

SUPPLEMENTARY DATA

Supplementary Appendix

Supplementary Methods

Study Medication Administration

Following the run-in phase, patients with HbA_{1c} ≥ 7.0 and $\leq 9.0\%$ (≥ 53 and ≤ 75 mmol/mol) at week -1 with mean fasting self-monitored plasma glucose (SMPG) ≤ 7.8 mmol/L (≤ 140 mg/dL) over the 7 days before day 1 were randomized to receive lixisenatide once daily (QD) or insulin glulisine QD or thrice daily (TID). If HbA_{1c} was ≥ 7.0 and $\leq 8.0\%$ (≥ 53 and ≤ 64 mmol/mol) at week -1 , insulin glargine dose was reduced by 20% on the day before randomization to avoid hypoglycemia when starting add-on treatment.

Patients randomized to insulin glulisine QD were administered a starting dose of 3–5 U QD titrated by the investigator to obtain a bedtime (if injected at the evening meal) or pre-lunch (if injected at breakfast) SMPG value >5.6 and ≤ 7.8 mmol/L (>100 and ≤ 140 mg/dL) while avoiding hypoglycemia. Injection time for lixisenatide and insulin glulisine QD was kept consistent throughout the study and was decided by the investigator based on the meal with the highest self-monitored median 2-h postprandial glucose (PPG) across three different days in the week before the week -1 visit. Patients randomized to receive insulin glulisine TID were administered a starting dose of 3–5 U at each meal that was titrated by the investigator to avoid hypoglycemia and to obtain an SMPG value >5.6 and ≤ 7.8 mmol/L (>100 and ≤ 140 mg/dL) before the next meal (if injected at breakfast or lunch) or at bedtime (if injected before the evening meal).

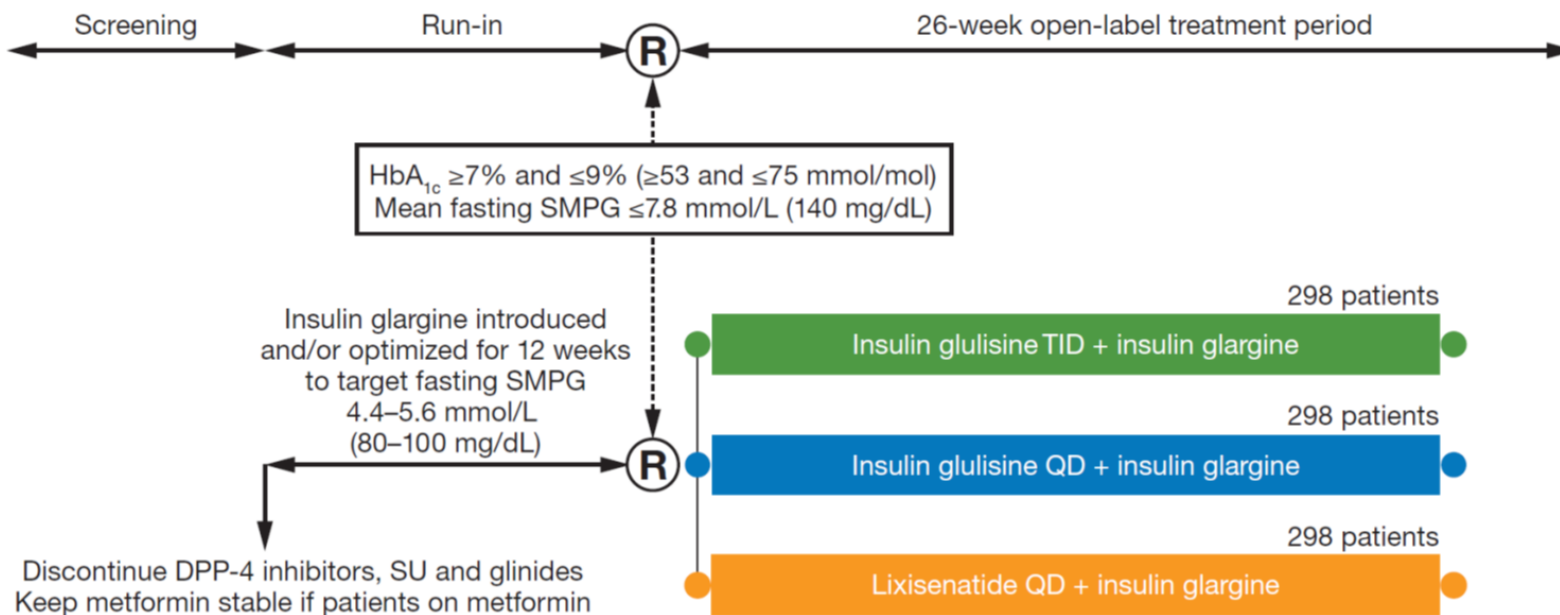
Assays

Blood samples for analysis of HbA_{1c} were collected at screening, at week -1 , at randomization (week 0), and at weeks 12, 20, and 26; blood samples for assessment of fasting plasma glucose (FPG) were taken during run-in (weeks -12 , -9 , -6 , and -1), at randomization, and at weeks 2, 6, 8, 12, 20, and 26. Standardized liquid test meals at breakfast to assess FPG, PPG, and PPG excursions were consumed at the investigation centers on day -1 (before randomization) and at week 26 by patients who had fasted overnight for at least 8 h. At the week-26 visit, lixisenatide was administered 30–60 min and insulin glulisine up to 15 min before the start of the breakfast meal test; the meal was then consumed within 15 min. Blood samples were collected immediately before administration of study medication, before the start of the meal test (0 min) and then 30, 60, and 120 min after the start of the meal.

SMPG was assessed with plasma glucose meters after training at the end of the screening phase. During seven-point SMPG measurement (on three different days in the week before the visits at weeks 0, 12, and 26), patients checked their plasma glucose with their glucose meter before and 2 h after breakfast, lunch, and the evening meal, and at bedtime. Patients used diaries to document their daily insulin doses and any missed injections. Body weight was measured at screening, during run-in (weeks -12 , -6 , and -1), at randomization, and at weeks 2, 6, 8, 12, 20, and 26.

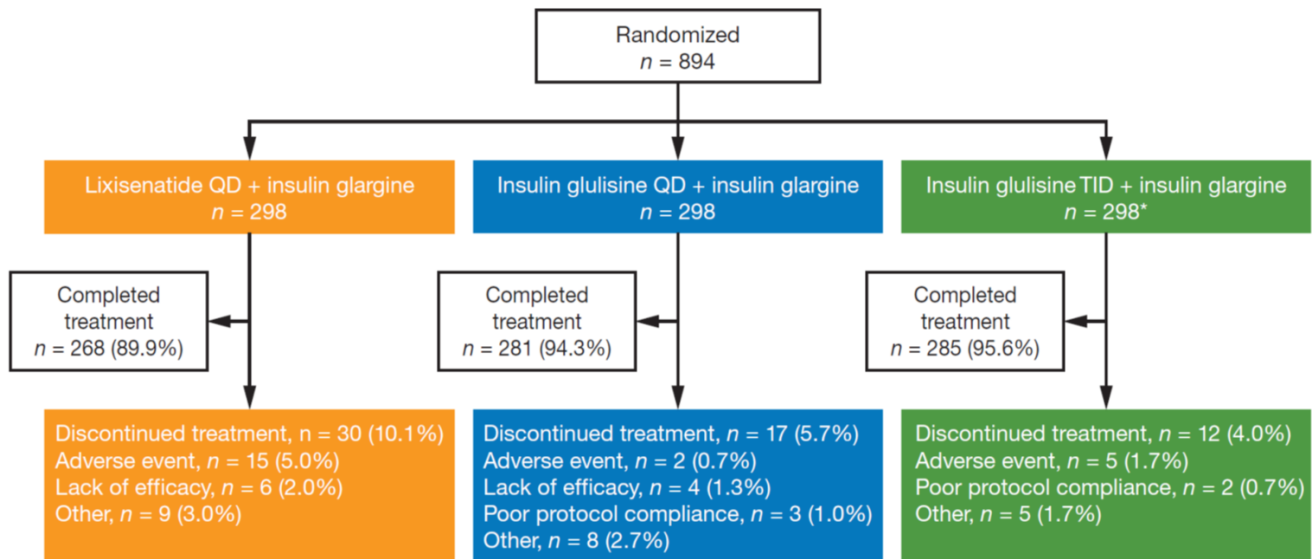
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Supplementary Figure 1. Study design. DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycated hemoglobin; QD, once daily; SMPG, self-monitored plasma glucose; SU, sulfonylurea; TID, thrice daily.



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Supplementary Figure 2. Summary of patient disposition. *One patient did not receive study treatment in the insulin glulisine TID arm. QD, once daily; TID, thrice daily.



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