Original Research

Effectiveness of iGlarLixi (Insulin Glargine-Lixisenatide) in People with Type 2 Diabetes According to the Time of Administration through the Day

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Authors and Affiliations:

Martin Haluzík[1], Jochen Seufert[2], Cristian Guja[3], Mireille Bonnemaire[4], Gregory Bigot[5], Mathilde Tournay[6], János Tibor Kis[7], Nick Freemantle[8]

[1]Institute for Clinical and Experimental Medicine and Charles University, Prague, Czech Republic.

[2]Division of Endocrinology and Diabetology, Department of Internal Medicine II, Medical Centre - Faculty of Medicine, University of Freiburg, Freiburg, Germany.

[3]Department of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

[4]General Medicines, Sanofi, Paris, France.

[5]IVIDATA Group, Paris, France.

[6]International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium.

[7]Department of Internal Medicine Centrum, Szent János Hospital, Budapest, Hungary.

[8]Institute of Clinical Trials and Methodology, University College London, London, UK

Correspondence: Mireille Bonnemaire; General Medicines, Sanofi, Paris, France. E-mail: mireille.bonnemaire@sanofi.com.

Abstract

Introduction: iGlarLixi (insulin glargine 100 U/mL plus lixisenatide) has demonstrated glycaemic efficacy and safety in adults with uncontrolled type 2 diabetes mellitus (T2DM). Per product label, iGlarLixi should be injected once a day within one hour prior to a meal, preferably the same meal every day when the most convenient meal has been chosen. It is however unknown whether iGlarLixi administration timing affects glycaemic control and safety, as clinical trial evidence is mainly based on pre-breakfast iGlarLixi administration. Accordingly, we assessed the effectiveness and safety of iGlarLixi in clinical practice, according to its administration timing.

Methods: Patient-level data were pooled from two prospective observational studies including 1,303 European patients with T2DM, uncontrolled on oral antidiabetics with or without basal insulin, who initiated iGlarLixi therapy for 24 weeks. Patients were classified into four subgroups based on daily timing of iGlarLixi injection: pre-breakfast (N=436), pre-lunch (N=262), pre-dinner (N=399), and those who switched iGlarLixi injection time during the study (N=206).

Results: Baseline characteristics did not differ between study groups. Least-squares (LS) mean reduction in haemoglobin A1c (HbA1c) from baseline to week 24 was important in all groups with the largest numerical decrease observed in the pre-breakfast group (1.57%) compared with pre-lunch (1.27%), pre-dinner (1.42%), or changed injection time (1.33%) groups. Pre-breakfast iGlarLixi injection also resulted in a greater proportion of patients achieving HbA1c <7.0% at week 24 (33.7% versus 19.0% for pre-lunch, 25.6% pre-dinner, and 23.2% changed injection time). iGlarLixi was well-tolerated across all groups, with low rates of gastrointestinal disorders and hypoglycaemia. Mean body weight also decreased similarly in all groups (by 1.3–2.3 kg).

Conclusion: iGlarLixi was effective and safe regardless of its daily administration time. However, pre-breakfast iGlarLixi injection resulted in greater HbA1c reductions.

Keywords: Fixed-ratio combination; Insulin glargine; Lixisenatide; Time of administration; Type 2 diabetes.

Key Summary Points

Why carry out this study?

- iGlarLixi (insulin glargine 100 U/mL and lixisenatide) should be injected once daily within one hour prior to a meal, preferably before the same meal every day, as per product label.
- It is however unknown whether the administration time of iGlarLixi affects glycaemic control and safety, as clinical trial evidence is mainly based on iGlarLixi administration before breakfast.
- By using data pooled from two prospective observational studies in patients with type 2 diabetes, uncontrolled on oral antidiabetics with or without basal insulin, we sought to evaluate in routine clinical practice the effectiveness and safety of iGlarLixi, according to its daily administration timing.

What was learned from the study?

- iGlarLixi was effective and safe at all administration times, allowing patients flexibility in the timing of iGlarLixi administration to suit their lifestyle.
- However, pre-breakfast iGlarLixi injection was associated with a significantly greater HbA1c reduction compared to pre-lunch injection and changed injection timing but not compared to pre-dinner injection.

Introduction

Due to its progressive nature, most people with type 2 diabetes mellitus (T2DM) will eventually require treatment intensification with injectable therapies, specifically glucagon-like peptide-1 (GLP-1) receptor agonists and basal insulin (Skolnik et al., 2021) [1]. By exploiting complementary mechanisms of action, iGlarLixi, a titratable, once-daily, fixed-ratio combination of insulin glargine 100 U/mL (iGlar) and lixisenatide, may represent a good option for therapy intensification in patients with uncontrolled T2DM (Giorgino et al., 2020) [2]. On one hand, lixisenatide is a short-acting GLP-1 receptor agonist that reduces postprandial plasma glucose (PPG) levels largely by delaying gastric emptying and decreasing postprandial glucagon levels. On the other hand, iGlar is a long-acting basal insulin analogue that primarily reduces fasting plasma glucose (FPG) (Giorgino et al., 2020) [2]. iGlarLixi also allows patients with T2DM to achieve glycaemic control in a simple regimen, due to its low injection burden and ease of use without the need for increased self-monitored plasma glucose (SMPG) measurements, which in turn may translate into better treatment adherence (Giorgino et al., 2020; McCrimmon et al., 2021) [2, 3].

Given its many potential benefits, iGlarLixi is currently recommended in different clinical guidelines for use in patients with T2DM inadequately controlled on basal insulin and/or oral antidiabetic drugs (OADs) (Davies et al., 2018; American Diabetes Association, 2022) [4, 5]. Indeed, the efficacy and safety of iGlarLixi has been consistently demonstrated in several large randomised controlled trials (RCTs) conducted in patients with uncontrolled T2DM, including the LixiLan clinical programme, consisting of LixiLan-O (Rosenstock et al., 2016) [6], LixiLan-L (Aroda et al., 2016) [7], and LixiLan-G (Blonde et al., 2019) [8], and more recently SoliMix (Rosenstock et al., 2021) [9]. The LixiLan RCTs demonstrated robust glycaemic benefit with

iGlarLixi versus iGlar, lixisenatide, or continuing prior GLP-1 receptor agonists, without an increased risk of hypoglycaemia (Rosenstock et al., 2016; Aroda et al., 2016; Blonde et al., 2019) [6-8]. iGlarLixi was also well-tolerated, and had a better gastrointestinal profile compared with lixisenatide alone and a more favourable body weight profile compared with iGlar alone (Rosenstock et al., 2016; Aroda et al., 2016) [6, 7]. Similarly, in SoliMix, which compared iGlarLixi to a premix insulin analogue, biphasic insulin aspart 30 (BIAsp 30), once-daily iGlarLixi provided better glycaemic control with body weight benefit and less hypoglycaemia than twice-daily premix BIAsp 30 (Rosenstock et al., 2021) [9].

Despite the extensive evidence from RCTs, there is currently limited data on the effectiveness and safety of iGlarLixi in routine clinical practice. It thus remains unknown whether the time of administration of iGlarLixi affects glycaemic control and safety, as in most RCTs iGlarLixi was subcutaneously administered within one hour before breakfast. However, the product monograph of iGlarLixi states, without specifying the injection time, that iGlarLixi should be injected once a day within one hour prior to a meal (or first meal as per US label), preferably before the same meal every day, when the most convenient meal has been chosen (European Medicines Agency [EMA], 2022) [10]. By using data pooled from two prospective observational studies, we sought to evaluate in routine clinical practice the effectiveness and safety of iGlarLixi in patients with T2DM uncontrolled on OADs with or without basal insulin, according to its time of administration (i.e., before breakfast, lunch, dinner, or in case the time of the prandial injection was changed during the study period).

Methods

Study Design

This analysis was a part of the larger, comprehensive, European REALI project including pooled data from several multicentre, prospective, open-label studies reflecting clinical practice in different European countries. The aim of REALI was to evaluate the effectiveness and safety of different injectable glucose-lowering medications, particularly insulin glargine 300 U/mL and iGlarLixi, in unselected patients with uncontrolled T2DM defined as haemoglobin A1c (HbA1c) ≥7.5% (≥58.5 mmol/mol) (Freemantle et al., 2020; Bonadonna et al., 2021; Gourdy et al., 2022) [11-13].

The present analysis pooled patient-level data from two 24-week observational studies including adults with T2DM inadequately controlled on OADs with or without basal insulin who initiated iGlarLixi upon the treating physician-investigator's decision. In both studies, iGlarLixi (Suliqua®, Sanofi, Paris, France) was self-administered subcutaneously once daily within one hour prior to a meal (preferably the same meal every day) for 24 weeks, using one of two SoloStar® pen injectors. The Suliqua® 30–60 pen, with a ratio of 3 units iGlar:1 µg lixisenatide, contains 100 U/mL of iGlar and 33 µg/mL of lixisenatide and delivers dose steps between 30 to 60 units of iGlar in combination with 10 to 20 µg of lixisenatide. The Suliqua® 10–40 pen, with a ratio of 2 units iGlar:1 µg lixisenatide, contains 100 U/mL of iGlar and 50 µg/mL of lixisenatide and delivers dose steps between 10 and 40 units of iGlar in combination with 5 to 20 µg of lixisenatide (EMA, 2022) [10]. The choice of iGlarLixi pen and starting dose were left at the discretion of the treating physician-investigator. iGlarLixi was titrated once a week to achieve a fasting self-monitoring plasma glucose (SMPG) of 80 to 110 mg/dL (4.4 to 6.1 mmol/L). All participants recorded the daily time of iGlarLixi injection.

For the purpose of these analyses, participants were classified into four subgroups based on the daily time of iGlarLixi injection: pre-breakfast, pre-lunch, pre-dinner, and in case the time of the iGlarLixi injection was changed during the study period. Both pooled studies were conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines, and were approved by the relevant institutional review boards/ethics committees. All participants gave written informed consent. Before data pooling, all patient information was de-identified. Consequently, no ethical approval was required for this pooled analysis.

Data Collection and Assessments

Study-related data were collected at baseline, at 12 weeks, and at 24 weeks. Baseline demographics and clinical characteristics in this analysis included age, sex, duration of diabetes, body weight and/or body mass index (BMI), diabetic complications and cardiovascular comorbidities, and details of prior glucose-lowering medications. Data on iGlarLixi treatment, such as iGlarLixi dose, timing of injection, used pen, and concomitant use of other glucose-lowering medications were also collected.

The primary endpoint of this analysis was the change in HbA1c from baseline to week 24. Secondary efficacy endpoints included HbA1c change from baseline to week 12, proportions of patients achieving HbA1c targets of <7.0% (<53 mmol/mol), <7.5% (<58.5 mmol/mol) and <8.0% (<63.9 mmol/mol) at week 24, and changes from baseline to weeks 12 and 24 in FPG and 2-hour PPG. Two-hour PPG was however collected in only one of the two pooled studies. Safety endpoints included the incidence of hypoglycaemic events (symptomatic and severe) and gastrointestinal adverse events (AEs). During the 24-week treatment period, hypoglycaemic events were reported as percentages of participants with at least one event and as annualised rates (events per patient-year), and were defined based on the American Diabetes Association classification

(Seaquist et al., 2013) [14]. The pooled analysis also evaluated changes in body weight and in iGlar dose provided by iGlarLixi (expressed in both U/day and in U/kg/day) from baseline to weeks 12 and 24.

Data Analysis

Data are expressed as mean ± standard deviation (SD) or as median (Q1–Q3) for continuous variables and as counts and percentages for categorical variables. The HbA1c change from baseline was evaluated using a mixed model for repeated measures (MMRM) with fixed effects of study, visit, subgroup category (pre-breakfast, pre-lunch, pre-dinner, and changed time of iGlarLixi injection), prior insulin use (insulin-naïve or insulin pre-treated), baseline HbA1c, age, baseline BMI, subgroup category-by-visit interaction, prior insulin use-by-visit interaction, baseline HbA1c value-by-visit interaction, age-by-visit interaction, and baseline BMI-by-visit interaction. Based on this MMRM, we estimated the least-squares (LS) mean HbA1c changes from baseline to weeks 12 and 24 with the corresponding 95% confidence intervals (CIs) for each subgroup.

All other efficacy and safety endpoints as well as baseline characteristics were assessed descriptively. No imputation of missing data was performed. All statistical tests were two-sided, with a p-value of <0.05 considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Participants

A total of 1,303 patients with T2DM, who were treated with iGlarLixi for 24 weeks, comprised the pooled study population. Of these patients, 436 (33.5%) self-administered iGlarLixi before

177 breakfast, 262 (20.1%) before lunch, 399 (30.6%) before dinner, and 206 (15.8%) switched the
178 time of iGlarLixi injection during the study period (**Fig. 1**). Overall, baseline characteristics did
179 not differ between the four study groups (**Table 1**). Patients had a mean age of 61 years, a mean
180 BMI of 32.2 kg/m^2, and a median diabetes duration of 9 years. A total of 590 patients (45.3%)
181 were previously treated with basal insulin for a median duration of 2.5 years, with insulin glargine
182 being the most common (67.8%) prior basal insulin used at baseline. More than half of the study
183 population (56.7%) previously received only one OAD. Except for metformin which use remained
184 stable during the 24-week observation period (administered in 98% of patients), there was an
185 important reduction in the use of all other OADs. For instance, sulphonylurea use was reduced
186 from 30.5% prior to iGlarLixi initiation to 4.5% after.

187 **Glycaemic Control**

188 In the overall study population, mean ± SD HbA1c decreased from 9.11% ± 1.37 at baseline to
189 7.70% ± 1.22 at week 24, corresponding to a LS mean change in HbA1c from baseline to week 24
190 of -1.43% (95% CI, -1.50 to -1.36). At week 24, pre-breakfast iGlarLixi injection resulted in
191 significantly greater LS mean reductions in HbA1c compared to pre-lunch injection (-1.57%
192 versus -1.27%; LS mean difference = 0.3%, p=0.002) or changed injection time (-1.33%; LS mean
193 difference = 0.24%, p=0.02). There was however no statistically significant difference in HbA1c
194 change between the pre-breakfast group and the pre-dinner group, which showed a LS mean
195 reduction in HbA1c from baseline to week 24 of -1.42% (LS mean difference = 0.15%, p=0.08)
196 (**Fig. 2**). At week 12, the LS mean change in HbA1c from baseline was -1.15% (95% CI, -1.21 to
197 -1.08) in the overall study population, ranging from -0.94% in the pre-lunch group to -1.30% in
198 the pre-breakfast group. Compared to other study groups, pre-breakfast iGlarLixi injection also
199 resulted in greater proportions of patients achieving HbA1c targets of <7.0%, <7.5%, and <8.0%

at week 24 (**Fig. 3**). There were however no significant differences in the changes in FPG (**Table 2**) and in 2-hour PPG (**Electronic Supplementary Material Table S1**) from baseline to week 24 between the four study groups.

Safety

iGlarLixi was well-tolerated in all study groups, with overall low reported rates of gastrointestinal AEs and of hypoglycaemic events (**Table 3**). Mean ± SD body weight showed a decrease from baseline to weeks 12 and 24 in all four groups. In the overall study population, the mean ± SD change in body weight from baseline to week 24 was -1.8 ± 4.6 kg (**Table 4**). iGlarLixi dose titration occurred primarily in the first 12 weeks of the study. The mean ± SD dose of iGlar increased from 18.9 ± 9.3 U/day (0.21 ± 0.11 U/kg/day) at baseline to 29.8 ± 11.2 U/day (0.34 ± 0.13 U/kg/day) at week 12 and 33.3 ± 12.7 U/day (0.38 ± 0.14 U/kg/day) at week 24, with comparable changes across study groups (**Table 4**).

Discussion

In patients with T2DM, PPG levels typically peak within two hours after the start of a meal (Kapitza et al., 2013) [15]. Hence, given the mode of action of lixisenatide, which specifically decreases post-meal hyperglycaemia, iGlarLixi should be injected within one hour before a meal, and preferably the main/largest meal (Kapitza et al., 2013; Haluzík et al., 2020) [15, 16]. The present pooled analysis, performed in 1,303 European patients with T2DM inadequately controlled on OADs with or without basal insulin, shows that iGlarLixi is effective at all administration times. Our findings support flexibility in the timing of iGlarLixi administration, which may be of benefit to both patients and healthcare providers. For instance, flexibility in iGlarLixi administration can improve patient adherence by suiting their lifestyle and can simplify treatment modalities

particularly for challenging patient populations with long-standing T2DM or other comorbidities, leading to overall improved health-related quality of life (Peyrot et al., 2012; Davies et al., 2013) [17, 18]. The favourable safety profile of iGlarLixi across all study groups of this analysis, reflected by its beneficial effect on body weight, the absence of serious AEs, and the occurrence of too few AEs leading to iGlarLixi discontinuation, may further enhance adherence to iGlarLixi therapy.

In line with the reported effectiveness and safety of iGlarLixi at all administration times in the current analysis, two 24-week RCTs, evaluating lixisenatide injected once daily at 20 µg in patients with T2DM inadequately controlled on metformin, demonstrated that the efficacy and safety of lixisenatide do not vary depending on whether it is administered before breakfast, lunch, or dinner (Ahrén et al., 2013, 2014) [19, 20]. Similarly, in a more recent in-silico simulation study comparing the effect of iGlarLixi administration before either breakfast or an evening meal on blood sugar profiles, both regimens were observed to have acceptable glucose level variability, with low hypoglycaemia rates in the simulation (Gautier et al., 2022) [21]. A comparable percentage of time over 24 hours was spent with blood glucose levels between 70 and 180 mg/dL when iGlarLixi was administered pre-breakfast or pre-evening (73% versus 71%, respectively) [21].

Although our overall findings confirm the effectiveness and safety of iGlarLixi regardless of its daily administration time, pre-breakfast iGlarLixi injection was associated with a significantly greater HbA1c reduction compared to pre-lunch injection and changed injection timing but not compared to pre-dinner injection. Hence, pre-breakfast iGlarLixi injection may be preferable if it is convenient for the individuals living with T2DM, with their lifestyle and their typical main/largest meal remaining the most important factors when choosing the timing of the

iGlarLixi injection (Haluzík et al., 2020) [16]. Morning administration of iGlarLixi is also supported by the facts that PPG levels are typically highest after breakfast in most patients and that iGlarLixi can cover PPG elevations after two meals if taken less than 4–5 hours apart. Thus, for pre-breakfast iGlarLixi administration, post-breakfast and post-lunch blood glucose levels are anticipated to be controlled by iGlarLixi assuming a time interval between the two meals of less than 4–5 hours (Haluzík et al., 2020) [16]. Of note, this assumption may not be supported by the pre-dinner group results which are not significantly different from those of pre-breakfast group.

To the best of our knowledge, this work represents the first analysis in which the daily administration time of iGlarLixi was prospectively recorded and data regarding glycaemic control were systematically collected and analysed. In such a way, our study addresses the clinical question concerning the impact of iGlarLixi administration timing on its effectiveness and safety. Among other strengths of this analysis are the large dataset coming from clinical practice and the analytical methods used to assess the change in HbA1c. Indeed, the change in HbA1c from baseline to week 24 was evaluated using a MMRM that adjusted for several factors including baseline HbA1c, age, baseline BMI, and prior insulin use. Despite this adjustment, caution is nevertheless advised when interpreting the differences in HbA1c reduction between the study groups, given the influence of unmeasured confounding factors. This analysis also has the limitation of the relatively short treatment duration. In addition, the incidences of AEs including hypoglycaemia may be underestimated, given that routine clinical practice settings are associated with less stringent titration and AE reporting. It should also be noted that since this is an analysis of European data, our results may not be generalisable to other patient populations, as it is possible that patients' management and response to iGlarLixi therapy could differ by culture and ethnicity (Dailey et al., 2019) [22]. Overall, our data are reassuring in that iGlarLixi was effective and safe,

irrespective of its administration time. These results hence support the use of iGlarLixi in a patient-centred approach tailored to patient preferences and meal patterns.

Conclusions

In European people with T2DM inadequately controlled on OADs with or without basal insulin, iGlarLixi was effective and safe regardless of its daily administration time. However, pre-breakfast iGlarLixi injection may be preferable when there is a choice, as it was associated with greater HbA1c numerical reductions compared to other administration times. These data add to the body of evidence on the optimal use of iGlarLixi in clinical practice.

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Authors' Contributions: (To complete)

AUTHORS' NAMES contributed to the project design and the analysis plan. Mathilde Tournay performed the statistical analysis of the data. All authors were involved in the interpretation of the data, writing and reviewing drafts of the manuscript, and approved the final version for submission.

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Compliance with Ethics Guidelines: This analysis did not involve primary data collection by the authors; consequently, ethical approval was not required. Both included studies were approved by the appropriate ethics committees, and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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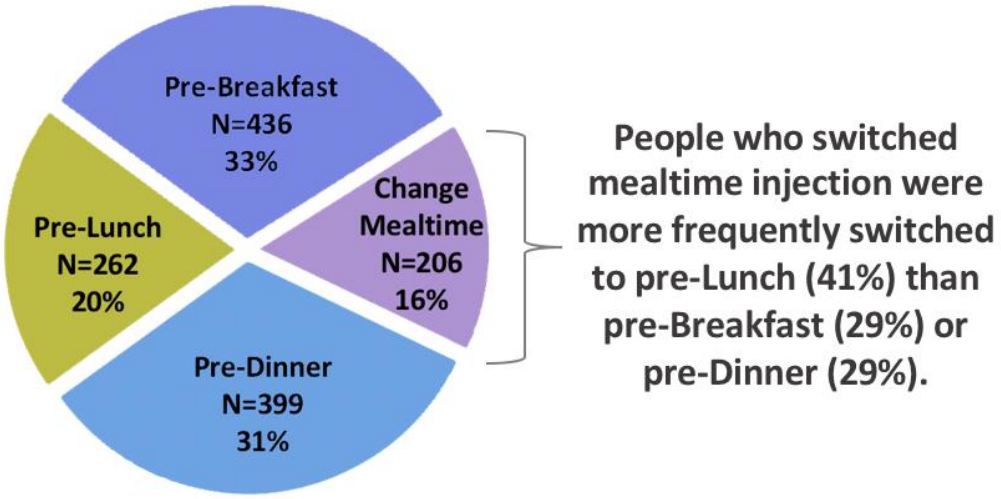

Fig. 1 Patient disposition in the pooled study population (N=1,303)

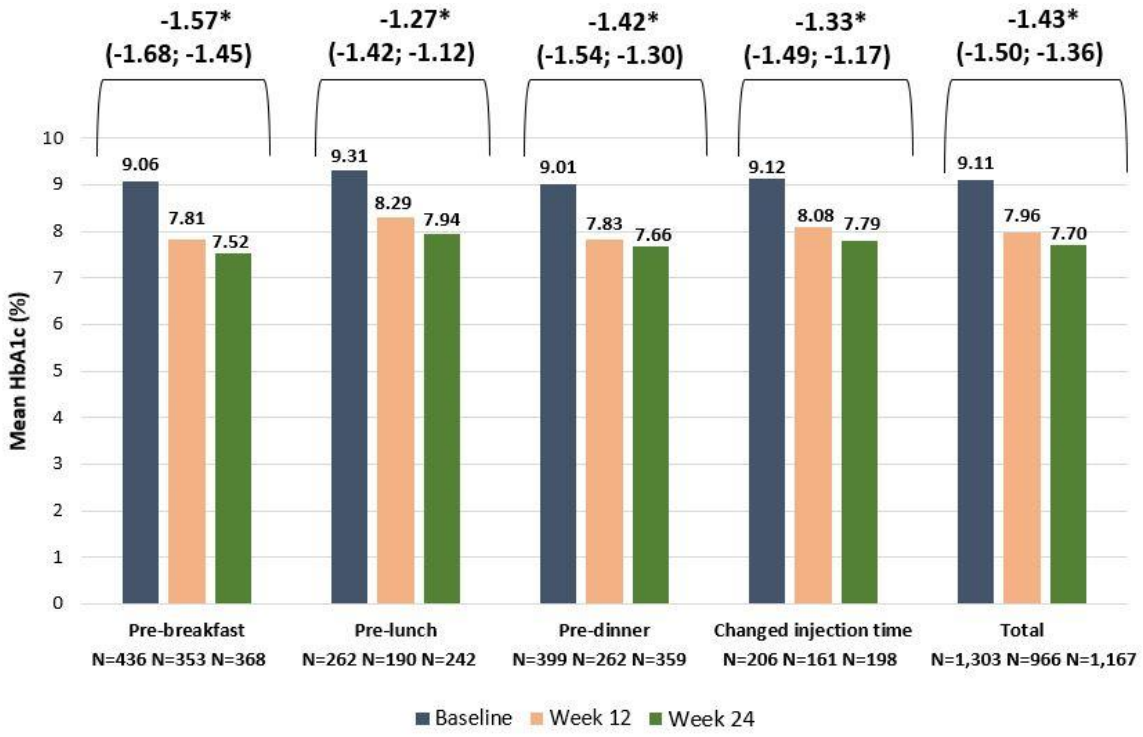

Fig. 2 Mean haemoglobin A1c (HbA1c) (%) over the 24-week study period according to iGlarLixi daily time of administration. N refers to the number of patients with available data at each timepoint. *Correspond to least-squares mean change (95% confidence interval) in HbA1c from baseline to week 24 issued from adjusted MMRM

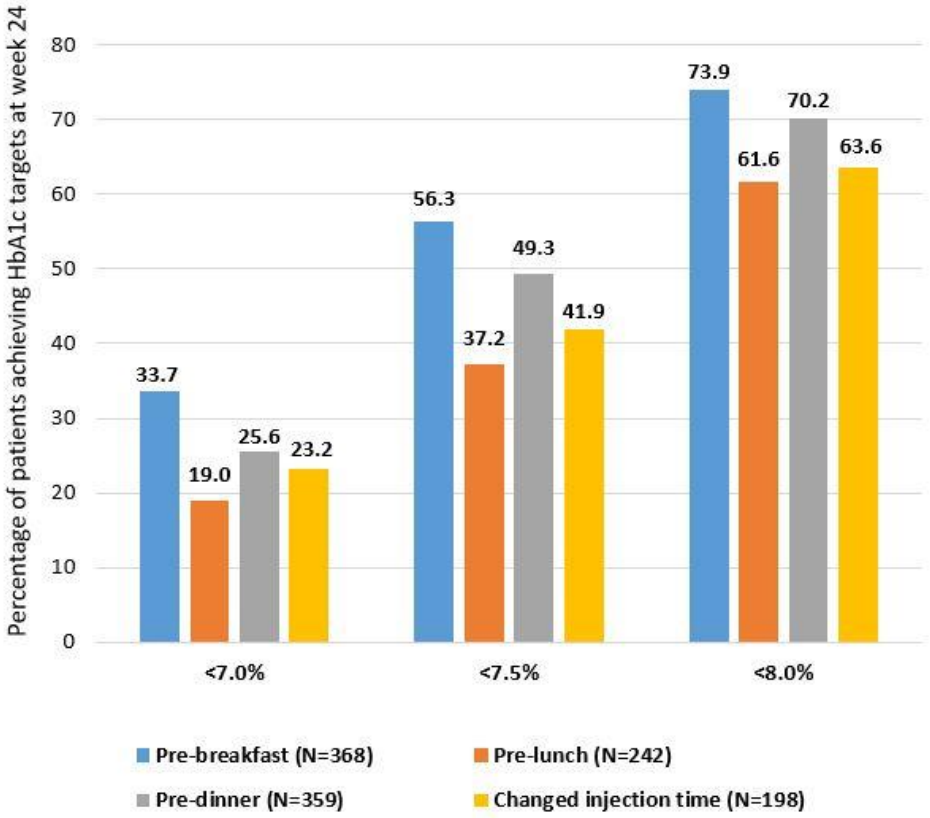

Fig. 3 Percentage (%) of patients achieving haemoglobin A1c (HbA1c) targets <7.0%, <7.5% and <8.0% at week 24 according to iGlarLixi daily time of administration

Table 1. Baseline characteristics according to iGlarLixi daily time of administration

	Pre-breakfast (N=436)	**Pre-lunch (N=262)**	**Pre-dinner (N=399)**	**Changed time (N=206)**	**Total (N=1,303)**
Age (years), mean ± SD	61.7 ± 9.2	62.5 ± 8.0	60.0 ± 9.3	59.5 ± 9.3	61.0 ± 9.0
Sex, n (%)					
Male	186 (42.7)	105 (40.1)	189 (47.4)	94 (45.6)	574 (44.1)
Female	250 (57.3)	157 (59.9)	210 (52.6)	112 (54.4)	729 (55.9)
Body mass index (kg/m^2), mean ± SD	32.4 ± 6.0	32.2 ± 5.1	32.2 ± 5.4	32.0 ± 5.1	32.2 ± 5.5
Body mass index in categories (kg/m^2), n (%)					
<30	162 (37.2)	91 (34.7)	152 (38.1)	79 (38.3)	484 (37.1)
≥30	274 (62.8)	171 (65.3)	247 (61.9)	127 (61.7)	819 (62.9)
Diabetes duration (years), median (Q1–Q3)	9.0 (4.5–13.0)	10.0 (5.0–14.0)	9.0 (4.0–12.0)	8.0 (5.0–12.0)	9.0 (5.0–13.0)
Previous basal insulin use, n (%)	209 (47.9)	129 (49.2)	168 (42.1)	84 (40.8)	590 (45.3)
Prior basal insulin, n (%)*					
Insulin glargine	142 (67.9)	99 (76.7)	102 (60.7)	57 (67.9)	400 (67.8)
NPH insulin	43 (20.6)	7 (5.4)	33 (19.6)	10 (11.9)	93 (15.8)
Insulin detemir	24 (11.5)	21 (16.3)	33 (19.6)	17 (20.2)	95 (16.1)
Duration of prior basal insulin treatment (years), median (Q1–Q3)	2.5 (1.2–4.5)	2.6 (1.3–4.1)	2.5 (1.1–3.8)	2.3 (1.5–4.7)	2.5 (1.3–4.2)
Prior basal insulin dose (U/day), mean ± SD	33.9 ± 12.4	35.7 ± 17.2	31.9 ± 11.4	34.2 ± 12.4	33.7 ± 13.3
Prior basal insulin dose (U/kg/day), mean ± SD	0.38 ± 0.15	0.41 ± 0.20	0.35 ± 0.13	0.39 ± 0.13	0.38 ± 0.15
Number of prior OADs, n (%)‡					
1	242 (55.5)	152 (58.0)	230 (57.6)	115 (55.8)	739 (56.7)
≥2	192 (44.0)	106 (40.5)	166 (41.6)	90 (43.7)	554 (42.5)
Previous OADs, n (%)†‡					
Biguanides	424 (97.2)	258 (98.5)	388 (97.2)	204 (99.0)	1,274 (97.8)
Sulphonylurea	133 (30.5)	81 (30.9)	118 (29.6)	66 (32.0)	398 (30.5)
DPP-4 inhibitors	58 (13.3)	27 (10.3)	49 (12.3)	22 (10.7)	156 (12.0)
SGLT-2 inhibitors	45 (10.3)	11 (4.2)	19 (4.8)	14 (6.8)	89 (6.8)
Other	2 (0.5)	2 (0.8)	3 (0.8)	2 (1.0)	9 (0.7)

	Pre-breakfast (N=436)	Pre-lunch (N=262)	Pre-dinner (N=399)	Changed time (N=206)	Total (N=1,303)
Comorbidities, n (%)†					
Diabetic neuropathy	182 (41.7)	124 (47.3)	135 (33.8)	86 (41.7)	527 (40.4)
Diabetic retinopathy	75 (17.2)	42 (16.0)	51 (12.8)	33 (16.0)	201 (15.4)
Diabetic nephropathy	56 (12.8)	25 (9.5)	42 (10.5)	17 (8.3)	140 (10.7)
Hypertension	213 (48.9)	182 (69.5)	186 (46.6)	116 (56.3)	697 (53.5)
Dyslipidaemia	209 (47.9)	169 (64.5)	184 (46.1)	109 (52.9)	671 (51.5)
Coronary heart disease	86 (19.7)	95 (36.3)	75 (18.8)	46 (22.3)	302 (23.2)
Peripheral arterial disease	57 (13.1)	38 (14.5)	38 (9.5)	32 (15.5)	165 (12.7)
Baseline HbA1c (%), mean ± SD	9.06 ± 1.36	9.31 ± 1.39	9.01 ± 1.36	9.12 ± 1.40	9.11 ± 1.37
Type of used iGlarLixi pen at baseline, n (%)					
Suliqua® 30–60	75 (17.2)	48 (18.3)	65 (16.3)	31 (15.0)	219 (16.8)
Suliqua® 10–40	356 (81.7)	211 (80.5)	329 (82.5)	175 (85.0)	1,071 (82.2)
Missing data	5 (1.1)	3 (1.1)	5 (1.3)	0	13 (1.0)

DPP-4, dipeptidyl peptidase-4; GLP1-RA, glucagon-like peptide-1 receptor agonist ; HbA1c, haemoglobin A1c; iGlarLixi, insulin glargine 100 U/mL and lixisenatide; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; Q, quartile; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2.

*The total number of patients who were previously treated with insulin in each subgroup was used as the denominator to calculate the percentages of patients who received prior insulin glargine, NPH insulin, or insulin detemir. For 2 patients, prior baseline insulin was unspecified.

‡Among these patients, 7 were reported receiving GLP1-RA.

†A participant can be counted in more than one category.

Table 2. Changes in fasting plasma glucose (FPG) from baseline according to iGlarLixi daily time of administration

FPG (mg/dL)	Pre-breakfast (N=436)	Pre-lunch (N=262)	Pre-dinner (N=399)	Changed time (N=206)	Total (N=1,303)
Baseline, n	436	262	399	206	1,303
Mean ± SD	179.63 ± 48.62	188.73 ± 49.07	186.80 ± 58.95	181.97 ± 48.11	184.03 ± 52.09
Week 12, n	403	248	372	206	1,229
Mean ± SD	139.44 ± 32.36	147.29 ± 37.74	137.64 ± 30.48	143.38 ± 37.57	141.14 ± 34.04
Change from baseline to week 12	-42.36 ± 48.97	-43.07 ± 47.10	-50.17 ± 58.95	-38.58 ± 51.37	-44.24 ± 52.34
Week 24, n	374	243	360	200	1,177
Mean ± SD	132.74 ± 27.30	138.66 ± 33.86	134.40 ± 33.19	137.38 ± 33.64	135.26 ± 31.71
Change from baseline to week 24	-48.47 ± 50.84	-51.09 ± 49.43	-53.26 ± 62.42	-45.48 ± 50.03	-49.97 ± 54.25

All data are expressed as mean ± standard deviation (SD). n refers to the number of patients with available data at each timepoint.

Table 3. Safety profile of iGlarLixi according to its daily time of administration

	Pre-breakfast (N=436)	**Pre-lunch (N=262)**	**Pre-dinner (N=399)**	**Changed time (N=206)**	**Total (N=1,303)**
Patients with any TEAE, n (%)	3 (0.7)	9 (3.4)	5 (1.3)	1 (0.5)	18 (1.4)
Patients with any serious TEAE, n (%)	0	0	0	0	0
Patients with any TEAE leading to treatment discontinuation, n (%)	0	2 (0.8)	0	0	2 (0.2)
Patients with any gastrointestinal AE, n (%)	4 (0.9)	10 (3.8)	4 (1.0)	1 (0.5)	19 (1.5)
Nausea	2 (0.5)	8 (3.1)	3 (0.8)	0	13 (1.0)
Vomiting	1 (0.2)	2 (0.8)	0	0	3 (0.2)
Any hypoglycaemia					
Patients with events, n (%)	17 (3.9)	5 (1.9)	22 (5.5)	8 (3.9)	52 (4.0)
Number of events per patient-year*	0.23	0.06	0.23	0.17	0.19
Symptomatic hypoglycaemia					
Patients with events, n (%)	17 (3.9)	3 (1.1)	21 (5.3)	7 (3.4)	48 (3.7)
Number of events per patient-year*	0.23	0.02	0.22	0.16	0.18
Severe hypoglycaemia					
Patients with events, n (%)	1 (0.2)	0	0	0	1 (0.08)
Number of events per patient-year*	0.005	0	0	0	0.002

TEAE, treatment-emergent adverse event.

*Calculated as number of events divided by total patient-years of exposure.

Table 4. Changes in body weight and in daily iGlar dose from baseline according to iGlarLixi time of administration

	Pre-breakfast (N=436)	Pre-lunch (N=262)	Pre-dinner (N=399)	Changed time (N=206)	Total (N=1,303)
Body weight (kg)					
Baseline	90.7 ± 18.6	88.8 ± 15.7	91.2 ± 16.8	89.7 ± 14.8	90.3 ± 16.9
Week 12	89.4 ± 17.8	87.3 ± 14.5	90.0 ± 16.5	88.6 ± 14.7	89.0 ± 16.3
Change from baseline to week 12	-1.6 ± 4.0	-1.5 ± 3.5	-1.2 ± 3.4	-1.1 ± 3.4	-1.4 ± 3.7
Week 24	88.5 ± 17.7	86.7 ± 14.4	89.8 ± 16.2	88.4 ± 15.0	88.5 ± 16.2
Change from baseline to week 24	-2.3 ± 4.6	-1.9 ± 3.9	-1.6 ± 5.1	-1.3 ± 4.4	-1.8 ± 4.6
Daily iGlar dose provided by iGlarLixi (U/day)					
Baseline	19.0 ± 9.8	18.9 ± 8.1	18.4 ± 9.1	19.4 ± 9.6	18.9 ± 9.3
Week 12	30.7 ± 12.0	29.2 ± 10.6	28.9 ± 10.4	30.2 ± 11.5	29.8 ± 11.2
Change from baseline to week 12	11.3 ± 10.0	9.9 ± 8.5	10.2 ± 9.1	11.0 ± 10.1	10.7 ± 9.5
Week 24	33.9 ± 13.1	33.4 ± 13.5	32.5 ± 11.6	33.8 ± 13.0	33.3 ± 12.7
Change from baseline to week 24	14.3 ± 11.5	14.3 ± 11.5	13.5 ± 11.3	14.7 ± 12.0	14.1 ± 11.5
Daily iGlar dose provided by iGlarLixi (U/kg/day)					
Baseline	0.21 ± 0.11	0.22 ± 0.09	0.21 ± 0.10	0.22 ± 0.12	0.21 ± 0.11
Week 12	0.35 ± 0.13	0.34 ± 0.13	0.33 ± 0.11	0.35 ± 0.13	0.34 ± 0.13
Change from baseline to week 12	0.13 ± 0.11	0.12 ± 0.10	0.12 ± 0.10	0.13 ± 0.11	0.12 ± 0.11
Week 24	0.39 ± 0.15	0.39 ± 0.16	0.36 ± 0.13	0.39 ± 0.15	0.38 ± 0.14
Change from baseline to week 24	0.17 ± 0.13	0.17 ± 0.13	0.15 ± 0.12	0.17 ± 0.13	0.16 ± 0.13

All data are expressed as mean ± standard deviation. iGlarLixi, insulin glargine 100 U/mL and lixisenatide.

Table S1. Changes in 2-hour postprandial plasma glucose (PPG) from baseline according to iGlarLixi daily time of administration

2-hour PPG (mg/dL)	Pre-breakfast (N=436)	Pre-lunch (N=262)	Pre-dinner (N=399)	Changed time (N=206)	Total (N=1,303)
Baseline, n	181	53	150	56	440
Mean ± SD	204.37 ± 38.39	217.97 ± 38.44	203.17 ± 48.78	203.34 ± 40.46	205.47 ± 42.59
Week 12, n	156	44	130	55	385
Mean ± SD	159.00 ± 29.14	174.12 ± 30.41	159.75 ± 25.90	164.57 ± 32.22	161.78 ± 29.00
Change from baseline to week 12	-48.27 ± 42.15	-43.02 ± 33.85	-42.30 ± 48.37	-39.83 ± 44.20	-44.45 ± 43.79
Week 24, n	140	43	118	52	353
Mean ± SD	150.44 ± 24.65	158.52 ± 24.33	154.24 ± 23.31	159.09 ± 36.71	153.97 ± 26.42
Change from baseline to week 24	-53.87 ± 37.97	-58.81 ± 38.34	-46.98 ± 51.12	-45.97 ± 49.71	-51.00 ± 44.62

All data are expressed as mean ± standard deviation (SD). n refers to the number of patients with available data at each timepoint. Two-hour PPG was reported in only one of the two pooled studies.