A multicentred, UK, retrospective observational study to assess the effectiveness of insulin glargine 300 units/mL in treating people with Type 1 diabetes mellitus in routine clinical practice (SPARTA)

Running title: Real-world evidence of switching to insulin glargine U300 in people with Type 1 DM

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Competing interests

- T. Pang has received speaker honoraria from Janssen, Eli Lilly, Napp Pharmaceuticals, and Sanofi; and advisory board and consultancy fees from Novo Nordisk.
- S.C. Bain has received speaker honoraria and advisory board fees from AstraZeneca, Boehringer Ingelheim/Lilly, Novo Nordisk, and Sanofi; and institutional investigator fees as chief and principal investigator for AstraZeneca, Novo Nordisk, and Sanofi.
- R.N.A Black has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Merck Sharp and Dohme, Novo Nordisk, and Sanofi; and educational support for conference attendance from Novo Nordisk and Sanofi.

- J.G. Boyle has received speaker honoraria from AstraZeneca and Napp Pharmaceuticals; advisory board fees from Novo Nordisk and Sanofi; and research investigator fees from Boehringer Ingelheim, Lexicon, and Sanofi.
- J. Elliott has received speaker fees from Lilly, Novo Nordisk, and Sanofi.
- A. Holcombe has received speaker fees from Sanofi.
- K.C.S. Lee is an employee of Sanofi.
- C. Mulligan has received speaker honoraria from Boehringer Ingelheim, Eli Lilly, and Sanofi; advisory board fees from Novo Nordisk; and educational support for conference attendance from Sanofi.
- L. Saunders is an employee of pH Associates which has received consultancy fees from Sanofi.
- A. Yousseif has received speaker honoraria from Sanofi, Novo Nordisk, and AstraZeneca; and advisory board fees from Novo Nordisk.
- M. Baxter is an employee of Sanofi.

Bulleted novelty statement

- This descriptive, retrospective study provides real-world data on the use of a second-generation basal insulin, insulin glargine 300 units/mL (U300) in Type 1 DM across the UK.
- Overall, participants who switched to U300 demonstrated improvements in HbA_{1c} without significant changes in basal insulin dose and weight from baseline.
- The number of participants with documented severe hypoglycaemia and diabetic ketoacidosis requiring A&E visits or hospitalization was low and similar prior to and after U300 initiation.
- Results from this real-world study demonstrate that observations made in randomized controlled trials translate to people with Type 1 DM treated with U300 in clinical practice in the UK.

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Abstract

Aim Insulin glargine 300 units/mL (U300) is a second-generation, once-daily basal insulin analogue. This open-label study provides UK real-world evidence from its use in Type 1 diabetes mellitus (DM).

Methods Participants with Type 1 DM prescribed U300 ≥6 months before data collection with glycated haemoglobin (HbA_{1c}) levels recorded within 3 months prior to U300 initiation (baseline) were included. The primary endpoint was change in HbA_{1c} from baseline to Month 6 after U300 initiation. Other endpoints included number of documented hypoglycaemic and diabetic ketoacidosis (DKA) episodes, and change in daily basal insulin dose.

Results A total of 298 people with Type 1 DM were included (mean age 42.1 years, mean HbA_{1c} 79 mmol/mol [9.4%]). After U300 initiation, mean reduction in HbA_{1c} from baseline to Month 6 was –4 mmol/mol (–0.4%; P<0.001; n=188). Total daily basal insulin dose at 6 months was 1.3 units higher compared with U300 initiation (P<0.001; n=275) but was not significantly different from prior basal insulin dose. There was no clinically significant difference in weight between baseline and Month 6 (mean difference +0.7 kg [95% CI –0.1, 1.5]; P=0.084; n=115). During the 6 months before and after U300 initiation, severe hypoglycaemic episodes were documented for 6/298 and 4/298 participants. DKA requiring A&E visits or hospitalizations were documented for 4/298 and 6/298 participants, before and after U300 initiation, respectively.

Conclusions In participants with Type 1 DM, a change in basal insulin to U300 was associated with clinically and statistically significant HbA_{1c} improvements, without significant changes in basal insulin dose and weight. Documented severe hypoglycaemia episodes and DKA requiring A&E visits or hospitalizations were low and similar before and after U300 initiation.

Keywords: Insulin glargine 300 units; Type 1 diabetes mellitus; real-world evidence; hypoglycaemia

Introduction

Insulin glargine 300 units/mL (U300; Toujeo®, Sanofi) is a second-generation, once-daily basal insulin analogue [1]. As a result of its distinct formulation, U300 has a discrete pharmacokinetic and pharmacodynamic profile when compared with insulin glargine 100 units/mL (U100; Lantus®, Sanofi) [2, 3]. The higher concentration of U300 generates precipitate with a smaller surface area following subcutaneous injection compared with U100 resulting in a steadier and extended glargine release and leading to a smoother pharmacokinetic profile and longer duration of action [1-3].

The use of U300 in people with Type 1 diabetes mellitus (DM) is supported by results from two phase III randomized controlled trials: EDITION 4 and EDITION JP 1 [4, 5]. However, no participants from the UK were included in these randomized controlled trials, and there is no real-world evidence on the use and utility of U300 in Type 1 DM in UK clinical practice.

This study was designed to provide evidence on the effectiveness of U300 in people with Type 1 DM across the UK over a 6-month observation period.

Methods

A retrospective, observational, single-arm study was conducted in eight NHS centres across the UK. Anonymized participant-level data, corresponding to a predefined core data set, were collected from electronic medical notes and paper charts and entered into a database (compliant with the Code of Federal Regulations 21 Part 11 [6] and approved for use in the NHS setting). This study was conducted in accordance with the principles laid out by the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013), and with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice, in accordance with local regulations, including local data protection regulations.

People with Type 1 DM who were prescribed their first dose of U300 ≥ 6 months before the date of data collection (01 August 2015) and had a glycated haemoglobin (HbA_{1c}) blood result within 3 months prior to starting U300 were included. Data were collected retrospectively from 11 October 2017 to 7 December 2017.

Participants with Type 2 DM or participants with Type 1 DM who were insulin naïve, using an insulin pump, pregnant or participating in a concurrent clinical trial were excluded from participation. For evaluation of HbA_{1c} at 3 months and all variables at 6 months, observation windows of 60–120 days (2–4 months) and 120–270 days (5–9 months) after U300 initiation, respectively, were permitted. Six-month treatment data prior to, and for 6

months following, initiation of U300 were analysed (Fig. 1). Participant eligibility was not determined by the availability of HbA_{1c} data at 6 months post-initiation of U300.

The primary endpoint was change in HbA_{1c} from baseline to Month 6 after U300 initiation. Secondary efficacy endpoints included change in HbA_{1c} from baseline to Month 3 after U300 initiation, change in basal, prandial and total (basal and prandial combined) daily insulin doses from previous insulin therapy (baseline) to Month 6 and from U300 initiation to Month 6, and change in weight from baseline to Month 6. Secondary safety endpoints including the number of hypoglycaemic episodes and diabetic ketoacidosis (DKA) episodes requiring A&E visits or hospitalizations during the 6 months prior to and following initiation of U300 were analysed, where documented. The following additional secondary endpoints were also extracted: reasons for switching or discontinuing previous diabetes therapy, and where appropriate, for discontinuing treatment with U300; the proportions of participants meeting the optimal titration dose of U300 (defined as the dose when the titration process was halted when adequate HbA_{1c} or fasting plasma glucose [FPG] levels were achieved) and meeting individualized HbA_{1c} targets during the observation period; diabetes education attendance; and change in insulin-to-carbohydrate ratio.

Reliability estimates for the primary outcome for sample sizes ranging from 100 to 400 participants suggested that, based on 99% confidence limits, the precision of estimates would not improve much above sample sizes of 200. For an observed HbA_{1c} reduction of 3 mmol/mol (0.3%) at this sample size, there would be 99% confidence that the true value would be greater than or equal to 2 mmol/mol (0.2%). As complete data records cannot be guaranteed in real-world settings, a sample size of 300 participants was considered sufficient to address the primary objective and to ensure inclusion of a wide variety of participants in terms of severity of disease, age, sex and geographical location.

In order to minimize biases associated with the study and to reflect, as accurately as possible, a cross-section of clinical experience throughout the UK, the following measures were taken: Sites were enrolled from different healthcare systems (i.e. from community and tertiary centres) and geographical locations. A minimum of ten participants was required per site to ensure good geographical representation, while an enrolment cap of 100 participants per site was chosen to minimize the potential for centre bias. In addition, in order to avoid selection bias, participants were recruited in reverse consecutive order from the last eligible participant seen during the most recent clinic visit. Data heterogeneity was evaluated using a one-way ANOVA comparing change in HbA_{1c} (the primary endpoint) between sites; no significant difference was found (P=0.137). Source data verification was performed to ensure quality, accuracy and consistency of the data collection.

Descriptive statistics (including the mean, standard deviation [SD], median and interquartile range) were calculated for quantitative variables with frequencies and percentages derived for qualitative variables (analysed using Stata v14 [StataCorp LLC]). Changes in participant measurements between time periods were evaluated using paired *t*-tests. Analyses involving a within-participant change from baseline used only those data available at both time points (paired values). In addition to analysing endpoints with the overall population, change in HbA_{1c} from baseline to 6 months (both univariate analysis and multivariate adjusting for sex, retinopathy and neuropathy) was also analysed for the 'completer-finisher' subgroup population, which included participants who remained on treatment for at least 6 months post-initiation of U300 and for whom paired HbA_{1c} data were available. Additional *post hoc* analyses included: a linear model comparing change in HbA_{1c} from baseline to 6 months versus baseline HbA_{1c}; change in HbA_{1c} from baseline to Month 6 for the subgroup of participants previously on once-daily basal insulin and for the subgroup of participants previously on twice-daily basal insulin (difference between subgroups calculated with and without an adjustment for baseline HbA_{1c}); and the proportion of participants taking U300 as per the Summary of Product Characteristics[1].

Results

Participant characteristics

Three hundred people were screened; two were excluded (one was <18 years at initiation of U300, and one did not have a HbA_{1c} measurement within 3 months of U300 initiation), leaving 298 participants with Type 1 DM eligible for inclusion in the final analysis (Fig. 1). Data are only listed for participants whose data were available in medical notes; therefore, not all the data points were present for all participants in the overall cohort (*n*=298). Participating NHS centres were located in England, Northern Ireland, Scotland and Wales (Table S1).

Participants' baseline characteristics are summarized in Table 1. The mean age of participants was 42.1 years, 51% were men and 72% were white. Participants had an average baseline HbA_{1c} of 79 mmol/mol (9.4%), weight of 81.2 kg and body mass index (BMI) of 28.3 kg/m^2. The mean time from diagnosis of diabetes to data collection was 21.6 years. At baseline, 86% of participants were on a basal-bolus insulin regimen, 7% were on a basal insulin only and 5% were on pre-mixed insulin (Table 1). The most common basal insulins were U100 (55%) and insulin detemir (35%); insulin aspart (64%) and insulin lispro (20%) were the most commonly used rapid-acting insulins (Table 1). A total of 35%

(105/298) of participants were on an insulin regimen that included a twice-daily basal insulin component.

The mean (SD) total daily insulin dose (basal and prandial insulin combined) at baseline was 68.4 (37.1) units/day; the combination of mean basal and prandial insulin dose was approximately 50:50 (basal insulin: 35.9 [21.6] units/day, prandial insulin: 35.0 [23.0] units/day; Table 1). Of the 188 participants with both baseline and 6-month insulin doses available, 59% (110/188) were on a once-daily dosing regimen and 39% (73/188) were on a twice-daily dosing regimen (3% [5/188] had no previous dosing regimen recorded).

Of diabetes-related comorbidities documented at baseline, retinopathy (33%) was the most common, followed by dyslipidaemia (23%), hypertension (18%) and depression (18%). Ninety-seven subjects (33%) provided no data on this measure (Table S2). Twenty-one (9%) participants with data recorded were documented as hypoglycaemic unaware at baseline (Table S3).

Efficacy

Change in HbA_{1c}

In the population for whom paired HbA_{1c} values were available (*n*=188), HbA_{1c} significantly decreased from baseline (78 mmol/mol [9.3%]) to Month 6 post-initiation of U300 (74 mmol/mol [8.9%]), with a mean difference of −4 mmol/mol (95% CI −6.0, −2.4; [−0.4%, 95% CI −0.5%, −0.2%]; *P*<0.001; primary endpoint; Fig. 2a). In the 'completer-finisher' subgroup population, which includes participants who remained on treatment for at least 6 months post-initiation of U300 and for whom paired HbA_{1c} data were available (*n*=175), a similar significant change in HbA_{1c} of −4 mmol/mol (95% CI −6.2, −2.4; [−0.4%, 95% CI −0.6%, −0.2%]; *P*<0.001) was observed (Fig. 2b).

A *post hoc* analysis of the change in HbA_{1c} from baseline to 6 months versus baseline HbA_{1c} indicated that for every 1 mmol/mol the baseline HbA_{1c} was higher, the mean reduction in HbA_{1c} at 6 months would increase by 0.27 mmol/mol (linear model; *P*<0.001; Fig. S1). This translates to an increased reduction of 0.27% for every increase in 1% in baseline HbA_{1c}. This general relationship holds even after adjusting the analysis for other covariates associated with change in HbA_{1c} (including sex, retinopathy and neuropathy).

For participants previously on once-daily basal insulin, according to a *post hoc* analysis, change in HbA_{1c} from baseline to Month 6 was –3 mmol/mol (95% CI –5.1, –1.1; [−0.3%, 95% CI –0.5%, –0.1%]; *P*<0.01; *n*=110; Fig. 2c). For participants previously on twice-daily basal insulin, change in HbA_{1c} from baseline to Month 6 was –6 mmol/mol (95% CI –9.8, –2.9; [−0.6%, 95% CI –0.9%, –0.3%]; *P*<0.001; *n*=73; Fig. 2d). HbA_{1c} reductions

were significantly larger for participants previously on twice-daily versus once-daily basal insulin treatment after adjusting for differences in baseline HbA_{1c} between the groups (unadjusted *P*=0.102; adjusted *P*=0.036).

At Month 3 post-initiation of U300, mean HbA_{1c} fell from 80 mmol/mol (9.5%) at baseline to 74 mmol/mol (8.9%) with a significant mean change of –6 mmol/mol (95% CI –9.8, –2.5; [–0.6%, 95% CI –0.9%, –0.2%]; *P*=0.001; *n*=95; Fig. 3).

Change in weight

There was no clinically significant difference in weight between baseline and Month 6 (mean difference +0.7 kg [95% CI –0.1, 1.5]; *P*=0.084; *n*=115; Fig. 4a). The distribution of participants' weight change and mean weight change from baseline to Month 6 after U300 initiation are presented in Table S4.

Change in basal, prandial and total daily insulin

There was a significant increase in basal insulin dose of 1.3 units (*P*<0.001; *n*=275) from U300 initiation to 6 months. This followed a significant reduction in basal insulin dose from previous basal insulin therapy (baseline) to U300 initiation of –2.4 units (*P*<0.001), in line with the Summary of Product Characteristics guidance when switching to U300. However, the change in basal insulin dose was not significant between previous basal insulin therapy and 6 months post-initiation of U300 (–1.1 units; *P*=0.155; *n*=237; Fig. 4b–4d).

A low number of dose changes of U300 were documented for participants after initiation; a mean (SD) of 0.8 (1.1) dose adjustments (median, 0.0 [range: 0–8]) was recorded.

There was no significant difference in total daily prandial insulin dose or total daily insulin dose (basal and prandial combined) between previous insulin therapy (baseline) and Month 6 or U300 initiation and Month 6 (Figure S2).

Most participants received U300 as part of a basal-bolus regimen 6 months post-initiation of U300 (89% [265/298]); the remainder received U300 alone, with no prandial insulin component (5% [15/298]) or discontinued therapy (6% [18/298]). A *post hoc* analysis confirmed that all participants taking U300 were using it once daily, as per the Summary of Product Characteristics [1].

Safety

Documented severe hypoglycaemic episodes were experienced by 6/298 (2%) participants and 4/298 (1%) participants during the 6 months prior to and post-initiation of U300,

respectively (Table 2). Severe episodes requiring A&E visits or hospitalization and mild-to-moderate hypoglycaemic episodes are shown in Table S5.

DKA episodes requiring A&E visit or hospitalization were documented in 4/298 (1%) participants in the 6 months prior to initiation of U300 and 6/298 (2%) in the 6 months following initiation (Table 2). No participants with documented DKA episodes discontinued U300 during the 6 months post-initiation.

Additional endpoints

Reasons for switching from previous diabetes therapy prior to starting U300 and for discontinuing treatment with U300 are shown in Figure 5. The most common reasons for discontinuing previous basal insulin were lack of efficacy (157/271 [58%]) and hypoglycaemia concerns (57/271 [21%]). Twenty four participants had 'not known' as reason for discontinuation recorded. A total of 18 (6%) participants discontinued U300 by Month 6, the most common reason being difficulty with dosing (6/18 [33%]).

The majority of participants (162/185 [88%]) did not meet recorded individualized HbA_{1c} targets (Table S6). Limited data were obtained on whether participants reached the optimal titration of U300, and therefore meaningful conclusions could not be made (Table S7). Participation in structured diabetes education was recorded for 17/298 (6%) participants in the 6 months pre-initiation of U300 and 19/298 (6%) participants post-initiation of U300 (Table S8). It is important to note that these proportions do not reflect the possibility that participants may have had structured education at an earlier point in their lives. Limited insulin-to-carbohydrate ratio data were available at baseline and at 6 months post-initiation of U300, and therefore definite conclusions could not be made about the level of insulin optimization achieved (Table S9).

Discussion

This descriptive, retrospective study documents the real-world experience of using U300 in people with Type 1 DM undergoing routine care across the UK. Overall, participants who switched to U300 demonstrated improvements in HbA_{1c}, without significant changes in insulin dose or weight from baseline. Documented severe hypoglycaemia episodes and DKA events requiring A&E visits or hospitalization prior to and post-initiation of U300 were low or similar. These real-world outcomes, reflecting the real-life experience in UK practice, are broadly similar to those observed for U300 in EDITION 4, a randomized, controlled, treat-to-target trial with comparable baseline characteristics of participants, with the exception of baseline HbA_{1c}, which was higher in our study [4]. The higher baseline HbA_{1c} observed in

this study was, however, similar to that reported by a National Diabetes Audit of UK practices [7], suggesting that this level of glycaemia is representative of the UK Type 1 DM population.

Following the switch to U300, improvements in glycaemic control occurred relatively quickly and were seen across the 6-month treatment observation period (3 months: 6 mmol/mol [0.6%] [*n*=95]; 6 months: 4 mmol/mol [0.4%] [*n*=188]). A *post hoc* analysis revealed a statistically significant greater reduction in HbA_{1c} at 6 months for those participants who had been on twice-daily versus once-daily basal insulin prior to U300 initiation when adjusted for baseline HbA_{1c} (–6 mmol/mol [*n*=73] vs –3 mmol/mol [*n*=110]). These data suggest that poorly controlled patients moving from a twice-daily regimen to once-daily U300 not only benefited from a improvement in HbA_{1c} but also a reduction in the number of daily injections.

There was a statistically significant increase (albeit small) in the mean daily dose of U300 from initiation to Month 6 of 1.3 units, which corresponded to an average of 0.8 dose adjustments per participant. Changes in total insulin (basal and prandial combined), basal insulin and prandial insulin dose from previous therapy dose (baseline) to 6 months were not significant, nor was the change in total insulin and prandial insulin dose from U300 initiation to Month 6. These observations were consistent with a pilot study (*n*=18) investigating the benefits of participants with Type 1 DM switching to U300 [8].

There was no clinically significant change in weight at Month 6 after U300 initiation compared to baseline (prior insulin therapy), Although these results must be interpreted with caution because the evaluable sample size was small (*n*=115), similar findings were reported in the U300 pilot study (*n*=18) [8].

In a *post hoc* analysis, it was observed that participants with a higher starting baseline HbA_{1c} achieved a greater reduction in HbA_{1c}, which is in line with observations reported for a number of therapeutic interventions in randomized controlled trials [9]. The linear relationship between baseline HbA_{1c} and HbA_{1c} reduction suggests that U300 provides a direct therapeutic benefit and that the reduction seen in the study after switching to U300 cannot be explained by a simple ‘placebo effect’ of changing therapy. The improved glycaemic control observed with U300 may be due to the beneficial pharmacokinetic-pharmacodynamic properties and improved 24-hour basal insulin coverage of U300 compared to U100 as demonstrated in a continuous glucose monitoring study [10].

The main reasons for switching from previous insulin for those participants with data recorded (*n*=247) were lack of efficacy (64%) and hypoglycaemia concerns (23%). This suggests that in clinical practice, improvement in glycaemic control remains an important

objective of treatment. After 6 months, 94% of participants remained on U300, indicating good tolerability of U300 when used in routine clinical practice. These observations are in agreement with the higher persistence observed with U300 in both Type 1 and Type 2 DM compared to other basal insulins in real-world study of basal insulin usage [11].

Despite the improvement in HbA_{1c} observed, few participants were described as achieving optimal titration or meeting individualized HbA_{1c} targets. In contrast to the primary reason for changing basal insulin being to improve glycaemic control, the corresponding low average number of dose adjustments observed suggests that effective titration of insulin in clinical practice, even in experienced centres, is not achieved or sustained. In our study, HbA_{1c} measurements were not systematically collected at the 6-month time point as was predicted to occur in routine practice given the National Institute for Health and Care Excellence guideline which recommends HbA_{1c} testing every 3–6 months [12].

It is possible that more motivated patients returned for 3-month and 6-month HbA_{1c} checks, which could have biased the results. However, the inconsistent collection and recording of HbA_{1c} measurements has also been seen in other UK data sets such as the National Diabetes Audit, where up to 17% of participants had HbA_{1c} measurements missing over the last 15 months [13]. In addition to the potential issues of clinical inertia [14], individual factors such as adherence and motivation may affect outcomes. Of note, this study reported low recorded participation in structured diabetes education prior to and post-initiation of U300, which may also have affected treatment response. Greater HbA_{1c} reduction may have been achievable if there had been more intensive dose optimization with U300.

It is well known that hypoglycaemia is under-reported and poorly recorded. Even severe hypoglycaemia may not be captured in clinical notes or routine clinical review; episodes requiring A&E visits or hospitalization have been demonstrated to go unreported to the direct care team in other real-world studies [15]. Data concerning hypoglycaemic events should be interpreted with caution in that 91% of participants prior to U300 initiation and 88% post-initiation of U300 had no documented mention of hypoglycaemia. Despite the low recorded hypoglycaemic frequency, hypoglycaemic concerns were cited in 21% of cases as the reason for basal insulin switch without documentation of events, adjustments of bolus insulin dose or referral to education. Compared to, and in parallel with the findings presented here, a recent prospective single-centre real-world study of participants with Type 1 DM in Belgium (n=116), which had a comparable population in terms of baseline BMI and weight but lower HbA_{1c} (65 mmol/mol [8.0%] vs 80 mmol/mol [9.5%]), demonstrated a significant reduction in nocturnal hypoglycaemia after switching to U300 [16].

Observational retrospective studies can be limited by real-world related biases with numerous (potentially unmeasureable) confounders. We have, however, sought to ameliorate these limitations through our study design. Following recruitment of 300 participants and a final eligible population of 298, there was a smaller than expected evaluable sample size for the primary endpoint (*n*=188). However, a statistically significant change in HbA_{1c} was observed, as the effect size was larger than anticipated. The smaller sample size marginally reduced the precision to answer descriptive endpoints. However, we performed an analysis to assess the homogeneity of the primary outcome and found that differences between sites were not significant; this suggests that the findings were robust across different centres. Additionally, source data verification was employed to enable correction of abstraction errors. Selected UK centres were known to be regular prescribers of U300 for participants with Type 1 DM; those that are not regular prescribers may have patients with different characteristics. Thus, generalizability was increased by ensuring adequate representation of UK sites and clinical settings, and a sample of 298 provides a good representative population and is a large sample size for this type of study [17]. In addition, we recognize that composite endpoints (e.g. those achieving a greater HbA_{1c} reduction and weight loss) could not be evaluated as data points on both measurements were not always available for each participant. However, the conclusions for each individual endpoints are valid.

In conclusion, statistically significant and clinically meaningful reductions in HbA_{1c} at Month 6 (4 mmol/mol [0.4%] reduction) were observed following U300 initiation in a population of participants with Type 1 DM representative of clinical practice in the UK. The relationship between baseline HbA_{1c} and the observed improvements in HbA_{1c} may indicate that the improvement in glycaemic control is a direct effect of U300 treatment and might be due to the beneficial pharmacokinetic-pharmacodynamic properties and improved 24-hour basal insulin coverage of U300. This UK-based real-world study also suggests that there is an opportunity to more effectively manage people with Type 1 DM through more intensive follow-up, focussing on increased frequency of HbA_{1c} measurements and insulin titration. Additionally, the observed missingness of data may be helpful in planning study size and power calculations in future real-world studies. Results of this real-world study demonstrate that observations made in randomized controlled trials on U300 in Type 1 DM translate to the population seen in everyday clinical practice within the UK.

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Table 1 Participant demographics and clinical characteristics at baseline*

Characteristics	Number of participants†	Population (*n*=298)
Age, mean (SD) years	298	42.1 (14.0)
Men, *n* (%)	298	152 (51)
Women, *n* (%)	298	146 (49)
Ethnicity, *n* (%)	298	
White		216 (72)
Other ethnic groups		16 (5)
Not recorded		66 (22)
Weight, mean (SD) kg	225	81.2 (20.9)
BMI, mean (SD) kg/m^2	161	28.3 (6.7)
Height, mean (SD) cm	203	169.7 (10.2)
Duration of diabetes at U300 initiation, years	272	
Mean (SD)		20.3 (12.9)
Median (IQR)		17.9 (10.4–29.7)
Duration of diabetes at data collection, years	272	
Mean (SD)		21.6 (13.0)
Median (IQR)		19.3 (11.4–31.0)
HbA_{1c}	298	
Mean (SD) mmol/mol		79 (20.2)
Mean (SD) %		9.4 (1.8)
Hypoglycaemia and DKA		
Participants experiencing severe hypoglycaemia in last 6 months, *n* (%)	298	6 (2)
Participants experiencing DKA in last 6 months, *n* (%)	298	4 (1)
Insulin regimen, *n* (%)	298	
Basal-bolus		257 (86)
Pre-mix		16 (5)
Basal insulin only		20 (7)
Bolus (prandial) only		5 (2)
Intermediate/long-acting insulin regimen, *n* (%)	277	
Basal-bolus with OD basal insulin		170 (61)
Basal-bolus with BD basal insulin		84 (30)
OD (basal insulin only)		9 (3)

BD (basal insulin only)		11 (4)
Not recorded		3 (1)
Rapid/short-acting insulin regimen, *n* (%)	262	
Basal-bolus/MDI		257 (98)
Bolus only		5 (2)
Pre-mix insulin regimen, *n* (%)	16	
OD		4 (25)
BD		10 (63)
Not recorded		2 (13)
Insulin regimen, *n* (%)	298	
Insulin analogues		
Insulin aspart		192 (64)
U100		164 (55)
Insulin detemir		103 (35)
Insulin degludec		6 (2)
Insulin lispro		59 (20)
Insulin glulisine		16 (5)
Novomix 30 (insulin aspart protamine-insulin aspart)		6 (2)
Humalog Mix 25/75 (insulin lispro protamine-insulin lispro)		3 (1)
Humalog Mix 50/50 (insulin lispro protamine-insulin lispro)		2 (1)
Human insulin		
Regular insulin		1 (<1)
Humulin 30/70 (human insulin NPH-human insulin regular)		3 (1)
Mixtard 30 (human insulin NPH-human insulin regular)		1 (<1)
Humulin M3 (human insulin-isophane insulin)		2 (1)
Insulatard (isophane insulin)		4 (1)
Isophane insulin		7 (2)
Insuman Comb (neutral insulin-isophane insulin)		1 (<1)
Daily insulin dose, mean (SD) units/day		
Basal insulin	237	35.9 (21.6)
Prandial insulin	136	35.0 (23.0)
Total daily insulin (basal insulin plus prandial)	133	68.4 (37.1)

BD, twice-daily; BMI, body mass index; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; IQR, interquartile range; MDI, multiple dose injection; NPH, Neutral Protamine

Hagedorn; OD, once-daily; SD, standard deviation; U100, insulin glargine 100 units/mL; U300, insulin glargine 300 units/mL.

*Baseline variables were defined as the most recent observation within the 6-month period prior to U300 initiation, with the exception of baseline HbA_{1c}, BMI, height and weight, which were defined as the most recent observation within the 3-month period prior to U300 initiation.

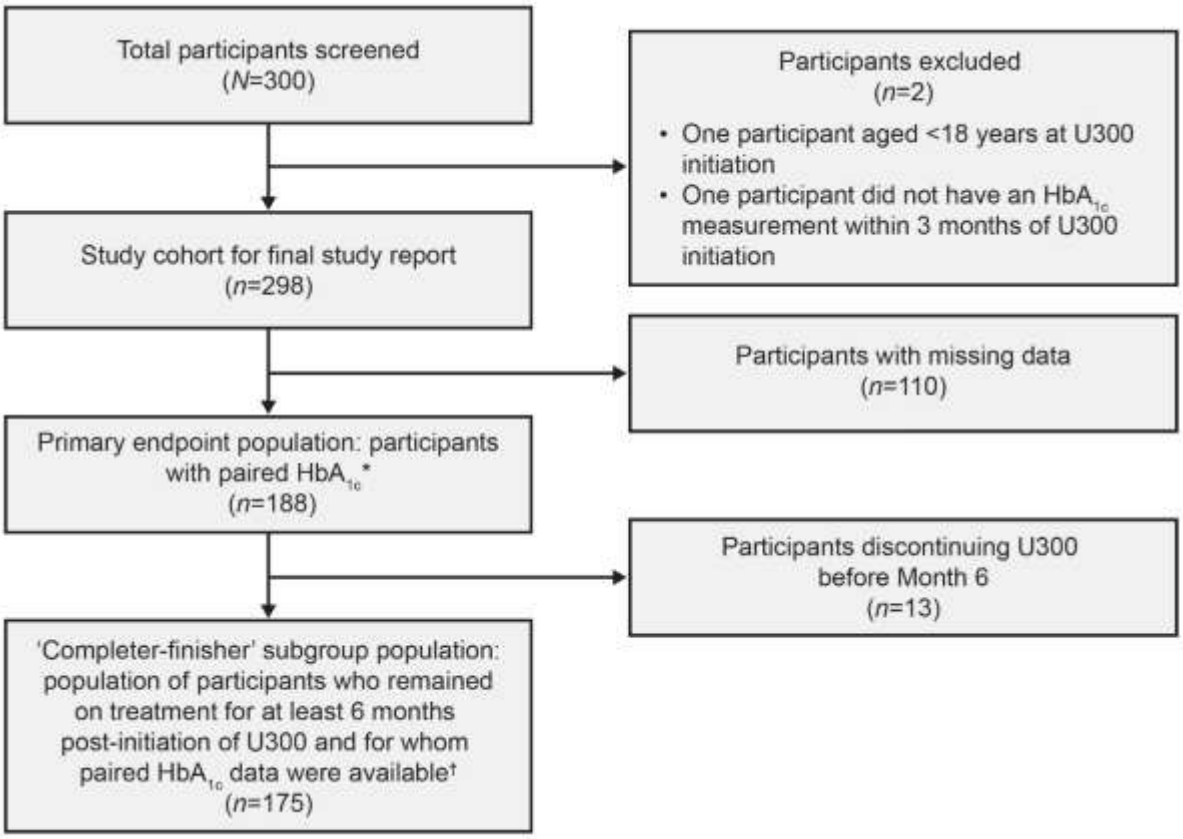
†Participants with data available at baseline.

Table 2 Incidence of severe hypoglycaemia and DKA episodes in the 6 months prior to and 6 months after U300 initiation

	Prior to U300 initiation		**Following U300 initiation**	
Severe documented hypoglycaemia episodes				
	n	**% (*n*=298)**	***N***	**% (*n*=298)**
Number of episodes	7		4	
Number of participants with episodes	6	2	4	1
Mean (SD) episodes per participant	0.02 (0.17)		0.01 (0.12)	
DKA episodes requiring A&E visits or hospitalization				
	n	**% (*n*=298)**	***N***	**% (*n*=298)**
Number of episodes	4		9	
Number of participants with episodes	4	1	6	2

A&E, Accident and Emergency Department; DKA, diabetic ketoacidosis; SD, standard deviation; U300, insulin glargine 300 units/mL.

FIGURE 1 Participant screening and eligibility.

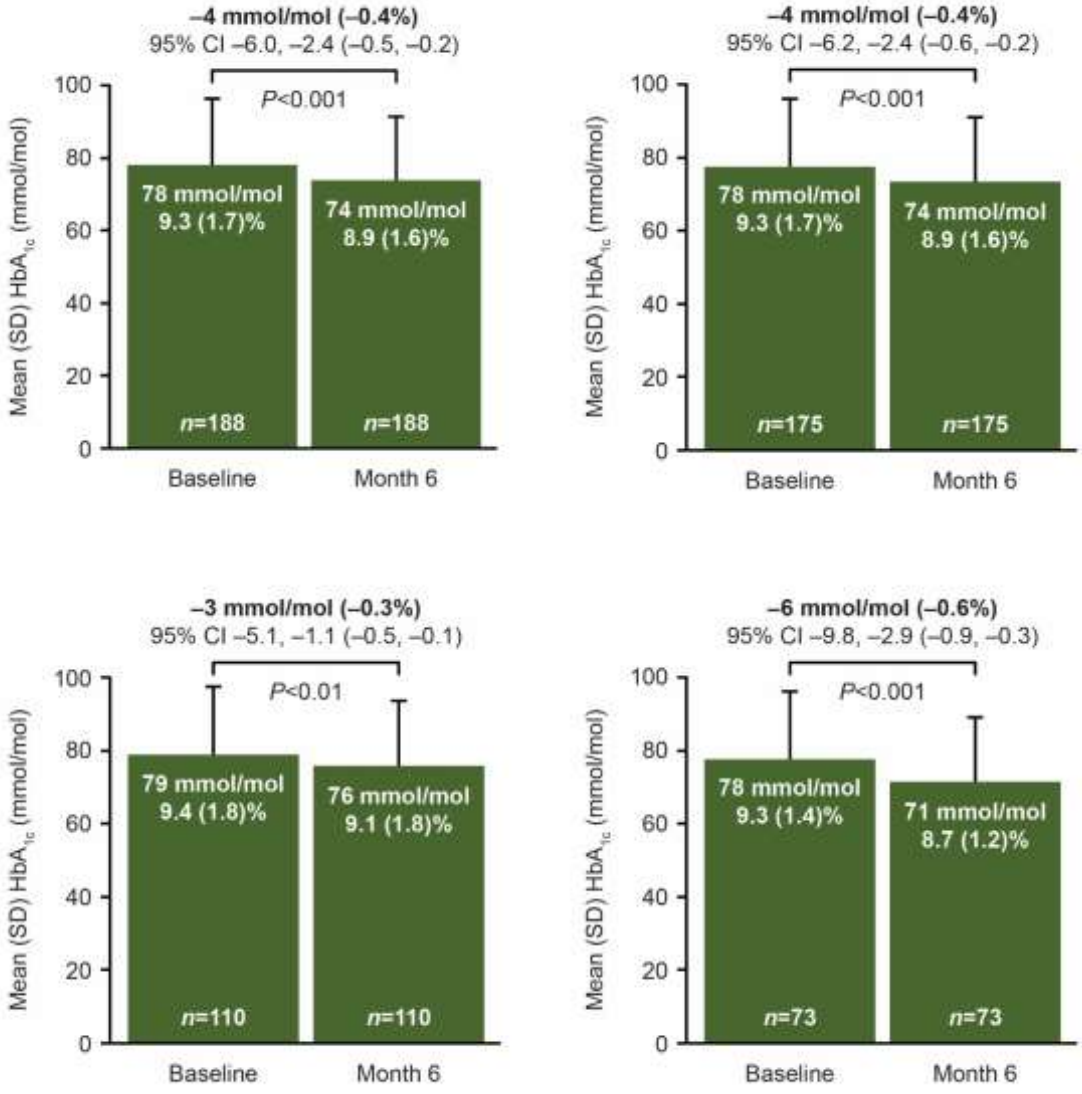


HbA_{1c}, glycated haemoglobin; U300, insulin glargine 300 units/mL.

*The primary endpoint population included all participants with HbA_{1c} available both within 3 months pre-initiation and at Month 6 post-initiation, irrespective of whether they had discontinued U300 by Month 6.

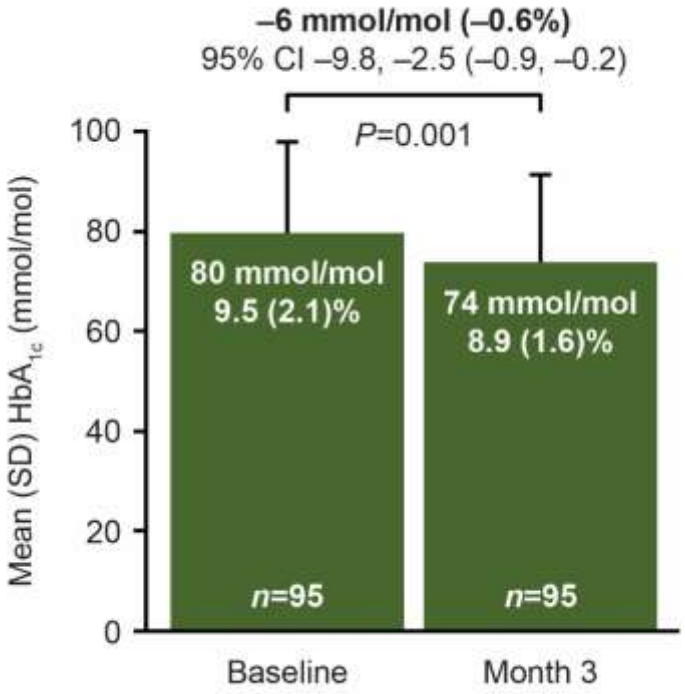
†The primary endpoint subpopulation included participants with ongoing U300 therapy at Month 6 with HbA_{1c} available both within 3 months pre-initiation and at Month 6 post-initiation if they remained on U300 at Month 6.

FIGURE 2 Change in HbA_{1c} from baseline to Month 6 post-initiation of U300 in (a) the overall population (primary endpoint), (b) the 'completer-finisher' subgroup population, (c) the subgroup of participants previously on once-daily basal insulin and (d) the subgroup of participants previously on twice-daily basal insulin.



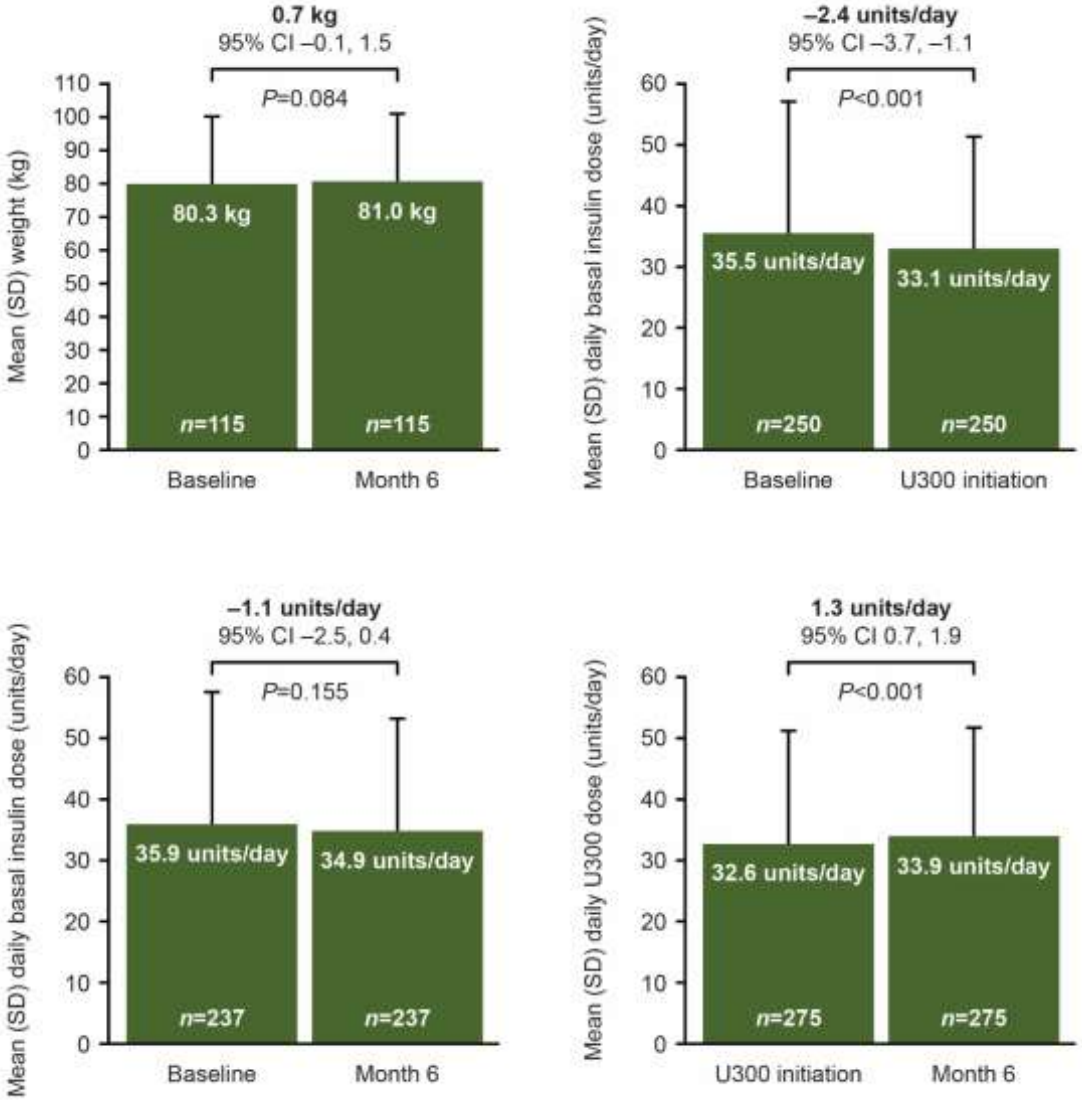
CI, confidence interval; HbA_{1c}, glycated haemoglobin; SD, standard deviation; U300, insulin glargine 300 units/mL.

FIGURE 3 Change in HbA_{1c} from baseline to Month 3 post-initiation of U300 in the overall population



CI, confidence interval; HbA_{1c}, glycated haemoglobin; SD, standard deviation; U300, insulin glargine 300 units/mL.

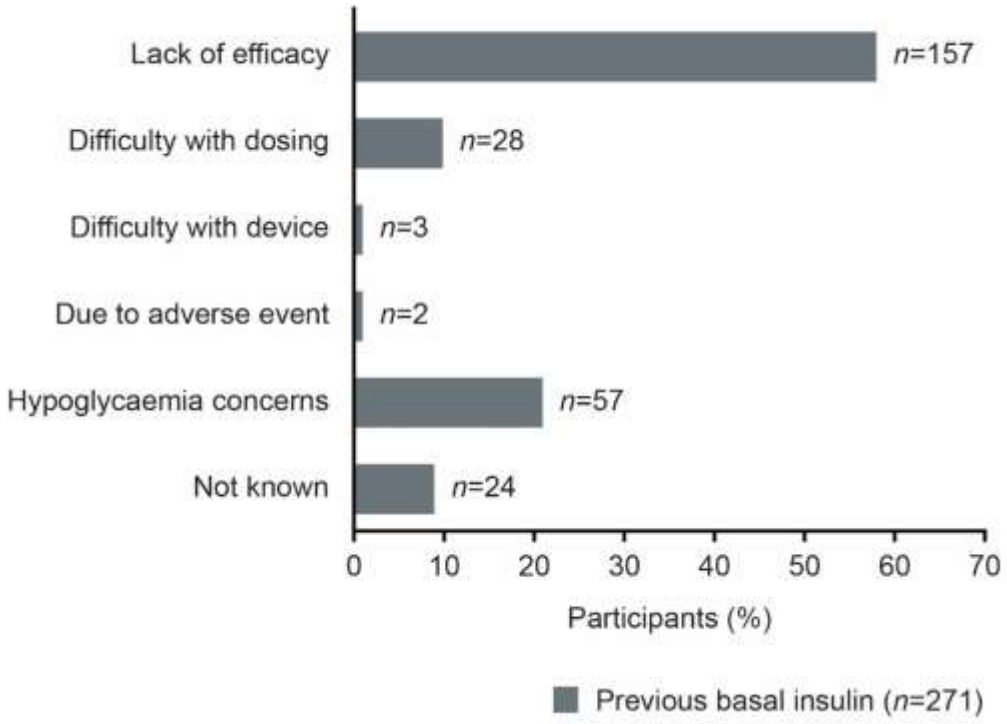
FIGURE 4 Change in (a) body weight from baseline to Month 6 post-initiation of U300, (b) total daily basal insulin dose from previous insulin therapy (baseline) to U300 initiation, (c) total daily basal insulin dose from previous insulin therapy (baseline) to Month 6 post-initiation of U300 and (d) total daily basal insulin dose from U300 initiation to Month 6 post-initiation of U300.

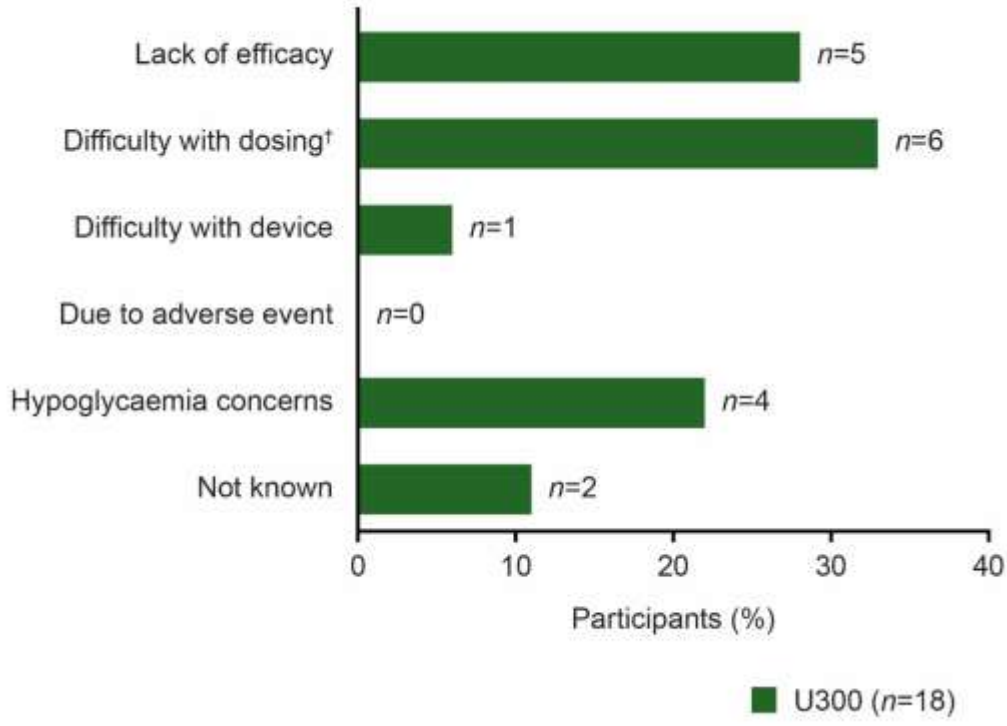


CI, confidence interval; HbA_{1c}, glycated haemoglobin; SD, standard deviation; U300, insulin glargine 300 units/m.

P values were calculated according to paired *t*-test.

FIGURE 5 Reason for (a) switching from previous basal insulin therapy to U300* and (b) discontinuing U300 after initiation.





U300, insulin glargine 300 units/mL.

*A total of 27 participants had no documented data available for reason for switching from previous basal insulin therapy to U300; these participants were not included in the total *n* value (*n*=271).

†No additional information was provided for the 6% who discontinued U300 due to dosing difficulty.

Supplementary Table S1 Proportion of participants by county

	Proportion of participants *n* (%) (*n*=298)
England	**171 (57)**
Essex	37 (12)
Surrey	32 (11)
Sheffield	59 (20)
West Midlands	43 (14)
Northern Ireland	**83 (28)**
County Down and Antrim	33 (11)
Derry and Antrim	50 (17)
Scotland	14 (5)
Glasgow	14 (5)
Wales	30 (10)
Swansea	30 (10)

Supplementary Table S2 Diabetes-related comorbidities at baseline

	Overall participant population (*n*=298)
Diabetes-related comorbidities per participant	
Number per participant, *n* (%)	
0	97 (33)
1	77 (26)
2	62 (21)
3	34 (11)
4	18 (6)
5	6 (2)
6	2 (1)
7	2 (1)
Mean (SD) per participant	1.4 (1.4)
Median per participant	1.0
IQR	0.0–2.0
Range	0.0–7.0
Diabetes-related comorbidities, n (%)	
Obesity	43 (14)
Dyslipidaemia	70 (23)
Hypertension	54 (18)
Cardiovascular disease	21 (7)
Depression	53 (18)
Kidney disease (nephropathy)	22 (7)
Retinopathy	99 (33)
Neuropathy	28 (9)
Coeliac disease	9 (3)
Thyroid disease	32 (11)
None recorded	97 (33)

Comorbidities are not mutually exclusive.

IQR, interquartile range; SD, standard deviation.

Supplementary Table S3 Hypoglycaemic awareness status at baseline

	Proportion of participants *n* (%)
Hypoglycaemic awareness status	***n*=298**
Hypoglycaemic aware	212 (71)
Hypoglycaemic unaware	21 (7)
Not known	65 (22)

Supplementary Table S4 Distribution of participants' weight change and mean weight change between baseline and Month 6 post-initiation of U300

Changes in weight from baseline to Month 6 post-initiation of U300	
Weight change in overall participant population (*n* = 298)	***n* (%)**
Lost weight	53 (18)
Gained weight	59 (20)
No weight change	3 (1)
Weight not recorded	183 (61)
Change in weight for participants losing or gaining weight	**Mean (SD)**
Weight lost, kg (*n*=53)	–3.0 (2.6)
Weight gained, kg (*n*=59)	4.7 (5.8)

SD, standard deviation; U300, insulin glargine 300 units/mL.

Baseline for weight was defined as the most recent observation within the 3-month period prior to U300 initiation.

Supplementary Table S5 Mild-to-moderate and severe hypoglycaemia episodes requiring A&E visits or hospitalization prior to and following U300 initiation

	Documented hypoglycaemia episodes (*n* = 298)	
	Number of episodes	**Proportion of participants**
	n	***n* (%)**
No documented episodes		
Prior to U300 initiation		270 (91)
Post U300 initiation		262 (88)
Mild-to-moderate hypoglycaemia		
Prior to U300 initiation	39	11 (4)
Post U300 initiation	86	27 (9)
Severe hypoglycaemia episodes requiring A&E visits or hospitalization		
Prior to U300 initiation	4	3 (1)
Post U300 initiation	1	1 (<1)

A&E, Accident and Emergency Department; U300, insulin glargine 300 units/mL.

All episodes refer to those that were documented. Mild-to-moderate and severe categories not mutually exclusive.

Supplementary Table S6 Proportion of participants who met an individualized HbA_{1c} target during the observation period following initiation of U300

	Proportion of participants ***n* (%)**
Proportion meeting documented HbA_{1c} targets	***n*=298**
Yes	23 (8)
No	162 (54)
Not known	113 (38)
Reasons where not known	***n*=113**
No target recorded	87 (29)
No post-initiation HbA_{1c}	0
No target and no post-initiation HbA_{1c}	26 (9)

HbA_{1c}, glycated haemoglobin; U300, insulin glargine 300 units/mL.

Supplementary Table S7 Proportion of participants meeting their optimal titration dose following initiation of U300

	Proportion of participants *n* (%)
Proportion reaching optimal titration	***n* = 298**
Yes	40 (13)
No	51 (17)
Not known	207 (69)
Glycaemic parameter on which optimal titration of dose was based	***n* = 40**
HbA_{1c}	8 (20)
FPG	21 (53)
Both	7 (18)
Not known	4 (10)

FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; U300, insulin glargine 300 units/mL.

*Optimal titration dose was defined as the dose at which a set target of HbA_{1c} or FPG was achieved.

Supplementary Table S8 The proportion of participants who attended structured diabetes education at baseline and within 6 months after the initiation of U300, and the types of education used

	Prior to U300 initiation *n* (%)	**Following U300 initiation *n* (%)**
Structured diabetes education	***n*=298**	***n*=298**
Yes	17 (6)	19 (6)
No	268 (90)	265 (89)
Not known	13 (4)	14 (5)
Type of education	***n*=17**	***n*=19**
DAFNE	5 (29)	9 (47)
BERTIE/CHOICE*	4 (24)	4 (21)
WICKED	0	0
STEPH	4 (24)	2 (11)
DAFYDD	2 (12)	2 (11)
One-to-one with dietitian	1 (6)	
3-h carbohydrate counting course		2 (11)
Not recorded	1 (6)	

*BERTIE and CHOICE are combined patient numbers

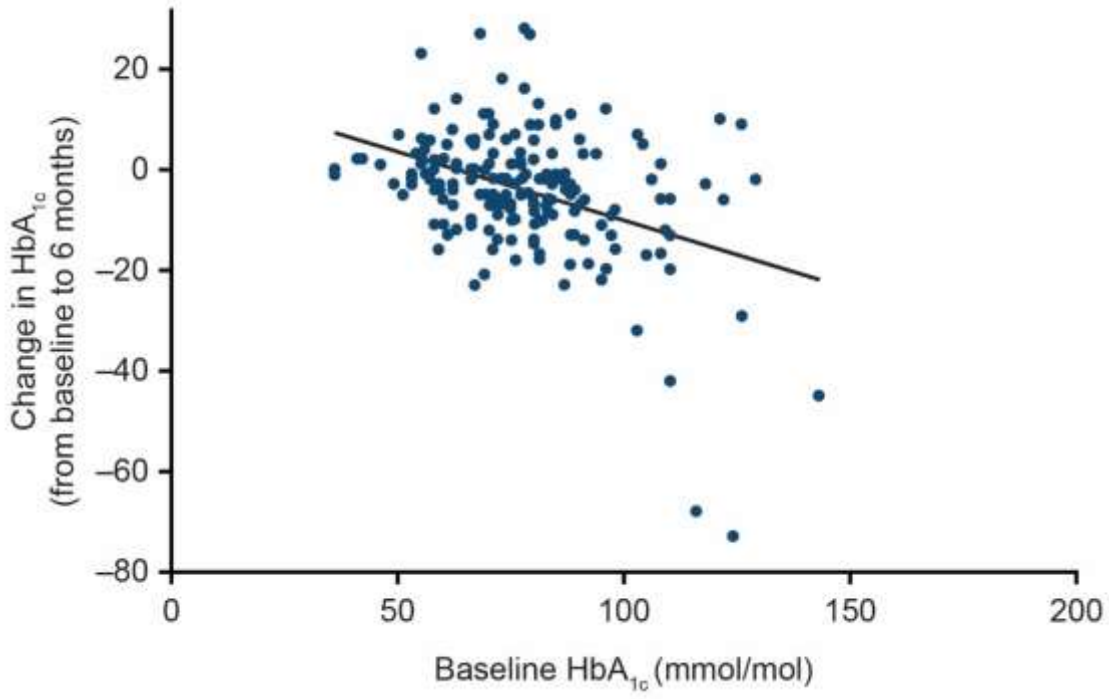
BERTIE, Beta Cell Education Resources for Training in Insulin and Eating; CHOICE, CHO and Insulin Calculation Education; DAFNE, Dose Adjustment for Normal Eating; DAFYDD, Dose Adjustment for your Daily Diet; STEPH, Structured Education for People with Type 1 Diabetes; U300, insulin glargine 300 units/mL; WICKED, Working with Insulin, Carbs, Ketones and Exercise to manage Diabetes.

Supplementary Table S9 Change in ICR from baseline to Month 6 post-initiation of U300

Change in ICR by Month 6	Overall participant population *n* (%)	Participants with ICR recorded *n* (%)
	***n*=298**	***n*=27**
Increased ICR	6 (2)	6 (22)
Decreased ICR	2 (1)	2 (7)
No change	19 (6)	19 (70)
ICR not recorded	271 (91)	

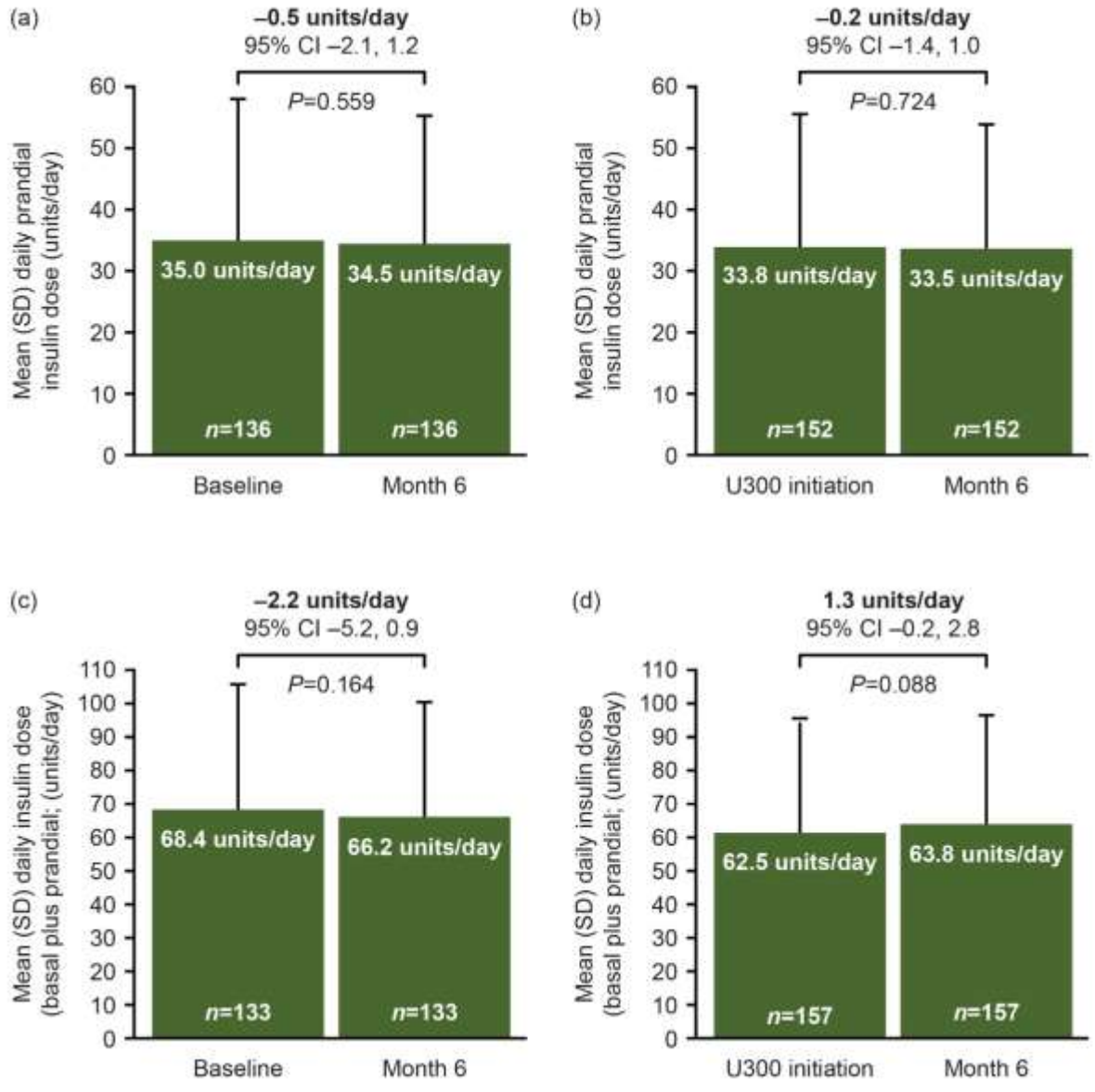
ICR, insulin-to-carbohydrate ratio; U300, insulin glargine 300 units/mL.

Supplementary Figure S1 Linear model comparing change in HbA_{1c} (from baseline to Month 6 post-initiation of U300) to baseline HbA_{1c}



HbA_{1c}, glycated haemoglobin; U300, insulin glargine 300 units/mL.

Supplementary Figure S2 Change in total daily prandial insulin dose and total daily insulin dose (basal plus prandial) from previous insulin therapy (baseline) to 6 months following U300 initiation, and from U300 initiation to Month 6 post-initiation



CI, confidence interval; SD, standard deviation; U300, insulin glargine 300 units/mL. Participants with paired data.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No.
Title and abstract			
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Included P.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Included, P.4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Included, P.5
Objectives	3	State specific objectives, including any prespecified hypotheses	Included, P.5
Methods			
Study design	4	Present key elements of study design early in the paper	Included, P.5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Included, P.5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Included, P.5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Data was paired - i.e. patients with starting and end measurement)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Included, P.6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	Included, P.7
Bias	9	Describe any efforts to address potential sources of bias	Included, P. 6 (also discussed in the discussion)
Study size	10	Explain how the study size was arrived at	Included, P.6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Included, P.7

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Included, P.7
		(*b*) Describe any methods used to examine subgroups and interactions	Included, P.7
		(*c*) Explain how missing data were addressed	Included, P.7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Data was paired - i.e. patients with starting and end measurement)
		(*e*) Describe any sensitivity analyses	Sensitivity analyses not performed
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and	Included, P.7
		(b) Give reasons for non-participation at each stage	Included, P.7
		(c) Consider use of a flow diagram	Included (See Figure 2)
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Included, P.7
		(b) Indicate number of participants with missing data for each variable of interest	Done through results text and/or in provided data tables
		(c) *Cohort study* - Summarise follow-up time (eg, average and total amount)	Results provided with timeframes
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results provided with timeframes
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Included, P.9
		(b) Report category boundaries when continuous variables were categorized	Results provided with timeframes
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Post hoc* analyses etc. reported within results section

Discussion			
Key results	18	Summarise key results with reference to study objectives	Included, P.10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Included, P.12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Done throughout discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Included, P.13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Included, P.3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.