**Table S1. Overview of key Gla-100 TTT clinical trials involving patients with T2DM with inadequate glycemic control on OADs alone.**

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| Study | Intervention | Efficacy and safety endpoints | Titration algorithm for Gla-100 | Outcomes |
| Fritsche A, *et al*. 2003 [1]  | Patients were randomized for 24 weeks to:* Morning Gla-100 plus glimepiride
* Bedtime NPH insulin plus glimepiride
* Bedtime Gla-100 plus glimepiride
 | **Efficacy:*** Change in HbA1c level from baseline to endpoint

**Safety:*** Frequency of patients experiencing hypoglycemic episodes
 | **Starting dose:** According to the formula of Holman and Turner [2]**Titration:** Conducted at every physician visit, based on whether patient’s FBG was greater than the below values for at least 1‒2 consecutive days prior to the physician visit**Target:** FBG ≤5.56 mmol/L**Algorithm:****FBG >5.6 mmol/L:** dose increased by 2 units**FBG >6.7 mmol/L:** dose increased by 4 units**FBG >7.8 mmol/L:** dose increased by 6 units**FBG >8.9 mmol/L:** dose increased by 8 units | **Efficacy:*** HbA1c levels improved by –1.24% with morning Gla-100, –0.96% with bedtime Gla-100, and by –0.84% with bedtime NPH insulin
* HbA1c improvements statistically greater with morning Gla-100 than the other treatment groups

**Safety:*** Nocturnal hypoglycemia less frequent with morning (17%) and bedtime Gla-100 (23%) than with bedtime NPH insulin (38%) (p <0.001)
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| The Treat-to-Target TrialRiddle MC, *et al.* 2003 [3]  | Overweight patients were randomized for 24 weeks to:* Bedtime Gla-100 with metformin
* Bedtime NPH with metformin
 | **Efficacy:*** Percentage of patients achieving HbA1c ≤7.0% without symptomatic nocturnal hypoglycemia (PG ≤4 mmol/L) and/or meeting criteria for severe hypoglycemia

**Safety:*** Overall rates of symptomatic hypoglycemia
 | **Starting dose:** 10 units/day**Titration:** Conducted weekly and based on the mean of SMFPG values from the preceding 2 days**Target:** FPG ≤5.5 mmol/L**Algorithm:****FPG 5.6–6.7 mmol/L:** dose increased by 2 units**FPG 6.7–7.8 mmol/L:** dose increased by 4 units**FPG 7.8–10.0 mmol/L**: dose increased by 6 units**FPG ≥10 mmol/L:** dose increased by 8 units  | **Efficacy:*** Nearly 25% more patients on Gla-100 attained HbA1c ≤7.0% without documented nocturnal hypoglycemia than with NPH (33.2% vs 26.7%; p <0.05)

**Safety:*** Rates of other categories of symptomatic hypoglycemia were 21–48% lower with Gla-100
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| LAPTOPJanka HU, *et al*. 2005 [4]  | Patients were randomized for 24 weeks to:* Morning Gla-100 plus glimepiride and metformin
* 70/30 premixed insulin b.i.d. without OADs
 | **Efficacy:*** Change in HbA1c level from baseline to endpoint

**Safety:*** Proportion of patients with hypoglycemic events
* Frequency of hypoglycemic events
 | **Starting dose:** 10 units/day**Titration:** Weekly adjustments for 8 weeks and at 2-week intervals thereafter, and based on daily SMCBG measurements using meters**Target:** FBG ≤5.6 mmol/L**Algorithm:****BG >100–120 mg/dL:** dose increased by 2 units**BG >120–140 mg/dL:** dose increased by 4 units**BG >140–160 mg/dL:** dose increased by 6 units**BG >160 mg/dL:** dose increased by 8 units | **Efficacy:*** Mean HbA1c decrease from baseline was significantly greater (–1.64% vs –1.31%; p = 0.0003) with Gla-100 plus OADs than with 70/30 premixed insulin
* More patients reached HbA1c ≤7.0% without confirmed nocturnal hypoglycemia (45.5% vs 28.6%; p = 0.0013) with Gla-100 plus OADs than with 70/30 premixed insulin

**Safety:*** Patients on Gla-100 plus OADs had fewer confirmed hypoglycemic episodes than those on 70/30 premixed insulin (mean 4.07 vs 9.87/patient-year; p <0.0001)
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| Eliaschewitz FG, *et al.* 2006 [5]  | Patients were randomized for 24 weeks to:* Glimepiride plus bedtime Gla-100
* Glimepiride plus bedtime NPH insulin
 | **Efficacy:*** Change in HbA1c levels between baseline and the end of the study

**Safety:*** Symptomatic hypoglycemic events
 | **Titration:** Conducted daily and based on the highest SMFBG value of the last 2 consecutive days **Target:** FBG ≤5.5 mmol/L**Algorithm:****6.7 mmol/L ≥ FBG >5.5 mmol/L**: dose increased by 2 units**7.8 mmol/L ≥ FBG >6.7 mmol/L**: dose increased by 4 units**8.9 mmol/L ≥ FBG >7.8 mmol/L**: dose increased by 6 units**FBG >8.9 mmol/L**: dose increased by 8 units  | **Efficacy:*** Similar HbA1c reductions achieved (–1.38 ± 1.32% for Gla-100 vs –1.44 ± 1.33% for NPH insulin; p = 0.795)

**Safety:*** Confirmed nocturnal hypoglycemia significantly lower with Gla-100 vs NPH insulin (16.9% vs 30.0%; p <0.01)
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| TRIPLERosenstock J, *et al.* 2006 [6]  | Patients were randomized for 24 weeks to:* Bedtime Gla-100 with continued sulfonylurea and metformin
* Rosiglitazone with continued sulfonylurea and metformin
 | **Efficacy:*** Comparison of glycemic control (measured by HbA1c) between Gla-100 and rosiglitazone

**Safety:*** AEs
* Hypoglycemia
* Body weight
 | **Starting dose:** 10 units/day**Titration:** Done weekly and based on FPG and monitored BG meter levels for the previous 2 consecutive days along with no severe hypoglycemia or BG (<4 mmol/l)**Target:** FPG ≤5.5–6.7 mmol/L**Algorithm:****6.7 mmol/L ≥ FPG ≥5.5 mmol/L:** dose increased by 0–2 units**7.8 mmol/L ≥ FPG ≥6.7 mmol/L:** dose increased by 2 units**8.9 mmol/L ≥ FPG ≥7.8 mmol/L:** dose increased by 4 units**10 mmol/L ≥ FPG ≥8.9 mmol/L:** dose increased by 6 units**FPG ≥10 mmol/L:** dose increased by 8 units | **Efficacy:*** Similar HbA1c improvements from baseline (–1.7% vs –1.5% for Gla-100 vs rosiglitazone, respectively)
* When baseline HbA1c was >9.5%, reduction in HbA1c with Gla-100 was greater than with rosiglitazone (p <0.05)

**Safety:*** More patients in the Gla-100 group had confirmed nocturnal hypoglycemia of <3.9 mmol/L (p = 0.02) and <2.8 mmol/L (p <0.05) than in the rosiglitazone group
* Patients on Gla-100 had fewer AEs than those on rosiglitazone (7% vs 29%;

p = 0.0001)* Patients on Gla-100 had less weight gain than with rosiglitazone (1.6 ± 0.4 vs 3.0 ± 0.4 kg; p = 0.02)
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| LANMETYki-Järvinen H, *et al.* 2006 [7]  | Patients were randomized for 36 weeks to:* Bedtime Gla-100 with metformin
* Bedtime NPH with metformin
 | **Efficacy:*** Change in HbA1c from baseline to endpoint

**Safety:*** Hypoglycemia
 | **Starting dose:** 10 units/day for patients who were using metformin alone, and 20 units/day for patients who had used both sulfonylurea and metformin (sulfonylurea was stopped as mandated by the study design)**Titration**: Based on FPG values for three consecutive mornings**Target:** FPG 4.0–5.5 mmol/L**Algorithm:****FPG >5.5 mmol/L:** dose increased by 2 units**FPG >10 mmol/L:** dose increased by 4 units  | **Efficacy:*** At 36 weeks, mean HbA1c was 7.14 ± 0.12% for Gla-100 and metformin, and 7.16 ± 0.14% for NPH and metformin; the difference between them was not significant

**Safety:*** Hypoglycemia was significantly lower during the first 12 weeks in the Gla-100 and metformin group (4.1 ± 0.8 episodes/patient-year) than in the NPH and metformin group (9.0 ± 2.3 episodes/patient-year; p <0.05), but not significantly different thereafter
* Glucose levels before dinner were higher in the NPH and metformin group (10.1 ± 0.3 mmol/L) than in the Gla-100 and metformin group (8.6 ± 0.3 mmol/L; p = 0.002) throughout the 36-week study
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| LEADPan CY, *et al*.2007 [8]  | Asian patients were randomized over 24 weeks to:* Bedtime Gla-100 plus glimepiride
* Bedtime NPH insulin plus glimepiride
 | **Efficacy:*** Change in HbA1c level from baseline to endpoint

**Safety:*** Hypoglycemic episodes
 | **Starting dose:** 0.15 units/kg/day**Titration:**Done at the discretion of the investigator, upwards by 2 units every 3 days until a target FBG of ≤6.7 mmol/L was achieved | **Efficacy:*** In the PP population HbA1c levels decreased in the Gla-100 and NPH groups (1.10% vs 0.92%), and difference between adjusted means (0.19%) demonstrated noninferiority
* In a superiority analysis, the difference between adjusted mean changes in the two groups was 0.22%, demonstrating the superiority of Gla-100 (p = 0.0319)

**Safety:*** Number of hypoglycemic episodes was significantly lower with Gla-100 vs NPH insulin (p <0.004), particularly severe (p <0.03) and nocturnal (p <0.001)
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| APOLLOBretzel RG, *et al.* 2008 [9]  | Patients were randomized for 44 weeks to:* Gla-100 taken once daily at the same time every day plus previous OAD(s)
* Insulin lispro administered three times per day plus previous OAD(s)
 | **Efficacy:*** Change in HbA1c from baseline to endpoint
* Baseline to endpoint changes in nocturnal BG
* BG profiles at eight points throughout the day

**Safety:*** The percentage of patients with nocturnal, severe, and symptomatic hypoglycemia
 | **Starting dose:** 10 units/day**Titration:** Conducted daily and based on SMFBG values for 2 consecutive days with no severe hypoglycemia**Algorithm:****FBG ≤5.5 mmol/L:** no titration needed**6.7 mmol/L ≥ FBG >5.5 mmol/L:** dose increased by 2 units**7.8 mmol/L ≥ FBG >6.7 mmol/L:** dose increased by 4 units**8.9 mmol/L ≥ FBG >7.8 mmol/L:** dose increased by 6 units**FBG >8.9 mmol/L:** dose increased by 8 units | **Efficacy:*** Mean HbA1c decrease in the Gla-100 group was –1.7% and –1.9% for insulin lispro (within the predefined limit of 0.4% for noninferiority)
* In the Gla-100 group, the fall in mean FBG (–4.3 mmol/L vs –1.8 mmol/L; p <0.0001) and nocturnal BG (–3.3 mmol/L vs –2.6 mmol/L;

p = 0.0041) was better than in the insulin lispro group* Insulin lispro better controlled postprandial BG throughout the day (p <0.0001)

**Safety:*** Incidence of hypoglycemic events was less with Gla-100 than with lispro (5.2 vs 24.0 events/patient-year; p <0.0001)
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| TULIPBlicklé JF, *et al.* 2009 [10]  | Patients were randomized for 9 months to:* Evening Gla-100 along with metformin and sulfonylurea
* Intensifying LM along with metformin and sulfonylurea
 | **Efficacy:*** Percentage of subjects achieving HbA1c <7% at the end of the study

**Safety:*** Occurrence of symptomatic hypoglycemia
* Change in weight between baseline and end of study
 | **Starting dose:** 0.1 units/kg/day**Titration**: Conducted based on FBG values from the last 2 consecutive days, as well as absence of severe hypoglycemic episodes or BG levels <3.9 mmol/L**Target:** FBG 3.9–5.5 mmol/L**Algorithm:****FBG <3.9 mmol/L:** dose reduced by 2–4 units**FBG ≥3.9 mmol/L:** no change in dose**FBG ≥5.5 mmol/L:** dose increased by 1 unit**FBG ≥6.7 mmol/L:** dose increased by 2 units**FBG ≥7.8 mmol/L:** dose increased by 4 units**FBG ≥8.8 mmol/L:** dose increased by 6 units | **Efficacy:*** More patients reached HbA1c <7% (66% vs 38%; p <0.0001) with Gla-100 vs LM

**Safety:*** Compared with the Gla-100 group, the LM group showed a decrease in weight (–0.9 ± 2.9 vs –2.5 ± 3.2 kg; p <0.0001), as well as lower symptomatic hypoglycemia (55.3% vs 25.0%; p <0.0001) and nocturnal hypoglycemia (20.4% vs 5.6%; p <0.0016)
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| L2T3Swinnen SG, *et al*. 2010 [11]  | Patients were randomized for 24 weeks to:* Gla-100 in the evening
* Insulin detemir b.i.d. at breakfast and dinner
 | **Efficacy:*** Percentage of patients reaching HbA1c <7% without symptomatic hypoglycemia (PG <3.1 mmol/L)

**Safety:*** Hypoglycemia
* Weight
* Insulin doses
 | Doses increased every 2 days by 2 units until FPG reached <5.6 mmol/L | **Efficacy:*** 27.5% and 25.6% of patients reached the primary outcome with Gla-100 and insulin detemir, respectively (noninferiority of Gla-100)

**Safety:*** Hypoglycemic risk similar between both treatment groups
* Weight gain higher for Gla-100 with a statistically significant increase of 0.77 kg
* Gla-100 doses lower than insulin detemir doses: 43.5 ± 29.0 vs 76.5 ± 50.5 units/day

(p <0.001) |
| EASIEAschner P, *et al*. 2012 [12]  | Patients were randomized for 24 weeks to:* Dinner/bedtime Gla-100 plus metformin
* Sitagliptin plus metformin
 | **Efficacy:*** Change in HbA1c from baseline to study end

**Safety:*** AEs reported by the patient or noted by the investigator
* Symptomatic hypoglycemia
 | **Starting dose:** 0.2 units/kg**Titration:** Conducted twice per week using the middle of the past three FPG values**Target:** 5.5 mmol/L ≥ FPG ≥4.0 mmol/L**Algorithm:****FPG <4.0 mmol/L with or without symptomatic hypoglycemia:** dose decreased by 2 units**FPG 5.6–7.7 mmol/L:** dose increased by 2 units**FPG >7.7 mmol/L**: dose increased by 4 units | **Efficacy:*** Adjusted mean reduction in HbA1c statistically greater (p <0.0001) for patients on Gla-100 (–1.72%) than for those on sitagliptin (–1.13%)

**Safety:*** Estimated rate of all symptomatic hypoglycemic episodes greater with Gla-100 than with sitagliptin (4.21 vs 0.50 events/patient-year; p <0·0001)
* 15 (6%) patients on Gla-100 versus 8 (3%) on sitagliptin had ≥1 serious TEAEs
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| EAGLED’Alessio D, *et al*. 2015 [13]  | Patients were randomized for 24 weeks to:* Gla-100 in combination with OADs and a lifestyle program
* Liraglutide in combination with OADs and a lifestyle program
 | **Efficacy:*** Percentage of subjects reaching HbA1c <7% at study end

**Safety:*** TEAEs reported by the patient or noted by the investigator
* Body weight
* Hypoglycemia
 | **Titration:** Done every 3 days and based on the intermediate FPG value of the past 3 days**Target:** FPG 4.0–5.5 mmol/L**Algorithm:****FPG ≤3.9 or symptomatic hypoglycemia:** dose decreased by 2 units**3.9 mmol/L < FPG ≤5.5 mmol/L:** no change in dose**5.5 mmol/L < FPG ≤7.7 mmol/L:** dose increased by 2 units**FPG >7.7 mmol/L:** dose increased by 4 units  | **Efficacy:*** Similar numbers of subjects in both groups attained HbA1c level <7% (48.4% vs 45.9%) and superiority of Gla-100 over liraglutide was not observed (p = 0.44)
* Subjects treated with Gla-100 had greater reductions of HbA1c (−1.94% vs −1.79%; p = 0.019)

**Safety:*** The liraglutide group reported a greater number of gastrointestinal TEAEs (p <0.001)
* The mean (SD) weight change was +2.0 (4.0) kg for Gla-100, and –3.0 (3.6) kg for liraglutide (p <0.001)
* Symptomatic hypoglycemia was more common with Gla-100 (p <0.001)
* A greater number of subjects in the liraglutide arm withdrew as a result of AEs (p <0.001)
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| LANCELOTHome PD, *et al*. 2015 [14]  | Patients were randomized for 36 weeks to:* Evening Gla-100 in combination with OADs
* Evening NPH insulin in combination with OADs

The protocol was designed to limit nocturnal hypoglycemia | **Efficacy:*** Change in HbA1c from baseline to study end

**Safety:*** Hypoglycemic episodes
 | **Starting dose:** 0.2 units/kg**Titration:** Conducted weekly during Weeks 1–4, twice weekly during Weeks 5–12, and then weekly up to Week 36 and based on the median of the last three pre-breakfast glucose measurements**Target:** Median pre-breakfast and NPG levels ≤5.5 mmol/L**For FPG *>*7.8 mmol/L:**NPG ≤4.4 mmol/L or symptomatic hypoglycemia: dose decreased by 2 units5.5 mmol/L ≥ NPG *>*4.4 mmol/L: no change in dose7.8 mmol/L ≥ NPG *>*5.5 mmol/L: dose increased by 2 unitsNPG *>*7.8 mmol/L: dose increased by 4 units**For 7.8 mmol/L ≥ FPG *>*5.5 mmol/L:**NPG ≤4.4 mmol/L or symptomatic hypoglycemia: dose decreased by 2 units5.5 mmol/L ≥ NPG *>*4.4 mmol/L: no change in dose7.8 mmol/L ≥ NPG *>*5.5 mmol/L: dose increased by 2 unitsNPG *>*7.8 mmol/L: dose increased by 2 units**For 5.5 mmol/L ≥ FPG *>*4.4 mmol/L:**NPG ≤4.4 mmol/L or symptomatic hypoglycemia: dose decreased by 2 unitsDose remained the same for the other NPG ranges**FPG ≤4.4 mmol/L or symptomatic hypoglycemia:** dose decreased by 2 units for all NPG ranges | **Efficacy:*** HbA1c values and the proportion of participants with HbA1c *<*7.0% were not significantly different for Gla-100 (7.1% and 50.3%) versus NPH (7.2% and 44.3%)

**Safety:*** The rate of symptomatic nocturnal hypoglycemia, confirmed by PG ≤3.9 or ≤3.1 mmol/L, was 29% and 48% less with Gla-100 than with NPH insulin, respectively

Even when titrating basal insulin to prevent nocturnal hypoglycemia, reduction was achieved in nocturnal hypoglycemia while attaining good glycemic control with Gla-100 compared with NPH |
| GALAPAGOSAschner P, *et al*. 2015 [15]  | Patients were randomized over 24 weeks to:* Dinnertime Gla-100 in combination with OADs and in certain patients with insulin glulisine
* Dinnertime/breakfast premixed insulin
 | **Efficacy:*** Proportion of patients achieving HbA1c <7.0% at the study end with no documented symptomatic hypoglycemia (confirmed by BG ≤3.1 mmol/L)

**Safety:*** Hypoglycemia
 | **Starting dose:** 0.2 units/kg**Titration:** Conducted every 3 days and based on the median of the last three SMBG values**Target:** SMFBG or premeal BG levels 4.4–5.5 mmol/L**Titration:****FPG <4.4 mmol/L or symptomatic hypoglycemia:** dose decreased by 2 units**5.5 mmol/L ≥ FPG *>*4.4 mmol/L:** no change in dose**7.8 mmol/L > FPG *>*5.6 mmol/L:** dose increased by 2 units**FPG >7.8 mmol/L:** dose increased by 4 units  | **Efficacy:*** HbA1c <7.0% with no documented symptomatic hypoglycemia was achieved by 33.2% of Gla-100 (± insulin glulisine) and 31.4% of premix patients. Superiority was not demonstrated, but noninferiority was (prespecified margin: 25% of premix rate)
* More patients using premixed insulin achieved target HbA1c <7% (52.6% vs 43.2%; p = 0.005)

**Safety:*** Symptomatic hypoglycemia was less with Gla-100 (1.17 vs 2.93 events/patient-year)
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AEs: adverse events; BG: blood glucose; b.i.d.: twice a day; FBG: fasting blood glucose; FPG: fasting plasma glucose; Gla-100: insulin glargine 100 U/mL; HbA1c: glycated hemoglobin; LM, lifestyle management; NPG: nocturnal plasma glucose; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic drug; PG: plasma glucose; PP: per-protocol; SD: standard deviation; SMBG: self-monitoring of blood glucose; SMCBG: self-monitored capillary whole blood glucose; SMFBG: self-monitored FBG; SMFPG: self-monitored FPG; T2DM: type 2 diabetes mellitus; TEAEs: treatment-emergent adverse events; TTT: treat-to-target.

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