Fixed-ratio combination of basal insulin and glucagon-like peptide-1 receptor agonists in the treatment of Japanese people with type 2 diabetes: An innovative solution to a complex therapeutic challenge

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Abstract
Over 10 million people in Japan have known or suspected type 2 diabetes (T2D), and this number is expected to rise. Although many people require therapy escalation because of the progressive nature of T2D, this appears to be suboptimal in Japanese real-world clinical practice. Insulin therapy tends to be introduced only when glycaemic control is very poor (mean glycated haemoglobin >9%). Although basal insulin therapy is effective in reducing fasting plasma glucose (FPG), postprandial plasma glucose often remains uncontrolled. Basal-bolus insulin regimens are complex and carry the risk of weight gain and hypoglycaemia. Recently, fixed-ratio combinations (FRCs) of BI and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown efficacy in reducing both FPG and postprandial plasma glucose with a single injection and without increased risk of hypoglycaemia or weight gain. IDegLira, a titratable FRC of insulin degludec (100 U/mL) and liraglutide, is currently available in Japan and the United States/European Union at a ratio of 1 U (unit):0.036 mg. iGlarLixi (insulin glargine 100 U/mL and lixisenatide at a ratio of 1:1 (20 U/20 μg) has recently been approved in Japan. Phase 3 trials in Japan for IDegLira (DUAL Japan) and iGlarLixi (LixiLan JP) have shown that both FRCs are efficacious. This review provides an overview of IDegLira and iGlarLixi (Japanese formulation) and considers their potential use as new therapeutic options to address the clinical need for early glycaemic control in Japanese people with T2D.

KEYWORDS
antidiabetic drug, GLP-1 analogue, glycaemic control, insulin therapy, type 2 diabetes
1  |  DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF TYPE 2 DIABETES IN JAPAN

1.1  |  Epidemiology and pathophysiology of diabetes in Japan

Globally, the prevalence of type 2 diabetes (T2D), which accounts for approximately 90% of diabetes, is expected to continue to rise, driven by obesity and an ageing population. As in other parts of the world, this rise in T2D prevalence is a significant issue in Japan. Based on a survey conducted by the Ministry of Health, Labor and Welfare, the number of people in Japan strongly suspected to have diabetes has grown from approximately 6.9 million in 1997 to 10 million in 2016. Japan has a rapidly ageing population, and according to the Japan Diabetes Clinical Data Management Study Group, the mean age of people with T2D in Japan has increased from 62.7 years in 2002 to 66.8 years in 2018. Body mass index (BMI) in Japanese people with T2D tends to be lower than in Western countries.

Although impaired β-cell function and insulin resistance are both common features of T2D, there appear to be differences across ethnicities in its pathophysiology. The Western T2D population is characterized by rising BMI, increasing insulin resistance and compensatory but ineffective hyperinsulinaemia. In the Japanese population, T2D is characterized by a prominent defect in insulin secretion, and a relatively mild increase in insulin resistance. Persistent hyperglycaemia further impairs insulin secretion and generates a cycle of glucose toxicity. As β-cell function declines, deterioration in glucose homeostasis progresses from the initial loss of postprandial plasma glucose control to elevation of fasting plasma glucose (FPG). Growing evidence suggests that individuals of East Asian descent, including people from Japan, have less β-cell functional capacity compared with white people. Therefore, treatment strategies that preserve β cells early in the course of diabetes are particularly critical for the Japanese population. Current therapies focus on reducing hyperglycaemia by supporting or supplementing insulin activity.

1.2  |  Characteristics of T2D therapy in Japan and unmet medical needs

Japan Diabetes Society (JDS) guidelines place particular emphasis on personalized therapy. Although a treatment target of glycated haemoglobin (HbA1c) <53 mmol/mol (<7%) is generally recommended to reduce risks of microvascular complications, the JDS guidelines advise setting targets tailored to the individual, taking into consideration age, type of medications and activities of daily living.

1.2.1  |  Oral antidiabetic drugs

Lifestyle modification, including improvement of diet and exercise, is fundamental to the management of T2D and is recommended by the JDS, and by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), as the initial intervention, either followed by or together with oral antidiabetic drugs (OADs) as appropriate. It is worth noting that there is a difference in the guidance with respect to specific OADs. ADA and EASD guidance suggest that metformin should be the first OAD agent used, and should be considered at the point of diagnosis. In contrast, the JDS guidance is not as prescriptive; lifestyle modification is recommended as an initial intervention where possible, with the decision on timing and OAD agent left to the clinician. Metformin, which lowers blood glucose primarily by improving insulin sensitivity and reducing hepatic gluconeogenesis, may not necessarily be considered the optimal initial oral therapy for Japanese people with T2D. In fact, only approximately 10% of Japanese people with T2D are placed on metformin as initial OAD therapy.

In Japan, dipeptidyl peptidase-4 (DPP-4) inhibitors are preferentially prescribed. According to Japanese claims-based studies, DPP-4 inhibitors are the most commonly (44.0%-54.8%) prescribed OAD as first-line medication. DPP-4 inhibitors increase portal concentrations of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino metric polypeptide (GIP) by inhibiting DPP-4, the enzyme that rapidly inactivates GLP-1 and GIP. This prolonged elevation of GLP-1 has effects on pancreatic β- and α-cell function (increasing insulin and decreasing glucagon), and delays gastric emptying, all of which contribute to a reduction in postprandial glucose rises.

Progression of therapy to an injectable agent is often required to improve glycaemic control in patients inadequately controlled on multiple OADs. Even so, initiation of injectable therapy is frequently delayed and utilized in patients with diabetes of longer duration and with suboptimal glycaemic control despite the use of multiple therapies, often including the newer hypoglycaemic agents.

1.2.2  |  Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide a non-insulin-based injectable option for people with T2D who require escalation from OAD therapy. GLP-1RAs are recommended in the 2018 ADA/EASD consensus as initial injectable therapies for most people with T2D. GLP-1RAs can lower postprandial glucose by enhancing insulin secretion, reducing glucagon secretion in response to a meal, and in the case of short-acting GLP-1RAs, by delaying gastric emptying. Importantly, GLP-1RAs provide an improvement in glycaemic control with a low risk of hypoglycaemia, and can facilitate body weight reduction. Their efficacy and safety have been demonstrated in the Japanese population and their use in Japan has been steadily growing: GLP-1RAs constituted 2.0% of treatments for T2D in 2012 and 4.2% in 2018. Nevertheless, in clinical practice, substantial proportions of patients fail to achieve glycaemic control with GLP-1RA therapy. This is probably influenced by multiple factors, which may include poor adherence due to gastrointestinal (GI) tolerability issues or hypoglycaemia and a significant "no response" rate. In Japanese people with T2D, the proportion achieving HbA1c <53 mmol/mol (<7%) with GLP-1RAs was 26.3% in 2018; among...
other real-world populations, the cumulative probability of achieving HbA1c <53 mmol/mol (<7%) within 12 months of initiating GLP-1RAs was 29.8%.\textsuperscript{33,34}

### 1.2.3 Insulin therapy

Insulin therapy is often reserved as a last option for people with T2D. In a Japanese database study where data between 2006 and 2009 were collected, the initiation rate of insulin therapy in people treated with OADs was estimated to be only 2.2/100 per year.\textsuperscript{35} The ALOHA-2 post-marketing surveillance study in Japan reported that for people with T2D receiving basal insulin (BI) and concomitant OAD therapy, the mean duration of T2D was 12.6 years and the mean HbA1c was 9.4% at insulin initiation.\textsuperscript{36,37} In ALOHA-2, 24 weeks of treatment with BI and concomitant OAD therapy resulted in a mean HbA1c reduction of −1.61%; only 26% of study participants reached the treatment target of HbA1c <53 mmol/mol (<7%).\textsuperscript{36,37} The low proportion of study participants achieving target HbA1c appeared to be partly attributable to delayed initiation and insufficient insulin dose titration. As ALOHA-2 was an observational trial in a real-world setting, the dosing of insulin was driven by physicians’ clinical judgement, rather than by fixed protocol or targeted FPG. The apparent clinical inertia may have been related to a fear of hypoglycaemia and/or weight gain, as well as lack of time, experience, and resources for physicians.\textsuperscript{38,39} Other observational studies also show low or modest proportions of insulin-treated patients with T2D achieving HbA1c target <53 mmol/mol (<7%), probably as a result of similar deficiencies in management strategies. In patients initiating BI, the cumulative probability of achieving this target over 12 months was 18.0% and approximately 38% in real-world studies in the United Kingdom and the United States, respectively.\textsuperscript{33,34} In 2018, the proportion of Japanese patients achieving HbA1c <53 mmol/mol (<7%) was 31% for those receiving insulin only and 28.5% for those treated with insulin plus OADs.\textsuperscript{9}

Long-acting BI therapy is effective in lowering FPG and is often selected as a next step following a variety of combinations of OADs. However, even among people who are able to achieve FPG targets on BI, HbA1c can remain above target because of the persistence of postprandial hyperglycaemia.\textsuperscript{40,41} Postprandial hyperglycaemia is not addressed with BI therapy. In an analysis of real-world studies of people with T2D on BI, 35.6% of study participants in Japan had “residual hyperglycaemia”, which is defined as HbA1c above target (≥53 mmol/mol ≥7%) despite FPG <7.2/7.8 mmol/L (130/140 mg/dL; the specific FPG target is according to country-specific recommendations).\textsuperscript{41}

Basal-bolus (BB) and premixed insulin therapies that address fasting and postprandial glycaemia can be more efficacious than BI alone in providing glycaemic control. In Japan, BB therapy is introduced as initial injectable therapy for people with T2D with high plasma glucose levels in an attempt to gain rapid glycaemic control and relieve glucose toxicity.\textsuperscript{42,43} However, BB therapy is complex, often requiring hospital admission for initiation. Moreover, because of the associated risk of hypoglycaemia and weight gain,\textsuperscript{44,45} BB therapy is difficult for most people with T2D to maintain outside of hospitals without ongoing medical support, resulting in de-escalation of therapy in many cases. In the JDDM 43 retrospective cohort study, among Japanese people with T2D who had intensified BI with BB or premixed therapy, mean HbA1c was 8.2% after 17 months;\textsuperscript{46} therefore, insulin intensification with such therapies is not sufficient to provide glycaemic control in many people with T2D.

Minimizing hypoglycaemia during insulin-based therapy is a critical component of diabetes care as all degrees of hypoglycaemia can have a negative impact on therapy adherence, overall diabetes control, and well-being. Furthermore, hypoglycaemia is associated with a wide range of adverse clinical outcomes, including cardiovascular diseases,\textsuperscript{47,48} cognitive decline\textsuperscript{49,50} and cardiac arrhythmia.\textsuperscript{51–53} It is possible that the problems with insulin treatment, most notably hypoglycaemia, along with the emergence of new therapeutic options, account for the decline in the proportion of people with T2D on insulin-based therapy in the past 10 years in Japan (from 23.2% in 2008 to 16.7% in 2018).\textsuperscript{4}

### 2 FIXED-RATIO COMBINATIONS OF BI AND GLP-1RAS

Titratable, fixed-ratio combinations (FRCs) of BI and GLP-1RAs allow administration of both components as a single, once-daily injection. FRCs provide people with T2D with a therapeutic option that reduces the injection burden of separate administration and allows accelerated escalation of treatment through the simultaneous up-titration of these complementary therapies delivered as a single therapeutic intervention.

The optimal ratio of GLP-1RA to BI may differ across ethnicities because of differences in insulin resistance and insulin dose requirements. In the United States and the European Union (EU), two FRCs are available, IDegLira [insulin degludec 100 U/mL and lixisenatide; 1 unit (U):0.036 mg ratio]\textsuperscript{54,55} and iGlarLixi [insulin glargine 100 U/mL (iGlar) and lixisenatide (Lixi); 2 U:1 μg (EU) and 3 U:1 μg ratios (United States and the EU)].\textsuperscript{56,57} These dose ratios drive relatively high doses of insulin to achieve effective doses of the GLP-1RA, and reflect the relatively high insulin needs of people with T2D in the United States and EU. Indeed, in phase 3 trials of IDegLira and iGlarLixi in global studies, the mean insulin doses administered were 38 to 47 U in the FRC arms.\textsuperscript{58–61}

In 2019 IDegLira was approved in Japan at the same dose ratio as approved in the United States and EU; up to 50 U of insulin degludec can be administered using IDegLira, delivering the maximum dose of liraglutide (1.8 mg) licensed in Japan.\textsuperscript{62} iGlarLixi was approved in 2020 in Japan at a dose ratio that is different from those approved in the United States and EU. The Japanese formulation contains iGlar and Lixi at a ratio of 1 U to 1 μg, which aims to correspond to the relatively low insulin needs of the Japanese population. In the ALOHA-2 study, the mean final insulin dose was 10.1 U/d (24 weeks following insulin initiation), and 97.3% of study participants received a mean insulin dose of 20 U/d or less during the study.\textsuperscript{37} The maximum dose of Lixi licensed in Japan is 20 μg;\textsuperscript{63} therefore, the maximum dose of GLP-1RA occurs at an insulin dose of 20 U, which was expected to be appropriate for the majority of Japanese people with T2D.
3 | OVERVIEW OF THE JAPANESE PHASE 3 TRIALS OF IGLARLIXI (LIXILAN JP) AND IDEGLIRA (DUAL JAPAN)

3.1 | DUAL Japan

Two phase 3 trials of IDegLira were conducted in Japan: DUAL I Japan and DUAL II Japan. DUAL I Japan was a 52-week, open-label, randomized, three-arm, parallel-group, multicentre trial that evaluated the efficacy and safety of IDegLira versus each of its components, insulin degludec and liraglutide, in people with T2D uncontrolled on one OAD.64 DUAL II Japan was a 26-week, double-blind, randomized, two-arm, parallel-group, multicentre trial of IDegLira versus insulin degludec, both in combination with metformin, in people with T2D uncontrolled on BI or premixed/combination insulin and metformin with or without another OAD (Table 1).68

Mean baseline HbA1c levels were 67.4 to 69.7 mmol/mol (8.3%–8.5%) in DUAL I Japan and 70.3 mmol/mol (8.6%) in DUAL II Japan.64,68 In both trials, IDegLira demonstrated significantly greater HbA1c reductions compared with comparators, insulin degludec and

| TABLE 1 | Study populations and designs of phase 3 trials of iGlarLixi and IDegLira in Japan |
|---|---|
| **LixiLan JP** | **DUAL Japan** |
| Study population | O1, O2: People with T2D inadequately controlled on one or two OADs\(^a\)  
L: People with T2D inadequately controlled on BI and one or two OADs | I: People with T2D inadequately controlled on one OAD  
II: People with T2D inadequately controlled on basal or premixed/combination insulin in combination with metformin with or without another OAD |
| Permitted pre-trial OADs | O1: Metformin, SUs, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, α-GIs, glinides  
O2: Metformin, SUs, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, α-GI, glinide | I: Metformin, SUs, TZDs, SGLT2 inhibitors, α-Gis, glinides  
II: Metformin + one OAD, SUs, TZDs, SGLT2 inhibitors, α-GI, glinides |
| Inclusion criteria | O1: HbA1c 58–86 mmol/mol (7.5%–10%); FPG ≤13.8 mmol/L (≤250 mg/dL)  
O2: HbA1c 58–80 mmol/mol (7.5%–9.5%); FPG ≤10.0 mmol/L (≤180 mg/dL)  
L: HbA1c 58–80 mmol/mol (7.5%–9.5%); FPG ≤10.0 mmol/L (≤180 mg/dL) at screening; SMPG 5.6 mmol/L (≤10.0 mmol/L) at run-in; mean iGlar dose at run-in ≤5 U and < 15 U | I: HbA1c 53–97 mmol/mol (7.0%–11.0%), 50% subjects to have HbA1c >67.2 mmol/mol (>8.3%); BMI ≥20 kg/m\(^2\)  
II: HbA1c 58–97 mmol/mol (7.5%–11%); BMI ≥23 kg/m\(^2\) |
| FRC arm | O1, O2: iGlarLixi + pre-trial OAD\(^b\)  
L: iGlarLixi + metformin\(^c\) | I: IDegLira + pre-trial OAD  
II: IDegLira + metformin\(^d\) |
| Comparator arm | O1: Lixisenatide + pre-trial OAD\(^p\)  
O2: iGlar + pre-trial OAD\(^p\)  
L: iGlar + metformin\(^e\) | I: Liraglutide + pre-trial OAD; insulin degludec + pre-trial OAD  
II: Insulin degludec + metformin\(^8\) |
| Study duration | 26 weeks of treatment (+26-week safety extension for JP-O1 only; 12-weeks run-in for JP-L only) | I: 52 weeks of treatment +1 week of follow-up  
II: 26 weeks of treatment +1 week of follow-up |
| Titration targets | O1, O2: SMPG 4.4–5.6 mmol/L (80–100 mg/dL)  
Dose cap at 20 U/20 μg (iGlarLixi), 20 U (iGlar)  
L: SMPG 4.4–5.6 mmol/L (80–100 mg/dL)  
Dose cap at 20 U/20 μg (iGlarLixi), 20 U (iGlar) | I: FPG 4.0–5.0 mmol/L (72–90 mg/dL)  
Dose cap at 50 dose steps for IDegLira, none for insulin degludec  
II: FPG 4.0–5.0 mmol/L (72–90 mg/dL)  
Dose cap at 50 dose steps for IDegLira, 50 U for insulin degludec |
| Definitions of hypoglycaemia | Severe hypoglycaemia (requiring assistance); Documented symptomatic hypoglycaemia (plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) | Severe (according to ADA classification) or blood glucose confirmed (<3.1 mmol/L [≤56 mg/dL]) hypoglycaemia; Severe (according to ADA classification) or blood glucose confirmed (<3.1 mmol/L [≤56 mg/dL]) symptomatic hypoglycaemia |

Abbreviations: ADA, American Diabetes Association; α-GI, alpha-glucosidase inhibitor; BI, basal insulin; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; FRC, fixed-ratio combination; HbA1c, glycated haemoglobin; iGlarLixi, insulin degludec plus liraglutide; iGlar, insulin glargine; iGlarLixi, insulin glargine plus lixisenatide; OAD, oral antidiabetic drug; SGLT2, sodium-glucose co-transporter-2; SMPG, self-measured plasma glucose; SU, sulphonylurea; T2D, type 2 diabetes; TZD, thiazolidinediones.

\(^a\)Any DPP-4 inhibitors were discontinued at randomization.

\(^b\)Metformin was to be continued or initiated as mandatory background therapy, and all other OADs were stopped.

\(^c\)For JP-O2, in case of use of DPP-4 inhibitors, participants could receive up to three OADs.

\(^d\)OAD other than metformin was discontinued at randomization.
**TABLE 2**  Key outcomes from phase 3 trials of iGlarLixi and IDegLira in Japan\(^{64–68,70}\)

| Inadequately controlled on OAD | Inadequately controlled on BI + OAD |
|-------------------------------|-----------------------------------|
| **LixiLan JP-O1 (26/52 weeks)** | **LixiLan JP-O2 (26 weeks)** | **DUAL Japan I (52 weeks)** | **LixiLan JP-L (26 weeks)** | **DUAL Japan II (26 weeks)** |
| iGlarLixi (n = 161) | iGlarLixi (n = 260) | IDegLira (n = 275) | iGlarLixi (n = 255) | IDegLira (n = 105) |
| Mean baseline age, years | 58.3 | 59.2 | 56.9 | 59.4 | 56.6 |
| Mean baseline BMI kg/m\(^2\) | 26.79 | 26.20 | 26.1 | 25.32 | 27.3 |
| Start dose: insulin/GLP-1RA | 5 U/5 \(\mu\)g | 5 U/5 \(\mu\)g | 10 U degludec/3.6 mg liraglutide\(^a\) | \(\geq\) 5 U/5 \(\mu\)g and \(\leq\) 10 U/10 \(\mu\)g\(^b\) | 10 U degludec/3.6 mg liraglutide\(^a\) |
| Mean final dose of insulin (FRC) | 16.69 U (26 weeks), 17.01 U (52 weeks) | 15.10 U | 27.7 dose steps\(^d\) | 16.78 U | 37.6 U |
| Mean final dose of insulin (comparator) | | 17.30 U | 34.8 dose steps\(^d\) | 17.03 U | 41.2 U |
| Mean baseline HbA1c, % | 8.39 | 8.08 | 8.5 | 8.25 | 8.61 |
| Mean HbA1c at study end, mmol/mol | 43.1 | 49.3 | 70.5 | 41.2 |
| Mean HbA1c at study end, % | 6.73 | 6.66 | 6.10 | 7.05 | 6.66 |
| Mean change in HbA1c from baseline to study end, % | LS mean –1.58 (26 weeks) | LS mean –1.40 (26 weeks) | –26.5 | LS mean –1.27 (26 weeks) | –1.95 |
| Difference in HbA1c change between FRC and comparator | LS mean difference –1.07% vs. Lixi (26 weeks) | LS mean difference –0.63% | Estimated treatment difference –6.91 mmol/mol (–0.63%) vs. IDeg –5.30 mmol/mol (–0.48%) vs. liraglutide | LS mean difference –0.74% vs. iGlar | Estimated treatment difference –13.98 mmol/mol (–1.28%) vs. IDeg |
| Percentage of participants with HbA1c <53 mmol/mol (<7%) at study end | 65.2 (26 weeks) | 71.5 | 89.1 | 51.8 | 71.4 |
| FPG at baseline, mmol/L | 9.83 | 8.71 | 9.9 | 7.75 | 8.95 |
| Mean change in FPG from baseline, mmol/L | –2.38 | –1.77 | –4.1 | –0.81 | –2.8 |
| Change in mean body weight, kg | +0.62 | LS mean + 0.26 | +2.9 | LS mean –0.51 | –0.7 |
| Difference in body weight change between FRC and comparator, kg | LS mean difference + 1.94 vs. Lixi (26 weeks) | LS mean difference –1.06 vs. iGlar | Estimated treatment difference –1.19 vs. IDeg; +3.89 vs. liraglutide | LS mean difference –1.05 vs. iGlar | Estimated treatment difference –1.41 vs. IDeg |
| Percentage of participants with GI AE | Nausea 14.9, diarrhoea 8.1, vomiting 6.2, constipation 2.5 (52 weeks) | Nausea 9.6 | Nausea 3.3, diarrhoea 5.5, constipation 9.8 | Nausea 16.9, diarrhoea 5.1, vomiting 6.6, constipation 8.6 | Nausea 9.5, diarrhoea 14.3, vomiting 8.6, constipation 8.6 |
| Documented symptomatic hypoglycaemia [plasma glucose ≤3.9 mmol/L (≤70 mg/dL)] | 18.0, 0.80 events per patient-year (52 weeks) | 14.2, 0.73 events per patient-year | NR | 18.8, 1.64 events per patient-year | NR |
| Severe (according to ADA classification) or blood glucose-confirmed (<3.1 mmol/L [<56 mg/dL]) symptomatic hypoglycaemia | NR | NR | 19.3%, 50.4 events per 100 patient-years | NR | 14.3%, 95.80 events per 100 patient-years |
liraglutide in DUAL I Japan and insulin degludec in DUAL II Japan (Table 2). In DUAL I Japan, mean changes in HbA1c from baseline with IDegLira were −26.5 mmol/mol (−2.42%) versus −19.7 mmol/mol (−1.80%) with insulin degludec and −19.6 mmol/mol (−1.80%) with liraglutide after 52 weeks of treatment (P < 0.0001 for both). In DUAL II Japan, mean changes in HbA1c from baseline were also significantly greater with IDegLira: −21.3 mmol/mol (−1.95%) versus −7.1 mmol/mol (−0.65%) with insulin degludec after 26 weeks of treatment (P < 0.0001).64,68 At study end, the proportions of participants achieving HbA1c <53 mmol/mol (<7%) with IDegLira were 89.1% (vs. 69.7% with insulin degludec and 76.2% with liraglutide) in DUAL I Japan and 71.4% (vs. 21.9% with insulin degludec) in DUAL II Japan.68,70

The incidence of severe or blood glucose−confirmed [<3.1 mmol/L (<56 mg/dL)] hypoglycaemia was lower with IDegLira versus insulin degludec: 38.5% versus 54.6% over 52 weeks in DUAL I Japan and 28.6% versus 30.5% over 26 weeks in DUAL II Japan, respectively. Incidences of severe or blood glucose−confirmed [<3.1 mmol/L (<56 mg/dL)] symptomatic hypoglycaemia were also lower with IDegLira versus insulin degludec: 19.3% versus 29.5% over 52 weeks in DUAL I Japan and 14.3% versus 17.1% over 26 weeks in DUAL II Japan, respectively. Mean changes in body weight with IDegLira were lower than with insulin degludec (+2.9 kg vs. +4.1 kg in DUAL I Japan and −0.7 kg vs. +0.7 kg in DUAL II Japan).64,68 The incidences of GI adverse events (AEs) were lower with IDegLira (34.9%) versus liraglutide (41.8%) in DUAL I Japan.64,68 The mean daily insulin doses at study end were lower for IDegLira than for insulin degludec: 27.7 U vs. 34.8 U in DUAL I Japan and 37.6 U vs. 41.2 U in DUAL II Japan.64,68

Outcomes with IDegLira treatment were also better than with iDeg in the equivalent global DUAL I60 and DUAL II61 trials with respect to reductions in HbA1c, changes in weight, and incidences of severe or blood glucose−confirmed hypoglycaemia. The final insulin doses were higher in these global populations than in Japanese patients in DUAL I and II Japan (−40% and 20%, respectively).

Changes in weight associated with IDegLira also differed in the global compared with the Japanese studies. Modest weight loss in DUAL I contrasted with weight gain in DUAL I Japan60,64; weight losses in DUAL I were greater than in DUAL II Japan.61,68 These findings were attributed to differences in the OAD background and/or ethnic differences in diabetes pathology (DUAL I) and the lower BMI of Japanese patients (DUAL II). Similar to the safety findings in Japanese patients, IDegLira in a global population was associated with lower frequencies of GI AEs than liraglutide.

### TABLE 2

| Inadequately controlled on OAD | Inadequately controlled on BI + OAD |
|-------------------------------|-----------------------------------|
| **LixiLan JP-O1 (26/52 weeks)** | **LixiLan JP-O2 (26 weeks)** | **DUAL Japan I (52 weeks)** | **LixiLan JP-L (26 weeks)** | **DUAL Japan II (26 weeks)** |
| Severe (according to ADA classification) or blood glucose−confirmed [<56 mg/dL (3.1 mmol/L)] hypoglycaemia | NR | NR | 38.5%, 174.3 events per 100 patient-years | NR | 28.6%, 228.45 events per 100 patient-years |

**Abbreviations:** ADA, American Diabetes Association; AE, adverse event; BI, basal insulin; BMI, body mass index; FRC, fixed-ratio combination; GI, gastrointestinal; HbA1c, glycated haemoglobin; IDeg, insulin degludec; IDegLira, insulin degludec plus liraglutide; iGlar, insulin glargine; iGlarLixi, insulin glargine plus lixisenatide; Lixi, lixisenatide; LS, least squares; NR, not reported; OAD, oral antidiabetic drug.

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**3.2 LixiLan JP**

Three phase 3 studies of iGlarLixi have been conducted in Japan [LixiLan JP-O1 (NCT02749890),66 -O2 (NCT02752828)67 and -L (NCT02752412)]65. All three trials were open-label, randomized, active-controlled, parallel-group, multicentre studies evaluating the efficacy and safety of iGlarLixi versus Lixi or iGlar (Table 1). LixiLan JP-O1 and -O2 evaluated iGlarLixi in people with T2D inadequately controlled on one or two OADs (vs. Lixi in JP-O1 and iGlar in JP-O2).65,67 LixiLan JP-L evaluated iGlarLixi versus iGlar in people with T2D inadequately controlled on BI (<15 U) and one or two OADs; this study also included a 12-week run-in period before randomization, during which study participants switched to or continued on iGlar treatment with dose titration to maintain acceptable glycaemic control, and continued or initiated metformin as mandatory background therapy and discontinued all other previously taken OADs. The primary endpoint for all three studies was HbA1c change from baseline after 26 weeks of treatment.

The three studies met their primary endpoint of significantly greater reduction in HbA1c from baseline to week 26 with iGlarLixi versus comparator [Lixi or iGlar; P < 0.0001 for all (Table 2)].65-67 Mean baseline HbA1c levels for each study population were 8.4% (JP-O1), 8.0% (JP-O2) and 8.3% (JP-L).65-67 Least squares (LS) mean HbA1c reductions were −1.58% (iGlarLixi) versus −0.51% (Lixi) in JP-O1, −1.40% (iGlarLixi) versus −0.76% (iGlar) in JP-O2, and −1.27% (iGlarLixi) versus −0.53% (iGlar) in JP-L.65 Furthermore, significantly greater proportions of participants achieved HbA1c <53 mmol/mol (<7%) with iGlarLixi (65.2% in JP-O1; 71.5% in JP-O2;
51.8% in JP-L) versus Lixi (19.4% in JP-O1) or iGlar (38.5% in JP-O1; 16.0% in JP-L; \(P < 0.0001\) for all studies).\(^{65-67}\) In JP-O1, HbA1c reductions with iGlarLixi were sustained over the 26-week extension period (up to week 52).\(^{66}\)

Incidence of documented symptomatic hypoglycaemia ([≤ 3.9 mmol/L (≤ 70 mg/dL)] were comparable between the iGlarLixi and iGlar groups (14.2% vs. 12.3% in JP-O2; 18.8% vs. 16.7% in JP-L over 26 weeks) despite greater HbA1c reductions with iGlarLixi.\(^{65,67}\)

No severe hypoglycaemia events were reported with iGlarLixi.\(^{65-67}\) iGlarLixi mitigated the weight gain induced by iGlar; while iGlar led to LS mean body weight increases from baseline of +1.33 kg in JP-O2 and +0.55 kg in JP-L, LS mean weight changes with iGlarLixi were +0.26 kg and −0.51 kg, respectively.\(^{65,67}\) In JP-O1, the incidence of GI AEs was lower with iGlarLixi versus Lixi (36.0% vs. 50.0%), which may be attributed to the FRC formulation, which allowed a lower initial dose of Lixi and gradual titration of both components.\(^{66}\) In participants treated with iGlarLixi, mean daily insulin doses at week 26 were 16.7 U in JP-O1, 15.1 U in JP-O2 and 16.8 U in JP-L, which were lower than for the iGlar comparators (17.3 U and 17.0 U, respectively).\(^{65-67}\)

Overall, these efficacy and safety findings are consistent with those from the equivalent global trials (LixiLan-O and LixiLan-L) of iGlarLixi 2 U:1 μg and 3 U:1 mg, in which final mean insulin doses (week 30) were more than double those in the Japanese studies.\(^{58,59}\) In these global trials, compared with iGlar, iGlarLixi treatment resulted in significantly greater reductions in HbA1c (the primary endpoints), similar incidences of documented symptomatic hypoglycaemia and favourable changes in weight (modest reductions vs. gains). Global populations were also similar to Japanese populations in having a lower frequency of GI events associated with LixiLan compared with Lixi. A post hoc analysis of the LixiLan-O trial showed that incremental HbA1c reduction was dependent on baseline HbA1c. In the subpopulation of patients with baseline HbA1c ≥9%, the mean decrease in HbA1c with iGlarLixi was 2.9%, and was 1.5% in the subpopulation with baseline HbA1c ≥53 mmol/mol (≥7%) and ≤9%. In this study population of difficult-to-treat patients receiving two OADs at screening, iGlarLixi was able to achieve a target HbA1c of 53 mmol/mol (7%) or lower in 72.4% of the cohort with a mean HbA1c of 6.6%.\(^{71}\)

### 3.3 Differences between the two phase 3 study designs

There are no direct head-to-head comparisons of iGlarLixi and IDegLira. Differences in study design, as outlined in Table 1, limit any indirect comparison between the study programmes. They also potentially confound any attribution of differences in study outcomes to the different characteristics of each type of insulin and GLP-1RA in the two FRCs. Real-world data not subject to the restrictions of a randomized controlled trial will be needed to provide insights into the relative effectiveness of the FRCs. It should be noted, however, that the components of the FRCs are different and these differences and other factors (study design, patient characteristics, etc.) may well give rise to differences in patterns of control of glycaemic profile. Continuous glucose monitoring studies would be interesting to determine if any clinically significant difference in glycaemic variability can be seen.

In addition, target FPG for titration was lower in the DUAL Japan trials [4.0–5.0 mmol/L (72–90 mg/dL)] compared with LixiLan JP trials [4.4–5.6 mmol/L (80–100 mg/dL)].\(^{65-67}\) Records of the FPG achieved in these studies are not available; however, the change in fasting blood glucose from baseline is shown in Table 2 (−2.38 mmol/L in JP-O1, −1.77 mmol/L in JP-O2, −4.1 mmol/L in DUAL I, −0.8 mmol/L in JP-L, and −2.8 mmol/L in DUAL II). The difference in incremental change supports the argument that more aggressive glucose-lowering was achieved in the DUAL JP studies compared with the LixiLan JP studies. In treat-to-target trials, lower FPG targets drive higher doses of insulin and greater HbA1c reduction, but can be complicated by higher rates of hypoglycaemia. In the DUAL Japan clinical trials and LixiLan JP trials, the respective mean doses of IDegLira (27.7 U and 37.6 U)\(^{64,68}\) were higher than those of iGlarLixi (15.1 U to 16.8 U),\(^{65-67}\) and the mean HbA1c reduction was also higher with IDegLira (−2.42% and −1.95%)\(^{64,68}\) compared with iGlarLixi (−1.27% to −1.58%).\(^{65-67}\)

In the LixiLan JP-O2 and JP-L trials, the incidence of symptomatic hypoglycaemia was similar between both treatment groups; similarly, there was no difference between IDegLira or degludec in severe or blood glucose-confirmed hypoglycaemic episodes or severe or blood glucose-confirmed symptomatic hypoglycaemic episodes in the DUAL II trial, but significantly fewer severe or blood glucose-confirmed hypoglycaemic episodes with IDegLira compared with degludec were seen in DUAL I. Indirect comparison between LixiLan JP and DUAL Japan trials of the data on hypoglycaemia is problematic and should be performed with caution. The comparison of hypoglycaemia between trials is complicated by the differences in the definitions used to report hypoglycaemia events in LixiLan JP and DUAL Japan. The LixiLan JP studies reported severe (defined as requiring assistance) hypoglycaemia and documented symptomatic hypoglycaemia with a plasma glucose ≤3.9 mmol/L (≤70 mg/dL). The DUAL Japan studies reported severe (defined according to ADA classifications) or blood glucose-confirmed [plasma glucose <3.1 mmol/L (<56 mg/dL)] hypoglycaemia, and severe (defined according to ADA classifications) or blood glucose-confirmed [plasma glucose <3.1 mmol/L (<56 mg/dL)] symptomatic hypoglycaemia. Given that the DUAL definitions of severe hypoglycaemia were more stringent than those for the LixiLan JP studies, the findings suggest that hypoglycaemia events were less severe for iGlarLixi compared with IDegLira. Notably, hypoglycaemia risk is related to insulin dose. In the ONCE Asia trial, which compared insulin degludec with insulin glargine 100 U/mL (or iGlar) over 26 weeks, the final mean dose for iGlar was significantly higher than for insulin degludec and this was consistent with its higher overall rate of hypoglycaemia.\(^{72}\)
4 | THERAPEUTIC POSSIBILITIES OF THE FRC CLASS IN JAPAN

4.1 | Therapeutic possibilities of the FRC class

According to the 2018 ADA/EASD consensus guidelines, an initial injectable combination with a GLP-1RA and BI can be considered for people with high HbA1c (>86 mmol/mol (>10%)) and/or 23 mmol/mol (2%) above target. These guidelines support the use of FRCs for combination therapy.

The efficacy and safety of iGlarLixi and IDegLira have been demonstrated in the global LixiLan and DUAL trial programmes. Head-to-head studies comparing FRCs versus the sequential addition of the components are not available. However, a propensity-score matching analysis has been conducted to compare indirectly the efficacy of iGlarLixi (formulated as 2 U:1 μg and 3 U:1 μg of iGlar 100 U/mL and Lixi) versus the sequential administration of iGlar and Lixi. This analysis suggested that simultaneous treatment of BI and a GLP-1RA in an FRC was more effective in reducing HbA1c than the two components administered sequentially. Furthermore, FRCs allow the initiation of GLP-1RA therapy at lower doses and can provide more gradual titration than GLP-1RAs administered alone. GI AEs, such as nausea and vomiting, which are associated with GLP-1RAs, may be mitigated with GLP-1RA therapy at lower doses and can provide more gradual titration of the components and moves away from personalized therapy emphasized in the JDS guidelines. However, FRCs allow titration based on the fasting plasma glucose level of the individual, with the added benefit of the simplicity of a single injection and titration that provides gradual simultaneous titration of the component drugs and could reduce potential adverse effects, while providing the dose of both insulin and a GLP-1RA to deliver optimum control to the individual patient. Treatment with iGlarLixi has also been shown to allow more people with T2D to reach glycaemic control at earlier timepoints compared with iGlar alone, with similar hypoglycaemia outcomes. Relative ease of dosing, coupled with the observation that FRCs offer a highly effective therapy for reducing HbA1c and rapidly bring the majority of people with T2D within glycaemic targets with a low risk hypoglycaemia, should be compelling.

In the real-world clinical setting, lack of physician’s time and resources for T2D management pose a barrier to optimal therapy intensification. Even though it is well established that people with poor glycaemic control are at an increased risk of diabetic complications, currently, initiation of insulin therapy tends to be delayed, and therapy is not sufficiently intensified despite the individual not achieving HbA1c goals. The high HbA1c and long duration of diabetes at baseline in Japanese people who initiated insulin therapy suggest that delaying treatment with insulin is prevalent in clinical practice in Japan. Intensive therapies such as BB therapy are complex and lead to a high risk of hypoglycaemia, making this a less attractive option for many people with T2D and for physicians.

Fixed-ratio combinations may help clinicians and people with T2D to overcome the barriers associated with therapy intensification and provide an innovative alternative treatment option for Japanese people with T2D (Table 3). FRCs have the potential to allow people with T2D to be treated more effectively, and help more people to achieve their glycaemic targets. It will be important to assess the real-world efficacy of FRCs in Japan; no such data are yet available owing to the only very recent approval of IDegLira (September 2019) and iGlarLixi (March 2020) in Japan.

5 | CONCLUSION

There is compelling evidence from global and Japanese clinical trials demonstrating that FRCs of GLP-1RAs and BI are highly effective at reducing HbA1c in people with T2D inadequately controlled on OADs or BI and OADs. These benefits on glycaemic control come without an increased risk of hypoglycaemia or weight gain compared with BI.
### TABLE 3
Advantages and disadvantages of fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonists

| Advantages | Disadvantages |
|------------|---------------|
| • Co-administration of two components in a single once-daily injection | • Uncertainty whether the fixed ratio is optimal for each individual |
| • Greater reduction in HbA1c (compared with each component alone) | • No option to adjust dose of a single component as needed |
| • No increased hypoglycaemic risk compared with BI alone | |
| • Mitigated weight gain (compared with BI alone) | |
| • Mitigated gastrointestinal symptoms due to gradual dose increment (compared with GLP-1RA alone) | |

Abbreviations: BI, basal insulin; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin.

The simultaneous administration of these components is not only associated with greater HbA1c reduction, but also has the potential to reduce the treatment burden associated with sequential or more complicated treatment regimens. This treatment simplicity may facilitate treatment adherence.

One key distinction between iGlarLixi and IDegLira is that the formulation of the former takes into account the lower insulin requirements of this patient population, allowing the maximal GLP-1RA dose (20 μg) to be reached at a lower and more commonly used dose of insulin. Therefore, the two FRCs need to be selected appropriately based on the requirements of BI and the risk of hypoglycaemia. Collectively, FRCs offer a simple, effective and tolerable treatment option, with the potential to address the need for glycaemic control in Japanese people with T2D.

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### AUTHOR CONTRIBUTIONS
M.B. and H.K. contributed to the review design. All authors contributed to writing of the manuscript.

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