Correct Use of a New Reusable Insulin Injection Pen by Patients with Diabetes: A Design Validation Study

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Abstract

Background:

Insulin pen devices are currently being used by approximately half of insulin users worldwide. ClikSTAR® (sanofi-aventis) is a novel reusable insulin pen for injecting either long-acting insulin glargine or short-acting insulin glulisine. The objective of this study was to demonstrate that individuals with diabetes could use the ClikSTAR pen correctly.

Methods:

In this open-label, single-center study, people with diabetes delivered three 40 U insulin doses after receiving training from a diabetes specialist (group A, $n = 256$) or after self-training (group B, $n = 47$). Administration of a dose of 75–115% of the intended dose was considered successful. Adverse events (AEs) and product technical complaints (PTCs) were recorded.

Results:

In group A (68% females, 93% Hispanic ethnicity, 97% type 2 diabetes mellitus, mean ± standard deviation age 52 ± 11 years, diabetes duration 11 ± 7 years), half of the participants had prior experience in using insulin pen devices. All except one participant (99.6%) in group A successfully delivered three insulin doses. The lower one-tailed 95% confidence limit for the success rate (98.2%) was higher than the predefined target of 90%. Demographic/baseline characteristics were similar in group B, but 70% had not previously used an injection pen. Group B also showed success; 93.6% of participants successfully completed three dose deliveries. No AEs were reported, although one participant (0.4%) in group A reported one PTC during the training period that was due to a blocked needle.

Conclusions:

This study successfully validated the ClikSTAR pen for use by individuals with diabetes.

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Abbreviations: (AE) adverse event, (PTC) product technical complaint, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus

Keywords: design validation, reusable insulin pen device, type 2 diabetes mellitus

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Effective management of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) relies on maintaining glycemic control within the normal range and keeping the hemoglobin A1c level below 7% or, preferably, 6.5%.[1] Insulin therapy is essential in T1DM and is becoming more commonly used in T2DM, particularly in light of the American Diabetes Association/European Association for the Study of Diabetes position statement, which describes that insulin therapy is the most effective method of lowering blood glucose levels and is capable of achieving glycemic control at any disease stage in T2DM.[2] Insulin can be administered via several methods such as vial and syringe, insulin pump, and insulin pen. In particular, insulin pens have increased the convenience and flexibility of insulin therapy compared with the traditional vial and syringe administration method.[3,4]

Despite the continuing advances in insulin administration technology, the potency of insulin therapy means that dosing errors can have adverse consequences for the health of patients with diabetes, whereas the accurate insulin dosing associated with insulin delivery devices has the potential to lead to better long-term outcomes. Insulin pen devices have repeatedly been demonstrated to exhibit greater dose accuracy compared with syringes.[5,6] Ongoing development to achieve further improvements in insulin pens and facilitate insulin injection is a major focus. In particular, developments have focused on prefilled pens such as SoloSTAR® (sanofi-aventis),[7,8] KwikPen® (Eli Lilly),[9–11] and FlexPen® (Novo Nordisk),[12,13] which have provided improvements in terms of ease of use, injection force, and patient preference. However, it is also important to acknowledge that 29% of insulin users worldwide administer insulin with a reusable pen,[14] for reasons that might include individual preference, cost or environmental impact, and that the advances made in prefilled pen technology are transferred to reusable pens.

ClikSTAR® (sanofi-aventis) is a novel, reusable insulin pen device developed as part of the ongoing development of insulin pens aimed at improving ease of use, injection force, differentiating features, and dose accuracy.[7,15] ClikSTAR insulin pens are fitted with cartridges for the injection of either the long-acting insulin glargine or the short-acting insulin glulisine. The aim of this study was to demonstrate that individuals with diabetes could use the ClikSTAR device correctly in a simulated real-world clinical setting after receiving active training from a diabetes specialist.

Methods

Participants

Individuals aged 13–79 years who had been diagnosed with T1DM or T2DM for at least 1 year and who were able to read and understand English were eligible for this study. Exclusion criteria included individuals who had unsuccessfully used, or attempted to use, insulin pens within the past 2 years; current addiction/abuse of alcohol or drugs; diagnosis of dementia or another mental condition rendering them incapable of understanding the nature, scope, and possible consequences of the study; severe visual or dexterity impairment; individuals unlikely to comply with the protocol; and participation in a clinical trial and/or device validation study within the past 3 months. All participants provided written, informed consent. Participants could voluntarily withdraw at any time before study completion, irrespective of the reason, or could be withdrawn at the investigator's discretion. Participants who showed extreme difficulty in handling the insulin pen or who were not able to remove the cap, insert the cartridge, or attach the needle during the initial training periods were excluded from the study before entering the validation phase, because they would generally be excluded from using insulin pens in clinical practice.

Study Design

This was an open-label, single-site (Diabetes and Glandular Disease Clinic, San Antonio, TX), single-visit, two-arm, design validation study. The participants included in the study were either trained by a diabetes specialist (group A) or self-trained (group B) before performing the validation tests. The study design is presented in **Figure 1**.

Participants in group A were given a face-to-face training session over 30–60 minutes, which was delivered by a trained diabetes specialist. The training could be performed in groups with no more than four patients per educator. During the training session, the participants were given a demonstration of the ClikSTAR device and instructions on how to insert the cartridge and needle, set and deliver a safety dose, and set and deliver a standard dose of insulin (40 U). The safety test involved

set up correctly and that air bubbles that may disrupt the test had been removed. The participants were then asked to perform two assistance-free demonstrations of using the ClikSTAR device, which included insertion of the insulin cartridge, attachment of the needle, execution of the safety test and dose delivery, and a review of the instructional leaflet. This scenario was designed to mimic clinical practice for people starting insulin pen injections (or switching to a different pen) in which a health care provider provides the patient with training on how to use the new pen correctly.

Participants in group B were given the instructional leaflet, the insulin pen, a cartridge, needles, and a telephone helpline number and were instructed to learn how to use the ClikSTAR device in the absence of direct training. This self-directed learning session lasted approximately 30 minutes. This scenario was designed to mimic a less likely practice environment, where the participant receives the insulin pen and instructional leaflet without any training by a diabetes specialist and learns how to use the device on their own. The participants in this group were allowed to telephone the diabetes specialist to request additional information. Participants were enrolled into group B once group A enrollment had been completed. Inclusion in both groups was not possible.

For device validation, after the appropriate training sessions, all participants were asked to insert a pen needle, perform a safety test, and inject a 40 U dose of insulin glargine into a receptacle, rather than as an actual injection. This procedure was to be repeated three times. The investigators were not allowed to assist or guide the participants, except to ensure that nobody injected themselves with insulin. The doses delivered were assessed by the investigator who visually inspected, weighed, and photographed the device on the weighing scale before and after each procedure. All digital photographs of the pen were evaluated by an independent expert reviewer to determine whether any errors were made by the investigator.

Participants were disqualified from the dose delivery demonstration according to the following criteria: (1) participant error—the participant was unable to remove the insulin pen cap or to attach the needle to permit a dosing measurement; (2) investigator error—the study investigator made a critical mistake that affected the conduct of the test or the system being tested, such as weighing the pen with the inner or outer cap attached,

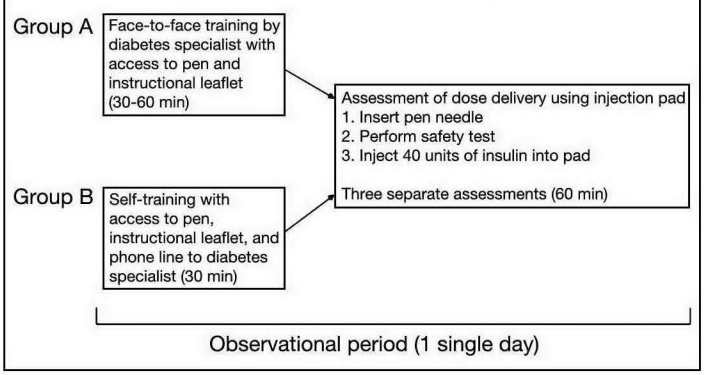

Figure 1. Study design.

as identified by photograph; (3) scale malfunction—malfunction of the scale used to weigh the pen device to calculate the insulin dose delivered; and (4) pen disqualification—if participants observed that a device was malfunctioning, they could request a new one. The malfunctioning pen together with the attached needle was sent for investigation following the product technical complaint (PTC) process. Since a visibly malfunctioning pen would normally be replaced in real practice before any injections were carried out, all dosing measurements with this pen were excluded from the analysis.

The primary analysis variable was the proportion of participants delivering a successful dose on all three dose delivery repetitions after active training by a diabetes specialist (group A). The main secondary analysis variable was the proportion of participants delivering a successful dose on all three dose delivery repetitions after self-training (group B). Additional secondary endpoints included correct insulin dose (75–115% of intended dose, i.e., 30 to 46 U for an intended dose of 40 U—based on advisory board recommendations); safety endpoints [adverse events (AEs) and PTCs]; the proportion of participants who requested additional instructions by calling the diabetes specialist during the training period (for the self-trained participants), who performed the safety test correctly before each of the three dose delivery repetitions, and who used the instructional leaflet during the dosing period; the proportion of dose delivery repetitions for which a successful dose was delivered; and the accuracy and precision of the device based on the three dose injections per participant.

Statistical Analyses

A total of 321 participants were planned for inclusion in this study (266 in group A and 55 in group B). Sample sizes were determined based on a 90% success

ensure that the one-sided 95% lower confidence bound would exclude 90% with a statistical power of 90%. Given an expected dropout rate or ineligible results of 5%, 266 participants were to be included in group A to provide 239 evaluable participants. For group B, only a descriptive analysis was planned, and with a success rate expected to range from 60–80%. Fifty participants were deemed sufficient to allow calculation of a one-sided 95% confidence interval with a precision of 9.3–11.4%, and 55 participants were to be included to ensure 50 evaluable participants. The lower limit of the one-sided 95% confidence intervals for the success rates was calculated according to the Clopper–Pearson method. Statistical analyses were performed using all evaluable participants, while safety was assessed in all included participants.

Results

Study Population

A total of 345 participants were enrolled in the study, 276 in group A and 69 in group B. In group A, 10 participants who experienced difficulties during the training period were withdrawn after training, and a further 10 participants were disqualified because of investigator error (for 1 participant, the printed weight was lost, and for 9 participants, photographs of the device taken during the validation session were missing). Consequently, 256 participants were included in the evaluation of group A. In group B, of the 69 participants enrolled, 1 participant did not wish to continue the study after self-training, 3 participants were disqualified due to investigator error (missing photographs), and 18 participants were disqualified because of participant errors (15 participants were unable to attach the needle, 2 participants performed only one dose assessment, and 1 participant was unable to insert the insulin cartridge or attach the needle). Therefore, 47 participants were included in the evaluation of group B; the safety population included all 276 participants in group A and all 69 participants in group B. The characteristics of the evaluable populations are shown in **Table 1** and were broadly comparable between both groups. In group A, 2.7% (n = 7) and 97.3% (n = 249) had T1DM and T2DM, respectively, and the respective proportions in group B were 6.4% (n = 3) and 93.6% (n = 44). However, a greater proportion of participants in group A versus group B reported that they had prior experience of using an insulin injection pen [46.5% (n = 119) versus 29.8% (n = 14), respectively; **Table 1**].

Participant Characteristics

	Statistics	Group A n = 256	Group B n = 47
Age (years)	Mean ± standard deviation, range	52.1 ± 10.7, 23–73	49.7 ± 13.6, 19–69
Age			
<18 years	n (%)	0	0
18–40 years	n (%)	36 (14.1)	9 (19.1)
40–65 years	n (%)	188 (73.4)	31 (66.0)
≥65 years	n (%)	32 (12.5)	7 (14.9)
Gender			
Male	n (%)	83 (32.4)	22 (46.8)
Female	n (%)	173 (67.6)	25 (53.2)
Ethnicity			
Hispanic	n (%)	237 (92.6)	42 (89.4)
Not Hispanic	n (%)	19 (7.4)	5 (10.6)
Duration of diabetes (years)	Mean ± standard deviation, range	10.9 ± 7.4, 1.1–39.4	8.9 ± 6.6, 1.5–26.5
Type of diabetes			
Type 1	n (%)	7 (2.7)	3 (6.4)
Type 2	n (%)	249 (97.3)	44 (93.6)
Experience with injection pen			
Yes	n (%)	119 (46.5)	14 (29.8)
No	n (%)	137 (53.5)	33 (70.2)

Assessment of Dose Delivery after Diabetes Specialist Training

The majority of participants in group A delivered three successful doses of 40 U (i.e., between 30 and 46 U) after diabetes specialist training [99.6% (n = 255); 95% lower bound: 98.2%; **Figure 2**]; only one subject did not deliver all three doses correctly (**Table 2**). This individual, a 52-year-old Hispanic female who had previously used an injection device, successfully delivered the first two doses (39.0 and 39.6 U) but not the third dose, delivering a dose of 48.8 U instead of 40 U. Overall, 767 of 768 individual doses (99.9%) were within the predefined target range of 30–46 U.

Assessment of Dose Delivery after Self-Training

As in group A, the majority of participants in group B delivered three successful doses after self-training [93.6% (n = 44); 95% lower bound: 84.3%; **Figure 2**]. Meanwhile, 3 participants (6.4%) did not deliver all three doses correctly (**Table 2**), with seven dose delivery failures. Of these 3 participants, 2 did not use the instruction leaflet during the insulin pen set up and did not dial the correct target dose of 40 U during each

safety test, and successfully delivered the required dose during the first and second dose assessments, but failed the safety test and dose delivery during the third assessment. Overall, 134 of 141 doses (95%) were within the predefined target range of 30–46 U.

Safety

None of the enrolled participants (n = 345) reported an AE during the study. One participant reported one PTC during the study. This PTC was investigated and was found to be due to a blocked needle rather than a fault with the pen.

Discussion

The results of this study demonstrate that the majority of participants were able to deliver three consecutive doses of insulin in a simulated clinical setting after receiving training from a diabetes specialist (group A) or after self-training (group B). Indeed, 99.6% of participants in group A correctly administered three doses with the ClikSTAR device after training from a diabetes specialist, and the 95% lower bound was 98.2%, which was above the predefined limit of 90%. Participants in group B appeared to be slightly underdosing, and the resulting success rate in group B was lower. This was to be expected because the participants relied on instruction manuals, a helpline, or their own experience and were not given feedback on whether their use of the device was correct before the validation test.

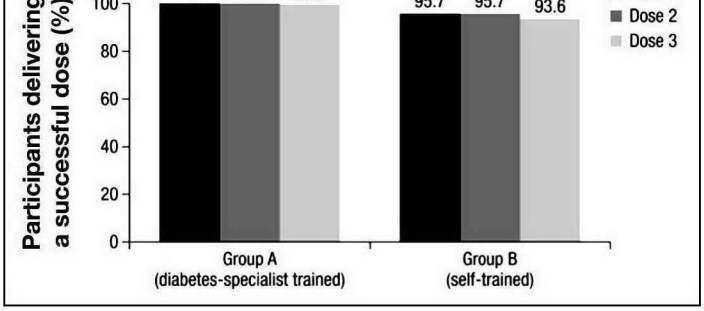

Figure 2. Participants delivering a successful dose.

Notably, there were no AEs reported in this study and no insulin pen malfunctions; the only PTC reported was subsequently attributed to a blocked needle rather than to the device itself. In actual clinical use, people using insulin pen devices are recommended to set and deliver a safety dose, thus confirming that the full system (device and needle) is functioning correctly, as demonstrated by the appearance of insulin at the tip of the needle. If no insulin is seen, the user should replace the needle and repeat the test before injecting, in addition to checking that there is sufficient insulin left in the cartridge. Performing such safety tests before injecting is an integral part of good treatment practice and can help to ensure that the dose will be delivered instead of no dose being delivered.

Accurate dose delivery is a key requirement for insulin delivery devices because of the potential for hypoglycemia with excessively high doses and for

Table 2.
Dose Delivery

	Group A			Group B		
	Dose 1 n = 256	Dose 2 n = 256	Dose 3 n = 256	Dose 1 n = 47	Dose 2 n = 47	Dose 3 n = 47
Safety test performed correctly						
No, n (%)	2 (0.8)	2 (0.8)	2 (0.8)	9 (19.1)	8 (17.0)	9 (19.1)
Yes, n (%)	254 (99.2)	254 (99.2)	254 (99.2)	38 (80.9)	39 (83.0)	38 (80.9)
Units displayed prior to the dose						
Mean ± standard deviation	40 ± 0.2	40 ± 0.2	40 ± 0.2	38 ± 7.3	38 ± 7.2	38 ± 7.3
Minimum/maximum	39/41	39/40	39/40	4/40	4/40	4/40
Dose delivered (U)						
Mean ± standard deviation	39.4 ± 0.81	39.6 ± 0.57	39.6 ± 0.83	37.4 ± 7.61	38.0 ± 7.20	37.2 ± 9.09
Minimum/maximum	32.9/40.9	36.9/42.3	35.1/48.8	1.7/40.5	3.6/40.5	0.0/40.3
Participants delivering a successful dose (30–46 U), n (%)	256 (100.0)	256 (100.0)	255 (99.6)	45 (95.7)	45 (95.7)	44 (93.6)

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