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Efficacy and safety of iGlarLixi versus IDegAsp: Results of a systematic literature review and indirect treatment comparison

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Abstract

Aim: To assess the efficacy and safety of iGlarLixi, a fixed-ratio combination of basal insulin glargine 100 U/mL and lixisenatide (glucagon-like peptide-1 receptor agonist) versus IDegAsp, a co-formulation of basal insulin degludec 100 U/mL with rapid-acting insulin aspart.

Materials and Methods: A systematic literature search of randomized controlled trials (RCTs) was performed. Outcomes from eligible RCTs were compared by an indirect treatment comparison using a Bayesian framework. Subanalyses of Japanese and international trials were performed.

Results: Eight RCTs (duration 26-30 weeks) were included. Mean difference in HbA1c change with iGlarLixi exceeded that for IDegAsp: −0.64 (95% credible interval −1.01, −0.28) %-units (−7.0 [−11.0, −3.1] mmol/mol) for all trials, −0.39 (−0.55, −0.23) %-units (−4.3 [−6.0, −2.5] mmol/mol) for international, and −0.88 (−1.11, −0.64) %-units (−9.6 [−12.1, −7.0] mmol/mol) for Japanese trials. HbA1c target achievement (<7.0%-units [<53 mmol/mol]) was greater for iGlarLixi in all trials (odds ratio 2.50 [1.06, 5.56]) and Japanese trials (2.17 [1.27, 3.70]), but not in international trials (2.17 [0.42, 11.11]). Analyses suggesting differences in mean postmeal self-measured plasma glucose were significantly lower by 1.0-2.0 mmol/L (18-36 mg/dL) with iGlarLixi in all analyses. Bodyweight change was more favourable (1-2 kg) for iGlarLixi versus IDegAsp for all analyses ($P < 0.05$). Comparisons of hypoglycaemia were inconclusive owing to differences in definitions between studies. Adverse events were more frequent with iGlarLixi because of gastrointestinal intolerance.

Conclusions: iGlarLixi appears to offer clinical benefit in glucose control and bodyweight change in people needing both basal and meal-time intervention.

KEYWORDS
GLP-1 analogue, insulin therapy, network meta-analysis, type 2 diabetes

1 | INTRODUCTION

Most individuals with type 2 diabetes (T2D) will eventually require injectable agents to maintain adequate glycaemic control.[1,2] This may be sequential, beginning with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or basal insulin, followed by addition of the other, or introduction of a more complex insulin regimen.[1,2] Alternatively, combination injectable therapy, such as basal insulin plus a GLP-1 RA or basal insulin plus meal-time insulin, may be employed either as separate injections or using combined injectable therapy.[1,2] Combined injectable therapy may provide a simplified, more convenient approach to separate administration and has been extensively studied in both insulin-naïve and insulin-experienced people with T2D.[3-5] iGlarLixi is a fixed-ratio combination (FRC) of insulin glargine 100 U/mL (iGlar) and lixisenatide (Lixi), with evidence of improved outcomes versus its components in both populations.[3,4] IDegAsp is a co-formulation of insulin degludec (IDeg) with insulin aspart (IAsp) in a 70:30 ratio. In a series of phase 3 studies, IDegAsp was generally non-inferior to biphasic insulin aspart, iGlar, and detemir-based meal-time plus basal regimens in HbA1c reductions, with advantage for hypoglycaemia in some studies and improved fasting plasma glucose (FPG) control.[5]

A previous network meta-analysis (NMA) recently compared efficacy and safety outcomes of two FRCs, namely iGlarLixi and IDegLira, an FRC of IDeg and liraglutide. The NMA suggested the two treatments offered similar benefits in HbA1c target achievement but differed by better glycaemia results, with seemingly more hypoglycaemia with IDegLira.[6] However, currently, no head-to-head trial data exist comparing FRCs of a basal insulin analogue plus GLP-1 RA with a basal insulin analogue plus a meal-time insulin. Accordingly, we performed a systematic review to identify relevant studies for the conduct of an indirect treatment comparison (ITC) comparing clinical outcomes with iGlarLixi once daily versus IDegAsp once daily as enhancement of therapy in people with T2D as first injectable or in people already using basal insulin alone.

2 | MATERIALS AND METHODS

2.1 | Systematic literature review and screening

The screening and selection process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[7] Relevant studies were identified by searching MEDLINE, Embase, and Cochrane Controlled Register of Trials (CENTRAL) via the OvidSP platform using predefined search strategies (Table Appendix S1). In addition, manual searches of major conferences of learned societies (American Diabetes Association, European Association for the Study of Diabetes, American Association of Clinical Endocrinologists, and the International Diabetes Federation) from 2018 to 2020 were performed, as was a search for unpublished trials via US and European clinical trials registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu).Two independent investigators reviewed abstracts and conference proceedings according to the predefined eligibility criteria, based on the Population, Intervention, Comparator, Outcomes (PICO) framework (Table S2). All identified eligible randomized controlled trials (RCTs) underwent full-text screening for eligibility by the same investigators. Studies that fulfilled the PICO criteria were selected for data extraction (study characteristics, participants, and outcomes) using a standardized data extraction table in Excel (Microsoft, Seattle, WA). Discrepancies between investigators were resolved by discussion, with adjudication by a third senior investigator if needed. Methodological quality of the studies was assessed based on the Cochrane Collaboration's Risk of Bias Tool for RCTs.[8]

2.2 | Outcomes

The primary outcome was change in HbA1c from baseline. Other outcomes included the proportion of participants reaching an HbA1c target of less than 7.0%-units (<53 mmol/mol); change in clinic-measured FPG, clinic-measured postprandial plasma glucose (PPPG), self-measured plasma glucose (SMPG) metrics, and bodyweight; final insulin dose; incidence and event rates of hypoglycaemia; and incidence of adverse events (AEs). All SMPG data were extrapolated from figures, as were bodyweight in the LixiLan-O trial (week 24)[4] and FPG in BOOST: JAPAN (week 26)[9] using Grab It! XP (v. 10.0; DataTrend; https://download.cnet.com/Grab-It-XP/3000-2053_4-41084.html). Only the first seven points of any nine-point profiles were used, discarding 03:00 AM-04:00 AM hours and second prebreakfast data (not given in most studies). For LixiLan-L,[3] the event-rate data for hypoglycaemia (<3.3 mmol/L [<60 mg/dL]) were taken from an unpublished clinical study report (CSR). For LixiLan JP-L,[10] incidence and event-rate data for hypoglycaemia (<3.3 mmol/L [<60 mg/dL]) were taken from an unpublished CSR. Data for all other outcomes were taken from published results or clinical trial registries.

2.3 | Data analysis

A Bayesian NMA was used to estimate differences in the treatment effects of iGlarLixi and IDegAsp and comparator therapies (iGlar and Lixi).[11] A Markov Chain Monte Carlo simulation with non-informative priors was used with a 30 000 iteration "burn-in" to calculate the posterior distribution for the indirect treatment assessment estimates. Inferences on treatment comparisons were made on the next 30 000 iterations, using two chains and a thinning rate of 1, and implemented in WinBUGS (v. 1.4.3, www.mrc-bsu.cam.ac.uk/wp-content/uploads/2018/11/winbugs143_unrestricted.zip). The heterogeneity of relative treatment effects meant that a random-effects model was required in the analyses.

Bucher ITC was used to compare changes relative to insulin glargine where no closed loop could be established.[12]

Based on the initial feasibility assessment, all studies included in the final analysis network presented outcomes following 24, 26, or 30 weeks of randomized treatment; therefore, analyses were performed for data from 24 to 30 weeks. Owing to differences in methodology and

population characteristics found in the included papers between international and Japanese studies (see Results), secondary analyses were performed using data for the two populations separately.

To analyse change in premeal glucose, mean values of premeal SMPG values (breakfast, lunch, and dinner) at study end were combined, and the resulting mean was subtracted from that calculated from the baseline SMPG premeal profiles. Change in postmeal SMPG was calculated the same way. Change in meal-time SMPG excursions used the difference in the premeal and postmeal values for individual meals at follow-up, minus the same metric at baseline.

Results were summarized as mean difference (MD) or odds ratio (OR), with confidence intervals (CIs) for the Bucher ITC findings and credible intervals (CrIs) for the Bayesian NMA estimates.

3 | RESULTS

3.1 | Study selection

Publication screening and selection (Figure Appendix S1) resulted in 99 publications identified for qualitative analysis; 21 were unique RCTs. Nine trials formed a relevant network, and all evaluated iGlarLixi or IDegAsp. One phase 2 study was comparatively small and had a disparately short follow-up (16 weeks) and, therefore, was not included for further analysis.[13] The characteristics of the eight remaining phase 3 RCTs are shown in Table 1; seven compared iGlarLixi or IDegAsp with iGlar, whereas one study[14] compared iGlarLixi with Lixi (Figure 1). Inclusion of this last study creates a network loop in combination with a Lixi versus iGlar comparison, thereby providing additional data on the comparison of iGlarLixi with iGlar.

3.2 | Evidence base

Half of the studies were international (see Table S3 for the country list), and half were from centres in Japan only. The participants in the latter studies are generally described as "Japanese". There was a reasonable balance between prior insulin-naïve or insulin-treated participants both in studies with iGlarLixi and with IDegAsp and between Japanese and international studies (Table 1). However, there were no studies in prior insulin-treated Japanese populations for IDegAsp.

Assessment of population characteristics revealed marked differences in body mass index (BMI) between all the international studies compared with all the Japanese studies (Table 1). Further, the final

TABLE 1 Summary of the characteristics of the included trials

	Population	Treatment duration (wk)	Randomized population (n)	Intervention/ comparator	Concomitant therapy[a]	Participant baseline characteristics			
						Age (y)	Male/ female (%)	Duration of diabetes (y)	BMI (kg/m^2)
Aroda et al. 2016[3]	International, insulin-pretreated (18 countries)	30	736	iGlarLixi/ iGlar	Metformin	59.6 60.3	45/55 49/51	12.0 12.1	31.3 31.0
Kaneto et al. 2020[10]	Japanese, insulin-pretreated	26	512	iGlarLixi/ iGlar	Metformin	59.4 60.2	62/38 57/43	11.9 12.0	25.3 24.9
Rosenstock et al. 2016[4]	International, insulin-naïve (23 countries)	30	1170	iGlarLixi/ iGlar/ Lixi	Metformin	58.2 58.3 58.7	47/53 51/49 57/43	8.9 8.7 8.9	31.6 31.7 32.0
Terauchi et al. 2020[17]	Japanese, insulin-naïve	26	521	iGlarLixi/ iGlar	≤2 OGLDs[b]	59.2 60.2	67/33 64/36	8.9 9.6	26.2 25.9
Watada et al. 2020[14]	Japanese, insulin-naïve	52	321	iGlarLixi/ Lixi	1–2 OGLDs[b]	58.3 57.7	65/35 64/36	8.1 9.2	26.8 26.9
Kumar et al. 2016[15]	International, insulin-naïve (8 countries)	52	530	IDegAsp/ iGlar	Metformin	57.4 56.4	47/53 52/48	8.7 9.6	30.9 30.5
Kumar et al. 2017[16]	International, insulin-pretreated (9 countries)	26	465	IDegAsp/ iGlar	Metformin ± pioglitazone ± DPP4i	57.8 58.4	59/41 55/45	11.6 11.4	30.1 30.1
Onishi et al. 2013[9]	Japanese, insulin-naïve	26	296	IDegAsp/ iGlar	≤2 OGLDs[c]	60.0 61.0	61/39 66/34	10.9 12.4	25.2 25.0

Abbreviations: BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; IDegAsp, a co-formulation of insulin degludec and insulin aspart; iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; Lixi, lixisenatide; OGLDs, oral glucose-lowering drugs; SGLT2, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea.

[a]Background therapy continued throughout the study unless otherwise stated.

[b]DPP4i discontinued at randomization; SU/SGLT2/glinide dose reduced 50% or discontinued if screening HbA1c <8%-units.

[c]SU, DPP4i, and glinides discontinued, other OGLDs continued.

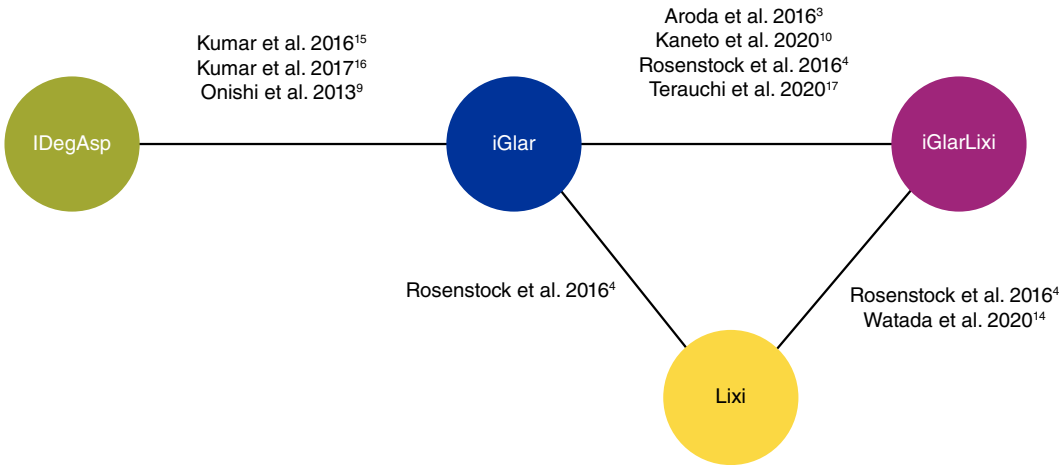

FIGURE 1 Diagram of the relationships between treatments in the included studies. Four trials directly compare iGlarLixi with iGlar, and three compare IDegAsp with iGlar. One of the former also compares iGlarLixi with Lixi, and one compares Lixi with iGlar, forming a loop. IDegAsp, a co-formulation of insulin degludec and insulin aspart; iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; Lixi, lixisenatide

insulin dose in any Japanese study using iGlar was lower than seen in the international studies (Table S4); whereas, in the iGlarLixi studies, a different ratio of lixisenatide to insulin glargine was used in the Japanese studies (1:1 [1 U of iGlar to 1 μg of Lixi]) than in international studies (2:1 or 3:1 [2 or 3 U of iGlar to 1 μg of Lixi]). Effect sizes appeared higher in the Japanese studies for both therapies. Accordingly, and despite possible power problems, secondary analyses separating the international and Japanese trials were required.

Distributions of age, baseline HbA1c, sex, and duration of diabetes varied among studies (Table 1). All insulin-containing regimens were titrated according to fasting/prebreakfast SMPG, the targets and algorithms for the three IDegAsp studies being the same, and were only marginally more aggressive (i.e. greater dose increments when the glucose target was exceeded) than those of the two international iGlarLixi studies (Table S5). All three iGlarLixi Japanese studies used a target similar to the international studies, but with a much less aggressive dose titration algorithm. However, achieved insulin doses at study endpoint were higher in the iGlar comparator arms of the IDegAsp studies compared with iGlarLixi studies (allowing for geographical differences; Table S4), perhaps because of dose capping in the international studies with iGlarLixi. Possible differences in methodology supporting dose titration remain undefined.

The once-daily injectable dose timing varied, being consistently before breakfast for iGlarLixi and Lixi study arms, but varying for IDegAsp, for which most of the studies used pre-evening meal injection (except for Kumar et al. [2016], in which morning injection was mandated except for the extension phase of the study).[15] In general, iGlar injection timing was not prespecified in any study but left to usual practice (typically before bedtime).

3.3 | Study design quality

In general, randomization was concealed (unclear for one study),[16] but all of the trials were open label (Table S6). As a result, dose titration could be subject to bias, as could SMPG, bodyweight, and hypoglycaemia and AE reports. However, HbA1c (the basis of the primary endpoint) would always be a remote laboratory measurement (although not generally so stated), as would FPG; no study confirmed that HbA1c was International Federation of Clinical Chemistry and Laboratory Medicine/National Glycohaemoglobin Standardization Programme standardized. Risk of attribution bias was generally low, with low non-completion rates, although one study had a more than 10% imbalance between treatment arms.[15] Reporting standards were poor in some studies.[15,16] Furthermore, bias could have arisen from use of last observation carried forward for missing data because of early termination in certain studies, whereas two studies used statistical modelling instead.[3,4]

3.4 | Insulin dose

iGlar doses within the iGlar treatment arms at study end were consistently higher for IDegAsp studies versus iGlarLixi studies when comparing international versus international and Japanese versus Japanese studies (Table S4). However, adjusting for differences in iGlar doses, there were no differences between IDegAsp and iGlarLixi dose change in any population (Figure 2C).

3.5 | Measures of glycaemic control

Compared with IDegAsp, iGlarLixi was associated with a statistically greater change in HbA1c (primary outcome) in the all-trials analysis (MD −0.64 [−1.01, −0.28] %-units, −7.0 [−11.0, −3.1] mmol/mol) (Figure 2A). Significantly greater reductions with iGlarLixi were also found in the international trials (MD −0.39 [−0.55, −0.23] %-units, −4.3 [−6.0, −2.5] mmol/mol) and appeared larger in the Japanese trials (MD −0.88 [−1.11, −0.64] %-units, −9.6 [−12.1, −7.0] mmol/mol) (Figure 2A).

iGlarLixi was associated with a significantly greater likelihood of achieving an HbA1c of less than 7.0%-units (<53 mmol/mol) compared with IDegAsp in the all-trials analysis (OR 2.50 [1.06, 5.56]) and the Japanese trials analysis (OR 2.17 [1.27, 3.70]). In the international studies, the effect size favouring iGlarLixi versus IDegAsp was of the same order but with very wide CrIs when using a random-effects model (OR 2.17 [0.42, 11.11]); however, MD was highly statistically significant with a fixed-effects model (OR 2.17 [1.56, 3.03]).

Change in clinic-measured FPG was similar for iGlarLixi and IDegAsp for the all-trials, international, and Japanese analyses (Figure 2D). Clinic-measured laboratory PPPG excursions were performed in four of the five iGlarLixi studies[3,4,10,17] but in none of the three IDegAsp studies.[9,15,16] Accordingly, it was not possible to assess objectively measured PPPG between IDegAsp and iGlarLixi.

In all studies, SMPG profiles were supplied in graphical form at baseline and endpoint. In one study, IDegAsp endpoint profiles were only given at 52 weeks; but, as HbA1c and clinic-measured FPG did not change significantly between 26 and 52 weeks in that study, these data are included in our analysis. Analysis of seven-point SMPG profiles indicated greater improvement with iGlarLixi versus IDegAsp for change in postbreakfast, prelunch, and postlunch time points across all analyses, and for IDegAsp versus iGlarLixi for the postdinner endpoint in the all-trials and Japanese analyses (Figure 3A). Analysis of difference in mean premeal SMPG change suggested the advantage for iGlarLixi compared with IDegAsp was approximately 1 mmol/L (~ 18 mg/dL) in the all-trials analysis and international analysis, but a similar difference in the Japanese studies analysis was not confirmed owing to wider confidence limits (Figure 3B, Table S7). Analysis of difference in mean postmeal SMPG change found it was significantly

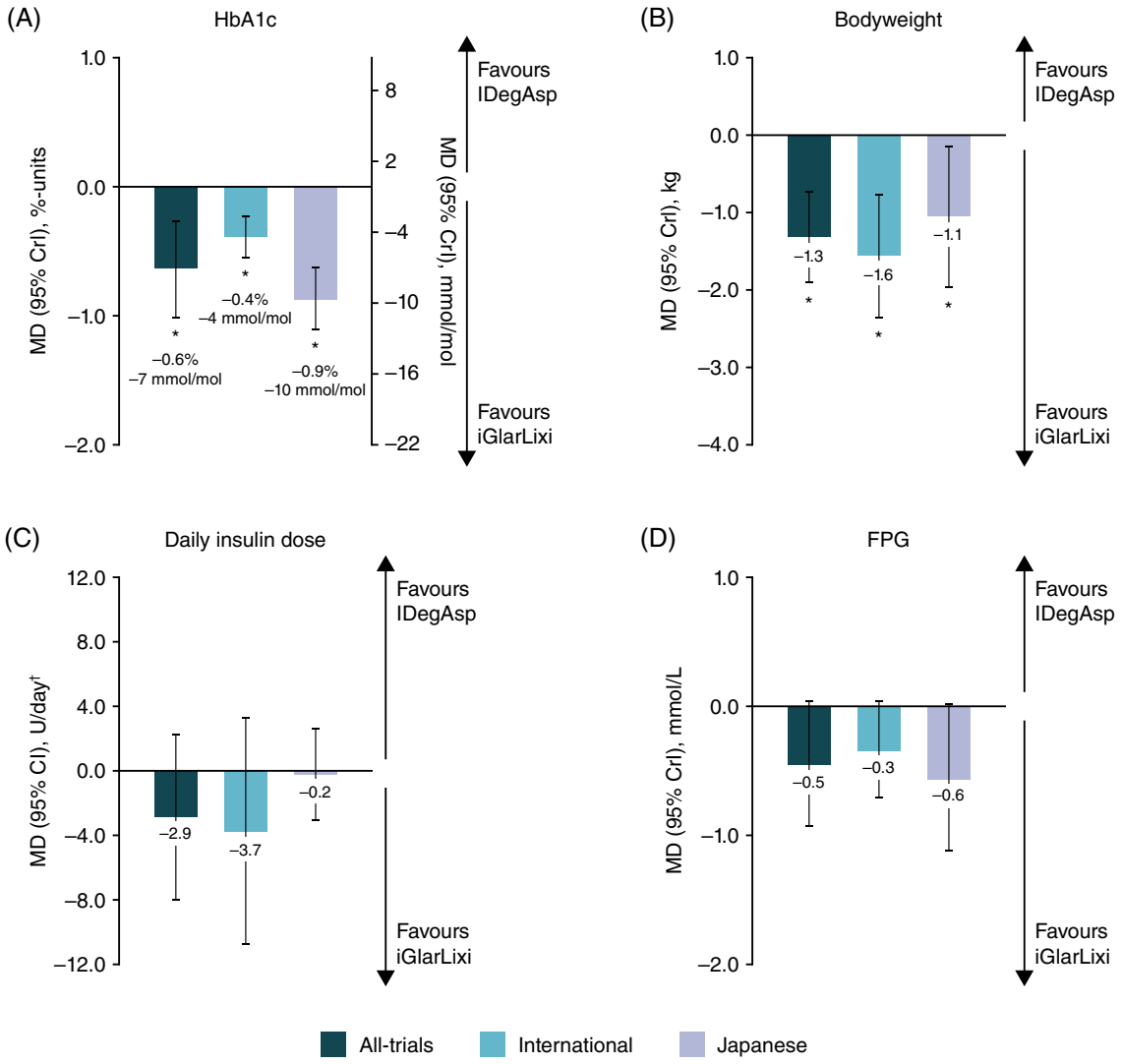

FIGURE 2 Mean treatment differences between iGlarLixi and IDegAsp in (A) HbA1c change from baseline; (B) bodyweight change from baseline; (C) daily insulin dose change from baseline†; and (D) fasting plasma glucose (FPG) change from baseline in the all-trials, international, and Japanese analyses. *$P < 0.05$; †assessed using a Bucher indirect treatment comparison (ITC). CI, confidence interval; CrI, credible interval; IDegAsp, a co-formulation of insulin degludec and insulin aspart; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; MD, mean difference; ITC, indirect treatment comparison; U, units

lower by 1.0-2.0 mmol/L (18-36 mg/dL) with iGlarLixi versus IDegAsp in all three geographical analyses (Figure 3B, Table S7). Analysis of mean change in SMPG glucose excursions after all meals gave inconclusive results because of wide CIs except for change in postbreakfast excursions that favoured iGlarLixi and change in postdinner excursions favouring IDegAsp (both in the Japanese studies; Table S7).

3.6 | Hypoglycaemia

Hypoglycaemia definitions varied between studies and were not always clearly stated. Data could be extracted from papers for IDegAsp using a threshold of less than 3.1 mmol/L (<56 mg/dL) and from clinical study reports for iGlarLixi using less than 3.3 mmol/L (<60 mg/dL). However, in the IDegAsp studies, symptomatic and asymptomatic episodes could not be disaggregated,[9,15,16] whereas the equivalent combined data could not be assembled for the iGlarLixi studies.[3,4,10,14,17] Statistical methods of comparing event rates also differed. Therefore, we were not able to provide valid comparative data by NMA/ITC. For transparency, we present a table of the study data (Table S8). Severe hypoglycaemia events were too few (0 in most study arms) to allow any assessment of between-treatment differences (Table S8).

3.7 | Bodyweight

iGlarLixi was associated with a statistically better bodyweight change from baseline to endpoint compared with IDegAsp in the all-trials analysis (MD −1.34 [95% CrI −1.92, −0.74] kg). Bodyweight change was also statistically more favourable with iGlarLixi than IDegAsp in both the international and Japanese trials analyses (Figure 2B).

3.8 | Adverse events

iGlarLixi was associated with an increased likelihood of a treatment-emergent AE compared with IDegAsp in the all-trials and the Japanese trials analyses, with a consistent finding in the international trials (Table 2). In the published results, the AE driving an excess of AEs with iGlarLixi compared with iGlar was always gastrointestinal intolerance (data not shown). There was no evidence of difference in the

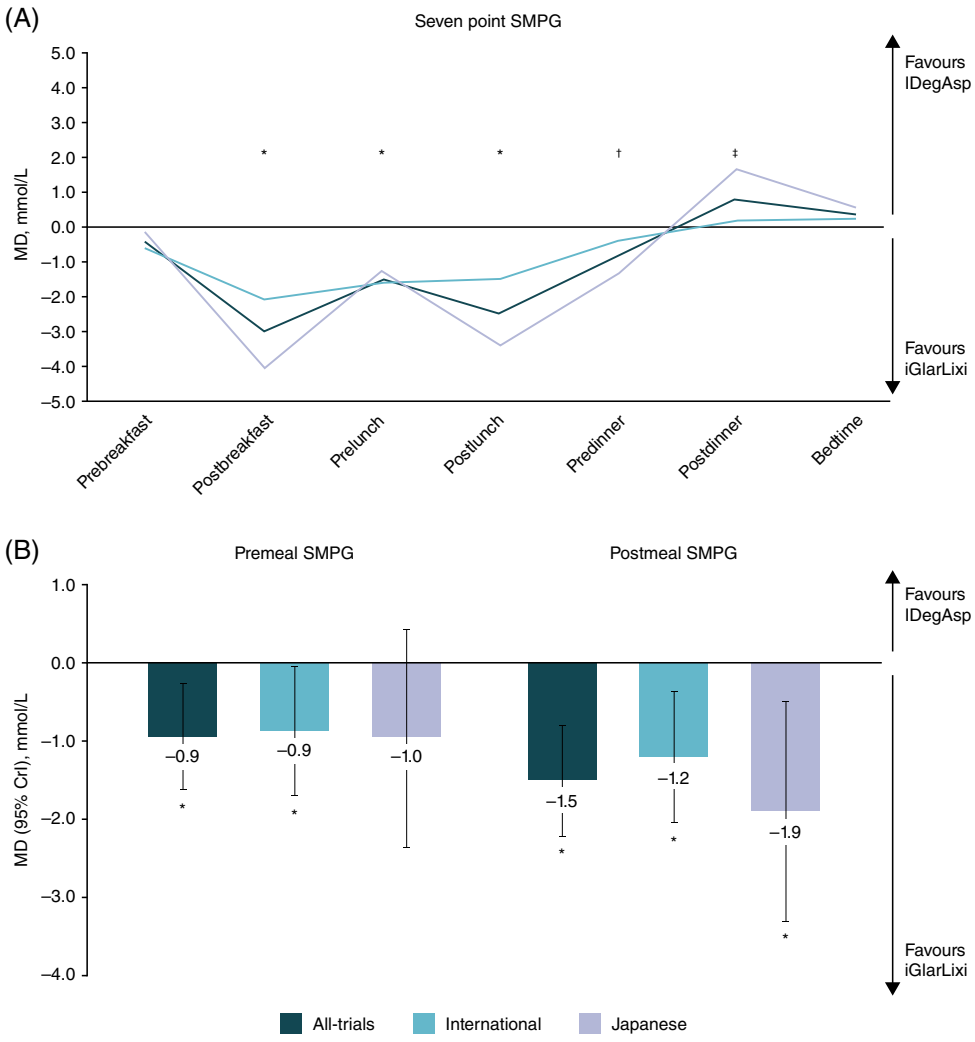

FIGURE 3 Mean differences in seven-point self-measured plasma glucose (SMPG) change from baseline (A), and mean differences in premeal and postmeal SMPG change from baseline (B), between iGlarLixi and IDegAsp in the all-trials, international, and Japanese analyses. *P < 0.05 versus 0.0 change favouring iGlarLixi in all three analyses; †P < 0.05 versus 0.0 change favouring iGlarLixi in all-trials and Japanese analyses; ‡P < 0.05 versus 0.00 change favouring IDegAsp in all-trials and Japanese analyses. 95% CrIs for data in the lower panel are given in Table S7. CrI, credible interval; MD, mean difference, SMPG, self-measured plasma glucose

TABLE 2 Adverse event odds ratios for iGlarLixi versus IDegAsp endpoints

Adverse events	OR (95% CrI)
Any	
All trials	1.64 (1.15, 2.38)[a]
International trials	1.52 (0.99, 2.27)
Japanese trials	2.33 (1.14, 5.00)[a]
Serious	
All trials	0.52 (0.17, 1.85)
International trials	ND[b]
Japanese trials	ND[b]

Abbreviations: CrI, credible interval; OR, odds ratio.
[a]Significant difference.
[b]ND, not done, insufficient data.

incidence of serious AEs (SAEs) in the all-trials analysis. There were insufficient data to assess SAEs in the international and Japanese analyses separately.

4 | DISCUSSION

iGlarLixi and IDegAsp, used once daily, offer a clinically simpler approach to provision of basal and meal-time glucose-lowering therapy. Lower daily injection frequency is associated with reduced treatment burden and improved adherence.[18] However, although the two approaches have shown good efficacy and safety profiles in both insulin-naïve and prior insulin-treated people with poorly controlled T2D,[3-5,9,10,14-17,19-23] there are currently no data from direct head-to-head comparisons of these two therapies. However, evidence suggests that separate injection of GLP-1 RAs on a background of basal insulin has clinical advantages compared with meal-time analogues plus basal insulin.[24-27]

4.1 | Glycaemic outcomes and bodyweight

The current analysis suggests that iGlarLixi was associated with better HbA1c change and bodyweight outcomes compared with IDegAsp, to a clinically useful extent (Figure 2). Target achievement was also better with iGlarLixi in the all-trials and Japanese trials analyses, although a numerical change of the same order was not statistically significant in the international trials when calculated using a random-effects model.

Although changes in clinic-measured FPG were similar between treatments in all analyses, change in mean premeal SMPG favoured iGlarLixi over IDegAsp in the all-trials and international analyses, and was of a similar order but not statistically significant in the less-powered Japanese analysis (Table S7). Differences in clinic-measured PPPG could not be assessed, as the IDegAsp studies did not include this metric. However, mean postmeal SMPG was consistently significantly lower with iGlarLixi versus IDegAsp in all analyses. When considering seven-point SMPG profiles, postdinner SMPG favoured IDegAsp in the Japanese and all-trials analyses; this greater impact on postdinner SMPG may reflect the fact that IDegAsp was administered before the main evening meal in all studies, except for Kumar et al.[15] Analyses of between-treatment differences in SMPG excursions across all meals were inconclusive. Unfortunately, hypoglycaemia could not be formally or qualitatively compared between the two treatments owing to heterogeneity in the reporting of hypoglycaemia. Furthermore, the proportion of participants experiencing hypoglycaemia appeared to be much higher among iGlar comparator arms in the IDegAsp studies than in the iGlarLixi studies (Table S8), suggesting differences in how hypoglycaemia was ascertained or dose-titration differences, potentially including the impact of the lack of dose capping of iGlar in the IDegAsp studies in contrast to the IGlarLixi studies. Overall, however, the findings in the studies suggest neither treatment showed an advantage or disadvantage compared with iGlar alone. Another explanation for differences between studies might be titration schedules (Table S5), which were more aggressive in the IDegAsp studies. This difference in titration regimens and dose capping may be reflected in the iGlar doses being consistently higher in IDegAsp versus iGlarLixi studies when comparing international with international or Japanese with Japanese studies (Table S4).

Taken together, the glucose-control findings appear to suggest usefully better postmeal glucose control with iGlarLixi compared with IDegAsp, leading to improved HbA1c findings.

4.2 | Safety

Except for the expected gastrointestinal intolerance with the GLP-1 RA–containing medication,[3,4,19,28] the two approaches were similar for incidence of AEs and SAEs. Gastrointestinal intolerance was not reported in the BOOST studies.[9,15,16] In the iGlarLixi studies, the gastrointestinal events resulted in very low levels of discontinuation (~1%).[3,4,10,14,17]

4.3 | Study strengths and limitations

The strengths of the current analysis include the comprehensive and methodical literature search involving three databases and manual searching of congress abstracts. Assessment of study quality suggested that most selected trials had a low risk of bias from participant selection and attrition, or other sources. However, all trials were open label, owing to use of bespoke injection devices. It is not possible to know whether any resulting bias would differ between the iGlarLixi and IDegAsp studies. Most trials of injectable antihyperglycaemic therapies are open label, and the bias is usually regarded as manageable for objective laboratory-measured endpoints. Furthermore, a comprehensive analysis of homogeneity was performed in a robust feasibility assessment.

The current study was limited by the small number of trials informing comparisons of iGlarLixi versus IDegAsp. Additionally, trial

length varied among studies (Table 1), although all included trials provided data over approximately 6 months of treatment, typical of phase 3 studies of diabetes medications. This allows for both dose titration and the delay of HbA1c in reaching steady state. The current analysis included studies of both insulin-naïve people and prior insulin users with T2D. These populations can have distinct clinical characteristics, such as longer duration of diabetes in the latter group, which might, for example, be predisposed to have a lesser response to a GLP-1 RA. Indeed, diabetes duration did appear to be longer in the identified prior insulin studies (Table 1). However, improvement in HbA1c in the iGlarLixi studies, when compared with iGlar alone, was numerically greater in the prior insulin-treated international and Japanese studies (MD –0.5 and −0.75%-units [−5.5 and −8.1 mmol/mol]) compared with the insulin-naïve studies (−0.3 and −0.63%-units [−3.3 and −6.9 mmol/mol]) (Table S4). Because of the absence of a Japanese IDegAsp prior insulin study and the small number of studies overall, we were not convinced of the merits of separate analyses of prior insulin versus no prior insulin, but a very recent publication selected the two international prior insulin studies we identified[3,16] and reported, by ITC, statistically significant HbA1c and bodyweight improvements of the same order we found, in addition to improvements in PPPG.[29]

One issue might be that iGlar doses were capped in the iGlarLixi studies but not in the IDegAsp studies, thus possibly giving a comparator advantage to iGlarLixi. However, this issue has been investigated for some of the LixiLan studies by Schmider et al., who reported that uncapping the iGlar dose would not have led to significant improvements in fasting self-monitored blood glucose or HbA1c.[30] Our results also showed that end of study mean doses did not approach the dose cap (Table S4). It could also be argued that the differences in insulin dose between iGlarLixi and IDegAsp studies, whether attributable to population selection, dose titration, or dose capping, could also favour iGlarLixi in regard to bodyweight change, as higher insulin doses in the uncapped IDegAsp studies could lead to greater bodyweight increases.[31] However, insulin-related bodyweight gain can be related to improved glucose control driving a reduction in glycosuria[31]; in this regard, IDegAsp would be favoured in bodyweight outcomes.[31] Conversely, it has also been suggested that hypoglycaemia may affect bodyweight through defensive eating, although because of the differing hypoglycaemic definitions between studies, it is unclear whether there were between-treatment differences that may have affected bodyweight.

Heterogeneity between treatment groups across studies can be a problem with all meta-analyses but may be exacerbated in NMAs owing to the more diverse pool of RCTs included. However, this issue is ameliorated by using the quantitative findings of the common comparators. We did, however, find it necessary to perform sensitivity analyses for the Japanese and international studies separately, noting distinct differences in clinical phenotype in the reported studies, including baseline BMI and insulin dose requirement. Further, the iGlarLixi formulation used in Japanese populations differs from that used in Western populations.[3,4,10,14,17] The outcome of the sensitivity studies was that the findings were directionally similar in the two populations for all metrics, albeit with seemingly greater postprandial differences between iGlarLixi and IDegAsp in Japan.

Not all of the included studies reported all endpoints of interest. Thus, we had to rely on SMPG data for postmeal glucose assessments, owing to absence of formal meal tests in the IDegAsp studies. Comparisons of hypoglycaemia incidence and event rate analyses were also not possible. However, there is no evidence in the published data that improved glucose control with iGlarLixi versus IDegAsp was achieved by more aggressive insulin dose titration; indeed, the insulin dose ratio in the studies compared with the iGlar alone comparator arms was not dissimilar (Table S4). Comparisons of reductions in postmeal SMPG should also be interpreted with some caution, as although most studies reported postmeal SMPG after a 120-minute interval, the IDegAsp studies used a 90-minute interval.[9,15,16]

Finally, all of the trials included in the current analysis were RCTs, with many excluding individuals with risk factors for hypoglycaemia, such as impaired renal function, previous episodes of severe hypoglycaemia within the 12 months prior to randomization, or hypoglycaemia unawareness.[3,9,15,16] As such, the results of these trials may not be generalizable to all individuals.

4.4 | Summary

The results of the current analyses provide comparative ITC data for iGlarLixi and IDegAsp that suggest that iGlarLixi provides improved glycaemic efficacy with improved bodyweight change compared with IDegAsp, with the risk of some gastrointestinal intolerance. This concurs with other evidence that, when used with basal insulin, a GLP-1 RA has advantages over meal-time insulin,[24-27] and supports clinical guidelines recommending a GLP-1 RA as first injectable therapy either alone or, for individuals with very poor glycaemic control, in combination with basal insulin.[1,2] Given the maximum daily dose limitations with iGlarLixi, these findings are generally relevant for adults with T2D not requiring more than 60 U/day (international population) or more than 20 U/day (Japanese population) iGlar equivalent dose as part of their FRC. Our findings also suggest that, overall, Japanese populations may derive a greater benefit with FRCs of basal insulin and a GLP-1 RA in HbA1c change and postmeal blood glucose control, whereas non-Japanese populations may have a greater bodyweight benefit. Further studies could examine subpopulations that might benefit from the potential for reduced hypoglycaemia risk with a GLP-1 RA versus a meal-time insulin analogue and those in particular need of lower postmeal glucose excursions. In summary, although limited by the small number of trials available for this NMA and study heterogeneity, these results suggest that where the convenience of a fixed-ratio preparation is chosen, one containing a GLP-1 RA may be preferred.

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CONFLICT OF INTEREST

The authors declare the following: PDH, or institutions with which he is associated, have received funding for his research, advisory and lecturing activities from Sanofi and Novo Nordisk, and also from other GLP-1 RA and insulin manufacturers including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Merck (MSD). RM has received funding for advisory and lecturing activities from Sanofi and Novo Nordisk and from AstraZeneca, Boehringer Ingelheim, Abbott, Amgen, Janssen, Silanes, and Stendahl. KASH has received funding for advisory and lecturing activities from Sanofi, Novo Nordisk, AstraZeneca, Boehringer Ingelheim, MSD, and Pfizer. OYG has received funding for advisory and lecturing activities from Sanofi and Novo Nordisk, STADA, Eli Lilly, Takeda, and Boehringer Ingelheim. AA is an employee of Sanofi and may hold shares and/or stock options in the company. PS and M-MP are employees of Evidinno, contracted by Sanofi.

AUTHOR CONTRIBUTIONS

All authors fulfilled authorship requirements according to ICMJE guidelines. PDH, AA, PS, and M-MP designed and conceptualized the study. PS and M-MP were responsible for the systematic review, data acquisition, and statistical analysis. Initial publication drafting was carried out by Hannah Brown, while extensive critical revision and interpretation was performed by PDH, RM, OYG, KASH, AA, PS, and M-MP. All authors approved the final draft for submission.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2021. *Diabetes Care*. 2021;44(Suppl 1):S111-S124.
2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701.
3. 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(11):1972-1980.
4. 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 monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care*. 2016;39(11):2026-2035.
5. Haahr H, Fita EG, Heise T. A review of insulin degludec/insulin aspart: pharmacokinetic and pharmacodynamic properties and their implications in clinical use. *Clin Pharmacokinet*. 2017;56(4):339-354.
6. 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(11):2170-2178.
7. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
8. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
9. Onishi Y, Ono Y, Rabøl R, Endahl L, Nakamura S. Superior glycaemic control with once-daily insulin degludec/insulin aspart versus insulin glargine in Japanese adults with type 2 diabetes inadequately controlled with oral drugs: a randomized, controlled phase 3 trial. *Diabetes Obes Metab*. 2013;15(9):826-832.
10. Kaneto H, Takami A, Spranger R, Amano A, Watanabe D, Niemoeller E. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) in Japanese patients with type 2 diabetes mellitus inadequately controlled on basal insulin and oral antidiabetic drugs: the LixiLan JP-L randomized clinical trial. *Diabetes Obes Metab*. 2020;22(Suppl. 4):3-13.
11. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33(5):607-617.
12. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50(6):683-691.
13. Heise T, Tack CJ, Cuddihy R, et al. A new-generation ultra-long-acting basal insulin with a bolus boost compared with insulin glargine in insulin-naive people with type 2 diabetes: a randomized, controlled trial. *Diabetes Care*. 2011;34(3):669-674.
14. Watada H, Takami A, Spranger R, Amano A, Hashimoto Y, Niemoeller E. Efficacy and safety of 1:1 fixed-ratio combination of insulin glargine and lixisenatide versus lixisenatide in Japanese patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs: the LixiLan JP-O1 randomized clinical trial. *Diabetes Care*. 2020;43(6):1249-1257.
15. Kumar A, Franek E, Wise J, Niemeyer M, Mersebach H, Simó R. Efficacy and safety of once-daily insulin degludec/insulin aspart versus insulin glargine (U100) for 52 weeks in insulin-naïve patients with type 2 diabetes: a randomized controlled trial. *PLOS ONE*. 2016;11(10):e0163350.
16. Kumar S, Jang HC, Demirağ NG, Skjøth TV, Endahl L, Bode B. Efficacy and safety of once-daily insulin degludec/insulin aspart compared with once-daily insulin glargine in participants with type 2 diabetes: a randomized, treat-to-target study. *Diabet Med*. 2017;34(2):180-188.
17. Terauchi Y, Nakama T, Spranger R, Amano A, Inoue T, Niemoeller E. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi 1:1) in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs: a randomized, 26-week, open-label, multicenter study: the LixiLan JP-O2 randomized clinical trial. *Diabetes Obes Metab*. 2020;22(Suppl 4):14-23.
18. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. *J Gen Intern Med*. 2005;20(5):479-482.
19. Blonde L, Anderson JE, Chava P, Dendy JA. Rationale for a titratable fixed-ratio co-formulation of a basal insulin analog and a glucagon-like peptide 1 receptor agonist in patients with type 2 diabetes. *Curr Med Res Opin*. 2019;35(5):793-804.

20. Philis-Tsimikas A, Astamirova K, Gupta Y, et al. Similar glycaemic control with less nocturnal hypoglycaemia in a 38-week trial comparing the IDegAsp co-formulation with insulin glargine U100 and insulin aspart in basal insulin-treated subjects with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2019;147:157-165.
21. Franek E, Haluzík M, Canecki Varžić S, et al. Twice-daily insulin degludec/insulin aspart provides superior fasting plasma glucose control and a reduced rate of hypoglycaemia compared with biphasic insulin aspart 30 in insulin-naïve adults with type 2 diabetes. *Diabet Med*. 2016;33(4):497-505.
22. Fulcher GR, Christiansen JS, Bantwal G, et al. Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial. *Diabetes Care*. 2014;37(8):2084-2090.
23. Kaneko S, Chow F, Choi DS, et al. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre−/self-mixed insulin: a 26-week, randomised, treat-to-target trial. *Diabetes Res Clin Pract*. 2015;107(1):139-147.
24. Rosenstock J, Nino A, Soffer J, et al. Impact of a weekly glucagon-like peptide 1 receptor agonist, albiglutide, on glycemic control and on reducing prandial insulin use in type 2 diabetes inadequately controlled on multiple insulin therapy: a randomized trial. *Diabetes Care*. 2020;43(10):2509-2518.
25. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. 2014;37(8):2317-2325.
26. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care*. 2014;37(10):2763-2773.
27. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab*. 2014;16(7):636-644.
28. Buse JB, Vilsbøll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care*. 2014;37(11):2926-2933.
29. Jammah AA. Indirect comparison of efficacy and safety of insulin glargine/lixisenatide and insulin degludec/insulin aspart in type 2 diabetes patients not controlled on basal insulin. *Prim Care Diabetes*. 2021;15(1):132-137.
30. Schmider W, Belder R, Lee M, Niemoeller E, Souhami E, Frias JP. Impact of dose capping in insulin glargine/lixisenatide fixed-ratio combination trials in patients with type 2 diabetes. *Curr Med Res Opin*. 2019;35(6):1081-1089.
31. McFarlane SI. Insulin therapy and type 2 diabetes: management of weight gain. *J Clin Hypertens*. 2009;11(10):601-607.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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