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ORIGINAL RESEARCH

Efficacy and Safety of Insulin Glargine 300 U/mL in People with Type 2 Diabetes Uncontrolled on Basal Insulin: The 26-Week Interventional, Single-Arm ARTEMIS-DM Study

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ABSTRACT

Introduction: The efficacy and safety of switching to insulin glargine 300 U/mL (Gla-300) in type 2 diabetes mellitus (T2DM) uncontrolled on basal insulin (BI) has been demonstrated in the North American and Western European populations; however, there is limited data from other geographical regions with different ethnicities. The ARTEMIS-DM study aimed to evaluate the efficacy and safety of Gla-300 in people with T2DM uncontrolled on BI from Asia, Latin America and Middle East Africa.

Methods: The ARTEMIS-DM was a 26-week, prospective, interventional, single-arm, phase IV study (NCT03760991). Adults with T2DM previously uncontrolled (glycated haemoglobin [HbA_{1c}] 7.5–10%) on BI were switched to Gla-300. The primary endpoint was change in HbA_{1c} from baseline to 26 weeks. Key secondary endpoints were changes in HbA_{1c} (week 12), fasting plasma glucose (FPG), self-monitored plasma glucose (SMPG) and BI dose from baseline to week 26. The safety and tolerability of Gla-300 were also assessed.

Results: A total of 372 (50% male) participants were included, with mean (standard deviation [SD]) age 60.9 (10.0) years, duration of diabetes 13.11 (7.48) years and baseline HbA_{1c} 8.67 (0.77)% (71.22 [8.44] mmol/mol). A total of 222 (59.7%) participants were using insulin glargine 100 U/mL and 107 (28.8%) were using neutral protamine Hagedorn insulin as previous BI. There were clinically significant reductions in mean HbA_{1c} (− 0.82%; primary endpoint), FPG and SMPG levels at week 26. With a pre-defined

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titration algorithm, mean Gla-300 dose increased from 27.48 U (0.35 U/kg) at baseline to 39.01 U (0.50 U/kg) at week 26. Hypoglycaemia events occurred in 20.4% of the participants; 1 (0.3%) participant had a severe hypoglycaemia event.
Conclusion: In people with T2DM uncontrolled on previous BI, switching to Gla-300 with optimal titration guided by an algorithm was associated with improved glycaemic control and low incidence of hypoglycaemia across multiple geographic regions.
ClinicalTrials.gov identifier: NCT03760991.

Keywords: Basal insulin; Glycaemic control; Hypoglycaemia; Insulin glargine 300 U/mL; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

Diabetes has become a global health challenge and the prevalence of diabetes has been rising more rapidly in low- and middle-income countries than in high-income countries.

The efficacy and safety of switching to insulin glargine 300 U/mL (Gla-300) in people with type 2 diabetes mellitus (T2DM) uncontrolled on basal insulin (BI) has been previously demonstrated in randomised controlled trials and real-world studies, albeit in populations from the USA and Europe.

There is limited data on efficacy and safety of Gla-300 use in wider geographic regions including populations of various ethnic backgrounds, lifestyles and clinical practices; the present study aimed to address this evidence gap.

What was learned from the study?

The 26-week ARTEMIS-DM study assessed the efficacy and safety of switching to Gla-300 in people with T2DM who were uncontrolled on previous BI therapy in Asia, Latin America and Middle East Africa.

The study results confirm that switching to Gla-300 treatment with optimal titration results in clinically significant reductions in glycated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) with low incidence of hypoglycaemia and minimal body weight change.

This interventional study confirms the efficacy and safety of Gla-300 in people with T2DM uncontrolled on previous BI across multiple geographic regions.

INTRODUCTION

Insulin glargine 300 U/mL (Gla-300) is a second-generation basal insulin (BI) which has the potential to provide similar or improved glycaemic control owing to its stable and prolonged pharmacokinetic (PK) and pharmacodynamic (PD) profiles compared with the first-generation basal insulin glargine 100 U/mL (Gla-100), with a low risk of hypoglycaemia in people with type 2 diabetes mellitus (T2DM) [1–4]. Previous randomised controlled trials (RCTs) and real-world evidence (RWE) studies have confirmed the efficacy and safety of Gla-300 in people with diabetes; however, these studies included participants mainly from North America and Western Europe [5–8].

The prevalence of diabetes has increased at an alarming rate in low- and middle-income countries over the past few decades [9]. The prevalence of diabetes has also been increasing in regions like Asia, Latin America and Middle East Africa, which has contributed to a significant increase in the diabetes population worldwide resulting in public health and economic challenges [9–11]. Ethnic differences across regions also play an important role in determining the prevalence of diabetes. The prevalence of T2DM is reported to be higher among people of Asian, African or Hispanic origin when compared with that in non-Hispanic Whites [12–14]. Further, diabetes onset is reported to occur at a younger age and lower body mass index (BMI) in Asian populations,

resulting in a longer duration of diabetes and high risk of complications [12–14]. The prevalence of T2DM is greater among Hispanic/Latin-American adults in the USA compared to non-Hispanic Whites, which may be attributed to the sociocultural as well as genetic factors that increase obesity and insulin resistance [15, 16]. The International Diabetes Management Practices Study, a large real-world observational study, included more than 66,000 participants over 12 years from 49 developing countries across geographic regions such as Asia, Middle East, Africa, Latin America and Eurasia. The study showed that glycaemic control remains suboptimal (15–25%) among insulin-treated people with T2DM, despite an increase in the proportion of participants on insulin therapy over time [17].

However, there is limited data on the efficacy of Gla-300 in people with T2DM uncontrolled on previous BI from geographic regions outside the USA and Europe, where the prevalence and risk of T2DM are high owing to differences in ethnicity and sociocultural factors. The present study aimed to evaluate the efficacy and safety of Gla-300 in participants with T2DM uncontrolled on current BI therapy in wider geographic regions, such as Asia, Latin America and Middle East Africa including populations with various ethnic backgrounds and differences in lifestyles and treatment practices.

METHODS

Study Design and Participants

This multinational, prospective, interventional, single-arm, phase IV study (ARTEMIS-DM; NCT03760991) was designed to evaluate the clinical efficacy and safety of Gla-300 over 26 weeks in adults with T2DM uncontrolled on BI. The study comprised of a screening period (2 weeks), treatment period (26 weeks) and a post-treatment follow-up visit at week 27. The maximum study duration per patient was to be 29 weeks. Six onsite visits (weeks − 2 [screening visit], 0, 4, 8, 12 and 26) and five contacts via telephone (three weekly calls during weeks 1–3, one call during weeks 18–20 and one follow-up call in week 27) were scheduled; additional onsite visits could be scheduled as needed (Supplementary Fig. 1). Participants were enrolled at 47 centres in 14 countries (Asia: Hong Kong, India, Indonesia, Malaysia, Philippines and Thailand; Latin America: Argentina, Colombia and Peru; Middle East Africa: Egypt, Lebanon, Saudi Arabia, South Africa and Turkey). The study included adult participants with T2DM who were treated with standard of care BI therapy (Gla-100, detemir, degludec or neutral protamine Hagedorn [NPH] insulin) for at least 6 months and having glycated haemoglobin (HbA_{1c}) between 7.5% (58 mmol/mol) and 10% (86 mmol/mol) during screening, with a median of the last three consecutive fasting self-monitored plasma glucose (SMPG) values greater than 130 mg/dL prior to baseline or at least two fasting SMPG values greater than 130 mg/dL in the week prior to baseline. Participants treated with any insulin other than BI and/or treated with unstable BI regimen during the last 8 weeks prior to the screening visit were excluded. The trial was conducted between January 2019 and October 2020, which included the coronavirus disease 2019 (COVID-19) pandemic period. The COVID-19 pandemic impacted the study monitoring, laboratory assessments and the delivery of the study drug to participants; however, there was limited impact on recruitment or data monitoring committees.

The study protocol and other relevant study-related documents were approved by an institutional review board (IRB) or independent ethics committee (IEC) at each study centre. The study was conducted in accordance with the approved protocol, ethical standards derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All participants provided written informed consent prior to participation in the study.

Study Treatment

Participants received Gla-300 once daily self-administered subcutaneously at any time of day (the timing of injection was established at the discretion of the patient/investigator at baseline and maintained throughout the study). The participants were trained to self-administer Gla-300 using the SoloSTAR® prefilled pen as per the local label. Per the dose titration algorithm (Table 1), the insulin dose was titrated at least weekly and preferably not more than every 3–4 days unless required for safety, based on the median value determined from the last three consecutives fasting SMPG values and with the aim to attain the American Diabetes Association/European Association for the Study of Diabetes recommended HbA_{1c} target [18].

At physician's discretion, participants were educated regarding the titration process and were allowed to adjust their dose in between the scheduled visits without prior consultation with the site personnel. After week 12, rescue antidiabetic therapy (including a new drug or increasing the dose of a non-study drug that was part of the participant's current regimen at the time of the study) was used at the physician's discretion and per local labelling for insufficient glucose control (fasting plasma glucose [FPG] > 200 mg/dL [11 mmol/L] and HbA_{1c} > 8.5% [69.4 mmol/mol]).

Study Endpoints

The primary endpoint was the change in HbA_{1c} from baseline to week 26. Secondary endpoints included change in HbA_{1c} from baseline to week 12, changes in FPG, SMPG and 7-point SMPG over 26 weeks, percentage of participants achieving glycaemic targets (HbA_{1c} < 7% and fasting SMPG 80 to 110 mg/dL [4.4–6.1 mmol/L]), percentage of participants achieving glycaemic target without any severe or symptomatic documented (≤ 3.9 mmol/L [70 mg/dL]) hypoglycaemia event, and the percentage of participants requiring rescue therapy during the study. Other study endpoints included changes in BI dose, body weight, Insulin Treatment Satisfaction Questionnaire (ITSQ) score and percentage of participants with healthcare resource utilisation (HCRU), hypoglycaemia incidence and rates, as well as incidence of adverse events during the 26-week treatment period.

Table 1 Gla-300 starting dose and titration algorithm

Gla-300 starting dose	
Previous BI	**Recommended Gla-300 starting dose**
Gla-100	Same as the total daily Gla-100 dose
Other BI	
Once daily dosing	Same as the total daily BI dose
Twice daily dosing	80% of the total daily dose of the previous BI
Gla-300 dose titration algorithm	
Median fasting SMPG from last 3 consecutive values	**Dose adjustment (U/day)**
> 160 mg/dL	+ 4 U/day
> 110 to ≤ 160 mg/dL	+ 2 U/day
> 80 mg/dL to ≤ 110 mg/dL (glycaemic target)	No change
≤ 80 mg/dL or occurrence of ≥ 2 symptomatic or 1 severe hypoglycaemia episode in the preceding week	− 2 or at the discretion of the investigator

BI basal insulin, *Gla-100* insulin glargine 100 U/mL, *Gla-300* insulin glargine 300 U/mL, *SMPG* self-monitored plasma glucose

Data Collection and Statistical Analysis

Participants were supplied with a glucometer and diary at the screening visit and were required to record their fasting SMPG at least three times per week and all Gla-300 doses throughout the study. For insulin treatment satisfaction, participants were requested to complete the ITSQ by themselves, independently from the investigator or site staff, at specific time points.

The sample size was based on the primary objective of assessing the change in HbA_{1c} from baseline to week 26 (calculation based on the two-sided 95% confidence interval [CI] for the least squares [LS] mean change). To reach an absolute precision of 0.11% assuming a standard deviation (SD) of 1.1 for the change from baseline in HbA_{1c}, 385 evaluable participants were needed. An absolute precision of 0.11% corresponds to a relative precision of approximately 20% (i.e. for a mean HbA_{1c} change from baseline of − 0.5%: relative precision of 22%; for a change from baseline of − 0.6%: relative precision of 18%). Descriptive statistics were used to analyse primary and secondary endpoints. The LS mean change from baseline with 95% CI in HbA_{1c}, FPG and fasting SMPG were analysed using a mixed-effect linear model with repeated measures approach in the evaluable population including all eligible participants with a baseline and at least one post-baseline value for the respective parameters. Changes in body weight, insulin dose and safety were analysed in the safety population including all eligible participants assigned to study intervention and who received at least one dose of the study drug and results were summarised descriptively.

RESULTS

A total of 372 eligible participants from Asia (n = 125), Latin America (n = 141) and Middle East Africa (n = 106) were included and treated with Gla-300. A majority (361 [97.0%]) of the participants completed the on-treatment period and 11 (3.0%) discontinued treatment. Major reasons for discontinuations were adverse events (n = 5), withdrawal by the subjects (n = 4), poor compliance to protocol (n = 1) and lost to follow-up (n = 1). The mean (± SD) age was 60.9 ± 10.0 years and 37.3% of participants were at least 65 years of age; the proportions of male and female participants were equal (50% each). The mean BMI was 29.6 kg/m^2 and most of the participants (82.0%) were obese or overweight (Table 2). More than half of the participants (66.1%) had diabetes for more than 10 years and the mean duration of diabetes was 13.11 years. Neuropathy (18.3%), nephropathy (11.0%) and retinopathy (8.6%) were the most frequently observed diabetes-related complications. Majority (98.7%) of the participants were on BI treatment, 59.7% were using Gla-100 U/mL and 28.8% were using NPH insulin. A total of 89.0% of participants were previously treated with noninsulin antihyperglycemic agents. Biguanides were the most commonly used oral antidiabetic drug (OADs) at baseline (81.7% of participants), followed by sulfonylureas (34.7%) and dipeptidylpeptidase 4 inhibitors (28.5%).

Glycaemic Endpoints

Glycated Haemoglobin (HbA_{1c})

The mean (± SD) HbA_{1c} reduced from 8.67 ± 0.77% (71.22 ± 8.44 mmol/mol) at baseline (n = 372) to 8.04 ± 1.11% (64.43 ± 12.17 mmol/mol) at week 12 (n = 329) and 7.87 ± 1.13% (62.50 ± 12.31 mmol/mol) at week 26 (n = 355). The LS mean change (95% CI) in HbA_{1c} was clinically significant at week 12, − 0.66% (− 0.77%, − 0.56%) and week 26 (primary endpoint), − 0.82% (− 0.93%, − 0.70%) (Fig. 1). At week 26, a total of 18.5% of participants reached the target $HbA_{1c} < 7.0\%$; and greater proportions of participants achieved the less stringent targets ($HbA_{1c} < 7.5\%$, 36.8% and $< 8.0\%$, 56.7%) compared to $HbA_{1c} < 6.5\%$ (7.0%).

Fasting Plasma Glucose and Fasting Self-Monitored Plasma Glucose

The mean (± SD) FPG reduced from 164.08 ± 54.58 mg/dL at baseline to 137.38 ± 50.17 mg/dL and 133.54 ± 50.34 mg/dL at week 12 and week 26, respectively. A

Table 2 Baseline and patient disease characteristics

Characteristics	Gla-300 (N = 372)
Age, mean (SD), years	60.9 (10.0)
< 65 years, *n* (%)	233 (62.6)
≥ 65 – < 75 years, *n* (%)	108 (29.0)
≥ 75 years, *n* (%)	31 (8.3)
Male	186 (50.0)
BMI, mean (SD) kg/m^2	29.57 (5.43)
Duration of diabetes, mean (SD) years	13.11 (7.48)
Median (range)	12.00 (0.6–49.0)
< 10 years, *n* (%)	126 (33.9)
≥ 10 years, *n* (%)	246 (66.1)
Diabetic complications[a]	
Neuropathy	68 (18.3)
Nephropathy	41 (11.0)
Retinopathy[b]	32 (8.6)
Previous BI treatment[c], *n* (%)	367 (98.7)
Insulin glargine 100 U/mL	222 (59.7)
Insulin detemir	21 (5.6)
NPH Insulin	107 (28.8)
Insulin degludec	17 (4.6)
Duration of previous BI treatment, mean (SD), years[d]	2.86 (3.66)
Any previous noninsulin antihyperglycaemic agents, *n* (%)[a, e]	331 (89.0)
Biguanides	304 (81.7)
SU	129 (34.7)
DPP4 inhibitors	106 (28.5)
SGLT2 inhibitors	50 (13.4)
GLP-1 RA	19 (5.1)
Thiazolidinediones	17 (4.6)
Alpha-glucosidase inhibitors	7 (1.9)
Glinides	1 (0.3)
Others	1 (0.3)
Duration of previous non-insulin antidiabetic treatment, mean (SD), years	5.40 (5.85)

BI basal insulin, *BMI* body mass index, *DPP4* dipeptidyl peptidase 4, *Gla-300* insulin glargine 300 units/mL, *GLP-1 RA* glucagon-like peptide 1 receptor agonists, *NPH* neutral protamine Hagedorn, *SGLT2* sodium-glucose co-transporter 2, *SU* sulfonylurea

[a]Participants could have been counted in several categories

[b]Participants could have multiple retinopathy occurrences, with different subtypes

[c]Refers to the whole duration participants were on BI before the study regardless of the type and dose changes

[d]Refers to the latest BI received at the time of visit 2

[e]Refers to the last treatment received at study entry

clinically relevant reduction in FPG from baseline was observed at week 12 (LS mean change [95% CI] − 25.86 [− 31.23, − 20.49] mg/dL) and at week 26 (− 29.88 [− 35.13, − 24.63] mg/dL) (Fig. 2A). Mean (± SD) fasting SMPG was 162.30 ± 33.38 mg/dL at baseline, 129.07 ± 35.28 mg/dL at week 12, and 126.35 ± 34.89 mg/dL at week 26 (Fig. 2B). A clinically relevant reduction in fasting SMPG from baseline was observed at week 12 (LS mean change [95% CI] − 33.20 [− 36.74, − 29.66] mg/dL) and at week 26 (− 36.03 [− 39.54, − 32.52] mg/dL). The fasting SMPG target of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) was achieved in 127 (34.1%) participants at week 12 and in 136 (36.6%) participants at week 26.

7-Point Self-monitored Plasma Glucose and Rescue Therapy

Reductions from baseline in 7-point SMPG were observed at pre-breakfast, 2 h post-breakfast, and at bedtime over 26 weeks. The improvement in 7-point SMPG at week 12 was consistent with the improvement at week 26, in-line with the expectation that full dose titration would be reached by 12 weeks (Fig. 2C). None of

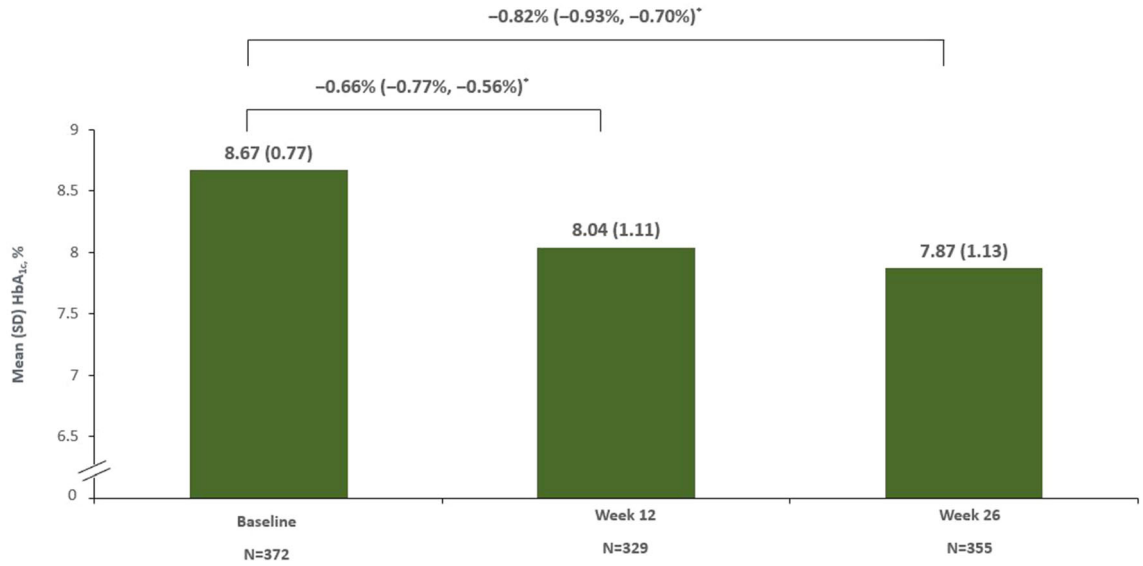

Fig. 1 Change in HbA_{1c} from baseline to week 12 and 26. *Treatment effects are shown as LS mean (95% CI) change from baseline (MMRM model). *Gla-300* insulin glargine 300 units/mL, *HbA_{1c}* glycated haemoglobin, *LS* least squares, *MMRM* mixed-effect model with repeated measures, *N* number of evaluable participants, *SD* standard deviation

the participants required rescue therapy between weeks 12 and 26.

Insulin Dose

The mean total daily BI dose was increased from 27.48 U at baseline to 36.71 U at week 12 and 39.01 U at week 26 with the recommended titration algorithm. The mean daily dose per kg body weight was 0.35 U/kg at baseline and increased to 0.47 U/kg and 0.50 U/kg at weeks 12 and 26, respectively (Fig. 2D).

Body Weight

The mean (± SD) weight was 78.43 ± 16.90 kg at baseline and 79.16 ± 16.92 kg at week 26, with a mean change from baseline of 0.82 ± 4.64 kg.

Insulin Treatment Satisfaction Score

Treatment satisfaction increased over time following the initiation of Gla-300 therapy. The mean (± SD) ITSQ total satisfaction score increased from baseline, 76.30 ± 15.63 (n = 345) to week 12, 83.51 ± 13.29 (n = 344) and week 26, 84.42 ± 13.15 (n = 337). Improvements were noted for all ITSQ domain scores, especially the glycaemic control score; mean (± SD) at baseline, 65.83 ± 23.94 (n = 352) to week 12, 80.92 ± 18.18 (n = 354) and week 26, 82.75 ± 17.09 (n = 350) (Supplementary Table 1).

Healthcare Resource Utilisation

Over a total of 183.0 patient-years during the 26-week treatment period, few participants required HCRU with no in-patient hospitalisations, three participants required emergency room visits (0.02 visits/patient-year), and 17 participants had outpatient office or specialty visits (a total of 29 visits, 0.16 visits/patient-year). None of the reported HCRU was related to diabetes or hypoglycaemia.

Safety

Hypoglycaemia

Overall, incidence of treatment-emergent hypoglycaemia was reported in 76 (20.4%) participants; of these 35 (9.4%) participants had

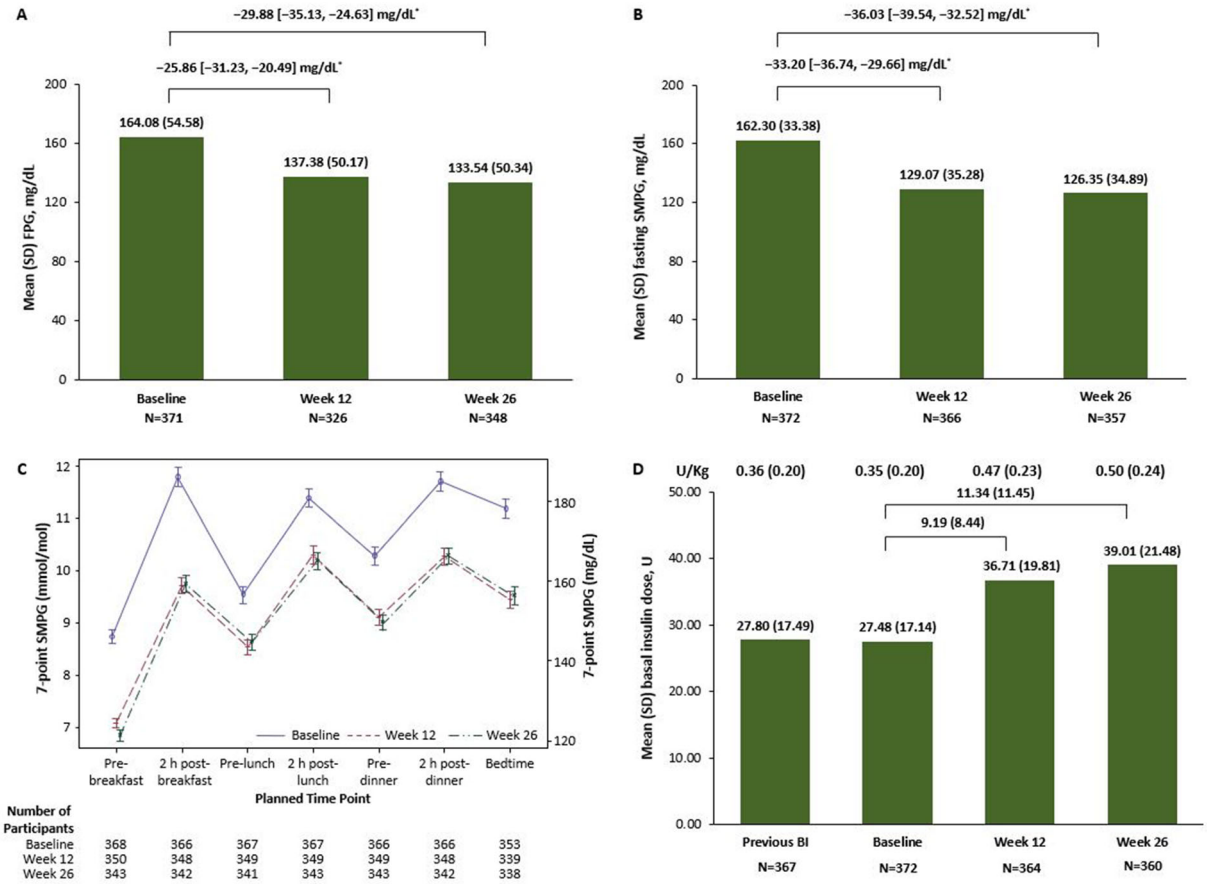

Fig. 2 Change in **A** FPG, **B** Fasting SMPG, **C** 7-point SMPG and **D** BI dose from baseline to week 12 and 26. *Treatment effects are shown as LS mean (95% CI) change from baseline (MMRM model); analysis included N=354 for FPG and N=366 for fasting SMPG. *BI* basal insulin, *FPG* fasting plasma glucose, *Gla-300* insulin glargine 300 units/mL, *h* hour, *MMRM* mixed-effect model with repeated measures, *N* number of evaluable participants, *SD* standard deviation, *SMPG* self-monitored plasma glucose

nocturnal hypoglycaemia events. The incidence of documented symptomatic (blood glucose ≤ 3.9 mmol/L) hypoglycaemia was 12.6% for all hypoglycaemia and 5.9% for nocturnal hypoglycaemia. Similarly, the incidence of documented symptomatic (blood glucose ≤ 3.0 mmol/L) was 3.8% for all hypoglycaemia and 0.5% for nocturnal hypoglycaemia. Severe hypoglycaemia was reported in one (0.3%) participant, and this occurred during nighttime (Table 3).

Adverse Events

Treatment-emergent adverse events (TEAEs) were reported in 110 (29.6%) participants; 15 (4.0%) participants had a treatment-emergent serious adverse event. One treatment-emergent serious adverse events (cardiac arrest) led to death during the study, which was not related to the study drug. The most frequently reported TEAEs were infections and infestations in 45 (12.1%) participants and gastrointestinal disorders in 16 (4.3%) participants. Treatment discontinuations due to TEAEs were reported in 4 (1.1%) participants. Five (1.3%) participants reported TEAEs related to COVID-19 infection.

DISCUSSION

The ARTEMIS-DM study enrolled participants from regions with previously limited

Table 3 Hypoglycaemia events (safety population)

Type of hypoglycaemia event, *n* (%)	All hypoglycaemia (*N* = 372)	Nocturnal hypoglycaemia[a] (*N* = 372)
Any hypoglycaemia event	76 (20.4)	35 (9.4)
Severe hypoglycaemia[b]	1 (0.3)	1 (0.3)
Symptomatic hypoglycaemia	55 (14.8)	26 (7.0)
Documented ≤ 3.9 mmol/L (≤ 70 mg/dL)	47 (12.6)	22 (5.9)
Documented ≤ 3.0 mmol/L (< 54 mg/dL)	14 (3.8)	2 (0.5)
Severe and/or symptomatic hypoglycaemia	55 (14.8)	26 (7.0)
Documented ≤ 3.9 mmol/L (≤ 70 mg/dL)	47 (12.6)	22 (5.9)
Documented ≤ 3.0 mmol/L (< 54 mg/dL)	14 (3.8)	2 (0.5)
Asymptomatic hypoglycaemia	33 (8.9)	13 (3.5)
≤ 3.9 mmol/L (≤ 70 mg/dL)	33 (8.9)	13 (3.5)
≤ 3.0 mmol/L (< 54 mg/dL)	3 (0.8)	2 (0.5)
Severe and/or confirmed hypoglycaemia[c]	70 (18.8)	31 (8.3)
≤ 3.9 mmol/L (≤ 70 mg/dL)	70 (18.8)	31 (8.3)
≤ 3.0 mmol/L (< 54 mg/dL)	16 (4.3)	4 (1.1)

[a]Nocturnal hypoglycaemia is any hypoglycaemia that occurs while the patient was asleep between bedtime and before getting up in the morning

[b]Severe hypoglycaemia includes any hypoglycaemia event that requires third party assistance

[c]Confirmed hypoglycaemia are symptomatic or asymptomatic events confirmed by glucose values ≤ 3.9 mmol/L (≤ 70 mg/dL) or ≤ 3.0 mmol/L (< 54 mg/dL)

participation in the Gla-300 clinical development programme (Asia, Middle East Africa and Latin America) to address evidence gaps regarding the efficacy and safety of Gla-300 in people with T2DM uncontrolled on BI. The mean age and BMI of the eligible participants were different from those in previous Gla-300 studies [19–21]. Participants in the ARTEMIS-DM study also had a long duration of T2DM (mean 13.1 years) and were on a broad range of previous BI, with the most commonly used previous BI being Gla-100 (59.7%) and NPH insulin (28.8%). Biguanides were the most commonly used previous OADs among the participants in this study. The regional populations in the ARTEMIS-DM study had varying patient characteristics, treatment practices, and were found to have delayed insulin initiation and suboptimal insulin dose titration.

The results of this study support the findings from other Gla-300 studies namely the EDITION 2 RCT [19], TRANSITION 2 interventional study [20] and DELIVER 2 RWE study [21] in people with T2DM. Although the Gla-300 arms of these studies evaluated the efficacy or effectiveness and safety of switching to Gla-300 in people with T2DM who were previously treated with other BI in RWE or interventional setting, it may not be possible to draw any direct comparisons with the present study owing to differences in the study designs. The EDITION 2 was a treat-to-target randomised open-label study comparing once daily Gla-300 versus Gla-100 in people with T2DM uncontrolled on BI and OADs [19]. TRANSITION 2 was a single country, interventional, single-arm, phase IV study to evaluate the efficacy and safety of Gla-300 in people with suboptimal

glucose control on BI with or without OADs [20]. Further, the DELIVER 2 study was a retrospective RWE study in the US population that investigated the effects of BI switch (to Gla-300 or another BI) in people with uncontrolled T2DM [21].

The ARTEMIS-DM study demonstrated reduction in HbA_{1c} from 8.67% at baseline to 7.87% at week 26 with a change of − 0.82% from baseline. The HbA_{1c} reduction observed at week 26 in the ARTEMIS-DM study was greater than that reported in the Gla-300 arm of the EDITION 2 study at 6 months (− 0.57%); this could be due to the higher baseline HbA_{1c} in the ARTEMIS-DM study (8.67%) than in the EDITION 2 study (8.26%) [19]. Previous studies have reported greater HbA_{1c} reduction in participants with higher baseline HbA_{1c} levels [22]. Further, the magnitude of HbA_{1c} reduction in the present study was also greater than that reported in the TRANSITION 2 (− 0.64%) and DELIVER 2 RWE (− 0.51%) studies despite comparable or greater baseline HbA_{1c} levels (TRANSITION 2, 8.64% and DELIVER 2, 8.95%) [20, 21]. The HbA_{1c} reduction in the ARTEMIS-DM study was greater at week 26 than in the TRANSITION 2 study, which is also an interventional study with participants close to the real-life practice, potentially due to a difference in titration algorithms. While a titration algorithm was recommended in the TRANSITION 2 study, the target FPG range was less stringent than the present study [20]. In the DELIVER 2 study, being a retrospective real-world study, there was no defined BI titration algorithm, and this may explain the difference in HbA_{1c} reduction compared with that seen in ARTEMIS-DM [21]. Collectively, the data suggest that both baseline HbA_{1c} level and optimal titration of Gla-300 dose play an important role in determining glycaemic improvements. Also, the Gla-300 formulation produces a smaller subcutaneous depot, resulting in more prolonged and constant release of insulin into the bloodstream, extending the blood glucose control well beyond 24 h [3, 4]. Switching to Gla-300 in patients previously uncontrolled on different basal or premix insulin regimens has been shown to improve glycaemic control in the EDITION 2 RCT, TRANSITION 2 and other real-world studies [19, 20, 24, 25]. The results of the ARTEMIS-DM study also confirm that switching to Gla-300 treatment with optimal titration results in clinically significant reductions in HbA_{1c} level.

Along with HbA_{1c} reductions, improvements were also seen in other glycaemic parameters such as FPG and fasting SMPG in the ARTEMIS-DM study. The FPG reduction observed in the ARTEMIS-DM study (− 29.88 mg/dL [− 1.66 mmol/L]) was greater than that reported in the EDITION 2 RCT (− 1.14 mmol/L) [19]. The changes from baseline to 6 months in FPG and fasting SMPG were not reported in TRANSITION 2 and DELIVER 2 studies [20, 21]. Despite the clinically significant HbA_{1c} reduction in the ARTEMIS-DM study, 18.5% of participants achieved target $HbA_{1c} < 7.0\%$. The same glycaemic target achievement was higher (30.6%) in the EDITION 2 RCT but was lower in the TRANSITION 2 (11.4%) and real-world DELIVER 2 (16.8%) studies [19–21]. While these differences could be partly explained by the controlled trial design and lower baseline HbA_{1c} in the EDITION 2 study and the lack of or less stringent BI titration in the TRANSITION 2 and DELIVER 2 studies, the results suggest that glycaemic control remains poor in majority of insulin-treated people with T2DM [19–21]. In the present study the mean duration of previous BI therapy was only 2.86 years despite the long duration of diabetes (> 12 years), indicating delayed treatment intensification. Taking into consideration the progressive nature of the disease, most people with T2DM require treatment intensification (either by increasing the dose of their current medication or addition of a new drug) to improve their glycaemic control.

In the present study, Gla-300 dose was increased by 11.3 U and from 0.35 U/kg at baseline to 0.5 U/kg at week 26. This showed that when guided by a titration algorithm, people with T2DM in these regions who need to switch to another BI could safely increase their BI dose. In the TRANSITION 2 study, the mean BI dose increased from 46.1 U/day from baseline to 57.8 U/day at week 24 [20]. Also, in the EDITION 2 study, the Gla-300 daily dose increased from 0.64 U/kg at baseline to 0.92 U/kg by the end of 6 months; however, it should

be noted that in the EDITION 2 study, the starting insulin dose was high because of the inclusion criteria (dose of previous BI required to be 42 U) [19]. While the starting BI dose and dose change in the ARTEMIS-DM study were still lower than the previous studies cited, the reduction in HbA_{1c} and glycaemic control observed is positively correlated with insulin dose titration and was consistent with previous studies [21, 21]. After 26 weeks of Gla-300 treatment, there were minimal changes in body weight, improvements in treatment satisfaction and reported HCRU were low. There were no HCRU related to diabetes or hypoglycaemia in addition to the scheduled study visits.

The incidence of hypoglycaemia and nocturnal hypoglycaemia observed in the ARTEMIS-DM study was 20.4% and 9.4%, respectively, which is lower compared to EDITION 2 and TRANSITION 2 studies [19, 21]. The EDITION 2 study reported 71.5% and 30.5% of participants experiencing any hypoglycaemia and nocturnal hypoglycaemia, respectively; whereas the TRANSITION 2 study reported 46.0% of the participants had at least one hypoglycaemia event and 12.2% experienced nocturnal hypoglycaemia [19, 20]. In the EDITION 2 and TRANSITION 2 studies, nocturnal hypoglycaemia was defined by hypoglycaemic events occurring during the night (00:00–05:59 hours), whereas in the ARTEMIS-DM study nocturnal hypoglycaemia was defined by the sleep status [19, 20]. The lower incidence of severe hypoglycaemia ($n = 1$) and nocturnal hypoglycaemia ($n = 35$) might be due to lower insulin dose and titration.

Strengths of this study include its large, diverse population from wide geographic regions with longer duration of diabetes uncontrolled on BI. The pre-defined titration algorithm used in the ARTEMIS-DM study may have facilitated good insulin titration and attainment of the observed glycaemic improvements. However, the starting dose of Gla-300 and magnitude of titration were low compared with that in previous RCTs, suggesting that further dose increments could be achieved without any significant safety concerns. The frequent follow-ups during the study period (six onsite visits and five contacts via telephone) may have had an impact on the study outcomes. Regular study follow-up visits/calls and patients' motivation to improve their health may lead to better treatment adherence in RCTs. A previous report has shown that medication adherence is a key factor contributing to improved glycaemic control in RCTs compared to RWE studies [26]. The main limitation of the ARTEMIS-DM study was the single arm study design with no direct comparators; however, it was a large interventional study conducted across multiple geographic regions and provides data from close to real-world clinical setting.

CONCLUSION

The ARTEMIS-DM is the first 26-week interventional study conducted in multiple geographic regions (Asia, Latin America and Middle East Africa) with limited prior data on T2DM uncontrolled on previous BI and transitioned to Gla-300. The results of this study showed a clinically meaningful HbA_{1c} reduction at week 26 with changes noted as early as after 12 weeks of treatment. Approximately 20% of the participants achieved the target of $HbA_{1c} < 7\%$ and more than 35% of participants achieved less stringent HbA_{1c} targets. The safety results were consistent with previous studies in terms of adverse events and hypoglycaemia, with no new or unexpected safety findings. The observed glycaemic improvements and low incidence of hypoglycaemia with the low starting Gla-300 dose and magnitude of titration suggest that a more stringent titration approach could enable more people to achieve glycaemic control. Thus, in people with T2DM uncontrolled on previous BI from multiple geographic regions, switching to Gla-300 with a standardised dose-titration algorithm was associated with improved glycaemic control and low risk of hypoglycaemia.

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Compliance with Ethics Guidelines. The study protocol and other relevant study-related documents were approved by an institutional review board (IRB) or independent ethics committee (IEC) at each study centre (Supplementary material Appendix II). The study was conducted in accordance with the approved protocol, ethical standards derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All participants provided written informed consent prior to participation in the study.

Data Availability. Qualified researchers may request access to patient-level data and related documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria of Sanofi, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

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