2:1 ratio of iGlar units to 1 μg Lixi (10 U iGlar/5 μg Lixi up to 40 U iGlar/20 μg Lixi) or a 3:1 ratio (30 U iGlar/10 μg Lixi up to 60 U iGlar/20 μg Lixi) depending on basal insulin needs; the 2:1 ratio was used as the starting dose for participants with a last pre-randomisation dose of basal insulin < 30 units, with the 3:1 ratio for participants transferring from ≥ 30 units. GLP-1 RA therapy was administered per local labelling, continuing the same regimen as before randomisation. Subsequent weekly titration was used to reach a target fasting plasma glucose level of 80–100 mg/dL (4.4–5.6 mmol/L).

SoliMix (EudraCT: 2017-003370-13) was a randomised open-label, parallel group, Phase 3b study that compared participants advancing from basal insulin to iGlarLixi versus those advancing to premix insulin (30 % insulin aspart and 70 % insulin aspart protamine; BIAsp 30) [24]. Eligible adults were those with suboptimally controlled T2D (HbA_{1c} ≥ 7.5–≤10.0 % [≥58–≤86 mmol/mol]) despite receiving basal insulin combined with OAD therapy (metformin/SGLT2is) [25]. Participants self-administered iGlarLixi once-daily using one of the two pen injectors (2:1 or 3:1 iGlar:Lixi, as above) depending on previous basal insulin dose at randomisation; for participants with previous daily basal insulin dose < 30 units, the starting dose was 20 units iGlar with 10 μg Lixi administered with the 10–40 units pen; for basal insulin of 30 to 50 units, the starting dose was 30 units iGlar with 10 μg Lixi administered with the 30–60 units pen. Starting total daily dose of BIAsp 30 was the same as the participant's previous basal insulin dose on a unit-to-unit basis and was split into two daily doses. Doses of iGlarLixi and BIAsp 30 were titrated weekly to achieve fasting plasma glucose levels 80–110 mg/dL (4.4–6.1 mmol/L).

LixiLan ONE CAN (NCT03767543) was an open-label, randomised, parallel-group, Phase 3b study conducted in Canada. Study participants were adults with T2D and an HbA_{1c} of ≥ 7.5–≤ 10.5 % (≥58–≤ 91 mmol/mol) who had been treated with basal insulin with or without OAD therapy (metformin/insulin secretagogues/dipeptidyl peptidase-4 inhibitors/SGLT2is) [23]. iGlarLixi was administered once daily, and participants self-titrated iGlarLixi on a once-daily or once-weekly regimen targeting a fasting self-monitored plasma glucose level of 79–101 mg/dL (4.4–5.5 mmol/L). The starting dose of iGlarLixi for participants transferring from once-daily basal insulin was 15 units for participants with basal insulin < 30 units, or 30 units for participants with basal insulin dose ≥ 30 units. For participants transferring from twice-daily basal insulin, the same rationale was applied following calculation of 80 % of the pre-trial total daily dose.

2.2. Endpoints

In LixiLan-G, the primary endpoint was HbA_{1c} change from baseline to Week 26. Secondary endpoints included the proportion of patients achieving HbA_{1c} < 7 % (<53 mmol/mol) and ≤ 6.5 % (≤48 mmol/mol), fasting plasma glucose (FPG) change from baseline, change in 2-hour post-prandial plasma glucose (PPG), and change in body weight [18]. In SoliMix, the primary endpoints were non-inferiority of iGlarLixi compared with BIAsp 30 in terms of HbA_{1c} reduction, or superiority in terms of body weight change from baseline to Week 26. Key secondary endpoints included achievement of HbA_{1c} < 7 % without weight gain and without hypoglycaemia (plasma glucose < 70 mg/dL [< 3.9 mmol/L]), and change in FPG [25]. In LixiLan ONE CAN, the primary endpoint was HbA_{1c} change from baseline to Week 26. Key secondary endpoints were change in body weight and proportion of patients achieving the composite endpoint of HbA_{1c} ≤ 7 % (≤53 mmol/mol) without weight gain and without severe hypoglycaemia (ADA Level 3) or documented symptomatic hypoglycaemia (plasma glucose < 70 mg/dL [< 3.9 mmol/L]) [23]. All three studies assessed Level 3 and documented symptomatic hypoglycaemia, as well as adverse events (AEs).

In this pooled patient-level analysis, the primary endpoints evaluated in SGLT2i users versus non-users were HbA_{1c} change and body weight change from baseline to Week 26. Further efficacy endpoints were change in FPG and 2-hour PPG from baseline to Week 26, and proportion of patients reaching glycaemic targets at Week 26. Safety endpoints included assessment of AEs, and incidence and rate of hypoglycaemia, including Level 1 (<70 mg/dL and ≥ 54 mg/dL [< 3.9 mmol/L and ≥ 3.0 mmol/L]), Level 2 (<54 mg/dL [<3.0 mmol/L]), Level 3

hypoglycaemia and documented symptomatic hypoglycaemia (≤70 mg/dL [≤ 3.9 mmol/L]).

2.3. Statistical analysis

Efficacy endpoints were assessed for the modified intention-to-treat population. The primary endpoints and FPG were analysed using a mixed model with repeated measures (MMRM). The MMRM included visit and study as fixed effects, and baseline value-by-visit interaction, as well as fixed continuous variables of baseline values as a covariate. For change in 2-hour PPG, descriptive statistics were used. Safety analyses were performed on the pooled safety population. Incidence of hypoglycaemia and confidence intervals were estimated using the Clopper-Pearson Exact method.

3. Results

There were 965 participants in the pooled randomised population (comprising 257 participants from LixiLan-G, 443 from SoliMix, and 265 from LixiLan ONE CAN). Of these participants, 219 were SGLT2i users (LixiLan-G, 24; SoliMix, 104; LixiLan ONE CAN, 91) and 746 were SGLT2i non-users (LixiLan-G, 233; SoliMix, 339; LixiLan ONE CAN, 174). Overall, there were no major differences in baseline characteristics between SGLT2i users and non-users (Table 1). The mean (standard deviation [SD]) age was 62.0 (9.9) years for SGLT2i users and 60.5 (10.7) years for non-users. There were more male participants in the SGLT2i-users group (62.1 %) than in the non-user group (50.8 %) and mean ± SD duration of diabetes was slightly longer for users (14.3 ± 7.1 years) than for non-users (13.2 ± 7.8 years).

3.1. Efficacy

Similar changes in HbA_{1c} levels and body weight from baseline to Week 26 were seen for SGLT2i users and non-users in the pooled population (Fig. 1). At baseline, mean ± SD HbA_{1c} values were 8.4 ± 0.7 % (68 ± 8 mmol/mol) and 8.3 ± 0.8 % (68 ± 9 mmol/mol) for SGLT2i users and non-users, respectively. Least squares mean change (LSMC; 95 % confidence interval [CI]) from baseline to Week 26 in HbA_{1c} was −1.2 % (−1.4 %, −1.1 %) for users and −1.2 % (−1.2 %, −1.1 %) for non-users. LSMC body weight changed from baseline to Week 26 by 0.4 (−0.2, 1.0) kg for SGLT2i users and by 0.5 (0.3, 0.8) kg for non-users.

Table 1
Baseline characteristics – Randomised population.

Baseline characteristics	SGLT2i users (n = 219)	SGLT2i non-users (n = 746)
Male, n (%)	136 (62.1)	379 (50.8)
Age, years	62.0 ± 9.9	60.5 ± 10.7
Weight at baseline, kg/m^2	85.0 ± 15.7	84.3 ± 17.5
Baseline BMI, kg/m^2	30.1 ± 4.5	30.5 ± 4.9
Duration of diabetes, years	14.3 ± 7.1	13.2 ± 7.8
<10 years, n (%)	60 (27.4)	263 (35.3)
≥10 years, n (%)	159 (72.6)	483 (64.7)
Age at onset of diabetes, years	48.2 ± 9.2	47.5 ± 9.7
HbA_{1c} at baseline, %	8.4 ± 0.7	8.3 ± 0.8
HbA_{1c} at baseline, mmol/mol	68 ± 8	68 ± 9
FPG at baseline, mg/dL	149 ± 40	156 ± 44
FPG at baseline, mmol/L	8.3 ± 2.2	8.7 ± 2.4
Receiving ≥ 1 OAD at baseline, n (%)	219 (100)	740 (99.2)
Participants receiving sulfonylurea at baseline, n (%)[a]	40 (18.3)	92 (12.3)

Data from pooled LixiLan-G, SoliMix and LixiLan ONE CAN studies. All data are mean ± SD unless stated otherwise. [a]LixiLan ONE CAN study only.
BMI, body mass index; FPG, fasting plasma glucose; OAD, oral anti-hyperglycaemic drug; SD, standard deviation; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Changes from baseline to Week 26 in secondary efficacy endpoints were likewise similar between the two groups (Fig. 2). No relevant differences were seen in change from baseline to Week 26 in FPG and 2-hour PPG. LSMCs (95 % CI) for FPG were −25.2 (−31.2, −19.3) mg/dL (−1.4 [−1.7, −1.1] mmol/L) for the user group and –30.4 (−33.5, −27.3) mg/dL (−1.7 [−1.9, −1.5] mmol/L) for the non-user group. Mean ± SD decreases in 2-hour PPG were −85.8 ± 64.2 mg/dL (−4.8 ± 3.6 mmol/L) and −71.0 ± 66.2 mg/dL (−3.9 ± 3.7 mmol/L) for users and non-users, respectively.

By Week 26, SGLT2i users were receiving a mean total daily insulin dose of 0.66 ± 0.29 U/kg whilst non-users were receiving 0.59 ± 0.25 U/kg, corresponding to a mean ± SD change from baseline to Week 26 of 0.16 ± 0.13 U/kg in SGLT2i users and 0.17 ± 0.13 U/kg in non-users. The proportions of participants reaching the target $HbA_{1c} < 7$ % at Week 26 were 42.8 % and 45.9 % for users and non-users, respectively. The proportions achieving the target $HbA_{1c} < 7$ % without weight gain were 23.7 % (users) and 23.9 % (non-users); furthermore, 28.4 % (users) and 27.8 % (non-users) achieved $HbA_{1c} < 7$ % without hypoglycaemia. Proportions achieving the target $HbA_{1c} < 7$ % without both weight gain and hypoglycaemia were 16.3 % and 14.0 % for users and non-users, respectively.

3.2. Safety

Treatment-emergent AEs were reported in 45.7 % of SGLT2i users and in 49.9 % of SGLT2i non-users, with nausea, diarrhoea or vomiting experienced by 10.0 % of SGLT2i users and 12.7 % of SGLT2i non-users (Table 2). Incidences of renal and urinary AEs and reproductive system disorders were low (Table 2). Treatment discontinuation rates were low, though a slightly higher proportion of participants in the non-user group discontinued the study because of a treatment-emergent AE than in the SGLT2i-user group (2.7 % [n = 20] versus 1.8 % [n = 4], respectively).

The proportion of participants experiencing at least one hypoglycaemia event of any kind at any time of day during the 26-week on-treatment period was similar at 37.9 % for SGLT2i users (n = 83, [95 % CI 31.4, 44.7]) and 40.5 % for non-users (n = 300, [95 % CI 37.0, 44.2]; Table 2). Documented symptomatic hypoglycaemia occurred in 25.1 % (n = 55) and 28.8 % (n = 213) of users and non-users, respectively. ADA Level 3 hypoglycaemia events were experienced by 1.4 % (n = 3; 95 % CI 0.3, 4.0) of SGLT2i users and 0.9 % (n = 7; 95 % CI 0.4, 1.9) of SGLT2i non-users. The corresponding rates of hypoglycaemia per patient-year were slightly lower for SGLT2i users than non-users for Level 1 and Level 2 hypoglycaemia, with no difference in rate for ADA Level 3 hypoglycaemia (Table 2). Sulfonylurea (SU) use was permitted in LixiLan ONE CAN; analyses of hypoglycaemia when excluding participants using SU at baseline showed that hypoglycaemia incidence was slightly lower in participants not receiving SU. (Supplementary Table 1).

4. Discussion

This pooled analysis of the LixiLan-G, SoliMix and LixiLan ONE CAN studies demonstrated the efficacy and tolerability of advancing therapy with iGlarLixi in people with T2D irrespective of concomitant SGLT2i therapy. In this analysis, there were no major differences in baseline characteristics between SGLT2i users and non-users. Across the three studies, when switching to iGlarLixi, glycaemic outcomes and hypoglycaemia rates were similar, regardless of concomitant SGLT2i status. Improvements in multiple glucometabolic outcomes, including HbA_{1c}, FPG, and 2-hour PPG levels were seen for both SGLT2i users and non-users by Week 26, with an HbA_{1c} change during the study period of −1.2 % for both groups. Body weight changes were small and comparable between groups. There was no increase in rates of hypoglycaemia in SGLT2i users, and gastrointestinal AEs were comparable between groups.

SGLT2i use for T2D management has increased in recent years [26]. In addition to the evidence from cardiovascular and renal outcomes

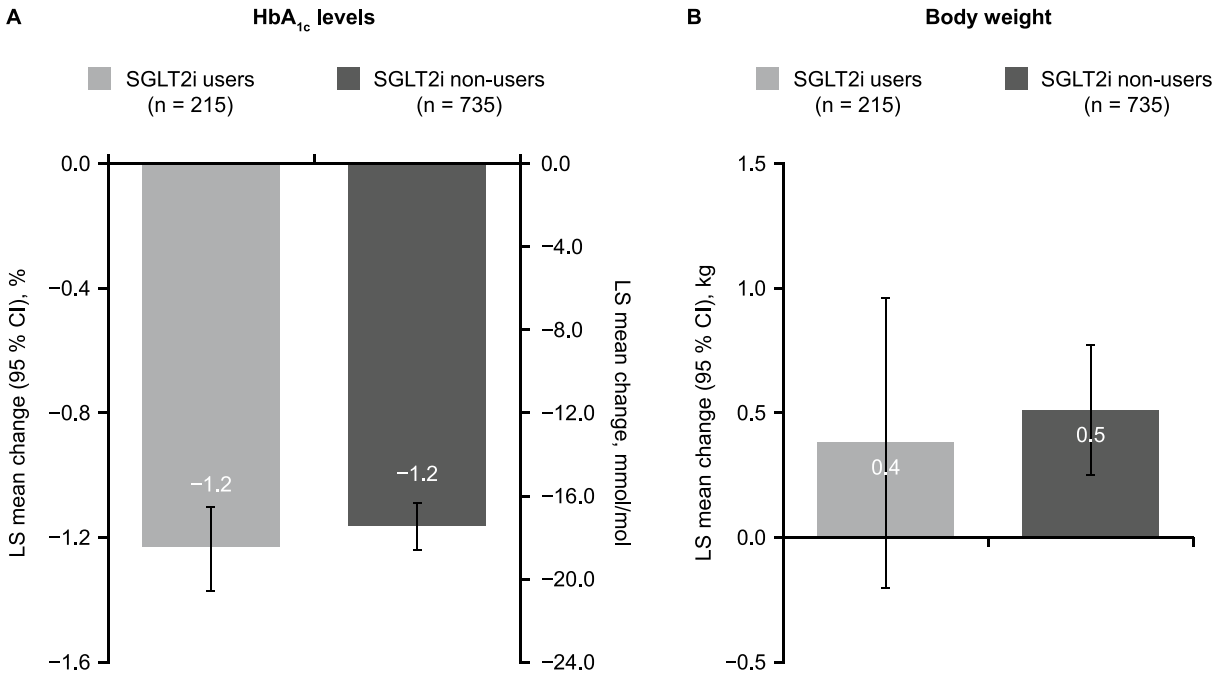

Fig. 1. Primary efficacy endpoints: (A) change in HbA_{1c} and (B) change in body weight from baseline to Week 26 – mITT population. Data from pooled LixiLan-G, SoliMix and LixiLan ONE CAN studies. Error bars represent 95 % CIs in units of HbA_{1c} %. CI, confidence interval; LS, least squares; mITT, modified intention-to-treat; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

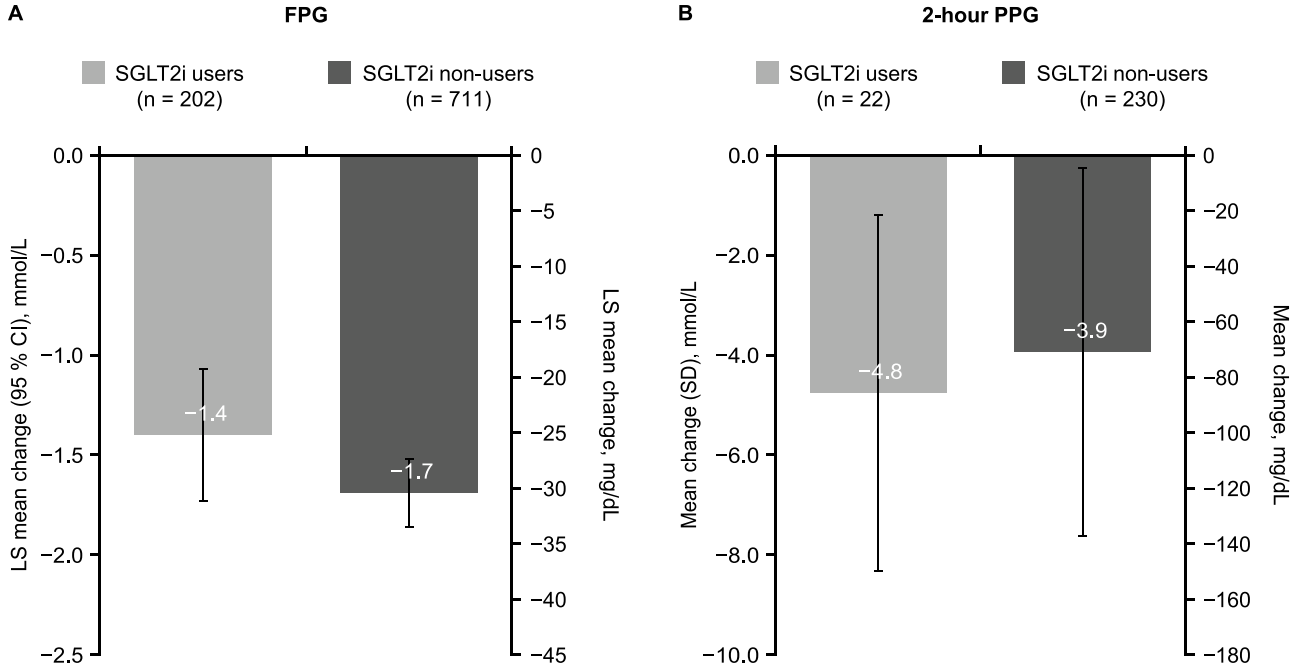

Fig. 2. Secondary efficacy endpoints: (A) change in FPG and (B) change in 2-hour PPG baseline to Week 26 – mITT population. (A) Data from pooled LixiLan-G, SoliMix and LixiLan ONE CAN studies. Error bars represent 95 % CI in units of mmol/L. (B) Data from LixiLan-G. Error bars represent SD in units of mmol/L. CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; mITT, modified intention-to-treat; PPG, post-prandial plasma glucose; SD, standard deviation; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

trials, real-world evidence has shown improvements in cardiorenal outcomes for participants receiving SGLT2i compared with other glucose-lowering therapies, with benefits occurring also in populations with a lower kidney-disease and heart failure risk [27,28]. This suggests that SGLT2is will be more widely used over a large spectrum of cardiorenal risk to achieve target organ protection in patients with T2D, also independently of glycaemic control [29]. In this context, therapy advancement for T2D may be primarily informed by the need for glycaemic control, with cardiorenal protection provided by SGLT2i treatment. This would also be of interest in those patients with T2D and more advanced kidney disease receiving SGLT2i for nephroprotection in whom the glycaemic efficacy of these agents is limited due to declining renal function [8].

The efficacy and tolerability of a fixed-ratio combination in

Table 2
Safety endpoints in the pooled population – Safety population.

Safety endpoints	SGLT2i users (n = 219; 105.23 PPY)	SGLT2i non-users (n = 740; 357.98 PPY)
Incidence of hypoglycaemia, % (95 % CI)		
Any hypoglycaemia event[a]	37.9 (31.4, 44.7)	40.5 (37.0, 44.2)
Documented symptomatic hypoglycaemia[a,b]	25.1 (19.5, 31.4)	28.8 (25.5, 32.2)
ADA Level 1 hypoglycaemia[a,c]	32.0 (25.8, 38.6)	33.8 (30.4, 37.3)
ADA Level 2 hypoglycaemia[a,d]	7.3 (4.2, 11.6)	11.8 (9.5, 14.3)
ADA Level 3 (severe) hypoglycaemia[a,e]	1.4 (0.3, 4.0)	0.9 (0.4, 1.9)
Rates of hypoglycaemia, PPY (95 % CI)		
Any hypoglycaemia	4.49 (4.09, 4.91)	4.60 (4.38, 4.83)
Documented symptomatic hypoglycaemia[b]	2.05 (1.79, 2.35)	2.72 (2.56, 2.90)
ADA Level 1 hypoglycaemia[c]	2.74 (2.43, 3.07)	3.29 (3.11, 3.49)
ADA Level 2 hypoglycaemia[d]	0.29 (0.19, 0.41)	0.48 (0.41, 0.56)
ADA Level 3 (severe) hypoglycaemia[e]	0.03 (0.01, 0.08)	0.03 (0.01, 0.05)
TEAEs, n (%)		
Any TEAE	100 (45.7)	369 (49.9)
Any serious TEAE	9 (4.1)	30 (4.1)
Any TEAE leading to discontinuation, n (%)	4 (1.8)	20 (2.7)
At least one gastrointestinal AE of nausea, diarrhoea, or vomiting	22 (10.0)	94 (12.7)
Nausea	14 (6.4)	73 (9.9)
Diarrhoea	11 (5.0)	25 (3.4)
Vomiting	4 (1.8)	21 (2.8)
AE in SOC of renal and urinary disorders	2 (0.9)	22 (3.0)
Urinary tract infection	0	7 (0.9)
AE in SOC of reproductive system and breast disorders	4 (1.8)	4 (0.5)
Vulvovaginal mycotic infection	1 (0.5)	2 (0.3)

Data from pooled LixiLan-G, SoliMix and LixiLan ONE CAN studies. [a]CIs estimated using Clopper-Pearson Exact method; [b] ≤ 70 mg/dL (≤3.9 mmol/L); [c] < 70 mg/dL and ≥ 54 mg/dL (<3.9 and ≥ 3.0 mmol/L); [d] < 54 mg/dL (<3.0 mmol/L); [e]requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
ADA, American Diabetes Association; AE, adverse event; CI, confidence interval; PPY, per patient-year; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SOC, system organ class; TEAE, treatment-emergent adverse event.

conjunction with SGLT2i therapy has been demonstrated with both iGlarLixi [16–18,25] and iDegLira [30]. Furthermore, results from iGlarLixi studies in different populations have shown that similar improvements in glycaemic control are seen for participants who are receiving SGLT2i and those who are not. In a Japanese population of people with T2D suboptimally controlled on OADs, the efficacy and safety of iGlarLixi were demonstrated irrespective of receipt of SGLT2is [31]. A pooled analysis of LixiLan-G and a real-world evidence study, with no prespecified inclusion or exclusion criteria other than iGlarLixi initiation, also found comparable glycaemic control and hypoglycaemia rates between SGLT2is users and non-users [19]. The results from this analysis, therefore, further support the efficacy and tolerability of iGlarLixi when taken concomitantly with an SGLT2i.

Strengths of the current analysis include a large and diverse pool of participants from different studies with a variety of background comorbidities and therapies. Having different study designs and exclusion criteria aids in generalisability of the data to a wider population of people with T2D. For example, SUs are commonly used to treat T2D and although not permitted in LixiLan-G and SoliMix, their use was permitted in the LixiLan ONE CAN study, which allowed analysis of hypoglycaemia by SU usage [23]. The trials were multinational and randomised, comparing iGlarLixi with existing comparators through different healthcare systems.

Limitations of this analysis include its post hoc nature and the combination of data originating from a variety of sources. The enrolment criteria for the three studies had different thresholds for baseline HbA_{1c} levels, which may influence the change from baseline measured as the primary endpoint. Variation in the number of patients included from each study (LixiLan-G, n = 257; SoliMix, n = 443; LixiLan ONE CAN, n = 265) may have resulted in bias due to the respective weighting of each population in the analyses.

In conclusion, a pooled analysis of three studies of adults with T2D showed that iGlarLixi provides improvements in glycaemic control, irrespective of the use of a concomitant SGLT2i, with no increase in rates of hypoglycaemia. Simultaneous use of these therapies may be of benefit to people with T2D with, or who are at risk of, cardiovascular or kidney disease, and/or heart failure, and require cardio- and reno-protective effects alongside improved glycaemic control.

LixiLan-G (NCT02787551), SoliMix (EudraCT: 2017-003370-13), LixiLan ONE CAN (NCT03767543).

Plain language summary

Collective analysis of iGlarLixi trials shows receiving iGlarLixi with or without SGLT2i treatment lowers blood glucose with few hypoglycaemia episodes (hypos) in adults with type 2 diabetes.

Overview

This analysis examined if taking two prescription medicines together, iGlarLixi (Soliqua; Sanofi, Paris, France) and an SGLT2i, which causes blood glucose to be excreted with the urine, is well tolerated and effective at lowering blood glucose in people with type 2 diabetes. We found that therapy with both iGlarLixi and an SGLT2i decreases blood glucose with no increase in the number of hypos.

What do you need to know?

While some people with type 2 diabetes can achieve their target glucose levels with diet alone, others need medicines, like insulin, to lower their glucose to healthy levels. People with type 2 diabetes are at risk of heart, blood-vessel and kidney complications. SGLT2is protect against such complications. iGlarLixi is made up of a long-acting insulin (insulin glargine) and a non-insulin injectable medicine called lixisenatide (a GLP-1 RA), and is given as a single daily injection.

What did we do?

This analysis reviewed data from three iGlarLixi trials. To take part in the trials people had to be diagnosed with type 2 diabetes and have blood glucose levels higher than the target range as reflected by HbA_{1c} values (a measure of glucose levels); some participants also took SGLT2i (users) while others did not (non-users).

What did we find?

HbA_{1c} went down by 1.2 % for both SGLT2i users and non-users. Glucose levels reached the target in 28.4 % of users and 27.8 % of non-users, without people experiencing hypos.

Overall, we found that people taking iGlarLixi, with or without an SGLT2i, experienced similar lowering of their glucose levels and a similar number of hypos.

What does this mean?

These results suggest that iGlarLixi is an effective treatment for

people with type 2 diabetes with or without an SGLT2i.

CRediT authorship contribution statement

Francesco Giorgino: Writing – review & editing, Writing – original draft. **Cristian Guja:** Writing – review & editing, Writing – original draft. **Hasan Aydın:** Writing – review & editing, Writing – original draft. **Felipe Lauand:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Lydie Melas-Melt:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Julio Rosenstock:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **FG:** has served as an advisor for Eli Lilly, Medtronic, Novo Nordisk, Roche Diabetes Care and Sanofi; has received payment of honoraria for lectures, presentations, manuscript writing or education events from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Medtronic, Novo Nordisk, Roche Diabetes Care and Sanofi; has patents planned, issued or pending for Roche Diabetes Care; has served as a research investigator for Eli Lilly, Novo Nordisk and Roche Diabetes Care, and has received grants from Eli Lilly and Roche Diabetes Care. **CG:** has participated in scientific advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi and has received consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Krka, Merck KGaA, MSD, Novo Nordisk, Sanofi and Servier. **HA:** Nothing to disclose. **FL** is an employee of Sanofi; may hold shares and/or stock options. **LMM**: Employee of Ividata Life Sciences, Levallois-Perret, France, contracted by Sanofi. **JR** has served on advisory panels for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Hanmi, Intarcia, Novo Nordisk, Oramed, Sanofi, Structure Therapeutics, Terns Pharma and Zealand, and has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Intarcia, Merck, Novo Nordisk, Oramed, Pfizer and Sanofi.

Data availability

Qualified researchers may request access to participant-level data and related study documents. Participant-level data will be anonymised, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

Acknowledgements

The authors thank the study participants, trial staff, and investigators for their participation. We thank Brant de Fanti, PhD (Sanofi) for coordinating the development, facilitating author discussions, and providing a courtesy review of this manuscript, and Elisabeth Souhami, MD (Sanofi) for scientific guidance and significant scientific contributions. Editorial and writing assistance was provided by Louise Gildea, PhD, and Hayley Ellis, PhD, of Fishawack Communications Ltd, part of Avalere Health.

Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors participated in the interpretation of the data, the writing, reviewing, and editing of the manuscript, and had final responsibility for approving the published version.

Role of the funding source

This work was supported by Sanofi, Paris, France. Assistance provided by Fishawack Communications Ltd, part of Avalere Health, was funded by Sanofi.

Compliance with ethics standards

This post hoc analysis used data from previously published studies, thus no additional approval was required. All participants provided informed consent in the individual clinical trials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111604.

References

[1] Pearson ER. Type 2 diabetes: a multifaceted disease. Diabetologia 2019;62:1107–12. https://doi.org/10.1007/s00125-019-4909-y.
[2] Pearson-Stuttard J, Holloway S, Polya R, Sloan R, Zhang L, Gregg EW, et al. Variations in comorbidity burden in people with type 2 diabetes over disease duration: a population-based analysis of real world evidence. EClinicalMedicine 2022;52:101584. https://doi.org/10.1016/j.eclinm.2022.101584.
[3] Karalliedde J, Gnudi L. Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. Nephrol Dial Transplant 2016;31:206–13. https://doi.org/10.1093/ndt/gfu405.
[4] American Diabetes Association. Standards of care in diabetes—2023. 6. Glycemic targets. Diabetes Care 2023;46:S97–s110. https://doi.org/10.2337/dc23-S006.
[5] American Diabetes Association. Standards of care in diabetes—2023. 9. Pharmacologic approaches to glycemic treatment. Diabetes Care 2023;46:S140–57. https://doi.org/10.2337/dc23-S009.
[6] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2022;2022(45):2753–86. https://doi.org/10.2337/dci22-0034.
[7] American Diabetes Association. Standards of care in diabetes—2023. 10. Cardiovascular disease and risk management. Diabetes Care 2023;46:S158–90. https://doi.org/10.2337/dc23-S010.
[8] American Diabetes Association. Standards of care in diabetes—2023. 11. Chronic kidney disease and risk management. Diabetes Care 2023;46:S191–202. https://doi.org/10.2337/dc23-S011.
[9] Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al. Association between use of sodium-glucose co-transporter 2 Inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA 2018;319:1580–91. https://doi.org/10.1001/jama.2018.3024.
[10] Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. Circulation 2022;146:1882–94. https://doi.org/10.1161/circulationaha.122.059595.
[11] Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653–62. https://doi.org/10.1016/s2213-8587(21)00203-5.
[12] Castellana M, Cignarelli A, Brescia F, Perrini S, Natalicchio A, Laviola L, et al. Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: a meta-analysis. Sci Rep 2019;9:19351. https://doi.org/10.1038/s41598-019-55524-w.
[13] Li S, Vandvik PO, Lytvyn L, Guyatt GH, Palmer SC, Rodriguez-Gutierrez R, et al. SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. BMJ 2021;373:n1091. https://doi.org/10.1136/bmj.n1091.
[14] González-González JG, Díaz González-Colmenero A, Millán-Alanís JM, Lytvyn L, Solis RC, Mustafa RA, et al. Values, preferences and burden of treatment for the initiation of GLP-1 receptor agonists and SGLT-2 inhibitors in adult patients with type 2 diabetes: a systematic review. BMJ Open 2021;11:e049130. https://doi.org/10.1136/bmjopen-2021-049130.
[15] 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;36:138–47. https://doi.org/10.2337/cd17-0065.
[16] Rosenstock J, Emral R, Sauque-Reyna L, Mohan V, Trescolí C, Al Sifri S, et al. Advancing therapy in suboptimally controlled basal insulin-treated type 2 diabetes: clinical outcomes with iGlarLixi versus premix BIAsp 30 in the soliMix randomized controlled trial. Diabetes Care 2021;44:2361–70. https://doi.org/10.2337/dc21-0393.

[17] Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G, 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;39:1972–80. https://doi.org/10.2337/dc16-1495.

[18] Blonde L, Rosenstock J, Del Prato S, Henry R, Shehadeh N, Frias J, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: the lixiLan-G randomized clinical trial. Diabetes Care 2019;42:2108–16. https://doi.org/10.2337/dc19-1357.

[19] Guja C, Giorgino F, Blonde L, Ali A, Prázný M, Meier JJ, et al. Concomitant iGlarLixi and sodium-glucose co-transporter-2 inhibitor therapy in adults with type 2 diabetes: lixiLan-G trial and real-world evidence results. Diabetes Ther 2022;13:205–15. https://doi.org/10.1007/s13300-021-01180-1.

[20] Hassanein M, Malek R, Shaltout I, Sahay RK, Buyukbese MA, Djaballah K, et al. Real-world safety and effectiveness of iGlarLixi in people with type 2 diabetes who fast during Ramadan: the soliRam observational study. Diabetes Metab Syndr 2023;17:102707. https://doi.org/10.1016/j.dsx.2023.102707.

[21] Bala C, Cerghizan A, Mihai B-M, Moise M, Guja C. Real-world evidence on the use of a fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) in people with suboptimally controlled type 2 diabetes in Romania: a prospective cohort study (STAR.Ro). BMJ Open 2022;12:e060852. https://doi.org/10.1136/bmjopen-2022-060852.

[22] McCrimmon RJ, Cheng AYY, Galstyan G, Djaballah K, Li X, Coudert M, et al. iGlarLixi versus basal plus rapid-acting insulin in adults with type 2 diabetes advancing from basal insulin therapy: the soliSimplify real-world study. Diabetes Obes Metab 2023;25:68–77. https://doi.org/10.1111/dom.14844.

[23] Hramiak I, Gerstein HC, Leiter LA, Yale JF, Bajaj HS, Stewart J, et al. Comparing a daily versus weekly titration algorithm in people with type 2 diabetes switching from basal insulin to iGlarLixi in the lixiLan ONE CAN randomized trial. Diabetes Obes Metab 2022;24:1998–2007. https://doi.org/10.1111/dom.14787.

[24] McCrimmon R, Al Sifri S, Emral R, Mohan V, Sauque-Reyna L, Trescolí C, et al. Advancing therapy with iGlarLixi versus premix BIAsp 30 in basal insulin-treated type 2 diabetes: design and baseline characteristics of the soliMix randomized controlled trial. Diabetes Obes Metab 2021;23:1221–31. https://doi.org/10.1111/dom.14354.

[25] Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. 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;39:2026–35. https://doi.org/10.2337/dc16-0917.

[26] Eberly LA, Yang L, Eneanya ND, Essien U, Julien H, Nathan AS, et al. Association of race/ethnicity, gender, and socioeconomic status with sodium-glucose co-transporter 2 inhibitor use among patients with diabetes in the US. JAMA Netw Open 2021;4:e216139. https://doi.org/10.1001/jamanetworkopen.2021.6139.

[27] Gonzalez Perez A, Vizcaya D, Sáez ME, Lind M, Garcia Rodriguez LA. Cardiovascular and renal outcomes among patients with type 2 diabetes using SGLT2 inhibitors added to metformin: a population-based cohort study from the UK. BMJ Open Diabetes Res Care 2023:11. https://doi.org/10.1136/bmjdrc-2022-003072.

[28] Blanco CA, Garcia K, Singson A, Smith WR. Use of SGLT2 inhibitors reduces heart failure and hospitalization: a multicenter, real-world evidence study. Perm J 2023;27:77–87. https://doi.org/10.7812/tpp/22.137.

[29] Schechter M, Melzer-Cohen C, Rozenberg A, Yanuv I, Chodick G, Karasik A, et al. Cardiorenal outcomes with sodium/glucose cotransporter-2 inhibitors in patients with type 2 diabetes and low kidney risk: real world evidence. Cardiovasc Diabetol 2021;20:169. https://doi.org/10.1186/s12933-021-01362-y.

[30] Philis-Tsimikas A, Billings LK, Busch R, Portillo CM, Sahay R, Halladin N, et al. Superior efficacy of insulin degludec/liraglutide versus insulin glargine U100 as add-on to sodium-glucose co-transporter-2 inhibitor therapy: a randomized clinical trial in people with uncontrolled type 2 diabetes. Diabetes Obes Metab 2019;21:1399–408. https://doi.org/10.1111/dom.13666.

[31] Terauchi Y, Nakama T, Spranger R, Amano A, Inoue T, Niemoeller E. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi 1:1) in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs: a randomized, 26-week, open-label, multicentre study: the lixiLan JP-O2 randomized clinical trial. Diabetes Obes Metab 2020;22(Suppl 4):14–23. https://doi.org/10.1111/dom.14036.