Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

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Lancet 2019; 394: 2012–24

Published Online November 11, 2019 https://doi.org/10.1016/S0140-6736(19)32517-6

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Summary

Background Non-alcoholic steatohepatitis (NASH) is characterised by hepatic steatosis, inflammation, hepatocellular injury, and progressive liver fibrosis. Resmetirom (MGL-3196) is a liver-directed, orally active, selective thyroid hormone receptor-β agonist designed to improve NASH by increasing hepatic fat metabolism and reducing lipotoxicity. We aimed to assess the safety and efficacy of resmetirom in patients with NASH.

Methods MGL-3196-05 was a 36-week randomised, double-blind, placebo-controlled study at 25 centres in the USA. Adults with biopsy confirmed NASH (fibrosis stages 1–3) and hepatic fat fraction of at least 10% at baseline when assessed by MRI-proton density fat fraction (MRI-PDFF) were eligible. Patients were randomly assigned 2:1 by a computer-based system to receive resmetirom 80 mg or matching placebo, orally once a day. Serial hepatic fat measurements were obtained at weeks 12 and 36, and a second liver biopsy was obtained at week 36. The primary endpoint was relative change in MRI-PDFF assessed hepatic fat compared with placebo at week 12 in patients who had both a baseline and week 12 MRI-PDFF. This trial is registered with ClinicalTrials.gov, number NCT02912260.

Findings 348 patients were screened and 84 were randomly assigned to resmetirom and 41 to placebo at 18 sites in the USA. Resmetirom-treated patients (n=78) showed a relative reduction of hepatic fat compared with placebo (n=38) at week 12 (–32·9% resmetirom *vs* –10·4% placebo; least squares mean difference –22·5%, 95% CI –32·9 to –12·2; p<0·0001) and week 36 (–37·3% resmetirom [n=74] *vs* –8·5 placebo [n=34]; –28·8%, –42·0 to –15·7; p<0·0001). Adverse events were mostly mild or moderate and were balanced between groups, except for a higher incidence of transient mild diarrhoea and nausea with resmetirom.

Interpretation Resmetirom treatment resulted in significant reduction in hepatic fat after 12 weeks and 36 weeks of treatment in patients with NASH. Further studies of resmetirom will allow assessment of safety and effectiveness of resmetirom in a larger number of patients with NASH with the possibility of documenting associations between histological effects and changes in non-invasive markers and imaging.

Funding Madrigal Pharmaceuticals.

Introduction

Non-alcoholic steatohepatitis (NASH) is the active, progressive form of non-alcoholic fatty liver disease (NAFLD), defined as the presence of 5% or more hepatic steatosis with inflammation and hepatocyte injury (eg, ballooning), with or without fibrosis.[1,2] NAFLD and NASH are both associated with a group of comorbid conditions that include metabolic syndrome, obesity, type 2 diabetes, hypertension, dyslipidaemia, and hypothyroidism. As with other metabolic conditions, NASH is associated with increased cardiovascular risk, including cardiovascular death.[3] Patients with more advanced NASH fibrosis also have increased morbidity and mortality from progression of their liver disease, including progression to cirrhosis, liver failure, and hepatocellular carcinoma.[4,5]

No approved therapy for NASH exists, and its prevalence has increased with the increasing global prevalence of obesity.[6,7] As with other metabolic diseases, lifestyle modifications are effective but difficult to achieve and maintain.[1,8] In small clinical trials,[9,10] pioglitazone (thought to address insulin resistance) and vitamin E (thought to address oxidative stress) improved liver histology. Obeticholic acid, a bile acid analogue that activates farnesoid X receptors, and elafibranor, a peroxisome proliferator-activated receptor (PPAR) α and δ agonist, improved liver histology in phase 2 studies.[11,12] Ongoing phase 3 studies (NCT02548351, NCT02704403) are assessing their long-term efficacy and safety.

Thyroid hormone receptor β (THR-β) is highly expressed in hepatocytes and is responsible for regulating the metabolic pathways in the liver that are frequently impaired in NAFLD and NASH.[13] Animal studies have shown that THR-β has an important role in the reduction of triglycerides and cholesterol, improving insulin sensitivity, promoting liver regeneration, and reducing apoptosis. Evidence suggests that NASH might

Research in context

Evidence before this study

Non-alcoholic fatty liver disease includes a spectrum of chronic hepatic diseases, with non-alcoholic steatohepatitis being the most aggressive phenotype, leading to an increased risk of developing cirrhosis. To identify clinical trials of the treatment of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, we searched PubMed for English language articles published from Jan 1, 2007, to July 1, 2019, with the search terms "NAFLD", "NASH", "fatty liver", "thyroid hormone", and "thyroid hormone receptor beta". We found no controlled clinical trials investigating a thyroid hormone analogue in the treatment of non-alcoholic steatohepatitis, and therefore the current study represents a first-in-class trial in this patient population. Resmetirom is a liver-directed molecule that is highly targeted towards thyroid hormone receptor-β designed to avoid the toxicities associated with an excess of systemic thyroid hormone, shown to be largely mediated through thyroid hormone receptor-α. On the basis of established preclinical and clinical biological activity and safety, resmetirom is being assessed for the treatment of non-alcoholic steatohepatitis with fibrosis in a phase 3 clinical trial.

Added value of this study

Liver biopsy is an invasive technique with associated morbidity. A goal of the field is to find non-invasive tests that predict outcome of non-alcoholic steatohepatitis treatments to avoid use of serial liver biopsies. In addition to improving the understanding of the pharmacology and safety of resmetirom in patients with non-alcoholic steatohepatitis, this study provides results of serial non-invasive imaging of liver fat content, serial biomarkers of liver injury and fibrosis, and serial liver biopsies at baseline and after 36 weeks of treatment, providing the potential to show associations between changes in non-invasive measures and liver histology.

Implications of all the available evidence

There is an unmet need for treatments of non-alcoholic steatohepatitis, and no European Medicines Agency or Food and Drug Administration-approved treatments exist. The results of our phase 2 study show the efficacy of resmetirom in rapidly decreasing liver fat content and markers of inflammation and fibrosis and non-alcoholic steatohepatitis with fibrosis on liver biopsy at week 36, highlighting its therapeutic potential in non-alcoholic steatohepatitis. A larger clinical trial of longer duration is ongoing to fully assess the safety and efficacy of resmetirom in patients with non-alcoholic steatohepatitis with advanced fibrosis.

be, in part, a condition of diminished liver thyroid hormone levels or hepatic hypothyroidism, and the incidence of clinical and subclinical hypothyroidism is higher in patients with NAFLD or NASH relative to age-matched controls.[13,14]

Resmetirom (MGL-3196) is a liver-directed, orally active agonist of THR that is around 28 times more selective than triiodothyronine for THR-β versus THR-α.[15] It is highly protein bound (>99%), has poor tissue penetration outside the liver, and shows specific uptake into the liver. In NASH, selectivity for THR-β might provide metabolic benefits of thyroid hormone that are mediated by the liver, while avoiding unwanted systemic actions of excess thyroid hormone in heart and bone that are largely mediated through THR-α.[13] In preclinical NASH animal models, thyroid analogues, including resmetirom, have been shown to reduce hepatic triglycerides, steatosis, lipid peroxidation, inflammatory and fibrosis markers, and alanine aminotransferase.[13,15] In an earlier study, resmetirom doses of 50–200 mg per day in healthy participants with mildly elevated LDL cholesterol were shown to be well tolerated and resulted in significant reductions in atherogenic lipids, including LDL cholesterol (up to 30%), apolipoprotein B (28%), and triglycerides (up to 60%) at doses of 80 mg and higher.[16]

This study was designed to determine the effect of resmetirom on hepatic fat compared with placebo at week 12 and week 36 in patients with NASH and stage 1–3 fibrosis. Steatosis was assessed by MRI-proton density fat fraction (MRI-PDFF), a sensitive measure of hepatic fat. Secondary objectives were to assess safety and tolerability and to assess the effects of resmetirom on liver histology, serum lipids, alanine aminotransferase, and biomarkers of inflammation and fibrosis.

Methods

Study design and participants

This double-blind, randomised, placebo-controlled study enrolled adults with biopsy-confirmed NASH in 25 medical centres across the USA. Patients were eligible for screening if they were at least 18 years of age, had a diagnosis suggestive of NASH based on the presence of metabolic syndrome, plus a vibration controlled transient elastography consistent with liver fibrosis and steatosis based on a controlled attenuation parameter, or metabolic syndrome plus a previous liver biopsy consistent with NASH with non-cirrhotic fibrosis. Patients were required to have at least 10% hepatic fat content on screening MRI-PDFF before obtaining a liver biopsy, with up to 10% of patients with at least 9% and less than 10% hepatic fat permitted to enrol. Eligible liver biopsies included stage 1–3 fibrosis with a NAFLD activity score (NAS) of 4 or more, including a score of 1 or more in each component according to the NASH clinical research network scoring system[17]—ie, steatosis, ballooning degeneration, and lobular inflammation, on screening or historic (within the previous 6 months) biopsy as determined by a single central reader (CDG).

Up to 10% of patients with NAS of 4 or more and fibrosis stage F0 or NAS of 3 with all NASH components plus fibrosis were allowed. Patients were excluded if they had a history of clinically significant alcohol consumption or use of drugs associated with NAFLD, hypothyroidism (thyroxine treatment at doses ≤75 µg daily was permitted during the study), uncontrolled type 2 diabetes (glycated haemoglobin ≥9·5%), or a requirement for glucagon-like peptide analogue (unless on a stable dose ≥6 months before screening). Statins (≤20 mg atorvastatin, ≤10 mg rosuvastatin, and ≤20 mg pravastatin) were permitted. Patients were also excluded if they had evidence of cirrhosis, hepatic decompensation, or other chronic liver disease, or if serum alanine aminotransferase or aspartate aminotransferase were more than five times the upper limit of normal. A full list of inclusion and exclusion criteria and key protocol amendments is provided in the appendix (pp 2–7).

See Online for appendix

All participants provided written informed consent before enrolment. This study was done in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the International Conference on Harmonisation Good Clinical Practice and applicable regulatory requirements. The institutional review board or independent ethics committee of each study centre approved the study and all amendments.

Randomisation and masking

A computer-generated simple randomisation schedule prepared by study administrators was used to randomly assign patients (2:1) to resmetirom 80 mg or matching placebo administered orally once a day. Patients, the sponsor, investigators, and site personnel involved with dispensing study medication, carrying out study procedures, evaluating patients, entering study data, or evaluating study data were masked to treatment assignment throughout the study using placebo identical to resmetirom in all ways except for the presence of active ingredient; these groups (patients and study personnel) were also masked to post-baseline lipid, thyroxine, sex hormone binding globulin (SHBG), sex hormone, and drug exposure measurements. Dose adjustments determined by an unmasked medical monitor were managed using an interactive web response system.

Procedures

Study drug was administered for 12 weeks in the initial treatment period (primary analysis) and continued without interruption to 36 weeks. Study visits occurred at weeks 2 and 4, then every 4 weeks to 24 weeks, then every 6 weeks to 36 weeks after randomisation. Follow-up visits after the study ended were scheduled for week 38 (ie, 2 weeks after treatment finished). MGL-3196-05 was a dose exploration study based on an adaptive exposure-based dosing scheme. Earlier phase 1 studies showed that daily doses of resmetirom between 50 mg and 200 mg resulted in statistically significant lowering of atherogenic lipids,[16] the effect appearing to be near maximal at 80 mg. All patients randomly assigned to resmetirom received an 80 mg dose for the first 4 weeks. In each resmetirom treated patient, the 24-h resmetirom area under the curve (AUC; ng*h/ml) was estimated on the basis of exposures measured at week 2, which included samples at pre-dose, 2 h, 4 h, 6 h, and 8 h after an 80 mg dose. At week 4, the resmetirom dose was adjusted by 20 mg up or down or remained at 80 mg on the basis of the week 2 estimated AUC. Of 79 patients who completed at least week 4 and had resmetirom exposure determined at week 2, 37 (47%) had an estimated total exposure to resmetirom plus inactive metabolite of more than 5500 ng*h/mL (resmetirom >3500 ng*h/ml, plus inactive metabolite) and had a dose reduction to 60 mg at week 4 (one decreased to 40 mg at week 4 based on amendment 3; appendix p 7). The remaining 42 (53%) remained on 80 mg or, if total exposure was 3000 ng*h/ml or less on 80 mg, had a dose increase to 100 mg (5 [6%]) at week 4 (per amendment 3) or a subsequent visit. Exposure data were blinded to study personnel. The decision on dose adjustment was made on the basis of the estimated AUC at week 4 by an unblinded monitor. On the basis of exposure at 80 mg or re-estimation of exposure at the week 4 adjusted dose, 44 (56%) were included in a prespecified high exposure subgroup at week 12 (resmetirom AUC ≥2700 ng*h/mL), the remainder were in the low exposure subgroup—an AUC of 2700 ng*h/mL, at which significant lipid lowering had been shown in a phase 1 study.[16] Additionally, the change in the concentration of SHBG, which is a specific liver target of THR-β, was assessed as a potential marker of the hepatic exposure to resmetirom, and two SHBG groups (high and low) defined before data analysis at weeks 12 and 36 based on percent change from baseline SHBG concentrations (≥75% at week 12 and ≥88% at week 36).

MRI-PDFF was done before the initiation of drug administration, and at 12 and 36 weeks.[18,19] Liver biopsies were done at baseline and 36 weeks. A historical biopsy was allowed if within 6 months of expected randomisation. Both MRI and liver biopsies were centrally read by blinded reviewers (MRB and CDG, respectively). Fibrosis stage, portal inflammation, and NAS were assessed. Vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory testing (haematology, chemistry, and urinalysis) and assessment of lipid parameters, thyroid hormone parameters, and other biomarkers were done at specified visits. Bone mineral density was assessed by dual-energy x-ray absorptiometry scan at baseline and week 36. Safety and tolerability were assessed at all timepoints and during follow-up. Patients were required to be instructed on diet and exercise at screening and every study visit (per American Association for the Study of Liver Diseases guidance[1]). The details of instruction were at the site investigator's discretion.

Outcomes

The primary endpoint was percent relative change from baseline in hepatic fat fraction by MRI-PDFF at 12 weeks for resmetirom versus placebo. Key secondary endpoints included the proportions of patients with 30% or more relative hepatic fat reduction at 12 weeks and 36 weeks, absolute hepatic fat reduction at 12 weeks and 36 weeks, relative fat reduction at 36 weeks (including change from 12 weeks to 36 weeks), and proportions of patients (resmetirom-treated versus placebo-treated) with a 2-point reduction in NAS, a 2-point reduction in NAS with at least 1-point reduction in ballooning or inflammation, with resolution of NASH (ballooning score of 0, lobular inflammation score of 0 or 1) without worsening of fibrosis with at least a 2-point reduction in NAS, including patients with less than 9·5% bodyweight loss from the time of screening, and with a 1-point reduction in fibrosis without worsening of NAS on liver biopsy. Other secondary endpoints included changes in liver enzymes, fibrosis biomarkers at 12 weeks and 36 weeks and lipids at 30 weeks or 36 weeks. Safety endpoints included laboratory tests, vital signs and anthropometrics, 12-lead ECG, dual-energy x-ray absorptiometry, physical examinations, adverse events, and clinical assessments. There were no changes to the primary outcome assessment, but there were minor updates to the liver biopsy and biomarker secondary and exploratory outcomes after study initiation, which were documented in the statistical analysis plan before unblinding. All endpoints, except where otherwise specified as post hoc (the only post-hoc analysis included the dose comparison; appendix p 9), were prespecified in the statistical analysis plan, which was finalised and signed before the week 12 interim (if relevant) or study unblinding after all patients completed the 36-week study. After all randomly assigned patients completed 12 weeks, the primary endpoint and other week 12 endpoints were read out, while the trial continued uninterrupted. At week 36, after all patients had either discontinued or completed their week 38 visits, the database was locked, and week 36 endpoints were read out.

Statistical analysis

The safety population included all randomly assigned patients who received at least one dose of study drug. The modified intention-to-treat population included all patients who were randomised in the study, received at least one dose of study drug, and had lipid and other efficacy measurements at week 4 or later visits (used for secondary efficacy analyses). The MRI-PDFF evaluable population included all patients who were randomised in the study, received study drug, finished the week 12 visit, and had MRI-PDFF measurements at both baseline and week 12. The liver biopsy-evaluable population included all individuals in the modified intention-to-treat population with paired, evaluable liver biopsies. For analyses by resmetirom exposure, patients were stratified by AUC, with high exposure defined as an AUC of 2700 ng*h/mL or more. Patients with less than 5% weight loss at 12 weeks and 36 weeks was a subgroup of special interest.

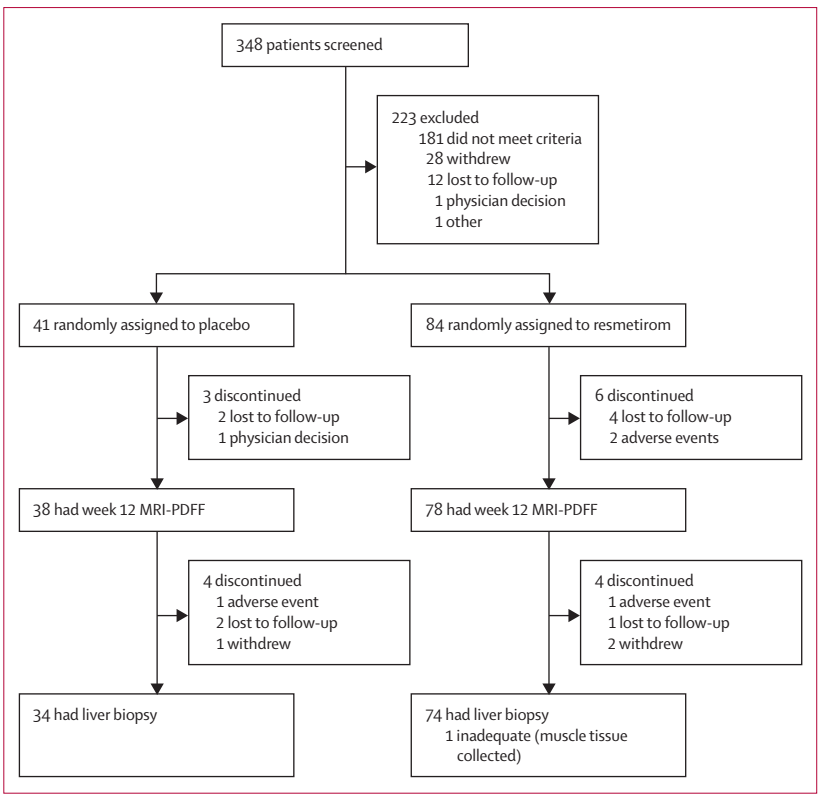

Figure 1: **Study profile**
MRI-PDFF=MRI-proton density fat fraction.

Around 117 patients, randomly assigned to 80 mg (two-thirds) or placebo (a third) treatments, and given an estimated treatment difference of 30% change in hepatic fat fraction from baseline to week 12 between any dose of resmetirom and the placebo group and a common SD for the percent change in hepatic fat fraction of 35%, would provide 90% power with a two-sample *t* test to achieve a significance of 0·025 for a two-dose multiplicity (after protocol amendment, the significance level was reset at 0·05 because a single-dose group was used). The enrolment size was designed to allow for 10% dropout before the week 12 visit, and as such, patients who dropped out of the study would not be replaced. Additionally, the sample size was expected to provide meaningful liver biopsy-related data. For the primary and secondary efficacy endpoints, the entire treatment group randomly assigned to 80 mg was compared with placebo, irrespective of dose adjustment at week 4. The primary endpoint used ANCOVA for the analysis of percent PDFF change endpoint and logistic regression and Fisher's exact test for the treatment goals endpoints and mixed-effect model repeated measure was used in the sensitivity analyses; secondary and exploratory endpoints used ANCOVA or ANOVA.

	Placebo, n=41	Resmetirom, n=84
Mean age, years (SD)	47·3 (11·7)	51·8 (10·4)
Sex		
Male	24 (59%)	38 (45%)
Female	17 (41%)	46 (55%)
Race or ethnicity		
White	37 (90%)	80 (95%)
Black	1 (2%)	1 (1%)
Asian	3 (7%)	2 (2%)
Other	0	1 (1%)
Hispanic or Latino	22 (54%)	37 (44%)
Metabolic risk factors and parameters		
Diabetes	13 (32%)	36 (43%)
Glycated haemoglobin, mmol/mol (%)	6·02 (0·82%)	6·36 (1·2%)
Homoeostasis model assessment-estimated insulin resistance	10·4 (22·9)	10·4 (10·2)
Hypertension	18 (43·9)	45 (53·6)
Bodyweight, kg	97·5 (22·5)	101·0 (21·2)
Body-mass index, kg/m^2	33·6 (5·8)	35·8 (6·2)
Waist circumference, cm	105·2 (20·8)	112·4 (16·8)
Baseline liver chemistries		
Alanine aminotransferase, IU/L	60·1 (32·2)	50·0 (29·2)
Aspartate aminotransferase, IU/L	38·0 (20·7)	35·1 (17·7)
Alkaline phosphatase, IU/L	80·1 (30·9)	68·8 (19·9)
Gamma-glutamyl transpeptidase, IU/L	68·1 (60·7)	48·5 (31·0)
Direct bilirubin, mg/dL	0·10 (0·051)	0·095 (0·04)
Total bilirubin, mg/dL	0·57 (0·25)	0·55 (0·23)
Baseline lipids		
Cholesterol, mg/dL	198·4 (37·3)	193 (39·3)
HDL cholesterol, mg/dL	45·2 (13·4)	43·8 (12·5)
LDL cholesterol, mg/dL	116·9 (30·0)	111·3 (30·4)
LDL cholesterol (baseline ≥100 mg/dL), n; mean mg/dL (SD)	26; 131·8 (25·1)	49; 130·2 (21·3)
Apolipoprotein B, mg/dL	104·1(21·7)	103·5 (22·8)
Apolipoprotein B (baseline LDL cholesterol ≥100 mg/dL), n; mean mg/dL (SD)	26; 114·1 (18·4)	49; 116·1 (17·5)
Triglycerides (mg/dL)	161·1 (75·2)	178·5 (82·4)
Triglycerides (baseline >150 mg/dL), n; mean mg/dL (SD)	19; 220·9 (62·2)	44; 229·5 (75·8)
Apolipoprotein CIII, mg/dL	9·80 (3·7)	10·6 (3·8)
Lipoprotein(a), nmol/L	36·9 (50·0)	29·1 (44·7)
Lipoprotein(a) (baseline >10 nmol/L), n; mean nmol/L (SD)	22; 61·5 (55·5)	40; 51·8 (53·5)

(Table 1 continues in next column)

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	Placebo, n=41	Resmetirom, n=84
Baseline hormones		
Free thyroxine, ng/dL	1·1 (0·2)	1·1 (0·15)
Free triiodothyronine, ng/L	3·2 (0·4)	3·2 (0·4)
Thyrotropin, IU/L	2·1 (1·3)	1·9(0·9)
Reverse triiodothyronine, ng/dL	18·5 (6·1)	19·3 (5·2)
Thyroxine binding globulin, mg/L	22·6 (6·9)	23·1(5·7)
Sex hormone binding globulin, nmol/L	46·6 (28·3)	48·8 (40·1)
Non-alcoholic steatohepatitis biomarkers		
N-terminal type III collagen propeptide, ng/ml	16·2 (59·0)	17·8 (10·3)
Enhanced liver fibrosis	9·2 (1·0)	9·2 (0·9)
Cytokeratin-18 fragments (M30), U/L	738·1 (495·9)	773·8 (522·7)
Adiponectin, mg/L	5·32 (3·52)	4·73 (2·24)
MRI-proton density fat fraction, % fat fraction (SD)	19·6% (8·2)	20·2% (6·8)
Liver biopsy		
Historical	4 (10%)	2 (2%)
NAS	4·8 (1·1)	4·9 (1·0)
NAS ≥5	19 (46%)	47 (58%)
Fibrosis stage 0	2 (5%)	1 (1%)
Fibrosis stage 1	19 (46%)	47 (56%)
Fibrosis stage 2	13 (32%)	18 (21%)
Fibrosis stage 3	7 (17%)	18 (21%)
Common concomitant drugs		
Proton pump inhibitors	10 (24%)	33 (39%)
Statins	4 (10%)	19 (23%)
Biguanides (metformin)	10 (24%)	28 (33%)
Insulin	3 (7%)	7 (8%)
Angiotensin-converting-enzyme inhibitors	10 (24%)	16 (19%)
Platelet aggregation inhibitors	4 (10%)	17 (20%)

Data are mean (SD) or n (%) unless otherwise stated. NAS=non-alcoholic fatty liver disease activity score.

Table 1: **Baseline characteristics**

Role of the funding source

The study was funded by Madrigal Pharmaceuticals. It was designed by expert consultants in the NASH field in conjunction with representatives of the funder. Data were collected by investigators, and managed, validated, and analysed by Medpace Research (Cincinnati, OH, USA). The corresponding author and the funder had full access to all data in the study and had final responsibility for the decision to submit for publication. The authors of the study were responsible for the data analysis, data interpretation, and writing of the report.

Results

348 individuals were screened at 25 sites in the US for enrolment (figure 1), with 125 patients from 18 sites randomly assigned between October 19, 2016, and July 28, 2017, to receive resmetirom (n=84) or placebo (n=41; figure 1). 125 patients were included in the safety analysis, 118 patients in the modified intention-to-treat

analysis for biomarkers, 116 patients in the week 12 MRI-PDFF assessment, and 108 patients in the week 36 liver biopsy assessment, of which one liver biopsy was not evaluable (muscle tissue only). 78 patients in the resmetirom group and 38 in the placebo group who completed the 12-week treatment period had both a baseline and week 12 MRI-PDFF. One patient in the placebo group had a follow-up liver biopsy after 26 weeks of treatment. All 74 patients in the resmetirom group who completed 36 weeks of treatment had a liver biopsy at week 36 and one patient in the placebo group who completed 36 weeks did not have a week 36 liver biopsy. 34 (83%) of 41 patients in the placebo group completed 36 weeks of treatments and 74 (88%) of 84 in the resmetirom group. The most common reason for discontinuing the study was lost to follow-up (5 [6%] in the resmetirom group and 4 [10%] in the placebo group).

Baseline demographics and disease characteristic were generally similar between groups (table 1). The resmetirom group had more women and more patients with diabetes than the placebo group. Mean age of the entire study population was 50·3 years (SD 11·0), most were white (117 [94%] of 125), with a large proportion of Hispanic or Latino individuals (59 [47%]), and most had a body-mass index greater than 30 kg/m² (99 [79%]). Mean baseline NAS was 4·9 in the resmetirom group and 4·8 in the placebo group, and nearly half (56 [45%]) the study population had fibrosis stage 2 or 3 at screening.

Resmetirom therapy was associated with significant reductions in relative and absolute hepatic fat fraction from baseline compared with placebo (figure 2; table 2). At week 12, the change in median relative fat from baseline was –36·3% (IQR –52·1 to –15·6) with a least square mean between-group difference of –23·1% (95% CI –33·5 to –12·7; p<0·0001; figure 2; table 2). Similar hepatic fat reductions compared with baseline and with placebo were observed at 36 weeks. The proportion of patients with a 30% or more relative fat reduction was also greater in the resmetirom group compared with the placebo group at 12 weeks (47 [60%] of 78 *vs* seven [18%] of 38, p<0·0001) and at 36 weeks (68% *vs* 30%, p=0·0008; table 3). Five of seven placebo responders (relative fat reduction ≥30%) had lost 5% or more of their bodyweight from screening to week 12. Patients with high resmetirom exposure (AUC ≥2700 ng*h/mL) or higher SHBG response (change from baseline ≥75% at week 12 and 88% at week 36) had greater relative hepatic fat reductions from baseline at 12 weeks (–39·7% [standard error 3·9]) and 36 weeks (–41·1% [4·8]) and greater absolute reductions from baseline at 12 weeks (–8·5% [0·7]) and 36 weeks (–9·2% [0·9]), showing that patients with higher plasma (drug exposure) and liver exposures (percentage change in SHBG from baseline) had better efficacy in lowering hepatic fat (table 2). A greater proportion of the high exposure group patients also met the treatment goal of at least 30% fat reduction at 12 weeks (33 [75%] of 44) and at 36 weeks (32 [74%] of 43; table 3). Subgroups based on liver fibrosis stage, diabetes status, and demographics showed similar results. In a per-protocol analysis, patients remaining on 80 mg or 100 mg past week 4 showed greater improvement in MRI-PDFF at week 36 than those on 60 mg, achieving 50·5% relative and 10·8% absolute fat reduction (appendix p 9).

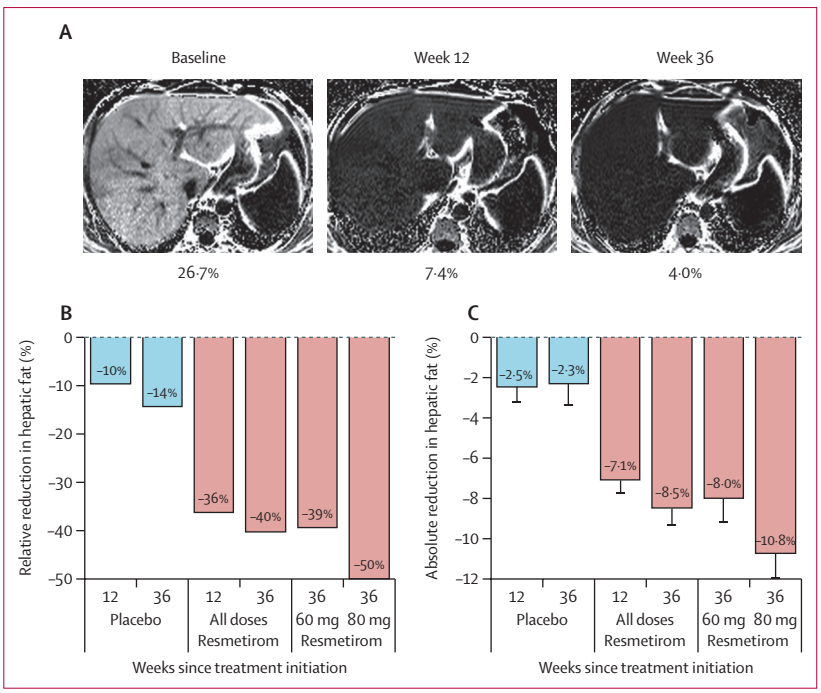

Figure 2: **MRI-PDFF**
(A) MRI-PDFF images with percentage fat fraction at baseline, week 12, and week 36. (B) Relative (median) fat reduction at week 12 and week 36 in placebo (n=38) and resmetirom (n=78). (C) Absolute (mean) fat reduction at week 12 and week 36 in placebo (n=34) and resmetirom (n=74). Week 36 resmetirom 60 mg n=36 and resmetirom 80 mg n=33 (post-hoc analysis; appendix p 8). MRI-PDFF=MRI-proton density fat fraction.

Multiple atherogenic lipids and lipoproteins were significantly reduced with resmetirom therapy compared with placebo (table 4), notably LDL cholesterol, apolipoprotein B, triglycerides, lipoprotein(a), and apolipoprotein CIII. Patients continuing on 80 mg had more robust lipid reductions than those in the 60 mg group (appendix p 9). Atherogenic lipoprotein particles were significantly reduced, particularly small LDL particles (–34·3%, p=0·011), and large VLDL particles and chylomicrons (>–50%, p<0·0001; appendix pp 10–11). There were no effects of resmetirom on other metabolic parameters including bodyweight, or metabolic indices (appendix p 12).

Markers of liver injury and fibrosis also improved. At week 12 there was no difference in alanine aminotransferase values between groups, although mean alanine aminotransferase values were significantly decreased from baseline in the resmetirom group (–8·2 U/L; p=0·0028 within group; table 4; appendix p 8). By week 36, the between-group difference was

	n	Placebo, % (standard error)	n	Resmetirom, % (standard error)	Least squares mean difference from baseline (95% CI)	p value
Week 12 change relative to baseline	38	−10·4% (4·3)	78	−32·9% (3·0)	−22·5% (−32·9 to −12·2)	<0·0001
High exposure group	..	..	44	−39·7% (3·9)	−29·3% (−40·6 to −18·0)	<0·0001
Low exposure group	..	..	34	−24·1% (4·4)	−13·8% (−25·8 to −1·7)	0·025
High SHBG group	..	..	48	−38·7% (3·7)	−28·3% (−39·4 to −17·2)	<0·0001
Low SHBG group	..	..	30	−23·7% (4·7)	−13·3% (−25·8 to −0·8)	0·037
F2–F3	19	−7·1% (5·3)	33	−30·9% (4·0)	−23·7% (−37·0 to −10·5)	0·0007
<5% weight loss group	31	−3·8% (4·5)	70	−31·5% (3·0)	−27·8% (−38·4 to −17·1)	<0·0001
Week 36 change relative to baseline	34	−8·9% (5·4)	74	−37·3% (3·7)	−28·4% (−41·3 to −15·4)	<0·0001
High exposure group	..	..	43	−41·1% (4·8)	−32·2% (−46·5 to −18·0)	<0·0001
Low exposure group	..	..	31	−31·8% (5·6)	−22·9% (−38·4 to −7·5)	0·0040
High SHBG group	..	..	44	−46·1% (4·6)	−37·1% (−50·7 to −23·4)	<0·0001
Low SHBG group	..	..	30	−24·3% (5·5)	−15·3% (−30·4 to −0·2)	0·047
F2–F3	18	−13·5% (6·2)	31	−34·7% (4·7)	−21·2% (−37·0 to −5·5)	0·0094
Week 12 absolute change from baseline	38	−2·7% (0·8)	78	−7·0% (0·6)	−4·3% (−6·3 to −2·4)	<0·0001
High exposure group	..	..	44	−8·5% (0·7)	−5·8% (−7·9 to −3·7)	<0·0001
Low exposure group	..	..	34	−5·1% (0·8)	−2·4% (−4·7 to −0·2)	0·035
High SHBG group	..	..	48	−8·0% (0·7)	−5·3% (−7·4 to −3·2)	<0·0001
Low SHBG group	..	..	30	−5·4% (0·9)	−2·7% (−5·1 to −0·3)	0·026
F2–F3	19	−1·6% (1·1)	33	−6·6% (0·8)	−5·0% (−7·8 to −2·2)	0·0007
<5% weight loss group	31	−1·6% (0·8)	70	−6·7% (0·5)	−5·1% (−7·0 to −3·1)	<0·0001
Week 36 absolute change from baseline	34	−2·8% (1·1)	74	−8·2% (0·7)	−5·3% (−7·8 to −2·8)	<0·0001
High exposure group	..	..	43	−9·2% (0·9)	−6·3% (−9·0 to −3·5)	<0·0001
Low exposure group	..	..	31	−6·9% (1·1)	−4·0% (−7·0 to −1·1)	0·0084
High SHBG group	..	..	44	−9·8% (0·9)	−6·9% (−9·6 to −4·3)	<0·0001
Low SHBG group	..	..	30	−5·9% (1·1)	−3·0% (−5·9 to −0·1)	0·048
F2–F3	18	−3·3% (1·3)	31	−7·7% (1·0)	−4·4% (−7·8 to −1·0)	0·012

The high exposure group consisted of individuals with 2700 ng*h/ml or more estimated AUC, and the low exposure group consisted of individuals with an estimated AUC of less than 2700 ng*h/ml. The high SHBG group consisted of individuals with 75% or greater change from baseline at week 12 and 88% or greater change from baseline at week 36. Exposure and SHBG groups were prespecified on the basis of blinded data and compared with all placebo patients (week 12 n=38, week 26 n=34). SHBG=sex hormone binding globulin. F2–F3=F2 or F3 fibrosis stage on baseline liver biopsy. AUC=area under the curve.

Table 2: **Change in MRI-proton density fat fraction from baseline**

	n	Placebo, n (%)	n	Resmetirom, n (%)	Odds ratio (95% CI)	p value
Week 12 ≥30% fat reduction	38	7 (18·4%)	78	47 (60·3%)	6·8 (2·6–17·6)	<0·0001
High exposure group	..	..	44	33 (75·0%)	13·8 (4·6–40·9)	<0·0001
Low exposure group	..	..	34	14 (41·2%)	3·08 (1·0–9·1)	0·042
High SHBG group	..	..	48	31 (64·6%)	8·33 (3·0–23·3)	<0·0001
Low SHBG group	..	..	30	16 (53·3%)	4·99 (1·7–15·0)	0·0043
F2–F3	19	2 (10·5)%	33	20 (60·6%)	14·61 (2·7–78·0)	0·0017
<5% weight loss group	31	2 (6·5%)	70	41 (58·6%)	27·9 (5·5–142·2)	<0·0001
Week 36 ≥30% fat reduction	34	10 (29·4%)	74	50 (67·6%)	4·9 (2·0–11·9)	0·0006
High exposure group	..	..	43	32 (74·4%)	6·9 (2·5–19·3)	0·0002
Low exposure group	..	..	31	18 (58·1%)	3·1 (1·1–8·9)	0·032
High SHBG group	..	..	44	34 (77·3%)	8·3 (2·9–23·5)	<0·0001
Low SHBG group	..	..	30	16 (53·3%)	2·5 (0·9–7·2)	0·084
F2–F3	18	4 (22·2%)	31	21 (67·7%)	7·3 (1·9–28·6)	0·0040

The high exposure group consisted of individuals with 2700 ng*h/ml or more estimated AUC, and the low exposure group consisted of individuals with an estimated AUC of less than 2700 ng*h/ml. The high SHBG group consisted of individuals with 75% or greater change from baseline at week 12 and 88% or greater change from baseline at week 36. Exposure and SHBG groups were prespecified on the basis of blinded data and compared with all placebo patients (week 12 n=38, week 26 n=34). SHBG=sex hormone binding globulin. F2–F3=F2 or F3 fibrosis stage on baseline liver biopsy. AUC=area under the curve.

Table 3: **Proportions of patients with at least 30% fat reduction at weeks 12 and 36**

statistically significant (p=0·0019). A similar pattern was seen in patients with elevated alanine aminotransferase at baseline (table 4). Alanine aminotransferase reductions were more pronounced in patients with evidence of higher exposure to drug or on-treatment SHBG concentrations, particularly in patients in whom baseline liver enzymes were elevated. Average reductions of 40% were observed at week 36 (p=0·013). At week 36, 44 [60%] of 74 patients in the resmetirom group had alanine aminotransferase concentrations of less than 30 U/L compared with 10 [30%] of 34 patients in the placebo group. Mean aspartate aminotransferase and gamma-glutamyl transpeptidase values were also significantly reduced from baseline and relative to the placebo group by week 36. Assessments of non-invasive fibrosis markers, enhanced liver fibrosis and N-terminal type III collagen propeptide (PRO-C3), which are markers of collagen formation and fibrogenic activity, showed

	n	Placebo	n	Resmetirom	Least squares mean difference (95% CI)	p value
Lipids, percentage change from baseline						
LDL cholesterol, mg/dL	39	6·2% (3·1)	79	−11·2% (2·1)	−17·3% (−24·8 to −9·9)	<0·0001
LDL cholesterol (baseline ≥100 mg/dL), mg/dL	24	6·1% (3·8)	47	−16·2% (2·7)	−22·3% (−31·6 to −12·9)	<0·0001
HDL cholesterol, mg/dL	39	2·2% (3·4)	79	6·0% (2·3)	3·8% (−4·4 to 12·0)	0·36
Lipoprotein(a) (baseline >10 nmol/L), nmol/L	20	15·3% (8·9)	40	−22·7% (6·3)	−37·9% (−59·7 to −16·2)	0·0009
Apolipoprotein B (baseline LDL cholesterol ≥100 mg/dL), n	24	7·4% (3·5)	47	−20·2% (2·5)	−27·6% (−36 to −19·1)	<0·0001
Triglycerides, mg/dL	39	20·5% (5·5)	79	−15·4% (3·8)	−36·0% (−49·2 to −22·7)	<0·0001
Triglycerides (baseline >150 mg/dL), mg/dL	15	9·5% (7·9)	41	−21·4% (4·8)	−30·8% (−49·4 to −12·2)	0·0016
Apolipoprotein CIII, mg/dL	37	24·5% (5·4)	76	−12·0% (3·7)	−36·5% (−49·6 to −23·5)	<0·0001
Liver enzymes						
Alanine aminotransferase, IU/L	39	..	79	..	..	..
Week 12	..	−5·2 (3·9)	..	−8·2 (2·7)*	−3·0 (−12·4 to 6·4)	0·53
Week 36	..	11·0 (6·8)	..	−15·4 (4·7)*	−26·4 (−42·8 to −9·9)	0·0019
High exposure group	..	..	44	−19·0 (6·2)*	−30·0 (−48·3 to −11·7)	0·0015
Low exposure group	..	..	35	−10·6 (7·1)	−21·5 (−41·2 to −1·9)	0·032
High SHBG group	..	..	44	−19·6 (6·25)*	−31·1 (−49·6 to −12·6)	0·0012
Low SHBG group	..	..	33	−8·9 (7·3)	−20·4 (−40·5 to −0·2)	0·048
Alanine aminotransferase (baseline >45 IU/L in men or >30 IU/L in women), IU/L	29	..	47	..	..	..
Week 12	..	−7·7 (5·3)	..	−13·5 (4·2)*	−5·8 (−19·3 to 7·7)	0·39
Week 36	..	11·9 (9·4)	..	−24·0 (7·3)*	−35·9 (−59·6 to −12·2)	0·0035
High exposure group	..	..	27	−27·8 (9·6)*	−39·7 (−66·6 to −12·8)	0·0044
Low exposure group	..	..	20	−18·8 (11·2)	−30·7 (−60·0 to −1·5)	0·0397
High SHBG group	..	..	29	−33·6 (10·1)*	−45·5 (−72·9 to −18·1)	0·0015
Low SHBG group	..	..	21	−11·6 (11·0)	−23·4 (−52·4 to 5·5)	0·11
Aspartate aminotransferase, IU/L						
Week 12	..	−1·1 (2·5)	..	−5·8 (1·8)	−4·8 (−10·9 to 1·4)	0·13
Week 36	..	3·6 (2·8)	..	−7·4 (1·9)*	−11·1 (−17·8 to −4·3)	0·0016
Gamma-glutamyl transpeptidase, IU/L	..	49·4 (15·2)	..	−9·1 (10·4)*	−58·5 (−95·2 to −21·8)	0·0020
Direct bilirubin, mg/dL	..	−0·005 (0·006)	..	0·014 (0·004)	0·020 (0·006 to 0·033)	0·0057
Total bilirubin, mg/dL	..	−0·033 (0·026)	..	0·013 (0·018)	0·046 (−0·017 to 0·11)	0·15
Alkaline phosphatase, IU/L	..	10·0 (2·75)	..	5·4 (1·88)	−4·6 (−11·2 to 2·1)	0·17
Other biomarkers						
Enhanced liver fibrosis (baseline ≥9)	21	−0·18 (0·16)	40	−0·66 (0·12)*	−0·48 (−0·88 to −0·09)	0·017
N-terminal type III collagen propeptide, ng/mL						
Baseline ≥10·0 ng/mL	25	7·4 (3·1)	53	−2·2 (2·1)*	−9·63 (−17·1 to −2·2)	0·012
Baseline ≥17·5 ng/mL	12	14·9 (5·6)	29	−6·5 (3·5)*	−21·4 (−34·9 to −7·9)	0·0027
Cytokeratin-18 (M30), U/L	36	−101·0 (47)	75	−272·0 (33)*	−171·0 (−285 to −57)	0·0035
Adiponectin (mg/L)	37	0·24 (0·24)	78	1·31 (0·16)*	1·07 (0·50 to 1·64)	0·0003
Reverse triiodothyronine (ng/dL)	36	−1·37 (0·73)	76	−4·26 (0·50)*	−2·88 (−4·64 to −1·12)	<0·0001

(Table 3 continues on next page)

	n	Placebo	n	Resmetirom	Least squares mean difference (95% CI)	p value
(Continued from previous page)						
Liver biopsy						
Change in NAS, mean (SE)	34	−1·0 (0·21)	73	−1·4 (0·14)	−0·4 (−0·9 to 0·1)	0·082
High exposure group	..	..	43	−1·6 (0·18)	−0·6 (−1·2 to −0·1)	0·029
Low exposure group	..	..	30	−1·2 (0·22)	−0·2 (−0·8 to 0·4)	0·51
High SHBG group	..	..	44	−1·7 (0·18)	−0·7 (−1·2 to −0·1)	0·016
Low SHBG group	..	..	29	−1·1 (0·22)	−0·1 (−0·7 to 0·5)	0·77
MRI-PDFF responder	..	..	46	−1·9 (0·16)	−0·9 (−1·4 to 0·4)	0·0006

Lipid, liver enzyme, and biomarker measurements are presented as last observation carried forward. Lipid statistics were based on week 30, a prespecified timepoint. For triglycerides, combined results from weeks 30–36 were used because of variability. Apolipoprotein CIII was measured at week 36. Least square means, SE, CIs, and p values come from a linear model with change from baseline as the dependent variable and treatment as a factor. For the analysis of change from baseline (lipids only), the baseline value is also included as a covariate. For liver biopsy assessments, all analyses were prespecified in the statistical analysis plan. Fisher's exact test was used in all responder analyses. Unless otherwise specified, MRI-PDFF responders are patients treated with resmetirom with ≥30% decrease in hepatic fat at week 12). SHBG=sex hormone binding globulin. NAS=non-alcoholic fatty liver disease activity score. MRI-PDFF=MRI-proton density fat fraction. *Least squares mean decrease from baseline p≤0·05 within group for liver enzymes and biomarkers. All lipids were statistically significantly decreased within resmetirom group. For liver enzymes and other biomarkers, week 36 measurements are presented (except as indicated at week 12). There was no change in high-sensitivity C-reactive protein.

Table 4: **Biomarkers and liver biopsy**

statistically significant decreases at 12 and 36 weeks with resmetirom treatment as compared with placebo (enhanced liver fibrosis −0·48, p=0·017; PRO-C3 −21·4 ng/ml, p=0·0027; table 4). Serum cytokeratin-18 fragments, detected using the M30 antibody and which might reflect hepatocyte apoptosis, were statistically significantly reduced within group (weeks 12 and 36) and relative to placebo at week 36. Concentrations of adiponectin, an adipokine associated with hepatic health, was increased, and reverse triiodothyronine, a marker of hepatic inflammation,[17] was decreased by resmetirom treatment (appendix p 8).

On liver biopsy, features of NASH were reduced with resmetirom therapy. NAS was reduced in resmetirom-treated patients compared with placebo-treated patients, particularly in patients with higher resmetirom exposure (table 4). The proportion of patients with a 2-point or greater reduction in NAS with at least a 1-point reduction in ballooning or inflammation on week 36 biopsy was significantly greater in the resmetirom group compared with placebo (28 [46%] of 61 *vs* 5 [19%] of 27, p=0·017) in the subgroup of patients who had <5% weight loss, the subgroup of patients with high resmetirom exposure (26 [60%] of 43 *vs* 11 [32%] of 34, p=0·021) and patients who were MRI-PDFF responders by week 12 (≥30% fat reduction; 30 [65%] of 46 *vs* 11 [32%] of 34, p=0·0063; appendix p 8). NASH resolution (ballooning score of 0, inflammation score of 0 or 1 with ≥2-point reduction in NAS) at 36 weeks was a prespecified secondary endpoint in the study. The evaluation of NASH resolution was done in patients with less than 9·5% weight loss (prespecified), among whom 20 (27%) of 73 patients in the resmetirom group had NASH resolution compared with two (6%) of 31 in the placebo group (p=0·018; table 4; appendix p 8). Of 46 patients in the resmetirom group who were MRI-PDFF responders at week 12, 18 (39%) had NASH resolution (p=0·0013). Similar percentages of resmetirom patients had NASH resolution with no fibrosis worsening compared with placebo. Seven (39%) of 18 patients in the resmetirom group with NASH resolution had a baseline NAS of 5 of more compared with 0 in the placebo group.

The mean fat reduction on MRI-PDFF in NASH resolution responders was 50·0% (standard error 4·6; relative) and 11·0% (0·69; absolute; appendix p 15). The few patients in the placebo group with NASH resolution also showed reduction in hepatic fat on MRI-PDFF, and this response was associated with weight loss. The MRI-PDFF response defined as 30% or more relative fat reduction at week 12 was associated with NASH resolution on liver biopsy (appendix p 15) in that 17 (37%) of 46 patients treated with resmetirom who were MRI-PDFF responders had NASH resolution, whereas two (4%) of 27 non-PDFF responders had NASH resolution. The MRI-PDFF response also correlated with decrease in both ballooning and inflammation, and in this study, only MRI-PDFF responders showed a decrease in both ballooning and inflammation (appendix pp 15–17).

The number of patients achieving at least 1-point reduction in fibrosis without worsening of NAS did not differ between groups (table 5). 11 (61%) of 18 patients in the resmetirom group with NASH resolution showed a reduction in fibrosis stage, and 10 (56%) of 18 patients with NASH resolution resolved their fibrosis (F0; table 5).

Resmetirom was generally well tolerated. The most common adverse events were diarrhoea and nausea (table 6). Diarrhoea was commonly an isolated episode described as loose stools at therapy initiation. Other than liver enzymes, which were reduced, and other laboratory tests reflecting the pharmacological action of resmetirom (eg, lipids and SHBG), laboratory tests did not differ from baseline and were similar between

	n	Placebo, n (%)	n	Resmetirom, n (%)	Odds ratio	p value
≥2-point NAS reduction	34	11 (32·4%)	73	41 (56·2%)	2·7 (1·1–6·3)	0·024
High exposure group	..	..	43	28 (65·1%)	3·9 (1·5–10·1)	0·0059
Low exposure group	..	..	30	13 (43·3%)	1·6 (0·6–4·4)	0·44
High SHBG group	..	..	44	28 (63·6%)	3·7 (1·4–9·4)	0·012
Low SHBG group	..	..	29	13 (44·8%)	1·7 (0·6–4·7)	0·44
MRI-PDFF responder	..	..	46	32 (69·6%)	4·8 (1·8–12·4)	0·0014
<5% weight loss group	27	5 (18·5%)	61	30 (49·2%)	4·3 (1·4–12·7)	0·0090
NASH resolution (without fibrosis worsening)	31	6 (6·5%)	73	18 (24·7%)	4·75 (1·03–21·9)	0·032
MRI-PDFF responder	..	..	46	17 (37·0%)	8·50 (1·80–40·2)	0·0026
Including weight loss >9·5%	34	5 (14·7%)	73	18 (24·7%)	1·9 (0·64–5·6)	0·32
MRI-PDFF responder (including weight loss >9·5%)	..	..	46	17 (37·0%)	3·4 (1·1–10·4)	0·042
Fibrosis responder	34	8 (23·5%)	73	21 (28·8%)	1·3 (0·51–3·36)	0·65
MRI-PDFF responder	..	..	46	15 (32·6%)	1·6 (0·58–4·29)	0·46
NASH resolution responder	..	..	18	11 (61·1%)	5·1(1·5–17·6)	0·014

Unless otherwise specified, MRI-PDFF responders are patients treated with resmetirom with ≥30% decrease in hepatic fat at week 12, fibrosis responders are patients with one stage or more reduction in fibrosis and no worsening of NAS, NASH resolution is ballooning score of 0 and inflammation score of 0 or 1, with at least a 2-point reduction in NAS and no worsening of fibrosis (assessed in patients with <9·5% weight loss), and NASH resolution responders were patients with NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis (resmetirom treatment group only). NAS=non-alcoholic fatty liver disease activity score. SHBG=sex hormone binding globulin. MRI-PDFF=MRI-proton density fat fraction. NASH=non-alcoholic steatohepatitis.

Table 5: **Biopsy responder analyses**

treatment groups. Treatment-emergent serious adverse events occurred in six patients in the resmetirom group and two in the placebo group. All were single occurrences and considered to be unrelated to the study drug. One placebo patient progressed from F2 at baseline to cirrhosis at week 36. No significant effects on thyroid stimulating hormone concentrations, bone mineral density, ECG, cardiovascular markers, or diabetes biomarkers were noted (not shown and appendix pp 12–13). A less than 3% reduction in mean diastolic blood pressure was noted at week 36 in patients in the resmetirom group that was significant within group relative to baseline but not relative to placebo. Quality of life questionnaire results showed no differences between resmetirom and placebo groups (data not shown).

	Placebo, n=41	Resmetirom, n=84
Patients with treatment-emergent adverse events, n (%)	28 (68%)	73 (86·9%)
Severe	2 (5%)	6 (7%)
Moderate	13 (32%)	27 (32%)
Mild	13 (32%)	40 (48%)
Patients with serious adverse events	2 (5%)	5 (6%)
Patients with drug-related serious adverse events	0	0
Adverse events occurring in ≥10%, n (%)		
Diarrhoea (baseline to week 12)	3 (7%)	28 (33%)
Nausea (baseline to week 12)	2 (5%)	12 (14%)
Diarrhoea (week 12–36)	1 (2%)	3 (4%)
Nausea (week 12–36)	1 (2%)	5 (6%)
Headache	6 (15%)	11 (13%)
Urinary tract infection	4 (10%)	9 (11%)
Dizziness	4 (10%)	6 (7%)
Fatigue	4 (10%)	4 (5%)
Grade 3 laboratory changes (CTCAE*)		
Alanine aminotransferase >5 times ULN	3 (7%)	1 (1%)†
Gamma-glutamyl transferase >5 times ULN	5 (12%)	1 (1%)

Data are n (%). Five times ULN was only reported if the value was at least two times greater than baseline. CTCAE=Common Terminology Criteria for Adverse Events. ULN=upper limit of normal. *CTCAE-based assessments were post hoc. †One resmetirom patient took a double dose (160 mg/day) for 2 weeks before the week 2 visit and showed increased liver enzymes to three times baseline at week 2; liver enzymes resolved during the study, with alanine aminotransferase decreasing from 77 IU/L at baseline to 17 IU/L on 80 mg/day.

Table 6: **Adverse events**

Discussion

In patients with documented NASH fibrosis, daily oral doses of resmetirom compared with placebo resulted in a sustained statistically significant reduction in hepatic fat as measured by MRI-PDFF, an accurate measurement of hepatic fat, including an average relative reduction of up to 50% and absolute reduction of 11% at higher doses and drug exposures Additionally, similar to what has been observed in healthy volunteers and patients with dyslipidaemia,[16] treatment with resmetirom resulted in statistically and clinically significant reductions in multiple atherogenic lipids and lipoproteins, including LDL cholesterol, apolipoprotein B, triglycerides, apolipoprotein CIII, and lipoprotein(a) (table 3; appendix pp 10–11). The reductions included effects on atherogenic lipoprotein particles known to be associated with cardiovascular disease, including small dense LDL particles and large VLDL or chylomicrons (appendix pp 10–11).

Liver enzymes were reduced, and biomarkers associated with inflammation and fibrosis were statistically significantly changed by resmetirom. Biomarkers of hepatic fibrogenesis (PRO-C3 and enhanced liver fibrosis),

cytokeratin-18, which has been associated with ballooning, and reverse triiodothyronine (associated with liver inflammation)[14] were reduced, and adiponectin was increased in resmetirom-treated patients. Adiponectin, an adipokine which is low in patients with NASH, is inversely correlated with liver fibrosis.[20] Because resmetirom actions occur in the liver, resmetirom could increase adiponectin by decreasing the hepatic turnover of adiponectin.

In secondary analyses, a significant improvement in NASH on liver biopsy compared with placebo was observed, including reduction in NAS and NASH resolution. The reduction in NAS was particularly correlated with higher dose and exposure to resmetirom. Comparison of the histological effects of resemetirom in NASH with other drugs is hampered by the use of variable liver biopsy endpoints and differences in NASH populations across studies. NASH resolution or NAS improvement has been defined as "pathologist determined",[10] absence of ballooning (without assessing inflammation),[21] 2-point NAS reduction,[11] or ballooning score of 0 and lobular inflammation score of 0 or 1 (post hoc).[12] Weight loss studies were done in patients with very early NASH that was more likely to resolve (60% F0) and, therefore, not comparable to studies in patients with more advanced NASH.[8] We defined NASH resolution as at least a 2-point reduction in NAS plus ballooning score of 0 with lobular inflammation score of 0 or 1. This definition avoids confounding data, in which NASH resolution might result from a single point reduction in ballooning in patients with baseline NAS, ballooning score of 1, and lobular inflammation score of 1, a potentially significant fraction of baseline biopsies, including not only F1 stage biopsies, but about 20% of the more advanced stage (F2–F3) biopsies in this study. The heterogeneity of the liver and discordance between pathology reviewers support that NASH resolution requires at least a 2-point NAS improvement.[22] Moreover, the confounding issue with liver biopsy as an objective measure of response adds value to changes in non-invasive data, such as liver enzymes, fibrosis biomarkers, and imaging, that are consistent with clinical improvement.

Resmetirom was well tolerated. It was associated with an increase in mild and a few moderate gastrointestinal adverse events, particularly loose stools. These adverse events were self-limited and did not result in study withdrawal (table 6). There were no increases in gastrointestinal adverse events in the later phases of the study. No adverse events related to the thyroid hormone pathway were noted, including no increase in adverse events related to the thyroid receptor α activity (cardiovascular, bone mineral density, thyroid axis suppression). Resmetirom's safety was consistent with its overall selectivity and high liver uptake, and few toxicities in non-clinical and animal toxicology studies.

It has been proposed that liver relative fat reduction of 29% or more correlates with NAS reduction on biopsy.[23] In this study, MRI-PDFF responders (defined by ≥30% relative fat reduction at week 12 compared with baseline) showed an enhanced NASH resolution response (appendix p 15) validating the proposal that 30% or more hepatic fat reduction is a valuable marker of the improvement in NASH in clinical trials. NASH resolution responders also showed a marked reduction in fibrosis (61% with ≥1-point reduction in fibrosis stage). This is consistent with findings that suggest that fibrosis reduction is most strongly predicted by NASH resolution, followed by NAS reduction, steatosis, and ballooning reduction.[24] Reduction in hepatic fat as assessed by MRI-PDFF was associated with a steatosis component response on biopsy, as would be expected, but also correlated with a reduction in NAS ballooning and inflammation components (appendix pp 15–17). This is the first report in which an MRI-PDFF response has been linked to a significant NASH resolution and improvement in other NAS components analysed separately from steatosis.[23] Because MRI-PDFF detects only hepatic triglycerides and not other lipid metabolites, reduction in PDFF might not directly reflect lipotoxic fat reduction or assess specific factors that might mediate NASH improvement.

Weight loss improves NASH, and might lead to NASH resolution when weight loss is 9–10%.[8,25] Patients were counselled on diet and exercise at each visit, and some patients (2 [20%] of 34 in the placebo group and 12 [16%] of 73 in the resmetirom group) had meaningful weight loss of 5% or more. Resmetirom had no effect on bodyweight. Weight loss of 5% or more was observed in the majority of MRI-PDFF responders in the placebo group and occurred in more than half of patients in the placebo group with a 2-point or greater reduction in NAS. Patients in the placebo group with 9·5% or more weight loss (n=3) or NASH resolution were from a single site (appendix p 14). In this study, whether patients were treated with placebo or resmetirom, weight loss of 5% or more was associated with improvement in NAS and some improvement in fibrosis (42% fibrosis reduction in all patients with ≥5% weight loss); the effect of weight loss on fibrosis was not independent of the effect on NAS. Although weight loss enhanced the response to resmetirom, assessment of efficacy relative to placebo in the subgroup with less than 5% weight loss showed that the effects of resmetirom on MRI-PDFF and NAS were not driven by weight loss.

This study used an adaptive dosing design that maintained a generally even exposure to resmetirom. Prespecified groups that were estimated to have higher plasma or liver (as determined with the pharmacodynamic marker SHBG) exposure to resmetirom included patients dosed with both 60 mg and 80 mg. High exposure groups showed more robust responses on MRI-PDFF, liver enzymes, lipids, NAS, and fibrosis biomarker reductions. In a post-hoc analysis, the 80 mg group, which included five patients on 100 mg, showed more

robust lipid lowering, MRI-PDFF reductions, and NASH resolution than those on 60 mg (appendix p 9). 60 mg is an effective dose in some patients who have higher plasma drug concentrations at 60 mg but, on the basis of these results, is not predicted to be a minimally effective dose, defined by at least 50% NASH or lipid response across the population. In the completed 36-week exploratory extension study of MGL-3196-05 and the ongoing phase 3 clinical trial, MAESTRO-NASH (NCT03900429), higher doses of 80 mg and 100 mg are used.

As a nuclear receptor hormone analogue, resmetirom's effects in the liver are pleiotropic. The mechanism by which resmetirom reduces hepatic fat is hypothesised to be largely through increased mitochondrial β oxidation and restoration of normal mitochondrial function in the livers of patients with NASH.[13] Although other nuclear hormone receptors have pleiotropic hepatic actions, such as farnesoid X receptor and PPAR agonists, the magnitude of resmetirom's effect on hepatic fat appears to be greater. Lowering of serum apolipoprotein B by resmetirom is hypothesised to be a consequence of a reduced VLDL production and secretion, leading to lower concentrations of plasma LDL cholesterol and triglycerides. Lipoprotein(a), a highly atherogenic lipoprotein, is reduced by a significant magnitude; the mechanism of lowering by resmetirom or THR-β agonism is unknown.[26] Data support apolipoprotein B (excreted from the liver as VLDL particles) as the major lipoprotein associated with cardiovascular risk.[27] Lipid lowering by resmetirom highlights a potential for providing cardiovascular benefit to patients with NASH, who die most frequently of cardiovascular disease. Other mechanisms to reduce hepatic steatosis are being studied in ongoing NASH trials to determine an effect on biopsy including NGM-282, an injectable FGF19 analogue, that significantly raises LDL cholesterol through CYP7a inhibition,[28] pegbelfermin, an injectable FGF21 analogue,[29] and GS-0976, a pan-acetyl-CoA carboxylase inhibitor that lowers hepatic fat, and also increases plasma triglycerides.[30] Resmetirom does not affect bile acid levels including C4, the product of CYP7a (data not shown).

The study had notable strengths, particularly with respect to testing multiple non-invasive endpoints that might be linked with changes in liver histology. In the treatment of NASH, validated, serial, non-invasive markers, rather than serial liver biopsies, are needed to monitor response to therapy. Resmetirom has significant, rapid, and sustained effects on readily assayed markers, such as lipids, liver enzymes, fibrosis markers, and non-invasive imaging, that make monitoring of the therapeutic response feasible. The study was well powered to test the primary endpoint—reduction of hepatic fat by MRI-PDFF—and key secondary endpoints—LDL cholesterol and apolipoprotein B lowering. However, largely because of the small sample size affecting the secondary liver biopsy endpoints, limitations included some imbalances in specific subgroups and site effects that resulted in confounding lifestyle changes. Because this was a phase 2 study, the analyses of secondary endpoints were not controlled for multiplicity. Evaluation of more advanced NASH was limited by the relatively low baseline NAS and small number of patients with advanced stages of fibrosis.

In conclusion, resmetirom showed statistically significant effects compared with placebo in reduction of hepatic fat, liver enzymes, atherogenic lipids, lipoprotein(a), markers of inflammation and fibrosis, and improving NASH on liver biopsy. These findings provide the rationale for the resmetirom phase 3 clinical trial (NCT03900429) that has been initiated in patients with NASH and stage F2–F3 fibrosis.

Contributors

SAH, RT, MBB, RZ, MRB, and CDG and participated in study design. SAH, JPF, NA, MBB, SEM, MRB, CDG, SB, and BAN-T were responsible for data collection. SAH, MRB, RT, RZ, CAM, and CDG participated in data analysis. All authors participated in data interpretation and manuscript review and writing. RZ, RT, and SAH were responsible for preparation of the tables and figures.

Declaration of interests

SAH reports grant and research support from Conatus, Galectin, Galmed, Genfit, Gsilead, Intercept, Madrigal, NGM Bio, Akero, Axcella, Metacrine, 3V Bio, Enyo, NorthSea, Genentech, Contravir, Cymabay, and Hightide and is a consulting adviser for the Chronic Liver Disease Foundation, Cirius, Echosens, Akero, Galmed, Genfit, Gilead, Intercept, Madrigal, NGM Bio, Novartis, Perspectum, Metacrine, Medpace, 3V Bio, Blade, Viking, Poxel, Axcella, Terns, HistoIndex, Hightide, Contravir, Innovate, CiVi, and Prometic. MRB reports grant and research support from General Electric, Madrigal, Metacrine, NGM Bio, Pinnacle Clinical Research, ProSciento, and Siemens and is a consulting advisor for MedPace. CDG reports grant and research support from Immuron, TaiwanJ, Madrigal, CymaBay, and NGM and is a consulting advisor for Immuron, TaiwanJ, Madrigal, CymaBay, and NGM. RZ is an employee of MedPace working under contract with Madrigal. CAM reports grant and research support from Galectin, Intercept, Genfit, Gilead, NGM Bio, TaiwanJ, Novartis, Allergan, Conatus, Immuron, Galmed, BMS, Novo Nordisk, Conatus, and Immuron and is a consulting advisor for Gilead and NuSirt. JPF reports grant and research support from Akcea, Allergan, BMS, Cirius, Cymabay, Eli Lilly, Genentech, Madrigal, NGM, Novartis, Novo Nordisk, Pfizer, Sanofi, Second Genome, and Theracos, speakers' bureau for Merck and Sanofi, and is a consulting advisor for Eli Lilly, Gilead, Merck, Novo Nordisk, and Sanofi. NA reports grant and research support from Akero, Albireo, Allergan, BMS, Conatus, Enyo, Galectin, Galmed, Genfit, Gilead, Hanmi, Intercept, Madrigal, Novartis, and Poxel, speakers' bureau for Alexion, Gilead, and Intercept, and is a consulting adviser for Allergan, Cirius, Gilead, and Pfizer. MBB reports grant and research support from the National Institutes of Health, Intercept, Allergan, and Madrigal and is a consulting advisor for Kinetix Group and Boehringer Ingelheim. SB reports grant and research support from Madrigal, speakers' bureau for Amgen, Lilly, Novo Nordisk, and Akcea, and is a consulting advisor for Sanofi, Amgen, GLG Group, Guidepoint Global, Regeneron, Novo Nordisk, Novartis, and Akcea. BAN-T reports consulting and advisor relationships with Allergan, Arrowhead, ARTham, Axcella, Blade, Boehringer Ingleheim, BMS, Coherus, Consynance, Durect, Enanta, Fortress, Gelesis, Gilead, Intercept, Lipocine, Madrigal, Medimmune, Merck, Metacrine, Mundipharma, NGM, pH-Pharma, Prometheus, and Siemens and institution research support from Allergan, BMS, Cirius, Cymabay, Enanta, Galectin, Genfit, Gilead, Intercept, Madrigal, NGM, and Prometheus. RT is an employee and shareholder of Madrigal. SEM reports research support from Madrigal.

Data sharing

Requests that are considered in scope for sharing will meet the following criteria: trials that completed after January, 2018, trials that are part of a programme in which Madrigal Pharmaceuticals currently has the legal

right to develop and commercialise the asset, and those that are part of a programme that has been approved for marketing; and 3 years have elapsed since study completion. All data requests will be reviewed internally by a qualified panel of Madrigal Pharmaceuticals experts who are familiar with the data. The Madrigal Pharmaceuticals study evaluation team will ensure that the proposal is complete, the scientific request is valid, and that the data are available, consistent with safeguarding patient privacy and informed consent.

Acknowledgments

We would like to thank all the patients and their families. This study was funded by Madrigal Pharmaceuticals, West Conshohocken, PA, USA.

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