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# A comparative effectiveness study of degludec and insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes

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**Aims:** To compare the real-world effectiveness of insulin degludec (degludec) and glargine 300 units/mL (glargine U300) in insulin-naïve adult patients with type 2 diabetes in routine US clinical practice.

**Materials and methods:** CONFIRM is a non-interventional comparative effectiveness study following US patients across the continuum of care, through electronic medical records from multiple health systems and integrated delivery networks. Propensity-score matching controlled for confounding. The primary endpoint, change in HbA1c from baseline to 180 days of follow-up, was estimated using a repeated-measure of covariance analysis with subject as random effect. Change in the rate of hypoglycaemic episodes (defined using International Classification of Diseases codes 9/10) and change in proportion of patients with hypoglycaemia were estimated using negative binomial and logistic regression, respectively. Time-to-discontinuation of the initial basal insulin/initiation with another prescribed basal insulin was analysed using a Cox Proportional Hazard model.

**Results:** Data concerning 4056 patients were analysed. After matching, baseline characteristics were comparable (n = 2028 in each group). After 180 days of follow-up, degludec was associated with a larger reduction in HbA1c (estimated treatment difference, −0.27%; $P = 0.03$), greater reductions in change in rate (rate ratio, 0.70; $P < 0.05$) and greater reductions in change in the likelihood of hypoglycaemia (odds ratio, 0.64; $P < 0.01$]) compared with glargine U300. In addition, patients treated with degludec were 27% less likely to discontinue treatment at follow-up compared with those treated with glargine U300 (hazard ratio, 0.73; $P < 0.001$).

**Conclusions:** Significantly improved HbA1c, larger reductions in rates and likelihood of hypoglycaemia and lower risk of treatment discontinuation were demonstrated with degludec vs glargine U300.

KEYWORDS

database research, glycaemic control, hypoglycaemia, insulin analogues, observational study, type 2 diabetes

## 1 | INTRODUCTION

Current guidelines for treatment of patients with type 2 diabetes (T2D) recommend initiation of basal insulin as part of dual or triple therapy, often within 3 months of failing to achieve glycaemic control with metformin monotherapy.[1] While restoration of glycaemic control is the primary aim of treatment, insulin can expose patients to an elevated risk of hypoglycaemia,[2] creating a barrier to treatment adherence and recovery of glycaemic control.[3]

Long-acting basal insulin analogues were developed with the goal of achieving glycaemic targets while lowering the risk of hypoglycaemia compared with previous basal insulin products, and this goal has been reached in the case of these insulin analogues as compared with neutral protamine Hagedorn (NPH) insulin.[4–6] For example, in studies in which HbA1c outcomes were similar, basal insulin analogues have resulted in reductions of 20%-50% in the relative risk of hypoglycaemia.[7] From a cost perspective, use of insulin analogues with lower rates of hypoglycaemia should translate into real-world cost-savings, not simply because of reductions in the immediate short-term costs of hypoglycaemia for healthcare providers,[8,9] but also through a reduction in the longer term costs that arise if patients fail to persist with insulin therapy, resulting in more time spent in acute care.[10]

The two most recently developed basal insulins, insulin degludec (degludec) and insulin glargine 300 units/mL (glargine U300) are longer acting than first-generation basal insulin analogues (glargine 100 units/mL [glargine U100] and insulin detemir [IDet]), and these longer acting insulins have been proven to lower the risk of hypoglycaemia further still.[11–18] Despite results from both the DELIVER D+ study[19] and the BRIGHT randomized controlled trial (RCT)[20] comparing use of degludec with glargine U300, there is presently no evidence from real-world clinical practice with insulin-naïve patients that indicates a clinical advantage of degludec vs glargine U300, or vice versa. This situation, insulin-naïve patients for whom real-world data are missing, is a gap that should be bridged. Compared with RCTs, real-world studies allow investigation of the comparative effectiveness of these insulins that is not confounded by trial protocols that fail to mirror real-world practices (eg, titration algorithms). Furthermore, an insulin-naïve population permits comparison without the additional confounding of prior experience with these insulins (ie, incident user design).[21] Prior to publication of the DELIVER D+[19] and BRIGHT[20] studies, it was anticipated that use of degludec would result in lower rates of hypoglycaemia than use of glargine U300, as is the case in comparisons of degludec with insulin glargine U100. This assumption was based on the pharmacodynamic evidence that degludec has a lower day-to-day and within-day variability of glucose-lowering effect than glargine U300, which may enable tighter glycaemic control with a lower risk of hypoglycaemia.[22] However, in the DELIVER D+[19] and BRIGHT[20] studies, no differences were found in rate of hypoglycaemia between degludec and glargine U300. Considering the methodological limitations of these studies, as outlined above, the potential to exploit the higher potency of degludec as compared to glargine U300, resulting in lower fasting plasma glucose and elevation of hypoglycemia rates,[20] and considering the lack of a real-world study in insulin-naïve patients, further investigations are warranted. The aim of the CONFIRM (Clinical Outcome assessmeNt of the eFfectiveness of Insulin degludec in Real-life Medical practice) study was to investigate the comparative effectiveness, using real-world data, of degludec vs glargine U300 in insulin-naïve adults with T2D in routine clinical practice in the USA.

## 2 | MATERIALS AND METHODS

The CONFIRM study is a non-interventional comparative effectiveness study of treatment with degludec (either 100 [U100] or 200 units/mL [U200], as these are bioequivalent)[23] vs glargine U300, following US patients across the continuum of care, through electronic medical records (EMRs).

### 2.1 | Study population

The CONFIRM study utilised an incident user design by comparing the effects of the two basal insulins in insulin-naïve adults, at least 18 years of age, who had suboptimal control of their T2D with oral antihyperglycaemic drugs, with or without a glucagon-like peptide-1 receptor agonist. A total of 30 441 patients were identified for inclusion in the CONFIRM study from the Explorys (IBM Watson Health) US database of EMRs during the identification period, from March 2015 to January 2018. The Explorys database includes de-identified patient data, provided with prior informed consent, collected from millions of patients and multiple, distinct healthcare systems/providers. These data are updated daily, are standardised and normalised, and are made accessible using an application on the Explorys Inc. platform. The date of first prescription of degludec or glargine U300 in the EMR was used to determine the date of insulin initiation. All available data for the assessed variables were collected prior to this time, representing the covariate assessment period.

Patients eligible for inclusion in the treatment cohorts included those with at least 360 days of data prior to initiation of insulin to ensure at least one HbA1c measurement at baseline. Patients were identified as exposed to treatment according to an on-treatment principle; to be included, patients must have had at least one prescription of degludec or glargine U300 during the identification period, with no other basal insulin during the follow-up period (ie, 90-180 days for analyses regarding HbA1c and 180 days for analyses regarding hypoglycaemia). Degludec and glargine U300 were identified via national drug codes used by the US Food and Drug Administration (FDA).

Overall, 24 066 patients were excluded, most commonly because of previous treatment with any basal or prandial insulin (n = 11 090). Other exclusion criteria in this insulin-naïve cohort included: age under 18 years (n = 2203), absence of gender registration (n = 1), prescription of an alternative insulin on the date of first prescription of degludec or glargine U300 (n = 3556), absence of baseline HbA1c measurement during the 90 days prior to and 7 days after initiation of basal insulin (n = 7136) and pregnancy registration during the study (n = 80) (Figure S1 in File S1). Subsequently, 6375 patients were eligible for inclusion and propensity-score matching, resulting in 4056 matched patients (n = 2028 in each group) (Table 1 and Table S1 in File S1).

### 2.2 | Data collection

EMRs from over 50 million patients, sourced from multiple health systems and integrated delivery networks, were utilised (>360 hospitals and > 330 000 providers). These are data recorded during routine care of patients for healthcare delivery purposes in ambulatory, inpatient and post-acute care settings. Patient demographics, diagnoses, procedures, prescribed drugs, and clinical and laboratory measurements are available from the database. Patients in the CONFIRM

**TABLE 1** Baseline demographics and characteristics

| | Patients meeting inclusion criteria | | | Propensity-matched patient population | | |
|---|---|---|---|---|---|---|
| | Degludec (n = 3135) | Glargine U300 (n = 3240) | SMD | Degludec (n = 2028) | Glargine U300 (n = 2028) | SMD |
| Demographics | | | | | | |
| Age at initiation of basal insulin, mean ± SD (years) | 57.8 ± 13.5 | 58.7 ± 12.9 | 0.07 | 57.5 ± 13.8 | 57.6 ± 13.0 | 0.01 |
| Male, N (%) | 1650 (52.6) | 1629 (50.3) | 0.05 | 1057 (52.1) | 1050 (51.8) | 0.01 |
| Provider specialty, N (%) | | | | | | |
| Endocrinology | 671 (21.4) | 849 (26.2) | 0.11 | 507 (25.0) | 462 (22.8) | 0.05 |
| Other | 325 (10.4) | 358 (11.0) | 0.02 | 244 (12.0) | 236 (11.6) | 0.01 |
| PCP | 1927 (61.5) | 1602 (49.4) | 0.24 | 1157 (57.1) | 1195 (58.9) | 0.04 |
| Unknown | 212 (6.8) | 431 (13.3) | 0.22 | 120 (5.9) | 135 (6.7) | 0.03 |
| Comorbidities and/or diabetic complications, N (%) | | | | | | |
| Hypertension | 2679 (85.5) | 2796 (86.3) | 0.02 | 1694 (83.5) | 1706 (84.1) | 0.02 |
| Hyperlipidaemia | 2746 (87.6) | 2828 (87.3) | 0.01 | 1747 (86.1) | 1754 (86.5) | 0.01 |
| Nephropathy | 722 (22.2) | 785 (23.8) | 0.04 | 419 (20.7) | 421 (20.9) | 0.003 |
| Neuropathy | 1094 (33.6) | 1225 (37.1) | 0.07 | 624 (30.9) | 623 (30.9) | 0.001 |
| Obesity | 1898 (67.0) | 1895 (69.2) | 0.05 | 1129 (65.6) | 1166 (69.0) | 0.07 |
| Retinopathy | 396 (12.2) | 498 (15.1) | 0.09 | 230 (11.4) | 250 (12.4) | 0.03 |
| Hypoglycaemia within 180 days prior to switch | | | | | | |
| Patients with hypoglycaemic episodes, N (%) | 240 (7.7) | 202 (6.2) | 0.06 | 135 (6.7) | 114 (5.6) | 0.04 |
| Number of hypoglycaemic episodes, PYE (mean ± SD) | 0.30 ± 1.29 | 0.26 ± 1.31 | 0.03 | 0.26 ± 1.22 | 0.22 ± 1.16 | 0.03 |
| Non-insulin anti-hyperglycaemic medication, N (%) | | | | | | |
| Number of anti-hyperglycaemics used (mean ± SD) | 1.4 ± 1.3 | 1.3 ± 1.3 | 0.07 | 1.2 ± 1.3 | 1.2 ± 1.3 | 0.00 |
| Metformin | 1479 (47.2) | 1447 (44.7) | 0.05 | 909 (44.8) | 906 (44.7) | 0.00 |
| Sulphonylureas | 779 (24.8) | 864 (26.7) | 0.04 | 504 (24.9) | 477 (23.5) | 0.03 |
| DPP-4 inhibitor | 696 (22.2) | 603 (18.6) | 0.09 | 392 (19.3) | 385 (19.0) | 0.01 |
| SGLT-2 inhibitor | 521 (16.6) | 448 (13.8) | 0.08 | 289 (14.3) | 298 (14.7) | 0.01 |
| GLP-1 receptor agonists | 556 (17.7) | 493 (15.2) | 0.07 | 228 (11.2) | 228 (11.2) | 0.00 |
| Other | 232 (7.4) | 258 (8.0) | 0.02 | 146 (7.2) | 149 (7.3) | 0.01 |
| Clinical characteristics, mean ± SD | | | | | | |
| Diabetes duration (years) | 4.9 ± 3.9 | 5.0 ± 4.4 | 0.03 | 4.8 ± 4.0 | 4.8 ± 4.0 | 0.00 |
| CDCC score | 2.4 ± 2.2 | 2.4 ± 2.2 | 0.00 | 2.2 ± 2.2 | 2.2 ± 2.2 | 0.00 |
| HbA1c (%) | 9.6 ± 2.2 | 9.4 ± 2.1 | 0.09 | 9.6 ± 2.2 | 9.5 ± 2.1 | 0.08 |
| HbA1c (mmol/mol) | 81.6 ± 23.9 | 79.4 ± 23.3 | 0.09 | 81.8 ± 24.3 | 79.8 ± 23.4 | 0.08 |
| Clinical characteristics[a], mean ± SD | | | | | | |
| Weight (kg) | 99.8 ± 26.1 | 101.1 ± 26.4 | 0.05 | 99.1 ± 26.6 | 101.5 ± 26.1 | 0.09 |
| BMI (kg/m$^2$) | 34.2 ± 8.4 | 34.7 ± 8.4 | 0.06 | 34.0 ± 8.4 | 34.7 ± 8.4 | 0.09 |

Abbreviations: BMI, body mass index; CDCC, Charlson/Deyo comorbidity; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; N, number of patients; PCP, primary care physician; PYE, patient years of exposure; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2; SMD, standardized mean difference.

[a] Characteristics not used for propensity-score matching because of missing baseline data: dose (n = 1270/4056) and weight/BMI (n = 3451/4056). Characteristics included in propensity-score matching but omitted here include: patients' race, insurance type and comorbidities and/or diabetic complications. Selected interaction terms were applied to the propensity-score analysis, eg, calendar year and US geographical region, to account for market access and formulary changes. Data listed are given as N (proportion [%]) or mean ± standard deviation.

study were managed primarily by primary care physicians (PCPs) and endocrinologists.

## 2.3 | Endpoints

### 2.3.1 | Primary and secondary endpoints

The primary endpoint was change in baseline HbA1c from initiation of basal insulin (−90 days to +7 days) until 180 days of follow-up, that is, the last HbA1c measurement in the +90—180 days following initiation of basal insulin (Figure 1). HbA1c values were identified using the Logical Observation Identifiers Names and Codes system code 4548-4.[24] Secondary endpoints included change in rates of hypoglycaemic episodes and change in proportion of patients with at least one episode of hypoglycaemia, and treatment discontinuation of degludec and glargine U300. Treatment discontinuation was measured as time-to-discontinuation of the first prescribed basal insulin and was defined as

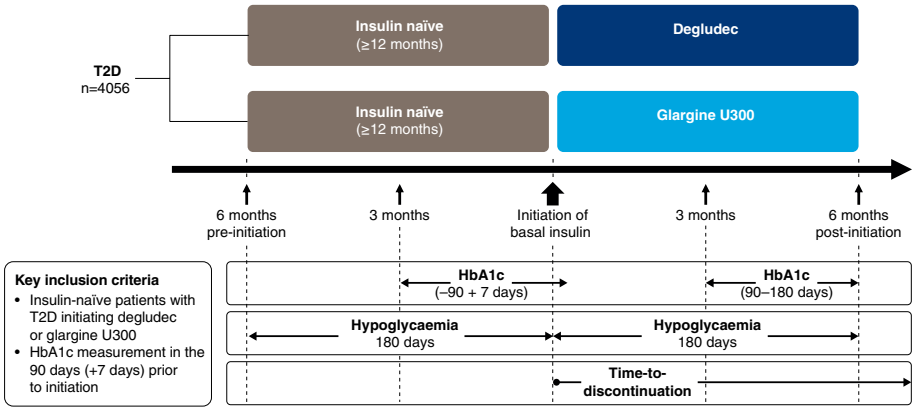


**FIGURE 1** Study design. Abbreviations: Glargine U300, insulin glargine 300 units/mL; T2D, type 2 diabetes

time from initiation of basal insulin until time of prescription of an alternative basal insulin (degludec, IDet, glargine U100, glargine U300 or NPH). Hypoglycaemia was defined according to International Classification of Diseases (ICD) clinical modification (CM) codes 9/10[4] (for additional detail, see Supporting Information, Methods and Figure S2 in File S1).

### 2.3.2 | Exploratory endpoints

Exploratory endpoints were change in body mass index (BMI) and mean end-of-study (EOS) basal insulin doses (units/day). Change in BMI was calculated from baseline to Day 180 of follow-up, using weight (kg) from the EMR. Mean EOS basal insulin doses were calculated from the last available prescription within 180 days of initiation.

## 2.4 | Statistical analyses

### 2.4.1 | Propensity-score matching

A non-parsimonious logistic-regression model[25] was used to derive propensity scores. Propensity scores were calculated using 42 patient and provider characteristics, based on availability of data from the Explorys database, as well as selected interaction terms, including calendar year and geographical region, to account for market access and formulary changes (Supporting Information, Methods in File S1). Each patient was assigned a propensity score that reflected the probability of initiating degludec. Using a greedy matching algorithm, each degludec initiator was matched 1:1, without replacement, to a glargine U300 initiator within a 0.1 calliper of propensity.[26] Unmatched patients, those with more than 0.1 calliper of propensity, were excluded (n = 2319). Balance between treatment groups was assessed using standardized mean differences (SMDs).[26]

Because of missing baseline data and/or concerns that bias would be introduced by including only patients with measurement of BMI/weight (Supporting Information, Methods in File S1), these characteristics (n = 3451/4056), as well as insulin dose (n = 1270/4056), were omitted from propensity-score matching. Inclusion of patients in the propensity-score analysis was based only on baseline characteristics, that is, regardless of whether patients dropped out at a later stage. Thus, patients without follow-up measurements were omitted from the analysis of primary and secondary endpoints, resulting in a smaller population than the propensity-matched cohort described in Table 1. The impact of this exclusion (missing data) was investigated in a sensitivity analysis. HbA1c, rate of hypoglycaemia, proportion of patients with hypoglycaemia and BMI were presented as the change from baseline to follow-up.

### 2.4.2 | Treatment comparisons

For each endpoint, the model included the covariates period (pre-, post-initiation) and basal insulin type (degludec, glargine U300) as factors, with subject included as a random effect. Baseline measurements for the endpoints described above were those taken prior to initiation of basal insulin. Treatment differences were estimated using adjusted least square means. If multiple measurements were available during the covariates period or at follow-up, the last available measurement was used.

The primary endpoint, change in HbA1c, was estimated using a repeated-measure analysis of covariance (ANCOVA). Standard errors were used to adjust for the potential dependence between repeated measures on individuals. Change in rate of hypoglycaemic episodes and change in proportion of patients with hypoglycaemia were estimated over 180 days, pre- or post-initiation of basal insulin, using negative binomial and logistic regression, respectively, and a generalized estimating equation approach. A Cox Proportional Hazard model was used to estimate the hazard ratio (HR) for time-to-discontinuation of the first prescribed basal insulin. Patients were censored on the last date for which data were available or on 22 January 2018. Change in BMI was estimated using the same methodology as that used for the primary endpoint. Dose ratio of mean prescribed EOS basal insulin doses was analysed using log-transformed dose and ANCOVA.

### 2.4.3 | Sensitivity analyses

Several sensitivity analyses were conducted to determine if results from the primary and secondary endpoints were dependent on specific characteristics of the treatment population. For the primary endpoint, these analyses included comparison of baseline HbA1c and HbA1c outcome in patients with and without HbA1c follow-up data at Day 180, and analyses of change in HbA1c by comparing patients stratified by degludec formulation (U100 or U200) with patients using glargine U300. Sensitivity analyses for secondary endpoints are described in Supporting Information, Methods in File S1.

## 3 | RESULTS

### 3.1 | Baseline characteristics: pre- vs post-propensity match

Baseline characteristics are shown in Table 1. Following propensity-score matching, treatment groups were broadly comparable at baseline, as indicated by the small (<0.1) SMDs (Table 1).[27] Notable differences included a higher proportion of patients treated by a PCP receiving degludec vs glargine U300, and a lower proportion treated by an unknown healthcare provider. In addition, despite a low SMD, there was a higher number of hypoglycaemic episodes and a higher proportion of patients with at least one episode of hypoglycaemia at baseline, when comparing those treated with degludec vs those treated with glargine U300. After propensity-score matching, SMDs for all examined characteristics were similar, including BMI/weight despite its exclusion from the model. On average, patients were 58 years old, with established diabetes for 5 years, and with suboptimal glycaemic control (HbA1c, 9.5%—9.6%). Patients were obese (mean BMI, 34—35 kg/m$^2$) and there was a high proportion of patients (>80%) with either hypertension or hyperlipidaemia. The main healthcare provider was a PCP (almost 60%) and most patients (41%) were undergoing oral antidiabetic drug (OAD) monotherapy with metformin or sulphonylureas, while the remaining patients were managed with dual (34%) or triple (or more) therapy (25%).

### 3.2 | Change in HbA1c

The mean exposure time from insulin initiation to HbA1c follow-up was similar when comparing degludec treatment (130.3 days) with glargine U300 treatment (127.8 days) ($P$ = 0.095). A minority of patients (n = 189/4056) treated with degludec (insulin aspart, n = 25; insulin lispro, n = 34) or with glargine U300 (insulin aspart, n = 50; insulin lispro, n = 80) received a prescription of prandial insulin during follow-up. Following initiation with degludec or glargine U300, HbA1c significantly reduced ($P$ < 0.01) over 180 days of treatment (Figure 2), resulting in a significantly greater lowering of HbA1c with degludec vs glargine U300 (estimated treatment difference [ETD], −0.27; $P$ = 0.03).

### 3.3 | Change in rate of hypoglycaemia and proportion of patients with hypoglycaemia

From initiation of basal insulin until Day 180 of follow-up, both the rate of hypoglycaemia and the proportion of patients experiencing at least one episode of hypoglycaemia increased significantly in these insulin-naïve patients (Table S2 in File S1). Degludec treatment resulted in a significantly lower change in rate vs glargine U300 treatment (rate ratio [RR], 0.70; $P$ < 0.05), increasing by a factor of 1.30 vs 1.85, respectively (Figure 3 and Table S2 in File S1). Similarly, degludec treatment resulted in a significantly lower change in the proportion of patients experiencing at least one episode of hypoglycaemia vs glargine U300 treatment (odds ratio, 0.64; $P$ < 0.01), increasing by a factor of 1.32 vs 2.06, respectively (Figure 3 and Table S2 in File S1).

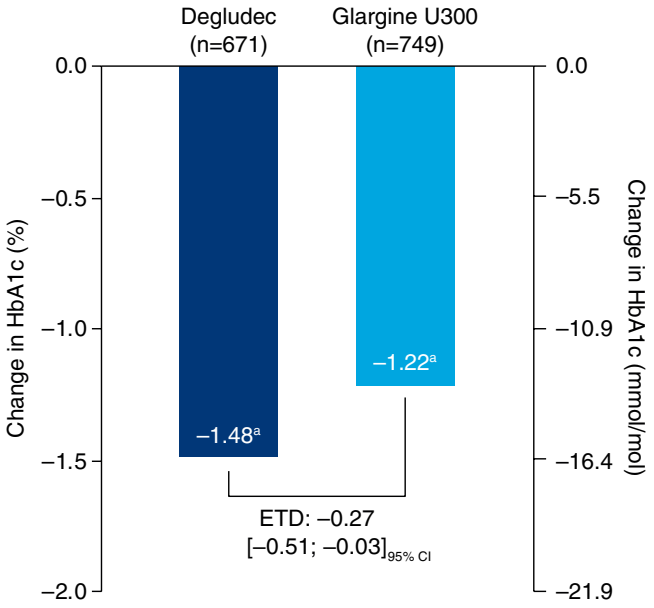


**FIGURE 2** Change in HbA1C over 180 days of treatment with degludec or glargine U300. Results are presented as means with associated ETD and $P$ value. ETD values may appear non-arithmetic as the result of rounding of data. Robust standard errors were used to adjust for potential dependence between repeated measures on individuals. [a]$P$ < 0.01 for change in HbA1c over 180 days of treatment. Abbrevations: ETD, estimated treatment difference; glargine U300, insulin glargine 300 units/mL

### 3.4 | Treatment discontinuation

Most patients continued treatment during the follow-up period (degludec, n = 1764/2028; glargine U300, n = 1602/2028) and were censored from the time-to-discontinuation analysis. A smaller proportion of patients discontinued treatment with degludec (n = 264/2028) vs treatment with glargine U300 (n = 426/2028), meaning that treatment with degludec was 27% less likely to result in treatment discontinuation than treatment with glargine U300 (HR, 0.73; $P$ < 0.001) (Figure 4). The subsequent basal insulin used was most commonly glargine U100 (patients discontinuing with: degludec, 44.7%; glargine U300, 52.1%) followed by IDet (patients discontinuing with: degludec, 36.0%; glargine U300, 21.6%), with the lowest proportion being patients who switched to NPH (patients discontinuing with: degludec, 1.9%; glargine U300, 3.8%). When comparing the proportion of patients who switched from degludec to glargine U300, and vice versa, a higher proportion of glargine U300 users switched to degludec (22.5%) vs the proportion of degludec users who switched to glargine U300 (17.4%) (Figure S3 in File S1).

### 3.5 | Exploratory endpoints

Change in BMI during the first 180 days of treatment (available for 25% of the cohort [1020/4056]) did not differ significantly between the two treatment groups (ETD, −0.08; $P$ = 0.81). EOS insulin doses were available for 31% of the cohort (n = 1270/4056), with a median duration from initiation of basal insulin until follow-up (last prescription within 180 days) of 77 days. EOS doses were 9% lower for

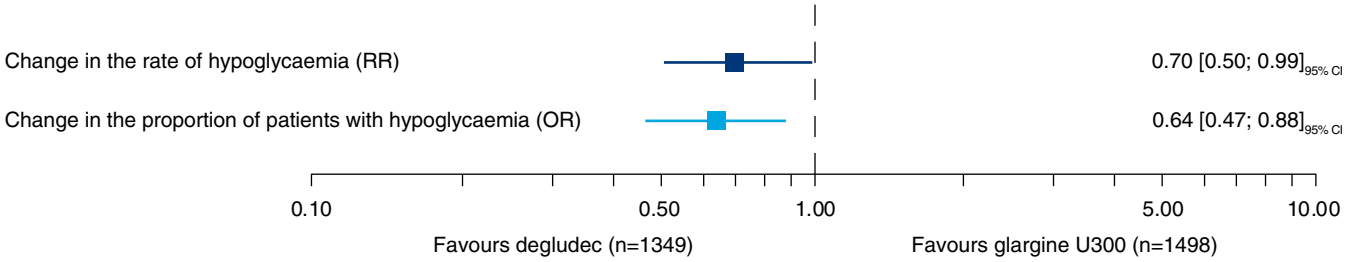


**FIGURE 3** Change in rate of hypoglycaemic episodes and change in proportion of patients with hypoglycaemia during treatment with degludec or glargine U300. Number of patients treated represents those for whom data were available at follow-up following propensity matching. Treatment group: degludec. Reference group: glargine U300. Abbreviations: CI, confidence interval; glargine U300, insulin glargine 300 units/mL; OR, odds ratio; RR, rate ratio

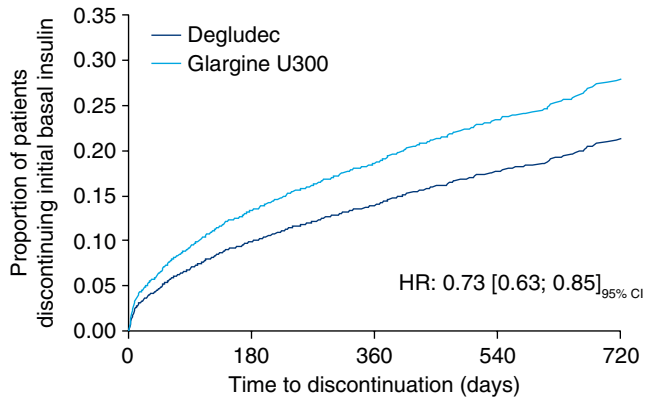


**FIGURE 4** Likelihood of discontinuation of basal insulin treatment in patients who initiated treatment with degludec or glargine U300. Treatment group: glargine U300. Reference group: degludec. Abbreviations: CI, confidence interval; glargine U300, insulin glargine 300 units/mL; HR, hazard ratio

degludec compared with those for glargine U300 (degludec, 40.8 U/day; glargine U300, 42.3 U/day; RR, 0.91; $P = 0.04$ [geometric mean: degludec, 29.6 U/day; glargine U300, 32.5 U/day]).

Sensitivity analyses, described in greater detail in Supporting Information, Results, did not change the results of primary and secondary endpoints (Table S3 in File S1).

## 4 | DISCUSSION

The present real-world study of insulin-naïve patients with T2D has demonstrated that patients initiating basal insulin treatment with degludec have significantly improved HbA1c; the magnitude of reduction as compared to that with glargine U300 [−0.27%] is close to the clinically significant reduction of 0.3%. They also have larger reductions in rates of hypoglycaemia and likelihood of hypoglycaemia, and a lower risk of treatment discontinuation compared with those initiating treatment with glargine U300. These data are consistent with previous observations from a pharmacokinetic/pharmacodynamic study of degludec and glargine U300 that identified the potential of degludec to result in a lower risk of hypoglycaemia and a relatively higher dose potency compared with glargine U300.[22]

Given the differences in the rates of hypoglycaemia between degludec and glargine U300 treatment, it might be anticipated that this may lead to changes in prescribing, as there was a shift previously towards the use of the longer-acting insulins (glargine U100 and IDet)[28] that had lower rates of hypoglycaemia compared with their predecessors.[11–18] Such a prediction is further supported by our finding that patients treated with degludec were less likely to discontinue treatment than were patients treated with glargine U300 and, furthermore, were less likely to switch to the other treatment if discontinuing, suggesting a greater likelihood of clinical success with degludec vs glargine U300.

The recently published results of the DELIVER D+[19] and BRIGHT[20] trials challenge this hypothesis, as both found that, with equivalent glycaemic control, rates of hypoglycaemia were similar with degludec and glargine U300. However, while the BRIGHT study found no significant differences in rates of hypoglycaemia between degludec and glargine U300 treatment during the full study period of the trial, lower rates with glargine U300 were noted during the titration phase. It is difficult, however, to compare these results from the BRIGHT study with those of the present study, as it was not possible to extract information specifically during the titration period of the basal insulins compared in the CONFIRM study. In addition, despite the use of a similar insulin-naïve population with T2D, the inclusion criteria of the BRIGHT study[20] make the results less generalizable to real-world clinical practice in which the protocols on insulin initiation, frequency of follow-up, treatment adherence and self-management differ from those in RCTs. By contrast with the BRIGHT study,[20] the DELIVER D+ study was a real-world study; however, the cohort was not insulin naïve as patients were switched from glargine U100 or IDet to glargine U300 or degludec and, therefore, the results may be subject to confounding.[19,21]

Despite these differences with the present study, data from both the DELIVER D+[19] and the BRIGHT[20] studies suggest certain advantages of degludec vs glargine U300. The DELIVER D+ study, as with the present study, found that rates of discontinuation were higher in patients treated with glargine U300 as compared to those treated with degludec.[19] The BRIGHT study found that equivalent glycaemic control was possible with degludec, at a 20% lower dose than that of glargine U300.[20] These results may suggest that there are potential economic benefits with the use of degludec vs glargine U300; however, this must be explored further in additional studies, with different healthcare systems and patient populations, to support the limited data currently available.[29]

In the present real-world study, degludec treatment resulted in greater reductions in the rate and likelihood of hypoglycaemia compared with glargine U300 treatment, findings that probably contributed to the ability of patients to reach lower HbA1c and to persist with the original insulin therapy with degludec vs glargine U300. Indeed, in real-world clinical practice, when hypoglycaemia occurs during the first 6 months of treatment, it has been demonstrated that the risk of discontinuation, as well as the risk of hospitalization and augmented healthcare costs, increases.[30] Although the financial impact of insulins is also considered to be a major driver of treatment discontinuation because of access to insurance schemes requiring reduced or no copayments,[31] in terms of differentiation among insulins, hypoglycaemia may be a more important driver. For example, despite the higher prescription costs of analogue insulins as compared to NPH,[32] analogue insulins are associated with a lower rate of discontinuation compared with that with NPH,[10,33] potentially explained by their lower rates of hypoglycaemia[6] and the associated healthcare resource utilization and costs.[34]

By contrast with the aforementioned DELIVER D+ study,[19,34] a strength of the present study from the CONFIRM trial was the use of an insulin-naïve population to ensure that comparison of degludec and glargine U300 is not clouded by inclusion of other insulin analogues, either before or after propensity-score matching, or by different populations of patients that may subsequently introduce bias.[21] In addition, the utilization of 1:1 propensity-score matching of treatment groups helped to minimize confounding by indication by producing well-balanced treatment groups after matching, illustrated by the standardized mean differences of baseline characteristics. Thus, the groups were similarly well matched when compared with randomized studies, including characteristics omitted from propensity matching. This was particularly important given the potential for differences in the use of anti-hyperglycaemic medications in the treatment groups and, consequently, potential differences in rates of hypoglycaemia. However, while propensity-score analyses offer the benefits of robust inferences, feasible balancing approaches and reduction in the potential for bias,[35] they can compensate only for measured confounders, and therefore cannot substitute for randomization, which also compensates for unmeasured confounders.[36]

Inclusion of several sensitivity analyses also added to the robustness of the study by demonstrating that the results and conclusions of this study were consistent and independent of the methodology. Furthermore, a sensitivity analysis in the present study supports the reported bioequivalence of degludec U100 and degludec U200[23] in real-world clinical practice by demonstrating that, following 6 months of treatment, HbA1c was comparable in patients treated with either formulation, with both degludec U100 and degludec U200 resulting in lower HbA1c compared with glargine U300.

A limitation of the study is the short period of follow-up. However, this duration corresponds to the period when the greatest changes in HbA1c occur, the first 90—180 days,[11] and it also corresponds to the commonly used follow-up periods of many clinical trials. Another limitation of this study is that it utilized EMR data, and this approach has its own inherent limitations, misclassification and/or measurement errors, for example, [37] as compared to the more careful and frequent collection of clinical trial data, although trial data may also limit the generalizability of the cohort of patients investigated to the wider population of patients receiving treatment with basal insulin for T2D. Because of the limited data collected from EMRs, inclusion of baseline characteristics and comorbidities typically communicated in RCTs (eg, more details concerning comorbidities and smoking status) or included in studies investigating adherence (eg, socioeconomic and educational status) have not been possible and, therefore, propensity matching criteria were identified according to the data available for matching. Lastly, although a validated coding algorithm was used to improve identification of hypoglycaemia,[38] as in other observational studies, hypoglycaemia may still have been under-reported in the present study. Interpretation of insulin dose data is also limited by the fact that dose information was available only for a subset of patients, and that reported basal insulin doses reflect doses prescribed by the PCP and may not correspond to what was actually taken by patients. In addition, the last available dose within 180 days in the EMR data was used as the basal insulin dose during follow-up, to be consistent with the primary endpoint of HbA1c. Therefore, despite relatively high HbA1c and BMI at baseline, only the last available dose during the follow-up period was evaluated and compared between degludec and glargine U300.

In conclusion, this comparative effectiveness study of insulin-naïve patients with T2D has demonstrated that treatment with degludec results in significantly larger reductions in HbA1c, with a 30% lower risk of hypoglycaemia and reduced likelihood of treatment discontinuation as compared to treatment with glargine U300.

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## CONFLICT OF INTEREST

J. T. serves as a consultant for Novo Nordisk A/S, Merck and AstraZeneca. M. H. B. has served on advisory panels for AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim and Eli Lilly and Company (the Alliance), Merck, Novo Nordisk A/S, Roche Pharmaceuticals and Sanofi. A. L. has received research support, honoraria for giving presentations and for attending advisory board meetings from AstraZeneca, Bayer, Becton Dickinson, Boehringer-Ingelheim, Bristol Myers Squibb, Lilly, Medtronic, MSD, Novo Nordisk, Roche and Sanofi. S. H., V. S. and M. L. W. are stockholders in and are employed by Novo Nordisk. H. W. R. has served on advisory panels for AstraZeneca Pharmaceuticals LP, Bayer Health Care LLC, Merck, Novo Nordisk A/S, and Sanofi; has served as a consultant for Lexicon, Merck and Sanofi; has received research support from AstraZeneca Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc., Janssen Pharmaceuticals, Lexicon, Eli Lilly and Company, Merck, Mylan, Novo Nordisk A/S, Regeneron and Sanofi; and has served as a speaker for AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc., Janssen, Eli Lilly and Company, Merck, Novo Nordisk A/S, and Sanofi.

## Author contributions

A. L. contributed to the analysis, writing and approval of the final manuscript. H. W. R. contributed to the study design, analysis, writing and approval of the final manuscript. M. H. B. contributed to the analysis, writing and approval of the final manuscript. J. T. contributed to the study design, analysis, writing and approval of the final manuscript. S. F. U. A., M. L. W. O. and V. T. S. A. contributed to the analysis, writing and approval of the final manuscript.

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## SUPPORTING INFORMATION

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

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