SUPPLEMENTARY DATA

The impact of liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial

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Online-only supplementary material

Supplementary Table S1. Completion of the 21-point checklist designed to assess clinical study publications reporting on the prevention and management of foot disease in patients with diabetes (13)

	Question	Answer for this posthoc analysis
Study design		
1	Are appropriate definitions included for the terms “ulcer”, “healing”, and all other required aspects of the population and the outcomes?	Yes (we defined foot ulcer as an open wound on the foot. As healing was not examined in this analysis, no definition of it was applied)
2	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?	N/A (this was a *posthoc*analysis of a prespecified endpoint within a CVOT. The study target population was appropriate for the CVOT and interventions (i.e. those at high risk of CV events), which would inherently have included patients at risk for DFU events; however, the trial was not designed to examine foot ulcers)
3	Was there a control population that was managed at the same time as those in the intervention group or groups?	Yes (there were 410 sites and each may have managed foot ulcers slightly differently, but with randomization the effects of between-site variation would be minimized)
4	Is the intervention sufficiently well described to enable another researcher to replicate the study?	Yes (these are well described in the primary paper[16])
5	Are the components of other aspects of care described for the intervention and comparator groups?	Yes (these are well described in the primary paper[16])
6	Were the participants randomized into intervention and comparator groups?	Yes
7	Were the participants randomized by an independent person or agency?	Yes
8	Was the number of participants studied in the trial based on an appropriate sample size calculation?	N/A (this was a *posthoc*analysis from a trial where the sample size calculation was for the primary endpoint of a three-point MACE and not DFU)
9	Was the chosen primary outcome of direct clinical relevance?	N/A (the trial was designed as a CVOT with the primary endpoint of a three-point MACE[CV death, non-fatal myocardial infarction and non-fatal stroke]; however, DFU was a prespecified endpoint)
10	Was the person who assessed the primary outcome or outcomes blinded to group allocation?	Yes
11	Were either the clinical researcher who cared for the wound at research visits or the	Yes (both the researchers and participants were blinded to group allocation)

	participants blinded to group allocation?	
Study conduct		
12	Did the study complete recruitment?	Yes
13	Was it possible to document the primary outcome in 75% or more of those recruited?	N/A (this was a *posthoc* analysis of a prespecified endpoint within a CVOT. However, DFU was a prespecified MESI. Therefore, at each visit, investigators were requested to report any new DFU events or worsening of existing DFU events present at baseline. Among the total trial population, 85% attended the 3-year visit and 8.9% died during the trial. The DFU data collection is therefore considered robust)
14	Were the results analysed primarily by intention-to-treat analysis?	Yes (all Cox analyses were done on the intention-to-treat population, so all randomized patients were included)
15	Were appropriate statistical methods used throughout?	Yes
Outcomes		
16	Was the performance in the control group of the order that would be expected in routine clinical practice?	Yes
17	Are the results from all participating centers comparable? Answer “yes” if the study was done in only one center	Unknown (an analysis of the DFU events by study center has not been undertaken. However, we would anticipate that, as per protocol,all investigators were working to best local practice, and any differences in outcomes was due to the study treatments only)
Study reporting		
18	Is the report free from errors of reporting—eg, discrepancies between data reported in different parts of the report?	Yes
19	Are the important strengths and weaknesses of the study discussed in a balanced way?	Yes
20	Are the conclusions supported by the findings?	Yes
21	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?	Yes (all conflicts of interest have been fully disclosed)
Total score		16/21

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DFU, diabetes-related foot ulcer; MACE, major adverse cardiovascular event; MESI, medical event of special interest; N/A, not applicable.

Identification of diabetes-related foot ulcer (DFU) events for this analysis

No standardized Medical Dictionary for Regulatory Activities (MedDRA) query exists to capture adverse events of DFU. Therefore, based on a blinded evaluation of DFU events prior to database lock, a MedDRA search string was designed to capture events related to foot ulcers and exclude unrelated events. Specific MedDRA terms were used to search all reported adverse events (Table S2). This automated search was followed by a blinded review of the case narrative of each event. Events that were not DFUs or were related to a previously reported DFU were excluded from the subsequent analyses.

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Supplementary Table S2. MedDRA terms included in the search for DFU events reported during the LEADER trial

High level terms included	Preferred terms included	Preferred terms excluded
1. Diabetic complications dermal	1. Wound	1. Arteriosclerosis
2. Limb therapeutic procedures	2. Skin necrosis	2. Arteriosclerotic gangrene
3. Musculoskeletal necrosis and vascular insufficiency		3. Compartment syndrome
4. Non-site-specific necrosis and vascular insufficiency		4. Steal syndrome
5. Skin and subcutaneous ulcerations		5. Vascular graft occlusion

DFU, diabetes-related foot ulcer; MedDRA, Medical Dictionary for Regulatory Activities.

Search results

The search using prespecified MedDRA terms identified 268 events in 181 patients treated with liraglutide and 304 events in 198 patients treated with placebo. A total of 21 events (eight in the liraglutide group and 13 in the placebo group) were excluded based on the blinded review of the case narratives (Figure S1). This total included 12 events in 12 patients (five in the liraglutide group and seven in the placebo group) being unrelated to DFU and nine events in nine patients (three in the liraglutide group and six in the placebo group) being complications to already reported DFU events. Importantly, for the latter nine events, information on complications to the DFU events was captured from the narrative review of the already reported events in these nine patients.

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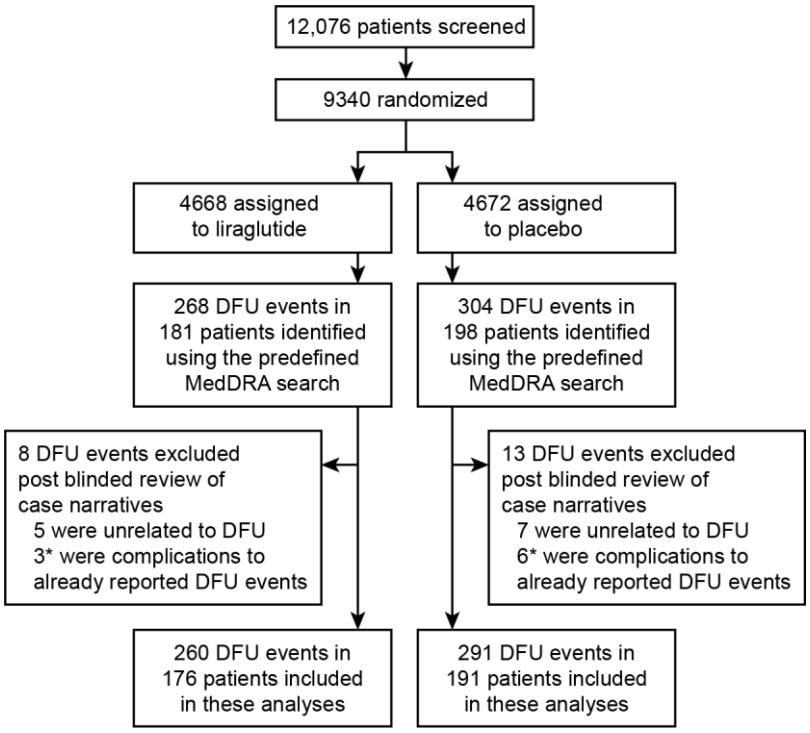
Supplementary Figure S1. Patient disposition in relation to the analysis of DFU events



*For these nine events (three with liraglutide and six with placebo), information on complications to the DFU events was captured from the narrative review of the already reported events in these nine patients. DFU, diabetes-related foot ulcer; MedDRA, Medical Dictionary for Regulatory Activities.

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Supplementary Table S3. Baseline characteristics, focusing on risk factors for DFU

	Patients with DFU events		Patients without DFU events	
	Liraglutide (N=176)	**Placebo (N=191)**	**Liraglutide (N=4492)**	**Placebo (N=4481)**
Age, years	64.7 ± 7.0	64.6 ± 7.8	64.2 ± 7.3	64.4 ± 7.2
Male, n (%)	130 (73.9)	140 (73.3)	2881 (64.1)	2852 (63.6)
Diabetes duration, years	15.6 ± 7.2	16.4 ± 8.4	12.7 ± 8.0	12.7 ± 8.0
HbA_{1c}, % (mmol/mol)	9.2 ± 1.9 (77 ± 21)	9.1 ± 1.7 (76 ± 18)	8.7 ± 1.5 (72 ± 17)	8.6 ± 1.5 (71 ±16)
Body weight, kg	98.0 ± 27.1	97.4 ± 23.6	91.7 ± 20.9	91.3 ± 20.6
BMI, kg/m^2	33.2 ± 7.8	32.9 ± 6.8	32.5 ± 6.3	32.4 ± 6.2
History of DFU, n (%)	71 (40.3)	69 (36.1)	137 (3.0)	127 (2.8)
DFU at baseline	29 (16.5)	26 (13.6)	40 (0.9)	33 (0.7)
Peripheral neuropathy, n (%)	120 (68.2)	127 (66.5)	1454 (32.4)	1452 (32.4)
Diabetes-related nephropathy, n (%)	109 (61.9)	108 (56.5)	1773 (39.5)	1809 (40.4)
Peripheral vascular artery disease, n (%)	48 (27.3)	60 (31.4)	519 (11.6)	540 (12.1)
Diabetes-related retinopathy, n (%)	62 (35.2)	81 (42.4)	916 (20.4)	818 (18.3)
Non-proliferative	37 (21.0)	46 (24.1)	701 (15.6)	609 (13.6)
Proliferative	23 (13.1)	23 (13.1)	200 (4.5)	184 (4.1)
Urinary albumin-to-creatinine ratio, geometric mean mg/g (Q1, Q3)	58.3 (8.1, 260.6)	47.0 (11.2, 161.0)	19.6 (4.6, 60.5)	20.6 (4.5, 64.0)
Antidiabetic medication, n (%)				
1 OAD	28 (15.9)	20 (10.5)	888 (19.8)	874 (19.5)
>1 OADs	40 (22.7)	50 (26.2)	1480 (32.9)	1431 (31.9)
Insulin with OAD(s)	71 (40.3)	89 (46.6)	1606 (35.8)	1665 (37.2)
Insulin without OAD(s)	29 (16.5)	27 (14.1)	332 (7.4)	350 (7.8)
None	8 (4.5)	5 (2.6)	186 (4.1)	161 (3.6)
Antihypertensive medication, n (%)	160 (90.9)	169 (88.5)	4169 (92.8)	4133 (92.2)

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Statins, n (%)	124 (70.5)	137 (71.7)	3281 (73.0)	3199 (71.4)
Smoking status, n (%)				
Current smoker	28 (15.9)	27 (14.1)	539 (12.0)	536 (12.0)
Previous smoker	66 (37.5)	66 (34.6)	1884 (41.9)	1854 (41.4)
Never smoked	82 (46.6)	98 (51.3)	2069 (46.1)	2091 (46.7)
SBP, mmHg	138.3 ± 22.6	135.9 ± 20.6	135.8 ± 17.6	135.9 ± 17.6
DBP, mmHg	76.1 ± 11.8	76.2 ± 10.7	77.3 ± 10.3	77.0 ± 10.1
LDL cholesterol, mmol/L	2.4 ± 0.9	2.4 ± 1.1	2.3 ± 0.9	2.3 ± 0.9

Values are mean ± standard deviation unless otherwise stated. BMI, body mass index; DBP, diastolic blood pressure; DFU, diabetes-related foot ulcer; HbA_{1c}, glycated hemoglobin; LDL, low-density lipoprotein; N, number of patients in the treatment group; n, number of patients reporting the characteristic in question; OAD, oral antidiabetic drug; Q1, quartile 1; Q3, quartile 3; SBP, systolic blood pressure; %, proportion of patients reporting the characteristic of the total treatment group.

Supplementary Table S4. Analysis of time to first DFU-related complication, which occurred after 1 year from randomization (i.e. excluding complications occurring within the first year of trial participation)

Complication	**Liraglutide, n (%)**	**Placebo, n (%)**	**HR (95% CI)**	***p*-value**
Amputation	32 (0·70)	58 (1·26)	0·55 (0·36, 0·84)	0·006
Infection	75 (1·63)	101 (2·20)	0·74 (0·55, 0·99)	0·044
Involvement of underlying structures	47 (1·02)	67 (1·46)	0·70 (0·48, 1·01)	0·06
Peripheral revascularization	11 (0·24)	20 (0·43)	0·55 (0·26, 1·14)	0·11

Percentages of patients are of the full analysis set (Liraglutide, N=4599; Placebo, N=4601). *p*-values calculated using Cox regression model with treatment as a fixed factor. CI, confidence interval; DFU, diabetes-related foot ulcer; HR, hazard ratio; n, number of patients.

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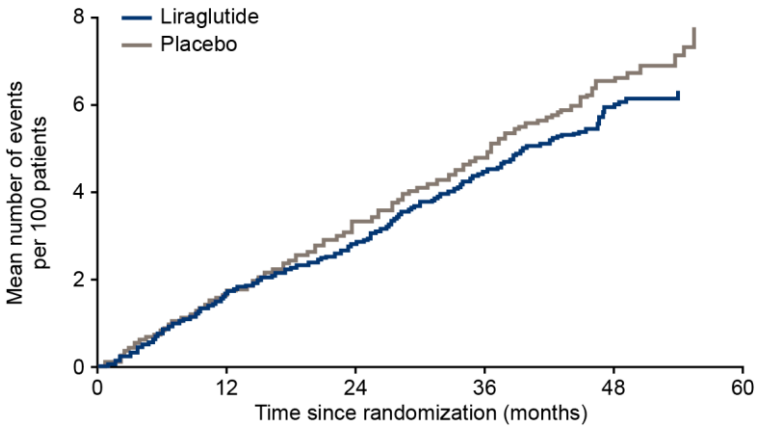
Supplementary Figure S2. Mean number of DFU events per 100 patients



This figure includes data from 260 DFU events in 176 liraglutide-treated patients and 291 DFU events in 191 placebo-treated patients. DFU, diabetes-related foot ulcer.