SUPPLEMENTARY DATA

Supplementary Table 1. Glycemic changes from baseline. Least squares mean reductions from baseline with last observation carried forward
LS=least squares. HbA_{1c}=glycated hemoglobin A_{1c}. FPG=fasting plasma glucose. SMPG=self-measured plasma glucose.

	Gla-300 (n=404)	**Gla-100 (n=400)**
HbA_{1c}		
Baseline, mean (SD) (%)	8.14 (0.78)	8.14 (0.76)
(mmol/mol)	65.5 (8.5)	65.5 (8.3)
Last visit, mean (SD) (%)	7.25 (0.85)	7.28 (0.92)
(mmol/mol)	55.7 (9.3)	56.1 (10.1)
Mean change (SD) (%)	–0.88 (0.81)	–0.86 (0.92)
(mmol/mol)	–9.6 (8.9)	–9.4 (10.1)
LS mean change (SE) (%)	–0.83 (0.06)	–0.83 (0.06)
(mmol/mol)	–9.1 (0.7)	–9.1 (0.7)
Participants attaining HbA_{1c} targets (%)		
<7.0% (53 mmol/mol)	39.6	40.9
≤6.5% (48 mmol/mol)	21.0	21.6
FPG, mean (mmol/L)		
Baseline (SD)	8.72 (2.83)	8.90 (2.94)
Last visit (SD)	7.24 (2.57)	7.21 (2.40)
Mean change (SD)	–1.48 (3.11)	–1.69 (3.21)
LS mean change	–1.29 (0.19)	–1.38 (0.19)
Participants attaining FPG targets (%)		
≤6.7 mmol/L	46.3	44.9
≤5.6 mmol/L	26.5	23.2
SMPG profiles		
All 8 measurements, mean (mmol/L)		
Baseline (SD)	9.28 (2.04)	9.45 (2.24)
Last visit (SD)	8.14 (2.05)	8.13 (1.98)
Mean change (SD)	–1.14 (2.23)	–1.32 (2.48)
LS mean change (SE)	–0.987 (0.16)	–1.073 (0.16)
Pre-breakfast, mean (mmol/L)		
Baseline (SD)	8.47 (2.06)	8.58 (2.10)
Last visit (SD)	7.05 (1.90)	6.69 (1.64)
Mean change (SD)	–1.42 (2.11)	–1.89 (2.17)
03:00 h, mean (mmol/L)		
Baseline (SD)	8.44 (3.34)	8.62 (3.26)
Last visit (SD)	7.57 (2.99)	7.46 (2.91)
Mean change (SD)	–0.87 (3.91)	–1.17 (3.8)
LS mean change (SE)	–0.98 (0.25)	–1.16 (0.25)
Pre-injection, mean (mmol/L)		
Baseline (SD)	10.31 (2.58)	10.44 (2.65)
Last visit (SD)	9.10 (2.42)	9.27 (2.44)
Change (SD)	–1.21 (2.83)	–1.17 (2.69)
LS mean change (SE)	–0.90 (0.18)	–0.84 (0.18)
Pre-injection, variability (coefficient of variation)		
Baseline (SD)	25.55 (12.41)	24.97 (11.82)
Last visit (SD)	22.21 (11.75)	21.60 (11.52)
Mean change (SD)	–3.33 (14.56)	–3.37 (14.57)
LS mean change (SE)	–1.10 (1.22)	–1.08 (1.22)

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Supplementary Table 2. Incidence of hypoglycemic events (% of participants affected) for Gla-300 versus Gla-100 during 6 months of treatment, by intervals of time of day.

	Hypoglycemia at any time of day or night (24 h)		**Nocturnal hypoglycemia (00:00–05:59)**		**Daytime hypoglycemia (06:00–23:59)**	
	No. participants (%)		***No. participants (%)***		***No. participants (%)***	
	Gla-300	**Gla-100**	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**
	(n=404)	**(n=402)**	**(n=404)**	**(n=402)**	**(n=404)**	**(n=402)**
Any hypoglycemia						
Baseline to month 6	337 (83.4)	356 (88.6)	183 (45.3)	240 (59.7)	328 (81.2)	345 (85.8)
Baseline to week 8	266 (65.8)	311 (77.4)	109 (27.0)	150 (37.3)	261 (64.6)	301 (74.9)
Week 9 to month 6	306 (75.7)	312 (77.6)	151 (37.4)	187 (46.5)	293 (72.5)	293 (72.9)
Documented symptomatic hypoglycemia ≤3.9 mmol/L						
Baseline to month 6	283 (70.0)	313 (77.9)	145 (35.9)	194 (48.3)	265 (65.6)	293 (72.9)
Baseline to week 8	200 (49.5)	248 (61.7)	79 (19.6)	105 (26.1)	186 (46.0)	226 (56.2)
Week 9 to month 6	249 (61.6)	252 (62.7)	115 (28.5)	149 (37.1)	229 (56.7)	229 (57.0)
Documented symptomatic hypoglycemia ≤3.0 mmol/L						
Baseline to month 6	151 (37.4)	167 (41.5)	49 (12.1)	68 (16.9)	131 (32.4)	141 (35.1)
Baseline to week 8	87 (21.5)	101 (25.1)	27 (6.7)	30 (7.5)	72 (17.8)	85 (21.1)
Week 9 to month 6	119 (29.5)	114 (28.4)	36 (8.9)	46 (11.4)	103 (25.5)	96 (23.9)
Asymptomatic hypoglycemia ≤3.9 mmol/L						
Baseline to month 6	255 (63.1)	274 (68.2)	84 (20.8)	102 (25.4)	245 (60.6)	263 (65.4)
Baseline to week 8	180 (44.6)	206 (51.2)	39 (9.7)	55 (13.7)	174 (43.1)	197 (49.0)
Week 9 to month 6	209 (51.7)	216 (53.7)	62 (15.3)	68 (16.9)	198 (49.0)	202 (50.2)
Severe hypoglycemia						
Baseline to month 6	20 (5.0)	23 (5.7)	8 (2.0)	10 (2.5)	17 (4.2)	16 (4.0)
Baseline to week 8	6 (1.5)	11 (2.7)	3 (0.7)	3 (0.7)	5 (1.2)	8 (2.0)
Week 9 to month 6	18 (4.5)	14 (3.5)	5 (1.2)	7 (1.7)	16 (4.0)	10 (2.5)
Confirmed (≤3.9 mmol/L) or severe hypoglycemia						
Baseline to month 6	331 (81.9)	353 (87.8)	180 (44.6)	231 (57.5)	321 (79.5)	339 (84.3)
Baseline to week 8	260 (64.4)	302 (75.1)	106 (26.2)	134 (33.3)	255 (63.1)	288 (71.6)
Week 9 to month 6	302 (74.8)	312 (77.6)	146 (36.1)	184 (45.8)	288 (71.3)	290 (72.1)
Confirmed (≤3.0 mmol/L) or severe hypoglycemia						
Baseline to month 6	181 (44.8)	201 (50.0)	63 (15.6)	82 (20.4)	164 (40.6)	171 (42.5)
Baseline to week 8	111 (27.5)	121 (30.1)	34 (8.4)	39 (9.7)	97 (24.0)	101 (25.1)
Week 9 to month 6	150 (37.1)	147 (36.6)	44 (10.9)	53 (13.2)	136 (33.7)	127 (31.6)

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Supplementary Table 3. Hypoglycemic events and event-rates (per participant-year of exposure) for Gla-300 versus Gla-100 during 6 months of treatment, by intervals of time of day.

	Hypoglycemia at any time of day or night (24 h)		**Nocturnal hypoglycemia (00:00–05:59)**		**Daytime hypoglycemia (06:00–23:59)**	
	Events (Events per participant-year)		***Events (Events per participant-year)***		***Events (Events per participant-year)***	
	Gla-300	**Gla-100**	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**
	(n=404)	**(n=402)**	**(n=404)**	**(n=402)**	**(n=404)**	**(n=402)**
Any hypoglycemia						
Baseline to month 6	5138 (26.37)	5430 (28.08)	646 (3.32)	883 (4.57)	4491 (23.05)	4545 (23.50)
Baseline to week 8	1822 (29.13)	2070 (33.40)	229 (3.66)	324 (5.23)	1593 (25.47)	1744 (28.14)
Week 9 to month 6	3316 (25.06)	3360 (25.56)	417 (3.15)	559 (4.25)	2898 (21.90)	2801 (21.31)
Documented symptomatic hypoglycemia ≤3.9 mmol/L						
Baseline to month 6	2626 (13.48)	2855 (14.76)	375 (1.92)	623 (3.22)	2251 (11.55)	2232 (11.54)
Baseline to week 8	925 (14.79)	1071 (17.28)	138 (2.21)	203 (3.28)	787 (12.58)	868 (14.01)
Week 9 to month 6	1701 (12.86)	1784 (13.57)	237 (1.79)	420 (3.20)	1464 (11.06)	1364 (10.38)
Documented symptomatic hypoglycemia ≤3.0 mmol/L						
Baseline to month 6	474 (2.43)	512 (2.65)	89 (0.46)	124 (0.64)	385 (1.98)	388 (2.01)
Baseline to week 8	175 (2.80)	186 (3.00)	34 (0.54)	41 (0.66)	141 (2.25)	145 (2.34)
Week 9 to month 6	299 (2.26)	326 (2.48)	55 (0.42)	83 (0.63)	244 (1.84)	243 (1.85)
Asymptomatic hypoglycemia ≤3.9 mmol/L						
Baseline to month 6	2220 (11.39)	2173 (11.24)	215 (1.10)	171 (0.88)	2005 (10.29)	2001 (10.35)
Baseline to week 8	785 (12.55)	805 (12.99)	71 (1.14)	73 (1.18)	714 (11.42)	731 (11.80)
Week 9 to month 6	1435 (10.84)	1368 (10.41)	144 (1.09)	98 (0.75)	1291 (9.76)	1270 (9.66)
Severe hypoglycemia						
Baseline to month 6	53 (0.27)	47 (0.24)	12 (0.06)	15 (0.08)	41 (0.21)	32 (0.17)
Baseline to week 8	11 (0.18)	15 (0.24)	6 (0.10)	4 (0.06)	5 (0.08)	11 (0.18)
Week 9 to month 6	42 (0.32)	32 (0.24)	6 (0.05)	11 (0.08)	36 (0.27)	21 (0.16)
Confirmed (≤3.9 mmol/L) or severe hypoglycemia						
Baseline to month 6	4966 (25.48)	5176 (26.76)	610 (3.13)	813 (4.20)	4356 (22.35)	4362 (22.55)
Baseline to week 8	1743 (27.87)	1934 (31.21)	217 (3.47)	281 (4.53)	1526 (24.40)	1652 (26.66)
Week 9 to month 6	3223 (24.36)	3242 (24.67)	393 (2.97)	532 (4.05)	2830 (21.39)	2710 (20.62)
Confirmed (≤3.0 mmol/L) or severe hypoglycemia						

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Baseline to month 6	737 (3.78)	698 (3.61)	122 (0.63)	156 (0.81)	615 (3.16)	542 (2.80)
Baseline to week 8	265 (4.24)	266 (4.29)	51 (0.82)	55 (0.89)	214 (3.42)	211 (3.40)
Week 9 to month 6	472 (3.57)	432 (3.29)	71 (0.54)	101 (0.77)	401 (3.03)	331 (2.52)

Supplementary Table 4. Assessment of treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)
LS=least squares.

Mean (SD)*	**Gla-300 (n=404)**			**Gla-100 (n=402)**		
	Baseline	**Month 6**	**Change from baseline**	**Baseline**	**Month 6**	**Change from baseline**
Current treatment	5.1 (1.3)	5.6 (0.7)	0.45 (1.2)	5.5 (1.1)	5.6 (0.6)	0.43 (1.1)
Convenience	4.8 (1.3)	5.3 (1.1)	0.47 (1.3)	4.9 (1.2)	5.3 (1.0)	0.44 (1.3)
Flexibility	4.8 (1.3)	5.2 (1.2)	0.46 (1.4)	4.8 (1.3)	5.2 (1.1)	0.42 (1.4)
Understanding	4.8 (1.2)	5.3 (0.9)	0.48 (1.2)	4.9 (1.2)	5.2 (0.8)	0.33 (1.1)
Recommend	5.2 (1.2)	5.6 (0.9)	0.43 (1.3)	5.2 (1.2)	5.6 (0.8)	0.35 (1.3)
Continue	5.1 (1.2)	5.6 (0.9)	0.46 (1.3)	5.2 (1.2)	5.6 (0.7)	0.43 (1.3)
Total Score	29.7 (5.9)	32.5 (4.4)	2.85 (5.6)	30.2 (5.7)	32.6 (3.8)	2.48 (5.5)
LS Mean change in total score (Baseline to Month 6)	2.32 95% CI 1.72 to 2.93			2.24 95% CI 1.63 to 2.85		

*Maximum score in each category is 6.

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Supplementary Table 5. Treatment-emergent serious adverse events.

	Gla-300 (n=404)	**Gla-100 (n=402)**
Any class	26 (6.4)	21 (5.2)
Infections and infestations	7 (1.7)	5 (1.2)
Cellulitis	0	1 (0.2%)
Erysipelas	1 (0.2)	0
Diverticulitis	0	1 (0.2)
Osteomyelitis	2 (0.5)	1 (0.2)
Endocarditis	1 (0.2)	0
Groin abscess	1 (0.2)	0
Bronchitis	1 (0.2)	0
Bronchopneumonia	1 (0.2)	0
Pneumonia	0	2 (0.5)
Sepsis	1 (0.2)	1 (0.2)
Septic embolus	1 (0.2)	0
Pyelonephritis acute	0	1 (0.2)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	3 (0.7)	1 (0.2)
Breast cancer	1 (0.2)	0
Chronic myeloid leukemia	0	1 (0.2)
Prostate cancer	1 (0.2)	0
Metastatic bronchial carcinoma	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	3 (0.7)
Hyperkalemia	0	1 (0.2)
Diabetes mellitus inadequate control	0	1 (0.2)
Hypoglycemia	1 (0·2)	1 (0.2)
Psychiatric disorders	0	1 (0.2)
Depression	0	1 (0.2)
Nervous system disorders	3 (0.7)	2 (0.5)
Transient ischemic attack	1 (0.2)	0
Hypoglycemic unconsciousness	2 (0.5)	0
Syncope	0	1 (0.2)
Guillain-Barré syndrome	0	1 (0.2)
Cardiac disorders	6 (1.5)	7 (1.7)
Bundle branch block left	0	1 (0.2)
Atrial fibrillation	1 (0.2)	1 (0.2)
Ventricular tachycardia	1 (0.2)	0
Aortic valve stenosis	0	1 (0.2)
Coronary artery disease	2 (0.5)	1 (0.2)
Acute coronary syndrome	1 (0.2)	0
Angina pectoris	0	1 (0.2)
Myocardial ischemia	1 (0.2)	1 (0.2)
Cardiac failure	0	1 (0.2)
Cardiac chronic failure	0	1 (0.2)

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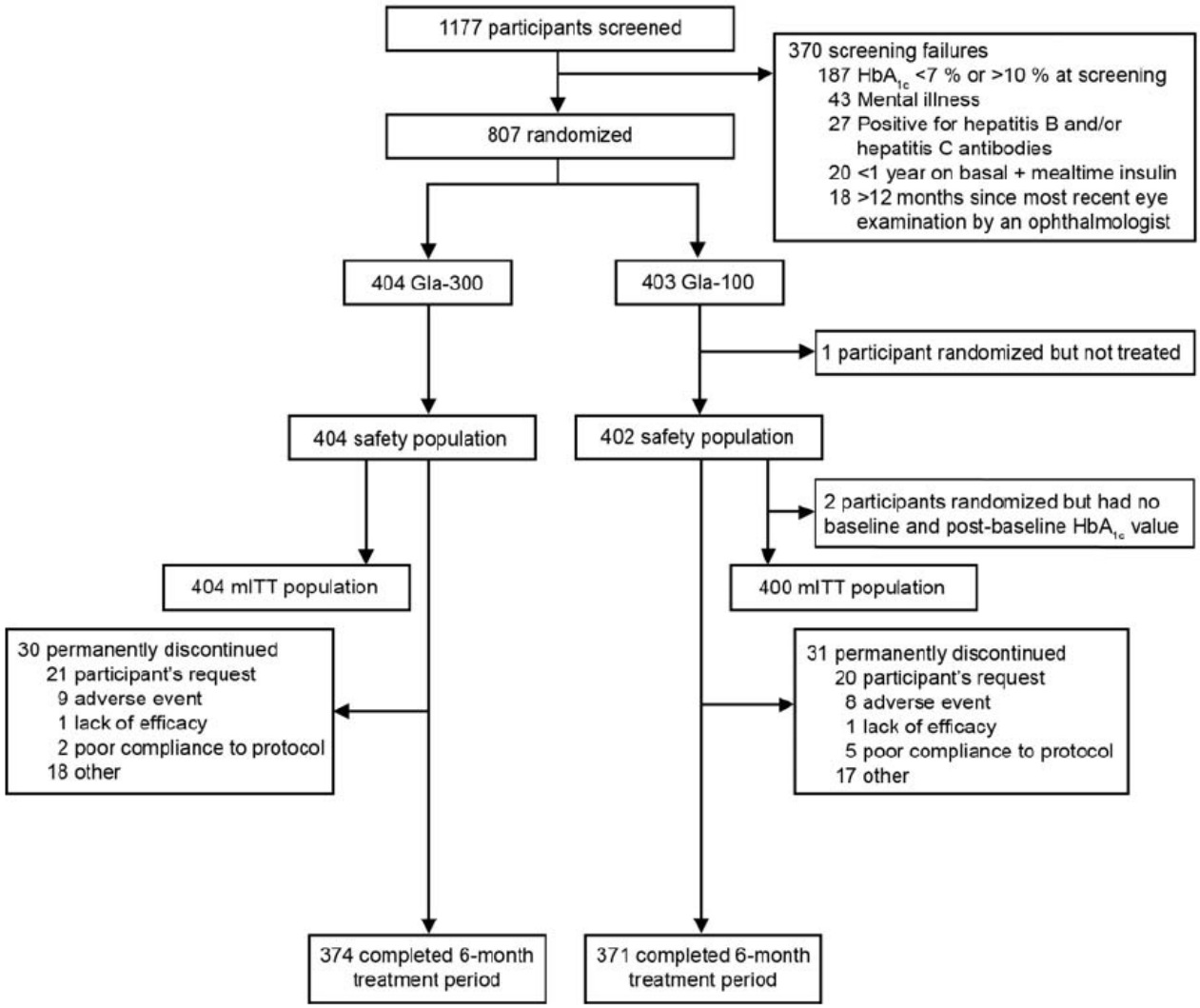
Vascular disorders	0	1 (0.2)
Aortic stenosis	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0
Dyspnea exertional	1 (0.2)	0
Gastrointestinal disorders	1 (0.2)	0
Ileus	1 (0.2)	0
Hepatobiliary disorders	0	1 (0.2)
Cholelithiasis	0	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)	0
Diabetic foot	1 (0.2)	0
Musculoskeletal and connective tissue disorders	2 (0.5)	2 (0.5)
Osteoarthritis	1 (0.2)	0
Spondylitis	0	1 (0.2)
Rhabdomyolysis	1 (0.2)	0
Musculoskeletal chest pain	0	1 (0.2)
Renal and urinary disorders	2 (0.5)	3 (0.7)
Urinary bladder polyp	1 (0.2)	0
Diabetic nephropathy	0	1 (0.2)
Renal failure acute	1 (0.2)	0
Renal failure chronic	0	2 (0.5)
Nephrolithiasis	0	1 (0.2)
Reproductive system and breast disorders	1 (0.2)	0
Metrorrhagia	1 (0.2)	0
General disorders and administration site conditions	1 (0.2)	1 (0.2)
Non-cardiac chest pain	1 (0.2)	1 (0.2)
Injury, poisoning and procedural complications	2 (0.5)	4 (1.0)
Meniscus lesion	1 (0.2)	0
Toxicity to various agents	0	1 (0.2)
Subdural hematoma	0	1 (0.2)
Fall	1 (0.2)	1 (0.2)
Head injury	0	1 (0.2)
Airway complication of anesthesia	0	1 (0.2)

SUPPLEMENTARY DATA

Supplementary Figure 1. Participant flow diagram.
HbA_{1c}=glycated hemoglobin A_{1c}. mITT=modified intention to treat.



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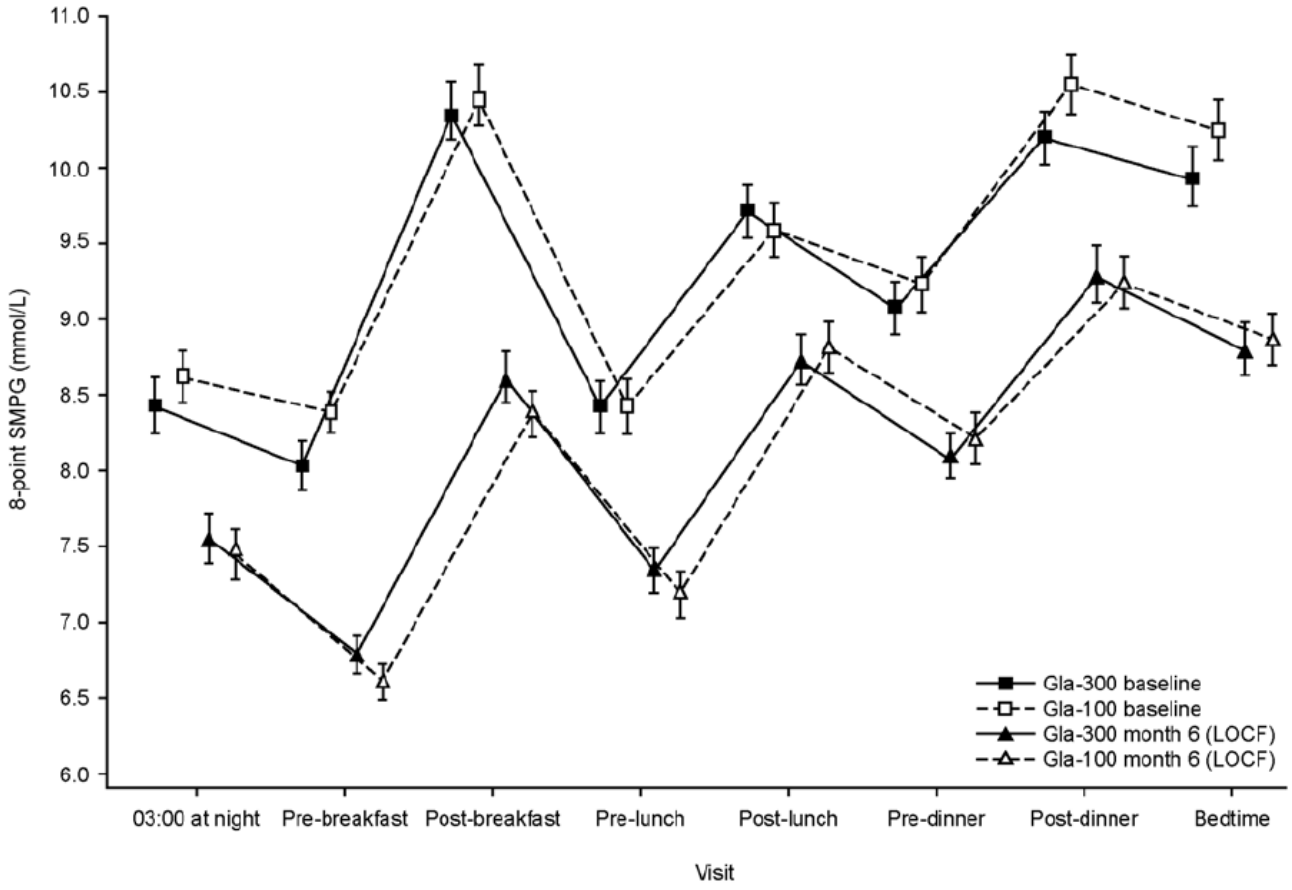
Supplementary Figure 2. Eight-point SMPG profile at baseline and at the end of treatment in the modified intent-to-treat population.
LOCF=last observation carried forward. SMPG=self-measured plasma glucose.



SUPPLEMENTARY DATA

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Protocol summary: 6-month, multicenter, randomized, open-label, parallel-group study comparing the efficacy and safety of a new formulation of insulin glargine and Lantus® both plus mealtime insulin in people with type 2 diabetes mellitus with a 6-month safety extension period (EDITION 1; NCT01499082)

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Study centers
Canada (2 centers), Czech Republic (10 centers), Estonia (6 centers), Finland (3 centers), France (2 centers), Germany (3 centers), Hungary (17 centers), Latvia (6 centers), Mexico (5 centers), The Netherlands (8 centers), Romania (9 centers), South Africa (7 centers), USA (95 centers).

Background
Long-acting basal insulin analogues, such as insulin glargine 100 U/mL (Gla-100) have significantly contributed to diabetes management over the last decade. The new insulin glargine 300 U/mL (Gla-300) has a flatter and more prolonged profile than Gla-100 and may further improve safety and tolerability.

Aims
The trial was conducted to compare the efficacy of the new insulin glargine Gla-300 with Gla-100 in people with type 2 diabetes receiving basal plus mealtime insulin in terms of change in HbA_{1c} and occurrence of nocturnal hypoglycemia from baseline to month 6.

Design
The study was a multicenter, randomized, open-label, parallel-group phase 3 study consisting of a ≤2 week screening period, a main 6-month treatment period, a 6-month on-treatment safety extension period, and a 4-week post-treatment follow-up period in a subset of participants. An additional 3-month substudy after the main 6-month study period was carried out in a subset of participants randomized and treated with Gla-300 to investigate the effect of adapting the interval between doses (24 ± 3 hour) vs a fixed 24 hour interval between doses. Adults (≥18 years) with type 2 diabetes and a HbA_{1c} level of 7–10 % using basal (≥42 U/day) plus mealtime insulin and self-monitoring their blood glucose were eligible for inclusion in the study. The key exclusion criteria were: ≤1 year on combined basal and mealtime insulin; using regular human insulin as a mealtime insulin in the 3 months, initiation of a new glucose-lowering therapy in 3 months or using an insulin pump in the 6 months before the screening visit; history or presence of significant diabetic retinopathy or macular edema requiring treatment or surgery and current; planned pregnancy during the study period. Participants were randomized to once-daily Gla-300 or Gla-100 taken in the evening in addition to their regular mealtime insulin (and metformin if required).

Randomization
Participants were randomized to Gla-300 or Gla-100 in a 1:1 ratio. Randomization was stratified by HbA_{1c} value at the screening stage prior to study commencement to guarantee a minimum of 20% randomized participants in each group per HbA_{1c} stratum.

SUPPLEMENTARY DATA

Primary and secondary endpoints

The primary endpoint was change in HbA_{1c} from baseline to month 6. The key secondary endpoints were: the incidence of participants with at least one confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe nocturnal hypoglycemic event between the start of week 9 and month 6, change in pre-injection plasma glucose and change in variability of pre-injection plasma glucose from baseline to month 6. Additional secondary endpoints were: percentage of participants with HbA_{1c} <7 % at month 6; change in fasting plasma glucose (FPG) between baseline and month 6; percentage of participants with FPG <100 mg/dL at month 6; change in 8-point self-monitored plasma glucose (SMPG) profile per timepoint from baseline to month 6; change in daily basal insulin dose from baseline to month 6 and change in treatment satisfaction score using the Diabetes Treatment Satisfaction Questionnaire (DTSQs) from baseline to month 6.

Analysis of safety and tolerability was based on the number of hypoglycemic events observed, local tolerability at injection site, hypersensitivity reactions, observed AEs and SAEs and other information including clinical laboratory data and vital signs such as body weight, 12-lead ECG and AIA results.

Statistics

A sample size of 800 evaluable participants was estimated to give 99% power for the upper confidence limit of the mean difference in change of HbA_{1c} between insulin formulations not to exceed 4.4 mmol/mol (0.4 %), assuming that the SD of change is 14.2 mmol/mol (1.3 %), for a true difference of 0.0 %.

Primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model with treatment, screening HbA_{1c} stratification (<8 % and ≥8 %) and country as fixed effects and baseline HbA_{1c} level as a covariate. Subgroup analyses were performed to assess consistency of treatment effect across baseline and demographic factors. Secondary endpoints were analyzed using analysis of variance (ANOVA), ANCOVA or Cochran-Mantel-Haenszel models as appropriate. No interim analyses were planned.

Ethics and trial registration

The study protocol and informed consent form were approved by local ethics committees and the trial was registered on the public registry website, www.clinicaltrials.gov in compliance with Sanofi public disclosure commitments. Each patient provided informed consent at study enrolment.

Study sponsor: Sanofi

Study start date: December 2011

Study end date: September 2013