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REVIEW ARTICLE

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Titratable fixed-ratio combination of basal insulin plus a glucagon-like peptide-1 receptor agonist: A novel, simplified alternative to premix insulin for type 2 diabetes

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Abstract

Despite novel therapeutic options, many people with type 2 diabetes (T2D) do not achieve their HbA1c targets. Given the progressive nature of T2D, many individuals not controlled with oral therapy will require advancement to injectable therapy using either a glucagon-like peptide-1 receptor agonist (GLP-1 RA), recently recommended as a first option, or traditionally a basal insulin. However, premix insulins remain frequently used, either as initial injectable therapy or as intensification from basal insulin. Premix insulin injections can potentially provide significant glycaemic improvements to basal insulin but at the expense of increased hypoglycaemia and weight gain and the need for multiple daily doses, which may affect treatment adherence. Real-world evidence suggests that glycaemic control often remains suboptimal with premix insulins. Fixed-ratio combinations (FRCs) of basal insulin and GLP-1 RAs provide a novel alternative to premix insulin for therapy intensification. While no direct comparisons between premix insulins and FRCs are available, results from meta-analyses suggest that FRCs may offer better HbA1c reductions, a lower risk of hypoglycaemia and less weight gain compared with premix insulin in a simplified treatment regimen. A head-to-head trial of T2D treatment intensification with premix insulin and a FRC of basal insulin plus a GLP-1 RA is currently in progress, which should help to clarify the outcomes for each treatment option. This review discusses the unmet needs of people with T2D treated with premix insulin and provides evidence supporting FRCs of basal insulin and GLP-1 RAs as an alternative treatment option.

KEYWORDS
basal insulin, GLP-1 analogue, glycaemic control, insulin therapy, type 2 diabetes

1 | INTRODUCTION

Despite advancements in type 2 diabetes (T2D) therapy, a considerable proportion of people with diabetes fail to reach standard and individualized glucose targets. A recent meta-analysis of global glycaemic control using 24 studies across 20 countries showed that the pooled average proportion of people with T2D achieving their HbA1c targets was 43%, both in primary and secondary care settings.[1] Similarly, the International Diabetes Management and Practices Study (IDMPS), a large observational, cross-sectional, real-world study in

low- to middle-income countries, highlighted that less than 50% of people with T2D reached an HbA1c level of <7% (<53 mmol/mol), and a small but significant decreasing trend in HbA1c target achievement over a 12-year period was apparent.[2] Based on this global evidence and the progressive nature of T2D, there is a need for timely optimization and intensification of therapy among people with T2D.

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines recommend advancing therapy in people with T2D inadequately controlled on oral antihyperglycaemic drugs (OADs) with the addition of an injectable therapy, such as a glucagon-like peptide-1 receptor agonist (GLP-1 RA) as a first injectable option.[3,4] Basal insulin or combined injectable therapy can also be considered as a first injectable therapy in people with T2D, depending on patient profiles, such as HbA1c level.[3,4] Should further intensification be required in these individuals, therapy can be advanced using the following treatment options: (a) the addition of either basal insulin or a GLP-1 RA as a second injectable (depending on whichever was initiated first) or switching to a fixed-ratio combination (FRC) of both agents; (b) switching to a basal insulin plus prandial insulin at mealtimes or a full basal-bolus regimen; or (c) switching to a premix insulin regimen.[3,4] The use of premix insulin has also been supported by the UK National Institute for Clinical Excellence (NICE), which recommends premix insulin as an option for insulin initiation in people with T2D, particularly if their HbA1c is ≥9.0% (≥75 mmol/mol).[5] Premix insulins are recommended as an option for intensification of basal insulin[5] despite the increased risk of hypoglycaemia and weight gain compared with basal insulin,[6] and limited published evidence for sustained efficacy.

Premix insulins have been widely used worldwide, as indicated by the observational MOSAIc study of 18 countries that showed use of premix insulin in 30% of people with T2D taking insulin globally and in more than 50% of those with T2D in China and India.[7] Premix insulin use observed in this study was lower in the United States (17%) but remained quite high in some European countries (44% in Germany and 36% in the UK). Results of the VISION 18-month observational study of insulin-use patterns showed that 46% of people with T2D in the Middle East and North Africa who initiated insulin therapy did so with premix insulin,[8] whereas only 27% of those in the Western Pacific region did the same.[9]

This review will address the limitations and concerns with the use of premix insulin, which is still a widely used treatment, and also discuss the potential of the novel FRCs of basal insulin and a GLP-1 RA as a potentially better option for people with uncontrolled T2D who are either initiating or intensifying their insulin therapy with premix insulin.

2 | COMPARATIVE STUDIES OF PREMIX INSULIN VERSUS BASAL INSULIN WITH OR WITHOUT PRANDIAL INSULIN

Evidence from randomized controlled trials (RCTs) has shown that people with uncontrolled T2D (≥7.0% to ≤10% [≥53 to ≤86 mmol/mol] or ≥7.5% to ≤12% [58 to 108 mmol/mol]) on basal insulin who switch to premix insulin had HbA1c reductions of between 0.8% (9 mmol/mol) and 1.9% (21 mmol/mol) upon study completion (24 or 26 weeks), depending on baseline HbA1c and study design.[10–15] A systematic review of RCTs comparing basal insulin (with or without prandial insulin) versus premix insulin showed that twice-daily administration of premix insulin resulted in HbA1c reductions of −1.0% (11 mmol/mol) to −2.8% (31 mmol/mol), while thrice-daily administration promoted reductions of −0.7% (8 mmol/mol) to −1.2% (13 mmol/mol) ($p < .01$) after 16–28 weeks of treatment.[6] However, premix insulins have also been associated with greater weight gain (0.8–5.4 kg for twice-daily premix vs. 0.1–3.5 kg for basal insulin; $p < .01$) and greater hypoglycaemia risk (3.4–8.2 events/year with twice-daily premix vs. 0.7–5.4 events/year with basal insulin; $p < .05$ for two of three studies).[6]

3 | REAL-WORLD EVIDENCE OF POOR GLYCAEMIC CONTROL WITH PREMIX INSULIN

Observational studies, such as PRESENT and IMPROVE, have shown that people with uncontrolled T2D with high HbA1c levels who switched from basal insulin to premix insulin therapy exhibited significant reductions in HbA1c, ranging from 1.4% (15 mmol/mol) to 1.7% (19 mmol/mol).[16,17]

However, numerous real-world evidence (RWE) studies have shown that glycaemic control remains less than optimal after initiating or switching therapy to premix insulin. A retrospective UK cohort study in people with uncontrolled T2D (HbA1c ≥ 9% [≥75 mmol/mol]) who switched from OADs to premix insulin (as per NICE recommendations[5]) reported that the cumulative probability of first achieving glycaemic targets on premix insulin was low (9%) over 6 months, with little additional clinical benefit beyond that (14% over 12 months; 16% over 24 months).[18] Another study using UK data from the Clinical Practice Research Datalink showed that people with uncontrolled T2D on basal insulin (mean HbA1c 9.6% ± 1.1% [81 ± 12 mmol/mol]) still had elevated HbA1c levels 6–12 months after switching to premix insulin (mean HbA1c: 8.9% ± 1.4% [74 ± 15 mmol/mol] at 6–12 months).[19] Similarly, a retrospective study of Japanese clinical practice data from the Computerized Diabetes Care (CoDiC; Japan Diabetes Clinical Data Management Study Group) database showed that mean HbA1c remained over 8% (8.2% ± 1.3%; 66 ± 14 mmol/mol) 17 months after intensification in people with T2D whose basal insulin therapy was intensified with either basal bolus or premix insulin.[20] These findings agree with data from waves 6 and 7 of the previously mentioned IDMPS, which indicated that approximately 80% of people with T2D treated with premix or basal insulin did not achieve adequate glycaemic control (HbA1c ≤ 7% [≤53 mmol/mol)].[21] Moreover, the IDMPS indicated that despite suboptimal glycaemic control in both groups, those receiving basal insulin achieved good glycaemic control, defined as an HbA1c level of ≤7% (≤53 mmol/mol), more frequently than those receiving premix insulin, with no difference in hypoglycaemia risk

having been observed between both insulin regimens following adjustment for potential confounders.[21]

Barriers to optimal adherence and titration of insulin therapy may explain why some people with T2D still remain uncontrolled after therapy intensification with premix insulin in real-life clinical practice. The most probable barrier is fear of hypoglycaemia,[22] as people who experience hypoglycaemia tend to be reluctant to continue adjusting insulin doses. Additional barriers include burdensome or complicated regimens, multiple injections, and fear of weight gain.[22–25] Therefore, the greater likelihood of weight gain and hypoglycaemia with premix insulin[3] combined with the need for multiple daily injections and frequent self-monitoring of blood glucose may suggest that the efficacy observed in RCTs is difficult to achieve in real-world practice.

4 | RATIONALE FOR COMBINATION THERAPY WITH BASAL INSULIN THERAPY AND GLP-1 RAS

GLP-1 RAs and basal insulin therapy present a promising combination therapy option for people with T2D given their different yet complementary mechanisms of action. Basal insulin therapy primarily reduces fasting plasma glucose (FPG) mainly by suppressing hepatic glucose production, whereas GLP-1 RAs improve glycaemic control by stimulating insulin release and suppressing glucagon secretion.[26] Furthermore, short-acting GLP-1 RAs provide further benefit by delaying gastric emptying, which is an important factor in reducing postprandial glucose.[26] GLP-1 RAs are also associated with weight reductions and may help mitigate the weight gain typically seen with basal insulin therapy.[26] Evidence from a network meta-analysis (NMA) of RCTs suggests that a combination therapy of basal insulin and a GLP-1 RA may provide similar glycaemic control with benefits in terms of weight gain and hypoglycaemia risk versus premix and basal-bolus insulin regimens,[27] while a RWE study reported greater HbA1c target achievement with basal insulin and GLP-1 RA therapy versus premix and basal plus prandial insulin regimens.[28]

5 | NOVEL TITRATABLE FRCS OF BASAL INSULIN AND GLP-1 RAS

Recently available therapeutic strategies, such as FRCs of basal insulin and a GLP-1 RA, can provide a clinically relevant alternative treatment option for people with uncontrolled T2D who are insulin-naïve or are currently receiving basal insulin therapy. Two once-daily titratable FRCs are currently available: (a) iGlarLixi, a combination of insulin glargine 100 units/mL (iGlar) and the GLP-1 RA lixisenatide (Lixi); and (b) IDegLira, a combination of insulin degludec (IDeg) and liraglutide (Lira).[29,30]

The LixiLan RCT programme compared the safety and efficacy of iGlarLixi with those of: iGlar alone and Lixi alone in people with T2D uncontrolled on OADs (LixiLan-O)[31]; basal insulin in people with T2D uncontrolled on basal insulin with OADs (LixiLan-L)[32]; or GLP-1 RA therapy in people with T2D uncontrolled on GLP-1 RAs (LixiLan-G).[33] Briefly, the results of these studies showed that iGlarLixi provided greater HbA1c reductions and improved glycaemic control compared with other regimens, with a similar risk of hypoglycaemia and more favourable weight change profiles compared with iGlar and fewer gastrointestinal adverse events compared with Lixi alone.[31–34] An NMA of 17 studies comparing gastrointestinal events with iGlarLixi compared with GLP-1 RAs during the first 12 weeks of therapy showed that fewer participants in the iGlarLixi treatment group reported nausea compared with short-acting GLP-1 RAs, and vomiting was also less common with iGlarLixi compared with use of a single-agent GLP-1 RA.[35]

The pivotal studies of the DUAL RCT programme compared the safety and efficacy of IDegLira versus either IDeg alone or Lira alone in people with T2D uncontrolled on OAD therapy (DUAL I),[36] versus continued use of IDeg in people with T2D uncontrolled on IDeg with OADs (DUAL II),[37] or versus continued use of GLP-1 RAs in people with T2D uncontrolled on GLP-1 RAs and OADs (DUAL III).[38] Other DUAL studies (DUAL IV–IX) further described the use of IDegLira versus comparators including continued OADs, iGlar or basal-bolus therapy in different populations of people with T2D.[39–44] Notably, the results of these pivotal studies in the DUAL RCT programme (DUAL I–III) were comparable with those of the LixiLan RCT programme (LixiLan-O, LixiLan-L and LixiLan-G[31–33]) and resulted in regulatory approval for both formulations. Briefly, IDegLira provided greater HbA1c reductions and improved glycaemic control compared with other regimens.[36,37] The risk of hypoglycaemia with IDegLira was lower than with IDeg[36] (and lower than that with iGlar [DUAL V][40]); although it should be noted that different definitions of hypoglycaemia were used in the DUAL studies than in the LixiLan studies, including a higher blood glucose threshold in the LixiLan trial programme (≤70 mg/dL [≤3.9 mmol/L]) compared with the DUAL programme (<56 mg/dL [<3.1 mmol/L]).[31–33,36,37] As such, indirect comparisons of hypoglycaemia are not possible. Fewer gastrointestinal adverse events were observed with IDegLira than with Lira, and weight changes from baseline significantly favoured IDegLira compared with basal insulin therapy.[36,37]

It should be noted that the LixiLan and DUAL RCT programmes were open-label in design. While this was a necessity because of the different injector pen devices being used for the FRCs and comparators, it is possible that the open-label study design could have resulted in bias. An additional limitation was the assessment of gastrointestinal events by self-report rather than by validated measures.

FRCs may therefore provide a novel, simple alternative therapy option to premix, either as an initial injectable therapy or for intensification from basal insulin. However, it should be noted that the two available FRC therapies are limited to a maximum of 60 dose steps (60 U iGlar, 20 μg Lixi) for iGlarLixi,[45,46] and 50 dose steps (50 U IDeg, 1.8 mg Lira) for IDegLira.[29,30] As such, these therapies may not be feasible options for individuals requiring higher insulin doses.

There are currently no head-to-head trials comparing the two FRCs. Results of a systematic review and meta-analysis by Cai et al. (2017) suggested no significant differences between iGlarLixi or IDegLira in HbA1c reductions or change in body weight.[47] Recently, two indirect treatment comparisons (ITCs) comparing the efficacy and

safety of these two therapies using data from RCTs have been published. Evans et al. (2018) compiled data from the LixiLan-L, DUAL II, DUAL V and SWITCH 2 phase 3 studies in individuals with T2D uncontrolled on basal insulin; the results suggested that IDegLira provided greater reductions in HbA1c and body weight at a similar dose of insulin compared with iGlarLixi.[48] Home et al. (2020) presented results of a systematic literature review and an ITC of two RCTs.[49] Results of this analysis suggested that, in patients uncontrolled with GLP-1 RA, advancing treatment with either FRC allowed a similar proportion of patients to achieve glycemic target, in addition to providing similar preprandial and postprandial self-measured plasma glucose and bodyweight change.[49] While IDegLira provided greater reductions in HbA1c and FPG, results suggested possibly fewer hypoglycaemia episodes with iGlarLixi; both results could be reflective of differences in study design and titration approaches.[49]

6 | EVIDENCE ON PREMIX INSULIN VERSUS FRCS OF BASAL INSULIN AND GLP-1 RAS

A systematic review and NMA, which compared the FRC, iGlarLixi, with other intensification options (i.e. basal-plus, basal-bolus, premix insulin), suggested that iGlarLixi was a clinically relevant treatment option for early intensification in people with T2D who were inadequately controlled on basal insulin with or without OADs (Table 1).[50]

TABLE 1 Premix insulin versus fixed-ratio combinations

Citation	Study description	Outcomes
Home et al.[50]	NMA of eight RCTs (n = 3538) comparing iGlarLixi, premix insulin or basal insulin in combination with mealtime insulin, in people inadequately controlled with basal insulin	Estimated HbA1c reductions with iGlarLixi were greater than premix and basal + 1x mealtime insulin and similar to 3x mealtime + basal insulin • vs. premix insulin: MD −0.50% (95% CrI: −0.93%, −0.06%), 98% probability of iGlarLixi being favourable • vs. 1x mealtime + basal insulin: MD −0.68 (95% CrI: −1.18, -0.17), >99% probability of iGlarLixi being favourable • vs. 3x mealtime + basal insulin: MD −0.35 (−0.89, 0.13), 94% probability of iGlarLixi being favourable[a]Estimated weight gain was significantly lower with iGlarLixi vs. premix insulin • vs. premix insulin: MD −2.2 (95% CrI: −4.6, −0.1), 98% probability of iGlarLixi being favourableAlthough not significant[a], compared with premix insulin, analyses suggested iGlarLixi had: • lower rates of confirmed hypoglycaemia: RR 0.87 (95% CrI: 0.64, 1.16), 85% probability of iGlarLixi being favourable • lower rates of documented symptomatic hypoglycaemia: RR 0.76 (95% CrI: 0.51, 1.14), 93% probability of iGlarLixi being favourable
Watada et al.[51]	Post hoc analysis of the DUAL II Japan RCT that assessed outcomes in Japanese people with T2D uncontrolled on premix insulin who switched to IDegLira (n = 39) Study length: 26 weeks	Mean (SD) HbA1c was 8.26% (67 mmol/mol) at baseline with premix insulin and 6.68% (49 mmol/mol) at week 26 following the switch to IDegLira (mean change −1.58%) Mean (SD) body weight was reduced by 1.5 ± 2.9 kg The rate of severe or confirmed hypoglycaemic events was 2.59 events/patient-year of exposure

Abbreviations: CrI, credible interval; IDegLira, a combination of IDeg and Lira; iGlarLixi, combination of insulin glargine 100 units/mL (iGlar) and the GLP-1 RA lixisenatide; Lira, liraglutide; NMA, network meta-analysis; P.Better, probability of better; RCT, randomized controlled trial; SD, standard deviation; T2D, type 2 diabetes.

[a]Although not significant, the probability of iGlarLixi being better than comparators was determined to be likely favourable if the CrI included 0.00 for continuous outcomes and 1.00 for binary outcomes but the P.Better values were 85% or more.

iGlarLixi exhibited a greater estimated difference in HbA1c reduction compared with premix insulin (−0.50% units [95% credible interval: −0.93, −0.06]), suggesting a 98% probability of iGlarLixi being superior to premix. Although no definite conclusions could be established given the comparatively low incidences and large intervals for relative risk, the study suggested that iGlarLixi likely promoted lower rates of both confirmed and documented symptomatic hypoglycaemia (probabilities of 85% and 93%, respectively) compared with premix insulin. iGlarLixi also exhibited a favourable weight profile compared with premix insulin (mean difference −2.2 [95% credible interval: −4.6, −0.1]) with a 98% probability of iGlarLixi being favourable to premix insulin.

Another post hoc analysis of Japanese individuals who switched from premix insulin to insulin IDegLira (n = 39) or IDeg (n = 38) showed that switching to IDegLira promoted a mean HbA1c decrease of −1.6% (17 mmol/mol), while switching to IDeg promoted a mean HbA1c decrease of −0.2% (2 mmol/mol).[51] Moreover, mean body weight decreased by 1.5 kg with IDegLira and increased by 0.1 kg with IDeg, while mean rates of confirmed (<3.1 mmol/L [<56 mg/dL]) hypoglycaemia were 2.6 and 4.0 events per patient-year in those who switched to IDegLira and IDeg, respectively.[51] These results suggest that FRCs may offer more clinical benefits over premix insulin as an intensification option for people with T2D who remain uncontrolled on OADs or basal insulin. However, head-to-head comparisons between FRCs and premix insulin are currently lacking.

As detailed above, premix insulins may therefore provide good glycaemic efficacy, but are associated with a higher risk of weight gain and hypoglycaemia compared with basal insulin therapies. However, a co-formulation of the basal insulin degludec (IDeg) and rapid-acting insulin aspart (IDegAsp) is available, which has previously been shown to generally provide HbA1c reductions similar to iGlar with similar or higher rates of confirmed hypoglycaemia and similar or lower rates of nocturnal hypoglycaemia in insulin-naïve or insulin-pretreated adults with T2D.[52–55] A recent RCT compared the efficacy and safety of IDegAsp, administered twice daily, with a free combination of the basal insulin degludec and the GLP-1 RA liraglutide, administered once daily in 52 individuals with T2D inadequately controlled on insulin therapy plus OADs.[56] Results showed that IDeg + Lira provided similar glycaemic control but superior weight loss versus IDegAsp.[56]

6.1 | Head-to-head RCT comparing iGlarLixi with premix insulin

While it has previously been highlighted that current guidelines suggest GLP-1 RAs as a first-line injectable therapy, basal insulins are still recommended by ADA guidelines as a first injectable therapy for some patients with T2D, based on patient preferences or clinical profiles[4]; and as first-line injectable therapy ahead of GLP-1 RAs for most individuals with T2D by NICE.[5] Furthermore, the long history of basal insulin use in individuals with T2D will probably mean that basal insulin will remain a prominent therapy option and that there will be a substantial population of individuals with T2D who are receiving basal insulin only and require intensification. As such, individuals on basal insulin represent an important global population and given the progressive nature of T2D, studies providing efficacy and safety data of novel intensification options for these individuals are warranted.

SoliMix, a head-to-head RCT comparing the efficacy and safety of an FRC of basal insulin and a GLP-1 RA, iGlarLixi, and premix insulin in a 30/70 ratio, biphasic insulin aspart 30/70 (BIAsp 30) in adults with T2D who have failed to reach their glycaemic targets with basal insulin plus one or two OADs, is currently in progress.[57] This 26-week, open-label, randomized, active-controlled, parallel-group, multicentre study will address a question that has previously not been properly tested in a prospective RCT, namely, assessing the comparative efficacy and safety of advancing basal insulin therapy by switching to a premix insulin regimen or by switching to a simpler once-daily FRC, such as iGlarLixi.

7 | CONCLUSIONS

Premix insulin was at one point a novel approach to simplify advancing NPH insulin, instead of manually mixing rapid insulin as the old split-mixed regimen. It is still often used as an intensification option in people with T2D who remain uncontrolled on OADs or basal insulin. Despite RCT data showing significant decreases in HbA1c following the initiation of premix insulin, often at the expense of more hypoglycaemia and weight gain, evidence from RWE studies highlights that glycaemic control remains poor in most individuals following therapy intensification with premix. As such there is an unmet need for further therapy options for those people with T2D who require treatment intensification. One commonly stated reason for choosing premix insulin is the unsolved need of postprandial control with basal insulin, with or without other antihyperglycaemic agents in people with advanced T2D. The ubiquitous actions of GLP-1 RAs have been shown to effectively reduce postprandial hyperglycaemia with considerable advantages over the addition of prandial insulin.[58] Therefore, FRCs of basal insulin and a GLP-1 RA can offer both components of glycaemic control (FPG and postprandial blood glucose) in a convenient and effective way. For those with T2D who require treatment intensification, FRCs may offer better glycaemic control with a lower risk of hypoglycaemia and weight gain compared with premix insulin. Furthermore, once-daily FRCs can provide a more convenient and simplified therapeutic option compared with multiple daily doses of premix insulin. Given that people with T2D often find it difficult to administer all insulin doses as prescribed, the ideal medication for improved adherence would be one that minimizes the number of daily injections required given that a lower treatment burden is a key predictor of better adherence.[23,24] Moreover, considering that fear of hypoglycaemia and weight gain are often cited as barriers to effective insulin treatment, therapies such as FRCs, which have lower risks for such adverse side effects compared with premix insulin, may promote improved treatment adherence and quality of life.[23]

However, the availability of medications is always an important consideration. Premix formulations are widely available, and represent a lower cost option compared with FRCs. Consequently, premix

insulins will still probably remain a commonly used therapy option, particularly in developing countries where resources are limited. However, it should be noted that the potential clinical benefits of FRCs over premix insulins may result in long-term reductions in complications relating to hyperglycaemia and fewer inpatient visits for hypoglycaemia. Cost-effectiveness analyses comparing these two therapy options are needed to determine the cost versus benefit of FRCs in relation to premix insulins.

While evidence suggests that FRCs offer clinical benefits compared with premix insulin, head-to-head RCTs comparing both approaches have been lacking. Nonetheless, this evidence gap should be addressed soon by the first head-to-head trial comparing iGlarLixi and premix BIAsp 30, testing important comparative questions.[57]

However, it should be noted that while data from such prospective RCTs are invaluable in providing comparative data on the efficacy and safety of therapies, results from RCTs are not always generalizable to real-life clinical practice because of high degrees of participant follow-up, stringent protocols and titration algorithms, and highly-selected populations.[59] As such, further real-world comparative effectiveness studies would be of interest to complement the results of the aforementioned RCT and explore whether the results seen in this trial are maintained in a real-life clinical practice setting.

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CONFLICT OF INTEREST

FG-P has acted as an advisor for Abbott Diabetes, AstraZeneca, Novartis, Novo Nordisk and Sanofi; has been an investigator in clinical trials for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi; and has acted as a speaker for Abbott Diabetes, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Novartis, Novo Nordisk and Sanofi. EA-O has no conflicts of interest to declare. EBJ has received advisory board honoraria and grant/research support from Sanofi and has received speaker honoraria from Bayer AG, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Takeda. XL has no conflicts of interest to declare. JR has been a consultant for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, Oramed and Sanofi, and has received grant/research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck, Novartis, Novo Nordisk, Oramed, Pfizer and Sanofi.

AUTHOR CONTRIBUTIONS

All the authors contributed to the conception and design of the analysis, as well as interpretation of the data. All the named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, had full access to all study data, and take complete responsibility for the integrity of the data and accuracy of the data analysis. All the authors participated in the writing and editing, critically reviewed and revised drafts of the manuscript, and had the responsibility of approving the final version for submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this review.

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SUPPORTING INFORMATION

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

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