New Medicine Assessment

Insulin Glargine 300 units/mL (Toujeo®▼)

Treatment of type 2 diabetes mellitus in adults

Recommendation: Amber 0

Insulin glargine 300 units/mL (Toujeo®) is recommended as an option in adults with type 2 diabetes mellitus (T2DM) only in accordance with the recommendations in NICE NG28 and in those who suffer from symptomatic nocturnal hypoglycaemia whilst being treated with a first-line long-acting insulin analogue.

In T2DM NICE NG28 recommends that when insulin is necessary, NPH (isophane) insulin is the preferred option unless the patient meets specific HbA1c or lifestyle criteria. Insulin detemir or insulin glargine can be considered as an alternative in those who require assistance to inject insulin and the use of these insulins would decrease the frequency of injections from twice to once daily or the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.

Patients should be considered for switching to insulin detemir or insulin glargine from NPH insulin in adults who fail to achieve adequate glycaemic control or continue to suffer from recurrent episodes of hypoglycaemia or cannot use the device but could if switched to one of the long-acting insulin analogues or who require assistance with insulin injections and for whom one of the long-acting insulin analogues would reduce the number of daily injections.

Insulin glargine 300 units/mL (Toujeo®) was non-inferior to insulin glargine 100 units/mL (Lantus®) for glycaemic control in three phase 3 trials, and significantly reduced the risk of confirmed or severe nocturnal hypoglycaemic events in the two trials that enrolled patients who were insulin-experienced.

Summary of supporting evidence:

- Insulin glargine 300 units/mL (Toujeo®) was non-inferior to insulin glargine 100 units/mL (Lantus®) for glycaemic control in three open-label phase 3 RCTs (Edition 1, 2 and 3), spanning insulin experienced and insulin-naïve patients. There are no data available assessing the effect of Gla-300 on the long-term complications of diabetes, such as micro- or macro-vascular events.
- The main secondary endpoint of the trials was the proportion of patients with at least one confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6. Insulin glargine 300 units/mL (Toujeo®) was statistically superior to insulin glargine 100 units/mL (Lantus®) for this endpoint in Edition 1 and Edition 2 (insulin-experienced patients), but not in Edition 3 (insulin-naïve patients). There were too few severe hypoglycaemic events in either treatment arm to permit meaningful comparisons, and the definition of confirmed hypoglycaemic events in this endpoint was based on self-monitored plasma glucose

≤3.9mmol/L, irrespective of whether this was symptomatic or not. The actual differences in rates of these events are small (<2 per patient per year) and as serious events were so rare, the clinical significance of these is unclear.

- Data from trial extension periods indicate the effect of insulin glargine 300 units/mL (Toujeo®) on glycaemic and other endpoints is maintained at 12 months. Small sub-studies in Edition 1 and 2 observed only small differences in HbA1c, and comparable rates of nocturnal and anytime hypoglycaemic events when administration of insulin glargine 300 units/mL (Toujeo®) was permitted to vary from the usual administration time by +/- 3 hours.
- It is suggested that the high strength formulation of insulin glargine may reduce the number of volume of injections and may be less painful in patients with large daily insulin requirements; however, there is no evidence from RCTs that injections were less painful with insulin glargine 300 units/mL (Toujeo®), and as the marketed pen device limits delivery to 80 units per injection, type 2 diabetes patients with large daily insulin requirements may still require more than one injection, which may negate this advantage. Collectively, it is not clear that insulin glargine 300 units/mL (Toujeo®) represents an innovative step-change in treatment and patient experience, or significantly addresses an unmet need.
- The frequency and pattern of adverse events were similar for insulin glargine 100 units/mL (Lantus®) and glargine 300 units/mL (Toujeo®) and there were no new safety signals with for injection site reactions, hypersensitivity, malignancy, or hepatic or cardiovascular events.
- An MHRA Drug Safety Update includes guidance to reduce the risk of possible medication errors that could occur with the availability of new high strength formulations of insulins, such as insulin glargine 300 units/mL (Toujeo®). This includes brand name prescribing, specifying the concentration, along with the recommended dose in units.
- Insulin glargine 300 units/mL (Toujeo®) is not bioequivalent with insulin glargine 100 units/mL (Lantus®) or other long-acting insulin analogues; in the Edition 1, 2 and 3 trials, patients with type 2 diabetes typically required a 10% greater number of units per day of insulin glargine 300 units/mL (Toujeo®) to achieve comparable glycaemic control with insulin glargine 100 units/mL (Lantus®).
- Should that insulin glargine 300 units/mL (Toujeo®) be used instead of the biosimilar insulin glargine 100 units/mL (Abasaglar®), this could potentially increase prescribing budgets by £60-£120 per patient per year.

Details of Review

Name of medicine (generic & brand name)**:** Insulin glargine 300 units/mL (Toujeo®) solution for injection [SANOFI]
Strength(s) and form(s): Insulin glargine 300 units/mL solution for injection in a pre-filled pen
Dose and administration: Insulin glargine is a basal insulin for once-daily administration at any time of the day, preferably at the same time every day. The dose regimen (dose and timing) should be adjusted according to individual response. The potency of this medicinal product is stated in units. These units are exclusive to Toujeo and are not the same as IU or the units used to express the potency of other insulin analogues
BNF therapeutic class / mode of action 6.1.1 Insulins / 6.1.1.2 Intermediate- and long-acting insulins
Licensed indication(s): Treatment of diabetes mellitus in adults
Proposed use (if different from, or in addition to, licensed indication above): This New Medicines Assessment considers use of insulin glargine 300 units/mL in patients with type 2 diabetes mellitus only
Course and cost: 3 x 1.5 mL SoloStar pre-filled pen=£33.13. Dose titration according to individual requirements
Current standard of care/comparator therapies: Other long-acting insulin analogues: Insulin glargine 100 units/mL Insulin detemir 100 units/mL Insulin degludec 100 unit/mL or 200 units/mL
Relevant NICE guidance: NICE NG28: Type 2 diabetes in adults: management (2015)

Background and context

The current NICE guideline on Type 2 diabetes in adults: management, NG28 [1], recommends that if insulin therapy is required, it should be chosen from a number of insulin types and regimens:

- Offer NPH insulin injected once or twice daily according to need.
- Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75mmol/mol [9.0%] or higher), administered either
    - separately **or**
    - as a pre-mixed (biphasic) human insulin preparation.
- Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if:
    - the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily **or**
    - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or**
    - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:
    - a person prefers injecting insulin immediately before a meal **or**
    - hypoglycaemia is a problem **or**
    - blood glucose levels rise markedly after meals

The NICE NG28 recommends that switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:

- who do not reach their target HbA1c because of significant hypoglycaemia **or**
- who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached **or**
- who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made **or**
- who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections.

Insulin glargine 300 units/mL (Toujeo®, Gla-300) is a recently-licensed, high strength formulation of the original insulin glargine 100 units/mL (Lantus®, Gla-100). The high strength formulation aims to reduce the number and/or volume of injections in people who have large insulin requirements; however, due to differences in their bioavailabilities, Gla-300 is not interchangeable on a per unit basis with Gla-100 or other long-acting insulin analogues [3].

GLa-300 is licensed for use in patients with type 1 or type 2 diabetes mellitus [3]. This New Medicine Assessment considers evidence for its use in patients with type 2 diabetes mellitus.

Summary of evidence

Summary of efficacy data in proposed use:

Key efficacy data in type 2 diabetes are available from three phase 3 randomised controlled trials (RCTs) (Edition 1, 2 and 3), which compared Gla-300 against Gla-100 [4-9]. Details of each trial are provided in **Table 1**, with a summary provided below. There are no trials comparing Gla-300 against other long-acting insulin analogues, and there are no data assessing the effect of Gla-300 on the long-term complications of diabetes, such as micro- or macro-vascular events.

Trial designs: Edition 1, 2 and 3 were large (n>800) phase 3, open-label trials that assessed the non-inferiority of Gla-300 against Gla-100 through an initial six-month treatment period. Each trial included an open-label six-month extension to provide a total of 12 months of comparative data. Edition 1 and 2 included a small sub-study of flexible Gla-300 dosing during the first three-months of their extension periods (not included in the published papers) [4].

Populations: The trials were conducted in three distinct populations of adults with Type 2 diabetes with HbA1c >53 mmol/moL (7.0%). Edition 1 enrolled patients treated with basal insulin (≥42 units/day) plus mealtime insulin [5]. Edition 2 enrolled patients treated with basal insulin (≥42 units/day) plus oral antidiabetic agents (OADs) [7]. Edition 3 enrolled insulin-naïve patients treated with OADs [9].

Interventions and Comparators: Patients in all trials were randomised (1:1) to once-daily Gla-300 or Gla-100, dosed using pre-filled pens at the same time of day for each individual in a period from before their evening meal to bedtime [5-9]. Insulin dose was generally adjusted weekly, aiming for a fasting self-monitored plasma glucose of 4.4-5.6 mmol/L, and adjustments were restricted by the protocol to changes divisible by 3 units. The pre-filled pens used for Gla-300 differed to the marketed device. In the three-month sub-study during the six-month extension periods of Edition 1 and 2, around 100 patients on Gla-300 were randomised (1:1) to the same fixed dosing time or to more flexible dosing (+/- 3 hours).

Outcomes: For the primary endpoint in all three trials, Gla-300 was non-inferior to Gla-100 for the mean change from baseline to six-months in HbA1c. The main secondary endpoint was the proportion of patients with at least one confirmed (self-monitored plasma glucose [SMPG] ≤3.9 mmol/L) or severe (needing assistance) nocturnal hypoglycaemic event (between the hours of midnight and 05:59), recorded between week 9 and month 6. Gla-300 was superior to Gla-100 for this endpoint in Edition 1 and 2, but not in Edition 3. Annualised event rates per participant year were consistent with these. There was no significant difference in the proportion of patients with confirmed or severe hypoglycaemic events throughout the whole 24 hours of the day in any of the three trials [5,7,9]. Gla-300 and Gla-100 were broadly comparable for exploratory endpoints, including proportion of patients achieving HbA1c <53 mmol/mol (7.0%) and weight changes.

Data from the trial extension periods indicated the effect of Gla-300 on HbA1c and other endpoints is maintained at 12 months [4,6,8]. The small sub-studies in Edition 1 and 2 observed only small differences in HbA1c, and comparable rates of nocturnal and anytime hypoglycaemic events, between more flexible and fixed Gla-300 dosing [4]. Over time, patients required more units of Gla-300 basal insulin compared with Gla-100-treated patients [4-9].

Other efficacy data:

A patient-level meta-analysis of six-month data from the Edition 1, 2 and 3 trials, sponsored by the manufacturer, has been published [10]. Based on pooling of the data from the three different trial populations, this concludes Gla-300 provides comparable glycaemic control to Gla-100, but with lower rates of confirmed or severe hypoglycaemia, and documented symptomatic hypoglycaemia, at any time of day and at night across the whole six month treatment period, and in the first eight weeks of treatment initiation. It also estimated significantly less weight gain with Gla-300 compared with Gla-100 (least squares mean difference −0.28, 95% CI −0.55 to −0.01; p=0.039) [10].

Summary of safety data:

The European Public Assessment Report (EPAR) concluded that the safety profile of Gla-300 is largely similar to that of Gla-100, with some evidence of a reduction in hypoglycaemia events in patients with type 2 diabetes [4], as noted above. The frequency and pattern of adverse events was similar and there were no new safety signals with Gla-300 for injection site reactions, hypersensitivity, malignancy, or hepatic or cardiovascular events. Treatment emergent adverse events were reported in 57.3% with Gla-300 and 53.7% with Gla-100, and few patients discontinued treatment due to treatment emergent adverse events (1.4% with Gla-300, 1.3% with Gla-100).

The potential for medication errors with the availability of a high strength formulation of insulin glargine is discussed below.

Strengths and limitations of the evidence:

Overall study design:

- The EMA considered the Edition 1, 2 and 3 trials to be sufficient to assess the non-inferiority of Gla-300 against Gla-100 [4].
- The open-label design was necessary due to differences in the pen devices, but may be associated with potential bias in either direction. The vast majority of patients in Edition 1 and 2 had prior experience with Gla-100 and so may have favoured a familiar device or, alternatively, the newer, high strength Gla-300 may have been perceived as an improved product. However, primary and other key endpoints are based largely on objective rather than subjective measures. Other than this, the trials appear to have good internal validity (Table 1).

Population:

- Patients enrolled in the Edition 1, 2 and 3 trials reflect broad populations of patients with Type 2 diabetes, ranging from those with long experience of insulin treatment through to insulin-naïve patients.
- None of the trials required patients to have particular issues with recurrent or severe

hypoglycaemia or problems injecting their insulin, as is required for use of long-acting insulin analogues in the current NICE clinical guideline [1].

- Edition 1 and 2 enrolled patients requiring at least 42 units of basal insulin 100units/mL; however, the mean baseline basal insulin doses were 65-70 units per day, which increased over the six-month treatment to in excess of 80 units per day for Glar-100 and to up to 103 units per day for Gla-300.

Intervention & Comparator:

- Gla-300 was dosed in Edition 1, 2 and 3 using a modified pen device, which only permitted dose adjustment in multiples of 3 units. Accordingly, dose titration and adjustment was protocol driven for both Gla-300 and Gla-100 [5,7,9]. As with the Gla-100 pen device, the marketed device for Gla-300 permits dose adjustment down to 1 unit.
- The three trials required patients to administer their basal insulin at the same time each day. Sub-studies of Edition 1 and 2 provide evidence that, when needed, patients may administer Gla-300 three hours before or after their usual administration time; however, these are limited by their short duration, in small numbers of patients, who had six months of experience with Gla-300.
- The required basal insulin dose increased throughout all three trials, but more so for patients treated with Gla-300. In Edition 1 and 2, in insulin experienced patients, the mean number of units/day of both Gla-300 and Gla-100 exceeded the maximum single dose deliverable with their respective marketed pen devices. (Gla-300 can deliver 80 units, and Gla-100 can deliver 60 units in one injection. The daily doses of basal insulin were greater than this in the Edition 1 and 2 trials by month 6).
- There are no trials comparing Gla-300 against other long-acting insulin analogues.

Outcomes:

- Outcomes data are limited to short-term measures of glycaemic control and hyperglycaemic symptoms; there are no data assessing the effect of Gla-300 on the long-term complications of diabetes, such as micro- or macro-vascular events.
- Gla-300 was consistently demonstrated to be non-inferior to Gla-100 for glycaemic control in the Edition trials, as may be expected from their “treat-to-target” protocols. The upper bound of the 95% confidence interval for the difference in the mean change from baseline in HbA1c was well within the pre-defined non-inferiority margin (0.4%) and the stricter margin (0.3%) that is now recommended [4]. The analysis was conducted using a modified intention-to-treat population, with last observation carried forward for missing data, which may bias the analysis towards equivalence [11]; a confirmatory per protocol analysis was not provided. In order to obtain a similar effect on HbA1c, the required dose of Gla-300 was approximately 10% higher than the Gla-100 dose [4].
- The main secondary endpoint of the trials was the proportion of patients with at least one confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6. Gla-300 was statistically superior to Gla-100 for this endpoint in Edition 1 and Edition 2 (insulin-experienced patients), but not in Edition 3 (insulin-naïve patients). There were too few severe hypoglycaemic events to permit meaningful comparisons, and the definition of

confirmed hypoglycaemic events in this endpoint was based on an SMPG ≤3.9 mmol/L, irrespective of whether this was symptomatic or not. A significant difference in rates of documented symptomatic hypoglycaemic events was observed in Edition 1, but not in Edition 2, between week 9 and month 6.

- When considered across the entire 6 month treatment period (including the initial eight-week treatment period in which dose titration was greatest), or when considered as annualised event rates per patient, nocturnal confirmed or severe hypoglycaemia remained lower with Gla-300 than Gla-100 in Edition 1 and 2 and was also lower in Edition 3. However, the actual differences in these event rates are small (<2 per patient per year) and as serious events were so rare, the clinical significance of these is unclear. Nonetheless, the EPAR considers these exploratory analyses support a lower risk of hypoglycaemia with Gla-300 in type 2 diabetes, particularly in those who are insulin experienced [4]. The lower rates of nocturnal hypoglycaemia were not accompanied by a significantly higher rate of daytime hyperglycaemic events.

Summary of evidence on cost effectiveness:

No published cost effectiveness analyses of Gla-300 of relevance to the UK have been identified.

The Scottish Medicines Consortium (SMC) assessed Gla-300 for the treatment of both type 1 and type 2 diabetes via its abbreviated submission process [12]. For patients with type 2 diabetes, SMC accepted Gla-300 for restricted use in NHS Scotland, in patients who suffer from recurrent episodes of hypoglycemia or require assistance with their insulin injections. Few details are provided; however, Gla-300 was considered to have similar efficacy, and at doses that provide comparable glycaemic control, is available at a similar cost to Gla-100 [12].

Prescribing and risk management issues:

Gla-300 is not bioequivalent to other long-acting insulin analogues, and Gla-300 is not interchangeable with Gla-100 or other insulins on a per unit basis. An MHRA Drug Safety Update includes guidance to reduce the risk of possible medication errors that could occur with the availability of new high strength formulations of insulins, such as Gla-300 [13]. This includes brand name prescribing, specifying the concentration, along with the recommended dose in units.

Switching between Gla-300 and Gla-100 requires dose adjustment and close blood glucose monitoring is recommended during switching and in the initial weeks thereafter [3].

Commissioning considerations:

Comparative unit costs:

Current NICE guidance recommends that if insulin is required in patients with type 2 diabetes, this should normally be initiated with twice daily NPH. Long-acting insulin analogues may be considered as an alternative if there are issues with injection frequency, need for assistance with injections or problemati hypoglaycaemia with NPH [1]. The availability of Gla-300 would not change this recommendation, and therefore, comparators to Gla-300 would be other long-acting insulin analogues, when used in line with the NICE recommendations.

Insulin dosing is individually tailored to patients. **Table 2** therefore provides only illustrative examples of acquisition costs for comparable dosing, assuming 50 to 100 units of Gla-300 daily to reflect the range of Gla-300 doses observed at 6 months in the Edition 1, 2 and 3 trials [5, 7, 9], and accounting for the fact that patients in these trials required approximately 10% more units of Gla-300 compared with Gla-100 to achieve comparable glycaemic control [4]. On this basis, Gla-300 has similar costs to the Lantus® brand of Gla-100 and to insulin detemir (Levemir®). A biosimilar version of Gla-100 (Abasaglar®) is available at a lower cost per (comparable) dose than other long-acting insulin analogues.

Table 2. Example annual acquisition costs of Gla-300 and other long-acting insulin analogues that may be used as basal insulins in patients with Type 2 diabetes

Drug	Example regimen	Pack costs	Cost per patient per year (ex VAT)	Difference in cost per patient per year (ex VAT)
Insulin glargine 300 units/mL (Toujeo®) pre-filled pen	**50-100 units once daily**	**3 x 1.5ml pre-filled pen: £33.13**	**£448 to £896**	**-**
Insulin glargine 100 units/mL (Lantus®)	45-90 units once daily	5 x 3ml pre-filled pen: £41.50	£454 to £909	-£6 to -£13
Biosimilar insulin glargine 100 units/mL (Abasaglar®)		5 x 3ml pre-filled pen: £35.28	£386 to £773	+£62 to +£123
Insulin detemir 100 units/mL (Levemir®)		5 x 3ml pre-filled pen: £42.00	£459 to £919	-£11 to -£23
Insulin degludec 100 units/mL (Tresiba®)*		5 x 3ml pre-filled pen: £72.00	£788 to £1,575	-£340 to -£679
Insulin degludec 200 units/mL (Tresiba®)**		3 x 3ml pre-filled pen: £86.40	£788 to £1,577	-£340 to -£679

Costs based on MIMS list prices October 2015
*Insulin degludec 100 units/mL is not recommended for use by the Lancashire Medicines Management Group
** Insulin deguldec 200 units/mL is restricted for use for West Lancashire and not recommended for use by the Lancashire Medicines Management Group.
This table does not imply therapeutic equivalence of drugs or doses. See respective Summaries of Product Characteristics for full dosing details

Associated additional costs or available discounts:

No associated additional costs are anticipated. No discounts are currently known.

Productivity, service delivery, implementation:

No impact is anticipated on productivity or service delivery. No specific requirements for implementation are envisaged.

Anticipated patient numbers and net budget impact:

High strength insulin products have been developed for patients with large daily insulin requirements to reduce the number and volume of injections [13]. Estimation of the number of patients with type 2 diabetes who would be potential candidates for Gla-300 is difficult. A NICE Evidence Summary: New Medicine review of Gla-300 in the treatment of type 1 diabetes reports the manufacturer's estimates of uptake in both type 1 and type 2 diabetes over the next 5 years for England as follows: 2015 (734 people), 2016 (9994 people), 2017 (27,900 people), 2018 (65,386 people), 2019 (80,948 people) and 2020 (90,581 people); however, the methodology used to arrive at these estimates is unclear [14].

Crudely assuming that 90% of people with diabetes mellitus cases have type 2 diabetes [4], and extrapolating these figures to the populations of CCGs in Lancashire would produce the estimates of uptake of Gla-300 in **Table 3**.

Table 3. Crude estimates of uptake of Gla-300 in people with type 2 diabetes

CCG	2016	2017	2018	2019	2020
NHS BLACKBURN WITH DARWEN CCG	28	79	185	228	256
NHS BLACKPOOL CCG	28	79	186	230	258
NHS CHORLEY AND SOUTH RIBBLE CCG	29	82	193	239	267
NHS EAST LANCASHIRE CCG	62	173	404	501	560
NHS GREATER PRESTON CCG	35	97	228	282	315
NHS LANCASHIRE NORTH CCG	26	73	172	213	238
NHS WEST LANCASHIRE CCG	19	52	121	150	168
NHS FYLDE & WYRE CCG	25	70	163	202	226
ALL LANCASHIRE CCGs	252	705	1652	2045	2288

From **Table 2**, the annual acquisition cost of Gla-300, based on mean daily doses observed in the Edition 1, 2 and 3 trials at 6 months, is similar to the acquisition costs of the Lantus® brand of Gla-100 and insulin detemir. The use of Gla-300 instead of these products in the above patients would therefore have an approximately neutral impact on prescribing budgets.

Should Gla-300 be used instead of the biosimilar Gla-100 (Abasaglar®) in the above patients, this could potentially increase prescribing budgets by £60-120 per patient per year.

The availability of Gla-300 should not influence the proportion of patients who would be treated with NPH as per NICE NG28 [1].

Innovation, need, equity:

Gla-300 is a high strength formulation of insulin glargine, which it is suggested may reduce the number of volume of injections and may be less painful in patients with large daily insulin requirements [4,13]. There is no evidence from the clinical trials that injections were less painful with Gla-300 compared with Gla-100, and as the marketed pen device limits delivery to 80 units per injection, type 2 diabetes patients with large daily insulin requirements may still require more than one injection, which may negate this advantage [4].

The EPAR considers Gla-300 has a lower risk of hypoglaycaemia compared with Gla-100 in patients with type 2 diabetes [4]. However, the actual differences in these event rates are small (<2 per patient per year) and as serious hypoglycaemic events were so rare with both Gla-300 and Gla-100, the clinical significance of these lower rates of hypoglycaemia observed with Gla-300 in the Edition trials is unclear.

In summary, it is not clear that Gla-300 represents an innovative step-change in treatment and patient experience, or significantly addresses an unmet need. There are no anticipated equity considerations.

References

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Table: Summary of key insulin glargine 300 unit/mL RCTs in type 2 diabetes mellitus

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Edition 1: Basal insulin and meal time insulin						
[5]	Open-label, randomised, 6-month, phase 3 trial Inclusion criteria: • Adults with T2DM • Use of basal and meal time insulin • Basal insulin ≥42 units/day • HbA1c 53 to 86mmol/mol (7.0 to 10.0%) Exclusions: • Human mealtime, or any non-glargine or non-NPH basal insulin • OADs other than metformin • Other injectable glucose-lowering agents • Other clinically important disease	• Mean age: 60 yrs • Male: 53% • White: 92% • Body weight: 106kg • Median T2DM duration: 16 yrs • Insulin duration: 6.5 yrs • Basal insulin dose: 0.67 units/kg/day; 70 units/day • Mealtime insulin dose: 0.54 units/kg/day; 57.5 units/day • Prior glargine use: 92% • Prior metformin use: 57% • HbA1c: 65.6 mmol/mol (8.15%)	• Insulin glargine 300 units/mL (Gla-300) (n=404; 374 completed 6 months) vs. • Insulin glargine 100 units/mL (Gla-100) (n=403; 372 completed 6 months) All dosed once daily at the same time for each individual from before dinner to bedtime, via pre-filled pens Initial doses determined by pre-randomisation dose Target pre-breakfast SMPG 4.4-5.6mmol/L	HbA1c change from baseline (least squares mean): Gla- 300: -9.1mmol/mol (-0.83%) GLa-100: -9.1mmol/mol (-0.83%) Difference: -0.00mmol/mol (95% CI -1.2 to 1.2) -0.0% (95%CI -0.11 to 0.11) **Non-inferiority criterion of <4.4mmol/mol (<0.4%) for upper bound of 95%CI met**	% with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events (week 9 to month 6): Gla-300: 36% Gla-100: 46% RR 0.79 (95%CI 0.67 to 0.93), p=0.0045 % with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events (week 9 to month 6): Gla-300: 74.8% Gla-100: 77.6% RR 0.96 (95%CI 0.89 to 0.1.04), p=NS % with HbA1c <53mmol/mol (<7.0%): Gla-300: 39.6% Gla-100: 40.9% Change in basal insulin doses: Gla-300: 33 units Gla-100: 23 units Total daily insulin doses:	Patient-oriented outcome measure?:No Allocation concealment?: Yes Blinded if possible?: Not possible due to differences in pen devices Intention to treat analysis?: Yes, but for non-inferiority trials a per protocol analysis is also usually specified. This was not presented. Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes (92%) Level 3 evidence based on no long term patient-oriented outcomes Risk of bias: unclear due to open-label design and extensive prior experience

					Gla-300: 1.53 units/kg/day Gla-100: 1.43 units/kg/day Change in body weight: Gla-300: +0.9kg Gla-100: +0.9kg	with Gla-100; however, primary and other key endpoints are largely objective rather than subjective
[6]	6-month pre-planned extension to above trial		• Insulin glargine 300 units/mL (Gla-300) (n=404 at baseline; 359 completed 12 months) vs. • Insulin glargine 100 units/mL (Gla-100) (n=403 at baseline; 355 completed 12 months)	Mean HbA1c at 12 months: Gla-300: 55.6mmol/mol (7.24%) Gla-100: 57.6mmol/mol (7.42%) Least squares mean difference: -1.9mmol/mol (95%CI -3.2 to -0.5) −0.17% (95% CI −0.30 to −0.05); p=0.007	% with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events (week 9 to month 12): Gla-300: 54% Gla-100: 65% RR 0.84 (95%CI 0.75 to 0.94) Annualised rates of confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events: Gla-300: 2.88 events ppy Gla-100: 3.19 events ppy RR 0.90 (95%CI 0.70 to 1.16); p=NS % with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events (week 9 to month 6): Gla-300: 85.9% Gla-100: 91.5% RR 0.94 (95%CI 0.89 to 0.99) Annualised rates of confirmed (≤3.9mmol/L) or severe	As above Greater potential for biased reporting of safety and efficacy when patients are not followed up as closely by investigators

					(needing assistance) anytime hypoglycaemic events: Gla-300: 22.34 events ppy Gla-100: 20.99 events ppy RR 1.06 (95%CI 0.89 to 1.27); p=NS Change in body weight: Gla-300: +1.2kg Gla-100: +1.4kg; p=NS	
Edition 2: Basal insulin and OADs						
[7]	Open-label, randomised, 6-month, phase 3 trial Inclusion criteria: • Adults with T2DM • Use of basal insulin and OADs • Basal insulin ≥42 units/day • HbA1c 53 to 86mmol/mol (7.0 to 10.0%) Exclusions: • Premixed insulins, insulin detemir or new glucose lowering agents • Human or mealtime insulin • Sulphonylurea use in previous 2 months • Other clinically significant disease	• Mean age: 58 yrs • Male: 46% • White: 94% • Body weight: 98kg • Mean T2DM duration: 13 yrs • Basal insulin duration: 3.8 yrs • Basal insulin dose: 0.67 units/kg/day; 65 units/day • Prior basal insulin glargine: 79% • Prior basal insulin NPH: 21% • Basal insulin once daily: 79% • Previous OAD treatment: Biguanides: 94% DPP4 inhibitors: 10% Sulphonylurea: 1.25% Thiazolidinediones: 2.5% Combinations: 1.9% • HbA1c: 66.5 mmol/mol	• Insulin glargine 300 units/mL (Gla-300) (n=404; 368 completed 6 months) vs. • Insulin glargine 100 units/mL (Gla-100) (n=407; 369 completed 6 months) All dosed once daily at the same time for each individual from before dinner to bedtime, via pre-filled pens Initial doses determined by pre-randomisation dose Target pre-breakfast SMPG 4.4-5.6mmol/L OAD continued at stable dose	HbA1c change from baseline (least squares mean): Gla- 300: -6.2mmol/mol (-0.57%) GLa-100: -6.1mmol/mol (-0.56%) Difference: -0.1mmol/mol (95% CI -1.5 to 1.3) -0.01% (95%CI -0.14 to 0.12) **Non-inferiority criterion of <4.4mmol/mol (<0.4%) for upper bound of 95%CI met**	% with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events (week 9 to month 6): Gla-300: 21.6% Gla-100: 27.9% RR 0.77 (95%CI 0.61 to 0.99), p=0.038 % with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events (week 9 to month 6): Gla-300: 59.3% Gla-100: 65.0% RR 0.91 (95%CI 0.82 to 1.02), p=NS % with HbA1c <53mmol/mol (<7.0%): Gla-300: 30.6% Gla-100: 30.4% Change in basal insulin doses:	Patient-oriented outcome measure?:No Allocation concealment?: Yes Blinded if possible?: Not possible due to differences in pen devices Intention to treat analysis?: Yes, but for non-inferiority trials a per protocol analysis is also usually specified. This was not presented. Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes (91%) Level 3 evidence based on no long term patient-oriented outcomes

		(8.24%)			Gla-300: +0.28 units/kg/day Gla-100: +0.18 units/kg/day Change in body weight: Gla-300: +0.08kg Gla-100: +0.66kg; p=0.015	Risk of bias: unclear due to open-label design and extensive prior experience with Gla-100; however, primary and other key endpoints are largely objective rather than subjective
[8]	6-month pre-planned extension to above trial		• Insulin glargine 300 units/mL (Gla-300) (n=404 at baseline; 315 completed 12 months) vs. • Insulin glargine 100 units/mL (Gla-100) (n=403 at baseline; 314 completed 12 months)	Mean HbA1c at 12 months: Gla-300: 59.8mmol/mol (7.62%) Gla-100: 60.0mmol/mol (7.64%) Least squares mean difference: -0.66mmol/mol (95%CI -0.24 to 1.1) −0.06% (95% CI −0.22 to 0.10); p=NS	% with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events (week 9 to month 12): Gla-300: 38% Gla-100: 45% RR 0.84 (95%CI 0.71 to 0.99) Annualised rates of confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events: Gla-300: 1.77 events ppy Gla-100: 2.77 events ppy RR 0.63 (95%CI 0.42 to 0.96); p=0.0308 % with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events (week 9 to month 6): Gla-300: 78% Gla-100: 82% p=NS Annualised rates of confirmed	As above Greater potential for biased reporting of safety and efficacy when patients are not followed up as closely by investigators

					(≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events: Gla-300: 11.6 events ppy Gla-100: 13.2 events ppy; p=NS Change in body weight: Gla-300: +0.4kg Gla-100: +1.2kg; p=0.009	
Edition 3: Insulin-naïve patients on OADs						
[9]	Open-label, randomised, 6-month, phase 3 trial Inclusion criteria: • Adults with T2DM • Use of OADs for ≥6 months • Insulin naive • HbA1c 53 to 97mmol/mol (7.0 to 11.0%) Exclusions: • OADs not approved for use in combination with insulin were discontinued at baseline	• Mean age: 58 yrs • Male: 58% • White: 78% • Body weight: 95kg • Mean T2DM duration: 6.4 yrs • Previous OAD treatment: Metformin: 91% DPP4 inhibitor: 22% Sulphonylurea: 59% Thiazolidinediones: 2.5% • HbA1c: 69.8 mmol/mol (8.5%)	• Insulin glargine 300 units/mL (Gla-300) (n=439; 377 completed 6 months) vs. • Insulin glargine 100 units/mL (Gla-100) (n=439; 364 completed 6 months) All dosed once daily at the same time for each individual from before dinner to bedtime, via pre-filled pens Initial dose 0.2U/kg Target pre-breakfast SMPG 4.4-5.6mmol/L OAD continued at stable dose	HbA1c change from baseline (least squares mean): Gla- 300: -15.5mmol/mol (-1.42%) GLa-100: -16.0mmol/mol (-1.46%) Difference: 0.4mmol/mol (95% CI -1.0 to 1.9) 0.04% (95%CI -0.09 to 0.17) **Non-inferiority criterion of <4.4mmol/mol (<0.4%) for upper bound of 95%CI met**	% with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) nocturnal (0h to 0559h) hypoglycaemic events (week 9 to month 6): Gla-300: 16% Gla-100: 17% RR 0.89 (95%CI 0.66 to 1.20), p=NS % with ≥1 confirmed (≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events (week 9 to month 6): Gla-300: 40% Gla-100: 46% RR 0.86 (95%CI 0.74 to 1.00) Annualised rates of confirmed (≤3.9mmol/L) or severe (needing assistance) anytime hypoglycaemic events: Gla-300: 6.4 events ppy Gla-100: 8.5 events ppy; RR 0.75 (95%CI 0.57 to 0.99);	Patient-oriented outcome measure?: No (HRQoL measured as additional outcome) Allocation concealment?: Yes Blinded if possible?: Not possible due to differences in pen devices Intention to treat analysis?: Yes, but for non-inferiority trials a per protocol analysis is also usually specified. This was not presented. Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes (84%) Level 3 evidence based

					p=0.042 % with HbA1c <53mmol/mol (<7.0%): Gla-300: 43.1% Gla-100: 42.1% Change in body weight: Gla-300: +0.49kg Gla-100: +0.71kg Mean basal insulin dose at 6 months: Gla-300: 0.62 unis/kg/day Gla-100: 0.53 units/kg/day	on no long term patient-oriented outcomes Risk of bias: unclear due to open-label design; however, primary and other key endpoints are largely objective rather than subjective
HRQoL=health-related quality of life; NS=not significant; OADs=Oral anti-diabetic drugs; ppy=per participant-year; SMPG=self-monitored plasma glucose						

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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