

METHODS FOR TREATING A FATTY LIVER DISEASE**Cross Reference to Related Applications**

[0001] This application claims the benefit of U.S. Patent Application No. 19/045,070, filed February 4, 2025, and U.S. Provisional Application Nos. 63/550,201, filed February 6, 2024, 63/564,803, filed March 13, 2024, 63/655,870, filed June 4, 2024, 63/719,257, filed November 12, 2024, 63/720,725, filed November 14, 2024, and 63/721,474, filed November 16, 2024, the disclosures of all of which are incorporated herein by reference in their entireties.

Technical Field of the Invention

[0002] This disclosure is related to the area of treatment of a fatty liver disease, such as, for instance, non-alcoholic steatohepatitis (NASH) (e.g., noncirrhotic non-alcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 and F3 fibrosis. In particular, the disclosure relates to method for the efficacious treatment of a fatty liver disease (e.g., NASH) utilizing the thyroid hormone receptor-beta (THR-beta) agonist resmetirom or a pharmaceutically acceptable salt thereof. In addition, the disclosure is related to the area of treatment of stages F2 and F3 liver fibrosis associated with a fatty liver disease. In particular, the disclosure relates to a method for the efficacious treatment of stages F2 and F3 liver fibrosis associated with a fatty liver disease, with improvement of liver fibrosis by up to one or two stages, utilizing resmetirom or a pharmaceutically acceptable salt thereof.

Background of the Invention

[0003] Thyroid hormones are critical for normal growth and development and for maintaining metabolic homeostasis. Circulating levels of thyroid hormones are tightly regulated by feedback mechanisms in the hypothalamus/pituitary/thyroid (HPT) axis. Thyroid dysfunction leading to hypothyroidism or hyperthyroidism clearly demonstrates that thyroid hormones exert profound effects on cardiac function, body weight, metabolism, metabolic rate, body temperature, cholesterol, bone, muscle, and behavior.

[0004] The development of thyroid hormone analogs which avoid the undesirable effects of hyperthyroidism and hypothyroidism while maintaining the beneficial effects of thyroid hormones would open new avenues of potential treatment for patients with metabolic disease such as obesity, hyperlipidemia, hypercholesterolemia, diabetes and other disorders and diseases such as liver steatosis and non-alcoholic steatohepatitis (NASH), atherosclerosis, cardiovascular diseases, hypothyroidism, thyroid cancer, thyroid diseases, resistance to thyroid hormone and related disorders and diseases.

[0005] Non-alcoholic steatohepatitis (NASH) is the most common chronic liver disease in the United States. NASH is a fatty inflammation of the liver and a major cause of fibrosis, cirrhosis and liver failure. The disease is progressive, starting as steatosis or nonalcoholic fatty liver disease (NAFLD), progressing to an inflamed fatty liver (NASH), and eventually leading to fibrosis and cirrhosis. The disease is generally asymptomatic until severe liver impairment occurs.

[0006] Human subjects with NASH may experience elevated liver volumes, which can be attributed to increased liver fat and fluid retention due to inflammatory processes in NASH. As NASH progresses to cirrhosis, liver fat decreases as the liver becomes increasingly fibrotic. Liver volume remains elevated in cirrhotic human subjects due to ongoing inflammation and venous congestion associated with portal hypertension. Reducing liver

volume in noncirrhotic non-alcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 and F3 fibrosis human subjects is important for maintaining perfusion of the diseased liver and reversing disease progression to cirrhosis. Liver volume reduction in NASH and cirrhosis is associated with histopathologic improvement of the liver.

[0007] The prevalence of NAFLD in the U.S. population is about 20-23%, and may be as high as 33%, and the prevalence of NASH in the U.S. population is about 2-3%. Some NASH patients will progress to late-stage disease: approximately 15-50% of NASH patients progress to severe fibrosis, and approximately 7-16% progress to cirrhosis. The rate of liver-specific mortality in NASH cirrhotics is approximately 10% per decade.

[0008] Obesity is a common characteristic of both NASH and cirrhosis, due to insufficient weight loss through diet and lifestyle modifications, this patient population is often prescribed interventional surgical procedures (e.g., bariatric surgery). Liver volume reduction immediately prior to surgery is aggressively pursued to improve surgical access to the stomach.

Summary

[0009] Resmetirom has previously been mentioned in connection with the treatment of a fatty liver disease, such as NASH. However, it has now been unexpectedly found that the 100 mg dose thereof leads to better outcomes than the 80 mg dose in human subjects that weigh at least 100 kg. The 80 mg dose is optimal for human subjects that weigh less than 100 kg to achieve better outcomes with discontinuation rates based upon adverse results in clinical trials similar to placebo. This weight-based dosing was recognized by the U.S. Food and Drug Administration (FDA) in the approval of REZDIFFRA™ (resmetirom), as reflected in the prescribing information

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217785s000lbl.pdf, incorporated herein by reference in its entirety) and also shown in FIG. 46.

[0010] Disclosed herein is a method of treating or improving a fatty liver disease, such as, for example non-alcoholic steatohepatitis (NASH) (e.g., noncirrhotic non-alcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 and F3 fibrosis) in a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement.

[0011] In particular, disclosed herein is a method of treating NASH. The method comprises: determining a weight of a human subject; and based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg.

[0012] In some embodiments, the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

[0013] In some embodiments, the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[0014] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

[0015] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stage F1.

[0016] In some embodiments, the method is of improving noncirrhotic nonalcoholic steatohepatitis.

[0017] In some embodiments, the solid oral dosage form comprises resmetirom.

[0018] In some embodiments, the solid oral dosage form is a tablet.

[0019] In some embodiments, the human subject is an adult human subject.

[0020] Also disclosed herein is a method of treating or improving liver fibrosis associated with a fatty liver disease (e.g., NASH) in a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement.

[0021] In particular, disclosed herein is a method of treating liver fibrosis. The method comprises: determining a weight of a human subject; and based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg;
and

wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

[0022] In some embodiments, the method is of improving the liver fibrosis.

[0023] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F1.

[0024] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F2.

[0025] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F3.

[0026] In some embodiments, the method is of improving the liver fibrosis by one stage in the human subject.

[0027] In some embodiments, the method is of improving the liver fibrosis by two stages in the human subject.

[0028] In some embodiments, the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

[0029] In some embodiments, the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[0030] In some embodiments, the solid oral dosage form comprises resmetirom.

[0031] In some embodiments, the solid oral dosage form is a tablet.

[0032] In some embodiments, the human subject is an adult human subject.

[0033] Also disclosed herein is a method of treating or improving a fatty liver disease (e.g., NASH) in a human subject (e.g., an adult human subject) who may be in need of such

treatment or improvement who may also be on a moderate CYP2C8 inhibitor regimen. In this instance, the human subject is administered resmetirom or a pharmaceutically acceptable salt thereof at a dosage that is reduced by 20 mg per day relative to what the same human subject would have otherwise been administered based on the determination of the weight. If the human subject was taking resmetirom or the pharmaceutically acceptable salt thereof prior to using a moderate CYP2C8 inhibitor, then the dose administered to the human subject as determined based on the weight of the human subject would be reduced by 20 mg per day to the reduced dosage, during the concomitant use of the moderate CYP2C8 inhibitor. If the human subject was not taking resmetirom or the pharmaceutically acceptable salt thereof prior to using a moderate CYP2C8 inhibitor, then the human subject would start with the reduced dosage and continue taking the reduced dosage, determined based on the weight of the human subject, during the concomitant use of the moderate CYP2C8 inhibitor.

[0034] In particular, disclosed herein is a method of treating NASH, which comprises: determining a weight of a human subject; and based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor.

[0035] In some embodiments, the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 80 mg per day.

[0036] In some embodiments, the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 60 mg per day.

[0037] In some embodiments, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

[0038] In some embodiments, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

[0039] In some embodiments, the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nifedipine, loratadine, eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate, spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin, troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, gemfibrozil, idelalisib, isoniazid, ketoprofen, letermovir, lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

[0040] In some embodiments, the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, and/or pioglitazone.

[0041] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

[0042] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with mild liver fibrosis consistent with stage F1.

[0043] In some embodiments, the method is of improving noncirrhotic nonalcoholic steatohepatitis..

[0044] In some embodiments, the solid oral dosage form comprises resmetirom..

[0045] In some embodiments, the solid oral dosage form is a tablet.

[0046] In some embodiments, the human subject is an adult human subject.

[0047] Also disclosed herein is a method of treating or improving liver fibrosis associated with a fatty liver disease (e.g., NASH) in a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement who may also be on a moderate CYP2C8 inhibitor regimen.

[0048] In particular, disclosed herein is a method of treating liver fibrosis, which comprises: determining a weight of a human subject; and based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor; and

wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

[0049] In some embodiments, the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising the resmetirom or a pharmaceutically acceptable salt thereof at the reduced dosage of 80 mg per day.

[0050] In some embodiments, the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 60 mg per day.

[0051] In some embodiments, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

[0052] In some embodiments, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

[0053] In some embodiments, the method is of improving the liver fibrosis.

[0054] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F1.

[0055] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F2.

[0056] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F3.

[0057] In some embodiments, the method is of improving the liver fibrosis by one stage in the human subject.

[0058] In some embodiments, the method is of improving the liver fibrosis by two stages in the human subject.

[0059] In some embodiments, the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nicardipine, loratadine, eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate, spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin, troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, gemfibrozil, idelalisib, isoniazid, ketoprofen, letermovir, lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

[0060] In some embodiments, the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, and/or pioglitazone.

[0061] In some embodiments, the solid oral dosage form comprises resmetirom.

[0062] In some embodiments, the solid oral dosage form is a tablet.

[0063] In some embodiments, the human subject is an adult human subject.

[0064] Also disclosed herein is resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating nonalcoholic steatohepatitis (NASH), the method comprising: determining a weight of a human subject; and based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

(i) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more;

or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg.

[0065] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

[0066] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stage F1.

[0067] In some embodiments, the method is of improving noncirrhotic nonalcoholic steatohepatitis.

[0068] Also disclosed herein is resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating liver fibrosis, the method comprising: determining a weight of a human subject; and based on determination of the weight of the human subject, administering orally to the human subject a solid oral dosage form comprising:

(i) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more;

or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg;

and

wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

[0069] In some embodiments, the method is of improving the liver fibrosis.

[0070] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F1.

[0071] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F2.

[0072] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F3.

[0073] In some embodiments, the method is of improving the liver fibrosis by one stage in the human subject.

[0074] In some embodiments, the method is of improving the liver fibrosis by two stages in the human subject.

[0075] In some embodiments, the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

[0076] In some embodiments, the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[0077] In some embodiments, the solid oral dosage form is a tablet.

[0078] In some embodiments, the human subject is an adult human subject.

[0079] Also disclosed herein is resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating noncirrhotic nonalcoholic steatohepatitis (NASH), the method comprising: determining a weight of a human subject; and based on determination of the weight of the human subject, administering orally to the human subject a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor.

[0080] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

[0081] In some embodiments, the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stage F1.

[0082] In some embodiments, the method is of improving noncirrhotic nonalcoholic steatohepatitis.

[0083] Also disclosed herein is resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating liver fibrosis, the method comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor; and wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

[0084] In some embodiments, the method is of improving the liver fibrosis.

[0085] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F1.

[0086] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F2.

[0087] In some embodiments, the human subject has liver fibrosis characterized as fibrosis stage F3.

[0088] In some embodiments, the method is of improving the liver fibrosis by one stage in the human subject.

[0089] In some embodiments, the method is of improving the liver fibrosis by two stages in the human subject.

[0090] In some embodiments, the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[0091] In some embodiments, the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 60 mg per day.

[0092] In some embodiments, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

[0093] In some embodiments, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

[0094] In some embodiments, the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nicardipine, loratadine,

eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate, spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin, troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, gemfibrozil, idelalisib, isoniazid, ketoprofen, letermovir, lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

[0095] In some embodiments, the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, and/or pioglitazone.

[0096] In some embodiments, the solid oral dosage form comprises resmetirom.

[0097] In some embodiments, the solid oral dosage form is a tablet.

[0098] In some embodiments, the human subject is an adult human subject.

Brief Description of the Drawings

[0099] The above and further features will be more clearly appreciated from the following detailed description when taken in conjunction with the accompanying drawings.

[00100] FIG. 1 is a graphical representation showing the correlation of liver volume reduction and proton density fat fraction (PDFF) reduction in placebo and resmetirom treated patients at 12 weeks in Example 1. "PBO" represents placebo patients and "RES" represents resmetirom-treated patients.

[00101] FIG. 2 is a graphical representation showing change in MRI-PDFF (Magnetic Resonance Imaging-PDFF) in several subgroups of patients treated with 100 mg resmetirom, once daily, for 52 weeks in Example 1. "High SHBG" corresponds with 2/3 study patients with the highest increase from baseline in sex hormone binding globulin (SHBG), a biomarker for resmetirom liver exposure.

[00102] FIG. 3 is a graphical representation showing change in liver volume in several subgroups of patients treated with 100 mg resmetirom, once daily, for 52 weeks in Example 1. "High SHBG" corresponds with 2/3 study patients with the highest increase from baseline in SHBG, a biomarker for resmetirom liver exposure.

[00103] FIG. 4 is a graphical representation showing resmetirom-mediated changes to the MRI-PDFF and liver volume (LV) at week 52 in Example 1.

[00104] FIG. 5 is a graphical representation showing percentage of patients at week 52 with 10% reduction or 10% increase in spleen volume (SV) in Example 1.

[00105] FIG. 6 is a graph showing the correlation between 52 week liver volume change and spleen volume change in patients who entered the study with baseline PDFF <8% in Example 1.

[00106] FIG. 7 is a graphical representation showing the study design in Example 2. CAP: controlled attenuation parameter; LDL-C: low-density lipoprotein cholesterol; MRE: magnetic resonance elastography; MRI-PDFF: magnetic resonance imaging-proton density fat fraction; VCTE: vibration-controlled transient elastography.

[00107] FIG. 8 is a schematic showing statistical testing process for primary and key secondary endpoints at week 52 in Example 2. LDL-C: low-density lipoprotein cholesterol.

[00108] FIG. 9 is a schematic showing patient disposition in Example 2. AE: adverse event; LTFU: lost to follow up. The primary reasons for screen failure included biopsy, withdraw of consent, MRI-PDFF <8%, HbA1c >9. The exploratory F1 group included baseline F1A/F1C patients (n = 84) that were considered only for exploratory efficacy and safety analyses. These patients received treatment but as prespecified in the statistical analysis plan, were not included in the primary analysis population.

[00109] FIGS. 10A-10C show primary and Key Secondary End Points in Example 2. The two primary end points at week 52 were resolution of nonalcoholic steatohepatitis (NASH) with no worsening of fibrosis (Panel A, FIG. 10A), and an improvement (reduction) in fibrosis by at least one stage with no worsening of the nonalcoholic fatty liver disease (NAFLD) activity score (Panel B, FIG. 10B). The key secondary end point was the percent change from baseline in the low-density lipoprotein (LDL) cholesterol level at week 24 (Panel C, FIG. 10C). The NAFLD activity score is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2). NASH resolution was defined as achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by at least 2 points. Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis). A total of 11 patients had a delay in their week 52 biopsy due to coronavirus disease 2019–related closure of the biopsy site or related reasons and were removed from the primary analysis population for liver-biopsy analyses.

[00110] FIGS. 11A-11D are graphical representations showing subgroup analyses of the dual primary endpoints at Week 52 in Example 2: Resolution of nonalcoholic steatohepatitis (FIG. 11A and FIG. 11C) and improvement in fibrosis (FIG. 11B and FIG. 11D). Data are

reported for the primary analysis population (n=955, after removal of the COVID impacted biopsies outside the Week 60 window). Eleven patients had a delay in their Week 52 biopsy due to COVID-19 biopsy site closure or related reasons and were removed from the analysis. Resolution of nonalcoholic steatohepatitis is defined as achievement of a ballooning score of 0, inflammation score of 0 or 1, and ≥ 2 -point reduction in the nonalcoholic fatty liver disease activity score with no worsening of fibrosis. Fibrosis improvement is defined as achievement of ≥ 1 -stage reduction in fibrosis with no worsening of the nonalcoholic fatty liver disease activity score. A 1-point improvement in fibrosis would be a change to F1A or F1C from F2 (a change of F2 to F1B is not considered a 1-point improvement). Forest plots include prespecified subgroups with minor modifications. Body weight subgroups based on ≤ 200 , >200 pounds or BMI (Body Mass Index) ≤ 35 , >35 were not informative. PDFF reduction in resmetirom groups are compared to all placebo patients with any Week 52 PDFF; % SHBG CFB in resmetirom groups is compared to all placebo patients with a Week 52 SHBG. A posthoc subgroup of ≤ 100 kg, >100 kg is shown in Table 21 that also includes subgroups for $\geq 30\%$ PDFF at Week 16, region (US-ExUS), weight gain $\geq 5\%$ F2/F3, F1B. Subgroup analyses by statin use and NAFLD Activity Score (NAS) were post-hoc analyses. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

[00111] FIG. 12 is a graphical representation showing percentage of patients who were F1B or F2 at baseline with worse (progressed to $\geq F3$), stable (no change), or improved fibrosis stage at week 52 based on liver biopsy in Example 2. In patients with a baseline and eligible Week 52 biopsy (80 mg, 100 mg; resmetirom). The two pathologists' assessments were similar and were averaged to generate a single output.

[00112] FIG. 13 is a graphical representation showing percent of patients with worsened, stable (no change), or improved individual components of the nonalcoholic fatty liver disease activity score (ballooning, inflammation, steatosis) in Example 2. In patients with a baseline and eligible Week 52 biopsy are shown. The two pathologists' assessments were similar and were averaged to generate a single output.

[00113] FIG. 14 is a graphical representation showing percent change from baseline in lipids and lipoproteins at weeks 24 and 52 in Example 2. ApoB: apolipoprotein B; ApoCIII: apolipoprotein CIII; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein a; non-HDL-C: non-high-density lipoprotein cholesterol. (80 mg, 100 mg: resmetirom)

[00114] FIGS. 15A and 15B are graphical representations showing percent change from baseline in hepatic fat as measured by magnetic resonance imaging-proton density fat fraction at weeks 16 and 52 (FIG. 15A), and steatosis as measured by FibroScan controlled attenuation parameter at week 52 (FIG. 15B) in Example 2 (80 mg, 100 mg: resmetirom). Based on observed data, patients with a baseline and week 52 assessment.

[00115] FIG. 16 is a graphical representation showing percentage of patients achieving a $\geq 25\%$ reduction from baseline in liver stiffness as measured by FibroScan vibration-controlled transient elastography at week 52 in Example 2. Based on observed data, patients with a baseline and week 52 assessment.

[00116] FIG. 17 is a graphical representation showing improvement or worsening from baseline in liver stiffness as measured by magnetic resonance elastography at week 52 in Example 2. (80 mg, 100 mg: resmetirom) Based on observed data, patients with a baseline and week 52 assessment.

[00117] FIGS. 18A and 18B are graphical representations showing percent change from baseline in liver volume (FIG. 18A) and spleen volume (FIG. 18B) at weeks 16 and 52 in Example 2. (80 mg, 100 mg: resmetirom) Based on observed data, patients with a baseline and week 52 assessment.

[00118] FIGS. 19A-19C are graphical representations showing change from baseline in the enhanced liver fibrosis score (FIG. 19A), TIMP-1 (FIG. 19B), and P3NP (FIG. 19C) in Example 2. (80 mg, 100 mg: resmetirom) Based on observed data.

[00119] FIG. 20 is a graphical representation showing time to onset of first gastrointestinal adverse event in Example 2.

[00120] FIG. 21 is a graphical representation showing duration of diarrhea: duration of diarrhea reported in first 12 weeks of randomization in Example 2.

[00121] FIG. 22 is a schematic showing prescreening and screening sequence in Example 2.

[00122] FIG. 23 is a schematic showing methodology for central pathologist evaluation of liver biopsies in Example 2.

[00123] FIG. 24A is a graphical representation showing the percentage of patients that achieved $\geq 120\%$ increase in SHBG at Week 52 in the resmetirom 80 mg and resmetirom 100 mg groups based on weight in Example 2. FIG. 24B is a graphical representation showing the percentage of patients that achieved $\geq 30\%$ reduction in MRI-PDFF at Week 52 in the resmetirom 80 mg and resmetirom 100 mg groups based on weight in Example 2.

[00124] FIG. 25A is a graphical representation showing the percentage of patients that achieved NASH Resolution (ballooning score=0, inflammation score=0/1, and ≥ 2 -point

reduction in NAS with no worsening of fibrosis) in the resmetirom 80 mg and resmetirom 100 mg groups based on weight in Example 2. FIG. 25B is a graphical representation showing the percentage of patients that achieved Fibrosis Improvement (≥ 1 -stage improvement in fibrosis with no worsening of NAS) in the resmetirom 80 mg and resmetirom 100 mg groups based on weight in Example 2.

[00125] FIG. 26A is a graphical representation showing the percentage of patients that achieved NASH Resolution (ballooning score=0, inflammation score=0/1, and ≥ 2 -point reduction in NAS with no worsening of fibrosis) in the resmetirom 80 mg and resmetirom 100 mg groups based on body mass index in Example 2. FIG. 26B is a graphical representation showing the percentage of patients that achieved Fibrosis Improvement (≥ 1 -stage improvement in fibrosis with no worsening of NAS) in the resmetirom 80 mg and resmetirom 100 mg groups based on body mass index in Example 2.

[00126] FIG. 27 is a graphical representation showing the percentage biopsy response for fibrosis improvement and NASH resolution in all resmetirom-treated patients (80 mg and 100 mg combined) and placebo patients based on the percentage change from baseline PDFF at Week 52 in Example 2. The graph shows that the greater the Week 52 PDFF reduction, the greater likelihood for fibrosis and NASH responses with resmetirom treatment.

[00127] FIG. 28 is a graphical representation showing the change over time from baseline to 48 weeks in SHBG in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in the MAESTRO-NASH Week 52 primary analysis population in Example 2.

[00128] FIG. 29A is a graphical representation showing the ALT response at Week 48 in all randomized patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in the MAESTRO-NASH Week 52 primary analysis population in Example 2. FIG. 29B is a

graphical representation showing the ALT response at Week 48 where the dose aligned with prescribing information recommended dose for patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in the MAESTRO-NASH Week 52 primary analysis population in Example 2.

[00129] FIG. 30A is a graphical representation showing the change over time in VCTE from baseline to year 3 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg group in Example 2. FIG. 30B is a graphical representation showing the change over time in CAP (dB/M) from baseline to year 3 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in Example 2.

[00130] FIG. 31 is a graphical representation showing the VCTE responder analyses at years 1-3 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in the MAESTRO-NASH population in Example 2.

[00131] FIG. 32A is a graphical representation showing the percentage of patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups that achieved ≥ 1 stage fibrosis improvement as determined by qFibrosis and pathologists in Example 2. FIG. 32B is a graphical representation showing the percentage of patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups that had progression of fibrosis as determined by qFibrosis and pathologists in Example 2.

[00132] FIG. 33A is a graphical representation showing the intersection portal tract change from baseline in the placebo and resmetirom (80 mg and 100 mg combined) groups at the F2 and F3 stages in Example 2. FIG. 33B is a graphical representation showing the string length portal tract change from baseline in the placebo and resmetirom (80 mg and 100 mg combined) groups at the F2 and F3 stages in Example 2.

[00133] FIG. 34A is a graphical representation showing the intersection portal tract change from baseline in pathologist fibrosis responders and non-responders in the placebo and resmetirom (80 mg and 100 mg combined) groups at the F2 and F3 stages in Example 2. FIG. 34B is a graphical representation showing the string length portal tract change from baseline in pathologist fibrosis responders and non-responders in the placebo and resmetirom (80 mg and 100 mg combined) groups at the F2 and F3 stages in Example 2.

[00134] FIG. 35A is a graphical representation showing the change from baseline in the number of long strings-portal tract in responders and non-responders in the placebo and resmetirom (80 mg and 100 mg combined) groups at the F2 and F3 stages in Example 2. FIG. 35B is a graphical representation showing the change from baseline in the number of short strings zone 2 in responders and non-responders in the placebo and resmetirom (80 mg and 100 mg combined) groups at the F2 and F3 stages in Example 2.

[00135] FIG. 36 is a graphical representation showing the percentage change from baseline in ALT at Week 48 compared to the percentage biopsy response in the patients who achieved resmetirom NASH resolution, resmetirom fibrosis improvement, placebo NASH resolution, and placebo fibrosis improvement in Example 2.

[00136] FIG. 37 is a graphical representation showing the CAP change over time from baseline to year 3 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in Example 2.

[00137] FIG. 38 is a graphical representation showing the percentage change from baseline in CAP at Week 52 compared to the percentage biopsy response in the patients who achieved resmetirom NASH resolution, resmetirom fibrosis improvement, placebo NASH resolution, and placebo fibrosis improvement in Example 2.

[00138] FIG. 39 is a graph showing the percentage change from baseline in PDFF at Week 52 compared to the percentage biopsy response in the patients who achieved resmetirom NASH resolution, resmetirom fibrosis improvement, placebo NASH resolution, and placebo fibrosis improvement in Example 2.

[00139] FIG. 40 is a graphical representation showing the VCTE change over time from baseline to year 3 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in Example 2.

[00140] FIG. 41 is a graphical representation showing the percentage change from baseline in VCTE at Week 52 compared to the percentage biopsy response in the patients who achieved resmetirom NASH resolution, resmetirom fibrosis improvement, placebo NASH resolution, and placebo fibrosis improvement in Example 2.

[00141] FIG. 42 is a graphical representation showing the importance of various response predictors of resmetirom NASH resolution response based on Week 52 data in Example 2.

[00142] FIG. 43 is a graphical representation showing the importance of various predictors of resmetirom fibrosis improvement biopsy response based on Week 52 data in Example 2.

[00143] FIG. 44 is a graphical representation showing the P3NP change vs. the PRO-C3 change at Week 52 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in Example 2.

[00144] FIG. 45 is a graphical representation showing the ELF change vs. the PRO-C3 change at Week 52 in patients in the placebo, resmetirom 80 mg, and resmetirom 100 mg groups in Example 2.

- [00145] FIG. 46 is a reproduction of an excerpt of the prescribing information of REZDIFFRA™ (resmetirom).
- [00146] FIG. 47 is an X-ray powder diffractogram (XRPD) pattern of resmetirom Form I.
- [00147] FIG. 48 is a differential scanning calorimetry (DSC) diagram of resmetirom Form I.
- [00148] FIG. 49 is an XRPD pattern of resmetirom Form λ.
- [00149] FIG. 50 is an XRPD pattern of resmetirom Form F.
- [00150] FIG. 51 is an XRPD pattern of resmetirom Form L.
- [00151] FIG. 52 is an XRPD pattern of resmetirom crystalline Form CSIV.
- [00152] FIG. 53 is a thermogravimetric analysis (TGA) diagram of resmetirom crystalline Form CSIV.
- [00153] FIG. 54 is a DSC diagram of resmetirom crystalline Form CSIV.
- [00154] FIG. 55 is an XRPD pattern of resmetirom Form R3-A.
- [00155] FIG. 56 is a solid state ¹³C NMR spectrum of resmetirom Form R3-A (full range 200-0 ppm).
- [00156] FIG. 57 is a solid state ¹³C NMR spectrum of resmetirom Form R3-A (200-100 ppm).
- [00157] FIG. 58 is a solid state ¹³C NMR spectrum of resmetirom Form R3-A (100-0 ppm).
- [00158] FIG. 59 is an XRPD pattern of resmetirom : nicotinamide (Form RC1-A).

[00159] FIG. 60 is a solid state ^{13}C NMR spectrum of resmetirom : nicotinamide (Form RC1-A) (full range 200-0 ppm).

[00160] FIG. 61 is a solid state ^{13}C NMR spectrum of resmetirom : nicotinamide (Form RC1-A) (200-100 ppm).

[00161] FIG. 62 is a solid state ^{13}C NMR spectrum of resmetirom : nicotinamide (Form RC1-A) (100-0 ppm).

[00162] FIG. 63 is an XRPD pattern of resmetirom : caffeine (Form RC2-A).

[00163] FIG. 64 is a solid state ^{13}C NMR spectrum of resmetirom : caffeine (Form RC2-A) (full range 200-0 ppm).

[00164] FIG. 65 is a solid state ^{13}C NMR spectrum of resmetirom : caffeine (Form RC2-A) (200-100 ppm).

[00165] FIG. 66 is a solid state ^{13}C NMR spectrum of resmetirom : caffeine (Form RC2-A) (100-0 ppm).

[00166] FIG. 67 is an XRPD pattern of resmetirom : caffeine (Form RC2-B).

[00167] FIG. 68 is a solid state ^{13}C NMR spectrum of resmetirom : caffeine (Form RC2-B) (full range 200-0 ppm).

[00168] FIG. 69 is a solid state ^{13}C NMR spectrum of resmetirom : caffeine (Form RC2-B) (200-100 ppm).

[00169] FIG. 70 is a solid state ^{13}C NMR spectrum of resmetirom : caffeine (Form RC2-B) (100-0 ppm).

- [00170] FIG. 71 is an XRPD pattern of resmetirom : 2-picolinic acid (Form RC3-A).
- [00171] FIG. 72 is an XRPD pattern of resmetirom : urea (Form RC4-A).
- [00172] FIG. 73 is an XRPD pattern of resmetirom : N-methyl morpholine salt (Form R1-A).
- [00173] FIG. 74 is an XRPD pattern of resmetirom : piperazine salt (Form R2-A).
- [00174] FIG. 75 is a solid state ^{13}C NMR spectrum of resmetirom : piperazine salt (Form R2-A) (full range 200-0 ppm).
- [00175] FIG. 76 is a solid state ^{13}C NMR spectrum of resmetirom : piperazine salt (Form R2-A) (200-100 ppm).
- [00176] FIG. 77 is a solid state ^{13}C NMR spectrum of resmetirom : piperazine salt (Form R2-A) (100-0 ppm).
- [00177] FIG. 78 is an XRPD pattern of resmetirom : benzathine salt (Form R4-A).
- [00178] FIG. 79 is a chart depicting weight loss in conjunction with resmetirom therapy's impact on biopsy endpoints in the MAESTRO-NASH study.
- [00179] FIG. 80 is a chart depicting weight loss in conjunction with resmetirom therapy's impact on MRI-PDFF results in the MAESTRO-NASH study.
- [00180] FIG. 81 is an XRPD pattern of resmetirom Form N8.
- [00181] FIG. 82 an ^1H NMR spectrum of resmetirom Form N8.
- [00182] FIG. 83 a combined DSC and TGA thermogram of resmetirom Form N8.
- [00183] FIG. 84 is an XRPD pattern of resmetirom Form 3.

- [00184] FIG. 85 is an XRPD pattern of resmetirom Form 9.
- [00185] FIG. 86 is an XRPD pattern of resmetirom Form CSV.
- [00186] FIG. 87 is a TGA diagram of resmetirom Form CSV.
- [00187] FIG. 88 is an XRPD pattern of resmetirom Form 2.
- [00188] FIG. 89 is an XRPD pattern of resmetirom Form 4.
- [00189] FIG. 90 is an XRPD pattern of resmetirom Form 6.
- [00190] FIG. 91 is an XRPD pattern of resmetirom Form 7.
- [00191] FIG. 92 is an XRPD pattern of resmetirom Form 8.
- [00192] FIG. 93 is an XRPD pattern of resmetirom Form 10.
- [00193] FIG. 94 is an XRPD pattern of resmetirom Form 11.
- [00194] FIG. 95 is an XRPD pattern of resmetirom Form 13.
- [00195] FIG. 96 is an XRPD pattern of resmetirom Form 14.
- [00196] FIG. 97 is an XRPD pattern of resmetirom Form 15.
- [00197] FIG. 98 is an XRPD pattern of resmetirom Form 16.
- [00198] FIG. 99 is an XRPD pattern of resmetirom Form 17.
- [00199] FIG. 100 is an XRPD pattern of resmetirom Form 19.
- [00200] FIG. 101 is an XRPD pattern of resmetirom Form 20.
- [00201] FIG. 102 is an XRPD pattern of resmetirom Form 21.

- [00202] FIG. 103 is an XRPD pattern of resmetirom Form 22.
- [00203] FIG. 104 is a solid state ^{13}C NMR spectrum of resmetirom Form 20 (full range 200-0 ppm).
- [00204] FIG. 105 is a solid state ^{13}C NMR spectrum of resmetirom Form 20 (200-100 ppm).
- [00205] FIG. 106 is a solid state ^{13}C NMR spectrum of resmetirom Form 20 (100-0 ppm).
- [00206] FIG. 107 is an XRPD pattern of resmetirom Form CSVI.
- [00207] FIG. 108 is a TGA diagram of resmetirom Form CSVI.
- [00208] FIG. 109 is an XRPD pattern of resmetirom Form CSVI.
- [00209] FIG. 110 is an XRPD pattern of an amorphous resmetirom Form E1 and/or E2.
- [00210] FIG. 111 is an XRPD pattern of an amorphous solid dispersion of resmetirom with copovidone Form E3 and/or E4.
- [00211] FIG. 112 is an XRPD pattern of resmetirom Form 3A.
- [00212] FIG. 113 is a TGA diagram of resmetirom Form 3A.
- [00213] FIG. 114 is a DSC diagram of resmetirom Form 3A.
- [00214] FIG. 115 is a Fourier Transform Infrared (FT-IR) diagram of resmetirom Form 3A.
- [00215] FIG. 116 is an XRPD pattern of resmetirom Form CSVII.
- [00216] FIG. 117 is a TGA diagram of resmetirom Form CSVII.
- [00217] FIG. 118 is a DSC diagram of resmetirom Form CSVII.

- [00218] FIG. 119 is an XRPD pattern of resmetirom Form Type K65.
- [00219] FIG. 120 is an XRPD pattern of resmetirom Form Type K65.
- [00220] FIG. 121 is an XRPD pattern of resmetirom Form Type K65 desolvate.
- [00221] FIG. 122 is an XRPD pattern of resmetirom Form 4A.
- [00222] FIG. 123 is a TGA diagram resmetirom Form 4A.
- [00223] FIG. 124 is a ^1H NMR spectrum of resmetirom Form 4A.
- [00224] FIG. 125 is an XRPD pattern of resmetirom Form 7A.
- [00225] FIG. 126 is a TGA diagram resmetirom Form 7A.
- [00226] FIG. 127 is a ^1H NMR spectrum of resmetirom Form 7A.
- [00227] FIG. 128 is an XRPD pattern of resmetirom Form 9A.
- [00228] FIG. 129 is a TGA diagram of resmetirom Form 9A.
- [00229] FIG. 130 is a ^1H NMR spectrum of resmetirom Form 9A.
- [00230] FIG. 131 is an XRPD pattern of resmetirom Form BSI.
- [00231] FIG. 132 is a DSC diagram of resmetirom Form BSI.
- [00232] FIG. 133 is a TGA diagram of resmetirom Form BSI.
- [00233] FIG. 134 is an XRPD pattern of resmetirom Form R1.
- [00234] FIG. 135 is an XRPD pattern of resmetirom Form R2.
- [00235] FIG. 136 is an XRPD pattern of resmetirom Form R3.

- [00236] FIG. 137 is an XRPD pattern of resmetirom Form R4.
- [00237] FIG. 138 is an XRPD pattern of resmetirom Form R5.
- [00238] FIG. 139 is an XRPD pattern of an amorphous solid dispersion of resmetirom with eudragit.
- [00239] FIG. 140 is an XRPD pattern of an amorphous form of resmetirom reported in IN202241066042A.
- [00240] FIG. 141 is an XRPD pattern of resmetirom Form RL.
- [00241] FIG. 142 is an XRPD pattern of resmetirom Form M1.
- [00242] FIG. 143 is an XRPD pattern of resmetirom Form M2.
- [00243] FIG. 144 is an XRPD pattern of resmetirom Form M3.
- [00244] FIG. 145 is an XRPD pattern of resmetirom Form M4.
- [00245] FIG. 146 is an XRPD pattern of resmetirom Form M5.
- [00246] FIG. 147 is an XRPD pattern of resmetirom Form M6.
- [00247] FIG. 148 is an XRPD pattern of resmetirom Form M7.
- [00248] FIG. 149 is an XRPD pattern of resmetirom Form U1.
- [00249] FIG. 150 is a combined DSC and TGA thermogram of resmetirom Form U1.
- [00250] FIG. 151 is an XRPD pattern of resmetirom Form U2.
- [00251] FIG. 152 is a combined DSC and TGA thermogram of resmetirom Form U2.

- [00252] FIG. 153 is an XRPD pattern of resmetirom Form U3.
- [00253] FIG. 154 is a combined DSC and TGA thermogram of resmetirom Form U3.
- [00254] FIG. 155 is an XRPD pattern of resmetirom Form U4.
- [00255] FIG. 156 is an XRPD pattern of resmetirom Form U5.
- [00256] FIG. 157 is an XRPD pattern of resmetirom Form U6.
- [00257] FIG. 158 is a combined DSC and TGA thermogram of resmetirom Form U6.
- [00258] FIG. 159 is an XRPD pattern of resmetirom Form U7.
- [00259] FIG. 160 is a combined DSC and TGA thermogram of resmetirom Form U7.
- [00260] FIG. 161 is an XRPD pattern of resmetirom Form U8.
- [00261] FIG. 162 is a combined DSC and TGA thermogram of resmetirom Form U8.
- [00262] FIG. 163 is an XRPD pattern of resmetirom Form U9.
- [00263] FIG. 164 is combined DSC and TGA thermogram of resmetirom Form U9.
- [00264] FIG. 165 is an XRPD pattern of resmetirom Form C1.
- [00265] FIG. 166 is an ^1H NMR spectrum of resmetirom Form C1.
- [00266] FIG. 167 is a combined DSC and TGA thermogram of resmetirom Form C1.
- [00267] FIG. 168 is an FTIR spectrum of resmetirom Form C1 (bottom) compared to an FTIR spectrum of Resmetirom Form I (top).

[00268] FIG. 169 is a Raman spectrum of resmetirom Form C1 (bottom) compared to a Raman spectrum of resmetirom Form I (top).

[00269] FIG. 170 is an XRPD pattern of resmetirom Form C2.

[00270] FIG. 171 is an ^1H NMR spectrum of resmetirom Form C2

[00271] FIG. 172 is a combined DSC and TGA thermogram of resmetirom Form C2.

[00272] FIG. 173 is an FTIR spectrum of resmetirom Form C2 (bottom) compared to an FTIR spectrum of Resmetirom Form I (top).

[00273] FIG. 174 is a Raman spectrum of resmetirom Form C2 (bottom) compared to a Raman spectrum of resmetirom Form I (top).

[00274] FIG. 175 is an XRPD pattern of resmetirom Form C3.

[00275] FIG. 176 is an XRPD pattern of resmetirom Form C4.

[00276] FIG. 177 is an ^1H NMR spectrum of resmetirom Form C4

[00277] FIG. 178 is a combined DSC and TGA thermogram of resmetirom Form C4.

[00278] FIG. 179 is an XRPD pattern of resmetirom Form C5.

[00279] FIG. 180 is an ^1H NMR spectrum of resmetirom Form C5.

[00280] FIG. 181 is a combined DSC and TGA thermogram of resmetirom Form C5.

[00281] FIG. 182 is an FTIR spectrum of resmetirom Form C5 (bottom) compared to an FTIR spectrum of resmetirom Form I (top).

[00282] FIG. 183 is a Raman spectrum of resmetirom Form C5 (bottom) compared to a Raman spectrum of resmetirom Form I (top).

[00283] FIG. 184 is an XRPD pattern of resmetirom Form C6.

[00284] FIG. 185 is an XRPD pattern of resmetirom 4-aminopyridine salt (Form C7).

[00285] FIG. 186 is an ^1H NMR spectrum of resmetirom 4-aminopyridine salt (Form C7).

[00286] FIG. 187 is a combined DSC and TGA thermogram of resmetirom 4-aminopyridine salt (Form C7).

[00287] FIG. 188 is an FTIR spectrum of resmetirom 4-aminopyridine salt (Form C7) (bottom) compared to an FTIR spectrum of resmetirom Form I (top).

[00288] FIG. 189 is a Raman spectrum of resmetirom 4-aminopyridine salt (Form C7) (bottom) compared to a Raman spectrum of resmetirom Form I (top).

[00289] FIG. 190 is an XRPD pattern of resmetirom imidazole salt (Form C8).

[00290] FIG. 191 is an ^1H NMR spectrum of resmetirom imidazole salt (Form C8).

[00291] FIG. 192 is a combined DSC and TGA thermogram of resmetirom imidazole salt (Form C8).

[00292] FIG. 193 is an FTIR spectrum of resmetirom imidazole salt (Form C8) (bottom) compared to an FTIR spectrum of resmetirom Form I (top).

[00293] FIG. 194 is a Raman spectrum of resmetirom imidazole salt (Form C8) (bottom) compared to a Raman spectrum of resmetirom Form I (top).

[00294] FIG. 195 is an XRPD pattern of resmetirom tromethamine salt (Form C9).

- [00295] FIG. 196 is an ^1H NMR spectrum of resmetirom tromethamine salt (Form C9).
- [00296] FIG. 197 is a combined DSC and TGA thermogram of resmetirom tromethamine salt (Form C9).
- [00297] FIG. 198 is an XRPD pattern of resmetirom Form N1.
- [00298] FIG. 199 is an ^1H NMR spectrum of resmetirom Form N1.
- [00299] FIG. 200 is an XRPD pattern of resmetirom Form N2.
- [00300] FIG. 201 is an ^1H NMR spectrum of resmetirom Form N2.
- [00301] FIG. 202 is a combined DSC and TGA thermogram of resmetirom Form N2.
- [00302] FIG. 203 is an XRPD pattern of resmetirom Form N3.
- [00303] FIG. 204 is an ^1H NMR spectrum of resmetirom Form N3.
- [00304] FIG. 205 is an XRPD pattern of resmetirom Form N4.
- [00305] FIG. 206 is an ^1H NMR spectrum of resmetirom Form N4.
- [00306] FIG. 207 is a combined DSC and TGA thermogram of resmetirom Form N4.
- [00307] FIG. 208 is an XRPD pattern of resmetirom Form N6.
- [00308] FIG. 209 is an ^1H NMR spectrum of resmetirom Form N6.
- [00309] FIG. 210 is an XRPD pattern of resmetirom Form N7.
- [00310] FIG. 211 is an ^1H NMR spectrum of resmetirom Form N7.
- [00311] FIG. 212 is a combined DSC and TGA thermogram of resmetirom Form N7.

[00312] FIG. 213 is an XRPD pattern of Resmetirom Form N9.

Detailed Description

[00313] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description is intended to describe particular embodiments only, and is not intended to limit the scope of the invention.

[00314] As used herein, the following terms have the meaning indicated, unless otherwise specifically noted in context. Unless otherwise defined herein, all technical terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[00315] As used herein, the term "MRI-PDFF" describes proton-density-fat-fraction determined by a magnetic resonance imaging (MRI)-based determination. MRI-PDFF is an MRI-based diagnostic imaging biomarker of the liver. MRI-PDFF is a measure to assess liver fat content and is proposed to be used as non-invasive method used as a pre-screening strategy in an adult population having clinical signs or risk factors suggesting nonalcoholic fatty liver disease, e.g., noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis consistent with stages F2 and F3 fibrosis. MRI-PDFF is also used as a monitoring tool to demonstrate efficacy and reduction in NASH over time. MRI-PDFF is an accurate quantitative imaging biomarker with high repeatability and reproducibility and has provided results from test and validation datasets with MRI-PDFF compared to liver histology to show optimal MRI-PDFF cut-offs in order to reduce the number of unnecessary biopsies.

[00316] As used herein, the term "portal hypertension," refers to an increase in the pressure within the portal vein (the vein that carries blood from the digestive organs (large and small intestines, stomach, pancreas, spleen) to the liver). The increase in pressure is caused by a blockage in the blood flow through the liver.

[00317] As used herein, the term "cirrhosis," refers to a late stage of scarring (fibrosis) of the liver caused by many forms of liver diseases and conditions, such as hepatitis and chronic alcoholism. The liver fat of a cirrhosis human subject (e.g., as measured by MRI-PDFF) is no more than 5%.

[00318] As used herein, "administering" or "administered to" refers to prescribing a medicine to a human subject, directing others to administer a medicine to a human subject, directing a human subject to self-administer a medicine, and/or the act of physically ingesting the medicine. A medicine containing resmetirom (or a pharmaceutically acceptable salt of resmetirom) as its active pharmaceutical ingredient, can therefore be administered by a physician or other medical professional who writes prescriptions for a medicine(s) or otherwise directs a patient to self-administer a prescription, and/or by the human subject who ingests the medicine and/or by a human subject's caretaker who provides the medicine to a human subject.

[00319] As used herein, the term "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[00320] As used herein, the term "daily" means every day, where each day is defined by a 24 hour period. For the avoidance of doubt, the 24 hour period defining "daily" can bridge

two calendar days, for example, Sunday-Monday; Monday-Tuesday; Tuesday-Wednesday; etc.

[00321] As used herein, the term "dose," "dosage" or "daily dosage" refers to the weight of an active ingredient (e.g., resmetirom).

[00322] As used herein, the term "reduced dosage" refers to a dose of resmetirom or the pharmaceutically acceptable salt thereof that is less than the dose that would otherwise be administered to the human subject based on the determination of the human subject's weight due to concomitant use of a moderate CYP2C8 inhibitor.

[00323] In some embodiments, the human subject who is administered resmetirom or the pharmaceutically acceptable salt thereof is concomitantly on a moderate CYP2C8 inhibitor regimen. Such a human subject is administered a reduced dosage of resmetirom or the pharmaceutically acceptable salt thereof per day compared to the daily dose that would otherwise be administered if this human subject were not on a moderate CYP2C8 inhibitor regimen.

[00324] In some embodiments, the human subject was already taking the moderate CYP2C8 inhibitor prior to being administered resmetirom or the pharmaceutically acceptable salt thereof.

[00325] As used herein, the term "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a formulation that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[00326] As used herein, the term "human subject" refers to a human subject who is an adolescent or an adult.

[00327] As used herein, an "adult human subject" refers to a human subject who is 18 years of age or older.

[00328] As used herein, an "adolescent human subject" refers to a human subject who is 12 years of age or older and younger than 18 years of age. A physician's prescription in connection with the treatment and/or improvement as disclosed herein to a human subject younger than 18 years old is considered to be off-label.

[00329] As used herein, the term "human subject in need thereof," refers to a human subject having a disease (to be treated) or having an increased risk of developing the disease (to be prevented). A human subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A human subject in need thereof can also be one who has (e.g., is suffering from) a disease or disorder disclosed herein. Alternatively, a human subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a human subject who is predisposed to developing such disorder relative to the population at large). A human subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that doesn't respond or hasn't yet responded to treatment). The human subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the human subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the human subject in need thereof received at least one prior therapy.

[00330] As used herein, the term "salt" or "pharmaceutically acceptable salt" refers to a derivative of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, e.g., glycine, alanine, phenylalanine, arginine, etc. Other examples of pharmaceutically acceptable salts include those derived from hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. Further examples of pharmaceutically acceptable salts include caffeine, urea, 2-picolinic acid, N-methyl-morpholine, piperazine, benzathine, and L-proline salts. The present disclosure also encompasses salts formed when an acidic proton present in the parent

compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3. It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) or co-crystals as defined herein, of the same salt. Some pharmaceutically acceptable salts of resmetirom—and methods for preparing the same—are reported in U.S. Patent Application Publication Nos. 2021/0122740 and 2023/0364099, both of which are incorporated herein by reference in their entireties.

[00331] As used herein, the term "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. That is, "treating" or "treatment" of a state, disorder, or condition therefore includes: (1) delaying the appearance of clinical symptoms of the state, disorder, or condition developing in a human that may be afflicted with the state, disorder, or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder, or condition, (2) inhibiting the state, disorder, or condition, i.e., arresting or reducing the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder, or condition or at least one of its clinical or subclinical symptoms.

[00332] As used herein, a "solvate" refers to a crystalline form that includes a solvent (e.g., an organic solvent) chemically incorporated with the parent molecule in various fractional or integral molar ratios.

[00333] As used herein, a "hydrate" refers to a crystalline form that includes water chemically incorporated with the parent molecule in various fractional or integral molar ratios.

[00334] As used herein, a "co-crystal" refers to a crystalline material including at least two, different, molecules in the same crystalline lattice and associated by non-ionic and /or non-covalent bonds in a defined stoichiometric ratio. In some embodiments, the co-crystal includes two molecules which are in natural state. As used herein, this at least one other molecule is referred to as a "co-crystal former." For example, a co-crystal may be resmetirom with at least one co-crystal former in a defined stoichiometric ratio.

[00335] As used herein, the notation "resmetirom : nicotinamide" refers to a distinct molecular species that includes resmetirom and nicotinamide. Resmetirom : nicotinamide may be a co-crystal of resmetirom and nicotinamide. Alternatively, resmetirom : nicotinamide may be a salt.

[00336] As used herein, the notation "resmetirom : caffeine" refers to a distinct molecular species that includes resmetirom and caffeine. Resmetirom : caffeine may be a co-crystal of resmetirom and caffeine. Alternatively, resmetirom : caffeine may be a salt.

[00337] As used herein, the notation "resmetirom : 2-picolinic acid" refers to a distinct molecular species that includes resmetirom and 2-picolinic acid. Resmetirom : 2-picolinic acid may be a co-crystal of resmetirom and 2-picolinic acid. Alternatively, resmetirom : 2-picolinic acid may be a salt.

[00338] As used herein, the notation "resmetirom : urea" refers to a distinct molecular species that includes resmetirom and urea. Resmetirom : urea may be a co-crystal of resmetirom and urea. Alternatively, resmetirom : urea may be a salt.

[00339] As used herein, the notation "resmetirom : N-methyl-morpholine salt" refers to a distinct molecular species that includes resmetirom and N-methyl-morpholine. Resmetirom : N-methyl-morpholine salt may be a co-crystal of resmetirom and N-methyl-morpholine salt. Alternatively, resmetirom : N-methyl-morpholine salt may be a salt.

[00340] As used herein, the notation "resmetirom : piperazine salt" refers to a distinct molecular species that includes resmetirom and piperazine salt. Resmetirom : piperazine salt may be a co-crystal of resmetirom and piperazine salt. Alternatively, resmetirom : piperazine salt may be a salt.

[00341] As used herein, the notation "resmetirom : benzathine salt" refers to a distinct molecular species that includes resmetirom and benzathine salt. Resmetirom : benzathine salt may be a co-crystal of resmetirom and benzathine salt. Alternatively, resmetirom : benzathine salt may be a salt.

[00342] As used herein, the notation "resmetirom : L-proline" refers to a distinct molecular species that includes resmetirom and L-proline. Resmetirom : L-proline may be a co-crystal of resmetirom and L-proline. Alternatively, resmetirom : L-proline may be a salt.

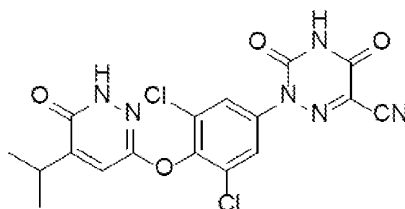
[00343] As used herein, an "amorphous form" refers to a non-crystalline material that lacks long-range order in its structure.

[00344] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in

practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[00345] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

[00346] Resmetirom is a compound having the chemical name 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile. Resmetirom has the chemical structure depicted below:



[00347] It is to be understood that resmetirom or the pharmaceutically acceptable salt thereof can exist in crystalline or amorphous form. It is also to be understood that resmetirom or the pharmaceutically acceptable salt thereof can exist as a hydrate, solvate, or co-crystal.

[00348] Various forms of resmetirom or the pharmaceutically acceptable salt thereof—and processes for preparing the same—are reported in the following patents, applications, and/or publications, all of which are incorporated herein by reference in their entireties:

- U.S. Patent No. 9,266,861
- U.S. Patent No. 10,376,517
- U.S. Patent Application Publication No. 2021/0122740
- U.S. Patent Application Publication No. 2023/0416234
- WO 2022/171200
- WO 2025/011259
- WO 2021/063367
- CN 115124515A
- IN 202241066042A
- U.S. Patent Application Publication No. 2024/0423993
- CN 118772117A
- MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof," found at https://www.tdcommons.org/cgi/viewcontent.cgi?article=8898&context=dpubs_series
- U.S. Patent Application Publication No. 2022/0372021
- U.S. Patent Application Publication No. 2023/0364099

[00349] It is to be understood that resmetirom or the pharmaceutically acceptable salt thereof may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[00350] In some embodiments, the resmetirom exists in a crystalline form.

[00351] In some embodiments, the resmetirom exists in an amorphous form.

[00352] In some embodiments, the resmetirom is in the form of a solvate.

[00353] In some embodiments, the solvate is selected from 1,1,1-trichloroethane, 1,1,2-trichloroethene, 1,1-dichloroethene, 1,2-dichloroethane, 1,2-dichloroethene, 1,2-dimethoxyethane, 1,3 dioxolane, 1,4-dioxane, 1-butanol, 1-pentanol, 1-propanol, 2,2,2-trifluoroethanol, 2-butanol, 2-ethoxyethanol, 2-methoxyethanol, 2-methyl-1-propanol, 2-propanol, 3-methyl-1-butanol, acetic acid, acetone, acetonitrile, acetyl acetone, anisole, benzene, benzyl alcohol, butyl acetate, carbon tetrachloride, chlorobenzene, chloroform, cumene, cyclohexane, cyclohexanone, cyclopentylmethyl ether, di(ethylene glycol) ethyl ether, dibutyl ether, dichloromethane, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, ethylene glycol, formamide, formic acid, heptane, hexafluoroisopropanol, hexane, isobutyl acetate, isopropyl acetate, methanol, methyl acetate, methyl tetrahydrofuran, methylbutyl ketone, methylcyclohexane, methylethyl ketone, methylisobutyl ketone, MIPK, N,N-dimethylformamide, N,N-dimethylacetamide, nitrobenzene, nitromethane, N-methylpyrrolidone, pentane, propionic acid, propionitrile, propyl acetate, pyridine, sulfolane, tert-butanol, tert-butylmethyl ether, tetrahydrofuran, tetralin, toluene, triethylamine, trifluorotoluene, Tween 2.1 wt%, and xylene.

[00354] In some embodiments, the solvate is 2,2,2-trifluoroethanol, cyclohexanone, methyl acetate, methylethyl ketone, N,N-dimethylformamide, nitromethane, N-methylpyrrolidone, tert-butanol, or xylene.

[00355] In some embodiments, the resmetirom is in the form of a hydrate.

[00356] In some embodiments, the resmetirom is in the form of a co-crystal along with a co-crystal former as part of the co-crystal.

[00357] In some embodiments, the co-crystal former is selected from 1-(2-hydroxyethyl)pyrrolidine, 1-hydroxy-2-naphthoic acid, 4-(2-hydroxyethyl)morpholine, acesulfame, acesulfame potassium, 4-acetamidobenzoic acid, acetic acid, acetoin,

acetylsalicylic acid, aconitic acid, adenine, adipic acid, alanine, alitame, alpha tocopherol, aluminum, 4-aminobenzoic acid, 4-aminopyridine, 4-aminosalicylic acid, ammonia, ammonium chloride, anethole, arginine, ascorbic acid, ascorbyl palmitate, asparagine, aspartame, aspartic acid, benzathine, benzaldehyde, benzamide, benzenesulfonic acid, benzoic acid, beta-cyclodextrin, betaine, betaine HCl, butylated hydroxyanisole, butylated hydroxytoluene, caffeine, calcium, calcium bromide, calcium chloride, camphoric acid, capric acid (decanoic acid), caprylic acid (octanoic acid), carbonic acid, carvone, cholic acid, choline, choline chloride, chrysin, cinnamic acid, citric acid, p-coumaric acid, creatine, creatinine, cyclamic acid, cysteine, cytosine, deanol, dehydroacetic acid, diacetyl, 2,2-dichloroacetic acid, diethanolamine, diethylamine, 2-diethylaminoethanol, 3,4-dihydroxybenzoic acid, dimethyl glycine, 2-dimethylaminoethanol, erythritol, ethane-1,2-disulfonic acid, 2-hydroxyethanesulfonic acid, ethanesulfonic acid, ethanolamine, ethyl maltol, ethyl paraben, ethyl vanillin, ethylenediamine, eugenol, ferric chloride, folic acid, folinic acid, formic acid, fructose, fumaric acid, gallic acid, genistein, gentisic acid, glucoheptonic acid, gluconic acid, glucosamine, glucosamine hydrochloride, glucose, D-glucuronic acid, glutamic acid, L-glutamine, glutaric acid, glycerin/glycerol, glycine, glycolic acid, guanine, HCl, hippuric acid, L-histidine, 4-hydroxybenzoic acid, hypoxanthine, 1H-imidazole, inositol, D-isoascorbic acid, isobutyric acid, isoleucine, isonicotinamide, ketoglutaric acid, lactic acid, lactitol, lactobionic acid, lactose, lauric acid, L-carnitine, leucine, linoleic acid, lithium, lysine, magnesium, magnesium bromide, magnesium chloride, maleic acid, malic acid, malonic acid, maltitol, maltol, maltose, mandelic acid, manganese chloride, mannitol, meglumine, methanesulfonic acid, methionine, methyl anthranilate, methyl paraben, monosodium glutamate (MSG), mucic (galactaric) acid, naphthalene-1,5-disulfonic acid, 2-naphthalenesulfonic acid, n-butyric acid, neotame, nicotinamide, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, pantothenic acid,

phenylalanine, phosphoric acid, picolinic acid, piperazine, piperonal, potassium, proline, propionic acid, propyl gallate, propyl paraben, propylene glycol, pyridoxine, pyroglutamic acid, quercetin, resveratrol, retinol, riboflavin, saccharin, sacrosine (N-methylglycine), salicylic acid, sebacic acid, serine, sodium, sodium chloride, sodium lauryl sulfate, sorbic acid, sorbitol, stannous chloride, stearic acid, succinic acid, sucralose, sucrose, sulfuric acid, tagatose, L-tartaric acid, taurine, theanine, theobromine, theophylline, thiamine chloride, thiamine nitrate, thiocyanic acid, threonine, thymine, p-toluenesulfonic acid, triacetin, tributyrin, triethanolamine, triethyl citrate, triethylamine, tromethamine, tromethamine hydrochloride, L-tryptophan, tyrosine, uracil, urea, valeric acid, valine, vanillic acid, vanillin, xanthine, xylitol, xylose, zinc, and zinc chloride.

[00358] In some embodiments, the co-crystal former is 4-aminopyridine, cytosine, 2,2-dichloroacetic acid, diethylamine, dimethyl glycine, 1H-imidazole, pantothenic acid (calcium pantothenate), triethyl citrate, or tromethamine.

[00359] In some embodiments, the co-crystal former is L-proline, caffeine, or 2-picolinic acid.

[00360] In some embodiments, resmetirom exists in a co-crystal form or a salt form including resmetirom : nicotinamide, resmetirom : caffeine, resmetirom : 2-picolinic acid, resmetirom : urea, resmetirom : N-methyl-morpholine salt, resmetirom : piperazine salt, resmetirom : benzathine salt, or resmetirom : L-proline.

[00361] All doses or dosages recited herein for resmetirom or the pharmaceutically acceptable salt thereof are based on the molecular weight of the compound itself, rather than the molecular weight of the pharmaceutically acceptable salt thereof, or the hydrate or solvate thereof, or the co-crystal thereof, or any excipients in the composition, unless otherwise

stated. For example, administration of resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 100 mg per day means administration of the equivalent of 100 mg of the compound itself per day, not 100 mg of the pharmaceutically acceptable salt thereof, or the hydrate or solvate thereof, or the co-crystal thereof, per day.

[00362] Resmetirom is described, for example, in Examples 4 and 5 of U.S. Patent No. 9,266,861 and WO 2014/043706. One aspect of the present disclosure relates to methods of treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) in which a solid dosage form administered to a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement contains resmetirom or a pharmaceutically acceptable salt thereof, existing in a morphic form (e.g., an amorphous form, a crystalline form, a solvate, or a hydrate) or a mixture of morphic forms.

[00363] In some embodiments, resmetirom exists in Form I. Form I is described in U.S. Patent No. 9,266,861 and WO 2014/043706 and can be synthesized as shown, for example, in Examples 6 and 7 of U.S. Patent No. 9,266,861 and WO 2014/043706.

[00364] Example 6 of U.S. Patent No. 9,266,861 and WO 2014/043706 describes conversion of resmetirom to Form I:

[00365] Purified resmetirom (4802 g) as a 1:1 MIBK solvate which was obtained from Int. 8 as described in Example 5 of U.S. Patent No. 9,266,861 and WO 2014/043706 above was added into a jacketed, 100 L reactor along with 24 liters of ethanol. The resulting slurry was heated to 80 ± 5 °C (reflux) over 1 h 25 min; the mixture was stirred at that temperature for 4 h 25 min. Analysis of the filtered solids at 2 h 55 min indicated that the form conversion was complete, with the XRPD spectra conforming to Form I. The mixture was cooled to 20 ± 5 °C over 45 min and stirred at that temperature for 15 min. The slurry was filtered and the

filter cake was washed twice with prefiltered ethanol (2 x 4.8 L). The wet cake (4.28 kg) was dried under vacuum at 40 ± 5 °C for 118 h to afford 3390 g of resmetirom Form I.

[00366] The X-ray Powder Diffraction study was performed on different lots of resmetirom morphic Form I generated by the process described above. XRPD after micronization confirms Form I.

[00367] The data for Form I is provided in the table below and the diffractograms of Form I are provided as FIG. 43.

[00368] Table 11 of U.S. Patent No. 9,266,861 and WO 2014/043706

2 θ (angle)	d value (Å)	Intensity (counts)	Intensity % (%)
3.0288	29.17117	1925.62	15.89
3.4596	25.5397	832.08	4.58
3.6702	24.07429	707.65	3.89
4.0027	22.07529	410.45	6.78
4.4466	19.87232	432.4	2.38
4.5794	19.29632	429.89	4.73
5.2533	16.82257	320.41	5.29
5.8566	15.09082	335.71	1.85
6.05	14.60887	224.56	9.89
6.8068	12.98624	287.97	3.17
7.2152	12.25213	293.93	4.04
7.6426	11.56781	239.85	2.64
8.2256	10.74918	1637.27	13.51
8.8542	9.98745	309.91	3.41
9.115	9.70221	244.6	2.02
9.576	9.23622	255.43	2.11
10.5373	8.39569	9763.54	100
11.1868	7.9096	2398.13	24.56
13.0814	6.76802	164.19	3.36
13.9013	6.37063	197.28	1.52
14.3022	6.19296	290.11	2.23
14.7284	6.01469	94.1	0.96
15.7399	5.63037	1305.28	16.71
16.4002	5.40513	804.24	10.3
16.732	5.2987	173.26	2.22
17.3055	5.12435	145.15	2.97
17.6872	5.01461	1400.39	17.93
18.3399	4.83761	1233.01	9.47
18.6986	4.7456	9825.6	100
18.9598	4.6808	572.69	3.5
19.3018	4.59864	278.53	1.7
19.6643	4.51468	97.55	0.4

2 θ (angle)	d value (Å)	Intensity (counts)	Intensity % (%)
20.0939	4.41912	64.71	2.63
21.0604	4.21845	333.65	2.72
22.2097	4.00268	833.43	8.48
22.6128	3.93224	1304.95	10.62
22.8964	3.88417	3375.42	34.35
23.066	3.856	976.63	5.96
23.5742	3.77401	3115.33	38.05
23.8662	3.72849	571.62	4.65
24.1	3.69284	572.34	6.99
24.5243	3.62991	1097.27	6.7
24.6502	3.61166	1580.95	16.09
25.4993	3.49329	225.6	2.76
26.4933	3.36443	506.03	5.15
26.7528	3.33239	244.51	1.99
27.1244	3.28756	130.69	1.06
27.4354	3.251	546.35	4.45
27.8382	3.20487	213.44	2.17
28.5208	3.12971	158.82	1.29
28.9064	3.08883	436.59	2.67
29.1352	3.06509	710.53	5.79
29.5077	3.02724	416.16	4.24
30.0267	2.97608	1470.29	17.96
30.3658	2.94361	260.89	1.59
30.6326	2.91858	132.13	0.54
31.316	2.85644	177.78	1.45
31.6013	2.83129	397.61	5.67
31.9237	2.80343	514.26	4.19
32.2125	2.77895	1293.04	18.42
32.8721	2.72469	434.37	2.65
33.3755	2.68474	295.36	2.4
33.8232	2.65022	358.99	3.65
34.8364	2.57542	140.57	1.72
35.1838	2.55079	739.55	7.53
35.7301	2.51303	98.13	1.2
36.0084	2.49424	110.57	1.35
36.4676	2.46389	316.07	2.57
37.2747	2.41237	199.99	4.07
38.3543	2.34691	34.08	0.42
39.1941	2.29854	63.88	1.3
39.9663	2.25589	211.73	1.29
40.6489	2.21957	96.61	0.59
41.194	2.19145	167.45	1.36
42.0276	2.14989	47.01	0.57

2 θ (angle)	d value (Å)	Intensity (counts)	Intensity % (%)
42.4477	2.12958	290.42	1.77
42.8091	2.11244	200.71	1.63
43.6289	2.07463	171.28	2.09

[00369] Form I was found to have a melting onset around 321 °C, followed by decomposition upon melting by DSC (FIG. 44).

[00370] Example 7 of U.S. Patent No. 9,266,861 and WO 2014/043706 describes preparation of resmetirom Form I: conversion of resmetirom solvate to Form I:

[00371] A 50 L, jacketed, glass vessel purged with N₂ was charged with resmetirom MIBK solvate (2.72 kg) from Example 5 of U.S. Patent No. 9,266,861 and WO 2014/043706 above and ethanol (13.6 L). The agitator was started and the batch temperature was adjusted from 16.8 °C to 79.4 °C over 1.3 h. The batch was held at 79.5 °C for 2 h and sampled for XRPD analysis. XRPD indicated Form I, and the batch was cooled to 24.9 °C over 1 h and 10 min. An 18" Nutsche filter equipped with tight-weave (0.67 CFM) polypropylene cloth was set up and the batch was filtered. The filtration took 4 min. Ethanol (2.8 L) was charged to the vessel and transferred to the filter cake. The cake was manually resuspended and the liquors were pulled through with vacuum. Ethanol (2.80 L) was charged to the filter cake and the cake was manually resuspended. The liquors were pulled through with vacuum and the cake was conditioned with vacuum and nitrogen for 1 h. The filter cake was transferred to drying pans and dried at 45 °C and 28 "/Hg for one day to give an 89% yield (1.96 kg) of resmetirom as a light yellow solid. HPLC analysis indicated a purity of 99.6%. XRPD analysis is consistent with Form I. Micronization of 300 g of this material on a 2" jet mill gave 284 g (95% yield) of micronized resmetirom. XRPD analysis confirmed that micronized resmetirom remained Form I.

[00372] Resmetirom DMAC solvate can be converted, via the dihydrate and the MIBK solvate, to Form I as described in Example 7 of U.S. Patent No. 9,266,861 and WO 2014/043706. Alternatively, the DMAC solvate was converted directly to Form I in 75% yield (yield calculated from Intermediate 8) by heating it with 8 volumes of ethanol to 80 °C for 2 hours followed by cooling to room temperature and filtering. In another reaction, a sample of resmetirom that was a mixture of the DMAC solvate and dihydrate was converted to Form I in 69% yield by heating it with 8 volumes of MIBK to 80°C followed by cooling to room temperature.

[00373] In some embodiments, Form I of resmetirom is characterized by an X-ray powder diffraction (XRPD) pattern including signals (e.g., peaks) at $10.5^{\circ}\pm 0.2^{\circ}$, $18.7^{\circ}\pm 0.2^{\circ}$, $22.9^{\circ}\pm 0.2^{\circ}$, $23.6^{\circ}\pm 0.2^{\circ}$, and $24.7^{\circ}\pm 0.2^{\circ}$ 2 θ . In some embodiments, the XRPD pattern further includes one or more signals (e.g., peaks) at $8.2^{\circ}\pm 0.2^{\circ}$, $11.2^{\circ}\pm 0.2^{\circ}$, $15.7^{\circ}\pm 0.2^{\circ}$, $16.4^{\circ}\pm 0.2^{\circ}$, $17.7^{\circ}\pm 0.2^{\circ}$, $30.0^{\circ}\pm 0.2^{\circ}$, and $32.2^{\circ}\pm 0.2^{\circ}$ 2 θ . The XRPD pattern of Form I of 2-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (resmetirom) is described, for example, in Table 11 of U.S. Patent No. 9,266,861 and WO 2014/043706 and FIG. 43.

[00374] In some embodiments, Form I of resmetirom is characterized by a differential scanning calorimetry (DSC) diagram comprising an endothermic peak at 329° C. In some embodiments, Form I of resmetirom is further characterized by an onset melting temperature of 321° C. The DSC diagram of Form I resmetirom is described for example in Example 6 of U.S. Patent No. 9,266,861 and WO 2014/043706 and FIG. 44.

[00375] In some embodiments, resmetirom or a pharmaceutically salt thereof exists in a morphic form (e.g., crystalline form), as described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068 (incorporated herein by reference in their entireties).

[00376] In some embodiments, resmetirom is Form λ , which is described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068.

[00377] Form λ can be produced as described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068:

[00378] A suspension of resmetirom and isopropyl acetate was stirred for 2 days then filtered. Heating to 100°C for 1 hour generated the desolvate. (Form λ , FIG. 45).

[00379] In some embodiments, Form λ of resmetirom is characterized by an X-ray powder diffraction pattern including peaks at $10.6^{\circ} \pm 0.2^{\circ}$, $12.0^{\circ} \pm 0.2^{\circ}$, $14.3^{\circ} \pm 0.2^{\circ}$, $16.2^{\circ} \pm 0.2^{\circ}$, $17.6^{\circ} \pm 0.2^{\circ}$, $18.0^{\circ} \pm 0.2^{\circ}$, and $24.3^{\circ} \pm 0.2^{\circ}$ 2θ , wherein the X-ray powder diffraction pattern is obtained using a $\text{CuK}\alpha$ radiation source (1.54 Å). In some embodiments, the X-ray powder diffraction pattern of Form λ can further include one or more peaks from Table 29 of U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068. In some embodiments, Form λ has an X-ray diffraction pattern substantially similar to that set forth in FIG. 45.

[00380] Table 29 of U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068 provides the following data:

2- θ	d (Å ²)	Height (counts)	Relative Intensity, %
8.85	9.97936	57	6
10.64	8.30722	834	94
11.24	7.86653	227	26
12.01	7.36601	291	33
14.33	6.1747	271	30
15.59	5.67972	261	29
16.20	5.46571	704	79
17.31	5.11846	206	23
17.60	5.03393	333	37
18.01	4.92036	528	59
19.56	4.53532	82	9
20.10	4.41393	151	17
22.34	3.97569	262	29
22.81	3.89618	50	6
24.26	3.66562	889	100
26.78	3.32625	117	13
27.68	3.22066	76	9
28.75	3.10234	183	21

[00381] In some embodiments, resmetirom is Form F, which is described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068.

[00382] Form F can be produced as described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068:

[00383] A suspension of resmetirom and ethyl acetate was stirred for 2 days then filtered. Heating to 100°C for 1 hour generated the desolvate (Form F, FIG. 46).

[00384] In some embodiments, Form F of resmetirom is characterized by an X-ray powder diffraction pattern including peaks at $10.1^{\circ} \pm 0.2^{\circ}$, $10.4^{\circ} \pm 0.2^{\circ}$, $11.4^{\circ} \pm 0.2^{\circ}$, $13.9^{\circ} \pm 0.2^{\circ}$, $16.2^{\circ} \pm 0.2^{\circ}$, $16.4^{\circ} \pm 0.2^{\circ}$, $17.1^{\circ} \pm 0.2^{\circ}$, $22.0^{\circ} \pm 0.2^{\circ}$, $23.8^{\circ} \pm 0.2^{\circ}$, and $29.5^{\circ} \pm 0.2^{\circ}$ 2θ , wherein the x-ray powder diffraction pattern is obtained using a CuK α radiation source (1.54 Å). In some embodiments, the X-ray powder diffraction pattern of Form F can further include one or more peaks from Table 8 of U.S. Patent Application Publication No. 2021/0122740 and WO

2020/010068. In some embodiments, Form F has an X-ray diffraction pattern substantially similar to that set forth in FIG. 46.

[00385] Table 8 of U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068 provides the following data:

XRPD Peak positions of Form F			
2- θ	d ($\text{\AA}^\circ$)	Height (counts)	Relative Intensity, %
7.28	12.13064	156	13
10.12	8.73306	925	78
10.41	8.4933	920	78
11.37	7.77672	292	25
13.91	6.36341	1179	100
16.20	5.46847	262	22
16.38	5.40798	331	28
17.05	5.19679	456	39
18.41	4.81512	162	14
18.90	4.69209	77	7
19.27	4.60216	129	11
20.94	4.23938	107	9
22.00	4.03681	396	34
22.51	3.94607	226	19
23.21	3.82963	73	6
23.81	3.73378	424	36
25.30	3.51739	74	6
25.85	3.44375	81	7
27.97	3.18771	227	19
29.53	3.02271	676	57
29.87	2.98899	83	7

[00386] In some embodiments, resmetirom is Form L, which is described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068.

[00387] Form L can be produced as described in U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068:

[00388] A suspension of resmetirom and acetonitrile was stirred for 2 days then filtered. XRPD analysis indicated the formation of the acetonitrile solvate (Form L, FIG. 47).

[00389] In some embodiments, Form L of resmetirom is characterized by an X-ray powder diffraction pattern including peaks at $10.5^{\circ} \pm 0.2^{\circ}$, $11.5^{\circ} \pm 0.2^{\circ}$, $11.9^{\circ} \pm 0.2^{\circ}$, $15.2^{\circ} \pm 0.2^{\circ}$, $15.7^{\circ} \pm 0.2^{\circ}$, $16.0^{\circ} \pm 0.2^{\circ}$, $16.9^{\circ} \pm 0.2^{\circ}$, $17.1^{\circ} \pm 0.2^{\circ}$, $18.4^{\circ} \pm 0.2^{\circ}$, $18.7^{\circ} \pm 0.2^{\circ}$, $22.0^{\circ} \pm 0.2^{\circ}$, $22.8^{\circ} \pm 0.2^{\circ}$, $23.5^{\circ} \pm 0.2^{\circ}$, and $26.4^{\circ} \pm 0.2^{\circ}$ degrees 2θ , wherein the x-ray powder diffraction pattern is obtained using a $\text{CuK}\alpha$ radiation source ($1.54 \text{ \AA}$). In some embodiments, the X-ray powder diffraction pattern of Form L can further include one or more peaks from Table 13 of U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068. In some embodiments, Form L has an X-ray diffraction pattern substantially similar to that set forth in FIG. 47.

[00390] Table 13 of U.S. Patent Application Publication No. 2021/0122740 and WO 2020/010068 provides the following data:

2- θ	d ($\text{\AA}^{\circ}$)	Height (counts)	Relative Intensity, %
8.11	10.88728	170	12
10.53	8.39548	319	23
11.49	7.6921	904	64
11.87	7.45234	1402	100
12.27	7.20569	141	10
15.21	5.82222	794	57
15.65	5.6584	470	34
16.04	5.52206	591	42
16.88	5.24756	455	32
17.10	5.18216	849	61
17.70	5.00658	143	10
18.43	4.81125	278	20
18.71	4.73921	332	24
21.32	4.16467	128	9
22.04	4.02938	413	29
22.81	3.89506	695	50
23.45	3.79117	422	30
24.08	3.69229	206	15
24.72	3.59921	266	19
26.37	3.37757	328	23
29.03	3.07381	91	6
29.49	3.02679	70	5

[00391] A number of forms of resmetirom have been reported in the art.

[00392] For example, one of the forms is Form CSIV reported in U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465.

[00393] Form CSIV may be characterized, for instance, by the X-ray powder diffraction pattern that comprises characteristic peaks at 2-theta values of $6.3^{\circ} \pm 0.2^{\circ}$, $18.1^{\circ} \pm 0.2^{\circ}$, and $25.3^{\circ} \pm 0.2^{\circ}$ using CuK α radiation. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $10.4^{\circ} \pm 0.2^{\circ}$, $14.5^{\circ} \pm 0.2^{\circ}$, $20.6^{\circ} \pm 0.2^{\circ}$, $24.6^{\circ} \pm 0.2^{\circ}$, and $28.6^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00394] Example 1 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465 describes preparation of resmetirom crystalline Form CSIV:

[00395] 145.2 mg of resmetirom solid was weighed into a glass vial. 1.5 mL of acetonitrile was added, and then stirred at room temperature for three days to form a suspension. The suspension was centrifuged to obtain a solid. The obtained solid was dried under vacuum at 100° C. for 3.5 hours to obtain resmetirom crystalline Form CSIV.

[00396] The XRPD pattern of resmetirom crystalline Form CSIV obtained in this example is shown in FIG. 48, and the XRPD data are listed in Table 2 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465.

[00397] Table 2 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465 provides the following data:

2 θ (°)	d spacing (Å)	Relative intensity %
6.26	14.13	15.68
7.88	11.21	3.93
10.40	8.50	6.46
14.48	6.12	19.94
14.57	6.08	18.19
15.32	5.78	7.55
15.51	5.72	8.63
16.39	5.41	2.88
17.08	5.19	3.69
18.10	4.90	71.67
19.65	4.52	13.55
20.60	4.31	17.34
20.98	4.23	10.25
23.21	3.83	20.11
23.85	3.73	16.01
24.58	3.62	74.11
25.31	3.52	100.00
26.08	3.42	7.51
27.11	3.29	4.29
28.55	3.13	21.78
30.05	2.97	14.73
31.02	2.88	6.02
31.67	2.83	10.20
32.94	2.72	14.56
34.03	2.63	7.50
34.76	2.58	5.80
35.50	2.53	5.77
36.76	2.45	2.33
37.43	2.40	2.42
38.80	2.32	5.18

[00398] The TGA curve of resmetirom crystalline Form CSIV is substantially as depicted in FIG. 49, which shows about 0.1% weight loss when heated to 200° C.

[00399] The DSC curve of resmetirom crystalline Form CSIV is substantially as depicted in FIG. 50, which shows an exothermic peak and an endothermic peak. The peak at around 245° C. (onset temperature) is an exothermic peak of crystal transformation, and the endothermic peak at around 334° C. (onset temperature) corresponds to melting.

[00400] The ¹H NMR data of resmetirom crystalline Form CSIV are: ¹H NMR (400 MHz, DMSO-d₆) δ 13.29 (s, 1H), 12.24 (s, 1H), 7.78 (s, 2H), 7.45 (s, 1H), 3.05 (m, 1H), 1.20 (d, J=6.9 Hz, 6H).

[00401] Example 2 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465 also describes preparation of resmetirom Crystalline Form CSIV:

[00402] A certain amount of resmetirom solid was put in 30 mL of acetonitrile and stirred at -20°C . for about 37.5 h. The obtained solid was separated and dried under vacuum at 50°C . for about 23.5 h to obtain resmetirom crystalline Form CSIV.

[00403] For example, one of the forms is Form CSV reported in WO 2021/129465.

[00404] Form CSV may be characterized, for instance, by the X-ray powder diffraction pattern that comprises characteristic peaks at 2-theta values of $11.9^{\circ}\pm 0.2^{\circ}$, $13.8^{\circ}\pm 0.2^{\circ}$, and $17.3^{\circ}\pm 0.2^{\circ}$ using $\text{CuK}\alpha$ radiation. The X-ray powder diffraction pattern may have any one, two, three, four, five, or six additional peaks selected from $19.9^{\circ}\pm 0.2^{\circ}$, $20.8^{\circ}\pm 0.2^{\circ}$, $21.2^{\circ}\pm 0.2^{\circ}$, $24.5^{\circ}\pm 0.2^{\circ}$, $26.2^{\circ}\pm 0.2^{\circ}$, and $27.0^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00405] Example 3 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465 describes preparation of resmetirom crystalline Form CSV:

[00406] 2.0742 g of resmetirom solid was weighed into a glass vial, 30 mL of dimethyl carbonate was added, and then stirred at 5°C . for 19 hours to form a suspension. The suspension was centrifugated and the separated solid was dried under vacuum at 50°C . for 4 hours to obtain a dry solid. 54.9 mg of the dry solid was weighed into a glass vial, 1 mL of isopropyl alcohol was added, and then stirred at 5°C . for 1.5 hours to obtain resmetirom crystalline Form CSV.

[00407] The XRPD pattern of resmetirom crystalline Form CSV obtained in this example is shown in FIG. 86, and the XRPD data are listed in Table 3 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465.

[00408] Table 3 of U.S. Patent Application Publication No. 2022/0372021 and WO 2021/129465 provides the following data:

2 θ (°)	d spacing (Å)	Relative intensity %
10.61	8.34	13.46
11.88	7.45	100.00
12.47	7.10	8.14
13.03	6.79	5.05
13.83	6.41	22.15
16.63	5.33	3.82
17.27	5.13	20.20
18.61	4.77	2.21
19.59	4.53	9.14
19.94	4.45	10.80
20.85	4.26	11.12
21.20	4.19	16.07
22.15	4.01	8.96
22.97	3.87	12.28
23.77	3.74	8.66
24.06	3.70	13.65
24.49	3.64	10.51
24.92	3.57	8.42
25.82	3.45	7.83
26.24	3.40	11.66
26.64	3.35	4.46
27.05	3.30	6.36
27.41	3.25	2.39
27.91	3.20	4.26
28.50	3.13	12.48
29.10	3.07	3.56
29.36	3.04	4.07
30.38	2.94	4.99
31.07	2.88	2.13
32.33	2.77	6.22
33.25	2.69	4.77
34.24	2.62	2.21
36.17	2.48	3.66
37.13	2.42	2.11
37.96	2.37	1.65
39.54	2.28	3.02

[00409] The TGA curve of resmetirom crystalline Form CSV is substantially as depicted in FIG. 87, which shows about 0.1% weight loss when heated to 200° C.

[00410] The ^1H NMR data of resmetirom crystalline Form CSV are: ^1H NMR (400 MHz, DMSO- d_6) δ 13.29 (s, 1H), 12.25 (s, 1H), 7.79 (s, 2H), 7.45 (s, 1H), 3.05 (m, 1H), 1.20 (d, $J=6.9$ Hz, 6H).

[00411] For example, one of the forms is Form CSVI reported in U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822.

[00412] Form CSVI may be characterized, for instance, by the X-ray powder diffraction pattern that comprises characteristic peaks at 2-theta values of $9.6^\circ \pm 0.2^\circ$, $10.1^\circ \pm 0.2^\circ$, and $18.9^\circ \pm 0.2^\circ$ using CuK α radiation. The X-ray powder diffraction pattern may have any one, two, three, four, five, or six additional peaks selected from $11.6^\circ \pm 0.2^\circ$, $13.7^\circ \pm 0.2^\circ$, $19.5^\circ \pm 0.2^\circ$, $20.6^\circ \pm 0.2^\circ$, $23.3^\circ \pm 0.2^\circ$, and $31.9^\circ \pm 0.2^\circ$ 2-theta.

[00413] Example 1 of U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822 describes preparation of resmetirom crystalline Form CSVI:

[00414] 1.5801 g of resmetirom was weighed into a glass bottle, followed by adding 25 mL of acetonitrile, and then stirred at room temperature for 4 days. The obtained solid was separated by filtration, and then blast dried the obtained solid at 40°C . for 15.5 h to obtain the resmetirom crystalline form CSVI.

[00415] The XRPD pattern of resmetirom crystalline Form CSVI obtained in this example is shown in FIG. 107, and the XRPD data are listed in Table 3 of U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822 .

[00416] Table 3 of U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822 provides the following data:

2 θ (°)	d spacing (Å)	Relative intensity (%)
6.49	13.62	2.06
9.57	9.25	65.84
10.11	8.75	100.00
11.58	7.65	7.89
12.77	6.93	0.88
13.68	6.48	3.39
13.98	6.33	0.91
14.75	6.00	2.41
16.19	5.48	4.32
17.64	5.03	1.13
18.10	4.90	2.23
18.94	4.68	10.63
19.50	4.55	19.67
19.81	4.48	4.75
20.33	4.37	1.63
20.61	4.31	7.02
21.62	4.11	2.74
21.86	4.07	2.96
22.66	3.92	4.89
22.91	3.88	2.66
23.29	3.82	8.60
23.72	3.75	1.44
24.14	3.69	0.98
24.80	3.59	3.03
24.98	3.57	4.96
25.69	3.47	1.87
26.12	3.41	3.40
21.86	4.07	2.96
22.66	3.92	4.89
22.91	3.88	2.66
23.29	3.82	8.60
23.72	3.75	1.44
24.14	3.69	0.98
24.80	3.59	3.03
24.98	3.57	4.96
25.69	3.47	1.87
26.12	3.41	3.40
26.75	3.33	4.17
27.31	3.27	2.57
27.57	3.24	1.94
28.01	3.19	1.85
29.19	3.06	1.72
29.79	3.00	2.09
31.13	2.87	1.30
31.90	2.81	4.91
32.68	2.74	1.98
33.48	2.68	1.87
33.77	2.65	1.24
34.37	2.61	1.29
35.45	2.53	1.92
36.44	2.47	1.70
38.27	2.35	1.43
39.14	2.30	3.36

[00417] The TGA curve of resmetirom crystalline Form CSVI is substantially as depicted in FIG. 108, which shows about 0.2% weight loss when heated to 250° C.

[00418] The ^1H NMR data of resmetirom crystalline Form CSVI are: ^1H NMR (400MHz, DMSO- d_6) δ 13.28(s, 1H), 12.23(s, 1H), 7.79(s, 2H), 7.44(d, $J=0.8\text{Hz}$, 1H), 3.04 (dq, $J=13.5$, 6.8 Hz, 1H), 1.20 (d, $J=6.9\text{ Hz}$, 6H).

[00419] Example 2 of U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822 describes preparation of resmetirom crystalline Form CSVI:

[00420] 22.0 mg of resmetirom was weighed into a glass bottle, followed by adding 2.0 mL of the solvent mixture of acetonitrile and water (95:5, V:V), and then dissolved at 50° C., filtered, then the filtrate was stirred at -20° C. for 4 h. The obtained solid was separated by filtration, and then dried the obtained solid at 25° C. under a vacuum for 2 h to obtain the resmetirom crystalline Form CSVI.

[00421] The XRPD pattern of resmetirom crystalline Form CSVI obtained in this example is shown in FIG. 109, and the XRPD data are listed in Table 4 of U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822 .

[00422] Table 4 of U.S. Patent Application Publication No. 2023/0416234 and WO 2022/052822 provides the following data:

2θ (°)	d spacing (Å)	Relative intensity (%)
6.48	13.65	9.15
9.55	9.26	51.51
10.09	8.76	100.00
11.56	7.65	10.22
13.00	6.81	1.45
13.67	6.48	6.38
13.97	6.34	1.56
14.71	6.02	2.42
16.18	5.48	9.37
17.61	5.04	0.98
18.11	4.90	1.81
18.93	4.69	22.10
19.49	4.56	18.39
19.82	4.48	2.83
20.61	4.31	4.81
21.61	4.11	3.08
21.84	4.07	7.91
22.64	3.93	4.23
22.88	3.89	3.26
23.27	3.82	12.36
24.97	3.57	3.66
25.62	3.48	1.81
26.11	3.41	3.28
26.73	3.34	3.74
27.28	3.27	2.52
27.59	3.23	2.25
27.96	3.19	5.37
29.20	3.06	1.70
29.76	3.00	1.82
31.13	2.87	3.79
31.91	2.81	5.06
32.69	2.74	2.33
33.43	2.68	3.01
34.36	2.61	2.57
35.41	2.53	1.64
36.43	2.47	1.33
38.18	2.36	1.33
39.15	2.30	2.37

[00423] For example, one of the forms is Form CSVII reported in WO 2025/011259.

[00424] Form CSVII may be characterized, for instance, by the X-ray powder diffraction pattern that comprises characteristic peaks at 2-theta values of $6.5^{\circ} \pm 0.2^{\circ}$, $7.7^{\circ} \pm 0.2^{\circ}$, and $23.4^{\circ} \pm 0.2^{\circ}$ using CuK α radiation. The X-ray powder diffraction pattern may have any one, two, three, four, five, or six additional peaks selected from $12.2^{\circ} \pm 0.2^{\circ}$, $19.7^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, $22.7^{\circ} \pm 0.2^{\circ}$, $24.2^{\circ} \pm 0.2^{\circ}$, and $25.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00425] Example 1 of WO 2025/011259 describes preparation of resmetirom crystalline Form CSVII:

[00426] 527.6 mg of resmetirom was weighed into a glass bottle, followed by adding 15 mL of methyl tert-butyl ether, and then stirred at room temperature for 1 day. The obtained solid was separated by filtration, and then dried under vacuum at 25° C. for 0.5 hour to obtain a dried solid. The partially dried solid was heated to 140° C. at 10° C./min under the protection of nitrogen and kept warm for 60 minutes, cooled to room temperature to obtain the resmetirom crystalline form CSVII.

[00427] The XRPD pattern of resmetirom crystalline Form CSVII obtained in this example is shown in FIG. 116, and the XRPD data are listed in Table 2 of WO 2025/011259.

[00428] Table 2 of WO 2025/011259 provides the following data:

Diffraction Angle 2θ	d value	Intensity%
5.1	17.2	2.5
6.5	13.7	13.1
7.7	11.4	100
12.2	7.3	2.9
14.2	6.2	1.1
17.1	5.2	1.2
19.7	4.5	3.5
21.1	4.2	1.1
22.7	3.9	1.7
23.4	3.8	6.2
24.2	3.7	3.8
25.4	3.5	2.3
26.6	3.3	2.1

[00429] The TGA curve of resmetirom crystalline Form CSVII is substantially as depicted in FIG. 117, which shows about 0.5% weight loss when heated to 100° C.

[00430] The DSC curve of resmetirom crystalline Form CSVII is substantially as depicted in FIG. 118, which shows an exothermic peak near 264° C. and an endothermic peak near 333° C.

[00431] The ¹H NMR data of resmetirom crystalline Form CSVII are: ¹H NMR (400MHz, DMSO-d₆) δ12.24(s, 1H), 7.79(s, 2H), 7.44(d, J=0.7Hz, 1H), 3.13-2.97 (m, 1H), 1.19 (d, J=6.9 Hz, 6H).

[00432] For example, one of the forms is Form Type K65 reported in WO 2025/011259.

[00433] Example 4 of WO 2025/011259 describes preparation of resmetirom crystalline Form Type K65:

[00434] 51.2 mg of resmetirom was weighed into a vial, a mixed solvent (volume ratio of 7:1) of 1.0 mL of acetonitrile and methanol was added, the mixture was suspended and stirred overnight at room temperature, and centrifugation was performed to obtain the resmetirom crystalline Form Type K65.

[00435] The XRPD pattern of resmetirom crystalline Form Type K65 obtained in this example is shown in FIG. 119, and the XRPD data are listed in Table 5 of WO 2025/011259.

[00436] Table 5 of WO 2025/011259 provides the following data:

Diffraction Angle 2 θ	d value	Intensity%
6.5	13.6	3.8
7.6	11.7	100.0
8.2	10.7	56.9
10.0	8.8	13.3
13.4	6.6	4.3
14.3	6.2	7.8
15.1	5.9	7.7
16.3	5.4	4.0
18.0	4.9	15.8
19.1	4.7	4.8
19.5	4.6	10.9
20.1	4.4	6.1
21.0	4.2	4.5
22.4	4.0	7.3
23.1	3.8	10.7
24.4	3.6	5.8
24.7	3.6	6.6
26.0	3.4	5.7
26.4	3.4	8.8
27.3	3.3	4.2
27.9	3.2	3.0
31.1	2.9	1.7
31.4	2.9	2.9
32.3	2.8	1.6
32.6	2.7	1.5
35.5	2.5	1.7
38.6	2.3	1.2

[00437] Example 5 of WO 2025/011259 describes preparation of resmetirom crystalline Form Type K65:

[00438] 10.1 mg of resmetirom was weighed into a vial, 0.2 mL of acetonitrile was added, sonicated at room temperature for about 1 minute, and centrifuged to obtain the resmetirom crystalline Form Type K65.

[00439] The XRPD pattern of resmetirom crystalline Form Type K65 obtained in this example is shown in FIG. 120, and the XRPD data are listed in Table 6 of WO 2025/011259.

[00440] Table 6 of WO 2025/011259 provides the following data:

Diffraction Angle 2 θ	d value	Intensity%
6.5	13.6	0.7
7.6	11.7	100.0
8.3	10.7	26.9
10.0	8.8	3.5
13.8	6.4	1.7
15.2	5.8	3.3
18.1	4.9	5.3
19.5	4.6	4.2
20.2	4.4	2.3
22.4	4.0	3.5
22.9	3.9	5.6
23.1	3.8	8.4
24.7	3.6	1.5
26.0	3.4	3.2
26.4	3.4	4.3
27.8	3.2	1.2
31.4	2.8	2.0
32.3	2.8	1.3
33.5	2.7	0.8
35.6	2.5	0.9
36.8	2.4	0.4
38.7	2.3	1.3

[00441] For example, one of the forms is Form Type K65 desolvate reported in WO 2025/011259.

[00442] Example 6 of WO 2025/011259 describes preparation of resmetirom crystalline Form Type K65 desolvate:

[00443] The crystalline Form Type K65 obtained in Example 4 was placed in a room temperature environment for about 5 h.

[00444] The XRPD pattern of resmetirom crystalline Form Type K65 desolvate obtained in this example is shown in FIG. 120, and the XRPD data are listed in Table 6 of WO 2025/011259.

[00445] Table 6 of WO 2025/011259 provides the following data:

Diffraction Angle 2 θ	d value	Intensity%
6.5	13.6	8.5
7.7	11.5	19.1
8.3	10.6	9.0
9.6	9.2	65.8
10.1	8.7	100.0
11.6	7.6	9.3
12.8	6.9	4.5
13.7	6.5	11.9
14.0	6.3	11.3
14.7	6.0	10.1
16.2	5.5	10.5
18.1	4.9	10.9
19.0	4.7	23.7
19.5	4.5	26.5
20.7	4.3	12.8
21.9	4.1	12.1
22.7	3.9	12.2
23.3	3.8	16.0
24.2	3.7	6.7
24.9	3.6	10.7
26.2	3.4	8.4
26.7	3.3	9.8
27.3	3.3	8.4
28.0	3.2	6.0
29.2	3.1	3.1
29.9	3.0	3.3
31.1	2.9	3.2
31.9	2.8	4.5
32.7	2.7	2.7
33.5	2.7	2.1
34.4	2.6	1.6
35.5	2.5	1.5
36.4	2.5	1.6
38.3	2.3	0.9
39.2	2.3	2.2

[00446] For example, one of the forms is Form R3-A reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00447] The crystalline Form R3-A may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 55; an X-ray powder diffraction pattern having peaks at $8.6^{\circ} \pm 0.2^{\circ}$, $9.3^{\circ} \pm 0.2^{\circ}$, $10.3^{\circ} \pm 0.2^{\circ}$,

16.9°±0.2° and 18.3°±0.2° 2-theta; a solid state ¹³C NMR spectrum with characteristic peaks at 161.7±0.2, 152.4±0.2, 135.1±0.2, 60.8±0.2 and 46.5±0.2 ppm; a solid state ¹³C NMR spectrum having the following chemical shift absolute differences from reference peak at 174.7 ppm ± 1 ppm: 13.0±0.1, 22.3±0.1, 39.6±0.1, 114.0±0.1 and 128.3±0.1 ppm; a solid state ¹³C NMR spectrum substantially as depicted in FIGS. 56, 57, or 58; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from 16.4°±0.2°, 20.1°±0.2°, 21.9°±0.2°, 24.8°±0.2° and 25.8°±0.2° 2-theta.

[00448] Example 22 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of resmetirom Form R3-A (resmetirom : L-proline Form R3-A):

[00449] Procedure A

[00450] 2-methoxy ethanol (3.5 ml, 26Vol) was added to L-proline (132 mg, 1.15 mmol) to give a slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Then, resmetirom (500 mg, 1.15 mmol) was added to the magnetically stirred clear hot solution at 80 °C to obtain a slurry. Next, the slurry was magnetically stirred at 80 °C to give a clear solution and after 15 minutes precipitation occurred. Next, the obtained slurry was cooled to room temperature and was magnetically stirred for 18 hours. Then the solid was filtered by Buchner and dried in vacuum oven at 45 °C for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 53.

[00451] Procedure B

[00452] 2-methoxy ethanol (0.66 ml, 55V) was added to L-proline (12 mg, 0.11 mmol) to give a slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain clear solution, followed by a hot mechanical filtration. Then, the obtained clear solution was placed in a 4 ml vial. Next, in another 4 ml vial, 2-methoxy ethanol (0.21 ml, 7V) was added to resmetirom (30 mg, 0.07 mmol) to give a slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain clear solution, followed by a hot mechanical filtration. Then, the resmetirom hot solution was added to the 4 ml vial that contained the L-Proline hot solution and the reaction was magnetically stirred at 80 °C for 15 minutes. Then, the clear solution was concentrated by rotor vapor. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom L-proline salt Form R3-A.

[00453] For example, one of the forms is Form RC1-A (resmetirom : nicotinamide) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00454] The crystalline Form RC1-A of resmetirom : nicotinamide may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 59; an X-ray powder diffraction pattern having peaks at $8.7^{\circ} \pm 0.2^{\circ}$, $18.6^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, $25.3^{\circ} \pm 0.2^{\circ}$ and $26.4^{\circ} \pm 0.2^{\circ}$ 2-theta; a solid state ^{13}C NMR spectrum with characteristic peaks at 159.9 ± 0.2 , 153.4 ± 0.2 , 136.2 ± 0.2 , 134.9 ± 0.2 and 119.1 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from reference peak at $170.2 \text{ ppm} \pm 1 \text{ ppm}$: 10.3 ± 0.1 , 16.8 ± 0.1 , 34.0 ± 0.1 , 35.3 ± 0.1 and 51.0 ± 0.1 ppm; a solid state ^{13}C NMR spectrum substantially as depicted in FIG. 60, 61, or 62 ; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $11.5^{\circ} \pm 0.2^{\circ}$, $12.6^{\circ} \pm 0.2^{\circ}$, $13.9^{\circ} \pm 0.2^{\circ}$, $20.1^{\circ} \pm 0.2^{\circ}$ and $22.0^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00455] Example 24 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form RC1-A (resmetirom : nicotinamide).

[00456] Procedure A

[00457] Resmetirom (200 mg, 0.46 mmol) was grinded by mortar and pestle with Nicotinamide (56.2 mg, 0.46 mmol, 1 eq.) for 1 minute. Dichloromethane was added to 50 mg of grinding mixture of resmetirom and nicotinamide to give slurry. The obtained slurry was seeded with 0.1-0.5% of resmetirom : nicotinamide Form RC1-A (prepared according to procedure B or C) and was magnetically stirred at room temperature for 18 hours. Then, the solid was separated by centrifuge and dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and the XRPD pattern is presented in FIG. 59.

[00458] Procedure B

[00459] 2-methoxy ethanol (0.25 ml, 5V) was added to resmetirom (50 mg, 0.115 mmol) to give slurry. The obtained slurry was stirred at 80° C. for 30 minutes to full dissolution of the solid. Next, nicotinamide (14.05 mg, 0.115 mmol, 1 eq.) was added to obtained hot clear solution to give slurry. Then, the obtained slurry was magnetically stirred at 80° C., for 30 min. to full dissolution of the solid. Next, the above mixture was dried in a vacuum oven at 45° C. for 18 hours to obtain yellow solid. Then, Dichloromethane (0.512 ml, 8V) was added to give slurry. The obtained slurry was magnetically stirred at 25° C. for 18 hours. Then the solid separated by centrifuge and dried in vacuum oven at 45° C. for 18 hours. The solid was analyzed by X-ray powder diffraction and characterized as resmetirom : nicotinamide Form RC1-A.

[00460] Procedure C

[00461] Resmetirom (50 mg, 0.115 mmol) was grinded by mortar and pestle with Nicotinamide (14.05 mg, 0.115 mmol, 1 eq.) for 1 minute. The obtained solids mixture was heated in 1.7 ml glass vial at 140° C. (10° C. higher than the melting point of co-former) for 2 hours. Then, the vial was cooled to 120° and heated at this temperature for 1 hour. Next, the vial was cooled to room temperature. The obtained solid was analyzed and characterized as resmetirom : nicotinamide Form RC1-A.

[00462] Procedure D

[00463] Dichloromethane (0.48 ml, 8V) was added to resmetirom methyltetrahydrofuran solvate (50 mg, 0.115 mmol) to give slurry. Next, nicotinamide (14 mg, 0.115 mmol, 1.0 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC1-A. Next, the slurry was magnetically stirred at room temperature for 4 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : nicotinamide crystal Form RC1-A.

[00464] Procedure E

[00465] Dichloromethane (0.48 ml, 8V) was added to resmetirom methylethyl ketone solvate (50 mg, 0.115 mmol) to give slurry. Next, nicotinamide (14 mg, 0.115 mmol, 1.0 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC1-A. Next, the slurry was magnetically stirred at room temperature for 3 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid

was analyzed by X-ray powder diffraction and identified as resmetirom : nicotinamide crystalline Form RC1-A.

[00466] For example, one of the forms is Form RC2-A (resmetirom : caffeine) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00467] The crystalline Form RC2-A of resmetirom: caffeine may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 63; an X-ray powder diffraction pattern having peaks at $6.0^{\circ} \pm 0.2^{\circ}$, $6.8^{\circ} \pm 0.2^{\circ}$, $10.4^{\circ} \pm 0.2^{\circ}$, $11.2^{\circ} \pm 0.2^{\circ}$ and $16.4^{\circ} \pm 0.2^{\circ}$ 2-theta; a solid state ^{13}C NMR spectrum with characteristic peaks at 139.5 ± 0.2 , 118.8 ± 0.2 , 106.7 ± 0.2 , 34.0 ± 0.2 and 29.6 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from reference peak at $161.0 \text{ ppm} \pm 1 \text{ ppm}$: 21.4 ± 0.1 , 42.2 ± 0.1 , 54.3 ± 0.1 , 127.0 ± 0.1 and 131.4 ± 0.1 ppm; a solid state ^{13}C NMR spectrum substantially as depicted in FIGS. 64, 65, or 66; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $14.6^{\circ} \pm 0.2^{\circ}$, $15.6^{\circ} \pm 0.2^{\circ}$, $17.8^{\circ} \pm 0.2^{\circ}$, $19.5^{\circ} \pm 0.2^{\circ}$ and $26.9^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00468] Example 25 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form RC2-A (resmetirom : caffeine).

[00469] Procedure A

[00470] 2-methoxy ethanol (0.2 ml, 6.7V) was added to resmetirom (30 mg, 0.07 mmol) to give a slurry. The obtained slurry was stirred at 80°C . during 30 minutes to full dissolution of the solid. Next, caffeine (13.4 mg, 0.07 mmol, 1 eq.) was added to obtained hot clear solution to give a slurry. Then, ethanol (0.2 ml, 6.7V) was added to the obtained slurry and was magnetically stirred at 80°C ., for 30 minutes to full dissolution of the solid. The mixture

was dried in a vacuum oven at 45° C. for 18 hours, to obtain yellow solid. Then, isopropanol (0.18 ml, 4V) was added to give slurry. The obtained slurry was magnetically stirred at 25° C. for 18 hours. Then the solid separated by centrifuge and dried in vacuum oven at 45° C. for 18 hours. The solid was analyzed by X-ray powder diffraction and the XRPD pattern is presented in FIG. 63.

[00471] Procedure B

[00472] Iso-propyl alcohol (0.45 ml, 6V) was added to resmetirom methyltetrahydrofuran solvate (50 mg, 0.115 mmol) to give slurry. Next, caffeine (24.2 mg, 0.126 mmol, 1.1 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC2-A. Next, the slurry was magnetically stirred at room temperature for 4 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : caffeine crystal Form RC2-A.

[00473] Procedure C

[00474] Iso-propyl alcohol (0.45 ml, 6V) was added to resmetirom methylethyl ketone solvate (50 mg, 0.115 mmol) to give slurry. Next, caffeine (24.2 mg, 0.126 mmol, 1.1 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC2-A. Next, the slurry was magnetically stirred at room temperature for 3 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : caffeine crystal Form RC2-A.

[00475] For example, one of the forms is Form RC2-B (resmetirom : caffeine) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00476] The crystalline Form RC2-B of resmetirom: caffeine may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 67; an X-ray powder diffraction pattern having peaks at $8.9^{\circ} \pm 0.2^{\circ}$, $10.6^{\circ} \pm 0.2^{\circ}$, $11.2^{\circ} \pm 0.2^{\circ}$, $14.5^{\circ} \pm 0.2^{\circ}$ and $17.1^{\circ} \pm 0.2^{\circ}$ 2-theta; a solid state ^{13}C NMR spectrum with characteristic peaks at 145.9 ± 0.2 , 142.7 ± 0.2 , 108.7 ± 0.2 , 33.5 ± 0.2 and 28.1 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from reference peak at $161.1 \text{ ppm} \pm 1 \text{ ppm}$: 15.2 ± 0.1 , 18.45 ± 0.1 , 52.4 ± 0.1 , 127.6 ± 0.1 and 133.0 ± 0.1 ppm; a solid state ^{13}C NMR spectrum substantially as depicted in FIGS. 68, 69, or 70; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $14.9^{\circ} \pm 0.2^{\circ}$, $20.0^{\circ} \pm 0.2^{\circ}$, $21.9^{\circ} \pm 0.2^{\circ}$, $24.5^{\circ} \pm 0.2^{\circ}$ and $28.2^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00477] Example 26 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form RC2-B (resmetirom : caffeine).

[00478] Procedure A

[00479] 2-methoxy ethanol (0.2 ml, 6.7V) was added to resmetirom (30 mg, 0.07 mmol) to give a slurry. The obtained slurry was stirred at 80°C . for 30 minutes to full dissolution of the solid. Next, caffeine (13.4 mg, 0.07 mmol, 1 eq.) was added to obtained hot clear solution to give slurry. Then, ethanol (0.2 ml, 6.7V) was added to the obtained slurry and was magnetically stirred at 80°C ., for 30 minutes to full dissolution of the solid. Next, the above mixture was dried in a vacuum oven at 45°C . for 18 hours, to obtain yellow solid. Then, toluene (0.18 ml, 4V) was added to give slurry. The obtained slurry was magnetically stirred

at 25° C. for 18 hours. Then the solid separated by centrifuge and dried in vacuum oven at 45° C. for 18 hours. The solid was analyzed by X-ray powder diffraction and the XRPD pattern is presented in FIG. 67.

[00480] Procedure B

[00481] Resmetirom (200 mg, 0.46 mmol) was grinded by mortar and pestle with caffeine (89 mg, 0.46 mmol, 1 eq.) for 1 minute. Toluene (4 Vol) was added to 250 mg of grinded mixture of resmetirom and caffeine to give a slurry. The obtained slurry was seeded with 0.1-0.5% of resmetirom : caffeine Form RC2-B (prepared according to procedure example 26, procedure A) and was magnetically stirred at 25° C. for 48 hours. Then, the solid was separated by centrifuge and dried in vacuum oven at 45° C. for 72 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as Form RC2-B.

[00482] Procedure C

[00483] Toluene (0.30 ml, 4V) was added to resmetirom methyltetrahydrofuran solvate (50 mg, 0.115 mmol) to give slurry. Next, caffeine (24.2 mg, 0.126 mmol, 1.1 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom : caffeine Form RC2-B. Next, the slurry was magnetically stirred at room temperature for 4 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : caffeine crystal Form RC2-B.

[00484] Procedure D

[00485] Toluene (0.30 ml, 4V) was added to resmetirom methylethyl ketone solvate (50 mg, 0.115 mmol) to give slurry. Next, caffeine (24.2 mg, 0.126 mmol, 1.1 eq.) was added to

the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom : caffeine Form RC2-B. Next, the slurry was magnetically stirred at room temperature for 3 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : caffeine crystal Form RC2-B.

[00486] For example, one of the forms is Form RC3-A (resmetirom : 2-picolinic acid) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00487] The crystalline Form RC3-A of resmetirom: 2-picolinic acid may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 71; an X-ray powder diffraction pattern having peaks at $6.0^{\circ} \pm 0.2^{\circ}$, $6.8^{\circ} \pm 0.2^{\circ}$, $12.9^{\circ} \pm 0.2^{\circ}$, $15.6^{\circ} \pm 0.2^{\circ}$ and $26.9^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $10.4^{\circ} \pm 0.2^{\circ}$, $14.8^{\circ} \pm 0.2^{\circ}$, $18.0^{\circ} \pm 0.2^{\circ}$, $18.5^{\circ} \pm 0.2^{\circ}$ and $24.7^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00488] Example 27 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form RC3-A (resmetirom : 2-picolinic acid).

[00489] Procedure A

[00490] 2-methoxy ethanol (0.375 ml, 7.5V) was added to resmetirom (50 mg, 0.115 mmol) to give a slurry. The obtained slurry was stirred at 80° C. during 30 minutes to full dissolution of the solid. Next, 2-picolinic acid (14.6 mg, 0.115 mmol, 1 eq.) was added to obtained hot clear solution to give a slurry. Then, the obtained slurry was magnetically stirred at 80° C., for 30 minutes to full dissolution of the solid. Next, the above mixture was dried in

a vacuum oven at 45° C. for 18 hours, to obtain yellow solid. The solid was analyzed by X-ray powder diffraction and the XRPD pattern is presented in FIG. 71.

[00491] Procedure B

[00492] Dichloromethane (0.5 ml, 8V) was added to resmetirom methyltetrahydrofuran solvate (50 mg, 0.115 mmol) to give slurry. Next, 2-picolinic acid (15.62 mg, 0.126 mmol, 1.1 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC3-A. Next, the slurry was magnetically stirred at room temperature for 4 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : 2-picolinic acid crystal Form RC3-A.

[00493] Procedure C

[00494] Dichloromethane (0.5 ml, 8V) was added to resmetirom methyltetrahydrofuran solvate (50 mg, 0.115 mmol) to give slurry. Next, 2-picolinic acid (15.62 mg, 0.126 mmol, 1.1 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC3-A. Next, the slurry was magnetically stirred at room temperature for 3 days. The precipitate was separated by centrifuge and then was dried in a vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : 2-picolinic acid crystal Form RC3-A.

[00495] For example, one of the forms is Form RC4-A (resmetirom : urea) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894. In some embodiments, the molar ratio of resmetirom and urea is about 1:1.

[00496] The crystalline Form RC4-A of resmetirom : urea may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 72; an X-ray powder diffraction pattern having peaks at $7.6^{\circ}\pm 0.2^{\circ}$, $12.6^{\circ}\pm 0.2^{\circ}$, $15.7^{\circ}\pm 0.2^{\circ}$, $16.4^{\circ}\pm 0.2^{\circ}$ and $16.9^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $15.2^{\circ}\pm 0.2^{\circ}$, $19.1^{\circ}\pm 0.2^{\circ}$, $19.6^{\circ}\pm 0.2^{\circ}$, $22.0^{\circ}\pm 0.2^{\circ}$ and $23.6^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00497] Example 28 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form RC4-A (resmetirom : urea).

[00498] Procedure A

[00499] Resmetirom (100 mg, 0.23 mmol) and urea (14 mg, 0.23 mmol) were dissolved in 2-methoxy ethanol (0.57 ml, 5.7 Vol) at 80°C . for 30 minutes. The obtained solution was dried in vacuum oven at 50°C . for 18 hours to give a solid and then was dried in vacuum oven at 80°C . for 18 hours. The obtained solid was characterized by X-ray powder diffraction as resmetirom : urea crystal Form RC4-A (FIG. 72).

[00500] Procedure B

[00501] Dichloromethane (0.48 ml, 8V) was added to resmetirom Me-THF solvate (50 mg, 0.115 mmol) to give slurry. Next, urea (7.7 mg, 0.128 mmol, 1.1 eq.) was added to obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and then was seeded with 0.1-0.5% of resmetirom Form RC4-A. The slurry was magnetically stirred at room temperature for 4 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45°C . for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : urea crystal Form RC4-A.

[00502] Procedure C

[00503] Dichloromethane (0.46 ml, 8V) was added to resmetirom methylethyl ketone solvate (50 mg, 0.115 mmol) to give slurry. Next, urea (7.7 mg, 0.128 mmol, 1.1 eq.) was added to the obtained slurry. Then, the obtained slurry was magnetically stirred at room temperature, and was seeded with 0.1-0.5% of resmetirom Form RC4-A. Next, this slurry was magnetically stirred at room temperature for 3 days. The precipitate was separated by centrifuge and then was dried in vacuum oven at 45° C. for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : urea crystal Form RC4-A.

[00504] For example, one of the forms is Form R1-A (resmetirom : N-methylmorpholine salt) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00505] The crystalline Form R1-A of resmetirom : N-methylmorpholine salt may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 73 ; an X-ray powder diffraction pattern having peaks at $8.2^{\circ} \pm 0.2^{\circ}$, $16.5^{\circ} \pm 0.2^{\circ}$, $17.8^{\circ} \pm 0.2^{\circ}$, $18.6^{\circ} \pm 0.2^{\circ}$ and $21.5^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $10.0^{\circ} \pm 0.2^{\circ}$, $14.5^{\circ} \pm 0.2^{\circ}$, $20.2^{\circ} \pm 0.2^{\circ}$, $22.4^{\circ} \pm 0.2^{\circ}$ and $27.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00506] Example 20 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form R1-A (resmetirom : N-methylmorpholine salt).

[00507] Procedure A

[00508] N-methylmorpholine [4-methylmorpholine] (4.0 ml, 20V) was added to resmetirom (200 mg, 0.26 mmol) to obtain a slurry. The slurry was magnetically stirred at

room temperature over a period of 48 hours. Next the solid was separated by centrifuge and dried in vacuum oven at 45° C. for 18 hours and was then analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 73.

[00509] For example, one of the forms is Form R2-A (resmetirom : piperazine salt) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00510] The crystalline Form R2-A of resmetirom : piperazine salt may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 74; an X-ray powder diffraction pattern having peaks at $10.7^{\circ}\pm 0.2^{\circ}$, $15.7^{\circ}\pm 0.2^{\circ}$, $19.5^{\circ}\pm 0.2^{\circ}$, $22.0^{\circ}\pm 0.2^{\circ}$ and $23.9^{\circ}\pm 0.2^{\circ}$ 2-theta; a solid state ^{13}C NMR spectrum with characteristic peaks at 161.1 ± 0.2 , 152.0 ± 0.2 , 138.0 ± 0.2 , 40.9 ± 0.2 and 39.9 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from reference peak at $164.6\text{ ppm}\pm 1\text{ ppm}$: 3.5 ± 0.1 , 12.6 ± 0.1 , 26.6 ± 0.1 , 123.7 ± 0.1 and 124.7 ± 0.1 ppm; a solid state ^{13}C NMR spectrum substantially as depicted in FIGS. 75, 76, or 77; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $12.0^{\circ}\pm 0.2^{\circ}$, $12.3^{\circ}\pm 0.2^{\circ}$, $12.6^{\circ}\pm 0.2^{\circ}$, $17.1^{\circ}\pm 0.2^{\circ}$ and $21.5^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00511] Example 21 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form R2-A (resmetirom : piperazine salt).

[00512] Procedure A

[00513] 2-methoxy ethanol (4.2 ml, 35.3V) was added to piperazine (119 mg, 1.38 mmol) to give a slurry. The slurry was magnetically stirred at 80° C. over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Then, resmetirom (600 mg, 1.38 mmol) was added to the magnetically stirring clear solution at 80° C. to give slurry.

Next, the slurry was magnetically stirred at 80° C. to give a clear solution and after 15 minutes a solid precipitation occurred. Next, obtained slurry was cooled to room temperature and then magnetically stirred at room temperature for 18 hours. Then the obtained solid was separated by centrifuge, dried in vacuum oven at 45° C. for 18 hours and analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 74.

[00514] Procedure B

[00515] 2-methoxy ethanol (0.42 ml, 70V) was added to piperazine (6 mg, 0.07 mmol) to give a slurry. The slurry was magnetically stirred at 80° C. over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Then, the obtained clear solution was placed in a 4 ml vial. Next, in another 4 ml vial, 2-methoxy ethanol (0.25 ml, 8.3V) was added to resmetirom (30 mg, 0.07 mmol) to give a slurry. The slurry was magnetically stirred at 80° C. over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Then, the resmetirom hot solution was added to 4 ml vial that contains the Piperazine hot solution and the reaction was magnetically stirred at 80° C. for 15 minutes. Then, the clear solution was concentrated in vacuum oven at 45° C. for 24 hours. The obtained solid was analyzed by X-ray powder diffraction and identified as resmetirom : piperazine salt form R2-A.

[00516] For example, one of the forms is Form R4-A (resmetirom : benzathine salt) reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00517] The crystalline Form R4-A of resmetirom : benzathine salt may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 78; an X-ray powder diffraction pattern having peaks at $8.8^{\circ} \pm 0.2^{\circ}$, $13.0^{\circ} \pm 0.2^{\circ}$, $17.6^{\circ} \pm 0.2^{\circ}$, $20.7^{\circ} \pm 0.2^{\circ}$, $22.3^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these

data. The X-ray powder diffraction pattern may have any one, two, three, four or five additional peaks selected from $11.1^{\circ}\pm 0.2^{\circ}$, $11.4^{\circ}\pm 0.2^{\circ}$, $17.1^{\circ}\pm 0.2^{\circ}$, $18.7^{\circ}\pm 0.2^{\circ}$ and $23.7^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00518] Example 23 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form R2-A (resmetirom : benzathine salt).

[00519] Procedure A

[00520] Ethanol (45 ml, 75V) was added to resmetirom (0.6 grams, 1.38 mmol) to give a slurry. The obtained slurry was heated to 75°C . and magnetically stirred at this temperature for 30 minutes to obtain a clear solution, followed a hot mechanical filtration. Then, benzathine (0.663 ml, 2.76 mmol) was added dropwise to the filtrated solution at 75°C . while magnetically stirred. Next, the obtained clear mixture was cooled to room temperature to give slurry and was stirred at room temperature for 18 hours. The obtained solid was filtered by Buchner and then dried in vacuum oven at 45°C . for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 78.

[00521] For example, one of the forms is Form 2 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00522] The crystalline Form 2 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 88; an X-ray powder diffraction pattern having peaks at $6.9^{\circ}\pm 0.2^{\circ}$, $10.0^{\circ}\pm 0.2^{\circ}$, $14.1^{\circ}\pm 0.2^{\circ}$, $19.1^{\circ}\pm 0.2^{\circ}$, and $21.9^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.0^{\circ}\pm 0.2^{\circ}$, $15.7^{\circ}\pm 0.2^{\circ}$, $22.7^{\circ}\pm 0.2^{\circ}$, $23.3^{\circ}\pm 0.2^{\circ}$, and $25.2^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00523] Example 2 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 2.

[00524] Procedure A

[00525] Methyl isopropyl ketone (MIPK) (1.25 ml, 50V) was added to resmetirom (25 mg, 0.06 mmol) to obtain a slurry. The slurry was heated to 80 °C and magnetically stirred at 80 °C over a period of 30 minutes to obtain complete dissolution, followed by a hot mechanical filtration. Next, diethyl ether as anti-solvent (5.6 ml) was added dropwise to the stirred clear solution at 80 °C. The obtained clear solution was stirred at 80 °C for 1 hour and then cooled to room temperature. Next, the solution was magnetically stirred at RT over 48 hours to obtain a solid precipitate. The solid was then separated by centrifuge and analyzed by X-ray powder diffraction. The XRPD pattern is presented in FIG. 88.

[00526] Procedure B

[00527] Methyl isopropyl ketone (MIPK) (4.0 ml, 20V) was added to resmetirom (200 mg, and 0.46 mmol) to give a slurry. The obtained slurry was heated to 80 °C and stirred at 80 °C temperature for a period of 48 hours. Then the slurry was cooled to room temperature and separated by centrifuge. Next, the obtained solid was dried in a vacuum oven at 25 °C for 2 hours and was analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 2.

[00528] For example, one of the forms is Form 3 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00529] The crystalline Form 3 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 84; an X-ray powder diffraction pattern having peaks at $6.9^{\circ} \pm 0.2^{\circ}$, $13.8^{\circ} \pm 0.2^{\circ}$, $15.0^{\circ} \pm 0.2^{\circ}$, $20.0^{\circ} \pm 0.2^{\circ}$,

and $20.8^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.1^{\circ}\pm 0.2^{\circ}$, $17.4^{\circ}\pm 0.2^{\circ}$, $17.8^{\circ}\pm 0.2^{\circ}$, $19.0^{\circ}\pm 0.2^{\circ}$, and $23.6^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00530] Example 3 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 3.

[00531] Procedure A

[00532] Dioxane (1.7 ml, 57V) was added to resmetirom (30 mg, 0.07 mmol) to obtain a slurry. The slurry was heated to 70° C. and magnetically stirred at 70° C. for a period of 30 minutes to obtain complete dissolution, followed by a hot mechanical filtration. Next, diethyl ether as anti-solvent (6.8 ml) was added dropwise to the stirred clear solution at 80° C. to obtain a solid precipitate. The obtained slurry was magnetically stirred at 80° C. for 1 hour and then cooled to room temperature with stirring. Next, the obtained slurry was magnetically stirred at room temperature for 18 hours. The solid was then separated by centrifuge and analyzed by XRPD. The obtained XRPD pattern is presented in FIG. 84.

[00533] Procedure B

[00534] Dioxane (2.0 ml, 10V) was added to resmetirom (200 mg, and 0.46 mmol) to give a slurry. The obtained slurry was heated to 80° C. and magnetically stirred at 80° C. for a period of 48 hours. Then, the slurry was cooled to room temperature and separated by centrifuge. The obtained solid was dried in a vacuum oven at 25° C. for 2 hours. The solid was analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 3.

[00535] For example, one of the forms is Form 4 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00536] The crystalline Form 4 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 89; an X-ray powder diffraction pattern having peaks at $11.5^{\circ} \pm 0.2^{\circ}$, $14.2^{\circ} \pm 0.2^{\circ}$, $18.0^{\circ} \pm 0.2^{\circ}$, $22.0^{\circ} \pm 0.2^{\circ}$, and $25.4^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.1^{\circ} \pm 0.2^{\circ}$, $12.5^{\circ} \pm 0.2^{\circ}$, $15.2^{\circ} \pm 0.2^{\circ}$, $21.0^{\circ} \pm 0.2^{\circ}$, and $23.0^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00537] Example 4 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 4.

[00538] Procedure A

[00539] Anisole (4.0 ml, 20V) was added to resmetirom (200 mg, and 0.46 mmol) to obtain a slurry. The slurry was heated to 80 °C and stirred at 80 °C for a period of 48 hours. Then, the slurry was separated by centrifuge. The obtained solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 89.

[00540] For example, one of the forms is Form 6 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00541] The crystalline Form 6 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 90; an X-ray powder diffraction pattern having peaks at $5.4^{\circ} \pm 0.2^{\circ}$, $8.5^{\circ} \pm 0.2^{\circ}$, $10.9^{\circ} \pm 0.2^{\circ}$, $16.4^{\circ} \pm 0.2^{\circ}$, and $23.9^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $19.1^{\circ} \pm 0.2^{\circ}$, $19.9^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, $22.3^{\circ} \pm 0.2^{\circ}$, and $25.7^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00542] Example 5 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 6.

[00543] Procedure A

[00544] N,N-Dimethylformamide (DMF) (1.3 ml, 4.3 V) was added to resmetirom (30 mg, 0.07 mmol) to obtain a slurry. The slurry was heated to 80 °C and magnetically stirred at 80 °C for a period of 30 minutes to obtain complete dissolution, followed by a hot mechanical filtration. Next, water as anti-solvent (2.6 ml) was added dropwise to the stirred clear solution at 80 °C to obtain a solid precipitate. The obtained slurry was stirred at 80 °C for 1 hour and cooled to room temperature. Next, the slurry was magnetically stirred at room temperature for 18 hours. The solid was then separated by centrifuge and was dried in a vacuum oven at 25 °C for 18 hours. The obtained solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 90.

[00545] For example, one of the forms is Form 7 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00546] The crystalline Form 7 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 91; an X-ray powder diffraction pattern having peaks at $6.1^{\circ} \pm 0.2^{\circ}$, $11.8^{\circ} \pm 0.2^{\circ}$, $14.6^{\circ} \pm 0.2^{\circ}$, $19.1^{\circ} \pm 0.2^{\circ}$, and $26.6^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $11.0^{\circ} \pm 0.2^{\circ}$, $20.6^{\circ} \pm 0.2^{\circ}$, $21.2^{\circ} \pm 0.2^{\circ}$, $23.2^{\circ} \pm 0.2^{\circ}$, and $25.7^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00547] Example 6 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 7.

[00548] Procedure A

[00549] Acetyl acetone (0.85 ml, 30V) was added to resmetirom (30 mg, 0.07 mmol) to obtain a slurry. The slurry was heated to 80 °C and magnetically stirred at 80 °C over a

period of 30 minutes to obtain complete dissolution, followed by a hot mechanical filtration. Next, hexane as anti-solvent (2.55 ml) was added dropwise to the stirred clear solution at 80 °C to obtain a solid precipitate. The obtained slurry was stirred at 80 °C for 1 hour and cooled to room temperature. Next, the slurry was magnetically stirred at room temperature during 18 hours. The solid was then separated by centrifuge analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 91.

[00550] Procedure B

[00551] Acetyl acetone (4.0 ml, 20V) was added to resmetirom (200 mg, and 0.46 mmol) to give a slurry. The obtained slurry was stirred at room temperature over a period of 48 hours. Then, the slurry was separated by centrifuge and dried in vacuum oven at 25 °C for 2 hours. The solid was analyzed by XRPD and identified as resmetirom crystalline Form 7.

[00552] For example, one of the forms is Form 8 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00553] The crystalline Form 8 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 92; an X-ray powder diffraction pattern having peaks at $11.0^{\circ} \pm 0.2^{\circ}$, $12.2^{\circ} \pm 0.2^{\circ}$, $17.5^{\circ} \pm 0.2^{\circ}$, $20.7^{\circ} \pm 0.2^{\circ}$, and $22.0^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $10.3^{\circ} \pm 0.2^{\circ}$, $14.1^{\circ} \pm 0.2^{\circ}$, $15.4^{\circ} \pm 0.2^{\circ}$, $23.9^{\circ} \pm 0.2^{\circ}$, and $25.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00554] Example 7 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 8.

[00555] Procedure A

[00556] Acetyl acetone (0.85 ml, 30V) was added to resmetirom (30 mg, 0.07 mmol) to obtain a slurry. The slurry was heated to 80 °C and was magnetically stirred at 80 °C over a period of 30 minutes to obtain complete dissolution, followed by a hot mechanical filtration. Next, propionitrile as anti-solvent (3.4 ml) was added dropwise to the stirred clear solution at 80 °C to obtain a solid precipitate. The obtained slurry was magnetically stirred at 80 °C for 1 hour and then cooled to room temperature. Next, the obtained slurry was magnetically stirred at room temperature for 18 hours. The solid was then separated by centrifuge and analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 8.

[00557] Procedure B

[00558] Propionitrile (0.80 ml, 20V) was added to resmetirom (40 mg, and 0.09 mmol) to give a slurry. The obtained slurry was heated to 80 °C and stirred at 80 °C over a period of 48 hours. Then, the slurry was left to cool to room temperature, separated by centrifuge and dried in vacuum oven at 25 °C for 2 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 92.

[00559] For example, one of the forms is Form 9 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00560] The crystalline Form 9 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 85; an X-ray powder diffraction pattern having peaks at $8.7^{\circ} \pm 0.2^{\circ}$, $13.4^{\circ} \pm 0.2^{\circ}$, $14.8^{\circ} \pm 0.2^{\circ}$, $15.5^{\circ} \pm 0.2^{\circ}$, and $22.8^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $11.1^{\circ} \pm 0.2^{\circ}$, $19.8^{\circ} \pm 0.2^{\circ}$, $20.3^{\circ} \pm 0.2^{\circ}$, $21.5^{\circ} \pm 0.2^{\circ}$, and $24.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00561] Example 8 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 9.

[00562] Procedure A

[00563] Nitrobenzene (2.0 ml, 10V) was added to resmetirom (200 mg, and 0.46 mmol) to give a slurry. The obtained slurry was heated to 80° C. and stirred at 80° C. over a period of 48 hours. Then, the slurry was left to cool to room temperature, separated by centrifuge and dried in vacuum oven at 25° C. for 2 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 85.

[00564] For example, one of the forms is Form 10 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00565] The crystalline Form 10 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 93; an X-ray powder diffraction pattern having peaks at $12.5^{\circ} \pm 0.2^{\circ}$, $14.9^{\circ} \pm 0.2^{\circ}$, $20.4^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, and $23.4^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $7.4^{\circ} \pm 0.2^{\circ}$, $13.4^{\circ} \pm 0.2^{\circ}$, $16.0^{\circ} \pm 0.2^{\circ}$, $22.5^{\circ} \pm 0.2^{\circ}$, and $24.8^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00566] Example 9 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 10.

[00567] Procedure A

[00568] Di(ethylene glycol)ethyl ether (2.0 ml, 10V) was added to resmetirom (200 mg, and 0.46 mmol) to give a slurry. The obtained slurry was stirred at room temperature over a

period of 48 hours. Then, the slurry was separated by centrifuge, analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 93.

[00569] For example, one of the forms is Form 11 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00570] The crystalline Form 11 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 94; an X-ray powder diffraction pattern having peaks at $5.9^{\circ}\pm 0.2^{\circ}$, $10.1^{\circ}\pm 0.2^{\circ}$, $11.8^{\circ}\pm 0.2^{\circ}$, $19.7^{\circ}\pm 0.2^{\circ}$, and $25.1^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.5^{\circ}\pm 0.2^{\circ}$, $16.4^{\circ}\pm 0.2^{\circ}$, $16.8^{\circ}\pm 0.2^{\circ}$, $17.9^{\circ}\pm 0.2^{\circ}$, and $22.2^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00571] Example 10 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 11.

[00572] Procedure A

[00573] 1,3-Dioxolane (1 ml, 33.3V) was added to resmetirom (30 mg, 0.07 mmol) and stirred at room temperature to give a clear solution. The clear solution was mechanically filtered and was left for 4 days for slow evaporation at room temperature. The obtained solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 94.

[00574] For example, one of the forms is Form 13 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00575] The crystalline Form 13 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 95; an X-

ray powder diffraction pattern having peaks at $14.4^{\circ} \pm 0.2^{\circ}$, $17.0^{\circ} \pm 0.2^{\circ}$, $20.0^{\circ} \pm 0.2^{\circ}$, $22.7^{\circ} \pm 0.2^{\circ}$, and $24.5^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $7.3^{\circ} \pm 0.2^{\circ}$, $13.0^{\circ} \pm 0.2^{\circ}$, $17.9^{\circ} \pm 0.2^{\circ}$, $18.7^{\circ} \pm 0.2^{\circ}$, and $19.0^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00576] Example 11 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 13.

[00577] Procedure A

[00578] Methyl ethyl ketone (3.33 ml, 33.3V) was added to resmetirom (100 mg, 0.23 mmol) to obtain a slurry. The slurry was heated to 60 °C and magnetically stirred at 60 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Next, di chloroethane as anti-solvent (10 ml) was added dropwise to the stirred clear solution at 60 °C to obtain a solid precipitate. The obtained slurry was stirred at 60 °C for 1 hour and cooled to room temperature. Next, the slurry was magnetically stirred at room temperature for 18 hours. The solid was then separated by centrifuge and dried in vacuum oven at 25 °C for 2 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 95.

[00579] Procedure B

[00580] 2-methoxy ethanol (0.15 ml, 5V) was added to resmetirom (30 mg, 0.07 mmol) to obtain a slurry. The slurry was heated to 80 °C and magnetically stirred at 80 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Next, di chloroethane as anti-solvent (0.6 ml) was added dropwise to the stirred clear solution at 80 °C to obtain a solid precipitate. The obtained slurry was stirred at 80 °C for 1 hour and cooled to room temperature. Next, the slurry was magnetically stirred at room temperature for 18

hours and was then separated by centrifuge. The solid was analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 13.

[00581] For example, one of the forms is Form 14 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00582] The crystalline Form 14 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 96; an X-ray powder diffraction pattern having peaks at $9.8^{\circ} \pm 0.2^{\circ}$, $11.1^{\circ} \pm 0.2^{\circ}$, and $23.2^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data.

[00583] Example 12 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 14.

[00584] Procedure A

[00585] Methyl tetrahydrofuran (3.3 ml, 10V) was added to resmetirom (100 mg, and 0.23 mmol) to give a slurry. The obtained slurry was stirred at 75 °C for 30 minutes to full dissolution of the solid, followed by a hot mechanical filtration. Next, the filtered clear solution was magnetically stirred at 4 °C for 18 hours to obtain a solid precipitate. The solid was then separated by centrifuge and dried in vacuum oven at 25 °C for 3 hours. The solid was analyzed by X-ray powder diffraction and the obtained pattern is presented in FIG. 96.

[00586] Procedure B

[00587] Methyl tetrahydrofuran (5 ml, 10V) was added to resmetirom (500 mg, and 0.15 mmol) to give a slurry. The obtained slurry was heated to 60 °C and magnetically stirred at this temperature for 48 hours. Then, the slurry was cooled to room temperature and separated

by centrifuge. The solid was dried in vacuum oven at 25 °C for 3 hours. The solid was analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 14.

[00588] For example, one of the forms is Form 15 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00589] The crystalline Form 15 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 97; an X-ray powder diffraction pattern having peaks at $10.0^{\circ} \pm 0.2^{\circ}$, $11.6^{\circ} \pm 0.2^{\circ}$, $13.0^{\circ} \pm 0.2^{\circ}$, $18.6^{\circ} \pm 0.2^{\circ}$, and $23.8^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $10.7^{\circ} \pm 0.2^{\circ}$, $17.0^{\circ} \pm 0.2^{\circ}$, $18.2^{\circ} \pm 0.2^{\circ}$, $22.0^{\circ} \pm 0.2^{\circ}$, and $23.3^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00590] Example 13 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 15.

[00591] Procedure A

[00592] Propionic acid (15 ml, 50V) was added to Resmetirom (300 mg, 0.7 mmol) to obtain a slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Next, the filtered clear solution was magnetically stirred at 4 °C for 72 hours to obtain a solid precipitate. The solid was then separated by centrifuge and dried in vacuum oven at 25 °C for 3 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 97.

[00593] For example, one of the forms is Form 16 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00594] The crystalline Form 16 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 98; an X-ray powder diffraction pattern having peaks at $8.7^{\circ}\pm 0.2^{\circ}$, $11.5^{\circ}\pm 0.2^{\circ}$, $13.3^{\circ}\pm 0.2^{\circ}$, $14.7^{\circ}\pm 0.2^{\circ}$, and $26.0^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $10.2^{\circ}\pm 0.2^{\circ}$, $12.8^{\circ}\pm 0.2^{\circ}$, $19.5^{\circ}\pm 0.2^{\circ}$, $25.3^{\circ}\pm 0.2^{\circ}$, and $26.4^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00595] Example 14 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 16.

[00596] Procedure A

[00597] Propionic acid (15 ml, 50V) was added to resmetirom (300 mg, 0.7 mmol) to obtain a slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain clear solution, followed by a hot mechanical filtration. Next, the filtered clear solution was magnetically stirred at 4 °C for 72 hours to obtain a solid precipitation. Next, the saturated solution was separated by centrifuge from the solid and then was concentrated by slow evaporation of the solvent at 80 °C for 48 hours to give a solid. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 99.

[00598] For example, one of the forms is Form 17 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00599] The crystalline Form 17 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 99; an X-ray powder diffraction pattern having peaks at $6.8^{\circ}\pm 0.2^{\circ}$, $8.7^{\circ}\pm 0.2^{\circ}$, $11.4^{\circ}\pm 0.2^{\circ}$, $14.5^{\circ}\pm 0.2^{\circ}$, and $29.7^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction

pattern may have any one, two, three, four, or five additional peaks selected from $10.1^{\circ} \pm 0.2^{\circ}$, $15.0^{\circ} \pm 0.2^{\circ}$, $15.4^{\circ} \pm 0.2^{\circ}$, $19.7^{\circ} \pm 0.2^{\circ}$, and $20.0^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00600] Example 15 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 17.

[00601] Procedure A

[00602] Methyl ethyl ketone (2 ml, 20V) was added to resmetirom (100 mg, 0.23 mmol) to obtain a slurry. The slurry was magnetically stirred at 72 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Next, the filtered clear solution was magnetically stirred at 4 °C during 18h to obtain a solid precipitate. The solid was then separated by centrifuge and dried in vacuum oven at 25 °C for 2 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 99.

[00603] Procedure B

[00604] Methyl ethyl ketone (20 ml, 20V) was added to resmetirom (1000 mg, 2.3 mmol) to obtain a slurry. The slurry was magnetically stirred at 72 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Next, the filtered clear solution was concentrated by rotor vapor to give a solid. The solid was dried in vacuum oven at 25 °C during 18 hours. The solid was analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 17.

[00605] For example, one of the forms is Form 19 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00606] The crystalline Form 19 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 100; an X-ray powder diffraction pattern having peaks at $8.5^{\circ} \pm 0.2^{\circ}$, $9.1^{\circ} \pm 0.2^{\circ}$, $12.6^{\circ} \pm 0.2^{\circ}$, $14.5^{\circ} \pm 0.2^{\circ}$, and $15.2^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.1^{\circ} \pm 0.2^{\circ}$, $15.7^{\circ} \pm 0.2^{\circ}$, $20.8^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, and $25.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00607] Example 16 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 19.

[00608] Procedure A

[00609] Methyl ethyl ketone (2.0 ml, 20V) was added to resmetirom (100 mg, 0.23 mmol) to obtain a slurry. The slurry was magnetically stirred at 70 °C over a period of 30 minutes to obtain a clear solution, followed by a hot mechanical filtration. Next, toluene as anti-solvent (8 ml) was added dropwise to the stirred clear solution at 70 °C to obtain a solid precipitate. The obtained slurry was stirred at 70 °C for 1 hour and cooled to room temperature. Next, the slurry was magnetically stirred at room temperature for 18 hours. The solid was then separated by centrifuge and dried in vacuum oven at 25 °C for 3 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 100.

[00610] Procedure B

[00611] Dimethylacetamide (DMAc) (2.5 ml, 5V) was added to resmetirom (500 mg, 1.15 mmol) to obtain a slurry. The slurry was heated to 80 °C and magnetically stirred at 80 °C over a period of 30 minutes to obtain complete dissolution, followed by a hot mechanical filtration. Next, isopropyl alcohol (IPA) as anti-solvent (10 ml) was added drop-wise to the

stirred clear solution at 80 °C. The obtained clear solution was stirred at 80 °C for 1 hour and then cooled to room temperature. Next, the solution was magnetically stirred at RT over 18 hours to obtain a solid precipitate. The solid was then separated by centrifuge, dried in vacuum oven at 25 °C for 18 hours.

[00612] Toluene (2.0 ml, 20V) was added to resmetirom obtained above (100 mg, and 0.23 mmol) to give a slurry. The obtained slurry was stirred at 80 °C over a period of 18 hours. Then, the slurry was cooled to room temperature, filtered by centrifuge, dried in vacuum oven at 45 °C during 18 hours and was analyzed by X-ray powder diffraction and identified as resmetirom crystalline Form 19.

[00613] For example, one of the forms is Form 20 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00614] The crystalline Form 20 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 101; an X-ray powder diffraction pattern having peaks at $6.5^{\circ} \pm 0.2^{\circ}$, $9.6^{\circ} \pm 0.2^{\circ}$, $10.1^{\circ} \pm 0.2^{\circ}$, $19.0^{\circ} \pm 0.2^{\circ}$, and $23.3^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data; a solid state ^{13}C NMR spectrum with characteristic peaks at 161.0 ± 0.2 , 155.0 ± 0.2 , 151.1 ± 0.2 , 145.3 ± 0.2 , and 121.8 ± 0.2 ppm; a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from reference peak at 162.4 ± 1 ppm: 1.4 ± 0.1 , 7.5 ± 0.1 , 11.3 ± 0.1 , 17.1 ± 0.1 , and 40.6 ± 0.1 ppm; a solid state ^{13}C NMR spectrum substantially as depicted in FIGS. 104, 105, or 106; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $11.6^{\circ} \pm 0.2^{\circ}$, $16.2^{\circ} \pm 0.2^{\circ}$, $19.5^{\circ} \pm 0.2^{\circ}$, $21.8^{\circ} \pm 0.2^{\circ}$, and $24.9^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00615] Example 17 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 20.

[00616] Procedure A

[00617] Acetonitrile (66 ml, 132V) was added to resmetirom (500 mg, 1.15 mmol) to obtain a slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain a cloudy solution, followed by a hot mechanical filtration. Next, the filtered clear solution was magnetically stirred at room temperature during 18h to obtain a solid precipitate. The solid was then separated by Buchner and dried in vacuum oven at 45 °C for 72 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 101.

[00618] For example, one of the forms is Form 21 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00619] The crystalline Form 21 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 102; an X-ray powder diffraction pattern having peaks at $7.0^{\circ} \pm 0.2^{\circ}$, $14.1^{\circ} \pm 0.2^{\circ}$, $15.9^{\circ} \pm 0.2^{\circ}$, $20.2^{\circ} \pm 0.2^{\circ}$, and $28.4^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.4^{\circ} \pm 0.2^{\circ}$, $17.0^{\circ} \pm 0.2^{\circ}$, $25.1^{\circ} \pm 0.2^{\circ}$, $25.8^{\circ} \pm 0.2^{\circ}$, and $29.3^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00620] Example 18 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 21.

[00621] Procedure A

[00622] Acetonitrile (10.8 ml, 120V) was added to resmetirom (100 mg, 0.23 mmol) to obtain slurry. The slurry was magnetically stirred at 80 °C over a period of 30 minutes to obtain clear solution, followed by a hot mechanical filtration. Next, the filtered clear solution was concentrated by rotor vapor to give a solid. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 102.

[00623] For example, one of the forms is Form 22 reported in U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894.

[00624] The crystalline Form 22 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 103; an X-ray powder diffraction pattern having peaks at $5.6^{\circ} \pm 0.2^{\circ}$, $15.0^{\circ} \pm 0.2^{\circ}$, $16.6^{\circ} \pm 0.2^{\circ}$, $17.4^{\circ} \pm 0.2^{\circ}$, and $23.0^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $11.5^{\circ} \pm 0.2^{\circ}$, $23.3^{\circ} \pm 0.2^{\circ}$, $26.1^{\circ} \pm 0.2^{\circ}$, $27.6^{\circ} \pm 0.2^{\circ}$, and $28.9^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00625] Example 18 of U.S. Patent Application Publication No. 2023/0364099 and WO 2022/086894 describes preparation of Form 22.

[00626] Procedure A

[00627] Ethylene glycol (10 ml, 20V) was added to resmetirom (500 mg, 1.15 mmol) to give a slurry. The obtained slurry was stirred at room temperature for 48 hours. Next, the obtained solid was separated by centrifuge and dried in vacuum oven at 45 °C for 18 hours. The solid was analyzed by X-ray powder diffraction and the obtained XRPD pattern is presented in FIG. 103.

[00628] Resmetirom crystalline Forms 2, 3, 5 and 20 may also be used for preparation of resmetirom crystalline Form 22.

[00629] For example, one of the forms is an amorphous Form E1 reported in U.S. Patent Application Publication No. 2024/0423993.

[00630] The amorphous Form E1 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 110.

[00631] Example-1 of U.S. Patent Application Publication No. 2024/0423993 describes preparation of the amorphous Form E1.

[00632] Methanol (3000 ml) and resmetirom (100 g) were added in RB flask at 25° C. to 35° C. and reaction mass was stirred for 15 to 20 minutes to get clear solution. The reaction mass was assembled in spray dryer. The reaction mass was spray dried under below conditions. The product was collected from cyclone and was further dried at 40° C. to 50° C. under vacuum for 4 hours to get amorphous form of resmetirom.

[00633] For example, one of the forms is an amorphous Form E2 reported in U.S. Patent Application Publication No. 2024/0423993.

[00634] The amorphous Form E2 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 110.

[00635] Example-2 of U.S. Patent Application Publication No. 2024/0423993 describes preparation of amorphous Form E2.

[00636] Methanol (300 ml) and resmetirom (100 g) were added at 25° C. to 35° C. The reaction mass was stirred for 10 to 15 minutes to get a clear solution. Methanol was distilled out under vacuum below 45° C. from above reaction mass, n-Heptane (500 ml) was added to residue at 25° C. to 35° C. The reaction mass was stirred for 15 to 20 minutes, filtered and washed with n-Heptane (100 ml) to get amorphous form of resmetirom.

[00637] For example, one of the forms is an amorphous solid dispersion Form E3 reported in U.S. Patent Application Publication No. 2024/0423993.

[00638] The amorphous solid dispersion Form E3 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 111.

[00639] Example-3 of U.S. Patent Application Publication No. 2024/0423993 describes preparation of the amorphous solid dispersion Form E3.

[00640] Methanol (3000 ml), resmetirom (100 g) and copovidone (Kollidone VA 64) (100 g) were added in RB flask at 25° C. to 35° C. and reaction mass was stirred for 15 to 20 minutes to get clear solution. The reaction mass was assembled in spray dryer. The reaction mass was spray dried under below conditions. The product was collected from cyclone and was further dried at 40° C. to 50° C. under vacuum for 4 hours to get amorphous solid dispersion of resmetirom.

[00641] For example, one of the forms is an amorphous solid dispersion Form E4 reported in U.S. Patent Application Publication No. 2024/0423993.

[00642] The amorphous solid dispersion Form E4 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 111.

[00643] Example-4 of U.S. Patent Application Publication No. 2024/0423993 describes preparation of the amorphous solid dispersion Form E4.

[00644] Methanol (3000 ml) and resmetirom (100 g) were added at 25° C. to 35° C. The reaction mass was stirred for 15 to 20 minutes to get a clear solution, copovidone (Kollidone

VA 64) (100 g) was added to the reaction mass and stirred for 15 to 20 minutes and after that reaction mass was filtered out. Methanol was distilled out below 50° C. from above reaction mass. Cyclohexane (400 ml) was added to residue at 25° C. to 35° C. The reaction mass was stirred for 15 to 20 minutes, filtered and washed with cyclohexane (100 ml) to get amorphous solid dispersion of resmetirom.

[00645] For example, one of the forms is Form 3A reported in WO 2022/171200.

[00646] The crystalline Form 3A may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 112; an X-ray powder diffraction pattern having peaks at $10.7 \pm 0.2^\circ$, $16.2 \pm 0.2^\circ$, $18.0 \pm 0.2^\circ$, $24.1 \pm 0.2^\circ$ and $24.3 \pm 0.2^\circ$ 2-theta; and combinations of these data; a FT-IR spectrum substantially as depicted in FIG. 115; a FT-IR spectrum with characteristic peaks at $1718 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1190 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1180 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $908 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, and $896 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$; a FT-IR spectrum with characteristic peaks at $1603 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1461 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1406 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1337 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $1230 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $952 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, $908 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$, and $896 \text{ cm}^{-1} \pm 2 \text{ cm}^{-1}$; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve additional peaks selected from $11.3 \pm 0.2^\circ$, $12.0 \pm 0.2^\circ$, $14.4 \pm 0.2^\circ$, $15.6 \pm 0.2^\circ$, $17.3 \pm 0.2^\circ$, $17.6 \pm 0.2^\circ$, $19.5 \pm 0.2^\circ$, $20.0 \pm 0.2^\circ$, $22.4 \pm 0.2^\circ$, $26.7 \pm 0.2^\circ$, $26.9 \pm 0.2^\circ$ and $28.7 \pm 0.2^\circ$ 2-theta.

[00647] WO 2022/171200 provides the following data:

2 θ	Intensity%
8 $\pm$ 0.2 $^{\circ}$	5.2
10.7 $\pm$ 0.2 $^{\circ}$	83.2
11.3 $\pm$ 0.2 $^{\circ}$	13.8
12 $\pm$ 0.2 $^{\circ}$	56
12.6 $\pm$ 0.2 $^{\circ}$	14.2
13.9 $\pm$ 0.2 $^{\circ}$	29.8
14.4 $\pm$ 0.2 $^{\circ}$	20.7
15.6 $\pm$ 0.2 $^{\circ}$	21.2
16.2 $\pm$ 0.2 $^{\circ}$	63.7
16.8 $\pm$ 0.2 $^{\circ}$	4.5
17.3 $\pm$ 0.2 $^{\circ}$	32.5
17.6 $\pm$ 0.2 $^{\circ}$	33.1
18 $\pm$ 0.2 $^{\circ}$	48.4
19.5 $\pm$ 0.2 $^{\circ}$	12.5
20 $\pm$ 0.2 $^{\circ}$	20.9
20.9 $\pm$ 0.2 $^{\circ}$	8.6
21.3 $\pm$ 0.2 $^{\circ}$	13.1
22.4 $\pm$ 0.2 $^{\circ}$	34.5
23 $\pm$ 0.2 $^{\circ}$	12.3
23.4 $\pm$ 0.2 $^{\circ}$	4.9
24.1 $\pm$ 0.2 $^{\circ}$	100
24.3 $\pm$ 0.2 $^{\circ}$	93.8
25 $\pm$ 0.2 $^{\circ}$	13.2
25.9 $\pm$ 0.2 $^{\circ}$	11.1
26.3 $\pm$ 0.2 $^{\circ}$	6.3
26.7 $\pm$ 0.2 $^{\circ}$	17.5
26.9 $\pm$ 0.2 $^{\circ}$	14.9
27.6 $\pm$ 0.2 $^{\circ}$	10.8
28.1 $\pm$ 0.2 $^{\circ}$	3.4
28.7 $\pm$ 0.2 $^{\circ}$	34.6
29.3 $\pm$ 0.2 $^{\circ}$	11.7
30.4 $\pm$ 0.2 $^{\circ}$	21.6
31.1 $\pm$ 0.2 $^{\circ}$	6.9
32.2 $\pm$ 0.2 $^{\circ}$	9
32.7 $\pm$ 0.2 $^{\circ}$	6.5
33.3 $\pm$ 0.2 $^{\circ}$	3.6
33.7 $\pm$ 0.2 $^{\circ}$	5.1
34.2 $\pm$ 0.2 $^{\circ}$	20.3
35.8 $\pm$ 0.2 $^{\circ}$	3.1
36.3 $\pm$ 0.2 $^{\circ}$	12.7
39 $\pm$ 0.2 $^{\circ}$	4.1

[00648] The TGA pattern of this crystalline Form 3A is substantially as shown in FIG. 113, with a weight loss of 0.3% before 100°C, and a decomposition temperature of 320°C.

[00649] The DSC pattern of the crystalline Form 3A is substantially as shown in FIG. 114, and the melting point is 324°C.

[00650] Example 1-1 of WO 2022/171200 describes preparation of the crystalline Form 3A.

[00651] Take 20 mg of resmetirom to form a suspension in 0.5 mL of n-propanol. After 5 days of crystal slurry at room temperature, centrifuge, and vacuum-dried at room temperature for 24 hours to obtain crystalline Form 3A.

[00652] Example 1-2 of WO 2022/171200 describes preparation of the crystalline Form 3A.

[00653] Take 51.80 mg of resmetirom to form a suspension in 1.0 mL of n-propanol. After slurring at room temperature for 2 days, centrifuge and vacuum dry at room temperature for 24 hours to obtain crystalline Form 3A.

[00654] Example 1-3 of WO 2022/171200 describes preparation of the crystalline Form 3A.

[00655] 200 mg of resmetirom was taken into 3 mL of n-propanol to form a suspension, and after 3 days of crystal slurry at room temperature, centrifuged, and vacuum-dried at room temperature for 24 hours to obtain crystalline Form 3A.

[00656] Example 1-4 of WO 2022/171200 describes preparation of the crystalline Form 3A.

[00657] Take 500 mg of resmetirom, form a suspension in 3.5 mL of n-propanol, slurried at room temperature for 16 hours, filtered, and vacuum-dried at room temperature for 67 hours to obtain crystalline Form 3A.

[00658] Example 2-1 of WO 2022/171200 describes preparation of the crystalline Form 3A.

[00659] Dissolve 20.15 mg of resmetirom in 2 mL of n-propanol at 60 °C, filter, add 3 mg of the crystal form 3 prepared in Example 1 as a seed crystal, stir at 4 °C for 1 day, and then

centrifuge. It was dried under vacuum at room temperature for 24 hours to obtain crystalline Form 3A.

[00660] Example 3-1 of WO 2022/171200 describes preparation of this crystalline Form 3A.

[00661] 20.92 mg of resmetirom was dissolved in 7 mL of n-propanol by ultrasonic wave, filtered, and 3 mg of crystalline Form 3 prepared in Example 1 was added as a seed crystal, and after 2 days of open volatilization at room temperature, crystalline Form 3A was obtained.

[00662] For example, one of the forms is Form 4A reported in CN115124515A.

[00663] The crystalline Form 4A may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 122; an X-ray powder diffraction pattern having peaks at $7.2\pm0.2^\circ$, $12.4\pm0.2^\circ$, $13.3\pm0.2^\circ$, $15.0\pm0.2^\circ$ and $23.1\pm0.2^\circ$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $8.6\pm0.2^\circ$, $13.9\pm0.2^\circ$, $19.6\pm0.2^\circ$, $22.5\pm0.2^\circ$, and $26.2\pm0.2^\circ$ 2-theta.

[00664] CN115124515A provides the following data:

	Intensity%
20	
7.2	100
7.9	8.5
8.6	21.1
10.8	4.8
12.4	28.6
13.3	42.9
13.9	25.5
14.3	15.1
15.0	43.9
15.9	6.5
17.3	15.5
17.7	16.9
18.0	19.4
18.6	15.3
19.6	26.2
20.5	4.8
20.8	5.1
21.5	7
21.8	3.5
22.5	21.7
22.8	18.5
23.1	55.1
24.0	16.1
24.4	4.1
24.9	16.5
25.4	5.9
25.8	12.2
26.2	24.4
29.4	6.1
29.8	16.4
29.9	9.9
30.3	11.5
30.8	3.4
31.4	3.6
31.8	6.2
32.1	7.7
33.0	3.4
34.0	3
34.7	2.9
35.1	5.9
35.5	5.5
35.7	5.8
38.0	4.3
39.1	3.

[00665] The TGA pattern of the crystalline Form 4A is substantially as shown in FIG. 123, with a weight loss of 10.5% before 150°C, and a decomposition temperature of 327.11°C.

[00666] The ¹H NMR spectrum of the crystalline Form 4A is substantially as shown in FIG. 124.

[00667] Example 1 of CN115124515A describes preparation of this crystalline Form 4A.

[00668] About 20 mg of resmetirom was sonicated in 2mL of acetone, filtered, 5.4mL of n-heptane was added with stirring to Form a suspension, which was stirred at room temperature for 3 hours, centrifuged, and dried under vacuum at room temperature for 24 hours to obtain crystalline Form 4A.

[00669] For example, one of the forms is Form 7A reported in CN115124515A.

[00670] The crystalline Form 7A may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 125; an X-ray powder diffraction pattern having peaks at $6.9 \pm 0.2^\circ$, $13.9 \pm 0.2^\circ$, $15.0 \pm 0.2^\circ$, $17.8 \pm 0.2^\circ$ and $20.0 \pm 0.2^\circ$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $12.2 \pm 0.2^\circ$, $16.0 \pm 0.2^\circ$, $20.9 \pm 0.2^\circ$, $22.6 \pm 0.2^\circ$, and $24.8 \pm 0.2^\circ$ 2-theta.

[00671] CN115124515A provides the following data:

2 θ	Intensity%
6.9	100
10.0	10.4
10.6	21.7
11.8	18.2
12.2	52
13.9	86.1
15.0	86.7
15.5	22.4
16.0	46.2
16.3	10.6
17.4	41
17.8	78.1
19.1	23.2
20.0	85.3
20.9	52.2
21.4	27.7
22.3	29.4
22.6	46.6
23.0	27.7
23.7	28.4
24.4	28.2
24.8	63.8
25.6	8.7
25.8	7.9
26.4	34.8
27.5	14.3
28.1	17.4
29.0	15.9
30.4	36.2
31.1	7.5
32.2	16.1
33.2	10.8
33.6	13.7
34.5	7.7
34.9	8.5
37.2	6.2
37.7	8.5

[00672] The TGA pattern of the crystalline Form 7A is substantially as shown in FIG. 126, with a weight loss of 19% before 150°C, and a decomposition temperature of 327°C.

[00673] The ^1H NMR spectrum of the crystalline Form 7A is substantially as shown in FIG. 127.

[00674] Example 2 of CN115124515A describes preparation of the crystalline Form 7A.

[00675] About 20 mg of resmetirom was suspended in 0.6 mL of 1, 4-dioxane/isopropyl ether (v: v2:1) and stirred at 40 °C for 5 days to obtain crystalline Form 7A.

[00676] Example 3 of CN115124515A describes preparation of the crystalline Form 7A.

[00677] About 20 mg of resmetirom was suspended in 0.5 mL 1, 4-dioxane/n-heptane (v: v4:1) and stirred at 40 °C for 5 days to obtain crystalline Form 7A.

[00678] Example 4 of CN115124515A describes preparation of the crystalline Form 7A.

[00679] About 20 mg of resmetirom was dissolved in 1.8 mL of 1, 4-dioxane/water (v: v2:1) mixed solvent at 60 °C, filtered, transferred to 4 °C and stirred to obtain crystalline Form 7A.

[00680] For example, one of the forms is Form 9A reported in CN115124515A.

[00681] The crystalline Form 9A may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 128; an X-ray powder diffraction pattern having peaks at $14.5 \pm 0.2^\circ$, $19.7 \pm 0.2^\circ$, $22.2 \pm 0.2^\circ$, $22.4 \pm 0.2^\circ$ and $23.9 \pm 0.2^\circ$ 2-theta; and combinations of these data, The X-ray powder diffraction pattern may have any one, two, three, four, or five additional peaks selected from $6.9 \pm 0.2^\circ$, $10.6 \pm 0.2^\circ$, $12.1 \pm 0.2^\circ$, $22.9 \pm 0.2^\circ$, and $25.0 \pm 0.2^\circ$ 2-theta.

[00682] CN115124515A provides the following data:

2θ	Intensity%
6.9	22.0
8.7	9.9
9.7	5.6
10.0	15.1
10.6	27.5
11.4	20.0
12.1	22.9
13.7	5.7
14.5	100.0
15.0	5.5
15.8	14.2
17.5	17.3
18.7	15.9
19.7	36.7
20.0	15.8
20.7	13.1
21.4	6.7
22.2	32.7
22.4	30.1
22.7	20.7
22.9	26.7
23.5	4.1
23.9	35.3
24.3	4.8
24.5	7.3
25.0	29.7
25.3	4.2
25.8	17.0
26.3	4.4
27.0	8.0
27.5	7.4
27.8	5.6
28.9	7.1
29.3	11.1
29.8	18.8
30.6	4.3
31.2	8.5
31.5	8.8
31.8	6.5
32.6	12.4
34.8	3.5
35.5	5.4
36.9	4.3

[00683] The TGA pattern of the crystalline Form 9A is substantially as shown in FIG. 129, with a weight loss of 13.2% before 160°C, and a decomposition temperature of 340°C.

[00684] The ^1H NMR spectrum of the crystalline Form 9A is substantially as shown in FIG. 130.

[00685] Example 5 of CN115124515A describes preparation of the crystalline Form 7A.

[00686] About 20 mg of resmetirom was suspended in 0.5mL butanone and stirred at room temperature for 6 days to obtain crystalline Form 9A.

[00687] For example, one of the forms is Form BSI reported in CN118772117A.

[00688] The crystalline Form BSI may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 131; an X-ray powder diffraction pattern having peaks at $6.6\pm0.2^\circ$, $7.8\pm0.2^\circ$, $9.7\pm0.2^\circ$, $10.2\pm0.2^\circ$, $13.7\pm0.2^\circ$, $16.3\pm0.2^\circ$, $17.8\pm0.2^\circ$, $18.2\pm0.2^\circ$, $19.0\pm0.2^\circ$, $19.6\pm0.2^\circ$, $20.7\pm0.2^\circ$, $22.0\pm0.2^\circ$, $23.4\pm0.2^\circ$, $24.9\pm0.2^\circ$, $25.8\pm0.2^\circ$, $26.8\pm0.2^\circ$, $27.5\pm0.2^\circ$, $28.0\pm0.2^\circ$, $30.0\pm0.2^\circ$, $31.2\pm0.2^\circ$, $32.0\pm0.2^\circ$, $34.5\pm0.2^\circ$, $36.5\pm0.2^\circ$, $38.3\pm0.2^\circ$, and $42.4\pm0.2^\circ$ 2-theta; and combinations of these data.

[00689] The DSC curve of the crystalline Form BSI is substantially as depicted in FIG. 132, which shows an endothermic peak near 334°C . and an exothermic peak near 238°C which is the crystal transition exothermic peak.

[00690] The TGA pattern of the crystalline Form BSI is substantially as shown in FIG. 133, with a decomposition temperature of 340°C .

[00691] Example 1 of CN118772117A describes preparation of Form BSI.

[00692] Taking 1 g of resmetirom, adding 5 mL of acetonitrile and 5 mL of toluene, stirring to form a suspension, stirring at room temperature for 3 days, filtering, and drying in

a vacuum oven (90-100 °C) for 6 hours to obtain 0.88g of the resmetirom crystalline form BSI.

[00693] Example 2 of CN118772117A describes preparation of Form BSI.

[00694] Taking 1 g of resmetirom, adding 5 mL of acetonitrile and 5 mL of cyclohexane, stirring to form a suspension, stirring at room temperature for 4 days, filtering, and drying in a vacuum oven (90-100 °C) for 6 hours to obtain 0.93 g of the resmetirom crystalline form BSI.

[00695] Example 3 of CN118772117A describes preparation of Form BSI.

[00696] Taking 1g of resmetirom, adding 5 mL of acetonitrile and 5 mL of n-hexane, stirring to form a suspension, stirring at room temperature for 3 days, filtering, and drying in a vacuum oven (90-100 °C) for 6 hours to obtain 0.90 g of the resmetirom crystalline form BSI.

[00697] Example 4 of CN118772117A describes preparation of Form BSI.

[00698] Taking 1 g of resmetirom, adding 4 mL of acetonitrile, 3 mL of toluene and 3 mL of cyclohexane, stirring to form a suspension, stirring at room temperature for 3 days, filtering, and drying in a vacuum oven (100-110 °C) for 7 hours to obtain 0.87 g of the resmetirom crystalline form BSI.

[00699] For example, one of the forms is Form R1 reported in IN202241066042A.

[00700] The crystalline Form R1 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 134; an X-ray powder diffraction pattern having peaks at $11.18^{\circ} \pm 0.2^{\circ}$, $12.48^{\circ} \pm 0.2^{\circ}$, $13.8^{\circ} \pm 0.2^{\circ}$, $15.02^{\circ} \pm 0.2^{\circ}$, $16.49^{\circ} \pm 0.2^{\circ}$, and $20.6^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray

powder diffraction pattern may have any one, two, three, four, five, or six additional peaks selected from $5.59^{\circ} \pm 0.2^{\circ}$, $10.56^{\circ} \pm 0.2^{\circ}$, $22^{\circ} \pm 0.2^{\circ}$, $22.76^{\circ} \pm 0.2^{\circ}$, $26.69^{\circ} \pm 0.2^{\circ}$, and $27.78^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00701] Example 1 of IN202241066042A describes preparation of Form R1.

[00702] A mixture of resmetirom (1 g) and formic acid (5 mL) was stirred for 3 days at room temperature. The resulting mixture was dried at room temperature for 2.5 hours followed by drying under VTD dryer for 1 day at 50 °C to obtain crystalline Form R1.

[00703] For example, one of the forms is Form R2 reported in IN202241066042A.

[00704] The crystalline Form R2 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 135; an X-ray powder diffraction pattern having peaks at $9.04^{\circ} \pm 0.2^{\circ}$, $22.56^{\circ} \pm 0.2^{\circ}$, and $25.5^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, or three additional peaks selected from $9.6^{\circ} \pm 0.2^{\circ}$, $15.9^{\circ} \pm 0.2^{\circ}$, and $26.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00705] Example 2 of IN202241066042A describes preparation of Form R2.

[00706] A mixture of resmetirom (1 g) and hexanoic acid (2 mL) was stirred for 20 hours at room temperature. Diisopropyl ether (25 mL) was added to the above mixture and stirred for 2 hours at the same temperature. The solid was filtered under vacuum under nitrogen atmosphere. The resulting solid was dried at room temperature for 2.5 hours followed by drying at 50 °C for 12 hours using VTD drier to obtain crystalline Form R2.

[00707] For example, one of the forms is Form R3 reported in IN202241066042A.

[00708] The crystalline Form R3 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 136; an X-ray powder diffraction pattern having peaks at $13.18^{\circ} \pm 0.2^{\circ}$, $27.2^{\circ} \pm 0.2^{\circ}$, $30^{\circ} \pm 0.2^{\circ}$, and $31.6^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, or three additional peaks selected from $9.68^{\circ} \pm 0.2^{\circ}$, $16.99^{\circ} \pm 0.2^{\circ}$, and $20.57^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00709] Example 3 of IN202241066042A describes preparation of Form R3.

[00710] A mixture of resmetirom (1 g) and sulfolane (2 mL) was stirred for 20 hours at room temperature. Water (25 mL) was added to the above mixture and stirred for 1 hours at the same temperature. The reaction mixture was filtered under vacuum under nitrogen atmosphere. The resulting solid was dried at room temperature for 2.5 hours followed by drying at 50°C for 12 hours using VTD drier to obtain crystalline Form R3.

[00711] For example, one of the forms is Form R4 reported in IN202241066042A.

[00712] The crystalline Form R4 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 137; an X-ray powder diffraction pattern having peaks at $7.02^{\circ} \pm 0.2^{\circ}$, $8.9^{\circ} \pm 0.2^{\circ}$, $9.35^{\circ} \pm 0.2^{\circ}$, and $14.09^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, or three additional peaks selected from $16.88^{\circ} \pm 0.2^{\circ}$, $22.56^{\circ} \pm 0.2^{\circ}$, and $28.77^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00713] Example 4 of IN202241066042A describes preparation of Form R4.

[00714] A mixture of resmetirom (1 g) and butyric acid (5 mL) was stirred for 2 days at room temperature. Heptane (25 mL) was added to the above mixture and stirred for 2 hours at the same temperature. The reaction mixture was filtered under vacuum under nitrogen

atmosphere. The resulting solid was dried at room temperature for 2.5 hours followed by drying at 50 °C for 12 hours using VTD drier to obtain crystalline Form R4.

[00715] For example, one of the forms is Form R5 reported in IN202241066042A.

[00716] The crystalline Form R5 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 138; an X-ray powder diffraction pattern having peaks at $12.0^{\circ} \pm 0.2^{\circ}$, $14.28^{\circ} \pm 0.2^{\circ}$, $15.5^{\circ} \pm 0.2^{\circ}$, and $22.43^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, or six additional peaks selected from $5.7^{\circ} \pm 0.2^{\circ}$, $10.6^{\circ} \pm 0.2^{\circ}$, $20.2^{\circ} \pm 0.2^{\circ}$, $21.09^{\circ} \pm 0.2^{\circ}$, $21.44^{\circ} \pm 0.2^{\circ}$, and $28.82^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00717] Example 5 of IN202241066042A describes preparation of Form R5.

[00718] A mixture of Resmetirom (1 g) and 1,2-Dimethoxyethane (2.5 mL) was stirred for 24 hours at 40 °C. After 24 hours of stirring at 40 °C, the reaction mixture is cooled to 25 °C. The solid was filtered and dried at under VTD dryer for 2 days at 50 °C to obtain crystalline Form R5.

[00719] For example, one of the forms is an amorphous solid dispersion of resmetirom and eudragit (1:2) reported in IN202241066042A.

[00720] The amorphous solid dispersion of resmetirom and eudragit may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIG. 139.

[00721] Example 6 of IN202241066042A describes preparation of the amorphous solid dispersion of resmetirom and eudragit.

[00722] A mixture of resmetirom (1.5 g) and eudragit (3 g) in methanol (500 mL) was heated 50 °C and stirred for 1 hour. The mixture was filtered and the resulting clear solution

was subjected to spray drying at 70 °C. The resulting solid was further dried at 40 °C under VTD dryer for 18 hours to obtain the amorphous solid dispersion of resmetirom and eudragit.

[00723] For example, one of the forms is an amorphous form of resmetirom reported in IN202241066042A.

[00724] This amorphous form of resmetirom may be characterized by an X-ray powder diffraction pattern substantially as depicted in FIG. 140.

[00725] Example 7 of IN202241066042A describes preparation of this amorphous form of resmetirom.

[00726] A mixture of resmetirom (3 g) and acetone (300 mL) was stirred for 2 hours at 40 °C. The mixture was filtered and the resulting clear solution was subjected to spray drying at 65 °C to obtain this amorphous form of resmetirom.

[00727] For example, one of the forms is Form RL reported in IN202241066042A.

[00728] The crystalline Form RL may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 141; an X-ray powder diffraction pattern having peaks at $18.42^{\circ} \pm 0.2^{\circ}$, $19.09^{\circ} \pm 0.2^{\circ}$, and $20.49^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one or two additional peaks selected from $11.24^{\circ} \pm 0.2^{\circ}$ and $17.12^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00729] Example 8 of IN202241066042A describes preparation of Form RL.

[00730] A mixture of resmetirom (1.7 g) and lysine (0.58 g) in acetone (15 mL) was stirred for 2 days at room temperature. The resulting solid was filtered and dried at under VTD dryer for 3 hours at room temperature to obtain crystalline Form RL.

[00731] For example, one of the forms is Form M1 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00732] The crystalline Form M1 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 142; an X-ray powder diffraction pattern having peaks at $10.6^{\circ} \pm 0.2^{\circ}$, $11.0^{\circ} \pm 0.2^{\circ}$, and $12.7^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, six, or seven additional peaks selected from $10.2^{\circ} \pm 0.2^{\circ}$, $11.5^{\circ} \pm 0.2^{\circ}$, $16.9^{\circ} \pm 0.2^{\circ}$, $18.8^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, $22.4^{\circ} \pm 0.2^{\circ}$, and $24.2^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00733] Example 1 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M1.

[00734] Dissolved resmetirom (0.5 g) in the mixture of acetic acid (12 ml) and ethyl acetate (18 ml) at 40-50°C, cooled the obtained solution to 25-30°C and stirred at the same temperature. Filtered the precipitated solid and dried to get the title compound to obtain crystalline Form M1.

[00735] For example, one of the forms is Form M2 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00736] The crystalline Form M2 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 143; an X-ray powder diffraction pattern having peaks at $5.0^{\circ} \pm 0.2^{\circ}$, $6.4^{\circ} \pm 0.2^{\circ}$, $7.7^{\circ} \pm 0.2^{\circ}$, $15.1^{\circ} \pm 0.2^{\circ}$, and $23.7^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder

diffraction pattern may have any one, two, three, four, five, or six additional peaks selected from $10.1^{\circ}\pm 0.2^{\circ}$, $12.1^{\circ}\pm 0.2^{\circ}$, $14.3^{\circ}\pm 0.2^{\circ}$, $17.8^{\circ}\pm 0.2^{\circ}$, $19.6^{\circ}\pm 0.2^{\circ}$, and $21.8^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00737] Example 2 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M2.

[00738] Dissolved resmetirom (0.5 g) in cyclohexanol (45 ml) at 60-70°C and filtered for particle free. Obtained filtrate is added to the methyl tertiary butyl ether (80 ml) at 25-30°C and stirred at the same temperature. Cyclohexane (100 ml) added to the mixture at 25-30°C and stirred at the same temperature. Filtered the precipitated solid and dried to obtain crystalline Form M2.

[00739] For example, one of the forms is Form M3 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00740] The crystalline Form M3 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 144; an X-ray powder diffraction pattern having peaks at $6.9^{\circ}\pm 0.2^{\circ}$, $8.6^{\circ}\pm 0.2^{\circ}$, $11.5^{\circ}\pm 0.2^{\circ}$, $13.9^{\circ}\pm 0.2^{\circ}$, $24.7^{\circ}\pm 0.2^{\circ}$, and $30.2^{\circ}\pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve additional peaks selected from $9.8^{\circ}\pm 0.2^{\circ}$, $10.3^{\circ}\pm 0.2^{\circ}$, $10.7^{\circ}\pm 0.2^{\circ}$, $12.2^{\circ}\pm 0.2^{\circ}$, $15.7^{\circ}\pm 0.2^{\circ}$, $17.4^{\circ}\pm 0.2^{\circ}$, $17.9^{\circ}\pm 0.2^{\circ}$, $18.7^{\circ}\pm 0.2^{\circ}$, $21.6^{\circ}\pm 0.2^{\circ}$, $22.7^{\circ}\pm 0.2^{\circ}$, $26.7^{\circ}\pm 0.2^{\circ}$, and $28.5^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00741] Example 3 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M3.

[00742] Dissolved resmetirom (0.5 g) in cyclohexanol (45 ml) at 60-70°C, cooled the obtained solution to 25-30°C and filtered for particle free. Obtained filtrate is added to cyclohexane (80 ml) at 25-30°C and stirred at the same temperature. Filtered the solid and dried to obtain crystalline Form M3.

[00743] For example, one of the forms is Form M4 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00744] The crystalline Form M4 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 145; an X-ray powder diffraction pattern having peaks at $3.9^{\circ} \pm 0.2^{\circ}$, $18.3^{\circ} \pm 0.2^{\circ}$, and $19.0^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen additional peaks selected from $9.6^{\circ} \pm 0.2^{\circ}$, $11.9^{\circ} \pm 0.2^{\circ}$, $13.2^{\circ} \pm 0.2^{\circ}$, $14.9^{\circ} \pm 0.2^{\circ}$, $15.2^{\circ} \pm 0.2^{\circ}$, $16.9^{\circ} \pm 0.2^{\circ}$, $17.6^{\circ} \pm 0.2^{\circ}$, $19.7^{\circ} \pm 0.2^{\circ}$, $21.8^{\circ} \pm 0.2^{\circ}$, $23.9^{\circ} \pm 0.2^{\circ}$, $25.2^{\circ} \pm 0.2^{\circ}$, $25.7^{\circ} \pm 0.2^{\circ}$, $29.8^{\circ} \pm 0.2^{\circ}$, and $36.9^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00745] Example 4 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M4.

[00746] Dissolved resmetirom (0.5 g) in acetic acid (7 ml) at 70-80°C. Obtained solution is added to cyclohexane (60 ml) at 25-30°C and stirred. The mixture was cooled to 0-5°C and

stirred the mixture at the same temperature. The mixture was heated to 35-40°C and stirred.

Filtered the solid and dried to obtain crystalline Form M4.

[00747] For example, one of the forms is Form M5 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00748] The crystalline Form M5 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 146; an X-ray powder diffraction pattern having peaks at $6.4^{\circ} \pm 0.2^{\circ}$, $7.5^{\circ} \pm 0.2^{\circ}$, $8.2^{\circ} \pm 0.2^{\circ}$, and $9.5^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, six, seven, eight, nine, or ten additional peaks selected from $10.0^{\circ} \pm 0.2^{\circ}$, $11.5^{\circ} \pm 0.2^{\circ}$, $16.1^{\circ} \pm 0.2^{\circ}$, $18.8^{\circ} \pm 0.2^{\circ}$, $19.4^{\circ} \pm 0.2^{\circ}$, $20.5^{\circ} \pm 0.2^{\circ}$, $21.7^{\circ} \pm 0.2^{\circ}$, $23.2^{\circ} \pm 0.2^{\circ}$, $24.7^{\circ} \pm 0.2^{\circ}$, and $27.2^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00749] Example 5 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M5.

[00750] Dissolved resmetirom (0.5 g) and isonicotinamide (0.286 g) in acetonitrile (12 ml) at 75-85°C and filtered for particle free at the same temperature. Obtained filtrate is cooled to 25-30°C and stirred at the same temperature. Filtered the precipitated solid and dried to obtain crystalline Form M5.

[00751] For example, one of the forms is Form M6 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00752] The crystalline Form M6 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 147; an X-ray powder diffraction pattern having peaks at $6.9^{\circ} \pm 0.2^{\circ}$, $8.5^{\circ} \pm 0.2^{\circ}$, $11.2^{\circ} \pm 0.2^{\circ}$, and $14.5^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder diffraction pattern may have any one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen additional peaks selected from $10.6^{\circ} \pm 0.2^{\circ}$, $12.1^{\circ} \pm 0.2^{\circ}$, $13.9^{\circ} \pm 0.2^{\circ}$, $15.3^{\circ} \pm 0.2^{\circ}$, $15.9^{\circ} \pm 0.2^{\circ}$, $16.4^{\circ} \pm 0.2^{\circ}$, $17.2^{\circ} \pm 0.2^{\circ}$, $17.9^{\circ} \pm 0.2^{\circ}$, $19.6^{\circ} \pm 0.2^{\circ}$, $19.9^{\circ} \pm 0.2^{\circ}$, $21.4^{\circ} \pm 0.2^{\circ}$, $22.4^{\circ} \pm 0.2^{\circ}$, $25.1^{\circ} \pm 0.2^{\circ}$, $27.5^{\circ} \pm 0.2^{\circ}$, $29.9^{\circ} \pm 0.2^{\circ}$, and $32.4^{\circ} \pm 0.2^{\circ}$ 2-theta.

[00753] Example 6 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M6.

[00754] Dissolved resmetirom (0.3 g) in a mixture (1:1) of acetonitrile and tetrahydrofuran (6.0 ml) at 55-65°C and filtered for particle free at the same temperature. Obtained filtrate is cooled to 25-30°C and stirred at the same temperature. Filtered the solid and dried to obtain crystalline Form M6.

[00755] For example, one of the forms is Form M7 reported in MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof".

[00756] The crystalline Form M7 may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in FIG. 148; an X-ray powder diffraction pattern having peaks at $9.1^{\circ} \pm 0.2^{\circ}$, $9.5^{\circ} \pm 0.2^{\circ}$, $10.5^{\circ} \pm 0.2^{\circ}$, $10.8^{\circ} \pm 0.2^{\circ}$, and $23.0^{\circ} \pm 0.2^{\circ}$ 2-theta; and combinations of these data. The X-ray powder

diffraction pattern may have any one, two, three, four, five, six, seven, eight, or nine additional peaks selected from $11.9^{\circ}\pm 0.2^{\circ}$, $15.7^{\circ}\pm 0.2^{\circ}$, $17.3^{\circ}\pm 0.2^{\circ}$, $18.8^{\circ}\pm 0.2^{\circ}$, $19.5^{\circ}\pm 0.2^{\circ}$, $21.5^{\circ}\pm 0.2^{\circ}$, $24.3^{\circ}\pm 0.2^{\circ}$, $24.9^{\circ}\pm 0.2^{\circ}$, and $28.8^{\circ}\pm 0.2^{\circ}$ 2-theta.

[00757] Example 7 of MSN Laboratories Private Limited, R&D Center, et al, "Solid-state forms of Resmetirom and processes for preparation thereof" describes preparation of Form M7.

[00758] A mixture of isobutyl acetate (15.0 ml) and resmetirom (0.3 g) is stirred at 25-30°C. Filtered the solid and dried to obtain crystalline Form M7.

[00759] The present disclosure also provides novel, previously unknown morphic forms, co-crystals, and salts of resmetirom, as well as methods for their preparation.

[00760] All XRPD patterns and peak listings for the novel forms described herein are based on a Cu-K α radiation wavelength (1.54 Å). A Rigaku Smart Lab X-Ray Diffractometer was configured in Bragg–Brentano reflection geometry equipped with a beam stop and knife edge to reduce incident beam and air scatter. Data collection parameters are shown in the table below:

Parameter	Value	Parameter	Value
Geometry	Bragg–Brentano	Receiving Slit 1 (mm)	18
Tube Anode	Cu	Receiving Slit 2 (mm)	20.1
Tube Type	Long Fine Focus	Start Angle 2θ (°)	2
Tube Voltage (kV)	40	End Angle 2θ (°)	40
Tube Current (mA)	44	Step Size (°)	0.02
Detector	HyPix-3000	Scan Speed (°/min)	6
Monochromator	Ni foil Cu K β Filter	Spinning (rpm)	11
Incident Slit (°)	1/3	Sample Holder	Low-background Si

[00761] All DSC analyses for the novel forms described herein were carried out using a TA Instruments Q2000 Discovery Series instrument. The instrument temperature calibrations were performed using indium. The DSC cell was kept under a nitrogen purge of about 50 mL per minute during the analysis. Each sample was placed in a standard, crimped aluminum pan and heated from approximately -30°C to 250/300°C or -30°C to 350/400°C at a rate of 10°C per minute.

[00762] All thermogravimetric analyses (TGA) were carried out using a TA Instruments Q5500 Discovery Series instrument. The instrument balance was calibrated using class M weights and the temperature calibration was performed using alumel. The nitrogen purge was about 10 mL per minute at the balance and about 25 mL per minute at the furnace. The sample was placed into a pre-tared platinum pan and heated from approximately 25 °C to 400 °C at a rate of 10 °C per minute.

[00763] All infrared (IR) spectroscopic analysis for the novel forms described herein was performed using a Thermo Scientific model iS50 Fourier-transform (FT) IR spectrophotometer equipped with a deuterated triglycine sulfate (DTGS) detector, a potassium bromide (KBr) beamsplitter, and a Polaris™ long-life IR source. A diamond attenuated total reflectance (ATR) sampling accessory with a spectral range of 4000 cm⁻¹ to 400 cm⁻¹ was used for ATR analysis. A SpectraTech drifts (Diffuse reflectance infra-red Fourier transform spectroscopy, DRIFTS) sampling accessory with a spectral range of 4000–400 cm⁻¹ was used for DRIFTS analysis. Each spectrum was the result of 128 co-added scans acquired at 2 cm⁻¹ resolution. A single beam background scan of air was acquired before the sample scan, allowing presentation of the spectra in log 1/R units. Wave-length calibration was performed using polystyrene. OMNIC v9.11 software package (Thermo-Nicolet) was used to acquire, process, and evaluate the spectral data.

[00764] All ^1H NMR spectra for the novel forms described herein were acquired on a Bruker Avance NEO 400 MHz spectrometer. Samples were prepared by dissolving material in DMSO- d_6 . The solutions were placed into individual 5 mm NMR tubes for subsequent spectral acquisition. Each spectrum was processed using TopSpin version 4.1.4 and referenced to the chemical shift of the residual DMSO- d_6 (2.5 ppm) peak.

[00765] All Raman spectroscopic analysis for the novel forms described herein was performed using a Nicolet iS50 Raman module that was equipped with a 1064 nm near-infrared laser. The system was configured with an indium gallium arsenide (InGaAs) detector and a calcium fluoride (CaF_2) beamsplitter. Each sample was placed onto the automated XYZ stage and analyzed using a laser power that was adjusted to optimize the signal intensity while avoiding damage to the sample. Raman spectra were collected with 256 signal-averaged scans at a resolution of 2 cm^{-1} over the spectral range from 3700 cm^{-1} to 100 cm^{-1} . Data acquisition and processing were performed using OMNIC v9.11 software.

[00766] Methods for synthesizing resmetirom can be found in U.S. Patent Nos. 7,452,882 and 9,266,861. Resmetirom Form I may be prepared according to the methods of U.S. Patent No. 9,266,861. Resmetirom Form D (acetone solvate) may be prepared according to the methods disclosed in U.S. Patent Application Publication No. 2021/0122740 A1. The contents of each of the foregoing are incorporated herein by reference in their entirety.

[00767] One aspect of the present disclosure relates to a morphic form, Form U1, of resmetirom. Form U1 is a methyl ethyl ketone (MEK) solvate. In some embodiments, Form U1 is characterized by an XRPD pattern including peaks at $10.0^\circ \pm 0.2^\circ$, $10.7^\circ \pm 0.2^\circ$, $13.8^\circ \pm 0.2^\circ$, $23.5^\circ \pm 0.2^\circ$, and $24.5^\circ \pm 0.2^\circ$ 2-theta. In some embodiments, Form U1 is characterized by an XRPD pattern including any three, four, or five peaks selected from $10.0^\circ \pm 0.2^\circ$, $10.7^\circ \pm 0.2^\circ$, $13.8^\circ \pm 0.2^\circ$, $23.5^\circ \pm 0.2^\circ$, and $24.5^\circ \pm 0.2^\circ$ 2-theta. In some

embodiments, the XRPD pattern of Form U1 further includes one or more additional peaks from Table U1 below $\pm 0.2^\circ$ 2-theta. In other embodiments, Form U1 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.149. In other embodiments, Form U1 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U1 below $\pm 0.2^\circ$ 2-theta.

TABLE U1

No.	2 theta(deg)	d(ang.)	Rel. int. I
1	3.3317	26.49745	4.64
2	3.5531	24.84711	2.36
3	6.668	13.24523	8.67
4	7.1212	12.4033	1.6
5	9.9779	8.85771	100
6	10.6615	8.29121	86.33
7	10.8591	8.14081	48.91
8	11.7777	7.50785	1.03
9	12.1375	7.28608	9.53
10	13.7755	6.42318	38.35
11	14.235	6.21683	3.99
12	14.536	6.08877	3.6
13	16.236	5.45489	3.45
14	17.2717	5.13004	8.23
15	17.8018	4.97847	4.68
16	18.3525	4.83029	4.24
17	21.3924	4.15028	10.58
18	21.8783	4.05918	7.12
19	23.4542	3.7899	45.25
20	24.0996	3.68983	36.58
21	24.4903	3.63185	47.96
22	26.4943	3.3615	5.34

23	26.8229	3.32106	8.54
24	27.8691	3.19873	16.26
25	29.3368	3.04195	30.14
26	30.2886	2.94849	7.75
27	31.4065	2.84604	4.82
28	32.3727	2.76327	24.16
29	32.4526	2.75666	9.87
30	33.0847	2.70541	2.9
31	33.8123	2.64884	1.02
32	34.6542	2.58639	1.21
33	35.4358	2.53112	2.64

[00768] In other embodiments, Form U1 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 150. In other embodiments, Form U1 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 150. In other embodiments, Form U1 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 150. In other embodiments, Form U1 is also or alternatively characterized by a TGA thermogram comprising a 7.9% weight loss upon heating to about 200 °C. In other embodiments, Form U1 is also or alternatively characterized by a DSC thermogram comprising an endothermic event at about 150 °C and about 334 °C.

[00769] Another aspect of the present disclosure relates to a morphic form, Form U2, of resmetirom. Form U2 is a t-butanol solvate. In some embodiments, Form U2 is characterized by an XRPD pattern including peaks at $12.9^{\circ} \pm 0.2^{\circ}$, $13.7^{\circ} \pm 0.2^{\circ}$, $16.9^{\circ} \pm 0.2^{\circ}$, $23.6^{\circ} \pm 0.2^{\circ}$, and $29.3^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U2 is characterized by an XRPD pattern including any three, four, or five peaks selected from $12.9^{\circ} \pm 0.2^{\circ}$, $13.7^{\circ} \pm 0.2^{\circ}$, $16.9^{\circ} \pm 0.2^{\circ}$, $23.6^{\circ} \pm 0.2^{\circ}$, and $29.3^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the

XRPD pattern of Form U2 further includes one or more additional peaks from Table U2 below $\pm 0.2^\circ$ 2-theta. In other embodiments, Form U2 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.151. In other embodiments, Form U2 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U2 below $\pm 0.2^\circ$ 2-theta.

TABLE U2

No.	2 theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	10.024	8.81707	2258.11	27.95
2	10.3407	8.54768	1448.4	28.58
3	10.7052	8.25745	954.45	14.59
4	11.7874	7.50165	981.1	9.64
5	12.8873	6.8638	3089.65	36.31
6	13.7178	6.45006	4456.4	85.52
7	16.1154	5.49544	1247.37	27.01
8	16.9335	5.23173	3796.48	49.29
9	17.8294	4.97081	488.35	5.96
10	19.165	4.6273	1274.94	9.47
11	21.0246	4.22205	712.07	5.8
12	21.6724	4.09729	1133.4	42.01
13	23.6398	3.76055	4090.96	100
14	27.7625	3.21077	1875.32	41.19
15	29.3737	3.03821	4153.83	83.48
16	32.0425	2.79099	711.74	16.84
17	33.7973	2.64998	199.23	2.71
18	34.6434	2.58717	193.36	4.36

[00770] In other embodiments, Form U2 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 152. In other embodiments, Form U2 is also or alternatively characterized by a TGA thermogram substantially similar to that

set forth in FIG. 152. In other embodiments, Form U2 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 152. In other embodiments, Form U2 is also or alternatively characterized by a TGA thermogram comprising about 5.7% weight loss upon heating to about 200 °C. In other embodiments, Form U2 is also or alternatively characterized by a DSC thermogram comprising an endothermic event at about 136 °C and about 328 °C.

[00771] Another aspect of the present disclosure relates to a morphic form, Form U3, of resmetirom. Form U3 is a N-methyl pyrrolidone solvate. In some embodiments, Form U3 is characterized by an XRPD pattern including peaks at $10.5^{\circ} \pm 0.2^{\circ}$, $11.2^{\circ} \pm 0.2^{\circ}$, $16.4^{\circ} \pm 0.2^{\circ}$, $22.7^{\circ} \pm 0.2^{\circ}$, and $23.2^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U3 is characterized by an XRPD pattern including any three, four, or five peaks selected from $10.5^{\circ} \pm 0.2^{\circ}$, $11.2^{\circ} \pm 0.2^{\circ}$, $16.4^{\circ} \pm 0.2^{\circ}$, $22.7^{\circ} \pm 0.2^{\circ}$, and $23.2^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form U3 further includes one or more additional peaks from Table U3 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form U3 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 153. In other embodiments, Form U3 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U3 below $\pm 0.2^{\circ}$ 2-theta.

TABLE U3

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	8.166	10.81854	437.49	3.53
2	8.6549	10.20845	1324.3	10.61
3	9.037	9.77769	1061.32	7.21
4	9.6583	9.15005	702.38	7.88
5	10.5353	8.39028	3681.53	26.44
6	11.2411	7.865	8477.05	88.53

7	12.5458	7.04984	2260.49	15.04
8	12.822	6.8986	607.32	6.63
9	13.1418	6.73144	1308.89	9.03
10	13.3994	6.60262	492.71	4.59
11	14.973	5.91204	1763.05	13.56
12	16.0276	5.52533	2332.87	28.75
13	16.1275	5.49134	4171.44	19.54
14	16.4378	5.38837	8985.84	100
15	16.7728	5.2815	3388.24	23.22
16	16.9806	5.21734	2507.91	15.42
17	17.3758	5.09955	1663.92	13.71
18	17.6663	5.01633	1535.01	27.44
19	18.1516	4.8833	1438.72	8.22
20	18.3921	4.81999	1587.36	16.64
21	19.1134	4.63969	624.46	4.28
22	19.3672	4.57946	2303.43	13.68
23	19.712	4.50012	1769.3	13.45
24	19.9106	4.45567	1429.51	11.11
25	20.4248	4.34464	1194.18	15.67
26	22.7744	3.90146	4551.75	73.04
27	23.214	3.82856	6676.84	54.38
28	23.6511	3.75878	2756.85	14.99
29	23.877	3.72372	913.22	13.7
30	24.4476	3.6381	3377.94	23.01
31	24.9267	3.56924	6051.85	42.54
32	25.5169	3.48801	1443.75	13.35
33	25.7931	3.45128	3659.82	52.49
34	26.5991	3.3485	672.38	8.17
35	26.9009	3.31162	1963.75	12.85
36	27.5064	3.24007	3096.59	27.81
37	28.12	3.17075	1575.39	23.11
38	28.6236	3.1161	838.12	6.66

39	28.8312	3.09414	606.01	6.74
40	30.0778	2.96867	772.97	6.95
41	32.0066	2.79404	2912.38	21.03
42	33.8727	2.64426	889.01	21.58
43	34.4956	2.59792	348.52	3.17
44	34.9783	2.56317	903.78	9.01
45	37.0354	2.42539	496.62	8.55
46	38.003	2.36583	824.61	5.71

[00772] In other embodiments, Form U3 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 154. In other embodiments, Form U3 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 154. In other embodiments, Form U3 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 154. In other embodiments, Form U3 is also or alternatively characterized by a TGA thermogram comprising about 20.0% weight loss upon heating to about 200 °C. In other embodiments, Form U3 is also or alternatively characterized by a DSC thermogram comprising endothermic events at about 169 °C, about 207 °C, and about 329 °C.

[00773] Another aspect of the present disclosure relates to a morphic form, Form U4, of resmetirom. Form U4 is a nitromethane solvate. In some embodiments, Form U4 is characterized by an XRPD pattern including peaks at $8.1^{\circ} \pm 0.2^{\circ}$, $12.9^{\circ} \pm 0.2^{\circ}$, $16.3^{\circ} \pm 0.2^{\circ}$, $23.8^{\circ} \pm 0.2^{\circ}$, and $29.5^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U4 is characterized by an XRPD pattern including any three, four, or five peaks selected $8.1^{\circ} \pm 0.2^{\circ}$, $12.9^{\circ} \pm 0.2^{\circ}$, $16.3^{\circ} \pm 0.2^{\circ}$, $23.8^{\circ} \pm 0.2^{\circ}$, and $29.5^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form U4 further includes one or more additional peaks from Table U4 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form U4 is also or alternatively characterized by a XRPD pattern

substantially similar to that set forth in FIG.155. In other embodiments, Form U4 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U4 below $\pm 0.2^\circ$ 2-theta.

TABLE U4

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	8.14	10.85305	4915.91	25.75
2	8.3515	10.5786	3662.1	13.77
3	10.2545	8.6194	2988.84	11.19
4	11.404	7.75304	1001.28	6.8
5	11.6122	7.61448	4048.09	10.2
6	12.1998	7.24899	1445.13	4.95
7	12.8758	6.86991	4789.66	27.24
8	13.1469	6.72884	6210.96	20.9
9	14.684	6.02776	1378.32	4.9
10	16.3138	5.42903	12975.16	100
11	16.5089	5.36534	2996.2	9.88
12	16.7149	5.29966	1824.01	9.88
13	17.4647	5.07378	2767.83	13.27
14	18.3584	4.82874	2743.75	17.07
15	19.2336	4.61096	4809.17	21.37
16	20.2142	4.38944	3085.63	30.99
17	20.5533	4.31778	1205.67	3.74
18	22.1947	4.00202	653.07	2.91
19	22.735	3.90813	3017.54	21
20	23.3293	3.8099	3893.23	16.67
21	23.8427	3.729	13662.49	60.8
22	24.0145	3.70272	11574.38	47.19
23	24.5005	3.63035	715.72	4.37
24	24.863	3.57824	2083.42	13.04
25	25.3906	3.50507	1252.35	3.17

26	25.9278	3.43365	613.49	2.52
27	26.4553	3.36637	1721.07	10.45
28	26.7375	3.33148	2721.8	15.26
29	27.4832	3.24276	2384.48	9.68
30	28.1679	3.16547	560.04	5.34
31	29.536	3.02188	3881.6	39.24
32	30.4967	2.92884	497.47	2.51
33	31.0859	2.87466	596.17	6.5
34	31.7109	2.81942	2123.7	6.75
35	32.0308	2.79199	955.4	19.76
36	32.9884	2.71309	1156.79	9.91
37	34.4978	2.59776	623.91	3.72
38	36.2583	2.47556	759.81	15.66

[00774] Another aspect of the present disclosure relates to a morphic form, Form U5, of resmetirom. Form U5 is an o-xylene solvate. In some embodiments, Form U5 is characterized by an XRPD pattern including peaks at $8.7^{\circ}\pm 0.2^{\circ}$, $11.1^{\circ}\pm 0.2^{\circ}$, $15.5^{\circ}\pm 0.2^{\circ}$, $24.5^{\circ}\pm 0.2^{\circ}$, and $32.4^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U5 is characterized by an XRPD pattern including any three, four, or five peaks selected from $8.7^{\circ}\pm 0.2^{\circ}$, $11.1^{\circ}\pm 0.2^{\circ}$, $15.5^{\circ}\pm 0.2^{\circ}$, $24.5^{\circ}\pm 0.2^{\circ}$, and $32.4^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form U5 further includes one or more additional peaks from Table U5 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form U5 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.156. In other embodiments, Form U5 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U5 below $\pm 0.2^{\circ}$ 2-theta.

TABLE U5

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
-----	--------------	---------	-------------	-------------

1	8.7671	10.07807	5444.62	43.05
2	9.8261	8.99414	370.22	2.35
3	11.1095	7.95784	8590.02	32.04
4	11.2145	7.88362	5529.61	29.39
5	11.3199	7.81039	6819.29	27.02
6	11.7163	7.54707	528.86	3.1
7	12.1226	7.29502	2969.31	14.93
8	12.6275	7.00441	1072.48	10.06
9	13.5633	6.5232	3636.75	15.5
10	15.4558	5.72846	15846.41	100
11	15.9914	5.53777	3287.57	23.02
12	17.8761	4.95795	1593.85	17.88
13	18.2048	4.86915	806.44	18.97
14	19.704	4.50192	754.89	2.73
15	20.0462	4.42584	2361.7	16.11
16	20.5008	4.32872	1881.55	8.21
17	20.6807	4.29147	2432.41	14.04
18	21.1724	4.1929	949.25	13.4
19	21.8626	4.06207	1868.82	6.54
20	22.775	3.90136	463.3	4.41
21	23.4014	3.79832	1275.66	6.28
22	23.6624	3.75702	3979.64	24.86
23	24.3813	3.64784	4167.45	19.84
24	24.5608	3.62159	3965.47	32.77
25	24.7244	3.59799	2743.56	7.98
26	25.2801	3.52014	740.11	10.39
27	25.7951	3.45102	404.93	8.94
28	26.6191	3.34603	1124.94	8.05
29	27.2918	3.26507	2777.97	10.46
30	27.6399	3.22473	834.35	3.34
31	28.1447	3.16803	420.62	4.63
32	28.7004	3.10794	833.96	8.61

33	29.0356	3.07282	1060.05	5.3
34	29.7716	2.9985	1050.39	8.7
35	31.4977	2.83801	661.31	10.7
36	32.3609	2.76425	2807.15	30.92
37	33.6289	2.66287	1555.13	12.9
38	34.4682	2.59992	540.68	4.12
39	35.5409	2.52387	525.66	5.04
40	38.7308	2.32303	618.14	4.43

[00775] Another aspect of the present disclosure relates to a morphic form, Form U6, of resmetirom. Form U6 is a trifluoroethanol (TFE) solvate. In some embodiments, Form U6 is characterized by an XRPD pattern including peaks at $10.6^{\circ}\pm 0.2^{\circ}$, $11.5^{\circ}\pm 0.2^{\circ}$, $18.8^{\circ}\pm 0.2^{\circ}$, $20.0^{\circ}\pm 0.2^{\circ}$, and $23.5^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U6 is characterized by an XRPD pattern including any three, four, or five peaks selected from $10.6^{\circ}\pm 0.2^{\circ}$, $11.5^{\circ}\pm 0.2^{\circ}$, $18.8^{\circ}\pm 0.2^{\circ}$, $20.0^{\circ}\pm 0.2^{\circ}$, and $23.5^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form U6 further includes one or more additional peaks from Table U6 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form U6 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.157. In other embodiments, Form U6 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U6 below $\pm 0.2^{\circ}$ 2-theta.

TABLE U6

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	10.2855	8.5935	1221.6	3.13
2	10.64	8.30793	4450.82	10.19
3	11.2786	7.8389	1006.48	2.56
4	11.5805	7.63527	8107.31	20.03

5	13.1776	6.71323	2867.25	6.9
6	16.3418	5.41981	2343.64	6.28
7	16.7821	5.27859	1792.64	5.49
8	17.539	5.05246	832.58	1.71
9	18.7949	4.71759	5015.16	13.29
10	20.0422	4.42672	6147.48	21.2
11	20.4209	4.34546	5634.03	14.83
12	20.7197	4.28347	2722.33	8.69
13	21.3405	4.16025	3181.13	9.25
14	22.2617	3.99013	3847.45	13.79
15	22.4369	3.95936	1528.74	3.58
16	23.4727	3.78694	24977.35	100
17	24.2408	3.66866	1763.31	4.53
18	25.3089	3.5162	3166.32	8.44
19	25.4237	3.50058	3181.91	10.15
20	25.9656	3.42874	1734.37	5.03
21	26.5704	3.35206	740.79	2.27
22	26.9475	3.30599	580.8	1.89
23	28.0752	3.17572	1381.74	4.35
24	28.7584	3.1018	512.02	1.04
25	29.4154	3.03401	849.8	5.18
26	30.1439	2.96232	2755.47	8.96
27	30.4676	2.93157	1898.21	7.55
28	31.2718	2.85799	2317.11	6.42
29	31.594	2.82958	1338.27	10.69
30	32.1368	2.78302	1777.92	6.28
31	33.8147	2.64866	1912.72	5.54
32	34.8863	2.56972	493.45	0.85
33	35.2723	2.54247	308.84	1.05
34	38.1646	2.35618	590.14	2.73

[00776] In other embodiments, Form U6 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 158. In other embodiments, Form U6 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 158. In other embodiments, Form U6 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 158. In other embodiments, Form U6 is also or alternatively characterized by a TGA thermogram comprising about 18.4% weight loss upon heating to about 150 °C. In other embodiments, Form U6 is also or alternatively characterized by a DSC thermogram comprising endothermic events at about 234°C and about 333 °C.

[00777] Another aspect of the present disclosure relates to a morphic form, Form U7, of resmetirom. Form U7 is a solvate comprising multiple solvents. In some embodiments, Form U7 is characterized by an XRPD pattern including peaks at $9.5^{\circ}\pm 0.2^{\circ}$, $11.5^{\circ}\pm 0.2^{\circ}$, $21.4^{\circ}\pm 0.2^{\circ}$, $23.0^{\circ}\pm 0.2^{\circ}$, and $23.8^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U7 is characterized by an XRPD pattern including any three, four, or five peaks selected from $9.5^{\circ}\pm 0.2^{\circ}$, $11.5^{\circ}\pm 0.2^{\circ}$, $21.4^{\circ}\pm 0.2^{\circ}$, $23.0^{\circ}\pm 0.2^{\circ}$, and $23.8^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form U7 further includes one or more additional peaks from Table U7 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form U7 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.159. In other embodiments, Form U7 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U7 below $\pm 0.2^{\circ}$ 2-theta.

TABLE U7

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	5.733	15.40315	609.05	19.81
2	9.4924	9.30957	1191.98	38.34
3	11.4559	7.71801	2220.15	60.36

4	15.2516	5.80469	507.63	18.74
5	16.3238	5.42573	615.58	26.67
6	16.7611	5.28515	571.82	77.56
7	18.8686	4.69932	766.07	62.06
8	20.1651	4.40002	241.05	10.6
9	21.4339	4.14233	1389.25	80.98
10	21.6493	4.10159	830.35	37.07
11	22.9737	3.86806	1112.38	100
12	23.8804	3.72321	389.29	46.21
13	25.4361	3.4989	405.43	39.04
14	28.7589	3.10175	170.48	18.31
15	29.58	3.01749	173.3	8.96
16	30.1465	2.96207	230.12	7.6
17	32.2998	2.76934	298.82	17.94
18	32.9596	2.7154	300.07	19.68
19	34.4843	2.59875	248.43	17.05
20	34.9241	2.56702	240.37	16.69
21	35.5067	2.52623	122.04	10.98

[00778] In other embodiments, Form U7 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 160. In other embodiments, Form U7 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 160. In other embodiments, Form U7 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 160. In other embodiments, Form U7 is also or alternatively characterized by a TGA thermogram comprising about 9.7% weight loss between about 100°C and about 150 °C. In other embodiments, Form U7 is also or alternatively characterized by a DSC thermogram comprising endothermic events at about 73°C, about 130 °C, and about 320°C.

[00779] Another aspect of the present disclosure relates to a morphic form, Form U8, of resmetirom. Form U8 is a cyclohexanone solvate. In some embodiments, Form U8 is characterized by an XRPD pattern including peaks at $13.9^{\circ}\pm 0.2^{\circ}$, $14.9^{\circ}\pm 0.2^{\circ}$, $21.6^{\circ}\pm 0.2^{\circ}$, $25.1^{\circ}\pm 0.2^{\circ}$, and $28.2^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, Form U8 is characterized by an XRPD pattern including any three, four, or five peaks selected from $13.9^{\circ}\pm 0.2^{\circ}$, $14.9^{\circ}\pm 0.2^{\circ}$, $21.6^{\circ}\pm 0.2^{\circ}$, $25.1^{\circ}\pm 0.2^{\circ}$, and $28.2^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form U8 further includes one or more additional peaks from Table U8 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form U8 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.161. In other embodiments, Form U8 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U8 below $\pm 0.2^{\circ}$ 2-theta.

TABLE U8

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	7.0126	12.59507	4556.49	17.58
2	10.0758	8.77188	2461.27	8.64
3	10.4677	8.44428	3024.26	11.46
4	10.6665	8.28734	3728.07	16.52
5	11.5336	7.6662	365.56	1.51
6	12.4455	7.10646	1640.65	6.28
7	13.8697	6.37975	28881.39	100
8	14.0057	6.31811	4180.07	10.8
9	14.8859	5.94643	5285.02	18.66
10	15.8756	5.57789	2038.42	7.06
11	16.6412	5.32297	1435.74	4.54
12	17.663	5.01727	964.9	10.4
13	17.9553	4.93625	2500.78	7.7
14	18.1664	4.87935	2884.34	8.09
15	18.6183	4.76193	7581.22	25.5

16	19.2347	4.61069	2947.7	9.26
17	19.5383	4.53974	3462.39	10.71
18	20.1985	4.39281	1721.77	7.1
19	20.5221	4.32427	3024.84	9.86
20	20.6546	4.29683	713.21	1.9
21	21.0499	4.21702	3209.58	12.77
22	21.1829	4.19085	1203.8	4.21
23	21.4096	4.14698	4280.37	14.99
24	21.6371	4.10389	13519.49	49.15
25	21.7673	4.07964	4176.77	14.23
26	22.7537	3.90495	11349.39	39.81
27	23.2209	3.82744	3995.98	13.49
28	24.5375	3.62496	1685.5	5.95
29	24.9789	3.5619	3929.99	13.88
30	25.143	3.53903	12533.09	44.16
31	25.4839	3.49245	10963.84	37.87
32	26.705	3.33547	950.15	3.72
33	26.9635	3.30407	2360.02	8.95
34	27.2095	3.27476	5024.1	26.45
35	27.5123	3.23939	652.76	2.13
36	27.7061	3.21717	969.93	2.87
37	27.9137	3.19372	5548.14	18.58
38	28.2795	3.15323	10331.67	51.2
39	28.9425	3.08249	1302.9	3.42
40	29.8159	2.99415	3287.86	17.79
41	29.9247	2.98351	4631.07	16.79
42	30.7063	2.90933	1156.34	4.26
43	31.0624	2.87679	4726.46	17.64
44	31.776	2.81379	2159.38	9.24
45	32.6672	2.73903	1577.76	7.2
46	33.0917	2.70486	1495.52	2.91
47	33.1863	2.69736	2249.17	15.01

48	34.0413	2.63154	699.14	1.98
49	34.6723	2.58508	456.82	3.63
50	35.1084	2.55397	627.8	2.63
51	35.4353	2.53115	658.28	1.97
52	36.0102	2.49205	1327.57	4.38
53	36.145	2.48306	503.07	3.46
54	37.5634	2.3925	479.48	1.36
55	37.8626	2.37428	603.7	4.4
56	38.1928	2.3545	808.06	2.72
57	38.928	2.31172	382.27	3.33
58	39.4781	2.28076	1343.97	6.09

[00780] In other embodiments, Form U8 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 162. In other embodiments, Form U8 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 162. In other embodiments, Form U8 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 162. In other embodiments, Form U8 is also or alternatively characterized by a TGA thermogram comprising about 18.4% weight loss upon heating to about 200 °C. In other embodiments, Form U8 is also or alternatively characterized by a DSC thermogram comprising endothermic events at about 192 °C and about 333°C.

[00781] Another aspect of the present disclosure relates to a morphic form, Form U9, of resmetirom. Form U9 is a methyl acetate solvate. In some embodiments, Form U9 is characterized by an XRPD pattern including peaks at $10.5^{\circ}\pm 0.2^{\circ}$, $11.0^{\circ}\pm 0.2^{\circ}$, $11.8^{\circ}\pm 0.2^{\circ}$, $19.8^{\circ}\pm 0.2^{\circ}$, and $24.4^{\circ}\pm 0.2^{\circ}$ 2-theta 2-theta. In some embodiments, Form U9 is characterized by an XRPD pattern including any three, four, or five peaks selected from $10.5^{\circ}\pm 0.2^{\circ}$, $11.0^{\circ}\pm 0.2^{\circ}$, $11.8^{\circ}\pm 0.2^{\circ}$, $19.8^{\circ}\pm 0.2^{\circ}$, and $24.4^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, the

XRPD pattern of Form U9 further includes one or more additional peaks from Table U9 below $\pm 0.2^\circ$ 2-theta. In other embodiments, Form U9 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.163. In other embodiments, Form U9 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table U9 below $\pm 0.2^\circ$ 2-theta.

TABLE U9

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	7.6885	11.48933	671.89	1.61
2	10.4601	8.45042	5836.26	18.4
3	10.8149	8.17399	5564.51	14.11
4	10.9786	8.05248	3695.47	16.74
5	11.7758	7.50902	4950.95	15.76
6	12.1382	7.28564	1508.91	6.41
7	13.0491	6.77906	1438.25	9.74
8	14.6314	6.04931	3218.99	8.71
9	16.0848	5.50583	136.28	1.75
10	17.1691	5.16048	3178.15	7.69
11	18.7268	4.73458	1085.39	3.47
12	19.5372	4.53998	1409.37	12.25
13	19.8037	4.47949	5716.78	13.73
14	20.2287	4.38632	731.55	3.39
15	21.1973	4.18802	925.59	2.2
16	21.7293	4.08668	2265.31	11.57
17	22.1518	4.00969	1982.76	7.52
18	22.3534	3.97398	3347.05	11.81
19	22.8432	3.88985	1906.28	6.41
20	23.7089	3.74975	1415.86	13.34
21	24.3676	3.64986	25497.61	100
22	25.4685	3.49453	1437.08	5.17
23	26.7314	3.33223	311.08	1.45

24	27.3642	3.2566	3329.09	13.02
25	27.8413	3.20186	1122.34	2.26
26	29.4889	3.0266	968.96	5.06
27	29.8906	2.98684	579.97	2.47
28	30.445	2.9337	1009.5	2.94
29	32.0635	2.78921	2122.14	22.17
30	32.8747	2.72222	557.57	0.99
31	33.8796	2.64373	554.21	2.18
32	35.8627	2.50196	1523.79	8.06
33	36.3251	2.47116	321.07	2.64
34	39.6202	2.27291	561.36	0.94

[00782] In other embodiments, Form U9 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 164. In other embodiments, Form U9 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 164. In other embodiments, Form U9 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 164. In other embodiments, Form U9 is also or alternatively characterized by a TGA thermogram comprising about 13.9% weight loss upon heating to about 175 °C. In other embodiments, Form U9 is also or alternatively characterized by a DSC thermogram comprising endothermic events at about 110 °C, about 154°C, and about 333 °C.

[00783] Another aspect of the present disclosure relates to a resmetirom triethyl citrate cocrystal, Form C1. In some embodiments, Form C1 is characterized by an XRPD pattern including peaks at $7.1^{\circ}\pm 0.2^{\circ}$, $9.3^{\circ}\pm 0.2^{\circ}$, $10.1^{\circ}\pm 0.2^{\circ}$, $12.5^{\circ}\pm 0.2^{\circ}$, and $23.5^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, Form C1 is characterized by an XRPD pattern including any three, four, or five peaks selected from $7.1^{\circ}\pm 0.2^{\circ}$, $9.3^{\circ}\pm 0.2^{\circ}$, $10.1^{\circ}\pm 0.2^{\circ}$, $12.5^{\circ}\pm 0.2^{\circ}$, and $23.5^{\circ}\pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form C1 further includes one or more

additional peaks from Table C1 below $\pm 0.2^\circ$ 2-theta. In other embodiments, Form C1 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.165. In other embodiments, Form C1 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C1 below $\pm 0.2^\circ$ 2-theta.

TABLE C1

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	6.9261	12.75215	7410	63.36
2	7.1357	12.37808	10474.93	80.71
3	9.325	9.4764	7092.72	66.8
4	10.1773	8.68462	7066.21	75.61
5	10.547	8.38096	3215.86	48.77
6	10.9581	8.0675	315.15	15.97
7	11.5424	7.66037	1551.33	10.22
8	12.1751	7.26368	627.35	4.87
9	12.5168	7.06613	11534.98	98.12
10	13.8824	6.37397	1669.18	16.77
11	14.2749	6.19958	1479.93	10.47
12	14.5907	6.06607	1782.76	13.47
13	15.5307	5.70098	2854.44	22.94
14	16.636	5.32462	3483.72	42.3
15	17.1764	5.15828	1873.39	19.28
16	17.4582	5.07567	5286.33	51.91
17	17.7624	4.9894	1480.41	11.67
18	18.0054	4.92261	3072.46	27.05
19	18.6068	4.76484	634.51	13.07
20	19.9126	4.45522	1548.48	8.69
21	20.4593	4.33741	7697.27	68
22	20.875	4.25197	3464.14	25.31
23	21.1905	4.18935	4196.07	35.78
24	21.3976	4.14927	2696.13	40.43

25	21.7908	4.07528	1683.43	12.75
26	21.9811	4.04044	4042.97	32.02
27	22.6241	3.92704	1400.15	15.29
28	22.9197	3.87705	2627.87	26.83
29	23.1943	3.83176	8670.52	78.2
30	23.5388	3.77645	9211.7	100
31	24.1116	3.68802	1048.25	10.9
32	24.4772	3.63376	2415.74	21.7
33	24.9164	3.5707	2119.26	21.68
34	25.4118	3.5022	4939.26	61.46
35	25.9764	3.42734	595.39	4.03
36	26.217	3.39643	775.31	3.36
37	26.8826	3.31382	855.66	18.43
38	28.2579	3.1556	1326.55	25.47
39	28.8017	3.09724	1233.57	20.31
40	29.1517	3.06084	3228.96	34.48
41	29.4566	3.02985	1361.99	24.88
42	30.3351	2.94408	4441.42	51.69
43	30.7001	2.9099	783.67	13.42
44	31.4059	2.8461	370.48	19.52
45	34.2481	2.61613	591.61	7.18
46	34.6407	2.58737	1385.6	13.73
47	35.0133	2.56069	1051.49	9.94
48	35.9659	2.49502	666.62	10.23
49	36.2324	2.47728	478.84	2.48
50	36.4846	2.46073	701.84	5.82
51	36.9727	2.42936	273.82	6.85
52	38.0376	2.36375	429.8	6.09

[00784] In other embodiments, Form C1 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 167. In other embodiments, Form

C1 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 167. In other embodiments, Form C1 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 167. In other embodiments, Form C1 is also or alternatively characterized by a TGA thermogram comprising about 37% weight loss by 250 °C. In other embodiments, Form C1 is also or alternatively characterized by a DSC thermogram comprising endothermic events at about 84 °C and about 330 °C.

[00785] In other embodiments, Form C1 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 166. In other embodiments, Form C1 is also or alternatively characterized by an FTIR spectrum substantially similar to the FTIR spectrum of Form C1 set forth in FIG. 168. In other embodiments, Form C1 is also or alternatively characterized by a Raman spectrum substantially similar to the Raman spectrum of Form C1 set forth in FIG. 169.

[00786] Another aspect of the present disclosure relates to a resmetirom cytosine cocrystal, Form C2. In some embodiments, Form C2 is characterized by an XRPD pattern including peaks at 8.7°±0.2°, 10.8°±0.2°, 13.6°±0.2°, 17.6°±0.2°, and 21.6°±0.2° 2-theta. In some embodiments, Form C2 is characterized by an XRPD pattern including any three, four, or five peaks selected from 8.7°±0.2°, 10.8°±0.2°, 13.6°±0.2°, 17.6°±0.2°, and 21.6°±0.2° 2-theta. In some embodiments, the XRPD pattern of Form C2 further includes one or more additional peaks from Table C2 below ±0.2° 2-theta. In other embodiments, Form C2 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.170. In other embodiments, Form C2 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C2 below ±0.2° 2-theta.

TABLE C2

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	4.2417	20.81454	6779.84	16.96
2	8.6536	10.20998	11155.15	26.7
3	9.88	8.94524	1601.25	3.14
4	10.8246	8.16668	23480.34	63.11
5	12.7804	6.92099	2165.61	5.18
6	13.5506	6.52925	13047.3	22.53
7	13.9824	6.32859	2944.7	8.07
8	16.2805	5.44007	4661.81	12.84
9	16.4467	5.38546	4174.67	6.97
10	16.5909	5.33898	3406.55	5.12
11	16.9747	5.21913	2233.45	4.96
12	17.6316	5.02614	28850.83	100
13	19.8626	4.46634	1194.58	2.11
14	20.1138	4.41111	5508.4	12.45
15	21.2616	4.1755	6253.95	23.38
16	22.22	3.99753	1835.84	4.59
17	23.8092	3.73418	810.52	3.98
18	24.0005	3.70485	2299.78	5.05
19	24.6804	3.6043	1487.54	4.33
20	25.0678	3.54947	1798.92	4.5
21	25.5959	3.47742	3463.58	11.26
22	26.1005	3.41132	3883.75	14.19
23	26.7606	3.32866	2333.38	6.98
24	27.0217	3.29709	3061.49	4.96
25	28.1868	3.16339	2407.88	7.84
26	28.8991	3.08702	1201.84	1.38
27	29.4837	3.02713	518.5	0.68
28	29.9913	2.97704	1513.51	7.16
29	30.4181	2.93623	2166.29	8.5
30	30.6672	2.91295	4648.41	13.13
31	31.1483	2.86904	2530.12	6.6

32	31.9573	2.79824	420.2	1.18
33	32.6534	2.74016	811.94	2.17
34	33.541	2.66965	1458.65	4.4
35	34.3951	2.60528	558.98	1.92
36	38.9825	2.30861	666.92	5.07

[00787] In other embodiments, Form C2 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 172. In other embodiments, Form C2 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 172. In other embodiments, Form C2 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 172. In other embodiments, Form C2 is also or alternatively characterized by a TGA thermogram comprising about 0.6% weight loss up to 200 °C. In other embodiments, Form C2 is also or alternatively characterized by a DSC thermogram comprising two major overlapping endothermic events with onset at 283 °C.

[00788] In other embodiments, Form C2 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 171. In other embodiments, Form C2 is also or alternatively characterized by an FTIR spectrum substantially similar to the FTIR spectrum of Form C2 set forth in FIG. 173. In other embodiments, Form C2 is also or alternatively characterized by a Raman spectrum substantially similar to the Raman spectrum of Form C2 set forth in FIG. 174.

[00789] Another aspect of the present disclosure relates to a resmetirom calcium pantothenate cocrystal, Form C3. In some embodiments, Form C3 is characterized by an XRPD pattern including peaks at 5.8°±0.2°, 11.5°±0.2°, 19.2°±0.2°, 20.0°±0.2°, and 23.4°±0.2° 2-theta. In some embodiments, Form C3 is characterized by an XRPD pattern

including any three, four, or five peaks selected from $5.8^{\circ} \pm 0.2^{\circ}$, $11.5^{\circ} \pm 0.2^{\circ}$, $19.2^{\circ} \pm 0.2^{\circ}$, $20.0^{\circ} \pm 0.2^{\circ}$, and $23.4^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form C3 further includes one or more additional peaks from Table C3 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form C3 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 175. In other embodiments, Form C3 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C3 below $\pm 0.2^{\circ}$ 2-theta.

TABLE C3

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	5.7696	15.30563	22440.66	100
2	7.4184	11.90701	862.12	2.97
3	9.5642	9.23984	871.39	2.57
4	10.4609	8.44977	1361.55	3.65
5	11.5407	7.6615	13739.68	58.04
6	13.7701	6.42567	653.77	2.22
7	14.2594	6.20627	2714.99	9.25
8	15.6688	5.65104	1684.12	5.92
9	17.2084	5.14878	825.37	6.69
10	18.0978	4.8977	379.21	6.95
11	18.6228	4.76079	3650.03	10.41
12	19.0191	4.66248	1534.7	4.89
13	19.2142	4.61556	4204.99	17.47
14	19.9543	4.44602	5981.2	36.07
15	20.3591	4.35851	765.78	1.61
16	20.964	4.2341	1179.54	3.44
17	22.5076	3.9471	3547.03	13.85
18	22.7854	3.8996	1760.47	11.8
19	23.4466	3.7911	5524.06	27.72
20	24.0248	3.70116	345.38	2.71

21	24.5578	3.62202	1921.27	8.97
22	26.5729	3.35174	680	4.09
23	26.9246	3.30876	863.39	3.19
24	27.7587	3.21119	2628.23	14.76
25	29.0589	3.07041	381.82	4.34
26	29.967	2.9794	778.9	5.55
27	30.3237	2.94516	433.23	1.04
28	30.7629	2.90411	464.56	3.75
29	33.3805	2.68211	409.05	2.18
30	35.3781	2.53511	318.03	5.11

[00790] Another aspect of the present disclosure relates to a resmetirom dimethylglycine cocrystal, Form C4. Form C4 also contains 0.7 molar equivalents of isopropanol (IPA). In some embodiments, Form C4 is characterized by an XRPD pattern including peaks at $11.3^{\circ} \pm 0.2^{\circ}$, $14.1^{\circ} \pm 0.2^{\circ}$, $18.0^{\circ} \pm 0.2^{\circ}$, $19.7^{\circ} \pm 0.2^{\circ}$, and $22.7^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form C4 is characterized by an XRPD pattern including any three, four, or five peaks selected from $11.3^{\circ} \pm 0.2^{\circ}$, $14.1^{\circ} \pm 0.2^{\circ}$, $18.0^{\circ} \pm 0.2^{\circ}$, $19.7^{\circ} \pm 0.2^{\circ}$, and $22.7^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form C4 further includes one or more additional peaks from Table C4 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form C4 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.176. In other embodiments, Form C4 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C4 below $\pm 0.2^{\circ}$ 2-theta.

TABLE C4

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	6.5477	13.48825	3665.71	19.03
2	7.1047	12.43206	613.6	13.75
3	7.8204	11.29578	415.18	5.6

4	9.7683	9.04724	1331.71	6.46
5	11.3349	7.80009	3765.11	28.22
6	12.9853	6.81224	1285.26	7.28
7	14.1252	6.26493	9971.23	48.39
8	15.5508	5.69367	937.65	3.07
9	16.2021	5.46621	3087.99	12.34
10	16.8237	5.26563	5629.33	33.77
11	17.476	5.07053	493.16	1.38
12	18.0202	4.9186	13001.49	58.77
13	18.6194	4.76166	3029.98	19.12
14	19.5498	4.5371	7380.09	33.49
15	19.6908	4.50491	23734.61	100
16	19.819	4.47607	11027.13	51.9
17	20.0724	4.42012	1617.62	12.73
18	20.3159	4.36768	1351.34	20.35
19	20.8841	4.25012	678.99	16.23
20	21.7405	4.0846	1191.74	9.65
21	21.8982	4.05554	5028.84	42.16
22	22.3505	3.97448	3487.88	23.18
23	22.7003	3.91402	13412.39	86.29
24	23.2407	3.82422	1329.08	8.33
25	24.061	3.69566	6030.99	45.22
26	24.451	3.6376	1758.21	6.11
27	24.7721	3.59117	2571.7	11.72
28	25.1048	3.54433	1084.58	6.78
29	25.3457	3.51118	1178.74	4.84
30	25.5582	3.48246	567.17	1.38
31	26.6289	3.34483	3771.59	18.38
32	26.842	3.31875	1603.75	5.43
33	26.9627	3.30416	2098.16	13.01
34	27.2087	3.27485	862.91	12.33
35	27.9475	3.18993	7483.08	31.47

36	28.2373	3.15785	6180.38	26.6
37	28.4273	3.13718	4393.75	24.02
38	28.991	3.07745	1304.24	16.97
39	29.5089	3.02461	2219.41	16.2
40	29.7641	2.99925	1589.71	9.27
41	29.9038	2.98555	1332.73	11.01
42	30.8447	2.89659	1328.55	5.14
43	31.1249	2.87115	846.5	2.94
44	31.3829	2.84813	1284.97	3.86
45	32.7435	2.73283	1299.62	9.56
46	33.2809	2.68992	1110.71	3.77
47	33.4806	2.67432	1371.34	5.11
48	34.0381	2.63179	868.41	3.68
49	34.7889	2.57669	404.6	7.43
50	35.14	2.55174	1963.14	10.98
51	35.6794	2.51439	1188.88	5.31
52	36.2797	2.47415	642.79	4.75
53	36.6985	2.44688	1037.1	5.49
54	37.2998	2.4088	636.75	2.79
55	37.7636	2.38028	505.16	3.48
56	38.9614	2.30981	546.34	1.46
57	39.3733	2.28659	426.2	2.55
58	39.7446	2.26608	282.9	1.15

[00791] In other embodiments, Form C4 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 178. In other embodiments, Form C4 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 178. In other embodiments, Form C4 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 178. In other embodiments, Form C4 is also or alternatively characterized by a TGA thermogram

comprising two weight loss steps: 4.4% by 75 °C (about 0.5 Eq IPA) and an additional 2.1% by 125 °C (about 0.2 Eq IPA) In other embodiments, Form C4 is also or alternatively characterized by a DSC thermogram comprising multiple overlapping endotherms with peaks at 68 °C (broad) and 130 °C (double endo-therms), with an apparent onset of decomposition after the last endotherm.

[00792] In other embodiments, Form C4 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 177.

[00793] Another aspect of the present disclosure relates to a resmetirom dichloroacetic acid cocrystal, Form C5. In some embodiments, Form C5 is characterized by an XRPD pattern including peaks at 3.5°±0.2°, 6.9°±0.2°, 10.3°±0.2°, 13.7°±0.2°, and 17.2°±0.2° 2-theta. In some embodiments, Form C5 is characterized by an XRPD pattern including any three, four, or five peaks selected from 3.5°±0.2°, 6.9°±0.2°, 10.3°±0.2°, 13.7°±0.2°, and 17.2°±0.2° 2-theta. In some embodiments, the XRPD pattern of Form C5 further includes one or more additional peaks from Table C5 below ±0.2° 2-theta. In other embodiments, Form C5 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.179. In other embodiments, Form C5 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C5 below ±0.2° 2-theta.

TABLE C5

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	3.4511	25.58093	14898.62	42.77
2	6.8779	12.84154	36701.69	100
3	10.3113	8.572	25333.87	59.04
4	11.914	7.42227	605.93	1.96
5	12.1102	7.30245	872.05	2.39
6	13.7568	6.43187	13014.53	31.58

7	13.8721	6.37867	2288.98	6.53
8	14.3149	6.18232	583.48	1.9
9	15.5631	5.68919	1715.74	4.91
10	17.2099	5.14833	17391.34	35.91
11	17.6458	5.02212	1484.29	17.1
12	18.1643	4.87992	999	2.82
13	18.975	4.67322	2927.02	11.41
14	19.3637	4.58028	3873.19	11.96
15	19.5949	4.52673	4027.44	11.54
16	19.7382	4.4942	2114.48	6.35
17	20.0838	4.41765	8676.18	27.84
18	20.6918	4.28918	560.83	0.89
19	20.8908	4.24878	498.86	1.98
20	21.5949	4.1118	1076.28	4.19
21	22.1406	4.01168	3740.36	11.82
22	22.7221	3.91032	2695.21	6.5
23	23.1472	3.83946	5468.96	20.51
24	23.8142	3.73341	2798.11	11.92
25	23.9408	3.71395	3221.06	13.84
26	24.2097	3.67331	936.41	2.71
27	24.3733	3.64902	3585.55	11.38
28	24.5021	3.63012	3181.48	11.93
29	24.8841	3.57525	1034.58	3.48
30	25.0516	3.55173	3168.92	10.97
31	25.9703	3.42813	507.45	1.1
32	26.3112	3.38448	3202.7	10.83
33	26.6386	3.34362	473.98	0.9
34	27.2874	3.26559	822.15	2.14
35	27.7066	3.21711	1197.9	2.5
36	28.0226	3.18156	4566.78	14.62
37	28.1932	3.16268	856.38	3.74
38	28.3486	3.14571	1303.11	3.27

39	29.2367	3.05214	1269.14	5.94
40	29.4214	3.0334	1637.5	10.47
41	29.976	2.97852	1095.54	7.86
42	31.2608	2.85898	1007.39	3.09
43	31.3496	2.85108	765.3	3.82
44	31.8788	2.80495	938.72	5.77
45	32.3037	2.76902	1994.52	7.75
46	32.5057	2.75227	938.01	3.2
47	32.7188	2.73483	912.41	5.07
48	34.1293	2.62496	900.17	4.41
49	34.8415	2.57292	4774.16	16.13
50	35.868	2.5016	476.97	3.08
51	36.3477	2.46968	503.12	2.87
52	36.8015	2.44026	936.64	2.77
53	37.3021	2.40865	468.91	4.06
54	37.9901	2.3666	1568.55	4.15
55	38.4547	2.33907	644.05	1.7
56	39.6403	2.2718	437.41	2.07
57	39.7744	2.26445	878.31	2.48

[00794] In other embodiments, Form C5 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 181. In other embodiments, Form C5 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 181. In other embodiments, Form C5 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 181. In other embodiments, Form C5 is also or alternatively characterized by a TGA thermogram comprising about 37.8% weight loss by about 200 °C and a subsequent onset of decomposition at 339 °C. In other embodiments, Form C5 is also or alternatively characterized by a DSC thermogram comprising a major endotherm at about 106 °C (onset),

a minor broad endotherm at about 186 °C (peak), and a major endotherm at about 319 °C (onset).

[00795] In other embodiments, Form C5 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 180. In other embodiments, Form C5 is also or alternatively characterized by an FTIR spectrum substantially similar to the FTIR spectrum of Form C5 set forth in FIG. 182. In other embodiments, Form C5 is also or alternatively characterized by a Raman spectrum substantially similar to the Raman spectrum of Form C5 set forth in FIG. 183.

[00796] Another aspect of the present disclosure relates to a resmetirom diethylamine cocrystal, Form C6. In some embodiments, Form C6 is characterized by an XRPD pattern including peaks at 10.0°±0.2°, 12.2°±0.2°, 13.1°±0.2°, 22.2°±0.2°, and 22.8°±0.2° 2-theta. In some embodiments, Form C6 is characterized by an XRPD pattern including any three, four, or five peaks selected from 10.0°±0.2°, 12.2°±0.2°, 13.1°±0.2°, 22.2°±0.2°, and 22.8°±0.2° 2-theta. In some embodiments, the XRPD pattern of Form C6 further includes one or more additional peaks from Table C6 below ±0.2° 2-theta. In other embodiments, Form C6 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.184. In other embodiments, Form C6 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C6 below ±0.2° 2-theta.

TABLE C6

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	5.2971	16.66952	956.19	6.93
2	10.0353	8.80712	10048.41	48.75
3	10.5941	8.34385	748.1	2.95
4	11.3562	7.78556	2933.07	13.66
5	11.6624	7.58182	618.08	1.97

6	12.201	7.24827	10453.06	51.23
7	12.8627	6.87684	8532	42.44
8	13.0877	6.75913	13507.33	62.99
9	13.5181	6.54488	703.62	2.69
10	14.9977	5.90237	417.24	1.56
11	15.9405	5.55533	1657.11	7.27
12	16.1198	5.49393	972.38	8.09
13	16.4983	5.36874	988.85	4.26
14	17.816	4.97451	2691.05	15.33
15	19.5738	4.53159	2042.05	13.69
16	20.1002	4.41407	7413.88	49.48
17	20.5808	4.31207	2067.3	8.2
18	21.0706	4.21292	779.55	2
19	21.3142	4.16532	2264.18	13.97
20	21.831	4.06787	713.14	1.49
21	22.157	4.00876	12628.99	61.1
22	22.7951	3.89796	16857.94	100
23	23.2212	3.82739	2627.77	10.72
24	23.4978	3.78295	2030.34	8.4
25	23.7006	3.75104	2169.77	10.18
26	24.0386	3.69905	3784.33	24.57
27	24.3971	3.64551	5226.85	51.43
28	24.6639	3.60667	2076.74	12.18
29	25.3796	3.50657	1219.38	5.27
30	25.6402	3.47152	1412.87	6.03
31	25.8604	3.44245	1943.82	8.18
32	26.222	3.3958	671.53	2.01
33	26.72	3.33362	1823.98	7.83
34	26.9607	3.30441	1500.07	5.82
35	27.5673	3.23306	7351.27	57.33
36	27.9076	3.19441	870.6	6.47
37	28.4923	3.13016	2089.22	14.3

38	28.6246	3.11599	2068.34	12.37
39	28.8681	3.09026	1242.14	7.72
40	29.2654	3.04921	590.16	2.03
41	29.9528	2.98078	559.87	3.61
42	30.4643	2.93188	1249.74	7.9
43	30.9511	2.88687	835.55	3.82
44	32.9726	2.71435	1417.52	12.43
45	33.4488	2.67679	1437.79	8.58
46	34.0547	2.63054	505.85	2.13
47	34.5804	2.59175	668.49	10.5
48	35.3935	2.53405	964.15	12.11
49	35.9588	2.49549	520.72	3.57
50	36.6043	2.45295	460.98	2.73
51	37.6447	2.38752	1029.39	7.36
52	38.2271	2.35247	723.81	5.14
53	38.4998	2.33643	392.41	1.68
54	39.2005	2.29627	801.46	3.68
55	39.9227	2.25638	390.97	1.63

[00797] Another aspect of the present disclosure relates to a resmetirom 4-aminopyridine salt, Form C7. In some embodiments, Form C7 is characterized by an XRPD pattern including peaks at $4.5^{\circ} \pm 0.2^{\circ}$, $8.9^{\circ} \pm 0.2^{\circ}$, $24.5^{\circ} \pm 0.2^{\circ}$, $27.3^{\circ} \pm 0.2^{\circ}$, and $16.9^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form C7 is characterized by an XRPD pattern including any three, four, or five peaks selected from $4.5^{\circ} \pm 0.2^{\circ}$, $8.9^{\circ} \pm 0.2^{\circ}$, $24.5^{\circ} \pm 0.2^{\circ}$, $27.3^{\circ} \pm 0.2^{\circ}$, and $16.9^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form C7 further includes one or more additional peaks from Table C7 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form C7 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.185. In other embodiments, Form C7 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C7 below $\pm 0.2^{\circ}$ 2-theta.

TABLE C7

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	4.4968	19.63459	5394.36	46.04
2	8.916	9.9101	10862.26	100
3	10.4586	8.45162	651.07	5.76
4	11.3466	7.79211	671.17	10.31
5	11.7719	7.5115	1096.16	17.91
6	13.4936	6.5567	2050.08	14.97
7	14.9666	5.91455	253.9	17.51
8	15.5118	5.7079	663.98	11.36
9	16.6027	5.33523	2135.36	24.32
10	16.9116	5.23845	1742.49	51.75
11	17.5071	5.06159	2399.38	25.68
12	19.2074	4.61718	679.33	8.17
13	20.6392	4.29999	857.59	10.58
14	21.4114	4.14664	737.24	6.01
15	22.4511	3.9569	800.23	15.59
16	23.5027	3.78218	1491.64	24.98
17	24.5506	3.62306	4901.5	88.91
18	26.2463	3.39271	1079.75	13.87
19	27.3535	3.25784	2638.14	61.44
20	28.7129	3.10662	799.05	12.02
21	31.7118	2.81934	364.03	24.05

[00798] In other embodiments, Form C7 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 187. In other embodiments, Form C7 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 187. In other embodiments, Form C7 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 187. In other embodiments, Form C7 is also or alternatively characterized by a TGA thermogram

comprising about 1.1% weight loss by 100 °C, a further 2.2% weight loss by 225 °C, and the onset of decomposition at 255 °C. In other embodiments, Form C7 is also or alternatively characterized by a DSC thermogram comprising a minor broad endotherm at 76 °C (peak), a minor endotherm at 178 °C (peak) overlapping with an exotherm at 181 °C (onset), followed by a broad endotherm at 216 °C (peak) and a sharp major endotherm at 267 °C (onset).

[00799] In other embodiments, Form C7 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 186. In other embodiments, Form C7 is also or alternatively characterized by an FTIR spectrum substantially similar to the FTIR spectrum of Form C7 set forth in FIG. 188. In other embodiments, Form C7 is also or alternatively characterized by a Raman spectrum substantially similar to the Raman spectrum of Form C7 set forth in FIG. 189.

[00800] Another aspect of the present disclosure relates to a resmetirom imidazole salt, Form C8. In some embodiments, Form C8 is characterized by an XRPD pattern including peaks at 6.3°±0.2°, 7.3°±0.2°, 17.4°±0.2°, 21.9°±0.2°, and 22.3°±0.2° 2-theta. In some embodiments, Form C8 is characterized by an XRPD pattern including any three, four, or five peaks selected from 6.3°±0.2°, 7.3°±0.2°, 17.4°±0.2°, 21.9°±0.2°, and 22.3°±0.2° 2-theta. In some embodiments, the XRPD pattern of Form C8 further includes one or more additional peaks from Table C8 below ±0.2° 2-theta. In other embodiments, Form C8 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 190. In other embodiments, Form C8 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C8 below ±0.2° 2-theta.

TABLE C8

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	6.2524	14.12472	3005.04	14.58

2	7.0862	12.4645	4809.14	27.85
3	7.3455	12.02511	8640.74	36.84
4	8.6787	10.18049	1756.62	8.2
5	10.3378	8.5501	569.97	6.24
6	12.9882	6.81068	2588.75	12.26
7	14.0702	6.2893	1703.76	8.4
8	14.4565	6.12208	2916.63	12.87
9	15.7439	5.62426	2342.27	8.12
10	15.9734	5.54396	2763.27	13.52
11	17.4447	5.07955	17484.1	100
12	19.1315	4.63533	1677.97	17.6
13	20.5562	4.31717	1229.52	8.28
14	21.2516	4.17744	1315.99	8.79
15	21.9175	4.052	9895.77	54.81
16	22.3273	3.97855	4961.51	37.18
17	22.7788	3.9007	3978.35	17
18	23.1023	3.84681	749.57	5.35
19	23.9212	3.71695	2296.43	8.15
20	24.32	3.65689	1810.96	6.88
21	24.6027	3.61552	2213.63	6.31
22	25.5351	3.48557	4733.93	36.97
23	25.9072	3.43634	1459.28	8.23
24	26.78	3.32629	886.59	3.55
25	27.1031	3.28737	1957.23	6.56
26	27.284	3.26598	1260.48	4.17
27	27.8688	3.19876	566.33	4.14
28	28.2819	3.15297	2235.96	8.73
29	29.0381	3.07256	3622.15	16.34
30	29.4019	3.03537	816.08	4.67
31	29.7999	2.99572	2357.71	10.22
32	30.1602	2.96076	1355.01	8.49
33	30.5964	2.91953	1061.22	5

34	30.9424	2.88767	857.8	4.12
35	31.6997	2.82038	716.21	2.58
36	32.2004	2.77766	792.45	3.07
37	33.7749	2.65169	1717.39	12.67
38	34.8224	2.57428	1682.15	10.95
39	35.3445	2.53745	250.46	1.79
40	37.7409	2.38165	422.24	2.84

[00801] In other embodiments, Form C8 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 192. In other embodiments, Form C8 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 192. In other embodiments, Form C8 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 192. In other embodiments, Form C8 is also or alternatively characterized by a TGA thermogram comprising about 3.1% weight loss by 175 °C, and an additional about 13.4% weight loss by about 275 °C. In other embodiments, Form C8 is also or alternatively characterized by a DSC thermogram comprising endotherms at 150 °C (onset) and at 231 °C (onset).

[00802] In other embodiments, Form C8 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 191. In other embodiments, Form C8 is also or alternatively characterized by an FTIR spectrum substantially similar to the FTIR spectrum of Form C8 set forth in FIG. 193. In other embodiments, Form C8 is also or alternatively characterized by a Raman spectrum substantially similar to the Raman spectrum of Form C8 set forth in FIG. 194.

[00803] Another aspect of the present disclosure relates to a resmetirom tromethamine salt, Form C9. In some embodiments, Form C9 is characterized by an XRPD pattern including peaks at 7.3°±0.2°, 9.0°±0.2°, 20.2°±0.2°, 21.1°±0.2°, and 22.5°±0.2° 2-theta. In some

embodiments, Form C9 is characterized by an XRPD pattern including any three, four, or five peaks selected from $7.3^{\circ} \pm 0.2^{\circ}$, $9.0^{\circ} \pm 0.2^{\circ}$, $20.2^{\circ} \pm 0.2^{\circ}$, $21.1^{\circ} \pm 0.2^{\circ}$, and $22.5^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form C9 further includes one or more additional peaks from Table C9 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form C9 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG.195. In other embodiments, Form C9 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table C9 below $\pm 0.2^{\circ}$ 2-theta.

TABLE C9

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	7.3512	12.01577	13097.05	2.93
2	8.0985	10.9086	3557.41	0.92
3	8.7713	10.07325	3101.57	0.67
4	8.9951	9.8231	7924.58	2.06
5	11.1154	7.95367	4332.3	1.16
6	13.4438	6.58088	195.72	0.03
7	14.2038	6.23046	3649.25	0.67
8	16.4904	5.3713	2546.23	1.5
9	16.732	5.29427	6407.22	1.19
10	17.1762	5.15834	3898.19	1.34
11	17.5949	5.03654	605.15	0.42
12	18.0216	4.91823	3108.23	0.74
13	18.2299	4.86249	2724.72	0.46
14	18.4071	4.81608	7067.73	1.51
15	19.2779	4.60047	3095.98	0.96
16	19.6314	4.51842	2335.22	0.68
17	20.1896	4.39474	574584	100
18	20.6108	4.30586	1554.1	0.36
19	21.1344	4.20036	10878.77	3.39
20	21.2529	4.1772	4419.81	0.99

21	21.6364	4.10402	8282.58	2.15
22	22.0944	4.01996	1015.2	0.73
23	22.5817	3.9343	21917.72	3.75
24	22.7283	3.90926	2576.55	1.03
25	23.2806	3.81775	6072.32	1.62
26	23.3777	3.80212	4980.11	1.41
27	24.1897	3.6763	1816.71	0.31
28	24.8801	3.57582	5794.71	1.32
29	25.218	3.52867	1445.35	0.22
30	25.3851	3.50582	1178.21	0.21
31	25.5263	3.48674	808.96	0.45
32	25.7	3.46357	1448.52	0.22
33	26.1444	3.4057	692.62	0.16
34	26.3835	3.37537	542.39	0.11
35	26.6178	3.3462	2028.37	0.31
36	26.9642	3.30398	1441.77	1.46
37	27.1471	3.28214	6605.28	1.23
38	27.9199	3.19302	3105.96	0.78
39	28.1809	3.16404	1750.19	0.39
40	28.3544	3.14507	2670.28	0.48
41	28.9084	3.08605	2151.67	0.53
42	29.0958	3.0666	1521.36	0.4
43	29.6323	3.01229	1755.39	0.32
44	29.9566	2.98041	687.13	0.12
45	30.1664	2.96016	1002.8	0.18
46	31.3726	2.84904	1365.64	0.25
47	32.1245	2.78405	1144.62	0.33
48	32.7628	2.73126	485.35	0.08
49	33.1783	2.698	759.38	0.12
50	33.4113	2.67971	787.78	0.19
51	33.6996	2.65745	1205.27	0.19
52	34.0362	2.63193	1639.99	0.34

53	34.1975	2.61988	1986.11	0.45
54	34.8657	2.57119	423.7	0.17
55	35.436	2.5311	718.19	0.17
56	36.0916	2.48662	688.05	0.26
57	36.4068	2.46581	871.63	0.21
58	37.2686	2.41074	2450.5	0.65
59	37.7721	2.37976	437.11	0.13
60	38.517	2.33543	1978.08	0.57

[00804] In other embodiments, Form C9 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 197. In other embodiments, Form C9 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 197. In other embodiments, Form C9 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 197. In other embodiments, Form C9 is also or alternatively characterized by a TGA thermogram comprising about 6.5% weight loss by about 130 °C, followed by onset of apparent decomposition at about 184 °C. In other embodiments, Form C9 is also or alternatively characterized by a DSC thermogram comprising a broad and sharp endotherm at 104°C and 134°C (onset), respectively, preceded by a minor endotherm with peak at 87 °C.

[00805] In other embodiments, Form C9 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 196.

[00806] Another aspect of the present disclosure relates to a morphic form, Form N1, of resmetirom. Form N1 is a methyl ethyl ketone (MEK) solvate. In some embodiments, Form N1 is characterized by an XRPD pattern including peaks at 10.9°±0.2°, 14.3°±0.2°, 17.0°±0.2°, 21.9°±0.2°, and 24.5°±0.2° 2-theta. In some embodiments, Form N1 is characterized by an XRPD pattern including any three, four, or five peaks selected from

10.9°±0.2°, 14.3°±0.2°, 17.0°±0.2°, 21.9°±0.2°, and 24.5°±0.2°. In some embodiments, the XRPD pattern of Form N1 further includes one or more additional peaks from Table N1 below ±0.2° 2-theta. In other embodiments, Form N1 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 198. In other embodiments, Form N1 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N1 below ±0.2° 2-theta.

TABLE N1

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	7.6195	11.59325	227.8	5.14
2	10.0757	8.77197	939.47	44.32
3	10.3428	8.54599	1278.89	15.51
4	10.8609	8.13944	3804.94	100
5	11.1045	7.96141	314.81	40.83
6	12.0455	7.34153	1613.84	50.39
7	13.1234	6.74086	819.86	19.74
8	13.8041	6.40995	1153.6	24.01
9	14.3283	6.17658	895.51	86.51
10	16.3568	5.41487	811.19	32.49
11	17.0277	5.20299	1731.67	94.67
12	18.1418	4.88592	289.14	28.46
13	19.4874	4.55148	1154.73	57.04
14	21.8941	4.05628	1031.23	95.25
15	23.626	3.76272	1020.71	43.47
16	24.4653	3.6355	2134.48	94.84
17	26.8413	3.31883	389.12	13.02
18	27.7525	3.2119	363.06	21.59
19	29.3571	3.0399	1668.9	73.24

[00807] In other embodiments, Form N1 is also or alternatively characterized by an ^1H NMR spectrum substantially similar to that set forth in FIG. 199.

[00808] Another aspect of the present disclosure relates to a morphic form, Form N2, of resmetirom. Form N2 is an unsolvated form. In some embodiments, Form N2 is characterized by an XRPD pattern including peaks at $14.5^\circ \pm 0.2^\circ$, $15.3^\circ \pm 0.2^\circ$, $23.8^\circ \pm 0.2^\circ$, $24.6^\circ \pm 0.2^\circ$, and $25.3^\circ \pm 0.2^\circ$ 2-theta. In some embodiments, Form N2 is characterized by an XRPD pattern including any three, four, or five peaks selected from $14.5^\circ \pm 0.2^\circ$, $15.3^\circ \pm 0.2^\circ$, $23.8^\circ \pm 0.2^\circ$, $24.6^\circ \pm 0.2^\circ$, and $25.3^\circ \pm 0.2^\circ$ 2-theta. In some embodiments, the XRPD pattern of Form N2 further includes one or more additional peaks from Table N2 below $\pm 0.2^\circ$ 2-theta. In other embodiments, Form N2 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 200. In other embodiments, Form N2 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N2 below $\pm 0.2^\circ$ 2-theta.

TABLE N2

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	6.2663	14.09334	2852.02	32.67
2	7.8732	11.2202	705.29	8.09
3	10.3922	8.50549	2528.98	24.35
4	14.535	6.08919	2143.29	43.99
5	15.3228	5.77788	2674.8	37.85
6	16.5117	5.36443	235.66	9.16
7	17.0883	5.18469	190.66	1.43
8	17.4241	5.08551	302.66	4.03
9	18.0852	4.90107	3321.2	47.44
10	19.6774	4.50795	1234.89	46.91
11	20.5752	4.31322	1913.72	34.23
12	20.9718	4.23255	2028.86	25.11

13	23.2086	3.82944	1766.15	42.79
14	23.8044	3.73492	2148.36	49.74
15	24.598	3.61619	3544.84	89.23
16	25.3153	3.51532	4617.71	100
17	26.0942	3.41214	353.47	5.67
18	27.0614	3.29233	363.11	4.07
19	28.5772	3.12106	432.66	9.95
20	30.0278	2.9735	625.61	10.38
21	31.6802	2.82208	510.09	7.54
22	33.0301	2.70977	437.49	11.47
23	38.8411	2.31668	130.71	4.5

[00809] In other embodiments, Form N2 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 201. In other embodiments, Form N2 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 202. In other embodiments, Form N2 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 202. In other embodiments, Form N2 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 202.

[00810] Another aspect of the present disclosure relates to a morphic form, Form N3, of resmetirom. Form N3 is an acetyl acetone solvate. In some embodiments, Form N3 is characterized by an XRPD pattern including peaks at $8.0^{\circ} \pm 0.2^{\circ}$, $9.9^{\circ} \pm 0.2^{\circ}$, $10.7^{\circ} \pm 0.2^{\circ}$, $11.4^{\circ} \pm 0.2^{\circ}$, and $13.7^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form N3 is characterized by an XRPD pattern including any three, four, or five peaks selected from $8.0^{\circ} \pm 0.2^{\circ}$, $9.9^{\circ} \pm 0.2^{\circ}$, $10.7^{\circ} \pm 0.2^{\circ}$, $11.4^{\circ} \pm 0.2^{\circ}$, and $13.7^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form N3 further includes one or more additional peaks from Table N3 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form N3 is also or alternatively characterized by a XRPD pattern

substantially similar to that set forth in FIG. 203. In other embodiments, Form N3 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N3 below $\pm 0.2^\circ$ 2-theta.

TABLE N3

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	0.8029	109.9342	13255.92	100
2	8.052	10.97144	1941.45	0.59
3	9.8654	8.95843	1918.38	0.54
4	10.7384	8.23202	1710.24	0.45
5	11.3642	7.78007	1652.69	0.51
6	13.6705	6.47226	3138.35	0.53
7	14.688	6.02614	733.35	0.14
8	15.3982	5.74976	531.38	0.1
9	16.7155	5.29946	635.32	0.12
10	16.9352	5.2312	1285.42	0.3
11	17.1356	5.1705	1834.66	0.64
12	17.4816	5.06893	311.92	0.27
13	17.8233	4.97249	1741.08	0.35
14	17.9328	4.94238	1669.72	0.4
15	18.089	4.90005	1025	0.41
16	18.584	4.77065	177.41	0.07
17	19.3373	4.58646	1761.37	0.32
18	19.5881	4.52829	752.74	0.09
19	19.7425	4.49323	790.84	0.34
20	20.0959	4.41501	498.21	0.14
21	20.7634	4.27456	843.34	0.19
22	21.5241	4.12518	416.29	0.05
23	21.9276	4.05017	1177.93	0.23
24	22.3843	3.96855	544.66	0.12
25	22.5487	3.93998	962.21	0.14

26	22.8701	3.88534	1861.79	0.6
27	23.4626	3.78855	571.89	0.09
28	23.6586	3.75761	1187.86	0.31
29	23.7975	3.73599	807.83	0.08
30	24.1026	3.68939	2275.47	0.35
31	24.3013	3.65966	520.61	0.12
32	24.572	3.61996	665.76	0.08
33	24.8865	3.57492	501.17	0.24
34	25.251	3.52413	516.61	0.16
35	26.0039	3.42378	678.55	0.16
36	26.3744	3.37652	515.35	0.06
37	26.9439	3.30643	870.97	0.16
38	27.24	3.27116	913.7	0.4
39	27.5016	3.24063	1037.98	0.18
40	28.1013	3.17282	450.67	0.06
41	28.5053	3.12877	877.34	0.16
42	29.1372	3.06233	672.38	0.1
43	29.4506	3.03045	636.92	0.14
44	29.6446	3.01106	380.14	0.13
45	29.8929	2.98662	685.66	0.27
46	32.6436	2.74096	722.41	0.22
47	32.8698	2.72261	330.99	0.05
48	33.101	2.70412	284.88	0.06
49	34.1844	2.62086	577.23	0.19
50	37.5755	2.39176	278.69	0.07
51	37.9901	2.3666	611	0.12

[00811] In other embodiments, Form N3 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 204.

[00812] Another aspect of the present disclosure relates to a morphic form, Form N4, of resmetirom. Form N4 is a methyl ethyl ketone (MEK) solvate. In some embodiments, Form

N4 is characterized by an XRPD pattern including peaks at $10.0^{\circ} \pm 0.2^{\circ}$, $10.9^{\circ} \pm 0.2^{\circ}$, $23.5^{\circ} \pm 0.2^{\circ}$, $24.1^{\circ} \pm 0.2^{\circ}$, and $24.5^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, Form N4 is characterized by an XRPD pattern including any three, four, or five peaks selected from $10.0^{\circ} \pm 0.2^{\circ}$, $10.9^{\circ} \pm 0.2^{\circ}$, $23.5^{\circ} \pm 0.2^{\circ}$, $24.1^{\circ} \pm 0.2^{\circ}$, and $24.5^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form N4 further includes one or more additional peaks from Table N4 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form N4 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 205. In other embodiments, Form N4 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N4 below $\pm 0.2^{\circ}$ 2-theta.

TABLE N4

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	3.3394	26.4363	985.77	3.77
2	6.6734	13.23459	835.05	11.91
3	10.0176	8.82271	8815.3	51.97
4	10.684	8.27379	5027.56	32.57
5	10.9303	8.08791	3162.64	95.6
6	11.4396	7.72899	812.45	18.87
7	12.1501	7.27855	780.16	18.18
8	12.6508	6.9916	630.65	5.62
9	12.9064	6.85369	1332.78	5.48
10	13.7232	6.44756	524.68	7.88
11	14.2752	6.19945	1827.56	9.81
12	14.5514	6.08236	813.57	9.69
13	17.3517	5.10657	781.98	8.53
14	17.7981	4.97948	588.71	12.09
15	18.3798	4.82318	899.08	7.06
16	18.7482	4.72923	1231.8	9.39
17	19.4199	4.56715	1106.92	6.34

18	19.602	4.52513	1258	7.09
19	19.9004	4.45794	1114.15	4.38
20	20.8246	4.26214	504.38	6.92
21	21.181	4.19122	1590.68	12.66
22	21.6474	4.10196	752.78	6.53
23	22.1078	4.01757	1195.45	9.09
24	22.8467	3.88926	755.07	5.16
25	23.4829	3.78532	10439.12	100
26	24.1299	3.68526	5932.55	83.63
27	24.4995	3.63051	4454.16	76.87
28	26.5045	3.36024	1332.57	6.42
29	26.8325	3.31991	1847.23	32.68
30	27.9827	3.186	634.44	7.75
31	29.0332	3.07306	883.81	19.05
32	30.3048	2.94696	955.02	6.76
33	31.3221	2.85353	2086.71	27.09
34	32.3763	2.76298	900.39	7.81
35	35.4855	2.52769	425.78	8.91

[00813] In other embodiments, Form N4 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 206. In other embodiments, Form N4 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 207. In other embodiments, Form N4 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 207. In other embodiments, Form N4 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 207.

[00814] Another aspect of the present disclosure relates to a morphic form, Form N6, of resmetirom. Form N6 is an acetyl acetone solvate. In some embodiments, Form N6 is characterized by an XRPD pattern including peaks at $5.1^{\circ} \pm 0.2^{\circ}$, $11.9^{\circ} \pm 0.2^{\circ}$, $19.9^{\circ} \pm 0.2^{\circ}$,

17.5°±0.2°, and 23.6°±0.2° 2-theta. In some embodiments, Form N6 is characterized by an XRPD pattern including any three, four, or five peaks selected from 5.1°±0.2°, 11.9°±0.2°, 19.9°±0.2°, 17.5°±0.2°, and 23.6°±0.2° 2-theta. In some embodiments, the XRPD pattern of Form N6 further includes one or more additional peaks from Table N6 below ±0.2° 2-theta. In other embodiments, Form N6 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 208. In other embodiments, Form N6 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N6 below ±0.2° 2-theta.

TABLE N6

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	5.1341	17.1987	466.75	75.02
2	11.8734	7.44754	346.64	64.17
3	12.612	7.01298	436.2	42.94
4	14.0022	6.31971	497.18	45.73
5	17.4594	5.07532	229.6	63.64
6	19.9044	4.45705	181.51	63.84
7	23.563	3.77264	237.26	100

[00815] In other embodiments, Form N6 is also or alternatively characterized by an ¹H NMR spectrum substantially similar to that set forth in FIG. 209.

[00816] Another aspect of the present disclosure relates to a morphic form, Form N7, of resmetirom. Form N7 is a propionic acid solvate. In some embodiments, Form N7 is characterized by an XRPD pattern including peaks at 6.3°±0.2°, 12.7°±0.2°, 19.4°±0.2°, 25.0°±0.2°, and 25.6°±0.2° 2-theta. In some embodiments, Form N7 is characterized by an XRPD pattern including any three, four, or five peaks selected from 6.3°±0.2°, 12.7°±0.2°, 19.4°±0.2°, 25.0°±0.2°, and 25.6°±0.2° 2-theta. In some embodiments, the XRPD pattern of

Form N7 further includes one or more additional peaks from Table N7 below $\pm 0.2^\circ$ 2-theta.

In other embodiments, Form N7 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 210. In other embodiments, Form N7 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N7 below $\pm 0.2^\circ$ 2-theta.

TABLE N7

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	6.3178	13.97864	12712.21	39.3
2	7.3283	12.05325	1774.14	6.4
3	8.4449	10.46183	1538.87	4.5
4	8.8831	9.94679	2417.5	7.97
5	9.666	9.14282	3757.75	10.27
6	10.396	8.50237	4779.69	18.44
7	10.6194	8.324	2389.58	7.74
8	11.4528	7.72011	4364.29	15.54
9	12.6669	6.98274	10608.15	35.44
10	13.5428	6.53304	1714.41	4.4
11	13.7857	6.41846	1377.76	4.38
12	14.9165	5.93433	3338.55	14.78
13	15.6065	5.67347	8720.38	36.67
14	15.818	5.59806	3966.16	9.07
15	16.4805	5.37451	8223.3	32.06
16	16.7886	5.27655	6613.06	14.68
17	16.9526	5.22588	5301.34	30.45
18	17.5771	5.0416	5208.7	16.08
19	18.4272	4.81089	7306.93	25.68
20	18.6153	4.76268	2097.19	10.12
21	18.8396	4.70648	2261.5	9.32
22	19.0323	4.65928	2192.56	5.27
23	19.4067	4.57021	13617.53	45.93

24	20.7005	4.2874	3424.33	10.52
25	21.4804	4.13348	5543.53	15.69
26	22.1286	4.01384	5635.25	19.59
27	22.3603	3.97276	2095.43	6.35
28	22.5155	3.94573	5708.92	14.36
29	22.8199	3.89378	814.19	2.34
30	22.9978	3.86406	2639	8.49
31	23.2465	3.82328	7995.02	23.35
32	23.6413	3.76032	2499.36	9.41
33	24.0019	3.70464	2367.41	7.19
34	25.0076	3.55787	5821.28	57.84
35	25.593	3.4778	30723.46	100
36	26.7473	3.33029	1509.95	9.04
37	26.9023	3.31145	1795.6	5.54
38	27.2727	3.26731	921.32	2.34
39	27.4815	3.24296	2204.74	4.98
40	27.6397	3.22475	6384.15	20.58
41	28.2391	3.15766	698.89	1.83
42	28.5226	3.12691	800.45	2.28
43	28.9	3.08693	1664.69	3.34
44	29.1066	3.06549	1090.41	2.46
45	29.2575	3.05001	2652.04	13.68
46	29.4237	3.03316	1878.14	6.27
47	30.7559	2.90475	2508.05	11.27
48	30.9834	2.88394	2069.19	4.77
49	31.1198	2.87161	835.9	8.46
50	31.4209	2.84477	1625.97	4.32
51	31.8821	2.80466	1613.2	11.01
52	34.2526	2.61579	796.5	1.87
53	34.7024	2.58291	2570.79	6.98
54	35.0846	2.55565	2315.87	8.31
55	35.5911	2.52043	2866.52	12.72

56	36.7629	2.44274	1056.94	3.54
57	37.8475	2.37519	1495.3	12.38
58	39.0419	2.30523	206.11	1.9

[00817] In other embodiments, Form N7 is also or alternatively characterized by an ^1H NMR spectrum substantially similar to that set forth in FIG. 211. In other embodiments, Form N7 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 212. In other embodiments, Form N7 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 212. In other embodiments, Form N7 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 212.

[00818] Another aspect of the present disclosure relates to a morphic form, Form N8, of resmetirom. Form N8 is an isopropanol (IPA) acid solvate. In some embodiments, Form N8 is characterized by an XRPD pattern including peaks at $6.9^\circ \pm 0.2^\circ$, $14.3^\circ \pm 0.2^\circ$, $20.4^\circ \pm 0.2^\circ$, $23.0^\circ \pm 0.2^\circ$, and $30.1^\circ \pm 0.2^\circ$ 2-theta. In some embodiments, Form N8 is characterized by an XRPD pattern including any three, four, or five peaks selected from $6.9^\circ \pm 0.2^\circ$, $14.3^\circ \pm 0.2^\circ$, $20.4^\circ \pm 0.2^\circ$, $23.0^\circ \pm 0.2^\circ$, and $30.1^\circ \pm 0.2^\circ$ 2-theta. In some embodiments, the XRPD pattern of Form N8 further includes one or more additional peaks from Table N8 below $\pm 0.2^\circ$ 2-theta. In other embodiments, Form N8 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 81. In other embodiments, Form N8 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N8 below $\pm 0.2^\circ$ 2-theta.

TABLE N8

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	6.904	12.79301	20282.41	100

2	7.7117	11.45477	6865.42	33.3
3	7.896	11.18791	7054.59	32.31
4	10.3208	8.56417	1441.85	6.14
5	12.0953	7.31142	1145.76	4.65
6	13.2707	6.66634	618.74	6.27
7	13.777	6.42249	4229.35	17.61
8	14.3094	6.18471	11764.48	50.07
9	14.5014	6.10322	2374.07	9.63
10	14.8647	5.95487	419.46	1.61
11	15.4166	5.74292	930.85	2.49
12	15.8031	5.60331	1720.24	6.37
13	15.9441	5.55407	633.63	2.65
14	16.2854	5.43845	1234.76	4.68
15	16.8727	5.25045	3638.49	13.76
16	18.1708	4.87819	3399.9	13.53
17	18.6565	4.75226	972.33	3.94
18	20.3902	4.35194	14827.48	73.72
19	20.5643	4.3155	5997.34	35.2
20	21.0629	4.21444	8435.88	34.55
21	22.131	4.0134	2663.12	10.53
22	22.4923	3.94974	822.04	1.62
23	22.9751	3.86782	17979.8	91.91
24	23.7858	3.73779	9399.76	41.67
25	23.9222	3.7168	8222.62	27.82
26	24.2299	3.67029	1013.53	2.57
27	24.4384	3.63944	344.47	5.54
28	24.7143	3.59943	1447.53	4.61
29	25.0883	3.54662	1605.06	5.3
30	25.4691	3.49445	2134.32	6.92
31	25.9404	3.43202	1562.02	8.74
32	26.5579	3.35361	597.46	1.25
33	27.5009	3.24071	2729.14	12.33

34	28.1641	3.1659	3226.83	15.14
35	29.201	3.05578	2603.33	13.14
36	30.1298	2.96367	8338.91	45.82
37	30.4981	2.92871	3380.11	16.36
38	31.2476	2.86016	2126.34	8.83
39	32.199	2.77778	1958.68	8.32
40	32.9167	2.71884	310.46	1.51
41	33.398	2.68075	1725.29	6.79
42	34.2009	2.61963	892.62	8.18
43	34.8248	2.57411	1065.35	5.78
44	35.0072	2.56112	1259.55	4.14
45	35.4402	2.53081	241.79	0.9
46	36.4618	2.46221	1144.07	4.6
47	36.8176	2.43923	1029.27	6.56
48	38.2441	2.35147	730.37	2.38
49	38.8354	2.31701	1543.2	7.08
50	39.2936	2.29104	719.76	3.4

[00819] In other embodiments, Form N8 is also or alternatively characterized by an ^1H NMR spectrum substantially similar to that set forth in FIG. 82. In other embodiments, Form N8 is also or alternatively characterized by a DSC thermogram substantially similar to that set forth in FIG. 83. In other embodiments, Form N8 is also or alternatively characterized by a TGA thermogram substantially similar to that set forth in FIG. 83. In other embodiments, Form N8 is also or alternatively characterized by TGA and DSC thermograms substantially similar to that set forth in FIG. 83.

[00820] Another aspect of the present disclosure relates to a morphic form, Form N9, of resmetirom. In some embodiments, Form N9 is characterized by an XRPD pattern including peaks at $4.8^\circ \pm 0.2^\circ$, $10.6^\circ \pm 0.2^\circ$, $16.9^\circ \pm 0.2^\circ$, $19.5^\circ \pm 0.2^\circ$, and $25.4^\circ \pm 0.2^\circ$ 2-theta. In some

embodiments, Form N9 is characterized by an XRPD pattern including any three, four, or five peaks selected from $4.8^{\circ} \pm 0.2^{\circ}$, $10.6^{\circ} \pm 0.2^{\circ}$, $16.9^{\circ} \pm 0.2^{\circ}$, $19.5^{\circ} \pm 0.2^{\circ}$, and $25.4^{\circ} \pm 0.2^{\circ}$ 2-theta. In some embodiments, the XRPD pattern of Form N9 further includes one or more additional peaks from Table N9 below $\pm 0.2^{\circ}$ 2-theta. In other embodiments, Form N9 is also or alternatively characterized by a XRPD pattern substantially similar to that set forth in FIG. 213. In other embodiments, Form N9 is also or alternatively characterized by an XRPD pattern having peaks substantially as provided in Table N9 below $\pm 0.2^{\circ}$ 2-theta.

TABLE N9

No.	2-theta(deg)	d(ang.)	Height(cps)	Rel. int. I
1	4.7901	18.43273	2365.25	100
2	6.4607	13.66982	6473.31	12.49
3	8.9134	9.91303	2210.43	10.45
4	9.768	9.04757	7500.83	16.74
5	10.5929	8.34475	5822.78	28.42
6	11.5579	7.65013	3047.72	12.42
7	12.8746	6.87056	8190.25	18.34
8	13.0019	6.80357	8566.8	8
9	13.5775	6.5164	4119.16	5.4
10	14.903	5.93966	2470.11	3.89
11	15.7368	5.62677	6027	13.25
12	15.9241	5.56102	7371.76	19.77
13	16.8472	5.25835	7133.08	40.36
14	17.1217	5.17464	7033.75	14.59
15	17.5796	5.04089	9767.3	14.91
16	18.4552	4.80364	1790.89	3.92
17	18.6799	4.74637	6497.96	13
18	19.5356	4.54035	11965.37	32.61
19	21.1115	4.20485	1761.37	3.67
20	21.6395	4.10343	3424.83	9

21	22.0923	4.02034	3861.82	11.85
22	22.5155	3.94573	2958.88	10.39
23	22.6757	3.91821	5314.41	8.37
24	23.3183	3.81166	6312.69	14.91
25	23.5726	3.77111	1374.55	6.74
26	24.0838	3.69222	2895.22	5.89
27	24.3069	3.65884	2081.01	3.97
28	25.1478	3.53836	5487.93	10.47
29	25.4007	3.5037	6544.9	31.86
30	25.7216	3.46071	12022.59	28.31
31	25.8601	3.44249	11972.59	21.33
32	28.097	3.1733	2366.65	4
33	29.1673	3.05925	2033.38	7.76
34	29.3534	3.04026	2136.73	5.47
35	30.3165	2.94584	788.4	4.46
36	31.1707	2.86704	2705.53	5.7
37	31.8952	2.80354	1984.63	6.92
38	35.6629	2.51552	899.81	5.75
39	36.9246	2.43241	920.41	2.5

[00821] The present disclosure provides a method of treating or improving a fatty liver disease (e.g., NASH), the method comprising administering to the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement resmetirom or a pharmaceutically acceptable salt thereof.

[00822] The present disclosure also provides a method of treating or improving liver fibrosis associated with a fatty liver disease (e.g., NASH), the method comprising administering to the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement resmetirom or a pharmaceutically acceptable salt thereof.

[00823] The present disclosure also provides resmetirom or a pharmaceutically acceptable salt thereof for use for treating or improving a fatty liver disease (e.g., NASH) in a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement.

[00824] The present disclosure also provides use of resmetirom or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or improving a fatty liver disease (e.g., NASH) in a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement.

[00825] In some aspects, the present disclosure provides a method of reducing liver volume in a human subject (e.g., an adult human subject) who may be in need of such a reduction and/or may be in need of treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis), the method comprising administering to this human subject resmetirom or a pharmaceutically acceptable salt thereof.

[00826] In some aspects, the present disclosure provides resmetirom or a pharmaceutically acceptable salt thereof for use for reducing liver volume in a human subject (e.g., an adult human subject) who may be in need of such a reduction and/or may be in need of treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis).

[00827] In some aspects, the present disclosure provides use of resmetirom or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for reducing liver volume in a human subject (e.g., an adult human subject) who may be in need of such a reduction and/or the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis).

[00828] In some aspects, the present disclosure provides resmetirom or a pharmaceutically acceptable salt thereof for use in treating or preventing NASH in a human subject (e.g., an adult human subject) who may be in need of such treatment or prevention .

[00829] In some aspects, the present disclosure provides resmetirom or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing NASH in a human subject (e.g., an adult human subject) who may be in need of such treatment or prevention.

[00830] Specifically, the present disclosure provides a method of treating NASH. The method comprises: determining a weight of an adult human subject in need thereof; and based on determination of the weight of the adult human subject in need thereof, administering to the adult human subject in need thereof a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the adult human subject in need thereof is determined to weigh 100 kg or more; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the adult human subject in need thereof is determined to weigh less than 100 kg.

[00831] In some embodiments, the adult human subject in need thereof is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

[00832] In some embodiments, the adult human subject in need thereof is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[00833] In some embodiments, the solid oral dosage form is a tablet.

[00834] In some embodiments, the solid oral dosage form comprises resmetirom.

[00835] Specifically, the present disclosure also provides a method of improving liver fibrosis. The method comprises: determining a weight of an adult human subject in need thereof; and based on determination of the weight of the adult human subject in need thereof, administering to the adult human subject in need thereof a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the adult human subject in need thereof is determined to weigh 100 kg or more; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the adult human subject in need thereof is determined to weigh less than 100 kg; and

wherein the adult human subject in need thereof has nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis consistent with stages F2 to F3.

[00836] In some embodiments, the adult human subject in need thereof is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

[00837] In some embodiments, the adult human subject in need thereof is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[00838] In some embodiments, the method is of improving the liver fibrosis by at least one stage in the adult human subject in need thereof.

[00839] In some embodiments, the solid oral dosage form is a tablet.

[00840] In some embodiments, the solid oral dosage form comprises resmetirom.

[00841] In some embodiments, the adult human subject in need thereof has liver fibrosis characterized as fibrosis stage F3.

[00842] In some embodiments, the adult human subject in need thereof has liver fibrosis characterized as fibrosis stage F2.

[00843] The present disclosure also provides a method of treating or improving a fatty liver disease (e.g., NASH). The method comprises: determining a weight of a human subject (e.g., an adult human subject); and based on determination of the weight of the human subject (e.g., an adult human subject), administering to the human subject (e.g., an adult human subject) a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject (e.g., an adult human subject) is determined to weigh 100 kg or more; or

(ii) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg.

[00844] The present disclosure also provides a method of improving a fatty liver disease (e.g., NASH). The method comprises: determining a weight of a human subject who may be in need of such improvement (e.g., an adult human subject); and based on determination of the weight of this human subject, administering to this human subject a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if this human subject is determined to weigh 100 kg or more; or
- (ii) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if this human subject is determined to weigh less than 100 kg.

[00845] The present disclosure also provides a method of treating a fatty liver disease (e.g., NASH). The method comprises: determining a weight of a human subject in need of such treatment (e.g., an adult human subject); and based on determination of the weight of the human subject in need of such treatment (e.g., an adult human subject), administering to the human subject in need of such treatment (e.g., an adult human subject) a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject in need of such treatment (e.g., an adult human subject) is determined to weigh 100 kg or more; or
- (ii) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject in need of such treatment (e.g., an adult human subject) is determined to weigh less than 100 kg.

[00846] The present disclosure also provides a method of treating or improving liver fibrosis associated with a fatty liver disease (e.g., NASH). The method comprises: determining a weight of a human subject (e.g., an adult human subject); and based on determination of the weight of the human subject (e.g., an adult human subject), administering to the human subject (e.g., an adult human subject) a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject (e.g., an adult human subject) is determined to weigh 100 kg or more; or
- (ii) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg.

[00847] The present disclosure also provides a method of treating liver fibrosis associated with a fatty liver disease (e.g., NASH). The method comprises: determining a weight of a human subject (e.g., an adult human subject) who may be in need of such treatment; and based on determination of the weight of this human subject, administering to this human subject a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if this human subject is determined to weigh 100 kg or more; or
- (ii) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if this human subject is determined to weigh less than 100 kg, and wherein this human subject has liver fibrosis associated with the fatty liver disease (e.g., NASH).

[00848] The present disclosure also provides a method of improving liver fibrosis associated with a fatty liver disease (e.g., NASH). The method comprises: determining a weight of a human subject (e.g., an adult human subject) in need of such improvement; and based on determination of the weight of the human subject (e.g., an adult human subject) in need of such improvement, administering to the human subject (e.g., an adult human subject) in need of such improvement a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject (e.g., an adult human subject) in need of such improvement is determined to weigh 100 kg or more; or
- (ii) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject (e.g., an adult human subject) in need of such improvement is determined to weigh less than 100 kg, and wherein the human subject (e.g., an adult human subject) in need of such improvement has liver fibrosis associated with the fatty liver disease (e.g., NASH).

[00849] In some aspects, the human subject (e.g., an adult human subject) who may be in need of such treatment and/or improvement (e.g., of NASH and/or liver fibrosis) is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or a pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

[00850] In some aspects, the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement (e.g., of NASH and/or liver fibrosis) is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or a pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

[00851] In some aspects, the fatty liver disease is NASH. In some aspects, the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement (e.g., of NASH and/or liver fibrosis) may have noncirrhotic non-alcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 and F3 fibrosis. In some aspects, the human subject (e.g., an adult human subject) who may be in need of such

treatment or improvement (e.g., of NASH and/or liver fibrosis) may have noncirrhotic non-alcoholic steatohepatitis with mild liver fibrosis consistent with stage F1.

[00852] In some aspects, the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement (e.g., of NASH and/or liver fibrosis) is administered the solid oral dosage form comprising resmetirom or a pharmaceutically acceptable salt thereof.

[00853] In some aspects, the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement (e.g., of NASH and/or liver fibrosis) has liver fibrosis characterized as fibrosis stage F2 or F3. In some aspects, the method is that of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

[00854] In some aspects, the method is of improving the liver fibrosis by one stage in the human subject (e.g., an adult human subject) who may be in need of such improvement. The human subject (e.g., an adult human subject) who may be in need of such improvement may have liver fibrosis characterized as fibrosis stage F2. The human subject (e.g., an adult human subject) who may be in need of such improvement may have liver fibrosis characterized as fibrosis stage F3.

[00855] In some aspects, the method is of improving the liver fibrosis by at least one stage (e.g., two stages) in the human subject (e.g., an adult human subject) who may be in need of such improvement. The human subject (e.g., an adult human subject) who may be in need of such improvement may have liver fibrosis characterized as fibrosis stage F2. The human subject (e.g., an adult human subject) who may be in need of such improvement may have liver fibrosis characterized as fibrosis stage F3.

[00856] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a body weight at or greater than 100 kilograms, and the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is or has been administered to such a human subject at a dosage of 100 mg per day.

[00857] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a body weight less than 100 kilograms, and the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is or has been administered to the human subject (e.g., an adult human subject) in need of such treatment (e.g., NASH/improving liver fibrosis) at a dosage of 80 mg per day.

[00858] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a body weight less than 100 kilograms, and the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is or has been administered to the human subject (e.g., an adult human subject) in need of such treatment (e.g., NASH/improving liver fibrosis) at a dosage of 60 mg per day.

[00859] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is administered to the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) with food. In other embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is administered to the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., NASH and/or liver fibrosis) without food.

[00860] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is taken daily.

[00861] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is taken once or twice daily.

[00862] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is taken once daily.

[00863] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof, is or has been taken without any drug holiday.

[00864] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is or has been taken with one or more drug holidays.

[00865] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is or has been administered for one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or for any number of weeks therebetween.

[00866] In some embodiments, the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof is or has been administered for longer than 52 weeks.

[00867] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof is not taking atorvastatin, pravastatin, rosuvastatin, or simvastatin. In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof is taking 20 mg or less rosuvastatin or simvastatin. In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof is taking 40 mg or less atorvastatin or pravastatin.

[00868] It was also found that concomitant use of resmetirom or the pharmaceutically acceptable salt thereof and a CYP2C8 inhibitor can increase resmetirom C_{max} and AUC. As a result, the daily dose of resmetirom or the pharmaceutically acceptable salt thereof can be reduced to a reduced dosage and yet continue to provide the desired treatment or improvement of a fatty liver disease (e.g., NASH) and/or of fibrosis associated with the fatty liver disease (e.g., NASH) with such concomitant use.

[00869] Specifically, the reduction in the daily dose of resmetirom or the pharmaceutically acceptable salt thereof is 20 mg for a human subject (e.g., an adult human subject) who may be in need of the treatment or improvement of a liver disease (e.g., NASH) or of liver fibrosis associated with such a liver disease as described in this disclosure, who is on a moderate CYP2C8 inhibitor regimen. For instance, if such a human subject would otherwise be administered a dose of 100 mg of resmetirom per day based on the determination that the

weight of this human subject is at least 100 kg, then the reduced dosage, due to the use of a moderate CYP2C8 inhibitor by this human subject, is 80 mg per day. If the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) would otherwise be administered a dose of 80 mg of resmetirom per day based on the determination that the weight of this human subject is less than 100 kg, then the reduced dosage, due to the use of a moderate CYP2C8 inhibitor by this human subject, is 60 mg per day.

[00870] If the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., NASH and/or liver fibrosis) was taking a moderate CYP2C8 inhibitor prior to using resmetirom or the pharmaceutically acceptable salt thereof then this human subject would start with the reduced dosage of 80 mg or 100 mg per day, depending on the weight determination. If the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as described herein (e.g., of NASH and/or liver fibrosis) was taking resmetirom or the pharmaceutically acceptable salt thereof at a dose of 100 mg per day or 80 mg per day, depending on the weight determination, but was not taking a moderate CYP2C8 inhibitor prior to using resmetirom or the pharmaceutically acceptable salt thereof then the dose would be reduced from 100 mg per day or 80 mg per day to a reduced dosage of 80 mg or 60 mg per day, respectively, depending on the weight determination, once this human subject is concomitantly using a moderate CYP2C8 inhibitor. If the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as described herein (e.g., of NASH and/or liver fibrosis) was using neither resmetirom or the pharmaceutically acceptable salt thereof nor a moderate CYP2C8 inhibitor prior to their concomitant use, then this human subject would start taking resmetirom or the pharmaceutically acceptable salt thereof with the reduced

dosage of 80 mg or 60 mg per day, depending on the weight determination, for this concomitant use.

[00871] Specifically, disclosed herein is a method of treating or improving a fatty liver disease (e.g., NASH or in particular noncirrhotic NASH), which method comprises: determining a weight of a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement; and based on determination of the weight of the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement, administering to this human subject (e.g., an adult human subject) who may be in need of such treatment or improvement a solid oral dosage form comprising:

- (i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is determined to weigh 100 kg or more and the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is using a moderate CYP2C8 inhibitor; or
- (ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is determined to weigh less than 100 kg and the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is using a moderate CYP2C8 inhibitor.

[00872] Also disclosed herein is a method of treating or improving liver fibrosis, which method comprises: determining a weight of a human subject (e.g., an adult human subject) who may be in need of such treatment or improvement ; and based on determination of the

weight of the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement, administering to the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is determined to weigh 100 kg or more and the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is using a moderate CYP2C8 inhibitor; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is determined to weigh less than 100 kg and the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement is using a moderate CYP2C8 inhibitor,

wherein the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

[00873] In some aspects, the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nicardipine, loratadine, eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate, spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin,

troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, idelalisib, isoniazid, ketoprofen, letermovir, lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

[00874] In some aspects, the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, teriflunomide, trimethoprim, and/or pioglitazone.

[00875] In some aspects, the fatty liver disease is NASH.

[00876] In some aspects, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) who is on a moderate CYP2C8 inhibitor regimen is administered the resmetirom compound.

[00877] In some aspects, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) was also previously on a moderate CYP2C8 inhibitor regimen.

[00878] In some embodiments, the reduced dosage of resmetirom or the pharmaceutically acceptable salt thereof is 80 mg per day.

[00879] In some embodiments, the reduced dosage of resmetirom or the pharmaceutically acceptable salt thereof is 60 mg per day.

[00880] In some embodiments, the method includes reducing the previously used oral dose of resmetirom or the pharmaceutically acceptable salt thereof to the reduced dosage.

[00881] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

[00882] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

[00883] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) uses the moderate CYP2C8 inhibitor concomitantly (e.g., together or on the same day) with the reduced dosage of resmetirom or the pharmaceutically acceptable salt thereof. In some embodiments, the moderate CYP2C8 inhibitor is used by the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) daily. In some embodiments, the moderate CYP2C8 inhibitor is used by the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) once daily.

[00884] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof (e.g., a reduced dosage), is not using a strong CYP2C8 inhibitor (e.g., gemfibrozil).

[00885] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof (e.g., a reduced dosage), is not using OATP1B1 (organic anion transporting polypeptide 1B1) or OATP1B3 (organic anion transporting polypeptide 1B3) inhibitors (e.g., cyclosporine).

[00886] In some embodiments, the concomitant use of the moderate CYP2C8 inhibitor is within 24 hours before the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) takes resmetirom or the pharmaceutically acceptable salt thereof.

[00887] In some embodiments, the concomitant use of the moderate CYP2C8 inhibitor is within 24 hours after the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) takes resmetirom or the pharmaceutically acceptable salt thereof.

[00888] In some embodiments, the concomitant use of the moderate CYP2C8 inhibitor by the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) is conducted simultaneously with the administration of resmetirom or the pharmaceutically acceptable salt thereof.

[00889] The reduced dosage of resmetirom or the pharmaceutically acceptable salt thereof may be administered via a solid oral dosage form.

[00890] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of such treatment or improvement as disclosed herein has a disease, disorder, or condition being NASH. It is understood that, in NASH, the fat accumulation may be associated with varying degrees of inflammation (hepatitis) and/or scarring (fibrosis) of the liver. In some embodiments, the fibrosis of the liver is a stage F2 fibrosis. In some embodiments, the fibrosis of the liver is a stage F3 fibrosis.

[00891] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein has a disease, disorder, or condition being liver inflammation.

[00892] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein has a disease, disorder, or condition being associated with an increased liver volume.

[00893] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein has a disease, disorder, or condition being portal hypertension.

[00894] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein has moderate hepatic impairment.

[00895] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein has autoimmune liver disease. In other embodiments, the human subject (e.g., an adult human subject) who may be

in need of the treatment or improvement as disclosed herein does not have autoimmune liver disease.

[00896] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein has moderate to severe hepatic impairment (e.g., Child-Pugh Class B or C). In other embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein does not have moderate to severe hepatic impairment.

[00897] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver volume being at least 5% greater, at least 10% greater, at least 20% greater, at least 30% greater, at least 40% greater, at least 50% greater, at least 60% greater, at least 70% greater, at least 80% greater, at least 90% greater, at least 100% greater, at least 150% greater, at least 200% greater, or any number therebetween, compared to the same human subject had this human subject not been affected by the disease, disorder, or condition (e.g., without NASH).

[00898] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by proton density fat fraction (PDFF)) being at least 5% greater, at least 10% greater, at least 20% greater, at least 30% greater, at least 40% greater, at least 50% greater, at least 60% greater, at least 70% greater, at least 80% greater, at least 90% greater, at least 100% greater, at least 150% greater, at least 200% greater, or any number therebetween, compared to the same human subject had this human subject not been affected by the disease, disorder, or condition (e.g., without NASH).

[00899] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by proton density fat fraction (PDFF)) being at most 200% greater, at most 150% greater, at most 100% greater, at most 90% greater, at most 80% greater, at most 70% greater, at most 60% greater, at most 50% greater, at most 40% greater, at most 30% greater, at most 20% greater, at most 10% greater, or at most 5% greater, or any number therebetween, compared to the same human subject had this human subject not been affected by the disease, disorder, or condition (e.g., without NASH).

[00900] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by proton density fat fraction (PDFF)) being 50% or less, 40% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, 4% or less, 3% or less, 2% or less, 1% or less, or any number therebetween.

[00901] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by proton density fat fraction (PDFF)) being 5% or less.

[00902] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by proton density fat fraction (PDFF)) greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 25%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, or any number therebetween.

[00903] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by proton density fat fraction (PDFF)) being greater than 5%.

[00904] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a spleen volume being at least 5% greater, at least 10% greater, at least 20% greater, at least 30% greater, at least 40% greater, at least 50% greater, at least 60% greater, at least 70% greater, at least 80% greater, at least 90% greater, at least 100% greater, at least 150% greater, at least 200% greater, or any number therebetween, compared to the same human subject had this human subject not been affected by the disease, disorder, or condition (e.g., without portal hypertension).

[00905] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof is not administered a strong CYP2C8 inhibitor (e.g., gemfibrozil).

[00906] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof is not administered OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine).

[00907] In some embodiments, the human subject (e.g., an adult human subject) i who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt

thereof is not administered atorvastatin, pravastatin, rosuvastatin, or simvastatin. In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof is taking 20 mg or less rosuvastatin or simvastatin. In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) administered a reduced daily dose of resmetirom or the pharmaceutically acceptable salt thereof is taking 40 mg or less atorvastatin or pravastatin.

[00908] In some embodiments, the administration eliminates, or reduces the severity of, the disease, disorder, or condition.

[00909] In some embodiments, the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween (e.g., over a period of 12 weeks or 52 weeks).

[00910] In some embodiments, the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween, over a period of 12 weeks.

[00911] In some embodiments, the administration reduces the liver volume by at least 10% over a period of 12 weeks.

[00912] In some embodiments, the administration reduces the liver volume by at least 15% over a period of 12 weeks.

[00913] In some embodiments, the administration reduces the liver volume by at least 20% over a period of 12 weeks.

[00914] In some embodiments, the administration reduces the liver volume by at least 25% over a period of 12 weeks.

[00915] In some embodiments, the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween, over a period of 52 weeks.

[00916] In some embodiments, the administration reduces the liver volume by at least 10% over a period of 52 weeks.

[00917] In some embodiments, the administration reduces the liver volume by at least 15% over a period of 52 weeks.

[00918] In some embodiments, the administration reduces the liver volume by at least 20% over a period of 52 weeks.

[00919] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween (e.g., over a period of 12 weeks or 52 weeks).

[00920] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween, over a period of 12 weeks.

[00921] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 10% over a period of 12 weeks.

[00922] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 15% over a period of 12 weeks.

[00923] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 20% over a period of 12 weeks.

[00924] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 25% over a period of 12 weeks.

[00925] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween, over a period of 52 weeks.

[00926] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 10% over a period of 52 weeks.

[00927] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 15% over a period of 52 weeks.

[00928] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver volume by at least 20% over a period of 52 weeks.

[00929] In some embodiments, the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 60% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or any number therebetween, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration.

[00930] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less, and the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 60% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or any number therebetween, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration.

[00931] In some embodiments, the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 20% or less, 15% or less, 10% or less, 5% or less, 4% or less, 3% or less, 2% or less, 1% or less, or any number therebetween, as compared to the liver volume of the human subject (e.g., an adult human subject) who may be in need of the

treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration.

[00932] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 60% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or any number therebetween, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween (e.g., over a period of 12 weeks or 52 weeks).

[00933] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 40% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 10% (e.g., over a period of 12 weeks or 52 weeks).

[00934] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein

(e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 35% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) in n who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 10% (e.g., over a period of 12 weeks or 52 weeks).

[00935] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 30% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 10% (e.g., over a period of 12 weeks or 52 weeks).

[00936] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 40% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) in who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 15% (e.g., over a period of 12 weeks or 52 weeks).

[00937] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein

(e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 35% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) in who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 15% (e.g., over a period of 12 weeks or 52 weeks).

[00938] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 30% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) in who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 15% (e.g., over a period of 12 weeks or 52 weeks).

[00939] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 40% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) in who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 20% (e.g., over a period of 12 weeks or 52 weeks).

[00940] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein

(e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 35% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 20% (e.g., over a period of 12 weeks or 52 weeks).

[00941] In some embodiments, prior to the administration the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) has a liver fat amount (e.g., as measured by MRI-PDFF) being 5% or less; the administration reduces the liver fat amount (e.g., as measured by MRI-PDFF) by 30% or less, as compared to the liver fat amount of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) prior to the administration; and the administration reduces the liver volume by at least 20% (e.g., over a period of 12 weeks or 52 weeks).

[00942] In some embodiments, the liver volume reduction is dependent from the liver fat amount (e.g., the liver fat amount prior to the administration).

[00943] In some embodiments, the liver volume reduction is independent from the liver fat amount (e.g., the liver fat amount prior to the administration).

[00944] In some embodiments, the liver volume reduction is dependent from the liver fat amount reduction.

[00945] In some embodiments, the liver volume reduction is independent from the liver fat amount reduction.

[00946] In some embodiments, the liver volume reduction is greater than the liver fat amount reduction.

[00947] In some embodiments, the liver volume reduction is at least 5% greater, at least 10% greater, at least 20% greater, at least 30% greater, at least 40% greater, at least 50% greater, at least 60% greater, at least 70% greater, at least 80% greater, at least 90% greater, at least 100% greater, at least 150% greater, at least 200% greater, at least 300% greater, at least 400% greater, at least 500% greater, at least 600% greater, at least 700% greater, at least 800% greater, at least 900% greater, at least 1000%, or any number therebetween, as compared to the liver fat amount reduction.

[00948] In some embodiments, the administration eliminates, or reduces the severity of, liver inflammation.

[00949] In some embodiments, the administration eliminates, or reduces the severity of, portal hypertension.

[00950] In some embodiments, the administration reduces the blood pressure in the portal vein of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis).

[00951] In some embodiments, the administration reduces the blood pressure in the portal vein of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis) by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween (e.g., over a period of 12 weeks or 52 weeks) as compared to before treatment.

[00952] In some embodiments, the administration reduces the spleen volume of the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis).

[00953] In some embodiments, the administration reduces the spleen volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or any number therebetween (e.g., over a period of 12 weeks or 52 weeks) as compared to before treatment.

[00954] In some embodiments, the administration reduces the spleen volume by at least 10% or at least 15% (e.g., over a period of 12 weeks or 52 weeks).

[00955] In some embodiments, the administration reduces the spleen volume by at least 10% or at least 15% over a period of 12 weeks.

[00956] In some embodiments, the administration reduces the spleen volume by at least 10% or at least 15% over a period of 52 weeks.

[00957] It has been unexpectedly determined that treatment with resmetirom or a pharmaceutically acceptable salt thereof can significantly improve NASH resolution and/or liver fibrosis if a human subject (e.g., an adult human subject) loses at least 5% of their body weight. Such weight loss can be achieved, for example, as a result of diet and/or exercise. Thus, a human subject (e.g., an adult human subject) in need of the treatment or improvement as described herein (e.g., of NASH and/or liver fibrosis) can be further instructed (e.g., counseled, instructed or prescribed) to perform diet and/or exercise in conjunction with said administration of a daily dose of resmetirom or the pharmaceutically acceptable salt thereof. In particular, this instruction can be to lose greater than or equal to 5% of their body weight, measured upon initiation of therapy.

[00958] In some embodiments, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as described herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof will be further instructed (e.g., counseled, instructed or prescribed) to perform diet and exercise in conjunction with said administration of a daily dose of resmetirom or the pharmaceutically acceptable salt thereof. In particular, the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as described herein (e.g., of NASH and/or liver fibrosis) administered a daily dose of resmetirom or the pharmaceutically acceptable salt thereof will be instructed (e.g., counseled, instructed or prescribed) to diet and exercise to lose greater than or equal to 5% of their body weight, measured upon initiation of therapy, in conjunction with said administration of a daily dose of resmetirom or the pharmaceutically acceptable salt thereof.

[00959] The pharmaceutical composition can be in a form suitable for oral use.

[00960] In some embodiments, the pharmaceutical composition is formulated in a solid oral dosage form. As used herein, the term "solid oral dosage form" refers to a dosage form that is taken by mouth in a solid form. The solid oral dosage form is designed to be swallowed and later dissolved in the gastrointestinal tract, allowing for systematic delivery of the medication to the human subject (e.g., an adult human subject) who may be in need of the treatment or improvement as disclosed herein (e.g., of NASH and/or liver fibrosis). The solid oral dosage form includes for example, a pill.

[00961] In some embodiments, the pharmaceutical composition is formulated in a pill. As used herein, the term "pill" includes for example, a capsule, a softgel, a sprinkle capsule, a tablet, a chewable tablet, or a caplet.

[00962] In some embodiments, the pharmaceutical composition is formulated in a tablet.

As used herein, the term "tablet" refers to a pill that is a solid formulation composed of medication and usually has no outer shell. Typically, the medication is in powder form where the medication and other inactive ingredients are compressed into a solid, smooth form. The tablet can be optionally coated.

[00963] The pharmaceutical compositions of the present disclosure may be manufactured in a manner that is generally known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[00964] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel[®], or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00965] In some embodiments, the active compounds are prepared with pharmaceutically acceptable excipients that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable excipients.

[00966] **EXAMPLES**

[00967] The following Examples are provided by way of illustration and not by way of limitation.

[00968] **Example 1**

[00969] **Liver Volume Reduction in Resmetirom-treated Non-cirrhotic and Cirrhotic NASH Patients**

[00970] Hepatomegaly may cause symptoms (e.g., pain) in NASH patients, and is thought to be driven primarily by high liver fat content. In a 36-week Phase 2 serial MRI-PDFF and liver biopsy study in adults with biopsy-confirmed NASH (NAS $\geq$ 4, F1-F3) and hepatic fat fraction $\geq$ 10%, resmetirom treated patients, compared with placebo, showed statistically significant liver fat reduction that was associated with NASH resolution on liver biopsy. This study was to assess the relationship between liver triglycerides as measured by MRI-PDFF and liver volume (LV) in placebo and resmetirom-treated patients.

[00971] MRI-PDFF and liver volume (LV) were assessed in, (n=117), and a NASH-cirrhotic active resmetirom treatment arm of MAESTRO-NAFLD-1 (n=73), in patients who

had at least baseline and one additional serial PDFF. LV was assessed using a validated artificial intelligence model for segmenting the liver on standard MR images.

[00972] LV at baseline was elevated in non-cirrhotic and cirrhotic NASH patients relative to literature values for healthy controls and was greater than predicted even after accounting for sex and body weight. PDFF correlated with LV at baseline in non-cirrhotic ($r^2=0.19$, $p<0.001$) and more weakly in cirrhotic NASH ($r^2=0.079$, $p=0.01$). Reduction in LV (CFB) correlated with reduction in PDFF in placebo ($r^2=0.25$, $p=0.001$) and resmetirom ($r^2=0.38$, $p<0.0001$) treated patients at 12 (and 36 (not shown)) weeks (see, e.g., FIG. 1). LV reduction was greater in resmetirom (-18.6 % (1.1), -20.5 % (1.2) compared to placebo (-0.4 % (1.5), 0.1 % (1.9) treated at 12 and 36 weeks, respectively ($p<0.0001$). A higher percentage of resmetirom (69.2%) than placebo (5.3%) patients had a $\geq 15\%$ reduction in liver volume ($p<0.0001$) at Week 12, and similarly at Week 36. The relationship between LV reduction and PDFF reduction was proportionately weaker in placebo compared to resmetirom treated non-cirrhotic NASH patients. In cirrhotic NASH patients treated with resmetirom (see FIG. 1), LV reduction was much greater than expected based on the small reduction in PDFF, especially in patients with $\text{PDFF} \leq 5\%$ at baseline (LV mean $\frac{3}{4}\text{CFB}$, -16.3% versus PDFF, mean $\frac{3}{4}\text{CFB}$, -2.5% at week 16). Resmetirom treated patients who had NASH resolution and/or fibrosis reduction on biopsy at week 36 all had a PDFF reduction $\geq 30\%$ and/or LV reduction of $\geq 15\%$ at week 12.

[00973] Without wishing to be bound by theory, reduction in liver volume in resmetirom treated patients may be explained in part by reduction in liver triglycerides (measured by MRI-PDFF), but it also may be driven by other changes related to its mechanism of action. LV reduction may be associated with histopathologic improvement of NASH that may be further assessed by data from Phase 3 MAESTRO-NASH study,

[00974] Biomarkers, imaging and safety in resmetirom 52 week non-cirrhotic**NASH Phase 3 clinical trial, completed open-label arm of MAESTRO-NAFLD-1**

[00975] MAESTRO-NASH NCT03900429 and MAESTRO-NAFLD-1 NCT04197479 are 52 week Phase 3 registrational double blind placebo controlled clinical trials to study the effect of resmetirom in more than 2,000 NASH patients. A goal of MAESTRO-NAFLD-1, a 1,200 patient "real life" NASH study is to identify non-invasive markers that correlate with patient response to resmetirom treatment. The 169 patient, 100 mg open label (OL) arm completed the 52 week study in July 2021.

[00976] Eligibility required at least 3 metabolic risk factors (Metabolic syndrome), fibroscan kilopascals (kPa) consistent with $\geq$ F1 fibrosis stage, and MRI-PDFF $\geq$ 8%. The primary and key secondary endpoints of MAESTRO-NAFLD-1 including safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), apolipoprotein B and triglycerides, fibroscan and 52 week endpoints were analyzed in the OL arm.

[00977] Mean age was 55.7 (11.5 Standard Deviation (SD)), female 69%, BMI 35.8 (6.0), diabetes 43%, hypertension 62%, dyslipidemia >70%, atherosclerotic cardiovascular disease (ASCVD) score 11.5%; fibroscan (kPa 7.7 (3.6)), and MRI-PDFF 17% (7%). Statistically significant ($p<0.0001$) reduction of MRI-PDFF -53% (3.3% (Standard Error)) overall, and in several subgroups were observed at week 52 (see, e.g., FIG. 2). Liver volume (LV) was elevated at baseline (2202 cm³ (535)) by -50% relative to normal controls and -15% after correction for BMI (Euro J of Radiol 106, 2018, 32-37). Resmetirom reduced LV -21% (1.0%), -23% (1.0%) respectively, at weeks 16 and 52 ($p<0.0001$), in all demographic groups (see, e.g., FIG. 3). LV reduction was 2-3 fold greater than predicted by % reduction in MRI-PDFF, a measure of liver fat content (Clin Gastroenterol Hepatol. 2015 13: 561-568); LY-

corrected mean MRI-PDFF reduction was -63% (2.4%). Weight loss $\geq 5\%$ occurred in ~25% and was linked to resmetirom exposure (SHBG). At week 52, magnetic resonance elastography (MRE) (-0.34, $p=0.03$); fibroscan controlled attenuation parameter (CAP) (-39 (4.6)) and vibration-controlled transient elastography (VCTE) (-1.87; -20%) ($p<0.0001$) were reduced relative to baseline. LDL-C (-22% (1.9%), apolipoprotein-B (-24% (1.6%)), triglycerides (-24% (2.6)) were statistically reduced ($p<0.0001$). Decreases from baseline in liver enzymes were ALT -20 International Unit (IU), aspartate aminotransferase (AST) -11 IU, gamma-glutamyl transferase (GGT) -25 IU ($p<0.0001$). Significant reductions in inflammatory and fibrosis biomarkers, reverse T3, enhanced liver fibrosis (ELF), and M30 (an apoptotic serum marker), and an increase in adiponectin were observed. No safety flags were identified; Blood pressure (systolic, diastolic) was reduced by ~2 mmHg, ($p=0.02$); bone mineral density (DEXA) was unchanged at 52 weeks.

[00978] In this 52 week Phase 3 OL study, noninvasively identified NASH patients treated with 100 mg per day of resmetirom for up to 52 weeks demonstrated rapid and sustained reduction in (1) hepatic fat and liver volume; (2) fibrosis as assessed by biomarkers, MRE, and fibroscan; (3) LDL and atherogenic lipids; and (4) liver enzymes inflammatory biomarkers, providing support for the use of non-invasive tests to monitor individual NASH patient response to resmetirom treatment.

[00979] Biomarkers, imaging and safety in a well-compensated NASH cirrhotic cohort treated with resmetirom for 52 weeks

[00980] As mentioned above, MAESTRO-NAFLD-1 is a 52-week patient Phase 3 randomized double blind placebo controlled NASH clinical trial that was conducted to study safety and biomarker effects of resmetirom in NASH patients with F1-F4 fibrosis identified

using non-invasive biomarkers and imaging (NCT04197479). The study included an open label active resmetirom treatment arm in well-compensated NASH cirrhotic patients.

[00981] Eligibility required at least 3 metabolic risk factors (metabolic syndrome), and NASH cirrhosis diagnosed on liver biopsy or according to accepted criteria. The primary and key secondary end points of the cirrhotic arm include safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein Band triglycerides, and markers of fibrosis. Patients received 80-100 mg daily dose of resmetirom for 52 weeks.

[00982] 105 well-compensated NASH cirrhotic patients were enrolled in the open label arm, 2/3 confirmed by liver biopsy. Demographics include mean age 62.7 (9.0 (SD)), female 64%, BMI 35.4 (7.4), diabetes 70%, hypertension 77%, dyslipidemia >70%, mean ASCVD score 16.1%, hypothyroid 32.4%, 51% on statins. MRE kPa, 5.7 (2.1); fibroscan kPa, 24.6 (14.9), CAP, 318 (59) and mean MRI-PDFF, 8.1% (5). Stage of cirrhosis was inversely correlated with baseline PDFF. At week 52 resmetirom lowered fibroscan CAP (-42 units ($p < 0.0001$) and kPa (-7.6 kPa, $p = 0.02$).

[00983] In patients with baseline PDFF >5% (5% = UL normal), resmetirom lowered PDFF by 37% ($p < 0.0057$). Resmetirom lowered MRE by 0.68 kPa at week 52, and 34% had an MRE reduction of $\geq 15\%$. GGT, -27%, $p = 0.04$ and alkaline phosphatase (ALP) -18%, $p = 0.04$ were reduced. Liver volume (LV), which was elevated in NASH cirrhosis patients at baseline, was reduced -15.9% (7.7%) at week 16 ($p < 0.0001$) independent of baseline PDFF. 73% of patients, independent of baseline cirrhosis severity, had $\geq 15\%$ reduction in LV at week 52 (see, e.g., FIG. 4). Reduction in PDFF was related to LV reduction only in patients with baseline (BL) PDFF $\geq 5\%$. Spleen volume (SV) changes were more variable than PDFF and LV reductions and were thus evaluated as a responder analysis (based on percentage of

patients with $\geq 10\%$ reduction or $\geq 10\%$ increase in SV) (see, e.g., FIGS. 5 and 6). Exposure to resmetirom was strongly correlated with LV and SV changes.

[00984] LV reduction was correlated with reduction in MRE, MRI-PDFF, tissue inhibitor of metalloproteinase (TIMP), type III procollagen peptide (P3NP), and the SHBG responses to resmetirom (see, e.g., Table 1). Resmetirom reduced LDL-C (20%), triglycerides (21%), apolipoprotein B (ApoB) (20%), lipoprotein a (Lp(a)) (30%), independent of cirrhosis stage. Blood pressure (BP) was reduced by 4-5 mm. Resmetirom was safe and well-tolerated.

Table 1:

CFB in:	Pearson		Spearman	
	%CFB LV	CFB LV	CFB LV	P-value
TIMP	0.500	0.350	0.369	0.007
P3NP	0.351	0.294	0.238	0.086
MRI-PDFF (W 16)	0.331	0.438	0.371	0.006
MRE (W 16)	0.327	0.273	0.347	0.014
AST (W 52)	0.197	0.254	0.191	0.170
SHBG	-0.282	-0.274	-0.344	0.012

CFB, change from baseline; LV, liver volume; TIMP, tissue inhibitor metalloproteinase; P3NP, amino terminal procollagen peptide; W, week.

[00985] Resmetirom treatment of patients with NASH cirrhosis for up to 52 weeks was safe and effective at lowering markers of CV risk and NASH fibrosis.

[00986] Mechanism of Action

[00987] Resmetirom is a partial agonist of the THR- β . Resmetirom produced 83.8% of the maximum response compared to triiodothyronine (T3), with an EC₅₀ of 0.21 μ M in an in vitro functional assay for THR- β activation. The same functional assay for thyroid hormone receptor-alpha (THR- α) agonism showed 48.6% efficacy for resmetirom relative to T3, with

an EC₅₀ of 3.74 µM. THR-β is the major form of THR in the liver, and stimulation of THR-β in the liver reduces intrahepatic triglycerides, whereas actions of thyroid hormone outside the liver, including in heart and bone, are largely mediated through THR-α.

[00988] Pharmacodynamics

[00989] Liver Fat Content

[00990] Resmetirom decreased liver fat content as measured by magnetic resonance imaging-protein density fat fraction (MRI-PDFF) or FibroScan controlled attenuation parameter (CAP). Reductions in liver fat content by MRI-PDFF were observed at 16 (the first assessment) and 52 weeks of treatment. Reductions in liver fat content by CAP were observed at 52 weeks of treatment.

[00991] Lipids

[00992] Resmetirom reduced LDL-C, apolipoprotein B, triglycerides and total cholesterol. Reductions in LDL C, apolipoprotein B, triglycerides and total cholesterol were observed at the first assessment at 1 month of treatment. Similar decreases were observed at longer durations of treatment, including 24 and 52 weeks.

[00993] Pharmacokinetics

[00994] Following once daily doses, steady state was typically reached within 3 to 6 days of dosing. Resmetirom steady state exposure increased in a dose proportional manner between doses of 40 mg (0.5 times the lowest approved recommended dose) and 100 mg. Resmetirom exposure increased in a greater than dose proportional manner between doses of 100 mg and 200 mg (2 times the highest approved recommended dose). Resmetirom exposure increased 1.5- to 3-fold following once daily dosing; however, the MGL-3623

metabolite did not accumulate. The estimated resmetirom systemic exposure at steady state in NASH patients are summarized in Table 2. Resmetirom exposure was similar between NASH patients with F2 stage fibrosis and F3 stage fibrosis.

Table 2: Resmetirom Estimated Systemic Exposure at Steady State in Patients with NASH with Fibrosis (F2 and F3)

Parameter	Resmetirom 80 mg Once Daily Mean (CV%)	Resmetirom 100 mg Once Daily Mean (CV%)
$C_{max,ss}$ (ng/mL) ^a	778 (41.5)	971 (40.9)
$AUC_{tau,ss}$ (ng*h/mL) ^a	5850 (60.5)	7780 (65.5)

^a $AUC_{tau,ss}$ = area under the concentration-versus-time curve over one dosing interval at steady state; $C_{max,ss}$ = maximum concentration at steady state; CV = arithmetic coefficient of variation

[00995] Absorption

[00996] Resmetirom median time to maximum plasma concentration (T_{max}) was approximately 4 hours following multiple daily doses of resmetirom 80 mg or 100 mg.

[00997] Effect of Food: No clinically significant differences in resmetirom pharmacokinetics were observed following administration with a high-fat meal (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). Concomitant food administration resulted in a 33% decrease in C_{max} , an 11% decrease in AUC, and a delay in median T_{max} by about 2 hours compared to underfasted condition.

[00998] Distribution

[00999] Resmetirom apparent volume of distribution (Vd/F) at steady-state was 68 (227%)

L. Resmetirom was greater than 99% protein-bound.

[001000] Elimination

[001001] Resmetirom median terminal plasma half-life ($t_{1/2}$) was 4.5 hours and the steady state apparent clearance (CL/F) was 17.5 (56.3%) L/h.

[001002] Metabolism: Resmetirom was metabolized by CYP2C8 and is not metabolized by other cytochrome P₄₅₀ (CYP) enzymes in vitro. MGL-3623 is a major metabolite with a 28-times lower potency for THR- β than resmetirom. MGL-3623 represented 33% to 51% of resmetirom AUC at steady state following administration of 100 mg once daily.

[001003] Excretion

[001004] Following oral administration of a 100 mg radio-labeled dose of resmetirom, approximately 67% of the total radioactive dose was recovered in the feces, mostly as metabolites and 24% of the total radioactive dose was recovered in the urine. Unchanged labeled resmetirom was not detected in feces and accounted for 1% of the dose recovered in urine. A metabolite MGL-3623 accounted for 3.3% and 16% of the dose recovered in feces and urine, respectively. Oxalic acid metabolite was observed in plasma but not in urine.

[001005] Specific Populations

[001006] No clinically significant differences in the pharmacokinetics of resmetirom were observed based on age (18 to 83 years), sex, race (White, Black, or Asian), or ATP-binding cassette super-family G member 2 (ABCG2) genotype (breast cancer resistance protein (BCRP) p.Gln141Lys, p.Val12Met).

[001007] Population pharmacokinetics (PK) analyses indicated no clinically significant difference in the pharmacokinetics of resmetirom by mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m², Modification of Diet in Renal Disease (MDRD)). The effect of severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², MDRD) on resmetirom pharmacokinetics is unknown.

[001008] **Efficacy Studies**

[001009] The efficacy of resmetirom was evaluated based on an efficacy analysis at Month 12 in Trial 1, a 54-month, randomized, double-blind, placebo-controlled trial. Enrolled patients had metabolic risk factors and a baseline or recent liver biopsy showing NASH with fibrosis stage 2 or 3 and a NAFLD Activity Score (NAS) of at least 4. Efficacy determination was based on the effect of resmetirom on resolution of steatohepatitis without worsening of fibrosis and one stage improvement in fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 12 months.

[001010] The Month 12 analysis included 888 F2 and F3 (at eligibility) patients randomized 1:1:1 to receive placebo (n = 294), resmetirom 80 mg once daily (n = 298), or resmetirom 100 mg once daily (n = 296), in addition to lifestyle counseling on nutrition and exercise. Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension.

[001011] Demographic and baseline characteristics were balanced between treatment and placebo groups. Overall, the median (Q1 to Q3) age of patients at baseline was 58 (51 to 65) years, 56% were female, 21% were Hispanic, 89% were White, 3% were Asian, and 2% were Black or African American. Median (Q1 to Q3) body mass index (BMI) was 35 (31 to 40)

kg/m² and median (Q1 to Q3) body weight was 99 (85 to 114) kg. Baseline characteristics are presented in Table 3.

Table 3: Baseline Characteristics in Patients with Stage 2 to Stage 3 Fibrosis in Trial 1

Characteristic	Overall N=888
Fibrosis stage, n (%)	
F2	328 (37)
F3	560 (63)
Type 2 Diabetes, n (%)	608 (69)
Hypertension, n (%)	700 (79)
Dyslipidemia, n (%)	633 (71)
Satin use, n (%)	434 (49)
Thyroxine use, n (%)	124 (14)
Vibration-controlled Transient Elastography (VCTE) (kPa), Median (Q1, Q3) ^{a, b}	11.8 (10, 15)
Controlled attenuation parameter (CAP) (Db/M), Median (Q1, Q3) ^a	349 (320, 378)
Fibrosis Index Based on 4 Factors (FIB-4), Median (Q1, Q3) ^a	1.3 (1, 1.8)
Enhanced Liver Fibrosis (ELF), Median (Q1, Q3) ^a	9.7 (9.2, 10.4)

^a Less than 5% missingness 476 in these variables is omitted.

^b kPa = kilopascal; Db/M = decibels per meter

[001012] Table 4 presents the Month 12 histopathology results comparing resmetirom with placebo on 1) the percentage of patients with resolution of steatohepatitis and no worsening of liver fibrosis and 2) the percentage of patients with at least one stage improvement in liver fibrosis and no worsening of steatohepatitis. Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient. Both the 80 mg once daily and the 100 mg once daily dosages of resmetirom demonstrated statistically significant improvement on histopathology endpoints for NASH and fibrosis at Month 12 compared to placebo.

[001013] Examination of age, gender, diabetes status (Yes or No), and fibrosis stage (F2 or F3) subgroups did not identify differences in response to resmetirom among these subgroups. The majority of patients in the trial were white (89%); there were too few patients of other races to adequately assess differences in response by race.

[001014] Table 4: Efficacy Results at Month 12 in Adult Patients with Noncirrhotic NASH with Stage 2 or Stage 3 Fibrosis in Trial 1

	Placebo N=294	Resmetirom 80 mg Once Daily N=298	Resmetirom 100 mg Once Daily N=296
Resolution of steatohepatitis and no worsening of liver fibrosis			
Response rate, Pathologist A (%)	13	27	36
Difference in response rate vs. placebo (95% CI)		14 (8, 20)	23 (16, 30)
Response rate, Pathologist B (%)	9	26	24
Difference in response rate vs. placebo (95% CI)		17 (11, 23)	15 (9, 21)
Improvement in liver fibrosis and no worsening of steatohepatitis			
Response rate, Pathologist A (%)	15	23	28
Difference in response rate vs. placebo (95% CI)		8 (2, 14)	13 (7, 20)
Response rate, Pathologist B (%)	13	23	24
Difference in response rate vs. placebo (95% CI)		11 (5, 17)	11 (5, 17)

CI: Confidence Interval

Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4. Resolution of steatohepatitis was defined as a score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. No worsening of steatohepatitis was defined as no increase in NAS for ballooning, inflammation, or steatosis. The prespecified primary endpoints were resolution of NASH (ballooning score 0, inflammation score 0,1) with at least

a 2-point reduction in NAS or at least a one stage improvement in fibrosis with no worsening of NAS. The effects on these prespecified endpoints were not different than the endpoints presented in Table 4.

Estimated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). 95% stratified Newcombe confidence intervals (CIs) are provided. Patients with missing liver biopsy at Month 12 were considered a non-responder.

[001015] On average, aminotransferase (ALT) and aspartate aminotransferase (AST) appeared to be reduced from baseline in resmetirom groups as compared to the placebo group starting at Month 3 through Month 12.

[001016] Pharmacokinetics

[001017] Various body weight cutoffs for dosing were evaluated.

Table 5: Distribution of Resmetirom Average Concentration at Steady State ($C_{ave,ss}$) Across Quartiles for the 80 and 100 mg Doses

$C_{ave,ss}$ (ng/mL) Range in Each Quartile	N	Percentage of $C_{ave,ss}$ in Each Quartile	
		80 mg	100 mg
Placebo	305	0%	0%
Q1: [20-155)	134	31%	19%
Q2: [155-219)	134	31%	19%
Q3: [219-321)	134	22%	28%
Q4: [321-1326]	134	17%	34%

Placebo; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile

Table 6: Model-Predicted and Observed Probabilities of Response (NASH Resolution or Fibrosis Response) According to Resmetirom $C_{ave,ss}$

$C_{ave,ss}$ (ng/mL)	N	Mean $C_{ave,ss}$ (ng/mL)	Estimated Probability (%)	Estimated 95% CI (%)	Observed Probability (%)	Observed 95% CI (%)
Placebo	305	0	27.3	(23.4 – 31.5)	19.0	(14.6 – 23.4)
Q1: [20-155)	134	120	33.6	(30.3 – 37.0)	45.5	(37.1 – 53.9)

Q2: [155-219)	134	186	37.3	(34.0 – 40.7)	44.0	(35.6 – 52.4)
Q3: [219-321)	134	263	41.9	(38.1 – 45.9)	41.8	(33.4 – 50.1)
Q4: [321-1326]	134	495	56.2	(48.9 – 63.3)	55.0	(47.6 – 64.4)

Placebo; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile

[001018] Descriptive statistics of exposure parameters of resmetirom for the 80 and 100 mg doses by 10 kg body weight increments are presented in Table 7.

Table 7: Descriptive Statistics of Exposure Parameters of Resmetirom for the 80 and 100 mg Dose by 10 kg Body Weight Increments

Assessment	Resmetirom 80 mg					Resmetirom 100 mg				
	<80 kg (N=56)	80-<90 kg (N=56)	90-<100 kg (N=59)	100-<110 kg (N=45)	≥110 kg (N=97)	<80 kg (N=50)	80-<90 kg (N=48)	90-<100 kg (N=56)	100-<110 kg (N=45)	≥110 kg (N=105)
AUC_{tau,ss} (ng.h/mL)										
Mean (CV%)	9230 (50.1%)	6660 (53.2%)	5790 (71.1%)	4740 (52.0%)	3750 (41.7%)	10800 (72.6%)	9660 (61.1%)	9010 (54.3%)	7430 (50.1%)	4940 (65.7%)
Median [Q05;Q95]	8180 [3950;18 200]	5750 [3400;13 400]	5030 [2530;10 900]	4400 [2860;74 40]	3550 [1840;623 0]	9610 [2440;2560 0]	7550 [5000;23 300]	7600 [4050;20 500]	6250 [3590;14 900]	3900 [2330;989 0]
Geometric Mean	8080	6010	5060	4370	3470	8680	8550	7990	6690	4330
C_{max,ss} (ng/mL)										
Mean (CV%)	1210 (33.3%)	869 (31.0%)	789 (29.8%)	654 (27.8%)	520 (32.3%)	1310 (46.0%)	1220 (28.3%)	1010 (30.2%)	958 (27.5%)	642 (42.0%)
Median [Q05;Q95]	1140 [664;189 0]	870 [428;127 0]	795 [358;1140]	644 [381;951]	504 [255;821]	1370 [288;2010]	1200 [689;178 0]	1060 [437;142 0]	966 [499;137 0]	647 [198;1040]
Geometric Mean	1120	816	745	624	489	1120	1160	954	905	575
C_{ave,ss} (ng.h/mL)										
Mean (CV%)	384 (50.1%)	277 (53.2%)	241 (71.1%)	197 (52.0%)	156 (41.7%)	451 (72.6%)	402 (61.1%)	375 (54.3%)	310 (50.1%)	206 (65.7%)
Median [Q05;Q95]	341 [165;759]	240 [142;560]	210 [105;455]	183 [119;310]	148 [76.5;259]	400 [102;1070]	315 [208;970]	316 [169;856]	261 [150;622]	163 [97.3;412]
Geometric Mean	337	250	211	182	145	362	356	333	279	180
C_{min,ss} (ng/mL)										
Mean (CV%)	72.8 (173.4%)	55.9 (196.0%)	52.0 (289.5%)	37.3 (244.6%)	26.0 (175.2%)	119 (195.1%)	100 (186.1%)	113 (174.0%)	65.4 (142.6%)	43.4 (212.6%)
Median [Q05;Q95]	25.5 [4.23;336]	18.4 [3.36;277]	12.0 [3.13;270]	14.1 [2.93;104]	9.77 [1.91;107]	29.7 [4.32;686]	22.2 [5.57;502]	51.0 [4.23;604]	22.1 [4.06;291]	12.8 [3.40;178]
Geometric Mean	26.7	20.7	14.2	13.2	11.5	31.4	32.0	41.7	26.5	16.2
t_{1/2α} (h)										
Mean (CV%)	1.27 (43.7%)	1.34 (46.0%)	1.21 (47.5%)	1.26 (50.3%)	1.30 (48.3%)	1.47 (48.8%)	1.30 (50.2%)	1.54 (43.6%)	1.30 (50.4%)	1.38 (48.2%)
Median [Q05;Q95]	1.15 [0.610;2. 24]	1.24 [0.599;2. 41]	1.02 [0.607;2. 48]	1.12 [0.567;2. 56]	1.11 [0.575;2.5 1]	1.44 [0.570;2.49]	1.08 [0.601;2. 55]	1.37 [0.655;2. 72]	1.34 [0.517;2. 35]	1.30 [0.655;2.7 3]
Geometric Mean	1.13	1.21	1.10	1.12	1.16	1.26	1.16	1.39	1.14	1.24
t_{1/2β} (h)										
Mean (CV%)	5.44 (51.6%)	6.04 (95.1%)	5.50 (81.5%)	5.86 (88.7%)	5.30 (50.5%)	6.85 (124.6%)	7.13 (124.0%)	8.49 (144.6%)	7.08 (145.9%)	6.33 (92.7%)
Median [Q05;Q95]	4.53 [3.68;11. 1]	4.41 [3.68;13. 4]	4.29 [3.69;14. 2]	4.50 [3.73;15. 8]	4.45 [3.63;10.0]	4.41 [3.52;15.8]	4.43 [3.78;15. 1]	5.29 [3.75;27. 3]	4.65 [3.77;11.6]	4.50 [3.75;17.0]
Geometric Mean	5.03	5.15	4.81	4.99	4.94	5.36	5.58	6.21	5.55	5.32

AUC_{tau,ss} = area under the curve over the dosing interval at steady state; C_{max,ss} = maximum concentration at steady state; C_{ave,ss} = average concentration at steady state; C_{min,ss} = minimum concentration at steady state; t_{1/2α} = distribution half-life; t_{1/2β} = elimination half-life; CV = coefficient of variation; Q05 = 5th quantile; Q95 = 95th quantile

[001019] The effect of body weight, as shown by increase in sex hormone binding globulin (SHBG), a measure of exposure, and response to resmetirom by dose in key efficacy measures, is presented in Table 8.

Table 8: Evaluation of Baseline Weight on Key Efficacy Outcomes with Resmetirom 80 mg and 100 mg

Assessment	Resmetirom 80 mg					Resmetirom 100 mg				
	80 - <90 <80 kg	90 - kg	100 - <100 kg	<110 kg	≥110 kg	80 - <90 <80 kg	90 - kg	100 - <100 kg	<110 kg	≥110 kg
≥120% increase in SHBG at Week 52	39 (72.2)	30 (56.6)	28 (52.8)	14 (34.1)	21 (28.0)	30 (68.2)	27 (62.8)	28 (63.6)	27 (62.8)	45 (50.6)
≥30% reduction in MRI-PDFF at Week 52	34 (73.9)	28 (63.6)	28 (62.2)	23 (67.6)	33 (51.6)	24 (64.9)	30 (76.9)	24 (70.6)	29 (70.7)	53 (74.6)
Week 52 MITT(1)										
Consensus Fibrosis Improvement Responder	17 (28.3)	20 (34.5)	15 (25.4)	8 (17.4)	17 (17.2)	16 (28.6)	13 (26.5)	12 (20.3)	14 (27.5)	27 (25.0)
Consensus NASH Resolution Responder	15 (25.0)	17 (29.3)	15 (25.4)	13 (28.3)	17 (17.2)	14 (25.0)	16 (32.7)	13 (22.0)	16 (31.4)	30 (27.8)
Week 52 Paired Biopsies										
Consensus Fibrosis Improvement Responder	17 (34.7)	20 (40.8)	15 (30.6)	8 (22.2)	17 (22.7)	16 (40.0)	13 (31.7)	12 (29.3)	14 (35.0)	27 (31.4)
Consensus NASH Resolution Responder	15 (30.6)	17 (34.7)	15 (30.6)	13 (36.1)	17 (22.7)	14 (35.0)	16 (39.0)	13 (31.7)	16 (40.0)	30 (34.9)
Discontinued Study Prior to Week 52	6 (10.0)	6 (10.3)	6 (10.2)	3 (6.5)	19 (19.2)	12 (21.4)	4 (8.2)	15 (25.4)	9 (17.6)	18 (16.7)

Note: (1) For NASH Resolution and Fibrosis Responder status, human subjects with composite clinical endpoints, missing responses and week 52 biopsies out of window were considered non-responders.

[001020] The pharmacokinetics of resmetirom were highly dependent on body weight and reflected in exposure response for liver biopsy and other study endpoints.

[001021] Example 2: A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

[001022] A phase 3 trial was conducted involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]).

Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no

worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

[001023] Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group). NASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group ($P < 0.001$ for both comparisons with placebo). Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group ($P < 0.001$ for both comparisons with placebo). The change in low-density lipoprotein cholesterol levels from baseline to week 24 was -13.6% in the 80-mg resmetirom group and -16.3% in the 100-mg resmetirom group, as compared with 0.1% in the placebo group ($P < 0.001$ for both comparisons with placebo). Diarrhea and nausea were more frequent with resmetirom than with placebo. The incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group.

[001024] Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage. (Funded by Madrigal Pharmaceuticals; MAESTRO-NASH ClinicalTrials.gov number, NCT03900429.).

[001025] Methods

[001026] Trial Design and Oversight

[001027] This phase 3, double-blind, randomized, placebo-controlled trial was conducted at 245 sites in 15 countries. The trial is ongoing and remains blinded to individual patient identification and trial-group assignments. The planned duration of the trial is 54 months; the two liver-biopsy primary end points were assessed at 52 weeks in the first 1050 patients who had undergone randomization, and the clinical-outcome primary end point is prespecified to be assessed at month 54. The planned duration of the trial is 54 months; the two liver-biopsy primary end points were assessed at 52 weeks in the first 1050 patients who had undergone randomization, and the clinical-outcome primary end point is prespecified to be assessed at month 54. The protocol was approved by the institutional review board and ethics committee at each participating site. The trial was and continues to be conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and all relevant regulations. All the patients provided written informed consent.

[001028] Patients

[001029] Eligible patients were 18 years of age or older who had at least three of five metabolic risk factors, according to a modified version of the International Diabetes Foundation criteria for the metabolic syndrome, and who had undergone prescreening vibration-controlled transient elastography (VCTE; FibroScan) within the past 3 months that showed a controlled attenuation parameter (CAP) of 280 dB per meter or more and a liver-stiffness measurement of 8.5 kPa or more (alternatively, a liver biopsy that was performed within 6 months before randomization could be confirmed to be eligible as a baseline biopsy by the central pathologist of the trial). Additional key inclusion criteria were histologic evidence of NASH and an NAFLD activity score of 4 or more (on a scale of 0 to 8, with higher scores indicating more severe disease), with a score of 1 or more for each component (steatosis [on a scale from 0 to 3], lobular inflammation [on a scale from 0 to 3], and

hepatocellular ballooning [on a scale from 0 to 2]). At least 50% of the total enrollment was required to have a fibrosis stage of F3. No more than 15% of the total enrollment could have a fibrosis stage of F1, primarily F1B (moderate fibrosis stage, pericentral area only), and no more than 3% of the total enrollment could have a fibrosis stage of F1A or F1C (only if the N-terminal type III collagen propeptide level was ≥ 14 ng per milliliter). Weight was required to be stable ($<5\%$ change in 3 months), and doses of glucagon-like peptide-1 agonists were required to be stable for at least 6 months before biopsy. Key exclusion criteria were alcohol consumption of more than 20 g per day for women and more than 30 g per day for men, a glycated hemoglobin level of more than 9.0% at screening, and causes of chronic liver disease other than noncirrhotic NASH. Full eligibility criteria are listed in the Supplementary Appendix.

[001030] Procedures

[001031] Patients were randomly assigned in a 1:1:1 ratio to receive resmetirom at a dose of 80 mg or 100 mg or placebo, administered orally once daily (FIG. 7). Randomization was performed with the use of an interactive Webresponse system. Patients were stratified according to status with respect to type 2 diabetes (presence or absence) and fibrosis stage (F1, F2, or F3). Throughout the trial, patients received nutrition and exercise counseling according to current recommendations. Patients were unaware of the trial-group assignments, as were site personnel, personnel of contract research organizations, and sponsor personnel who were conducting the trial, administering the investigational product, and performing clinical assessments. Selected persons were aware of the trial-group assignments to facilitate dispensation of resmetirom or placebo. All trial personnel were unaware of the results of postbaseline tests that could reveal the trial-group assignments, including levels of total and

free thyroxine (T4), sex hormone-binding globulin, and lipids as well as magnetic resonance imaging proton density fat fraction (MRI-PDFF).

[001032] Screening biopsy results were used as baseline values for histologic variables, and a second biopsy was performed at week 52. Biopsy specimens on glass slides were assessed centrally by two independent expert pathologists (the second and third authors) to determine the NAFLD activity score and fibrosis stage (according to NASH Clinical Research Network criteria). For the primary analysis, all screening or baseline biopsy specimens and week 52 biopsy specimens on glass slides were reread independently by both pathologists in large unpaired groups of screening or baseline biopsy specimens (50 to 100 slides per group, spiked with biopsy specimens obtained from patients who had screening failure) or a separate matched set of week 52 biopsy specimens (50 to 100 slides per group). The pathologists were unaware of the trial-group assignments, patient characteristics, and each other's assessments. A consensus review was conducted as a supportive analysis wherein the two pathologists read blinded (to time of biopsy and identification code) digitized images for cases in which there was disagreement on the primary read with respect to response status for the two primary end points or a reduction in fibrosis by at least two stages. Only the NAFLD activity scores or fibrosis components that determined the response for which there was disagreement between the pathologists were reread. Details are provided in the Supplementary Appendix.

[001033] End Points

[001034] The two primary end points at week 52 were NASH resolution (achievement of a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by ≥ 2 points) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score. The key secondary end point was the percent change from baseline in the low-

density lipoprotein (LDL) cholesterol level at week 24. Safety end points included adverse events, biochemical assessments, and clinical assessments. Selected serious adverse events (including deaths, cardiovascular events, and potential drug-induced liver injury) were adjudicated by independent, external event-adjudication committees whose members were unaware of the trial-group assignments. A complete list of primary and secondary end points is provided in Table 13.

[001035] Statistical Analysis

[001036] On the basis of a sample size of at least 780 patients, the trial had more than 90% power to detect a difference between each dose of resmetirom and placebo with the use of a stratified Cochran–Mantel–Haenszel test, under the assumption that NASH resolution with no worsening of fibrosis would occur in 7.2% of the patients receiving placebo and 19.8% of those receiving resmetirom and that fibrosis improvement by at least one stage with no worsening of the NAFLD activity score would occur in 14% of the patients receiving placebo and 26% of those receiving resmetirom. No comparisons were planned between the two resmetirom dose groups. The trial recruited additional patients to further expand the safety profile of resmetirom, support more robust subgroup analyses, and allow for uncertainty in the assumed treatment effects relative to placebo. Multiplicity was controlled with the use of a weighted Bonferroni approach ($\alpha = 0.04$ at week 52 and $\alpha = 0.01$ at month 54) (FIG. 8). In addition, a two-stage gatekeeping procedure was used to control α at 0.04 for the week 52 family of end points. Recycling of α to the month 54 analysis, as appropriate, is planned.

Table 9: Demographic and Clinical Characteristics of the Patients at Baseline (Primary Population).*

Characteristic	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)
Age – yr	55.9±11.5	57.0±10.8	57.1±10.5
Male sex — no. (%)†	140 (43.5)	141 (43.7)	143 (44.5)
Race or ethnic group — no. (%)†			
White	291 (90.4)	291 (90.1)	281 (87.5)
Black	5 (1.6)	5 (1.5)	9 (2.8)
Asian	10 (3.1)	9 (2.8)	9 (2.8)
Other‡	12 (3.7)	11 (3.4)	18 (5.6)
Missing data	4 (1.2)	7 (2.2)	4 (1.2)
Hispanic or Latino ethnic group — no. (%)†	71 (22.0)	81 (25.1)	52 (16.2)
Body weight — kg	100.1±22.3	101.9±22.9	100.2±23.1
Body-mass index	35.5±6.4	36.2±7.4	35.3±6.5
Type 2 diabetes — no. (%)	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension — no. (%)	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidemia — no. (%)	229 (71.1)	236 (73.1)	224 (69.8)
Hypothyroidism — no. (%)§	39 (12.1)	46 (14.2)	45 (14.0)
History of ASCVD — no. (%)	20 (6.2)	23 (7.1)	14 (4.4)
Estimated 10-yr risk of ASCVD — %¶	14.7±12.0	14.5±12.1	15.4±11.6
FibroScan liver-stiffness measurement – kPa //			
Mean	13.3±6.8	13.6±7.1	12.9±5.5
Median (IQR)	11.5 (9.5– 14.9)	11.9 (9.5– 15.9)	11.7 (9.4–14.8)
FibroScan controlled attenuation parameter — dB/m**	346.1±37.2	349.4±38.7	347.2±37.0
MRI-PDFF — %††	18.2±6.8	17.2±6.6	17.8±6.8
Liver stiffness on MRE — kPa	3.5±0.9	3.7±1.1	3.5±1.0
Fibrosis-4 index score‡‡	1.4±0.7	1.5±0.7	1.4±0.7
LDL cholesterol level — mg/dl	106.6±37.4	103.0±36.8	106.8±41.1

Alanine aminotransferase level — U/liter	52.8±27.3	56.3±34.0	54.7±34.8
Aspartate aminotransferase level — U/liter	38.2±19.3	42.5±25.2	40.7±24.6
γ-Glutamyltransferase level — U/liter	84.3±111.3	84.6±99.0	75.7±85.0
Liver-biopsy findings — no. (%)			
NAFLD activity score ≥5§§	266 (82.6)	288 (89.2)	253 (78.8)
Fibrosis stage¶¶			
F1B	16 (5.0)	15 (4.6)	18 (5.6)
F2	107 (33.2)	100 (31.0)	112 (34.9)
F3	199 (61.8)	208 (64.4)	191 (59.5)

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. ASCVD denotes atherosclerotic cardiovascular disease, IQR interquartile range, LDL low-density lipoprotein, and MRE magnetic resonance elastography.

† Data on sex, race, and ethnic group were reported by the patient.

‡ "Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and all other nonspecified race or ethnic group categories.

§ Shown are patients who were receiving thyroxine-replacement therapy at screening.

¶ The risk of cardiovascular events was derived from multiple risk factors, including age, sex, race, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, LDL cholesterol, history of diabetes, smoking status, hypertension treatment, statin treatment, and aspirin therapy. Persons are preliminarily classified on the basis of estimated risk: a 10-year risk of ASCVD of less than 5% is low risk; 5 to 7.4% is borderline risk; 7.5 to 19.9% is intermediate risk; and 20% or more is high risk.

// Liver stiffness was measured by means of vibration-controlled transient elastography. Values of more than 8.5 are considered to be indicative of fibrosis of stage F2 or higher.

** Controlled attenuation parameter is a method for the noninvasive assessment of steatosis, which measures the increased attenuation of ultrasound waves when traveling through steatotic hepatic tissue, as compared with normal liver tissue. The maximum value is 360 dB per meter; for this trial, a reading of more than 280 dB per meter was considered to be high.

†† Magnetic resonance imaging proton density fat fraction (MRI-PDFF) is a magnetic resonance imaging-derived noninvasive, quantitative biomarker to assess liver fat content. A reading of more than 5% is considered to be high.

‡‡ The Fibrosis-4 index score is derived from platelet count, aspartate aminotransferase level, age, and alanine aminotransferase level. Scores of more than 2.67 are considered to be indicative of advanced fibrosis and an elevated risk of liver-related events.

§§ The nonalcoholic fatty liver disease (NAFLD) activity score is assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure are steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2). NAFLD activity scores of 4 or more are considered to indicate at-risk nonalcoholic steatohepatitis (NASH).

¶¶ Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis). A stage of F1B indicates moderate fibrosis, pericentral area only. Five patients in each group who were scored as

having F3 fibrosis at eligibility and who were rescored as having F4 fibrosis at baseline by one or both central pathologists were evaluated in the F3 group.

[001037] The primary statistical analysis model used the Cochran–Mantel–Haenszel test to determine response with respect to the biopsy end points. Patients with missing biopsies were considered to have not had a response. Disagreement was incorporated into a statistical Cochran–Mantel–Haenszel model that provided partial credit for cases in which pathologists disagreed on response status for any biopsy end point. Multiple sensitivity analyses were conducted, including multiple imputation and tipping-point analysis. Details of secondary, exploratory, and safety analyses were specified in the statistical analysis plan (available with the protocol). All reported P values are two-sided. For end points not included in the hierarchical plan to adjust for multiple testing, 95% confidence intervals are reported without P values; 95% confidence intervals should not be used in place of hypothesis tests.

[001038] **Results**

[001039] **Patients**

[001040] From March 2019 through July 2021, a total of 1050 patients underwent randomization; 966 patients who had a fibrosis stage of F1B, F2, or F3 at baseline (primary population for safety and efficacy) were randomly assigned to receive 80 mg of resmetirom (322 patients), 100 mg of resmetirom (323 patients), or placebo (321 patients) (FIG. 9). A total of 84 patients who had a fibrosis stage of F1A or F1C at baseline were randomly assigned to receive 80 mg of resmetirom (30 patients), 100 mg of resmetirom (26 patients), or placebo (28 patients) (exploratory population for safety and efficacy) (Tables 19 and 20). A total of 11 of 966 patients had a delay in their week 52 biopsy for reasons related to coronavirus disease 2019 (Covid-19), were considered to have missing data completely at random, and were removed from the primary biopsy analysis population, a decision

consistent with regulatory guidance regarding Covid-19. As such, the primary biopsy analysis population consisted of 955 patients: 316 in the 80-mg resmetirom group, 321 in the 100-mg resmetirom group, and 318 in the placebo group.

[001041] The demographic and clinical characteristics of the patients at baseline were similar across the trial groups (Table 9 and Table 14). Most patients were White (89.3%), with a high incidence of metabolic risk factors (hypertension, 78.1%; dyslipidemia, 71.3%; and type 2 diabetes, 67.0%). A total of 21.1% of the patients were Hispanic; only 2.0% of the patients were Black. (The representativeness of the trial population is described in Table 15.) The mean ($\pm$ SD) age of the patients was 56.6 $\pm$ 10.9 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 35.7 $\pm$ 6.8. Baseline biopsies indicated that 83.5% of the patients had an NAFLD activity score of 5 or more; 5.1% had F1B fibrosis, 33.0% had F2 fibrosis, and 60.4% had F3 fibrosis. The use of medications at baseline was generally balanced across the trial groups. The demographic and clinical characteristics of the patients at baseline according to fibrosis stage are reported in Table 16. At the time of database lock for the week 52 end points, adherence to the trial regimen was high (92% with >80% adherence).

Table 10: Biopsy End Points*

Endpoint	Resmetirom 80 mg (N=316)	Resmetirom 100 mg (N=321)	Placebo (N=318)	Difference between Resmetirom, 80mg, and Placebo (95% CI)†	P- value	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†	P- value
	percent with response			percentage points		percentage points	
Primary endpoints							
NASH resolution with no worsening of	25.9	29.9	9.7	16.4 (11.0- 21.8)	<0.001	20.7 (15.3- 26.2)	<0.001

fibrosis							
Fibrosis improvement by ≥ 1 stage with no worsening of NAFLD activity score	24.2	25.9	14.2	10.2 (4.8-15.7)	<0.001	11.8 (6.4-17.2)	<0.001
Other endpoints							
≥ 2 -Point improvement in NAFLD activity score, including ≥ 1 -point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis	41.3	44.9	21.2	20.2 (13.8-26.5)		23.8 (17.4-30.2)	
≥ 2 -Point improvement in NAFLD activity score, including ≥ 1 -point improvement in hepatocellular ballooning or lobular inflammation, with improvement in fibrosis	18.8	21.2	8.5	10.5 (5.8-15.3)		13.0 (8.3-17.7)	
Improvement in each component of NAFLD activity score	23.3	27.9	7.2	16.1 (11.1-21.0)		20.9 (15.8-25.9)	
Improvement in fibrosis by ≥ 2 stages	8.3	10.1	2.8	5.6 (2.5-8.7)		7.4 (3.9-10.8)	
Both NASH resolution and fibrosis improvement	14.2	16.0	4.9	9.5 (5.4-13.6)		11.6 (7.5-15.8)	

by ≥ 1 stage							
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*Of the 966 patients in the primary population, 11 patients (6 in the 80-mg resmetirom group, 3 in the 100-mg resmetirom group, and 2 in the placebo group) had a delay in their week 52 biopsy for reasons related to coronavirus disease 2019 (Covid-19) and were not evaluated for the endpoints shown here. NASH resolution was defined as a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by at least 2 points.

†The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 11: Key Secondary and Other Secondary Endpoints (Primary Population)*

Measurement	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg, (N=323)	Placebo (N=321)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†
	<i>least-squares mean percent change from baseline</i>			<i>percentage points</i>	
LDL cholesterol level at wk 24‡§	-13.6±1.7	-16.3±1.7	0.1±1.7	-13.7 (-17.5 to -10.0) ¶	-16.4 (-20.1 to -12.6) ¶
Apolipoprotein B level at wk 24§	-16.8±1.3	-19.8±1.3	0.39±1.3	-17.2 (-20.0 to -14.4)	-20.2 (-22.9 to -17.4)
Triglyceride level at wk 24§	-22.7±4.0	-21.7±4.3	-2.6±4.1	-20.1 (-28.3 to -11.8)	-19.1 (-27.8 to -10.3)
Lipoprotein(a) level at wk 24§**	-30.4±3.8	-35.9±4.0	-0.84±3.5	-29.5 (-37.6 to -21.5)	-35.1 (-43.5 to -26.6)
MRI-PDFF at wk 52	-35.4±2.8	-46.6±2.8	-8.7±2.7	-26.7 (-32.9 to -20.6)	-37.9 (-44.2 to -31.7)
Alanine aminotransferase level at wk 48††	-26.6±3.7	-33.2±3.9	-6.9±3.8	-19.7 (-27.7 to -11.6)	-26.3 (-34.5 to -18.1)
Aspartate aminotransferase	-22.1±3.9	-28.3±3.9	-2.9±3.8	-19.3 (-27.2 to -11.3)	-25.4 (-33.5 to -17.4)

level at wk 48††					
y- Glutamyltransfer ase level at wk 48††	-25.0±5.5	-31.9±6.3	3.3±5.2	-28.3 (-37.3 to -19.3)	-35.2 (-45.5 to -25.0)

*Multiple imputation analyses were used for lipids and liver enzymes. Details on the change from baseline in levels of lipids, lipoproteins, and lipid particles at weeks 24 and 52 are provided in Table 8.

†The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

‡ The key secondary endpoint was the percent change from baseline in the LDL cholesterol level at week 24. LDL cholesterol was directly measured.

§ Data were missing for one patient in the 80-mg resmetirom group.

¶ P<0.001.

|| Data are for patients with a baseline triglyceride level of more than 150 mg per deciliter.

** Data are for patients with a baseline lipoprotein(a) level of more than 10 nmol per liter.

†† Data are for patients with a baseline alanine aminotransferase level of 30 U per liter or more.

[001042] Efficacy

[001043] NASH resolution with no worsening of fibrosis was achieved in significantly more patients who received resmetirom than in those who received placebo (25.9% in the 80-mg group and 29.9% in the 100-mg group, vs. 9.7% in the placebo group; P<0.001 for both comparisons with placebo) (FIG. 10A and Table 10). An improvement in fibrosis by at least one stage with no worsening of the NAFLD activity score was also achieved in significantly more patients who received resmetirom than in those who received placebo (24.2% in the 80-mg group and 25.9% in the 100-mg group, vs. 14.2% in the placebo group; P<0.001 for both comparisons with placebo) (FIG. 10B and Table 10). A consensus read (sensitivity analysis) of digitized images of biopsy specimens for which there was disagreement between the pathologists as to whether there was a response with respect to either primary end point yielded results similar to those of the primary analysis (Table 17A). Similar results were obtained individually by each pathologist and in multiple sensitivity analyses (Tables 17B, 17C, and 18).

[001044] Subgroup analyses of the primary end points showed generally consistent results across the subgroups (defined according to baseline fibrosis stage, baseline NAFLD activity score, status with respect to type 2 diabetes, age, and sex), with more patients who received resmetirom having either NASH resolution or fibrosis improvement than those who received placebo (FIGS. 11A through 11D). The results of additional biopsy end points and sensitivity analyses were generally supportive of the results of the primary analyses of the two primary end points (FIGS. 12 and 13 and Tables 10, 21 and 22).

[001045] LDL cholesterol levels were reduced from baseline at week 24 among patients who received resmetirom (−13.6% in the 80-mg group and −16.3% in the 100-mg group) and not in those who received placebo (0.1%) ($P < 0.001$ for both comparisons with placebo) (Table 11 and FIG. 10C); these effects seemed to be maintained at week 52 (Table 23 and FIG. 14). At week 24 and week 52, levels of triglycerides (in patients with baseline triglyceride levels of >150 mg per deciliter), non–high-density lipoprotein (HDL) cholesterol, apolipoprotein B, apolipoprotein C-III, and lipoprotein(a) appeared to decrease more from baseline in the resmetirom groups than in the placebo group. Levels of additional lipids and lipoproteins appeared to decrease more from baseline in the resmetirom groups than in the placebo group at week 52 (Table 24).

[001046] In addition, levels of liver enzymes — including alanine aminotransferase, aspartate aminotransferase, and γ -glutamyltransferase — seemed to decrease more in the resmetirom groups than in the placebo group (Table 11). Results of multiple noninvasive tests, including the MRI-PDFF at weeks 16 and 52 and Fibroscan CAP at week 52, suggested improvements associated with resmetirom treatment (Table 11 and FIGS. 15A and 15B). Liver stiffness (as assessed by VCTE or magnetic resonance elastography) appeared to decrease more from baseline with resmetirom treatment than with placebo (FIGS. 16 and 17).

By week 16, both liver volume and spleen volume appeared to decrease more from baseline with resmetirom treatment; this effect was maintained at week 52 (FIGS. 18A and 18B).

[001047] The Enhanced Liver Fibrosis test score and components of the score appeared to be improved by resmetirom treatment relative to placebo (FIGS. 19A-19C). In addition, there seemed to be improvements in levels of cytokeratin 18, adiponectin, and reverse triiodothyronine among patients who received resmetirom as compared with those who received placebo.

[001048] Safety

[001049] Overall, 91.6 to 91.9% of the patients who received resmetirom and 92.8% of those who received placebo reported an adverse event (Table 12). Most adverse events were mild or moderate in severity. The most frequent adverse events were gastrointestinal (diarrhea and nausea) (Table 25) and Covid-19. Diarrhea and nausea occurred more frequently in the resmetirom group than in the placebo group. The onset of diarrhea and nausea occurred at the initiation of resmetirom (FIG. 20). Approximately 50% of the cases of diarrhea were described as "worsening of preexisting diarrhea" or "intermittent/loose stool(s)"; no episodes of severe diarrhea were reported. The median duration of diarrhea was approximately 15 to 20 days, independent of resmetirom dose (FIG. 21).

Table 12: Safety Summary (Primary Population)

Event	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)
	number of patients (percent)		
≥1 Adverse event	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1: mild	73 (22.7)	66 (20.4)	77 (24.0)

Grade 2: moderate	180 (55.9)	183 (56.7)	169 (52.6)
Grade 3 or higher: severe	43 (13.4)	47 (14.6)	52 (16.2)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)
Adverse event leading to trial discontinuation before wk 52†	6 (1.9)	22 (6.8)	7 (2.2)
Adverse event leading to trial discontinuation during entire treatment period†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal adverse event	1 (0.3)	2 (0.6)	1 (0.3)
Major adverse cardiovascular event‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event‡	0	1 (0.3)	3 (0.9)
Adverse events affecting >10% of patients in any group			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)

* Shown are events that were considered by investigators to be related to resmetirom or placebo.

† Data are for events that emerged after the first dose of resmetirom or placebo and within 30 days after the last dose.

‡ Major adverse cardiovascular events were defined as nonfatal stroke, nonfatal myocardial infarction, and death from cardiovascular causes. All cardiovascular events were adjudicated.

[001050] The incidence of serious adverse events was similar across the trial groups:

10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg group, and 11.2% in the placebo

group (Tables 12 and 26). Serious adverse events that were considered by investigators to be related to the trial regimen occurred in two patients in the 80-mg resmetirom group and one in the placebo group (Table 12). Cancer was reported in 1.2% of the patients in the 80-mg group, 3.4% of those in the 100-mg group, and 3.7% of those in the placebo group (Table 27). There was no incidence of drug-induced liver injury. At week 52, trial discontinuations due to adverse events were more common in the 100-mg resmetirom group than in the other two trial groups (6.8% in the 100-mg resmetirom group, 1.9% in the 80-mg resmetirom group, and 2.2% in the placebo groups). Thereafter, trial discontinuations were similar across the trial groups.

[001051] Resmetirom treatment had no effect on heart rate or body weight and was not associated with arrhythmias (Table 28). Blood pressure appeared slightly reduced among patients who received resmetirom. Levels of sex hormones were little changed from baseline (Table 29). Independent of thyroxine-replacement status, resmetirom treatment reduced levels of prohormone free T4 (FT4) by approximately 16 to 19%, with no effect on levels of thyrotropin or the active thyroid hormone, free triiodothyronine (FT3) (Table 30). There were no increases in fractures or substantial changes in bone mineral density T scores (Table 31). Diarrhea AEs and AE discontinuations were higher in the 100 mg resmetirom group; overall discontinuations at 100 mg were higher in the lower body weight groups (<100 kg). Discontinuations at 80 mg resmetirom were similar to placebo. Discontinuations related to the COVID pandemic (lost to follow up/patient decision) resulted in higher than expected discontinuation at week 52 in all treatment arms (placebo 11% discontinuation at week 52).

[001052] Discussion

[001053] Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to the two primary histologic end points (NASH resolution with no

worsening of fibrosis, and an improvement in fibrosis by ≥ 1 stage with no worsening of the NAFLD activity score) at week 52. These are consistent with the end points proposed by the FDA as reasonably likely to predict clinical benefit in a phase 3 trial involving adults with NASH and liver fibrosis. The primary analyses were supported by multiple sensitivity analyses. The effects that were observed with resmetirom treatment were consistent across key subgroups. Multiple noninvasive tests for NASH, steatosis, and fibrosis (including blood biomarkers and imaging) showed a similar direction of effects favoring resmetirom treatment, which supports the findings for the primary end points.

[001054] Among patients with NASH (the majority of whom have diabetes), cardiovascular risk and mortality are high. Levels of a broad range of atherogenic lipids and lipoproteins, including LDL cholesterol, non-HDL cholesterol, triglycerides, apolipoprotein B, and lipoprotein(a), appeared to be reduced by resmetirom relative to placebo, findings consistent with those of earlier studies. Although not yet shown for resmetirom, reductions in apolipoprotein B and LDL cholesterol levels of this magnitude have been associated with improvement in cardiovascular outcomes.

[001055] More patients in the 100-mg resmetirom group than in the other two trial groups discontinued the trial because of adverse events (6.8% in the 100-mg resmetirom group, 1.8% in the 80-mg resmetirom group, and 2.2% in the placebo group). Diarrhea and nausea occurred more frequently in the resmetirom groups than in the placebo group. The safety profile of resmetirom in the MAESTRO-NASH trial is consistent with that in previous phase 2 or 3 trials in which the most common adverse events were generally self-limited diarrhea and nausea at treatment initiation. The incidence of serious adverse events was similar in the three trial groups (10.9% to 12.7%).

[001056] Noninvasive testing to identify patients with NASH for treatment and to monitor treatment response will be important in clinical practice in which liver biopsy is infrequently used. The MAESTRO-NASH trial used a screening paradigm consistent with guidelines that identified a highrisk NASH population (metabolic risk factors, FibroScan thresholds, additional imaging, and biomarkers). In this trial, achievement of a 30% reduction in hepatic fat (MRI-PDFF) or a 120% increase in the sex hormone-binding globulin level appeared to be associated with biopsy responses (FIGS. 11C and 11D).

[001057] A current limitation in the data from the MAESTRO-NASH trial is the lack of clinical-outcomes data to correlate with histologic data. The safety of long-term use of resmetirom has not yet been assessed. The trial is planned to continue to 54 months in order to accrue and evaluate liver-related outcomes, including progression to cirrhosis.

[001058] Data for the first 1050 patients from the MAESTRO-NASH trial, together with data from completed resmetirom trials, support the potential for resmetirom to provide benefit to patients with NASH and liver fibrosis. Both the 80-mg dose and the 100-mg dose of resmetirom were shown to be efficacious with respect to the two primary histologic end points in patients with NASH and liver fibrosis.

[001059] *Supplementary Appendix*

[001060] *Supplementary Methods*

[001061] *Patient Prescreening Criteria (FIG. 22)*

[001062] Potential patients to be screened for this study should:

- Not have any history of significant alcohol consumption (Exclusion Criterion #1)

- Have at least 3 metabolic risk factors using a slightly modified version of the International Diabetes Foundation (IDF) criteria (Synopsis Table 2)
- Have either
- Both AST and fibroscan requirements
- AST >17 IU (women) and AST >20 IU (men)

AND

- A fibroscan within 3 months of planned screening showing KpA ≥ 8.5 CAP ≥ 280 . Fibroscan is a potential alternative to a historic eligible liver biopsy to meet inclusion 5 and should be obtained during the prescreening period if possible.

OR

- Have a historic liver biopsy <2 years old demonstrating fibrosis stage 1B, 2 or 3 with NASH (NAS ≥ 4 , all components)

NOTE: Meets inclusion #5. Prior biopsy reflects documentation of NASH fibrosis and is not necessarily eligible as a baseline biopsy which must have been obtained 6 months prior to randomization with NAS and fibrosis score confirmed as eligible by the central pathology reader.

[001063] The IDF risk factors may be assessed by the investigator based on historic values and/or use of concomitant medications for dyslipidemia, hypertension, and diabetes.

Metabolic risk factors and the addition of an elevated serum AST value and fibroscan help ensure a higher degree of certainty that a patient will have biopsy-confirmed NASH, NAS ≥ 4 with Stage 1A/1C (high-risk), 1B, 2, or 3 fibrosis with primary emphasis on identifying patients who will have Stage 2 or 3 fibrosis on liver biopsy.

[001064] A patient with a historical liver biopsy <2 years with confirmed NASH fibrosis as described above does not require an elevated AST or fibroscan with KpA ≥ 8.5 . In patients

with historic liver biopsies, a baseline fibroscan KkpA obtained within 3 months of screening or during screening is still needed prior to randomization, but the fibroscan value does not determine eligibility. A baseline fibroscan in all randomized patients obtained during prescreening or screening is used to compare with serial fibroscans during the study.

[001065] Inclusion and Exclusion Criteria

[001066] Inclusion Criteria

[001067] Only evaluate patients for study participation if they meet the Prescreening Criteria. Patients who do not initially meet eligibility criteria may be retested, based on Investigator judgment, to determine if they qualify to participate. Patients who meet all of the following criteria will be eligible to participate in the study:

- Must be willing to participate in the study and provide written informed consent.
- Male and female adults ≥ 18 years of age.
- Female patients are eligible if they are of reproductive potential and have a negative serum pregnancy test (beta human chorionic gonadotropin), are not breastfeeding, and do not plan to become pregnant during the study and agree to use 2 highly effective birth control methods during the study OR if they are not of child bearing potential (i.e., surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]). Highly effective birth control methods include condoms with spermicide, diaphragm with spermicide, hormonal and non-hormonal intrauterine device, hormonal contraception (estrogens stable ≥ 3 months), a vasectomized or sterile male partner, or sexual abstinence (defined as refraining from heterosexual intercourse), from Screening throughout the study and for at least 30 days after study drug administration. Reliance on abstinence from heterosexual intercourse is acceptable only if it is the human subject's habitual practice.
- Male human subjects who are sexually active with a partner of child-bearing potential must either be sterile (vasectomy with history of a negative sperm count at least 90 days following the procedure); practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable); use a male condom with any sexual activity; or agree

to use a birth control method considered to be appropriate by the Investigator (such as one of the methods identified above for female human subjects of childbearing potential) from the time of Screening until 30 days after the last dose of study drug administration. Male human subjects must agree not to donate sperm for a period of 30 days after the last dose of study drug administration.

- Suspected or confirmed diagnosis of NASH fibrosis suggested by the historical data. Meet one of the following criteria that is consistent with NASH liver fibrosis:
- Historical biochemical test for fibrosis: N-terminal type III collagen propeptide (PRO-C3) >14 ng/mL; or ELF ≥ 9 (ELF is based on a historic value and is not obtained at screening; PRO-C3 is based on the historic PRO-C3 and not the screening PRO-C3).
- Fibroscan with transient elastography ≥ 8.5 kPa; and controlled attenuation parameter ≥ 280 dB.m-1 (Fibroscan does not need to be repeated at screening if done at prescreening and/or a historical Fibroscan was done in the prior 3 months).
- Historical liver biopsy obtained <2 years before expected randomization showing Stage 1B, 2 or 3 fibrosis with NASH (all 3 components) based on existing pathology review, with no significant change in body weight $>5\%$ or medication that might affect NAS or fibrosis stage.

NOTE: A biopsy that was > 6 months before the time of anticipated randomization is not eligible for study entry; a biopsy done ≤ 6 months is potentially eligible for study entry as a baseline biopsy only after confirmation of eligibility based on Inclusion #7 by the central pathology reviewer. If a Fibroscan is not used to meet Inclusion #5 (as in the case of historic eligible PRO-C3/ELF or liver biopsy), a baseline Fibroscan should be obtained prior to randomization. If other criteria are used to meet inclusion #5 and the MRI-PDFF $\geq 8\%$ OR an eligible historical liver biopsy ≤ 6 months) has been confirmed by the central reader, and with confirmed no significant change in metabolic status since the time of that biopsy, the baseline Fibroscan can be KpA <8.5 , CAP <280 .

NOTE: Eligibility based on meeting Inclusion #5 should be determined based on historic medical and laboratory (PRO-C3/ELF, Fibroscan, liver biopsy) data and should be determined prior to informed consent and screening visit.

- MRI-PDFF fat fraction $\geq 8\%$ obtained during the screening period (Baseline MRI-PDFF).

NOTE: To be eligible to perform the screening MRI-PDFF (Baseline MRI-PDFF) a patient must first meet Criterion #5. An eligible MRI-PDFF with fat fraction $\geq 8\%$ must be obtained prior to performing the baseline liver biopsy (Criterion #7). Patients with contraindications to

an MRI-PDFF (eg, metal prosthetics or uncontrolled claustrophobia) examination or screened at an investigative site where MRI-PDFF is not available are eligible for a liver biopsy if they have a Fibroscan with CAP ≥ 280 .

NOTE: An MRE and/or cT1 assessment will occur at sites with MRE equipment and/or multiparametric software. A historical MRI-PDFF $\geq 8\%$ is eligible as a baseline MRI-PDFF if obtained ≤ 8 weeks prior to randomization.

NOTE: In cases with an eligible historical biopsy (≤ 6 months) confirmed by central reader, and with confirmation that there were no significant change in metabolic status since the time of the biopsy, MRI-PDFF $< 8\%$ may be eligible. These cases would require review by Sponsor for confirmation.

- Biopsy-proven NASH baseline liver biopsy) based on a liver biopsy obtained ≤ 6 months before anticipated date of randomization (if the biopsy is deemed acceptable for interpretation by the central reader) with fibrosis stage 1A/1C, 1B, 2, or 3 on liver biopsy and NAS of ≥ 4 with a score of at least 1 in each of the following NAS components:

Steatosis (scored 0 to 3)

Ballooning degeneration (scored 0 to 2)

Lobular inflammation (scored 0 to 3)

Fibrosis stage 1A/1C patients must also have elevated PRO-C3 (> 14 ng/mL) obtained at Screening to be eligible to participate. Numbers of eligible F1A/F1C, F1B and F2 patients are defined in Number of Patients and Target Population.

NOTE: A historical biopsy obtained ≤ 6 months prior to anticipated date of randomization may be eligible as a baseline biopsy if the patient has had: (1) no significant change in metabolic status (diabetes control, lipid metabolism, and/or $> 5\%$ weight gain or loss); (2) no change in the use of any prohibited medication(s) listed as exclusionary within 12 weeks prior to the anticipated date of randomization (3) no change in the use of a NASH therapeutic (e.g., therapeutic with documented impact on liver biopsy or GLP-1 agonist) since the time of the biopsy.

The historical biopsy must be evaluated for eligibility by the central pathology reader and confirmed as eligible. The biopsy should be sent for review by the central reader after screening labs and medical history/conmeds confirm I/E requirements are met. In cases where the MRI-PDFF is $< 8\%$ but based on the local interpretation of the historical biopsy (≤ 6 months) the investigator believes that the human subject would qualify then sending the biopsy for review by the central reader may be an option if discussed with the Sponsor.

NOTE: In cases with an eligible historical biopsy (≤ 6 months) confirmed by central reader, and with confirmed no significant change in metabolic status since the time of the biopsy, MRI-PDFF $< 8\%$ may be eligible. These cases would require review by Sponsor for confirmation.

- Estimated glomerular filtration rate (GFR) ≥ 45 by the Modification of Diet in Renal Disease 6-variable formula (MDRD-6).

[001068] Exclusion Criteria

[001069] Patients who meet any of the following criteria will be excluded from participation in the study. Patients who do not initially meet eligibility criteria may be retested or rescreened, based on Investigator judgment, to determine if they qualify to participate.

- History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to Screening.

NOTE: Significant alcohol consumption is defined as equal to or greater than approximately 2 alcoholic drinks per day for males, and approximately 1.5 alcoholic drinks per day for females. One alcoholic drink is equal to 12 ounces (355 mL) of 5% alcohol by volume (ABV) beer, 5 ounces (148 mL) of 12% ABV wine, or 1.5 ounces (44.4 mL) of 40% ABV distilled spirits.

- Regular use of drugs historically associated with NAFLD, which include, but are not limited, to the following: amiodarone, methotrexate, systemic oral glucocorticoids, tamoxifen, estrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids except testosterone replacement, valproic acid, and known hepatotoxins for more than 4 weeks within the last 8 weeks prior to the initial Screening.

- Thyroid diseases:

Active hyperthyroidism

NOTE: Patients with a history of hyperthyroidism are eligible to participate.

Untreated clinical hypothyroidism defined by thyroid stimulating hormone (TSH) > 7 mIU/L with symptoms of hypothyroidism or > 10 mIU/L without symptoms.

NOTE: TSH may be repeated once, and, if > 10 mIU/L, even with normal FT4, patients may be stabilized on ≤ 75 μg thyroxine replacement therapy per day and rescreened for

eligibility. Patients with TSH >7 and <10 with no symptoms of hypothyroidism are eligible, and TSH may be monitored normally. Subclinical hypothyroidism and patients on stable thyroxine (T4) therapy up to 75 µg per day are eligible to participate. NOTE: Patients enrolled in the 'Subsequent 900' population or patients who have completed the Week 52 visit in the study may be on 100 µg/day. Other thyroid replacement therapies equivalent to up to 100 µg thyroxine are allowed (e.g. Armour thyroid).

Patients who have had a thyroidectomy and are on replacement thyroxine doses >75 µg per day are allowed.

- History of bariatric surgery or intestinal bypass surgery within the 5 years prior to randomization or planned during the conduct of the study.
- Weight gain or loss $\geq 5\%$ total body weight within 12 weeks prior to randomization. (NOTE: This includes the Screening period.)
- Hemoglobin A1C (HbA1c) $>9.0\%$.

NOTE: Patients with HbA1c $>8.0\%$ and $\leq 10.0\%$ should have documented efforts to control HbA1C to ≤ 8 . If no prior documentation of efforts to control HbA1c, patients with HbA1C $>8\%$ and $\leq 9.0\%$ may be treated with new or higher doses of existing diabetic medication(s) and continue screening. If screening HbA1C was $>9.0\%$ and a new antidiabetic therapy was initiated, they may have a repeat HbA1C 4 weeks after initiating a new antidiabetic therapy. Patients must be on stable treatment for all diabetes medications, including any new doses or medications, for ≥ 30 days prior to randomization.

NOTE: Insulin doses may be altered by up to 10% during the screening period. For screening HbA1C $>9\%$ and previous attempts to control HbA1C (no new therapy), HbA1C may be repeated once.

Glucagon-like peptide 1 [GLP-1] agonist therapy (eg, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide and albiglutide) unless stable dose for 24 weeks prior to biopsy. (NOTE: GLP-1 therapeutics may not be initiated or doses increased during the first 52 weeks of the study. However, GLP-1 therapeutics may be initiated or increased after the Week 52 visit is completed.)

- Use of high dose vitamin E (>400 IU/day) unless stable for ≥ 24 weeks prior to an eligible screening liver biopsy. Vitamin E can be discontinued but dose cannot be increased during the first 52 weeks of the study.
- Presence of cirrhosis on liver biopsy defined as stage 4 fibrosis.
- Diagnosis of hepatocellular carcinoma (HCC).

- Model for End-Stage Liver Disease (MELD) score ≥ 12 , as determined at Screening, due to liver disease.

NOTE: MELD of ≥ 12 on screening labs must be the result of liver disease to be exclusionary, NOT isolated lab abnormalities such as elevated creatinine due to chronic kidney disease, international normalized ratio (INR) abnormality secondary to anticoagulants or lab error, or bilirubin elevation due to Gilbert's Syndrome.

- Hepatic decompensation or impairment defined as presence of any of the following:

History of esophageal varices, ascites, or hepatic encephalopathy

Serum albumin < 3.5 g/dL, except as explained by non-hepatic causes

INR > 1.4 unless due to therapeutic anticoagulants or laboratory error; NOTE: INR may be repeated once to reassess eligibility.

Total bilirubin $> 1.5 \times$ upper limit of normal. NOTE: Patients with Gilbert's Syndrome are eligible with a total bilirubin above $1.5 \times$ upper limit of normal (ULN) if reticulocyte count is within normal limits (typically 0.5% to 2.5%), hemoglobin is within normal limits (typically 13.5 to 17.5 g/dL for men; 12.0 to 15.5 g/dL for women), and direct bilirubin is $< 20\%$ of total bilirubin.

- Chronic liver diseases:

Primary biliary cholangitis

Primary sclerosing cholangitis

Hepatitis B positive

Hepatitis C as defined by presence of hepatitis C virus (HCV) antibody (HCV Ab) and positive HCV RNA (tested for known cured HCV infection, or positive HCV Ab at Screening). NOTE: Patients who are HCV antibody positive and HCV RNA negative who have a history of clearly documented HCV infection (history of positive HCV RNA) are eligible to participate if prior treatment for HCV was given, and they have a documented sustained virologic response (SVR) of at least two years prior to the baseline liver biopsy.

History or evidence of current active autoimmune hepatitis History or evidence of Wilson's disease

History or evidence of alpha-1-antitrypsin deficiency Evidence of genetic hemochromatosis (hereditary, primary)

Evidence of drug-induced liver disease, as defined on the basis of typical exposure and history Known bile duct obstruction

Suspected or proven liver cancer.

Has an active autoimmune disease, including actively treated lupus, rheumatoid arthritis, inflammatory bowel disease, or autoimmune hepatitis, requiring systemic treatment within the past 12 weeks or a documented history of clinically severe autoimmune disease, including autoimmune liver disease, or a syndrome that requires systemic steroids or immunosuppressive agents. NOTE: Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators, topical, inhaled, or intranasal corticosteroids or local steroid injections are not excluded from the study.

Serum ALT >250 U/L.

NOTE: Given the intrinsic variability in ALT and AST in NASH patients, investigators should use the following guide in an attempt to establish a relatively stable baseline for ALT and AST. Investigator discretion is allowed. Documented historical (3 weeks to ≤ 6 months prior to study entry) ALT and AST levels consistent with the Screening ALT and AST values may help establish a stable baseline. This consistency may be established based on the following:

If the historical and Screening ALT and AST values are both $\leq 1.5 \times \text{ULN}$, there is no limit to the difference between the values.

Patients who do not have historical ALT and AST evaluations available will have their ALT and AST repeated during the Screening Period to help establish no worsening of >30% (both assessments during Screening period) with >2 weeks between assessments. If the historic ALT/AST are $>1.5 \times$ elevated and Screening ALT and AST are markedly improved (>50% decreased or normalized) relative to historic, then a third ALT/AST determination will be made during Screening to help establish a stable Baseline.

If at least 1 of the values is $>1.5 \times \text{ULN}$ and the second value is greater than the first value, the difference in the mean of ALT and AST values must be $\leq 30\%$. If the second value is greater than the first value by >30%, a third value assessed >2 weeks after the second value should be determined to help establish a lack of worsening trend in ALT/AST. If a worsening trend is confirmed (3 consecutive worsening values with difference from first value and second value >30% and difference between second and third value >30%), patient will be a screen failure, but may be rescreened if ALT and AST stabilize.

- Statins and/or other lipid-lowering therapies unless dose(s) is stable for ≥ 30 days prior to anticipated randomization. Statins must be taken in the evening for at least 2 weeks prior to randomization, and permitted statins include rosuvastatin up to 20 mg/day, atorvastatin up to

40 mg/day, pravastatin up to 40 mg/day, simvastatin up to 20 mg/day, pitavastatin up to 2 mg/day and lovastatin up to 40 mg/day. Other stable dyslipidemia therapies not specifically listed as excluded or dose-restricted such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are allowed. Higher doses and other statins are excluded. Stable doses of bile acid sequestrants (eg, cholestyramine (Questran, Prevalite), colestipol (Colestid, Flavored Colestid), and colesevelam (Welchol)) are permitted only if taken at least 4 h after or at least 4 h before the dose of study drug.

Fenofibrate unless dose is stable for at least 6 weeks prior to anticipated randomization and unless taking fenofibrate for a history of and/or ongoing very high triglycerides (triglycerides >500 mg/dL).

NOTE: Patients already enrolled who are taking fenofibrate even if not for very high triglycerides may remain in the study, because there are no safety concerns in most patients taking fenofibrate (Section 8.6.1).

- Pioglitazone >15 mg per day. Pioglitazone treatment must be stable for ≥ 24 weeks prior to the eligible liver biopsy.
 - Platelet count $< 140,000/\text{mm}^3$. Patients with platelets $< 140,000$ and $\geq 120,000/\text{mm}^3$ are eligible if Fib-4 < 3.5 .
 - Inability to safely obtain a liver biopsy.
 - History of biliary diversion.
 - Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure > 170 mmHg or a diastolic blood pressure > 100 mmHg at Screening.
 - New York Heart Association Class III or IV heart failure or known left ventricular ejection fraction $< 30\%$.
 - Uncontrolled cardiac arrhythmia.
 - Confirmed QT interval corrected using Fridericia's formula (QTcF) > 450 sec for males and > 470 msec for females at the Screening ECG assessment; At least 2/3 ECGs must show a prolongation and the average of the 3 ECGs must be prolonged to meet criteria for exclusion. Prolonged QTcF may be repeated and confirmed following machine calibration if needed.
- NOTE: Patients with bundle branch block or other conditions in which a QTcF cannot be calculated are allowed.
- Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 12 weeks prior to randomization.
 - Use of illicit intravenous drugs within 5 years prior to randomization or a urine drug screen

result positive for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, or phencyclidine at Screening, unless a prescribed drug accounts for the positive test.

- Active, serious medical disease with a likely life expectancy <2 years.
- Participation in an investigational new drug trial in the 60 days or 5 half-lives, whichever is longer, prior to randomization. Patients previously treated with NASH therapeutics in an investigational trial are allowed if follow up liver biopsy at the end of trial continued to show active NASH fibrosis meeting eligibility criteria, and they have been off the NASH therapeutic for at least 24 weeks prior to expected randomization. If a potential NASH therapeutic studied revealed no safety issues, and, in fact, was not a NASH therapeutic (no effect on liver biopsy compared to placebo) participation may occur 60 days or 5 half-lives, whichever is longer, after discontinuation of therapy.
- History of major surgery (ie, surgery involving a risk to the life of the patient; specifically, an operation upon an organ within the cranium, chest, abdomen, or pelvic cavity) within 6 weeks prior to randomization.
- History of cancer within the last 5 years (other than treated and believed to be cured basal or squamous cell carcinoma of the skin or resected carcinoma of the cervix).
- Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes.
- Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation, who are known to be positive for HIV, or who have recurrent or chronic systemic bacterial, fungal, viral, or protozoal infections.
- Hypersensitivity to resmetirom or to any of the excipients or to placebo.

[001070] Compliance

[001071] We calculated compliance as the number of doses (pills) taken as a percentage of the number of days patients were identified as receiving IP. Compliance was defined in standard way, at least 80%. Overall compliance was high and no per protocol analysis was conducted.

[001072] Methodology for Central Pathologist Evaluation of Liver Biopsies (FIG. 23)

[001073] A liver biopsy review manual detailed the methodology for review of the liver biopsies. Briefly, glass slides were read by a central pathologist who was blinded to patient characteristics for eligibility at the time of screening based on the protocol definition of eligible biopsy. Approximately 4% of screening biopsies were considered technically inadequate. Biopsies were obtained using a 16-gauge needle when possible and average biopsy length was ~22 mm at baseline and Week 52 as determined by both pathologists. Biopsy adequacy was confirmed for each biopsy by both pathologists. Week 52 biopsies blinded to patient ID were read by the central pathologist at the time the biopsy was obtained to determine if the biopsy showed cirrhosis. If cirrhosis was detected, the result was reported to the Sponsor and clinical site. The glass slides were digitized and stored at the digitization facility. For the primary analysis, each pathologist read all baseline and Week 52 glass slides as up to 100 slide batches of baseline and 100 slide Week 52 slides from the same patient to assure that baseline and Week 52 slides from the same patient were evaluated in batches at roughly the same time. Slides were read in the 6 months prior to the last patient Week 52 biopsy from the primary analysis population (966 patients with F1B, F2, or F3 fibrosis at baseline).

[001074] A secondary read was conducted of digitized images (read as patient pairs, blinded to time of biopsy). As a supportive analysis, consensus reads were conducted of digitized biopsies on which there was disagreement between the pathologists on responder status for the primary endpoints or the 2- stage fibrosis reduction.

[001075] Intrareader agreement (weighted kappa) was assessed between screening eligibility read and primary read for Path A, and for both pathologists between glass and digital reads. Interreader agreement was assessed for baseline and Week 52, respectively, for each component; steatosis 0.50, 0.60; lobular inflammation 0.30, 0.37; ballooning 0.34,

0.53 and fibrosis, 0.49, 0.65 (7 fibrosis components). The weighted kappa statistic appeared to underestimate the degree of correlation between the two pathologists' scores, because Pathologist A consistently scored steatosis higher and Pathologist B consistently scored ballooning higher.

[001076] Baseline fibrosis stage was assigned the higher stage, when the two pathologists disagreed and scored F1B only when there was agreement between the two pathologists. Baseline F1a/F1c patients (n=84) were considered only for exploratory efficacy and safety analyses.

[001077] Patient's outcomes were classified and scored based on the following approach:

(1,1): Both pathologist's scores indicated the patient was a Responder – score of 1

(1,0): Path A's scores indicated patient was a responder; Path B's scores indicated a Non-Responder- score of 0.5

(0,1): Path B's scores indicated patient was a responder; Path A's scores indicated a Non-Responder- score of 0.5

(0,0): Both pathologist's scores indicated the patient was a Non-Responder – score of 0. For each treatment, an average response rate was computed.

[001078] The primary analysis utilized a Cochran-Mantel-Haenszel (CMH) test, stratified for type 2 diabetes status and baseline fibrosis stage. Estimates of risk difference and confidence interval were provided. Biopsies conducted at baseline and within 60 weeks of randomization and read as "adequate" on glass slides were considered valid. For patients without a Week 52 biopsy, response was imputed as "non-response".

[001079] Primary Liver Biopsy Analysis, Sensitivity Analyses Rationale and Methodology

[001080] The primary statistical analysis calculates within each pathologist the response rate using the Cochran-Mantel-Haenszel (CMH) model stratified for type 2 diabetes status and fibrosis stage. A single estimate of response difference from placebo is then obtained by averaging the difference obtained from each pathologist. The scoring of (1,1), (1,0), (0,1) and (0,0) provides higher weight to patients that are considered responders by both pathologists relative to when they disagree. The p-value was obtained from the CMH test using table scores to compare the active and placebo treatments. Patients with no valid biopsy within the Week 52 window that extended to Week 60 were considered non-responders for the Week 52 analysis, as were patients who experience a composite clinical endpoint (e.g., liver transplant, death) prior to their Week 52 biopsy.

[001081] Consensus Reads of Digitized Images of Glass Slides

[001082] Consensus reads of digitized images of glass slides by the two central pathologists were conducted in cases where the two pathologists scores disagreed as to whether there was a response for either NASH resolution (ballooning 0,1; 2-point NAS reduction and no worsening of fibrosis) OR ≥ 1 stage fibrosis reduction with no worsening of NAS (primary endpoints) OR a 2-stage reduction in fibrosis with no worsening of NAS. The study pathologists remained blinded to all clinical data, patient ID, and slide/image identity or time of biopsy. Study personnel remain blinded to patient level data and detailed group analyses. In total 387 total assessments took place requiring four Zoom meetings between the pathologists. The consensus meetings were conducted by an unblinded reviewer who showed the pathologists the initial scores on a spread sheet, and then the pathologists decided on the consensus score for the disagreed component.

[001083] Additional Sensitivity and Supportive Analyses of the Dual Primary Endpoints

[001084] Multiple additional sensitivity and supportive analyses were conducted on the dual primary endpoints.

[001085] Tipping Point Analyses: This analysis imputed missing placebo responses for NASH resolution (in increments from 0% to 100% placebo imputation) and fibrosis response (in increments from 0% up to 35% placebo imputation) at Week 52 as successful responses in order to determine how many missing responses (which were counted in the primary analysis labels as non-responders) could be imputed before losing statistical significance. Of note, the 100-mg treatment group continued to demonstrate significant improvement in NASH resolution (up to 100% missing placebo imputation) (nominal $p = 0.0246$) and fibrosis response (up to 35% missing placebo imputation) (nominal $p = 0.0378$) (Table 18).

[001086] Multiple Imputation Analysis: Multiple imputation analyses were conducted where data for patients with missing response at Week 52 were imputed under the missing at random assumption. Data for patients with missing response data at Week 52 were imputed under the missing at random assumption by running a simulation (100 times) which produces a correlated pair of binary 0/1 data for each patient that represents the patient's response status for each pathologist. The statistics were then calculated for each imputation using the same approach as for the primary endpoint. The normalized results from each dataset were combined using Rubin's rule. (Table 17).

[001087] General Estimating Equation (GEE) Model Analysis: A generalized estimation equation (GEE) analysis was performed as a sensitivity analysis. This approach treated the biopsy scores from the two pathologists as repeated measures (i.e. correlated binary outcomes) within a patient. Baseline diabetes status, fibrosis stage and interaction term between pathologist and treatment were also included in the model.

[001088] Sensitivity analyses were performed using a GEE model in which the odds ratios favored both the 100- and 80-mg resmetirom treatment groups compared with placebo for NASH resolution (Tables 17A and 17B).

[001089] Summary of Observed Cases Using In-window Week 52 Paired Liver Biopsies: Supportive analyses were performed on patients with in-window paired Week 52 biopsies. Missing Week 52 biopsies were not imputed.

[001090] Statistical Analysis of Change in LDL-C at Week 24

[001091] Within the study, we provided analyses based on an analysis of covariance (ANCOVA) model after having performed single imputation for LDL-C as described in the statistical analysis plan (SAP). The ANCOVA model estimated least-squares means using treatment and baseline LDL-C as covariate.

[001092] To this end, the Week 24 LDL-C assessment and assessments at any visit in which LDL-C is measured (Weeks 4, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52) that has been impacted by kit shortage at the prior visit (unavailability of inpatient (IP) during the 4 weeks preceding the visit due to the COVID-19 pandemic as indicated on the electronic case report form (eCRF)), were considered missing and were imputed from an unaffected assessment at surrounding visits or using data from subjects unaffected by this intercurrent event as described in Section 11.2 of the SAP. In summary, single imputation utilizing adjacent and valid LDL-D measurements were imputed.

[001093] For missing lipid data that are still missing after the single imputation approach described, those missing lipid data were imputed using the non-missing lipid values (including the singly imputed data) based on missing at random (MAR)-based (MI). When

applying the MAR-based MI, data were imputed separately by randomized treatment group and baseline stratification factors.

Table 13: Complete List of Endpoints/Objectives for 52 Week Analyses

Type of Endpoint	Endpoint	Reported	Rationale
Dual Primary (#1)	Proportion of NASH Resolution Responders as assessed by two pathologists at Week 52.	Included	N/A
Dual Primary (#2)	Proportion of Fibrosis Responders as assessed by two pathologists at Week 52.	Included	N/A
Key Secondary	Percent change from baseline in directly measured LDL-C at Week 24.	Included	N/A
Secondary	Proportion of patients meeting each of the criteria below at Week 52: - At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation with no worsening of fibrosis. - At least a 2-point improvement in NAS with at least 1-point improvement in ballooning or lobular inflammation and at least a 1-point improvement in fibrosis. - An improvement in each histologic NAS component (ballooning, inflammation, steatosis) by at least 1 point; or improvement by at least 1 point in both ballooning and inflammation with an MRI-PDFF response ($\geq 30\%$ relative fat reduction) at Week 16 or at Week 52 if no data available at Week 16. - The resolution of fibrosis (reduction to F0). - A 2-stage Fibrosis Responders (a ≥ 2-point reduction in fibrosis patients with no worsening of NAS) in patients with baseline fibrosis F2 or more severe. - A composite of NASH Resolution Responder and Fibrosis Responder. - No worsening of fibrosis is defined as no progression ≥ 1-stage (for patients with an F1B baseline stage, a change to F2 is not considered worsening). This analysis includes patients with paired biopsies (i.e., baseline and Week 52).	Included	N/A
Secondary	Change from baseline to week 52 in NAS component score for each of the NAS components (improvement, worsening, no change [change is defined by at least a 1-point change]), NAS (total of the 3 components), and individual components, lobular inflammation, ballooning steatosis and fibrosis and the change from baseline in fibrosis (assuming a value of 1.8 for F1B). A change from F2 to F1B is not considered a decrease and from F1B to F2 is not considered an increase. Based on the paired liver biopsy population for each pathologist (based on glass slide [primary analysis]).	Included	N/A

	For fibrosis, only the subset of patients with baseline F1B or F2 (combined) to be evaluated.		
Secondary	Absolute change and percent change from baseline to Week 52 in MRI-PDFF in all patients with baseline and a Week 52 assessment.	Included	N/A
Secondary	Proportion of patients at Week 16 and Week 52 with $\geq 30\%$ or $\geq 50\%$ relative reduction from baseline in MRT-PDFF (analysis includes patients with paired data; that is a baseline assessment and an assessment at Week 16 and/or at baseline and at Week 52).	Included	N/A
Secondary	Absolute change and percent change from baseline to Week 48 in liver parameters, including ALT, AST, and GGT, in patients with baseline ALT ≥ 30 TUL/ml.	Included	N/A
Secondary	Percent change from baseline at Week 24 and Week 52 in directly measured LDL-C, ApoB, triglycerides in patients with baseline triglycerides > 150 mg/dL, ApoCIII, non-HDL-C, and Lp(a) in patients with baseline Lp(a) > 10 nmol/L.	Included	N/A
Secondary	Absolute change from baseline in directly measured LDL-C in patients with baseline LDL-C ≥ 100 mg/dL, ApoB, ApoB in patients with baseline LDL-C ≥ 100 mg/dL, triglycerides in patients with baseline triglycerides > 150 mg/dL, Lp(a) in patients with baseline Lp(a) > 10 nmol/L. Note: Percent change from baseline in LDL-C at Week 24 is a key secondary endpoint.	Not included	%CFB only is included as the more relevant measurement
Secondary	Proportion of patients at Week 24 and Week 52 with directly measured LDL-C > 100 mg/dL at Baseline who achieve < 100 mg/dL.	Not included	Endpoint not relevant to study objectives
Secondary	Proportion of patients at Week 24 and Week 52 with > 70 mg/dL directly measured LDL-C at Baseline who achieve < 70 mg/dL.	Not included	Endpoint not relevant to study objectives
Secondary	Percent change from baseline at Week 24 and Week 52 in HDL-C, ApoCIII, and lipoprotein particles.	Included	NA
Secondary	Absolute change and percent change from baseline to Week 52 in NASH inflammation and fibrosis biomarkers, including: adiponectin, reverse T3, CK-18, and ELF test with 3 direct components (ELF baseline ≥ 9.8 ; PTTTNP ≥ 9 $\mu\text{g/L}$; TTMP-1 ≥ 240 $\mu\text{g/L}$; HA ≥ 50 $\mu\text{g/L}$).	Included	NA
Secondary	Absolute change from baseline to Week 52 for NAFLD/NASH CLDQ, SF-LDQOL, and WPAI-NASH (QOL assessments).	Not included	This subanalysis will be presented separately

Secondary	Proportion of patients with baseline MRE as ≥ 2.9 kPa receiving serial (baseline and at least one of the following: Week 16, Week 52) MRE with $\geq 19\%$ reduction from baseline and the proportion with $\geq 19\%$ increase from baseline. F3, F1B, and F2 assessed separately.	Included	N/A
Secondary	Proportion of patients receiving serial (baseline and Week 52) FibroScan with $\geq 25\%$ and $\geq 30\%$ reduction from baseline in FibroScan VCTE over time. F3, F1B, and F2 assessed separately.	Included	N/A
Secondary	Absolute change from baseline at Week 52 in FibroScan CAP.	Included	N/A
Secondary	Percent change from baseline at Week 16 and Week 52 in liver volume in patients with baseline MRI-PDFF and at least one post baseline MRI-PDFF.	Included	N/A
Exploratory	Absolute change from baseline at Week 52 in other metabolic, liver, and cardiovascular assessments, including: • Markers of insulin resistance and glucose homeostasis such as adiponectin, HOMA-IR, HbA1c, glucose, and insulin. • Body weight, BMI. • Systolic and diastolic blood pressure. • Heart rate as determined by ECG.	Included	N/A
Exploratory	Agreement between: • The 2 pathologists in the assessment of NASH CRN scores (ballooning, inflammation, steatosis, fibrosis), NAS score, NASH Resolution Response, and Fibrosis Response. • The eligibility and Baseline liver biopsy assessments of NASH CRN scores (ballooning, inflammation, steatosis, fibrosis), NAS score, NASH Resolution Response, and Fibrosis Response for each pathologist.	Included	N/A
Exploratory	Proportion of patients at Week 52 defined as any improvement, no change, or any worsening in fibrosis stage.	Included	N/A
Exploratory	Change from baseline in fracture risk as assessed by T and Z scores at each of 3 sites: hip, femoral neck, and spine based on DEXA scan.	Included	
Exploratory	Adjudicated Events • MACE as adjudicated by an independent EAC in all patients. MACE includes cardiovascular mortality, myocardial infarction, cerebral vascular accident. • Events adjudicated as positive by an adjudication committee related to cardiovascular disease including a composite of 1) heart failure events, 2) hospitalization for unstable angina, and 3) urgent or emergent coronary revascularization. Drug-induced liver injury (DILI) events adjudicated as positive by an adjudication committee	Included	
Exploratory	DILI events (adjudicated)	Included	

Table 14: Additional Demographic and Baseline Characteristics (Primary Analysis

Population)*

	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
HbA1c, %	6.6 ± 1.1	6.6 ± 1.1	6.5 ± 1.0
Total cholesterol, mg/dL	179.6 ± 43.4	176.9 ± 46.0	180.0 ± 50.0
HDL-C, mg/dL	43.8 ± 12.6	44.0 ± 12.9	43.8 ± 13.3
ApoB, mg/dL	98.4 ± 27.8	95.9 ± 27.8	97.8 ± 32.0
Lp(a), nmol/L	44.7 ± 61.1	43.8 ± 60.8	42.2 ± 62.7
Enhanced liver fibrosis score	9.7 ± 0.89	9.8 ± 0.86	9.7 ± 0.86
Triglycerides, mg/dL	189.2 ± 112.5	188.7 ± 153.8	184.1 ± 125.8
Alkaline phosphatase, U/L	74.9 ± 27.1	73.9 ± 23.0	71.5 ± 23.7
Bilirubin, mg/dL†	0.63 ± 0.27	0.66 ± 0.32	0.66 ± 0.31
Platelets, 10 ⁹ /L†	236.6 ± 67.9	230.6 ± 59.1	233.6 ± 60.4
Albumin, g/dL†	4.4 ± 0.32	4.3 ± 0.27	4.4 ± 0.29
HOMA-IR	11.9 ± 11.8	10.6 ± 8.3	11.0 ± 12.3
GLP-1 RA, no. (%)	54 (16.8)	41 (12.7)	42 (13.1)
SGLT2i, no. (%)	55 (17.1)	39 (12.1)	36 (11.2)
Insulin, no. (%)	40 (12.4)	41 (12.7)	37 (11.5)
Statin, no. (%)	149 (46.3)	166 (51.4)	158 (49.2)

*Plus-minus signs are mean ±SD. †Safety population.

ApoB, apolipoprotein B; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance; Lp(a), lipoprotein (a); SD, standard deviation; SGLT2i, sodium/glucose cotransporter-2 inhibitor.

Table 15: Representativeness of Study Participants.

Category	Details
Disease	Nonalcoholic steatohepatitis (NASH)
Special considerations related to	
Age	NASH is prevalent in ages 45-65
Gender and sex	NASH is common in both men and women
Geography	NASH is common globally, with estimated 30% of US population has NAFLD
Race or ethnic group	NASH is highly prevalent in Hispanic and Latino communities and is less common in black patients

Other special considerations	NASH is more common in patients with multiple metabolic risk factors: Large waist or Body mass index (BMI) ≥ 30 , Dyslipidemia (raised TGs >150 or receiving treatment for elevated lipids), Dyslipidemia (reduced HDL cholesterol), hypertension (BP $>140/90$ on two occasions or receiving BP lowering medications), Type 2 diabetes or evidence of insulin resistance derived by HOMA-IR.
Overall total representation in MAESTRO- NASH trial	This trial included participants of the expected age range and ≥ 3 metabolic comorbid conditions. The study was conducted globally, with the majority of patients from USA. Approximately 55% of participants were women. Representative of the USA population, approximately 20% of participants were Hispanic or Latino.

Table 16: Demographic and Baseline Characteristics by Baseline Fibrosis Stage (Intent-to-Treat Population (n=1050))*

	F1 (n = 84)	Primary (N = 966)	F1B (n = 49)	F2 (n = 319)	F3 (n = 598)
Age, years	57.2 $\pm$ 13.3	56.6 $\pm$ 10.9	55.4 $\pm$ 12.8	55.0 $\pm$ 11.5	57.6 $\pm$ 10.3
Sex, male, no. (%)†	39 (46.4)	424 (43.9)	25 (51.0)	134 (42.0)	265 (44.3)
Body mass index, kg/m ²	35.5 $\pm$ 6.6	35.7 $\pm$ 6.8	36.2 $\pm$ 7.6	36.0 $\pm$ 6.7	35.4 $\pm$ 6.7
Type 2 diabetes, no. (%)	45 (53.6)	647 (67.0)	33 (67.3)	189 (59.2)	425 (71.1)
Hypertension, no. (%)	62 (73.8)	754 (78.1)	39 (79.6)	225 (70.5)	490 (81.9)
Dyslipidemia, no. (%)	57 (67.9)	689 (71.3)	37 (75.5)	212 (66.5)	440 (73.6)
Hypothyroidism, no. (%)‡	12 (14.3)	130 (13.5)	6 (12.2)	48 (15.0)	76 (12.7)
History of ASCVD, no. (%)	3 (3.6)	57 (5.9)	6 (12.2)	15 (4.7)	36 (6.0)
FibroScan VCTE/LSM, kPa	10.4 $\pm$ 3.5	13.3 $\pm$ 6.5	11.3 $\pm$ 4.8	11.6 $\pm$ 5.6	14.4 $\pm$ 6.8
MRE, kPa	2.7 $\pm$ 0.44	3.6 $\pm$ 1.0	3.0 $\pm$ 0.58	3.1 $\pm$ 0.71	3.9 $\pm$ 1.0
FIB-4	1.2 $\pm$ 0.59	1.4 $\pm$ 0.70	1.2 $\pm$ 0.54	1.3 $\pm$ 0.64	1.5 $\pm$ 0.72
Enhanced liver fibrosis score	9.6 $\pm$ 0.93	9.8 $\pm$ 0.87	9.4 $\pm$ 0.78	9.5 $\pm$ 0.76	9.9 $\pm$ 0.88
Statin, no. (%)	33 (39.3)	473 (49.0)	32 (65.3)	128 (40.1)	313 (52.3)

*Plus-minus signs are mean $\pm$ SD.

†Sex was self-reported by the patient.

‡Patients on thyroxine replacement therapy at screening.

Note: "Primary" column denotes the primary analysis population and includes F1B (by consensus); F2 and F3 populations. The F1 population was scored as baseline F1A or F1C by both pathologists or F1A/F1B or F1C/F1B. The F1 population was an exploratory population and excluded from the primary analysis population because their NASH is not felt to be at risk for progression to advanced fibrosis.

ASCVD, atherosclerotic cardiovascular disease; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; SD, standard deviation; VCTE, vibration-controlled transient elastography.

Table 17A: Sensitivity Analysis of Primary Endpoints: Consensus and Multiple Imputation

	% Response Resmetirom 80 mg (n = 316)	% Response Resmetirom 100 mg (n = 321)	% Response Placebo (n = 318)	% Difference Resmetirom 80 mg from PBO (95% CI)	% Difference Resmetirom 100 mg from PBO (95% CI)
NASH resolution					
Consensus (sensitivity)	24.4	27.7	7.9	16.8(11.3, 22.4)	20.7(15.0, 26.3)
Multiple imputation (sensitivity)	31.0	36.0	13.5	17.7 (11.3, 24.1)	23.2 (16.8, 29.6)
Fibrosis improvement					
Consensus (sensitivity)	24.4	25.5	12.3	12.2(6.3, 18.2)	13.4(7.4, 19.3)
Multiple imputation (sensitivity)	29.2	31.9	17.9	11.4 (5.1, 17.8)	14.1 (7.9, 20.4)

Data for patients with missing response data at Week 52 were imputed under the missing at random assumption by running a simulation (100 times) which produces a correlated pair of binary 0/1 data for each patient that represents the patient's response status for each pathologist. The statistics were then calculated for each imputation using the same approach as for the primary endpoint. The normalized results from each dataset were combined using Rubin's rule. Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either

pathologist are included in this analysis.

CI, confidence interval; NASH, nonalcoholic steatohepatitis; PBO, placebo. Unless otherwise stated "NASH resolution" means ballooning 0,1 with at least a 2-pt reduction in NAS and no worsening of fibrosis; "Fibrosis improvement" means at least 1-stage reduction in fibrosis with no worsening of NAS. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 17B: Sensitivity Analysis of Primary Endpoint (NASH Resolution): Generalized Estimating Equation Model

	Resmetirom 80 mg (n = 316)	Resmetirom 100 mg (n = 321)	Placebo (n = 318)
NASH resolution at Week 52, no. (%) [*]			
(1,1)	62 (19.6)	62 (19.3)	18 (5.7)
(1,0)	24 (7.6)	55 (17.1)	22 (6.9)
(0,1)	16 (5.1)	13 (4.0)	4 (1.3)
(0,0)	214 (67.7)	191 (59.5)	274 (86.2)
OR of resmetirom group to placebo [†]	3.5	4.2	
95% CI of the OR	(2.3, 5.2)	(2.8, 6.2)	
Difference in percentage of responders, CMH, resmetirom group – placebo (SD) [†]	17.5 (3.0)	21.3 (3.0)	
95% CI of the difference	(11.7, 23.3)	(15.4, 27.2)	

^{*}The ordered pair indicates (result according to pathologist A, result according to pathologist B). 1 indicates yes/responder; 0 indicates no/non-responder.

[†]The OR and difference in percentage of responders, 95% CIs, and p-values were obtained by fitting a GEE model with treatment arm, baseline type 2 diabetes status, baseline fibrosis stage, and pathologist by treatment interaction as factors, logit link function and a compound symmetric covariance structure, under the assumption that the scores from the two pathologists are repeated measurements for the same patient with some within-patient correlation structure.

Patients with no valid biopsy within the Week 52 window are considered non-responders for the Week 52 analysis, as are patients who experience a composite clinical endpoint (e.g., liver transplant, death) prior to their Week 52 biopsy.

Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis.

CI, confidence interval; GEE, generalized estimating equation; NASH, nonalcoholic steatohepatitis; OR, odds

ratio; SD, standard deviation. Unless otherwise stated "NASH resolution" means ballooning 0,1 with at least a 2-pt reduction in NAS and no worsening of fibrosis; "Fibrosis improvement" means at least 1- stage reduction in fibrosis with no worsening of NAS. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 17C: Sensitivity Analysis of Primary Endpoint (Fibrosis Improvement): Generalized Estimating Equation Model

	Resmetirom 80 mg (n = 316)	Resmetirom 100 mg (n = 321)	Placebo (n = 318)
Fibrosis improvement at Week 52, no. (%) [*]			
(1,1)	52 (16.5)	51 (15.9)	28 (8.8)
(1,0)	21 (6.6)	34 (10.6)	21 (6.6)
(0,1)	28 (8.9)	30 (9.3)	13 (4.1)
(0,0)	215 (68.0)	206 (64.2)	256 (80.5)
OR of resmetirom group to placebo [†]	2.0	2.1	
95% CT of the OR	(1.4, 2.9)	(1.5, 3.0)	
Difference in percentage of responders, CMH, resmetirom group - placebo (SD) [†]	9.7 (2.7)	11.0 (2.7)	
95% CT of the difference	(4.4, 15.0)	(5.7, 16.3)	

^{*}The ordered pair indicates (result according to pathologist A, result according to pathologist B). 1 indicates yes/responder; 0 indicates no/non-responder.

[†]The OR and difference in percentage of responders, 95% CTs, and p-values were obtained by fitting a GEE model with treatment arm, baseline type 2 diabetes status, baseline fibrosis stage, and pathologist by treatment interaction as factors, logit link function and a compound symmetric covariance structure, under the assumption that the scores from the two pathologists are repeated measurements for the same patient with some within-patient correlation structure.

Patients with no biopsy within the Week 52 window or experience a composite clinical endpoint (e.g., liver transplant, death) prior to their Week 52 biopsy are considered non-responders for the Week 52 analysis.

Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis.

CI, confidence interval; GEE, generalized estimating equation; OR, odds ratio; SD, standard deviation. Unless otherwise stated "NASH resolution" means ballooning 0,1 with at least a 2-pt reduction in NAS and no worsening of fibrosis; "Fibrosis improvement" means at least 1-stage reduction in fibrosis with no worsening of

NAS. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 18: Sensitivity Analysis of Primary Endpoints: Tipping Point

	% Response Resmetirom 80 mg (n = 316)	% Response Resmetirom 100 mg (n = 321)	% Response Placebo (n = 318)	% Difference Resmetirom 80 mg from PBO (95% CI) [†]	p-value	% Difference Resmetirom 100 mg from PBO (95% CI) [†]	p-value
NASH resolution							
Placebo – 0% imputed responders (Primary Analysis)	25.9	29.9	9.7	16.4 (11.0, 21.8)*	<0.001	20.7 (15.3, 26.2)*	<0.001
Placebo – 30% imputed responders	25.9	29.9	13.7	12.4 (6.5, 18.3)	<0.001	16.7 (10.9, 22.6)	<0.001
Placebo – 60% imputed responders	25.9	29.9	17.8	8.3 (2.2, 14.4)	0.0154	12.7 (6.6, 18.8)	<0.001
Placebo – 67% imputed responders	25.9	29.9	18.8	7.4 (1.2, 13.5)	0.0377	11.7 (5.6, 17.9)	<0.001
Placebo – 90% imputed responders	25.9	29.9	21.9	4.2 (-2.0, 10.4)	0.3693	8.6 (2.4, 14.8)	0.0130
Placebo – 100% imputed responders	25.9	29.9	23.4	2.6 (-3.5, 8.8)	0.4047	7.0 (0.9, 13.2)	0.0246
Fibrosis improvement							
Placebo – 0% imputed responders (Primary Analysis)	24.2	25.9	14.2	10.2 (4.8, 15.7)*	<0.001	11.8 (6.4, 17.2)*	<0.001
Placebo – 10% imputed responders	24.2	25.9	15.6	8.8 (3.2, 14.4)	0.0048	10.4 (4.8, 15.9)	<0.001
Placebo – 20% imputed responders	24.2	25.9	16.8	7.5 (1.8, 13.3)	0.0201	9.1 (3.4, 14.8)	0.0038

Placebo – 25% imputed responders	24.2	25.9	17.5	6.9 (1.1, 12.7)	0.0398	8.5 (2.7, 14.2)	0.0084
Placebo – 30% imputed responders	24.2	25.9	18.1	6.2 (0.3, 12.1)	0.0762	7.8 (1.9, 13.6)	0.0181
Placebo – 35% imputed responders	24.2	25.9	18.9	5.5 (-0.5, 11.5)	0.1410	7.1 (1.2, 13.0)	0.0378

*Calculated using a stratified CMH approach. Patients with missing response at Week 52 are considered non-responders in both active and placebo groups.

†Active patients with missing response at Week 52 are considered non-responders. Placebo patients with missing response at Week 52 had their response imputed by running a simulation (100 times) which produces a correlated pair of binary 0/1 data that represents the patient's response for each pathologist. The statistics were then calculated for each imputation using the same approach as in preceding footnote. The normalized results from each dataset were combined using Rubin's rule.

Note: Patients who experience a composite clinical endpoint (e.g., liver transplant, death) prior to their Week 52 biopsy. Patients that were F3 at eligibility and re-evaluated as F4 at baseline by either pathologist are included in this analysis. To account for multiplicity, 0.037 is considered to be the threshold for significance in this table. CI, confidence interval; NASH, nonalcoholic steatohepatitis; PBO, placebo. Unless otherwise stated "NASH resolution" means ballooning 0,1 with at least a 2-pt reduction in NAS and no worsening of fibrosis; "Fibrosis improvement" means at least 1-stage reduction in fibrosis with no worsening of NAS. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 19: Baseline Characteristics, F1 Patients

	Resmetirom 80mg (N=30)	Resmetirom 100mg (N=26)	Placebo (N=28)
Age, years	55.4 ± 13.0	57.8 ± 13.0	58.5 ± 14.3
Sex, male, no. (%)	14 (46.7%)	11 (42.3%)	14 (50%)
White	28 (93.3%)	23 (88.5%)	27 (96.4%)
Ethnicity, Hispanic or Latino, no. (%)	8 (26.7%)	8 (30.8%)	2(7.1%)
Body weight, kg	165.5 ± 9.2	97.6 ± 17.0	99.8 ± 25.2
Body mass index, kg/m²	36.2 ± 6.9	35.5 ± 6.6	34.8 ± 6.4
Type 2 diabetes, no. (%)	13 (43.3%)	16 (61.5%)	16 (57.1%)
Hypertension, no. (%)	23 (76.6%)	18 (69.2%)	21 (75.0%)
Dyslipidemia, no. (%)	22 (73.3%)	15 (57.7%)	20 (71.4%)
Hypothyroidism, no. (%)[§]	3 (10%)	3 (11.5%)	6 (21.4%)

History of ASCVD, no. (%)	0	1 (3.8%)	2 (7.1%)
10-year ASCVD risk score	12.7 ± 15.9	14.7 ± 12.9	17.1 ± 13.0
FibroScan VCTE/LSM, kPa	9.8 ± 3.0	11.0 ± 7.1	12.9 ± 5.5
Median (Q1, Q3)	9.8 (8.8, 11.7)	10.0 (9.1, 11.1)	9.7 (9.1, 10.9)
FibroScan CAP, dB/m	364.4 ± 34.3	355.2 ± 40.4	340.2 ± 41.0
MRI-PDFF, % fat fraction	18.6 ± 7.2	24.2 ± 8.9	20.2 ± 6.8
MRE, kPa	2.7 ± 0.42	2.9 ± 0.30	2.6 ± 0.52
FIB-4	1.2 ± 0.49	1.3 ± 0.74	1.2 ± 0.53
LDL-C, mg/dL	113.0 ± 48.1	113.3 ± 33.9	124.8 ± 48.8
Alanine aminotransferase, U/L	47.3 ± 28.4	58.1 ± 50.4	62.5 ± 48.2
Aspartate aminotransferase, U/L	30.4 ± 13.6	37.3 ± 20.2	38.0 ± 24.6
Gamma-glutamyl transferase, U/L	67.7 ± 54.8	68.3 ± 55.3	66.6 ± 65.7
Screening NAS ≥5, no. (%)	18 (60%)	17 (65.4%)	19 (67.9%)

Table 20: Endpoints and Safety Data, F1 Patients

	Resmetirom 80 mg (N=30) n (%)	Resmetirom 100 mg (N=26) n (%)	Placebo (N=28) n (%)
Biopsy endpoints			
Nash resolution endpoint	38.3	25.0	7.4
relative to placebo	31.9 (11.2, 52.5)	17.6 (-0.9, 36.2)	
Fibrosis improvement endpoint	21.7	15.4	11.1
	9.9 (-7.3, 27.0)	(-12.2, 21.1)	
SAFETY			
Any TEAE	28 (93.3)	21 (80.8)	26 (92.9)
Any Serious TEAE	6 (20.0)	6 (23.1)	4 (14.3)
Any TEAEs leading to Study Discontinuation	4 (13.3)	3 (11.5)	1 (3.6)
Grade 1	6 (20.0)	5 (19.2)	6 (21.4)
Grade 2	16 (53.3)	12 (46.2)	17 (60.7)
Grade 3	5 (16.7)	4 (15.4)	3 (10.7)
AEs >5%			
Diarrhea	8 (26.7)	5 (19.2)	7 (25.0)
Constipation	4 (13.3)	2 (7.7)	3 (10.7)

Nausea	5 (16.7)	2 (7.7)	2 (7.1)
Abdominal pain upper	2 (6.7)	1 (3.8)	4 (14.3)
Vomiting	1 (3.3)	3 (11.5)	2 (7.1)
Abdominal pain	1 (3.3)	2 (7.7)	2 (7.1)
Arthralgia	6 (20.0)	2 (7.7)	6 (21.4)
Back pain	4 (13.3)	3 (11.5)	4 (14.3)
Osteopenia	0	2 (7.7)	3 (10.7)
COVID-19	6 (20.0)	6 (23.1)	3 (10.7)
Urinary tract infection	2 (6.7)	4 (15.4)	1 (3.6)
Pruritus	2 (6.7)	4 (15.4)	1 (3.6)
Fatigue	3 (10.0)	2 (7.7)	2 (7.1)
Pyrexia	2 (6.7)	0	3 (10.7)
Headache	4 (13.3)	0	2 (7.1)
Dizziness	2 (6.7)	2 (7.7)	1 (3.6)
Rash	3 (10.0)	2 (7.7)	2 (7.1)
Type 2 diabetes mellitus	1 (3.3)	1 (3.8)	5 (17.9)
Weight decreased	1 (3.3)	3 (11.5)	1 (3.6)
Cough	0	1 (3.8)	4 (14.3)
Hypertension	1 (3.3)	0	4 (14.3)

Table 21: Histologic Response in Patients with Eligible Biopsies at Baseline and Week 52

	% Response Resmetirom 80 mg (N = 316)	% Response Resmetirom 100 mg (N = 321)	% Response Placebo (N = 318)	% Difference Resmetirom 80 mg from PBO (95% CI)	% Difference Resmetirom 100 mg from PBO (95% CI)
	(N = 258)	(N = 248)	(N = 276)		
NASH resolution* (in window including a baseline and Week 52 biopsy)					
% Response	31.8	38.7	11.2	20.9 (14.4, 27.2)	28.6 (22.2, 35.0)
Fibrosis improvement* (in window including a baseline and Week 52 biopsy)					
% Response	29.7	33.5	16.3	13.6 (7.3, 19.9)	17.2 (10.9, 23.6)
NASH resolution* OR fibrosis improvement* (in-window including a baseline and Week 52 biopsy)					
% Response	42.2	50.4	19.2	23.1 (15.4, 30.7)	31.2 (23.4, 39.0)

* NASH resolution or Fibrosis Improvement used the same definition as the primary endpoints (NASH resolution with ballooning 0, inflammation 0,1, with at least a 2-point improvement in NAS and no worsening of fibrosis stage; At least 1 stage fibrosis improvement with no worsening of NAS). Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 22: Additional Subgroups, Primary Endpoints

Additional Prespecified Subgroups				
	Relative to Placebo			
Assessment (%) (CI)	Resmetirom 80 mg		Resmetirom 100 mg	
Nash Resolution	N	Result	N	Result
≥5% Weight Gain from Baseline at Week 52	18	10.5 (-14.9, 36.0)	19	14.5 (-8.5, 37.4)
<5% Weight Gain from Baseline at Week 52	258	19.5 (13.4, 25.7)	248	26.9 (20.5, 33.2)
≥30% PDFF Reduction at Week 16	135	20.0 (12.6, 27.4)	157	26.2 (18.9, 33.5)
<30% PDFF Reduction at Week 16	90	13.8 (6.2, 21.3)	60	17.3 (8.6, 26.1)
Region: US	201	15.8 (9.0, 22.6)	224	19.9 (13.2, 26.7)
Region: Non-US	115	18.7 (9.4, 28.0)	97	22.9 (13.7, 32.1)
F2/F3	300	16.7 (11.1, 22.3)	306	20.9 (15.3, 26.5)
F1B	16	11.3 (-11.3, 34.0)	15	16.7 (-6.9, 40.2)
BMI <35 kg/m ²	164	22.4 (14.2, 30.6)	162	21.0 (13.4, 28.7)
BMI ≥35 kg/m ²	152	9.8 (3.1, 16.6)	159	20.0 (12.3, 27.7)
BW ≤200 pounds	120	17.4 (7.8, 26.9)	108	20.6 (11.0, 30.1)
BW >200 pounds	196	16.2 (9.6, 22.7)	212	21.1 (14.5, 27.8)
Fibrosis Improvement				
≥5% Weight Gain from Baseline at Week 52	18	0.9 (-22.6, 24.4)	19	16.0 (-7.9, 39.9)
<5% Weight Gain from Baseline at Week 52	258	12.8 (6.5, 19.0)	248	15.0 (8.8, 21.3)
≥30% PDFF Reduction at Week 16	135	13.5 (5.5, 21.5)	157	15.5 (8.0, 23.1)
<30% PDFF Reduction at Week 16	90	3.3 (-4.7, 11.4)	60	2.7 (-6.8, 12.2)
Region: US	201	7.8 (0.9, 14.6)	224	10.4 (3.6, 17.1)
Region: Non-US	115	14.6 (5.3, 23.9)	97	14.4 (5.5, 23.4)
F2/F3	300	10.2 (4.6, 15.9)	306	11.4 (5.8, 16.9)
F1B	16	10.5 (-11.4, 32.4)	15	19.6 (-2.6, 41.9)
BMI <35 kg/m ²	164	13.0 (5.2, 20.8)	162	11.8 (4.2, 19.4)
BMI ≥35 kg/m ²	152	7.0 (-0.7, 14.7)	159	11.1 (3.4, 18.9)
BW ≤200 pounds	120	15.6 (6.1, 25.1)	108	13.1 (3.9, 22.3)
BW >200 pounds	196	7.0 (0.4, 13.7)	213	10.8 (4.1, 17.6)
Body Weight Impact on Biopsy Responses SHBG and MRI-PDFF by Dose (post hoc)				

	Resmetirom 80 mg		Resmetirom 100 mg	
Assessment (%) (CI)	≤100 kg	>100 kg	≤100 kg	>100 kg
N	178	174	167	156
≥120% Increase in SHBG at Week 52	60.9 (52.9, 68.5)	29.6 (21.4, 38.8)	64.2 (55.4, 72.3)	55.0 (46.0, 63.8)
≥30% Reduction in MRI-PDFF at Week 52	66.9 (58.3, 74.7)	56.7 (46.3, 66.7)	71.7 (62.4, 79.8)	72.5 (63.1, 80.6)
Week 52 Primary Population *				
Consensus Fibrosis Improvement ¹	29.2 (22.7, 36.5)	17.4 (11.6, 24.6)	25.1 (18.8, 32.4)	25.6 (19.0, 33.2)
Consensus NASH Resolution ¹	26.4 (20.1, 33.5)	20.8 (14.5, 28.4)	26.9 (20.4, 34.4)	28.2 (21.3, 36.0)
Week 52 Paired Biopsies[†]				
N	147	111	125	123
Consensus Fibrosis Improvement	35.4 (27.7, 43.7)	22.5 (15.1, 31.4)	33.6 (25.4, 42.6)	32.5 (24.4, 41.6)
Consensus NASH Resolution	32.0 (24.5, 40.2)	27.0 (19.0, 36.3)	36.0 (27.6, 45.1)	35.8 (27.3, 44.9)

CT = 95% Clopper-Pearson confidence interval; BW = body weight

* For NASH Resolution and Fibrosis Responder status, missing responses and Week 52 biopsies out of window are considered non-responders.

[†] Patients with a baseline and valid Week 52 biopsy. PDFF reduction in resmetirom groups are compared to all placebo patients with any Week 16 PDFF.

¹ Unless otherwise stated "NASH resolution" means ballooning 0,1 with at least a 2-pt reduction in NAS and no worsening of fibrosis; "Fibrosis improvement" means at least 1-stage reduction in fibrosis with no worsening of NAS. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 23: Change From Baseline in Lipids, Lipoproteins, and Lipid Particles at Weeks 24 and 52 (Primary Analysis Population)

	Least Squares Mean %CFB (Standard Error) Resmetirom 80 mg (n = 322)	Least Squares Mean %CFB (Standard Error) Resmetirom 100 mg (n = 323)	Least Squares Mean %CFB (Standard Error) Placebo (n = 321)	Least Squares Mean %CFB Difference Resmetirom 80 mg from PBO (95% CI)	Least Squares Mean %CFB Difference Resmetirom 100 mg from PBO (95% CI)
LDL-C, mg/dL (baseline LDL-C >100 mg/dL)					
Week 24 – no.	148	133	150		

Baseline mean (SD)	135.6 (26.5)	134.4 (27.3)	136.8 (34.0)		
Week 24 (%CFB)	-21.3 (2.0)	-20.6 (2.0)	-5.9 (1.9)	-15.4 (-19.3, -11.6)	-14.7 (-18.6, -10.8)
Week 52 – no.	147	125	144		
Baseline mean (SD)	135.2 (26.0)	133.3 (27.4)	136.9 (34.2)		
Week 52 (%CFB)	-25.3 (2.2)	-27.1 (2.3)	-9.6 (2.1)	-15.7 (-20.0, -11.4)	-17.5 (-22.0, -13.1)
ApoB, mg/dL (baseline LDL-C >100 mg/dL)					
Week 24 – no.	148	133	150		
Baseline mean (SD)	117.9 (22.2)	116.9 (24.0)	118.3 (29.8)		
Week 24 (%CFB)	-21.9 (1.7)	-22.1 (1.8)	-3.7 (1.6)	-18.1 (-21.4, -14.9)	-18.4 (-21.8, -15.0)
Week 52 – no.	147	125	144		
Baseline mean (SD)	117.4 (20.9)	115.7 (24.1)	118.1 (29.9)		
Week 52 (%CFB)	-25.0 (2.0)	-26.6 (2.0)	-6.5 (1.9)	-18.5 (-22.4, -14.6)	-20.1 (-24.1, -16.1)
ApoCIII					
Week 24 – no.	282	272	288		
Baseline mean (SD)	10.9 (4.7)	10.7 (5.3)	10.5 (5.6)		
Week 24 (%CFB)	-10.6 (3.6)	-14.1 (3.1)	8.1 (3.1)	-18.7 (-27.1, -10.4)	-22.2 (-29.0, -15.4)
Week 52 – no.	272	255	279		
Baseline mean (SD)	10.9 (4.7)	10.7 (5.5)	10.3 (5.5)		
Week 52 (%CFB)	-10.0 (3.8)	-17.1 (3.3)	9.8 (3.3)	-19.8 (-28.4, -11.1)	-26.9 (-34.1, -19.6)
Non-HDL-C					
Week 24 – no.	285	280	294		
Baseline mean (SD)	135.6 (43.2)	131.8 (44.7)	135.7 (50.6)		
Week 24 (%CFB)	-15.2 (1.5)	-17.7 (1.6)	0.16 (1.5)	-15.4 (-18.8, -12.0)	-17.9 (-21.2, -14.5)
Week 52 – no.	276	262	284		
Baseline mean (SD)	136.1 (43.1)	132.4 (46.7)	135.2 (50.6)		
Week 52 (%CFB)	-15.7 (1.7)	-22.1 (1.7)	-0.40 (1.6)	-15.3 (-19.0, -11.7)	-21.7 (-25.2, -18.1)
HDL-C					
Week 24 – no.	285	280	294		
Baseline mean (SD)	43.9 (12.5)	43.5 (12.8)	43.8 (13.5)		
Week 24 (%CFB)	2.7 (1.5)	2.9 (1.5)	1.7 (1.5)	0.98 (-2.3, 4.2)	1.2 (-2.1, 4.5)

Week 52 – no.	276	262	284		
Baseline mean (SD)	44.1 (12.5)	43.6 (12.7)	44.1 (13.3)		
Week 52 (%CFB)	4.7 (1.4)	4.6 (1.5)	2.7 (1.4)	2.1 (-0.99, 5.1)	2.0 (-1.2, 5.1)
HDL particles, umol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	30.5 (6.5)	31.0 (6.0)	30.8 (6.2)		
Week 52 (%CFB)	5.2 (1.3)	2.3 (1.3)	1.6 (1.2)	3.6 (0.80, 6.3)	0.69 (-2.1, 3.5)
HDL particle size, nm					
Week 52 – no.	266	252	275		
Baseline mean (SD)	8.9 (0.46)	9.0 (0.46)	9.0 (0.45)		
Week 52 (%CFB)	0.90 (0.28)	0.40 (0.28)	0.30 (0.27)	0.60 (-0.01, 1.2)	0.10 (-0.51, 0.71)
LDL particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	1322.9 (438.5)	1273.5 (440.1)	1282.5 (476.1)		
Week 52 (%CFB)	-16.8 (1.7)	-20.0 (1.7)	-0.69 (1.6)	-16.1 (-19.8, -12.4)	-19.4 (-23.1, -15.6)
LDL particle size, nm					
Week 52 – no.	260	251	273		
Baseline mean (SD)	20.4 (0.59)	20.3 (0.59)	20.4 (0.60)		
Week 52 (%CFB)	-0.32 (0.17)	-0.35 (0.17)	0.04 (0.16)	-0.36 (-0.73, 0.01)	-0.39 (-0.76, 0.02)
Large HDL particles, umol/L					
Week 52 – no.	265	251	275		
Baseline mean (SD)	5.5 (2.9)	5.5 (2.9)	5.8 (2.9)		
Week 52 (%CFB)	12.3 (5.5)	4.5 (5.6)	12.2 (5.3)	0.06 (-11.9, 12.0)	-7.7 (-19.8, 4.4)
Large LDL particles, nmol/L					
Week 52 – no.	234	213	239		
Baseline mean (SD)	366.8 (263.0)	330.2 (265.6)	355.7 (257.3)		
Week 52 (%CFB)	47.8 (25.3)	55.6 (26.0)	86.4 (24.3)	-38.6 (-93.6, 16.3)	-30.8 (-87.0, 25.4)
Large VLDL and chylomicron particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	8.2 (5.8)	8.2 (8.9)	8.3 (8.7)		
Week 52 (%CFB)	-5.7 (4.9)	-9.1 (5.0)	11.2 (4.7)	-16.8 (-27.5, -6.2)	-20.2 (-31.1, -9.4)
Medium HDL particles, umol/L					
Week 52 – no.	260	245	271		
Baseline mean (SD)	5.5 (4.1)	5.7 (4.6)	5.1 (4.1)		
Week 52 (%CFB)	88.2 (28.0)	130.2 (28.7)	65.1 (27.1)	23.1 (-38.2, 84.4)	65.2 (2.9, 127.5)

Medium VLDL particles, nmol/L					
Week 52 – no.	253	240	260		
Baseline mean (SD)	25.0 (25.2)	23.2 (25.6)	23.1 (27.6)		
Week 52 (%CFB)	-18.7 (52.0)	-27.4 (53.5)	115.8 (50.6)	-134.5 (-249.6, -19.5)	-143.2 (-259.8, -26.7)
Small LDL particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	880.7 (336.3)	882.0 (360.3)	850.0 (356.9)		
Week 52 (%CFB)	-3.3 (9.2)	6.6 (9.5)	21.7 (8.9)	-25.0 (-45.2, -4.7)	-15.0 (-35.5, 5.5)
Small VLDL particles, nmol/L					
Week 52 – no.	260	250	270		
Baseline mean (SD)	25.8 (15.0)	27.1 (17.0)	27.4 (15.3)		
Week 52 (%CFB)	62.9 (38.2)	26.3 (39.0)	41.6 (36.9)	21.3 (-62.8, 105.4)	-15.3 (-100.2, 69.5)
VLDL and chylomicron particles, nmol/L					
Week 52 – no.	266	252	275		
Baseline mean (SD)	57.2 (32.4)	57.1 (38.8)	57.1 (38.2)		
Week 52 (%CFB)	-11.2 (4.3)	-20.2 (4.4)	8.2 (4.1)	-19.4 (-28.8, -10.0)	-28.4 (-37.9, -18.9)
VLDL particle size, nm					
Week 52 – no.	266	252	274		
Baseline mean (SD)	55.5 (6.5)	55.3 (6.9)	54.7 (7.3)		
Week 52 (%CFB)	1.9 (0.92)	3.4 (0.94)	2.0 (0.89)	-0.05 (-2.1, 2.0)	1.4 (-0.65, 3.4)
VLDL and chylomicron triglycerides, mg/dL					
Week 52 – no.	266	252	275		
Baseline mean (SD)	114.1 (68.6)	113.5 (92.1)	113.6 (91.7)		
Week 52 (%CFB)	-14.7 (3.1)	-17.9 (3.1)	4.9 (3.0)	-19.6 (-26.3, -12.9)	-22.8 (-29.6, -16.0)

ApoB, apolipoprotein B; ApoCIII, apolipoprotein CIII; CFB, change from baseline; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; PBO, placebo; RLP, remnant-like protein; SD, standard deviation; SE, standard error; VLDL, very low-density lipoprotein. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 24: Additional Secondary Endpoints (Primary Analysis population)

	Least Squares Mean %CFB (Standard Error)	Least Squares Mean %CFB (Standard Error)	Least Squares Mean %CFB	Least Squares Mean %CFB Difference Resmetirom 80	Least Squares Mean %CFB Difference Resmetirom 100
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	Resmetirom 80 mg (n = 321)	Resmetirom 100 mg (n = 323)	(Standard Error) Placebo (n = 321)	mg from PBO (95% CI)	mg from PBO (95% CI)
LDL-C (mg/dL)					
Week 24* – no.	285	280	294		
Baseline mean (SD)	106.6 (37.8)	102.9 (37.6)	106.2 (41.4)		
Week 24 (%CFB)	-13.6 (1.7)	-16.3 (1.7)	0.11 (1.7)	-13.7 (-17.5, - 10.0)	-16.4 (-20.1, - 12.6)
p value				<0.001	<0.001
Week 52 – no.	276	262	284		
Baseline mean (SD)	106.9 (37.9)	102.9 (36.8)	106.1 (41.7)		
Week 52 (%CFB)	-13.7 (1.8)	-19.5 (1.8)	-0.4 (1.7)	-13.3 (-17.3, - 9.3)	-19.0 (-23.0, - 15.1)
ApoB (U/L)					
Week 24 – no.	285	280	294		
Baseline mean (SD)	98.4 (28.1)	95.9 (28.3)	97.5 (32.1)		
Week 24 (%CFB)	-16.8 (1.3)	-19.8 (1.3)	0.39 (1.3)	-17.2 (-20.0, - 14.4)	-20.2 (-22.9, - 17.4)
Week 52 – no.	276	262	284		
Baseline mean (SD)	98.5 (27.6)	95.6 (27.8)	97.1 (32.1)		
Week 52 (%CFB)	-16.2 (1.5)	-22.3 (1.5)	0.59 (1.4)	-16.8 (-20.0, - 13.7)	-22.9 (-26.0, - 19.7)
Triglycerides (mg/dL) (baseline triglycerides >150 mg/dL)					
Week 24 – no.	170	146	144		
Baseline mean (SD)	237.9 (120.7)	244.7 (132.8)	261.5 (146.0)		
Week 24 (%CFB)	-22.7 (4.0)	-21.7 (4.3)	-2.6 (4.1)	-20.1 (-28.3, - 11.8)	-19.1 (-27.8, - 10.3)
Week 52 – no.	165	134	140		
Baseline mean (SD)	241.0 (122.4)	252.1 (160.2)	256.5 (145.7)		
Week 52 (%CFB)	-22.5 (4.2)	-28.4 (4.4)	-3.5 (4.2)	-19.0 (-27.9, - 10.1)	-24.9 (-34.1, - 15.7)
Lp(a) (nmol/L) (baseline Lp(a) >10 nmol/L)					
Week 24 – no.	200	187	200		

Baseline mean (SD)	62.0 (67.5)	58.7 (64.6)	57.9 (70.2)		
Week 24 (%CFB)	-30.4 (3.8)	-35.9 (4.0)	-0.84 (3.5)	-29.5 (-37.6, -21.5)	-35.1 (-43.5, -26.6)
Week 52 – no.	193	172	194		
Baseline mean (SD)	64.5 (68.4)	57.6 (62.7)	57.7 (70.0)		
Week 52 (%CFB)	-34.0 (4.9)	-37.5 (5.6)	-5.0 (4.6)	-29.5 (-39.4, -19.6)	-32.4 (-43.1, -21.8)
MRI-PDFF, % fat fraction					
Week 16 – no.	228	218	224		
Baseline mean (SD)	18.2 (6.8)	17.2 (6.5)	17.9 (6.6)		
Week 16 (%CFB)	-37.8 (2.2)	-42.1 (2.2)	-6.4 (2.2)	-31.4 (-36.3, -26.4)	-35.7 (-40.7, -30.7)
Week 52 – no.	233	222	230		
Baseline mean (SD)	18.2 (6.8)	17.2 (6.7)	17.9 (6.6)		
Week 52 (%CFB)	-35.4 (2.8)	-46.6 (2.8)	-8.7 (2.7)	-26.7 (-32.9, -20.6)	-37.9 (-44.2, -31.7)
ALT (U/L)#					
Baseline – no.	265	264	244		
Baseline mean (SD)	59.1 (25.4)	65.4 (33.5)	63.1 (26.7)		
Week 48 (CFB)	-20.4 (2.2)	-24.8 (2.3)	-8.5 (2.3)		
Week 48 (%CFB)	-26.6 (3.7)	-33.2 (3.9)	-6.9 (3.8)	-19.7 (-27.7, -11.6)	-26.3 (-34.5, -18.1)
AST (U/L)					
Baseline – no.	265	264	244		
Baseline mean (SD)	41.5 (18.6)	48.5 (26.0)	44.9 (20.8)		
Week 48 (CFB)	-13.9 (1.7)	-15.8 (1.7)	-6.0 (1.7)		
Week 48 (%CFB)	-22.1 (3.9)	-28.3 (3.9)	-2.9 (3.8)	-19.3 (-27.2, -11.3)	-25.4 (-33.5, -17.4)
GGT (U/L)					
Baseline – no.	265	264	244		
Baseline mean (SD)	87.3 (122.2)	92.4 (109.4)	80.1 (87.2)		
Week 48 (CFB)	-31.3 (3.9)	-32.7 (4.0)	-7.3 (3.9)		
Week 48 (%CFB)	-25.0 (5.5)	-31.9 (6.3)	3.3 (5.2)	-28.3 (-37.3, -19.3)	-35.2 (-45.5, -25.0)
FibroScan CAP, dB/m					
Week 52 – no.	256	252	267		
Baseline mean (SD)	346.7 (37.4)	348.4 (40.3)	347.0 (36.9)		

Week 52 (CFB)	-39.6 (4.3)	-41.3 (4.4)	-14.5 (4.1)	-25.2 (-34.5, -15.9)	-26.9 (-36.2, -17.5)
FibroScan VCTE/LSM, kPa					
FIB – no.	12	10	17		
Baseline mean (SD)	11.1 (5.5)	12.5 (5.7)	10.9 (4.4)		
Week 52 (CFB)	-3.7 (1.0)	-3.7 (1.3)	-0.62 (0.87)	-3.1 (-5.8, -0.33)	-3.1 (-6.1, -0.02)
Responder Analysis – no.	12	10	17		
Improving $\geq 25\%$ – no. (%)	6 (50.0)	7 (70.0)	4 (23.5)	3.7 (0.70, 19.1)	10.0 (1.3, 75.3)
Improving $\geq 30\%$ – no. (%)	5 (41.7)	6 (60.0)	4 (23.5)	2.7 (0.50, 14.0)	4.5 (0.78, 25.5)
Worsening $\geq 25\%$ – no. (%)	1 (8.3)	0	5 (29.4)	0.17 (0.02, 2.0)	0
Worsening $\geq 30\%$ – no. (%)	1 (8.3)	0	5 (29.4)	0.17 (0.02, 2.0)	0
F2 – no.	84	76	89		
Baseline mean (SD)	11.6 (5.5)	10.9 (3.3)	10.7 (3.3)		
Week 52 (CFB)	-2.3 (0.44)	-2.4 (0.46)	-1.3 (0.43)	-1.1 (-2.3, 0.12)	-1.2 (-2.4, 0.04)
Responder Analysis – no.	84	76	89		
Improving $\geq 25\%$ – no. (%)	37 (44.0)	38 (50.0)	31 (34.8)	1.5 (0.80, 2.7)	1.9 (1.0, 3.6)
Improving $\geq 30\%$ – no. (%)	28 (33.3)	31 (40.8)	23 (25.8)	1.4 (0.75, 2.8)	2.0 (1.0, 3.8)
Worsening $\geq 25\%$ – no. (%)	10 (11.9)	8 (10.5)	13 (14.6)	0.80 (0.33, 1.9)	0.68 (0.26, 1.8)
Worsening $\geq 30\%$ – no. (%)	7 (8.3)	5 (6.6)	12 (13.5)	0.57 (0.21, 1.5)	0.47 (0.16, 1.4)
F3 – no.	163	167	162		
Baseline mean (SD)	14.2 (6.2)	14.7 (8.4)	13.8 (5.1)		
Week 52 (CFB)	-2.0 (0.41)	-3.2 (0.41)	-1.1 (0.41)	-0.86 (-2.0, 0.25)	-2.1 (-3.2, -1.0)
Responder Analysis – no.	163	167	162		
Improving $\geq 25\%$ – n (%)	67 (41.1)	80 (47.9)	43 (26.5)	2.0 (1.2, 3.1)	2.5 (1.6, 4.0)
Improving $\geq 30\%$ – n (%)	56 (34.4)	65 (38.9)	29 (17.9)	2.5 (1.5, 4.2)	2.9 (1.7, 4.7)
Worsening $\geq 25\%$ – n (%)	24 (14.7)	18 (10.8)	30 (18.5)	0.77 (0.43, 1.4)	0.53 (0.28, 1.0)
Worsening $\geq 30\%$ – n (%)	21 (12.9)	17 (10.2)	21 (13.0)	1.0 (0.53, 1.9)	0.76 (0.39, 1.5)
MRE, kPa					
FIB – no.	7	10	11		
Baseline mean (SD)	3.1 (0.53)	2.8 (0.44)	3.2 (0.71)		
Week 52 (%CFB)	-5.7 (7.2)	2.4 (6.2)	7.5 (5.5)	-13.2 (-31.3, 4.8)	-5.1 (-21.9, 11.8)
Responder Analysis – no.	5	5	6		
$\geq 19\%$ increase from BL – no. (%)	0	1 (20.0)	2 (33.3)	0	0.50 (0.03, 9.0)
$\geq 19\%$ reduction from BL – no. (%)	1 (20.0)	0	0	NA	--
F2 – no.	47	42	61		

Baseline mean (SD)	3.0 (0.69)	3.0 (0.71)	3.0 (0.61)		
Week 52 (%CFB)	-1.9 (3.1)	1.1 (3.2)	2.1 (2.7)	-4.0 (-12.0, 4.0)	-0.99 (-9.2, 7.3)
Responder Analysis – no.	20	22	33		
≥19% increase from BL – no. (%)	0	0	2 (6.1)	0	0
≥19% reduction from BL – no. (%)	7 (35.0)	5 (22.7)	8 (24.2)	1.6 (0.45, 5.6)	0.89 (0.25, 3.2)
F3 – no.	94	96	91		
Baseline mean (SD)	3.8 (0.92)	4.0 (1.1)	3.9 (1.1)		
Week 52 (%CFB)	-8.9 (1.9)	-5.2 (1.9)	-0.38 (1.9)	-8.6 (-13.7, -3.4)	-4.8 (-10.0, 0.30)
Responder Analysis – no.	84	86	80		
≥19% increase from BL – no. (%)	3 (3.6)	7 (8.1)	13 (16.3)	0.19 (0.05, 0.70)	0.46 (0.17, 1.2)
≥19% reduction from BL – no. (%)	22 (26.2)	27 (31.4)	10 (12.5)	2.5 (1.1, 5.5)	3.2 (1.4, 7.2)
Enhanced liver fibrosis score (baseline enhanced liver fibrosis score ≥9.8)					
no.	122	123	122		
Baseline mean (SD)	10.5 (0.59)	10.5 (0.53)	10.5 (0.59)		
Week 52 (CFB)	-0.34 (0.092)	-0.35 (0.094)	-0.11 (0.091)	-0.22 (-0.40, - 0.05)	-0.24 (-0.41, - 0.07)
PIIINP, ng/mL (baseline PIIINP ≥9 ng/mL)					
no.	193	200	200		
Baseline mean (SD)	14.0 (4.4)	13.6 (4.4)	13.4 (3.9)		
Week 52 (%CFB)	-10.7 (2.8)	-10.3 (2.7)	-0.99 (2.6)	-9.7 (-15.5, -3.8)	-9.3 (-15.1, -3.5)
Week 52 (CFB)	-2.0 (0.38)	-2.1 (0.37)	-0.66 (0.36)	-1.4 (-2.2, -0.56)	-1.4 (-2.2, -0.61)
TIMP-1, ng/mL (baseline TIMP-I ≥240 ng/mL)					
no.	174	172	183		
Baseline mean (SD)	304.0 (64.7)	309.3 (73.4)	303.7 (64.0)		
Week 52 (%CFB)	-9.3 (2.0)	-10.1 (2.0)	-3.6 (1.9)	-5.7 (-9.6, -1.8)	-6.5 (-10.4, -2.6)
Week 52 (CFB)	-31.0 (6.2)	-35.7 (6.2)	-13.3 (6.0)	-17.7 (-30.1, - 5.3)	-22.3 (-34.8, -9.9)
Hyaluronic acid, ug/L (baseline hyaluronic acid ≥50 ng/mL)					
no.	156	152	155		
Baseline mean (SD)	114.9 (99.2)	122.9 (88.4)	125.3 (111.0)		
Week 52 (%CFB)	17.2 (7.8)	11.8 (8.1)	24.8 (7.8)	-7.6 (-23.1, 7.8)	-13.0 (-28.5, 2.5)

Week 52 (CFB)	1.1 (9.7)	-2.9 (10.1)	0.55 (9.7)	0.58 (-18.7, 19.9)	-3.5 (-22.9, 16.0)
CK-18, U/L					
no.	279	264	277		
Baseline mean (SD)	834.8 (476.3)	849.2 (520.3)	857.9 (519.0)		
Week 52 (CFB)	-278.2 (29.2)	-309.5 (29.8)	-143.9 (28.5)	-134.3 (-198.1, -70.5)	-165.7 (-230.3, -101.0)
Adiponectin, ug/mL					
no.	277	266	279		
Baseline mean (SD)	4.1 (2.6)	4.2 (2.5)	3.9 (2.3)		
Week 52 (CFB)	0.86 (0.19)	1.1 (0.19)	-0.10 (0.18)	0.97 (0.56, 1.4)	1.3 (0.83, 1.7)
rT3, ng/dL					
no.	278	269	282		
Baseline mean (SD)	18.5 (5.4)	19.2 (6.2)	18.4 (5.6)		
Week 52 (CFB)	-4.6 (0.31)	-5.1 (0.32)	0.17 (0.30)	-4.7 (-5.4, -4.1)	-5.2 (-5.9, -4.6)
Liver volume					
Week 16 – no.	229	217	226		
Baseline mean (SD)	2447.0 (615.7)	2376.0 (642.8)	2404.5 (666.0)		
Week 16 (%CFB)	-18.8 (0.90)	-21.4 (0.91)	-0.29 (0.87)	-18.5 (-20.5, -16.5)	-21.1 (-23.1, -19.1)
Week 52 – no.	235	225	235		
Baseline mean (SD)	2410.1 (598.9)	2368.8 (645.5)	2406.6 (683.9)		
Week 52 (%CFB)	-21.6 (1.1)	-25.8 (1.1)	-1.0 (1.0)	-20.5 (-22.9, -18.2)	-24.8 (-27.2, -22.4)
Spleen volume					
Week 16 – no.	229	217	226		
Baseline mean (SD)	373.4 (170.6)	357.2 (164.9)	361.8 (193.5)		
Week 16 (%CFB)	-2.4 (0.95)	-3.6 (0.96)	1.5 (0.92)	-3.9 (-6.0, -1.8)	-5.0 (-7.2, -2.9)
Week 52 – no.	235	225	235		
Baseline mean (SD)	364.0 (168.3)	355.8 (163.8)	360.2 (189.8)		
Week 52 (%CFB)	-5.9 (1.1)	-6.1 (1.1)	3.2 (1.1)	-9.0 (-11.5, -6.5)	-9.3 (-11.8, -6.7)

*Key secondary endpoint. # multiply imputed values. Direct LDL-C was measured.

CI, confidence interval; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic

steatohepatitis; PBO, placebo. BL, baseline; CAP, controlled attenuation parameter; CFB, change from baseline; CI, confidence interval; CK-18, cytokeratin 18; FIB-4, fibrosis-4 index; LS, least squares; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; OR, odds ratio; rT3, reverse triiodothyronine; VCTE, vibration-controlled transient elastography; SD, standard deviation; SE, standard error. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 25: Adverse Events Reported in $\geq 5\%$ of Patients (Safety Population)

Preferred Term, no. (%)	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
Abdominal pain upper	23 (7.1)	27 (8.4)	29 (9.0)
Headache	30 (9.3)	25 (7.7)	27 (8.4)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)
Type 2 diabetes	24 (7.5)	26 (8.0)	25 (7.8)
Abdominal pain	23 (7.1)	29 (9.0)	18 (5.6)
Constipation	21 (6.5)	28 (8.7)	17 (5.3)
Muscle spasms	14 (4.3)	22 (6.8)	22 (6.9)
Hypertension	16 (5.0)	13 (4.0)	25 (7.8)
Dizziness	20 (6.2)	19 (5.9)	11 (3.4)
Nasopharyngitis	14 (4.3)	20 (6.2)	14 (4.4)
Pain in extremity	12 (3.7)	12 (3.7)	23 (7.2)
Upper respiratory tract infection	23 (7.1)	8 (2.5)	17 (5.3)
Rash	12 (3.7)	21 (6.5)	12 (3.7)
Cough	14 (4.3)	18 (5.6)	12 (3.7)
Abdominal distension	14 (4.3)	13 (4.0)	17 (5.3)
Procedural pain	16 (5.0)	9 (2.8)	19 (5.9)
Gastroesophageal reflux disease	16 (5.0)	7 (2.2)	8 (2.5)
Decreased appetite	5 (1.6)	16 (5.0)	4 (1.2)
Sinusitis	10 (3.1)	13 (4.0)	17 (5.3)

Table 26: Serious Adverse Events

System Organ Class*	Resmetirom 80 mg (N=322) n (%)	Resmetirom 100 mg (N=323) n (%)	Placebo (N=321) n (%)
Patients with at least one TE-SAEs	35 (10.9)	41 (12.7)	37 (11.5)

Infections and infestations	12 (3.7)	5 (1.5)	13 (4.0)
COVID-19	1 (0.3)	1 (0.3)	2 (0.6)
COVID-19 pneumonia	2 (0.6)	0	3 (0.9)
Gastrointestinal disorders	3 (0.9)	7 (2.2)	7 (2.2)
Acute Gallstone-related disorders[#]	3 (0.9)	3 (0.9)	1 (0.3)
Injury, poisoning and procedural complications	3 (0.9)	8 (2.5)	4 (1.2)
Post procedural haemorrhage	1 (0.3)	1 (0.3)	2 (0.6)
Cardiac disorders	3 (0.9)	3 (0.9)	7 (2.2)
Respiratory, thoracic and mediastinal disorders	3 (0.9)	4 (1.2)	6 (1.9)
Musculoskeletal and connective tissue disorders	7 (2.2)	1 (0.3)	4 (1.2)
Nervous system disorders	3 (0.9)	2 (0.6)	6 (1.9)
General disorders and administration site conditions	2 (0.6)	5 (1.5)	3 (0.9)

* Included SAEs where category was not unblinding # Includes a combination of acute cholecystitis, gallstone related pancreatitis, or choledolithiasis. Individual SAEs that were unblinding for treatment of individual patients are not shown because MAESTRO-NASH is a blinded ongoing 54-month outcome study.

Table 27: Malignancies

	Resmetirom 80 mg (N=322) n (%)	Resmetirom 100 mg (N=323) n (%)	Placebo (N=321) n (%)
Patients with any malignancy	4 (1.2)	11 (3.4)	12 (3.7)
Basal cell carcinoma	2 (0.6)	3 (0.9)	2 (0.6)
Breast carcinoma	1 (0.3)	2 (0.6)	1 (0.3)
Malignant melanoma	0	1 (0.3)	1 (0.3)
Skin cancer (squamous cell)	1 (0.3)	1 (0.3)	3 (0.9)

* Malignancies that were unblinding for treatment of individual patients are not shown because MAESTRO-

NASH is a blinded ongoing 54-month outcome study.

Table 28: Change From Baseline in Metabolic Factors at Week 52 (Primary Analysis Population)

	Least Squares Mean %CFB (Standard Error) Resmetirom 80 mg (n = 322)	Least Squares Mean %CFB (Standard Error) Resmetirom 100 mg (n = 323)	Least Squares Mean %CFB (Standard Error) Placebo (n = 321)	Least Squares Mean %CFB Difference Resmetirom 80 mg from PBO (95% CI)	Least Squares Mean %CFB Difference Resmetirom 100 mg from PBO (95% CI)
Body weight, kg					
no.	281	265	286		
Baseline mean (SD)	98.6 (21.9)	102.1 (22.6)	99.5 (22.4)		
Week 52 (%CFB)	-1.2 (0.37)	-1.8 (0.38)	-0.87 (0.36)	-0.35 (-1.2, 0.45)	-0.88 (-1.7, -0.07)
SBP, mmHg					
no.	281	265	286		
Baseline mean (SD)	129.7 (13.6)	129.8 (15.1)	130.2 (14.4)		
Week 52 (%CFB)	-1.9 (0.70)	-2.1 (0.71)	0.74 (0.67)	-2.7 (-4.2, -1.2)	-2.9 (-4.4, -1.4)
DBP, mmHg					
no.	281	265	286		
Baseline mean (SD)	79.4 (8.8)	79.1 (9.7)	80.8 (9.5)		
Week 52 (%CFB)	-1.6 (0.71)	-2.0 (0.72)	-0.17 (0.69)	-1.5 (-3.0, 0.08)	-1.9 (-3.4, -0.32)
Heart rate, beats/min (based on electrocardiogram)					
no.	278	267	280		
Baseline mean (SD)	70.4 (10.7)	69.0 (10.4)	69.7 (10.9)		
Week 52 (%CFB)	-1.7 (0.83)	-2.6 (0.84)	-0.19 (0.81)	-1.5 (-3.3, 0.28)	-2.4 (-4.2, -0.57)
Glucose (mg/dL)					
no.	277	261	285		
Baseline mean (SD)	131.7 (40.8)	129.4 (35.0)	128.4 (38.8)		
Week 52 (%CFB)	-0.72 (1.8)	-3.4 (1.9)	2.2 (1.7)	-2.9 (-6.8, 1.0)	-5.6 (-9.5, -1.6)
Insulin (mIU/L)					
no.	277	261	285		
Baseline mean (SD)	34.5 (24.5)	31.5 (20.1)	33.2 (30.6)		
Week 52 (%CFB)	2.8 (5.0)	3.3 (5.1)	5.1 (4.8)	-2.3 (-13.0, 8.4)	-1.8 (-12.6, 9.1)
HOMA-IR					

no.	276	261	285		
Baseline mean (SD)	11.8 (11.1)	10.3 (8.0)	11.0 (12.7)		
Week 52 (%CFB)	9.1 (7.1)	3.4 (7.2)	14.4 (6.8)	-5.3 (-20.5, 9.9)	-11.0 (-26.4, 4.4)
HbA1c (%)					
no.	277	262	285		
Baseline mean (SD)	6.6 (1.1)	6.6 (1.1)	6.5 (1.0)		
Week 52 (%CFB)	1.7 (0.88)	1.5 (0.89)	1.5 (0.85)	0.19 (-1.7, 2.1)	0.05 (-1.9, 1.9)

CFB, change from baseline; CI, confidence interval; ECG, electrocardiogram; PBO, placebo; SD, standard deviation; SE, standard error. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 29: Change From Baseline in Sex Hormones at Week 52 (Safety Population)

	Least Squares Mean %CFB or CFB (Standard Error) Resmetirom 80 mg (n = 322)	Least Squares Mean %CFB or CFB (Standard Error) Resmetirom 100 mg (n = 323)	Least Squares Mean %CFB or CFB (Standard Error) Placebo (n = 321)	Least Squares Mean Difference Resmetirom 80 mg from PBO (95% CI)	Least Squares Mean Difference Resmetirom 100 mg from PBO (95% CI)
Estradiol, ng/L (female)					
no.	160	147	155		
Baseline mean (SD)	28.6 (37.0)	32.1 (56.3)	32.8 (65.9)		
Week 52 CFB (Standard Error)	17.7 (8.0)	30.6 (8.3)	1.8 (8.0)	15.9 (-1.3, 33.1)	28.8 (11.3, 46.3)
Estradiol, ng/L (male)					
no.	118	118	128		
Baseline mean (SD)	28.0 (11.6)	27.6 (10.9)	29.3 (12.1)		
Week 52 CFB (Standard Error)	8.9 (1.3)	11.0 (1.3)	-0.15 (1.2)	9.0 (6.3, 11.8)	11.2 (8.4, 13.9)
FSH, mIU/mL (female)					
no.	160	148	155		
Baseline mean (SD)	39.2 (25.7)	39.3 (22.6)	39.8 (23.2)		
Week 52 CFB (Standard Error)	-0.54 (0.89)	0.63 (0.92)	-1.3 (0.89)	0.79 (-1.1, 2.7)	2.0 (0.02, 3.9)
FSH, mIU/mL (male)					
no.	118	119	128		

Baseline mean (SD)	8.1 (7.7)	7.8 (9.7)	7.2 (6.5)		
Week 52 CFB (Standard Error)	1.1 (0.24)	1.7 (0.24)	0.01 (0.22)	1.1 (0.57, 1.6)	1.7 (1.1, 2.2)
LH, mIU/mL (female)					
no.	160	148	155		
Baseline mean (SD)	23.5 (14.1)	24.2 (13.2)	23.3 (12.0)		
Week 52 CFB (Standard Error)	-0.93 (0.69)	0.80 (0.72)	-0.60 (0.70)	-0.33 (-1.8, 1.2)	1.4 (-0.11, 2.9)
LH, mIU/mL (male)					
no.	118	119	128		
Baseline mean (SD)	6.3 (4.1)	6.0 (4.6)	6.1 (4.0)		
Week 52 CFB (Standard Error)	1.7 (0.30)	1.9 (0.30)	-0.10 (0.28)	1.8 (1.1, 2.4)	2.0 (1.4, 2.7)
Testosterone, ug/L (female)					
no.	160	147	156		
Baseline mean (SD)	0.2 (0.17)	0.2 (0.16)	0.1 (0.24)		
Week 52 CFB (Standard Error)	0.15 (0.019)	0.19 (0.020)	0 (0.019)	0.15 (0.10, 0.19)	0.19 (0.14, 0.23)
Testosterone, ug/L (male)					
no.	118	118	128		
Baseline mean (SD)	3.5 (1.6)	3.7 (2.0)	3.3 (1.5)		
Week 52 CFB (Standard Error)	2.6 (0.26)	3.5 (0.25)	0.44 (0.24)	2.2 (1.6, 2.8)	3.0 (2.5, 3.6)
Free testosterone, nmol/L (female)					
no.	121	110	106		
Baseline mean (SD)	0 (0.01)	0 (0.01)	0 (0.01)		
Week 52 CFB (Standard Error)	0 (0.001)	0 (0.001)	0 (0.001)	0	0
Free testosterone, nmol/L (male)					
no.	116	108	127		
Baseline mean (SD)	0.2 (0.09)	0.2 (0.11)	0.2 (0.07)		
Week 52 CFB (Standard Error)	0.04 (0.009)	0.03 (0.009)	0.02 (0.008)	0.02 (0, 0.04)	0.01 (-0.01, 0.03)
SHBG, nmol/L					
no.	275	262	283		
Baseline mean (SD)	48.8 (56.7)	45.6 (37.9)	47.2 (43.7)		
Week 52 %CFB (Standard Error)	157.5 (10.2)	217.4 (10.3)	9.0 (9.8)	148.5 (126.6, 170.4)	208.4 (186.3, 230.5)

Week 52 CFB (Standard Error)	60.2 (4.0)	80.7 (4.1)	1.3 (3.9)	58.9 (50.3, 67.5)	79.4 (70.7, 88.1)
SHBG, nmol/L (female)					
no.	159	145	155		
Baseline mean (SD)	58.2 (71.7)	48.9 (44.5)	55.7 (54.6)		
Week 52 %CFB (Standard Error)	193.0 (15.3)	251.8 (16.0)	15.6 (15.5)	177.4 (144.3, 210.5)	236.2 (202.3, 270.0)
Week 52 CFB (Standard Error)	74.1 (6.0)	94.0 (6.3)	0.82 (6.1)	73.3 (60.3, 86.2)	93.2 (79.9, 106.5)
SHBG, nmol/L (male)					
no.	116	117	128		
Baseline mean (SD)	36.0 (17.2)	41.4 (27.1)	37.0 (20.8)		
Week 52 %CFB (Standard Error)	108.0 (11.2)	174.0 (10.9)	0.74 (10.1)	107.3 (83.4, 131.2)	173.3 (149.4, 197.2)
Week 52 CFB (Standard Error)	41.9 (4.2)	60.8 (4.1)	1.5 (3.8)	40.4 (31.4, 49.4)	59.3 (50.3, 68.3)

CFB, change from baseline; CI, confidence interval; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LS, least squares; SD, standard deviation; SE, standard error; SHBG, sex hormone binding globulin. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 30: Change From Baseline in Thyroid Hormones at Week 52 (Safety Population)

	Least Squares Mean %CFB or CFB (Standard Error) Resmetirom 80 mg (n = 322)	Least Squares Mean %CFB or CFB (Standard Error) Resmetirom 100 mg (n = 323)	Least Squares Mean %CFB or CFB (Standard Error) Placebo (n = 321)	Least Squares Mean Difference Resmetirom 80 mg from PBO (95% CI)	Least Squares Mean Difference Resmetirom 100 mg from PBO (95% CI)
FT3, ng/L					
no.	279	265	286		
Baseline mean (SD)	3.0 (0.41)	3.0 (0.48)	3.0 (0.41)		
Week 52 CFB (Standard Error)	-0.01 (0.030)	-0.08 (0.031)	-0.03 (0.029)	0.02 (-0.05, 0.08)	-0.05 (-0.12, 0.01)
FT3, ng/L (not on thyroxine)					
no.	248	229	245		
Baseline mean (SD)	3.0 (0.40)	3.0 (0.42)	3.1 (0.39)		

Week 52 CFB (Standard Error)	-0.01 (0.032)	-0.08 (0.033)	-0.02 (0.031)	0.01 (-0.06, 0.08)	-0.06 (-0.13, 0.01)
FT3, ng/L (thyroxine-treated)					
no.	31	36	41		
Baseline mean (SD)	2.7 (0.38)	2.8 (0.72)	2.8 (0.41)		
Week 52 CFB (Standard Error)	0.04 (0.089)	-0.03 (0.081)	-0.02 (0.079)	0.05 (0.13, 0.23)	-0.01 (-0.19, 0.17)
FT4, ng/dL					
no.	279	265	286		
Baseline mean (SD)	1.1 (0.19)	1.1 (0.21)	1.1 (0.17)		
Week 52 %CFB (Standard Error)	-13.9 (0.96)	-18.1 (0.97)	2.6 (0.92)	-16.6 (-18.6, -14.5)	-20.7 (-22.8, -18.6)
Week 52 CFB (Standard Error)	-0.17 (0.011)	-0.22 (0.011)	0.02 (0.010)	-0.19 (-0.21, -0.16)	-0.24 (-0.26, -0.21)
FT4, ng/dL (not on thyroxine)					
no.	248	229	245		
Baseline mean (SD)	1.1 (0.18)	1.1 (0.18)	1.1 (0.16)		
Week 52 %CFB (Standard Error)	-13.8 (0.97)	-17.6 (1.0)	2.5 (0.95)	-16.3 (-18.4, -14.2)	-20.0 (-22.2, -17.9)
Week 52 CFB (Standard Error)	-0.16 (0.011)	-0.21 (0.011)	0.02 (0.010)	-0.18 (-0.20, -0.16)	-0.23 (-0.25, -0.20)
FT4, ng/dL (thyroxine-treated)					
no.	31	36	41		
Baseline mean (SD)	1.3 (0.23)	1.2 (0.31)	1.2 (0.21)		
Week 52 %CFB (Standard Error)	-14.0 (3.6)	-20.6 (3.3)	3.8 (3.1)	-17.9 (-25.2, -10.5)	-24.4 (-31.6, -17.3)
Week 52 CFB (Standard Error)	-0.18 (0.041)	-0.26 (0.037)	0.02 (0.036)	-0.21 (-0.29, -0.12)	-0.29 (-0.37, -0.21)
rT3, ng/dL					
no.	278	269	282		
Baseline mean (SD)	18.5 (5.4)	19.2 (6.2)	18.4 (5.6)		
Week 52 CFB (Standard Error)	-4.6 (0.31)	-5.1 (0.32)	0.17 (0.30)	-4.73 (-5.4, -4.1)	-5.2 (-5.9, -4.6)
rT3, ng/dL (not on thyroxine)					
no.	247	232	244		
Baseline mean (SD)	18.3 (5.3)	18.7 (5.7)	18.3 (5.6)		
Week 52 CFB (Standard Error)	-4.5 (0.33)	-4.9 (0.34)	0.19 (0.33)	-4.5 (-5.4, -3.9)	-5.1 (-5.9, -4.8)

rT3, ng/dL (thyroxine-treated)					
no.	31	37	38		
Baseline mean (SD)	20.7 (6.1)	22.2 (8.1)	19.1 (5.6)		
Week 52 CFB (Standard Error)	-5.1 (0.94)	-6.3 (0.85)	-0.01 (0.84)	-5.1 (-7.1, -3.1)	-6.3 (-8.2, -4.4)
FT3/rT3					
no.	278	269	282		
Baseline mean (SD)	0.18 (0.058)	0.17 (0.054)	0.18 (0.058)		
Week 52 CFB (Standard Error)	0.06 (0.004)	0.06 (0.004)	0 (0.004)	0.06 (0.05, 0.07)	0.07 (0.06, 0.08)
FT3/rT3 (not on thyroxine)					
no.	247	232	244		
Baseline mean (SD)	0.18 (0.057)	0.18 (0.051)	0.18 (0.057)		
Week 52 CFB (Standard Error)	0.06 (0.005)	0.06 (0.005)	0 (0.005)	0.06 (0.05, 0.07)	0.07 (0.06, 0.08)
FT3/rT3 (thyroxine-treated)					
no.	31	37	38		
Baseline mean (SD)	0.14 (0.051)	0.14 (0.058)	0.16 (0.065)		
Week 52 CFB (Standard Error)	0.05 (0.011)	0.06 (0.010)	-0.01 (0.010)	0.06 (0.04, 0.09)	0.06 (0.04, 0.09)
TSH, mIU/L					
no.	279	265	286		
Baseline mean (SD)	2.0 (1.1)	2.1 (1.2)	2.0 (1.1)		
Week 52 CFB (Standard Error)	-0.28 (0.059)	-0.20 (0.060)	-0.10 (0.057)	-0.18 (-0.31, -0.05)	-0.10 (-0.23, 0.03)
TSH, mIU/L (not on thyroxine)					
no.	248	229	245		
Baseline mean (SD)	2.0 (1.0)	2.0 (1.1)	1.9 (0.98)		
Week 52 CFB (Standard Error)	-0.23 (0.056)	-0.20 (0.058)	-0.08 (0.055)	-0.15 (-0.27, -0.03)	-0.12 (-0.24, 0)
TSH, mIU/L (thyroxine-treated)					
no.	31	36	41		
Baseline mean (SD)	2.0 (1.9)	2.6 (1.5)	2.2 (1.8)		
Week 52 CFB (Standard Error)	-0.63 (0.27)	-0.13 (0.25)	-0.22 (0.24)	-0.41 (-0.97, 0.15)	0.09 (-0.46, 0.63)
TBG, mg/L					
no.	269	261	283		
Baseline mean (SD)	24.4 (7.3)	24.5 (8.1)	24.3 (8.1)		

Week 52 CFB (Standard Error)	-0.32 (0.45)	-0.60 (0.45)	1.6 (0.43)	-1.9 (-2.8, -0.91)	-2.2 (-3.1, -1.2)
TBG, mg/L (not on thyroxine)					
no.	238	225	244		
Baseline mean (SD)	24.4 (7.5)	24.1 (7.7)	23.8 (7.7)		
Week 52 CFB (Standard Error)	-0.19 (0.47)	-0.21 (0.49)	1.6 (0.45)	-1.8 (-2.8, -0.74)	-1.8 (-2.8, -0.74)
TBG, mg/L (thyroxine-treated)					
no.	31	36	39		
Baseline mean (SD)	24.9 (5.8)	26.6 (9.8)	27.5 (9.7)		
Week 52 CFB (Standard Error)	-1.1 (1.4)	-3.1 (1.3)	1.5 (1.3)	-2.6 (-5.5, 0.43)	-4.6 (-7.5, -1.8)

CFB, change from baseline; CI, confidence interval; LS, least squares; rT3, reverse triiodothyronine; SE, standard error; FT3, free triiodothyronine; FT4, free thyroxine; TBG, thyroxine binding globulin; TSH, thyroid-stimulating hormone. Confidence interval widths have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 31: Shift Table of Bone Mineral Density T Score Risk Category

	Baseline								
	Resmetirom 80 mg (N = 78)			Resmetirom 100 mg (N = 61)			Placebo (N = 82)		
	Normal N (%)	Low Density N (%)	Possible Osteoporosis N (%)	Normal N (%)	Low Density N (%)	Possible Osteoporosis N (%)	Normal N (%)	Low Density N (%)	Possible Osteoporosis N (%)
Week 52									
Femoral Neck									
Normal	40 (51.3)	2 (2.6)	0	32 (52.5)	3 (4.9)	0	41 (50.0)	2 (2.4)	0
Low Density	6 (7.7)	25 (32.1)	0	2 (3.3)	21 (34.4)	0	4 (4.9)	31 (37.8)	0
Possible Osteoporosis	0	1 (1.3)	1 (1.3)	0	1 (1.6)	0	0	0	0
Hip									
Normal	67 (85.9)	1 (1.3)	0	47 (77.0)	0	0	64 (78.0)	1 (1.2)	0
Low Density	1 (1.3)	6 (7.7)	0	2 (3.3)	10 (16.4)	0	2 (2.4)	11 (13.4)	0
Possible Osteoporosis	0	0	0	0	0	0	0	0	0
Spine									
Normal	54 (69.2)	2 (2.6)	0	45 (73.8)	2 (3.3)	0	52 (63.4)	2 (2.4)	0
Low Density	2 (2.6)	14 (17.9)	0	1 (1.6)	8 (13.1)	0	4 (4.9)	18 (22.0)	0

Possible	0	1 (1.3)	1 (1.3)	0	1 (1.6)	3 (4.9)	0	0	2 (2.4)
Osteoporosis									

Note: Category Criteria: Normal = T Score ≥ -1.0 ; Low Density = T Score ≥ -2.5 and < -1.0 ; Possible

Osteoporosis = T Score < -2.5

Observed Data (Primary Analysis Population, Subgroup: Female Human Subjects Not Taking Thyroxine at Baseline, Estradiol < 30 ng/L at Baseline, and Weight Loss

$< 5\%$ at Week 52; Spine Adjusted Total; L1-L4

Note: Column headers are baseline status and row headers are status at the post-baseline visit.

[001094] Related Assessments

[001095] Assessment of Resmetirom Efficacy (80 mg vs. 100 mg) Stratified by Baseline Body Mass Index and Weight in Patients from the MAESTRO-NASH Trial

[001096] Resmetirom was approved in March 2024 in the United States for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). At Week 52, both primary endpoints were met at both clinical doses.

[001097] The recommended dosage of resmetirom is based on actual body weight (see FIG. 46). For patients weighing < 100 kg, the recommended dosage is 80 mg orally once daily. For patients weighing ≥ 100 kg, the recommended dosage is 100 mg orally once daily. In the MAESTRO-NASH study, randomization to 80 mg and 100 mg doses was equal across all body weights. Analyses were conducted to provide additional evidence of a relationship between resmetirom dose, baseline body weight and body mass index (BMI), and safety/efficacy readouts. The baseline body mass index mean (SD) for the resmetirom 80 mg, resmetirom 100 mg, and placebo groups were 35.5 kg/m^2 (6.4), 36.2 kg/m^2 (7.4), and 35.3 kg/m^2 (6.5), respectively. The baseline body weight for each group was 100.1 kg (22.3), 101.9 kg (22.9), and 100.2 kg (23.1), respectively.

[001098] Pharmacokinetic modeling concluded that higher exposure to resmetirom was associated with higher hepatic target engagement as reflected by higher SHBG responses and higher MRI-PDFF reduction (FIGS. 24A and 24B). The only variable that determined exposure to resmetirom in the NASH population was body weight. More patients treated with resmetirom 100 mg when compared with resmetirom 80 mg achieved targets for SHBG and PDFF, and differences between doses occurred primarily in patients ≥ 100 kg.

[001099] Exposure modeling indicated that higher NASH and fibrosis responses on biopsy were associated with higher exposure to resmetirom. Study median body weight was 100 kg. In the population with both a baseline and Week 52 liver biopsy, equivalent biopsy responses were achieved in patients who were < 100 kg at 80 mg and 100 mg (see FIGS. 25A and 25B). Lower responses were achieved at 80 mg in the ≥ 100 kg patients (FIGS. 25A and 25B). Study median BMI was 35 kg/m^2 . Higher BMI patients maintained the biopsy response at 100 mg; patients with BMI ≥ 35 had a lower response when randomized to 80 mg (FIGS. 26A and 26B).

[001100] The results show that the greater the week 52 PDFF reduction, the greater likelihood for fibrosis and NASH responses with resmetirom treatment (FIG. 27). PDFF reduction in resmetirom-treated patients was highly associated with both NASH resolution and fibrosis improvement. Placebo patients with more PDFF reduction had more NASH reduction but not fibrosis improvement. At least a 30% PDFF response was observed in 96% and 88% of resmetirom 100 mg responders for NASH resolution and fibrosis improvement, respectively. The percentage reduction in PDFF rather than resmetirom dose impacted the response on biopsy. The response on biopsy at resmetirom 80 mg and resmetirom 100 mg was equally correlated with the magnitude of PDFF response. Doses were combined in this predictive model.

[001101] Sensitive biomarkers SHBG, PDFF, and LDL/ApoB showed a persistent dose response over time with a difference between resmetirom 80 mg and resmetirom 100 mg (FIG. 28). Other tests like ALT showed an equally high response at both doses, irrespective of baseline body weight (FIGS. 29A and 29B). VCTE improved over time (1-3 years) relative to placebo in resmetirom-treated patients, both doses showing a similar durable response (FIG. 30A). New data indicates that less than 10 kPa correlates with less liver-related events. Garewh et al. (2024). CAP was stable over time, both doses showing a similar durable response (FIG. 30B). VCTE Responder analyses at 1-3 years in the MAESTRO-NASH population reflect improvement relative to placebo and <10% resmetirom-treated patients had worsening of VCTE (FIG. 31).

[001102] Pharmacokinetic modeling concluded that higher exposure to resmetirom was associated with higher hepatic target engagement as reflected by higher SHBG responses and higher MRI-PDFF reduction. The only variable that influenced exposure to resmetirom in the NASH population was body weight. Slightly lower rates of fibrosis improvement and NASH resolution on biopsy were observed in patients who were ≥ 100 kg or BMI ≥ 35 in patients treated with resmetirom 80 mg versus resmetirom 100 mg. Other biomarkers such as ALT, FibroScan, CAP and VCTE showed similar improvements relative to placebo at resmetirom 80 mg and resmetirom 100 mg. Responses on FibroScan in resmetirom-treated patients were durable out to 3 years of treatment and showed improvement and less worsening than placebo.

[001103] **Identification and Validation of Pre-Identified Morphological Baseline Features for Prediction of Fibrosis Progression in MAESTRO-NASH**

[001104] At Week 52, both primary endpoints were met at both clinical doses. Month 54 measured clinical outcomes including histologic conversion to cirrhosis. A second clinical

outcomes study, MAESTRO-NASH-OUTCOMES (NCT05500222), studied approximately 700 well-compensated NASH cirrhosis patients.

[001105] Fibrosis stage predicts clinical outcomes in NASH/metabolic-associated steatohepatitis (MASH), with liver biopsies as the regulatory standard. Ordinal fibrosis staging on stained slides may limit the ability to visualize dynamic fibrosis features throughout the liver lobule. qFibrosis, an AI-driven fibrosis assessment methodology that utilizes laser driven (SHG) collagen detection on unstained biopsy slides, has identified 30 specific fibrotic features on NASH liver biopsies that may be predictive of liver-related clinical outcomes, progression to cirrhosis and decompensated cirrhosis based on the SteatoSITE population. Non-invasive measures such as baseline MRE or FibroScan VCTE, ELF, and other non-invasive fibrosis markers also predict progression to cirrhosis and decompensated cirrhosis.

[001106] SteatoSITE contains integrated clinical and pathological data from 940 cases across the NAFLD spectrum with outcome data from electronic health record and pathologist-assigned fibrosis stage and RNA on baseline biopsy. In the SteatoSITE liver biopsy cohort, the level of the baseline fibrosis feature #IntersectionPT, the number of intersections of all strings for portal tract fibrosis per unit tissue area, was validated as predictive of liver decompensation events.

[001107] Baseline biopsy RNA analyses and annotated patient timelines in high-risk fibrosis stages (F3 and F4) showed that low THR- β liver regulon activity identifies patients at higher risk for hepatic decompensation. F3 to F4 patients with low baseline THR- β activity in their liver had the highest chance of progression to decompensated cirrhosis. Kendall et al, Nature Medicine (2023). At Week 52 biopsy, total qFibrosis scores showed a highly

significant improvement in fibrosis with resmetirom treatment and less progression of fibrosis as compared with placebo, similar to pathologist scoring (FIGS. 32A and 32B).

[001108] Resmetirom Week 52 results showed reduction from baseline in the qFibrosis progression features compared to placebo (FIGS. 33A and 33B). Fibrosis responders as determined by pathologists had greater improvement in qFibrosis features compared with non-responders in each treatment group (FIGS. 34A and 34B). Placebo fibrosis responders were few in number and had similar improvements in some qFibrosis progression features (FIGS. 35A and 35B). Fibrosis biomarkers and imaging tests (MRE, FibroScan VCTE, AST, GGT) showed improvements that were correlated with reduction in qFibrosis progression features. Change in MRE showed the highest correlation with change in qFibrosis progression features. The most marked reductions in scores of qFibrosis progression features occurred in the resmetirom F3 population.

[001109] Baseline and Week 52 biopsies from MAESTRO-NASH were analyzed for 30 qFibrosis features identified by SteatoSITE that are associated with progression of NASH fibrosis to liver decompensation, and six features with the strongest correlations between baseline pathologist scoring and non-invasive tests were identified. MRE followed by FibroScan showed strong correlations with the six qFibrosis features at baseline. Resmetirom treatment relative to placebo, particularly in F3, reduced qFibrosis features associated with progression to decompensated cirrhosis. SteatoSITE demonstrated that the thyroid hormone receptor beta regulon activity in the liver is a critical suppressor of NASH fibrosis progression; qFibrosis features are associated with progression in the SteatoSITE Cohort. qFibrosis data provide support for resmetirom's potential in benefiting patients with NASH with advanced liver fibrosis by reversing fibrosis and preventing progression to more advanced liver disease.

[001110] Non-Invasive Predictive Markers of Resmetirom Biopsy Response

[001111] A total of 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Histologic endpoints were assessed after 52 weeks. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥ 1 -stage reduction in fibrosis with no worsening of NAS (FR). The non-invasive correlates of response in the MAESTRO-NASH trial are summarized below.

[001112] Adults with ≥ 3 metabolic risk factors, liver stiffness ≥ 8.5 kPa, hepatic fat $\geq 8\%$, biopsy-confirmed NASH with F1B-F3 fibrosis, and NAS ≥ 4 were eligible to participate in MAESTRO-NASH. In this analysis, the relationship of changes in (1) FibroScan CAP, (2) FibroScan VCTE, and (3) alanine aminotransferase (ALT) to histological response (NR and/or FR) in the resmetirom 80 mg, resmetirom 100 mg, and placebo groups was assessed. The data used in these analyses were based on those 782 patients who had a paired biopsy at baseline and Week 52.

[001113] Both doses of resmetirom significantly reduced ALT approximately 30% relative to placebo (FIG. 36). In resmetirom-treated patients, higher percentage reductions in ALT were associated with slightly higher NASH resolution and fibrosis improvement on biopsy. For resmetirom-treated patients without a reduction in ALT or with worsening of ALT, the NASH resolution and fibrosis improvement responses were higher than the mean placebo biopsy responses. CAP improved with resmetirom treatment and improvement was stable over 3 years (FIG. 37). CAP improvement in individual resmetirom patients predicted both NASH resolution and fibrosis improvement responses; however, even no change in CAP predicted biopsy responses higher than the mean for placebo (FIG. 38). A CAP improvement in placebo patients did not predict a fibrosis improvement on biopsy.

[001114] PDFF reduction in resmetirom-treated patients was highly associated with both NASH resolution and fibrosis improvement (FIG. 39). Placebo patients with more PDFF reduction had more NASH reduction but not fibrosis improvement. At least a 30% PDFF response was observed in 96% and 88% of resmetirom 100 mg responders for NASH resolution and fibrosis improvement, respectively. Any PDFF response was associated with biopsy improvement higher than placebo. VCTE was improved over time (1-3 years) relative to placebo in resmetirom-treated patients (FIG. 40). There was a greater relative response at year 2 versus year 1. Resmetirom-treated patients, even those with no VCTE improvement, had higher NASH resolution and fibrosis improvement responses than the mean placebo response rates (FIG. 41). VCTE improvement at 1 year was not predictive of a placebo fibrosis improvement or NASH resolution response. Worsening of VCTE in placebo patients predicted a lower-than-average NASH resolution and fibrosis improvement.

[001115] Data identifying important biomarkers/imaging that are associated with resmetirom response on NASH and fibrosis on serial biopsies at baseline and Week 52 was generated. Random Forest model was utilized to determine the biomarkers and imaging tests both at baseline and change from baseline that had the most important association with response on biopsy for NASH resolution and/or fibrosis improvement. The data was based on baseline characteristics and change from baseline of more than 40 variables: biomarkers, clinical features, and imaging. This analysis confirmed the importance of MRI-PDFF (FIGS. 42-43).

[001116] In conclusion, biomarkers and imaging tests from the MAESTRO-NASH and NAFLD-1 clinical trials can be used to generate predictive models of baseline fibrosis stage in patients with NASH. Biomarker and imaging tests were examined for association with resmetirom biopsy responses. The study confirmed the importance of MRI-PDFF for both

NASH and fibrosis responses. It also identified changes in CAP, adiponectin and triglycerides as important factors for NASH response, and changes in M30 (CK18), CAP, ALT and ELF as important factors for fibrosis response. ALT, CAP, and VCTE were reduced by resmetirom relative to placebo. However, biopsy responses were not always associated with changes in these biomarkers. As confirmed by both logistic regression and random forest AI models, reduction in CAP showed a good relationship to biopsy response on fibrosis and NASH; reduction in ALT showed a relationship to fibrosis; and change in VCTE at Week 52 was not strongly associated with a fibrosis response on biopsy.

[001117] Resmetirom Treatment of a Subgroup of Patients with Possible METALD Enrolled in MAESTRO-NASH, a Phase 3 NASH/MASH Serial Liver Biopsy Study

[001118] 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥ 1 -stage improvement in fibrosis with no worsening of NAS (FI). The benefit of resmetirom in patients with and without indicators of increased alcohol consumption above protocol-allowed limits for NASH/MASH was assessed on biopsy endpoints and MRI-PDFF (liver fat reduction).

[001119] Analyses were performed on 782 patients who had both a baseline and Week 52 biopsy. Patients with a self-declared consumption of alcohol ≤ 2 drinks/day for men and ≤ 1.5 drinks/day for women were included as per usual MASH diagnostic recommendations. However, in attempt to objectify undisclosed moderate alcohol consumption above those limits, at baseline or during the trial, CDT measurements were performed longitudinally in all patients over 52 weeks. Post-randomization, a phosphatidylethanol (PEth) test was performed in patients tested for alcohol consumption based on increased liver enzymes ALT, AST

and/or GGT (<2%). Those with increased PEth were included as MetALD. Patients with baseline or post-baseline CDT >2.5% (ULN 2.47) and/or a PEth >20 ng/mL (ULN 20 ng/mL) were assigned to a "possible MetALD" subgroup (possible increased alcohol consumption).

[001120] Of the 782 patients, 75 patients (9.6%) were included in the MetALD subgroup. Baseline characteristics that were different in the MetALD group included higher percentage male sex; slightly lower BMI; lower percentage type 2 diabetes; higher FIB-4, AST, GGT and CDT; slightly higher percentage with F3 fibrosis (Table 32). For the group of patients with low or no alcohol consumption, out of those treated with resmetirom 80 mg (n=224) and resmetirom 100 mg (n=228), 29.9% and 36% had NASH resolution; 29% and 33.3% had fibrosis improvement; and 59.2% and 71.2% showed a $\geq 30\%$ reduction from baseline in MRI-PDFF, respectively (Table 33). For patients treated with placebo (n=255), the corresponding results were 10.3%, 13.7%, and 24.5% (Table 33). For the patients in the possible MetALD group, out of those treated with resmetirom 80 mg (n=34) and resmetirom 100 mg (n=20), 29% and 35% had NASH resolution; 35% and 30% had fibrosis improvement; and 88% and 81% showed a $\geq 30\%$ reduction from baseline in MRI-PDFF, respectively (Table 33). For patients treated with placebo (n=21), the corresponding results were 10%, 19%, and 14% (Table 33).

[001121] In conclusion, a total of 75 (9.6%) of patients had possible MetALD during the first 52 weeks of MAESTRO-NASH. Baseline characteristics showed more males; higher mean AST, CDT, GGT, and FIB-4 score; and fewer patients with type 2 diabetes in the MetALD versus low alcohol group. Response rates to resmetirom in patients with suspected MetALD were similar to those without MetALD.

[001122] Table 32:

	N=782	
	MASH/NASH (low alcohol) n=707 (90.4%)	MetALD (possible increased alcohol) n=75 (96%)
Age, years	60.1 (10.7)	57.7 (10.5)
Males, %	42	59
Type 2 Diabetes, %	67.9	50.7
Carbohydrate Deficient Transferrin (CDT) %	1.6 (0.3)	2.2 (1.0)
Body Mass Index (BMI), kg/m ²	35.8 (6.6)	33.0 (5.5)
FIB-4 Score	1.37 (0.66)	1.67 (0.69)
Aspartate aminotransferase (AST), U/L	40.3 (22.9)	45.6 (21.8)
Alanine transaminase (ALT), U/L	55.5 (32.2)	55.2 (24.8)
Gamma Glutamyl Transpeptidase (GGT), IU/L	75.3 (85.6)	117.9 (170.8)
Bilirubin, umol/L	0.65 (0.29)	0.69 (0.31)
Mean corpuscular volume (MCV), um ³	90.3 (5.6)	92.3 (5.8)
F3 fibrosis, %	62.5	66.7
MRI-PDFF (%)	17.4 (6.5)	21.7 (7.4)
VCTE (mean kPa)	13.2 (6.6)	13.4 (6.7)

¹Met protocol defined alcohol requirements for NASH/MASH. ²Based on elevated CDT and/or PEth, alcohol intake possibly exceeding protocol allowance. ³NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis stage. ⁴≥1 stage fibrosis improvement with no worsening of NAS.

[001123] Table 33:

		Resmetirom 80 mg (n=224)	Resmetirom 100 mg (n=228)	Placebo (n=255)
Subgroup	Endpoints			
MASH/NASH¹ (low alcohol)	NASH Resolution ³	67 (29.9%)	82 (36%)	23 (10.3%)
	Fibrosis Improvement ⁴	65 (29%)	76 (33.3%)	35 (13.7%)
	MRI-PDFF $\geq 30\%$ reduction	109/184 (59.2%)	136/191 (71.2%)	50/204 (24.5%)
		(n=34)	(n=20)	(n=21)
MetALD² (possibly increased alcohol)	NASH Resolution	10 (29%)	7 (35%)	2 (10%)
	Fibrosis Improvement	12 (35%)	6 (30%)	4 (19%)
	MRI-PDFF $\geq 30\%$ reduction	23/26 (88%)	13/16 (81%)	2/14 (14%)

¹Met protocol defined alcohol requirements for NASH/MASH. ²Based on elevated CDT and/or PETH, alcohol intake possibly exceeding protocol allowance. ³NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis stage. ⁴ ≥ 1 stage fibrosis improvement with no worsening of NAS.

[001124] Analysis of Biomarkers PRO-C3 and ELF in Resmetirom-Treated Patients from the MAESTRO-NASH Trial, a 52-Week NASH/MASH Serial Liver Biopsy Study

[001125] 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥ 1 -stage improvement in fibrosis with no worsening of NAS

(FI). The baseline and effect of resmetirom compared with placebo on fibrosis biomarkers PRO-C3 and P3NP/ELF were evaluated.

[001126] Pearson's correlation was used to examine the association between 2 PRO-C3 enzyme-linked immunosorbent assay (ELISA) assay methods (ELISA GEN1 and ELISA GEN2, NORDIC BIOSCIENCE) using PRO-C3 baseline data (N=919). The remainder of the analyses used the ELISA GEN2 assay. Mean SD or SE and median [Q1, Q3] were calculated to summarize PRO-C3 data. ANCOVA was used for comparisons between resmetirom 80 or 100 mg vs. placebo in PRO-C3 change from baseline at Week 52, while controlling for baseline PRO-C3 level. Mean difference with 95% CI and nominal P-values were obtained from the ANCOVA. Scatterplots and Spearman's correlations with 95% CIs were used to assess the associations between P3NP/ELF and PRO-C3 both at baseline and change from baseline at Week 52.

[001127] The two PRO-C3 assays ELISA GEN1 and ELISA GEN2 data were positively associated with a Pearson's correlation of 0.78 (P-value <0.0001). At baseline, PRO-C3 was mean (SD) 137 (71.7) ng/mL. At Week 52, PRO-C3 change from baseline for resmetirom 100 mg was -23.05 (4.76), resmetirom 80 mg was -17.93 (4.61), and placebo was -0.19 (4.07) (Table 34). The mean difference (95% CI) in PRO-C3 change from baseline at Week 52 was -16.9 (-27.0, -6.76; p= 0.0011) between resmetirom 80 mg and placebo, and -22.1 (-32.3, -11.84; p < 0.0001) between resmetirom 100 mg and placebo. Larger reductions in PRO-C3 mean (SD) on the resmetirom arms were observed in F3 patients. Resmetirom 80 mg reduced by -22.42 (6.38), resmetirom 100 mg reduced by -27.42 (6.72), and placebo reduced by -0.50 (5.46) (Table 37). Baseline P3NP and ELF were correlated with PRO-C3 (0.563 and 0.458, respectively). The change from baseline at Week 52 in P3NP was positively associated with change from baseline at Week 52 in PRO-C3 (0.557, 0.548 and 0.524 for resmetirom 100

mg, resmetirom 80 mg and placebo, respectively) (FIG. 44 and Table 38). A weaker positive correlation between the change from baseline at Week 52 for ELF and PRO-C3 (0.483, 0.484 and 0.487 for resmetirom 100 mg, resmetirom 80 mg and placebo, respectively) were also observed (FIG. 45 and Table 39).

[001128] In conclusion, two PRO-C3 assays (ELISA GEN1 and ELISA GEN2, NORDIC BIOSCIENCE) were correlated at baseline, indicating ELISA GEN2 assay was reasonable for measuring PRO-C3 levels. For PRO-C3 ELISA GEN2, drug effects were statistically significantly reduced at both doses of resmetirom vs. placebo. A greater magnitude of reduction with resmetirom was observed in F3 patients, who exhibited a higher baseline PRO-C3. ELF and PRO-C3 were less strongly correlated than P3NP and PRO-C3.

Table 34: Change from Baseline in PRO-C3 at Week 52 (Overall)

	Resmetirom 100 mg (n=261)	Resmetirom 80 mg (n=272)	Placebo (n=283)
Baseline Mean (SD)	138 (72.3)	138 (73.5)	136 (69.5)
Mean (Standard Error)	-23.05 (4.76)	-17.93 (4.61)	-0.19 (4.07)
Median (Q1, Q3)	-13.40 (-56.10, 10.20)	-11.95 (-41.78, 12.72)	-5.20 (-30.55, 29.30)

Table 35: Change from Baseline in PRO-C3 at Week 52 (F1B patients only)

	Resmetirom 100 mg (n=11)	Resmetirom 80 mg (n=13)	Placebo (n=18)
Baseline Mean (SD)	94.8 (54.8)	101 (32.3)	114 (58.6)
Mean (Standard Error)	-7.20 (16.34)	-0.69 (8.58)	21.33 (12.09)
Median (Q1, Q3)	0.40 (-1.15, 18.60)	4.30 (-21.90, 16.40)	0.60 (-15.60, 61.72)

Table 36: Change from Baseline in PRO-C3 at Week 52 (F2 patients only)

	Resmetirom 100 mg (n=79)	Resmetirom 80 mg (n=86)	Placebo (n=93)
Baseline Mean (SD)	116 (47.5)	124 (56.8)	122 (57.4)
Mean (Standard Error)	-15.79 (5.47)	-11.51 (6.75)	-3.78 (6.77)
Median (Q1, Q3)	-10.10 (-39.40, 11.25)	-13.65 (-34.55, 15.40)	-6.00 (-32.10, 18.70)

Table 37: Change from Baseline in PRO-C3 at Week 52 (F3 patients only)

	Resmetirom 100 mg (n=171)	Resmetirom 80 mg (n=173)	Placebo (n=172)
Baseline Mean (SD)	150 (79.4)	147 (80.9)	146 (74.8)
Mean (Standard Error)	-27.42 (6.72)	-22.42 (6.38)	-0.50 (5.46)
Median (Q1, Q3)	-18.30 (-63.75, 8.45)	-11.90 (-43.70, 7.00)	-5.80 (-30.93, 29.95)

Table 38: P3NP Correlation with PRO-C3

Group	Spearman Correlation (95% CI)	Pearson's Correlation (95% CI)
Resmetirom 100 mg (N=243)	0.557 (0.454, 0.645)	0.428 (0.320, 0.526)
Resmetirom 80 mg (N=255)	0.548 (0.445, 0.635)	0.535 (0.442, 0.618)
Placebo (N=260)	0.524 (0.414, 0.624)	0.538 (0.445, 0.619)

Table 39: ELF Correlation with PRO-C3

Group	Spearman Correlation (95% CI)	Pearson's Correlation (95% CI)
Resmetirom 100 mg	0.483 (0.384, 0.575)	0.346 (0.234, 0.450)

(N=256)		
Resmetirom 80 mg (N=265)	0.484 (0.377, 0.583)	0.453 (0.352, 0.544)
Placebo (N=276)	0.487 (0.388, 0.581)	0.467 (0.369, 0.555)

[001129] Analysis of Weight Loss

[001130] As shown in FIG. 79, a greater than or equal to 5% weight loss was observed more frequently in resmetirom treated patients as compared with placebo treated patients and was associated with high rates of NASH resolution (~60%) and fibrosis improvement (~40%) in resmetirom treated patients. 17% of patients treated with 80 mg and 22% of patients treated with 100 mg in the resmetirom arms of the MAESTRO-NASH study achieved a greater than or equal to 5% weight loss at Week 52 compared with 12% on placebo. Higher weight loss achieved with resmetirom was statistically significant (nominal). Median weight loss was 7% in the greater than or equal to 5% weight loss groups. In the 100 mg arm of the MAESTRO-NASH study, weight loss $\geq 5\%$ observed in about 22% of patients on resmetirom (12% of patients taking placebo) increased the percentage of patients with fibrosis improvement (42%) and NASH resolution (58%) on liver biopsy and maintained the difference from patients taking placebos with similar weight loss. Similar results were achieved in the 80 mg arm.

[001131] Weight loss greater than or equal to 5% achieved by diet and exercise occurred in about 22% of patients on resmetirom (12% of placebo patients). Resmetirom maintained the favorable difference on NASH and fibrosis endpoints from placebos with all weight changes (no weight change, greater than or equal to 5% weight loss or greater than or equal to 5% weight gain). A greater than or equal to 5% weight loss was found to significantly and synergistically improve NASH resolution and fibrosis improvement in resmetirom treated patients as compared to resmetirom treatment without such greater than or equal to 5%

weight loss or a placebo. Approximately 3X more resmetirom than placebo patients with greater than or equal to 5% weight loss had NR or F1.

[001132] As shown in FIG. 80, PDFF-reduction in patients taking resmetirom with greater than or equal to 5% weight loss improved at Week 52 relative to Week 16, but there was no change between Week 16 and Week 52 in patients without weight loss. Resmetirom therapy retains separation from placebo in both weight loss groups. In the resmetirom arm, at least a 30% PDFF response was observed in 98% of patients with greater than or equal to 5% weight loss.

[001133] **Example 3. Preparation of Resmetirom Form U1**

[001134] The starting material for this and other examples, resmetirom Form I, may be prepared according to the methods of U.S. Patent No. 9,266,861.

[001135] A saturated solution of resmetirom Form I was prepared in methyl ethyl ketone at about 80 °C. The sample was stirred briefly before being filtered into a warm receiving vial using a 0.22 µm PTFE syringe filter. The resulting solution was left uncapped at about 80 °C to evaporate the solution. Off-white, largely agglomerated material was recovered after overnight evaporation. XRPD, DSC, and TGA analysis indicated the formation of Form U1.

[001136] **Example 4. Preparation of Resmetirom Form U2**

[001137] A saturated solution of resmetirom Form I was prepared in tert-butanol at about 80 °C. The sample was stirred briefly before being filtered into a warm receiving vial using a 0.22 µm PTFE syringe filter. The resulting solution was left uncapped at about 80 °C to evaporate the solution. After two days of evaporation, white handleable solids and slightly yellow harder material stuck at the bottom of the vial were recovered and submitted as a

single sample for analysis. XRPD, DSC, and TGA analysis indicated the formation of Form U2.

[001138] Example 5. Preparation of Resmetirom Form U3

[001139] Resmetirom Form I was dissolved in N-methyl-2-pyrrolidone. The resulting solution was placed uncapped into a larger vial containing water. The larger vial was capped to allow vapor diffusion to occur. After seven days of storage at room temperature, solids were observed to have formed in the inner vial. The inner vial was removed from the larger vial, decanted, and the resulting solids were dried briefly under a stream of air prior to analysis. XRPD, DSC, and TGA analysis indicated the formation of Form U3.

[001140] Example 6. Preparation of Resmetirom Form U4

[001141] The starting material for this and other examples, resmetirom Form D (acetone solvate), was prepared according to the methods disclosed in U.S. Patent App. Pub. 2021/0122740 A1.

[001142] 78.2 mg of resmetirom Form D was added to about 1 mL of nitromethane and additional material was added to ensure a visually saturated solution with excess solids was observed. The sample was allowed to stir at room temperature for two weeks. Solids were isolated from the resulting white slurry via vacuum filtration using Whatman #1 filter paper. XRPD analysis indicated the formation of Form U4.

[001143] Example 7. Preparation of Resmetirom Form U5

[001144] A saturated solution of resmetirom Form D was prepared in o-xylene such that excess undissolved solids were observed. The sample was left to stir at room temperature for

two weeks. The resulting white suspension was vacuum filtered using Whatman #1 filter paper. XRPD analysis indicated the formation of Form U5.

[001145] Example 8. Preparation of Resmetirom Form U6

[001146] A saturated solution of resmetirom Form D was prepared in trifluorotoluene such that excess undissolved solids were observed. The sample was left to stir at room temperature for two weeks. The resulting white suspension was vacuum filtered using Whatman #1 filter paper. XRPD, DSC, and TGA analysis indicated the formation of Form U6.

[001147] Example 9. Preparation of Resmetirom Form U7

[001148] A saturated solution of resmetirom Form A was prepared in 2,2,2-trifluoroethanol at about 80 °C by adding excess solids such that undissolved material remained in suspension. After about 1 hour of equilibration, the slurry was hot filtered into a warm receiving vial using a 0.22 µm PTFE syringe filter. The hot filtered solution was added to a chilled solution of methyl tert-butyl ether that had been equilibrated in a refrigerator. The resulting solution was left to stir at room temperature for four days. The sample remained a clear solution and was uncapped to allow for evaporation at room temperature. After four days, the sample evaporated leaving a limited amount of solids. XRPD, DSC, and TGA analysis indicated the formation of Form U7.

[001149] Example 10. Preparation of Resmetirom Form U8

[001150] A saturated solution of resmetirom Form D was prepared in cyclohexanone at about 104 °C. After three days of equilibration an off-white/tan slurry was observed. The sample was hot filtered using Whatman #1 filter paper. XRPD, DSC, and TGA analysis indicated the formation of Form U8.

[001151] Example 11. Preparation of Resmetirom Form U9

[001152] A saturated solution of resmetirom Form D was prepared in methyl acetate at RT. After sixteen days of equilibration the sample was observed to be primarily a clear solution with a ring of solids submerged beneath the solvent line. The solvent was decanted and the damp sample recovered. XRPD, DSC, and TGA analysis indicated the formation of Form U9.

[001153] Example 12. Preparation of Resmetirom Form C1

[001154] 29.4 mg of resmetirom Form I was combined with 18.0 μ L of triethyl citrate (1.1 equivalents) and 10.0 μ L of diethyl ether were combined in a polyether ether ketone (PEEK) grinding cup containing a stainless-steel ball. The sample was milled using a Retsch mill at 25 Hz for 15 minutes resulting in a wet white residue that was dried uncapped at room temperature. XRPD, ^1H NMR, DSC, TGA, FTIR, and Raman analysis indicated the formation of Form C1.

[001155] Example 13. Preparation of Resmetirom Form C2

[001156] 49.8 mg of resmetirom Form I was combined with 25.4 mg of cytosine (2 equivalents) and 0.25 mL of isopropanol. The sample was allowed to slurry at room temperature. After overnight stirring the sample was observed to be a significantly thicker slurry so an additional 0.25 mL of isopropanol was added. After stirring an additional six days the sample was observed to be an off-white slurry. The sample was centrifuged and the supernatant was pipetted out and the wet sample was collected for analysis. XRPD, ^1H NMR, DSC, TGA, FTIR, and Raman analysis indicated the formation of Form C2.

[001157] Example 14. Preparation of Resmetirom Form C3

[001158] 49.6 mg of resmetirom Form I was combined with 108.6 mg of calcium d-pantothenate (2 equivalents) and 0.25 mL of isopropanol. The sample was allowed to slurry at room temperature. After overnight stirring, caked white solids were observed. The solids were dislodged with a spatula and an additional 0.5 mL of isopropanol was added. After stirring an additional six days the sample was observed to be a plugged white solid. Additional IPA was added and the vial vortexed before centrifuging and removing the supernatant leaving the wet solids for analysis. PXRD analysis indicated the formation of Form C3.

[001159] **Example 15. Preparation of Resmetirom Form C4**

[001160] 50.1 mg of resmetirom Form I was combined with 23.7 mg of dimethylglycine (2 equivalents) and 0.25 mL of isopropanol. The sample was allowed to slurry at room temperature. After overnight stirring the sample was observed to be a significantly thicker slurry so an additional 0.25 mL of isopropanol was added. After stirring an additional six days the sample was observed to be an off-white slurry. The sample was centrifuged and the supernatant was pipetted out and the wet sample was collected for analysis. XRPD, ¹H NMR, DSC, and TGA analysis indicated the formation of Form C4.

[001161] **Example 16. Preparation of Resmetirom Form C5**

[001162] 49.4 mg of resmetirom Form I was combined with 0.5 mL of dichloroacetic acid producing an almost clear yellow solution. The sample was allowed to stir at room temperature. After eleven days of stirring, a thin light-yellow slurry was observed. The sample was centrifuged and the supernatant was pipetted out and the wet solids were collected for analysis. analysis indicated the formation of Form C5. The supernatant was left uncapped in a vacuum oven at room temperature for evaporation. After three days the

sample was observed to be an off-white powder. XRPD, ¹H NMR, DSC, TGA, FTIR, and Raman analysis indicated the formation of Form C5.

[001163] Example 17. Preparation of Resmetirom Form C6

[001164] 50.9 mg of resmetirom Form I was combined with 0.5 mL of diethylamine producing a yellow slurry. The sample was allowed to stir at room temperature for eleven days producing a yellow solution with an off-white residue on the walls of the vial. The sample was centrifuged and the supernatant was pipetted out and the wet solids were collected for analysis. XRPD analysis indicated the formation of Form C6.

[001165] Example 18. Preparation of Resmetirom 4-Aminopyridine Salt (Form C7)

[001166] 30.9 mg of resmetirom Form I was combined with 7.4 mg of 4-aminopyridine (1.1 equivalents) and 20 µL of diethyl ether were combined in a polyether ether ketone (PEEK) grinding cup containing a stainless-steel ball. The sample was milled using a Retsch mill at 25 Hz for 15 minutes resulting in off-white solids. XRPD, ¹H NMR, DSC, TGA, FTIR, and Raman analysis indicated the formation of a resmetirom 4-aminopyridine salt (Form C7).

[001167] Example 19. Preparation of Resmetirom Imidazole Salt (Form C8)

[001168] 30.4 mg of resmetirom Form I was combined with 5.2 mg of 1H imidazole (1.1 equivalents) and 20 µL of diethyl ether were combined in a polyether ether ketone (PEEK) grinding cup containing a stainless-steel ball. The sample was milled using a Retsch mill at 25 Hz for 15 minutes resulting in off-white solids. XRPD, ¹H NMR, DSC, TGA, FTIR, and Raman analysis indicated the formation of a resmetirom imidazole salt (Form C8).

[001169] Example 20. Preparation of Resmetirom Tromethamine Salt (Form C9)

[001170] 51.0 mg of resmetirom Form I was combined with 28.4 mg of tromethamine (2 equivalents) and 0.25 mL of isopropanol. The sample was allowed to slurry at room temperature. After overnight stirring the sample was observed to be a significantly thicker slurry so an additional 0.25 mL of isopropanol was added. After stirring an additional six days the sample was observed to be an off-white slurry. The sample was centrifuged and the supernatant was pipetted out and the wet sample was collected for analysis. XRPD, ¹H NMR, DSC, and TGA indicated the formation of a resmetirom tromethamine salt (Form C9).

[001171] **Example 21. Preparation of Resmetirom Form N1**

[001172] 100 mg of resmetirom Form I was placed in a 1-dram glass vial. 5 mL of methyl tetrahydrofuran were added the slurry was heated to 60 °C while stirring magnetically. After 30 minutes of stirring, the solution was hazy with no solids. The solution was filtered into a 1-dram glass vial which had been kept at 60 °C. The vial was placed at 4 °C and stirring continued for 18 hours, during which time precipitation occurred. The vial was centrifuged, and the mother liquor was decanted. The solid was dried in a vacuum oven at 25 °C for 2 hours.

[001173] **Example 22. Preparation of Resmetirom Form N2**

[001174] 500 mg of resmetirom Form I was placed in a 125 mL Erlenmeyer flask. 66 mL of acetonitrile was added and the slurry was heated to 80 °C while stirring magnetically. After 30 minutes of stirring, the solution was clear with no solid. The solution was filtered into a 125 mL Erlenmeyer flask which had been kept at 80 °C. The vial was placed at room temperature and stirring continued. Precipitation occurred upon cooling. After stirring for 18 hours, the solid was recovered by vacuum filtration. The solid was dried in a vacuum oven at 45 °C for 3 days.

[001175] Example 23. Preparation of Resmetirom Form N3

[001176] 30 mg of resmetirom Form I was placed in a 1-dram glass vial. 0.85 mL of acetyl acetone was added and the slurry was heated to 80 °C while stirring magnetically. After 30 minutes of stirring, the solution was clear. The solution was filtered into a 1-dram glass vial, which had been kept at 80 °C. 3.4 mL propionitrile was added dropwise, and the solution remained clear. Stirring continued for 18 hours, and the solution remained clear. The slurry was cooled to room temperature and stirring continued for 22 hours, during which time precipitation occurred. The vial was centrifuged, and the mother liquor was decanted. The solid was not dried.

[001177] Example 24. Preparation of Resmetirom Form N4

[001178] 1000 mg of resmetirom Form I was placed in a 50 mL Erlenmeyer flask. 20 mL of methyl ethyl ketone was added and the slurry was heated to 72 °C while stirring magnetically. After 30 minutes of stirring, much solid remained. 6 mL of methyl ethyl ketone were added and the solid dissolved. Stirring continued for 30 minutes. The solution was filtered into a 50 mL Erlenmeyer flask which had been kept at 72 °C. The solution was transferred to a 50 mL round bottom flask and the solvent was removed by rotary evaporation at room temperature, resulting in a white solid.

[001179] Example 25. Preparation of Resmetirom Form N6

[001180] Resmetirom Form N3 (produced by Example 23 above) was left in a capped 1-dram glass vial at room temperature for 2 weeks, resulting in Form N6.

[001181] Example 26. Preparation of Resmetirom Form N7

[001182] 300 mg of resmetirom Form I was placed in a 20 mL glass vial. 15 mL of propionic acid was added and the slurry was heated to 80 °C while stirring magnetically. All of the solid dissolved upon reaching 80 °C. Stirring continued for 30 minutes. The solution was filtered into a 20 mL glass vial which had been kept at 80 °C. The vial was placed at 4 °C and stirring continued for 4 days, during which time precipitation occurred. The vial was centrifuged, and the mother liquor was decanted. The solid was dried in a vacuum oven at 25 °C for 3 hours.

[001183] **Example 27. Preparation of Resmetirom Form N8**

[001184] 2.0744 g of resmetirom Form I was placed in a 50 mL Erlenmeyer flask. 30 mL of dimethyl carbonate was added and then the mixture was cooled to 5 °C while stirring magnetically. Stirring continued for 19 hours. The vial was centrifuged, and the mother liquor was decanted. The solid was dried in a vacuum oven at 50 °C for 3 hours. 55 mg of the resulting solid was placed in a 1-dram glass vial. 1 mL of isopropanol was added and then the mixture was cooled to 5 °C while stirring magnetically. Stirring was continued for 90 minutes. The solid was recovered by vacuum filtration.

[001185] **Example 28. Preparation of Resmetirom Form N9**

[001186] Form N7 (produced by Example 26 above) was placed in a 1-dram glass vial. A cap was loosely placed on the vial, but not tightened. The vial was placed in an oven (no vacuum) at 60 °C for 2 weeks.

[001187] Any patents or publications mentioned in this specification are indicative of the levels of those skilled in the art to which the disclosure of the present invention pertains. These patents and publications are herein incorporated by reference for the indicated information to the same extent as if each individual publication was specifically and

individually indicated to be incorporated by reference for such information. In case of conflict, the present specification, including definitions, will control.

[001188] One skilled in the art will readily appreciate that the present disclosure is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The present disclosure described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention as defined by the scope of the claims.

CLAIMS

1. A method of treating nonalcoholic steatohepatitis (NASH),
comprising:
determining a weight of a human subject; and
based on determination of the weight of the human subject, administering to
the human subject a solid oral dosage form comprising:
 - (i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100
mg per day, if the human subject is determined to weigh 100 kg or more; or
 - (ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of
80 mg per day, if the human subject is determined to weigh less than 100 kg.
2. The method according to claim 1, wherein the human subject is
determined to weigh 100 kg or more and is administered the solid oral dosage form
comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100
mg per day.
3. The method according to claim 1, wherein the human subject is
determined to weigh less than 100 kg and is administered the solid oral dosage form
comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg
per day.
4. The method according to any one of the preceding claims, wherein the
method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced
liver fibrosis consistent with stages F2 to F3.

5. The method according to any one of the preceding claims, wherein the method is of improving noncirrhotic nonalcoholic steatohepatitis.

6. The method according to any one of the preceding claims, wherein the solid oral dosage form comprises resmetirom.

7. A method of treating liver fibrosis comprising:
determining a weight of a human subject; and
based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:
(i) resmetirom or a pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more; or
(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg; and
wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

8. The method according to claim 7, wherein the method is of improving the liver fibrosis.

9. The method according to claim 7 or 8, wherein the human subject has liver fibrosis characterized as fibrosis stage F2.

10. The method according to claim 7 or 8, wherein the human subject has liver fibrosis characterized as fibrosis stage F3.

11. The method according to any one of claims 8-10, wherein the method is of improving the liver fibrosis by one stage in the human subject.

12. The method according to claim 10, wherein the method is of improving the liver fibrosis by two stages in the human subject.

13. The method according to any one of claims 7-12, wherein the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

14. The method according to any one of claims 7-12, wherein the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

15. The method according to any one of claims 7-14, wherein the solid oral dosage form comprises resmetirom.

16. The method according to any one of claims 1-15, wherein the solid oral dosage form is a tablet.

17. The method according to any one of claims 1-16, wherein the human subject is an adult human subject.

18. A method of treating noncirrhotic nonalcoholic steatohepatitis (NASH), comprising:

determining a weight of a human subject; and

based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor.

19. The method according to claim 18, wherein the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 80 mg per day.

20. The method according to claim 18, wherein the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 60 mg per day.

21. The method according to claim 19, wherein the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

22. The method according to claim 20, wherein, the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

23. The method according to any one of claims 18-22, wherein the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nicardipine, loratadine, eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate, spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin, troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, gemfibrozil, idelalisib, isoniazid, ketoprofen, letemovir, lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

24. The method according to any one of claims 18-22, wherein the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, and/or pioglitazone.

25. The method according to any one of claims 18-24, wherein the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

26. The method according to any one of claims 18-25, wherein the method is of improving noncirrhotic nonalcoholic steatohepatitis.

27. The method according to any one of claims 18-26, wherein the solid oral dosage form comprises resmetirom.

28. The method according to any one of claims 18-27, wherein the solid oral dosage form is a tablet.

29. The method according to any one of claims 18-28, wherein the human subject is an adult human subject.

30. A method of treating liver fibrosis comprising:
determining a weight of a human subject; and
based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor; and

wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

31. The method according to claim 30, wherein the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 80 mg per day.

32. The method according to claim 30, wherein the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 60 mg per day.

33. The method according to claim 31, wherein the human subject used the resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

34. The method according to claim 32, wherein the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

35. The method according to any one of claims 30-34, wherein the method is of improving the liver fibrosis.

36. The method according to any one of claims 30-35, wherein the human subject has liver fibrosis characterized as fibrosis stage F2.

37. The method according to any one of claims 30-35, wherein the human subject has liver fibrosis characterized as fibrosis stage F3.

38. The method according to any one of claims 35-37, wherein the method is of improving the liver fibrosis by one stage in the human subject.

39. The method according to claim 36, wherein the method is of improving the liver fibrosis by two stages in the human subject.

40. The method according to any one of claims 30-39, wherein the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nicardipine, loratadine, eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate,

spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin, troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, gemfibrozil, idelalisib, isoniazid, ketoprofen, letermovir, lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

41. The method according to any one of claims 30-39, wherein the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, and/or pioglitazone.

42. The method according to any one of claims 30-41, wherein the solid oral dosage form comprises resmetirom.

43. The method according to any one of claims 30-42, wherein the solid oral dosage form is a tablet.

44. The method according to any one of claims 30-43, wherein the human subject is an adult human subject.

45. Resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating nonalcoholic steatohepatitis (NASH), the method comprising:

determining a weight of a human subject; and

based on determination of the weight of the human subject, administering to the human subject a solid oral dosage form comprising:

(i) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg.

46. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 45, wherein the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

47. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 45, wherein the method is of improving noncirrhotic nonalcoholic steatohepatitis.

48. Resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating liver fibrosis, the method comprising:

determining a weight of a human subject; and

based on determination of the weight of the human subject, administering orally to the human subject a solid oral dosage form comprising:

(i) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 100 mg per day, if the human subject is determined to weigh 100 kg or more; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a dosage of 80 mg per day, if the human subject is determined to weigh less than 100 kg; and wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

49. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 48, wherein the method is of improving the liver fibrosis.

50. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 48 or 49, wherein the human subject has liver fibrosis characterized as fibrosis stage F2.

51. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 48 or 49, wherein the human subject has liver fibrosis characterized as fibrosis stage F3.

52. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 49-51, wherein the method is of improving the liver fibrosis by one stage in the human subject.

53. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 51, wherein the method is of improving the liver fibrosis by two stages in the human subject.

54. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 48-53, wherein the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 100 mg per day.

55. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 48-53, wherein the human subject is determined to weigh less than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the dosage of 80 mg per day.

56. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 45-55, wherein the solid oral dosage form is a tablet.

57. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 45-56, wherein the human subject is an adult human subject.

58. Resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating noncirrhotic nonalcoholic steatohepatitis (NASH), the method comprising:

determining a weight of a human subject; and

based on determination of the weight of the human subject, administering orally to the human subject a solid oral dosage form comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor.

59. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 58, wherein the method is of treating noncirrhotic nonalcoholic steatohepatitis with moderate to advanced liver fibrosis consistent with stages F2 to F3.

60. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 58 or 59, wherein the method is of improving noncirrhotic nonalcoholic steatohepatitis.

61. Resmetirom or a pharmaceutically acceptable salt thereof for use in a method of treating liver fibrosis, the method comprising:

(i) resmetirom or a pharmaceutically acceptable salt thereof at a reduced dosage of 80 mg per day, if the human subject is determined to weigh 100 kg or more and the human subject is using a moderate CYP2C8 inhibitor; or

(ii) resmetirom or the pharmaceutically acceptable salt thereof at a reduced dosage of 60 mg per day, if the human subject is determined to weigh less than 100 kg and the human subject is using a moderate CYP2C8 inhibitor; and

wherein the human subject has liver fibrosis associated with nonalcoholic steatohepatitis (NASH).

62. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 61, wherein the method is of improving the liver fibrosis.

63. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 61 or 62, wherein the human subject has liver fibrosis characterized as fibrosis stage F2.

64. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 61 or 62, wherein the human subject has liver fibrosis characterized as fibrosis stage F3.

65. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 62-64, wherein the method is of improving the liver fibrosis by one stage in the human subject.

66. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 64, wherein the method is of improving the liver fibrosis by two stages in the human subject.

67. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 58-66, wherein the human subject is determined to weigh 100 kg or more and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 80 mg per day.

68. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 58-66, wherein the human subject is determined to weigh less

than 100 kg and is administered the solid oral dosage form comprising resmetirom or the pharmaceutically acceptable salt thereof at the reduced dosage of 60 mg per day.

69. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 67, wherein the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 100 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 100 mg per day is reduced to the reduced dosage of 80 mg per day.

70. Resmetirom or the pharmaceutically acceptable salt thereof for use according to claim 68, wherein the human subject used resmetirom or the pharmaceutically acceptable salt thereof at an oral dose of 80 mg per day before starting to use the moderate CYP2C8 inhibitor, and the oral dose of 80 mg per day is reduced to the reduced dosage of 60 mg per day.

71. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 58-70, wherein the moderate CYP2C8 inhibitor is selected from the group consisting of rosiglitazone, trimethoprim, tamoxifen, irbesartan, quinine, efavirenz, rabeprazole, crisaborole, nabilone, bexarotene, ritonavir, nicardipine, loratadine, eltrombopag, diltiazem, enzalutamide, ketoconazole, fluvastatin, levothyroxine, oxybutynin, medroxyprogesterone acetate, spironolactone, amlodipine, saquinavir, abiraterone, genistein, lenvatinib, pioglitazone, clotrimazole, nilotinib, teriflunomide, topiroxostat, lovastatin, troglitazone, amitriptyline, pirtobrutinib, belinostat, bezafibrate, candesartan, cholecalciferol, cimetidine, colchicine, dabrafenib, deferasirox, diethylstilbestrol, enasidenib, erlotinib, ethinylestradiol, fenofibrate, gemfibrozil, idelalisib, isoniazid, ketoprofen, letermovir,

lumacaftor, mefenamic acid, midostaurin, montelukast, nilutamide, opicapone, phenelzine, piroxicam, pyrimethamine, quercetin, raloxifene, repaglinide, rifampicin, rofecoxib, salmeterol, sorafenib, sulfaphenazole, tegaserod, terbinafine, terfenadine, thiazolidinediones, ticlopidine, trametinib, triazolam, troleandomycin, valproic acid, verapamil, vismodegib, clopidogrel, and zafirlukast.

72. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 58-70, wherein the moderate CYP2C8 inhibitor is clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, and/or pioglitazone.

73. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 45-72, wherein the solid oral dosage form comprises resmetirom.

74. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 58-73, wherein the solid oral dosage form is a tablet.

75. Resmetirom or the pharmaceutically acceptable salt thereof for use according to any one of claims 58-74, wherein the human subject is an adult human subject.