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Research: Treatment

A multicentre, 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)

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Abstract

Aim To conduct an open-label study to provide UK real-world evidence regarding the use of insulin glargine 300 units/ml (U300) in people with Type 1 diabetes mellitus.

Methods People with Type 1 diabetes who had been prescribed U300 ≥6 months before data collection and had HbA_{1c} levels recorded within 3 months prior to U300 (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 episodes, and change in daily basal insulin dose.

Results A total of 298 people with Type 1 diabetes were included [mean age 42.1 years, mean HbA_{1c} 79 mmol/mol (9.4%)]. After U300 initiation, the mean reduction in HbA_{1c} from baseline to month 6 was –4 mmol/mol (–0.4%; $P<0.001$; $n=188$). The total daily basal insulin dose at 6 months was 1.3 units higher than at the time of U300 initiation ($P<0.001$; $n=275$) but was not significantly different from the 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. Diabetic ketoacidosis episodes requiring Accident and Emergency department visits or hospitalization were documented for 4/298 and 6/298 participants, before and after U300 initiation, respectively.

Conclusions In people with Type 1 diabetes, 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 diabetic ketoacidosis requiring Accident and Emergency department visits or hospitalization were low and similar before and after U300 initiation.

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Introduction

Insulin glargine 300 units/ml [U300 (Toujeo®); Sanofi, Paris, France] is a second-generation, once-daily basal insulin analogue [1]. Because 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 a precipitate with a smaller surface area after 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 is supported by results from two phase III randomized controlled trials: EDITION 4 and EDITION JP 1 [4,5]; however,

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What's new?

- 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 diabetes 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 Accident and Emergency department visits or hospitalization was low and similar before and after U300 initiation.
- Results from this real-world study show that observations made in randomized controlled trials translate to people with Type 1 diabetes treated with U300 in clinical practice in the UK.

no participants from the UK were included in these randomized controlled trials, and there is no real-world evidence regarding the use and utility of U300 in Type 1 diabetes in UK clinical practice.

The present study was designed to provide evidence regarding the effectiveness of U300 in people with Type 1 diabetes across the UK over a 6-month observation period.

Participants and 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 dataset, 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 diabetes who were prescribed their first dose of U300 ≥ 6 months before the date of data collection (1 August 2015) and had an HbA_{1c} blood result within 3 months prior to starting U300 were included. Data were collected retrospectively for the period from 11 October 2017 to 7 December 2017.

People with Type 2 diabetes and those with Type 1 diabetes 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 after, 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 episodes requiring Accident and Emergency department visits or hospitalization during the 6 months before and after 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 proportion 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 levels were achieved) and the proportion 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 ≥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.

To minimize biases associated with the study and to reflect, as accurately as possible, a cross-section of clinical experience throughout the UK, sites were chosen from different healthcare systems (i.e. from community and tertiary centres) and from different geographical locations. A minimum of 10 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 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.

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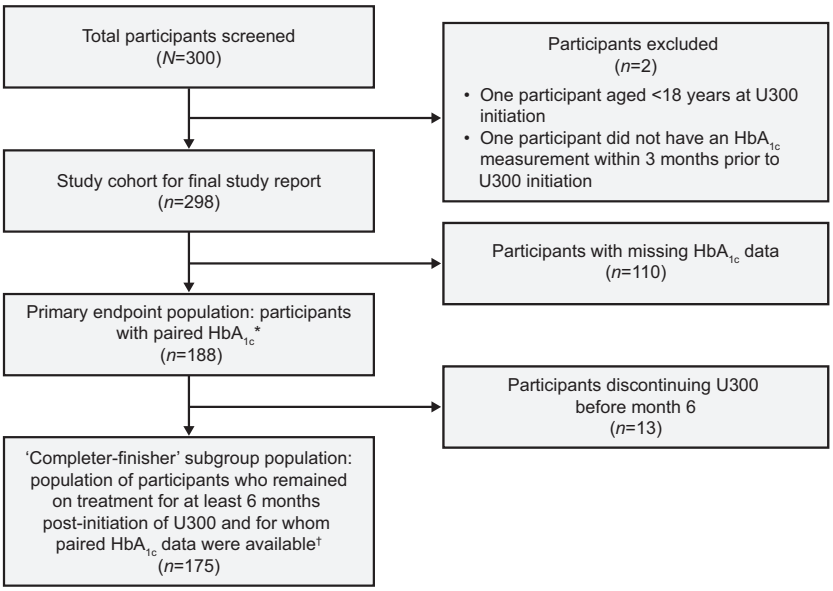

FIGURE 1 Participant screening and eligibility. *The primary endpoint population included all participants with HbA_{1c} available both within 3 months pre-initiation and at month 6 post-initiation, irrespective of whether they had discontinued insulin glargine 300 units/ml (U300) by month 6. †The primary 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.

Descriptive statistics [mean (SD), median and interquartile range] were calculated for quantitative variables, with frequencies and percentages derived for qualitative variables [analysed using STATA v14 (StataCorp LLC, College Station, TX, USA)]. 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 in univariable analysis and multivariable analysis 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 vs 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

A total of 300 people were screened; two were excluded (one was aged <18 years at initiation of U300, and one did not have an HbA_{1c} measurement within 3 months of U300 initiation), leaving 298 participants with Type 1 diabetes 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 a mean baseline HbA_{1c} of 79 mmol/mol (9.4%), weight of 81.2 kg and 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% of participants (105/298) 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].

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Table 1 Participant demographics and clinical characteristics at baseline*

Characteristics	
Age, mean (SD) years	42.1 (14.0)
N = 298	
Men, *n* (%)	152 (51)
N = 298	
Women, *n* (%)	146 (49)
N = 298	
Ethnicity, *n* (%)	
N = 298	
White	216 (72)
Other ethnic groups	16 (5)
Not recorded	66 (22)
Weight, mean (SD) kg	81.2 (20.9)
N = 225	
BMI, mean (SD) kg/m^2	28.3 (6.7)
N = 161	
Height, mean (SD) cm	169.7 (10.2)
N = 203	
Duration of diabetes at U300 initiation, years	
N = 272	
Mean (SD)	20.3 (12.9)
Median (IQR)	17.9 (10.4–29.7)
Duration of diabetes at data collection, years	
N = 272	
Mean (SD)	21.6 (13.0)
Median (IQR)	19.3 (11.4–31.0)
HbA_{1c}	
N = 298	
Mean (SD) mmol/mol	79 (20.2)
Mean (SD) %	9.4 (1.8)
Hypoglycaemia and diabetic ketoacidosis	
N = 298	
Participants experiencing severe hypoglycaemia in last 6 months, *n* (%)	6 (2)
Participants experiencing diabetic ketoacidosis in last 6 months, *n* (%)	4 (1)
Insulin regimen, *n* (%)	
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* (%)	
N = 277	
Basal-bolus with once-daily basal insulin	170 (61)
Basal-bolus with twice-daily basal insulin	84 (30)
Once daily basal insulin only	9 (3)
Twice daily basal insulin only	11 (4)
Not recorded	3 (1)
Rapid/short-acting insulin regimen, *n* (%)	
N = 262	
Basal-bolus/MDI	257 (98)
Bolus only	5 (2)
Pre-mix insulin regimen, *n* (%)	
N = 16	
Once daily	4 (25)
Twice daily	10 (63)
Not recorded	2 (13)
Insulin regimen, *n* (%)	
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	35.9 (21.6)
N = 237	
Prandial insulin	35.0 (23.0)
N = 136	
Total daily insulin (basal insulin plus prandial)	68.4 (37.1)
N = 133	

IQR, interquartile range; MDI, multiple dose injection; 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.
N = participants with data available at baseline.

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

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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 (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 vs baseline HbA_{1c} indicated that for every 1 mmol/mol that 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 1% increment 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 vs 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, the 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 is 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–d)].

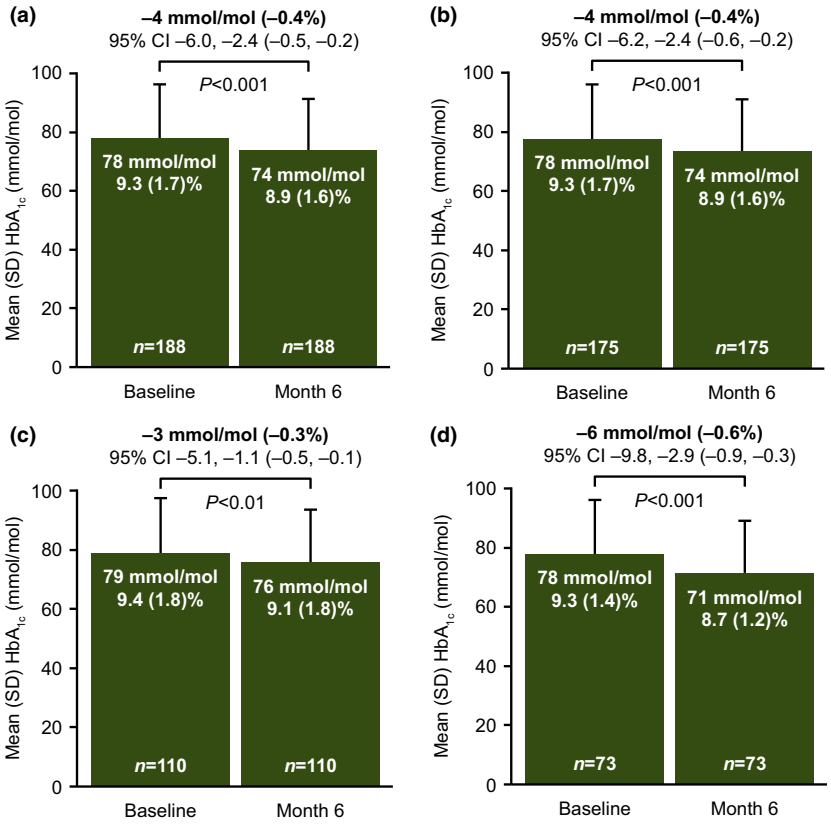

FIGURE 2 Change in HbA_{1c} from baseline to month 6 post-initiation of insulin glargine 300 units/ml (U300) in (a) the overall population (primary endpoint), (b) the 'completer-finisher' subgroup population, (c) the subgroup of participants previously on once-daily basal insulin and (d) the subgroup of participants previously on twice-daily basal insulin.

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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 (range) 0.0 (0–8)] was recorded.

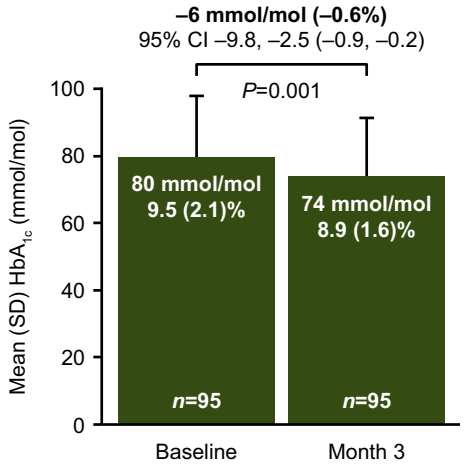

FIGURE 3 Change in HbA_{1c} from baseline to month 3 post-initiation of insulin glargine 300 units/ml (U300) in the overall population.

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 (Fig. 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 participants (2%) and 4/298 participants (1%) during the 6 months before and after initiation of U300, respectively (Table 2). Severe episodes requiring Accident and Emergency department visits or hospitalization and mild-to-moderate hypoglycaemic episodes are shown in Table S5.

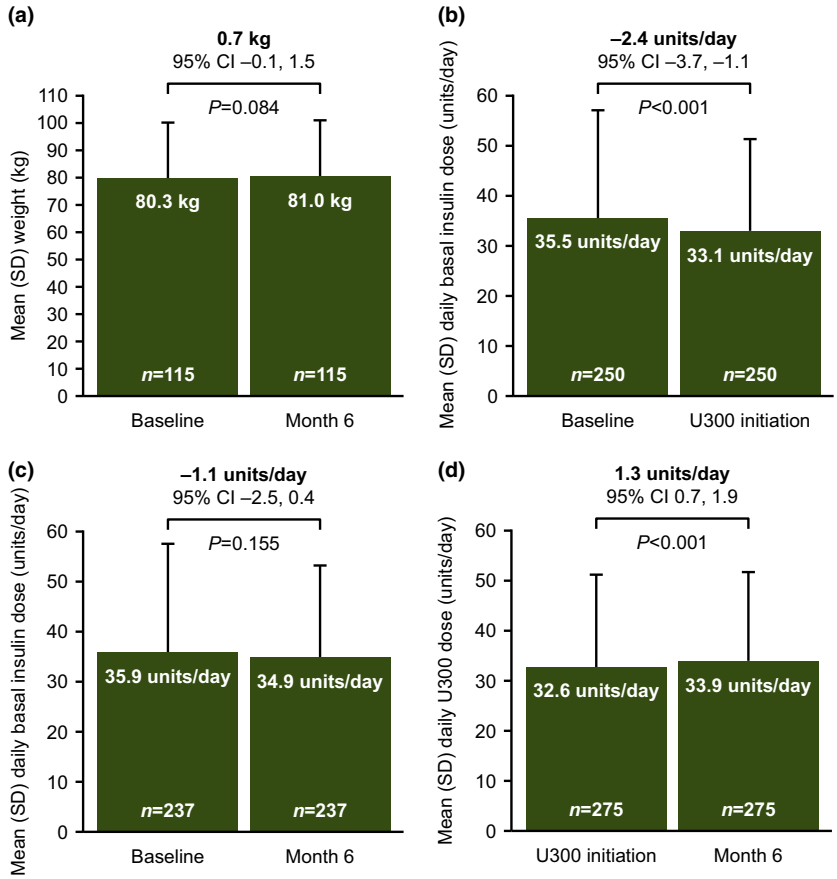

FIGURE 4 Change in (a) body weight from baseline to month 6 post-initiation of insulin glargine 300 units/ml (U300), (b) total daily basal insulin dose from previous insulin therapy (baseline) to U300 initiation, (c) total daily basal insulin dose from previous insulin therapy (baseline) to month 6 post-initiation of U300 and (d) total daily basal insulin dose from U300 initiation to month 6 post-initiation of U300. *P* values were calculated according to paired *t*-test.

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Diabetic ketoacidosis episodes requiring Accident and Emergency department visits or hospitalization were documented in 4/298 participants (1%) in the 6 months prior to initiation of U300 and in 6/298 participants (2%) in the 6 months after initiation (Table 2). No participants with documented diabetic ketoacidosis 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 Fig. 5. The most common reasons for discontinuing previous basal insulin were lack of efficacy [157/298 (53%)] and hypoglycaemia concerns [57/298 (19%)]. Fifty-one participants had 'not known or not recorded' as reason for discontinuation recorded. A total of 18 participants (6%) 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 participants (6%) in the 6 months pre-initiation of U300 and 19/298 participants (6%) 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 drawn about the level of insulin optimization achieved (Table S9).

Discussion

The present descriptive, retrospective study documents the real-world experience of using U300 in people with Type 1 diabetes 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 diabetic ketoacidosis events requiring Accident and Emergency department visits or hospitalization before and after U300 initiation 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 the present study [4]. The higher baseline HbA_{1c} observed in the present 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 diabetes population.

After 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 vs 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 benefitted 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 diabetes switching to U300 [8].

There was no clinically significant change in weight at month 6 after U300 initiation compared with baseline (prior insulin therapy). Although these results must be interpreted with caution because the evaluable sample size was small

Table 2 Incidence of severe hypoglycaemia and diabetic ketoacidosis episodes in the 6 months prior to and 6 months after insulin glargine 300 units/ml initiation (*N* = 298)

	Before U300 initiation	After U300 initiation
Severe documented hypoglycaemia episodes		
Number of episodes	7	4
Number of participants with episodes, *n* (%)	6 (2)	4 (1)
Mean (SD) episodes per participant	0.02 (0.17)	0.01 (0.12)
Diabetic ketoacidosis episodes requiring Accident and Emergency department visits or hospitalization		
Number of episodes	4	9
Number of participants with episodes, *n* (%)	4 (1)	6 (2)

U300, insulin glargine 300 units/ml.

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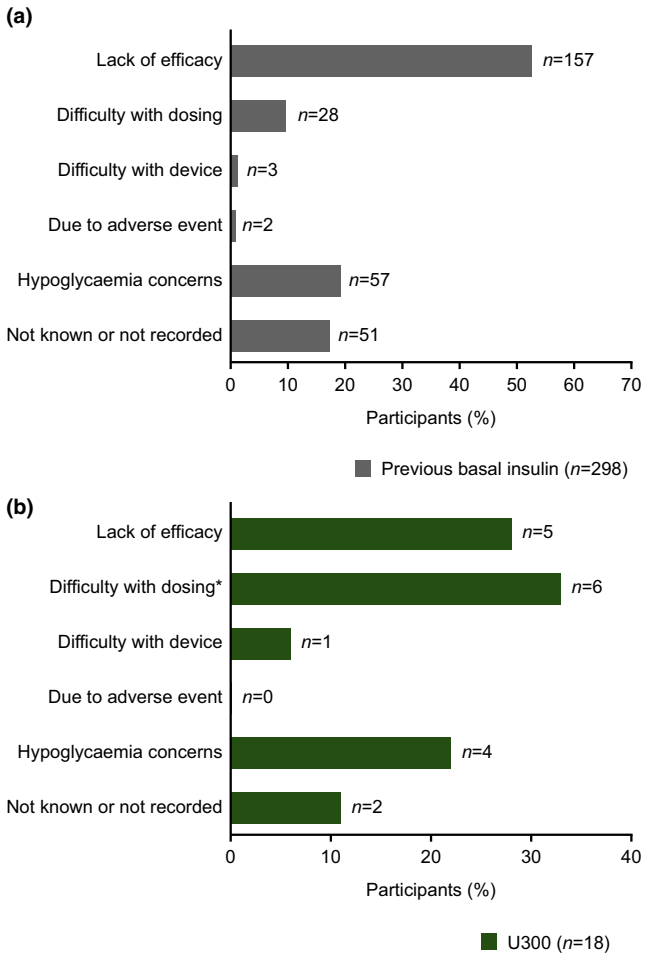

FIGURE 5 Reason for (a) switching from previous basal insulin therapy to insulin glargine 300 units/ml (U300) and (b) discontinuing U300 after initiation. *No additional information was provided for the participants who discontinued U300 because of difficulty with dosing.

(*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 attributable 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 (*n*=298) were lack of efficacy (53%) and hypoglycaemia concerns (19%). 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 consistent with the higher persistence observed with U300 in both Type 1 and Type 2 diabetes compared with 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 optimum 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 the present 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 datasets, such as the National Diabetes Audit, where up to

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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. Notably, the present study reported low recorded participation in structured diabetes education before and after U300 initiation, 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 Accident and Emergency department visits or hospitalization have been shown 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, concerns about hypoglycaemia 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 with, and parallel to the findings presented here, a recent prospective single-centre real-world study of participants with Type 1 diabetes in Belgium (n=116), which had a similar 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 unmeasurable) confounders. We have, however, sought to ameliorate these limitations through our study design. After 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 in answering 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 diabetes; 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 because 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 after U300 initiation in a population with Type 1 diabetes 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 attributable 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 manage people with Type 1 diabetes more effectively through more intensive follow-up, focusing 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. The results of this real-world study show that observations made in randomized controlled trials on U300 in Type 1 diabetes translate to the population seen in everyday clinical practice within the UK.

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Competing interests

T.P. has received speaker honoraria from Eli Lilly, Janssen, Napp Pharmaceuticals and Sanofi, and advisory board and consultancy fees from Novo Nordisk. S.C.B. has received speaker honoraria and advisory board fees from AstraZeneca, Boehringer Ingelheim/Eli Lilly, Novo Nordisk and Sanofi, and institutional investigator fees as chief and principal investigator for AstraZeneca, Novo Nordisk and Sanofi. R.N.A.B. 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.B. 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.E. has received speaker fees from Eli Lilly, Novo Nordisk and Sanofi. A.H. has received speaker fees from Sanofi. K.C.S.L. is an employee of Sanofi. C.M. 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.S. is an employee of pH Associates, which has received consultancy fees from Sanofi. A.Y. has received speaker honoraria from AstraZeneca, Novo Nordisk and Sanofi, and advisory board fees from Novo Nordisk. M.B. is an employee of Sanofi.

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Supporting Information

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

Table S1. Proportion of participants by county.
Table S2. Diabetes-related comorbidities at baseline.
Table S3. Hypoglycaemic awareness status at baseline.
Table S4. Distribution of participants' weight change and mean weight change between baseline and Month 6 post-initiation of U300.
Table S5. Mild-to-moderate and severe hypoglycaemia episodes requiring A&E visits or hospitalization prior to and following U300 initiation.
Table S6. Proportion of participants who met an individualized HbA_{1c} target during the observation period following initiation of U300.
Table S7. Proportion of participants meeting their optimal titration dose following initiation of U300.
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.
Table S9. Change in ICR from baseline to Month 6 post-initiation of U300.
Figure S1. Linear model comparing change in HbA_{1c} (from baseline to Month 6 post-initiation of U300) to baseline HbA_{1c}.
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.

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