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ORIGINAL RESEARCH

Glycaemic Control in People with Type 2 Diabetes Treated with Insulin Degludec: A Real-World, Prospective Non-interventional Study—UPDATES Saudi Arabia

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ABSTRACT

Introduction: Insulin degludec (degludec) has proven benefits in type 2 diabetes (T2D), in terms of improved glycaemic control, low risk of hypoglycaemia, and flexibility in dosing time. This prospective non-interventional UPDATES study aimed to investigate whether results obtained from randomised clinical trials and other real-world studies with degludec are generalisable to patients with T2D in routine clinical practice in Saudi Arabia.

Methods: Eligible adults ($n = 561$) with T2D received degludec for 26–34 weeks, at physicians' discretion and in accordance with local routine clinical practice. The primary endpoint was mean change in HbA_{1c} from baseline to end of study (EOS). Secondary endpoints included mean change from baseline to EOS in fasting

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plasma glucose (FPG), daily insulin dose and rate of hypoglycaemia.
Results: At baseline, mean age, HbA_{1c} and FPG were 55.7 years, 9.4% and 185.6 mg/dL, respectively. Mean (standard error [SE]) changes from baseline to EOS (crude analysis) were statistically significant for HbA_{1c} (− 1.1 [0.08] %-points, 95% CI − 1.29, − 0.98; $P < 0.0001$), FPG (− 39.1 [3.42] mg/dL, 95% CI − 45.9, − 32.4; $P < 0.0001$) and total daily insulin dose (+ 4.7 [1.6] units, 95% CI 1.63, 7.86; $P = 0.003$, insulin-experienced population). In exploratory analysis of patients switching from insulin glargine U100 or U300 to degludec, similar reductions were seen in HbA_{1c} and FPG. The rate of hypoglycaemia was significantly reduced with degludec versus previous treatment, with no apparent or unexpected safety and tolerability issues. The number of insulin-experienced patients utilising resources associated with severe hypoglycaemia was also reduced. Most patients (95.5%) were willing to continue treatment at EOS, and expressed a preference for degludec over their previous regimen (93.0%).
Conclusion: Patients with T2D treated with degludec in routine clinical practice in Saudi Arabia experienced clinically significant improvements in glycaemic control and a lower rate of hypoglycaemia compared with baseline, with no new safety concerns reported.
Clinical Trial Registration: NCT03785522.

Keywords: Insulin degludec; Glycaemic control; Type 2 diabetes

Key Summary Points

Why carry out this study?

Insulin degludec (degludec) is a basal insulin analogue with an ultra-long duration of action and low day-to-day variability in blood glucose-lowering effect compared with insulin glargine (glargine) U100 and U300.

Despite proven glycaemic benefits of degludec, accompanied by a low risk of hypoglycaemia and flexibility in dosing time, no clinical trials or observational studies have been conducted to date with degludec in Saudi Arabia.

The prospective non-interventional UPDATES study assessed clinical parameters in people with type 2 diabetes (T2D) treated with degludec in routine clinical practice in Saudi Arabia.

What was learned from the study?

In people with T2D treated with degludec in routine clinical practice, significant reductions were seen in HbA_{1c}, FPG and rate of hypoglycaemia, with no unexpected safety concerns; similar reductions were also seen in exploratory analysis of people switching from insulin glargine U100 and U300 to degludec.

Results support that previously published data with degludec are generalisable to a broad population of people with T2D in routine clinical practice in Saudi Arabia.

INTRODUCTION

Chronic hyperglycaemia has been linked to the development of long-term micro- and macrovascular complications, whose progression is accelerated by poor glycaemic control [1–3]. Thus, the primary treatment goal in people with diabetes is to prevent these complications, which can be accomplished through good glycaemic control [1–3]. Antidiabetic treatment aims to balance optimal control of both fasting plasma glucose (FPG) and postprandial glucose levels with the risk of hypoglycaemia [4]. Following lifestyle modification and treatment with oral antidiabetic drugs, with or without glucagon-like peptide 1 receptor agonists, insulin is eventually required in many people with type 2 diabetes (T2D) to manage their blood glucose levels [5–7]. Basal insulin is recommended, often subsequently intensified

by the inclusion of a rapid-acting insulin analogue, or with a tailored basal–bolus regimen or premixed insulin [5–7].

Insulin degludec (degludec) is a basal insulin analogue with an ultra-long duration of action and low day-to-day variability in blood glucose-lowering effect compared with insulin glargine (glargine) U100 and U300 [8–10]. Randomised, controlled, treat-to-target trials have demonstrated the beneficial effects of degludec in terms of improved glycaemic control, low risk of hypoglycaemia and flexibility in dosing time [8, 9, 11–13], and the cardiovascular safety profile of degludec has been confirmed as being non-inferior to that of glargine U100 [14]. Furthermore, data from real-world studies with degludec have reinforced its clinical benefits in terms of improving glycaemic control and lowering the risk of hypoglycaemia when switching from alternative insulin regimens in an everyday clinical setting [10, 15–18].

The prevalence of T2D in Saudi Arabia is rising, with the national prevalence of diabetes in adults currently estimated to be 18.7% [4]. Degludec was approved in Saudi Arabia in May 2016 and launched in September 2016, and is currently indicated for treatment of diabetes in adults, adolescents, and children from the age of 1 year [19]. No clinical trials or observational studies have been conducted with degludec in Saudi Arabia. Real-world evidence studies are increasingly recognised as important to complement data generated from randomised controlled trials [20–24].

The UPDATES study aimed to investigate whether results obtained from randomised clinical trials and other real-world studies with degludec would be generalisable to patients with T2D in routine clinical practice in Saudi Arabia. The primary objective was to investigate glycaemic control during treatment with degludec according to local clinical practice in adult patients with T2D in Saudi Arabia. The secondary objective was to investigate other clinical outcomes in this setting. Exploratory objectives included investigation of local resource utilisation due to severe hypoglycaemic episodes, and patient treatment preference.

METHODS

Study Design and Population

This was an approximately 26-week, multicentre, prospective, open-label, non-interventional study (NCT03785522) investigating glycaemic control and other clinical outcomes in adult patients with T2D treated with degludec in routine clinical practice. The study was conducted in a real-world setting across 19 sites in Saudi Arabia. The study was considered non-interventional as the decision to initiate degludec was at the treating physician's discretion and was independent from the decision to include the patient in the study. The study initiated with first patient first visit on 23 December 2018 and ended with last patient last visit on 30 November 2020. Eligible patients were male or female aged 18 years or older, diagnosed with T2D and treated with any anti-hyperglycaemic medication(s), except degludec, for at least 26 weeks prior to study enrolment, and with an available HbA_{1c} value measured within 12 weeks prior to study enrolment. Patients were excluded if they had mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation, or known hypersensitivity to the active substance or any of the excipients specified in the degludec local label.

Patients were treated with commercially available degludec in a pre-filled pen injector (FlexTouch®, Novo Nordisk A/S, Bagsvaerd, Denmark) according to routine clinical practice and in accordance with the local label. The physician determined the starting dose of degludec as well as any dose adjustments thereafter. During the study, addition, dose adjustments or discontinuation of glucose-lowering medications, including degludec, were at the treating physician's discretion, with no input from the study sponsor. The study included an informed consent and treatment initiation visit (baseline), multiple intermediate visits in accordance with local clinical practice and an end of study (EOS) visit (the first visit with the window from week 26 to 34). A treatment discontinuation visit was applied only for patients

who received at least one dose of degludec and then permanently discontinued treatment. Data related to clinical outcomes, other than laboratory measurements, were based on patient recollection reported during the relevant visit. This approach reflects routine clinical practice. Institutional review board (IRB) approval was received, with the study approved by local IRBs at all participating institutions. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients provided informed consent to participate in the study.

Study Objectives and Endpoints

Most endpoints compared change from baseline to EOS values. Baseline was defined as a period of 12 weeks or less prior to treatment initiation, with the most recent value used if multiple values were available. The primary endpoint was mean change in laboratory-measured HbA_{1c} (%-points) from baseline to EOS. Secondary endpoints were mean change from baseline to EOS in FPG and daily insulin dose (basal, prandial and total insulin); change in number and rate (episodes/person-year) of patient-reported overall severe, overall non-severe and nocturnal non-severe hypoglycaemia pre and post initiation of degludec (between 26 weeks before baseline until baseline and between 26 weeks before EOS until EOS for severe, and between 4 weeks before baseline until baseline and between 4 weeks before EOS until EOS for non-severe events); reason(s) for discontinuing treatment with degludec, and adverse event (AE) and safety data; patient preference for degludec compared with previous treatment, and willingness to continue treatment, assessed at EOS; and healthcare resource utilisation (HRU) associated with patient-reported severe hypoglycaemia, pre and post initiation of degludec (from 26 weeks before baseline until baseline and from 26 weeks before EOS until EOS). Pre-specified response options were number of outpatient visits, number of episodes requiring an ambulance, number of emergency room visits, number of inpatient hospitalisations, number of work days missed and number of episodes requiring administration of glucagon. Non-severe hypoglycaemia was defined as an episode with symptoms and/or self-monitored blood glucose value less than 3.9 mmol/L (70 mg/dL). The definition of nocturnal was based on the patient's perception of whether it was night, i.e. their answer to the question 'How many of these occurred between midnight and early morning?' Severe hypoglycaemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective action [25].

Exploratory endpoints included mean change from baseline to EOS in HbA_{1c}, FPG and basal daily insulin dose in patients switching from glargine U100 or U300; and estimated incidence rate ratio for overall severe, overall non-severe and nocturnal non-severe hypoglycaemia, in patients switching from glargine U100 or U300. Given that patients could commence prandial insulin during the study, two further exploratory endpoints were the assessment of mean change from baseline to EOS in HbA_{1c} and FPG in patients switching from another basal insulin and using degludec as their only insulin during the study, as well as the mean change from baseline to EOS in HbA_{1c} in patients treated with prandial insulin versus non-prandial insulin during the study. These endpoints were designed to assess change unconfounded by the influence of additional prandial insulin.

Statistical Methods

All assessments were made on the full analysis set (FAS), defined as all eligible patients who gave informed consent and initiated treatment with degludec. Two treatment period estimands were considered: the on-treatment period, in which patients were considered treated with degludec, commencing at baseline and ending with either EOS, date of the last dose of degludec according to the treating physician, withdrawal of consent, death or last patient-physician contact (defined by the physician for patients lost to follow-up); and the in-study period, during which patients were in the study,

regardless of adherence to degludec, commencing at baseline and ending at the earliest of the EOS, withdrawal of consent, death or last patient–physician contact. A complete on-treatment analysis set (COT) was also recognised for those patients being treated with degludec at EOS (and with no missing data for the endpoint at EOS visit). This was used for secondary analysis of the primary endpoint and the hypoglycaemia endpoints. Patients discontinuing degludec were censored at date of discontinuation but contributed their data until discontinuation. Any HbA_{1c} values measured after discontinuation were disregarded.

Descriptive statistics were used for patient characteristics, and safety information on AEs. The primary analysis was performed on the basis of the 'FAS, on-treatment observation period' using a mixed model for repeated measures (MMRM) with both crude and adjusted models made. The crude model included baseline HbA_{1c} and time of HbA_{1c} measurement as covariates. The adjusted model additionally included, as baseline covariates, age, sex, diabetes duration, body mass index (BMI) and baseline treatment regimen (insulin naïve and insulin experienced). Study sites were also included in the model to account for within-site correlation. The primary analysis included all FAS patients with at least one post-baseline HbA_{1c} measurement. The primary analysis was performed for patients overall and stratified by baseline treatment regimen (insulin naïve and insulin experienced). For the stratified analysis in the adjusted model, baseline treatment regimen was omitted as a covariate. Two secondary analyses were performed for the primary endpoint, the 'FAS, in-study observation period' analysis and the COT analysis. The former was similar to the primary analysis except patients were not censored if they discontinued degludec. The COT analysis assessed baseline-adjusted change using an analysis of covariance (ANCOVA) model with change in HbA_{1c} as the dependent variable, and covariates including baseline HbA_{1c}, age, sex, diabetes duration and baseline treatment regimen. As a result of the coronavirus 2019 disease (COVID-19) pandemic, some patients had their EOS visit outside the target window (week 26–34) and minor protocol deviations (PDs) were filed for those patients. If at least 10% of patients had their EOS visit after week 34, sensitivity analyses were performed for the primary endpoint, to assess the impact of PD. These were analyses of mean change in HbA_{1c} from baseline in patients having an EOS visit within the window (i.e. removing all PD cases), or considering all PD cases to be 'part of normal practice' and using the median exposure week of insulin degludec as EOS. Primary analyses of secondary endpoints were performed on the basis of the 'FAS, on treatment analysis set'. Change in laboratory-measured FPG was performed using MMRM as per the primary endpoint, but a stratified analysis by baseline treatment regimen was carried out for insulin-experienced patients only since data were available for fewer than 30 insulin-naïve patients. Changes in daily insulin doses (total, basal and prandial) were analysed using both the MMRM and ANCOVA models (crude and adjusted) by stratified baseline treatment regimen only. The adjusted model was the same as that used for the primary endpoint, except baseline treatment regimen was omitted as a covariate. Changes in number of patient-reported hypoglycaemic episodes (severe, overall non-severe, nocturnal non-severe) from baseline to EOS (or discontinuation) were assessed only in insulin-experienced patients using negative binomial regression models. Both crude (period only) and adjusted (all possible variables included in the same model) incidence rate ratios were calculated with corresponding 95% confidence intervals [CIs] and *P* values. These hypoglycaemia endpoints were also analysed using the COT analysis set. Reasons for discontinuing degludec were assessed with descriptive statistics. HRU was assessed using the 'FAS in-study observation period', with data given as descriptive statistics. Treatment preference was assessed using the FAS, with descriptive statistics.

The exploratory endpoints for the subset of patients switching from glargine U100 or U300 were assessed using the statistical methods described above for each respective endpoint. The exploratory endpoints for patients switching from another basal insulin and using degludec as their only insulin during the study

were assessed using the statistical methods described above for each respective endpoint. The exploratory endpoints comparing patients treated with prandial insulin versus non-prandial insulin during the study were assessed using adjusted MMRM.

RESULTS

Study Population Disposition and Clinical Characteristics

Patient disposition is summarised in Supplemental Fig. 1. Of 562 patients enrolled, 561 commenced treatment with degludec and were included in the FAS. In total, 75.2% completed the study, with 413 (73.6%) in the COT. Baseline characteristics are summarised in Table 1. At baseline, the mean age was 55.7 years, mean BMI was 31.7 kg/m^2, mean duration of T2D was 15.2 years, mean HbA_{1c} was 9.4% and mean FPG was 185.6 mg/dL. The proportion of patients already using insulin (90.6%) with HbA_{1c} levels less than 7% was only 7.3% at baseline. The reasons given by physicians for starting degludec were to improve patient's glycaemic control (91.1%), issues with hypoglycaemia on current treatment (36.7%), convenience (30.1%) and other reasons (5.9%). Reasons for premature discontinuation of degludec treatment were hypoglycaemia (n = 2), insufficient effect on hypoglycaemic control (n = 1), unknown reasons (n = 3) or other reasons (n = 11).

Glycaemic Control

Primary endpoint In the primary analysis, estimated mean (standard error [SE]) change in HbA_{1c} from baseline to EOS was − 1.1 (0.08) %-points (95% CI − 1.29, − 0.98; $P < 0.0001$) using the crude MMRM (Fig. 1). Similar results were obtained with the adjusted model (Supplemental Fig. 2). At EOS, 54.1%, 34.6% and 16.9% of patients reached an HbA_{1c} level of $< 8\%$, $< 7.5\%$ and $< 7\%$ respectively, and 49.2% of patients had at least a 1%-point reduction in HbA_{1c}.

For insulin-naïve patients (n = 32), the estimated mean change in HbA_{1c} from baseline to EOS was − 1.6%-points (− 2.00, − 1.11; $P < 0.0001$), and for insulin-experienced patients (n = 336), the change was − 1.1 (− 1.26, − 0.94; $P < 0.0001$) (crude MRMM) (Fig. 1). The change in estimated HbA_{1c} in the COT subset (n = 264) was − 1.1%-points (− 1.23, − 0.90; $P < 0.0001$).

A total of 85 patients out of 561 (FAS) had their EOS visit outside the window period (26−34 weeks) because of COVID-19 and were considered as minor PDs. In order to assess the impact of COVID-19 on the study, sensitivity analyses were performed. For patients having their EOS visit within the specified window, the estimated mean (SE) HbA_{1c} change from baseline to EOS using the crude MMRM model was − 1.2 (0.08) %-points [− 1.32, − 1.00] 95% CI; $P < 0.0001$. Results were similar for the adjusted MMRM model (− 1.1 (0.08) %-points [− 1.30, − 0.97] 95% CI; $P < 0.0001$) and for insulin-naïve ($P < 0.0001$—crude and adjusted) and insulin-experienced ($P < 0.0001$—crude and adjusted) subgroups. For patients for whom median exposure week of insulin degludec was used as the EOS target week, the estimated mean (SE) HbA_{1c} change from baseline to EOS using the crude MMRM model was − 1.1 (0.08) %-points [− 1.27, − 0.95] 95% CI; $P < 0.0001$). Results were similar for the adjusted MMRM model (− 1.1 (0.08) %-points [− 1.26, − 0.92] 95% CI; $P < 0.0001$) and for insulin-naïve ($P < 0.0001$—crude and adjusted) and insulin-experienced ($P < 0.0001$—crude and adjusted) subgroups.

The change in estimated mean (SE) fasting plasma glucose from baseline to EOS in the overall population was − 39.1 (3.42) mg/dL (95% CI − 45.9, − 32.4; $P < 0.0001$) using the crude MMRM (Fig. 1), with similar results obtained using the adjusted model (Supplemental Fig. 2). For insulin-experienced patients (n = 274) the change was − 37.5 (3.70) mg/dL (95% CI − 44.8, − 30.2; $P < 0.0001$) (crude MRMM) (Fig. 1).

Table 1 Patient baseline characteristics

	Insulin naïve (*N* = 53)	**Insulin experienced (*N* = 508)**	**All (*N* = 561)**
Age, mean (SD)	56.2 (11.7)	55.7 (11.8)	55.7 (11.7)
Male, *n* (%)	38 (71.7)	282 (55.5)	320 (57.0)
Duration of T2D (years), mean (SD)	12.1 (7.45)	15.6 (8.33)	15.2 (8.30)
FPG (mg/dL), mean (SD)	198.4 (55.82)	184.3 (73.35)	185.6 (71.92)
HbA_{1c}, %, mean (SD)	10.0 (1.55)	9.4 (1.91)	9.4 (1.89)
HbA_{1c}, *N* (%)			
$< 7.0\%$	0	37 (7.3)	37 (6.6)
$\geq 7.0\%$ to $< 7.5\%$	0	37 (7.3)	37 (6.6)
7.5% to $< 10\%$	29 (54.7)	271 (53.3)	300 (53.5)
$\geq 10\%$	24 (45.3)	163 (32.1)	187 (33.3)
Presence of diabetic complications, *n* (%)			
Diabetic retinopathy	5 (9.4)	110 (21.7)	115 (20.5)
Diabetic neuropathy	9 (17.0)	157 (30.9)	166 (29.6)
Diabetic nephropathy	6 (11.3)	98 (19.3)	104 (18.5)
Body weight (kg), mean (SD)	80.7 (14.48)	85.7 (17.12)	85.3 (16.94)
BMI (kg/m^2), mean (SD)	29.7 (4.75)	31.9 (6.30)	31.7 (6.20)
Previous non-insulin glucose-lowering medications, *n* patients (%)			
Biguanide	39 (73.6)	254 (50.0)	
Sulfonylurea	26 (49.1)	72 (14.2)	
DPP4 inhibitor	31 (58.5)	143 (28.1)	
SGLT2 inhibitor	24 (45.3)	133 (26.2)	
Other[a]	7 (13.2)	67 (13.2)	
Previous insulin used, *n* patients (%)			
Basal insulin		422 (83.1)	
Lantus®		241 (47.4)	
Toujeo®		110 (21.7)	
Levemir®		32 (6.3)	
Unknown basal insulin		27 (5.3)	
Vivaro®		9 (1.8)	
Other		3 (0.6)	
Premix insulin		74 (14.6)	
NovoMix® 30		48 (9.4)	
Mixtard® 30		10 (2.0)	

Table 1 continued

	Insulin naïve (N = 53)	Insulin experienced (N = 508)	All (N = 561)
Humalog® Mix25		8 (1.6)	
Other[b]		8 (1.6)	
Prandial insulin		181 (35.6)	
Novorapid®		155 (30.5)	
Apidra®		17 (3.3)	
Humalog®		7 (1.4)	
Other		2 (0.4)	

Full analysis set—in-study observation period

BMI body mass index, *FAS* full analysis set, *FPG* fasting plasma glucose, *SD* standard deviation, *T2D* type 2 diabetes, *DPP4* dipeptidyl peptidase 4, *SGLT2* sodium/glucose cotransporter 2, *GLP-1* glucagon-like peptide 1

[a]Thiazolidinedione, GLP-1 receptor agonist or meglitinide

[b]Humalog® Mix 50/50, Humalin® 70/30 or NovoMix® 50

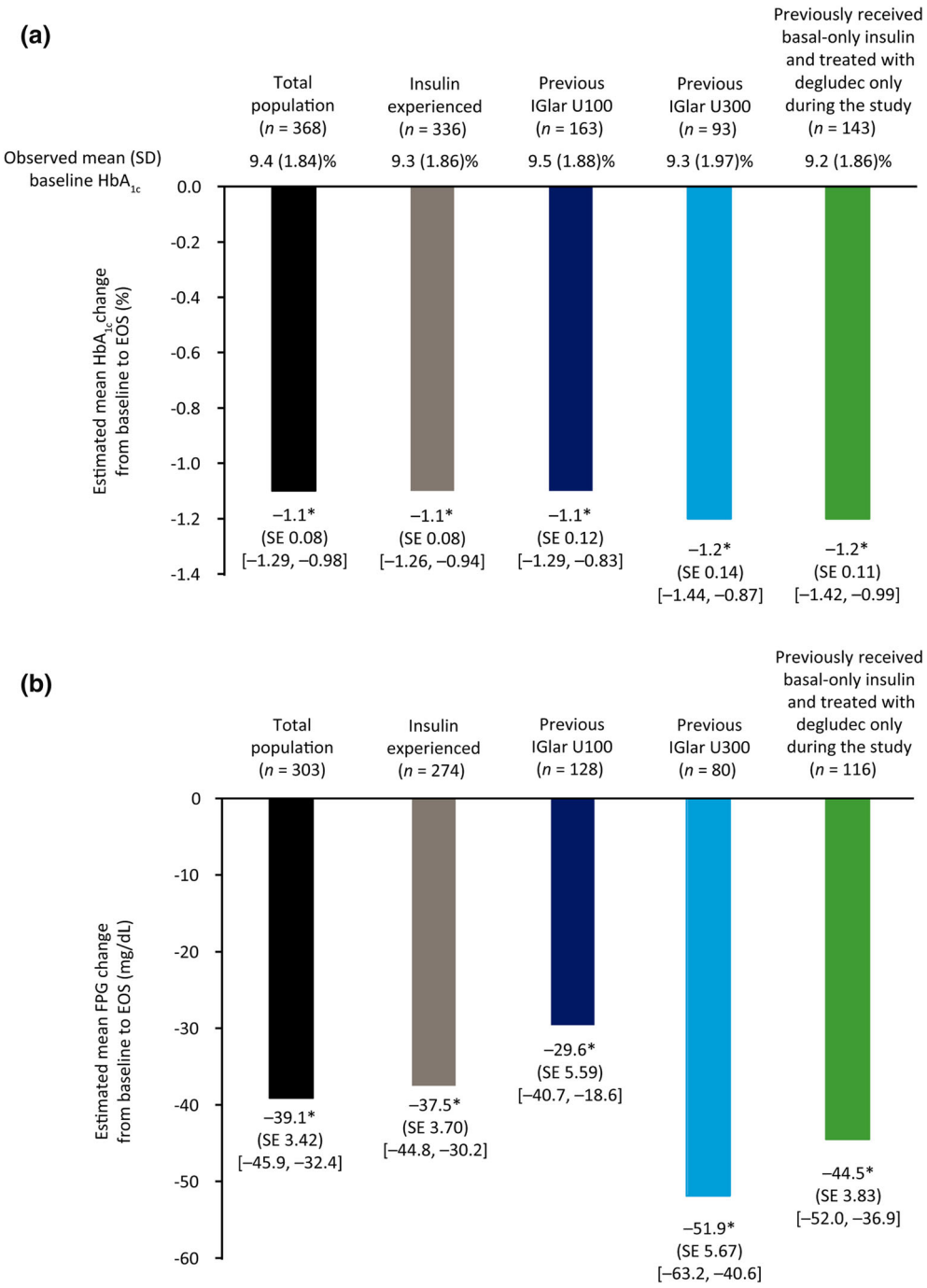
Insulin Dose

Degludec was initiated at a mean dose of 17.6 units (0.2/kg) in insulin-naïve patients, and 32.8 units (0.4/kg) in insulin-experienced patients. According to the crude MMRM, the estimated mean (SE) total insulin dose increased from baseline to EOS by 24.2 (2.93) units (95% CI 18.32, 30.14; $P < 0.0001$) in insulin-naïve patients (n = 41), and by 4.7 (1.58) units (95% CI 1.63, 7.86; $P = 0.003$) in insulin-experienced patients (n = 424). For insulin-experienced patients, the change in estimated mean (SE) basal insulin dose was − 0.3 (0.59) (− 1.49, 0.82; $P = 0.57$) with the crude MMRM. For insulin-experienced patients, the change in estimated mean (SE) prandial insulin dose was 3.7 (1.88) units (− 0.01, 7.42; $P = 0.051$) with the crude MMRM. Similar results were obtained using the adjusted model (Supplemental Fig. 3).

Hypoglycaemia

The primary analysis of hypoglycaemia data (based on the FAS, including rate ratios calculated using negative binomial regression) are summarised in Fig. 2. In the insulin-experienced population, the rate of patient-reported overall severe, overall non-severe and nocturnal non-severe hypoglycaemic events decreased significantly from baseline (0.2, 21.3 and 7.1 episodes/participant-years of exposure [PYE], respectively) to EOS (0.03, 4.1 and 0.7 episodes/PYE). The corresponding rate ratios (RRs) were 0.14 (95% CI 0.04, 0.54; $P = 0.0042$) for overall severe hypoglycaemia, 0.19 (95% CI 0.13, 0.28; $P < 0.0001$) for overall non-severe hypoglycaemia and 0.10 (95% CI 0.05, 0.18; $P < 0.0001$) for nocturnal non-severe hypoglycaemia. The results from the adjusted analysis were

Fig. 1 Change in **a** HbA_{1c} and **b** FPG from baseline to EOS. *$P < 0.0001$. Data presented are estimated mean change (SE) [95% CI]. The primary analysis was performed on the basis of the 'FAS, on-treatment observation period' using MMRM with both crude and adjusted models. The crude model (presented here) included baseline HbA_{1c} and time of HbA_{1c} measurement as covariates. The adjusted model additionally included, as baseline covariates, age, sex, diabetes duration, BMI and baseline treatment regimen (insulin naïve and insulin experienced). Change in laboratory-measured FPG was performed using MMRM as per the primary endpoint. *BMI* body mass index, *CI* confidence interval, *EOS* end of study, *FAS* full analysis set, *FPG* fasting plasma glucose, *IGlar U100* insulin glargine U100, *IGlar U300* insulin glargine U300, *MMRM* mixed model for repeated measures, *SE* standard error


(a)
Total population (n = 368)
Insulin experienced (n = 336)
Previous IGlar U100 (n = 163)
Previous IGlar U300 (n = 93)
Previously received basal-only insulin and treated with degludec only during the study (n = 143)
Observed mean (SD) baseline HbA1c
9.4 (1.84)%
9.3 (1.86)%
9.5 (1.88)%
9.3 (1.97)%
9.2 (1.86)%
Estimated mean HbA1c change from baseline to EOS (%)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
−1.1* (SE 0.08) [−1.29, −0.98]
−1.1* (SE 0.08) [−1.26, −0.94]
−1.1* (SE 0.12) [−1.29, −0.83]
−1.2* (SE 0.14) [−1.44, −0.87]
−1.2* (SE 0.11) [−1.42, −0.99]
(b)
Total population (n = 303)
Insulin experienced (n = 274)
Previous IGlar U100 (n = 128)
Previous IGlar U300 (n = 80)
Previously received basal-only insulin and treated with degludec only during the study (n = 116)
Estimated mean FPG change from baseline to EOS (mg/dL)
0
-10
-20
-30
-40
-50
-60
−39.1* (SE 3.42) [−45.9, −32.4]
−37.5* (SE 3.70) [−44.8, −30.2]
−29.6* (SE 5.59) [−40.7, −18.6]
−51.9* (SE 5.67) [−63.2, −40.6]
−44.5* (SE 3.83) [−52.0, −36.9]

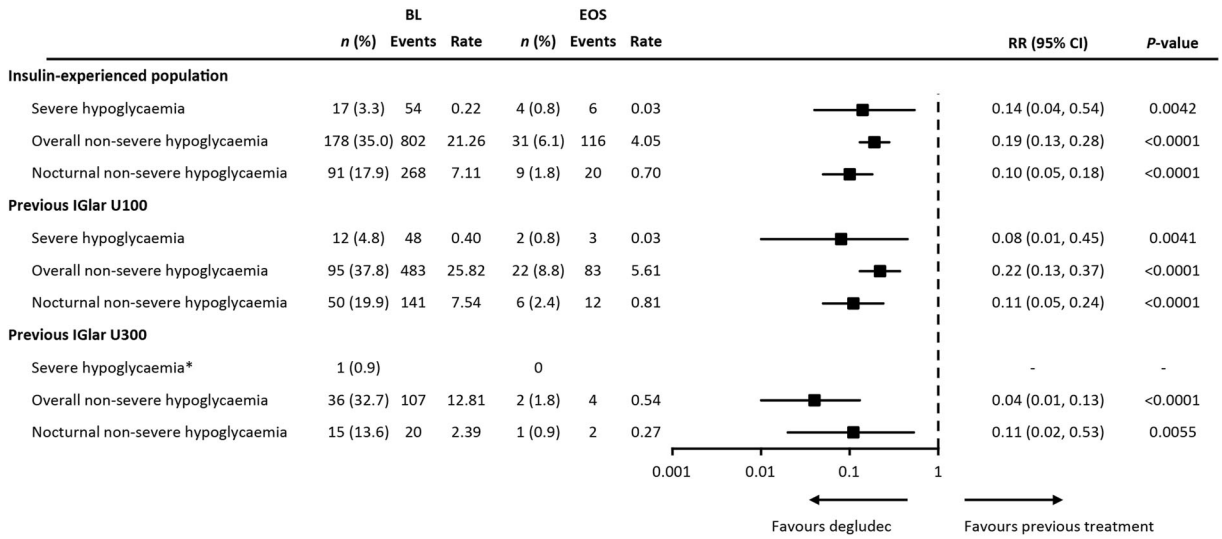


Fig. 2 Change in rate of patient-reported hypoglycaemia in the insulin-experienced population from baseline to EOS. Primary analysis of hypoglycaemic episodes, performed on the FAS. *No statistical analysis was performed, as one event occurred prior to degludec initiation and no patient experienced severe hypoglycaemia at EOS. A crude negative binomial regression model specifying a log-transformed follow-up time offset term was used to examine the incidence rate of hypoglycaemia. *BL* baseline, *CI* confidence interval, *EOS* end of study, *FAS* full analysis set, *IGlar U100* insulin glargine U100, *IGlar U300* insulin glargine U300, *RR* rate ratio

consistent with the results of the crude analysis. The event rates (and proportion of patients) for all categories were also significantly reduced after switching to degludec in patients previously treated with either IGlar U100 or IGlar U300 (Fig. 2). Results from a secondary analysis of hypoglycaemic episodes based on the COT subset were also consistent with the results of the primary analysis (Supplemental Fig. 4).

Body Weight

The observed mean (standard deviation [SD]) body weight was 85.3 (16.94) kg at baseline and 85.9 (15.38) kg at EOS.

Healthcare Resource Utilisation

HRU data before and after use of degludec are summarised in Table 2. The number of patients utilising resources associated with severe hypoglycaemia dropped from 19 patients within 26 weeks prior to degludec initiation to 4 patients within 26 weeks prior to EOS, all of whom were insulin experienced.

Adverse Events

No apparent or unexpected safety and tolerability issues were identified for degludec. A summary of AEs is provided in Table 3. A total of 19 patients (3.4%) experienced 25 AEs during the study. Of these, 7 were serious AEs and were reported in 6 patients and 18 were non-serious AEs and were reported in 13 patients. Of the 18 recorded non-serious AEs, 16 were hypoglycaemic events, with one case of urinary albuminuria and one of dizziness. It should be noted, however, that not all hypoglycaemic events were reported as adverse events. Of the seven serious AEs, three were cases of coronary artery disease, one was a case of large intestinal haemorrhage, one a case of diabetic foot infection, one a procedural complication and one a case of hypoglycaemia (moderate severity, this being the only serious event considered as probably caused by treatment and resolved by dose reduction).

Table 2 Health resource utilisation associated with severe hypoglycaemia

	Insulin naïve (*N* = 53)		Insulin experienced (*N* = 508)		Overall population (*N* = 561)	
	26 weeks prior to baseline	26 weeks prior to EOS	26 weeks prior to baseline	26 weeks prior to EOS	26 weeks prior to baseline	26 weeks prior to EOS
Patients utilising resource	1	0	18	4	19	4
Patients who self-reported:						
Additional outpatient visit	1 (1.9)	0	5 (1.0)	0	6 (1.1)	0
Emergency room visit	0	0	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
In-patient hospitalisations	0	0	2 (0.4)	0	2 (0.4)	0
Work days missed	1 (1.9)	0	2 (0.4)	0	3 (0.5)	0
Patients who self-reported episodes requiring:						
Assistance by non-medical person	1 (1.9)	0	13 (2.6)	3 (0.6)	14 (2.5)	3 (0.5)
Assistance from an ambulance	0	0	3 (0.6)	0	3 (0.5)	0
Administration of carbohydrates by another person	1 (1.9)	0	15 (3.0)	2 (0.4)	16 (2.9)	2 (0.4)
Administration of other treatment by another person	0	0	5 (1.0)	2 (0.4)	5 (0.9)	2 (0.4)

Full analysis set—in-study observation period. Values are *n* (%)
EOS end of study

Exploratory Endpoint: Willingness to Continue Degludec

Degludec treatment was well regarded by patients with 95.5% (*n* = 426) overall expressing a willingness to continue treatment at EOS, reflecting a willingness of 92.7% in previously insulin-naïve patients (*n* = 41) and 95.8% in insulin-experienced patients (*n* = 385). The respective proportions of patients expressing a preference for degludec over their previous regimen (overall, insulin-naïve, insulin-experienced) were 93.0%, 90.2% and 93.2%.

Exploratory Endpoint: Outcomes in Patients Switching From Glargine U100 and U300

The estimated mean (SE) change in HbA_{1c} (crude MMRM) was − 1.1 (0.12) %-points (95% CI − 1.29, − 0.83; $P < 0.0001$) for patients previously using glargine U100 (*n* = 163), and − 1.2 (0.14) %-points (95% CI − 1.44, − 0.87; $P < 0.0001$) for patients previously using glargine U300 (*n* = 93) (Fig. 1). Similar results were obtained with the adjusted model. The estimated mean (SE) change in FPG (crude MMRM) was − 29.6 (5.59) mg/dL (95% CI − 40.7, − 18.6; $P < 0.0001$) for patients previously using glargine U100 (*n* = 128), and − 51.9 (5.67) mg/dL

Table 3 Summary of adverse events

	Serious		Non-serious		Total	
	n (%)	Events	*n* (%)	Events	*n* (%)	Events
Adverse events	6 (1.1)	7	13 (2.3)	18	19 (3.4)	25
Metabolism and nutrition disorders	1 (0.2)	1	11 (2.0)	16	12 (2.1)	17
Hypoglycaemia	1 (0.2)	1	11 (2.0)	16	12 (2.1)	17
Cardiac disorders	3 (0.5)	3			3 (0.5)	3
Coronary artery disease	1 (0.2)	1			1 (0.2)	1
Myocardial infarction	1 (0.2)	1			1 (0.2)	1
Myocardial ischaemia	1 (0.2)	1			1 (0.2)	1
Gastrointestinal disorders	1 (0.2)	1			1 (0.2)	1
Large intestinal haemorrhage	1 (0.2)	1			1 (0.2)	1
Infections and infestations	1 (0.2)	1			1 (0.2)	1
Diabetic foot infection	1 (0.2)	1			1 (0.2)	1
Injury, poisoning and procedural complication	1 (0.2)	1			1 (0.2)	1
Procedural complication	1 (0.2)	1			1 (0.2)	1
Investigations			1 (0.2)	1	1 (0.2)	1
Albuminuria			1 (0.2)	1	1 (0.2)	1
Nervous system disorders			1 (0.2)	1	1 (0.2)	1
Dizziness			1 (0.2)	1	1 (0.2)	1

Full analysis set—in-study observation period

(95% CI − 63.2, − 40.6; $P < 0.0001$) for patients previously using glargine U300 ($n = 80$) (Fig. 1). Similar results were obtained with the adjusted model. There was little change in daily basal insulin dose in patients switching from glargine (+ 0.4 units, 95% CI − 0.87, 1.71; $P = 0.522$ for glargine U100, and − 1.1 units, 95% CI − 3.05, 0.90; $P = 0.2833$ for glargine U300).

As per the overall analysis, the rate of hypoglycaemia declined significantly in patients switching from glargine. In patients switched from glargine U100, the respective rate ratios (negative binomial regression) for overall non-severe, nocturnal non-severe and severe hypoglycaemic events were 0.22 (95% CI 0.13, 0.37; $P < 0.0001$), 0.11 (95% CI 0.05, 0.24; $P < 0.0001$) and 0.08 (95% CI 0.01, 0.45; $P = 0.0041$) (Fig. 2). Similar results were obtained with the adjusted MMRM. In patients switched from glargine U300, the respective rate ratios (crude MMRM) for overall non-severe and nocturnal non-severe hypoglycaemia were 0.04 (0.01, 0.13; $P < 0.0001$) and 0.11 (0.02, 0.53; $P = 0.0055$) (Fig. 2), with similar results obtained from the adjusted model. The rate ratio for severe hypoglycaemia was not calculated for patients switching from glargine U300 as only one event was reported before switching, and no events were reported after switching.

Exploratory Endpoint: Outcomes in Patients Using Basal Insulin as Their Only Insulin Before and After Switching to Degludec as Their Only Insulin, and in Those Taking Prandial Insulin During the Study

The change in estimated mean (SE) HbA_{1c} in patients providing data ($n = 143$) who only received basal insulin prior to degludec and who were using degludec as their only insulin during the study (crude MMRM) was − 1.2 (0.11) %-points (95% CI − 1.42, − 0.99; $P < 0.0001$) (Fig. 1), with similar results obtained in the adjusted model. The change in estimated mean (SE) FPG in patients providing data ($n = 116$) who only received basal insulin (crude MMRM) was − 44.5 (3.83) mg/dL (95% CI − 52.0, − 36.9; $P < 0.0001$) (Fig. 1), with similar results obtained in the adjusted model. The difference in estimated change from baseline to EOS in HbA_{1c} between patients who did and did not use prandial insulin was 0.17%-points (95% CI − 0.16, 0.50; $P = 0.3243$).

DISCUSSION

This study showed that patients with T2D in a real-world setting in Saudi Arabia who switched from a previous regimen to one including degludec benefitted from significant reductions in HbA_{1c}, FPG and hypoglycaemia rate. These outcomes reflected the clinical objectives of the physicians since the largest drivers of the decision to use degludec were the desires to improve glycaemic control, and to overcome issues with hypoglycaemia in current treatments. The study also revealed excellent patient acceptance of degludec, with high percentages preferring it to previous regimens and expressing a wish to continue its use, with no unexpected patterns of adverse events.

The study findings are in general agreement with those from randomised clinical trials and other real-world studies with degludec. The mean decrease seen from baseline to EOS in HbA_{1c} after switching to degludec (− 1.1%-points; $P < 0.0001$) was not dissimilar to results from other recent real-world studies of insulin-experienced patients with T2D switching to degludec. For example, in a retrospective chart review by Ponzani et al., HbA_{1c} decreased by − 0.6%-points from baseline to EOS ($P < 0.0001$) [17] and, in a non-interventional retrospective cohort study by Melzer Cohen and colleagues, the corresponding decrease was − 0.6%-points ($P < 0.001$) [18]. Mean HbA_{1c} also decreased by a similar amount from baseline to EOS, in this setting, in the large, retrospective, non-interventional EU-TREAT study (− 0.5%-points; $P < 0.001$) [10]. Importantly, the UK Prospective Diabetes Study (UKPDS) showed that a reduction in HbA_{1c} of 1%-point is associated with a relative risk reduction of 21% for any diabetes-related endpoint, 21% for deaths related to diabetes, 14% for myocardial infarction and 37% for microvascular complications [1].

Most patients in this study were already using insulin at baseline ($n = 424$). In the insulin-experienced population, the estimated mean (SE) total insulin dose increased from baseline to EOS by 4.7 (1.6) units ($P = 0.003$; crude analysis). This increase may potentially have been a result of patients being able to titrate more effectively than on their previous regimen. The basal insulin dose, however, remained relatively unchanged (mean (SE) − 0.3 (0.6) units; $P = 0.57$), with a small overall increase in prandial insulin dose (mean (SE) 3.7 (1.9) units; $P = 0.05$). In the retrospective chart review by Ponzani et al., in patients with T2D switching to degludec the estimated mean change from baseline to EOS in basal insulin was + 2.3 units and in prandial insulin was − 1.4 units [17]. In the non-interventional retrospective cohort study by Melzer Cohen and colleagues, the corresponding increase in mean daily basal insulin was 2 units ($P = 0.003$) [18]. In the EU-TREAT study, daily basal insulin dose was unchanged from baseline to 6 months; however, daily prandial insulin dose and total daily insulin dose decreased by − 2.0 units ($P = 0.015$) and − 2.5 units ($P = 0.006$), respectively [10].

The striking reduction seen in hypoglycaemia rate was achieved despite the basal insulin dose remaining relatively unchanged, and there being a small overall increase in

prandial insulin dose. This risk reduction could reflect the pharmacokinetic/pharmacodynamic profile of degludec, characterised by low variability over 24 h and from dose to dose [9], and arising from the ultra-long glucose-lowering action and unique protraction mechanism of degludec [26]. In some cases, the flexibility of dose timing afforded by degludec may have allowed dosing at more appropriate times of the day. The greatly reduced hypoglycaemia rate ratios reported were consistent with the large reduction in HRU associated with severe hypoglycaemia after switching to degludec (Table 2).

The majority of patients who switched from another basal insulin to degludec did so from glargine U100 or U300, so it was unsurprising that the improvements in glycaemic control and hypoglycaemia risk seen in the main analyses were also seen in the exploratory analyses of glargine switchers.

Because the use of prandial insulin (including its initiation) was permitted during the study, it is possible that this would have confounded the influence of degludec on glycaemic control. We therefore conducted an exploratory analysis involving only those patients who had received only basal insulin prior to the study, and who then received degludec as their only insulin during the study. The reductions in HbA_{1c} and FPG in these patients were very similar to the overall results, suggesting that degludec could be a major driver of the clinical benefits observed in this study.

The study had both strengths and limitations. The limitations included the open-label, uncontrolled design of the study (with patients being empirically selected with an anticipation of improvement with degludec), limited control for use of concurrent treatments, a relatively high loss to follow-up, and reliance on patient recall for endpoints such as hypoglycaemia. On the other hand, the study enrolled a large cohort in a single nation and showed that degludec was associated with the achievement of intended outcomes when used for selected patients in a real-world setting. The analysis of the main endpoints using different statistical models supports the robustness of the findings. Loss to follow-up may have been exacerbated by COVID-19, which was declared as a global pandemic by the World Health Organization on 11 March 2020 [27], with travel and other restrictions applied in Saudi Arabia. This might also have impacted titration, and in some cases (n = 85) caused the patient's EOS visit to occur outside of the 26–34-week target window. However, a sensitivity analysis for the primary endpoint (in which these protocol deviations were considered either as 'part of normal practice' [and median exposure week of insulin degludec as EOS] or in which they were removed altogether [and week 26 considered as the target week]) showed that COVID-19 had negligible impact on the overall result.

CONCLUSIONS

Patients treated with degludec experienced clinically significant improvements in glycaemic control and a lower rate of hypoglycaemia compared with baseline, with no new safety concerns. These results support that previously published data with degludec are generalisable to a broad population of patients with T2D in routine clinical practice in Saudi Arabia.

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Disclosures. Mussa H AlMalki has no conflicts of interest to declare. Hossam Aldesokey has received speaker honoraria from Sanofi, AstraZeneca, Pfizer, and Novo Nordisk, and has received honoraria as an advisory board member from Sanofi, Pfizer, and Novo Nordisk. Dania AlKhafaji has received speaker honoraria from Novo Nordisk, Sanofi, AstraZeneca, Eli Lilly and MSD, and has received honoraria and travel support as an advisory board member from Novo Nordisk, Sanofi, AstraZeneca and MSD. Abdulrahma Al Shaikh has been a researcher with Sanofi and Novo Nordisk and has received honoraria from AstraZeneca, Novo Nordisk and Sanofi as an advisory board member. Lars Lang Lehrskov and Uffe Christian Braae are shareholders and employees of Novo Nordisk. Waleed Magawry has no conflicts of interest to declare. Moataz Yahia is an employee of Novo Nordisk. Ahmed Haroun has received honoraria and travel support as an advisory board member from Novo Nordisk, Eli Lilly, Sanofi, Novartis, Servier, MSD, and GSK, and has received speaker honoraria from Novo Nordisk, Eli Lilly, Sanofi, Novartis, Servier, GSK, Amgen, Boehringer Ingelheim, Pfizer, AstraZeneca, MSD, Pfizer, Tabuk, Spimaco, and al Hikma.

Compliance with Ethics Guidelines. The trial protocol and any applicable protocol amendments were submitted for review, according to local requirements, by an independent ethics committee (IEC)/institutional review board (IRB) (see Supplemental Material). Approval was received from the IEC/IRB at all participating sites (King Fahad Medical city [v2.0-2018-09-17 approved 5, 11, 25, 29 November and 12 December 2018, and 4 July, 20 August, 11 September, and 2 October 2019], Al Habib Research centre [v2.0-2018-09-17 approved 12 October 2018], Security Forces Hospital IRB [v1.0-2018-08-14 and v2.0-2018-09-17 approved 23 October 2018], Specialized Medical Centre IRB [v1.0-2018-08-14 approved 14 October 2018; v2.0-2018-09-17 approved 10 January 2019], Imam Abdulrahman Bin Faisal University IRB [v2.0-2018-09- 17 approved 25 April 2019], King Abdullah International Medical Research Center IRB [v2.0-2018-09-17 approved 04 March 2020], King Abdulziz Univesity Bioethical Committee [v2.0-2018-09-17 approved 15 May and 30 July 2019]. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients provided informed consent to participate in the study.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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