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BRIEF REPORT

Low incidence of gastrointestinal adverse events over time with a fixed-ratio combination of insulin glargine and lixisenatide versus lixisenatide alone

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Please click on this **video link** to hear more about this post hoc evaluation of gastrointestinal adverse events in the LixiLan trials.

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This post hoc analysis of gastrointestinal (GI) adverse events (AEs) from the phase 3 LixiLan-L (NCT02058160) and LixiLan-O (NCT02058147) trials aimed to determine the frequency and timing of nausea, vomiting, and diarrhoea for iGlarLixi, a titratable, fixed-ratio combination of insulin glargine 100 units/mL (iGlar) and lixisenatide, versus iGlar alone or iGlar and lixisenatide alone, in patients with type 2 diabetes uncontrolled with oral antidiabetes drugs (OADs) or basal insulin ± OADs. In iGlarLixi-treated patients, the rate of GI AEs during the initial weeks of treatment was lower versus patients treated with lixisenatide alone (9.6% and 11.7% of iGlarLixi-treated patients in LixiLan-L and LixiLan-O, respectively, vs. 27.5% of lixisenatide-treated patients in LixiLan-O). Beyond day 60, these rates were generally low and similar to those of lixisenatide. These lower rates are likely due to the gradual titration of lixisenatide in iGlarLixi. Median durations of intermittent GI AEs in the iGlarLixi arms were 6.0, 2.0 and 2.5 days (LixiLan-L), and 5.0, 1.0 and 3.5 days (LixiLan-O), respectively. iGlarLixi-associated GI AEs were transient, mostly mild or moderate in severity, and occurred mainly during initial titration.

KEYWORDS

fixed-ratio combination, gastrointestinal adverse events, insulin glargine, lixisenatide

1 | INTRODUCTION

For many patients with type 2 diabetes, treatment with basal insulin ± oral antidiabetes drugs (OADs) will eventually be insufficient to maintain glycated HbA1c targets, and additional treatment will be required to control residual hyperglycaemia.[1]

A recent guideline's recommended approach for intensifying basal insulin is the addition of glucagon-like peptide-1 receptor agonists (GLP-1RAs),[1,2] which act on both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) by enhancing glucose-dependent insulin secretion and decreasing glucagon secretion while slowing gastric emptying and increasing satiety.[3] Shorter-acting GLP-1RAs show greater reductions in PPG versus longer-acting agents.[3]

Coadministration of basal insulin and GLP-1RAs results in equivalent or improved HbA1c levels, weight loss or no weight gain, and decreased or no increased hypoglycaemia risk, compared with basal insulin alone[4–9] or in combination with rapid-acting insulins (basal-plus and basal-bolus).[10–12] However, gastrointestinal (GI) adverse events (AEs) are common side effects of GLP-1RAs.[1,2]

iGlarLixi (SOLIQUA 100/33), a titratable, fixed-ratio combination of insulin glargine 100 units/mL (iGlar) and GLP-1RA lixisenatide 33 μg/mL, is indicated in the USA as a once-daily injection for patients with type 2 diabetes inadequately controlled with basal insulin (<60 units/day) or lixisenatide.[13] In the LixiLan phase 3 trials, iGlarLixi led to greater reductions in HbA1c than either iGlar or lixisenatide alone, with the benefit of weight loss or neutrality, and without

increased risk of hypoglycaemia versus iGlar alone. iGlarLixi was associated with low rates of nausea, vomiting, and diarrhoea compared with lixisenatide alone, but with higher rates of these events compared with iGlar alone.[5,6]

Discontinuation rates due to GI AEs associated with iGlarLixi were very low (<1.5%), and fewer patients receiving iGlarLixi in LixiLan-O withdrew versus those receiving lixisenatide alone. No patients treated with iGlar discontinued treatment due to GI AEs in either trial.[5,6]

GI AEs associated with iGlarLixi and lixisenatide appeared to subside over time in the LixiLan trials. This post hoc analysis aimed to assess the frequency and timing of GI AEs in these trials evaluating iGlarLixi in patients with type 2 diabetes.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a post hoc analysis of data from two open-label, randomized, parallel-group, multinational, multicentre phase 3 clinical trials.[5,6]

LixiLan-L (NCT02058160) compared iGlarLixi (n = 367) with iGlar (n = 369) in patients showing suboptimal glycaemic control on basal insulin ± 0–2 OADs. All patients continued/switched to iGlar (any other insulin or OAD other than metformin was stopped), which was titrated over 6 weeks. Patients with FPG ≤140 mg/dL and HbA1c 7.0%–10.0% (53–86 mmol/mol) receiving an iGlar dose of 20-50 units/day were then randomized to either iGlarLixi or iGlar for 30 weeks. The initial dose of iGlarLixi was determined based on the last iGlar dose received before randomization (20 units/10 μg or 30 units/10 μg for iGlar <30 or ≥30 units, respectively) and remained stable for 2 weeks; the initial dose of iGlar after randomization was the one before randomization. iGlarLixi and iGlar doses were titrated by 2–4 units once-weekly to reach and maintain the FPG target of 80–100 mg/dL, based on a 3-day average of fasting self-measured plasma glucose levels, and capped at 60 units/day of iGlar in both arms.[6]

LixiLan-O (NCT02058147) compared iGlarLixi (n = 469) with iGlar (n = 467) and lixisenatide (n = 234) in patients with type 2 diabetes not adequately controlled with metformin monotherapy or metformin plus a second OAD. Patients discontinued the second OAD during the run-in phase, and metformin dose was optimized (1500 or 2000 mg) as tolerated. Patients with an HbA1c of 7.0%–10.0% (53–86 mmol/mol) and FPG ≤250 mg/dL were randomly assigned to receive iGlarLixi, iGlar or lixisenatide for 30 weeks. iGlarLixi and iGlar doses were titrated and capped as described for LixiLan-L. iGlarLixi was administered within 60 min before breakfast, iGlar at any time of the day but at roughly the same time each day, and lixisenatide within 60 min before breakfast or dinner. Ten μg of lixisenatide was administered during the first 2 weeks, rising to 20 μg over 30 weeks.[5]

In both trials, the safety population included all randomized patients who received at least one dose of iGlarLixi, iGlar or lixisenatide.[5,6]

2.2 | Statistical analysis

The incidence, timing, and duration of selected GI AEs (nausea, vomiting and diarrhoea) arising from the start to the end of the trials (~210 days) were evaluated. Results were summarized by treatment group using descriptive statistics. *P* values were calculated from a two-sample *t*-test comparing patients who did and did not experience GI AEs.

The severity of the GI AEs was determined by the investigators. Mild events were generally transient, requiring only minimal treatment/intervention and not generally interfering with daily activities; moderate events could be alleviated with additional treatment/intervention and interfered with daily activities, but did not pose significant/permanent risk of harm; severe events required intensive treatment/intervention and interrupted common daily activities or affected clinical status, posing a significant risk of harm. For intermittent/periodic events, the highest intensity for the overall duration of the event was recorded; GI AEs were reported only once using the overall duration of the event as the time between the start and the stop date for the event.

3 | RESULTS

3.1 | Baseline patient characteristics

All patients in the safety population were included in the analysis: 736 patients from LixiLan-L and 1170 patients from LixiLan-O. No significant differences in age, HbA1c levels, body mass index or disease duration were seen between patients experiencing GI AEs versus those not reporting GI AEs in both trials (see the supporting information for this article, Table S1 in File S1).

3.2 | Incidence of GI AEs over time

The number of patients with a first complaint of nausea, vomiting or diarrhoea peaked within the first 60 days (8 weeks) and subsequently decreased over time in the iGlarLixi and lixisenatide groups (Figure 1). In LixiLan-L, the incidences of nausea and vomiting were low throughout the trial for iGlarLixi, and almost null for the iGlar arm (Figure 1A). Nausea and vomiting were marked during the initial weeks of treatment with lixisenatide in LixiLan-O (Figure 1B).

3.3 | Severity of GI AEs

Most GI AEs in the LixiLan trials were mild to moderate in severity for all treatment groups (Figure 2). In the group of iGlarLixi-treated patients with reported GI AEs (62/365 patients [17.0%] and 102/469 patients [21.7%] overall in LixiLan-L and LixiLan-O, respectively),[5,6] 53%–78% of the events were classified as mild and 22%–44% as moderate (Figure 2), with only one reported severe event (1/47 [2.13%]) of nausea in LixiLan-L (Figure 2A). In LixiLan-O, however, there were five reported severe nausea events (5/77 [6.49%]) with lixisenatide.

3.4 | Duration of GI AEs

Median durations of nausea and vomiting were lower with iGlarLixi versus lixisenatide in LixiLan-O, while the shortest durations of GI AEs were seen with iGlar treatment in both trials (Table S2 in File S1).

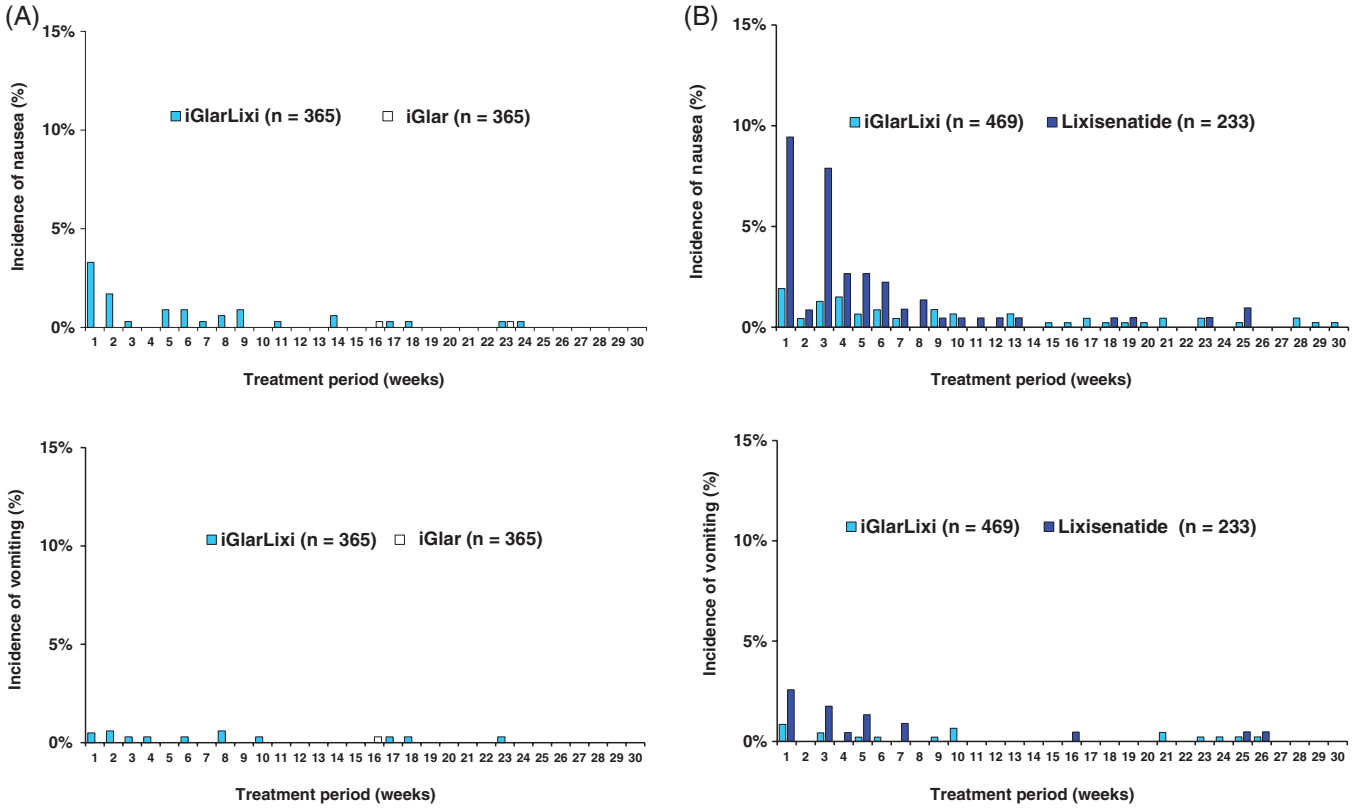

FIGURE 1 Incidence of nausea and vomiting per week with iGlarLixi A, versus iGlar in Lixilan-L and B, versus lixisenatide in Lixilan-O. Each subject could contribute with multiple events over time, but only the first event was counted each week

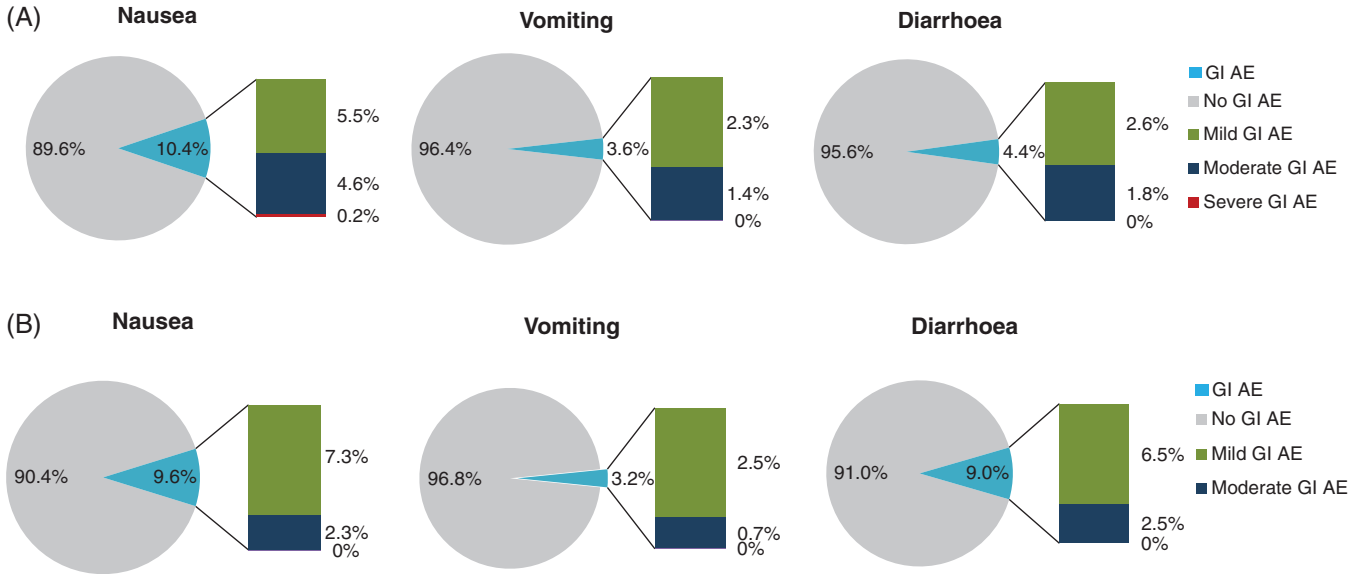

FIGURE 2 Severity of nausea, vomiting and diarrhoea with iGlarLixi in A, LixiLan-L and B, LixiLan-O. AE, adverse event; GI, gastrointestinal. The pie charts show the percentage of patients with/without a GI AE; the bars show the percentage of events (i.e. one patient can contribute with multiple events)

3.5 | Daily doses of iGlar and lixisenatide

The mean daily doses of iGlar and lixisenatide administered as part of the combination, as well as iGlar administered individually, increased throughout the trials. There were no statistically significant differences in daily iGlar doses between patients experiencing GI AEs versus those not reporting them in the iGlarLixi and the iGlar arms in either of the trials (Table S3 in File S1).

4 | DISCUSSION

GI AEs are expected side effects associated with the use of GLP-1RAs and among the main reasons given by patients for discontinuing treatment. In this post hoc analysis of the LixiLan trials, patients with type 2 diabetes treated with iGlarLixi showed a higher rate of GI AEs compared with those treated with iGlar

only, but lower compared with lixisenatide alone, which may be due to the gradual titration of lixisenatide in the combination arm. This gradual increase in the lixisenatide dose, paralleling the iGlar titration, may mitigate the risk of GI AEs seen when lixisenatide is administered separately as a fixed dose of 10 μg and increased after 2 weeks to the maintenance dose of 20 μg. Similar findings were obtained in the open-label, phase 3 trial (DUAL-I) comparing a combination of insulin degludec with liraglutide versus the individual components.[14]

Rates of GI AEs with iGlarLixi were also lower than those reported for other GLP-1 agents administered alone, which can exceed 20% and are mainly related to nausea.[15] The rates for GI AEs reported with the iGlarLixi combination in LixiLan-L were lower than those observed in the lixisenatide plus basal insulin arm in the GetGoal-L trial.[7] However, the incidences of GI AEs in the iGlar arms in both LixiLan-L and -O trials were consistent with those reported for the insulin arms in other clinical trials in insulin-experienced[7,9] and -naive patients,[8] suggesting that variability in patient populations across trials did not influence GI outcomes.

In this analysis, GI AEs were transient, predominantly arising during the initial 8 weeks of treatment; similarly, in DUAL-I, nausea was most prevalent in the first 10 weeks of treatment.[14] Beyond this period, the incidences of GI AEs with iGlarLixi and lixisenatide were similar and low.

Overall, the majority of GI AEs reported for all treatment groups in the current analysis were mild or moderate in severity in both trials, with only one reported severe nausea event with iGlarLixi. The median durations of nausea and vomiting were lower with iGlarLixi versus lixisenatide in LixiLan-O.

Treatment with iGlarLixi has been shown to achieve significantly greater reductions in HbA1c levels than iGlar alone.[5,6] Although adherence to medication is a major determinant of glycaemic control in type 2 diabetes,[16,17] real-world data show that approximately 35% of patients discontinue treatment with GLP-1RAs after 6 months.[18] Therefore, the improved glycaemic control and reduced frequency/severity of GI AEs with iGlarLixi compared with alternatives showing higher rates of GI AEs may improve treatment adherence and outcomes.

This study presents the usual limitations associated with post hoc analyses. Since this was an analysis of patients in highly controlled, randomized clinical trials, it is unclear whether the data are fully generalizable to the wider population with type 2 diabetes managed in routine care. The open-label design of the LixiLan trials and the fact that the severity of the GI AEs was categorized at the investigator's discretion may have introduced bias in the evaluation of AEs. The individual components were compared separately, not concomitantly. The authors' analysis is descriptive only and does not allow for testing for inferiority/superiority of the combination versus the single agents. Additionally, non-iGlarLixi/lixisenatide-related events that could potentially cause GI AEs were not captured in this analysis. It must also be taken into consideration that the LixiLan studies evaluated different patient populations with distinct baseline characteristics.

In summary, patients with type 2 diabetes treated with iGlarLixi in the LixiLan trials showed low rates of GI AEs versus lixisenatide alone. GI AEs associated with iGlarLixi tended to be transient and mild/moderate in severity; the majority occurred early in the course of treatment, with most patients no longer experiencing them beyond 8 weeks. iGlarLixi thus offers an alternative to treatment progression for patients not at target after lifestyle changes and treatment with oral agents by adding a GLP-1RA or basal insulin alone. Titration of iGlarLixi is similar to basal insulin titration and shows greater potential to achieve glycaemic targets with fewer GI AEs than either a GLP-1RA alone or a GLP-1RA plus basal insulin as a free combination.

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Conflict of interest

J. M. T. reports past participation in advisory boards and being a consultant for Sanofi Inc. M. R. reports being an employee of Sanofi US, Inc. T. D. reports being an employee and stock/shareholder of Sanofi US, Inc. J. C. reports being an employee of Xinyi, Inc., which is under contract with Sanofi US, Inc. J. W. reports past participation in advisory boards for Novo Nordisk, Inc. and Sanofi Inc. J. L. reports past participation in advisory boards for Eli Lilly and Company, Novo Nordisk, Inc., and Sanofi Inc., and being a member of the speakers bureau for Novo Nordisk, Inc.

Author contributions

J. M. T., M. R., T. D., J. W. and J. L. co-developed the concept of the study, interpreted the data, critically reviewed the manuscript drafts, and provided final approval of the version of the manuscript to be submitted. J. C. collected the data, performed the analyses and provided the data tables, interpreted the data, critically reviewed the manuscript drafts, and provided final approval of the version of the manuscript to be submitted. J. M. T. is the guarantor of this work and, as such, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

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

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