More patients reach glycaemic control with a fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) than with basal insulin at 12 weeks of treatment: A post hoc time-to-control analysis of LixiLan-O and LixiLan-L

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INTRODUCTION

Fixed-ratio combinations (FRCs) of basal insulin (BI) and a glucagon-like peptide-1 receptor agonist (GLP-1RA) are a relatively recent addition to the treatment intensification options for type 2 diabetes (T2D), with demonstrated efficacy and tolerability compared to either treatment alone.1,2 iGlarLixi is a titratable FRC of insulin glargine U100 (iGlar) and the short-acting GLP-1RA lixisenatide (Lixi), administered as a single daily injection.3,4 iGlarLixi provides complementary effects, with iGlar primarily improving fasting plasma glucose (FPG), and Lixi reducing postprandial plasma glucose via enhanced glucose-stimulated insulin secretion, suppression of glucagon secretion and delayed gastric emptying.2,5 In the LixiLan-O and LixiLan-L trials, which evaluated iGlarLixi in patients with T2D uncontrolled on oral antidiabetic drugs (OADs) or on BI, respectively, patients on iGlarLixi demonstrated improved glycaemic control compared with those taking iGlar, without weight gain or increased risk of hypoglycaemia.2,6 The safety profile of iGlarLixi was consistent with those of its components, but the GLP-1RA-associated gastrointestinal effects were lower compared with lixisenatide.2,6

In both LixiLan-O and LixiLan-L, patients on iGlarLixi showed greater reductions in glycated haemoglobin (HbA1c) from baseline to...
study end at 30 weeks compared with those on iGlar (LixiLan-O: −1.6% vs −1.3% [P < .0001]; LixiLan-L: −1.1% vs −0.6% [P < .0001]). Additionally, the proportion of patients who reached the glycaemic target (HbA1c <7% [<53 mmol/mol]) at study end was greater with iGlarLixi than with iGlar in both trials (LixiLan-O: 74% vs 59% [P < .0001]; LixiLan-L: 55% vs 30% [P < .0001]). To investigate time to control with iGlarLixi compared with initiation or continued titration of iGlar, a post hoc analysis of data from LixiLan-O and LixiLan-L was performed, focusing on efficacy and hypoglycaemia outcomes at early study visits (weeks 8 and 12), and time to reach standard American Diabetes Association (ADA) glycaemic targets (HbA1c <53 mmol/mol [<7%] or FPG ≤7.2 mmol/L [<130 mg/dL]).

2 | METHODS

2.1 | Trial designs

The full methodologies of the LixiLan-O (NCT02058147) and LixiLan-L (NCT02058160) trials were described previously2,6 and are summarized in Figure S1 and the Supporting Information Methods, Appendix S1.

2.2 | Post hoc analysis

The primary endpoint of the LixiLan-O and LixiLan-L trials was HbA1c change from baseline at 30 weeks; in this post hoc analysis, efficacy and hypoglycaemia outcomes were assessed at earlier time points. For all assessments, outcomes were compared only between the iGlarLixi and iGlar arms. Changes from baseline in HbA1c, FPG, 7-point self-measured plasma glucose (SMPG) and body weight at week 12 were assessed for the iGlarLixi and iGlar groups, along with the iGlar dose and the occurrence of documented symptomatic hypoglycaemia and severe hypoglycaemia. Documented symptomatic hypoglycaemia was defined as an event with hypoglycaemia and measured plasma glucose concentration ≤3.9 mmol/L (≤70 mg/dL). Severe hypoglycaemia was defined as requiring another person’s assistance to administer carbohydrate, glucagon or other resuscitative actions.

The proportion of patients achieving HbA1c ≤53 mmol/mol (<7%) or FPG ≤7.2 mmol/L (≤130 mg/dL; responders) at weeks 8 and 12 was measured. The median time to glycaemic control, defined as the time for 50% of patients to reach the target, was evaluated using HbA1c measured at scheduled visits at weeks 8, 12, 24 and 30, and FPG measured at scheduled visits at weeks 4, 8, 12, 24 and 30 of treatment, as well as any unscheduled visits.

2.3 | Statistical analysis

Responder analysis was based on the modified intention-to-treat (mITT) population (all randomized patients with a baseline assessment and at least one post-baseline assessment of any efficacy variable, irrespective of compliance with protocol and procedures). If no assessment was available for a given visit, patients were treated as non-responders for that visit. P values were calculated with weighted average of proportion difference between treatment groups from each strata (randomization strata of HbA1c [≤64, ≥64 mmol/mol (<8.0%, ≥8.0%]) and second OAD [LixiLan-O] or metformin use [LixiLan-L] at screening [Yes, No]) using Cochran–Mantel–Haenszel weights. The Kaplan–Meier method was used to estimate time to control, defined as time (days) to first achieving HbA1c ≤53 mmol/mol (<7%) or FPG ≤7.2 mmol/L (≤130 mg/dL). If the target was not reached during the study, the patient was censored at his/her last study visit. Time-to-control analysis was based on the mITT population. P values were calculated using the stratified log-rank test. Hazard ratios (HRs) were estimated using a stratified Cox regression model with treatment as the model factor and stratified by the randomization strata.

3 | RESULTS

3.1 | Patient baseline characteristics

In LixiLan-O, 469 and 467 patients were randomized to the iGlarLixi and iGlar groups, respectively. In LixiLan-L, 367 and 369 patients were randomized to the iGlarLixi and iGlar groups, respectively. Patient baseline characteristics in both studies have been described previously2,6 and were similar across treatment groups within each trial (Table S1, Appendix S1).

3.2 | Efficacy and hypoglycaemia outcomes at week 12

3.2.1 | Changes in HbA1c from baseline

In both LixiLan-O and LixiLan-L, patients achieved a greater reduction in HbA1c from baseline to week 12, and lower mean HbA1c at week 12 with iGlarLixi than with iGlar (Table 1); indeed, in LixiLan-O, mean HbA1c at week 12 with iGlarLixi had already reached the target: ≤53 mmol/mol (<7%; ie, 51.1 ± 8.1 mmol/mol [6.8% ± 0.7%]).

3.2.2 | Changes in FPG and SMPG

In LixiLan-O and LixiLan-L, the mean FPG at week 12 was comparable between treatment groups, and was below the 2015 ADA-recommended target7 of ≤7.2 mmol/L (≤130 mg/dL). In both trials, reductions in FPG from baseline were similar between treatment groups (Table 1), and mean change in average 7-point SMPG at week 12 was greater with iGlarLixi than with iGlar (Table 1). The differences in mean SMPG between the iGlarLixi and iGlar groups were pronounced at post-meal time points (Figure S2 and Table S2, Appendix S1).

3.2.3 | Insulin dose

Mean insulin doses at week 12 were similar for iGlarLixi vs iGlar within each trial (Table 1).

3.2.4 | Body weight

iGlarLixi mitigated body weight gain compared with iGlar alone in both studies (Table 1).

3.2.5 | Hypoglycaemia outcomes

By week 12 in LixiLan-O, 10.9% and 8.6% of patients experienced documented symptomatic hypoglycaemia (plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) with iGlarLixi and iGlar, respectively; in LixiLan-L, these
TABLE 1  Efficacy and hypoglycaemia outcomes at week 12 in the LixiLan-O and LixiLan-L trials

|                    | iGlarLixi | iGlar  |
|--------------------|-----------|--------|
| LixiLan-O          |           |        |
| Efficacy outcomesa |           |        |
| HbA1c, mmol/mol (%)| n = 455   | n = 455|
| At week 12         | 51.1 ± 8.1| 54.4 ± 8.8 |
| (6.8 ± 0.7)        | (7.1 ± 0.8)|        |
| Change from baseline to week 12 | -13.6 ± 8.7 | -10.3 ± 8.8 |
| (1.2 ± 0.8)        | (-0.9 ± 0.8)|        |
| FPG, mmol/L        | n = 455   | n = 451|
| At week 12         | 6.8 ± 1.7 | 7.0 ± 1.7 |
| Change from baseline to week 12 | -3.0 ± 2.5 | -2.8 ± 2.6 |
| 7-point SMPG, mmol/L|        |        |
| At week 12         | 7.6 ± 1.4 | 8.2 ± 1.5 |
| (n = 365)          | (n = 361)|        |
| Change from baseline to week 12 | -2.8 ± 2.2 | -2.1 ± 2.1 |
| (n = 358)          | (n = 351)|        |
| iGlar dose, U      | n = 424   | n = 429|
| At week 12         | 30.0 ± 10.1 | 30.5 ± 10.1 |
| Weight, kg         | n = 456   | n = 456|
| At week 12         | 88.8 ± 17.3 | 90.1 ± 16.2 |
| Change from baseline to week 12 | -0.6 ± 2.3 | 0.2 ± 2.5 |
| Hypoglycaemia eventsb |        |        |
| Number of patients in safety population | 469 | 467 |
| Documented symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL]), n (%)c | 51 (10.9) | 40 (8.6) |
| Severe hypoglycaemia, n (%)c | 0 | 0 |
| LixiLan-L          |           |        |
| Efficacy outcomesa |           |        |
| HbA1c, mmol/mol (%)| n = 357   | n = 360|
| At week 12         | 54.6 ± 8.8 | 59.1 ± 9.4 |
| (7.1 ± 0.8)        | (7.6 ± 0.9)|        |
| Change from baseline to week 12 | -10.1 ± 7.7 | -5.6 ± 8.3 |
| (0.9 ± 0.7)        | (-0.5 ± 0.8)|        |
| FPG, mmol/L        | n = 355   | n = 357|
| At week 12         | 7.0 ± 1.9 | 6.9 ± 1.9 |
| Change from baseline to week 12 | -0.3 ± 2.3 | -0.5 ± 2.5 |
| 7-point SMPG, mmol/L|        |        |
| At week 12         | 8.0 ± 1.7 | 8.6 ± 1.8 |
| (n = 301)          | (n = 295)|        |
| Change from baseline to week 12 | -1.2 ± 1.9 | -0.4 ± 1.7 |
| (n = 291)          | (n = 285)|        |
| iGlar dose, U      | n = 346   | n = 357|
| At week 12         | 41.4 ± 10.5 | 44.0 ± 11.6 |
| Weight, kg         | n = 359   | n = 362|
| At week 12         | 87.1 ± 14.4 | 87.4 ± 14.9 |
| Change from baseline to week 12 | -0.8 ± 2.1 | 0.3 ± 1.9 |
| Hypoglycaemia eventsb |        |        |
| Number of subjects in safety population | 365 | 365 |
| Documented symptomatic hypoglycaemia (≤3.9 mmol/L [≤70 mg/dL]), n (%)c | 86 (23.6) | 107 (29.3) |
| Severe hypoglycaemia, n (%)c | 2 (0.5) | 1 (0.3) |

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; iGlar, insulin glargine U100; iGlarLixi, insulin glargine and lixisenatide; mITT, modified intention-to-treat; SMPG, self-measured plasma glucose.

a Data are mean ± SD, based on mITT population.

b Hypoglycaemia events occurring on or before study day 84.

c Number of patients (%) with events, based on safety population.

rates were 23.6% and 29.3%, respectively (Table 1). In LixiLan-O, no patient receiving iGlarLixi or iGlar experienced severe hypoglycaemia by week 12, and in LixiLan-L, 0.5% and 0.3% of patients experienced severe hypoglycaemia with iGlarLixi and iGlar, respectively (Table 1).

3.3 Time to achieve glycaemic control

3.3.1 Responder analysis

In LixiLan-O and LixiLan-L, more patients achieved HbA1c <53 mmol/mol (<7%) at 8 and 12 weeks with iGlarLixi than with iGlar (P < .0001; Table 2). The proportions of patients with assessments available at 8 and 12 weeks were similar between the iGlarLixi and iGlar groups, and the amount of missing data was small (ranging from 2% to 3.5%; Table S3, Appendix S1).

3.3.2 Time to control

In LixiLan-O, the HbA1c target was achieved by 50% of patients in approximately half the time with iGlarLixi vs iGlar (median time 85.0 vs 166.0 days; HR 1.5; P < .0001 [Table 2 and Figure S3A, Appendix S1]). In LixiLan-L, the median time to achieve HbA1c <53 mmol/mol (<7%) was 153.0 days with iGlarLixi, whereas the target was not reached by 50% of patients with iGlar during the study period (HR 2.1; P < .0001 [Table 2 and Figure S3B, Appendix S1]).

In both trials, the proportions of patients achieving FPG ≤7.2 mmol/L (≤130 mg/dL) were similar between treatment arms (Table 2). The median time to achieve target FPG was similar with iGlarLixi vs iGlar in LixiLan-O, while in LixiLan-L, the FPG target was already achieved by >50% of patients at baseline in the iGlarLixi and iGlar groups (following at least 6 months of BI therapy prior to trial enrolment and a 6-week run-in phase with iGlar; Table 2; Figure S3C and D, Appendix S1).

4 DISCUSSION

This post hoc analysis of LixiLan-O and LixiLan-L showed that in patients with T2D who were intensifying from OADs or BI, more patients achieved glycaemic control early in treatment with iGlarLixi compared with iGlar, as defined by the percentage of patients reaching HbA1c <53 mmol/mol (<7%) at 8 and 12 weeks of therapy. Consistently, iGlar doses and FPG changes were similar across treatment arms in both studies, indicating that the BI component was solely responsible for fasting glucose control, and insufficient for reaching glycaemic control in the majority of patients. Earlier and more widespread achievement of target HbA1c with iGlarLixi was probably attributable to the postprandial plasma glucose coverage provided by the short-acting GLP-1RA component, underscoring the advantage of targeting multiple pathophysiological defects in T2D. Indeed, similar results to those reported in the
In both LixiLan-O and LixiLan-L, drug titrations were based on the same intent-to-treat; NE, non-evaluable; NR, not reached (ie, target not reached by 50% of patients); OAD, oral antidiabetic drug.

**TABLE 2**  Achievement of glycaemic targets (mITT population)

|                               | iGlarLixi | iGlar |
|-------------------------------|-----------|-------|
| **Target HbA1c <53 mmol/mol (≤7%)** |           |       |
| Patients achieving HbA1c target, n (%)<sup>a</sup> |           |       |
| At week 8                     | 186 (39.7) | 128 (27.5) |
| P                             | <.0001     |       |
| At week 12                    | 279 (59.6) | 209 (44.8) |
| P                             | <.0001     |       |
| **Days to first target HbA1c, median (95% CI)<sup>c</sup>** |           |       |
| HR (95% CI)                   | 1.5 (1.3, 1.8) | .1876 |
| P                             | <.0001     |       |
| **Target FPG ≤7.2 mmol/L (≤130 mg/dL)** |           |       |
| Patients achieving FPG target, n (%)<sup>b</sup> |           |       |
| At week 8                     | 263 (56.2) | 249 (53.4) |
| At week 12                    | 309 (66.0) | 293 (62.9) |
| P                             | .3126      |       |
| **Days to first target FPG, median (95% CI)<sup>c</sup>** |           |       |
| HR (95% CI)                   | 1.1 (1.0, 1.3) | .1876 |
| P                             | <.0001     |       |
| LixiLan-La<sup>a</sup>        | n = 366    | n = 365 |
| **Target HbA1c <53 mmol/mol (≤7%)** |           |       |
| Patients achieving HbA1c target, n (%)<sup>b</sup> |           |       |
| At week 8                     | 116 (31.7) | 73 (20.0) |
| P                             | <.0001     |       |
| At week 12                    | 168 (45.9) | 87 (23.8) |
| P                             | <.0001     |       |
| **Days to first target HbA1c, median (95% CI)<sup>c</sup>** |           |       |
| HR (95% CI)                   | 2.1 (1.7, 2.5) | .2271 |
| P                             | <.0001     |       |
| **Target FPG ≤7.2 mmol/L (≤130 mg/dL)** |           |       |
| Patients achieving FPG target, n (%)<sup>b</sup> |           |       |
| At week 8                     | 205 (56.0) | 225 (61.6) |
| At week 12                    | 218 (59.6) | 219 (60.0) |
| P                             | .9083      |       |
| **Days to first target FPG, median (95% CI)<sup>c</sup>** |           |       |
| HR (95% CI)                   | 1.0 (1.0, 2.6) | .2271 |
| P                             | <.0001     |       |

**Abbreviations:** CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HR, hazard ratio; iGlar, insulin glargine U100; iGlarLixi, insulin glargine and lixisenatide; mITT, modified intent-to-treat; NE, non-evaluable; NR, not reached (ie, target not reached by 50% of patients); OAD, oral antidiabetic drug.

<sup>a</sup> In both LixiLan-O and LixiLan-L, drug titrations were based on the same algorithm.

<sup>b</sup> Responder analysis based on the mITT population: estimated by proportion of patients achieving targets at weeks 8 and 12. P value calculated using weighted average of proportion difference between treatment groups from each strata (randomization strata of HbA1c [<64, ≥64 mmol/mol (<8.0%, ≥8.0%)]), second OAD [LixiLan-O] or metformin use [LixiLan-L] at screening [Yes, No] using Cochran–Mantel–Haenszel weights. If no assessment was available for a given visit, patients were treated as non-responders for that visit.

<sup>c</sup> Median time to control: defined as 50% of patients reaching target as estimated by Kaplan–Meier method. Analysis based on the mITT population. HR for time-to-control analysis estimated using a stratified Cox regression model with treatment as the model factor and stratified by the randomization strata. P value calculated using stratified log-rank test.

<sup>d</sup> More than 50% of patients were below the target at baseline.

The present paper was observed with IDegLira, an FRC of insulin degludec and the long-acting GLP-1RA liraglutide. In a post hoc analysis, IDegLira reduced plasma glucose faster and to a greater extent than its components within the first 12 weeks of therapy, without weight gain or an increased risk of hypoglycaemia. Together, these results support the hypothesis that FRCs allow patients with T2D to achieve glycaemic targets earlier than with insulin alone.

Despite the importance of early glycaemic control, clinical inertia is common for patients with inadequate response to OADs, BI or GLP-1RAs. In a retrospective analysis of patients with T2D and inadequate glycaemic control despite ≥2 non-insulin antidiabetic drugs, lack of treatment intensification was observed in 1 out of 5 patients followed up by primary care physicians, and the median time to first intensification was 17 months in patients with HbA1c >8.0%–9.9%, and 10 months in those with HbA1c >10%. In addition to improvement in efficacy, FRC treatment with BI and a GLP-1RA offers simplified titration and administration. These factors, along with lower rates of hypoglycaemia, the potential for mitigation of insulin-induced weight gain and a favourable gastrointestinal tolerability profile, may help combat clinical inertia, improve patient satisfaction and persistence, and minimize periods of hyperglycaemia often associated with the approach of adding on therapies in a sequential manner.

One limitation of the present analysis is that it was performed post hoc; therefore, the sample size and power calculations performed to address the studies’ primary endpoints may not apply to this analysis. Ideally, these findings would be further validated by prospectively planned studies that focus on early efficacy and durability. Additionally, the present study examined patients enrolled in clinical trials; follow-up of trial populations tends to be different from that performed in routine clinical practice. Pragmatic real-world studies will be required to confirm early glycaemic control in more patients with iGlarLixi vs BI in everyday clinical practice.

In conclusion, iGlarLixi allows more patients intensifying either OADs or BI to achieve glycaemic control at early treatment time points (8 and 12 weeks) than BI alone. The efficacy, low rates of hypoglycaemia and the treatment simplicity with this FRC may help to address clinical inertia and allow more patients to safely reach their glycaemic targets earlier.

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Conflict of interest
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REFERENCES
1. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and lirolaglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2:885–893.
2. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide versus insulin glargine and lixisenatide monocomponts in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016;39:2026–2035.
3. Sanofi. Soliqua®: US prescribing information. http://products.sanofi.us/Soliqua100-33/Soliqua100-33.pdf. Accessed January 17, 2018.
4. Sanofi. Press Release: Suliqua™ approved in the European Union for the treatment of adults with type 2 diabetes. http://mediaroom.sanofi.com/suliquatm-approved-in-the-european-union-for-the-treatment-of-adults-with-type-2-diabetes/. Accessed January 17, 2018.
5. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8:728–742.
6. Aroda VR, Rosenstock J, Wysham C, 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;39:1972–1980.
7. American Diabetes Association. Standards of medical care in diabetes-2015. Diabetes Care. 2015;38(suppl 1):S1–S93.
8. Vilsboll T, Vora J, Jarlov H, Kvist K, Blonde L. Type 2 diabetes patients reach target glycemic control faster using IDegLira than either insulin degludec or lirolaglutide given alone. Clin Drug Investig. 2016;36:293–303.
9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–1589.
10. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000:321:405–412.
11. Thomas MC. Glycemic exposure, glycemic control, and metabolic karma in diabetic complications. Adv Chronic Kidney Dis. 2014;21:311–317.
12. Blak BT, Smith HT, Hards M, Curtis BH, Ivanyi T. Optimization of insulin therapy in patients with type 2 diabetes mellitus: beyond basal insulin. Diabet Med. 2012;29:e13–e20.
13. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab. 2016;18:401–409.
14. Montvild O, Klein K, Kumar S, Khunti K, Paul SK. Addition of or switch to insulin therapy in people treated with glucagon-like peptide-1 receptor agonists: a real-world study in 66 583 patients. Diabetes Obes Metab. 2017;19:108–117.
15. Mata-Cases M, Franch-Nadal J, Real J, et al. Therapeutic inertia in patients treated with two or more antidiabetics in primary care: factors predicting intensification of treatment. Diabetes Obes Metab. 2018;20:103–112.

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