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ORIGINAL RESEARCH

Ease of Use of the iGlarLixi SoloStar Pen from the LixiLan ONE CAN Pen Sub-Study: Questionnaire Findings from People Living with Type 2 Diabetes and Their HealthCare Providers

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ABSTRACT

Introduction: For people with type 2 diabetes mellitus who do not achieve glycated hemoglobin A1C targets after treatment with basal insulin therapies, additional therapy with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) may be required. One option is to use a once-daily fixed-ratio combination (FRC) of basal insulin and a GLP-1 RA such as iGlarLixi (which is composed of insulin glargine 100 U/ml and lixisenatide). However, the ease of transitioning from basal insulin to an FRC has not been studied.

Methods: This sub-study of the LixiLan ONE CAN trial (NCT03767543) was conducted to assess the ease of transitioning from insulin glargine 100 U/ml to the FRC, iGlarLixi, using the iGlarLixi SoloStar® pen. Patients completed a validated, ten-item questionnaire, and healthcare professionals (HCPs) completed a five-item questionnaire. Both questionnaires used either five-point Likert scales or yes/no answers as appropriate, and both were completed after 4 weeks of using the iGlarLixi SoloStar pen.

Results: Overall, 95.1% of patients reported that the iGlarLixi Solostar pen was "easy" or

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"very easy" to use. Similarly, 100% of HCPs reported that it was "easy" or "very easy" to train people to use the pen. Nearly all participants (97.5% of patients and 94% of HCPs) responded that they would recommend the iGlarLixi Solostar pen to others.

Conclusions: These results suggest that during the transition from insulin glargine 100 U/ml to iGlarLixi, there were no difficulties associated with using the iGlarLixi SoloStar pen injector regarding instruction for use by HCPs or actual use by the majority of patients. The results indicate a broad consensus between patients and HCPs on the relative simplicity of transitioning from self-administration of insulin glargine 100 U/ml to iGlarLixi.

Trial Registration: ClinicalTrials.gov identifier, NCT03767543; Date of registration: December 6, 2018; Retrospectively registered.

PLAIN LANGUAGE SUMMARY

Many people take basal insulin to control their blood sugar, but for those in whom basal insulin injections do not work well enough to achieve their target blood glucose, treatment needs to be advanced. One option to do this is with a fixed-ratio combination therapy that combines basal insulin with a GLP-1 receptor agonist, such as iGlarLixi. Both basal insulin and fixed-ratio combination therapies are administered using injection pens, but the ease of transitioning from a basal insulin pen to a fixed-ratio combination pen has not been assessed. In this study, people with type 2 diabetes who had previously received the basal insulin insulin glargine 100 U/ml using a SoloStar® pen, and who transitioned to the iGlarLixi SoloStar pen, were asked to complete a questionnaire to rate their experience of using the new pen injector after 4 weeks of use. Their doctors also completed a questionnaire at the same time. Over 95% of patients reported that the iGlarLixi SoloStar® pen was "easy" or "very easy" to use, and all of the doctors reported that it was "easy" or "very easy" to train people to use it. Nearly all of those who completed questionnaires (97.5% of patients and 94% of doctors) said that they would recommend use of the iGlarLixi Solostar pen to others. These results suggest that both patients and their doctors thought that it was relatively easy to transition from self-administration of insulin glargine 100 U/ml to iGlarLixi using the SoloStar pen injector.

Keywords: Fixed-ratio combination; iGlarLixi; Injection; Insulin glargine 100 U/ml; Questionnaire; SoloStar; Type 2 diabetes

Key Summary Points

Why carry out this study?

When people with type 2 diabetes (T2D) do not achieve glycated hemoglobin A1C < 7% with basal insulin, one option to advance treatment is to use a basal insulin/glucagon-like peptide-1 receptor agonist fixed-ratio combination therapy (FRC), such as iGlarLixi.

FRCs are provided as prefilled disposable pens similar to those used for basal insulins, but ease of transition from basal insulin to iGlarLixi has not been investigated.

This questionnaire-based study was performed to assess the ease of use of the iGlarLixi SoloStar® pen when transitioning from insulin glargine 100 U/ml, both for people (patients) with T2D and healthcare professionals (HCPs).

What was learned from this study?

Overall, 95.1% of patients reported that the iGlarLixi Solostar pen was "easy" or "very easy" to use, and 100% of HCPs reported that it was "easy" or "very easy" to train people to use the iGlarLixi SoloStar pen; 97.5% of patients and 94% of HCPs would recommend it to others.

These results indicate a broad consensus between patients and HCPs of the relative simplicity of transitioning from self-administration of insulin glargine 100 U/ml to iGlarLixi using the SoloStar pen injector.

INTRODUCTION

Fewer than 30% of people with type 2 diabetes (T2D) achieve the recommended glycated hemoglobin (A1C) level of < 7% after treatment with basal insulin [1–3]. One option to advance therapy is to use a glucagon-like peptide-1 receptor agonist (GLP-1 RA) in a fixed-ratio combination (FRC) formulation with basal insulin [4, 5].

Two basal insulin/GLP-1 RA FRC agents are available as once-daily injections. iGlarLixi is a combination of insulin glargine 100 U/ml (Gla-100) and lixisenatide 33 μg/ml, available in the US and Canada as a 3:1 ratio, with each unit of Gla-100 given with approximately 0.33 μg of lixisenatide. iGlarLixi can deliver Gla-100 over a range of 15–60 U/day in 1-U steps [6]. IDegLira is a combination of insulin degludec (IDeg) 100 U/ml and liraglutide 3.6 mg/ml, delivering IDeg doses of 10–50 U/day; each U of IDeg is administered with 0.036 mg of liraglutide [7]. FRC medications are provided as prefilled disposable pens that contain a fixed ratio of the basal insulin and the GLP-1 receptor agonist. Doses are titrated according to the insulin component of the medication; although patients and healthcare professionals (HCPs) may find FRC pens similar to insulin pens, there are differences in that as the insulin dose in an FRC pen is increased, the GLP-1 RA dose also increases in a fixed ratio. iGlarLixi is administered using a 3-ml subcutaneous injection pen (SoloStar®, sanofi-aventis US LLC, Bridgewater, NJ) [6]. Results of the Phase 3 LixiLan-L trial in individuals with T2D inadequately controlled on basal insulin plus metformin revealed that treatment with iGlarLixi conferred significantly greater reduction from baseline in A1C compared with insulin glargine (– 1.1 vs. – 0.6%, $p < 0.0001$ for a mean final A1C of 6.9% vs. 7.5%) and more participants achieved A1C target of < 7.0% (55% vs. patients 30%, respectively) [8]. When advancing treatment after basal insulin, iGlarLixi can provide a simpler treatment option compared with complex insulin regimens [9], but the ease of transition from basal insulin to iGlarLixi has not been investigated. LixiLan ONE CAN was a phase 3b, 26-week, open-label, randomized, parallel group, multicenter study conducted in Canada (ClinicalTrials.gov identifier, NCT03767543) that compared the efficacy and safety of daily versus weekly titration algorithms for iGlarLixi in people with T2D suboptimally controlled on basal insulin and oral antihyperglycemic agents [10]. All participants used the SoloStar pen (3:1 ratio of Gla-100:lixisenatide; 15–60 U Gla-100). The study met its primary endpoint, with daily titration of iGlarLixi achieving both non-inferiority and superiority versus weekly titration in change from baseline in A1C at week 26; least squares mean difference: 0.32% (95% confidence interval [CI]: 0.07–0.57%); $p < 0.0001$. This sub-study of LixiLan ONE CAN was performed to better understand the experiences of both people living with T2D and HCPs when transitioning from Gla-100 (Lantus®, sanofi-aventis US LLC, Bridgewater, NJ) to the iGlarLixi SoloStar pen.

COMPLIANCE WITH ETHICS GUIDELINES

The study protocol was approved by Institutional Review Board/Independent Ethics Committees (Advarra [IRB00000971], Nova Scotia Health Authority Research Ethics Board [IRB00010873], Western University Health Sciences Research Ethics Board [HSREB; IRB00000940]). The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Council for Harmonization guidelines for Good Clinical Practice and all applicable laws, rules, and regulations. Informed consent was obtained prior to conducting any study-related procedures.

METHODS

Eligibility criteria for the LixiLan ONE CAN trial have been previously published [9]. Briefly, adults with T2D (A1C ≥ 7.5% and ≤ 10.5%) who had received basal insulin with or without oral antihyperglycemic agents for ≥ 6 months

were switched from basal insulin to daily treatment with iGlarLixi. Study participants were randomized 1:1 to daily or weekly titration and taught to self-titrate iGlarLixi either once daily (1 unit/day) or once weekly (2 or 4 units/week) to achieve a target self-monitored fasting plasma glucose concentration of 4.4–5.6 mmol/l (80–100 mg/dl). The demographic characteristics of the primary population have been previously published [10]. Briefly, participants had a mean (standard deviation [SD]) age of 64.1 (11.0) years, and 62.3% were male. Mean (SD) baseline A1C was 8.51 (0.81)%, and mean (SD) duration of T2D was 16.5 (8.0) years. The pen sub-study was pre-specified with the specific objective of assessing the ease of use of iGlarLixi SoloStar pen injector by both patients and HCPs after 4 weeks of transitioning from Gla-100. Based on 73 patients, the width of the 95% CI was 5%. Considering dropouts, the plan was to include responses from approximately 80 patients, but the number for inclusion was not capped. To be eligible for inclusion, participants had to be receiving Gla-100 using the SoloStar pen prior to study entry. Those treated with basal insulin other than Gla-100 were excluded. Training for HCPs on use of the iGlarLixi SoloStar pen was standardized with detailed information on dose selection, initiation, handling, pen components, safety test, injection technique, and troubleshooting. Titration data were collected during study visits/telephone calls. Any questions/issues were addressed by a Titration Committee. Participants were provided with an instruction leaflet and were trained to use the pen by study staff at the time of randomization, with periodic reinforcement thereafter.

Ease of use of the iGlarLixi SoloStar pen was assessed by patients via completion of a ten-item questionnaire (Table 1). As no validated questionnaires were identified in the literature, one was developed in English following a literature review of questionnaires used to evaluate ease of use of injectable pens for the treatment of diabetes. As with any patient-reported outcome questionnaire, content validity was evaluated to ensure that the whole questionnaire (i.e., instructions, questions, and answers) was fully understood by patients, that they interpreted all questions correctly, and that they considered the content relevant for pen injector users. People with T2D from the US with experience in using different insulin pen injectors ($n = 12$) reviewed the questionnaire and shared their thoughts by completing a survey and then through an Image Annotation exercise ($n = 11$). Most participants ($n = 9$) found the questionnaire easy to understand and determined that the content appropriate and consistent with their pen experience ($n = 10$). Following patients' recommendations, minor adaptations were made to the wording to improve clarity. As the questionnaire was intended to be used and indeed was used as a purely descriptive analysis at the item level, there was no intention to create a specific global score from the single items; therefore, it was not deemed necessary to perform psychometric validity and/or evaluate the psychometric properties of the questionnaire scores. The HCP questionnaire was developed by the clinical team based on previous literature and clinical expert opinion. Study participants completed the questionnaire 4 weeks after randomization, before any interaction with site staff at this study visit. Patients were asked to complete the questionnaire by themselves, independently from investigator and site staff, and without any help from friends or relatives. The HCP questionnaire comprised five questions (Table 1); these were also completed 4 weeks after randomization. HCPs completed a questionnaire for each patient; only HCP questionnaires relating to patients who had completed a patient questionnaire were included in the analysis. HCPs may have also trained patients who had used other basal insulin analogs and thus were asked about their comparative experience (see Table 1, HCP Question [Q]3).

Descriptive analyses were used to report the results relating to general use of the SoloStar pen (Q1–8 of the patient questionnaire and Q1–4 of the HCP questionnaire). For Q9–10 of the patient questionnaire and Q5 of the HCP questionnaire, the percentage of "yes" responses was calculated. For the patient questionnaire, correlations were calculated for all ten questions. Three stepwise regressions ($p < 0.05$) were performed to determine which characteristics

Table 1 Questionnaire details

Patient questionnaire		
Question (Q)	**How easy or difficult is it to…**	**Response options**
Q1	Learn to use the SoloStar pen	5-point Likert scale:
Q2	Select the dose needed	(1) very easy
Q3	Read the dose selected	(2) easy
Q4	Change the dose	(3) neither easy/nor difficult
Q5	Grip the pen while injecting	(4) difficult
Q6	Push down the injection button	(5) very difficult
Q7	Know that the full dose has been injected	
Q8	Use the pen, overall	
	Would you…	
Q9	Like to continue to use the pen after the study?	Yes/no
Q10	Recommend the pen to others?	
HCP questionnaire		
Question (Q)	**How easy or difficult is it…**	**Response options**
Q1	To train patients to use the SoloStar pen	5-point Likert scale:
Q2	For patients to learn to use the pen	(1) very easy
Q3	To train patients to use the pen if transitioning from Gla-100 vs. other insulins	(2) easy (3) neither easy/nor difficult (4) difficult (5) very difficult
Q4	How long did it take to train the patient to use the pen?	Time
Q5	Would you recommend the pen to others?	Yes/no

were associated with responses to Q8–10. Thus, overall ease of use of the pen (Q8), whether patients would continue to use the pen after the study (Q9), and whether they would recommend the pen to others (Q10) were the dependent variables and Q1–7 the independent variables.

RESULTS

Among the 93 participants who met the criteria for the sub-study, 11 did not complete the questionnaire. One patient was randomized, but did not receive treatment, and six discontinued the study on or before day 28 (four due to adverse events [AEs]; two withdrew consent), one patient discontinued on day 43 because of an AE, and three further patients who completed the study did not complete the questionnaire. Adverse events reported in the primary study [10] were comparable for daily and weekly titration of iGlarLixi and consistent with Phase 3 studies [8, 11].

For the seven questions about general use of the pen (learning to use it; selecting, reading,

and changing the dose; gripping and pushing down the injector button; knowing that the full dose had been injected), most patients responded that it was "easy" or "very easy" to do so, with the range being 87–94% (Fig. 1a). For overall ease of use (Q8), 95.1% (78/82) of patients reported that overall, the pen was "easy" or "very easy" to use, and the remaining four patients (4.9%) rated it "neither easy nor difficult." A response of "difficult" was given rarely; 1.2% of patients thought it was difficult to read the dose selected (Q3); 1.2% thought it was difficult to know if the full dose had been injected (Q7), and 2.4% thought it was difficult to push down the injection button (Q6). None of the patients gave the response of "very difficult" for any question. Ease/difficulty of learning to use the SoloStar pen (Q1) had the highest proportion of "very easy" responses (63/82); ease/difficulty of pushing down the injection button (Q6) had the lowest proportion of "very easy" responses (40/82) and the highest proportion of "difficult" responses (2/82).

When asked if they would continue to use the iGlarLixi SoloStar pen after the study (Q9), 80/82 patients (97.5%) said "yes", and the same proportion (97.5%) said they would recommend it to others (Q10). Responses to questions relating to general use of the pen (Q1–8) did not differ according to whether titration was performed daily or weekly (data not shown).

Results of the regression analysis indicated that patient responses to ease/difficulty of gripping the pen while injecting ([Q5]; $p < 0.0001$) and to ease/difficulty of pushing down the injection button ([Q6]; $p < 0.0001$) were associated with the overall ease/difficulty of using the pen (Q8). Given that answers to whether patients would continue to use the pen after the study (Q9) and whether they would recommend pen to others (Q10) were "yes" in nearly all cases, the regression model could not establish any associations for those responses.

Seventy HCPs at 18 study sites completed the HCP questionnaire for a total of 81 patients; these were then matched to those patients who completed the patient questionnaire. All HCPs (100%) reported that it was "easy" or "very easy" to train patients to use the iGlarLixi SoloStar pen (Q1), and 100% thought it was "easy" or "very easy" for patients to learn to use the pen (Q2) (Fig. 1b). Additionally, 89% of HCPs said that it was easier to train patients to use the iGlarLixi SoloStar pen if they had been transitioning from Gla-100 compared with other types of basal insulin (Q3). The "difficult" or "very difficult" responses were never used by HCPs. HCPs reported it took them 11.4 (± 4.8) min on average to train patients to use the pen. Similar to the results with patients, a high proportion of HCPs (66/70 [94.3%]) said they would recommend the pen to others.

DISCUSSION

The results of this pre-planned sub-study of the LixiLan ONE CAN trial suggest that people with suboptimally controlled T2D who switched from Gla-100 to iGlarLixi reported that the iGlarLixi SoloStar pen was easy or very easy to use. HCPs who provided training on pen use reported a similar view of its ease of use and described the training per the study protocol as being easy, taking about 11 min. Nearly all respondents (both patients and HCPs) said they would recommend the pen to others. Most HCPs considered it easier to train patients transitioning from Gla-100 versus other basal insulin analogs.

Studies have confirmed that the majority of people prefer insulin pens over the vial/syringe method and find them easier to use [12, 13]. Furthermore, insulin pens have been shown to be associated with increased persistence and adherence [14–16], fewer emergency department and physician visits, and lower all-cause treatment costs than the vial/syringe method [17]. However, use of insulin pens is very much dependent on both HCP and patient perceptions, with encouragement of use by the HCP, and patient perceptions that pen use will facilitate self-care (rather than convenience per se), and no increases in pen cost, being the most important factors influencing pen use [18].

When advancement of therapy becomes necessary to overcome poor glycemic control, increasing the complexity of treatment has been shown to reduce adherence [19–21]. The results of this pen use sub-study indicate a broad

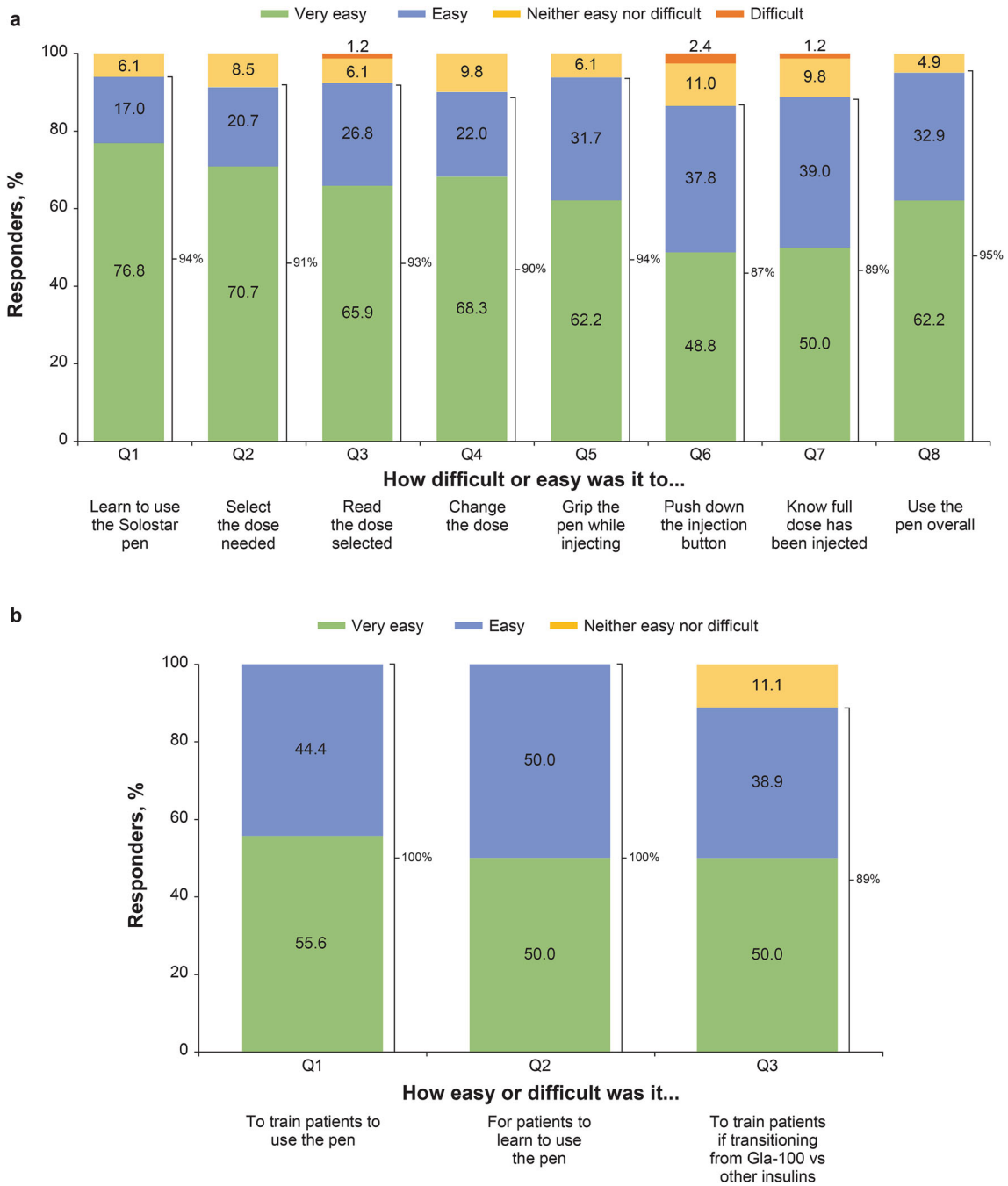

Fig. 1 Questionnaire results: **a** patient questionnaire (questions 1–8) for overall population ($N = 82$); **b** healthcare provider questionnaire (questions 1–3) ($N = 70$)

consensus between patients and HCPs about the relative simplicity of transitioning from self-administration of Gla-100 to iGlarLixi using the SoloStar pen injector. Existing familiarity of using a similar type of pen is likely to increase confidence to use a new pen, with the added benefit of minimal retraining. This has the advantage of advancing insulin therapy with the addition of GLP-1 RA while retaining a similar titration concept with which users are

already familiar. This is likely to improve adherence to and persistence with therapy, which may translate to a positive impact on real-world effectiveness that is consistent with the outcomes of the LixiLan-O and LixiLan-L studies [8, 11].

The key limitations of this sub-study were the relatively small number of patients and HCPs included in the analysis and that the pens (i.e., including Gla-100) were the same SoloStar format. Although protocol-defined, the fact that participation by patients was limited to those who had previously received Gla-100 using the SoloStar pen limits the generalizability of these results to patients switching from other basal insulins and insulin pens.

CONCLUSION

The results reported here indicate that when advancement of therapy is needed to overcome suboptimal glycemic control, transition from Gla-100 to iGlarLixi both using a SoloStar pen, there were no difficulties with the instruction and use of the pen for either HCPs or the vast majority of patients.

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Compliance with Ethics Guidelines. The study protocol was approved by Institutional

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

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