Efficacy and safety of iGlarLixi versus IDegLira in adults with type 2 diabetes inadequately controlled by glucagon-like peptide-1 receptor agonists: a systematic literature review and indirect treatment comparison

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Abstract
Aims: To estimate the relative treatment effect between the fixed-ratio combinations iGlarLixi and IDegLira (glucagon-like peptide 1 receptor agonist with basal insulin) in people with type 2 diabetes inadequately controlled on a glucagon-like peptide 1 receptor agonist.

Materials and Methods: A systematic literature review of randomized controlled trials followed by an indirect treatment comparison was performed to compare the efficacy and safety of the available fixed-ratio combinations. Main outcomes were glycated haemoglobin (HbA1c) change and target achievement [<6.5% and <7.0% (<48 and <53 mmol/mol)], fasting plasma glucose, self-monitored plasma glucose, body weight, and incidence and rate of hypoglycaemia.

Results: From 4850 abstracts screened, 78 qualified for full-text article review and two randomized controlled trials were included. Baseline characteristics were similar in the two studies. The mean difference at 26 weeks between IDegLira and iGlarLixi was −0.36 (95% credible intervals −0.58, −0.14) % [−3.9 (−6.3, −1.5) mmol/mol] for HbA1c and −1.0 (−1.6, −0.4) mmol/L for fasting plasma glucose. No significant differences were found in HbA1c target attainment, preprandial or postprandial self-monitored plasma glucose, body weight, and incidence and rate of hypoglycaemia.

Conclusions: Results of this indirect treatment comparison using two studies suggest iGlarLixi and IDegLira appear to offer similar benefits for HbA1c target achievement. However, the findings suggest differences in other glycaemia results and hypoglycaemia, which may reflect differences in study design and titration approaches.

* At time study was conducted.

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1 | INTRODUCTION

Oral agents usually become inadequate with time, thus for optimal control of blood glucose in type 2 diabetes (T2D) most people eventually require injectable therapy to meet their individual treatment targets.\(^1\) The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) now recommend a glucagon-like peptide-1 receptor agonist (GLP-1RA) as the first injectable for people with glycated haemoglobin (HbA1c) above their individual target.\(^2\) However, evidence indicates that about 50% of people discontinue GLP-1RA therapy within 1 year,\(^3\) and inadequate glycaemic control is the most commonly reported reason, by individuals, for discontinuing therapy.\(^4\)

The ADA and EASD recommend the addition of basal insulin in those inadequately controlled on GLP-1RAs.\(^5\) For the aforementioned people needing additional therapies and for those with HbA1c >10.0% (86 mmol/mol), these organizations recommend consideration of a fixed-ratio combination (FRC) treatment consisting of a basal insulin and a GLP-1RA as a potential option. The currently-available FRCs are iGlarLixi, a once-daily titratable FRC of insulin glargine 100 units/mL and lixisenatide, and IDegLira, insulin degludec with liraglutide.\(^6\) The efficacy and safety of these agents has been established through the LixiLan (iGlarLixi) and DUAL (IDegLira) programmes.\(^10\)–\(^15\)

However, there are no published head-to-head trials comparing iGlarLixi with IDegLira. The present study set out to compare the clinical efficacy and safety of iGlarLixi versus IDegLira in people with T2D inadequately controlled on GLP-1RAs by an indirect network meta-analysis (NMA), which evolved into an indirect treatment comparison (ITC) because only two relevant studies were identified through systematic literature review of relevant articles.

2 | MATERIALS AND METHODS

2.1 | Systematic literature review and screening

Literature searches were conducted in MEDLINE (Medical Literature Analysis and Retrieval System Online), Embase and CENTRAL (Cochrane Central Register of Controlled Trials) databases to identify articles published between January 2005 and January 2019, using a range of Medical Subject Headings and key words (Table S1). Recent conference proceedings searched in Embase included those from the International Diabetes Federation, ADA and EASD from 2017 to 2018. Additional literature was identified by ‘hand search’ review of the reference lists of the articles found via the database search.

Identified abstracts and proceedings were independently screened by two investigators, and papers eligible for inclusion were full-text screened. Study eligibility was determined according to the population, intervention, comparator and outcome (PICO) framework described in the Cochrane Handbook for Systematic Reviews of Interventions (Table S2).\(^6\) Randomized controlled trials (RCTs) were chosen as the eligible study design for this review. The intervention component of the PICO inclusion criteria required that the study compare an FRC, basal insulin or GLP-1RA with each other, or with premix insulin, all in a population already using a GLP-1RA.

Articles eligible after full-text screening were included for data extraction. Data on the characteristics of the studies, participants and interventions, as well as outcomes were extracted using a standardized data extraction table. At each stage of the screening process, disagreements due to differences in interpretation between the two investigators were resolved by a third investigator to reach a consensus. Internal validity of individual trials was assessed using Cochrane Collaboration’s tool for assessing risk of bias in randomized trials, including selection, performance, detection, attrition and reporting bias.\(^16\)

2.2 | Outcomes

The following outcomes were extracted: change in HbA1c; proportion reaching HbA1c <6.5% (<48 mmol/mol) and HbA1c <7.0% (<53 mmol/mol) targets relative to the respective GLP-1RA arm, change in fasting plasma glucose (FPG); parameters derived from self-monitored plasma glucose (SMPG) profiles; change in body weight; and incidence and event rate of hypoglycaemia, including total, symptomatic, severe, confirmed and combinations thereof. Treatment-emergent adverse events (AEs) were also captured.

2.3 | Data analysis

Extracted data were planned to be analysed by NMA using Bayesian fixed-effect modelling to estimate the comparative efficacy and safety of iGlarLixi versus IDegLira in the relevant studies identified. However, due to the small number of eligible publications identified and a lack of closed network loops, an ITC became necessary for the only two FRC versus GLP-1RA direct comparisons. A feasibility assessment for the ITC was therefore performed to assess the comparability of the two RCTs identified, and to plan the appropriate analyses. Analyses were conducted using WinBUGS (v1.4.3) software.\(^17\)

Comparison of the treatments for the clinical outcomes of interest were presented as mean difference or relative risk, with 95%
credible intervals (CrI). For binary outcomes, analyses used a binomial likelihood distribution and a logit link, whereas for continuous outcomes, analyses used a non-informative, normal previous distribution (mean of 0.000 and standard deviation of 0.001) and an identity link. Drugs in the GLP-1RA class were treated as a single node. Binary outcomes for which there were no events for the GLP-1RA group were not included in the analyses to avoid computational error and bias.

If a publication presented data points of interest only as a figure without data labels, data points were captured using Grab-It software (Datatrend, Minnetonka, Minnesota), a Microsoft Excel-based application that calibrates x- and y-axes to estimate the x- and y-value of the required data point. Author-reported values were given priority over Grab-It-estimated values. Daily average preprandial and postprandial SMPG were calculated at baseline and week 26 from the pre- and postmeal time points, respectively, and change was calculated by subtracting baseline values from the week 26 values. Pre- and post-breakfast points of the SMPG curve were also estimated, and if a profile included a next day measurement, only the first pre-breakfast estimate was included. Standard error was estimated assuming a correlation of $r = 0.70$ between each time point. Safety endpoints were assessed descriptively.

3 | RESULTS

3.1 | Study selection

Of 6422 publications identified by the search, 4850 were screened by title and abstract after de-duplication, and 78 publications were included for full-text screening (Figure S1). In total, 73 of these records were excluded: the reasons were population (n = 71; in particular for no previous use of GLP-1RA), outcome (n = 1) and not in English (n = 1).

Only two of the five remaining publications tested a relevant FRC product; the other two trials in three publications were of insulins compared with a GLP-1RA, but had no other link to the FRCs, which could have informed an NMA (Table S3). Accordingly, there were two studies remaining that were included in the ITC: DUAL III (NCT01676116) comparing IDegLira with continued use of previous liraglutide or exenatide therapy, and LixiLan-G (NCT02787551) comparing iGlarLixi with unchanged previous GLP-1RA therapy (Figure S2). Therefore, an ITC was performed, rather than an NMA analysis, to compare iGlarLixi versus IDegLira, with a common link through their GLP-1RA treatment arms. With one trial per treatment pair, a fixed-effects model was then employed, as in this circumstance, the choice of method was inconsequential.

3.2 | Participant disposition and baseline characteristics

DUAL III recruited 438 participants from 81 sites in five countries (Australia, France, Hungary, Slovakia and the USA); LixiLan-G included 514 participants from 112 sites in nine countries (Canada, Estonia, Germany, Israel, Romania, Slovakia, Spain, Italy and USA). Baseline characteristics were comparable between the two trials (Table 1). Both trials followed participants for a 26-week treatment period, although LixiLan-G included a single-arm 26-week extension, which was not reported in the included publication. Liraglutide was the most commonly used GLP-1RA at baseline in both trials and in both active and control arms. People assigned to the GLP-1RA arms continued with their previous GLP-1RA and oral agents. However, participants in LixiLan-G were not permitted sulphonylurea use from 3 months before the study period, while in DUAL III 23.3% of participants were using sulphonylureas pre-trial and could continue it. Neither publication reported previous comorbidities.

3.3 | Fixed-ratio combination dosing

In DUAL III, the starting dose of IDegLira was 16 U of insulin degludec per day, titrated to an FPG target of 4.0-5.0 mmol/L (72-90 mg/dL). The final mean daily dose was 43 U insulin degludec. In LixiLan-G, the starting dose of iGlarLixi (10 U of insulin glargine) was titrated to an FPG target of 4.4-5.6 mmol/L (80-100 mg/dL). After 26 weeks, the mean dose was 43.5 U of insulin glargine per day.

3.4 | Blood glucose control

The mean HbA1c reduced from 7.8 ± 0.6% (62 ± 7 mmol/mol) at baseline to 6.4 ± 0.8% (46 ± 9 mmol/mol) at week 26 for IDegLira and from 7.8 ± 0.6% (62 ± 7 mmol/mol) at baseline to 6.7 ± 0.8% (50 ± 9 mmol/mol) at week 26 for iGlarLixi (Table 2). However SMPG levels at −3.9 to −6.3 mmol/mol; Figure 1A). In both trials, HbA1c targets were ≤6.5% (≤48 mmol/mol) and <7.0% (<53 mmol/mol); more participants reached HbA1c targets with IDegLira or iGlarLixi than GLP-1RAs, but absolute attainment differed between studies for the GLP-1RA arms (Table 2). Adjusting for this, the relative risk of IDegLira compared with iGlarLixi for the ≤6.5% target was 0.94 (95% CrI 0.85, 1.37) and for the <7.0% target was 1.04 (95% CrI 0.85, 1.27; Figure 1B).

The mean difference between IDegLira and iGlarLixi for change in FPG from baseline to week 26 was significant in favour of IDegLira: 1.00 (95% CrI 1.57, −0.43) mmol/L. In LixiLan-G, participants collected a seven-point SMPG profile (postprandial 2 h after meals) on two separate days at baseline and week 26. In DUAL III, participants measured a nine-point SMPG profile adding a 04:00 h and following-day breakfast test (postprandial 90 min after meals), at baseline and week 26. In both trials, pre- and post-breakfast and mean pre- and postprandial SMPG values were significantly lower with the FRC than the GLP-1RA comparator (Table S4). However SMPG levels at baseline and week 26 were highly variable in the GLP-1RA arms. Mean differences in pre- and post-breakfast, as well as daily average
pre- and postprandial SMPG did not favour either FRC statistically, but credible intervals were wide (Figure 1A).

### 3.5 Body weight

In both trials, mean weight increased in the FRC group relative to the GLP-1RA group (Table 2)\textsuperscript{12,15}; however, comparative analyses did not suggest differences in weight at week 26 between IDegLira and iGlarLixi.

### 3.6 Hypoglycaemia

Table 3 presents the proportions of participants with hypoglycaemia and event rates as reported in the DUAL III and LixiLan-G trials\textsuperscript{12,15}. Comparisons of hypoglycaemic episodes were limited by differing definitions and plasma glucose cut-offs for hypoglycaemia, sulphonylurea use in DUAL III but not in LixiLan-G, and the very low rates of hypoglycaemia in the GLP-1RA comparator arms (Table 3). Accordingly, hypoglycaemia results are only presented descriptively. In DUAL III, hypoglycaemia was defined as confirmed hypoglycaemia with...
Incidence of confirmed hypoglycaemia (≤3.1 mmol/L) in participants with no sulphonylurea use was 28% for IDegLira in DUAL III versus 0% for the GLP-1RA arm. Incidence of documented symptomatic hypoglycaemia (<3.0 mmol/L) was 9.4% for iGlarLixi in LixiLan-G versus 0.4% for its GLP-1RA arm. Hypoglycaemia event

### TABLE 2  Glucose control and body weight outcomes in DUAL III and LixiLan-G

|                     | LixiLan-G | GLP-1RA | DUAL III | GLP-1RA |
|---------------------|----------|---------|----------|---------|
| HbA1c, %            |          |         |          |         |
| Baseline            | 7.8 ± 0.6| 7.8 ± 0.6| 7.8 ± 0.6| 7.7 ± 0.5|
| Week 26             | 6.7 ± 0.8| 7.4 ± 0.8| 6.4 ± 0.8| 7.4 ± 1.0|
| LS mean difference, P | −0.6 (−0.8, −0.5), <0.0001 | NC | −0.94 (−1.11, −0.78), <0.001 |
| Difference, P       | NC       |         | NC       |         |
| HbA1c, mmol/mol     |          |         |          |         |
| Baseline            | 62 ± 7   | 62 ± 7  | 62 ± 6   | 61 ± 7  |
| Week 26             | 50 ± 9   | 57 ± 9  | 46 ± 9   | 57 ± 11 |
| LS mean difference, P | −7 (−9, −6), <0.0001 | NC | −10 (−12, −9), <0.001 |
| Difference, P       | NC       |         | NC       |         |
| HbA1c target attainment (26 weeks) |          |         |          |         |
| ≤6.5% (≤48 mmol/mol), % | 41       | 10      | 63       | 23      |
| Difference, P       | 30.6 (23.6, 37.6), <0.0001 | NC | 7.5 (4.6, 12.4), <0.001 |
| Estimated odds ratio, P | NC |         | 6.84 (4.28 to 10.94), <0.001 |
| <7.0% (<53 mmol/mol), % | 61.9   | 26.6   | 75       | 36      |
| Difference, P       | 36.1 (28.1, 44.0), <0.001 | NC |         |         |
| Odds ratio, P       | NC       |         | 6.84 (4.28 to 10.94), <0.001 |
| FPG, mmol/L         |          |         |          |         |
| Baseline, mean ± SD | 9.1 ± 2.1| 9.5 ± 1.9| 9.0 ± 2.1| 9.4 ± 2.3|
| Week 26, mean ± SD  | 6.9 ± 1.7| 8.7 ± 2.0| 6.0 ± 1.6| 8.8 ± 2.7|
| LS mean difference, P | −1.7 (−2.0 to −1.3), <0.0001 | NC | −2.6 (−3.0 to −2.3), <0.001 |
| Difference, P       | NC       |         | NC       |         |
| FPG, mg/dL          |          |         |          |         |
| Baseline, mean ± SD | 163 ± 38 | 170 ± 35| 162 ± 38b| 169 ± 42b|
| Week 26, mean ± SD  | 124 ± 30 | 156 ± 36| 108 ± 29b| 158 ± 49b|
| LS mean difference, P | −30 (−36 to −24), <0.0001 | NC | −48 (−55 to −41)b, <0.001 |
| Difference, P       | NC       |         | NC       |         |
| Body weight, kg     |          |         |          |         |
| Baseline, mean ± SD | NR       | NR      | 95.6 ± 16.6| 95.5 ± 17.3|
| Week 26, mean ± SD  | +1.9 ± NR| −1.2 ± NR| +2.0 ± 3.9| −0.8 ± 3.0|
| LS mean difference, P | +3.0 (2.42 to 3.64), NR | NC | +2.9 (2.2 to 3.6), <0.001 |
| Difference, P       | NC       |         | NC       |         |

Note: Data are mean ± SD, %, difference (95% CrI), or P value.
Note: The table includes only data as presented in the LixiLan-G and DUAL III publications, except week 26 FPG and FPG treatment difference data for DUAL III, which was only provided in mg/dL and then converted during our analyses to mmol/L. HbA1c mmol/mol data were also converted from percentage data.
Abbreviations: CrI, credible interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LS, least squares; NC, not calculated in publication; NR, not reported in publication; SD, standard deviation.

aNot reported in the manuscript but calculated from reported % data.
bCalculated from mmol/L data.

plasma glucose ≤3.1 mmol/L (≤56 mg/dL) or severe hypoglycaemia that required third-party assistance, whereas in LixiLan-G, hypoglycaemia was documented symptomatic with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and for a separate analysis <3.0 mmol/L (<54 mg/dL).
rate for those who switched to iGlarLixi was 0.25 per patient-year for documented symptomatic hypoglycaemia (<3.0 mmol/L). The event rates for confirmed hypoglycaemia (≤3.1 mmol/L) with IDegLira were 6.34 per patient-year among those treated with sulphonylurea and 1.75 per patient-year among those not treated with sulphonylurea (Table 3). One case of severe hypoglycaemia...
occurred in each FRC arm of each study, versus none in the comparator groups.12,15

3.7 | Safety

In LixiLan-G, 63.9% of participants in the iGlarLixi group and 47.3% in the GLP-1RA group reported at least one AE. The most commonly reported AEs across treatment groups were nasopharyngitis, nausea and diarrhoea. Nausea occurred in 8.6% and 2.3% of participants in the iGlarLixi and GLP-1RA groups. Serious AEs were reported in 3.9% of the iGlarLixi group and 3.5% of the GLP-1RA group. Discontinuations due to an AE occurred in 3.5% and 0% of participants, respectively.12 In DUAL III, AEs were reported by 65.6% of participants in the IDegLira group and 63.4% in the GLP-1RA group. The most commonly reported AEs across treatment groups were nasopharyngitis, upper respiratory tract infection, increased lipase, headache and diarrhoea. Nausea occurred in 3.1% of participants in the IDegLira group and 4.1% of the GLP-1RA group. Serious AEs were reported in 3.1% of the IDegLira group and 2.1% of the GLP-1RA group. One participant treated with IDegLira and two with GLP-1RA discontinued due to AEs.15 No unexplained or unexpected serious AEs occurred in either trial.12,15

4 | DISCUSSION

The results of the current systematic literature review and the consequential ITC analysis, although limited by being based on the only two linked RCTs of IDegLira and iGlarLixi versus GLP-1RA, finds no significant differences between the FRC combinations in terms of the proportions of study participants reaching target HbA1c levels, SMPG derived parameters or body weight change. However, IDegLira showed greater reductions in HbA1c from baseline to week 26, though importantly, both FRCs showed clinically effective HbA1c reductions such that the proportions of participants reaching the HbA1c target (<7.0%) relative to the GLP-1RA arms were similar. While the hypoglycaemia data cannot be directly compared, in part owing to differences in allowance and use of sulphonylureas, an evaluation in the subset of participants not treated with sulphonylureas revealed lower incidence and event rates of hypoglycaemia with iGlarLixi in the LixiLan-G study than those seen with IDegLira in the DUAL III study. However, a direct comparison is difficult given differences in study background medications, trial design and conduct. For example, IDegLira was initiated at a higher insulin dose and titrated to a lower FPG target than iGlarLixi.14,17 However, the final mean insulin doses were similar, so the HbA1c and hypoglycaemia findings might also reflect a difference in effective GLP-1RA/insulin ratio between the preparations. Nevertheless, final mean HbA1c was well below 7.0% (53 mmol/mol) in both studies, and hypoglycaemia rates were low, suggesting both agents are clinically efficacious.12,15

In contrast with our study, which compared outcomes in people on previous GLP-1RA therapy, another ITC compared the enhancement of treatment regimens with the two FRCs in people with T2D inadequately controlled on basal insulin.19 In that study, IDegLira (assessed in the DUAL II14 and DUAL V20 trials) was associated with greater reductions in Hba1c and body weight, and a greater proportion of people reaching the HbA1c target (<7.0%) relative to the GLP-1RA arms without weight gain or hypoglycaemia compared with iGlarLixi (assessed in the LixiLan-L trial15), with no significant differences between FRCs in documented hypoglycaemia.19 However, the baseline Hba1c in LixiLan-L was notably lower than in DUAL II or DUAL V, probably biasing the findings14,21 This may explain the contrast with the current ITC, wherein baseline Hba1c was similar in all treatment arms [7.7-7.9% (61-63 mmol/mol)] and intensification of a GLP-1RA regimen with IDegLira versus iGlarLixi led to greater reductions in Hba1c and FPG with IDegLira but no differences in weight change or HbA1c goal attainment. These study differences may warrant further exploration. A meta-analysis of studies of the two agents, but not including the recently published LixiLan-G trial12 studied in the current paper, could not find clinically significant differences between the two preparations.22

Following screening for suitable studies, the current analysis only included two trials, reflecting the limited evidence available. Medications within the GLP-1RA class were assumed comparable and were reduced to a single node to ensure connectivity. However, the comparator arm for iGlarLixi included 39% of participants receiving once-weekly GLP-1RAs (from the LixiLan-G trial); these were not used in DUAL III, which rather had 21% of participants using short-acting exenatide.12,15 This limitation was mitigated by liraglutide being the most commonly used GLP-1RA in both RCTs.12,15 Another limitation was the restriction of the systematic literature review to only English language publications. The SMPG analyses were limited by having to capture the data points from figures. Finally, hypoglycaemia analyses were limited by the different definitions of hypoglycaemia in the two trials (type and plasma glucose cut-off), the inclusion of sulfonylurea in DUAL III but not LixiLan-G, and by the small numbers of episodes in the GLP-1RA arms of each study; thus, these results were only presented descriptively.

FRCs showed good clinical efficacy and safety profiles for people with T2D who require treatment intensification from oral antihyperglycaemic drugs, basal insulin or GLP-1RAs.10–15 In the absence of head-to-head comparison trials, results of this ITC suggest that, in people with T2D inadequately controlled on a GLP-1RA, intensification to iGlarLixi permits a similar likelihood of individuals reaching their glycaemic goals as intensification to IDegLira, with possibly fewer hypoglycaemic episodes but somewhat lesser effect on HbA1c. These analyses provide further data-driven confidence in iGlarLixi and IDegLira as clinically effective and simplified treatment options in people who do not reach glycaemic control with oral antihyperglycaemic medications after a trial of GLP-1RA therapy.

ACKNOWLEDGMENTS

Editorial assistance was provided by Tamsin Brown, MSc, and Rebecca Franklin, PhD, of Fishawack Communications Ltd, and was
funded by Sanofi. All authors take complete responsibility for the interpretation of the data in this paper.

CONFLICT OF INTEREST
Philip Home or institutions with which he is associated have received funding for his research, advisory and lecturing activities from Sanofi, and from other GLP-1RA and insulin manufacturers including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck (MSD) and Novo Nordisk. Vanita R. Aroda has served as a consultant for Adocia, Astra Zeneca, Applied Therapeutics, Becton Dickinson and Company, Novo Nordisk, Sanofi and Zafgen, and has received research support from Applied Therapeutics, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Caliba, Eisai, Fractyl/Premier, Janssen, Novo Nordisk, Sanofi and Theracos. Mir Sohali Fazeli and Mir-Masoud Pourrahmat are employees of Evidinno Outcomes Research Inc., which is contracted by Doctor Evidence, LLC. Patricia Goyut is an employee of Sanofi. Hardik Goswami and Alka Shaunik were employees of Sanofi during the analyses, and Alka Shaunik is now an employee of CSL Behring. Lawrence Blonde declares grant/research support to himself and/or his institution from: Janssen Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Inc., Merck & Co., Novo Nordisk and Sanofi; speaker for: Janssen Pharmaceuticals, Inc., Novo Nordisk, Sanofi; Consultant: AstraZeneca; Gilead Sciences, Inc., Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk and Sanofi. Sanjay Kalra has received lecture fees from Novo Nordisk and Sanofi, outside of the submitted work.

AUTHOR CONTRIBUTIONS
All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article and 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. PG, AS, MSF, HG and M-MP designed and conceptualized the study. MSF, HG and M-MP contributed to the acquisition of data. MSF and M-MP contributed to the analysis of data. 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.

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

How to cite this article: Home PD, Aroda VR, Blonde L, et al. Efficacy and safety of iGlarLixi versus IDegLira in adults with type 2 diabetes inadequately controlled by glucagon-like peptide-1 receptor agonists: a systematic literature review and indirect treatment comparison. Diabetes Obes Metab. 2020;22:2170–2178. https://doi.org/10.1111/dom.14136