Insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) compared with premix or addition of meal-time insulin to basal insulin in people with type 2 diabetes: A systematic review and Bayesian network meta-analysis

Philip Home DM1 | Lawrence Blonde MD2 | Sanjay Kalra MD3 |
Linong Ji MD4 | Patricia Guyot PhD5 | Claire Brulle-Wohlhueter MD6 |
Erin Murray MPH7 | Roshan Shah MS7 | Toby Sayre MS7 | Alka Shaunik MD5

1Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
2Ochsner Diabetes Clinical Research Unit, Frank Riddick Diabetes Institute, Department of Endocrinology, Ochsner Medical Center, New Orleans, Louisiana
3Department of Endocrinology, Bharti Hospital, Karnal, India
4Peking University People’s Hospital, Beijing, China
5Global Medical Affairs, Sanofi, Bridgewater, New Jersey
6Global Medical Affairs, Sanofi, Paris, France
7Doctor Evidence, Santa Monica, California

Correspondence
Philip Home, Translational and Clinical Research Institute, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK.
Email: philip.home@newcastle.ac.uk

Funding information
The systematic review and statistical analysis were funded by Sanofi.

Abstract
Aim: To assess the efficacy and safety of iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide, relative to premix insulin and other insulin options through network meta-analysis.

Methods: A systematic literature search identified randomized controlled trials (RCTs) comparing iGlarLixi, premix insulin or basal insulin (BI) in combination with meal-time insulin, in people inadequately controlled with BI. Eligible RCTs were compared using Bayesian network meta-analysis.

Results: Eight RCTs, some open-label, involving 3538 participants, with a study duration of 24-30 weeks were included. The estimated difference in HbA1c reduction with iGlarLixi compared with premix insulin was $-0.50\%-\text{units}$ (95% credible interval: $-0.93$ to $-0.06$) with 98% probability of iGlarLixi being superior to premix. Estimates for iGlarLixi versus meal-time + BI (thrice-daily meal-time insulin + basal) and basal-plus (once-daily meal-time insulin + basal) were $-0.35$ ($-0.89$ to $+0.13$)%-units and $-0.68$ ($-1.18$ to $-0.17$)%-units with probabilities of real difference of 94% and 99%, respectively. Safety outcome analysis suggested that iGlarLixi had lower rates of both confirmed and documented symptomatic hypoglycaemia compared with premix insulin (probabilities of 85% and 93%, respectively) and lower weight gain (probability 98%).

Conclusions: iGlarLixi showed similar or improved efficacy and safety versus other intensification choices from BI included in this study, providing a clinically relevant treatment option in people with type 2 diabetes not well controlled on BI.

KEYWORDS
basal insulin, GLP-1 analogue, insulin therapy, network meta-analysis, systematic review, type 2 diabetes
1 | INTRODUCTION

Basal insulin is commonly recommended when glycaemic control can no longer be achieved with oral or other injectable glucose-lowering drugs. Individual randomized controlled trials (RCTs) of basal insulin report that up to 70% of insulin-naive people with type 2 diabetes (T2D) may reach HbA1c levels of less than 7.0% (<53 mmol/mol).1,2 However, in a pooled analysis of 45 RCTs, only ~40% (7.5%-70%) of individuals achieved this.3 This is similar to data from clinical practice, where ~38% of insulin-naive people achieve an HbA1c level of less than 7.0% in the first year after starting basal insulin, and only 8% thereafter.4 Thus, there is often a clinical need to advance to more complex insulin regimens for those not well controlled on basal insulin. The 2015 National Institute for Health and Care Excellence UK guidelines recommend the addition of meal-time insulin in the circumstance where glycaemic control is not achieved on basal insulin.5 By contrast, the 2018 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus statement recommended glucagon-like peptide-1 receptor agonists (GLP-1RAs) as the first injectable therapy for T2D patients unless basal insulin is preferred or is more suitable for the individual patient (e.g. in those with HbA1c > 11.0% [>97 mmol/mol]).6,7 When the HbA1c target is not achieved with either injectable therapy with or without oral glucose-lowering drugs (OGLDs), the ADA statement recommends combining the GLP-1RA and basal insulin as a preferred alternative to adding a meal-time insulin.8

RCT data show that the combination of GLP-1RA and basal insulin therapies usually leads to effective glucose lowering with a moderate risk of hypoglycaemia and modest weight gain.6,9,10 However, real-world evidence shows that less than 50% of patients reach their target, leaving a high unmet medical need.11,12 The fixed-ratio combinations (FRCs) of basal insulin and GLP-1RAs provide the benefit of single administration, and may be expected to promote better adherence compared with regimens requiring separate injections of the insulin and GLP-1RA.13–16

iGlarLixi, an FRC containing insulin glargine 100 U/mL and lixisenatide in a disposable pen-injector, reduced HbA1c and attenuated insulin-related body weight gain versus basal insulin without increasing the risk of hypoglycaemia in people whose HbA1c was inadequately controlled on basal insulin (with or without OGLDs).17 Although RCTs have established the benefits of iGlarLixi compared with basal insulin,17,18 specific comparisons of its benefits compared with other insulin regimens are not available. To address this question, we performed a systematic literature review and network meta-analysis (NMA) to compare iGlarLixi with basal insulin, premix insulin or addition of meal-time insulin in people with T2D who have inadequate glucose control on basal insulin.

2 | MATERIALS AND METHODS

2.1 | Study selection

A systematic literature search of MEDLINE (via PubMed), Embase (via OVID) and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed in June 2018 to find English language publications of RCTs on iGlarLixi, premix insulin and basal insulin alone or in combination with OGLDs or meal-time insulin in people whose T2D was inadequately controlled (defined as HbA1c > 7.0% [>53 mmol/mol]) on basal insulin. The search strategy used population, intervention and study design terms from the Population, Intervention, Comparator, Outcome and Study (PICO) protocol (Table S1),19 and included keywords and MeSH headings for T2D, basal insulin, premix insulin, iGlarLixi and inadequate glycaemic control (Tables S1 and S2). In addition, a search of conference abstracts via Embase (January 2014 to June 2018 inclusive) and a manual search of the reference lists of eligible studies was performed.

Trial inclusion was guided by predefined criteria for the PICO design. Trials were included if they: (a) had an adult (aged ≥18 years) T2D population in which participants had previously been treated with basal insulin alone or in combination with an OGLD, but still had a HbA1c level of ≥7.0% (≥53 mmol/mol); (b) compared iGlarLixi, premix insulin, or a basal insulin either alone or in combination with OGLDs or meal-time insulin (1-3 times per day); (c) had treatment arms of ≥20 weeks; and (d) reported at least one of the following: change in HbA1c, proportion of participants reaching an HbA1c target of ≤7.0% (≤53 mmol/mol), total insulin dose, change in body weight, hypoglycaemia or gastrointestinal adverse events. Trials were excluded if they (a) included people who had type 1 diabetes or an HbA1c level of less than 7.0%-units (<53 mmol/mol) at baseline or were using meal-time insulin or (b) compared interventions of interest (iGlarLixi, premix insulin or basal insulin) to any non-intervention or placebo. Comparisons of different premix insulin, basal insulin or meal-time insulin to one another were also excluded. Further details are given in Table S1.

Standard methodology for systematic reviews, as defined in the Cochrane Handbook for Systematic Reviews of Interventions, was used.19 Results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.20

2.2 | Data extraction

Screening was performed at both title and abstract level and again at the full-text level, documenting reasons for exclusion. Screening was conducted by one screener (S.K.) and confirmed by a second screener (A.S.), with discrepancies identified and resolved by an independent third reviewer (E.M.).

The primary efficacy outcomes extracted included the change in HbA1c levels from baseline and the proportion reaching a target HbA1c of ≤7.0% (≤53 mmol/mol). Additional secondary outcomes included total insulin dose at trial endpoint, change in body weight from baseline, hypoglycaemia incidence during the treatment period and gastrointestinal events (diarrhoea, nausea and vomiting). Data were extracted using the DOC Extract 2.0 platform (Doctor Evidence, DOC Data Version 2.0, Santa Monica, CA, USA). The included trials were assessed for risk of bias using the Cochrane Collaboration’s tool.21
2.3 | Statistical methods

Data were analysed using Bayesian NMA to combine both direct and indirect evidence to compare the efficacy and safety of iGlarLixi relative to premix insulin, basal insulin and meal-time + basal insulin regimens. A very weak, non-biased prior was set automatically between each direct comparison in a network for each outcome analysed.22

We performed 5000 burn-in followed by 20 000 iterations with a thinning of 10 for two chains. The convergence was assessed using the Brooks-Gelman-Rubin method.23,24 Both fixed- and random-effects models were used. For the random-effects model, the standard deviation was sampled from a uniform distribution. Model selection was based on the Deviance Information Criteria (DIC).25,26 When the DIC were within five points of each other, the random-effects model results were preferred.27 The baseline characteristics (age, sex, inclusion and exclusion criteria, treatment period, duration of diabetes, body mass index [BMI], weight, HbA1c and fasting plasma glucose) of the included studies were qualitatively reviewed. The direct pairwise comparison results for the two studies comparing basal-plus versus premix and for the two studies comparing intensified basal versus premix were also qualitatively reviewed. Network inconsistency was tested using the Bucher method to measure differences in the direct and indirect estimates within closed loops in the networks.28

Change in HbA1c levels, total final insulin dose and change in body weight were modelled using a normal likelihood and identity link function and were represented as mean differences with associated 95% credible intervals (CrIs). A target HbA1c of less than 7.0% (<53 mmol/mol), hypoglycaemia and gastrointestinal events were modelled using binomial likelihoods and logarithmic link function and were represented as risk ratios (RRs) with associated 95% CrIs.

Probability thresholds were used to determine whether a given therapeutic approach was better, probably better, comparable, probably worse or worse. Probability of better (P(better)) was calculated based on the proportion of Markov chain Monte Carlo cycles in which the specific treatment estimate was numerically better than the comparator. A treatment option was taken to be ‘more effective’ than the comparator if the point estimate favoured the treatment and the 95% CrI did not include 0.00 (continuous outcomes) or 1.00 (binary outcomes). Other efficacy findings (‘likely to be favourable’, ‘comparable’) depended on the P(better) being ≥85% or 15%-85%, respectively, but with no requirement for the CrI to exclude 0.00 or 1.00.29 Additional details on the probability thresholds used for interpretation of the results can be found in Table S3. All analyses were conducted using R30 (Bell Laboratories, Open Source) and the GeMTC31 package, the latter using the JAGS program for Bayesian modelling.

3 | RESULTS

3.1 | Evidence base

A total of 5284 publications were identified and screened using title and abstract (Figure 1). No relevant conference abstracts were identified. Of these, 246 were full-text, and 16 studies describing 16 clinical trials were included in the qualitative analysis. The main reasons for exclusion were non-RCTs, choice of comparators or population. Eight trials were then excluded because they could not be linked to the overall network, leaving eight open-label trials included in the meta-analysis.17,32–38

A base-case network was constructed to compare iGlarLixi with premix insulin or adding meal-time insulin once per day (basal-plus) or at three meal-times (≥3× meal-time + basal). The base-case analysis was constructed with all interventions of one type (eg premix) combined into a single node, except for meal-time + basal insulin regimens which were separated according to the number of meal-time insulin injections per day (Figure 2). Basal insulin with and without an OGLD was included as a reference regimen baseline so as to indirectly relate iGlarLixi to the other comparators within the network. As a sensitivity analysis, an additional network explored the effect of pooling the meal-time insulin additions (basal-plus and ≥3× meal-time) into a single node (Figure S1).

The base-case analysis included seven RCTs17,32,33,35–38 published during 2008-2017 with treatment periods of 24-30 weeks. Additionally, one trial was included in a sensitivity analysis (Figure S1).34 Complete trial and participant characteristics are given in Table 1 and Tables S4-S7. Overall, 3538 participants contributed to the analysis (mean age range 51.9-61.6 years; male 38.6%-72.6%; duration of diabetes 10.9-13.5 years; baseline BMI range 29.4-34.8 kg/m²; baseline HbA1c range 7.7%-9.0% [60.7-74.9 mmol/mol]). The use of OGLDs at baseline varied between trials (Table S7).

Assessments for risk of bias conducted on the eight trials17,32–38 showed that there were no low-quality trials. However, as these were studies of injectables, all were open-label, and while the primary outcome (change in HbA1c from baseline) was objective and blinded until analysis, risk of bias is inherent. Quality assessments are given in Table S8 and Figure S2.

3.2 | NMA findings

The base-case network grouped trial interventions into five different treatment nodes (Figure 2). Direct evidence was available for five of the 10 potential pairwise comparisons. No outlier was identified in terms of baseline characteristics. The direct pairwise comparison results for the two studies comparing basal-plus versus premix and for the two studies comparing intensified basal versus premix were overlapping in all cases. None of the Bucher tests confirmed evidence of inconsistency within any of the closed loops (all P > .05). We therefore concluded that the exchangeability assumption was valid.

Deviance Information Criterion (DIC) estimates for the fixed- and random-effects models were within five points difference (Figure 3, Table 2, Table S9), and thus the random-effects models were favoured for the primary analysis of all outcomes. Analysis was not feasible for gastrointestinal events because of inconsistent reporting in the non-GLP-1RA trials.
3.3 | HbA1c

All the included trials reported HbA1c outcomes suitable for analysis. Based on analysis, there was greater reduction in HbA1c with iGlarLixi compared with premix insulin (mean difference $-0.50 \ [95\% \text{ CrI } -0.93 \text{ to } -0.06\%\text{-units} \ [-5.5 \text{ to } -10.2 \text{ to } -0.7 \text{ mmol/mol}])$, with a 98% probability of iGlarLixi being more effective ($P_{\text{better}} 98\%$; Figure 3A). However, no difference was established for iGlarLixi versus addition of thrice-daily meal-time insulin ($-0.35 \ [-0.89 \text{ to } +0.13\%\text{-units} \ [-3.8 \text{ to } -9.7 \text{ to } +1.4 \text{ mmol/mol}]$; $P_{\text{better}} 94\%$); iGlarLixi was better compared with basal-plus regimens ($-0.68 \ [-1.18 \text{ to } -0.17\%\text{-units} \ [-7.4 \text{ to } -12.9 \text{ to } -1.9 \text{ mmol/mol}]$; $P_{\text{better}} > 99\%$).

Therapies were found to be similar in achieving an HbA1c level of less than 7.0% ($<53 \text{ mmol/mol}$) with iGlarLixi compared with premix (relative risk 1.64 [95% CrI 0.92 to 2.83]; $P_{\text{better}} 96\%$; Figure 3B). Results were similar for iGlarLixi compared with both 3x meal-time + basal regimens (1.36 [0.69 to 2.55]-%-units; $P_{\text{better}} 87\%$) and basal-plus regimens (1.86 [0.96 to 3.49]-%units; $P_{\text{better}} 97\%$).

3.4 | Total insulin dose

Five trials reported total insulin dose.17,33,35–37 Total insulin dose was probably lower but not confirmed as such at the end of the trial for participants using iGlarLixi compared with premix insulin ($-50.0 \ [95\% \text{ CrI } -127.7 \text{ to } 28.6] \text{ U/day;} \ P_{\text{better}} 93\%$). Similar results were found for iGlarLixi compared with thrice-daily meal-time + basal regimens ($-63.7 \ [-156.7 \text{ to } 22.3] \text{ U/day;} \ P_{\text{better}} 95\%$) and basal-plus ($-52.0 \ [-145.6 \text{ to } 32.5] \text{ U/day;} \ P_{\text{better}} 92\%$) (Table 2).

3.5 | Change in body weight

All eight trials reported body weight. Overall, weight benefit relative to premix among participants receiving iGlarLixi was $-2.2 \ (95\% \text{ CrI } -4.6 \text{ to } -0.1 \text{ kg}; \ P_{\text{better}} 98\%)$. This finding was not confirmed for thrice-daily meal-time + basal ($-2.5 \ [-5.3 \text{ to } 0.2] \text{ kg;} \ P_{\text{better}} 97\%$) and basal-plus regimens ($-1.8 \ [-4.4 \text{ to } 0.6] \text{ kg;} \ P_{\text{better}} 95\%$) (Table 2).

3.6 | Hypoglycaemia

Different definitions of hypoglycaemia were used in the ascertained RCTs (Table S3). Four trials reported the number of participants (incidence) who experienced confirmed hypoglycaemia during the trial.17,32,35,37 Incidence was low and thus credible intervals for relative risk were large, such that possible differences were not confirmed (Table 2). Seven trials reported documented symptomatic hypoglycaemia,17,32,33,35–38 and results were similar to confirmed hypoglycaemia incidence for both RR and $P_{\text{better}}$ (Table 2).
| Trial | Interventions | Background OGLD | Treatment period (weeks) | Randomized (n) | Age (years) | Male (%) | Duration of diabetes (years) | Baseline HbA1c (% [mmol/mol]) |
|-------|---------------|-----------------|--------------------------|----------------|-------------|----------|-----------------------------|-------------------------------|
| Intensified basal vs. iGlarLixi [Aroda et al. (2016)]<sup>17</sup> | Glargine 100 U/mL (QD) | Metformin | 30 | 369 | 60.3 | 48.5 | 12.1 | 8.1 [65] |
| &nbsp; &nbsp; iGlarLixi (QD) | | | 367 | | 59.6 | 45.0 | 12.0 | 8.1 [65] |
| Intensified basal vs. premix [Kumar et al. (2017)]<sup>32</sup> | Glargine 100 U/mL (QD) | Metformin +/- pioglitazone +/− DPP-4i | 26 | 233 | 58.4 | 54.5 | 11.4 | 8.4 [68] |
| &nbsp; &nbsp; IdegAsp (QD) | | | 232 | | 57.8 | 58.7 | 11.6 | 8.3 [67] |
| Intensified basal vs. premix [Ligthelm et al. (2011)]<sup>33</sup> | Glargine 100 U/mL (QD) | Metformin + secretagogues +/- TZD | 24 | 143 | 53.5 | 58.7 | 11.2 | 8.9 [74] |
| &nbsp; &nbsp; BIAsp 30/70 (BID) | | | 137 | | 51.9 | 54.7 | 11.1 | 9.0 [75] |
| Meal-time + basal vs. premix [Rodbard et al. (2016)]<sup>34</sup> | Degludec + aspart (2-4x per day) | Pre-existing OGLDs other than sulphonylureas | 26 | 136 | 59.6 | 63.2 | 11.7 | 8.3 [67] |
| &nbsp; &nbsp; IdegAsp (BID) | | | 138 | | 59.6 | 52.9 | 13.5 | 8.3 [67] |
| 3x meal-time + basal vs. basal-plus [Rosenstock et al. (2016)]<sup>35</sup> | Glargine 100 U/mL + glulisine (TID) | +/- Metformin | 26 | 298 | 59.4 | 44.3 | 12.4 | 7.8 [62] |
| &nbsp; &nbsp; Glargine 100 U/mL + glulisine (QD) | | | 298 | | 60.2 | 45.3 | 12.3 | 7.7 [61] |
| 3x meal-time + basal vs. premix [Rosenstock et al. (2008)]<sup>36</sup> | Glargine 100 U/mL + lispro (TID) | Metformin and/or TZD | 24 | 187 | 54.0 | 52.0 | 11.2 | 8.9 [74] |
| &nbsp; &nbsp; Lispro protamine/lispro 50/50 | | | 187 | | 55.4 | 53.0 | 10.9 | 8.8 [73] |
| Basal-plus vs. premix [Tinahones et al. (2014)]<sup>37</sup> | Glargine 100 U/mL + lispro (QD) | Metformin +/- pioglitazone | 24 | 242 | 57.7 | 40.8 | 11.3 | 8.6 [70] |
| &nbsp; &nbsp; Lispro/lispro protamine 25/75 (BID) | | | 236 | | 57.4 | 49.2 | 12.2 | 8.7 [71] |
| Basal-plus vs. premix [Vora et al. (2015)]<sup>38</sup> | Glargine 100 U/mL + glulisine (QD) | Metformin | 24 | 170 | 61.6 | 72.4 | 12.9 | 8.6 [70] |
| &nbsp; &nbsp; Aspart/aspart protamine 30/70 (BID) | | | 165 | | 61.6 | 72.6 | 13.0 | 8.6 [70] |

Abbreviations: BID, twice daily; DPP-4i: dipeptidyl peptidase-4 inhibitor; OGLD, oral glucose-lowering drugs; QD, once daily; TID, three times daily; TZD: thiazolidinedione.

**FIGURE 2** Base-case network. Lines connecting each treatment node indicate a direct comparison. No trials comparing iGlarLixi with premix, or intensified basal with basal-plus, were identified.
FIGURE 3  Bayesian network meta-analysis results of HbA1c outcomes at 24–30 weeks. A, reduction in HbA1c (%-units). B, likelihood of achieving HbA1c < 7.0%. CFB, change from baseline; CrI, credible interval; DIC, deviance information criterion.

TABLE 2  Summary of base-case random-effects Bayesian network meta-analysis results: secondary outcomes

| Intervention (Relative to iGlarLixi) | Total insulin dose (U/day) MD (95% CrI) DIC: 20.1 P.bettera | CFB in body weight (kg) MD (95% CrI) DIC: 24.1 P.bettera | Confirmed hypoglycaemia RR (95% CrI) DIC: 15.8 P.bettera | Documented hypoglycaemia RR (95% CrI) DIC: 27.1 P.bettera |
|-------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| iGlarLixi vs. premix               | −50.0 (−127.7, 28.6) 93% | −2.2 (−4.6, −0.1) 98% | 0.87 (0.64, 1.16) 85% | 0.76 (0.51, 1.14) 93% |
| iGlarLixi vs. intensified basal     | 0.2 (−54.4 to 57.0) 49% | −1.4 (−3.2 to 0.5) 95% | 0.94 (0.77 to 1.15) 74% | 0.94 (0.68 to 1.31) 68% |
| iGlarLixi vs. basal-plus            | −52.0 (−145.6 to 32.5) 92% | −1.8 (−4.4 to 0.6) 95% | 0.85 (0.60 to 1.17) 85% | 0.79 (0.51 to 1.23) 88% |
| iGlarLixi vs. 3x meal-time + basal  | −63.7 (−156.7 to 22.3) 95% | −2.5 (−5.3 to 0.2) 97% | 0.87 (0.62 to 1.19) 83% | 0.73 (0.44 to 1.15) 93% |

Abbreviations: CFB, change from baseline; CrI, credible interval; DIC, deviance information criterion; MD, mean difference; RR, relative risk.
aProbability threshold that iGlarLixi is the better treatment.
3.7 Sensitivity analysis

A sensitivity analysis was performed to review whether the effect of combining the thrice-daily meal-time + basal and basal-plus nodes into a single meal-time insulin + basal insulin treatment node showed similar results for all outcomes. Although HbA1c reduction was greater with iGlarLixi treatment compared with premix insulin, the results were no longer confirmed (difference $-0.50$ [95% CrI $-1.21$ to $0.19$]-units; $P$ better 94%), a result which differed from the base-case analysis. The probability that participants would achieve an HbA1c level of less than 7.0% (<53 mmol/mol) on iGlarLixi compared with premix or meal-time + basal remained unconfirmed. Comparison of total insulin dose for participants at the end of treatment also remained inconclusive. It was still more probable for participants receiving iGlarLixi versus premix to have less weight gain; however, the CrI expanded to include 0.0 kg, leading to increased uncertainty, but with a higher central estimate ($-2.3 [-4.9$ to $0.2]$ kg; $P$ better 97%). Results for both hypoglycaemia definitions remained inconclusive (Table S10).

4 DISCUSSION

This systematic literature review and NMA sought to provide an evidence-based approach to understand the clinical efficacy of iGlarLixi versus other insulin options, including premix insulin and addition of meal-time insulin, for people with inadequate glucose control on basal insulin alone. The network of evidence led to estimates suggesting that efficacy and safety were improved or similar when using iGlarLixi relative to these other insulin options. In the absence of head-to-head trials, an NMA of RCTs provides insight into the relative efficacy of each of the interventions using the highest level of evidence available.

The 2018 Consensus Report by the ADA and EASD recommends that the combination of GLP-1RA and basal insulin may be considered for people with inadequate glucose control while taking a GLP-1RA or using basal insulin.6,7 In such patients, an FRC can be useful, decreasing the number of medications and the complexity of therapy. When individuals cannot maintain glycaemic control with basal insulin, conventional practice has been to move to a multiple-daily insulin injection regimen or to premix insulin.39 The latter remains a commonly used option globally.40 The results of the current study suggest that the FRC of GLP-1RA and basal insulin may be more favourable than premix (‘more effective’). It also has a high probability of an advantage in three domains (HbA1c, hypoglycaemia and weight gain) compared with adding meal-time insulin to basal insulin (‘likely to be favourable’).

Indeed, the HbA1c point estimates when iGlarLixi is compared with premix and basal-plus are greater than a clinically significant difference threshold of 0.30%-units, with CrIs which do not include 0.00%-units, although the upper bound of the CrI is above zero when iGlarLixi is compared with a regimen consisting of thrice-daily meal-time plus basal insulin (Figure 3). There was no evidence that use of iGlarLixi might increase the risk of weight gain or hypoglycaemia (was ‘comparable’) compared with changing to premix and/or adding meal-time insulin.

A sensitivity analysis was performed to determine the effect of pooling meal-time insulin additions (basal-plus and 3x meal-time) into a single network node and showed results similar to the base-case findings, now missing conventional statistical significance. However, this analysis may not be valid given the difference in primary outcomes between the two insulin regimens found in the base-case analysis. For HbA1c reduction and body weight outcomes, the relative effect of iGlarLixi compared with premix insulin was diminished from a ‘more effective’ difference to a ‘likely to be favourable’ difference between the two interventions, meaning the findings were less statistically robust. This could be because of a greater relative efficacy for premix based on the combination of the more favourable treatment thrice-daily meal-time + basal insulin (vs. premix) with the less efficacious basal-plus regimen (vs. premix). The inclusion of the study by Rodbard et al., which uses a step-wise approach to meal-time insulin addition, may also have contributed to the difference in relative efficacy between premix and meal-time insulin.34 Nevertheless, these results reinforce that even if treatment with meal-time insulin is not separated by frequency, iGlarLixi remains more efficacious than premix insulin.

Previous studies and meta-analyses have investigated other specific insulin strategies when moving from basal insulin, such as meal-time insulin plus basal versus premix or meal-time insulin versus GLP-1RA addition to basal insulin.10,41 One recent NMA compared the efficacy and safety of adding lixisenatide to basal insulin as an alternative to other insulin regimens.52 The results were similar to those of the present study. Reductions from baseline in HbA1c for lixisenatide plus basal insulin were similar to those for premix, basal-plus and basal-bolus, but lixisenatide plus basal insulin showed a significantly lower risk of symptomatic hypoglycaemia compared with premix and basal-bolus insulin regimens.42 However, these previous analyses have either not included fixed ratio GLP-1RA + basal insulin combinations or have included heterogeneous populations, such as both insulin-naive and insulin-exposed people.10,41 The current study, however, specifically investigates people with inadequate glycaemic control on basal insulin with or without OGLDs, a relevant clinical scenario eventually faced by a high proportion of people with T2D.39

A gap search was performed on Embase, including an index of MEDLINE, to identify any studies relevant to the present NMA published from June 2018 to April 2020. More than 900 publications were returned and, following further screening, two were deemed relevant. Both studies showed similar results to those of the studies already included in the present NMA. The first compared once-daily insulin degludec/insulin aspart (premix) versus once-daily insulin glargine 100 U/mL plus once-daily insulin aspart (basal-plus) over 26 weeks.43 This study would add to the link between the intensified basal and premix nodes (Figure 2). Similar to Tinahones et al.37 and Vora et al.,38 Philis-Tsimikas et al. found that although both treatment regimens afforded similar glycaemic control, premix was favoured because of significantly less nocturnal hypoglycaemia than with insulin glargine 100 U/mL plus once-daily insulin aspart.45 The second very recent
publication compared once-daily iGlarLixi versus once-daily insulin glargine 100 U/mL, both with metformin, over 26 weeks, in a single country.\textsuperscript{44} This study would add to the link between the iGlarLixi and intensified basal nodes (Figure 2). The results were similar to those shown by Aroda et al.,\textsuperscript{17} where iGlarLixi was favoured over insulin glargine 100 U/mL in terms of improving glycaemic control, with no increased risk of hypoglycaemia.\textsuperscript{44}

The strengths of the current study include formal evidence extraction from original publication of data reporting and analysis, the use of validated PRISMA and NMA methods developed by others, and the reliance on RCTs defined as high quality by the Cochrane risk of bias tool (except for the use of open-label therapy because of bespoke pen-injection devices). The use of a sensitivity analysis and consistency of direct and indirect evidence further corroborates the main findings of the analysis.

The analyses were subject to some limitations. First, the selection of outcomes was limited to those evaluated in the LixiLan-L trial.\textsuperscript{17} Indeed, the network link between iGlarLixi and the other therapies depended on the findings of that one trial, and the other links depended on just one or two trials each. While insulin glargine 100 U/mL as basal insulin was both the common link and is the more widely used insulin in that role, the premix and meal-time comparators varied between trials, as did the oral agents allowed in the study designs. However, the sensitivity analysis did not suggest notable problems arising from inclusion of different meal-time insulin regimens in the same treatment node. Second, the RCT evidence was from comparatively short-term trials, whereas T2D is progressive over years. Additionally, almost all of the RCTs included were open-label, which could introduce a risk of bias. However, it should be noted that most RCTs involving injectable therapies for T2D are open-label and the bias is usually regarded as manageable for objective endpoints. Furthermore, without inclusion of these studies, the NMA could not have been performed. The search of conference abstracts also retrieved no additional studies, further limiting the evidence base available. Third, the analysis of hypoglycaemia incidence was limited by low incidence and differences in hypoglycaemia definitions used in the trials, and severe hypoglycaemia was too infrequent to allow meaningful analysis. In addition, not all of the other predefined outcomes were available. There was poor recording of gastrointestinal events, a tolerability concern that could affect people taking GLP-1RA + basal insulin FRCs. These limitations should be taken into consideration when interpreting the results.

Results of head-to-head studies comparing iDegLira (the other available FRC) to meal-time insulin plus insulin glargine 100 U/mL are similar to the findings presented herein: that is, comparable or superior efficacy and safety compared with meal-time insulin + basal insulin.\textsuperscript{39,45} iDegLira has not been compared, either directly in a head-to-head trial or indirectly to premix insulin, so it is unclear whether the results presented here represent the FRC class of therapy. However, a recent meta-analysis found similar efficacy for glucose control and body weight for iGlarLixi compared with iDegLira.\textsuperscript{46} Therefore, a similar study of iDegLira indirectly compared with other intensification options may provide useful confirmatory information.

In conclusion, this systematic review and NMA present supporting evidence that iGlarLixi, compared with other intensification options such as adding meal-time insulin or switching to premix insulin, is a clinically relevant treatment option for early intensification in individuals with T2D inadequately controlled on basal insulin with or without OGLDs. This NMA suggests superior HbA1c reduction with iGlarLixi compared with premix, and a lower risk of hypoglycaemia and weight gain. Compared with meal-time insulin, iGlarLixi is at least comparable, with a higher probability of being favourable in these same outcome domains. FRCs offer patients who wish to use GLP-1RAs and basal insulin the opportunity to do so with a less complex regimen of a single daily injection, convenient dose timing and less plasma glucose monitoring than is necessary when meal-time insulin is added to basal insulin. These factors may lead to improved quality of life and treatment adherence.

ACKNOWLEDGMENTS
The authors are grateful to Doctor Evidence and Amanda Justice for medical writing support funded by Sanofi. The systematic review and statistical analysis were funded by Sanofi and performed by Doctor Evidence.

CONFLICT OF INTEREST
The authors declare the following: P.H. or institutions with which he is associated have received funding for his research, advisory and lecturing activities from Sanofi, and also from other GLP-1RA and insulin manufacturers including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck (MSD), and Novo Nordisk. S.K. has received lecture fees from Novo Nordisk and Sanofi, outside of the submitted work. L.B. declares grant/research support to Dr. Blonde and/or his institution: Janssen Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Inc., Merck & Co., Novo Nordisk and Sanofi; speaker at: Janssen Pharmaceuticals, Inc., Novo Nordisk, Sanofi; consultant: AstraZeneca, Gil-ead Sciences, Inc., Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk and Sanofi. L.J. reports receiving consulting and lecture fees from Boehringer Ingelheim, AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Novartis, Novo Nordisk, Merck (MSD), Bayer, Takeda, Sanofi and Roche Diagnostics, and research grants from Roche Diagnostics, Sanofi, Merck (MSD) and Novartis. P.G. and C.B.-W. are employees of Sanofi. A.S. was an employee of Sanofi at the time the study was conducted (current affiliation: CSL Behring, King of Prussia, PA, USA). T.S., E.M. and R.S. report employment and/or affiliation with GLP-1RA and insulin manufacturers such as Sanofi, Merck (MSD) and Novo Nordisk. P.G. and C.B.-W. are employees of Sanofi, Roche Diagnostics and Sanofi; speaker at: Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Roche Diagnostics; consultant: AstraZeneca, Eli Lilly, Boehringer Ingelheim; research grants from Sanofi, Novo Nordisk, Roche, Sanofi, Takeda, Merck & Co, Novo Nordisk and Roche Diagnostics; research grants from Roche Diagnostics. L.J. reports research grants from Janssen, Merck, Roche, and Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS
All authors fulfilled authorship requirements according to ICMJE guidelines. Design: A.S. and T.S. designed and conceptualized the study. Conduct/data collection: E.M., R.S. and T.S. were responsible for the systematic review and data acquisition. Analysis: E.M., R.S. and T.S. were responsible for the statistical analysis. Writing manuscript: initial publication drafting was performed by E.M., R.S. and T.S. while critical revision and interpretation were performed by P.H., L.B., A.S.,
REFERENCES

1. Hermansen K, Davies M, Derezenski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006;29(6):1269-1274.

2. Riddle MC, Rosenstock J, Gerich J. Insulin Glargine study I. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26(11):3080-3086.

3. Esposito K, Chiodini P, Bellastella G, Maioirino ML, Giugliano D. Proportion of patients at HbA1c target <7% with eight classes of anti-diabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. Diabetes Obes Metab. 2012;14(3):228-233.

4. Blonde L, Meneghini L, Peng XV, et al. Probability of achieving glycemic control with basal insulin in patients with type 2 diabetes in real-world practice in the USA. Diabetes Ther. 2018;9(3):1347-1358.

5. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management (NICE Guideline 28). 2015. https://www.nice.org.uk/guidance/ng28. Accessed April 22, 2019.

6. 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.

7. Buse JB, Wexler DJ, Tsapas A, et al. Update to: 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. 2020;43(2):487-493.

8. American Diabetes Association. 9. Pharmacologic approaches to glycemic control: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S90-S102.

9. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384(9961):2228-2234.

10. Maioirino ML, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care. 2017;40(4):614-624.

11. Sayre TSR, Thomas J, Murray E, Brulle-Wohlueter C, Shaunk A, Perfetti R. Network meta-analysis of iGlarLixi, a fixed-ratio combination GLP-1 RA and basal insulin, versus insulin premix. Paper presented at International Diabetes Federation (IDF) Congress 2017, Abu Dhabi, UAE.

12. Baser O, Tangirala K, Wei W, Xie L. Real-world outcomes of initiating insulin glargine-based treatment versus premixed analog insulins among US patients with type 2 diabetes failing oral antidiabetic drugs. Clinicoecon Outcomes Res. 2013;5:497-505.

13. Blonde L, San Juan ZT. Fixed-dose combinations for treatment of type 2 diabetes mellitus. Adv Ther. 2012;29(1):1-13.

14. Han S, Iglay K, Davies MJ, Zhang Q, Radican L. Glycemic effectiveness and medication adherence with fixed-dose combination or coadministered dual therapy of antihyperglycemic regimens: a meta-analysis. Curr Med Res Opin. 2012;28(6):969-977.

15. Hutchins V, Zhang B, Florence RL, Krishnarajah G, Graham J. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin. 2011;27(6):1157-1168.

16. Lokhandwala T, Smith N, Senthuvud C, Sorstadius E, Lee WC, Mukherjee J. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs. loose-dose combination of oral anti-diabetes drugs. J Med Econ. 2016;19(3):203-212.

17. 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.

18. Rosenstock J, Aronson R, Gronburger 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.

19. Lefebvre C, Glanville J, Bricоеe S, et al. Chapter 4: Searching for and selecting studies. In: Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions. 6th ed. Chichester, UK: John Wiley & Sons; 2019:67-107.

20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.

21. Higgins JPT, Savovic J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions. 6th ed. Chichester, UK: John Wiley & Sons; 2019:205-228.

22. van Valkenhoef G, Bujkiewicz S, Eftimeiou O, Reid D, Stroomberg C, de Keijser J. GeMTC Manual. https://gemtc.drugis.org/manual.html#prior-distributions. Accessed June 2020.

23. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. J Comput Graph Stat. 1998;7(4):434-455.

24. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Statist Sci. 1992;7(4):457-472.

25. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian Approaches to Clinical Trials and Health Economic Outcome Assessments. Chichester, UK: John Wiley & Sons; 2004.

26. Spiegelhalter DJ, Best NG, Carlin BP, Linde A. Deviance information criterion: 12 years on. J R Statist Soc B. 2014;76(3):485-493.

27. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian Measuring Statistical Significance. Chichester, UK: John Wiley & Sons; 2004.

28. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Multiple Sequences. 6th ed. Chichester, UK: John Wiley & Sons; 2019:205-228.

29. Cope S, Donohue JF, Jansen JP, et al. Comparative efficacy of long-acting bronchodilators for COPD: a network meta-analysis. Respirology. 2018;23(4):525-534.

30. Viechtbauer W. Metafor: Meta-analysis Package for R. 2018. https://cran.r-project.org/web/packages/metafor/index.html. Accessed July 13, 2018.
32. Kumar S, Jang HC, Demirag 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.

33. Ligthelm RJ, Gylvin T, DeLuzio T, Raskin P. A comparison of twice-daily biphasic insulin aspart 70/30 and once-daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: a randomized, open-label study. *Endocr Pract.* 2011;17(1):41-50.

34. Rodbard HW, Carioù B, Pieber TR, Endahl LA, Zacho J, Cooper JG. Treatment intensification with an insulin glargine–liraglutide (IDeg)/insulin aspart (IAsp) co-formulation twice daily compared with basal IDeg and prandial IAsp in type 2 diabetes: a randomized, controlled phase III trial. *Diabetes Obes Metab.* 2016;18(3):274-280.

35. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care.* 2006;31(1):20-25.

36. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin Glargine therapy: testing Lixisenatide plus basal insulin versus insulin GLulinsine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial. *Diabetes Care.* 2016;39(8):1318-1328.

37. Tinahones FJ, Gross JL, Onaca A, Cleall S, Rodriguez A. Insulin lispro low mixture twice daily versus basal insulin glargine once daily and prandial insulin lispro once daily in patients with type 2 diabetes requiring insulin intensification: a randomized phase IV trial. *Diabetes Obes Metab.* 2014;16(10):963-970.

38. Vora J, Cohen N, Evans M, Hockey A, Speight J, Whately-Smith C. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). *Diabetes Obes Metab.* 2015;17(12):1133-1141.

39. Home PD, Dain MP, Freemantle N, et al. Four-year evolution of insulin regimens, glycaemic control, hypoglycaemia and body weight after starting insulin therapy in type 2 diabetes across three continents. *Diabetes Res Clin Pract.* 2015;108(2):350-359.

40. Home P, Naggar NE, Khamseh M, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A1chieve study. *Diabetes Res Clin Pract.* 2011;94(3):352-363.

41. Giugliano D, Chiodini P, Maiorino M, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Endocrine.* 2016;51(3):417-428.

42. Men P, Qu S, Luo W, Li C, Zhai S. Comparison of lixisenatide in combination with basal insulin vs other insulin regimens for the treatment of patients with type 2 diabetes inadequately controlled by basal insulin: systematic review, network meta-analysis and cost-effectiveness analysis. *Diabetes Obes Metab.* 2020;22(1):107-115.

43. 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.

44. Kaneto H, Takami A, Spranger R, Amano M, 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. https://doi.org/10.1111/diab.14005.

45. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care.* 2018;41(5):1009-1016.

46. Cai X, Gao X, Yang W, Ji L. Comparison between insulin degludec/liraglutide treatment and insulin glargine/lixisenatide treatment in type 2 diabetes: a systematic review and meta-analysis. *Expert Opin Pharmacother.* 2017;18(17):1789-1798.

**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 P, Blonde L, Kalra S, et al. Insulin glargine/lixisenatide fixed-ratio combination (iGlarLixi) compared with premix or addition of meal-time insulin to basal insulin in people with type 2 diabetes: A systematic review and Bayesian network meta-analysis. *Diabetes Obes Metab.* 2020;22:2179–2188. [https://doi.org/10.1111/diab.14148](https://doi.org/10.1111/diab.14148)