An indirect treatment comparison of the efficacy of semaglutide 1.0 mg versus dulaglutide 3.0 and 4.5 mg

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Funding information
Novo Nordisk A/S

Abstract
Aim: To compare the effects of semaglutide 1.0 mg versus dulaglutide 3.0 and 4.5 mg on HbA1c and body weight in patients with type 2 diabetes.

Materials and Methods: A Bucher indirect comparison was conducted to compare efficacy outcomes of semaglutide 1.0 mg versus dulaglutide 3.0 and 4.5 mg using published results from the SUSTAIN 7 and AWARD-11 trials. Sensitivity analyses using individual patient data from SUSTAIN 7 and aggregate data from AWARD-11 were conducted to explore the impact of adjustment for cross-trial imbalances in baseline characteristics.

Results: Semaglutide 1.0 mg significantly reduced HbA1c versus dulaglutide 3.0 mg, with an estimated treatment difference (ETD) of −0.24%-points (95% confidence interval [CI] −0.43, −0.05), with comparable reductions in HbA1c versus dulaglutide 4.5 mg with an ETD of −0.07%-points (95% CI −0.26, 0.12). Semaglutide 1.0 mg significantly reduced body weight versus dulaglutide 3.0 and 4.5 mg with an ETD of −2.65 kg (95% CI −3.57, −1.73) and −1.95 kg (95% CI −2.87, −1.03), respectively. Sensitivity analyses supported the primary analysis findings.

Conclusions: This indirect comparison showed significantly greater reductions in HbA1c with semaglutide 1.0 mg versus dulaglutide 3.0 mg and comparable HbA1c reductions versus dulaglutide 4.5 mg. Semaglutide 1.0 mg significantly reduced body weight versus both dulaglutide 3.0 and 4.5 mg. With several glucagon-like peptide-1 receptor agonists available, information regarding their comparative efficacy can be valuable to clinicians.

Keywords
dulaglutide, GLP-1 receptor agonist, indirect comparison, semaglutide, type 2 diabetes

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are an established treatment option for people with type 2 diabetes (T2D), offering glycaemic control alongside beneficial effects on body weight and cardiovascular disease. Semaglutide and dulaglutide are both long-acting GLP-1 RAs with once-weekly (QW) dosing regimens and are recommended as treatment options for patients not adequately
controlled on metformin alone, as well as those with established cardiovascular disease regardless of HbA1c. However, semaglutide differs from dulaglutide in molecular structure and is smaller in size, which may lead to differences in metabolic effects.

Semaglutide was approved for use at maintenance doses of 0.5 and 1.0 mg by the Food and Drug Administration (FDA) in 2017 and subsequently by the European Medicines Agency (EMA) in 2018. Dulaglutide was initially approved at doses of 0.75 and 1.5 mg by the FDA and EMA in 2014. Semaglutide and dulaglutide have been extensively investigated as part of the SUSTAIN and AWARD clinical trial programmes, respectively. SUSTAIN 7 compared the efficacy and safety of semaglutide 0.5 mg versus dulaglutide 0.75 mg and semaglutide 1.0 mg versus dulaglutide 1.5 mg in patients with T2D inadequately controlled with metformin. The superiority of semaglutide compared with dulaglutide was shown with regard to reducing HbA1c and body weight at week 40. Semaglutide and dulaglutide had similar safety profiles, with comparable proportions of patients experiencing gastrointestinal (GI) adverse events and discontinuing treatment as a result of adverse events. Because of the progressive nature of T2D, treatment intensification is often required to achieve and maintain good glycaemic control and to minimize complications. SUSTAIN 7 and other trials illustrate that higher doses of GLP-1 RAs are associated with greater reductions in HbA1c, although there is a need to balance treatment benefits with adverse events, particularly GI adverse events. This has prompted the study of higher QW doses of both semaglutide and dulaglutide. The efficacy and safety of semaglutide 2.0 mg for the treatment of T2D is currently being assessed in the SUSTAIN FORTE trial. Higher doses of dulaglutide (3.0 and 4.5 mg) were investigated in AWARD-11 and subsequently approved in 2020 and 2021 by the FDA and EMA, respectively. In AWARD-11, treatment with dulaglutide 3.0 or 4.5 versus 1.5 mg at week 36 showed dose-related reductions in HbA1c and body weight, with increased weight loss observed with higher doses. Dulaglutide 3.0 and 4.5 mg showed similar safety profiles to dulaglutide 1.5 mg and GI tolerability generally consistent with that previously established for dulaglutide.

There are currently no head-to-head data comparing semaglutide 1.0 mg with doses of dulaglutide of more than 1.5 mg/week. Following FDA and EMA approval of dulaglutide at more than 1.5 mg/week, information on the relative efficacy of semaglutide 1.0 mg and dulaglutide at more than 1.5 mg/week would be useful for clinicians, to help guide selection of the most suitable GLP-1 RA for patients with T2D uncontrolled on metformin. Therefore, the objective of this analysis was to compare the efficacy of semaglutide 1.0 mg with dulaglutide 3.0 or 4.5 mg, using an indirect comparison based on results from SUSTAIN 7 and AWARD-11 randomized controlled trials (RCTs). The Bucher method is an established approach for performing indirect treatment comparisons (ITCs), and has been used previously for the comparison of glucose-lowering treatments. The method accounts for cross-trial differences by measuring treatment effects relative to a common comparator arm and requires only the availability of summary-level data for each trial. The Bucher method is appropriate if the relative treatment effect can be assumed to be the same across the two trial populations. In the current setting, this translates to assuming that the comparative efficacy results of SUSTAIN 7 would have been the same had SUSTAIN 7 been performed in an AWARD-11 population. This is considered an appropriate assumption based on previous analyses of the impact of patient characteristics on clinical outcomes in SUSTAIN 7. Moreover, both SUSTAIN 7 and AWARD-11 RCTs were conducted in patients inadequately controlled on metformin monotherapy. Bucher indirect comparisons were calculated in SAS version 9.4. Further details of the Bucher methodology are provided in the supporting information. Sensitivity analyses are described in detail in section 2.4.

## Methods

An indirect comparison using the Bucher method was conducted to compare efficacy outcomes of dulaglutide 3.0 and 4.5 mg with semaglutide 1.0 mg using available published results from the SUSTAIN 7 and AWARD-11 randomized controlled trials (RCTs). The Bucher method is an established approach for performing indirect treatment comparisons (ITCs), and has been used previously for the comparison of glucose-lowering treatments. The method accounts for cross-trial differences by measuring treatment effects relative to a common comparator arm and requires only the availability of summary-level data for each trial. The Bucher method is appropriate if the relative treatment effect can be assumed to be the same across the two trial populations. In the current setting, this translates to assuming that the comparative efficacy results of SUSTAIN 7 would have been the same had SUSTAIN 7 been performed in an AWARD-11 population. This is considered an appropriate assumption based on previous analyses of the impact of patient characteristics on clinical outcomes in SUSTAIN 7. Moreover, both SUSTAIN 7 and AWARD-11 RCTs were conducted in patients inadequately controlled on metformin monotherapy. Bucher indirect comparisons were calculated in SAS version 9.4. Further details of the Bucher methodology are provided in the supporting information. Sensitivity analyses are described in detail in section 2.4.
Outcomes assessed

Outcomes assessed in the ITCs were change from baseline in HbA1c and change from baseline in body weight, corresponding to the primary and secondary confirmatory outcomes in both SUSTAIN 7 and AWARD-11. These outcomes were assessed at 40 and 36 weeks in SUSTAIN 7 and AWARD-11, respectively. For these continuous outcomes, mean treatment differences with associated 95% confidence intervals (CIs) were calculated. The proportions of patients achieving HbA1c less than 7.0% were also assessed and, for this dichotomous outcome, treatment odds ratios (ORs) with associated 95% CIs were calculated.

Study and patient characteristics

Inclusion criteria of the SUSTAIN 7 and AWARD-11 trials used in the analysis are shown in Table 1. SUSTAIN 7 was an open-label, multinational, Phase IIIb trial and AWARD-11 was a double-blind, multinational, Phase III trial. Although there were some differences in terms of trial design and inclusion criteria, baseline characteristics were generally similar between the two trials, with both SUSTAIN 7 and AWARD-11 RCTs conducted in patients inadequately controlled on metformin monotherapy, with slightly higher mean baseline HbA1c, body weight and T2D duration in AWARD-11 compared with SUSTAIN 7 (Table 2). However, the indirect comparisons of semaglutide 1.0 mg versus dulaglutide 3.0 and 4.5 mg were anchored to dulaglutide 1.5 mg, making it possible to conduct a robust analysis without further adjustment for differences in prognostic factors across trials. In addition, based on a post hoc analysis investigating the impact of clinically relevant characteristics on relative treatment effects of semaglutide versus dulaglutide, there is no evidence to suggest that differences in baseline characteristics (age, sex, diabetes duration, glycaemic control and body mass index [BMI]) result in effect modification for semaglutide compared with dulaglutide.17 Direct comparisons between treatments for change from baseline in HbA1c and change from baseline in body weight as reported in AWARD-11 and SUSTAIN 7 are shown in Table S2.

For the primary analysis, indirect comparisons were based on results for the trial product estimand (referred to as efficacy estimand in AWARD-11), which was defined in both trials as including patients on treatment without rescue therapy and was the primary analysis population in SUSTAIN 7. The trial product estimand targets the treatment effect if all patients had continued to use the trial product for the planned duration of the trial without rescue medication, thus reflecting effect when treatment is used as intended.19

Sensitivity analyses

The Bucher indirect comparison used for the primary analysis assumes that the relative treatment effect is the same in the
| Trial name | SUSTAIN 7 |  |  |  | AWARD-11 |  |  |  |  |  |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Treatment  | Semaglutide | Dulaglutide | Pooled treatment arms | Dulaglutide | Dulaglutide | Dulaglutide | Pooled treatment arms |  |  |
|            | 1.0 mg (n = 300) | 1.5 mg (n = 299) | (semaglutide 1.0 mg and dulaglutide 1.5 mg) (n = 599) | 3.0 mg (n = 616) | 4.5 mg (n = 614) | 1.5 mg (n = 612) | (dulaglutide 3.0 mg, 4.5 mg and 1.5 mg) (n = 1842) |
| Mean age (SD), y | 55 (10.6) | 56 (10.6) | 55.6 (10.6) | 56.9 (10.2) | 56.6 (10.2) | 57.8 (9.7) | 57.1 (10.0) |
| Mean baseline HbA1c (SD), % | 8.2 (0.9) | 8.2 (0.9) | 8.2 (0.9) | 8.6 (1.0) | 8.6 (0.9) | 8.6 (0.9) | 8.6 (1.0) |
| Fasting glucose (SD), mg/dL | 177.1 (46.5) | 172.5 (41.2) | 174.8 (44.0) | 184 (54.4) | 183.4 (48.0) | 185 (52.0) | 184.1 (51.5) |
| Mean body weight (SD), kg | 95.5 (20.9) | 93.4 (21.8) | 94.5 (21.4) | 96.3 (20.1) | 95.4 (20.6) | 95.5 (20.2) | 95.7 (20.3) |
| Mean BMI (SD), kg/m² | 33.6 (6.5) | 33.1 (6.6) | 33.3 (6.5) | 34.3 (6.2) | 34.0 (6.2) | 34.4 (6.4) | 34.2 (6.3) |
| Mean T2D duration (SD), y | 7.3 (5.7) | 7.6 (5.6) | 7.5 (5.7) | 7.6 (5.5) | 7.7 (5.8) | 7.6 (5.8) | 7.6 (5.7) |
| Female, n (%) | 138 (46.0) | 128 (43.0) | 268 (44.4) | 288 (46.8) | 296 (48.2) | 314 (51.3) | 898 (48.8) |
| Race, n (%) |  |  |  |  |  |  |  |
| White | 243 (81.0) | 220 (74.0) | 463 (77.3) | 521 (84.6) | 530 (86.3) | 529 (86.4) | 1580 (85.8) |
| Black or African American | 18 (6.0) | 18 (6.0) | 36 (6.0) | 31 (5.0) | 23 (3.7) | 28 (4.6) | 82 (4.5) |
| Asian | 38 (13.0) | 55 (18.0) | 93 (15.5) | 18 (2.9) | 14 (2.3) | 13 (2.1) | 45 (2.4) |
| Other/multiple | 1 (<1) | 6 (2.0) | 7 (1.17) | 46 (7.5) | 47 (7.7) | 42 (6.9) | 135 (7.3) |
| Mean eGFR (SD), mL/min/1.73m² | 97 (17.2) | 95 (18.0) | 96 (17.6) | 93.3 (17.8) | 93.7 (18.3) | 93.4 (18.2) | 93.5 (18.1) |
| Mean SBP (SD), mmHg | 133 (14.5) | 132 (13.6) | 132.6 (14.1) | 131.1 (14.1) | 132.1 (14.0) | 132.1 (14.2) | 131.8 (14.1) |
| Mean DBP (SD), mmHg | 82 (9.1) | 80 (8.7) | 80.8 (8.9) | 78.4 (8.7) | 79 (9.0) | 78.8 (9.3) | 78.7 (9.0) |
| Mean HR (SD), bpm | 76 (10.6) | 75 (10.9) | 75.5 (10.6) | 75.3 (9.5) | 75.5 (10.3) | 75.6 (10.1) | 75.5 (10.0) |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FSG, fasting serum glucose; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation; T2D, type 2 diabetes.

*FPG recorded in SUSTAIN 7 and FSG recorded in AWARD-11.
SUSTAIN 7 population as in the AWARD-11 population, that is, there are no differences in the trial populations that could materially impact the effect of semaglutide versus dulaglutide. While this assumption is well supported in the literature, four different sensitivity analyses were conducted to assess the findings of the main analysis (Table 3).

### TABLE 3

| Analysis                        | Estimand                        | Aggregate data/IPD | Time point |
|---------------------------------|---------------------------------|--------------------|------------|
|                                 | Baker (unweighted)               | MAIC (weighted)    |            |
|                                 | Trial product                    | Treatment policy   |            |
|                                 | Aggregate                        | IPD                |            |
| Primary analysis                | X                               | X                  |            |
| SA1                             | X                               | X                  | SUSTAIN 7  |
|                                 | X (AWARD-11)                     | X (subgroup of patients meeting inclusion criteria in AWARD-11) | AWARD-11  |
| SA2                             | X                               | X                  | SUSTAIN 7  |
|                                 | X (AWARD-11)                     | X (SUSTAIN 7)      |            |
| SA3                             | X                               | X                  | SUSTAIN 7  |
|                                 | X (AWARD-11)                     | X (SUSTAIN 7)      |            |
| SA4                             | X                               | X                  | SUSTAIN 7  |

Abbreviations: IPD, individual patient data; MAIC, matching-adjusted indirect comparison; SA, sensitivity analysis.

### FIGURE 2

Efficacy outcomes of semaglutide (Sema) 1.0 mg versus dulaglutide (Dula) 3.0 and 4.5 mg. (A) Change in HbA1c from baseline; (B) change in bodyweight (kg) from baseline. Primary Baker analysis, sensitivity analyses 1-4

SUSTAIN 7 population as in the AWARD-11 population, that is, there are no differences in the trial populations that could materially impact the effect of semaglutide versus dulaglutide. While this assumption is well supported in the literature, four different sensitivity analyses were conducted to assess the findings of the main analysis (Table 3).
For the first sensitivity analysis (sensitivity analysis 1), Bucher analysis was used to account for a subgroup of subjects in SUSTAIN 7 who adhered to the inclusion criteria in AWARD-11 (n = 414). In another sensitivity analysis (sensitivity analysis 2), a matching-adjusted indirect comparison (MAIC) approach was used to adjust for potential effect modification attributable to baseline HbA1c, BMI and diabetes duration. A further sensitivity analysis (sensitivity analysis 3) used a MAIC approach utilizing SUSTAIN 7 results corresponding to week 36 (obtained from linear interpolation between the week 28 and week 40 visits) to assess the impact of the difference in time points at which outcomes were reported in the trials. The final sensitivity analysis (sensitivity analysis 4) used Bucher analysis of the results from the treatment policy estimand (referred to as treatment-regimen estimand in AWARD-11), which included efficacy data for patients regardless of treatment discontinuation or rescue medication and served to account for the potential effects of treatment discontinuation in the ITCs. Further details of the MAIC methodology are provided in the supporting information.

3 | RESULTS

In total, 1842 patients were randomly assigned to a dulaglutide dose in the AWARD-11 trial (3.0 mg, n = 616; 4.5 mg, n = 614; 1.5 mg, n = 612), with 599 out of 1199 patients randomly assigned to the highest available doses of semaglutide or dulaglutide in the SUSTAIN 7 trial (semaglutide 1.0 mg, n = 300; dulaglutide 1.5 mg, n = 299).

3.1 | Change in HbA1c

In the primary analysis, semaglutide 1.0 mg was significantly more effective at reducing HbA1c from baseline compared with dulaglutide 3.0 mg with an estimated treatment difference (ETD) of −0.24%-points (95% CI −0.43, −0.05). Semaglutide 1.0 mg offered comparable reductions in HbA1c from baseline versus dulaglutide 4.5 mg with an ETD of −0.07%-points (95% CI −0.26, 0.12) (Figure 2A). In the primary analysis, the proportion of patients achieving HbA1c less than 7.0% was comparable for semaglutide 1.0 mg versus dulaglutide 3.0 mg with an OR of 1.31 (95% CI 0.79, 2.19) and, compared with 4.5 mg, an OR of 0.88 (95% CI 0.52, 1.48) (Figure S1).

Sensitivity analyses adjusting for inclusion criteria (sensitivity analysis 1), baseline characteristics (sensitivity analysis 2), follow-up length (sensitivity analysis 3) and treatment discontinuation (sensitivity analysis 4) supported the findings of the primary analysis (Figure 2A and Figure S1).

3.2 | Change in body weight

In the primary analysis, semaglutide 1.0 mg was significantly more effective at reducing body weight from baseline compared with dulaglutide 3.0 and 4.5 mg with ETDs of −2.65 and −1.95 kg, respectively (95% CI −3.57, −1.73 and −2.87, −1.03, respectively) (Figure 2B).

Sensitivity analyses adjusting for inclusion criteria (sensitivity analysis 1), baseline characteristics (sensitivity analysis 2), follow-up length (sensitivity analysis 3) and treatment discontinuation (sensitivity analysis 4) supported the findings of the primary analysis (Figure 2B).

4 | DISCUSSION

This study indirectly compared the effect of two GLP-1 RAs (semaglutide 1.0 mg vs. dulaglutide 3.0 and 4.5 mg) on reducing HbA1c and body weight from baseline in patients with T2D inadequately controlled on metformin therapy.

The primary analysis showed that semaglutide 1.0 mg was significantly more effective than dulaglutide 3.0 mg and comparable with dulaglutide 4.5 mg in reducing HbA1c from baseline. Semaglutide 1.0 mg was also significantly more effective at reducing body weight versus dulaglutide 3.0 and 4.5 mg. No significant difference was shown in the proportion of patients achieving HbA1c less than 7.0% for any comparison. All sensitivity analyses supported the findings of the primary analysis.

This is the first comparison of semaglutide 1.0 mg with dulaglutide 3.0 and 4.5 mg in patients with T2D inadequately controlled on metformin. With multiple products in the GLP-1 RA class now available, information regarding their comparative effectiveness has become clinically relevant. Higher HbA1c levels are associated with a greater risk of complications from T2D, with only 26.4% of patients with T2D achieving the target HbA1c of less than 6.5%. Approximately 90% of people with T2D are overweight or have obesity. Diabetes and obesity together increase the risk of a range of chronic health conditions including cardiovascular disease, kidney disease and risk of mortality. Weight loss in patients with T2D has been shown to reduce HbA1c levels and improve cardiovascular risk factors. Weight loss is therefore an important consideration in the treatment of T2D. Hence, there is a need for treatment strategies for reducing body weight, in addition to improving glycaemic control, in patients with T2D.

The significantly greater reductions in body weight shown with semaglutide 1.0 mg versus dulaglutide 3.0 and 4.5 mg in this indirect comparison may therefore be a factor to consider for clinicians determining the most appropriate GLP-1 RA for individual patients. A higher dose of semaglutide (2.0 mg) for the treatment of T2D is currently being investigated in SUSTAIN FORTE. The strengths of this study include the comparison method used, with findings of the primary analysis supported by sensitivity analyses. Based on the available trial data and the method including anchoring with dulaglutide 1.5 mg, a conventional Bucher ITC approach was considered the most appropriate primary analysis in this study. Specifically, the Bucher approach assumed that the effect of semaglutide versus dulaglutide would be the same in the SUSTAIN 7 population as in the AWARD-11 population. Improvements in HbA1c and body weight with semaglutide versus dulaglutide have been reported in the
literature regardless of patient characteristics, supporting the use of
the Bucher method in this current study.\textsuperscript{17} To further explore this
assumption, IPD from SUSTAIN 7 were used to perform sensitivity
analyses adjusting for differences between trial populations and
follow-up length. These analyses supported the findings of the pri-
mary analysis.

This ITC utilized two statistical methods to strengthen the conclu-
sions; however, these findings can only be validated in a head-to-head
trial. The current study focused on the indirect comparison of efficacy
did not evaluate safety outcomes. A quantitative, indirect com-
parison of safety outcomes is intrinsically more difficult, because of
cross-trial differences in the assessment of adverse events. Both SUS-
TAIN 7 and AWARD-11 reported a similar safety profile across treat-
ment arms; semaglutide 1.0 mg resulted in comparable adverse events
versus dulaglutide 1.5 mg, and dulaglutide 1.5 mg resulted in compa-
rable adverse events versus dulaglutide 3.0 and 4.5 mg. A limitation of
this study is comparison of estimands across trials, as there are subtle
differences in the handling of intercurrent events, with different
criteria for initiation of rescue medication. It should also be noted that
baseline HbA1c levels differed between the two studies. However,
potential confounding resulting from this difference was mitigated
through anchoring of analyses via dulaglutide 1.5 mg. As a result of
this approach, the comparison made was between the relative treat-
ment effects shown in each of the trials (dulaglutide 1.5 mg -
semaglutide 1.0 mg compared with dulaglutide 1.5 mg - dulaglutide
3.0/4.5 mg). Further, when baseline HbA1c was adjusted for in sensi-
tivity analysis 2, the impact on the results was minimal. Another limi-
tation of this study is the comparison of data from trials with different
follow-up length. An MAIC was conducted as a sensitivity analysis
specifically to account for differences in follow-up between SUSTAIN
7 and AWARD-11, and supported the findings of the main analysis.

Despite these limitations, this study allows for a robust indirect
comparison of reduction of HbA1c and body weight with semaglutide
1.0 versus 3.0 mg and 4.5 mg dulaglutide in patients with T2D inade-
quately controlled on metformin.

In conclusion, this indirect comparison showed significantly
greater reductions from baseline in HbA1c with semaglutide 1.0 mg
versus dulaglutide 3.0 mg and a comparable HbA1c reduction with
semaglutide 1.0 mg versus dulaglutide 4.5 mg. Treatment
with semaglutide 1.0 mg also showed significantly greater reductions
in body weight compared with both dulaglutide 3.0 and 4.5 mg. The
findings of this study may help to guide clinician decisions on the most
suitable product within the GLP-1 RA treatment class for the treat-
ment of individual patients with T2D.

ACKNOWLEDGEMENTS
The authors would like to thank Danielle Vaughan, PhD, from DRG
Abacus (part of Clarivate), for providing medical writing support,
which was funded by Novo Nordisk A/S.

CONFLICT OF INTEREST
RP reports consulting fees from AstraZeneca; consulting fees from
Glytec, LLC; grants from Hanni Pharmaceutical Co.; grants and
consulting fees from Janssen; consulting fees from Merck; grants from
Metavention; consulting fees from Mundipharma; grants, speaker fees
and consulting fees from Novo Nordisk; consulting fees from Pfizer;
grants from Poxel SA; grants and consulting fees from Sanofi; consult-
ing fees from Scopia Pharma Inc.; consulting fees from Sun Pharma-
ceutical Industries; and personal consulting fees from Sanofi US
Services, Inc. Except for consulting fees in February 2018 and June
2018 from Sanofi US Services, Inc., RP’s services were paid for
directly to AdventHealth, a non-profit organization. AMC is an
employee and shareholder of Novo Nordisk A/S. IL has received
research funding, advisory/consulting fees and/or other support from
Novo Nordisk, Eli Lilly, Sanofi, AstraZeneca, Boehringer Ingelheim,
Janssen, Intercept, Intarcia, TARGETPharma, Merck, Pfizer, Novartis,
GI Dynamics, Mylan, Mannkind, Valeritas, Bayer and Zealand Pharma.
AV has conducted research studies funded by, served as advisor for,
and received lecture honoraria from Amgen, AstraZeneca, Boehringer,
Daiichi, Eli Lilly, Napp, Novartis, Novo Nordisk, MannKind, Pfizer,
Regeneron, Sanofi, Takeda and Tosoh. AP received consultancy fees
to develop a statistical analysis plan for the analyses presented in this
manuscript; she has also received personal fees from Novo Nordisk,
Sanofi and Ultragenyx. JL is an employee of Novo Nordisk A/S. BC is
an employee and a shareholder of Novo Nordisk A/S. AGR is an
employee and minor stakeholder in Novo Nordisk A/S. NM is
an employee of Novo Nordisk A/S.

AUTHOR CONTRIBUTIONS
All the authors contributed to the conception, drafting and critical
editing of the manuscript. AP contributed to the planning of analyses
and AGR conducted the statistical analyses.

PEER REVIEW
The peer review history for this article is available at https://publons.
.com/publon/10.1111/dom.14497.

DATA AVAILABILITY STATEMENT
Data will be shared with researchers who submit a research proposal
approved by an independent review board. Access request proposals
can be found at novonordisk-trials.com. Data will be made available
after research completion and approval of the product and product
use in the EU and the USA. Individual participant data will be shared
in datasets in a de-identified and anonymised format. There will not
be any limitations on how these data can be used.

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SUPPORTING INFORMATION

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