Supplementary text:

MRI Section:

Briefly, MRI-PDFF utilizes a gradient echo sequence with low flip angle (FA) to minimize T1 bias, and it acquires multiple echoes at echo times at which fat and water signals are nominally in phase or out of phase relative to each other. Data obtained at each of the echo times are passed to a nonlinear least-squares fitting algorithm that estimates and corrects T2* effects, models the fat signal as a superposition of multiple frequency components, and estimates fat and water proton densities from which the fat content is calculated(1). By minimization of T1 bias, correction of T2* effects, and modeling the fat signal as a superposition of multiple frequency components, MRI-PDFF is a standardized, accurate, and precise biomarker of liver fat content as shown by us and others(2-4).

Time interval between MRI and liver biopsy: The average (± sd) time interval between the MRI and liver biopsy was 48.1 ± 79.9 days.

Magnetic resonance elastography:

Rationale for including 2D and 3D MRE in the trial:

1. MRE-stiffness is known to have a strong cross-sectional correlation with fibrosis.

2. MRE-stiffness has a known cross-sectional correlation with inflammation and necro-inflammation, but the strength of this association is not well understood, in part because MRE-stiffness and histologic analysis are thought to reflect different components of inflammation (please see 3) and in part because inflammation and necro-inflammation may have greater temporal variability than fibrosis (some discordance between MRE and histology likely is due to interim change in inflammation between MRE and biopsy procedures).

3. MRE-stiffness is thought to reflect edema/swelling ± hyperemia while histology reflects inflammatory cell infiltration. It is possible that MRE-stiffness more closely reflects our intuitive concept of "inflammation" than histology.

4. Although histology is the gold standard for assessing inflammation, it has limitations: (a) does not reflect all components of inflammation (see 3), (b) scored subjectively in broad brackets, (c) prone to sampling error.

5. By comparison, MRE-estimated stiffness (a) reflects key components of inflammation not assessed by histology (i.e., edema/swelling ± hyperemia), (b) is scored objectively using a continuous parameter, (c) covers large portions of the liver, thereby reducing sampling variability. 3D MRE is particularly attractive because it covers the entire liver and therefor virtually eliminates sampling variability for assessing longitudinal change.

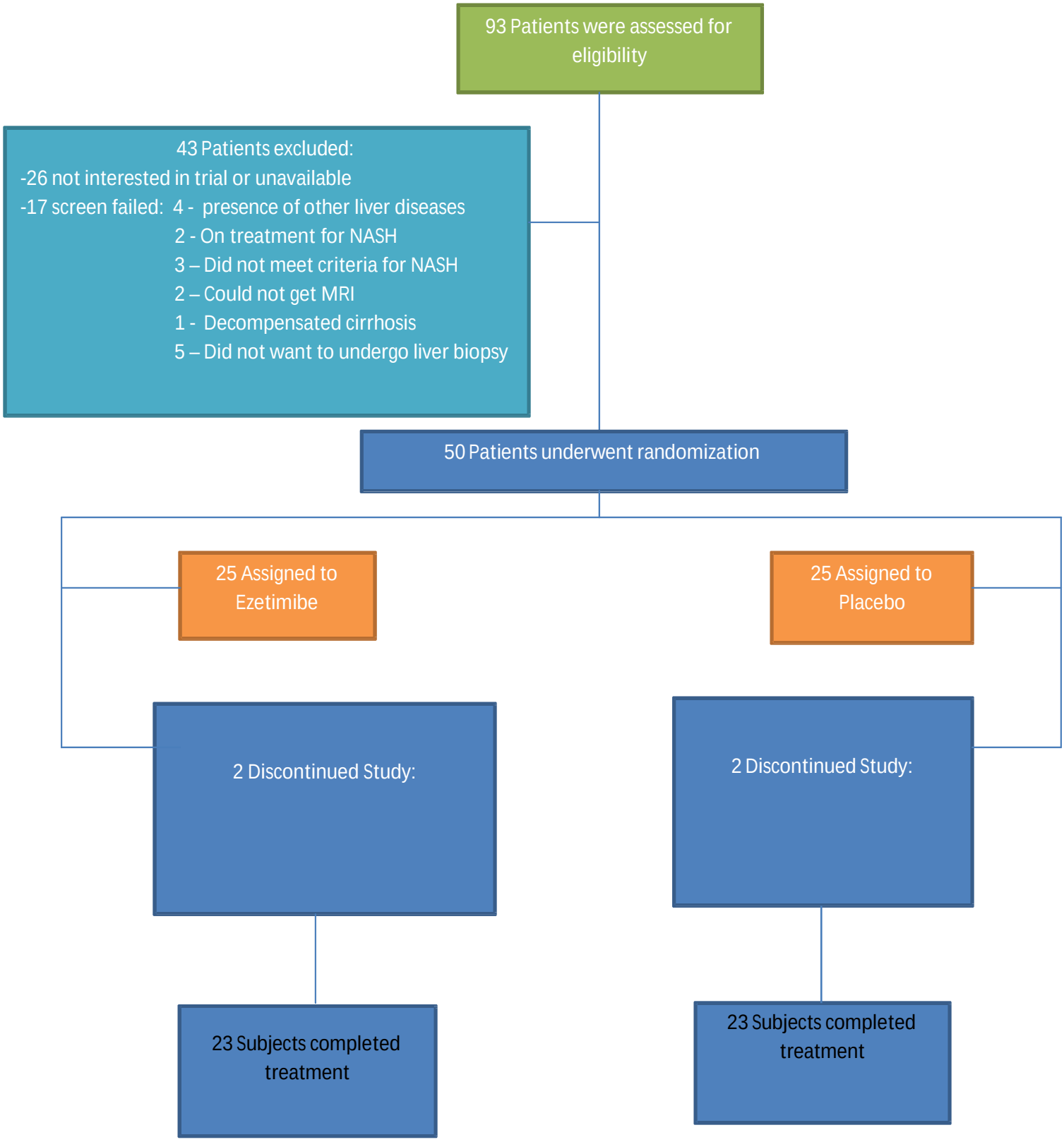
6. In the MOZART trial, we show the feasibility of implementing MRE in a prospective clinical trial in NASH."

MRE values in normal individuals: The mean 2D MRE-derived stiffness value among normal adults who underwent living-related liver donation was 2.05 Kpa (5). The mean 3D MRE-derived stiffness value among healthy volunteers was 1.27 Kpa (6).

References:

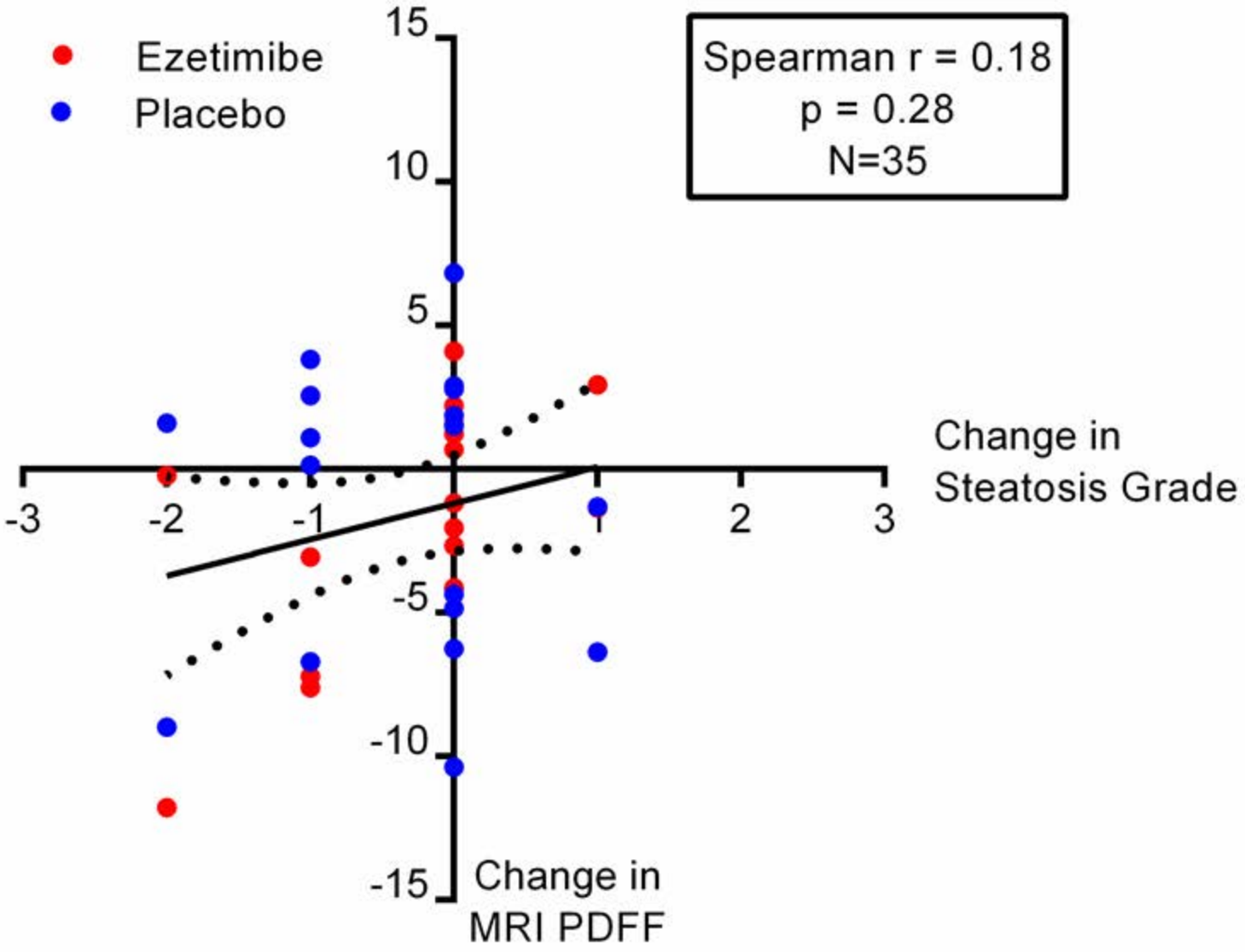
1. Tang A, Tan J, Sun M, Hamilton G, Bydder M, Wolfson T, Gamst AC, et al. Nonalcoholic Fatty Liver Disease: MR Imaging of Liver Proton Density Fat Fraction to Assess Hepatic Steatosis. Radiology 2013.
2. Kuhn JP, Hernando D, Munoz del Rio A, Evert M, Kannengiesser S, Volzke H, Mensel B, et al. Effect of multipeak spectral modeling of fat for liver iron and fat quantification: correlation of biopsy with MR imaging results. Radiology 2012;265:133-142.
3. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging 2011;34:729-749.

4. Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le TA, Bettencourt R, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013;58:1930-1940.
5. Lee DH, Lee JM, Han JK, Choi BI. MR elastography of healthy liver parenchyma: Normal value and reliability of the liver stiffness value measurement. J Magn Reson Imaging 2013;38:1215-1223.
6. Guo J, Hirsch S, Streitberger KJ, Kamphues C, Asbach P, Braun J, Sack I. Patient-activated three-dimensional multifrequency magnetic resonance elastography for high-resolution mechanical imaging of the liver and spleen. Rofo 2014;186:260-266.

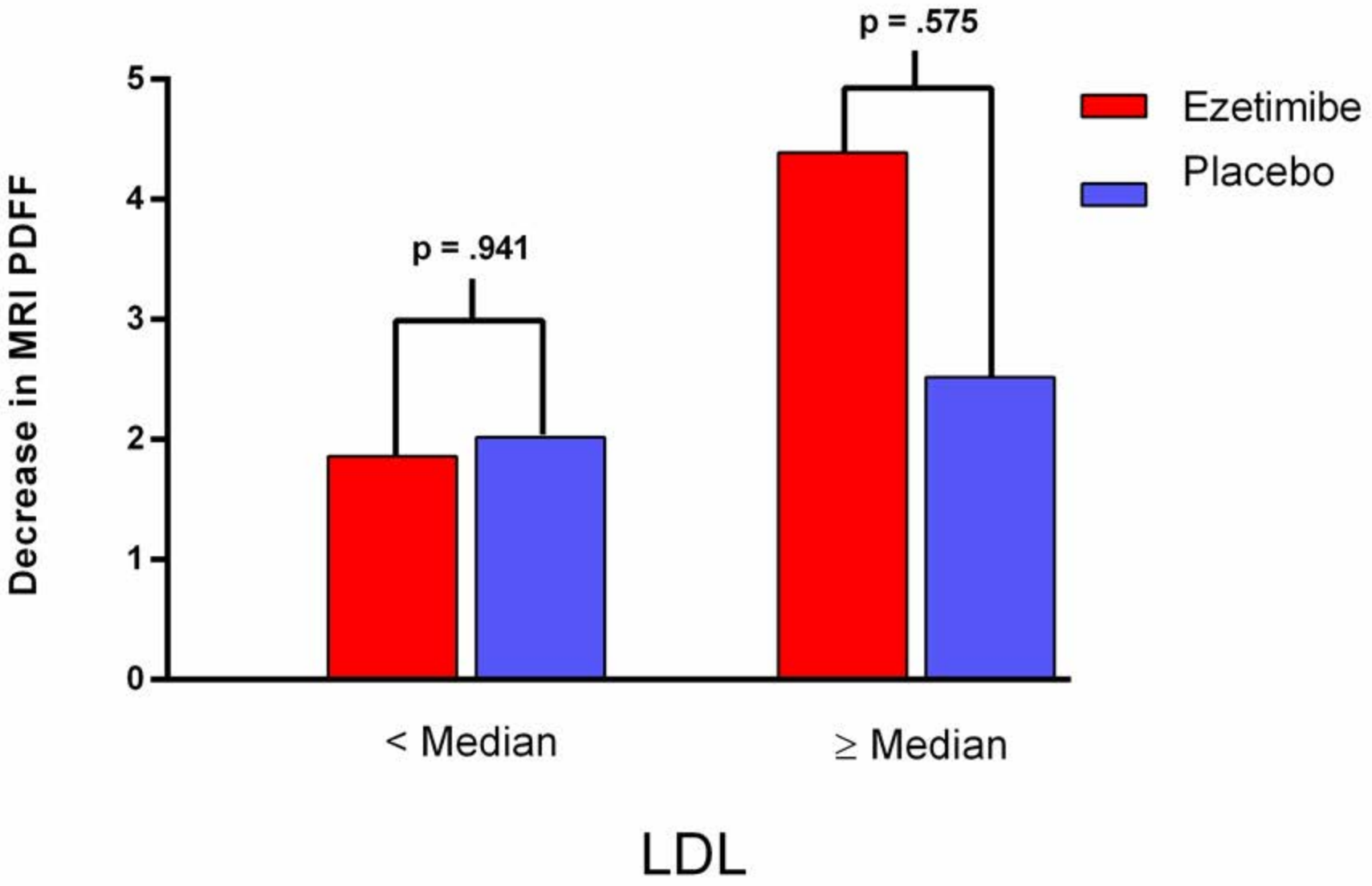


Supplementary Figure 1. Derivation of the MOZART trial study subjects and study flow

Supplementary Figure 2: Changes in MRI-PDFF and steatosis grade on biopsy



Supplementary figure 3: Ezetimibe versus placebo: Decrease in MRI-PDFF stratified by baseline LDL cholesterol



Supplementary Table 1: CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5, 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5 – no change
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	5 – no change
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	5 – no interim analysis
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8

	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, Suppl. Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	11 trial ended per protocol
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	11, Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12 Tables 1 & 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11-12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12 Table 4
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-14
Other information			
Registration	23	Registration number and name of trial registry	5-6
Protocol	24	Where the full trial protocol can be accessed, if available	attached and also found at fattyliver.ucsd.edu
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

Supplementary table 2: Adverse events in ezetimibe and placebo arms.

Adverse events	Ezetimibe	Placebo
General		
Fatigue	1	0
Allergies	0	0
Anxiety	0	0
Insomnia	0	0
Gastrointestinal		
Bloating	0	0
Flatus	0	0
Diarrhea	1	1
Constipation	1	1
Heartburn	0	0
Abdominal discomfort	0	0
Ulcerative colitis flair	0	0
Nausea/vomiting	0	0
Dark stool	0	0
Blood in stool	0	0
Gallbladder perforation	1	0
Dermatologic		
Increased facial hair	0	0
Rash	0	0
Genito-urinary		
Urinary tract infection	0	0
Otolaryngology		
Dry tongue	0	0
Nasal pain	0	0
Cardiovascular		
Dizziness	1	0
Hypertension	0	0
Vertigo	0	0
Atrial fibrillation	0	0
Shortness of breath	0	0
Leg edema	0	0
Chest pain	0	0
Pulmonary		
Possible pneumonia	0	0
Asthma exacerbation	0	0
Upper respiratory infection	0	0
Cough	0	0
Sleep apnea worsening	0	0
Musculoskeletal		
Fracture toe	0	0

Pain in hand or feet	0	0
Muscle pain	0	1
Muscle weakness	1	0
Restless leg syndrome	0	0
Back pain	0	0
Tendonitis	0	0
Joint pain	0	0
Sprain joint	0	0
Ophthalmological		
Blurry vision	0	0
Retinal detachment	0	0
Stye-right eye	0	0
Conjunctivitis	0	0
Infectious disease		
Tooth infection	0	0
Tooth ache	0	0
Flu	0	0
Neurological		
Headache	0	0
Nerve-damage neck	0	0
Weakness of thigh	0	0
Endocrine		
Worsening blood sugars	0	0
Feeling cold	0	0
New hot flash	0	0