Efficacy of Liraglutide versus Oral Antidiabetic Drugs in Patients with Type 2 Diabetes Uncontrolled with Metformin: A Randomized Clinical Trial in Primary Care (LIRA-PRIME)

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Online-only supplementary material

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Methods

Definition of serious adverse events

A serious adverse event (AE) is an experience that at any medication dose results in any of the following:

- Death;
- A life-threatening experience;
- In-patient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability or incapacity;
- A congenital anomaly or birth defect;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as serious AEs when, based on appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of serious AEs.

Suspicion of transmission of infectious agents via the trial product must always be considered a serious AE.

The term ‘life threatening’ in the definition of serious AE refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe.

The term ‘hospitalization’ is used when a patient:

- Is admitted to a hospital or in-patient facility, irrespective of the duration of physical stay; or
- Hospital stay for treatment or observation for more than 24 hours.

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalization. Hospitalizations for administrative, trial-related and social purposes do not constitute AEs and should therefore not be reported as AEs or serious AEs. Hospital admissions for surgical procedures planned before trial inclusion are not considered AEs or serious AEs.

A substantial disruption of a patient’s ability to conduct normal life functions (e.g. following the event or clinical investigation, the patient has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

For example, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definitions of treatment-emergent AEs and hypoglycemic episodes

A treatment-emergent AE was defined as an event with an onset date (or increase in severity) on or after the first day of trial product administration and no later than 7 days after the last trial product administration. Hypoglycemic episodes were defined as treatment-emergent if their onset occurred on or after the first day of trial product administration and no later than the day after the last day of trial product administration.
**Inclusion criteria**

The full inclusion criteria were as follows:

- Informed consent obtained before trial-related activities;
- Aged ≥18 years at the time of signing informed consent;
- Clinical diagnosis of type 2 diabetes ≥90 days prior to the screening visit;
- Stable daily dose of metformin ≥1500 mg or maximum tolerated dose as monotherapy for ≥60 days prior to the screening visit;
- HbA1c 7.5–9.0% (59–75 mmol/mol) (both inclusive) measured ≤90 days prior to the screening visit;
- Patients in which Victoza® and oral antidiabetic drug (OAD) treatment are indicated according to approved local label.

**Exclusion criteria**

The full exclusion criteria were as follows:

- Previous participation in this trial, defined as signed informed consent;
- Pregnancy, breast-feeding, intention to become pregnant or of childbearing potential and not using adequate contraceptive methods (as required by local regulation or practice);
- Receipt of any investigational medicinal product within 30 days of screening;
- Treatment with any medication for the indication of diabetes other than metformin within 60 days of screening (except short-term treatment of ≤7 days in total) with insulin in connection with intercurrent illness.

**Sample size calculation**

The sample size was calculated to detect a difference in the time to inadequate glycemic control between the liraglutide and OAD arms with 90% power. The following assumptions were made:

- Mean post-baseline glycated hemoglobin (HbA1c) in liraglutide arm of 6.9% (51.9 mmol/mol) and standard deviation (SD) of the within-subject error of 0.85% (9.3 mmol/mol);
- Mean treatment difference in HbA1c of 0.3% (3.3 mmol/mol), which is considered clinically relevant;
- Divergence in HbA1c levels between the two treatment arms after Week 65;
- 20% of patients discontinuing treatment prematurely by Week 26 without having inadequate glycemic control. These patients were assumed to discontinue before the Week 26 visit and thus not to contribute to the primary analysis.
Figure S1. Patient disposition

- Excluded (n=82)
  - Not meeting inclusion criteria (n=39)
  - Declined to participate (n=9)
  - Other reasons\(^*\) (n=34)

Randomized\(^a\) (n=1991)

**Allocation**

- Allocated to liラグリチド (n=996)
  - Exposed to liラグリチド (n=980)
  - Did not receive allocated intervention (n=18)
    - Withdrew by subject (n=14)
      - Do not want injection (n=5)
      - Drug safety concern (n=3)
      - No reason given (n=6)
    - Lost to follow-up (n=1)
    - Protocol violation (internal and external criteria) (n=2)
    - Other (family concerned) (n=1)

- Allocated to OAD (n=995)
  - Exposed to OAD (n=984)
  - Did not receive allocated intervention (n=9)
    - Withdrew by subject (n=5)
      - Refuse to take allocated drug (n=1)
      - Drug safety concern (n=1)
      - No reason given (n=1)
    - Lost to follow-up (n=1)
    - Protocol violation (internal and external criteria) (n=4)
    - Other (investigator's discretion) (n=1)

**Follow-up**

- Withdrawn due to meeting primary endpoint of inadequate glycemic control (n=368)
  - Withdrawn for another reason (n=182)
    - Adverse event (n=79)
    - Withdrew consent (n=45)
    - Lost to follow-up (n=25)
    - Protocol violation (n=23)
    - Lack of efficacy before Week 38 (n=4)
    - Pregnancy (n=0)
    - Died (n=1)
    - Other (n=5)

- Completed 104 weeks of treatment (n=446)\(^a\)

- Withdrawn due to meeting primary endpoint of inadequate glycemic control (n=473)
  - Withdrawn for another reason (n=160)
    - Adverse event (n=41)
    - Withdrew consent (n=42)
    - Lost to follow-up (n=21)
    - Protocol violation (n=30)
    - Lack of efficacy before Week 38 (n=13)
    - Pregnancy (n=1)
    - Died (n=8)
    - Other (n=4)

- Completed 104 weeks of treatment (n=362)\(^a\)

**Analysis**

- Analyzed (n=996)
  - Safety analysis set (n=980)

- Analyzed (n=995)
  - Safety analysis set (n=984)

\(^a\)Other reasons’ mostly included withdrawal of consent by the patient or lost to follow-up. \(^b\)Six patients (n=3 patients from each arm) were excluded from all analyses as their casebooks were not signed by the investigator, which is legally binding. \(^c\)Includes patients with inadequate glycemic control at Week 104. n, number of patients; OAD, oral antidiabetic drug.
Figure S2: First and last dose of medication compared with defined daily dose

A. Liraglutide and OAD subgroups

Safety analysis set. OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Inadequate glycemic control is defined as HbA1c >7.0% (53 mmol/mol) at 2 consecutive scheduled visits after the first 26 weeks of treatment and up to 104 weeks. First possible occurrence at Week 38. Premature discontinuation includes discontinuation due to any reason other than inadequate glycemic control. Week 104 includes subjects who met inadequate glycemic control at Week 104. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. For the DDD per drug, see Supplementary Table S1. DDD, defined daily dose; disc., discontinuation; glyc., glycemic control; OAD, oral antidiabetic drug.
B. Individual OAD class subgroups

Safety analysis set. Inadequate glycemic control is defined as HbA1c >7.0% (53 mmol/mol) at 2 consecutive scheduled visits after the first 26 weeks of treatment and up to 104 weeks. First possible occurrence at Week 38. Premature discontinuation includes discontinuation due to any reason other than inadequate glycemic control. Week 104 includes subjects who met inadequate glycemic control at Week 104. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDD, defined daily dose; disc., discontinuation; DPP-4i, dipeptidyl peptidase 4 inhibitor; glyc., glycemic control; SGLT2i, sodium-glucose cotransporter-1 inhibitor; SU, sulfonylurea.
Figure S3. Change in HbA1c over time

OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione; both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. Data are mean ± standard error of the mean. Numbers of patients contributing to the data points are shown in the bottom panel. HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug.

Figure S4. Change in body weight over time

OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione; both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. Data are mean ± standard error of the mean. Numbers of patients contributing to the data points are shown in the bottom panel. OAD, oral antidiabetic drug.
Figure S5. Changes in lipids over time

OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione; both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. Data are geometric means (symbols) ± standard error of the mean on a log-scale, back transformed (error bars). Numbers of patients contributing to the data points are shown in the bottom panels. LDL cholesterol was largely calculated from total cholesterol,
HDL cholesterol, and triglycerides using the Friedewald formula. When triglycerides were >4.52 mmol/L, direct LDL cholesterol was measured. HDL, high density lipoprotein; LDL, low density lipoprotein; OAD, oral antidiabetic drug.
Table S1. Defined daily dose (DDD) for liraglutide and oral antidiabetics

| Category and name | ATC code | DDD   |
|-------------------|----------|-------|
| GLP-1 RAs         |          |       |
| Liraglutide       | A10BJ02  | 1.2 mg|
| Sulfonylureas     |          |       |
| Glibenclamide     | A10BB01  | 7 mg  |
| Chlorpropamide    | A10BB02  | 0.375 g|
| Tolbutamide       | A10BB03  | 1.5 g |
| Tolazamide        | A10BB05  | 0.5 g |
| Glipizide         | A10BB07  | 10 mg |
| Gliquidone        | A10BB08  | 60 mg |
| Gliclazide        | A10BB09  | 60 mg |
| Glimepiride       | A10BB12  | 2 mg  |
| α-glucosidase inhibitors |       |       |
| Acarbose          | A10BF01  | 0.3 g |
| Miglitol          | A10BF02  | 0.3 g |
| Voglibose         | A10BF03  | 0.6 mg|
| Thiazolidinediones|          |       |
| Rosiglitazone     | A10BG02  | 6 mg  |
| Pioglitazone AT   | A10BG03  | 30 mg |
| Dipeptidyl peptidase-4 inhibitors | | |
| Sitagliptin       | A10BH01  | 0.1 g |
| Vildagliptin      | A10BH02  | 0.1 g |
| Saxagliptin       | A10BH03  | 5 mg  |
| Alogliptin        | A10BH04  | 25 mg |
| Teneligliptin     | A10BH08  | 20 mg |
| Linagliptin       | A10BH05  | 5 mg  |
| SGLT-2 inhibitors |          |       |
| Dapagliflozin     | A10BK01  | 10 mg |
| Canagliflozin     | A10BK02  | 0.2 g |
| Empagliflozin     | A10BK03  | 17.5 mg|
| Other blood glucose-lowering drugs, excl. insulins | | |
| Repaglinide       | A10BX02  | 4 mg  |
| Nateglinide       | A10BX03  | 0.36 g|

The defined daily dose (DDD) is the assumed average maintenance dose per day or a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Values of DDD given in the table were taken from the World Health Organization (WHO) website at the time the trial was carried out. Please refer to [https://www.whocc.no/atc_ddd_index/](https://www.whocc.no/atc_ddd_index/) for more information. ATC code, Anatomical Therapeutic Chemical code; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter-2.
### Table S2. Oral antidiabetic medication distribution

|                      | OAD, N (%) |
|----------------------|------------|
| Full analysis set    | 984 (100.0)|
| SGLT-2 inhibitor     | 471 (47.9)|
| DPP-4 inhibitor      | 391 (39.7)|
| Sulfonylurea         | 106 (10.8)|
| Thiazolidinedione    | 11 (1.1)  |
| α-glucosidase inhibitor | 5 (0.5)  |

The allocated OAD was chosen by the investigator; OADs in the following classes were prescribed in the study: α-glucosidase inhibitor, DPP-4i, SGLT-2i, sulfonylurea or thiazolidinedione. DPP-4, dipeptidyl peptidase-4; N, number of patients; OAD, oral antidiabetic drug; SGLT-2, sodium-glucose cotransporter-2; %, percentage of patients.
|                                      | Liraglutide | OAD       | Total     |
|--------------------------------------|-------------|-----------|-----------|
| Full analysis set, N                | 996         | 995       | 1991      |
| **Sex**                             |             |           |           |
| Female, N (%)³                      | 476 (47.8)  | 471 (47.3)| 947 (47.6)|
| Male, N (%)                          | 520 (52.2)  | 524 (52.7)| 1044 (52.4)|
| **Age (years)**                      |             |           |           |
|                                    | 57.6 (11.0) | 57.1 (10.7)| 57.4 (10.8)|
| **Body weight (kg)**                 |             |           |           |
|                                    | 93.8 (23.5) | 95.9 (25.3)| 94.8 (24.4)|
| **BMI (kg/m²)**                      |             |           |           |
|                                    | 33.2 (7.2)  | 33.7 (7.6)| 33.5 (7.4)|
| **Diabetes duration (years)**        |             |           |           |
|                                    | 7.3 (5.9)   | 7.1 (5.9) | 7.2 (5.9) |
| **HbA₁c (%)**                        |             |           |           |
|                                    | 8.2 (1.0)   | 8.1 (0.9) | 8.2 (1.0) |
| **HbA₁c (mmol/mol)**                 |             |           |           |
|                                    | 66.0 (11.0) | 65.5 (10.3)| 65.7 (10.7)|
| **FPG (mmol/L)**                     |             |           |           |
|                                    | 9.5 (2.8)   | 9.4 (2.7) | 9.5 (2.7) |
| **Metformin ≥1500 mg, N (%)**        |             |           |           |
|                                    | 886 (89.0)  | 887 (89.1)| 1773 (89.1)|
| **eGFR (mL/min/1.73m²)**            |             |           |           |
|                                    | 94.7 (26.6) | 96.0 (26.3)| 95.4 (26.4)|
| **Diabetes complications,³ N (%)**  |             |           |           |
| Diabetic nephropathy                 | 51 (5.1)    | 41 (4.1)  | 92 (4.6)  |
| Diabetic neuropathy                  | 160 (16.1)  | 145 (14.6)| 305 (15.3)|
| Diabetic retinopathy                 | 40 (4.0)    | 26 (2.6)  | 66 (3.3)  |
| Macroangiopathy                      | 61 (6.1)    | 41 (4.1)  | 102 (5.1) |
| **Race**                             |             |           |           |
| White                                | 724 (72.7)  | 714 (71.8)| 1438 (72.2)|
| Asian                                | 149 (15.0)  | 141 (14.2)| 290 (14.6)|
| Black or African American            | 101 (10.1)  | 106 (10.7)| 207 (10.4)|
| American Indian or Alaska Native     | 3 (0.3)     | 6 (0.6)   | 9 (0.5)   |
| Native Hawaiian or Other Pacific Islander | 3 (0.3) | 2 (0.2) | 5 (0.3) |
| Other                                | 16 (1.6)    | 26 (2.6)  | 42 (2.1)  |
| **Ethnicity**                        |             |           |           |
| Hispanic or Latino                   | 176 (17.7)  | 189 (19.0)| 365 (18.3)|
| Not Hispanic or Latino               | 820 (82.3)  | 806 (81.0)| 1626 (81.7)|
| **Smoking status**                   |             |           |           |
| Never smoked                         | 628 (63.1)  | 581 (58.4)| 1209 (60.7)|
| Previous smoker                      | 217 (21.8)  | 243 (24.4)| 460 (23.1)|
| Current smoker                       | 151 (15.2)  | 171 (17.2)| 322 (16.2)|

Full analysis set. Data are mean (SD) unless otherwise stated. ³Investigators also documented whether females were of childbearing potential, as this was relevant to an exclusion criterion. ³Data for diabetes complications are from the screening visit. BMI, body mass index; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; FPG, fasting plasma glucose; HbA₁c, glycated hemoglobin; N, number of patients; OAD, oral antidiabetic drug; SD, standard deviation.
Table S4. HbA\textsubscript{1c} at Week 104 or at premature treatment discontinuation

|                              | Liraglutide | OAD\textsuperscript{†} | \(P\)-value |
|------------------------------|-------------|-------------------------|-------------|
| Full analysis set, N         | 996         | 995                     |             |

Analysis of covariance model

|                              | Liraglutide | OAD\textsuperscript{†} | \(P\)-value |
|------------------------------|-------------|-------------------------|-------------|
| N                            | 872         | 900                     |             |
| HbA\textsubscript{1c}, %     |             |                         |             |
| Estimated LS mean (SE)       | 7.17 (0.037) | 7.50 (0.036) |             |
| Estimated LS mean (SE) change from baseline | -0.99 (0.037) | -0.66 (0.036) |             |
| Estimated liraglutide – OAD treatment difference (95\% CI) | -0.33 (-0.43; -0.23) | <0.0001 |     |

|                              | Liraglutide | OAD\textsuperscript{†} | \(P\)-value |
|------------------------------|-------------|-------------------------|-------------|
| N                            | 877         | 901                     |             |
| HbA\textsubscript{1c}, mmol/mol |             |                         |             |
| Estimated LS mean (SE)       | 54.83 (0.400) | 58.45 (0.394) |             |
| Estimated LS mean (SE) change from baseline | -10.80 (0.400) | -7.18 (0.394) |             |
| Estimated liraglutide – OAD treatment difference (95\% CI) | -3.62 (-4.73; -2.52) | <0.0001 |     |

Mixed model for repeated measures

|                              | Liraglutide | OAD\textsuperscript{†} | \(P\)-value |
|------------------------------|-------------|-------------------------|-------------|
| N                            | 877         | 901                     |             |
| HbA\textsubscript{1c}, %     |             |                         |             |
| Estimated LS mean (SE)       | 7.12 (0.044) | 7.46 (0.048) |             |
| Estimated LS mean (SE) change from baseline | -0.90 (0.044) | -0.57 (0.048) |             |
| Estimated liraglutide – OAD treatment difference (95\% CI) | -0.34 (-0.47; -0.21) | <0.0001 |     |

|                              | Liraglutide | OAD\textsuperscript{†} | \(P\)-value |
|------------------------------|-------------|-------------------------|-------------|
| N                            | 877         | 901                     |             |
| HbA\textsubscript{1c}, mmol/mol |             |                         |             |
| Estimated LS mean (SE)       | 54.36 (0.484) | 58.07 (0.523) |             |
| Estimated LS mean (SE) change from baseline | -9.89 (0.484) | -6.18 (0.523) |             |
| Estimated liraglutide – OAD treatment difference (95\% CI) | -3.70 (-5.09; -2.31) | <0.0001 |     |

\textsuperscript{†}OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione; both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. HbA\textsubscript{1c} and change from baseline in HbA\textsubscript{1c} at Week 104 or at premature treatment discontinuation were analyzed 1) using an analysis of covariance model with treatment and country as fixed factors and baseline HbA\textsubscript{1c} as a covariate and 2) using a linear mixed model for repeated measures with an unstructured residual covariance matrix and including treatment arm as a fixed factor and baseline HbA\textsubscript{1c} as a covariate. Two-sided \(P\)-value for test of no treatment difference. CI, confidence interval; HbA\textsubscript{1c}, glycated hemoglobin; LS, least squares; N, number of patients contributing to the analysis; OAD, oral antidiabetic drug; SE, standard error of the mean.
| Table S5. Treatment-emergent hypoglycemic episodes | Liraglutide | OAD† |
|-----------------------------------------------|------------|------|
|                                               | N | % | E | R | N | % | E | R |
| Safety analysis set                           | 980 |  |  |  | 984 |  |  |  |
| Events                                        | 113 | 11.5 | 224 | 165.3 | 101 | 10.3 | 315 | 250.3 |
| Severe or BG-confirmed symptomatic             | 18 | 1.8 | 24 | 17.7 | 21 | 2.1 | 44 | 35.0 |
| Severe or BG-confirmed                         | 26 | 2.7 | 32 | 23.6 | 27 | 2.7 | 52 | 41.3 |
| ADA classification                              |     |     |     |     |     |     |     |     |
| Severe                                        | 1 | 0.1 | 1 | 0.7 | 6 | 0.6 | 6 | 4.8 |
| Asymptomatic                                   | 38 | 3.9 | 47 | 34.7 | 37 | 3.8 | 100 | 79.5 |
| Documented symptomatic                         | 50 | 5.1 | 98 | 72.3 | 53 | 5.4 | 155 | 123.2 |
| Pseudo                                        | 24 | 2.4 | 31 | 22.9 | 17 | 1.7 | 32 | 25.4 |
| Probable symptomatic                           | 32 | 3.3 | 45 | 33.2 | 13 | 1.3 | 21 | 16.7 |
| Unclassifiable                                 | 1 | 0.1 | 2 | 1.5 | 1 | 0.1 | 1 | 0.8 |

†OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. A treatment-emergent hypoglycemic event was defined as an event with an onset date on or after the first day of trial product administration, and no later than the day after the last trial product administration. Prespecified endpoints involving hypoglycemic episodes are listed in the Methods section. Due to differences in exposure time between the liraglutide and OAD groups (1355.5 vs 1258.5 PYE, respectively), R is the most relevant parameter for between-group comparisons. ADA, American Diabetes Association; BG, blood glucose; E, number of events; N, number of patients with ≥1 event; OAD, oral antidiabetic drug; PYE, patient-years of exposure (1 PYE = 365.25 days); R, rate (number of events divided by patient-years of exposure multiplied by 1000); %, percentage of patients with ≥1 event.

Table S6. Analysis of treatment-emergent hypoglycemic episodes using negative binomial regression

|                                | Liraglutide – OAD ratio | 95% CI     | P-value* |
|--------------------------------|-------------------------|------------|----------|
| Severe episodes (ADA)          | 0.154                   | 0.019; 1.284 | 0.08     |
| Severe or BG-confirmed symptomatic episodes | 0.589                   | 0.310; 1.118 | 0.11     |
| Documented symptomatic episodes (ADA) | 0.607                   | 0.358; 1.029 | 0.06     |

OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. *Two-sided P-value for test of no treatment difference. The number of events was analyzed using a negative binomial regression model (log link) with the logarithm of the treatment-emergent exposure time (1000 years) as an offset. The model included treatment as a fixed factor and baseline HbA1c as a covariate. ADA, American Diabetes Association; BG, blood glucose; CI, confidence interval; OAD, oral antidiabetic drug.
Table S7. Treatment-emergent adverse events leading to permanent discontinuation of trial product (by SOC and occurring in ≥1% of patients in any group)

| Event Category                          | Liraglutide | OAD† |
|-----------------------------------------|-------------|------|
|                                         | N   | %  | E    | R    | N   | %  | E    | R    |
| Events                                  | 77  | 7.9 | 188  | 138.7| 41  | 4.2 | 98   | 77.9 |
| Gastrointestinal disorders              | 54  | 5.5 | 101  | 74.5 | 9   | 0.9 | 14   | 11.1 |
| Nervous system disorders                | 12  | 1.2 | 15   | 11.1 | 7   | 0.7 | 13   | 10.3 |
| Infections and infestations             | 6   | 0.6 | 6    | 4.4  | 10  | 1.0 | 12   | 9.5  |
| General disorders and administration site conditions | 11  | 1.1 | 11   | 8.1  | 3   | 0.3 | 4    | 3.2  |

†OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. Treatment-emergent adverse event: defined as an event with an onset date (or increase in severity) on or after the first day of trial product administration, and no later than 7 days after the last trial product administration. E, number of events; N, number of patients with ≥1 event; OAD, oral antidiabetic drug; R, rate (number of events divided by patient-years of exposure multiplied by 1000); SOC, system organ class; %, percentage of patients with ≥1 event.

Table S8. Change from baseline in biochemistry values (excluding amylase and lipase) at end of trial

| Parameter                        | Liraglutide | OAD† |
|----------------------------------|-------------|------|
| Safety analysis set, N           | 980         | 984  |
| Alanine aminotransferase, U/L    | -3.4 (17.05)| -2.9 (15.91) |
| Aspartate aminotransferase, U/L  | -1.4 (13.35)| -1.0 (11.27) |
| Creatinine, µmol/L               | 2.4 (12.18) | 1.7 (12.52)  |
| eGFR, mL/min/SSA                 | -3.3 (17.73)| -2.2 (14.95) |
| Potassium, mmol/L                | -0.1 (0.60) | -0.0 (0.60)  |
| Total bilirubin, µmol/L          | 0.3 (4.01)  | 0.3 (3.57)   |

†OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. Data are mean (SD). eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; N, number of patients; OAD, oral antidiabetic drug; SD, standard deviation; SSA, specific surface area.
Table S9. Amylase and lipase at Week 104 or at premature treatment discontinuation

|                                | Liraglutide | OAD† |
|--------------------------------|-------------|------|
| Safety analysis set, N         | 980         | 984  |
| **Amylase, U/L**               |             |      |
| N                              | 624         | 526  |
| Median                         | 7.0         | 4.0  |
| Min; max                       | -353.0; 147.0 | -131.0; 212.0 |
| **Lipase, U/L**                |             |      |
| N                              | 624         | 526  |
| Median                         | 9.0         | 1.0  |
| Min; max                       | -766.0; 448.0 | -486.0; 338.0 |

†OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. Amylase/lipase and changes from baseline in amylase/lipase at Week 104 or at premature treatment discontinuation were analyzed using an analysis of covariance model with treatment and country as fixed factors, and the baseline value of the variable of interest as a covariate. The response and baseline values included in the analysis were log transformed, due to distribution of these parameters. Two-sided P-value for test of no treatment difference. CI, confidence interval; N, number of patients contributing to the analysis; OAD, oral antidiabetic drug.
Table S10. Demographics and baseline characteristics of the liraglutide and post hoc OAD subgroups

|                     | Liraglutide | SGLT-2i | DPP-4i | SU |
|---------------------|-------------|---------|--------|----|
| **Full analysis set, N** | 996         | 471     | 391    | 106|
| **Sex**             |             |         |        |    |
| Female, N (%)a      | 476 (47.8)  | 218 (46.3)| 195 (49.9)| 45 (42.5)|
| Male, N (%)         | 520 (52.2)  | 253 (53.7)| 196 (50.1)| 61 (57.5)|
| **Age (years)**     | 57.6 (11.0) | 56.7 (10.5)| 57.4 (10.9)| 57.7 (10.9)|
| **Body weight (kg)**| 93.8 (23.5) | 98.8 (25.1)| 94.2 (25.6)| 91.2 (24.7)|
| **BMI (kg/m²)**     | 33.2 (7.2)  | 34.4 (7.5)| 33.6 (7.7)| 32.0 (7.7)|
| **Diabetes duration (years)** | 7.3 (5.9) | 6.9 (5.7)| 7.6 (6.3)| 6.7 (5.2)|
| **HbA₁c (%)**       | 8.2 (1.0)   | 8.2 (0.9)| 8.1 (0.9)| 8.3 (1.0)|
| **HbA₁c (mmol/mol)**| 66.0 (11.0) | 65.8 (10.3)| 64.6 (10.3)| 67.7 (10.9)|
| **FPG (mmol/L)**    | 9.5 (2.8)   | 9.5 (2.7)| 9.3 (2.6)| 9.7 (3.0)|
| **Metformin ≥1500 mg, N (%)** | 886 (89.0) | 423 (89.8)| 347 (88.7)| 94 (88.7)|
| **eGFR (mL/min/1.73m²)** | 94.7 (26.6) | 95.7 (24.5)| 96.7 (28.2)| 94.9 (27.1)|
| **Race**            |             |         |        |    |
| White               | 724 (72.7)  | 338 (71.8)| 296 (75.7)| 60 (56.6)|
| Asian               | 149 (15.0)  | 69 (14.6)| 43 (11.0)| 23 (21.7)|
| Black or African American | 101 (10.1) | 48 (10.2)| 37 (9.5)| 20 (18.9)|
| American Indian or Alaska Native | 3 (0.3) | 1 (0.2)| 3 (0.8)| 2 (1.9)|
| Native Hawaiian or Other Pacific Islander | 3 (0.3) | 1 (0.2)| 0 | 1 (0.9)|
| Other               | 16 (1.6)    | 14 (3.0)| 12 (3.1)| 0 |
| **Ethnicity**       |             |         |        |    |
| Hispanic or Latino  | 176 (17.7)  | 76 (16.1)| 82 (21.0)| 23 (21.7)|
| Not Hispanic or Latino | 820 (82.3) | 395 (83.9)| 309 (79.0)| 83 (78.3)|
| **Smoking status**  |             |         |        |    |
| Never smoked        | 628 (63.1)  | 276 (58.6)| 229 (58.6)| 59 (55.7)|
| Previous smoker     | 217 (21.8)  | 113 (24.0)| 94 (24.0)| 27 (25.5)|
| Current smoker      | 151 (15.2)  | 82 (17.4)| 68 (17.4)| 20 (18.9)|

Both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. Data are mean (SD) unless otherwise stated. SGLT-2i, DPP-4i and SU were the three most commonly prescribed OADs in the LIRA-PRIME trial. Other OADs prescribed were thiazolidinedione (n=11) and α-glucosidase inhibitor (n=5).

aInvestigators also documented whether females were of childbearing potential, as this was relevant to an exclusion criterion. BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; FPG, fasting plasma glucose; HbA₁c, glycated hemoglobin; N, number of patients; OAD, oral antidiabetic drug; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea.
Table S11. Time to inadequate glycemic control and time to premature treatment discontinuation with liraglutide versus post hoc OAD subgroups†

| Endpoint                                      | Liraglutide (N=996) | SGLT-2i (N=471) | DPP-4i (N=391) | SU (N=106) |
|-----------------------------------------------|---------------------|-----------------|----------------|------------|
| **Time to inadequate glycemic control**       |                     |                 |                |            |
| Patients with event, N (%)                    | 416 (41.8)          | 256 (54.4)      | 214 (54.7)     | 66 (62.3)  |
| Median (25th; 75th percentile), weeks         | 108.9 (37.7; n/a)   | 64.9 (35.1; n/a) | 78.1 (35.4; n/a) | 53.1 (36.6; n/a) |
| **Time to premature treatment discontinuation**|                     |                 |                |            |
| Patients with event, N (%)                    | 532 (53.4)          | 296 (62.8)      | 240 (61.4)     | 75 (70.8)  |
| Median (25th; 75th percentile), weeks         | 80.4 (35.7; n/a)    | 51.7 (35.1; n/a) | 62.6 (35.4; n/a) | 38.0 (35.9; n/a) |

†Both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. The primary endpoint of time to inadequate glycemic control was defined as HbA1c >7.0% at two consecutive scheduled visits after the first 26 weeks of treatment and up to 104 weeks. The first possible occurrence was at Week 38. Time to inadequate glycemic control with liraglutide versus individual OADs was analyzed using a generalized log rank test for interval-censored failure time data. The analysis was not based on any model assumptions or adjusted for any covariates. Possible event times were considered as a continuous variable. Similar methods were used to analyze time to premature treatment discontinuation. 25%, median (50%) and 75% percentiles for the cumulative distribution function were obtained from the Kaplan-Meier survival function. Some 75% percentiles were not estimated as the trial ended after the 104-week treatment period and 1-week follow-up period. DPP-4i, dipeptidyl peptidase-4 inhibitor; N, number of patients; n/a, not applicable; OAD, oral antidiabetic drug; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea.
Table S12. HbA1c and body weight values and changes from baseline at Week 104 or at premature treatment discontinuation in liraglutide and post hoc OAD subgroups

|                  | Liraglutide | SGLT-2i | DPP-4i | SU |
|------------------|-------------|---------|--------|----|
| Full analysis set, N | 996         | 471     | 391    | 106|

| HbA1c (%) | | | | |
|-----------|-----------|---------|--------|
| N         | 872       | 431     | 352    | 100|
| Estimated LS mean (SE) | 7.17 (0.036) | 7.30 (0.051) | 7.66 (0.057) | 7.71 (0.106) |
| Estimated LS mean (SE) change from baseline | -0.99 (0.036) | -0.85 (0.051) | -0.50 (0.057) | -0.45 (0.106) |
| Estimated liraglutide – OAD treatment difference (95% CI) | n/a | -0.14 (-0.26; -0.01) | -0.49 (-0.62; -0.36) | -0.54 (-0.76; -0.32) |

| HbA1c (mmol/mol) | | | | |
|------------------|-----------|---------|--------|
| N         | 872       | 431     | 352    | 100|
| Estimated LS mean (SE) | 54.83 (0.393) | 56.33 (0.560) | 60.20 (0.622) | 60.75 (1.163) |
| Estimated LS mean (SE) change from baseline | -10.80 (0.393) | -9.30 (0.560) | -5.43 (0.622) | -4.88 (1.163) |
| Estimated liraglutide – OAD treatment difference (95% CI) | n/a | -1.49 (-2.84; -0.15) | -5.37 (-6.81; -3.92) | -5.92 (-8.32; -3.51) |

| Body weight (kg) | | | | |
|------------------|-----------|---------|--------|
| N         | 930       | 460     | 376    | 103|
| Estimated LS mean (SE) | 92.40 (0.162) | 91.43 (0.232) | 94.09 (0.256) | 95.64 (0.489) |
| Estimated LS mean (SE) change from baseline | -2.80 (0.162) | -3.78 (0.232) | -1.11 (0.256) | 0.43 (0.489) |
| Estimated liraglutide – OAD treatment difference (95% CI) | n/a | 0.97 (0.42; 1.53) | -1.69 (-2.29; -1.10) | -3.24 (-4.25; -2.23) |

Both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. Changes from baseline in HbA1c and body weight at Week 104 or at premature treatment discontinuation were analyzed using an analysis of covariance model with treatment and country as fixed factors and the baseline value of the variable of interest as a covariate. Estimated differences between liraglutide and individual OADs were calculated, together with 95% CIs. CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated hemoglobin; LS, least squares; N, number of patients contributing to the analysis; n/a, not applicable; OAD, oral antidiabetic drug; SE, standard error of the mean; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea.
Table S13. Treatment-emergent hypoglycemic episodes in liraglutide and post hoc OAD subgroups

|                  | Liraglutide | SGLT-2i | DPP-4i | SU  |
|------------------|-------------|---------|--------|-----|
|                  | N  | %   | E | R | N  | %   | E | R | N  | %   | E | R | N  | %   | E | R |
| Safety analysis set | 980 |       | 471 |     | 391 |     | 106 |    | 106 |    |
| Events           | 113 | 11.5 | 224 | 165.3 | 32 | 6.8 | 42 | 70.2 | 34 | 8.7 | 72 | 140.3 | 34 | 32.1 | 200 | 1566.3 |
| Severe or BG-confirmed symptomatic | 18 | 1.8 | 24 | 17.7 | 4 | 0.8 | 4 | 6.7 | 5 | 1.3 | 6 | 11.7 | 12 | 11.3 | 34 | 266.3 |
| Severe or BG-confirmed severe or BG-confirmed asymptomatic | 26 | 2.7 | 32 | 23.6 | 7 | 1.5 | 7 | 11.7 | 7 | 1.8 | 8 | 15.6 | 13 | 12.3 | 37 | 289.8 |
| ADA classification |     |        |     |       |     |        |     |       |     |        |     |       |     |        |     |       |
| Severe           | 1  | 0.1 | 1 | 0.7 | 2 | 0.4 | 2 | 3.3 | 2 | 0.5 | 2 | 3.9 | 2 | 1.9 | 2 | 15.7 |
| Asymptomatic     | 38 | 3.9 | 47 | 34.7 | 11 | 2.3 | 16 | 26.8 | 14 | 3.6 | 32 | 62.3 | 12 | 11.3 | 52 | 407.2 |
| Documented symptomatic | 50 | 5.1 | 98 | 72.3 | 11 | 2.3 | 14 | 23.4 | 17 | 4.3 | 28 | 54.5 | 24 | 22.6 | 112 | 877.1 |
| Pseudo           | 24 | 2.4 | 31 | 22.9 | 4 | 0.8 | 5 | 8.4 | 5 | 1.3 | 8 | 15.6 | 8 | 7.5 | 19 | 148.8 |
| Probable symptomatic | 32 | 3.3 | 45 | 33.2 | 5 | 1.1 | 5 | 8.4 | 2 | 0.5 | 2 | 3.9 | 6 | 5.7 | 14 | 109.6 |
| Unclassifiable   | 1  | 0.1 | 2 | 1.5 | 0 |     | 0 |     | 0 |     | 0 |     | 1 | 0.9 | 1 | 7.8 |

Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. A treatment-emergent hypoglycemic event was defined as an event with an onset date on or after the first day of trial product administration, and no later than the day after the last trial product administration. Prespecified endpoints involving hypoglycemic episodes are listed in the main manuscript. ADA, American Diabetes Association; BG, blood glucose; DPP-4i, dipeptidyl peptidase-4 inhibitor; E, number of events; N, number of patients with ≥1 event; OAD, oral antidiabetic drug; R, rate (number of events divided by patient-years of exposure multiplied by 1000); SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; %, percentage of patients with ≥1 event.
Table S14. Treatment-emergent adverse events (serious, fatal, leading to permanent discontinuation and events of special interest) in liraglutide and post hoc OAD subgroups

|                  | Liraglutide | SGLT-2i | DPP-4i | SU  |
|------------------|-------------|---------|--------|-----|
|                  | N   | %    | E   | R   | N   | %    | E   | R   | N   | %    | E   | R   | N   | %    | E   | R   |
| Safety analysis set | 980 |       | 471 |     | 391 |       | 106 |     |
| Serious          | 92  | 9.4  | 145 | 107.0 | 33  | 7.0  | 61  | 102.0 | 31  | 7.9  | 56  | 109.1 | 14  | 13.2 | 20  | 156.6 |
| Fatal            | 0   |       | 3   | 0.6  | 2   | 0.5  | 2   | 3.9  | 0   |       |     |      |     |      |
| Leading to permanent discontinuation | 77  | 7.9  | 188 | 138.7 | 24  | 5.1  | 47  | 78.6 | 14  | 3.6  | 48  | 93.5 | 1   | 0.9  | 1   | 7.8  |

Both liraglutide and OADs were prescribed in combination with metformin. Safety analysis set. A treatment-emergent adverse event was defined as an event with onset or increase in severity on or after the time of first trial product administration and no later than seven days (7 times 24 hours) after the time of last trial product administration. DPP-4i, dipeptidyl peptidase-4 inhibitor; E, number of events; N, number of patients with ≥1 event; OAD, oral antidiabetic drug; R, rate (number of events divided by patient-years of exposure multiplied by 1000); SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; %, percentage of patients with ≥1 event.
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