


BRIEF REPORT

Comparison of the injection-site experience of the starting doses with semaglutide and dulaglutide: A randomized, double-blind trial in healthy subjects

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Abstract

This double-blind, randomized, single-site, crossover trial compared the injection-site experience with the starting doses of semaglutide and dulaglutide. Healthy subjects (aged 18–75 years; body mass index ≥ 25 kg/m²; n = 104) were randomized 1:1, using a pregenerated list, to semaglutide 0.25 mg as the first injection and dulaglutide 0.75 mg as the second injection or vice versa; each was administered using their proprietary pen-injectors, according to instructions for use. The primary endpoint was intensity of injection-site pain, measured using a visual analogue scale (VAS; 0 mm = no pain, 100 mm = unbearable pain). Exploratory endpoints included intensity category, duration and quality of injection-site pain, and comparative assessment of injection-site pain with the two injections. The point estimate of the VAS score for injection-site pain intensity was 11.5 mm with dulaglutide versus 5.6 mm with semaglutide; mean (95% confidence interval) estimated treatment difference 5.9 (3.6; 8.2) mm; $p < .0001$. Other endpoints corroborated a less painful injection experience with semaglutide versus dulaglutide. Safety was consistent with reported data for the drugs. In conclusion, the injection-site experience with semaglutide was rated as less painful than that with dulaglutide.

KEYWORDS

antidiabetic drug, clinical trial, GLP-1 analogue

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are used to treat type 2 diabetes (T2D); one member of the class (liraglutide) is also indicated for weight management.^{1,2} The latest generation of subcutaneously administered GLP-1 RAs are indicated for once-weekly use, offering the convenience of less frequent dosing than the previous generation.³ However, it is also important to

the user experience that any injection-site pain is reduced as much as possible. In a report by Sikirica et al.⁴ based on a survey conducted in 2014 among patients who had discontinued one of the then-available GLP-1 RA treatments (exenatide [including extended release], lixisenatide or liraglutide) within the last 6 months, 20.1% of patients cited 'injections hurt too much' as a contributing factor for ending treatment. However, it was not reported whether there were differences between the drugs in this regard.⁴

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To test the hypothesis that once-weekly GLP-1 RAs may vary in their potential to cause injection-site pain, the present trial compared injection-site pain experience with the starting doses of the two most frequently prescribed once-weekly GLP-1 RAs, semaglutide 0.25 mg and dulaglutide 0.75 mg.

2 | METHODS

This double-blind, randomized, cross-over trial (clinicaltrials.gov number: NCT04189848; EudraCT number: 2019-83 003 844-57) was conducted at a single site in Groningen, the Netherlands. The trial was approved by an independent ethics committee prior to any subject-related activities (see the supporting information for further details), and all subjects gave written, informed consent prior to any trial procedures. The trial was conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland in June 1964, and subsequent amendments.

2.1 | Participants

Eligible subjects were adults aged 18–75 years with a body mass index (BMI) of 25 kg/m² or higher and general good health. Key exclusions are listed in the supporting information.

2.2 | Trial design

The crossover trial design is shown in Figure 1. Subjects were randomized 1:1 according to a list provided by the sponsor, to receive semaglutide 0.25 mg as the first injection and dulaglutide 0.75 mg as the second injection or vice versa. Semaglutide and dulaglutide were given as marketed, using their proprietary pen-injectors, according to the manufacturers' instructions for use. Semaglutide comes in a multi-dose pen-injector, containing four once-weekly doses, co-packed with NovoFine Plus 4 mm × 32G needles, with which it was used in the present trial. The 0.25 mg dose is delivered in a 0.19 mL volume.⁵ Dulaglutide comes in a single-dose auto-injector with an integrated, hidden 29G needle; the 0.75 mg dose is delivered in a 0.5 mL volume.⁶ The two pen-injectors used in the trial are shown in Figure S1.

The two injections were given 30 min apart in the right or left anterior aspect of the abdominal wall. Independently of treatment sequence, the right/left sequence was randomized. Subjects were blinded to treatment and instructed to wear a blindfold immediately before each injection. A non-blinded site staff member performed the injection and, for each subject, both injections were administered by the same staff member. After the injections, the subject removed the blindfold and a member of the site staff, blinded to the injection sequence, conducted the assessments. The blinded member of the site staff was not in the room when the injection was given and was therefore blind to both visual and auditory cues during the injection. Subjects were discharged on the same day and followed up by telephone 4–5 weeks after discharge for any adverse events (AEs).

2.3 | Endpoints

The primary endpoint was intensity of injection-site pain, measured using a visual analogue scale (VAS). Exploratory endpoints included categorical assessment of intensity of injection-site pain, assessment of duration of injection-site pain, assessment of injection-site pain quality and comparative assessment of injection-site pain between the two injections.

2.4 | Assessments

Subjects were provided with basic instructions only during the assessments, to avoid any guidance that might bias the responses. One minute after receiving each injection, subjects rated the intensity of pain during the injection experience on a 100-mm VAS, where 0 mm was marked 'no pain' and 100 mm was marked 'unbearable pain', followed by a categorical rating of pain intensity ('none', 'very mild', 'mild', 'moderate', 'severe' or 'very severe'). Subjects then selected all applicable pain qualities on a list taken from the revised Short-Form McGill Pain Questionnaire (SF-MPQ-2).⁷ All inventories were professionally translated into Dutch. To assess the duration of pain, the subject was instructed to indicate when the pain had completely subsided.

After the second injection, the assessments of pain were repeated, followed by a comparative assessment, in which subjects were asked to choose one of the following five options: 'The last injection hurt much more than the first injection'; 'The last injection hurt more than the first injection'; 'They hurt about the same

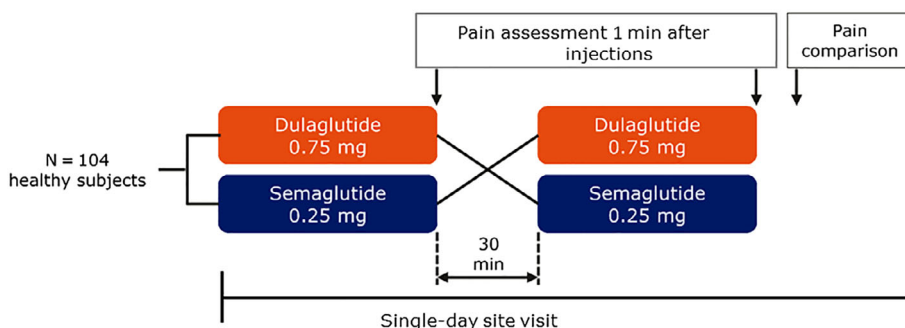


FIGURE 1 Trial design

(including: neither of them hurt); ‘The last injection hurt less than the first injection’; or ‘The last injection hurt much less than the first injection’. Subjects were not given access to their prior ratings when rating any aspect of the second injection.

2.5 | Statistical analysis

The sample size calculation is shown in the supporting information. The primary endpoint, pain intensity measured on a VAS, was assessed using an analysis of variance model with the VAS score as the dependent variable, and product, injection side (right/left), injection number (first/second) and subject as fixed effects. From the model, the mean difference in VAS score between the products was estimated and is presented with 95% confidence intervals (CI) and a *p*-value. The duration of pain was assessed using an analysis of variance model with duration of pain as the dependent variable, and product, injection side (right/left), injection number (first/second) and subject as fixed effects.

3 | RESULTS

Clinical activities took place in 2019–2020. One hundred and four subjects were randomized. All subjects received both treatments and completed all assessments. Subjects were 60% female, with a mean ± standard deviation (SD) age of 37 ± 17.5 years (Figure S2) and a mean ± SD BMI of 30 ± 3.8 kg/m².

The distribution of the VAS scores is shown in Figure 2A. Median VAS scores were 7.5 mm for dulaglutide and 1 mm for semaglutide. The distribution of the within-subject VAS score differences is shown in Figure 2B. The point estimate of the VAS score for injection-site pain intensity was higher for dulaglutide than for semaglutide (11.5 vs. 5.6 mm) with a mean (95% CI) estimated treatment difference (dulaglutide–semaglutide) of 5.9 (3.6; 8.2) mm (*p* < .0001; Figure 2C).

The results of the categorical assessment of injection-site pain intensity and the reported pain qualities from SF-MPQ-2 are shown in Figure 2D,E.

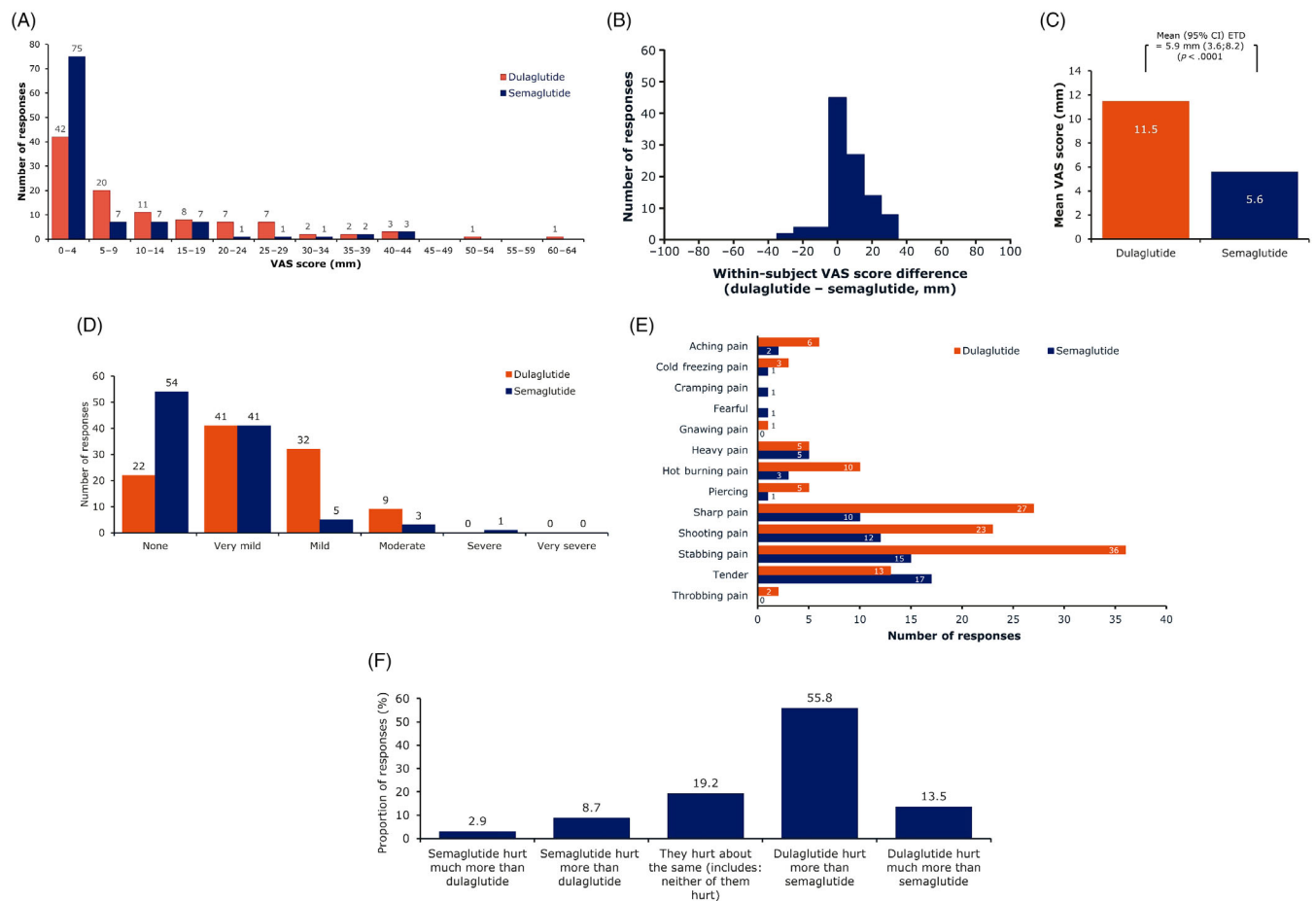


FIGURE 2 (A) Distribution of visual analogue scale (VAS) scores for injection-site pain intensity; (B) distribution of within-subject VAS score differences between dulaglutide and semaglutide (dulaglutide – semaglutide); (C) mean VAS score for injection-site pain intensity (0 = ‘no pain’ and 100 = ‘unbearable pain’); (D) categorical assessment of injection-site pain intensity (*n* = 104 for each treatment); (E) assessment of pain qualities using the modified short-form McGill Pain Questionnaire-2 inventory (*n* = 104 for each treatment; subjects could select more than one quality); and (F) comparison of injection-site pain. CI, confidence interval; ETD, estimated treatment difference. In Figure 2C, values are least squares means estimates

Including subjects who reported a duration of pain of 0 s, the mean pain duration was 31.9 s for dulaglutide and 16.1 s for semaglutide (mean difference 15.8 s; $p = .01$).

The results of the comparative assessment are shown in Figure 2F.

3.1 | Safety

Of the 70 treatment-emergent AEs reported, mild gastrointestinal disorders were the most common. No serious AEs were reported during the trial.

4 | DISCUSSION

All endpoints indicated that dulaglutide was associated with greater injection-site pain than semaglutide.

The VAS score for pain intensity was, on average, 5.9 mm higher for dulaglutide compared with semaglutide and more intense pain categories were generally reported for dulaglutide compared with semaglutide. The most common pain-intensity category for dulaglutide was 'very mild', whereas it was 'none' for semaglutide. Furthermore, the three most frequently reported pain qualities—'stabbing pain', 'sharp pain' and 'shooting pain'—were all reported approximately twice as frequently for dulaglutide compared with semaglutide, and the mean duration of pain postinjection was approximately twice as long for dulaglutide compared with semaglutide.

We further examined differences between the two drugs by comparative recall. The comparative recall method has been used to assess the clinical importance of differences in pain rating over time in an emergency room setting.⁸ If there is a numerical difference between two time points but the patient (without access to their prior score) reports 'no change', then the change is considered to be below the minimal clinically important difference.⁸ We believe our findings passed the comparative recall test in that less than 20% of the subjects found that the two drugs hurt 'about the same' while the remainder, by a six-to-one margin, found semaglutide less painful than dulaglutide (hurt 'less' or 'much less'). It should be noted, however, that both treatments in the present trial scored in the low end of the 0–100 mm VAS and that intensity categories greater than 'mild' were rare.

Some differences between the tested, marketed products that may or may not explain the findings deserve comment. First, the needle is larger with dulaglutide than semaglutide, and needle size is known to affect injection-site experience.^{6,9–11} Second, the starting dose of semaglutide is delivered in a smaller volume (0.19 mL)^{12,13} than the starting dose of dulaglutide (0.5 mL).^{14,15} However, volume differences are unlikely to have played a crucial role because volume does not seem to influence injection-site pain ratings unless it exceeds approximately 1 mL.¹⁶

The trial has some potential limitations. First, only the starting doses were examined, and larger dose sizes of semaglutide come in a larger volume. However, the starting doses are of interest because some patients may decide whether a treatment is acceptable based

on their experience during the first few injections. Further, no dose of semaglutide comes in a volume larger than 0.74 mL.^{12,13} Second, healthy subjects may differ in their perception of pain from people with T2D. The rationale for using healthy subjects was to avoid prior expectations of injection-related pain or pain tolerance; but notably, only subjects with a body habitus typical of patients with T2D ($BMI \geq 25 \text{ kg/m}^2$) were enrolled. Third, the injections were not administered by the subject but by a site-staff member, while the subject was wearing a blindfold. However, the trial was designed to avoid use errors and ensure that subjects were not distracted by the novelty of the injection task. Fourth, the subject was not blinded to auditory cues during injection, which differ between the two products. However, simultaneous visual and auditory blinding was believed to add undue stress, and it was unlikely that the subjects had prior knowledge of the sonic signatures of the pen-injectors. Finally, the trial included only a single injection of each drug. A decreasing trend in mean reported pain level from 1.2 to 0.8 (on a 0–10 integer scale) over the course of four injections was observed in patients who injected themselves once weekly with a placebo-filled dulaglutide pen-injector.⁶ However, it is plausible that a similar decrement would apply to semaglutide.

In conclusion, healthy, overweight or obese subjects rated the injection-site experience of semaglutide as less painful than that of dulaglutide when given the starting doses of both drugs on the same day by qualified medical personnel. Further studies are required to determine the extent to which patients' treatment satisfaction and adherence are influenced by injection-site experience, relative to clinical efficacy, side-effect profile and user interface.

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CONFLICT OF INTEREST

SS, AA, BB and TS are employees of Novo Nordisk A/S; BB and TS own Novo Nordisk A/S stock. SvM is an employee of PRA Health Sciences, which was funded by Novo Nordisk A/S to conduct this trial.

AUTHOR CONTRIBUTIONS

Design: A. Andersen, B. Berg, S. van Marle, S. Snitker, T. Sparre. Conduct/data collection: B. Berg, S. van Marle. Analysis: A. Andersen, S. Snitker, T. Sparre. Writing manuscript: A. Andersen, B. Berg, S. van Marle, S. Snitker, T. Sparre.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14349>.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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SUPPORTING INFORMATION

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

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