**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) |
| The Treat-to-Target Trial  Riddle 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 |
| LAPTOP  Janka 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) |
| 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) |
| TRIPLE  Rosenstock 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) |
| LANMET  Yki-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 |
| LEAD  Pan 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) |
| APOLLO  Bretzel 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) |
| TULIP  Blicklé 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) |
| L2T3  Swinnen 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) |
| EASIE  Aschner 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 |
| EAGLE  D’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) |
| LANCELOT  Home 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 units  5.5 mmol/L ≥ NPG *>*4.4 mmol/L: no change in dose  7.8 mmol/L ≥ NPG *>*5.5 mmol/L: dose increased by 2 units  NPG *>*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 units  5.5 mmol/L ≥ NPG *>*4.4 mmol/L: no change in dose  7.8 mmol/L ≥ NPG *>*5.5 mmol/L: dose increased by 2 units  NPG *>*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 units  Dose 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 |
| GALAPAGOS  Aschner 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) |

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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