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RESEARCH LETTER

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Comparison of the injection-site experience of semaglutide in a single-dose and a multidose pen-injector

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KEYWORDS: clinical trial, excipient, pain, phenol, propylene glycol, subcutaneous injection

1 | BACKGROUND

Subcutaneous injectable semaglutide, a glucagon-like peptide-1 receptor agonist, is approved for the treatment of type 2 diabetes (T2D) at maintenance doses up to 2 mg once weekly (OW; Ozempic®; Novo Nordisk A/S, Bagsvaerd, Denmark),[1,2] and for weight management, at a maintenance dose of 2.4 mg OW (Wegovy®; Novo Nordisk A/S).[3,4] For T2D use, semaglutide is delivered by a multidose pen-injector (MPI) holding four OW doses, except in Japan, where it is approved in a single-dose pen-injector (SPI).[5] The same SPI is used for the weight management indication (Figure 1).[6]

The formulation used in the SPI for T2D (semaglutide C) was derived from that used in the MPI (semaglutide MPI) by removing the preservative, phenol, which is not needed in an SPI, and increasing the concentration of the tonicity regulator propylene glycol to 1.9%. As phenol is a known analgesic, we hypothesized that semaglutide C would be associated with greater injection-site discomfort than semaglutide MPI.[7] When that hypothesis was confirmed, we hypothesized that the injection-site discomfort with semaglutide C was explained by the propylene glycol and could be minimized by replacing propylene glycol with sodium chloride in a formulation called semaglutide D.

We report studies of the injection-site experience with semaglutide C and semaglutide D, each compared with semaglutide MPI, a benchmark for low injection-site pain.[8]

2 | METHODS

The semaglutide C and semaglutide D trials (clinicaltrials.gov numbers: NCT04007107 and NCT04143945, respectively; EudraCT numbers: 2019-002284-10 and 2019-003654-83, respectively) were conducted at a single site following Independent Ethics Committee/Institutional Review Board approval. All participants gave written, informed consent. The trials complied with International Conference

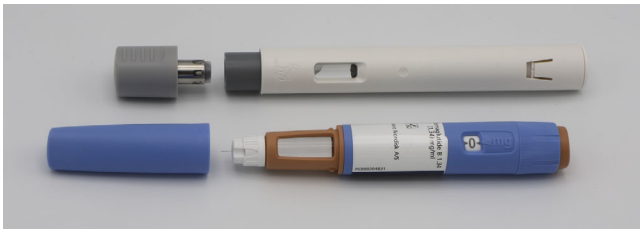

FIGURE 1 Semaglutide multidose pen-injector with the NovoFine® Plus 32G × 4 mm needle with which it is co-packed (foreground) and the semaglutide single-dose pen-injector (background), as used in the two trials reported here. The multidose pen-injector for clinical trials was used; it differs from the marketed version only by its colour scheme and labelling

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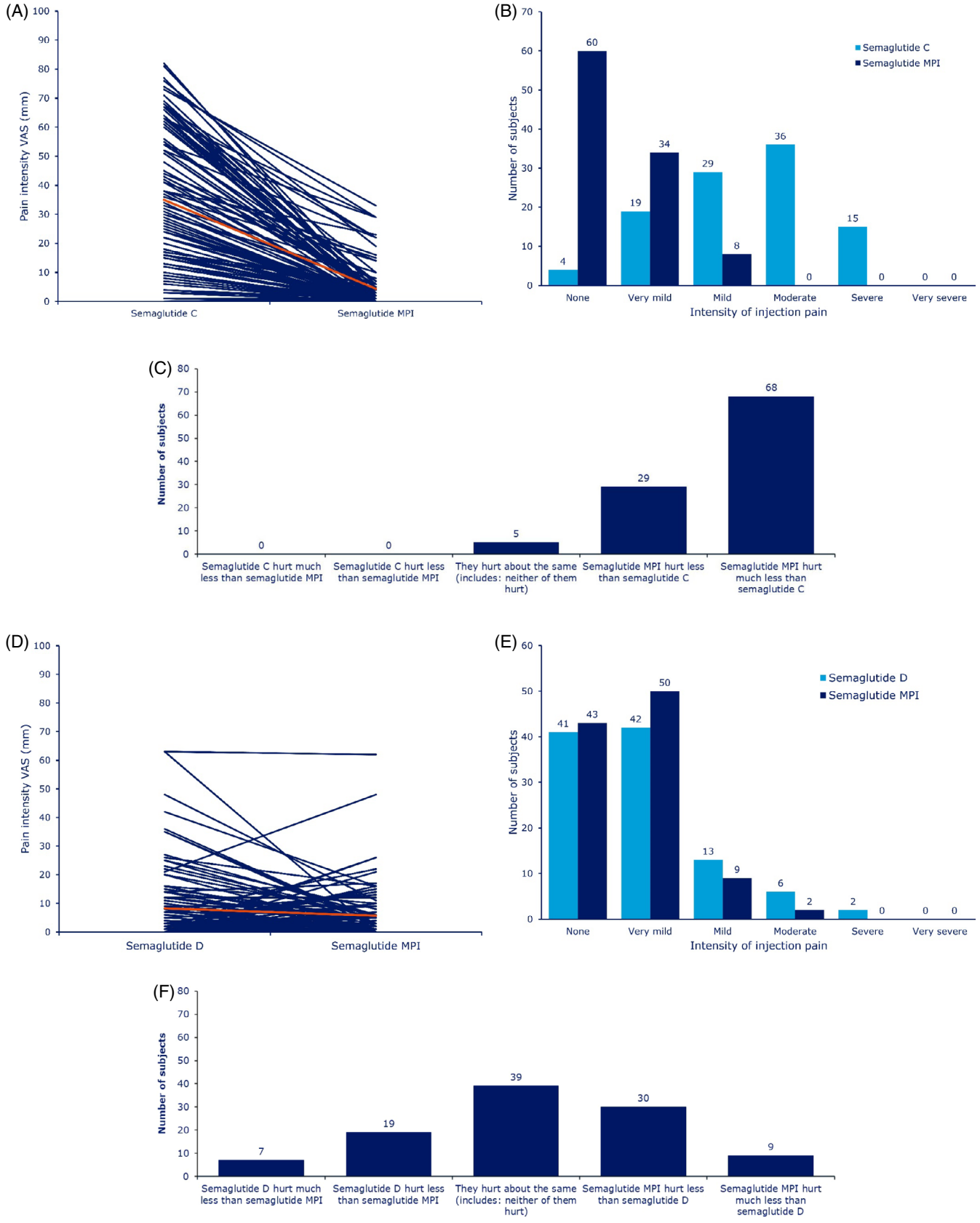

FIGURE 2 A, Individual VAS scores with semaglutide C and semaglutide MPI ($n = 103$ who received both treatments; dark orange line indicates mean values). B, Comparison of injection-site pain between semaglutide C and semaglutide MPI. C, Categorical assessment of injection-site pain intensity with semaglutide C and semaglutide MPI. D, Individual VAS scores with semaglutide D and semaglutide MPI ($n = 104$ who received both treatments; dark orange line indicates mean values). E, Categorical assessment of injection-site pain intensity with semaglutide D and semaglutide MPI. F, Comparison of injection-site pain between semaglutide D and semaglutide MPI. MPI, multidose pen-injector; SPI, single-dose pen-injector; VAS, visual analogue scale

on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.[9]

Eligible individuals were aged 18-75 years with a body mass index (BMI) ≥25 kg/m^2 and in general good health. Key exclusion criteria were glycated haemoglobin ≥6.5% (48 mmol/mol) and use of painkillers.

The trials were conducted in a similar manner to our study comparing dulaglutide with semaglutide MPI.[8] In the semaglutide C trial, subjects received, in randomized order, 30 min apart, one injection of 0.25 mg semaglutide C and one injection of 0.25 mg semaglutide MPI in the anterior aspect of the abdomen. The protocol was repeated with semaglutide D instead of semaglutide C in the second trial. The formulations and the needles used are described in Table S1.

One minute after receiving each injection, subjects rated the intensity of pain associated with the injection experience using a 100-mm visual analogue scale (VAS), where 0 mm was marked 'no pain' and 100 mm was marked 'unbearable pain'. Subjects then rated pain intensity using a categorical scale ('none', 'very mild', 'mild', 'moderate', 'severe' or 'very severe'), selected all applicable pain qualities from the revised Short-Form McGill Pain Questionnaire (Figure S1)[10] and assessed duration of pain.

After the second injection, the ratings were repeated, followed by a comparative recall assessment, in which subjects chose one of 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 (includes: neither of them hurt)'; 'The last injection hurt less than the first injection'; or 'The last injection hurt much less than the first injection'.

3 | RESULTS

In the semaglutide C trial, 103 subjects were randomized. All except one received both injections and completed all assessments. The mean ± SD age of subjects was 41 ± 18 years and the BMI was 29 ± 3.5 kg/m^2; 64% were women, and 95% stated their race as 'White.'

The mean VAS score for injection-site pain intensity was higher for semaglutide C than for semaglutide MPI (35.1 mm vs. 4.4 mm), with a mean (95% confidence interval) estimated treatment difference of 30.7 mm (26.6; 34.8) (p< .0001) (Figure 2A). The most frequently reported pain categories with semaglutide C were 'moderate' and 'mild'; with semaglutide MPI they were 'none' and 'very mild' (Figure 2B). The results from the pain qualities inventory are shown in Figure S2A. In the comparative recall, 95% of subjects reported that semaglutide C hurt more than semaglutide MPI (Figure 2C).

In the semaglutide D trial, 104 subjects were randomized. All received both injections and completed all assessments. The mean ± SD age was 39 ± 18.3 years and the BMI was 30.0 ± 3.8 kg/m^2; 57% were women, and 96% stated their race as 'White'.

The mean VAS score for injection-site pain intensity was slightly higher for semaglutide D than for semaglutide MPI (8.3 mm vs. 5.7 mm), with a mean estimated treatment difference (95% confidence interval) of 2.6 mm (0.1; 5.1) (p = .04) (Figure 2D). The median VAS score was 2 mm for both products. The most frequently reported pain categories with semaglutide D and semaglutide MPI were 'none' and 'very mild' (Figure 2E). Results from the pain qualities inventory are shown in Figure S2B. The mean pain duration was 26.1 and 23.1 s for semaglutide D and semaglutide MPI, respectively (p = .36). Thirty-eight per cent of subjects reported that semaglutide D hurt more than semaglutide MPI, 38% reported that semaglutide D and semaglutide MPI hurt 'about the same' and 25% reported that semaglutide D hurt less than semaglutide MPI (Figure 2F).

Safety data from the trials are shown in Tables S2 and S3.

4 | DISCUSSION

The mean VAS score for the initial SPI formulation, semaglutide C, was considerably higher than for semaglutide MPI.

To understand the clinical significance of the differences in VAS score, we used comparative recall, a method that has been used to assess the clinical importance of differences in pain rating over time in an emergency-room setting.[11] If there is a numeric difference between pain ratings obtained 30 min apart and the patient (without access to their previous score) reports 'no change', the change is considered below the minimal clinically important difference.[11] Only 5% of subjects reported 'hurt about the same'; the remaining 95% found semaglutide MPI less painful than semaglutide C.

Semaglutide D differs from semaglutide C in that the tonicity regulator propylene glycol has been replaced with sodium chloride. Propylene glycol at a concentration of 35% injected intradermally induces burning pain that subsides within minutes.[12] That concentration, however, is much higher than the 1.9% in semaglutide C.

In the semaglutide D trial, the mean VAS scores with semaglutide D and semaglutide MPI were 8.3 mm and 5.7 mm, respectively. The categorical assessments of pain intensity ratings and number of pain quality reports were slightly less favourable with semaglutide D than with semaglutide MPI, but there was no statistically significant difference in pain duration. In the comparative recall, responses were distributed rather symmetrically, with 38% reporting no difference and the remainder split 3:2 in favour of semaglutide D or semaglutide MPI hurting more, suggesting that the slightly higher mean VAS score with semaglutide D compared with semaglutide MPI is of limited clinical relevance.

In conclusion, our studies suggested room for improvement in the injection-site experience of semaglutide C compared with semaglutide MPI. The injection-site experience with semaglutide D was almost indistinguishable from semaglutide MPI, with >80% of injections with either product associated with no or very mild injection-site pain. Consequently, semaglutide D is used for the SPI for the weight management indication and is in development for the SPI for the T2D indication.

AUTHOR CONTRIBUTIONS

SS, AA, PSL, SvM, BFS and TS performed the design. PSL, SvM and BFS conducted the study and collected the data. AA, SS and TS

analysed the data. SS, AA, PSL, SvM, BFS and TS wrote the manuscript.

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CONFLICT OF INTEREST

SS, AA and TS are employees of Novo Nordisk A/S. TS owns Novo Nordisk A/S stock. PSL and BFS were employees of Novo Nordisk A/S at the time the study was conducted. SvM is an employee of PRA Health Sciences, which was funded by Novo Nordisk A/S to conduct this trial.

DATA AVAILABILITY STATEMENT

Data available upon reasonable request to authors

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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