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RESEARCH LETTER

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Ease-of-use and acceptability of the novel semaglutide 2.4 mg single-dose pen-injector in people with overweight or obesity in the STEP 8 phase III trial

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1 | INTRODUCTION

Subcutaneous semaglutide 2.4 mg, a glucagon-like peptide-1 analogue, is indicated for weight management and is administered once-weekly (at any time of day, with or without meals), in the abdomen, thigh or upper arm.[1,2] Its efficacy and safety were established through the Semaglutide Treatment Effect in People with obesity (STEP) phase III trial programme.[3-7]

An autoinjector-type single-dose pen-injector (SPI; Figure S1) has been developed for semaglutide 2.4 mg. Its first use in a phase III trial was during STEP 8, the primary endpoint of which was to compare the weight loss with once-weekly semaglutide 2.4 mg with that of once-daily liraglutide 3.0 mg in adults with overweight/obesity.[7] Because the semaglutide 2.4 mg SPI is the first autoinjector used for weight management, the aim of the present study, performed according to a STEP 8 protocol amendment, was to examine the patient-reported outcomes (PROs) ease-of-use and acceptability, including comparisons of the SPI with hypothetical once-daily oral treatment. In addition, we examined ease-of-training as reported by site healthcare professionals (HCPs).

2 | METHODS

STEP 8 (NCT04074161) was conducted from 2019 to 2021 at 19 United States sites, following Independent Ethics Committee/Institutional Review Board approval.[7] All participants gave written, informed consent. The trial complied with International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

2.1 | Participants

As previously described,[7] participants were aged 18 years or older with a body mass index of 30.0 kg/m^2 or higher or of 27.0 kg/m^2 or higher with at least one weight-related co-morbidity (hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease), at least one unsuccessful dietary weight loss effort and without type 2 diabetes (T2D).

2.2 | Design and procedures

The design of STEP 8 is reported elsewhere.[7] Participants were randomized to 68 weeks of once-weekly semaglutide 2.4 mg or matching placebo, or once-daily liraglutide 3.0 mg or matching placebo (Figure S2).

Liraglutide/matching placebo was administered once-daily in a multidose pen-injector (MPI). The same MPI was used for once-weekly semaglutide/matching placebo during weeks 0 to 44. Following a protocol amendment, at week 44 participants receiving

semaglutide/matching placebo were switched from the MPI to the SPI (Figure S2), and PRO questionnaires were added to assess ease-of-training, ease-of-use and acceptability of the SPI. Training in SPI use was performed by site staff consistent with the instructions for use of the approved product[1] (Figure S1). As a training aid, each site was given one demonstration pen-injector of the type provided free-of-charge to healthcare providers. The demonstration pen looks like the actual SPI but lacks a needle and liquid medium, and has a mechanism that can be reloaded for repeated simulated injections.

2.3 | Assessments

At week 44, immediately following training in SPI use, the site staff member who had administered the training assessed the ease-of-training for each participant by responding to the question 'How difficult or easy was it for you to train the subject?', using a five-point scale (Methods S1). At week 68, participants rated the ease-of-use and acceptability of the SPI using the 21-item Injection Device Experience and Acceptability (IDEA) instrument (eight items relating to ease-of-use [Part 1] and 13 to acceptability [Part 2]; Methods S2). Use errors were evaluated with the Device Use Error Form (Methods S3). Separate to the Device Use Error Form, adverse events were recorded throughout the trial (to week 75). Injection-site adverse events were identified by searching adverse event data for relevant Medical Dictionary for Regulatory Activities (MedDRA; version 23.1) terms.

3 | RESULTS

One hundred and fifty-five participants switched to the SPI at week 44 (Table 1).

TABLE 1 Baseline characteristics of participants initiating treatment with the SPI at week 44

Characteristic at baseline	Participants switched to SPI ($N = 155$) [semaglutide 2.4 mg, $n = 115$; matched placebo, $n = 40$]
Age, mean ± SD, y	50.0 ± 13.3
Sex, *n* (%)	
Female	122 (78.7)
Male	33 (21.3)
Race, *n* (%)	
Asian	5 (3.2)
Black/African American	28 (18.1)
White	117 (75.5)
Other[a]	5 (3.2)
Hispanic/Latino ethnicity, *n* (%)	14 (9.0)
Body weight, mean ± SD, kg	102.8 ± 22.6
BMI, kg/m^2	
Mean ± SD	37.1 ± 6.2
Distribution by BMI category, *n* (%)	
<30	12 (7.7)
≥30-<35	53 (34.2)
≥35-<40	50 (32.3)
≥40	40 (25.8)
Waist circumference, mean ± SD, cm	112.4 ± 14.2

Abbreviations: BMI, body mass index; SD, standard deviation; SPI, single-dose pen-injector.
[a]Native American, Alaska Native, Native Hawaiian, Other Pacific Islander, or other.

At week 44, site staff rated training as 'very easy' for 75.3% of participants, 'easy' for 21.4%, 'neither difficult nor easy' for 3.2% and 'difficult' or 'very difficult' for none.

At week 68, 151 participants completed the IDEA questionnaire. For all items in the IDEA Part 1 (ease-of-use) questionnaire, the most frequent participant responses were 'very easy' followed by 'easy', which together were selected by 80.8%-97.4% of participants across items (Figure 1A). For all items, few participants rated ease-of-use as 'difficult' or 'very difficult', with the exception that 'use the pen' and 'give yourself an injection' were rated as difficult by ~10% of participants (Figure S3).

For the items on the IDEA Part 2 (acceptability) questionnaire representing positive attributes, the most frequent response was 'strongly agree' for all items, followed by 'agree' for the majority of items (Figures 1B and S4). Conversely, the most frequent responses for the sole negative attribute, 'Injecting with the pen was painful', were 'strongly disagree' (38.4%) or 'disagree' (22.5%).

The cumulative percentage of 'strongly agree' and 'agree' was 78.8% for overall satisfaction and 90.7% for confidence in own ability to use the pen. For the items rating how well the pen fit into everyday life/schedule, 87.4%-93.4% strongly agreed/agreed, while for items rating lack of discomfort using the pen/the pen being less painful than anticipated, 58.3%-72.8% strongly agreed/agreed. On the items comparing the ease-of-use of the pen with pills and preference for the once-weekly pen versus once-daily pills, 70.9%-79.5% answered in favour of the pen.

The 155 participants reported injecting themselves 3864 times; 17 participants reported errors on 22 occasions, most commonly 'liquid was observed on the skin or pen-injector' (Figure S5). No injection-site adverse event reactions were reported. The use errors were most frequently reported between the changeover date and the following visit 6 weeks later (data not shown).

4 | DISCUSSION

The semaglutide SPI is the first autoinjector used for weight management. Experience with the device was assessed during the STEP 8 trial.

For almost all participants, site staff rated ease-of-training as 'easy'/'very easy'. Similarly, most participants considered use of the SPI to be 'easy'/'very easy'. While 11% of participants reported use of the SPI to be 'difficult', very few found it 'very difficult', and only 2% reported any difficulty in injecting once weekly. Collectively, these

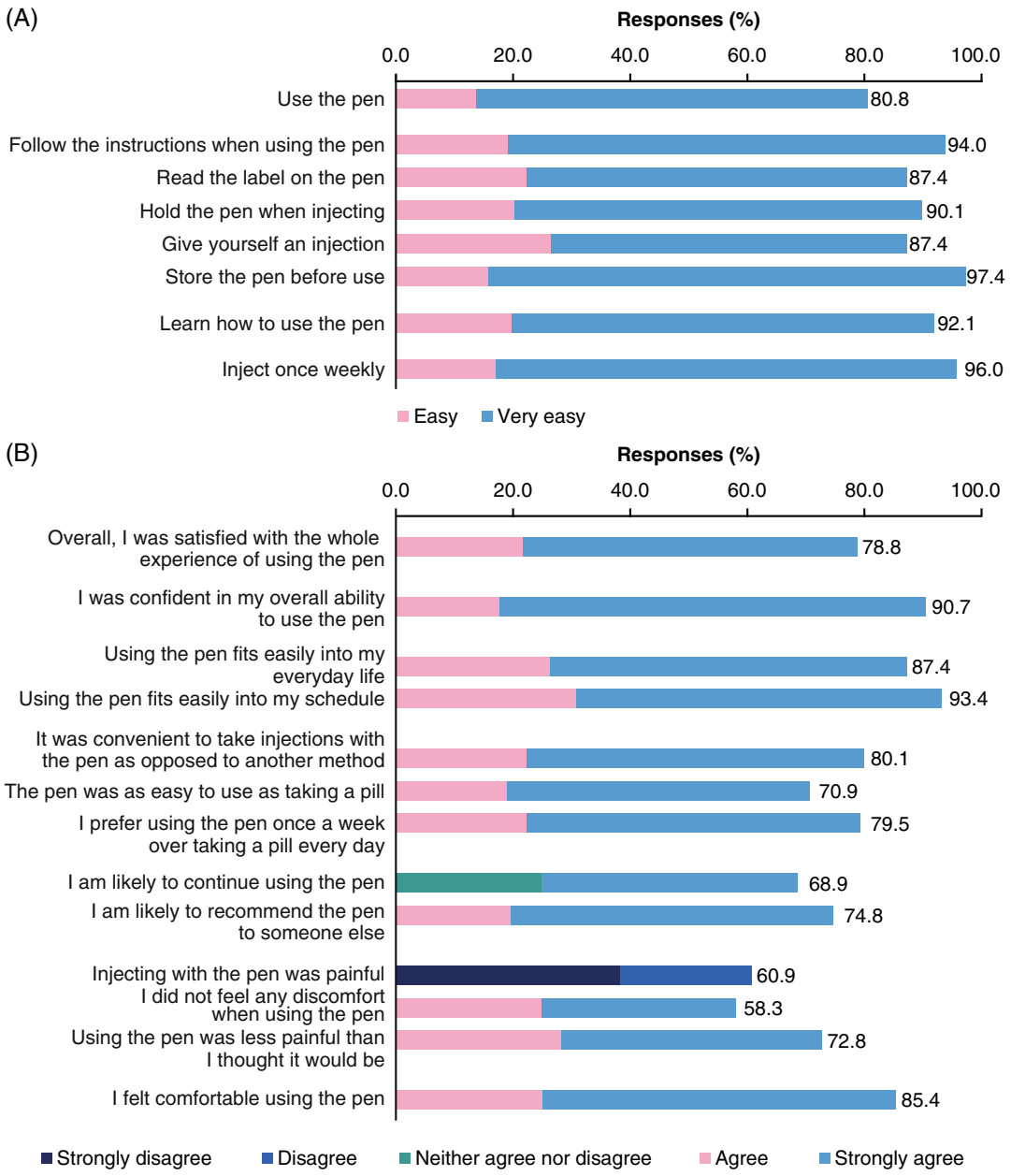

FIGURE 1 Cumulative frequency of the two most frequent participant responses at week 68 for each item in the IDEA Part 1 (ease-of-use) questionnaire (A) and Part 2 (acceptability) questionnaire (B), reordered according to relatedness. Based on responses from 151 participants. IDEA, Injection Device Experience and Acceptability

results suggest that the SPI is easy to use for participants, with minimal training burden for HCPs. Participants were familiar with self-injection with the MPI when they switched to the SPI, which could have reduced their need for training. However, prior summative usability testing results indicated that the SPI was easy to use for patients regardless of prior pen-injector experience and was not associated with serious use errors.[8,9]

Results also favoured the acceptability of the SPI for the majority of participants for all items in the IDEA acceptability questionnaire. Notably, items relating to overall satisfaction, confidence and comfort with using the pen were rated as 'agree'/'strongly agree' by a high proportion of participants. However, only 59% answered 'agree'/'strongly agree' to the item 'I am likely to continue using the pen', potentially reflecting the fact that participants were receiving an investigational product unavailable post-trial. This interpretation is supported by the observation that most participants indicated they were likely to recommend the pen to others.

Interestingly, 79.5% of participants preferred the weekly SPI over a daily pill. With the caveat of differences in populations, this is consistent with a discrete-choice experiment in which patients with T2D who previously received injectable medication preferred injectable to oral treatment, and weekly to daily administration.[10]

With regard to injection pain and discomfort, most participants disagreed that using the pen was painful, and agreed the pen did not

cause discomfort and was less painful than expected. In a previous double-blind comparison of the SPI and MPI, most participants rated injection-site pain as 'none' or 'mild' with both products.[11] The MPI has also been compared with dulaglutide injection.[12] While semaglutide 2.4 mg is to be stored in the refrigerator, its instructions for use do not preclude allowing it to warm up to room temperature prior to injection.[1,2] Further studies could investigate whether injection at room temperature may improve the injection experience, as recommended for insulin.[13]

Potential limitations include the lack of a direct comparator; however, taking a pill every day is a common experience, and thus the IDEA questionnaire items contrasting the SPI with oral therapy provide implied comparative data. Comparison between the SPI and MPI was hindered by the SPI being unavailable at the STEP 8 outset, which made randomization of the SPI/MPI sequence unfeasible.

In conclusion, HCPs found it easy to train STEP 8 participants on use of the semaglutide SPI. Most participants found the pen easy to use and convenient, and were satisfied with the overall experience of using it. No injection-site adverse events were reported. Use errors usually happened during the first few injections, seeming to disappear with practice.

AUTHOR CONTRIBUTIONS

SS and TS conceived of the study. SS developed the first draft of the manuscript; all authors contributed to the subsequent critical revision of the manuscript. All authors contributed to data analysis and/or interpretation.

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CONFLICT OF INTEREST

All authors are employees of Novo Nordisk, Søborg, Denmark, and TS owns stock in the company.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in data sets in a de-identified and anonymized format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found at novonordisk-trials.com.

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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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