SUPPLEMENTAL MATERIAL

Table of Contents

Supplementary Methods .................................................................................................................. 2
Inclusion criteria ................................................................................................................................. 2
Exclusion criteria ............................................................................................................................... 2
PET/CT imaging ................................................................................................................................. 3
Coronary artery calcium score (CACS) ............................................................................................... 4
Ultrasound carotid intima media thickness (CIMT) .......................................................................... 4
Endothelial function ........................................................................................................................... 5
Blood and urine analysis ................................................................................................................. 5
Height, Weight and Blood Pressure .................................................................................................. 5
Safety assessment ............................................................................................................................. 5
Statistical analysis plan ...................................................................................................................... 6

Supplementary Tables ....................................................................................................................... 7
Table I. Reasons for exclusion from the optimal efficacy population ............................................... 7
Table II: Overview of missing data for primary and secondary endpoints and key clinical characteristics .......................................................... 8
Table III. Arterial vascular inflammation in different vascular beds ............................................... 9
Table IV. Changes in circulating biomarkers ...................................................................................... 9
Table V. Arterial vascular inflammation. Optimal efficacy population ............................................. 10
Table VI. Arterial vascular inflammation in different vascular beds. Optimal efficacy population .... 11
Table VII. Adverse events divided by treatment allocation and organ system ................................ 12
Table VIII. Serious adverse events divided by treatment allocation and organ system .................... 13
Table IX. Capillary blood glucose ..................................................................................................... 14
Table X. Arterial vascular inflammation adjusted for blood glucose at time of imaging .................... 15
Table XI. Changes in biomarkers in patients with and without cardiovascular disease ..................... 16
Supplementary Methods

Inclusion criteria

1. Given written informed consent
2. Male or female patients >50 years with type 2 diabetes (WHO criteria)
3. HbA1c ≥ 48 mmol/mol (6.5 %)
4. eGFR ≥ 30 ml/min/1.73 m2 (estimated by CKD-epi formula)
5. Stable glucose-lowering medication (excluding oral glucocorticoids, calcineurin inhibitors, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon like peptide-1 agonists and other agents, which in the investigator’s opinion could interfere with the effect of liraglutide) for at least 4 weeks before the baseline PET/CT
6. Stable/no treatment of hypercholesterolemia 4 weeks before baseline PET/CT
7. Must be able to communicate with the investigator and understand informed consent.

Exclusion criteria

1. Type 1 diabetes mellitus
2. Chronic pancreatitis / previous acute pancreatitis
3. Known or suspected hypersensitivity to trial product(s) or related products
4. Treatment 90 days prior to screening with oral glucocorticoids, calcineurin inhibitors, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon like peptide-1 agonists and other agents, which in the investigator’s opinion could interfere with the effect of liraglutide
5. Cancer or any other clinically significant disorder, except for conditions associated with type 2 diabetes history, which in the investigators opinion could interfere with the results of the trial
6. Clinical signs of diabetic gastroparesis
7. Previous bowel resection
8. Impaired liver function (transaminases > two times upper reference levels)
9. Inflammatory bowel disease
10. Weight >150 kg
11. Females of childbearing potential who are pregnant, breast-feeding, intend to become pregnant or are not using adequate contraceptive methods
12. Known or suspected abuse of alcohol or narcotics
13. Subjects with personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia type 2
PET/CT imaging

We used a combined PET/CT-scanner (Siemens Biograph mCT64, Siemens, Berlin, Germany). Patients were fasting six hours prior to injection of 4 MBq/kg $^{18}$F-FDG; except for insulin treated patients. Patients with insulin dependent diabetes were allowed to eat a small meal up to two hours before the examination. Fast acting insulin was not to be taken the last two hours before the examination. Blood glucose was measured before injection of the FDG. Patients were scanned two hours ($\pm$15 min) after $^{18}$F-FDG injection, to ensure a low FDG content in the blood as recommended for vascular imaging.1 The PET was acquired in three-dimensional list mode for five min per field of view from head to groin. A low dose CT scan (120 keV, mAs 50) was applied for attenuation correction and anatomical location of the aorta, and a diagnostic CT scan (120 keV, reference mAs 225 (care dose)) of the neck was performed to identify the carotid arteries. The PET images were reconstructed using CT based attenuation correction, with both resolution-recovery (point spread function, TrueX) and time-of-flight (2 iterations, 21 subsets, zoom 1.0) giving 400×400 image slices (voxel size 2.00×2.04×2.04). A 2 mm full-width-at-half-maximum Gaussian filter was then applied. The PET quantification was done using OsiriX MD 11.0 (Pixmeo, Bernex, Switzerland). For analyses the baseline and follow-up examinations were analyzed in parallel to ensure correct alignment between timepoints, however the reader was blinded to the order of the examinations. The carotid arteries, the thoracic aorta and the abdominal aorta was identified and traced with free hand or ellipse regions of interest (ROI) on the axial CT slices without use of the PET images. This was done to diminish any bias the PET signal could cause in the identification of the arteries. Afterwards the ROIs were copied onto the spatially aligned PET examination. The carotids were traced from two cm proximal of the bifurcation and as far distal as the internal carotid artery was identifiable on the non-contrast enhanced CT. The thoracic aorta was traced from the bulb to the diaphragm. The abdominal aorta was traced from the most distal renal artery and to the bifurcation into the iliac arteries. For background correction three ROIs were placed in the lumen of the jugular vein (for carotid correction) and the superior cava vein (for aortic correction).

For each ROI, we quantified the FDG uptake as the standardized uptake value (SUV) by measuring a maximum pixel activity value (SUV$_{max}$). SUV$_{max}$ for each ROI was calculated as time- and dose-corrected tissue radioactivity divided by body weight. We calculated target-to-background ratio (TBR) as a ratio of SUV$_{max}$ and the average blood SUV estimated from venous blood in the superior cava vein or the jugular vein.

On basis of the TBR calculation, we applied three different approaches for the assessment of the arterial FDG uptake as previously described(ref 32):
• In the first approach (active segments) we identified all vessel slices with a TBR value >1.6 on the baseline scan. These slices were averaged to have a single baseline TBR value per patient. The anatomically identical slices were then identified on the follow-up scan and likewise averaged to a single follow-up TBR value per patient.

• In the second approach (most diseased segment) we identified a single small vessel segment (five consecutive slices) around the one vessel-slice with the maximum TBR on the baseline scan. These five slices were averaged to have a single baseline TBR value per patient. The anatomically identical five slices were then identified on the follow-up scan and likewise averaged to a single follow-up TBR value per patient.

• The third approach (whole vessels) included all vessel slices at both baseline and follow-up. TBR from all slices were averaged to have a single baseline TBR value per patient at both baseline and follow-up.

**Coronary artery calcium score (CACS)**

The CACS images were acquired as per clinical routine from a non-contrast breath-hold ECG gated CT immediately before the PET acquisition. The CACS was calculated according to the Agatston method using a threshold of 130 Hounsfield units (ref. 33).

**Ultrasound carotid intima media thickness (CIMT)**

CIMT of the carotid artery was measured along a 10 mm segment of the common carotid artery 10 mm proximal of the sinus caroticus by ultrasound GE Logiq e (GE Healthcare, Chicago, IL) with a linear 12L RS probe (GE Healthcare, Chicago, IL) using a 6.5 MHz transducer with integrated automatic software. The measurement was performed three times on each side and all six readings were averaged.
Endothelial function

Endothelial function was evaluated as 1) reactive hyperemia index using the EndoPat™ (Itamar Medical, Israel) as previously described (ref. 34); and as 2) glycocalyx integrity using a non-invasive handheld Side Dark Field imaging video microscope (Microvision, Medical Inc., Wallingford PA, USA), with integrated software (GlycoCheck® device, Maasticht, The Netherlands). The perfused boundary region, calculated as the distance between the median and the outer edge of the red blood cell perfused lumen in the sublingual capillaries (average over red blood cell columns 5- to 25-μm wide), was used as a measure of glycocalyx integrity. Larger perfused boundary region indicated thinner glycocalyx. Perfused boundary region was measured three times at each visit and averaged.

Blood and urine analysis

Routine blood tests were analysed at the Steno Diabetes Center Copenhagen accredited laboratory. High performance liquid chromatography was used to measure HbA1c, an enzymatic method (Hitachi 912, Roche Diagnostics, Mannheim, Germany) to measure plasma creatinine. To calculate eGFR we used the CKD-EPI equation. Urinary albumin creatinine rate (UACR) was measured by an enzyme immunoassay in two consecutive morning urine samples.

High sensitivity C-Reactive Protein, pro-Brain Natriuretic Peptide, Troponine T, and lipoprotein (a) was measured in lithium-heparin-plasma using Cobas 8000 e801 (Roche Diagnostics, Switzerland) assays following the manufacturer’s instructions. Results below the limit of detection was set at a value between zero and the limit of detection for the statistical analysis. Plasma levels of Vascular Cell Adhesion Molecule 1 (VCAM-1), Intercellular Adhesion Molecule 1 (ICAM-1), Plasminogen Activator Inhibitor-1 (PAI-1), Interleukin-6 (IL-6), Interleukin-18 (IL-18), Tumor Necrosis Factor Alpha (TNF-α), Monocyte Chemoattractant Protein-1 (MCP-1) and Osteopontin (OPN) were determined using Bio-Plex ProTM Magnetic Bead kits (Bio-Rad, Denmark) and the Luminex 200 instrument (Luminex Corporation, USA). Plasma EDTA samples were used. VCAM-1 and ICAM-1 were run in duplex (100-fold dilution of plasma samples), PAI-1 and OPN were run in triplex (3-fold dilution) and IL-6, IL-18, TNF-α and MCP-1 were run in 5-plex (4-fold dilution).

Height, Weight and Blood Pressure

Height and weight were measured at each visit. Blood pressure was measured in the sitting position with a validated device and appropriate cuff size, three measures were obtained and averaged.

Safety assessment

Efficacy and safety parameters were monitored at all visits. Safety assessments included physical examination, vital signs, laboratory tests and adverse event monitoring. Information on adverse events was collected by study personnel and recorded in the case report form. Adverse events included any untoward medical occurrence, unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease.
**Statistical analysis plan**

Primary endpoint: vascular inflammation assessed by FDG PET/CT

Analyses are performed on the carotid arteries (common carotid arteries and beginning of the internal carotid artery) and the aorta (including the ascending thoracic aorta, the aortic arch, the descending thoracic aorta, and the abdominal aorta). Regions of interest (ROI) are manually placed on the entire vasculature obtained from the consecutive coregistered transaxial PET/CT images, each 2 mm in thickness.

The intensity of the FDG uptake is quantified by measuring the standardized uptake value (SUV) within each ROI, by using the maximum pixel activity value (SUVmax). The SUV score for each ROI is calculated as a time- and dose-corrected tissue radioactivity divided by body weight.

The SUVmax score is further corrected for blood activity by dividing the SUV score for each ROI with the average blood SUV estimated from venous blood. This blood corrected artery SUV is also known as target-to-background ratio (TBR).

The arterial FDG-uptake is evaluated and presented as an average for the two carotid arteries and the aorta using three approaches:

1) Active slice analysis: Change in TBR in all “active segments” defined as ROIs with a TBR > 1.6 at baseline.
2) Whole vessel analysis: Change in TBR of “all segments”.
3) Most diseased segment analysis: Change in TBR in the “most diseased segment” defined as five segments containing the ROI with highest TBR value at baseline plus the axial ROIs directly above and below.

The active slice analysis is the primary endpoint. The alternative approaches of FDG evaluations are secondary endpoints.

Other secondary endpoints

- Change from baseline to end of treatment in CACS
- Change from baseline to end of treatment in CIMT
- Change from baseline to end of treatment in endothelial function
- Change from baseline to end of treatment in circulating biomarkers of inflammation and atherosclerosis (IL6, IL-18, TNF-alfa, MCP-1, sVCAM, sICAM-1, PAI-1, hsCRP, TNT, pro-BNP).
### Table I. Reasons for exclusion from the optimal efficacy population

| Reasons for Exclusion                                      | Liraglutide | Placebo |
|------------------------------------------------------------|-------------|---------|
| **Reduced dose of study medication (n=20)**                |             |         |
| Gastrointestinal symptoms                                 | 11          | 1       |
| Hypoglycemia                                               | 1           |         |
| Concurrent illness                                         | 1*          | 2**     |
| Compliance                                                 | 1           | 3†      |
| **Changed lipid-lowering therapy regimen (n=7)**            |             |         |
| Change in dose                                             | 1           | 2       |
| Discontinued therapy                                       | 3           | 1       |
| **Discontinued study medication (n=12)**                   |             |         |
| Gastrointestinal symptoms                                 | 7†          |         |
| Sneeze attack                                              | 1           |         |
| Shoulder pain related to study examination                 |             | 1       |
| Concurrent illness                                         | 1*          | 1***    |
| Motivation                                                 |             | 1†      |
| **Total**                                                  | 27          | 12      |

Numbers of participants with specified event are reported. *Gastro-intestinal disorder; **Cancer, herniated disc; ***Cancer. †1 Participant not FDG/PET CT scanned at follow-up and not part of the intention-to treat population (in total n=3).
Table II: Overview of missing data for primary and secondary endpoints and key clinical characteristics

|                          | Baseline Liraglutide | Baseline Placebo | End-of-treatment Liraglutide | End-of-treatment Placebo |
|--------------------------|----------------------|------------------|----------------------------|--------------------------|
| FDG PET                  | 0                    | 0                | 1                          | 2                        |
| HbA1c                    | 0                    | 0                | 2                          | 3                        |
| Body weight              | 0                    | 0                | 2                          | 3                        |
| Systolic blood pressure  | 0                    | 0                | 2                          | 3                        |
| LDL-cholesterol          | 2                    | 0                | 5                          | 5                        |
| Reactive Hyperemia Index | 0                    | 5                | 0                          | 7                        |
| Glycocalyx integrity*    | 29                   | 28               | 30                         | 28                       |
| Carotid intima media thickness | 0       | 1                | 1                          | 2                        |
| Coronary artery calcium score | 6       | 7                | 3                          | 5                        |
| Biomarkers**             |                      |                  |                            |                          |
| High-sensitivity C-Reactive Protein | 0     | 2                | 0                          | 3                        |
| Pro Brain Natriuretic Peptide | 0     | 0                | 2                          | 3                        |
| Interleukin-6            | 3                    | 5                | 7                          | 10                       |
| Monocyte Chemoattractant Protein-1 | 0     | 0                | 2                          | 3                        |
| Vascular Cell Adhesion Molecule 1 | 1     | 0                | 3                          | 2                        |
| Intercellular Adhesion Molecule 1 | 1     | 0                | 3                          | 2                        |
| Interleukin-18           | 0                    | 0                | 2                          | 3                        |
| Plasminogen Activator Inhibitor-1 | 0     | 0                | 2                          | 3                        |
| Osteopontin              | 0                    | 0                | 2                          | 3                        |
| Tumor Necrosis Factor Alpha | 6      | 9                | 4                          | 7                        |
| Troponine T              | 0                    | 0                | 2                          | 3                        |
| Lipoprotein (a)          | 0                    | 0                | 2                          | 3                        |

*Technical issues with the Glycocheck device resulted in low number of measurements **Samples for biomarker analysis was available for all patients at baseline, and for 49 patients at follow up, and missing values besides these are due to technical difficulties related to the measurements. Only observed data were part of the analyses, no imputation was made and if data was missing exclusion was case-wise
Table III. Arterial vascular inflammation in different vascular beds

| Group | Mean TBR (SD) | P value | Δ TBR (95% CI) | P value |
|-------|--------------|---------|---------------|---------|
|       | Baseline     | End-of-treatment |            |         |
| **Carotid arteries** |              |                 |            |         |
|       |              | **Active segments** | Liraglutide, n = 47 | 1.9 (0.34) | 1.8 (0.30) | 0.02 | -0.15 (-0.28; -0.03) | 0.96 |
|       |              | Placebo, n = 43  | 1.9 (0.25) | 1.7 (0.38) | 0.03 | -0.15 (-0.28; -0.02) |         |
|       |              | **Most diseased segment** | Liraglutide, n = 50 | 2.1 (0.62) | 1.9 (0.44) | 0.02 | -0.21 (-0.39; -0.04) | 0.62 |
|       |              | Placebo, n = 49  | 2.0 (0.60) | 1.7 (0.47) | 0.008 | -0.28 (-0.49; -0.08) |         |
|       |              | **Whole vessels** | Liraglutide, n = 50 | 1.8 (0.41) | 1.7 (0.29) | 0.55 | -0.03 (-0.17; 0.09) | 0.85 |
|       |              | Placebo, n = 49  | 1.7 (0.35) | 1.7 (0.38) | 0.72 | -0.02 (-0.14; 0.10) |         |
| **Aortic arch** |              | **Active segments** | Liraglutide, n = 50 | 2.0 (0.33) | 2.1 (0.39) | 0.89 | 0.01 (-0.13; 0.15) | 0.48 |
|       |              | Placebo, n = 48  | 2.0 (0.33) | 1.9 (0.33) | 0.33 | -0.05 (-0.16; 0.05) |         |
|       |              | **Most diseased segment** | Liraglutide, n = 50 | 2.4 (0.47) | 2.2 (0.54) | 0.07 | -0.16 (-0.33; 0.01) | 0.47 |
|       |              | Placebo, n = 48  | 2.2 (0.54) | 1.9 (0.44) | 0.003 | -0.24 (-0.40; -0.09) |         |
|       |              | **Whole vessels** | Liraglutide, n = 50 | 1.9 (0.39) | 2.0 (0.39) | 0.27 | 0.08 (-0.06; 0.22) | 0.52 |
|       |              | Placebo, n = 48  | 1.9 (0.40) | 1.9 (0.34) | 0.73 | 0.02 (-0.10; 0.13) |         |
| **Abdominal aorta** |              | **Active segments** | Liraglutide, n = 49 | 2.1 (0.40) | 2.1 (0.60) | 0.89 | -0.01 (-0.18; 0.15) | 0.24 |
|       |              | Placebo, n = 49  | 2.0 (0.34) | 1.9 (0.34) | 0.02 | -0.13 (-0.24; -0.02) |         |
|       |              | **Most diseased segment** | Liraglutide, n = 50 | 2.3 (0.74) | 2.2 (0.70) | 0.15 | -0.13 (-0.32; 0.05) | 0.53 |
|       |              | Placebo, n = 49  | 2.2 (0.57) | 2.0 (0.51) | 0.009 | -0.21 (-0.36; -0.06) |         |
|       |              | **Whole vessels** | Liraglutide, n = 50 | 1.9 (0.49) | 2.0 (0.58) | 0.17 | 0.12 (-0.05; 0.29) | 0.33 |
|       |              | Placebo, n = 49  | 1.8 (0.42) | 1.9 (0.32) | 0.76 | 0.02 (-0.10; 0.13) |         |

Data are mean (SD) and change (95% CI). Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of the change from baseline to end-of-treatment between the two groups. TBR=Target-to-background-ratio.
Table IV. Changes in circulating biomarkers

| Group                                      | Median [IQR] Baseline          | End-of-treatment          | P value | Median change [IQR] | P value |
|--------------------------------------------|-------------------------------|---------------------------|---------|--------------------|---------|
| Vascular Cell Adhesion Molecule 1 (VCAM-1) ng/ml |                               |                           |         |                    |         |
| Liraglutide, n=47                          | 376.1 [285.7; 490.5]          | 409.0 [323.7; 471.2]      | 0.84    | 39.8 [-40.1; 75.8] | 0.34    |
| Placebo, n=49                              | 377.8 [301.2; 452.8]          | 389.4 [340.5; 446.7]      | 0.03    | 36.0 [-22.7; 93.6] |         |
| Intercellular Adhesion Molecule 1 (ICAM-1) ng/ml |                               |                           |         |                    |         |
| Liraglutide, n=47                          | 64.8 [52.8; 84.9]             | 74.6 [62.6; 83.5]         | 0.54    | 7.8 [-11.3; 19.4]  | 0.12    |
| Placebo, n=49                              | 64.1 [53.2; 81.3]             | 71.6 [65.4; 89.6]         | 0.0001  | 11.9 [11.1; 20.2]  |         |
| Interleukin-18 (IL-18) pg/ml               |                               |                           |         |                    |         |
| Liraglutide, n=49                          | 67.2 [39.7; 85.7]             | 45.7 [34.0; 62.8]         | <0.0001 | -14.9 [-27.8; -2.6] | 0.08    |
| Placebo, n=48                              | 60.1 [42.1; 78.0]             | 50.2 [36.1; 64.4]         | <0.0001 | -9.3 [-19.9; 0.57] |         |
| Plasminogen Activator Inhibitor-1 (PAI-1) pg/ml |                               |                           |         |                    |         |
| Liraglutide, n=49                          | 1296 [634; 2085]              | 1327 [900; 1807]          | 0.19    | 55 [-243; 316]     | 0.29    |
| Placebo, n=48                              | 1180 [619; 1696]              | 1438 [808; 1901]          | 0.005   | 252 [-173; 594]    |         |
| Osteopontin (OPN) ng/ml                    |                               |                           |         |                    |         |
| Liraglutide, n=49                          | 23.3 [19.1; 27.8]             | 28.3 [25.0; 32.1]         | <0.0001 | 4.8 [1.8; 9.6]     | 0.74    |
| Placebo, n=48                              | 21.4 [18.7; 26.0]             | 27.3 [22.8; 34.0]         | <0.0001 | 6.0 [1.1; 13.1]    |         |
| Tumor Necrosis Factor Alpha (TNF-α) pg/ml  |                               |                           |         |                    |         |
| Liraglutide, n=41                          | 13.0 [9.2; 16.7]              | 10.7 [8.2; 20.0]          | 0.92    | -0.39 [-6.0; 4.6]  | 0.78    |
| Placebo, n=37                              | 13.0 [9.2; 15.8]              | 13.2 [8.2; 18.1]          | 0.62    | -1.0 [-3.7; 5.1]   |         |
| Tropinone T (TNT) ng/L                     |                               |                           |         |                    |         |
| Liraglutide, n=49                          | 6.5 [6.5; 13.5]               | 6.5 [6.5; 16.4]           | 0.03    | 0 [0; 0]           | 0.62    |
| Placebo, n=48                              | 6.5 [6.5; 13.5]               | 6.5 [6.5; 14.0]           | 0.11    | 0 [0; 0]           |         |
| Lipoprotein (a) [Lp(a)] mg/L               |                               |                           |         |                    |         |
| Liraglutide, n=49                          | 41.5 [41.5; 120.2]            | 41.5 [41.5; 105.8]        | 0.99    | 0 [0; 0]           | 0.47    |
| Placebo, n=48                              | 41.5 [41.5; 89.4]             | 41.5 [41.5; 41.5]         | 0.41    | 0 [0; 0]           |         |

Data are median [IQR] or median change [IQR]. Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of the change from baseline to end-of-treatment between the two groups (change in log2 values).

There was no effect of liraglutide on a weighted sum score of the 7 markers of inflammation (High-sensitivity C-reactive Protein, Interleukin-18, Interleukin-6, Vascular Cell Adhesion Molecule 1, Intercellular Adhesion Molecule 1, Monocyte Chemoattractant Protein-1 and Tumor Necrosis Factor Alpha), results not shown.
Table V. Arterial vascular inflammation. Optimal efficacy population

| Group               | Mean TBR (SD)          | P value | Δ TBR (95% CI)   | P value |
|---------------------|------------------------|---------|------------------|---------|
|                     | Baseline | End-of-treatment |          |                     |         |
| Active segments     |           |                  |          |                     |         |
| Liraglutide, n = 24 | 2.0 (0.23) | 2.1 (0.47) | 0.34 | 0.09 (-0.10; 0.28) | 0.052* |
| Placebo, n = 39     | 2.0 (0.30) | 1.9 (0.29) | 0.053 | -0.11 (-0.22; -0.002) |         |
| Most diseased segment |           |                  |          |                     |         |
| Liraglutide, n = 24 | 2.6 (0.69) | 2.5 (0.79) | 0.64 | -0.05 (-0.29; 0.18) | 0.27    |
| Placebo, n = 39     | 2.4 (0.57) | 2.2 (0.50) | 0.02 | -0.21 (-0.39; -0.04) |         |
| Whole vessels       |           |                  |          |                     |         |
| Liraglutide, n = 24 | 1.9 (0.29) | 2.0 (0.42) | 0.052 | 0.17 (-0.00; 0.35) | 0.08    |
| Placebo, n = 39     | 1.8 (0.36) | 1.8 (0.28) | 1.0 | -0.00 (-0.11; 0.11) |         |

Data are mean (SD) or change (95 % CI). Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of the change from baseline to end-of-treatment between the two groups. *Primary endpoint. TBR=Target-to-background-ratio.
Table VI. Arterial vascular inflammation in different vascular beds. Optimal efficacy population

| Group | Mean TBR (SD) | P value | ∆ TBR (95% CI) | P value |
|-------|---------------|---------|----------------|---------|
|       | Baseline | End-of-|               |         |
|       | treatment | treatment |               |         |
| Carotid arteries | | | | |
| **Active segments** | | | | |
| Liraglutide, n = 24 | 1.9 (0.21) | 1.8 (0.28) | 0.39 | -0.06 (-0.19; 0.08) | 0.35 |
| Placebo, n = 39 | 1.8 (0.18) | 1.7 (0.36) | 0.03 | -0.15 (-0.28; -0.02) | | |
| **Most diseased segment** | | | | |
| Liraglutide, n = 24 | 1.9 (0.48) | 1.8 (0.42) | 0.32 | -0.09 (-0.06; 0.20) | 0.18 |
| Placebo, n = 39 | 1.9 (0.43) | 1.7 (0.31) | 0.002 | -0.01 (-0.13; 0.10) | | |
| **Whole vessels** | | | | |
| Liraglutide, n = 24 | 1.7 (0.29) | 1.7 (0.28) | 0.26 | 0.07 (-0.06; 0.17) | 0.34 |
| Placebo, n = 39 | 1.6 (0.30) | 1.6 (0.36) | 0.82 | -0.03 (-0.15; 0.09) | | |
| Aortic arch | | | | |
| **Active segments** | | | | |
| Liraglutide, n = 24 | 2.0 (0.28) | 2.1 (0.45) | 0.29 | 0.10 (-0.10; 0.30) | 0.10 |
| Placebo, n = 39 | 2.0 (0.35) | 1.9 (0.32) | 0.23 | -0.07 (-0.19; 0.05) | | |
| **Most diseased segment** | | | | |
| Liraglutide, n = 24 | 2.3 (0.45) | 2.3 (0.52) | 0.43 | -0.08 (-0.29; 0.13) | 0.20 |
| Placebo, n = 39 | 2.2 (0.59) | 2.0 (0.45) | 0.006 | -0.26 (-0.45; -0.08) | | |
| **Whole vessels** | | | | |
| Liraglutide, n = 24 | 1.9 (0.36) | 2.1 (0.44) | 0.13 | 0.16 (-0.05; 0.36) | 0.16 |
| Placebo, n = 39 | 1.9 (0.42) | 1.9 (0.33) | 0.97 | -0.002 (-0.13; 0.13) | | |
| Abdominal aorta | | | | |
| **Active segments** | | | | |
| Liraglutide, n = 24 | 2.1 (0.37) | 2.3 (0.71) | 0.11 | 0.21 (-0.05; 0.46) | 0.02 |
| Placebo, n = 39 | 2.0 (0.36) | 1.9 (0.33) | 0.05 | -0.13 (-0.26; -0.003) | | |
| **Most diseased segment** | | | | |
| Liraglutide, n = 24 | 2.3 (0.74) | 2.4 (0.84) | 0.27 | 0.13 (-0.11; 0.34) | 0.04 |
| Placebo, n = 39 | 2.2 (0.61) | 2.0 (0.51) | 0.06 | -0.17 (-0.36; -0.01) | | |
| **Whole vessels** | | | | |
| Liraglutide, n = 24 | 1.9 (0.43) | 2.2 (0.69) | 0.02 | 0.31 (0.06; 0.57) | 0.05 |
| Placebo, n = 39 | 1.8 (0.44) | 1.9 (0.31) | 0.68 | 0.03 (-0.11; 0.16) | | |

Data are mean (SD) and change (95 % CI). Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of the change from baseline to end-of-treatment between the two groups. TBR=Target-to-background-ratio.
Table VII. Adverse events divided by treatment allocation and organ system

| Organ System                                      | Liraglutide, n=51 | Placebo, n=51 |
|---------------------------------------------------|-------------------|---------------|
| Gastro-intestinal symptoms                       | 41                | 18            |
| Dizziness                                         | 3                 | 4             |
| Headache                                          | 5                 | 1             |
| Tiredness                                         | 5                 | 5             |
| Hypoglycemia                                      | 1                 | 0             |
| Blood and lymphatic system disorders              | 1                 | 0             |
| Cardiac disorders                                 | 5                 | 7             |
| Ear and labyrinth disorders                       | 4                 | 1             |
| Endocrine disorders                               | 1                 | 1             |
| Eye disorders                                     | 3                 | 0             |
| General disorders and administration site conditions | 1                 | 1             |
| Hepatobiliary disorders                           | 0                 | 1             |
| Infections and infestations                       | 5                 | 9             |
| Injury, poisoning and procedural complications     | 0                 | 3             |
| Eye disorders                                     | 3                 | 0             |
| Nervous system disorders                          | 1                 | 0             |
| Metabolic and nutrition disorders                 | 0                 | 1             |
| Musculoskeletal and connective tissue disorders    | 1                 | 6             |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 1 | 0 |
| Renal and urinary disorders                       | 1                 | 1             |
| Respiratory, thoracic and mediastinal disorders    | 2                 | 2             |
| Skin and subcutaneous tissue disorders            | 2                 | 2             |
| Surgical and medical procedures                   | 2                 | 3             |
| Total                                             | 95                | 68            |

Adverse events within the same organ system has been reported once for each patient.
Table VIII. Serious adverse events divided by treatment allocation and organ system

| Organization of the Body System                                      | Liraglutide, n=51 | Placebo, n=51 |
|---------------------------------------------------------------------|-------------------|---------------|
| Blood and lymphatic system disorders                                | 0                 | 1             |
| Gastrointestinal disorders                                          | 2                 | 0             |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 2                 | 3             |
| Surgical and medical procedures                                     | 0                 | 1             |
| **Total**                                                           | **4**             | **5**         |
Table IX. Capillary blood glucose

| Group               | Mean Capillary blood glucose (SD) (mmol/l) | P value | Δ Capillary blood glucose (95% CI) | P value |
|---------------------|-------------------------------------------|---------|-----------------------------------|---------|
|                     | Baseline | End-of-treatment |                     |         |
| Liraglutide, n = 43 | 7.9 (1.9) | 7.7 (2.6) | 0.64 | -0.2 (-0.9; 0.6) | 0.30 |
| Placebo, n = 46    | 7.5 (2.5) | 7.9 (2.9) | 0.32 | 0.4 (-0.4; 1.2) |
| P value            | 0.42     | 0.74     |       |                     |

Data are mean (SD) or change (95 % CI). Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of level at baseline and end-of-treatment in the two treatment groups and of the change from baseline to end-of-treatment between the two groups.
Table X. Arterial vascular inflammation adjusted for blood glucose at time of imaging

| Group                  | Mean TBR (SD) | P value | Δ TBR (95% CI) | P value |
|------------------------|--------------|---------|----------------|---------|
|                        | Baseline     | End-of-treatment |
| **Active segments**    |              |          |                |         |
| Liraglutide, n = 43    | 3.3 (1.04)   | 3.0 (1.04) | 0.18 | -0.23 (-0.57; 0.11) | 0.18 |
| Placebo, n = 46        | 2.9 (1.00)   | 2.9 (0.99) | 0.90 | -0.01 (-0.34; 0.30) | 0.37 |
| **Most diseased segment** |          |          |                |         |
| Liraglutide, n = 42    | 4.3 (1.69)   | 3.7 (1.71) | 0.04 | -0.52 (-1.03; -0.02) | 0.04 |
| Placebo, n = 46        | 3.5 (1.37)   | 3.3 (1.12) | 0.32 | -0.21 (-0.62; 0.21) | 0.33 |
| **Whole vessels**      |              |          |                |         |
| Liraglutide, n = 43    | 3.0 (0.92)   | 3.0 (0.99) | 0.74 | -0.06 (-0.39; 0.28) | 0.64 |
| Placebo, n = 46        | 2.7 (0.92)   | 2.8 (0.93) | 0.31 | 0.15 (-0.14; 0.44) | 0.35 |

Data are mean (SD) or change (95% CI). Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of the change from baseline to end-of-treatment between the two groups. TBR=Target-to-background-ratio.
Table XI. Changes in biomarkers in patients with and without cardiovascular disease

| Group                                    | Median [IQR] Baseline | End-of-treatment | P value | Median change [IQR] | P value |
|------------------------------------------|-----------------------|------------------|---------|---------------------|---------|
| Vascular Cell Adhesion Molecule 1 (VCAM-1) ng/ml | 433.2 [322.1; 610.6] | 459.3 [324.9; 584.4] | 0.46 | 28.2 [-40.2; 47.4] | 0.995 |
| Liraglutide, n=12                        | 359.5 [310.6; 389.3] | 349.4 [289.0; 389.4] | 0.71 | 29.9 [-39.9; 48.8] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Interleukin-6 (IL-6) pg/ml                | 1.3 [0.87; 2.2]       | 0.94 [0.78; 1.7] | 0.11 | -0.26 [-1.1; 0.03] | 0.18   |
| Liraglutide, n=11                        | 1.0 [0.83; 1.1]       | 1.0 [0.66; 1.3] | 0.70 | 0.04 [-0.21; 0.08] |         |
| Placebo, n=6                             |                       |                  |         |                     |         |
| Interleukin-8 (IL-18) pg/ml              | 56.7 [39.7; 68.3]     | 42.8 [33.3; 48.5] | 0.09 | -5.8 [-22.6; -1.1] | 0.62   |
| Liraglutide, n=13                        | 48.1 [31.5; 75.2]     | 43.5 [29.3; 60.3] | 0.16 | -4.6 [-17.8; 1.5]  |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Monocyte Chemoattractant Protein-1 (MCP-1) pg/ml | 20.6 [15.0; 23.1]  | 14.4 [10.4; 16.5] | <0.0001 | -10.1 [-11.5; -4.0] | 0.16   |
| Liraglutide, n=13                        | 21.3 [15.4; 22.7]     | 13.6 [12.2; 16.8] | 0.0001 | -5.4 [-6.2; -3.0]  |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Plasminogen activator inhibitor-1 (PAI-1) pg/ml | 1196 [1130; 1725] | 1424 [1093; 1766] | 0.998 | -68 [-189; 119] | 0.55   |
| Liraglutide, n=13                        | 872 [531; 1288]       | 1139 [706; 1292] | 0.47 | 175 [-255; 368] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Osteopontin (OPN) ng/ml ng/ml             | 23.0 [19.0; 25.3]     | 27.7 [24.9; 31.4] | 0.09 | 4.7 [1.1; 9.6] | 0.42   |
| Liraglutide, n=13                        | 19.3 [16.8; 23.6]     | 26.0 [23.9; 35.3] | 0.04 | 7.7 [0.3; 12.9] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Tumor Necrosis Factor Alpha (TNFα) pg/ml  | 13.0 [9.2; 22.1]      | 11.9 [7.9; 20.3] | 0.41 | -4.8 [-6.5; 1.8] | 0.84   |
| Liraglutide, n=8                         | 12.0 [9.2; 14.8]      | 8.2 [6.9; 14.4]  | 0.44 | -2.9 [-7.9; 5.2] |         |
| Placebo, n=6                             |                       |                  |         |                     |         |
| High-sensitivity C-reactive Protein (hsCRP) mg/L | 2.1 [1.1; 3.3] | 1.8 [1.0; 2.9] | 0.67 | -0.17 [-0.91; 0.58] | 0.50   |
| Liraglutide, n=13                        | 0.75 [0.49; 1.5]      | 0.63 [0.53; 0.92] | 0.24 | -0.13 [-0.46; 0.14] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Pro Brain Natriuretic Peptide (proBNP) pmol/L | 9.9 [6.7; 18.5] | 7.4 [3.0; 13.9] | 0.61 | -0.54 [-0.01] | 0.47   |
| Liraglutide, n=13                        | 10.5 [7.2; 15.7]      | 12.8 [3.0; 39.0] | 0.61 | 2.3 [0; 9.2] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Tropomin T (TNT) ng/L                    | 6.5 [6.5; 13.5]       | 6.5 [6.5; 18.2]  | 0.06 | 0 [0; 5.7] | 0.40   |
| Liraglutide, n=13                        | 6.5 [6.5; 6.5]        | 6.3 [6.5; 13.6] | 0.47 | 0 [0; 0] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |
| Lipoprotein (a) (Lp(a)) mg/L             | 41.5 [41.5; 120.2]    | 41.5 [41.5; 105.8] | 0.19 | 0 [-14.4; 0] | 0.28   |
| Liraglutide, n=13                        | 41.5 [41.5; 123.7]    | 41.5 [41.5; 98.6] | 0.52 | 0 [0; 0] |         |
| Placebo, n=9                             |                       |                  |         |                     |         |

Data are median [IQR] or median change [IQR]. Paired t-test for comparisons between baseline and end-of-treatment within groups and unpaired t-test for comparison of the change from baseline to end-of-treatment between the two groups (change in log2 values)

In the subgroup of patients with and without cardiovascular disease, there was no effect of liraglutide on a weighted sum score of the 7 markers of inflammation (High-sensitivity C-reactive Protein, Interleukin-18, Interleukin-6, Vascular Cell Adhesion Molecule 1, Intercellular Adhesion Molecule 1, Monocyte Chemoattractant Protein-1 and Tumor Necrosis Factor Alpha), results not shown.
