SUPPLEMENTARY DATA

**Supplementary Table S1. Titration algorithm for iGlarLixi**

| **The lowest fasting SMPG value from the last three measurements, which may include the value measured on the day of titration** | **iGlarLixi dose adjustments (U/day)** |
|---|---|
| >140 mg/dL (>7.8 mmol/L ) | +4 |
| >100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L) | +2 |
| Glycemic target | |
| 80–100 mg/dL (4.4–5.6 mmol/L), inclusive | No change |
| ≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L) | –2 |
| <60 mg/dL (<3.3 mmol/L) or occurrence of two (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week | –2 to –4 or at the discretion of the investigator or medically qualified designee |

In this study, iGlarLixi was available in two pens, providing different dosing options.

- The first pen was used to deliver doses from 10 to 40 units of insulin glargine in combination with 5 to 20 µg of lixisenatide.
- The second pen was used to deliver doses from 30 to 60 units of insulin glargine in combination with 10 to 20 µg of lixisenatide.

The starting dose for all patients was 10 units of insulin glargine combined with 5 µg of lixisenatide, administered with the first (10–40 U) pen. The dose was then titrated based on the insulin dose required to reach and maintain fasting SMPG values of 80–100 mg/dL. The 10–40 U pen was to be used to administer doses up to 40 units/20 µg. If during titration, doses of 41 units of insulin or more were required, then the second (30–60 U) pen was used.

iGlarLixi, fixed-ratio combination of insulin glargine U100 and lixisenatide; SMPG, self-monitored plasma glucose.

SUPPLEMENTARY DATA

**Supplementary Table S2. Additional study details**

| **Inclusion criteria – GLP-1 RA doses** | |
|---|---|
| **GLP-1 RA** | **Required dose** |
| Liraglutide | 1.8 mg QD, or 1.2 mg QD if 1.8 QD was not well tolerated |
| Exenatide | 10 µg BID, or 5 µg BID if 10 µg BID was not well tolerated |
| Exenatide extended release | 2 mg QW |
| Albiglutide | 50 mg QW, or 30 mg QW if 50 mg QW was not well tolerated |
| Dulaglutide | 1.5 mg QW, or 0.75 mg QW if 1.5 mg QW was not well tolerated |
| All GLP-1 RA doses were in combination with metformin (daily dose ≥1500 mg/day or maximum tolerated dose), with or without pioglitazone, with or without SGLT2 inhibitor, all at a stable dose for at least 3 months prior to screening. | |

| **Additional statistical details** |
|---|
| The MMRM model included treatment group (iGlarLixi or GLP-1 RA), randomization strata of $HbA_{1c}$ (<8%, ≥8% [<64, ≥64 mmol/mol]) at screening, randomization strata of GLP-1 RA subtype (QD/BID vs. QW formulations) at screening, visit (Week 8, Week 12, Week 18, Week 22, and Week 26), treatment-by-visit interaction, and world region as fixed effects, and baseline $HbA_{1c}$ value-by-visit interaction as the covariate. |

SUPPLEMENTARY DATA

| **Doses at baseline/screening*** **mean ± SD** | **iGlarLixi** | **GLP-1 RA** |
|---|---|---|
| Liraglutide dose at baseline (mg) | 1.66 (0.25) | 1.66 (0.28) |
| Exenatide dose at baseline (μg) | 18.33 ± 3.83 | 17.78 ± 4.41 |
| Exenatide extended release dose at baseline (mg) | 2.00 ± 0.00 | 2.00 ± 0.00 |
| Albiglutide dose at baseline (mg) | 50.00 ± 0.00 | 45.00 ± 10.00 |
| Dulaglutide dose at baseline (mg) | 1.43 ± 0.22 | 1.40 ± 0.26 |
| Pioglitazone dose at screening (mg) | 31.25 ± 10.03 | 32.73 ± 8.83 |

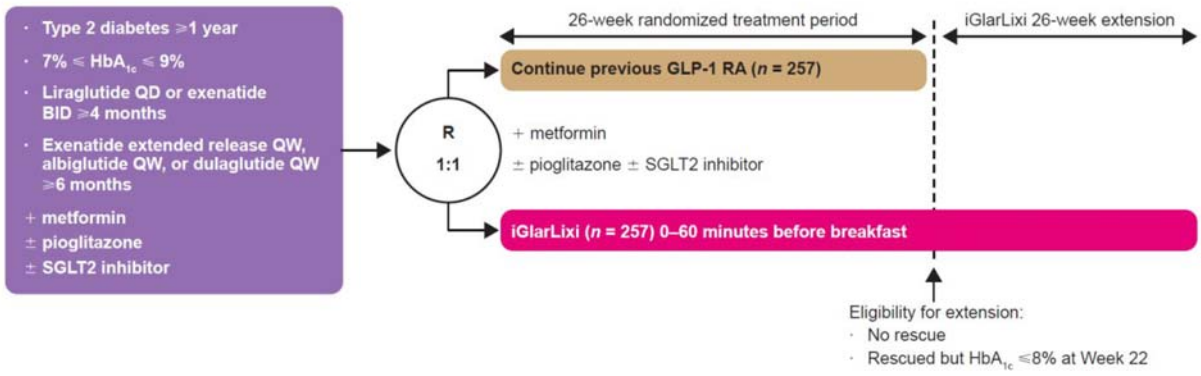
**Important changes to methods after trial commencement**

| Date | Change |
|---|---|
| September 22, 2016 | • Single-arm, 26-week extension for iGlarLixi added<br>• PK and antibody assessments for iGlarLixi added |
| May 12, 2017 | • Inclusion of patients receiving background treatment of SGLT2 inhibitors allowed |

*****Please see Table 1 for *n* (%) of patients receiving these treatments.
BID, twice daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iGlarLixi, fixed-ratio combination of insulin glargine U100 and lixisenatide; MMRM, mixed-effect model with repeated measures; PK, pharmacokinetic; QD, once daily; QW, once weekly; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2.

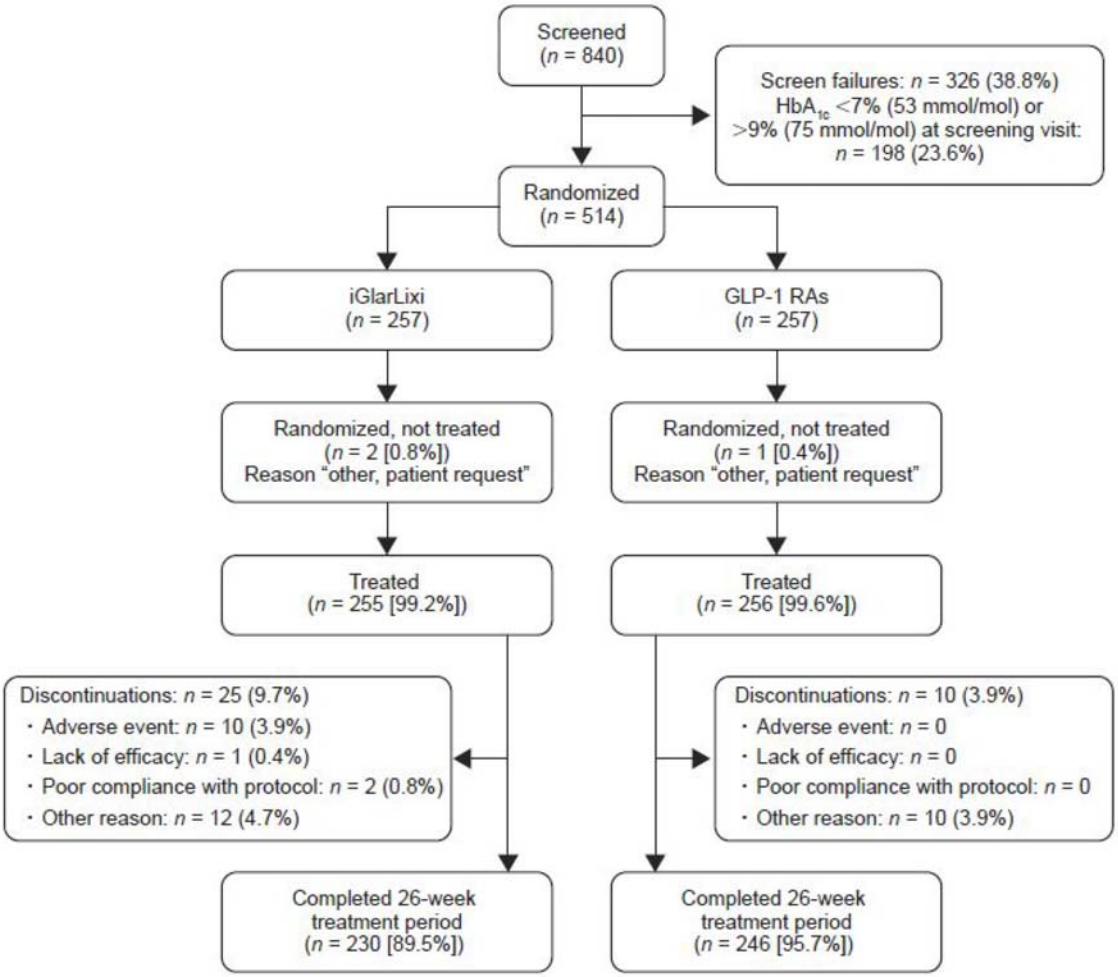
SUPPLEMENTARY DATA

**Supplementary Figure S1.** Study design. QD, once daily; BID, twice daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iGlarLixi, fixed-ratio combination of insulin glargine U100 and lixisenatide; R, randomization; SGLT2, sodium-glucose cotransporter-2.



SUPPLEMENTARY DATA

**Supplementary Figure S2.** Patient disposition. GLP-1 RA, glucagon-like peptide-1 receptor agonist; iGlarLixi, fixed-ratio combination of insulin glargine U100 and lixisenatide.



SUPPLEMENTARY DATA

**Supplementary Figure S3.** Change in body weight over the 26-week randomized treatment period. GLP-1 RA, glucagon-like peptide-1 receptor agonist; iGlarLixi, fixed-ratio combination of insulin glargine U100 and lixisenatide; SE, standard error.