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

Contents:

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[a] experience;
- In-patient hospitalization[b] or prolongation of existing hospitalization;
- A persistent or significant disability or incapacity;[c]
- A congenital anomaly or birth defect;
- Important medical events that may not result in death, be life-threatening,[a] or require hospitalization[b] 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.[d]

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

[a]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.

[b]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.

[c]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).

[d]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;
- HbA_{1c} 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:

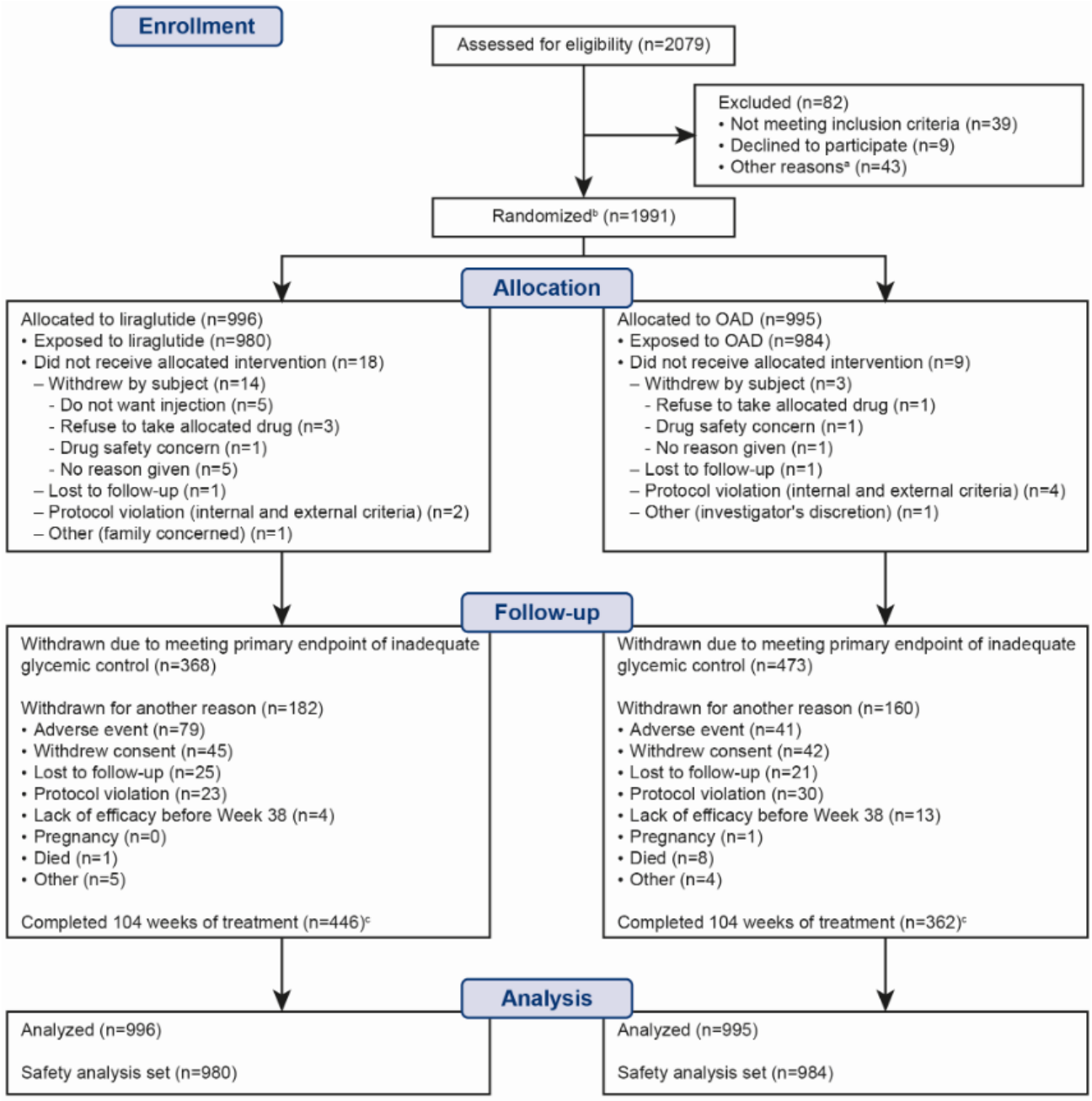
- Previous participation in this trial, defined as signed informed consent;
- Pregnancy, breast-feeding, intention to become pregnant or of childbearing potential and not using adequate contraceptive methods (as required by local regulation or practice);
- Receipt of any investigational medicinal product 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 (HbA_{1c}) 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 HbA_{1c} of 0.3% (3.3 mmol/mol), which is considered clinically relevant;
- Divergence in HbA_{1c} 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.

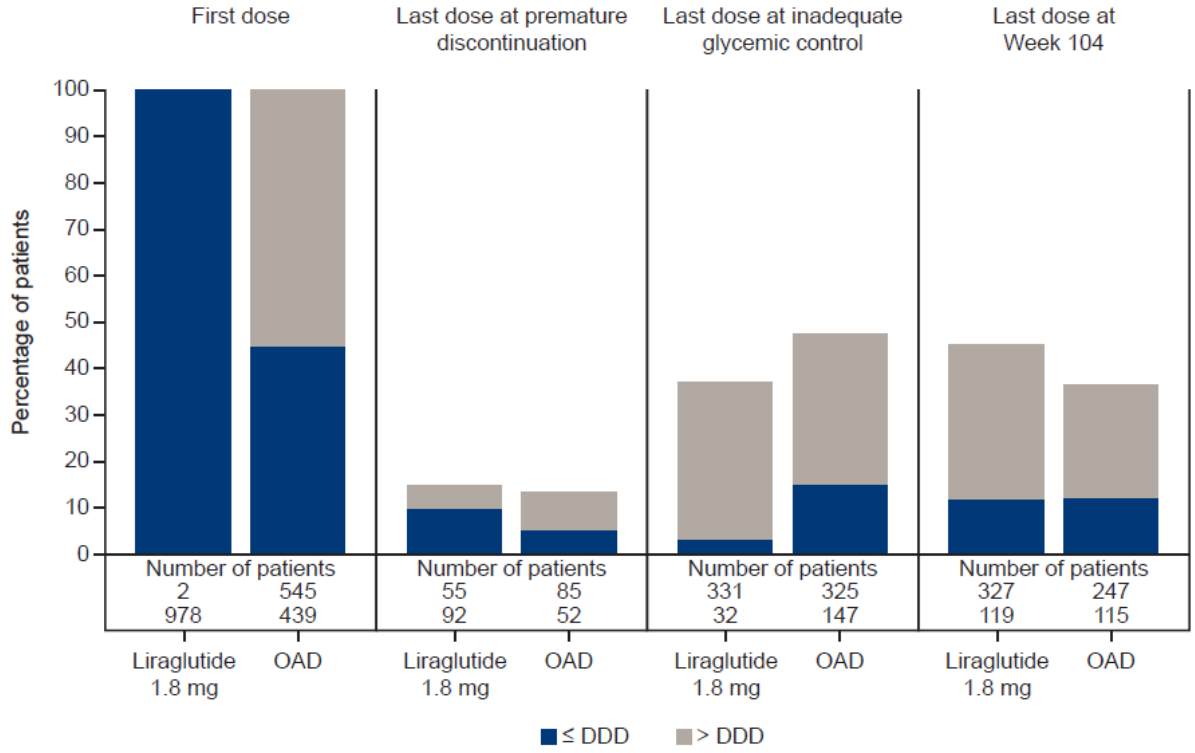
Figure S1. Patient disposition



[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.

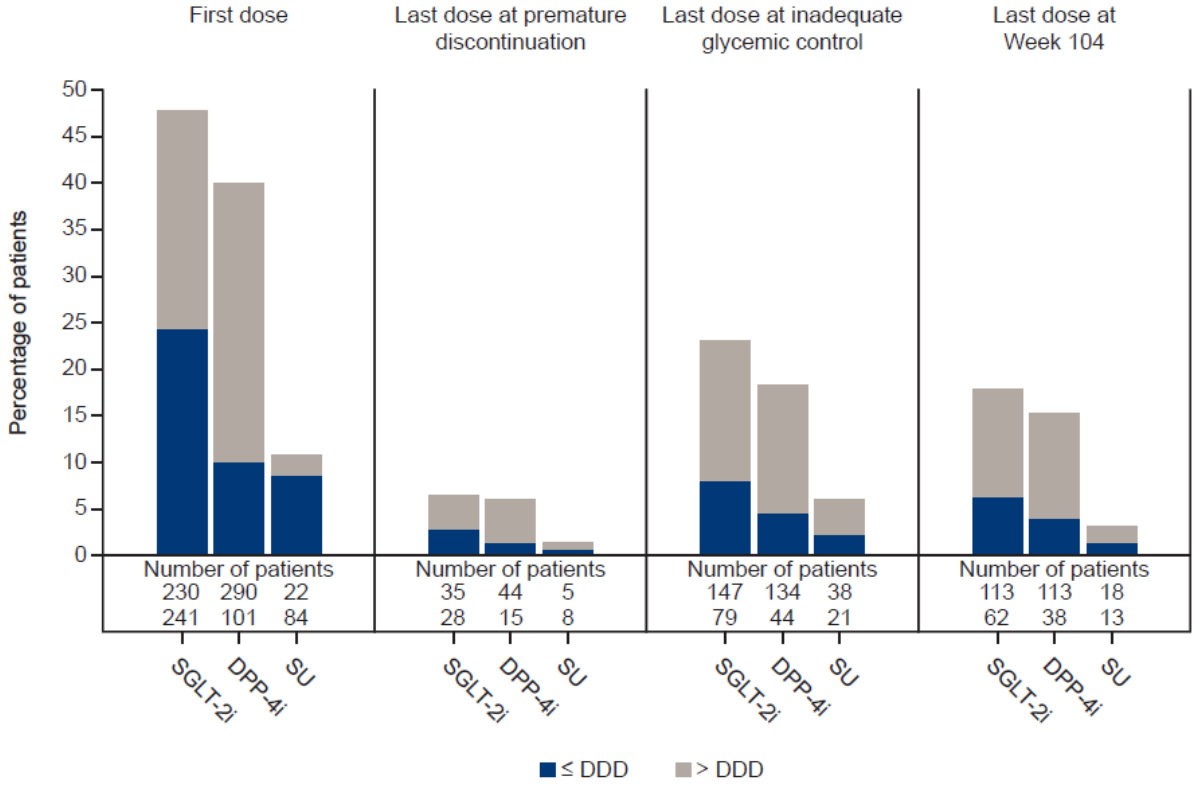
Figure S2: First and last dose of medication compared with defined daily dose

A. Liraglutide and OAD subgroups



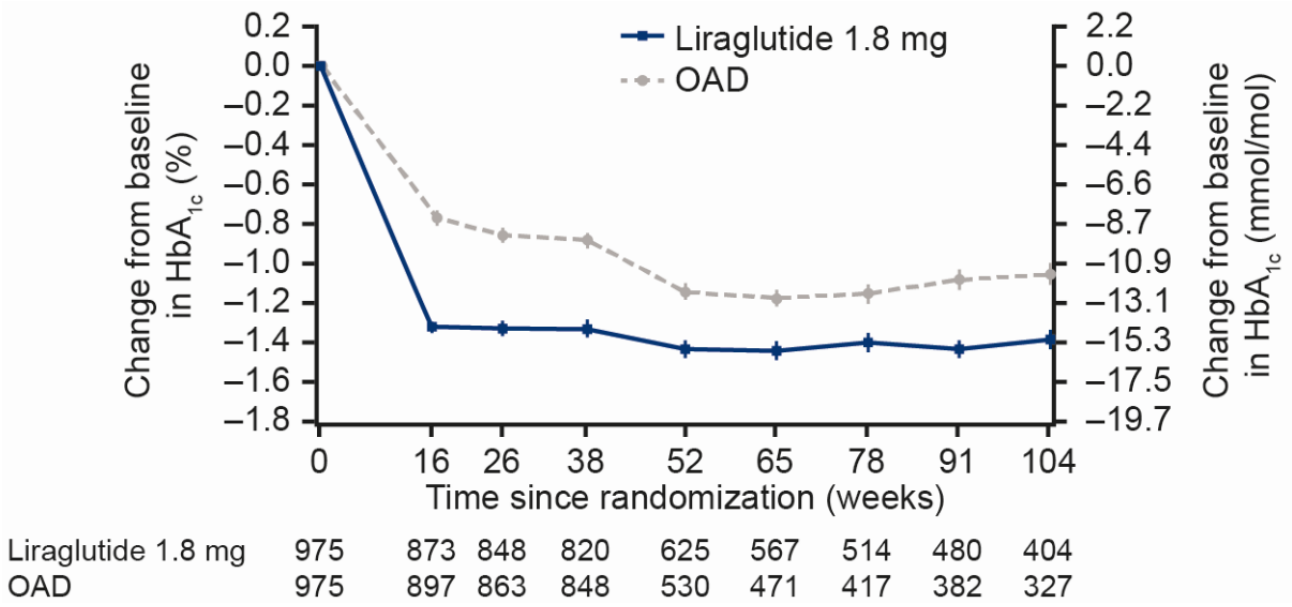
Safety analysis set. OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione. Inadequate glycemic control is defined as HbA_{1c} >7.0% (53 mmol/mol) at 2 consecutive 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



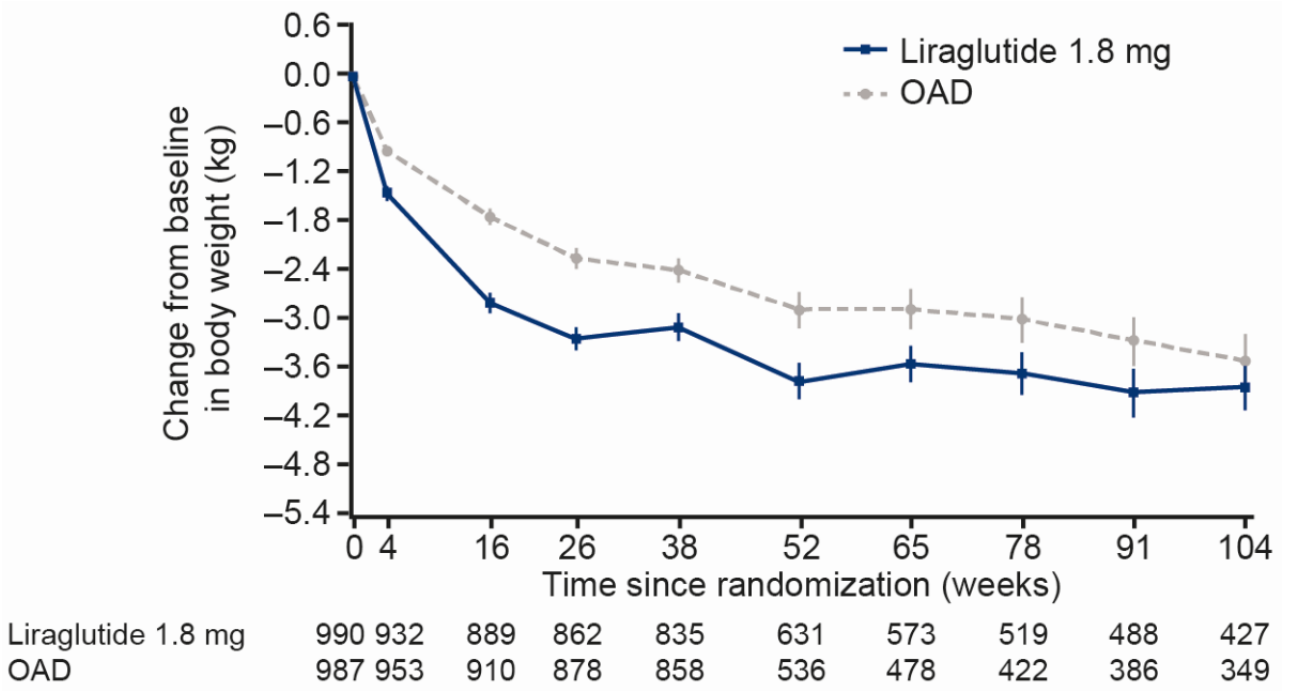
Safety analysis set. Inadequate glycemic control is defined as HbA_{1c} >7.0% (53 mmol/mol) at 2 consecutive scheduled visits after the first 26 weeks of treatment and up to 104 weeks. First possible occurrence at Week 38. Premature discontinuation includes discontinuation due to any reason other than 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 HbA_{1c} over time



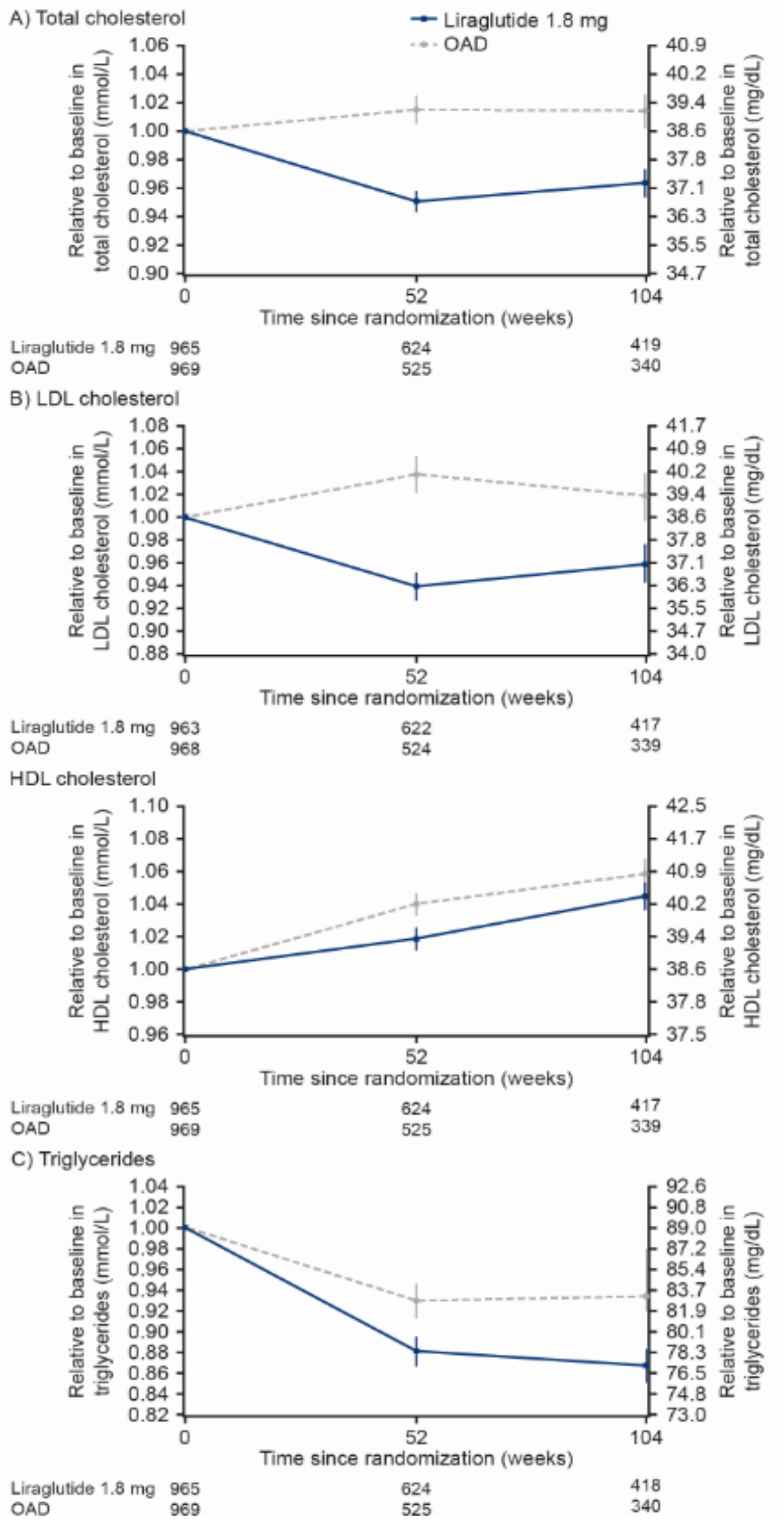
OADs included investigator-selected drugs from the classes: α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor, sulfonylurea or thiazolidinedione; both liraglutide and OADs were prescribed in combination with metformin. Full analysis set. Data are mean ± standard error of the mean. Numbers of patients contributing to the data points are shown in the bottom panel. HbA_{1c}, 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/ 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.

Table S3. Demographics and baseline characteristics of liraglutide and OAD subgroups

	Liraglutide	OAD	Total
Full analysis set, N	996	995	1991
Sex			
Female, N (%)[a]	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/m^2)	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)
HbA_{1c} (%)	8.2 (1.0)	8.1 (0.9)	8.2 (1.0)
HbA_{1c} (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 ($mL/min/1.73m^2$)	94.7 (26.6)	96.0 (26.3)	95.4 (26.4)
Diabetes complications,[b] 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. [a]Investigators also documented whether females were of childbearing potential, as this was relevant to an exclusion criterion. [b]Data 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; HbA_{1c}, glycated hemoglobin; N, number of patients; OAD, oral antidiabetic drug; SD, standard deviation.

Table S4. HbA_{1c} at Week 104 or at premature treatment discontinuation

	Liraglutide	OAD[†]	*P*-value
Full analysis set, N	996	995	
Analysis of covariance model			
N	872	900	
HbA_{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
HbA_{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			
N	877	901	
HbA_{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
HbA_{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

[†]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_{1c} and change from baseline in HbA_{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_{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_{1c} as a covariate. Two-sided *P*-value for test of no treatment difference. CI, confidence interval; HbA_{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[a]**
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. [a]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 HbA_{1c} 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)

	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/m^2)	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)
HbA_{1c} (%)	8.2 (1.0)	8.2 (0.9)	8.1 (0.9)	8.3 (1.0)
HbA_{1c} (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 ($mL/min/1.73m^2$)	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).
[a]Investigators 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; HbA_{1c}, 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 (25^{th}; 75^{th} 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 (25^{th}; 75^{th} 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 HbA_{1c} >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. HbA_{1c} 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
HbA_{1c} (%)				
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)
HbA_{1c} (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 HbA_{1c} 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; HbA_{1c}, 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			
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	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				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	3	5.0	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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