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# A model-based simulation of glycaemic control and body weight when switching from semaglutide to 3.0- and 4.5-mg doses of once-weekly dulaglutide

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## Abstract

**Aim:** To evaluate HbA1c and body weight changes when semaglutide 0.5- or 1.0-mg once-weekly (QW) is switched to dulaglutide 3.0- or 4.5-mg QW via exposure-response modelling.

**Methods:** HbA1c and body weight time-course models were developed and validated with data from the SUSTAIN 1 to 10 trials for semaglutide and the AWARD-11 trial for dulaglutide. Simulations were conducted for HbA1c and body weight over 52 weeks. In the initial 26 weeks, semaglutide was initiated at 0.25-mg and titrated to 0.5- or 1.0-mg QW via 4-weekly stepwise titration, followed by 26 weeks of dulaglutide initiated at 0.75- or 1.5-mg QW and escalated to 3.0- or 4.5-mg QW via 4-weekly stepwise titration.

**Results:** At 26 weeks, model-predicted mean changes from baseline in HbA1c and weight for semaglutide 0.5 mg were up to −1.55% and −3.44 kg, respectively. After switching to dulaglutide 3.0 mg, further reductions were 0.19% and 1.40 kg, respectively, at 52 weeks. Predicted mean HbA1c and weight changes for semaglutide 1.0 mg at 26 weeks were −1.84% and −4.96 kg, respectively; after switching to dulaglutide 4.5 mg, HbA1c was maintained with additional weight reduction of up to 0.57 kg at 52 weeks. Glycaemic control was preserved when switching from semaglutide 1.0 mg to dulaglutide 3.0 mg.

**Conclusion:** Switching from semaglutide 0.5 mg to dulaglutide 3.0 or 4.5 mg with dose escalation potentially yields additional HbA1c and weight reductions; switching from semaglutide 1.0 mg to dulaglutide 4.5 mg may enhance weight loss.

KEYWORDS

dulaglutide, glycaemic control, incretin therapy, pharmacodynamics, pharmacokinetics, type 2 diabetes

## 1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of antihyperglycaemic medication that stimulate the secretion of insulin in a glucose-dependent manner and are approved for the treatment of patients with type 2 diabetes (T2D).[1] Some medications within the class have also been shown to reduce the risk of major adverse cardiovascular events.[2,3] In addition, GLP-1 RAs can stimulate weight reduction in patients, mainly because of the effect of slower gastric emptying and increased satiety.[4] Multiple GLP-1 RAs are available on the market with different dosages and dosing schedules.[5] Several GLP-1 RAs are administered subcutaneously with a weekly dosing schedule, such as exenatide extended release, dulaglutide, and semaglutide.

Switching between GLP-1 RAs may be considered if a patient with T2D is not achieving the expected glycaemic target or weight reduction, or for reduction of the risk of major adverse cardiovascular events in adults with T2D and high cardiovascular risk, to improve adherence, or to reduce the incidence or severity of adverse events.[5-8]

Dulaglutide is a once-weekly (QW) GLP-1 RA with originally approved doses of 0.75 and 1.5 mg and, subsequently, additional approved doses of 3.0 and 4.5 mg, for the treatment of T2D.[9] Several head-to-head studies have compared GLP-1 RA treatment effects; however, there are a lack of data regarding the impact of switching from one GLP-1 RA to another upon HbA1c target and body weight expectations.[6] A retrospective analysis of 164 patients in the REALISE-DM study showed that switching from liraglutide or dulaglutide to semaglutide QW reduced HbA1c by 0.65% and body weight by 1.69 kg, on average, after 6 months.[10] Real-world evidence suggests that dulaglutide increases adherence postswitch compared with liraglutide, exenatide, or semaglutide.[11,12] An evaluation of glycaemic control and weight effects using a modelling approach concluded that switching from liraglutide, dulaglutide, or exenatide to semaglutide QW could induce further HbA1c and body weight reductions.[13]

Switching from one once-weekly GLP-1 RA to another is a probable scenario in the clinical setting for reasons that may include optimization of patient care, formulary or insurance plan changes, and even patient preference. Therefore, the aim of this analysis is to evaluate changes in HbA1c and body weight in patients with T2D after switching from semaglutide 0.5-mg QW to dulaglutide 3.0-mg QW, or semaglutide 1.0-mg QW to dulaglutide 4.5-mg QW, using pharmacokinetic (PK)/pharmacodynamic (PD) models built from the SUSTAIN 1 through 10 trials for semaglutide and the AWARD-11 trial for dulaglutide. Additionally, dosing scenarios switching from semaglutide 0.5-mg QW to dulaglutide 4.5-mg QW and semaglutide 1.0-mg QW to dulaglutide 3.0-mg via stepwise dose escalation were also assessed.

A modelling approach was undertaken to evaluate various switching scenarios using semi-mechanistic exposure response-driven PK/PD models for HbA1c and body weight, which are robust models developed and validated using observed data comprising drug doses and concentrations, treatment durations, baselines of HbA1c and body weight as covariates and time courses of HbA1c or body weight measurements from the patient population in each clinical trial. Hence, such PK/PD models can be utilized to simulate and provide reliable predictions of drug effects under different clinical scenarios.

## 2 | MATERIALS AND METHODS

### 2.1 | Data

The population PK and PK/PD time-course models for HbA1c and body weight for subcutaneous semaglutide were built on and validated with published treatment-level data from the phase 3 SUSTAIN 1 through 10 trials. Data were captured if values were reported in the literature or via digitization of figures in the listed publications.[14-23] The corresponding PK and PK/PD models for dulaglutide were based on patient-level data from the AWARD-11 trial.[9] Model schematics are illustrated in Figure S1. A summary of the trial descriptions and patient baseline demographics of these 11 model-building phase 3 trials in patients with T2D are listed in Table 1.

### 2.2 | Population PK and PK/PD models

The population PK and PK/PD modelling for dulaglutide and semaglutide were conducted using a non-linear mixed effects modelling approach on NONMEM software (version 7.4.2; ICON Development Solutions, Ellicott City, MD). Dulaglutide's population PK model was structurally similar to the previously published model by Geiser et al.,[25] except that model final estimates were updated with inclusion of data from AWARD-11, which compared dulaglutide 3.0- and 4.5-mg QW doses with dulaglutide 1.5-mg QW, as an add-on to metformin in patients with T2D.[9] The population PK model estimates and variabilities for semaglutide were based on the models described by Overgaard et al.[13] and Petri et al.[26] It is assumed that previously published PK model structures for semaglutide and dulaglutide are robust and can be adapted for use.

The exposure-response models for GLP-1 RAs consisted of a joint PK/PD model where HbA1c change was driven mainly by fasting glucose (FG) and a body weight model (Figure S1). The time course of HbA1c response was influenced by FG concentration through a linked concentration-response model that fitted both FG and HbA1c data jointly. A disease progression model, together with an offset compartment introducing drug effect, were utilized to describe FG concentration over time. The HbA1c time course was in turn represented using a classical indirect response model driven by FG, as previously described by Landersdorfer and Jusko.[27] Independent PK/PD models driven by the time course of drug concentrations, FG, and HbA1c were developed separately for dulaglutide and semaglutide.

As weight changes are often a delayed response relative to drug exposure, the PK/PD time course of body weight was described using an indirect response model, where drug effect was introduced as an

**TABLE 1** Summary of randomized, controlled phase 3 trials for semaglutide and dulaglutide included in the model-building dataset

| | Baseline characteristics as mean (SD) or % | | | | | |
|---|---|---|---|---|---|---|
| Trial descriptor (identifier) | N | Diabetes duration (y) | Age (y) | Sex (% male) | HbA1c (%) | Body weight (kg) |
| AWARD-11<br>A randomized, double-blind, parallel arm study of the efficacy and safety of investigational dulaglutide doses when added to metformin in patients with type 2 diabetes (AWARD-11: Assessment of weekly AdministRation of LY2189265 in Diabetes-11)<br>(ClinicalTrials.gov identifier: NCT03495102)[9] | 1842 | 7.6 (5.7) | 57.1 (10.0) | 51.2 | 8.6 (1.0) | 95.7 (20.3) |
| SUSTAIN 1<br>Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomized, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial<br>(ClinicalTrials.gov identifier: NCT02054897)[14] | 387 | 4.18 (5.52) | 53.7 (11.3) | 54 | 8.05 (0.85) | 91.93 (23.83) |
| SUSTAIN 2<br>Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomized trial<br>(ClinicalTrials.gov identifier: NCT01930188)[15] | 1225 | 6.6 (5.1) | 55.1 (10.0) | 50.6 | 8.1 (0.9) | 89.5 (20.3) |
| SUSTAIN 3<br>Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial<br>(ClinicalTrials.gov identifier: NCT01885208)[16] | 809 | 9.2 (6.3) | 56.6 (10.7) | 55.3 | 8.35 (0.95) | 95.8 (21.5) |
| SUSTAIN 4<br>Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulphonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomized, open-label, parallel-group, multicentre, multinational, phase 3a trial<br>(ClinicalTrials.gov identifier: NCT02128932)[17] | 1082 | 8.6 (6.3) | 56.5 (10.4) | 53 | 8.2 (0.9) | 93.5 (21.8) |
| SUSTAIN 5<br>Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized controlled trial<br>(ClinicalTrials.gov identifier: NCT02305381)[18,24] | 396 | 13.3 (7.8) | 58.8 (10.1) | 56.1 | 8.37 (0.83) | 91.7 (20.97) |
| SUSTAIN 6<br>Semaglutide and cardiovascular outcomes in patients with type 2 diabetes<br>(ClinicalTrials.gov identifier: NCT01720446)[19] | 3297 | 13.9 (8.1) | 64.6 (7.4) | 60.7 | 8.7 (1.5) | 92.1 (20.6) |
| SUSTAIN 7<br>Semaglutide versus dulaglutide once-weekly in patients with type 2 diabetes (SUSTAIN 7): a randomized, open-label, phase 3b trial<br>(ClinicalTrials.gov identifier: NCT02648204)[20] | 1199 | 7.4 (5.7) | 56 (10.6) | 55.2 | 8.2 (0.9) | 95.2 (22.6) |
| SUSTAIN 8<br>Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomized controlled trial<br>(ClinicalTrials.gov identifier: NCT03136484)[21] | 788 | 7.4 (5.6) | 56.6 (10.9) | 54.0 | 8.3 (1.0) | 90.2 (22.6) |
| SUSTAIN 9<br>Semaglutide once-weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomized, placebo-controlled trial | 302 | 9.7 (6.1) | 57.0 (9.5) | 58.3 | 8.0 (0.8) | 91.7 (21.0) |

**TABLE 1** (Continued)

| Trial descriptor (identifier) | Baseline characteristics as mean (SD) or % | | | | | |
|---|---|---|---|---|---|---|
| | N | Diabetes duration (y) | Age (y) | Sex (% male) | HbA1c (%) | Body weight (kg) |
| (ClinicalTrials.gov identifier: NCT03086330)[22] | | | | | | |
| SUSTAIN 10<br>Efficacy and safety of once-weekly semaglutide 1.0 mg versus once-daily liraglutide 1.2 mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10)<br>(ClinicalTrials.gov identifier: NCT03191396)[23] | 577 | 9.3 (5.9) | 59.5 (10.2) | 56.7 | 8.2 (1.0) | 96.9 (21.3) |

inhibitory effect on the build-up of body weight.[28] As with the FG-HbA1c model, separate models describing dulaglutide and semaglutide time-course effects on body weight were developed. Depending on the trial design, a placebo time-course effect was also incorporated in the FG-HbA1c and body weight models, where applicable.

Because the PK/PD models were developed using actual time courses of HbA1c and body weight, there was no need to assume that drug effects can be directly compared across different phase 3 clinical trials, where differences in trial duration, timing of primary endpoints, sample size, and patient inclusion criteria often exist.

## 2.3 | Model validations

Before the PK/PD models were utilized for simulations, visual predictive checks (VPCs)[29-31] comparing model-predicted change-from-baseline time courses of the key efficacy outcomes of HbA1c and body weight using observed data up to the 36-week primary endpoint of the AWARD-11 trial for dulaglutide (Figure S2) and SUSTAIN 1 through 10 trials for semaglutide (Figure S3) were conducted to ensure each PK/PD model adequately described the observed data. Model predictions agreed well with observed FG, HbA1c, and weight data and are included in Figure S2. The observed median, fifth, and 95th percentiles were generally within their respective model-predicted 95% confidence intervals. Therefore, model predictions agree well with observations.

## 2.4 | Simulation of switch scenarios

For the purpose of evaluating the key clinical outcomes of glycaemic control and body weight in patients who switch treatment from semaglutide to either 3.0- or 4.5-mg QW of dulaglutide, simulations were conducted with semaglutide dosing initiated at 0.25 mg on week 0 for 4 weeks, then escalated to 0.5-mg QW and either maintained at 0.5-mg QW until week 25 or further escalated to 1.0-mg QW before maintaining at this dose until week 25. Semaglutide effects for glycaemic control and body weight were reported at week 26 following a total of 26 semaglutide doses, inclusive of the dose-titration regimen. The dose-titration scheme employed for semaglutide followed general product label recommendations.[2,32] To simulate a switch at week 26 onwards to dulaglutide, dulaglutide dosing commenced at week 26 using various common prescribing scenarios, where dulaglutide could be initiated at either 0.75-mg QW or 1.5-mg QW for 4 weeks before escalation to 3.0-mg QW, and either maintained at 3.0-mg QW until week 51 or further escalated to 4.5-mg QW after 4 weeks and maintaining this dose until week 51, to reach a total duration of dulaglutide treatment of 26 weeks. Dose escalation of dulaglutide also followed general product label recommendations.[3,33] In a similar manner, dulaglutide effects were summarized at week 52 following a total of 26 dulaglutide doses. A total of 26 doses per treatment was chosen as this duration was deemed sufficient to allow full demonstration of the drug effect for the targeted dose to reach steady state.

Simulations of 100 trials with 100 patients per treatment scenario were created to evaluate each switching scenario (Figure 1), and the means from these 100 trials were plotted as the time course of change for each efficacy endpoint. To create the virtual patient datasets for the simulations so that the patient populations resemble as closely as possible actual patients who would switch to dulaglutide 3.0 or 4.5 mg, each simulation dataset was generated by sampling patients repeatedly from the AWARD-11 study dataset (bootstrap method), which contained 1842 patients with inadequately controlled T2D while on concomitant metformin therapy. At baseline, the mean age was 57.1 years, mean weight was 95.7 kg, and mean HbA1c was 8.6% in the AWARD-11 patient population (Table 1).[9] All model simulations and graphical outputs were conducted with R version 3.6.3 (Core Team R 2019). Considering that model-driven simulations are dependent on the input data for variability in the model-building dataset, and trial-level data were used for semaglutide versus patient-level data for dulaglutide, it was deemed most appropriate to report and compare simulation outcomes as population typical mean values from a bootstrap approach for the evaluation of each simulation.

Mean HbA1c and body weight changes from baseline were reported at weeks 26 and 52 to enable evaluation of various switching scenarios, starting with 26 weeks of weekly dosing of semaglutide followed by 26 weeks of weekly dulaglutide (Figure 1). A total treatment duration of 26 weeks was assumed to be adequate for each of semaglutide and dulaglutide to show their drug effects for meaningful comparisons after taking into consideration dose-escalation regimens.

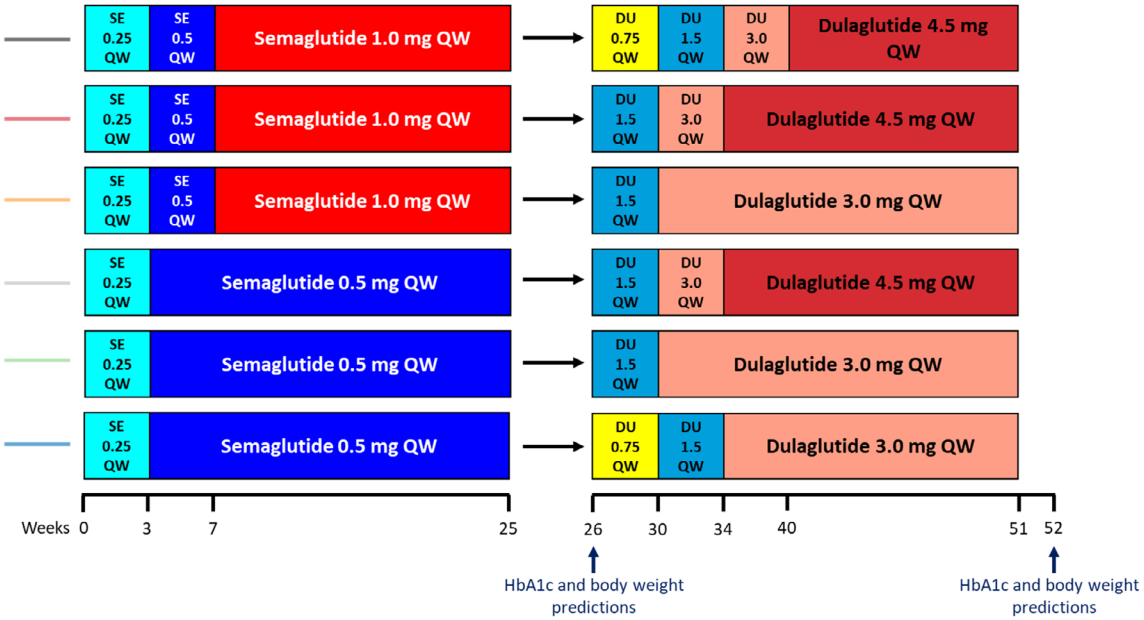


**FIGURE 1** Simulation scenarios for switching from semaglutide 0.5 or 1.0 mg to dulaglutide 3.0 or 4.5 mg. DU, dulaglutide; QW, once-weekly; SE, semaglutide

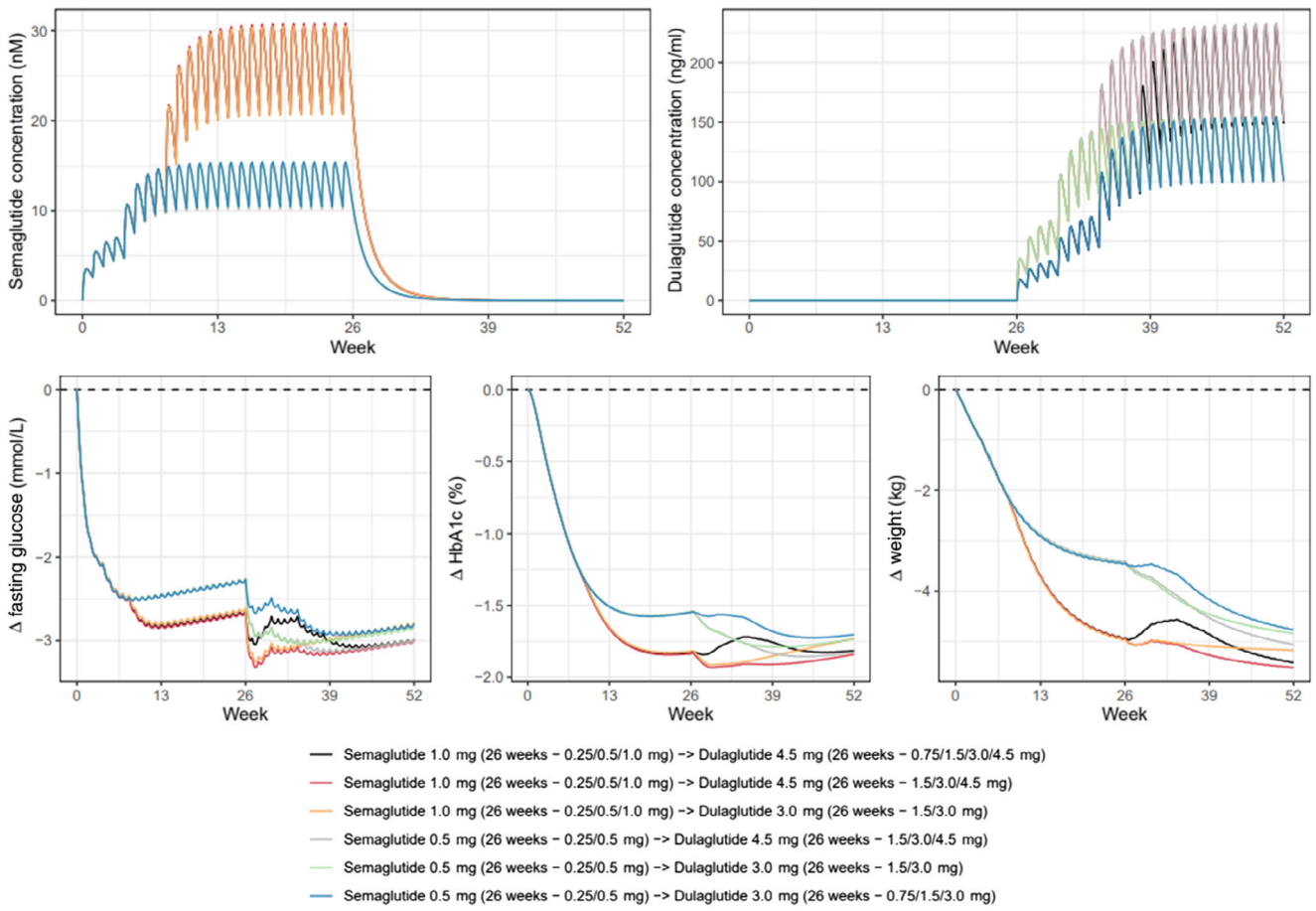


**FIGURE 2** Mean change from baseline in fasting glucose, HbA1c, and body weight after switching from semaglutide 0.5 or 1.0 mg to dulaglutide 3.0 or 4.5 mg. The top panels depict semaglutide (left) and dulaglutide (right) pharmacokinetic concentrations. The bottom panels depict fasting glucose (left), HbA1c (middle), and body weight (right) mean changes relative to baseline after 26 once-weekly doses of semaglutide followed by 26 once-weekly doses of dulaglutide. Δ, change from baseline

## 3 | RESULTS

Because the AWARD-11 dataset was used to generate the 100 simulation datasets, baseline demographics of each simulation dataset closely mimicked those of the AWARD-11 patients, as shown in Table 1. The time course of PK concentrations of semaglutide and dulaglutide and the mean changes from baseline in FG, HbA1c, and body weight are shown in Figure 2, illustrating the full 52-week time course of the expected outcomes through each transition scenario.

### 3.1 | HbA1c and weight outcomes after switching from semaglutide 0.5-mg QW to dulaglutide 3.0-mg QW via stepwise dose escalation

For patients initiated at semaglutide 0.25-mg QW and titrated to 0.5-mg QW 4 weeks later, model-predicted mean changes from baseline in HbA1c and body weight after 26 weeks on semaglutide were −1.55% and −3.44 kg, respectively (Table 2, Figure 2). Following a switch to dulaglutide initiated at 0.75-mg QW, then escalated to 1.5-mg QW after 4 weeks and finally to 3.0-mg QW after another 4 weeks, the predicted mean changes from baseline in HbA1c and body weight at week 52 were −1.70% and −4.76 kg, respectively (Table 2, Figure 2).

When switching from semaglutide 0.5-mg QW to dulaglutide 3.0-mg QW, via the alternative dosing regimen where dulaglutide was initiated at 1.5-mg QW, the week 52 mean changes from baseline in HbA1c and body weight showed additional improvements versus semaglutide 0.5-mg QW. These improvements were comparable regardless of dulaglutide dosing being initiated at 0.75-mg QW or 1.5-mg QW (Table 2, Figure 2).

In general, model predictions indicated that switching from semaglutide 0.5 mg to dulaglutide 3.0 mg should not result in any loss of glycaemic control and may in fact have a small positive impact on both HbA1c and body weight reductions for patients with T2D.

### 3.2 | HbA1c and weight outcomes after switching from semaglutide 0.5-mg QW to dulaglutide 4.5-mg QW via stepwise dose escalation

For semaglutide 0.5-mg QW patients who switched to dulaglutide after 26 weeks of treatment, where dulaglutide was dose-escalated every 4 weeks to 4.5-mg QW, the predicted mean changes in HbA1c

**TABLE 2** Summary of model-predicted mean changes from baseline in HbA1c and body weight at weeks 26 and 52 for each dosing scenario

| Dosing scenario | Change from week 0 baseline HbA1c (%) (mean, 90% CI) at week 26 after semaglutide treatment | Change from week 0 baseline HbA1c (%) (mean, 90% CI) at week 52 after switching to dulaglutide treatment | Mean HbA1c change from week 26 to week 52 (%) |
|---|---|---|---|
| Semaglutide 0.25/0.5/1.0 mg to dulaglutide 0.75/1.5/3.0/4.5 mg | −1.83 (−2.04, −1.59) | −1.82 (−2.0, −1.62) | 0.01 |
| Semaglutide 0.25/0.5/1.0 mg to dulaglutide 1.5/3.0/4.5 mg | −1.84 (−2.06, −1.59) | −1.84 (−2.01, −1.68) | 0 |
| Semaglutide 0.25/0.5/1.0 mg to dulaglutide 1.5/3.0 mg | −1.82 (−2.02, −1.53) | −1.73 (−1.9, −1.53) | 0.09 |
| Semaglutide 0.25/0.5 mg to dulaglutide 1.5/3.0/4.5 mg | −1.55 (−1.71, −1.39) | −1.83 (−2.0, −1.64) | −0.28 |
| Semaglutide 0.25/0.5 mg to dulaglutide 1.5/3.0 mg | −1.54 (−1.75, −1.34) | −1.73 (−1.90, −1.58) | −0.19 |
| Semaglutide 0.25/0.5 mg to dulaglutide 0.75/1.5/3.0 mg | −1.55 (−1.74, −1.36) | −1.70 (−1.88, −1.51) | −0.15 |
| **Dosing scenario** | **Change from week 0 baseline weight (kg) (mean, 90% CI) at week 26 after semaglutide treatment** | **Change from week 0 baseline weight (kg) (mean, 90% CI) at week 52 after switching to dulaglutide treatment** | **Mean weight change from week 26 to week 52 (kg)** |
| Semaglutide 0.25/0.5/1.0 mg to dulaglutide 0.75/1.5/3.0/4.5 mg | −4.93 (−5.36, −4.6) | −5.41 (−6.45, −4.65) | −0.48 |
| Semaglutide 0.25/0.5/1.0 mg to dulaglutide 1.5/3.0/4.5 mg | −4.94 (−5.40, −4.53) | −5.51 (−6.41, −4.72) | −0.57 |
| Semaglutide 0.25/0.5/1.0 mg to dulaglutide 1.5/3.0 mg | −4.96 (−5.30, −4.61) | −5.17 (−5.91, −4.31) | −0.21 |
| Semaglutide 0.25/0.5 mg to dulaglutide 1.5/3.0/4.5 mg | −3.40 (−3.63, −3.17) | −5.06 (−5.85, −4.48) | −1.66 |
| Semaglutide 0.25/0.5 mg to dulaglutide 1.5/3.0 mg | −3.43 (−3.66, −3.19) | −4.83 (−5.56, −4.15) | −1.40 |
| Semaglutide 0.25/0.5 mg to dulaglutide 0.75/1.5/3.0 mg | −3.44 (−3.72, −3.18) | −4.76 (−5.66, −3.91) | − 1.32 |

Abbreviation: CI, confidence interval.

and body weight at week 52 were −1.83% and −5.06 kg, respectively (Table 2, Figure 2), suggesting potential for greater improvement in glycaemic control and weight reduction compared with dulaglutide 3.0-mg QW in the previous dosing scenario.

### 3.3 | HbA1c and weight outcomes after switching from semaglutide 1.0-mg QW to dulaglutide 4.5-mg QW via stepwise dose escalation

For patients initiated at semaglutide 0.25-mg QW and titrated every 4 weeks to 0.5-mg QW and eventually to 1.0-mg QW, switching to dulaglutide initiated at either 0.75- or 1.5-mg QW and dose-escalated to 4.5-mg QW eventually, there may be transient changes in glycaemic control, but once dosed to steady state at the targeted 4.5-mg QW, no loss in glycaemic control is expected and some additional weight loss of about 0.5 kg may be possible (Table 2, Figure 2).

### 3.4 | HbA1c and weight outcomes after switching from semaglutide 1.0-mg QW to dulaglutide 3.0-mg QW via stepwise dose escalation

In a scenario where a patient currently on semaglutide 1.0-mg QW is switched to dulaglutide 3.0-mg QW following dose escalation, the expected mean change from baseline in HbA1c and body weight at week 52 would be −1.73% and −5.17 kg, respectively. These outcomes are still comparable with predicted mean changes in HbA1c and body weight of −1.82% and −4.96 kg, respectively, at 26 weeks, indicating there should be no clinical concerns for change in efficacy when switching from semaglutide 1.0-mg QW to dulaglutide 3.0-mg QW.

## 4 | DISCUSSION

This model-based approach evaluated several possible real-world scenarios where patients with T2D on an injectable QW GLP-1 RA (semaglutide 0.5 and 1.0 mg) switch to one of the more recently approved additional doses of another QW GLP-1 RA (dulaglutide 3.0 and 4.5 mg) via stepwise dose escalation. A drug-specific, exposure-response PK/PD model was developed for semaglutide and dulaglutide separately and validated using actual clinical trial data for each clinical endpoint of interest. While this approach is more tedious, it obviates the need to make potency assumptions between drugs to enable switching between them if the same exposure-response model was used across different drugs,[13] and ensures the model describes the unique disposition and PD behaviour of each individual drug adequately. By utilizing modelling and simulation approaches, the clinical impact of all clinically relevant doses and multiple dosing scenarios can be assessed without the need to subject patients to additional clinical studies.

A recent publication by Pratley et al. indirectly compared semaglutide 1 mg to dulaglutide 3 and 4.5 mg using the Bucher indirect comparison approach. However, this publication did not include a comparison of semaglutide 0.5 mg to either dulaglutide dose.[34] The Bucher method is based on a network meta-analysis approach that utilizes data selectively from the SUSTAIN 7 and AWARD-11 trials, an approach which tends to ignore differences in trial durations and inclusion criteria between studies. Our PK/PD modelling approach fully utilizes information from all data points along the time course, as reported in all of the SUSTAIN trials. More importantly, baseline HbA1c and body weight can be implemented as covariate effects in the models to enable adjustment for differences in patient baseline demographics potentially caused by differing inclusion criteria between trials. Therefore, simulation outputs from a PK/PD modelling approach show drug effects representative of the overall population mean at any chosen time point along the time course, and at the same time, account for subtle differences in patient factors.

Based on the VPCs created for the SUSTAIN 1 to 10 trials (Figure S3), mean change from baseline HbA1c model-fits versus observed data were slightly better than FG model-fits because there were more HbA1c data points reported in the published literature to enable better capture of the HbA1c time course compared with FG. For example, in the predicted mean time course for SUSTAIN 6, the PK/PD model seemed to have underpredicted mean changes in FG and HbA1c after week 52. SUSTAIN 6 may be an exception for the typical time-course behaviour for FG and HbA1c for reasons that may include the longer study duration of 104 weeks compared with other trials that did not exceed 52 weeks in duration; there were no FG values reported other than at baseline and week 104, so there were a lack of data to guide the FG trajectory; and because actual doses of insulins were unavailable, it was not possible to fully account for the impact of insulins on the PD endpoints. There appears to be a slight loss of glycaemic control over time in the SUSTAIN trials at the 52-week or later time points, potentially attributable to T2D disease progression over time, which was not as evident in AWARD-11 for dulaglutide. Considering the inter-trial variability within the patient population across the 10 SUSTAIN trials, where body weight was underpredicted for some (e.g. SUSTAIN 5 and 7) but overpredicted for others (e.g. SUSTAIN 1 and 8), these misspecifications of individual trials would not affect the overall model conclusions because conclusions are based on population mean predictions. Overall, the PD time courses for body weight across the 10 SUSTAIN trials were considered adequately described by the PK/PD model and would represent the mean population drug effect well.

As the PK/PD models account for the effect of baseline FG, HbA1c, and body weight on the magnitude of drug effect in their respective models, any difference in baseline demographics between patient cohorts in the SUSTAIN phase 3 trials, or between the SUSTAIN and AWARD-11 trials, should be captured accordingly before generating model outputs.

Because switching scenarios from semaglutide 1.0-mg QW to previously approved dulaglutide doses of 0.75-mg QW or 1.5-mg QW are out of scope, the model-building dataset did not include data from the AWARD 1 through 10 trials, which investigated dulaglutide 0.75-mg QW and/or 1.5-mg QW doses. Another limitation of the model-building dataset was the use of trial-level data from the semaglutide SUSTAIN trials. To circumvent the lack of inter-individual

variability information for semaglutide in the model-building dataset because of the collection of model-building data from trial-level results reported in the SUSTAIN 1 through 10 publications, all simulation datasets were created using virtual patients by sampling with replacement from the AWARD-11 patient population. This has two advantages. First, individual patient-level heterogeneity can now be introduced into the simulation datasets without the need to assume variability based on covariate distribution. This alleviates the concern that the PK/PD models cannot replicate inter-patient variability adequately because treatment-level mean data reported in the literature from the SUSTAIN 1 through 10 trials had been utilized to build the semaglutide model. Second, sampling patients from the AWARD-11 dataset directly mimicked the target patient population investigated in the phase 3 study for the additional doses of dulaglutide.

As the most informative outcome for this model-based evaluation was to report the typical mean time courses of FG, HbA1c, and body weight, any difference in individual patient effects would have been minimized, as the reporting of results for each scenario was based on the aggregated average of 100 simulated trials at each time point.

Because there appeared to be a slight loss of effect in FG and HbA1c by the week-52 or later time points across some of the SUSTAIN trials with longer durations, the treatment duration of 26 weeks on each drug was chosen as the endpoint for efficacy evaluation as this length of treatment for either drug is considered adequate for them to exhibit their optimal PD effects on glycaemic control and body weight in patients with T2D based on published phase 3 time-course data.

Upon closer examination of the data in the immediate weeks after week 26, where the last dose of semaglutide would have been administered at week 25 and the first dose of dulaglutide would have been administered at week 26, the model predictions indicated potential but transient aberrations in glycaemic control or weight effects depending on the doses involved in each switch scenario. This is the result of an overlap of a washout of semaglutide effect postdose with the onset of dulaglutide's drug effect as the latter's PK exposures build up following a transition. By initiating dulaglutide at 1.5-mg QW instead of 0.75-mg QW, the higher dulaglutide exposures are anticipated to provide a better buffer for transient change in glycaemic or weight control during the period immediately after a GLP-1 RA switch. Both 0.75-mg QW[3] and 1.5-mg QW[33] are commonly prescribed doses for the initiation of dulaglutide treatment.

To summarize, model-based evaluations suggest that switching from semaglutide 0.5-mg QW to dulaglutide 3.0-mg QW and from semaglutide 1.0-mg QW to dulaglutide 4.5-mg QW[34] via stepwise dose escalation, can potentially yield additional and comparable HbA1c reduction, respectively, with greater weight loss. The ability of robust exposure-response time-course models developed from and validated with actual observed clinical trial data to explore a myriad of clinical dosing scenarios draws on the flexibility of modelling and simulations as tools to answer questions on prescribing scenarios, which may otherwise have to be evaluated separately with clinical trials. The learnings drawn from this model-based approach serve to provide guidance to prescribers should a patient need to switch from QW semaglutide to dulaglutide, also given at the same weekly dosing frequency. In this scenario, model predictions showed that glycaemic control and weight benefits should be preserved, if not enhanced. The simulation results should also augment the understanding for different dosing scenarios in order to minimize the risk of losing efficacy during the transition and manage expectations for treatment outcomes.

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## CONFLICT OF INTEREST

L.S.T., C.C.T., M.K., and A.Y.M.K. are employees and stockholders of Eli Lilly and Company. K.M.P. declares speaker honoraria from AstraZeneca, Corcept Therapeutics, Merck, and Novo Nordisk; consultant honoraria from AstraZeneca, Bayer, Corcept Therapeutics, Diasome, Novo Nordisk, and Merck; and research support from Bayer, Novo Nordisk, and Merck. K.D. declares research support from Novo Nordisk, Sanofi, Abbott, and Viacyte; consulting fees from Eli Lilly and Company, Jansen, Novo Nordisk, and Tolerion; and honoraria from UpToDate, Elsevier, Cardiometabolic Health Conference, and the Academy for Continued Healthcare Learning. K.M. declares no conflicts of interest.

## AUTHOR CONTRIBUTIONS

L.S.T., A.Y.M.K., and M.K. contributed to the study concept and design, data interpretation and manuscript preparation and critical review. C.C.T. contributed to the data analysis, manuscript preparation and critical review. K.M.P., K.D. and K.M. contributed to the study concept, data interpretation, manuscript preparation and critical review. All authors have provided final approval of the manuscript. Some of the data were presented at the 81st Annual scientific meeting of the American Diabetes Association held virtually 25-29 June 2021.

## DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at vivli.org.

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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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