ORIGINAL RESEARCH

Impact of Participant Characteristics on Clinical Outcomes with iGlarLixi in Type 2 Diabetes: Post Hoc Analysis of SPARTA Japan

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ABSTRACT

Introduction: The real-world SPARTA Japan study confirmed the effectiveness and safety of the fixed-ratio combination of insulin glargine 100 U/mL plus lixisenatide (iGlarLixi) once daily over 6 months in Japanese people with type 2 diabetes (T2D). This post hoc analysis examined the impact of participant characteristics on the achievement of age-defined glycaemic targets with iGlarLixi therapy.

Methods: The retrospective, observational SPARTA Japan study included adults with T2D who initiated iGlarLixi. In this analysis, data from insulin-naïve and insulin-experienced participants were separately assessed to compare glycated haemoglobin (HbA1c), body weight and safety outcomes between those who achieved ('achieved' group) and those who did not achieve ('not-achieved' group) age-defined glycaemic targets after 6 months of iGlarLixi. The not-achieved group was further stratified by whether or not their iGlarLixi dose was increased during treatment.

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Results: In total, 418 participants were included in this analysis (138 insulin naïve and 280 insulin experienced). Among both insulin-naïve and insulin-experienced participants, those in the achieved group were older and had lower baseline HbA1c than those in the not-achieved group. Compared with the not-achieved group, the achieved group showed significantly greater HbA1c reductions from baseline (in both insulin-naïve and insulin-experienced participants) and significantly greater body weight reductions (in insulin-naïve participants), despite some participants in the not-achieved group receiving significantly higher insulin glargine doses than those in the achieved group. In both insulin-naïve and insulin-experienced participants, the incidence of hypoglycaemia and gastrointestinal-related adverse events was similar in the achieved and not-achieved groups. In a multivariate analysis, glycaemic target achievement was significantly more likely in older individuals and those who lost weight during iGlarLixi treatment.

Conclusions: Achievement of age-defined glycaemic targets with iGlarLixi treatment for 6 months was significantly affected by increased age and body weight loss, regardless of prior insulin exposure.

Trial Registration: UMIN-CTR Trials Registry, UMIN000044126; registered 10 May 2021.

PLAIN LANGUAGE SUMMARY

iGlarLixi is an injectable product used to treat type 2 diabetes that contains a fixed combination of two drugs, insulin glargine (at a concentration of 100 U/mL) and lixisenatide. The SPARTA Japan study investigated the effectiveness of controlling blood glucose levels and the safety of iGlarLixi in Japanese people when taken once daily for over 6 months as part of their routine medical care. The analysis reported in this article looked back at data from SPARTA Japan to assess whether certain characteristics of the people who took part in the study affected how well blood glucose targets were met. People who had previously taken insulin and those who had not were identified, and their results were assessed separately. The people were divided into those who had met their blood glucose level target (with the target defined as the glycated haemoglobin level for each person based on their age) and those who had not met their target. It was found that people who achieved their blood glucose target while receiving iGlarLixi were more likely to be older, to have had a lower glycated haemoglobin level before starting iGlarLixi, and to have lost weight during treatment than those who did not achieve their target, whether or not they had previously been treated with insulin. Side effects of excessively low blood glucose levels or gastrointestinal upset with iGlarLixi treatment occurred in a similar number of people who achieved or did not achieve their blood glucose target.

Key Summary Points

Why carry out this study?

The real-world SPARTA Japan study confirmed the effectiveness and safety of iGlarLixi (a fixed-ratio combination of insulin glargine 100 U/mL plus lixisenatide) in Japanese people with type 2 diabetes (T2D).

This post hoc analysis of SPARTA Japan assessed demographics and clinical characteristics of participants who achieved or did not achieve their age-defined glycaemic targets after 6 months' iGlarLixi treatment, both in insulin-naïve and insulin-experienced participants, with further comparison of those in the 'not-achieved' group by whether or not the iGlarLixi dose was increased.

What has been learned from this study?

Participants who achieved their age-defined glycaemic targets with iGlarLixi were older and had lower baseline glycated haemoglobin (HbA1c) than those in the not-achieved group, regardless of prior insulin exposure.

iGlarLixi provided significantly greater HbA1c reductions among participants in the achieved versus not-achieved groups, despite significantly higher insulin glargine doses in some participants in the not-achieved group.

The incidence of hypoglycaemia or gastrointestinal-related adverse events with iGlarLixi treatment was similar in participants who achieved or did not achieve their glycaemic targets.

INTRODUCTION

Maintenance of good glycaemic control is essential in people with type 2 diabetes (T2D) to reduce the risk of long-term macro- and microvascular complications [1, 2]. However, many individuals with T2D do not achieve adequate glycaemic control with oral antidiabetic drugs (OADs) alone [3]. As a result of the progressive nature of diabetes, treatment intensification and titration are often required to maintain glycaemic targets [4]. The United Kingdom Prospective Diabetes Study (UKPDS) [2] and Kumamoto study [5] were landmark trials that demonstrated the benefits of intensive glucose-lowering therapy for reducing the risk of diabetes-related complications in people with T2D. However, intensified glucose-lowering therapy may lead to an increased risk of severe hypoglycaemia, particularly in older individuals with T2D, in whom severe hypoglycaemia may impair cognitive function and increase the risk for cardiovascular events [6]. Therefore, the Japan Diabetes Society (JDS) guidelines recommend age-defined glycaemic targets that carefully consider the individual's age, duration of disease, risk for hypoglycaemia, and available support, as well as their cognitive function, comorbidities/functional impairment and basic/instrumental activities of daily living [7].

For individuals who have suboptimal glycaemic control with OADs alone, the American Diabetes Association (ADA) and the JDS guidelines recommend addition of one or more injectable agents, including glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and basal insulin (BI) [3, 7]. Further, the JDS recommends considering GLP-1 RAs and sodium-glucose transport protein 2 (SGLT2) inhibitors when selecting antidiabetic drugs for treatment intensification given the additional cardiorenal benefits of these drug classes [8, 9].

Treatment complexity with injectable agents and concern about insulin-related adverse events (AEs) may cause delays in treatment intensification, with this clinical inertia leading to poor glycaemic control and an increased risk of long-term complications [10, 11]. Further, titration of injectable therapy, which is essential for the achievement of glycaemic control, is often inadequate [12, 13]. To help address this issue, several titratable, fixed-ratio combinations of BI plus a GLP-1 RA have been

developed, with the goal of providing simplified dosing regimens that increase treatment adherence, thereby improving glycaemic control [14].

The fixed-ratio combination of insulin glargine 100 U/mL plus lixisenatide (iGlarLixi) is now available in Japan for individuals requiring intensification of T2D treatment [15]. The efficacy and safety of once-daily iGlarLixi has been demonstrated in randomised clinical trials in Japanese people with suboptimally controlled T2D previously treated with OADs alone (LixiLan JP-O1 and LixiLan JP-O2) [16, 17] or with BI plus OADs (LixiLan JP-L) [18]. Moreover, the addition of a BI to a GLP-1 RA has also been shown to provide more effective glycaemic control than either of its individual components, reducing glycaemic variability and both fasting and postprandial glucose levels, without increasing the risk of hypoglycaemia [19, 20].

The retrospective, observational SPARTA Japan study confirmed the real-world effectiveness and safety of iGlarLixi in Japan [21]. iGlarLixi administered for 6 months significantly reduced glycated haemoglobin (HbA1c) from baseline [21], with improvements in glycaemic control observed in all but one prior treatment subgroup (GLP-1 RA + BI) [22]. However, JDS guideline age-defined glycaemic targets [7] were achieved by only 28.9% of participants in the overall population, including 17.9% of those who switched from GLP-1 RA therapy, 40.7% of those previously on OADs and 21.4–50.0% of insulin-experienced participants [22]. In addition, the daily dose of iGlarLixi was only slightly increased after 6 months [22].

The aim of this post hoc analysis of SPARTA Japan was to compare baseline characteristics between participants who achieved or did not achieve their age-defined glycaemic targets after 6 months' iGlarLixi treatment, both among insulin-naïve and insulin-experienced participants. Among participants who did not achieve their glycaemic target, baseline characteristics were also compared between subgroups with or without an increase in iGlarLixi dose.

METHODS

Study Design, Participants and Outcomes

The study design and methods of the SPARTA Japan study (UMIN-CTR Trials Registry identifier UMIN000044126) have been reported in detail previously [21]. Briefly, data from the medical records of adults with T2D who initiated treatment with iGlarLixi at one of 27 medical institutions across Japan were retrospectively collected. Participants had to have initiated iGlarLixi treatment ≥ 6 months before data collection, have available HbA1c data from within 3 months prior to iGlarLixi initiation and within 6 months after treatment initiation, and have body weight data available from within 6 months prior to iGlarLixi initiation.

The primary endpoint of SPARTA Japan was the change in HbA1c from baseline to 6 months after the initiation of iGlarLixi treatment [21]. Exploratory endpoints included changes from baseline to 6 months in body weight and iGlarLixi dose, and the incidence of hypoglycaemia and gastrointestinal-related adverse events (AEs).

Post Hoc Analysis

For this post hoc analysis of SPARTA Japan, data from insulin-naïve and insulin-experienced participants were separately analysed to compare demographics and clinical characteristics of participants who achieved age-defined glycaemic targets after 6 months of iGlarLixi treatment and those who did not achieve these targets. The age-defined glycaemic targets were defined according to 2019 JDS guidelines [7], as follows: (i) HbA1c < 7.0% for participants aged < 65 years; (ii) HbA1c < 7.5% for participants aged ≥ 65 to < 75 years; and (iii) HbA1c < 8.0% for participants aged ≥ 75 years. Of note, the age-defined glycaemic targets did not include lower HbA1c limits; cognitive function and activities of daily living were also not considered when these targets were determined.

Data from participants in the 'not-achieved' group were further stratified according to

whether or not the iGlarLixi dose had been increased in the 6 months after treatment initiation. A dose increase was defined as an average increase of ≥ 4 dose steps of iGlarLixi (where 1 dose step = insulin glargine [iGlar] 100 U/mL: 1 µg lixisenatide) over the 6-month observational period, based on the median dose increase observed in the overall SPARTA population [21]. Participants who initiated treatment with > 17 dose steps were excluded, as the maximum approved dose of iGlarLixi in Japan is 20 dose steps.

Statistical Analysis

Descriptive statistics were used for this post hoc analysis, with continuous variables presented as means and standard deviations (SD), and categorical values presented as number and proportion of participants.

To determine differences in baseline characteristics and study outcomes between the study participants who achieved age-defined glycaemic targets and those who did not, the t test was used for continuous variables, the Fisher's exact test was used for two category variables and the Cochran–Armitage test for trends in categorical variables in the ordinal scale.

To determine differences in baseline characteristics and study outcomes in the multiple group comparison (i.e. the comparison of participants who achieved age-defined glycaemic targets vs those who did not achieve with an increased iGlarLixi dose and those who did not achieve without an increased iGlarLixi dose), multiplicity was considered, with the Tukey test used for continuous variables and the Steel–Dwass test used for categorical variables. Adjusted least squares mean (LSM) and 95% confidence interval (CI) changes in HbA1c from baseline to 6 months were calculated using analysis of covariance, with age, disease duration and baseline HbA1c as covariates. Adjusted odds ratios (OR) and their 95% CIs were calculated by multivariate logistic regression analyses with/ without achievement of age-defined targets as the objective variable and preselected background factors (age category, baseline body mass index [BMI] category, duration of T2D

category, baseline HbA1c category, body weight loss, and concomitant use of insulin secretagogues) as explanatory variables. p values of < 0.05 were considered statistically significant.

Statistical analyses were performed using SAS® Version 9.4 (SAS Institute; Cary, NC, USA).

Ethical Approval

SPARTA Japan was a retrospective observational study and, as such, compliance with the Declaration of Helsinki 1964 was not required. However, the study protocol for SPARTA Japan was approved on 24 February 2021 by a central ethics committee (Sone Clinic in Tokyo, Japan) for some institutions and by their own institutional ethics committees in other institutions. Written informed consent for the use of participant data was also obtained.

RESULTS

Participants

Of the 469 participants enrolled in SPARTA Japan, 432 were eligible for the full analysis set, and 418 met the criteria for inclusion in this post hoc analysis (Fig. 1). Of these 418 participants, 138 were insulin naïve and were treated with either diet and exercise therapy alone, OADs, or a GLP-1 RA before initiating iGlarLixi. The remaining 280 participants were insulin experienced and had been treated with either OADs plus BI (also known as BI-supported oral therapy [BOT]), a GLP-1 RA plus BI, or had received intensive insulin or other insulin therapy (including a combination of three or more injectable drugs or combination of insulin plus a GLP-1 RA) before initiating iGlarLixi.

In the insulin-naïve cohort, statistically significant differences in baseline age (66.1 vs 57.6 years; $p < 0.001$), body weight (67.8 vs 74.1 kg; $p = 0.034$) and HbA1c (8.91% vs 9.57%; $p = 0.019$) were observed between participants who achieved ($n = 49$) and those who did not achieve ($n = 89$) their age-defined glycaemic target (Table 1). Furthermore, at baseline, significantly fewer participants in the achieved
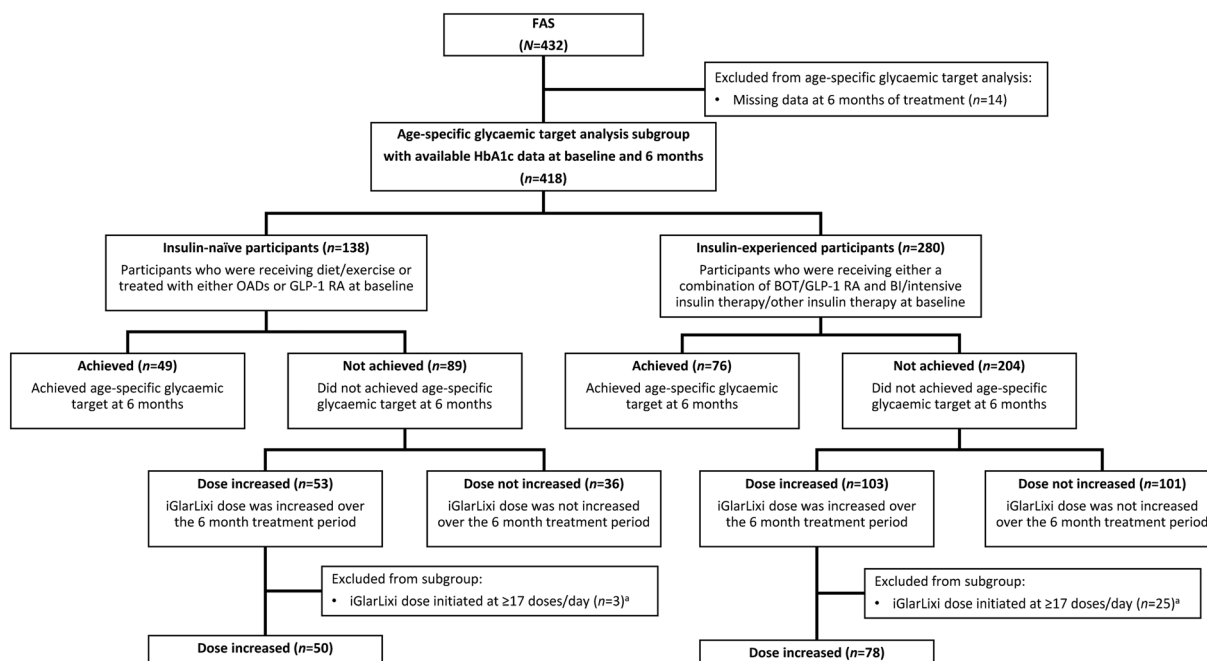
Fig. 1 Number of participants in each subgroup. Age-defined glycaemic targets were glycated haemoglobin (HbA1c) < 7.0% for participants aged < 65 years, HbA1c < 7.5% for participants aged ≥ 65 to < 75 years and HbA1c < 8.0% for participants aged ≥ 75 years. *BI* basal insulin, *BOT* basal insulin-supported oral therapy,

FAS full analysis set, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *iGlarLixi* insulin glargine 100 U/mL plus lixisenatide, *OAD* oral antidiabetic agent. [a]These participants were excluded as they could not increase their insulin dose by ≥ 4 doses/day

group were receiving a GLP-1 RA ± OAD (14.3% vs 36.0%; $p = 0.010$). Statistically significant differences in the proportion of participants receiving concomitant SGLT2 inhibitors (24.5% vs 64.0%; $p < 0.001$) and in the number of concomitant OADs received ($p = 0.044$ for trend) were also seen between the achieved and not-achieved groups (Table 1).

In the insulin-experienced cohort, significant differences in baseline age (66.5 vs 60.5 years; $p < 0.001$) and HbA1c (8.21% vs 9.01%; $p < 0.001$) were observed between participants in the achieved ($n = 76$) and not-achieved groups ($n = 204$; Table 1). At baseline, significantly more participants were receiving intensive insulin therapy in the achieved versus the not-achieved group (34.2% vs 17.2%; $p = 0.003$). The proportion of participants receiving concomitant biguanides (46.1% vs 68.1%; $p < 0.001$), SGLT2 inhibitors (39.5% vs 61.9%; $p < 0.001$) or three or more concomitant

OADs (7.9% vs 24.5%; $p < 0.001$) were all significantly lower in the achieved versus not-achieved group (Table 1).

When comparing baseline characteristics by whether or not the iGlarLixi dose was increased in the not-achieved group (Supplementary Table S1; Electronic Supplementary Material), in insulin-naïve participants, there were significant differences between the not-achieved/-dose-increased group ($n = 50$) and the achieved group in mean age (54.4 vs 66.1 years; $p < 0.001$), body weight (75.8 vs 67.8 kg; $p = 0.043$) and baseline HbA1c (9.86% vs 8.91%; $p = 0.007$). In the not-achieved/dose-not-increased group ($n = 36$), background characteristics were generally similar to those in the not-achieved/dose-increased group, with the exception of age (61.9 vs 54.4 years; $p = 0.022$) and duration of T2D category (< 10 years duration, 30.6% and 62.0% vs ≥ 10 years duration, 69.4% and 38.0%; $p = 0.012$ for trend).

Table 1 Baseline demographics and characteristics by age-defined glycaemic target achievement

Characteristic	Insulin naïve		P value	Insulin experienced		P value
	Achieved (n = 49)	Not achieved (n = 89)		Achieved (n = 76)	Not achieved (n = 204)	
Age, years	66.1 ± 14.9	57.6 ± 11.9	< 0.001[a]	66.5 ± 11.9	60.5 ± 12.6	< 0.001[a]
Age category, n (%)			< 0.001[b]			< 0.001[b]
< 65 years	19 (38.8)	61 (68.5)		28 (36.8)	130 (63.7)	
≥ 65 to < 75 years	15 (30.6)	25 (28.1)		25 (32.9)	52 (25.5)	
≥ 75 years	15 (30.6)	3 (3.4)		23 (30.3)	22 (10.8)	
Sex, n (%)			0.854[b]			0.052[b]
Male	30 (61.2)	57 (64.0)		55 (72.4)	121 (59.3)	
Female	19 (38.8)	32 (36.0)		21 (27.6)	83 (40.7)	
Body weight, kg	67.8 ± 16.3	74.1 ± 16.9	0.034[a]	70.4 ± 18.3	72.1 ± 14.2	0.428[a]
BMI, kg/m^2	25.6 ± 5.2	27.2 ± 4.7	0.060[a]	26.4 ± 5.0	27.0 ± 4.2	0.288[a]
BMI category, n (%)			0.067[b]			0.081[b]
< 25 kg/m^2	21 (42.9)	26 (29.2)		32 (42.1)	59 (28.9)	
≥ 25 to < 30 kg/m^2	19 (38.8)	38 (42.7)		25 (32.9)	94 (46.1)	
≥ 30 kg/m^2	8 (16.3)	24 (27.0)		14 (18.4)	44 (21.6)	
Duration of T2D, years	11.5 ± 9.3	12.6 ± 11.6	0.558[a]	13.5 ± 12.1	14.0 ± 9.9	0.717[a]
Duration of T2D category, n (%)			1.000[b]			0.496[b]
< 10 years	25 (51.0)	45 (50.6)		35 (46.1)	83 (40.7)	
≥ 10 years	24 (49.0)	44 (49.4)		41 (54.0)	121 (59.3)	
HbA1c, %	8.91 ± 1.53	9.57 ± 1.55	0.019[a]	8.21 ± 2.06	9.01 ± 1.45	< 0.001[a]
HbA1c category, n (%)			0.005[b]			< 0.001[b]
< 7%	0	0		17 (22.4)	6 (2.9)	
≥ 7 to < 8%	12 (24.5)	8 (9.0)		32 (42.1)	42 (20.6)	
≥ 8 to < 9%	19 (38.8)	30 (33.7)		11 (14.5)	65 (31.9)	
≥ 8%	18 (36.7)	51 (57.3)		16 (21.1)	91 (44.6)	
Prior treatments, n (%)						
Diet/exercise	7 (14.3)	8 (8.9)	0.396[c]	0	0	–
OAD	35 (71.4)	49 (55.1)	0.070[c]	0	0	–
GLP-1 RA ± OAD	7 (14.3)	32 (36.0)	0.010[c]	0	0	–
BOT	0	0	–	18 (23.7)	65 (31.9)	0.239[c]
GLP-1 RA + BI	0	0	–	15 (19.7)	50 (24.5)	0.431[c]

Table 1 continued

Characteristic	Insulin naïve		P value	Insulin experienced		P value
	Achieved (n = 49)	Not achieved (n = 89)		Achieved (n = 76)	Not achieved (n = 204)	
Intensive insulin therapy	0	0	–	26 (34.2)	35 (17.2)	0.003[c]
Other insulin therapies	0	0	–	17 (22.4)	54 (26.4)	0.539[c]
History of DPP4 inhibitor use, n (%)	19 (38.8)	22 (24.7)	0.119[c]	23 (30.3)	43 (21.1)	0.115[c]
Type of concomitant OADs, n (%)						
Biguanide	28 (57.1)	65 (73.0)	0.061[c]	35 (46.1)	139 (68.1)	< 0.001[c]
SGLT2 inhibitors	12 (24.5)	57 (64.0)	< 0.001[c]	30 (39.5)	141 (69.1)	< 0.001[c]
Sulfonylureas	15 (30.6)	15 (16.9)	0.084[c]	5 (6.6)	24 (11.8)	0.272[c]
Glinides	9 (18.4)	19 (21.4)	0.826[c]	14 (18.4)	49 (24.0)	0.340[c]
α-Glucosidase inhibitors	11 (22.5)	12 (13.5)	0.233[c]	11 (14.5)	31 (15.2)	1.000[c]
Thiazolidinediones	1 (2.0)	5 (5.6)	0.422[c]	6 (7.9)	8 (3.9)	0.216[c]
Number of concomitant OADs, n (%)			0.044[b]			< 0.001[b]
None	9 (18.4)	9 (10.1)		17 (22.4)	26 (12.8)	
1	19 (38.8)	19 (21.4)		27 (35.5)	37 (18.1)	
2	9 (18.4)	38 (42.7)		26 (34.2)	91 (44.6)	
≥ 3	12 (24.5)	23 (25.8)		6 (7.9)	50 (24.5)	

Data are presented as mean ± SD or n (%). Age-defined glycaemic targets were HbA1c < 7.0% for participants aged < 65 years, HbA1c < 7.5% for participants aged ≥ 65 to < 75 years and HbA1c < 8.0% for participants aged ≥ 75 years

BI basal insulin, *BMI* body mass index, *BOT* basal insulin-supported oral therapy, *DPP4* dipeptidyl peptidase 4, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *HbA1c* glycated haemoglobin, *OAD* oral antidiabetic agent, *SD* standard deviation, *SGLT2* sodium-glucose transport protein 2, *T2D* type 2 diabetes

[a]Calculated using the *t* test

[b]Calculated using the Cochran–Armitage test for trend across categories

[c]Calculated using Fisher's exact test

In insulin-experienced participants, significant differences in age (66.5 vs 60.0 years; p = 0.003), duration of T2D category (10 years duration, 23.1% vs 46.1%; ≥ 10 years duration, 76.9% vs 54.0%; p = 0.008 for trend) and HbA1c (8.98% vs 8.21%; p = 0.011) were seen between the not-achieved/dose-increased group (n = 78) and the achieved group (Supplementary Table S1; Electronic Supplementary Material).

Significant differences between the not-achieved/dose-not-increased (n = 101) and the not-achieved/dose-increased groups were observed in BMI (25.9 vs 27.8 kg/m^2; p = 0.014), BMI category (< 25 kg/m^2, 37.6% vs 24.4%; ≥ 25 to < 30 kg/m^2, 45.5% vs 42.3%; ≥ 30 kg/m^2, 14.9% vs 28.2%; p = 0.044 for trend) and duration of T2D category (< 10 years duration, 45.5% vs

23.1%; $\geq$ 10 years duration, 54.5% vs 76.9%; p = 0.006 for trend).

HbA1c Reductions

In the insulin-naïve cohort, the adjusted reduction in HbA1c at 6 months after initiating iGlarLixi was significantly greater in the achieved group (LSM change $-$ 2.37%; 95% CI $-$ 2.68, $-$ 2.06) than in the not-achieved group ($-$ 0.76%; 95% CI $-$ 0.99, $-$ 0.54; p < 0.001; Fig. 2a). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, the adjusted change in HbA1c at 6 months was still greater in the achieved group than in the not-achieved/dose-not-increased (LSM change $-$ 0.86%; 95% CI $-$ 1.21, $-$ 0.50) and not-achieved/dose-increased ($-$ 0.72%; 95% CI $-$ 1.03, $-$ 0.41) groups (both p < 0.001).

Similar results were observed in the insulin-experienced cohort, with a significantly greater adjusted reduction in HbA1c at 6 months after initiating iGlarLixi observed in the achieved group (LSM change $-$ 1.90%, 95% CI $-$ 2.15, $-$ 1.66) than in the not-achieved group ($-$ 0.13%; 95% CI $-$ 0.27, 0.02; p < 0.001), irrespective of whether the iGlarLixi dose was increased ($-$ 0.02%; 95% CI $-$ 0.24, 0.20; p < 0.001) or not increased ($-$ 0.18%; 95% CI $-$ 0.37, 0.01; p < 0.001) over the study period (Fig. 2b).

The relationships between achievement of age-defined glycaemic targets and iGlarLixi dose increases in insulin-naïve and insulin-experienced participants are presented in Fig. 3. Among the 49 insulin-naïve participants who achieved their glycaemic targets, 13 (26.5%) had increased their iGlarLixi dose by $\geq$ 4 dose steps (Fig. 3a). Of the participants in the not-achieved group, HbA1c levels ranged from 7.5% to 14.0% in the not-achieved/dose-not-increased group and from 7.0% to 11.6% in the not-achieved/dose-increased group. Among the 76 insulin-experienced participants who achieved their glycaemic targets, 17 (22.4%) had increased their iGlarLixi dose by $\geq$ 4 dose steps (Fig. 3b). In the not-achieved group, HbA1c levels were 7.0–13.1% in the not

achieved/dose-not-increased group and 7.0–12.4% in the not-achieved/dose-increased group (Fig. 3b).

Body Weight Changes

Among insulin-naïve participants, those in the achieved group had significantly greater reductions in body weight from baseline (mean $\pm$ SD change $-$ 1.19 $\pm$ 3.38 kg) at 6 months after initiating iGlarLixi compared with participants in the not-achieved group ($+$ 1.01 $\pm$ 2.83 kg; p < 0.001; Fig. 2a). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, a significant difference in the change in body weight versus the achieved group was observed in both the not-achieved/dose-increased (mean $\pm$ SD change $+$ 1.35 $\pm$ 2.65 kg; p < 0.001) and not-achieved/dose-not-increased ($+$ 0.61 $\pm$ 3.14 kg; p = 0.028) groups (Fig. 2a).

In insulin-experienced participants, there was a numerically greater reduction in body weight from baseline to 6 months in the achieved group (mean $\pm$ SD change $-$ 1.37 $\pm$ 3.72 kg) than in the not-achieved group ($-$ 0.61 $\pm$ 3.10 kg; p = 0.096; Fig. 2b). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, there was no statistically significant difference between the not-achieved/dose-increased and not-achieved/dose-not-increased groups (Fig. 2b).

Dose Changes

In the insulin-naïve cohort, the mean $\pm$ SD initial iGlarLixi dose was significantly lower in the achieved group (5.4 $\pm$ 1.8 dose steps) than in the not-achieved group (6.7 $\pm$ 3.5 dose steps; p = 0.015; Fig. 2a). At the end of the study, the mean $\pm$ SD dose was 7.8 $\pm$ 3.0 and 12.5 $\pm$ 5.2 dose steps, respectively (p < 0.001). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, compared with the achieved group, participants in the not-achieved/dose-increased group had a similar initial iGlarLixi dose (mean $\pm$ SD 6.0 $\pm$ 2.3 dose steps) and a significantly higher

(a)

□ Baseline ■ At 6 months
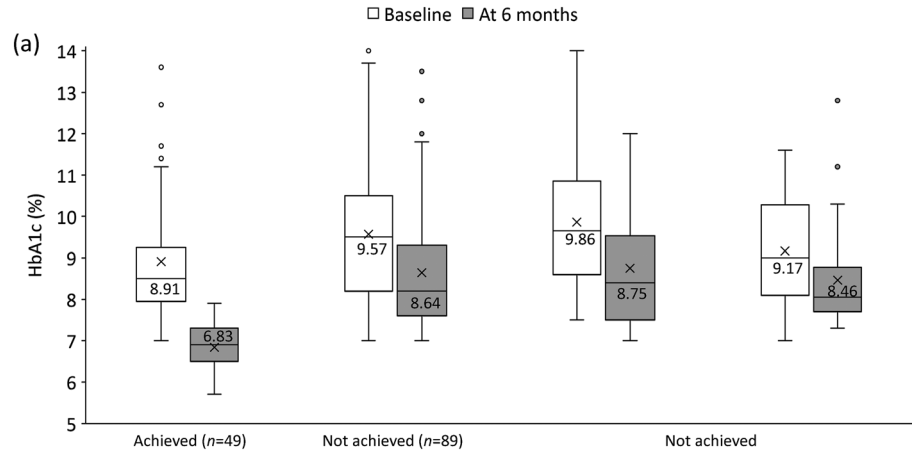
	Achieved (*n*=49)	Not achieved (*n*=89)	Not achieved/dose increased (*n*=50)[a]	Not achieved/dose not increased (*n*=36)
Mean (95% CI) change in HbA1c, %	−2.37 (−2.68, −2.06)	−0.76 (−0.99, −0.54)	−0.72 (−1.03, −0.41)	−0.86 (−1.21, −0.50)
Mean ± SD change in body weight, kg	−1.19 ± 3.38**	+1.01 ± 2.83	+1.35 ± 2.65†††	+0.61 ± 3.14†
Mean ± SD iGlarLixi dose				
At treatment initiation	5.4 ± 1.8*	6.7 (3.5)	6.0 ± 2.3	6.6 ± 2.8†
At end of study	7.8 ± 3.0**	12.5 ± 5.2	15.5 ± 3.7†††‡	7.6 ± 2.5
Incidence of hypoglycaemia, n (%)	9 (18.4)	9 (10.1)	1 (2.0)††	8 (22.2)
Incidence of GI disorders, n (%)	11 (22.4)	14 (15.7)	9 (18.0)	5 (13.9)

(b)

□ Baseline ■ At 6 months
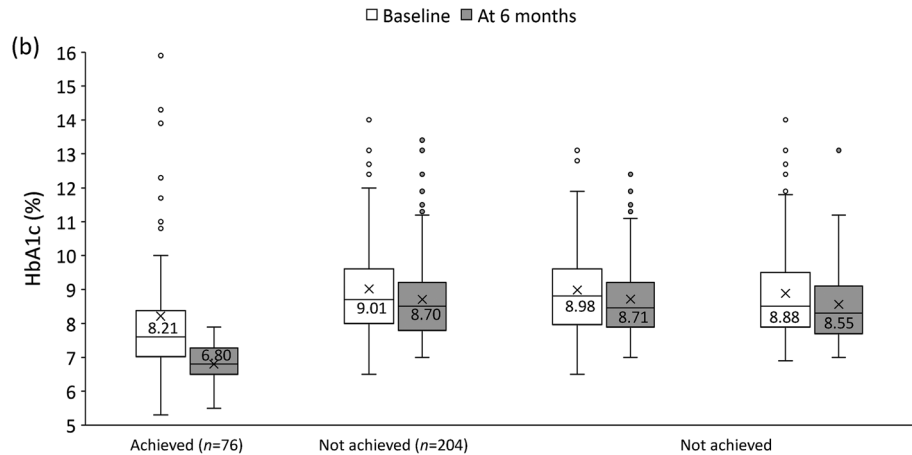
	Achieved (*n*=76)	Not achieved (*n*=204)	Not achieved/dose increased (*n*=78)[b]	Not achieved/dose not increased (*n*=101)
Mean (95% CI) change in HbA1c, %	−1.90 (−2.15, −1.66)	−0.13 (−0.27, +0.02)	−0.02 (−0.24, +0.20)	−0.18 (−0.37, +0.01)
Mean ± SD change in body weight, kg	−1.37 ± 3.72	−0.61 ± 3.10	−0.65 ± 2.87	−0.56 ± 3.10
Mean ± SD iGlarLixi dose				
At treatment initiation	8.1 ± 3.3**	10.3 (4.6)	8.0 ± 2.4	9.7 ± 3.5††
At end of study	9.8 ± 4.2**	14.1 ± 4.9	16.8 ± 3.3†††‡	10.6 ± 3.8
Incidence of hypoglycaemia, n (%)	16 (21.1)	25 (12.3)	9 (11.5)	14 (13.9)
Incidence of GI disorders, n (%)	13 (17.1)	30 (14.7)	16 (20.5)	14 (13.9)

◄ **Fig. 2** Box and whiskers plots of glycated haemoglobin (HbA1c) at baseline and 6 months in participants who achieved or did not achieve age-defined glycaemic targets after 6 months of iGlarLixi treatment, with an overall summary of HbA1c reductions, changes in body weight and dose, and the incidence of hypoglycaemia and gastrointestinal disorders in **a** insulin-naïve participants and **b** insulin-experienced participants. Age-defined glycaemic targets were HbA1c < 7.0% for participants aged < 65 years, HbA1c < 7.5% for participants aged ≥ 65 to < 75 years and HbA1c < 8.0% for participants aged ≥ 75 years. *CI* confidence interval, *GI* gastrointestinal, *iGlarLixi* insulin glargine 100 U/mL plus lixisenatide, *SD* standard deviation. *$p < 0.05$, **$p < 0.001$ vs not-achieved subgroup. †$p < 0.05$, ††$p < 0.01$, †††$p < 0.001$ vs achieved subgroup. ‡$p < 0.001$ vs not-achieved/dose-not-increased subgroup. [a]Three participants were excluded from this subgroup as their iGlarLixi dose was initiated at ≥ 17 doses/day; therefore, they could not increase their insulin dose by ≥ 4 doses/day. [b]Twenty-five participants were excluded from this subgroup as their iGlarLixi dose was initiated at ≥ 17 doses/day; therefore, they could not increase their insulin dose by ≥ 4 doses/day

iGlarLixi dose at the end of the study (15.5 ± 3.7 dose steps; $p < 0.001$). In contrast, participants in the not-achieved/dose-not-increased group had a higher initial dose (6.6 ± 2.8 dose steps; $p = 0.045$) than those in the achieved group. At the end of the study, there was no difference in iGlarLixi dose between the not-achieved/dose-not-increased group (7.6 ± 2.5 dose steps) and the achieved group. As expected, significant differences in the mean dose at study end were observed between the not-achieved/dose-increased groups and not-achieved/dose-not-increased ($p < 0.001$; Fig. 2a).

In the insulin-experienced cohort, the initial daily iGlarLixi dose was significantly lower in the achieved group (mean ± SD 8.1 ± 3.3 dose steps) than in the not-achieved group (10.3 ± 4.6 dose steps; $p < 0.001$; Fig. 2b). At the end of the study, the mean ± SD dose was 9.8 ± 4.2 and 14.1 ± 4.9 dose steps, respectively ($p < 0.001$). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, participants in the not-achieved/dose-increased group had a similar

initial dose (mean ± SD 8.0 ± 2.4 dose steps) and a significantly higher dose at the end of the study (16.8 ± 3.3 dose steps) compared with the achieved group ($p < 0.001$). Compared with the achieved group, the not-achieved/dose-not-increased group had a significantly higher initial iGlarLixi dose (mean ± SD 9.7 ± 3.5 dose steps; $p = 0.002$), while the dose at the end of the study showed no difference (10.6 ± 3.8 dose steps). Again, as expected, a significant difference in the iGlarLixi dose at study end was observed between the not-achieved/dose-not-increased and not-achieved/dose-increased groups ($p < 0.001$; Fig. 2b).

Safety

During 6 months of iGlarLixi treatment, the incidence of hypoglycaemia did not differ between the achieved and not-achieved groups, with hypoglycaemia reported in 18.4% ($n = 9/49$) and 10.1% ($n = 9/89$) of insulin-naïve participants, respectively ($p = 0.192$; Fig. 2a), and 21.1% ($n = 16/76$) and 12.3% ($n = 25/204$) of insulin-experienced participants, respectively ($p = 0.086$; Fig. 2b). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, a significantly lower proportion of participants experienced hypoglycaemia among insulin-naïve participants in the not-achieved/dose-increased group (2.0% [$n = 1/50$]) versus the achieved group ($p = 0.020$) or the not-achieved/dose-not-increased group (22.2% [$n = 8/36$]; $p = 0.008$; Fig. 2a).

The incidence of gastrointestinal-related AEs in the achieved and the not-achieved groups during 6 months of iGlarLixi treatment was 22.4% ($n = 11/49$) and 15.7% ($n = 14/89$) of participants in the insulin-naïve cohort, respectively ($p = 0.360$; Fig. 2a), and 17.1% ($n = 13/76$) and 14.7% ($n = 30/204$) of participants in the insulin-experienced cohort, respectively ($p = 0.710$; Fig. 2b). When assessed by whether or not the iGlarLixi dose was increased in the not-achieved group, there was no statistically significant difference in the incidence of gastrointestinal-related AEs between the not-achieved/dose-increased and

(a)

(b)
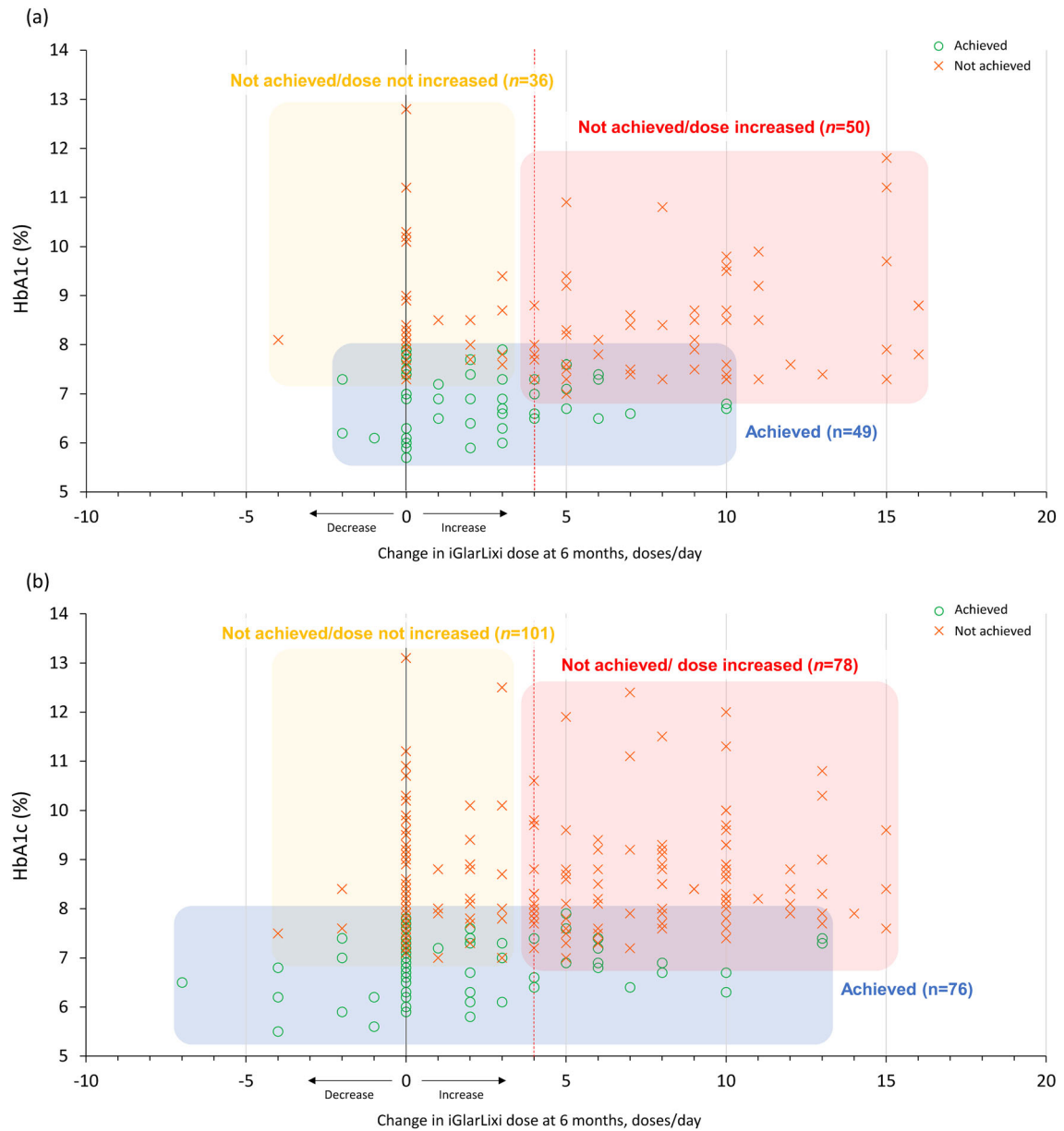
Fig. 3 Relationship between achievement of age-defined glycaemic targets after 6 months of iGlarLixi and an increase in iGlarLixi dose in **a** insulin-naïve participants and **b** insulin-experienced participants. The vertical red dotted line indicates the threshold for iGlarLixi dose increase (≥ 4 dose steps). Age-defined glycaemic targets were glycated haemoglobin (HbA1c) < 7.0% for participants aged < 65 years, HbA1c < 7.5% for participants aged ≥ 65 to < 75 years and HbA1c < 8.0% for participants aged ≥ 75 years. *iGlarLixi* insulin glargine 100 U/mL plus lixisenatide

not-achieved/dose-not-increased groups among insulin-naïve or insulin-experienced participants.

Multivariate Analysis

In the insulin-naïve cohort, multivariate analysis showed that achievement of age-defined

glycaemic targets was associated with age, with participants aged ≥ 75 years being significantly more likely to achieve targets than those aged < 65 years (OR 23.42; 95% CI 4.80, 11.24; $p < 0.001$; Fig. 4a). In addition, participants who lost body weight (i.e. ≥ 3% reduction from baseline) during iGlarLixi treatment were significantly more likely to achieve age-defined glycaemic targets than those who did not lose body weight (OR 6.74; 95% 2.39, 19.01; $p < 0.001$). Higher baseline BMI, longer duration of T2D and higher baseline HbA1c showed a trend towards lower odds of glycaemic target achievement, but the ORs for these characteristics did not reach statistical significance.

In the insulin-experienced cohort, achievement of age-defined glycaemic targets within 6 months of initiating iGlarLixi was significantly associated with age, duration of T2D, baseline HbA1c and body weight loss (Fig. 4b). Older participants (i.e. those aged ≥ 65 to < 75 years or ≥ 75 years) were significantly more likely to achieve their glycaemic target (OR 3.02; 95% CI 1.25, 7.27; $p = 0.014$; and OR 9.03; 95% CI 3.34, 24.38; $p < 0.001$, respectively) than younger participants (i.e. those aged < 65 years). Participants with a longer disease duration (i.e. ≥ 10 years) were significantly less likely to achieve their target than those with a shorter disease duration (i.e. < 10 years; OR 0.36; 95% CI 0.17, 0.78; $p = 0.009$). Compared with participants with a baseline HbA1c < 7%, age-defined glycaemic target achievement was significantly less likely in those who had a baseline HbA1c ≥ 7% to < 8% (OR 0.19; 95% CI 0.05, 0.65; $p = 0.008$), ≥ 8% to < 9% (OR 0.04; 95% CI 0.01, 0.16; $p < 0.001$) or ≥ 9% (OR 0.03; 95% CI 0.01, 0.12; $p < 0.001$). Participants who lost body weight during iGlarLixi treatment were significantly more likely to achieve age-defined glycaemic targets than those who did not lose body weight (OR 3.43; 95% 1.59, 7.40; $p = 0.002$).

DISCUSSION

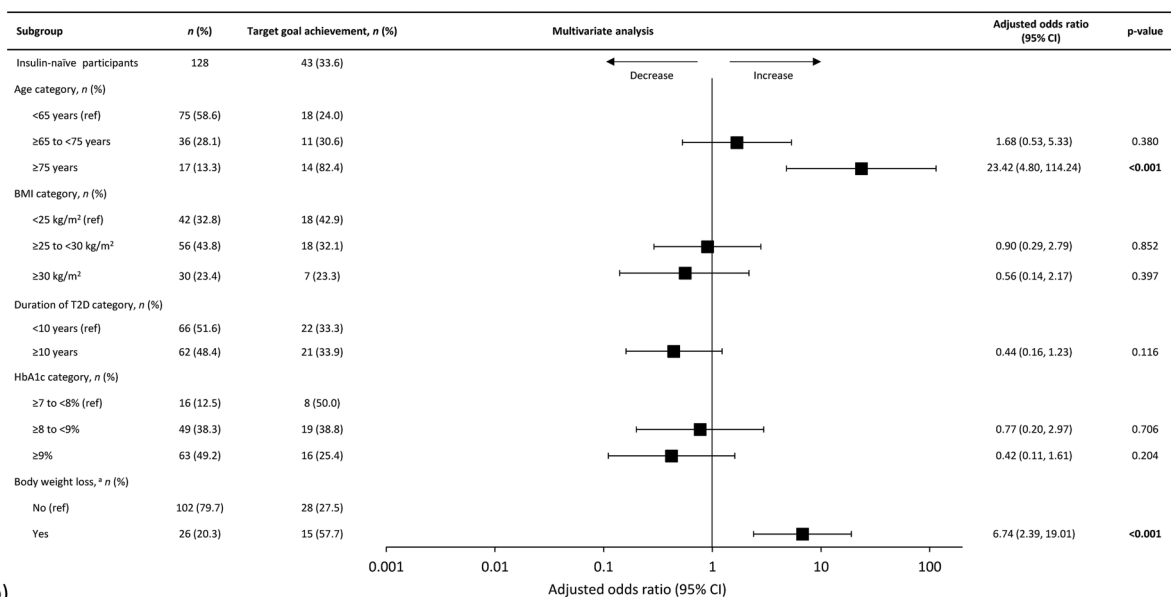The SPARTA Japan study provided real-world data on the effectiveness and safety of iGlarLixi treatment for individuals with T2D in routine clinical practice in Japan [21]. This post hoc subgroup analysis provides further information on the potential association between baseline characteristics and the achievement of glycaemic targets with 6 months of iGlarLixi treatment among both insulin-naïve and insulin-experienced individuals with T2D.

Among both the insulin-naïve and insulin-experienced cohorts in the current study, those who achieved their age-defined glycaemic target during iGlarLixi treatment were older and had lower baseline HbA1c compared with those in the not-achieved group. In addition, among insulin-experienced participants in the not-achieved group, more participants were receiving three or more concomitant OADs, biguanides or SGLT2 inhibitors at baseline compared with the achieved group. These findings are consistent with a post hoc analysis of the global LixiLan-L study [23], which found that maximum doses of iGlarLixi (i.e. 60 U/day) were required to achieve glycaemic targets in insulin-experienced individuals with a more insulin-resistant phenotype (i.e. younger with higher baseline BMI, fasting plasma glucose and insulin dose).
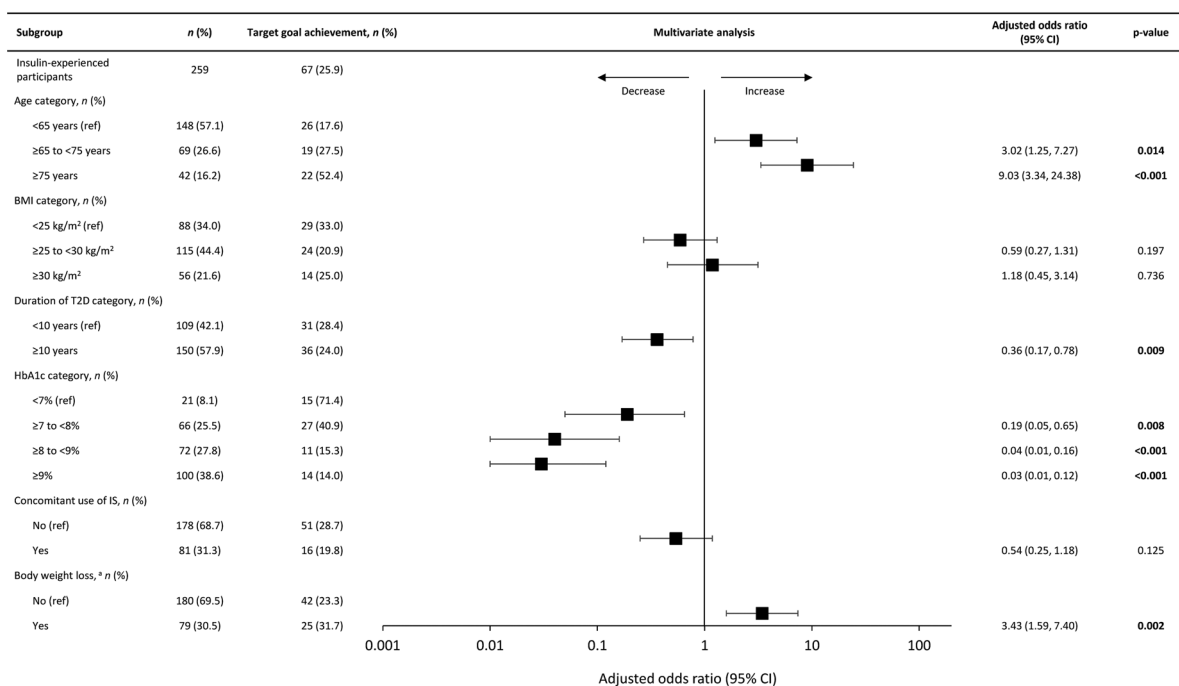
Significantly greater reductions in HbA1c from baseline to 6 months were observed in the achieved versus the not-achieved group in both the insulin-naïve and insulin-experienced cohorts. Insulin-naïve participants in the achieved group also had significantly greater reductions in body weight from baseline compared with the not-achieved group.

Insulin-naïve participants in the not-achieved group who increased their iGlarLixi dose were younger and had higher baseline HbA1c and body weight compared with the achieved group, but had generally similar characteristics to those in the not-achieved/dose-not-increased group. Smaller HbA1c reductions from baseline were observed in the not-achieved/dose-increased versus the achieved group, despite the iGlarLixi dose being significantly higher after 6 months of treatment in the not-achieved/dose-increased group. Compared with the achieved group, the not-achieved/dose-not-increased group had a higher initial iGlarLixi dose, but smaller dose increases,

(a)

Subgroup	n (%)	Target goal achievement, n (%)	Multivariate analysis	Adjusted odds ratio (95% CI)	p-value
Insulin-naïve participants	128	43 (33.6)			
Age category, n (%)					
<65 years (ref)	75 (58.6)	18 (24.0)			
≥65 to <75 years	36 (28.1)	11 (30.6)		1.68 (0.53, 5.33)	0.380
≥75 years	17 (13.3)	14 (82.4)		23.42 (4.80, 114.24)	**<0.001**
BMI category, n (%)					
<25 kg/m² (ref)	42 (32.8)	18 (42.9)			
≥25 to <30 kg/m²	56 (43.8)	18 (32.1)		0.90 (0.29, 2.79)	0.852
≥30 kg/m²	30 (23.4)	7 (23.3)		0.56 (0.14, 2.17)	0.397
Duration of T2D category, n (%)					
<10 years (ref)	66 (51.6)	22 (33.3)			
≥10 years	62 (48.4)	21 (33.9)		0.44 (0.16, 1.23)	0.116
HbA1c category, n (%)					
≥7 to <8% (ref)	16 (12.5)	8 (50.0)			
≥8 to <9%	49 (38.3)	19 (38.8)		0.77 (0.20, 2.97)	0.706
≥9%	63 (49.2)	16 (25.4)		0.42 (0.11, 1.61)	0.204
Body weight loss, [a] n (%)					
No (ref)	102 (79.7)	28 (27.5)			
Yes	26 (20.3)	15 (57.7)		6.74 (2.39, 19.01)	**<0.001**

Adjusted odds ratio (95% CI)

(b)

Subgroup	n (%)	Target goal achievement, n (%)	Multivariate analysis	Adjusted odds ratio (95% CI)	p-value
Insulin-experienced participants	259	67 (25.9)			
Age category, n (%)					
<65 years (ref)	148 (57.1)	26 (17.6)			
≥65 to <75 years	69 (26.6)	19 (27.5)		3.02 (1.25, 7.27)	**0.014**
≥75 years	42 (16.2)	22 (52.4)		9.03 (3.34, 24.38)	**<0.001**
BMI category, n (%)					
<25 kg/m² (ref)	88 (34.0)	29 (33.0)			
≥25 to <30 kg/m²	115 (44.4)	24 (20.9)		0.59 (0.27, 1.31)	0.197
≥30 kg/m²	56 (21.6)	14 (25.0)		1.18 (0.45, 3.14)	0.736
Duration of T2D category, n (%)					
<10 years (ref)	109 (42.1)	31 (28.4)			
≥10 years	150 (57.9)	36 (24.0)		0.36 (0.17, 0.78)	**0.009**
HbA1c category, n (%)					
<7% (ref)	21 (8.1)	15 (71.4)			
≥7 to <8%	66 (25.5)	27 (40.9)		0.19 (0.05, 0.65)	**0.008**
≥8 to <9%	72 (27.8)	11 (15.3)		0.04 (0.01, 0.16)	**<0.001**
≥9%	100 (38.6)	14 (14.0)		0.03 (0.01, 0.12)	**<0.001**
Concomitant use of IS, n (%)					
No (ref)	178 (68.7)	51 (28.7)			
Yes	81 (31.3)	16 (19.8)		0.54 (0.25, 1.18)	0.125
Body weight loss, [a] n (%)					
No (ref)	180 (69.5)	42 (23.3)			
Yes	79 (30.5)	25 (31.7)		3.43 (1.59, 7.40)	**0.002**

Adjusted odds ratio (95% CI)

Fig. 4 Multivariate analysis of preselected baseline characteristics affecting achievement of age-defined glycaemic targets after 6 months of iGlarLixi treatment in **a** insulin-naïve participants and **b** insulin-experienced participants. Age-defined glycaemic targets were glycated haemoglobin (HbA1c) < 7.0% for participants aged < 65 years, HbA1c < 7.5% for participants aged ≥ 65 to < 75 years and HbA1c < 8.0% for participants aged ≥ 75 years. *BMI* body mass index, *CI* confidence interval, *iGlarLixi* insulin glargine 100 U/mL plus lixisenatide, *IS* insulin secretagogues; *OR* odds ratio, *ref* reference, T2D type 2 diabetes. [a]Defined as ≥ 3% reduction in body weight from baseline

and had smaller HbA1c reductions from baseline to 6 months.

With regard to baseline characteristics, insulin-experienced participants in the not-achieved/dose-increased group were younger, and a higher proportion had a longer duration of T2D (i.e. ≥ 10 years) compared with the achieved group. Baseline body weight and the proportion of participants with a longer duration of T2D were also higher in the not-achieved/dose-increased versus the not-achieved/dose-not-increased group.

In both insulin-naïve and insulin-experienced participants, the not-achieved/dose-increased group had smaller HbA1c reductions despite receiving a higher mean iGlarLixi dose at the study end compared with the achieved group. This possibly suggests that age-defined glycaemic targets may be difficult to achieve because of higher levels of insulin resistance in some individuals. Indeed, a previous study reported extensive inter-individual variation in insulin secretion and sensitivity among people with metabolic syndrome or T2D [24].

With regard to safety, BI therapy is associated with an increased risk of hypoglycaemia [25], while GLP-1 RA therapy is often associated with a risk of gastrointestinal AEs [26]. In both insulin-naïve and insulin-experienced participants, the incidence of hypoglycaemia and gastrointestinal-related AEs during iGlarLixi treatment showed no significant difference between the achieved versus the not-achieved group, although a numerical trend towards an increased incidence of both AEs was observed in participants who achieved their age-defined glycaemic target. The incidence of hypoglycaemia and gastrointestinal-related AEs was similar in the achieved and not-achieved groups, and as discussed above, insulin-naïve and insulin-experienced participants in the not-achieved/dose-not-increased groups had small increases in iGlarLixi dose compared with the not-achieved/dose-increased group, despite having significantly higher baseline HbA1c levels. This suggests the existence of clinical inertia among Japanese individuals with T2D, particularly with regard to the uptitration of iGlarLixi dose. These results are in line with those of a previous real-world study, which demonstrated clinical inertia among Japanese individuals with early-stage T2D on OADs [11].

In the multivariate analysis, achievement of age-defined glycaemic targets in insulin-naïve participants appeared more likely in older participants (i.e. aged ≥ 75 years) and those who lost $\geq 3\%$ body weight from baseline during iGlarLixi treatment. A non-significant trend towards lower odds of age-defined glycaemic target achievement was observed in participants with higher baseline BMI and HbA1c and longer duration of T2D. In insulin-experienced participants, achievement of glycaemic targets with iGlarLixi was significantly related to age, duration of T2D, baseline HbA1c and body weight loss during treatment. These findings may indicate that older individuals and those with a shorter duration of T2D (i.e. < 10 years) more favourably benefit from iGlarLixi treatment. The significant association between body weight loss and target achievement in both insulin-naïve and insulin-experienced participants may support the importance of a healthy diet and exercise for body weight control, in addition to medication, for optimal glycaemic control in individuals with T2D. This observation is also not surprising, given that overweight and obese individuals with T2D are less likely to achieve glycaemic control than those with normal body weight [27].

The limitations of this study include its retrospective, observational study design that did not include a comparator control group, meaning that several potential non-measurable confounders may have influenced the results. In addition, the participants of this study were from selected medical institutions and, therefore, may not reflect the general Japanese T2D population. It should also be noted that as the current analysis was not pre-planned, the number of participants varied across subgroups, which could have affected the results. For example, in some subgroups, participant numbers were not large enough to show statistical significance. Moreover, the study's short duration (6 months) did not allow for assessment of long-term outcomes, such as severe cardiovascular disease and dementia, and treatment adherence was not systematically assessed; therefore, these findings should be interpreted

with caution. Although this analysis used age-defined glycaemic targets, as recommended by the JDS guidelines [7], these targets are not always applicable to individuals with T2D in routine clinical practice, where treatment goals are often adapted according to each individual's condition and needs. Further, this study assessed achievement of glycaemic targets at 6 months after iGlarLixi initiation; however, it is likely that most participants were not expected to achieve this target within this timeframe. The proportion of participants with glycaemic target achievement may have been improved with an extended period of evaluation. Lastly, the threshold for iGlarLixi dose increase was set at a mean of $\geq$ 4 dose steps based on the results of the total SPARTA Japan study population [21]; however, this threshold may not have been appropriate for all participants, and for some participants in the not-achieved/dose-increased group, this increase was not sufficient to achieve their glycaemic target, most likely because of differences in the individual's insulin resistance and β-cell function.

CONCLUSIONS

In routine clinical practice in Japan, achievement of age-defined glycaemic targets with iGlarLixi treatment for 6 months was associated with age and body weight loss, both in insulin-naïve individuals and in those who had received prior BI therapy. These results may add support to the importance of effective body weight control with a healthy diet and exercise for optimal glycaemic control with iGlarLixi treatment. Participants who did not achieve their target after 6 months of iGlarLixi treatment had smaller HbA1c reductions than those who did achieve their target, despite some participants receiving significantly higher iGlarLixi doses. This may highlight the importance of uptitration when needed during iGlarLixi treatment in order to achieve age-defined glycaemic targets in individuals with T2D.

acquisition and analysis and interpretation. All authors contributed to the development and critical review of the manuscript, and approved the final draft.

Data Availability. The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Daisuke Yabe has received consulting/lecture fees from Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim, Eli Lilly Japan K.K. and Kyowa Kirin Co., Ltd; and grants from Arkray Inc., Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim, Taisho Pharmaceutical Co. Ltd. and Terumo Corporation. Munehide Matsuhisa has received honoraria from Sanofi K.K., Takeda Pharmaceutical, Eli Lilly Japan, Mitsubishi Tanabe Pharma Corporation, Astellas Pharma Inc., Novo Nordisk Pharmaceuticals Ltd., Sumitomo Pharm, Orizuru Therapeutics, Abbott Japan and MSD; research funding from Sysmex and Nissui; and subsidies or donations from Novartis Pharma, Sanofi K.K. and Novo Nordisk Pharmaceuticals Ltd. Yoko Takahashi and Yukiko Morimoto are employees of Sanofi K.K. (and do not hold shares/stock options in the company). Yasuo Terauchi has received honoraria for serving on advisory boards for MSD, Boehringer Ingelheim, Mitsubishi Tanabe Pharma Co., Daiichi Sankyo, Novo Nordisk, Eli Lilly Japan, Sanofi K.K., Astellas Pharma and AstraZeneca; honoraria for lectures from MSD, Ono Pharmaceuticals, Boehringer Ingelheim, Mitsubishi Tanabe Pharma Co., Daiichi Sankyo, Sanwa Kagaku Kenkyusho, Novo Nordisk, Eli Lilly Japan, Sanofi K.K., Sumitomo Pharma Co., Ltd., Shionogi, Bayer Yakuhin, Astellas and AstraZeneca; and research funding from MSD, Ono Pharmaceuticals, Boehringer Ingelheim, Novartis, Takeda, Daiichi Sankyo, Novo Nordisk, Eli Lilly Japan, Sanofi K.K. and Sumitomo Pharma Co., Ltd.

Ethical Approval. SPARTA Japan was a retrospective observational study and, as such, compliance with the Declaration of Helsinki 1964 was not required. However, the study protocol for SPARTA Japan was approved on 24 February 2021 by a central ethics committee (Sone Clinic in Tokyo, Japan) for some institutions and by their own institutional ethics committee in other institutions. Written informed consent for the use of participant data was also obtained.

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