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ORIGINAL ARTICLE

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iGlarLixi (insulin glargine 100 U/ml plus lixisenatide) is effective and well tolerated in people with uncontrolled type 2 diabetes regardless of age: A REALI pooled analysis of prospective real-world data

Cristian Guja MD[1] | János Tibor Kis MD[2] | Martin Haluzík MD[3] | Mireille Bonnemaire MD[4] | Gregory Bigot MSc[5] | Mathilde Tournay MSc[6] | Nick Freemantle PhD[7] | Jochen Seufert MD[8]

[1]Department of Diabetes, Nutrition and Metabolic Disease, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

[2]Department of Internal Medicine Centrum, Szent János Hospital, Budapest, Hungary

[3]Institute for Clinical and Experimental Medicine and Charles University, Prague, Czech Republic

[4]General Medicines, Sanofi, Paris, France

[5]IVIDATA, Paris, France

[6]International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium

[7]Institute of Clinical Trials and Methodology, University College London, London, UK

[8]Division of Endocrinology and Diabetology, Department of Internal Medicine II, Medical Centre – Faculty of Medicine, University of Freiburg, Freiburg, Germany

Correspondence
Mireille Bonnemaire, MD, General Medicines, Sanofi, Paris, France.
Email: mireille.bonnemaire@sanofi.com

Funding information
Sanofi

Abstract

Aim: To evaluate the effectiveness and safety in routine clinical practice of insulin glargine/lixisenatide (iGlarLixi) in people with type 2 diabetes (T2D) according to age.

Methods: Patient-level data were pooled from 1316 adults with T2D inadequately controlled on oral antidiabetic drugs with or without basal insulin who initiated iGlarLixi for 24 weeks. Participants were classified into age subgroups of younger than 65 years (N = 806) and 65 years or older (N = 510).

Results: Compared with participants aged younger than 65 years, those aged 65 years or older had a numerically lower mean body mass index (31.6 vs. 32.6 kg/m^2), a longer median diabetes duration (11.0 vs. 8.0 years), were more likely to receive prior basal insulin (48.4% vs. 43.5%) and had a lower mean HbA1c (8.93% [74.10 mmol/mol] vs. 9.22% [77.28 mmol/mol]). Similar and clinically relevant reductions in HbA1c and fasting plasma glucose from baseline to week 24 of iGlarLixi therapy were observed regardless of age. At 24 weeks, least-squares adjusted mean (95% confidence interval [CI]) change in HbA1c from baseline was −1.55% (−1.65% to −1.44%) in those aged 65 years or older and −1.42% (−1.50% to −1.33%) in those aged younger than 65 years (95% CI: −0.26% to 0.00%; P = .058 between subgroups). Low incidences of gastrointestinal adverse events and hypoglycaemic episodes were reported in both age subgroups. iGlarLixi decreased mean body weight from baseline to week 24 in both subgroups (−1.6 kg in those aged ≥ 65 years and −2.0 kg in those aged < 65 years).

Conclusions: iGlarLixi is effective and well tolerated in both younger and older people with uncontrolled T2D.

KEYWORDS
age, elderly, fixed-ratio combination, iGlarLixi, insulin glargine, lixisenatide, real-world data, type 2 diabetes

1 | INTRODUCTION

Management of type 2 diabetes (T2D) in older adults is challenging because of the presence of co-morbidities and polypharmacy, a reduced functional status and increased disability, as well as an increased risk of hypoglycaemia.[1-3] Avoiding excessive weight loss is also important in the elderly to prevent accelerated muscle wasting and frailty.[4] Hence, older adults with T2D can especially benefit from simple but effective treatment regimens with a low risk of hypoglycaemia, associated with slight weight loss.

Insulin glargine/lixisenatide (iGlarLixi) is a titratable, fixed-ratio combination of insulin glargine 100 U/ml (iGlar) and the short-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) lixisenatide (Lixi). The rationale for the combination of iGlar with Lixi is based on the complementary effects of the two agents and on the potential for mitigating side effects and barriers to their individual use. iGlar improves fasting plasma glucose (FPG), and Lixi decreases postprandial glycaemia without increasing hypoglycaemia risk and may attenuate the risk of weight gain experienced with basal insulin (BI) alone. In addition, the gastrointestinal side effect profile that is typically observed with GLP-1RAs can be potentially mitigated by the gradual Lixi dose increments that follow iGlarLixi titration.[5]

The efficacy and safety of iGlarLixi in people with inadequately controlled T2D have been consistently shown in several large randomized controlled trials (RCTs).[6-10] There remains, however, a need to evaluate the effectiveness and safety of iGlarLixi in older people with T2D encountered in daily clinical practice. Indeed, there are currently only two published prospective studies, one from Hungary[11] and one from Romania,[12] examining the effectiveness and safety of iGlarLixi in routine clinical practice. By pooling data from the two aforementioned studies,[11,12] we sought to perform an age-specific evaluation of the real-world effectiveness and safety of iGlarLixi in older (≥ 65 years) and younger (< 65 years) people with uncontrolled T2D.

2 | METHODS

2.1 | Study design and participants

This analysis was conducted using pooled patient-level data from two 24-week, prospective, observational studies conducted in Europe,[11,12] which included adults up to 83 years of age with T2D inadequately controlled on oral antidiabetic drugs (OADs) with or without BI for at least 3 months. In both studies, the decision to initiate iGlarLixi treatment and the titration of iGlarLixi were kept at the discretion of the treating physician. iGlarLixi (Suliqua; Sanofi, Paris, France) was self-administered subcutaneously once daily within 1 hour prior to a meal for 24 weeks. In this subgroup analysis, participants were classified by age into those younger than 65 years and those aged 65 years or older. A further description of safety was performed in the latter group in those aged 65-69 years and those aged 70 years or older.

Both studies[11,12] were conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines and were approved by the relevant institutional review boards/ethics committees. All participants gave written informed consent prior to study inclusion, and all patient information was to be de-identified before data pooling. Consequently, no ethical approval was required for this pooled analysis.

2.2 | Outcomes

In each age subgroup, changes in HbA1c and FPG from baseline to weeks 12 and 24, as well as the percentages of patients achieving HbA1c targets at week 24 of iGlarLixi treatment, were determined. Safety outcomes included the incidence of hypoglycaemia and of gastrointestinal adverse events (AEs). Hypoglycaemic episodes were reported as numbers, percentages and event rates. The current subgroup analysis also evaluated changes in body weight and the iGlar dose provided by iGlarLixi (expressed in both U/d and in U/kg/d) from baseline to weeks 12 and 24.

2.3 | Statistical analysis

Effectiveness and safety analyses were performed on all included patients who received at least one iGlarLixi dose. The changes in HbA1c and FPG from baseline to weeks 12 and 24 of iGlarLixi treatment were analysed using a mixed model for repeated measures (MMRM) adjusted for baseline HbA1c and FPG, respectively. Based on this MMRM, which used an unstructured covariance matrix, we estimated the least-squares (LS) mean changes in HbA1c and FPG in the two age subgroups and the corresponding 95% confidence intervals (CIs). All other variables were assessed descriptively, with categorical variables presented as counts and percentages, and continuous variables as mean ± standard deviation or as median (quartile 1-quartile 3). No imputation of missing data and no adjustment for multiple testing were made. All statistical tests were two-sided, and *P* values were provided. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

3 | RESULTS

3.1 | Participants

A total of 1316 participants were included in this REALI pooled analysis, 1315 of whom (99.9%) received at least one iGlarLixi dose and were hence part of the effectiveness and safety analyses. Of the 1316 included participants, 806 (61.2%) were aged younger than 65 years and 510 (38.8%) were aged 65 years or older, including 286 aged 65-69 years and 224 aged 70 years or older. Demographic and baseline characteristics are reported in Table 1 and Table S1. Compared with participants aged younger than 65 years, those aged

TABLE 1 Baseline characteristics according to age

	Age < 65 y (N = 806)	Age ≥ 65 y (N = 510)	Total (N = 1316)
Age (y)			
Mean ± SD	55.4 ± 6.6	69.7 ± 4.0	61.0 ± 9.0
Median (Q1-Q3)	57.0 (51.0-61.0)	69.0 (67.0-72.0)	62.0 (55.0-67.0)
Women, n (%)	431 (53.5)	306 (60.0)	737 (56.0)
BMI (kg/m^2), mean ± SD	32.6 ± 5.8	31.6 ± 4.9	32.2 ± 5.5
BMI in categories (kg/m^2), n (%)			
< 30	277 (37.4)	211 (41.4)	488 (37.1)
≥ 30	529 (65.6)	299 (58.6)	828 (62.9)
Diabetes duration (y), median (Q1-Q3)	8.0 (4.0-12.0)	11.0 (6.0-16.0)	9.0 (5.0-13.0)
Prior use of BI, n (%)[a]	351 (43.5)	247 (48.4)	598 (45.4)
Insulin glargine	243 (69.2)	165 (66.8)	408 (68.2)
Insulin detemir	56 (16.0)	39 (15.8)	95 (15.9)
NPH insulin	51 (14.5)	42 (17.0)	93 (15.6)
Prior BI dose (U/d), mean ± SD	34.2 ± 13.4	32.9 ± 13.4	33.7 ± 13.4
Prior use of non-insulin glucose-lowering drugs, n (%)[b]	800 (99.3)	506 (99.2)	1306 (99.2)
Biguanides	792 (99.0)	495 (97.8)	1287 (98.5)
Sulphonylureas	241 (30.1)	166 (32.8)	407 (31.2)
DPP-4 inhibitors	80 (10.0)	76 (15.0)	156 (11.9)
SGLT-2 inhibitors	59 (7.4)	31 (6.1)	90 (6.9)
GLP-1 receptor agonists	4 (0.5)	3 (0.6)	7 (0.5)
Number of prior non-insulin drugs, n (%)[b]			
1	459 (57.4)	283 (55.9)	742 (56.8)
≥ 2	341 (42.6)	223 (44.1)	564 (43.2)
Patients with ≥ 1 diabetes complication, n (%)	384 (47.6)	284 (55.7)	668 (50.8)
Diabetic neuropathy	312 (38.7)	221 (43.3)	533 (40.5)
Diabetic retinopathy	111 (13.8)	92 (18.0)	203 (15.4)
Diabetic nephropathy	72 (8.9)	68 (13.3)	140 (10.6)
Patients with ≥ 1 CV risk factor or event, n (%)	496 (61.5)	319 (62.5)	815 (61.9)
Hypertension	418 (51.9)	290 (56.9)	708 (53.8)
Dyslipidaemia	415 (51.5)	267 (52.4)	682 (51.8)
Ischaemic heart disease	168 (20.8)	136 (26.7)	304 (23.1)
Peripheral arterial disease	93 (11.5)	72 (14.1)	165 (12.5)
Previous stroke	30 (3.7)	31 (6.1)	61 (4.6)
HbA1c (%; mmol/L), mean ± SD	9.22 ± 1.42; 77.31 ± 15.51	8.93 ± 1.29; 74.10 ± 14.04	9.11 ± 1.38; 76.06 ± 15.03
Fasting plasma glucose (mg/dl; mmol/L), mean ± SD	187.6 ± 54.3; 10.34 ± 2.99	179.7 ± 50.5; 9.90 ± 2.78	184.5 ± 53.0; 10.17 ± 2.91

Abbreviations: BI, basal insulin; BMI, body mass index; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NPH, neutral protamine Hagedorn; Q, quartile; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2.

[a]The total number of patients who were previously treated with BI in each group was used as the denominator to calculate the percentages of patients who received prior insulin glargine, detemir or NPH insulin.

[b]The total number of patients who were previously treated with non-insulin glucose-lowering drugs in each group was used as the denominator to calculate the percentages of patients in each drug class and the percentages of those receiving 1 or ≥ 2 glucose-lowering drugs.

65 years or older were more often women, had a slightly lower body mass index (BMI), a longer diabetes duration, were more probable to be previously treated with BI, and to exhibit diabetes complications and cardiovascular risk factors or events. Mean baseline HbA1c and FPG were both numerically lower in participants aged 65 years or older compared with those aged younger than 65 years. The types of

previously used OADs were overall similar across the two age subgroups. Except for biguanides, whose use remained stable during the 24-week observation period (administered in 99% of patients), there was a reduction in the use of all other OADs.

3.2 | Glycaemic control

Similar and clinically meaningful LS mean reductions in HbA1c from baseline to week 24 of iGlarLixi therapy were observed in the two age subgroups (Figure 1). At 24 weeks, the LS mean (95% CI) change in HbA1c from baseline was −1.55% (−1.65% to −1.44%) in the 65 years or older subgroup and −1.42% (−1.50% to −1.33%) in the younger than 65 years subgroup, corresponding to a non-significant between-group difference of −0.13% (95% CI: −0.26% to 0.00%; $P = .058$). Likewise, at 12 weeks, the LS mean (95% CI) change in HbA1c from baseline was −1.22% (−1.33% to −1.12%) in the 65 years or older subgroup and −1.16% (−1.25% to −1.08%) in the younger than 65 years subgroup, corresponding to a between-group difference of −0.06% (95% CI: −0.19% to 0.07%; $P = .373$).

Compared with those aged younger than 65 years, a numerically higher proportion of participants in the 65 years or older subgroup reached HbA1c levels of less than 7.0% at 24 weeks of iGlarLixi therapy (30.7% vs. 23.6%). The achievements of HbA1c targets of less

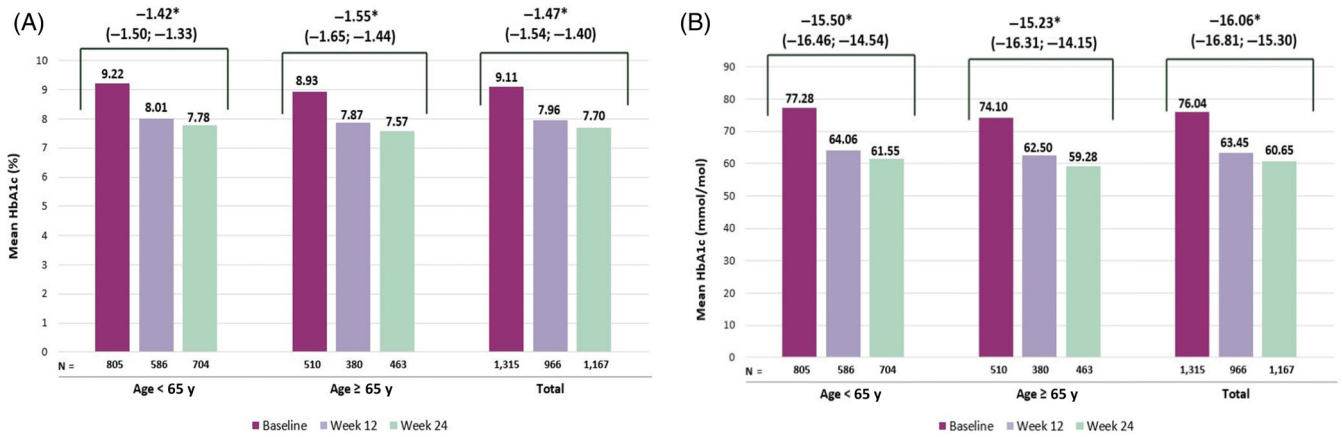

FIGURE 1 Observed mean HbA1c changes in A, %, and B, mmol/mol over the 24-week iGlarLixi treatment period. N refers to the number of patients with available data at each time point. *Corresponds to least-squares mean change (95% confidence interval) in HbA1c from baseline to week 24 derived from a mixed model for repeated measures

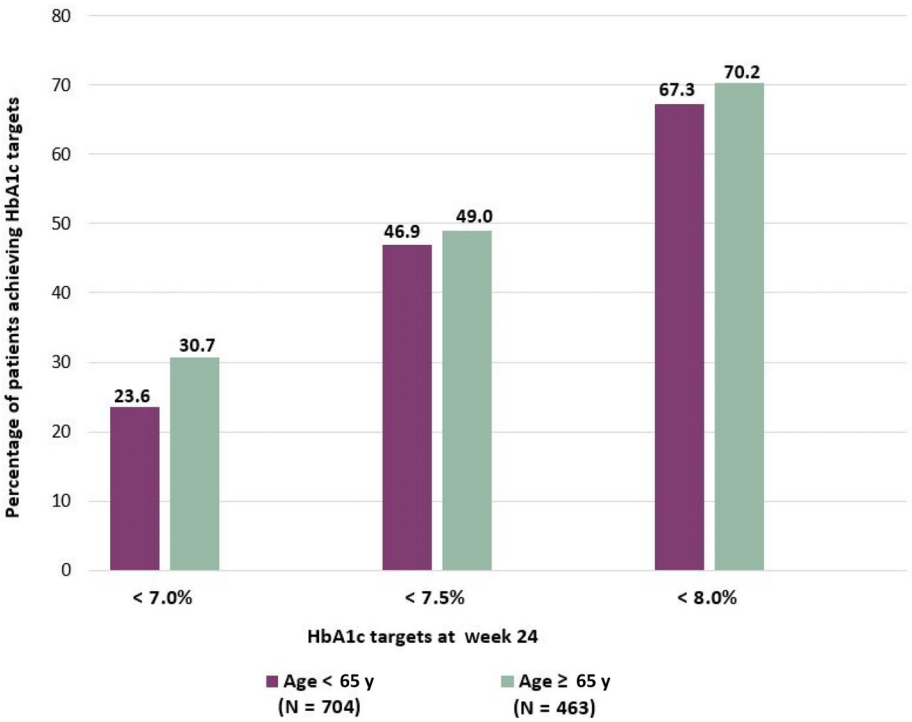

FIGURE 2 Percentage of patients achieving HbA1c targets at week 24 of iGlarLixi treatment. N refers to the number of patients with available data at week 24

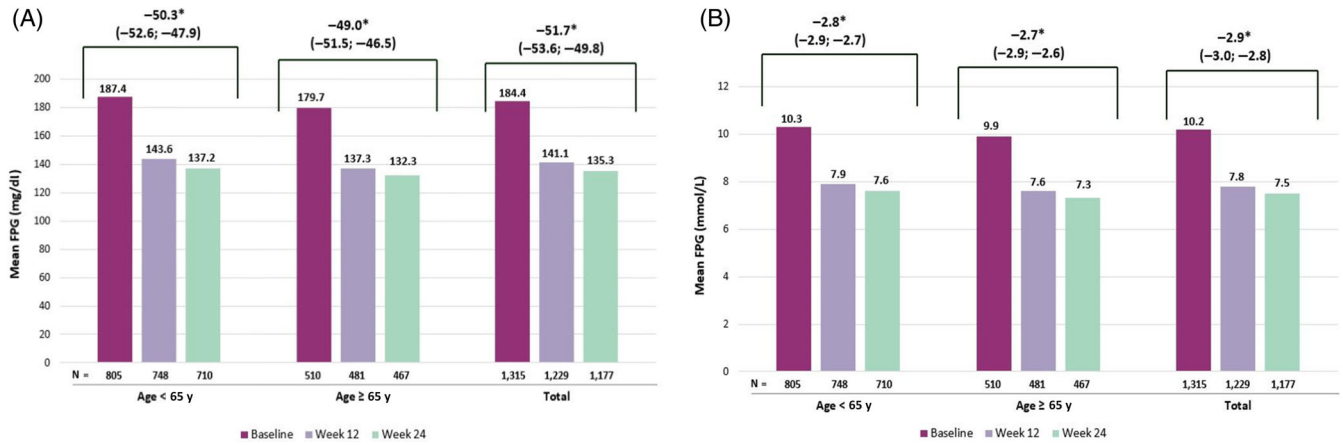

FIGURE 3 Observed mean fasting plasma glucose (FPG) changes in A, mg/dl, and B, mmol/L over the 24-week iGlarLixi treatment period. N refers to the number of patients with available data at each time point. *Corresponds to least-squares mean change (95% confidence interval) in FPG from baseline to week 24 derived from a mixed model for repeated measures

TABLE 2 Safety profile of iGlarLixi according to age

	Age < 65 y (N = 805)	Age ≥ 65 y (N = 510)			Total population (N = 1315)
		Age 65-69 y (N = 286)	Age ≥ 70 y (N = 224)	Total (N = 510)	
Patients with any gastrointestinal AE ≥ 1%, n (%)	11 (1.4)	5 (1.7)	0	5 (1.0)	16 (1.2)
Nausea	9 (1.1)	4 (1.4)	0	4 (0.8)	13 (1.0)
Total patient-year exposure	377.79	138.16	106.52	244.68	622.47
Any hypoglycaemia					
Patients with events, n (%)	35 (4.3)	9 (3.1)	8 (3.6)	17 (3.3)	52 (4.0)
Total number of events (event rate)	80 (0.21)	24 (0.17)	11 (0.10)	35 (0.14)	115 (0.18)
Symptomatic hypoglycaemia					
Patients with events, n (%)	32 (4.0)	9 (3.1)	7 (3.1)	16 (3.1)	48 (3.7)
Total number of events (event rate)	75 (0.20)	24 (0.17)	10 (0.09)	34 (0.14)	109 (0.18)
Severe hypoglycaemia					
Patients with events, n (%)	1 (0.1)	0	0	0	1 (0.1)
Total number of events (event rate)	1 (0.003)	0	0	0	1 (0.002)

Note: The event rate is calculated as the total number of events divided by total patient-year exposure.

than 7.5% and of less than 8.0% were, however, comparable in the two age subgroups (Figure 2). In line with changes in HbA1c, the LS mean decrease in FPG from baseline to week 24 of iGlarLixi therapy was also clinically meaningful and similar across the age subgroups (Figure 3).

3.3 | Safety, body weight and iGlarLixi dose

iGlarLixi was well tolerated, with overall low rates of gastrointestinal AEs and of symptomatic and severe hypoglycaemic events in both age subgroups, including in those aged 70 years or older (Table 2). Nausea was the most common gastrointestinal AE, reported in 1.1% and 0.8% of participants in the younger than 65 years and 65 years or older subgroups, respectively. There was only one patient, aged 65-69 years, who discontinued iGlarLixi therapy because of a gastrointestinal AE, namely nausea.

Treatment with iGlarLixi also reduced body weight from baseline to week 24 (Table 3) by a mean of −2.0 kg in the younger than 65 years subgroup and of −1.6 kg in the 65 years or older subgroup (−1.7 kg in those aged 65-69 years and −1.6 kg in those aged ≥ 70 years).

The mean dose of iGlar followed a similar pattern from baseline in both age subgroups. The mean increase in the daily iGlar dose provided by iGlarLixi from baseline to week 24 was 0.17 U/kg/d (15.3 U/d) in those aged younger than 65 years versus 0.15 U/kg/d (12.3 U/d) in

TABLE 3 Changes from baseline in daily iGlarLixi dose and in body weight according to age

	Age < 65 y (N = 805)	Age ≥ 65 y (N = 510)	Total (N = 1315)
Daily iGlar dose provided by iGlarLixi (U/d)			
Baseline	19.1 ± 9.6	18.6 ± 8.7	18.9 ± 9.2
Week 12	30.8 ± 11.4	28.2 ± 10.7	29.8 ± 11.2
Change from baseline to week 12	11.4 ± 9.8	9.5 ± 8.8	10.7 ± 9.5
Week 24	34.8 ± 12.9	31.1 ± 12.2	33.3 ± 12.7
Change from baseline to week 24	15.3 ± 11.9	12.3 ± 10.7	14.1 ± 11.5
Daily iGlar dose provided by iGlarLixi (U/kg/d)			
Baseline	0.21 ± 0.11	0.22 ± 0.10	0.21 ± 0.11
Week 12	0.34 ± 0.13	0.33 ± 0.13	0.34 ± 0.13
Change from baseline to week 12	0.13 ± 0.11	0.12 ± 0.10	0.12 ± 0.11
Week 24	0.39 ± 0.14	0.37 ± 0.14	0.38 ± 0.14
Change from baseline to week 24	0.17 ± 0.13	0.15 ± 0.12	0.16 ± 0.13
Body weight (kg)			
Baseline	92.6 ± 17.6	86.6 ± 15.0	90.3 ± 16.9
Week 12	91.2 ± 16.8	85.6 ± 15.0	89.0 ± 16.3
Change from baseline to week 12	-1.4 ± 3.6	-1.4 ± 3.7	-1.4 ± 3.7
Week 24	90.6 ± 16.7	85.2 ± 14.8	88.5 ± 16.2
Change from baseline to week 24	-2.0 ± 4.8	-1.6 ± 4.4	-1.8 ± 4.6

Note: All data are expressed as mean ± standard deviation.
Abbreviation: iGlar, insulin glargine 100 U/ml.

those aged 65 years or older. Of note, the titration of iGlar, as a component of iGlarLixi, occurred primarily in the first 12 weeks of treatment (Table 3).

4 | DISCUSSION

In this REALI pooled analysis of prospective real-world studies,[11,12] iGlarLixi was effective and well tolerated in both younger (age < 65 years) and older (age ≥ 65 years) people with T2D inadequately controlled on OADs with or without BI. Indeed, despite some differences in baseline characteristics (mainly sex ratio, BMI, diabetes duration and prior BI use) between patients aged 65 years or older and those aged younger than 65 years, similar and clinically meaningful reductions in HbA1c and FPG were observed in both age subgroups. Safety endpoints were also comparable between the age subgroups, with a low incidence of reported hypoglycaemic events and gastrointestinal AEs, including in participants aged 70 years or older.

The findings of this REALI analysis are consistent with those of a post hoc analysis of the LixiLan-O and LixiLan-L RCTs, in which the glucose-lowering efficacy of iGlarLixi was similar in T2D patients aged 65 years or older and those younger than 65 years, with no significant differences in the frequency of hypoglycaemia or gastrointestinal AEs.[10]

Beyond its glycaemic benefits, favourable safety profile and modest weight loss effect, iGlarLixi may be an attractive treatment option in older patients with T2D because of its simple injection regimen and once-daily dosing. In a single-arm, interventional, prospective study of 65 adults aged 65 years or older with T2D on multiple daily insulin injections who underwent simplification of their regimen by changing to once-daily iGlar with or without non-insulin glucose-lowering agents, simplifying the insulin regimen was found to improve diabetes-related distress and to reduce the risk of hypoglycaemia without compromising glycaemic control.[13] Thus, iGlarLixi has the potential to improve not only glycaemic control, but also overall patient well-being and adherence. Further investigations are warranted to confirm the positive impact of iGlarLixi therapy on patient adherence in older adults.

Corresponding to real-life clinical practice, no forced titration of iGlarLixi was followed in the two pooled studies.[11,12] This may have contributed to the lower final mean dose of iGlar observed in this analysis (33.3 U/d at week 24) compared with the LixiLan RCTs (39.8 and 46.7 U/d at week 30 in LixiLan-O and LixiLan-L, respectively).[6,7] This might also explain the lower percentage of patients reaching HbA1c targets in this REALI analysis compared with the LixiLan RCTs.[6,7] For instance, the percentage of patients aged 65 years or older who achieved HbA1c of less than 7.0% at the end of the LixiLan-L and LixiLan-O trials was 51.8% and 78.0%, respectively,[10] whereas it was 30.7% in the current analysis. The mean HbA1c at baseline reported in our analysis (9.1%) was also notably higher compared with the LixiLan RCTs (8.1%), which may further explain the lower rates of HbA1c target achievement at the end of this REALI analysis compared with the LixiLan RCTs.[6,7]

The present analysis is strengthened by the large number of participants coming from routine clinical practice, the application of standardized endpoint definitions and the prospective data collection.

There are, however, limitations to this pooled analysis, including its post hoc nature, the lack of assessments of cognitive function, functional capacity or frailty and the absence of a comparator arm. In addition, selection bias cannot be ruled out, because inclusion of patients in the two pooled studies[11,12] was at the sole decision of the prescribing physician. There may also be a potential reporting bias, which is inherent to observational studies, and which could result in under-reporting of AEs, including hypoglycaemia. On the same note, the two pooled studies[11,12] did not collect glucose sensor data, which could also result in under-reporting of hypoglycaemia. Lastly, it should be noted that the 24-week treatment duration may be short for full titration of the iGlarLixi dose in real-life clinical practice. Nevertheless, this REALI analysis provides valuable evidence for the treatment of older adults with T2D and offers insights into the real-life effectiveness and safety of iGlarLixi according to age.

In conclusion, in people with T2D inadequately controlled on OADs with or without BI, iGlarLixi was well tolerated and improved HbA1c, FPG and body weight, regardless of age. These data confirm the effectiveness and safety of iGlarLixi and its suitability as a therapeutic option for both younger and older people with T2D.

AUTHOR CONTRIBUTIONS

All authors contributed to the project design and the analysis plan. MT performed the statistical analysis of the data. All authors were involved in the interpretation of the data, writing and reviewing drafts of the manuscript, and approved the final version for submission.

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CONFLICT OF INTEREST

CG has participated in scientific advisory boards for and received consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Krka, Merck KGaA, MSD, Novo Nordisk, Sanofi and Servier. JTK has received research funding from Sanofi. MH has received honoraria for talks and/or consultancy and/or research funding from Eli Lilly, Novo Nordisk, Sanofi, AstraZeneca, Mundipharma, Bristol-Meyers Squibb, Amgen, Boehringer Ingelheim, Janssen and Johnson & Johnson. MB is a Sanofi employee. GB is an IVIDATA employee. MT is an IDDI employee, and has acted as a biostatistics contractor for Sanofi. NF has received research support and has acted as a consultant for Allergan, Ipsen, Sanofi, AstraZeneca, Vertex, Aimmune, ALK, Gedeon Richter, Abbott Singapore, Galderma, Thea and Novartis. JS has received honoraria for talks and/or consultancy and/or research funding from Apitope, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, GI-Dynamics, GlaxoSmithKline, Intarcia, Ipsen, Janssen, LifeScan, MedScape, MSD, Novartis, Novo Nordisk, Omniamed, Pfizer, Roche, Sanofi, Servier, Takeda and Ypsomed.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Cristian Guja https://orcid.org/0000-0002-8703-0522
Nick Freemantle https://orcid.org/0000-0001-5807-5740
Jochen Seufert https://orcid.org/0000-0001-5654-7310

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SUPPORTING INFORMATION

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

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