THE LANCET
Gastroenterology & Hepatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Loomba R, Abdelmalek MF, Armstrong MJ, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2023; published online March 16. https://doi.org/10.1016/S2468-1253(23)00068-7.

Supplementary Appendix

Contents

Further information on laboratory measurements

Very low-density lipoprotein cholesterol was calculated and low-density lipoprotein was measured; testcodes were used for this in the study.

Free Fatty Acids were measured using an enzymatic method at ICON Laboratories.

Pro-collagen 3 peptide was measured using an ELISA method at the referral laboratory (Nordic Biosciences).

High-sensitivity C-reactive protein was measured using a turbidimetric/immunoturbidimetric method at ICON Laboratories.

All other laboratory parameters were measured and validated according to standard procedures.

Further information on statistical analyses

Analysis of endpoints was based on the full analysis set for efficacy and the safety analysis set for adverse events.

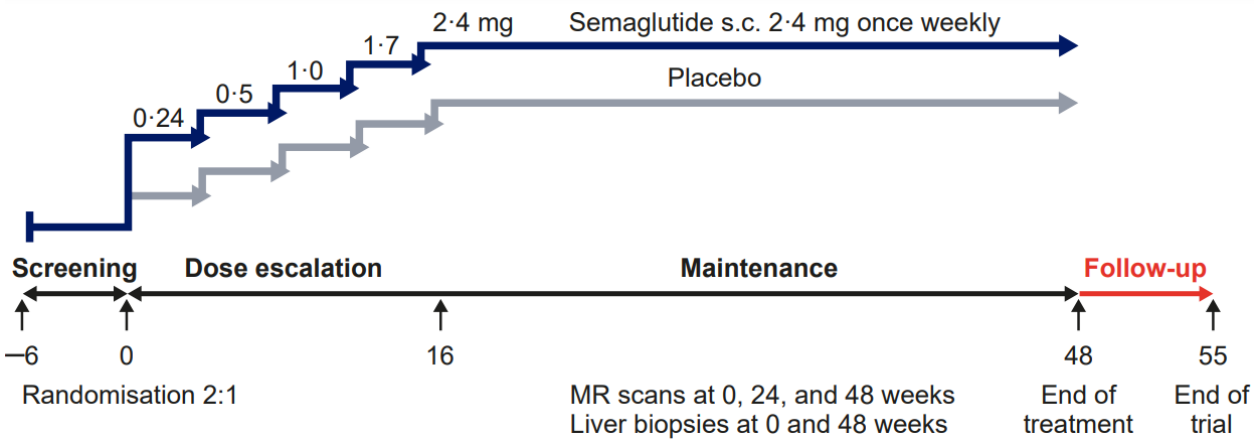
The primary analysis was analysed based on the Cochran–Mantel–Haenszel test. The common odds ratio between semaglutide and placebo, adjusting for baseline type 2 diabetes, was estimated along with exact 95% confidence interval (CI) based on conditioning on the marginal 2×2 tables. To test for superiority, the exact two-sided p-value was calculated as the sum of probabilities of outcomes having equal or lower probability than the observed outcome under the null hypothesis conditioning on the marginal 2×2 tables.

A sensitivity analysis was performed in which missing data were handled by reference-based multiple imputation informed by data from patients receiving placebo. It was assumed that, regardless of treatment group, patients with missing data for an observed outcome had the same chances of meeting the endpoint as patients in the placebo group who had an observed outcome. A supportive complete case on-treatment analysis, in which patients with missing week 48 data or for whom the data were collected after the on-treatment period were excluded, was also conducted.

Continuous endpoints were analysed using an analysis of covariance (ANCOVA) with missing outcomes handled by unconditional reference-based imputation. An ANCOVA model with baseline diabetes status as factor and baseline body weight and baseline value of the corresponding biomarker as covariates was fitted to the change from baseline to week 48 for the placebo group only. Using the fitted model, 500 sets of values of the model parameters (regression coefficients and residual variance) were drawn from the posterior distribution of the estimators. For each draw of parameter values, missing week 48 outcomes across treatment groups were imputed as predicted values from the linear combination of drawn model parameters and data. Patients with missing covariates, eg, baseline measurement, were not included. For each of the 500 complete data sets, the treatment effect on change from baseline to week 48 was estimated using an ANCOVA model with treatment and baseline diabetes status as factors, and baseline body weight and baseline biomarker as covariates. The estimated treatment differences and standard errors were pooled using Rubin's rule. From the pooled estimates and standard errors, 95% CIs for treatment difference and associated two-sided p-values were calculated. In cases where a log-transformation was deemed relevant, the treatment effect is given by the estimated treatment ratio.

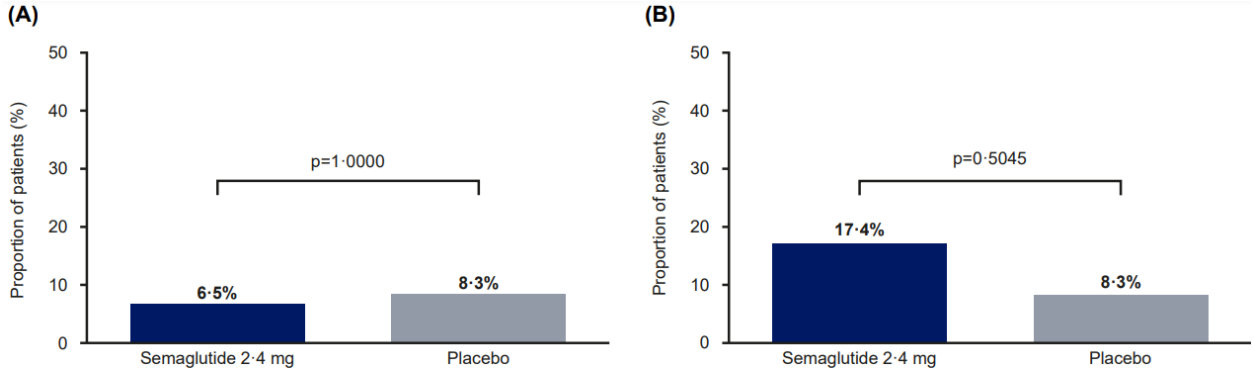
For the supportive secondary endpoints, ordinal histological feature scores (ie, excluding hepatic collagen) were analysed by ordered logistic regression with the histological scores at week 48 as response; treatment and baseline diabetes status as factors; and baseline body weight and corresponding histological score at baseline as covariates. The results are presented as the estimated cumulative odds ratio between semaglutide and placebo. Change in hepatic collagen from baseline to week 48 was analysed using ANCOVA and mixed model for repeated measures. Binary histological endpoints including non-alcoholic steatohepatitis (NASH) resolution after 48 weeks (NASH Clinical Research Network value of hepatocyte ballooning of 0 and lobular inflammation score 0–1) were analysed in the same way as the primary endpoint. Safety outcomes were analysed descriptively.

***Supplementary Figure S1*: Trial design**



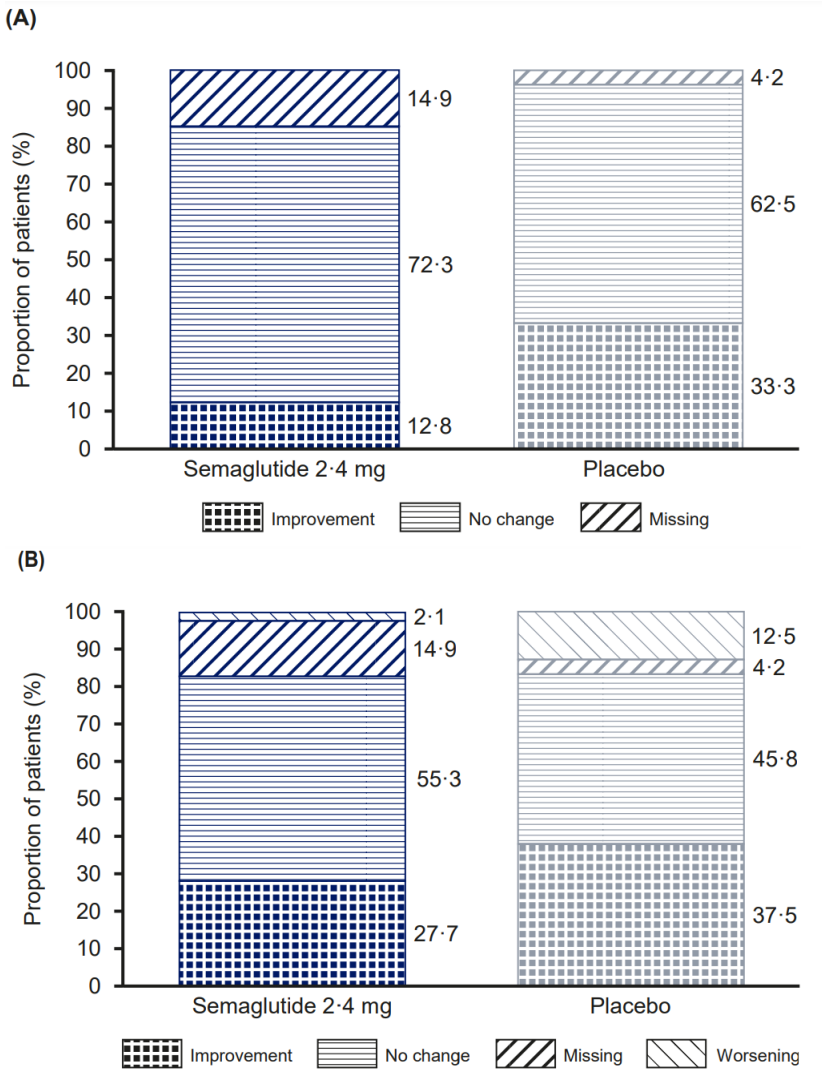
MR=magnetic resonance. s.c.=subcutaneous.

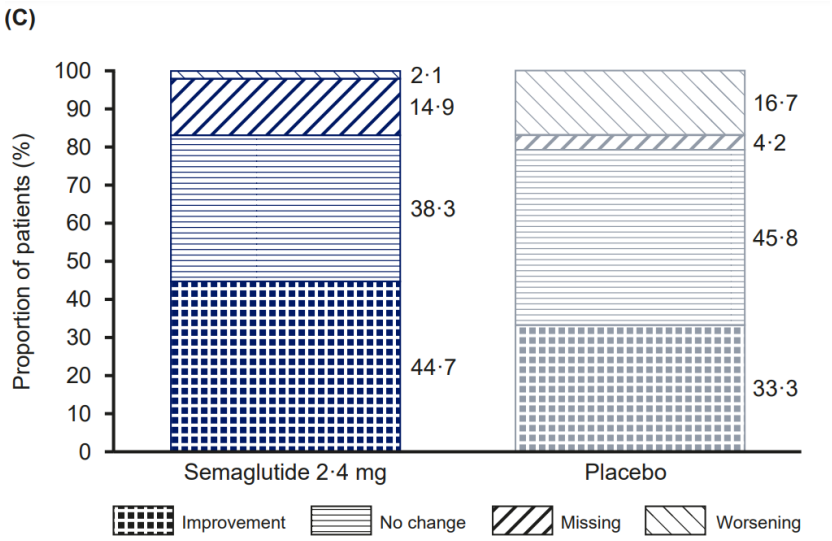
Supplementary Figure S2: **Histological outcomes assessed by PathAI machine learning software after 48 weeks' treatment: (A) improvement in fibrosis and no worsening of NASH (primary endpoint) and (B) NASH resolution (key secondary endpoint)**

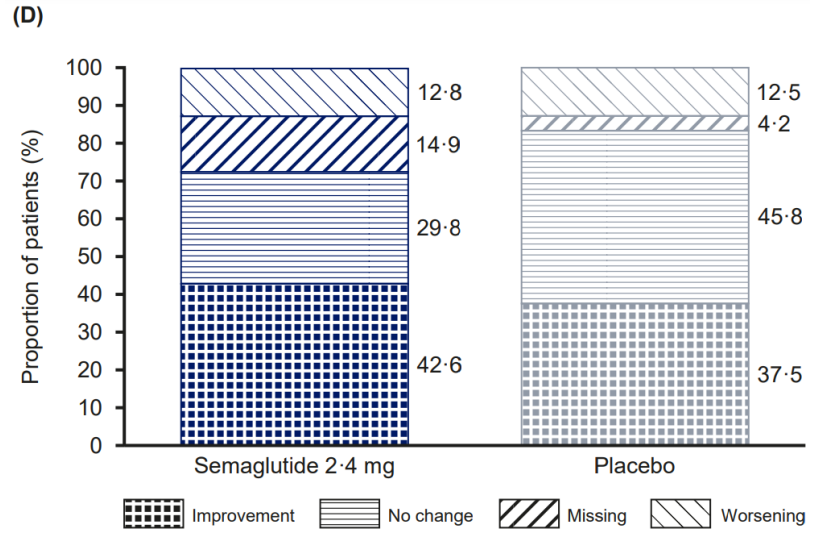


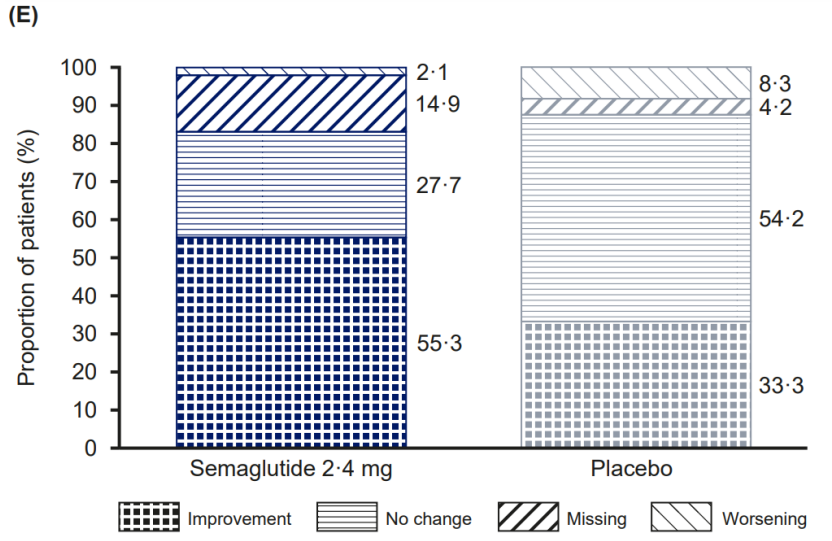
Data based on in-trial period. Two-sided p-values from a Cochran–Mantel–Haenszel test. Patients with missing data handled as non-responders. N=70 evaluated by PATH-AI (the biopsy of one patient in the semaglutide group could not be assessed) and 71 evaluated by pathologist. NASH=non-alcoholic steatohepatitis.

Supplementary Figure S3: **Change from baseline to week 48 in ordinal histological endpoints: (A) NASH CRN fibrosis stage, (B) Ishak fibrosis score, (C) steatosis grade, (D) lobular inflammation, (E) hepatocyte ballooning, (F) NAS, (G) SAF score**

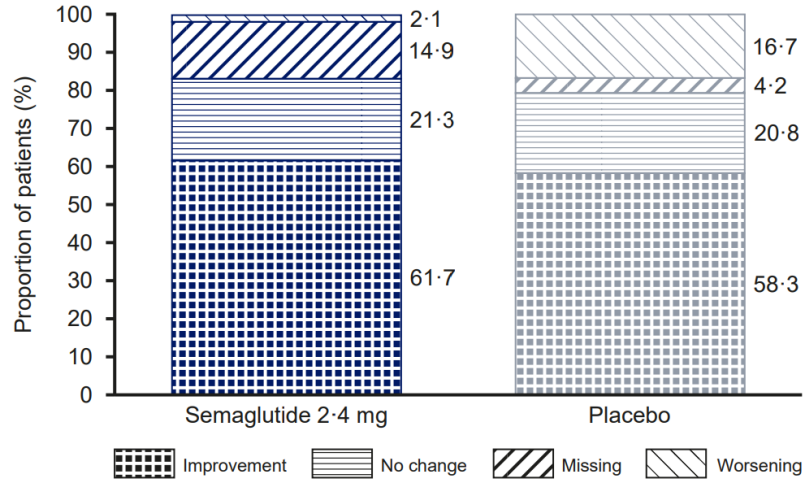



(C)
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
2·1
14·9
38·3
44·7
16·7
4·2
45·8
33·3
Semaglutide 2·4 mg
Placebo
Improvement
No change
Missing
Worsening

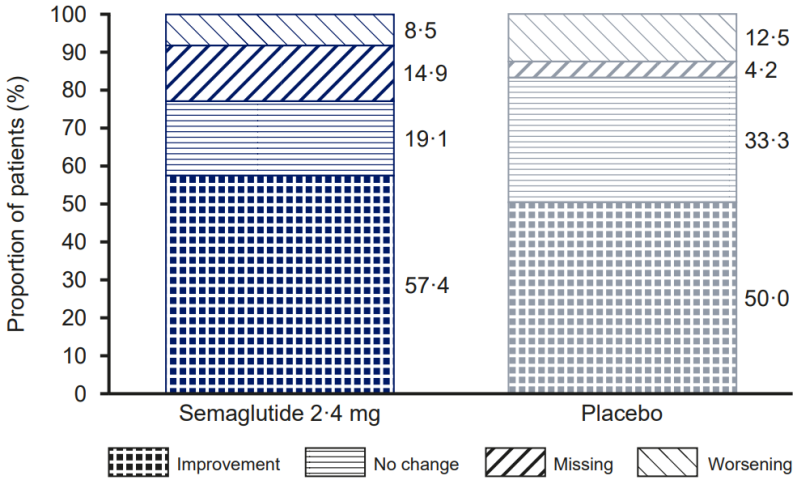

(D)
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
12·8
14·9
29·8
42·6
12·5
4·2
45·8
37·5
Semaglutide 2·4 mg
Placebo
Improvement
No change
Missing
Worsening


(E)
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
2·1
14·9
27·7
55·3
8·3
4·2
54·2
33·3
Semaglutide 2·4 mg
Placebo
Improvement
No change
Missing
Worsening

(F)

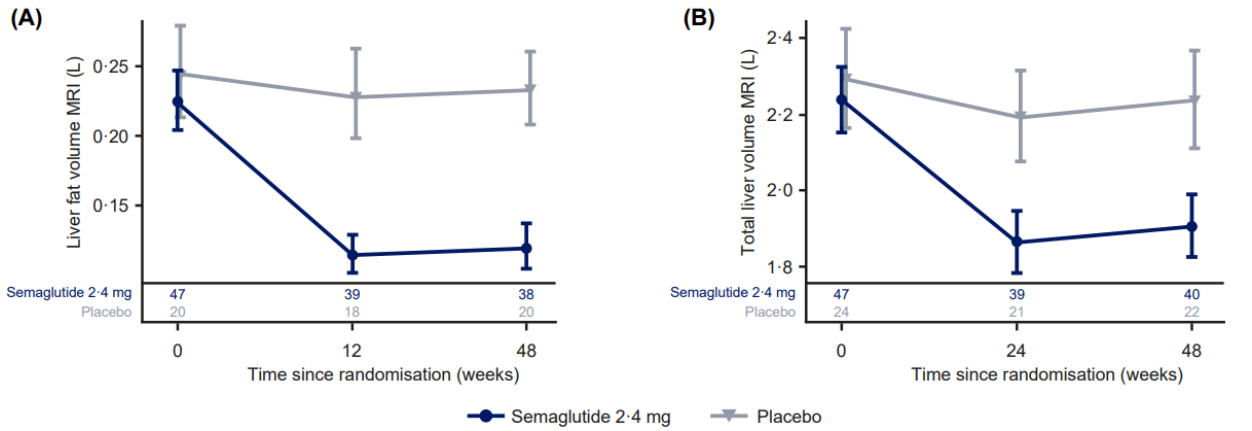


(G)



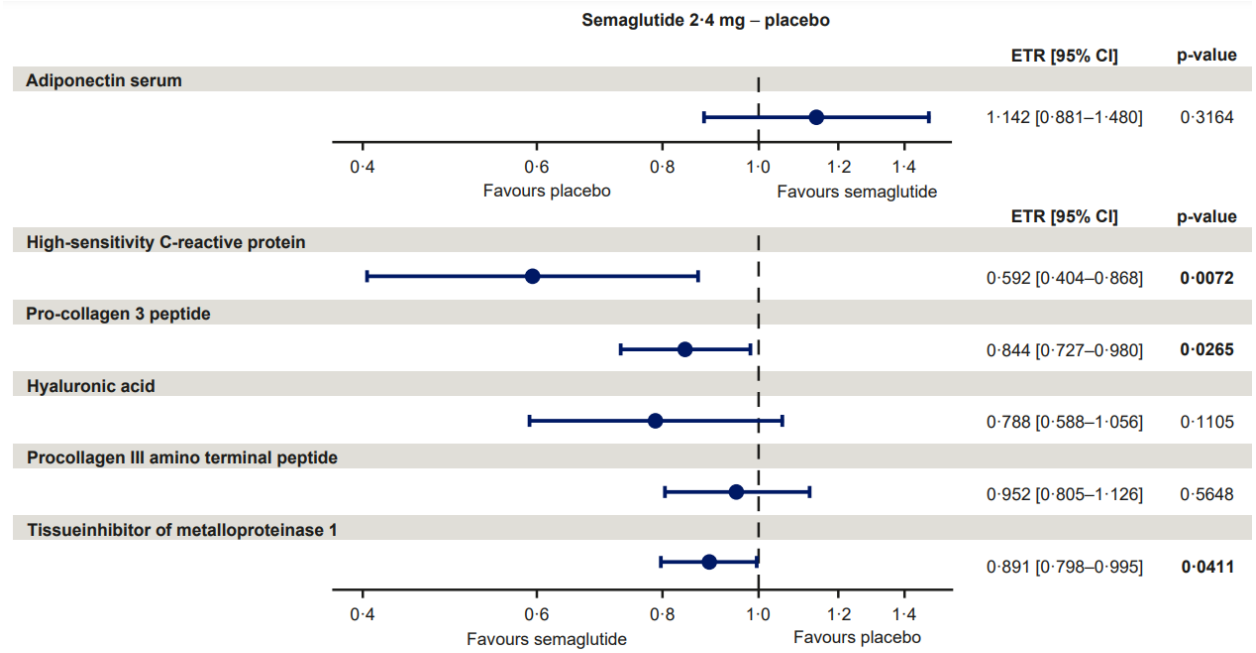
CRN=Clinical Research Network. NAS=non-alcoholic fatty liver disease activity score. NASH=non-alcoholic steatohepatitis. SAF=steatosis-activity-fibrosis.

Supplementary Figure S4: **Supportive liver imaging outcomes at baseline, week 24, and week 48: (A) liver fat volume and (B) total liver volume**



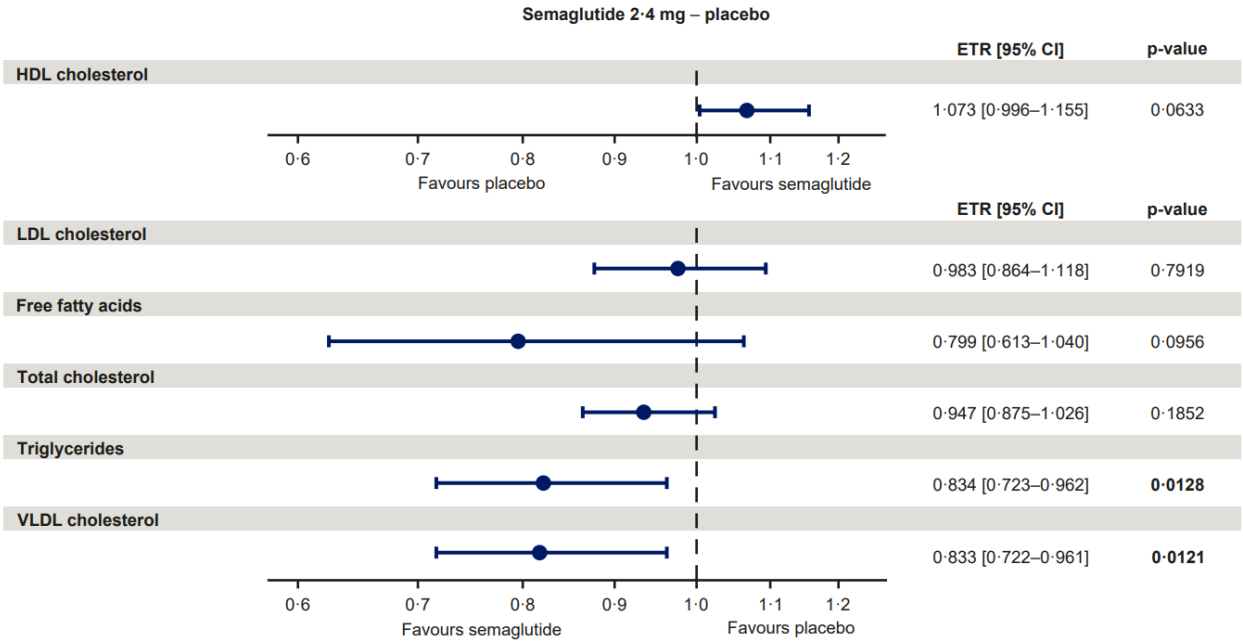
Numbers shown in the lower panel represent the number of patients contributing to the data at each time point. Data are estimated means at the landmark visit from an analysis of covariance with multiple imputation. Error bars show the standard error of the mean of observed values and 95% confidence limits of estimated means. MRI=magnetic resonance imaging.

***Supplementary Figure S5*: Exploratory biomarkers**



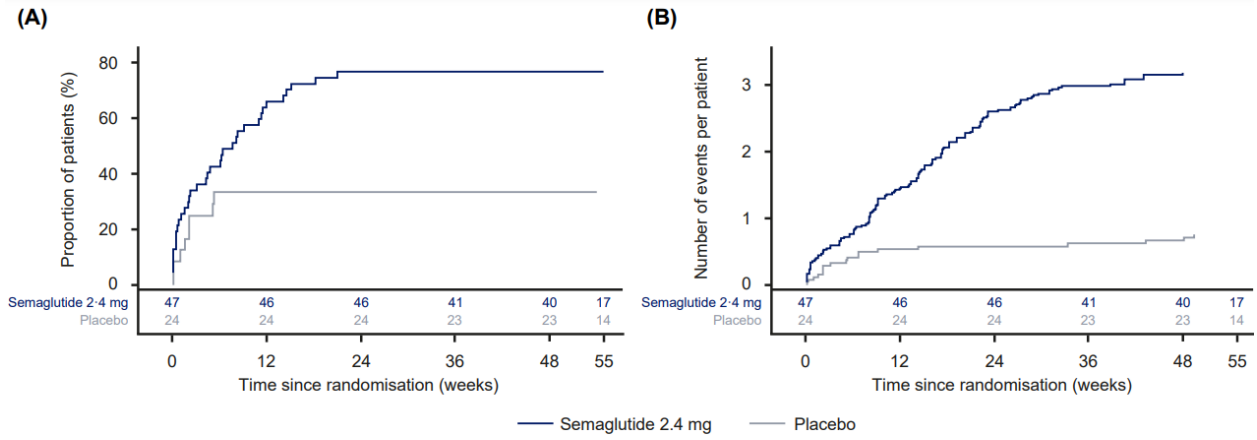
ETRs with 95% CIs are from an ANCOVA on log-transformed data with treatment and baseline diabetes status as factors; and baseline body weight and value of the analysed parameter as covariates. Missing data were imputed from the observed data in the placebo group on the log scale and back-transformed to original scale to give the ETR, using the same ANCOVA model but without treatment as factor. Treatment differences were estimated. ANCOVA=analysis of covariance. CI=confidence interval. ETR=estimated treatment ratio.

***Supplementary figure S6*: Change in lipids**



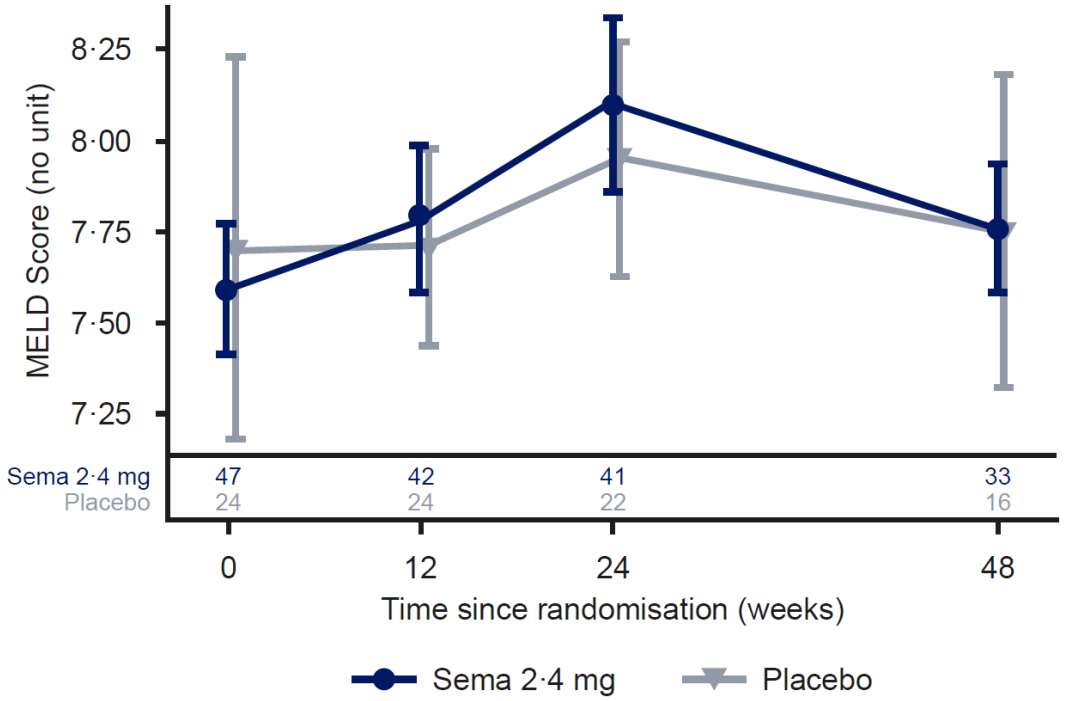
ETRs with 95% CIs are from an ANCOVA on log-transformed data with treatment and baseline diabetes status as factors, and baseline body weight and value of the analysed parameter as covariates. Missing data were imputed from the observed data in the placebo group on the log scale and back-transformed to original scale to give the ETR, using the same ANCOVA model but without treatment as factor. Treatment differences were estimated. ANCOVA=analysis of covariance. CI=confidence interval. ETR=estimated treatment ratio. HDL=high-density lipoprotein. LDL=low-density lipoprotein. VLDL=very low-density lipoprotein.

Supplementary Figure S7: **Proportion of patients with at least one on-treatment gastrointestinal adverse event over time: (A) time to onset of first event; (B) time to onset of any event**



Numbers shown in the lower panel represent the number of patients contributing to the data at each time point.

Supplementary Figure S8: **MELD score by week, on-treatment analysis**



Observed mean ± standard error. Numbers shown in the lower panel represent the number of patients contributing to the data at each time point. MELD=model for end-stage liver disease.

Supplementary Table S1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Informed consent obtained before any trial-related activities. Trial-related activities were any procedures carried out as part of the trial, including activities to determine suitability for the trial. 2. Male or female, aged 18–75 years (both inclusive) at the time of signing informed consent. 3. Histologic evidence of NASH and fibrosis stage 4 according to the NASH Clinical Research Network classification based on central pathologist evaluation of a liver biopsy obtained within 360 days prior to screening.* 4. A histological NAFLD activity score ≥3 with a score of ≥1 in both lobular inflammation and hepatocyte ballooning, based on central pathologist evaluation. 5. Body mass index ≥27 kg/m^2.	**Liver related:** 1. Presence or history of chronic liver disease other than NAFLD. 2. Presence or history of hepatic decompensation (eg, ascites, variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis) or liver transplantation. 3. Presence or history of gastroesophageal varices within the past 360 days prior to screening.† 4. Known or suspected abuse of alcohol (>12 g/day for women or >24 g/day for men) or alcohol dependence assessed by the Alcohol Use Disorders Identification Test (questionnaire). 5. Presence or history of hepatocellular carcinoma. 6. Treatment with vitamin E (at doses ≥800 IU/day) or pioglitazone which has not been at a stable dose in the opinion of the investigator in the period from 90 days prior to screening. 7. Treatment with medications (for more than 14 consecutive days) with known effect on liver steatosis (eg, treatment with corticosteroids [topical and inhaled are allowed], methotrexate, tamoxifen, valproic acid, amiodarone, or tetracycline) which had not been stable in the opinion of the investigator in the period from 28 days prior to screening. 8. Alanine aminotransferase >5 times UNL. 9. Aspartate aminotransferase >5 times UNL. 10. Total bilirubin >1·5 mg/dL.‡ 11. INR of prothrombin time >1·4. 12. Thrombocytes <100 000/μL. 13. MELD score ≥12 points. 14. Child–Pugh score ≥7 points. 15. Albumin <3·4 g/dL. 16. Positive result to test for hepatitis B surface antigen or hepatitis C antibodies. In case screening test for hepatitis C was positive, the confirmative test was decisive. 17. Diagnostic test results positive for HIV-1 or HIV-2 infection. **Glycaemia related:** 18. Presence or history of type 1 diabetes. 19. HbA_{1c} >9·5%. 20. Treatment with glucagon-like peptide-1 receptor agonists in the period from 90 days prior to screening. 21. Treatment with other glucose-lowering agent(s) or weight loss medication not stable in the opinion of the investigator in the period from 28 days prior to screening. **Obesity related:** 22. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device.§ **General safety:** 23. Presence or history of malignant neoplasms other than described in exclusion criterion 5 within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ were allowed. 24. Presence of acute pancreatitis within the 180 days prior to the day of screening. 25. History or presence of chronic pancreatitis. 26. For patients with type 2 diabetes only, uncontrolled and potentially unstable diabetic retinopathy or maculopathy verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation.‖

	27. Personal or first-degree relative(s) with history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. 28. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within the 90 days prior to the day of screening and between screening and randomisation. 29. Classification of heart failure New York Heart Association Class IV. 30. Presence or history of suffering from claustrophobia precluding magnetic resonance imaging. 31. Presence of metallic implants, pacemaker, defibrillator, artificial valves in heart, internal electrical devices (eg, cochlear implant, nerve stimulator, brain stimulator, gastric pacemaker, bladder stimulator etc.), aneurysm clips, permanent makeup, or tattoos precluding magnetic resonance imaging. 32. Unstable body weight defined as >5% self-reported change in body weight in the 28 days prior to screening. 33. Any condition which, in the investigator's opinion might jeopardise patient safety or compliance with the protocol. 34. Mental incapacity, language barriers, or unwillingness to comply with the requirements of the protocol, which may preclude adequate understanding or cooperation during the trial as judged by the investigator. 35. Surgery scheduled for the trial duration period, except for surgical procedures that were minor in the opinion of the investigator. 36. Known or suspected hypersensitivity to trial product or related products. 37. Previous participation in this trial. Participation defined as randomisation. 38. Participation in another interventional clinical trial within 60 days before screening. 39. Female who was pregnant, breast feeding, or intended to become pregnant, or of child-bearing potential and not using a highly effective contraceptive method (measures as required by local regulation or practice). 40. Calcitonin ≥100 ng/L. 41. Estimated glomerular filtration rate <30 mL/min/1·73 m^2.

*In patients who had never had a liver biopsy showing NASH and fibrosis stage 4, liver stiffness >14 kPa by FibroScan® at screening had to be documented before patients could have a trial-related liver biopsy. †For patients with no known history of gastroesophageal varices and with a FibroScan® ≥20 kPa and thrombocytes ≤150 000, esophagogastroduodenoscopy was performed to evaluate presence of gastroesophageal varices. ‡Total bilirubin level >1·5 mg/dL allowed if conjugated bilirubin <1·5 × UNL. §The following were allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening; (2) lap banding, if the band had been removed >1 year before screening; (3) intragastric balloon, if the balloon had been removed >1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve had been removed >1 year before screening. ‖Pharmacological pupil dilation was a requirement unless using a digital fundus photography camera specified for non-dilated examination. HbA_{1c}=glycated haemoglobin. HIV=human immunodeficiency virus. INR=international normalised ratio. MELD=model for end-stage liver disease. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic fatty liver disease. UNL=upper normal limit.

***Supplementary Table S2*: Summary of glucose-lowering medications not stopped before the day of randomisation**

	Semaglutide 2·4 mg, n (%)	**Placebo, n (%)**
Number of patients	**47**	**24**
Insulin and analogues for injection, fast-acting	0 (0·0)	1 (4·2)
Insulin glulisine	0 (0·0)	1 (4·2)
Insulin (human)	6 (12·8)	5 (20·8)
Insulin	1 (2·1)	0 (0·0)
Insulin aspartat	2 (4·3)	1 (4·2)
Insulin human	1 (2·1)	1 (4·2)
Insulin human; insulin human injection, Isophane	0 (0·0)	1 (4·2)
Insulin lispro	2 (4·3)	2 (8·3)
Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	0 (0·0)	1 (4·2)
Insulin human; insulin human injection, isophane	0 (0·0)	1 (4·2)
Insulins and analogues for injection, long-acting	7 (14·9)	5 (20·8)
Insulin degludec	0 (0·0)	1 (4·2)
Insulin glargine	7 (14·9)	4 (16·7)
Biguanides	24 (51·1)	11 (45·8)
Metformin	22 (46·8)	10 (41·7)
Metformin hydrochloride	2 (4·3)	1 (4·2)
Sulfonylureas	6 (12·8)	3 (12·5)
Glibenclamide	2 (4·3)	0 (0·0)
Gliclazide	0 (0·0)	1 (4·2)
Glimepiride	2 (4·3)	0 (0·0)
Glipizide	2 (4·3)	2 (8·3)
Combinations of oral blood glucose lowering drugs	2 (4·3)	3 (12·5)
Empagliflozin; metformin hydrochloride	0 (0·0)	2 (8·3)
Metformin hydrochloride; saxagliptin hydrochloride	0 (0·0)	1 (4·2)
Metformin hydrochloride; sitagliptin phosphate monohydrate	2 (4·3)	0 (0·0)
Thiazolidinediones	0 (0·0)	3 (12·5)
Pioglitazone	0 (0·0)	3 (12·5)
DPP-4 inhibitors	4 (8·5)	2 (8·3)
Sitagliptin	2 (4·3)	0 (0·0)
Sitagliptin phosphate	2 (4·3)	2 (8·3)
SGLT2 inhibitors	4 (8·5)	0 (0·0)
Empagliflozin	3 (6·4)	0 (0·0)
Ertugliflozin pidolate	1 (2·1)	0 (0·0)

DPP-4=dipeptidyl peptidase 4. SGLT2=**S**odium-glucose co-transporter 2.

Supplementary Table S3: **Results of sensitivity and supportive analyses for the primary endpoint**

	Semaglutide 2·4 mg (n=47), n (%)	**Placebo (n=24), n (%)**	**Odds ratio (95% CI); p value**
Primary analysis	5 (10·6)	7 (29·2)	0·28 (0·06–1·24); p=0·0867
Sensitivity analysis: MI based on unconditional reference	6 (13·1)	7 (29·2)	0·35 (0·10–1·27); p=0·1105
Supportive analysis: complete case on-treatment	4 (10·5)	7 (30·4)	0·23 (0·04–1·17); p=0·0722

Cochran–Mantel–Haenszel test stratified by baseline diabetes status. Patients with missing outcomes were imputed using MI based on unconditional reference (sensitivity analysis) or as non-responders (Covid-19 analysis). CI=confidence interval. FAS=full analysis set. MI=multiple imputation. n (%)=number and percentage of patients after imputation.

Supplementary Table S4: **Liver imaging and liver enzymes: continuous endpoints (in trial)**

	Semaglutide 2·4 mg (n=47)	Placebo (n=24)
Hepatic collagen (%)		
Baseline, mean (SD)	11·5 (7·3)	9·4 (4·8)
Week 48, mean (SD)	10·1 (6·0)	8·0 (4·8)
Change from baseline	–1·17	–2·23
ETD (95% CI); p-value	1·05 (–1·71 to 3·82); p=0·4546	
Liver stiffness, MRE, kPa		
Baseline, mean (SD)	6·65 (1·89)	6·08 (1·99)
Week 48, mean (SD)	6·02 (2·42)	6·22 (2·87)
Ratio to baseline	0·90	0·97
ETR (95% CI); p-value	0·93 (0·80 to 1·07); p=0·3027	
Liver steatosis, MRI-PDFF, %		
Baseline, mean (SD)	11·34 (5·04)	11·65 (5·23)
Week 48, mean (SD)	7·84 (5·14)	11·08 (4·33)
Ratio to baseline	0·68	1·02
ETR (95% CI); p-value	0·67 (0·51 to 0·88); p=0·0042	
Liver fat volume, L		
Baseline, mean (SD)	0·27 (0·19)	0·28 (0·15)
Week 48, mean (SD)	0·17 (0·15)	0·26 (0·13)
Ratio to baseline	0·58	1·00
ETR (95% CI); p-value	0·58 (0·42 to 0·81); p=0·0011	
Total liver volume, L		
Baseline, mean (SD)	2·32 (0·69)	2·38 (0·68)
Week 48, mean (SD)	1·98 (0·60)	2·31 (0·62)
Ratio to baseline	0·86	0·98
ETR (95% CI); p-value	0·87 (0·82 to 0·93); p<0·0001	
ALT, U/L		
Baseline, mean (SD)	56·1 (39·4)	41·8 (23·5)
Week 48, mean (SD)	35·9 (20·7)	43·7 (30·1)
Ratio to baseline	0·70	0·92
ETR (95% CI); p-value	0·76 (0·61 to 0·93); p=0·0090	
AST, U/L		
Baseline, mean (SD)	51·9 (24·2)	42·9 (20·3)
Week 48, mean (SD)	35·9 (15·5)	44·4 (26·3)
Ratio to baseline	0·72	0·94
ETR (95% CI); p-value	0·77 (0·65 to 0·92); p=0·0046	
GGT, U/L		
Baseline, mean (SD)	126·0 (110·3)	167·6 (229·0)
Week 48, mean (SD)	96·1 (95·1)	179·8 (267·3)
Ratio to baseline	0·72	0·98
ETR (95% CI); p-value	0·74 (0·62 to 0·88); p=0·0007	

ALT=alanine aminotransferase. AST=aspartate aminotransferase. CI=confidence interval. ETD=estimated treatment difference. ETR=estimated treatment ratio. GGT=gamma glutamyltransferase. MRE=magnetic resonance elastography. MRI-PDFF=magnetic resonance imaging proton density fat fraction.

Supplementary table S5. **Changes from baseline in selected variables for patients who completed the study on treatment**

	Semaglutide 2·4 mg (n=47)	Placebo (n=24)
BMI, kg/m^2		
Baseline, mean (SD)	34·6 (5·9)	35·5 (6·0)
Week 48, mean (SD)	31·5 (6·8)	34·3 (3·6)
Change from baseline	–3·05	–0·13
ETD (95% CI); p-value	–2·92 (–4·15 to –1·68); p<0·0001	
Waist circumference, cm		
Baseline, mean (SD)	112·9 (11·8)	118·3 (14·8)
Week 48, mean (SD)	105·7 (14·2)	117·0 (11·8)
Change from baseline	–6·19	0·82
ETD (95% CI); p-value	–7·01 [–11·01 to –3·02); p=0·0006	
Lipids, mg/dL		
LDL cholesterol		
Baseline, mean (SD)	100·0 (34·4)	88·1 (41·7)
Week 48, mean (SD)	92·8 (30·5)	100·5 (44·8)
Ratio to baseline	0·99	1·01
ETR (95% CI); p-value	0·98 (0·86 to 1·12); p=0·7919	
Free fatty acids		
Baseline, mean (SD)	15·6 (7·9)	15·9 (8·1)
Week 48, mean (SD)	17·5 (7·7)	21·8 (7·9)
Ratio to baseline	1·10	1·38
ETR (95% CI); p-value	0·80 (0·61 to 1·04); p=0·0956	
HDL cholesterol		
Baseline, mean (SD)	44·7 (10·0)	45·8 (12·6)
Week 48, mean (SD)	45·3 (10·0)	47·4 (18·5)
Ratio to baseline	1·06	0·99
ETR (95% CI); p-value	1·07 (1·00 to 1·15); p=0·0633	
Triglycerides		
Baseline, mean (SD)	168·9 (98·3)	151·6 (56·2)
Week 48, mean (SD)	158·1 (89·3)	187·3 (94·2)
Ratio to baseline	0·91	1·09
ETR (95% CI); p-value	0·83 (0·72 to 0·96); p=0·0128	
VLDL cholesterol		
Baseline, mean (SD)	32·5 (17·4)	29·6 (11·0)
Week 48, mean (SD)	30·2 (15·4)	36·6 (18·4)
Ratio to baseline	0·91	1·09
ETR (95% CI); p-value	0·83 (0·72 to 0·96); p=0·0121	
Total cholesterol		
Baseline, mean (SD)	177·2 (34·9)	163·4 (47·5)
Week 48, mean (SD)	168·3 (32·6)	184·5 (45·9)
Ratio to baseline	0·99	1·04

	Semaglutide 2·4 mg (n=47)	Placebo (n=24)
ETR (95% CI); p-value	0·95 (0·87 to 1·03); p=0·1852	
Blood pressure, mmHg		
Diastolic		
Baseline, mean (SD)	78·7 (9·6)	78·0 (6·6)
Week 48, mean (SD)	80·6 (10·6)	76·9 (9·3)
Change from baseline	0·62	–1·29
ETD (95% CI); p-value	1·91 (–2·84 to 6·67); p=0·4307	
Systolic		
Baseline, mean (SD)	132·6 (13·7)	135·8 (14·7)
Week 48, mean (SD)	128·7 (15·4)	136·3 (13·8)
Change from baseline	–4·72	0·22
ETD (95% CI); p-value	–4·94 (–12·79 to 2·92); p=0·2183	

BMI=body mass index. CI=confidence interval. ETD=estimated treatment difference. ETR=estimated treatment ratio. HDL=high-density lipoprotein. LDL=low-density lipoprotein. SD=standard deviation. VLDL=very low-density lipoprotein.

Supplementary Table S6: **Treatment-related hepatic and gallbladder disorders (on treatment)**

	Semaglutide 2·4 mg (n=47)			Placebo (n=24)		
	n (%)	**E**	**R**	**n (%)**	**E**	**R**
Patients with at least one event	6 (12·8)	10	21·7	1 (4·2)	1	4·1
Gastrointestinal disorders	4 (8·5)	4	8·7	0 (0·0)	0	0·0
Ascites*	2 (4·3)	2	4·3	··	··	··
Portal hypertensive gastropathy	1 (2·1)	1	2·2	··	··	··
Varices oesophageal[†]	1 (2·1)	1	2·2	··	··	··
Investigations[‡]	3 (6·4)	5	10·9	0 (0·0)	0	0·0
ALT increased	1 (2·1)	1	2·2	··	··	··
AST increased	1 (2·1)	1	2·2	··	··	··
Blood bilirubin increased	1 (2·1)	1	2·2	··	··	··
GGT increased	1 (2·1)	1	2·2	··	··	··
MELD score increased	1 (2·1)	1	2·2	··	··	··
Hepatobiliary disorders	1 (2·1)	1	2.2	1 (4·2)	1	4·1
Hepatic lesion[§]	··	··	··	1 (4·2)	1	4·1
Cholelithiasis	1 (2·1)	1	2·2	··	··	··

*Diagnosed in one patient by a small amount of fluid on imaging, without need for treatment or study treatment discontinuation; appeared in the second patient when diuretics were reduced but resolved after diuretics were increased. [†]Random finding of new oesophageal varices during endoscopic procedure, with no evidence of development during the patient's enrolment in the trial. [‡]Data available in clinical study report. [§]Occurred due to biopsy complication and detected by ultrasound. ALT=alanine aminotransferase. AST=aspartate aminotransferase. E=number of events. GGT=gamma-glutamyltransferase. MELD=model of end-stage liver disease. R=rate of events.

Supplementary Table S7: **Ratios of selected laboratory values from baseline to week 48 (on treatment)**

	Semaglutide 2·4 mg (n=47)	**Placebo (n=24)**
Albumin, g/dL, geometric mean (CV)	1·0 (6·5)	1·0 (5·3)
Bilirubin, mg/dL, geometric mean (CV)	1·0 (30·5)	1·0 (24·9)
Thrombocytes, 10^9/L, geometric mean (CV)	1·0 (16·9)	1·0 (15·0)
INR, treatment ratio	1·01	1·01

CV=coefficient of variation. INR=international normalised ratio.

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