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APPLICATION NUMBER:

211288Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217785
Priority or standard	Priority
Submit date(s)	7/14/2023
Received date(s)	7/14/2023
PDUFA goal date	3/14/2024
Division/office	Division of Hepatology and Nutrition (DHN)
Review completion date	3/14/2024
Established/proper name	resmetirom
(Proposed) proprietary name	REZDIFFRA
Pharmacologic class	Thyroid hormone receptor-beta (THR-β) agonist
Other product name(s)	N/A
Applicant	Madrigal Pharmaceuticals, Inc.
Dosage form(s)/formulation(s)	Tablet
Applicant-proposed dosing regimen	(b) (4)
Applicant-proposed indication(s)/ population(s)	REZDIFFRA is a thyroid hormone receptor beta (THR- β) selective agonist indicated for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis
SNOMED CT code for proposed indication disease term(s)[1]	Nonalcoholic steatohepatitis (442685003)
Regulatory action	Accelerated approval
Approved dosage (if applicable)	The recommended dosage is based on actual body weight. For patients weighing: <100 kg, the recommended dosage is 80 mg orally once daily. ≥100 kg, the recommended dosage is 100 mg orally once daily. Administer REZDIFFRA with or without food.
Approved indication(s)/ population(s) (if applicable)	REZDIFFRA is a thyroid hormone receptor beta (THR-β) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).
SNOMED CT code for approved indication disease term(s)[1]	See above proposed SNOMED indication

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ABCG2	adenosine triphosphate binding cassette subfamily G member 2
AE	adverse event
AESI	adverse event of special interest
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANA	antinuclear antibody
ANCOVA	analysis of covariance
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
aPTT	activated partial thromboplastin time
AR	adverse reaction
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{tau,ss}$	area under the curve over the dosing interval at steady state
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve from time zero extrapolated to infinity
$AUC_{0\text{-}24}$	area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule
BA	bioavailability
BCRP	breast cancer resistance protein
BMD	bone mineral density
BMI	body mass index
BW	body weight
CAP	controlled attenuation parameter
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CRF	case report form
CRN	clinical research network
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DB	direct bilirubin
DI-ALH	drug-induced autoimmune-like hepatitis
DDI	drug-drug interaction
DHN	Division of Hepatology and Nutrition
DILI	drug-induced liver injury
DXA	dual X-ray absorptiometry
EAIR	exposure-adjusted incidence rate
EBV	Epstein–Barr virus
EC_{50}	half maximal effective concentration

ECG	electrocardiogram
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
E_{max}	maximum effect of time on CL/F
EPC	established pharmacologic class
E-R	exposure-response
ETA	name given to a PK parameter
F[#]	fibrosis stage (i.e., F0, F1A, F1B, F2…)
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FT3	free triiodothyronine
FT4	free thyroxine
GD	gestation day
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	good laboratory practice
HAV	hepatitis A virus
HCC	hepatocellular carcinoma
HDL	high-density lipoprotein
HFD	high-fat diet
HGB	hemoglobin
HI	hepatic impairment
HLM	human liver microsomes
HPLC	high-performance liquid chromatography
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IgM	Immunoglobulin M
INR	international normalized ratio
IR	information request
K_2EDTA	dipotassium (K_2) ethylene diamine tetraacetic acid
IND	investigational new drug
LC	liquid chromatography
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LLOQ	lower limit of quantitation
LSM	least squares mean
LSMA	Leadscope Model Applier
MACE	major adverse cardiovascular events
MAR	missing-at-random
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
MOA	mechanism of action
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction

MRP2	multidrug resistance protein 2
MS/MS	tandem mass spectrometry
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OLNC	open-label noncirrhotic
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetic
PND	postnatal day
PopPK	population PK
PPND	pre- and postnatal developmental
PRO	patient-reported outcome
PRO-C3	N-terminal type III collagen propeptide
PT	preferred term
PY	person-years
qAM	every morning
QC	quality control
QD	once daily
RBC	red blood cell
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SEE	substantial evidence of effectiveness
SHBG	sex hormone binding globulin
SOC	system organ class
T3	triiodothyronine
T4	tetraiodothyronine
TB	total bilirubin
TBM	to-be-marketed
TEAE	treatment-emergent adverse event
TH	thyroid hormone
THR	thyroid hormone receptor
THR-α	thyroid hormone receptor α
THR-β	thyroid hormone receptor β
T_{max}	median time to maximum concentration
TSH	thyroid stimulating hormone
TT3	total T3
UGT	uridine 5’-diphospho (UDP) glucuronosyltransferase
ULN	upper limit of normal

VCA	viral capsid antigen

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Resmetirom, (trade name REZDIFFRA) is being approved as a thyroid hormone receptor beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). The approved dosage is 80 mg orally once daily (for patients weighing less than 100 kg) or 100 mg orally once daily (for patients weighing 100 kg or more), with or without food. The approved indication and dosage are different from those initially proposed by the Applicant but were agreed upon during the NDA review. The NDA was reviewed by the multidisciplinary review team whose reviews and recommendations are reflected in this integrated review. Each discipline recommends approval, and the signatory authority for this application concurs with those recommendations.

Substantial evidence of effectiveness for resmetirom in patients with NASH was established using data from one adequate and well-controlled trial with confirmatory evidence (CE). Trial MGL-3196-11 is the single adequate and well-controlled investigation supporting the effectiveness of resmetirom. Both 80 and 100 mg dose arms demonstrated statistical significance on prespecified histologic endpoints as surrogate endpoints to support an accelerated approval. These results, based on prespecified 52-week liver biopsy endpoints, were persuasive. Confirmatory evidence includes MGL-3196-05, a phase 2, double-blind, placebo-controlled trial that enrolled adult patients with noncirrhotic biopsy-proven NASH, who were randomized 2:1 to resmetirom 80 mg (n=84) or placebo (n=41). The primary endpoint was the percent change in hepatic fat fraction by MRI-PDFF at 12 weeks, with 36-week liver biopsy and MRI-PDFF as secondary endpoints. Treatment with resmetirom reduced hepatic fat fraction at 12 and 36 weeks and was associated with improved NASH activity scores, higher rates of NASH resolution, and reduction of fibrosis stage compared to treatment with placebo.

This indication will be approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication will be contingent upon verification and description of clinical benefit in confirmatory trials. Specifically, Trial MGL-3196-11 continues to enroll additional subjects for a total of approximately 1700 subjects. All subjects will be followed for up to 54 months to assess clinical outcomes: a composite clinical endpoint of progression to cirrhosis, liver decompensation events, liver transplant, and all-cause mortality.

The available safety data show that resmetirom is safe for its intended use. Common adverse reactions include gastrointestinal events (diarrhea, nausea, vomiting, constipation, abdominal pain), pruritus and dizziness. Rare, serious adverse reactions include gallbladder-related adverse reactions (cholecystitis or gallstone pancreatitis) and drug induced liver injury (DILI). The DILI was determined to be most consistent with drug-induced autoimmune-like hepatitis phenotype (DI-ALH), including one observed case meeting Hy's Law criteria which spontaneously resolved

with dechallenge. Although modest changes in thyroid function tests were observed, there were no clinical findings associated with effects on thyroid function.

The signatory authority concurs with the team's assessment that identified risks can be mitigated through labeling and further evaluated through the following post-marketing requirements (PMRs) and post-marketing commitments (PMCs). Post-marketing requirements include completion of the ongoing MGL-3196-11 trial to confirm clinical benefit and further characterize the long-term safety of resmetirom. In addition, required PMRs under the Pediatric Research Equity Act (21 U.S.C.355c) will include studies to evaluate the safety, pharmacokinetics (PK), and efficacy of REZDIFFRA in post-pubertal and pre-pubertal pediatric patients down to age 6. Safety-related PMRs under FDCA Section 505(o) include a descriptive pregnancy safety study to assess risk of pregnancy and maternal complications on the developing fetus and infant, a clinical lactation study to measure concentration of REZDIFFRA in breast milk, and a study to evaluate the effects of severe renal impairment on the PK of REZDIFFRA. PMCs include additional drug-drug interaction studies and completion of the environmental fate and ecotoxicity studies for REZDIFFRA.

The overall benefit-risk is favorable for the intended population, as described in the Benefit-Risk Framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in Part II and the Product Quality review.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Substantial evidence of effectiveness for resmetirom in patients with NASH was established using data from one adequate and well-controlled trial, MGL-3196-11, with confirmatory evidence (CE). Trial MGL-3196-11 is the single adequate and well-controlled investigation supporting the effectiveness of resmetirom. The efficacy of resmetirom was evaluated based on an prespecified interim analysis at Month 12 of Trial MGL-3196-11, a 54-month, randomized, double-blind, placebo-controlled trial. Enrolled subjects 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 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.

The Month 12 analysis included 888 F2 and F3 subjects 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.

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 improvement on both histopathology endpoints at Month 12 compared to placebo.

A total of 26% to 27% of subjects who received 80 milligrams of resmetirom and 24% to 36% of subjects who received 100 milligrams of resmetirom experienced NASH resolution and no worsening of fibrosis, compared to 9% to 13% of those who received placebo. In addition, a total of 23% of subjects who received 80 milligrams of resmetirom and 24% to 28% of subjects who received 100 milligrams of resmetirom experienced an improvement in liver fibrosis and no worsening of NASH, compared to 13% to 15% of those who received placebo. The range of responses reflects the two pathologist's readings.

In a statistical analysis incorporating both pathologists' independent readings, resmetirom achieved statistical significance on both histopathology endpoints for both doses (Refer to Table 18).

In summary, results demonstrated statistical significance on prespecified endpoints on a surrogate endpoint to support an accelerated approval. These results were persuasive.

Confirmatory evidence includes MGL-3196-05, a phase 2, double-blind, placebo-controlled trial that enrolled adult patients with noncirrhotic biopsy-proven NASH, who were randomized 2:1 to resmetirom 80 mg (n=84) or placebo (n=41). The primary endpoint was the percent change in hepatic fat fraction by MRI-PDFF at 12 weeks, with 36-week liver biopsy and MRI-PDFF as secondary endpoints. Treatment with resmetirom reduced hepatic fat fraction at 12 and 36 weeks and was associated with improved NASH activity scores, higher rates of NASH resolution, and reduction of fibrosis stage compared to treatment with placebo. Refer to Section 6.3.4 for further discussion of establishing SEE.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Nonalcoholic steatohepatitis (NASH) is a severe form of nonalcoholic fatty liver disease (NAFLD) in which the liver develops inflammation and ballooning along with excess fat (≥5%). NASH is associated with the metabolic syndrome. Type 2 diabetes is associated with NAFLD/NASH. The relationship between the two seems to be bidirectional. – Approximately 16.8 million people potentially have NASH, and it is estimated that at least 6 million people in the United States have NASH with fibrosis stage 2 or 3 (target population). – NASH is slowly progressive over many years, but the time to development of severe liver disease increases per stage of fibrosis (average of 9.3 years to liver decompensation with F2 fibrosis and an average of 2.3 years with F3 fibrosis). – NASH-related cirrhosis and hepatocellular carcinoma (HCC) are projected to be the leading indication for liver transplant by 2030. – Cardiovascular events are the most common cause of mortality in NASH patients, with the second most common being nonliver-related cancers. Mortality related to liver-related outcomes ranks third. • Liver histopathology reading is the only way to diagnose and accurately grade NASH (disease activity), and stage (fibrosis) but in clinical practice most patients would prefer to not undergo biopsy.	• NASH is a serious condition and once a person progresses to cirrhosis the disease can be life-threatening. • If left untreated the disease may progress to liver failure necessitating liver transplant or leading to death. • There is an increasing medical burden on the U.S. health care system for care of these patients. • Progression of disease is variable and slow in the majority of the NASH population; however, in a subset of patients, NASH progresses rapidly, and disease progression is unpredictable. • Liver biopsy to diagnose and stage NASH carries risks. It is not feasible to biopsy millions of patients to identify those who have NASH with stage 2 or 3 fibrosis. Currently most noninvasive tests are not accurate in identifying specific stage and grade of the disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Non-invasive tests (NITs) (circulating and imaging biomarkers) are being developed to diagnose and stage NASH. However, NITs lack accuracy in identifying patients with NASH with stage 2 or 3 fibrosis.	
Current treatment options	• There are no FDA-approved drugs to treat NASH, although there are multiple drugs in development for NASH and liver fibrosis. • Off-label treatments include use of vitamin E and pioglitazone for NASH with fibrosis. • Weight loss in patients with obesity is associated with reduced steatosis and fibrosis. • Bariatric surgery, generally performed in morbidly obese patients, has demonstrated weight loss, and is associated with reduction in steatohepatitis and improvement in fibrosis.	• There are no approved drug therapies for NASH, and the clinical benefit of off-label therapies is uncertain. • Lifestyle changes to effect weight loss are effective but infrequently sustainable. • Bariatric surgery is an invasive procedure associated with potential for significant complications. Not all NASH patients are candidates for bariatric surgery, (e.g., due to more advanced liver disease or other comorbid conditions). • There is an unmet medical need for treatment for patients with NASH who have liver fibrosis.
Benefit	• Trial MGL-3196-11 is an ongoing phase 3, double-blind, randomized, placebo-controlled multicenter study of resmetirom 80 mg daily and 100 mg daily versus placebo in patients with NASH and fibrosis (stages 1 to 3). The prespecified primary efficacy endpoint was analyzed in patients with stages F2 and F3 fibrosis (n=888) at Week 52. • Two pathologists, independently read the liver biopsies for each patient. Both the 80 mg once daily and the 100 mg once daily dosages of resmetirom demonstrated improvement on both histopathology endpoints at Month 12 compared to placebo. – 26% to 27% of subjects who received 80 milligrams of resmetirom and 24% to 36% of subjects who received 100 milligrams of resmetirom experienced NASH resolution, compared to 9% to 13% of those who received placebo. – 23% of subjects who received 80 milligrams of resmetirom and 24% to 28% of subjects who received 100 milligrams of resmetirom experienced an improvement in liver fibrosis and no worsening of NASH, compared to 13% to 15% of those who received placebo.	• Both dosages of resmetirom (80 mg and 100 mg daily) demonstrated superiority compared to placebo on both histologic surrogate endpoints at 52 weeks. • Despite differences between the two pathologists' determination of whether individual subjects were responders or nonresponders, both pathologists reached the same conclusion when reading the histology in a blinded, independent manner – the drug demonstrated benefit over placebo on both histologic endpoints. • The efficacy of resmetirom was demonstrated on a surrogate endpoint, considered reasonably likely to predict clinical benefit, therefore some uncertainty remains as to whether patients will experience clinical benefit with long-term treatment. • Trial MGL-3196-11 will continue through 54 months to evaluate clinical outcomes in the pivotal trial population. The composite clinical endpoint is composed of: all-cause mortality, liver transplant, or significant hepatic events (including liver decompensation events [ascites, encephalopathy, or variceal hemorrhage], histological

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– The range of responses reflects the two pathologist's readings. • There can be differences between the two pathologists' determinations of whether a subject was a responder. The Agency's primary analysis at Week 52 was a modification of the Applicant's pre-specified primary analysis, which results in a model-based response rate calculated using a Mantel-Haenszel method, stratified by baseline type 2 diabetes status and fibrosis stage (F2 or F3). • In the model-based primary analysis, both resmetirom 80 mg and 100 mg arms demonstrated superiority to placebo at 52 weeks on both histologic surrogate endpoints: (1) resolution of NASH and no worsening of fibrosis (11% in placebo arm compared with 26% in the 80 mg arm and 30% in the 100 mg arm) and (2) improvement of fibrosis and no worsening of NASH (14% in the placebo arm compared with 23% in the 80 mg arm and 26% in the 100 mg arm). These results were statistically significant. • The estimated risk difference (95% CI) for resolution of NASH and no worsening of liver fibrosis was 15% (10%, 21%) comparing resmetirom 80 mg to placebo, and 19% (13%, 25%) comparing resmetirom 100 mg to placebo. The estimated risk difference (95% CI) for improvement of fibrosis and no worsening of NASH was 9% (4%, 15%) comparing resmetirom 80 mg to placebo, and 12% (7%, 18%) comparing resmetirom 100 mg to placebo. • The results of sensitivity analyses were consistent with the primary analysis. • The recommended weight-tiered dosage is 80 mg daily for patients weighing less than 100 kg and 100 mg daily for patients with body weight of 100 kg or higher. These cutoffs were chosen because body weight was an important covariate affecting the PK of resmetirom, and response rates trended downward in subjects in higher body-weight categories.	progression to cirrhosis, and increase of model for end-stage liver disease (MELD) score from <12 to ≥15).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• Trials MGL-3196-11 and MGL-3196-14 largely comprised the safety database, including a total of 673 patients receiving resmetirom 100 mg, 679 patients receiving resmetirom 80 mg, and 667 patients receiving placebo for a minimum of 52 weeks. One-third of patients were treated for more than 60 weeks. Safety analyses were performed to evaluate percentages of adverse events overall and exposure-adjusted incidence rates. • Study drug discontinuations and moderate AEs were more common in the treatment arms than in the placebo arm. Six deaths occurred among the pooled study population (five in active treatment arms and one in the placebo arms), none of which were considered related to study drug. • Adverse events of special interest (AESIs) included adjudicated MACE; adjudicated non-MACE cardiovascular events; fractures; gallstone-related adverse events; malignancies; liver enzyme elevations, including drug-induced liver injury (DILI); and adverse events related to hypothyroidism and hyperthyroidism. • MACE and other cardiovascular events were rare and occurred at similar rates across treatment and placebo arms. • Gastrointestinal (GI) adverse events (diarrhea, nausea, vomiting, and abdominal pain), dizziness, and pruritus were more common in the treatment arms than placebo arms. GI adverse events were the most common cause of drug-related treatment discontinuation). • Gallbladder-related adverse reactions (cholelithiasis, cholecystitis, and obstructive gallstone pancreatitis) were rare (<1 event per 100 PY, but occurred more commonly in treatment arms than in the placebo arms. • Because resmetirom is a THR-β agonist, thyroid function abnormalities were AESIs. A minority of subjects experienced decreases in free T4, and TSH/T3 remained normal in these subjects. A minority of subjects had abnormal TSH levels (low or high), and these were largely transient changes. Subjects who were on thyroxine replacement at baseline had a higher	• Resmetirom at 80 mg or 100 mg daily was reasonably well tolerated, with GI adverse reactions as the most common events, higher in treatment arms than placebo. Dizziness and pruritus were also more common in the active treatment arms than placebo. • Discontinuation of study drug due to adverse reactions was uncommon(6.8 events per 100 person-years (PY) in resmetirom 80 mg daily; 7.4 events per 100 PY in resmetirom 100 mg/daily; 3.9 events per 100 PY in placebo). • Review of MACE events, malignancies, and fractures did not suggest any imbalance between treatment and placebo groups. • Function of the hypothalamic-pituitary-thyroid axis was maintained during resmetirom treatment, despite small transient fluctuations in thyroid hormone levels observed in a small number of subjects. • Transient elevations of transaminases at week 4 resolved by week 8, and decreased below baseline afterwards in the treatment arms. Serious elevations of transaminases were uncommon and balanced across treatment and placebo arms. • A subject receiving resmetirom 80 mg daily developed hepatotoxicity with a DI-ALH phenotype which resolved with drug discontinuation. Enhanced pharmacovigilance will be requested in order to facilitate efficient reporting of postmarket hepatotoxicity cases. • Women of childbearing potential are among the population with NASH and moderate/advanced liver fibrosis, and NASH may increase the risk of pregnancy and postpartum complications. Because there are no clinical data to support safe use of resmetirom during pregnancy and lactation, a postmarket descriptive pregnancy safety study (DPSS) and a milk-only lactation study are planned. Enhanced pharmacovigilance will be requested to facilitate reporting of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	incidence of TSH abnormalities than those who were not on baseline thyroxine. • Resmetirom is known to increase the synthesis of sex hormone binding globulin (SHBG), and these increases were seen in treated subjects. Increases in all sex hormones, except free testosterone, were noted in subjects treated with resmetirom , but the incidence of sex hormone-related adverse events was low. • The mean transaminase (ALT, AST) levels were increased from baseline at the 4-week evaluation in subjects treated with resmetirom compared to placebo, but returned to baseline by 8 weeks, and dropped below baseline thereafter. Mean alkaline phosphatase (ALP) and total bilirubin levels were unchanged. • One case of DILI meeting Hy's Law criteria was observed in Trial MGL-3196-14 in a subject receiving 80 mg resmetirom daily. The subject had positive dechallenge and more rapid and severe injury withrechallenge, but the liver analytes returned to normal off resmetirom without additional intervention. This case was reviewed independently by four FDA hepatologists, who considered it to be a probable DILI with features of a drug-induced autoimmune-like hepatitis (DI-ALH). • Nonclinical studies suggest a margin of safety at dosages of resmetirom intended for humans. Pregnant and lactating persons were not enrolled in MGL-3196-11 or MGL-3196-14. As such, the clinical safety profile of resmetirom in pregnancy and lactation is unknown.	results of any pregnancies that occur prior to the initiation of the DPSS.

Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular events; MGL-3196, resmetirom; PK, pharmacokinetic; THR-β, thyroid hormone receptor β; TSH, thyroid stimulating hormone

2.2. Conclusions Regarding Benefit-Risk

Nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stage F2 and F3) is a common condition, which can be progressive—on average, patients with NASH progress one fibrosis stage every 7 years. NASH prevalence has increased worldwide, and there are currently no approved pharmacologic therapies that have been shown to reduce steatohepatitis and/or fibrosis.

Resmetirom, a first-in-class new molecular entity, is a partial agonist of the thyroid hormone receptor β. In the pivotal trial (MGL-3196-11) reviewed to support efficacy, after one year of treatment, the population had statistically significant improvements in liver histology, both for steatohepatitis and fibrosis. These data were sufficiently persuasive for accelerated approval of resmetirom on the basis of a single adequate and well-controlled trial plus confirmatory evidence. Completion of the pivotal trial, including assessment of clinically meaningful endpoints that demonstrate progression of liver disease is of critical importance, to ensure that histologic improvement is accompanied by clinically meaningful benefit as well as to evaluate long-term safety. The 54-month assessment also may elucidate whether resmetirom treatment over a longer period is required to reverse fibrosis and/or steatohepatitis, and whether long term treatment has a clinically meaningful benefit on preventing progression to cirrhosis or hepatic decompensation events, including death and need for liver transplant.

The Applicant enrolled participants who had NASH with stages F1, F2, and F3 fibrosis, but the primary analysis and the indicated population is patients with NASH with moderate to advanced liver fibrosis, consistent with stage F2 and F3. Progression to cirrhosis and other clinically meaningful liver endpoints in patients with lower stages of fibrosis (F0 and F1) is too slow and indolent to be able to demonstrate benefits in the context of a clinical trial and would require a greater assurance of safety to support a favorable benefit:risk assessment for long-term use. (b) (4)

Safety data were reviewed from the pivotal trial along with an additional placebo-controlled, randomized safety study. This safety database was adequate. Serious adverse events were similar across treatment arms. The most common adverse events were gastrointestinal, including diarrhea and nausea, which were also the most common causes of treatment discontinuation. Based on the mechanism of action, thyroid function testing laboratory and clinical data were carefully reviewed, and clinically significant abnormalities in thyroid function were not detected. Although one case of probable drug-induced liver injury met Hy's law, this case resolved with drug discontinuation without further intervention. Elevated autoimmune markers and immunoglobulin G suggested a drug induced autoimmune hepatitis like injury, which is more likely to respond to treatment (e.g., corticosteroids) than other types of idiosyncratic drug-induced liver injury, if the injury does not spontaneously resolve with drug discontinuation. Adopting an enhanced pharmacovigilance strategy for the first 2 years after approval will expedite reporting of any additional hepatotoxicity cases for Agency review.

Based on review of all available efficacy and safety data, the benefits of resmetirom outweigh the risks of treatment in adult NASH patients with moderate to advanced liver fibrosis to support an accelerated approval based on improvement of NASH and fibrosis. Continued approval for

this indication may be contingent upon verification and description of clinical benefit in the confirmatory Trial, MGL-3196-11.

II. Interdisciplinary Assessment

3. Introduction

This review serves as the interdisciplinary assessment for REZDIFFRA (NDA 217785), submitted for approval under the accelerated approval pathway (subpart H) based on a surrogate endpoint reasonably likely to predict clinical benefit. REZDIFFRA contains resmetirom, which, as proposed by the Applicant, is indicated for treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Analysis of Condition

NASH is a severe form of nonalcoholic fatty liver disease (NAFLD). NAFLD is characterized by the presence of macrovesicular steatosis in ≥5% of hepatocytes and includes a spectrum of disease from bland steatosis (nonalcoholic fatty liver or NAFL) to more severe forms, i.e., NASH with stage 3 liver fibrosis, and in a proportion of patients may progress to cirrhosis. NAFLD is a diagnosis of exclusion, as other causes of steatosis, including but not limited to medications, starvation, or monogenic disorders, must be excluded in individuals who have little or no alcohol consumption (defined as <20 g/d for women and <30 g/d for men). NASH is characterized by the presence of steatosis, inflammatory changes, and ballooning degeneration of hepatocytes, with or without fibrosis (Rinella et al. 2023b).

The prevalence of NAFLD and NASH is rising worldwide, paralleling the increases in the prevalence of obesity and metabolic comorbid disease. The prevalence of NAFLD in adults is estimated to be between 25 to 30% of the general population. NASH prevalence in the general population is difficult to estimate, given the need for histological confirmation. Historically, reported prevalence estimates for NASH range from 1.5% to 6.45%, but in one recent study NASH was identified in 14% of asymptomatic patients undergoing colon cancer screening, suggesting an increase in prevalence of NASH. NAFLD and NASH incidence data from the general population is lacking, but it has been estimated that the incidence of NAFLD ranges from 28.01 per 1000 person-years (PY) (95% CI: 19.34, 40.57) to 52.34 per 1000 PY (95% CI: 28.31, 96.77) (Younossi 2018; Hamid et al. 2022; Rinella et al. 2023b). There are differences in prevalence between racial and ethnic subpopulations, with the highest prevalence in Americans of Hispanic/Latino descent, followed by white Americans, and Black/African Americans (Sayiner et al. 2016).

There is a bidirectional association between NAFLD and metabolic abnormalities (central obesity, insulin resistance, dyslipidemia, and hypertension) wherein NAFLD can often precede development of metabolic abnormalities, and having several metabolic abnormalities increases the risk of histological progression of NASH (Rinella et al. 2023b). The presence and severity of obesity are associated with NAFLD and progression of disease. In fact, 90% of morbidly obese persons have NAFLD and the prevalence of NASH among obese individuals is estimated to be 25% to 30%. Patients with type 2 diabetes mellitus are at the greatest risk for NAFLD and NASH. The prevalence of NASH among the patients with type 2 diabetes mellitus is estimated to be as high as 65%.

Though NAFLD and NASH are more common in obese individuals, NAFLD and NASH can occur in the absence of obesity. The prevalence of NAFLD in lean individuals in the United States is estimated to be about 7%, compared to prevalence in Asian countries, where it can be as high as 25% to 30% (Younossi 2018; Younossi and Henry 2022; Rinella et al. 2023b).

The degree of fibrosis has been linked to development of liver-related outcomes and death. Patients with stage 2 fibrosis and higher are at increased risk for all-cause mortality (Rinella et al. 2023b). Progression of fibrosis is associated with a higher likelihood of liver-related events. (Angulo et al. 2015; Ekstedt et al. 2015; Sanyal et al. 2021). The rate of fibrosis progression is higher in patients with NASH (one stage per 7 years) compared to those with NAFL (one stage per 14 years) (Singh et al. 2015).

From a natural history perspective, NAFL is generally considered as a benign condition, whereas NASH is considered a progressive disease that can advance to cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, or death. Approximately 10 to 15% of NASH patients will progress to cirrhosis, but this progression is nonlinear and some patients with NASH fibrosis may spontaneously regress (Younossi 2018). Progression to cirrhosis places NASH patients at high risk for developing decompensated cirrhosis (variceal bleeding, hepatic encephalopathy, ascites). Among patients with cirrhosis, progression to clinical decompensation ranges from 3% to 20% per year. HCC as a complication of NASH is the second most common indication for HCC-related liver transplantation, after hepatitis C-associated HCC. NASH is the second most common indication for listing for liver transplantation and the leading indication for liver transplant among women in the United States (Younossi and Henry 2022). The most common causes of death in NAFLD are cardiovascular disease and nonhepatic malignancy, followed by liver disease (Rinella et al. 2023b).

Current Treatment Options

There are currently no FDA-approved pharmacological treatments for NASH. Lifestyle management with reduced calorie diet and increased exercise are currently considered the standard of care. Bariatric surgery as a therapeutic option can be considered in patients who meet criteria for metabolic weight loss surgery as it can resolve NAFLD or NASH in the majority of patients without cirrhosis. NASH resolution was seen in 80% of patients 1 year following surgery and was maintained at 5 years. However, bariatric surgery is a high-risk procedure with a risk of surgical complications. It is not recommended in NASH patients with cirrhosis and is contraindicated in patients who have decompensated cirrhosis from any cause. Glucagon-like peptide 1 agonists like semaglutide can be considered for their approved indications (type 2 diabetes mellitus/obesity) in patients with concomitant NASH for their cardiovascular and metabolic benefits, but no glucagon-like peptide 1 agonist is approved for the treatment of NASH. Other medications used off label include vitamin E and pioglitazone, but these have not demonstrated an antifibrotic benefit (Rinella et al. 2023b).

Therefore, pharmacological treatment for NASH remains an unmet medical need.

Resmetirom

Resmetirom, a new molecular entity (NME), is a partial agonist of the thyroid hormone receptor β (THR-β). See Section 5.2 for details on mechanism of action (MOA). The Applicant has

proposed two dosages of resmetirom, 80 mg or 100 mg, to be administered orally, once daily (QD).

Rationale for Thyroid Hormone Receptor β Agonism

Lipotoxicity is a key driver in the pathogenesis of NASH, driven by excess free fatty acids coupled with increased de novo lipogenesis. Thyroid hormones (THs) regulate hepatic lipid metabolism. In experimental studies, mice fed a Western diet developed increased steatosis, inflammation, and fibrosis, and subsequently demonstrated decreased intrahepatic tetraiodothyronine (T4), and triiodothyronine (T3). In a dietary mouse model of NASH, THs decreased hepatic triglyceride content and hydroxyproline. Thyroid hormones also restored autophagy and mitochondrial biogenesis to increase β-oxidation of fatty acids, and reduced lipotoxicity, oxidative stress, hepatic inflammation, and fibrosis (Bruinstroop et al. 2021; Zhou et al. 2022).

Despite the known role of THs in regulation of hepatic lipid metabolism, the association between hypothyroidism and NAFLD from an epidemiological perspective remains unclear. In a large meta-analysis, hypothyroidism was significantly associated with presence and severity of NAFLD, whereas in another meta-analysis, no association between NAFLD and hypothyroidism was noted, along with no difference between TH levels between subjects with or without NAFLD (Jaruvongvanich et al. 2017; Mantovani et al. 2018).

The two main forms of THs—T3, the active form of TH, and T4, a prohormone activated by deiodinases at the cellular and circulatory level—exert their actions via the thyroid hormone receptor (THR), which is primarily a nuclear receptor that acts as a ligand-dependent transcription factor. There are two major THR genes, THRA and THRB. THR-α1 and THR-α2 are two major THRA receptor splice variants encoded by the THRA gene, whereas THR-β1and THR-β2 are two major THRB isoforms generated by alternate promoter choice on the THRB gene. THR-α1 is highly expressed in the heart, bone, and skeletal muscle, whereas THR-α2 is widely expressed throughout the whole body. THR-β1 is predominately expressed in the brain, liver, and kidney, whereas THR-β2 is found in the pituitary, retina, and cochlea (Singh and Yen 2017). Thyroid hormone receptor α (THR-α) has also been found in hepatic stellate cells. Thus, increased T3 and T4 levels could induce profibrogenic effects by activation of stellate cells (Ritter et al. 2020; Hatziagelaki et al. 2022).

The THR-β pathway regulates de novo lipogenesis, β-oxidation of fatty acids, mitophagy, mitochondrial oxidation, and cholesterol synthesis. In animal studies, hepatomegaly and hepatic steatosis were noted in mice with dominant negative mutations in the gene encoding THR-β, secondary to decreased THR-mediated fatty acid β-oxidation, which leads to lipid accumulation (Sinha et al. 2018). Given that THR-β is highly expressed in the liver, there is significant interest in development of THR analogs that can separate the beneficial actions on the liver mediated by THR-β (reduction of triglycerides and cholesterol) from the harmful actions on heart and bone, mediated by THR-α.)

In nonclinical studies, resmetirom demonstrated a stronger activation of THR-β compared to THR-α. It also showed rapid and robust lowering of non-high-density lipoprotein cholesterol,

triglycerides and liver triglycerides, with reduction in inflammatory and fibrosis gene transcripts.[1]

Brief Regulatory History

See Section 12 for a full summary of the regulatory history.

An IND application for resmetirom for the treatment of NASH was opened on July 25, 2016, and the IND-opening study was deemed safe to proceed on August 24, 2016. Fast Track Designation was granted to resmetirom on October 18, 2019, based on phase 2 trial (MGL-3196-05) results, which demonstrated reduction in hepatic fat fraction as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF). On April 11, 2023, resmetirom was granted breakthrough designation based on preliminary efficacy data obtained from Trial MGL-3196-11 (phase 3 pivotal trial), and on May 22, 2023, the Applicant was granted rolling review.

Change in Nomenclature for NAFLD/NASH

An international Delphi consensus process led to revised nomenclature for NAFLD and NASH which was introduced in 2023. The proposed nomenclature for NAFLD is metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is diagnosed if a patient has hepatic steatosis (>5% hepatocytes) with at least one cardiometabolic risk factor. Screening for other potential causes of steatotic liver disease is still indicated. The new nomenclature for NASH is metabolic dysfunction-associated steatohepatitis (MASH) with no change in histopathological criteria. The FDA considers the terms NAFLD and NASH, interchangeable with MASLD and MASH, respectively (December 2018; Rinella et al. 2023a).

The FDA has maintained the former nomenclature for NASH in this review and labeling. Most non-hepatology clinicians may be unfamiliar with the new nomenclature, and it is too early to know whether there will be universal acceptance of this new nomenclature. Additionally, the term NASH was used in the regulatory designations for the IND and NDA for resmetirom, i.e., fast track, breakthrough therapy designation, and priority review.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Efficacy Analysis Includes Subjects With Stage F2 and F3 Fibrosis

Among the inclusion criteria for phase 3 noncirrhotic NASH trials is that patients have more than stage 1 and less than stage 4 fibrosis at enrollment, to ensure that patients have clear evidence of steatohepatitis without cirrhosis (December 2018). From the first version of the MGL-3196-11 protocol submitted in 2019, the explicit intention was to include only patients with NASH and F2 and F3 fibrosis in the primary efficacy analyses. Despite clear communications, the Applicant included patients with F1B fibrosis in their primary efficacy analysis. There were 49 patients out

[1] Source: Applicant provided MGL-3196-11 clinical study report in module 5.

of 1,050 in the overall patient population enrolled in MGL-3196-11 who had F1B fibrosis at baseline using the baseline fibrosis stage specified by the Applicant. Refer to Section 6.3.1 for the full analysis of this key efficacy review issue.

3.1.1.2. Definition and Analysis of Histologic Primary Endpoints

Primary analyses of the histologic surrogate endpoints (primary endpoints) for Week 52 interim analyses were not agreed upon with the Agency during the IND development program. Primary histologic endpoints as defined by the Applicant differ from those defined in the FDA guidance for industry (December 2018). Refer to Section 6.3.2 for the full analysis of this key efficacy review issue.

3.1.1.3. Liver Histology as a Reasonably Likely Surrogate Endpoint

The Applicant is seeking accelerated approval under 21 CFR part 314, Subpart H, based on demonstrating an effect on surrogate endpoints. Refer to Section 6.3.3 for the full analysis of this key efficacy review issue.

3.1.1.4. Framework for Demonstrating Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) for resmetirom is based on a single adequate and well-controlled investigation (Trial MGL-3196-11) together with confirmatory evidence. Refer to Section 6.3.4 for the full analysis of this key efficacy review issue.

3.1.2. Key Safety Review Issues

3.1.2.1. Hepatotoxicity: Drug-Induced Liver Injury

Resmetirom is a thyromimetic, partial agonist of THR-β, with actions on the hepatocyte purported to provide beneficial metabolic effects on reducing lipotoxicity, primarily through action on THR-β, the predominant hepatocyte THR. However, resmetirom also has some action on THR-α (see Section 5.2). Thyromimetics are associated with safety signals related to the liver. In the pooled trial safety database (Trials MGL-3196-11 and MGL-3196-14), there were 10 potential Hy's law cases in both drug arms, but after detailed review, only one case of probable drug-induced liver injury (DILI) was observed. Refer to Section 7.7.1 for the full analysis of this key safety review issue.

3.1.2.2. Treatment-Related Changes in Thyroid Hormones

Resmetirom is intended to act in the liver while avoiding unwanted systemic actions of TH in heart and bone mediated through THR-α. Although a THR- ß agonist, resmetirom does have some agonist activity on THR-α receptors (see Section 5.2), therefore may have potential effects on the TH axis. Refer to Section 7.7.2 for the full analysis of this key safety review issue.

3.1.2.3. Treatment-Related Gallstone Adverse Events

There is a strong association between gallstone disease and NAFLD/NASH. Because resmetirom is a thyromimetic compound, targeting hepatic THR-ß, it is expected to promote bile formation and secretion, increase cholesterol metabolism, formation of bile acids, and increase secretion of cholesterol, increasing the potential for gallstone formation. Refer to Section 7.7.3 for the full analysis of this key safety review issue.

3.1.2.4. Treatment-Related Gastrointestinal Adverse Events

Gastrointestinal (GI) AEs were the most common treatment-emergent adverse event (TEAE) reported during the development program. Refer to Section 7.7.4 for the full analysis of this key safety review issue.

3.1.2.5. Treatment-Related Pruritus

Although pruritus has not been considered a common problem for patients with NASH, NASH with advanced fibrosis (F3/F4) can be associated with clinically significant pruritus. Pruritus has been found to be a TEAE in clinical trials evaluating other potential therapies for NASH, such as FXR agonists. Refer to Section 7.7.5 for the full analysis of this key safety review issue.

3.1.2.6. Deficiencies in the Pre- and Postnatal Development Study in Rats

The PPND study in rats is deficient based on current ICH standards. Refer to Section 7.7.6 for the full analysis of this key safety review issue.

3.1.2.7. Treatment-Related Changes in Sex Hormones

The impact of changes in sex hormone binding globulin (SHBG) and associated sex hormones (including estradiol, testosterone, FSH, and LH) in the setting of pharmacological intervention for NASH was unknown. Refer to Section 7.7.7 for the full analysis of this key safety review issue.

3.1.2.8. Treatment-Related Changes in Bone Metabolism

Resmetirom is a THR-ß partial agonist with high selectivity for hepatic THR-ß. However, potential off-target adverse effects of resmetirom via THR-α agonism may affect bone metabolism. Thyroid stimulating hormone (TSH) also has direct action on bone. Refer to Section 7.7.8 for the full analysis of this key safety review issue.

3.1.2.9. Major Cardiovascular Events

Even though resmetirom is a partial THR-ß agonist, no thyromimetic is a pure THR-β or THR-α agonist. Therefore, there is a possibility of off-target effects, which include cardiotoxicity as the

effect of THs on the heart is mediated by THR-α. Refer to Section 7.7.9 for the full analysis of this key safety review issue.

3.1.2.10. Malignancy

Patients with NASH are at increased risk of malignancies, including HCC. Comorbid obesity also increases malignancy risk. Thyroid hormones and THRs have been linked to various malignancies. Given resmetirom is a thyromimetic, malignancy was considered an adverse event of special interest (AESI). Refer to Section 7.7.10 for the full analysis of this key safety review issue.

3.2. Approach to the Clinical Review

For this submission, the review team assessed efficacy from Trial MGL-3196-11, the pivotal trial in adult patients with biopsy-proven NASH with fibrosis. The efficacy analysis, evaluating both resmetirom doses (80 mg and 100 mg) compared to placebo, was performed for subjects with stage F2 and F3 fibrosis at baseline (Section 6.2).

The primary safety analysis was conducted using data from Trials MGL-3196-11 and MGL-3196-14, including all subjects receiving placebo or resmetirom at 80 mg or 100 mg. The safety data from Trials MGL-3196-18 and MGL-3196-05 were also reviewed to support the primary safety analysis but are not described in detail in this review.

3.3. Approach to Establishing Substantial Evidence of Effectiveness

- REZDIFFRA is a thyroid hormone receptor beta (THR-β) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).
- SEE was established with one adequate and well-controlled clinical investigation and confirmatory evidence (May 1998; December 2019; September 2023).

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Resmetirom

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
MGL-3196-11 (Phase 3) (Pivotal) (Ongoing; data cutoff date: 2022-07-31)	Adult patients with NASH and fibrosis (noncirrhotic)	Control Type: placebo-controlled Randomization: randomized Randomization ratio: 1:1:1 Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	Drug (established name): resmetirom Dose: 80 and 100 mg Number treated: • Resmetirom 80 mg (N=352) • Resmetirom 100 mg (N=349) • Placebo (N=349) Duration (quantity and units): Up to 54 months (Subjects who experienced a composite clinical outcome event by the time of the Week 52 liver biopsy (cirrhosis) or after Week 52 and prior to Month 54 may enter an open-label active treatment arm of the Study.)	Primary: 1.) The proportion of subjects who achieved a NASH resolution associated with a 2-point reduction in NAS with no worsening of fibrosis by liver biopsy as assessed independently by two central reader pathologists at Week 52 on the primary glass slide read. 2.) The proportion of subjects with at least a 1-point improvement in fibrosis with no worsening of NAS (referred to as *fibrosis improvement*) by liver biopsy, as assessed by two pathologists at Week 52 Secondary: The mean treatment difference in percent change LDL-C at Week 24 due to randomized treatment.	Planned: 2,000 Actual: 1,050	Centers: 172 Countries: 14

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
MGL-3196-14 (Phase 3 safety) (Completed)	Adult patients with NAFLD, (noncirrhotic) who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH"	Control type: Placebo-controlled with open-label arm Randomization: randomized Randomization ratio: The first 34 participants were assigned to the OLNC 100 mg arm. Participants thereafter were randomized 1:1:1:1, until approximately 175 participants were enrolled in the OLNC 100 mg arm. Patients thereafter were randomized 1:1:1 to the remaining arms. Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	Drug (established name): resmetirom Dose: 80 and 100 mg Number treated: • Resmetirom 80 mg (N=327) • Resmetirom 100 mg (N=324) • OLNC 100 mg (N=171) • Placebo (N=318) Duration (quantity and units): 52 weeks	Primary: The incidence of treatment-emergent adverse events during 52 weeks of treatment. Secondary: 1.) The percent change in LDL-C from baseline to Week 24 2.) The percent change from aseline to Week 24 in ApoB 3.) The percent change from baseline to Week 16 in the hepatic fat fraction variable based on MRI-PDFF (tested differently from lipids). 4.) The percent change from baseline to Week 24 in TGs in subjects with baseline TGs >150 mg/dL. 5.) The change from baseline to Week 52 in PRO	Planned: 1,400 Actual: 1,143	Centers: 77 Countries: 1

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
MGL-3196-18 (Phase 3) (Ongoing; data cutoff date: 2022-09-30)	Adult patients with NAFLD (noncirrhotic)	Control type: Open-label extension Randomization: None Randomization ratio: NA Blinding: partial double-blind lead-in for 12 weeks Biomarkers: no biomarkers Innovative design features: none	Drug (established name): resmetirom Dose: 80 and 100 mg Number treated: • Placebo to resmetirom 80 mg (N=86) • Placebo to resmetirom 100 mg (N=86) • Any resmetirom to resmetirom 80 mg (N=171) • Any resmetirom to resmetirom 100 mg (N=170) • Open-label 100 mg (N=102) Duration (quantity and units): 52 weeks	Primary: The incidence of treatment-emergent adverse events in the 52-week treatment period of the extension study. Secondary: 1.) Safety of 80 mg versus 100 mg resmetirom for the first 12 weeks of extension treatment. 2.) The change and percent change of 80 mg versus 100 mg resmetirom from baseline in lipid parameters such as LDL cholesterol (direct and calculated), total cholesterol, ApoB, ApoA1, HDL-C, Lp(a), non-HDL-C, triglycerides, ApoCIII, lipoprotein particles (LDL, VLDL, HDL), VLDL-C, and TRL-C at extension Week 12. 3.) The change and percent change from baseline in lipid parameters such as LDL cholesterol (direct and calculated), total cholesterol, ApoB, ApoA1, HDL-C, Lp(a), non-HDL-C, triglycerides, ApoCIII, lipoprotein particles (LDL, VLDL, HDL), VLDL-C, and TRL-C at extension Weeks 28 and 52.	Planned: 1,080 Actual: 615	Centers: 57 Countries: 1

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
MGL-3196-05 (Phase 2)	Adult patients with NASH (noncirrhotic)	Control type: placebo-controlled Randomization: randomized Randomization ratio: 2:1 Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	Drug (established name): resmetirom Dose: 80 mg (adaptive) Number treated: • Resmetirom (N=84) • Placebo (N=41) • Duration (quantity and units): 36 weeks	Primary: The percent change in hepatic fat fraction by MRI-PDFF from baseline at 12 weeks. Secondary: 1.) Proportion of subjects who had 30% or more reduction in hepatic fat fraction by MRI-PDFF from baseline at Week 12, that is, the percent change from baseline to Week 12 is ≤30%. 2.) Proportion of subjects who had 5% or more absolute reduction in hepatic fat fraction by MRI-PDFF from baseline at Week 12, that is, the change from baseline to Week 12 is ≤5% in hepatic fat. 3.) Proportion of subjects who had 5% or less hepatic fat fraction by MRI-PDFF at Week 12, that is, the hepatic fat fraction measurement at Week 12 is ≤5%.	Planned: 117 Actual: 125	Centers: 18 Countries: 1

Source: Clinical Study Report and adsl.xpt. Generated by clinical data scientist at the FDA

[1] Includes all submitted clinical trials, even if not reviewed in depth, except for phase 1 and pharmacokinetic studies.

Abbreviations: ApoA1, apolipoprotein A-1; ApoB, apolipoprotein B; ApoCIII, apolipoprotein C-III; FDA, U.S. Food and Drug Administration; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NA, not applicable; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; N, total number of subjects; OLNC, open-label non-cirrhotic; PDFF, proton density fat fraction; PRO, patient-reported outcome; TG, triglyceride; TRL-C, triglyceride rich lipoprotein-cholesterol; VLDL, very low density lipoprotein; VLDL-C, very low-density lipoprotein cholesterol

4. Patient Experience Data

In Trial MGL-3196-11, effects on selected patient-reported outcomes (PROs) were considered exploratory objectives. Baseline, Week 24, and Week 52 scores of the following PRO instruments were reported:

- Short Form Liver Disease Quality of Life, total score
- Short Form Liver Disease Quality of Life, physical functioning subscale
- Chronic Liver Disease Questionnaire for NAFLD NASH

No meaningful changes were observed across placebo and drug treatment groups between baseline and week 52. These data are not discussed in the review.

The Applicant did not seek labeling based on any of the collected patient experience data.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	N/A
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Source: Generated by the FDA review team

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The potential effectiveness of resmetirom was tested in vitro (cell-free functional assay) and in vivo (mouse model). The dataset did not include any in vivo models that produced all the histological features of NASH (i.e., steatosis, inflammation, hepatocyte ballooning, and fibrosis). However, from a nonclinical perspective, the data are considered as adequate for supporting approval from pharmacology/toxicology perspective. In summary:

- In the THR-β cell-free functional assay performed by the Applicant, the half maximal effective concentration (EC_{50}) value for resmetirom was 0.70µM (see details in Section 13.2). The published EC_{50} value for resmetirom for the same assay was 0.21 µM. The published EC_{50} value is included in Section 12.1 of the label.
- In the THR-α cell-free functional assay performed by the Applicant, the EC_{50} value for resmetirom was 3.83µM (see details in Section 13.2). The published EC_{50} value for resmetirom for the same assay was 3.74uM. The published EC_{50} value is included in Section 12.1 of the label.
- The potency of resmetirom in the THR-β cell-free functional assay was 17.8 times the potency for THR-α activation based on the published EC_{50} values, and 5.5 times the potency for THR-α activation based on the EC_{50} values from the same assay performed independently by the Applicant.
- Decreases in liver weight and severity of liver vacuolation were observed in mice fed an admixture of resmetirom (RO4923659) and high-fat diet (HFD) for 25 weeks compared to placebo+HFD admixture-fed control animals. In liver, transcripts for some inflammatory genes and major fibrosis-associated genes were downregulated in resmetirom+HFD admixture-fed animals to levels that were similar to those measured in normal control animals. Resmetirom administration had the expected effects on THR-regulated genes (mitochondrial glycerol-3-phosphate dehydrogenase, malic enzyme, deiodinase 1, thyroid binding globulin) in the liver.
- Established pharmacologic class (EPC): Resmetirom is a first-in-class NME. The recommended EPC for resmetirom is *thyroid hormone receptor-beta (THR-β) agonist*. The review team agrees that the selected EPC meets the criteria of being scientifically valid and clinically meaningful, in accordance with the FDA guidance for industry, *Labeling for Human Prescription Drug and Biological Products—Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information* (October 2009). The recommended EPC differs slightly from the EPC proposed by the Applicant, *thyroid hormone receptor beta (THR-β) selective agonist*.

In Vitro Potency and Selectivity of Resmetirom

Data Report for Pharmacology Services (Thyroid Hormone Receptor/RXR Heterodimer Coactivator Recruitment Assay Functional Assay [Study TW04-0015410])

MGL-3196 (resmetirom) and the major human metabolite MGL-3623 were evaluated in a cell-free in vitro functional assay. MGL-3196, MGL-3623, or T3 (reference compound) was allowed to bind to the THR-retinoid X receptor (RXR) heterodimer complex, which mediates TH signaling. The functional assay measured the ability of MGL-3196, MGL-3623, or T3 to stimulate recruitment of the biotin-linked coactivator peptide, glucocorticoid receptor-interacting protein-1, through activation of the THR-RXR heterodimeric complex. For THRβ-RXRα heterodimer activation, MGL-3196 produced 81% of the maximum response compared to T3, with an EC_{50} of 0.70µM. The metabolite MGL-3623 produced 67% of the maximum response compared to T3 for THRβ-RXRα heterodimer activation, with an EC_{50} of 19.3µM. For THRα-RXRα heterodimer activation, MGL-3196 produced 85% efficacy relative to T3, with an EC_{50} of 3.83µM. MGL-3623 produced 59% of the maximum response compared to T3 for THRα-RXRα heterodimer activation, with an EC_{50} of 75.9µM. The EC_{50} values for MG-3196 are generally similar to the values published in (Kelly et al. 2014). (THRβ-RXRα heterodimer activation EC_{50}=0.21µM and THRα-RXRα heterodimer activation EC_{50}=3.74µM).

In Vivo Effects of Resmetirom

25-Week Study of RO4923659 and Rosiglitazone Given as Food Admixtures to Diet-Induced Obese Male C57Bl/6J Mice (Study THR-74)

After 25 weeks of oral RO4923659 (resmetirom) administration (0.1, 0.3, 1, and 3 mg/kg) to mice in an HFD admixture, effects on the liver were observed. Absolute and relative liver weight were decreased up to -44% and -24%, respectively, at 3 mg/kg (human equivalent dose=0.24 mg/kg) compared to placebo+HFD admixture-fed control animals. Liver histology showed a decrease in the degree of hepatocyte vacuolation (minimal vacuolation at 3 mg/kg versus moderate to severe vacuolation in placebo admixture-fed control animals). Other effects included decreased plasma cholesterol at ≥0.1 mg/kg and decreased plasma triglycerides at 3 mg/kg.

In liver, transcripts for some inflammatory genes, including C-reactive protein, serum amyloid A 1 and 2, and others, were upregulated in placebo+HFD admixture-fed control animals and downregulated in RO4923659+HFD admixture-fed animals (human equivalent doses of 0.024 to 0.24 mg/kg) to levels that were similar to those measured in the normal control animals. Likewise, transcripts for major fibrosis-associated genes, including TIMP1, smooth muscle actin, connective tissue growth factor, and collagen genes, were upregulated in placebo+HFD admixture-fed control animals and downregulated in RO4923659+HFD admixture-fed animals (human equivalent doses of 0.024 to 0.24 mg/kg) to levels that were similar to those measured in the normal control animals. Other effects on liver gene expression in RO4923659+HFD admixture-fed animals included upregulation of genes that are rate-limiting steps in cholesterol metabolism, bile acid synthesis and clearance; upregulation of genes involved in cholesterol biosynthesis; downregulation of peroxisome proliferator activated receptor γ; upregulation of cyclin D11 and adenosine triphosphate binding cassette subfamily B member 11 (bile salt export pump); and changes in a substantial number of cytochrome P450 genes (↑CYP450 7A1 [catalyzes first and rate limiting step in cholesterol metabolism in liver], ↑CYP7B1 [catalyzes

first reaction in conversion of cholesterol to bile acid], and ↓CYP3A11 [CYP3A4]). Thyroid hormone receptor-regulated genes were regulated by treatment with RO4923659 as expected (↑mitochondrial glycerol-3-phosphate dehydrogenase, ↑malic enzyme, ↑deiodinase 1, and ↓thyroid-binding globulin in RO4923659+HFD admixture-fed animals).

5.2. Clinical Pharmacology/Pharmacokinetics

Clinical Pharmacology recommends approval of resmetirom for the treatment of adults with NASH with moderate to advanced liver fibrosis. Key clinical pharmacology information about resmetirom is summarized in Table 5.

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Thyroid hormone receptor-beta (THR-β) agonist
Mechanism of action	Resmetirom is a partial agonist of THR-β. Resmetirom produced 83.8% of the maximum response compared to triiodothyronine (T3) in an in vitro functional assay for THR-β activation, with an EC_{50} of 0.21µM (Kelly et al. 2014)Resmetirom produced 83.8% of the maximum response compared to triiodothyronine (T3) in an in vitro functional assay for THR-β activation, with an EC_{50} of 0.21µM (Kelly et al. 2014).
Active moieties	Resmetirom
QT prolongation	In a thorough QT study, resmetirom did not prolong the QTcF interval at a dosage of 200 mg once daily (2 times the maximum recommended dose) (refer to the IRT-QT review in DARRTS under IND 122865, dated June 15, 2023).
General Information	
Bioanalysis	Plasma concentrations of resmetirom and metabolite MGL-3623 were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Bioanalytical methods were adequately validated.
Healthy subjects vs. patients	PK in NASH patients with fibrosis stage F2 or F3 was consistent with that in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 6. Mean (CV%) Resmetirom Estimated Systemic Exposure Parameters at Steady State in Subjects With NASH by Dose** **PK Parameter** — **Resmetirom 80 mg QD** — **Resmetirom 100 mg QD** C_{max} (ng/mL) — 778 (41.5) — 971 (40.9) AUC_{tau} (ng*h/mL) — 5850 (60.5) — 7780 (65.5) Source: Table 4, Population PK Report MADR-PMX mgL3196-2382_PK Note: Fibrosis stage was not found to impact resmetirom PK. Resmetirom exposure is similar between NASH patients with fibrosis stages F2 and F3 (estimated effect of fibrosis stage F3 on resmetirom CL/F=-0.02 [95% CI: -0.09, 0.05]) Abbreviations: AUC_{tau}, area under the concentration-time curve from time 0 to the dosing interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic; QD, once daily
Range of effective dose(s) or exposure	In phase 3 study, Trial MGL-3196-11, resmetirom 80 and 100 mg QD were evaluated. Histopathology results at Month 12 indicated that both doses demonstrated improvement over placebo in (1) the proportion of subjects with resolution of steatohepatitis and no worsening of liver fibrosis, and (2) the percentage of subjects with improvement

Characteristic	Drug Information
	in liver fibrosis with no worsening of steatohepatitis. A dose-dependent increase in response rate was not observed between 80 mg and 100 mg.
Maximally tolerated dose or exposure	A maximally tolerated dose was not determined. In MGL-3196-11, among subjects treated with resmetirom, a greater proportion of subjects in the 100 mg arm discontinued relative to subjects in the 80 mg arm. Diarrhea was determined to be the most common cause for treatment discontinuation, and the exposure-adjusted incidence rate for diarrheal episodes leading to treatment discontinuation was greater in the 100 mg arm relative to the 80 mg arm. In healthy subjects, multiple doses up to 200 mg once daily were studied and were well tolerated.
Dose proportionality	Resmetirom exposure increased in an approximately dose-proportional manner—approximately a 2.5-fold and 2.9-fold increase in mean C_{max} and AUC, respectively—between doses of 40 and 100 mg (2.5-fold increase in dose), and in a greater-than-dose-proportional manner—approximately a 5.6-fold increase in mean AUC and a 4.3-fold in mean C_{max}—between doses of 100 and 200 mg (2-fold increase in dose).
Accumulation	Following repeated once-daily dosing of 80 or 100 mg, resmetirom exhibited 1.5- to 3-fold accumulation in healthy subjects. Following once-daily dosing, the % ratio of $AUC_{(0-24)}$ for MGL-3623/resmetirom decreased from 73.5% at 60 mg to 17.1% at 200 mg, suggesting saturation of metabolism of resmetirom to MGL-3623 at higher doses.
Time to achieve steady state	3 to 6 days with once-daily dosing
Bridge between to-be-marketed and clinical trial/study formulations	The proposed to-be-marketed formulation differs from that used in the phase 3 studies via implementation of a tablet color change. The Applicant provided comparative dissolution data to compare these formulations. The biopharmaceutics review found the comparative dissolution data acceptable to bridge the phase 3 tablet formulation and the to-be-marketed tablet formulation. Refer to the Integrated Quality Review in DARRTS, dated January 29, 2024 (reference ID: 5318570).
Absorption	
Bioavailability	Absolute bioavailability was not determined.
T_{max}	The median T_{max} in healthy subjects was approximately 4 hours
Food effect (fed/fasted) Geometric least square mean and 90% CI	A food effect on PK of resmetirom was assessed in healthy subjects at steady state at a resmetirom dosage of 100 mg QD. In the fed state, a high-fat breakfast was administered approximately 30 minutes before administration of resmetirom. Compared to dosing under fasted condition on Day 9, the PK after dosing under fed-condition on Day 14 decreased mean $_{Cmax}$ by 33% and AUC by about 10%. By Day 9, steady state should have been attained. **Table 7. Geometric Mean Ratios (90% CI) (Fed/Fasted) for C_{max} and AUC_{0-24}, and Effect on T_{max}** C_{max} | AUC_{0-24} | T_{max} 0.67 (0.50, 0.89) | 0.89 (0.79, 1.01) | Median T_{max} delayed from 4 hours (fasted) to 6 hours (fed) Source: Clinical Study Report for MGL-3196-09 Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; MGL-3196, resmetirom; T_{max}, median time to maximum concentration
Distribution	
Volume of distribution	The mean (CV%) apparent Vd at steady state (Vd/F) in patients with NASH was 68 L (227%)

Characteristic	Drug Information
Plasma protein binding	>99% protein-bound
Drug as substrate of transporters	Resmetirom is a substrate for OATP1B1, OATP1B3, and BCRP, but not for MRP-2
Elimination	
Mass balance results	In a mass balance study, of the administered radioactive dose, about 67% was recovered in feces, mostly as metabolites, and 24% was recovered in 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. No individual metabolite accounted for more than 10% of the total radiolabeled administered dose in feces. In plasma, MGL-3196 was the major radioactive component (55.22% based on AUC) with MGL-3623 as the most abundant metabolite (16%). Oxalic acid metabolite was observed in plasma (14.5%) but not in urine. Mean plasma $t_{1/2}$ of total radioactivity was 34 hours. Per the Applicant, circulating human plasma levels of oxalic acid are about twice as high as those formed from a 100 mg dose of MGL-3196 (0.5-1.9 micromol).
Clearance	The mean (CV%) steady state CL/F in patients with NASH was 17.5 L/h (56.3%).
Half-life	The median terminal plasma $t_{1/2}$ of resmetirom in NASH subjects was 4.5 hours.
Metabolic pathway(s)	Resmetirom is extensively metabolized following oral administration. Resmetirom is a substrate of CYP2C8. In a clinical DDI study, administration of steady state resmetirom in the presence of steady state clopidogrel, a moderate CYP2C8 inhibitor, led to a 1.7-fold increase in resmetirom AUC.
Primary excretion pathways (% dose)	Following administration of a radiolabeled resmetirom in oral suspension of 100 mg resmetirom at steady state, the average percent recovery of radioactivity was 91%, mostly within 72 hours postdose. Fecal excretion was the primary excretion pathway (67% of the dose). Biliary excretion was observed in animal studies.
Intrinsic Factors and Specific Populations	
Body weight	Body weight is a significant covariate of PK. Resmetirom exposure is lower in patients with higher body weight. A weight-based dosage is recommended in patients with a body weight cutoff of 100 kg. Refer to Section 8.1.
Age	No clinically significant differences in PK based on age (>65 years old).
Renal impairment	Population PK analyses indicated no clinically significant differences in PK based on mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2). Resmetirom has not been studied in patients with severe renal impairment.
Hepatic impairment	Resmetirom AUC was 1.3-fold, 2.7-fold, and 19-fold higher in subjects with mild, moderate, and severe hepatic impairment (Child-Pugh A, B, and C), respectively, compared to subjects with normal hepatic function. Resmetirom C_{max} was 1.2-fold, 1.7-fold, and 8.1-fold higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function Following repeated once-daily dosing with 80 mg, 1.2- to 2.8-fold accumulation in resmetirom AUC_{tau} was observed among non-NASH subjects with hepatic impairment.

Characteristic	Drug Information

Table 8. Mean (CV%) PK Parameters of Resmetirom and Major Metabolite in Subjects With Normal Hepatic Function and Non-NASH Patients With Hepatic Impairment Following 80 mg Once-Daily for 6 Days

Drug or Metabolite PK Parameter	Normal Hepatic Function (N=7)	Mild HI (Child-Pugh A) (N=10)	Moderate HI (Child-Pugh B) (N=9)	Severe HI (Child-Pugh C) (N=3)
Resmetirom				
$C_{max,ss}$ (ng/mL)	1070 (51.0)	1390 (67.8)	1830 (47.5)	7730 (17.4)
$AUC_{tau,ss}$ (ng*h/mL)	5100 (51.5)	5570 (66.4)	15100 (65.8)	97600 (39.0)
$AUC_{last,ss}$ (ng*h/mL)	5090(51.8)	5560 (66.5)	14600 (82.1)	148000 (51.8)
MGL-3623				
$C_{max,ss}$ (ng/mL)	420 (38)	635 (47.5)	566 (18)	826 (26)
$AUC_{tau,ss}$ (ng*h/mL)	2490 (35.5)	3210 (39.7)	4900 (57)	14500 (38.8)
$AUC_{last,ss}$ (ng*h/mL)	2480(35.7)	3210 (39.7)	5510 (65.4)	25200 (47.8)

Source: Table 3, Report MC19R-0032 for Trial MGL-3196-10

Abbreviations: $AUC_{last,ss}$, area under the plasma concentration curve from time 0 to the last detectable time point at a steady state; $AUC_{tau,ss}$, area under the curve over the dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; CV, coefficient of variation; HI, hepatic impairment; MGL-3196, resmetirom; N, number of subjects in treatment arm; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic

In Trial MGL-3196-10, mean AUC and C_{max} in NASH cirrhosis patients with mild hepatic impairment (Child-Pugh Class A; n=20) were 18% lower and 19% lower, respectively, compared to noncirrhotic NASH subjects (n=8) following repeated 100 mg once-daily dosing of resmetirom for 6 days. One NASH cirrhosis subject with moderate HI (Child-Pugh B) had 11-fold higher AUC (114000 ng*h/mL) compared to mean AUC of 9780 ng*h/mL in cirrhotic NASH with mild HI (n=10).

Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	In vitro, resmetirom is an inhibitor of CYP2C8, UGT1A4, and UGT1A9. In a clinical DDI study, the AUC of pioglitazone, a moderate sensitive CYP2C8 substrate, increased 1.4-fold when co-administered with resmetirom.

Characteristic	Drug Information
Inhibition/induction of transporter systems	In vitro studies predict DDI potential via inhibition of BCRP by resmetirom. Resmetirom inhibits OATP1B1, OATP1B3, OAT3, and BSEP transporters. In clinical DDI studies, resmetirom increased exposure to multiple statins, which may have been mediated via inhibition of OATP1B1 and/or OATP1B3: • Atorvastatin: 1.4-fold increase in AUC in the presence of 100 mg QD resmetirom • Pravastatin: 1.4-fold increase in AUC in the presence of 100 mg QD resmetirom • Rosuvastatin: 1.8-fold increase in AUC in the presence of 200 mg QD resmetirom • Simvastatin: 1.7-fold increase in AUC in the presence of 100 mg QD resmetirom

Source: Module 2.7.2, Summary of Clinical Pharmacology; Module 2.7.1, Summary of Biopharmaceutic Studies; Population PK Report MADR-PMX mgL3196-2382_PK; Clinical Study Reports for MGL-3196-07 and MGL-3196-09)

Abbreviations: AUC, area under the concentration-time curve; $AUC_{tau,ss}$, area under the curve over the dosing interval at steady state; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CL/F, apparent clearance; CYP, cytochrome P450; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; eGFR, estimated glomerular filtration rate; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; QD, once daily; T_{max}, median time to maximum concentration; UGT, uridine 5'-diphospho (UDP) glucuronosyltransferase; Vd/F, apparent volume of distribution

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

In the placebo-controlled, phase 3 trial conducted in subjects with biopsy-proven NASH and fibrosis, MGL-3196-11, two dosages of resmetirom were evaluated: 80 and 100 mg QD. These dosages were also evaluated in a separate placebo-controlled, phase 3 trial conducted in subjects with NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH", MGL-3196-14.

Dose Rationale for Phase 3

Phase 2 Trial (MGL-3196-05)

The doses for the pivotal phase 3 study were selected based on the results of phase 2 study, Trial MGL-3196-05. MGL-3196-05 was a randomized, double-blind, placebo-controlled study conducted in subjects with biopsy-proven NASH and fibrosis stage 1 to 3 (main study) with an open-label extension study. All subjects were randomized 2:1 to receive 80 mg resmetirom or placebo QD for 36 weeks. At Week 4, doses were adjusted based on measurements of pharmacokinetics (PK) and SHBG that were drawn at Week 2 (Table 9). Subsequently, in a protocol amendment, doses could be further adjusted later than Week 4 or based on levels of free T4 (refer to Section 14.2.13).

Table 9. Dose Adjustment Scheme at Week 4, Trial MGL-3196-05

Conditions at Week 2	Week 4 Dose
Combined AUC_{inf} (resmetirom+MGL-3623) >11000 ng*h/mL AND SHBG change from baseline >150%	40 mg
Combined AUC_{inf} (resmetirom+MGL-3623) >11000 ng*h/mL with SHBG change from baseline <150%	60 mg[a]
Combined AUC_{inf} (resmetirom+MGL-3623) >5500 ng*h/mL	60 mg
Combined AUC_{inf} (resmetirom+MGL-3623) ≤5500 ng*h/mL	80 mg
Combined AUC_{inf} (resmetirom+MGL-3623) ≤3000 ng*h/mL	100 mg

Source: Reviewer-generated table derived from CSR for Trial MGL-3196-05
[a.] Under this condition, predose concentrations and SHBG were measured at Week 4. At Week 4, if SHBG change from baseline was >150% and predose concentrations were >40 ng/mL for both resmetirom and MGL-3623, then the dose was reduced to 40 mg at Week 8
Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 to infinity; SHBG, sex hormone binding globulin

A total of 125 subjects were enrolled in the main study, including 84 subjects randomized to resmetirom, and 41 subjects randomized to placebo. At Week 4, most subjects in the resmetirom arm either had doses reduced to 60 mg or continued at a dose of 80 mg (N=73). By the end of the treatment period, 31 subjects received 60 mg and 29 subjects remained on 80 mg resmetirom.

Of note, the dosage adjustment based on PK may have allowed knowledge of treatment and dose. However, the Applicant indicated that dose adjustments were determined by an unmasked medical monitor, while the Applicant, subjects, investigators, and study personnel were masked to treatment assignment throughout the study.

At Week 36, subjects randomized to resmetirom had greater absolute and relative reductions in hepatic fat fraction, as measured by MRI-PDFF, relative to subjects randomized to placebo. Reductions were greater for subjects who received resmetirom relative to placebo and were numerically greater among subjects who received 80 mg relative to subjects who had doses adjusted to 60 mg at Week 4 (mean [standard error] absolute change from baseline of -8.0 (1.2) and -10.8 (1.2) for 60- and 80 mg groups, respectively, relative to -2.5 (1.1) for the placebo group). In addition, a greater proportion of subjects who received resmetirom relative to those receiving placebo were considered NASH resolution responders (ballooning score of 0 and inflammation score of 0 or 1, with at least a 2-point reduction in the NAFLD Activity Score [NAS] without an increase in fibrosis) based on liver biopsies collected at Week 36. NASH resolution response was greater for subjects who received resmetirom relative to placebo and was numerically greater for subjects receiving 80 mg resmetirom relative to subjects who had doses adjusted to 60 mg at Week 4 (19.4% and 39.4% for the 60 and 80 mg groups, respectively, relative to 6.5% for the placebo group) (refer to Section 14.2.13).

Subjects who completed the main study and met inclusion criterion for significant elevation in liver enzymes at Week 30 were eligible for enrollment in the 36-week open-label extension study. Subjects who received resmetirom in the main study remained on the same dose of resmetirom or had a prespecified increase in dose. Subjects who initially received placebo received 80 mg resmetirom with an option for dose adjustment to 40 to 120 mg based on measurements of PK and SHBG at Week 2 (refer to Section 14.2.13).

In the 36-week open-label extension study, 31 subjects were enrolled, including 17 subjects and 14 subjects who initially received resmetirom or placebo, respectively. Six out of 31 subjects received 100 mg, and had numerically greater reductions in MRI-PDFF relative to subjects on 80 mg. The interpretation of dose-response relationship between 80 mg and 100 mg is limited due to the differences in total duration of treatment, limited sample size at 100 mg, and open-label nature of the assessment (refer to Section 14.2.13).

Based on data from Trial MGL-3196-05, doses of 80 and 100 mg were selected for evaluation in phase 3.

Dose/Exposure-Response Relationships in Phase 3 Trial (MGL-3196-11)

Dose-Response

Trial MGL-3196-11 enrolled a total of 1,050 subjects, including 352 subjects randomized to 80 mg QD resmetirom, 349 subjects randomized to 100 mg QD resmetirom, and 349 subjects randomized to placebo. Most of the randomized population presented with fibrosis stage F2 (332/1,050; 32%) or F3 (558/1,050; 53%) on baseline histology. Compared to placebo treatment, both 80 mg and 100 mg showed statistically significant effects on both primary endpoints, i.e., resolution of steatohepatitis with no worsening of liver fibrosis (NASH resolution), or improvement in liver fibrosis and no worsening of steatohepatitis (fibrosis response) at month 12. However, there was no dose-dependent increase in response rate in either primary endpoint based on consensus biopsy reads. Refer to Sections 6.2 and 6.3.2 for additional details on efficacy results.

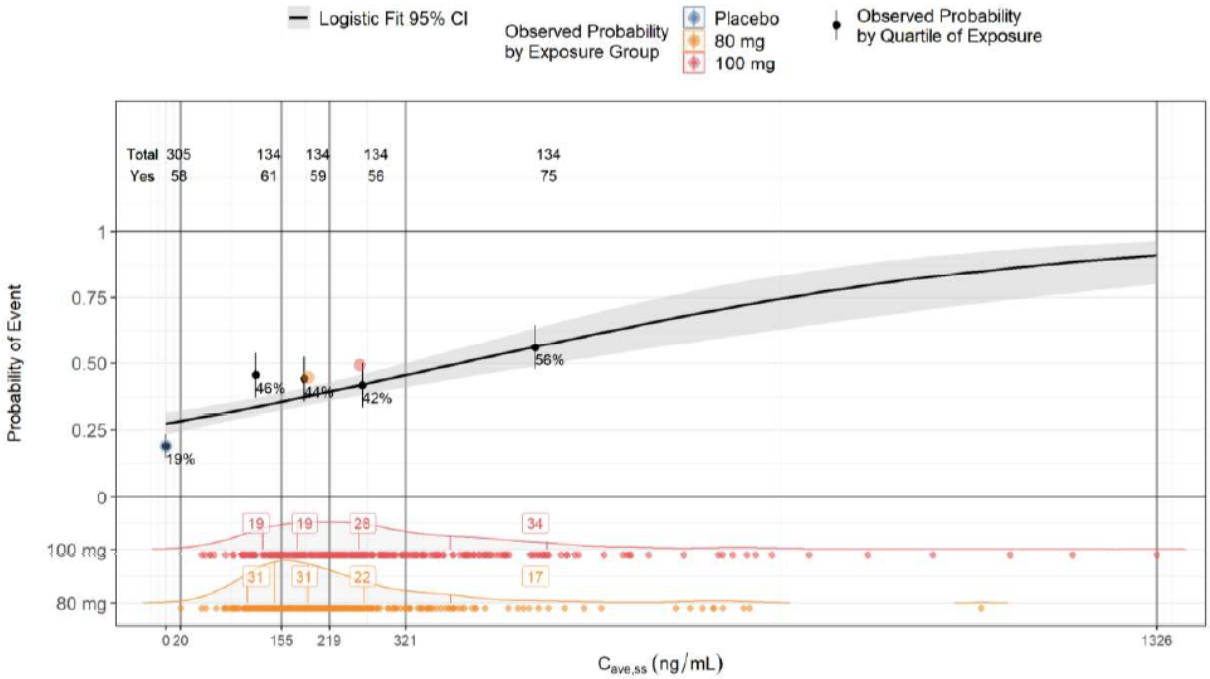
In MGL-3196-11, absolute and percent reductions in hepatic fat fraction at Month 12, as measured by MRI-PDFF, were greater for subjects receiving resmetirom relative to placebo and

were numerically greater for subjects in the 100 mg arm relative to subjects in the 80 mg arm (mean [standard error] absolute change from baseline of -7.1 (0.5) and -8.5 (0.5) for 80 and 100 mg groups, respectively, relative to -2.0 (0.4) for the placebo group). However, change from baseline to Month 12 in hepatic steatosis as measured by FibroScan controlled attenuation parameter was comparable between both arms (refer to Section 14.2.14).

Exposure-Response

The Applicant conducted exposure-response (E-R) analyses based on the probability of achieving NASH resolution or fibrosis response at Week 52 in Trial MGL-3196-11 (Figure 1). There was a shallow E-R relationship, primarily driven by the highest exposure quartile, showing the probability of achieving NASH resolution or fibrosis response increases with increasing average concentration at steady state ($C_{ave,ss}$). Subjects in all exposure quartiles had greater probability of achieving efficacy over placebo. The systemic exposure between two dose groups was largely overlapped as expected for a small difference between doses with a larger PK variability, although a greater proportion of subjects in the 100 mg dose group fell into the highest exposure quartile relative to those in the 80 mg dose group (34% versus 17%, respectively). Note that the 25% difference in the dose between 80 and 100 mg falls within the observed PK variability for maximum plasma concentration (C_{max}) (41% to 42%) and area under the concentration-time curve (AUC) (61% to 66%).

Figure 1. Exposure-Response for the Probability of NASH Resolution or Fibrosis Response at Week 52, Trial MGL-3196-11



Source: Figure 16, page 42, Exposure-Response Report MADR-PMX mgL3196-2382-ER
Note: The efficacy response (yes/no) was a combination of NASH resolution and fibrosis response. A subject was considered a responder if one of the conditions was held.
Note: The upper panel presents the total number of subjects in each quartile and total response ("Yes") in each quartile.
Note: The middle panel includes model-predicted probability of response (black line) with 95% CI (gray shaded area). The observed response for placebo and each exposure quartile is presented with a black circle. The orange and red circles show the observed probability in the 80 and 100 mg dose groups, respectively.
Note: The lower panel shows the distribution of $C_{ave,ss}$ for the 80 and 100 mg doses at Week 52. Numbers in the boxes represents the percentage of subjects in each quartile. The orange and red circles represent individual values for the 80 and 100 mg doses at Week 52, respectively.
Abbreviations: $C_{ave,ss}$, average concentration at steady state

The E-R relationship for the pharmacodynamic (PD) biomarker, liver fat content measured by MRI-PDFF, was also explored using pooled PK and PD data from Trials MGL-3196-11 and MGL-3196-14 based on the probability of achieving at least 30% or at least 50% reduction in MRI-PDFF at Week 52. The probability of achieving at least 30% or at least 50% reduction in the liver fat content MRI-PDFF increases with increasing $C_{ave,ss}$ (refer to Section 14.5.2.3). Note that MGL-3196-14 enrolled subjects with NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH."[2] Thus, subjects enrolled in MGL-3196-14 may represent a different population from that enrolled in MGL-3196-11, as subjects did not need to demonstrate biopsy-confirmed NASH.

[2] Eligible patients were defined as having a FibroScan ≥5.5 to <8.5 kPa; CAP ≥280 $dB \cdot m^{-1}$ OR MRE ≥2.0 to <4.0 kPa with MRI-PDFF ≥8% liver fat. Patients with biopsy-proven NASH/NAFLD with steatosis were also eligible for enrollment.

Dose Recommendation

The recommended weight-tiered dosage is 80 mg daily for patients weighing less than 100 kg and 100 mg daily for patients with body weight (BW) of 100 kg or higher. Resmetirom can be administered with or without food.

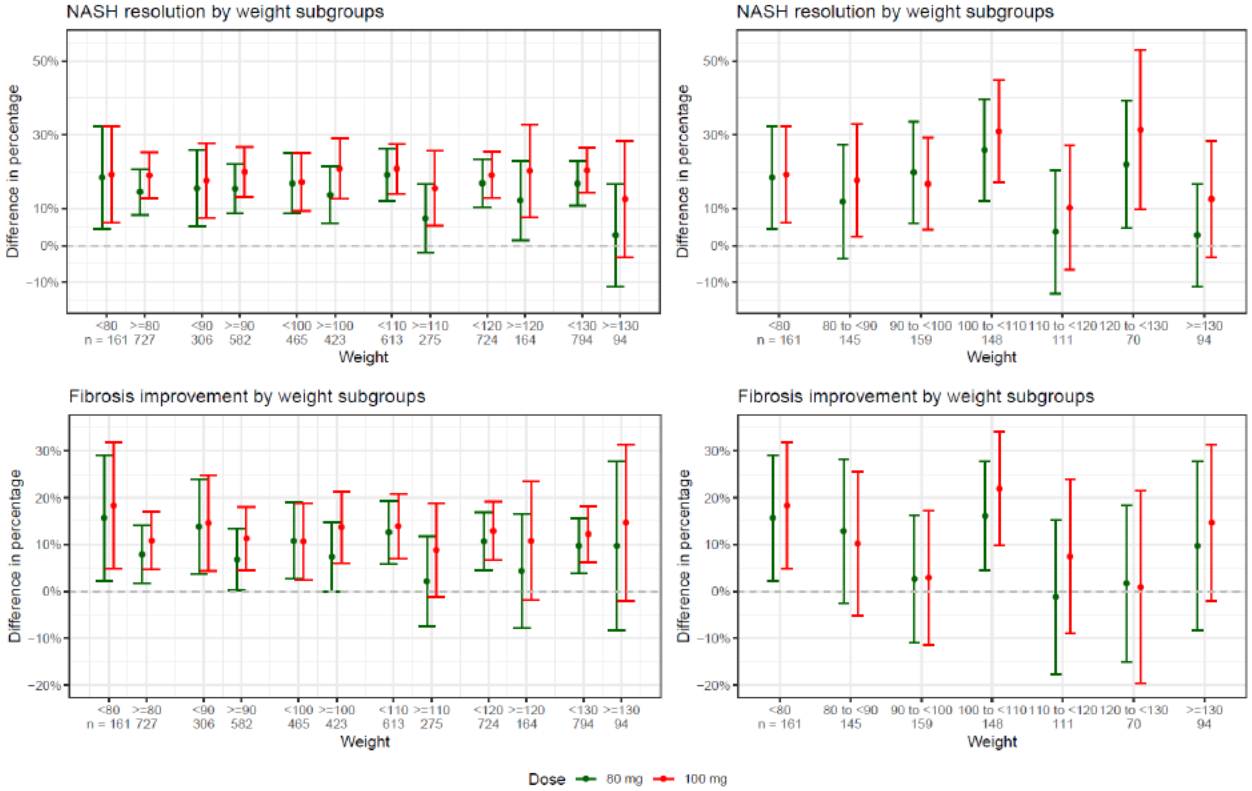
Of note, the clinical benefit of resmetirom will be further confirmed in the ongoing study (Trial MGL-3196-11), in which both 80 mg and 100 mg will continue to be studied. Doses higher than 100 mg have not been studied in NASH patients.

(b) (4)

In Trial MGL-3196-11, there was no clear dose-dependent trend between dosages of 80 and 100 mg in achieving either the primary endpoint of NASH resolution or fibrosis response. Refer to Section 6.3.2. Thus, 80 mg is the *lowest effective dose* and is an appropriate dose for the general patient population.

However, BW was identified as a significant covariate affecting the PK of resmetirom, such that subjects with higher BW have lower exposure to resmetirom (refer to Section 14.5). There were no appreciable differences between two doses for efficacy (i.e., NASH resolution or fibrosis response) across BW subgroups (Figure 2) (refer to Section 6.2.1.4). Nevertheless, the response rates trended down in subjects weighing >110 kg (Figure 2). Meanwhile, an analysis of resmetirom exposure by BW indicated that a higher dosage of 100 mg administered to subjects weighing 100 kg or greater will yield comparable PK across patients of all BW. Therefore, 100 mg dose for patients weighing >100 kg is recommended, considering a potentially suboptimal efficacy in this weight group.

Figure 2. Difference in the Responder Percentages Comparing Resmetirom Group to Placebo Group by Body Weight Subgroups—Lefthand Graphs, Comparison Between Subgroups by Different Body Weight Cutoff; Righthand Graphs, Efficacy Across Body Weight Cohorts



Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Note: These estimates/bars represent treatment effects compared to placebo (i.e., the difference in the responder percentages comparing resmetirom group to placebo group).
Abbreviations: NASH, nonalcoholic steatohepatitis

(b) (4)

Per protocol, dosage reductions in MGL-3196-11 and MGL-3196-14 were based on levels of free T4 and occurred in few numbers of subjects (N=22 in double-blind arms). Similarly, there was only one dosage adjustment for intolerance, however, criteria for intolerance (b) (4) are not well defined. Thus, the data are insufficient to recommend any dosage reductions for intolerance.

No dosage adjustment for patients ≥65 years is recommended as no trend in efficacy or safety was observed across age subgroups (refer to Section 6.2.1.4, 7.6.2.9 and 7.6.1.9). In addition, age was not identified as a significant covariate affecting the PK of resmetirom (refer to Section 14.5).

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

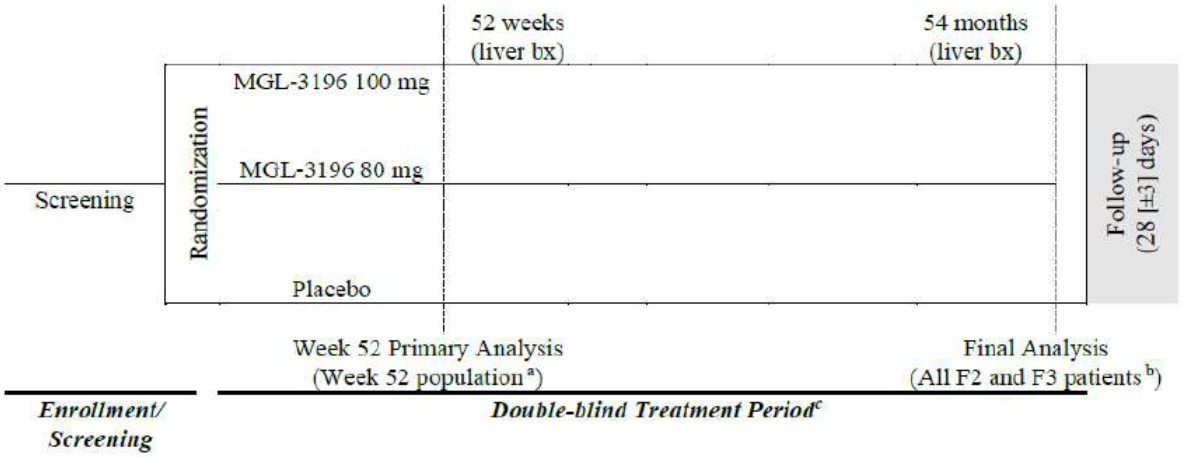
6.2.1. Trial MGL-3196-11

6.2.1.1. Design, Trial MGL-3196-11

Trial MGL-3196-11 is an ongoing double-blind, randomized, placebo-controlled, multicenter, phase 3 trial evaluating resmetirom 80 mg daily and resmetirom 100 mg daily versus placebo. The trial consists of an up-to-8-week screening period, a 54-month treatment period, and a 28 (±3)-day follow-up period. An interim analysis of surrogate endpoints at Week 52, which are considered reasonably likely to predict clinical benefit in the target patient population, was conducted to support an accelerated approval and is the focus of this review. The trial is ongoing to capture events that comprise the composite clinical benefit endpoint evaluated at the end of the trial to support a traditional approval.

Eligible participants with a histological diagnosis of NASH with liver fibrosis based on a screening biopsy were randomized in a 1:1:1 ratio to receive resmetirom 100 mg, resmetirom 80 mg, or matching placebo for the duration of the study. Randomization was stratified by type 2 diabetes status (presence/absence) and fibrosis stage (1, 2, or 3). Resmetirom or placebo was given orally QD in the morning. Figure 3 depicts the trial design.

Figure 3. Schematic, Trial MGL-3196-11



Source: Protocol MGL-3196-11 Version 6.0 Figure 2 (page 82)
Note: Liver bx = biopsy will be required 52 weeks and 54 months after randomization.
a. The Week 52 primary analysis to assess the NASH resolution response and fibrosis response conducted on the mITT-LB-W52 population.
b. The final primary analysis of the composite clinical outcome endpoint will occur when all subjects have completed the study (or discontinued early).
Abbreviations: F2, fibrosis stage 2; F3, fibrosis stage 3; LB, liver biopsy; mITT, modified intent-to-treat; NASH, nonalcoholic steatohepatitis

The first participant was enrolled on June 20, 2019. The Week 52 interim analysis was planned to occur after all participants with fibrosis stage 1B, 2, and 3 who were randomized on or before July 31, 2021, reached their Week 52 visit and completed liver biopsy (including subjects who

discontinued before reaching the planned Week 52 visit). The database lock for this planned Week 52 interim analysis occurred on November 18, 2022.

Liver biopsies were planned at screening, Week 52, and Month 54. Two pathologists (pathologists A and B, if referred to individually) read the liver biopsies in Trial MGL-3196-11. To determine the participant eligibility for enrollment in the trial, a single pathologist (pathologist A or pathologist B) evaluated the screening liver biopsy (hereinafter referred to as the "eligibility read").

Table 10 presents the NASH clinical research network (CRN) scoring system used to determine eligibility at enrollment and for assessment of the histological endpoints. The first three histological features in the table are the three components for which the scores are added to calculate the NAFLD activity score (NAS): steatosis, ballooning, and lobular inflammation. The last histological feature in the table shows the stage of fibrosis, which ranges from stage 0, indicating no fibrosis, to stage 4, indicating cirrhosis. Eligibility criteria (refer to Section 6.2.1.2) included participants with fibrosis stage 1A/1C, 1B, 2, or 3, in addition to NAS greater than or equal to 4, with a score of at least 1 on steatosis, ballooning, and lobular inflammation.

Table 10. NASH CRN Scoring System for Histological Assessment

Histological feature	Score	Category definition
Steatosis	0	<5%
	1	5–33%
	2	34–66%
	3	>66%
Hepatocyte ballooning	0	None
	1	Few
	2	Many
Lobular Inflammation	0	None
	1	1–2 foci per ×20 field
	2	2–4 foci per ×20 field
	3	>4 foci per ×20 field
Fibrosis	0	No fibrosis
	1A	Zone 3 mild perisinusoidal fibrosis
	1B	Zone 3 moderate perisinusoidal fibrosis
	1C	Periportal/portal fibrosis only
	2	Zone 3+periportal/portal fibrosis
	3	Bridging fibrosis
	4	Cirrhosis

Source: Protocol MGL-3196-11 Version 6.0 Table 6 (page 141)
Note: A score of ≥4 with steatosis and hepatocyte ballooning is generally considered diagnostic of NASH, but patients can still have NASH with lower NAS scores if steatosis and hepatocyte ballooning are present.
Abbreviations: CRN, clinical research network; NAS, nonalcoholic fatty liver disease (NAFLD) activity score; NASH, nonalcoholic steatohepatitis

Primary Endpoints for Week 52 Interim Analysis

The primary endpoints prespecified by the Applicant for the Week 52 interim analysis were:

- Resolution of NASH (0 for ballooning, 0 to 1 for inflammation) with an at least 2-point reduction in NAS and no worsening of fibrosis.
- At least a 1-point improvement in fibrosis stage and no worsening of NAS, where no worsening of NAS was defined as no worsening in the total of three NAS components (ballooning, inflammation, and steatosis).

The definitions of these endpoints differed from the endpoints specified in FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018). For the definition of the first endpoint, the guidance does not require "at least 2-point reduction in NAS." For the definition of the second endpoint, the guidance requires no increase in NAS for any individual component (ballooning, inflammation, and steatosis) instead of the Applicant's definition requiring no increase in total NAS. Refer to Section 6.3.2 for further discussion of the primary endpoints for Week 52 interim analysis.

Demonstrating statistical significance on at least one of the two Week-52 primary endpoints with appropriate control of type I error due to multiple endpoints was considered acceptable for accelerated approval.

Other Endpoints for Week 52 Interim Analysis

A key secondary endpoint, percent change in low-density lipoprotein-cholesterol (LDL-C) from baseline to Week 24, was prespecified to be included in the multiplicity adjustment for Week 52 interim analysis. During the IND development program, the Agency did not agree with this as a key efficacy endpoint, and communicated to the Applicant that effects on LDL-C would be considered as safety data or for exploratory purposes only.

Other secondary and exploratory endpoints based on biomarkers, noninvasive tests, and liver biochemistry were specified for the Week 52 interim analysis. Multiplicity adjustments for these endpoints were not prespecified. Therefore, these endpoints are considered exploratory. The Agency review focuses on the following secondary endpoints prespecified by the Applicant:

- Resolution of NASH (0 for ballooning, 0 to 1 for inflammation) with an at least 2-point reduction in NAS and at least a 1-point improvement in fibrosis stage.
- At least a 2-point improvement in fibrosis stage and no worsening of NAS, where no worsening of NAS was defined as no worsening in the total of three NAS components (ballooning, inflammation, and steatosis).
- Fibrosis stage reduced to stage 0.

The Agency also evaluated the following endpoints that were not prespecified by the Applicant to further understand the treatment effect:

- Resolution of NASH (0 for ballooning, 0 to 1 for inflammation) and at least a 1-point improvement in fibrosis stage (i.e., Applicant's endpoint above without the criterion for at least a 2-point reduction in NAS)

- At least a 2-point improvement in fibrosis stage and no worsening of NAS, where no worsening in NAS was defined as no worsening in any of the NAS components (ballooning, inflammation, and steatosis)
- Resolution of NASH (0 for ballooning, 0 to 1 for inflammation).
- At least a 2-point reduction in NAS.
- An improvement in ballooning by at least one point.
- An improvement in inflammation by at least one point.
- An improvement in steatosis by at least one point.
- At least a 2-point improvement in fibrosis stage.
- At least a 1-point improvement in fibrosis stage.

Primary Composite Clinical Benefit Endpoint to be Assessed at End of Study

The composite clinical endpoint was agreed upon between the Applicant and the Agency during the development program, and is considered a clinically meaningful composite, incorporating measures of worsening liver disease, such as progression to cirrhosis, hepatic decompensation events, liver transplant and all-cause mortality. The primary composite clinical benefit endpoint will be evaluated upon trial completion and is measured as the time to first occurrence of any of the following adjudicated events:

- Death (all cause)
- Liver transplant
- Significant hepatic events, including hepatic decompensation events:
  - Ascites
  - Encephalopathy
  - Gastroesophageal variceal hemorrhage
- Histological progression to cirrhosis
- Confirmed increase of model of end-stage liver disease score from <12 to ≥15

The trial is ongoing and participants continue to be assessed for these outcomes.

6.2.1.2. Eligibility Criteria, Trial MGL-3196-11

Participants were prescreened to include adults with at least three metabolic risk factors, elevated aspartate aminotransferase (AST), and no history of significant alcohol consumption. Either a historic liver biopsy within 2 years demonstrating NASH with fibrosis or FibroScan KpA ≥8.5 controlled attenuation parameter ≥280 was required to continue screening.

A complete listing of inclusion and exclusion criteria is in Section 15.

Key Inclusion Criteria

- Must be willing to participate in the study and provide written informed consent.
- Male and female adults ≥18 years.

- Contraception requirements for female participants of reproductive potential or male participants sexually active with a partner of childbearing potential.
- Suspected or confirmed NASH fibrosis suggested by historical data; meet one of the following criteria:
  - Historical biochemical test for fibrosis: N-terminal type III collagen propeptide (PRO-C3) >14 ng/mL; or enhanced liver fibrosis ≥9 (enhanced liver fibrosis 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, based on existing pathology review, with no significant change in BW >5% or medication that might affect NAS or fibrosis stage.
- MRI-PDFF fat fraction ≥8% obtained during the screening period (baseline MRI-PDFF).
- Biopsy-proven NASH based on 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, and 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), and lobular inflammation (scored 0 to 3).
- Estimated glomerular filtration rate (eGFR) ≥45 by the Modification of Diet in Renal Disease 6-variable formula.

Key Exclusion Criteria

- History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening.
- Regular use of drugs historically associated with NAFLD and known hepatotoxins for more than 4 weeks within the last 8 weeks prior to initial screening.
- Thyroid disease, including active hyperthyroidism or untreated hypothyroidism.
- 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 ≥5% total BW within 12 weeks prior to randomization.
- HbA1c >9.0%.
- Glucagon-like peptide 1 agonist therapy or high-dose Vitamin E (>400 IU/day) unless stable dosing for 24 weeks prior to biopsy.
- Presence of cirrhosis on liver biopsy defined as stage 4 fibrosis.
- Diagnosis of HCC.
- Model of end-stage liver disease score ≥12, as determined at screening, due to liver disease.
- Hepatic decompensation or impairment

- Chronic liver diseases, including primary biliary cholangitis, primary sclerosing cholangitis, Hepatitis B or C, and others.
- Active autoimmune diseases.
- Serum alanine aminotransferase (ALT) >250 U/L
- Stable doses for statins (doses for statin were restricted), fenofibrate, and pioglitazone (>15 mg were excluded).
- Platelet count <140,000/mm3
- Inability to safely obtain a liver biopsy.
- History of biliary diversion.
- Uncontrolled hypertension, arrhythmia, elevated QTcF interval, heart failure (New York Heart Association Class II or IV heart failure or known left ventricular ejection fraction <30%), or heart disease

6.2.1.3. Statistical Analysis Plan, Trial MGL-3196-11

Statistical Analysis Plan Amendments

There were major changes to the analysis plan for the Week 52 primary endpoints shortly before unblinding the results of the interim analyses. There were multiple correspondences between the Applicant and Agency shortly before unblinding regarding these changed analyses. These late changes were concerning as there was little to no time for FDA to review, and some changes were made after unblinding by the contract research organization (e.g., modification of the analysis of the key secondary endpoint and clarifications on sensitivity analyses in the second addendum of the SAP signed after unblinding and in the study report; refer to Table 23 and Section 16.3). This Section 6.2.1.3 presents the analyses as described in the final statistical analysis plan (SAP) and will point out major changes between the final and previous versions. Various analyses will be presented to investigate the impact of these changes on the overall conclusions.

Refer to Table 23 in Section 6.3.2 for relevant dates related to submission of the SAP. SAP Version 3.0 and the first SAP addendum was submitted to the Agency on the same day as unblinding of the trial, and the second SAP addendum was submitted to the Agency months after unblinding.

Histopathology Readings

To evaluate histologic outcomes for the Week 52 interim analysis, the two pathologists performed a *primary read* and *consensus read* of both the screening and Week 52 liver biopsies. Table 11 describes these different histopathology readings. Refer to Section 16.1 for additional details of the primary read.

Table 11. Histopathology Readings for Screening and Week 52 Liver Biopsies for Week 52 Interim Analysis, Trial MGL-3196-11

Reading Timepoint	Reading Process
At Screening	
Eligibility read	One pathologist read screening liver biopsy. Pathologist A, or pathologist B in absence of pathologist A, was planned to perform eligibility read. For Week 52 interim analysis, pathologist A performed all eligibility reads.
Evaluation for Week 52 Analyses	
Primary read	Two pathologists independently read batches of screening and batches of Week 52 liver biopsies. Pathologists were blinded to treatment assignment. The screening and Week 52 liver biopsies for each participant were not paired and the pathologists were unblinded to the timing of the liver biopsies.
Consensus read[1]	If the two pathologists agreed on the responder status according to the Applicant's prespecified primary endpoints for the Week 52 interim analysis based on the primary read, the consensus responder status corresponded to the pathologists' primary read assessment. If the two pathologists disagreed on the responder status, the two pathologists read the liver biopsies together to reach consensus on the responder status. Only scores for the histological features that caused responder status disagreement were reread. The two pathologists were not blinded to scores from the primary read but blinded to who rated the scores at primary read. The allowable scores for the consensus scores were bounded by the minimum and the maximum scores from the primary read. Given that the Applicant's process for an additional reading by consensus only occurred if there was a disagreement on responder status for the primary endpoints, there was not a consensus score (neither a consensus read nor agreement between the two pathologists) for approximately 25% of screening liver biopsies. Following the Agency's request, a post hoc consensus read for these additional participants' baseline fibrosis stage was performed but did not include the three histological features in NAS.

Source: Statistical reviewer
Abbreviation: NAS, nonalcoholic steatohepatitis (NASH) activity score
[1] The consensus read process for responder status for the Week 52 endpoints occurred shortly before and after the Applicant unblinded the study; there was some additional consensus reading of baseline fibrosis stage among unaligned cases months after unblinding. Refer to Table 23 and Section 6.3.2 for additional details on the timing and other concerns with the consensus read process.

Refer to Section 6.3.2 for a discussion of concerns with the histopathology reading process for scoring the screening and Week 52 liver biopsies, and how that affects the definition of the analysis populations and primary efficacy endpoints for Week 52 interim analysis. Section 16.2.7 includes a summary of the prespecified evaluation of intra- and inter-rater reliability for the reading of liver biopsies.

Analysis Populations

The Applicant specified the primary analysis population for the histology endpoints to be the Week 52 liver biopsy modified intent-to-treat population, defined as all F1B, F2, and F3 participants who were randomized on or before July 31, 2021; this is excluding participants who

were missing a Week 52 biopsy due to the COVID-19 pandemic that resulted in study discontinuation and/or inability or delay (outside biopsy window) in obtaining the Week 52 biopsy. Refer to Section 6.3.1 regarding the inclusion of F1B in the analysis population.

Primary read refers to the two pathologists' reading at end of treatment, as described in Table 11; this includes a rereading of the baseline/enrollment liver biopsy. For the analysis population defined in SAP Version 3.0, participants with F3 fibrosis were defined as those where at least one pathologist rated the screening liver biopsy as F3 at primary read, and those where both pathologists rated as F4 at primary read; participants with F2 fibrosis were defined as those where one pathologist rated the screening liver biopsy as F2 and the other pathologist rated as F2 or lower at primary read; participants with F1B fibrosis were defined as those where both pathologists rated the screening liver biopsy as F1B at primary read.

The criterion excluding participants with a missing a Week 52 biopsy due to the COVID-19 pandemic was first proposed in an SAP submitted on October 20, 2022 (shortly before unblinding). The Agency did not agree with excluding such participants from the analysis and communicated this to the Applicant.

Refer to Section 6.3.2 for a discussion of the different ways of defining the primary analysis population. The primary analysis population used by the Agency includes all F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021—this includes participants with a missing Week 52 biopsy due to the COVID-19 pandemic in the analysis; the prespecified methods are used to handle missing data. The Agency's analyses will focus on this analysis population, and analyses using alternative definitions of the analysis populations are also explored for completeness in Section 6.3.2.

Primary Analysis Method for Week 52 Primary Endpoints

The Applicant's prespecified primary analysis considers a participant's outcome to be 1 if the two pathologists agree that the participant is a responder, 0.5 if the two pathologists disagree, and 0 if the two pathologists agree that the participant is a nonresponder. During the IND interactions, the Agency expressed concern with the clinical interpretability of the case where the pathologists disagree with the response status and a value of 0.5 is used in the analysis. The Applicant prespecified additional analyses evaluating the consensus reads or individual pathologist's reads where outcomes of 1 or 0 indicate responders or nonresponders, respectively.

For both types of analyses (evaluating outcomes 1, 0.5, 0 or 1, and 0), the prespecified primary efficacy analysis method was a Cochran-Mantel-Haenszel test stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (stage 2 or 3) comparing resmetirom 80 mg to placebo and resmetirom 100 mg to placebo.

For the analyses evaluating outcomes of 1, 0.5, and 0, the SAPs specified that 95% Wald CIs based on Mantel-Haenszel mean score statistic would be provided (Stokes et al. 2012). For analyses evaluating outcomes of 1 or 0, the SAPs specified that 95% stratified Newcombe CIs would be provided. The SAPs did not provide justification for the different choices of CIs.

Participants who experienced an intercurrent event of any components of the primary composite clinical benefit endpoint defined in Section 6.2.1.1 prior to the Week 52 biopsy would be handled using the composite strategy and considered a nonresponder. The SAP specified that the main efficacy results would use the treatment policy strategy to handle intercurrent events of

treatment discontinuation, i.e., data collected after treatment discontinuation would be included in the analysis. The Agency conducted additional analyses using a composite strategy to handle intercurrent events of treatment discontinuation, i.e., participants who discontinued study treatment are considered as nonresponders.

Section 6.3.2 discusses the concerns with the prespecified primary analysis for the Week 52 primary endpoints and presents results for the different choices of the primary analysis.

Missing Data and Sensitivity Analyses for the Week 52 Primary Endpoints

Primary Method for Handline Missing Data

The SAPs specified that the target study week (day) for Week 52 primary endpoints was Weeks 36 to 60 (Days 252 to 420). Participants without a liver biopsy or with a liver biopsy outside of the target analysis window were considered having missing values and were considered nonresponders in the primary analyses of the Week 52 primary endpoints.

Multiple Imputation Sensitivity Analysis

The SAPs specified a sensitivity analysis using multiple imputation (MI), though the details of the analysis changed across different SAP Addenda. Therefore, the Agency considered the results of multiple MI analyses to further assess the results of the primary analysis. Details of the MI analyses specified by the Applicant and analyses conducted by the Agency are described in Section 16.2.2.

Tipping Point Analysis

The SAPs did not prespecify a tipping point analysis for the Week 52 primary endpoints; however, the SAP Addenda (signed and submitted after unblinding the interim analysis) specified a tipping point analysis. The first SAP Addendum specified that tipping point analysis would be handled in the same way as MI except that the number of responders in each treatment group would be varied independently within the imputations for each pathologist, and no additional details were provided. The second SAP Addendum specified that the missing values in the resmetirom groups would be imputed as nonresponders, and the missing values in the placebo group would be imputed by varying the proportion of responders. The proportion of responders in the placebo group would vary from 0 to a proportion where the comparison to the resmetirom group becomes insignificant.

Because the tipping point analysis should ideally be two-dimensional (i.e., proportions of responders in both the treatment and the placebo groups should be varied), the Agency conducted its own tipping point analysis, evaluating different combinations of the proportions of responders in the treatment and the placebo groups for missing values in primary endpoints varying from 0% to 100% by 10% increments. The results from the Cochran-Mantel-Haenszel test used in the primary analysis are first transformed using the Wilson & Hilferty transformation (Wilson and Hilferty 1931) as described in (Ratitch et al. 2013) and then pooled across 100 imputed datasets using Rubin's rule (Rubin 1987).

Other Analyses

The SAPs prespecified an additional analysis for the Week 52 primary endpoints using a generalized estimating equation model, assuming that the scores from the two pathologists are repeated measurements (i.e., correlated binary outcomes) for the same subject with some within-subject correlation structure. Participants with missing values were considered nonresponders. Refer to Section 16.2.3 for details of the model specified by the Applicant. This analysis was the proposed primary analysis method in the Applicant's submission of the SAP to the IND on July 7, 2022, prior to the change in primary analysis, as described above, in the submission dated October 20, 2022.

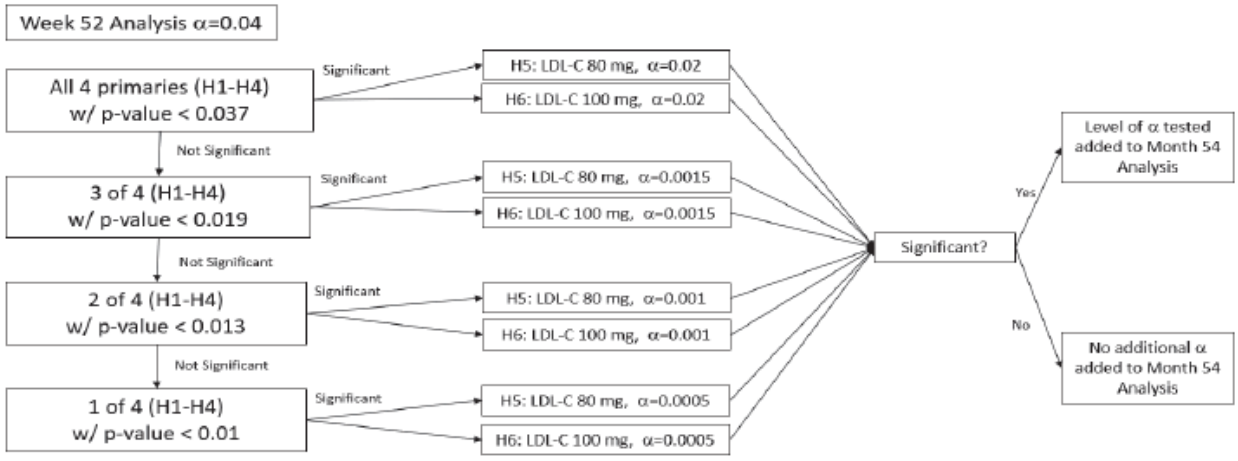
Type I Error Control

The testing hierarchy in Trial MGL-3196-11 is illustrated in Figure 4. The overall type I error rate for the study is controlled at the two-sided alpha=0.05 significance level. An alpha level of 0.04 was allocated to evaluate histological endpoints for the Week 52 interim analysis and an alpha level of 0.01 was allocated to the clinical outcome endpoint at the end of the trial, with the potential for propagation of alpha from the interim analysis to the final analysis.

A two-stage parallel gatekeeping procedure was used to test the primary and the key secondary endpoints for the two dose groups at Week 52 interim analysis. In the first stage, the two dose groups of resmetirom and the two histologic surrogate endpoints (i.e., four hypotheses) were tested using the truncated Hochberg procedure with a truncation parameter of 0.9. The remaining alpha from the first stage would be propagated to the second stage to test the key secondary endpoint for the two dose groups. Therefore, the key secondary endpoint would not be tested if none of the hypotheses in the first stage were significant. The key secondary endpoint would be tested for the two dose groups using the Bonferroni method.

An alpha of 0.01 plus any alpha propagated from the Week 52 interim analysis will be used for testing the composite clinical benefit endpoint at Month 54. The two dose groups will be tested using the Hochberg procedure for the Month 54 analysis.

Figure 4. Statistical Testing Process, Trial MGL-3196-11



Source: Statistical Analysis Plan MGL-3196-11 Version 3.0 Figure 2 (page 50)
Abbreviation: LDL-C, low-density lipoprotein cholesterol

Analysis of Key Secondary Endpoint

The SAP and second SAP addendum specified different methods for analyzing the key secondary endpoint evaluating the percent change from baseline to Week 24 in LDL-C. While the Agency has stated that this endpoint is not adequate to support efficacy, it is critical to know whether the key secondary endpoint reached statistical significance, as this determines whether alpha from the interim analysis can be propagated to the Month 54 analysis of clinical benefit endpoint.

Refer to details of the different analysis specifications in Section 16.3. The Agency conducted the analysis in multiple ways to ensure the results were not driven by the choice of a single statistical methodology.

Analysis of Other Endpoints

Other prespecified secondary endpoints and Agency-specified endpoints listed in Section 6.2.1.1 were analyzed using the same Cochran-Mantel-Haenszel test for the primary analysis of the Week 52 primary endpoints.

Analysis of Liver Enzymes

To evaluate the trend of liver enzymes in Trial MGL-3196-11, the Agency summarized ALT and AST by treatment groups from baseline to Week 52 using means and 95% Wald CIs.

6.2.1.4. Results of Analyses, Trial MGL-3196-11

Demographics, Baseline Histopathology Characteristics, and Subject Disposition

A total of 1,050 participants were enrolled and were randomized on or before July 31, 2021, in Trial MGL-3196-11, across 172 sites and 14 countries.

Table 12 presents the primary analysis population for histological endpoints specified by both the Applicant and by the Agency.

- The analysis population specified by the Applicant was defined as all F1B, F2, and F3 participants (as defined by the Applicant's algorithm based on primary reads) who were randomized on or before July 31, 2021, excluding participants who were missing a Week 52 biopsy due to the COVID-19 pandemic. This population included 955 participants, which excluded 84 participants who did not have baseline fibrosis stage 1B, 2, or 3 as defined by the Applicant based on primary reads, and additionally excluded 11 participants (3 in placebo arm, 6 in resmetirom 80 mg arm, and 2 in resmetirom 100 mg arm) who were missing a Week 52 biopsy due to the COVID-19 pandemic.
- The analysis population used by the Agency was defined as all F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021. This population included 888 participants.

Table 12. Study Populations, Trial MGL-3196-11

Study Population	Placebo n	Resmetirom 80 mg n	Resmetirom 100 mg n	Total n
Randomized by cutoff[1]	349	352	349	1,050
Analysis population specified by Applicant[2]	318	316	321	955
Analysis population used by Agency[3]	294	298	296	888

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt.
1. July 31, 2021.
2. Week 52 liver biopsy modified intent-to-treat population specified by the Applicant, which was defined as all F1B, F2, and F3 participants (as defined by Applicant's algorithm) who were randomized on or before July 31, 2021, excluding participants who were missing a Week 52 biopsy due to the COVID-19 pandemic. F3 fibrosis was defined as those where at least one pathologist rated the screening liver biopsy as F3 at primary read, and those where both pathologists rated as F4 at primary read; F2 fibrosis was defined as those where one pathologist rated the screening liver biopsy as F2 and the other pathologist rated as F2 or lower at primary read; F1B fibrosis was defined as those where both pathologists rated as F1B at primary read.
3. All F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021.
Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; F4, fibrosis stage 4; n, number of subjects in study population

Baseline fibrosis stage for all enrolled participants on or before July 31, 2021 is summarized in Table 13 by both the Applicant's algorithm described in the first bullet above and by eligibility read, as used to define the Agency's primary analysis population.

Table 13. Baseline Fibrosis Stage, All Enrolled Subjects Randomized on or Before July 31, 2021, Trial MGL-3196-11

Assessment Method Baseline Fibrosis Stage	Placebo N=349 n (%)	Resmetirom 80 mg N=352 n (%)	Resmetirom 100 mg N=349 n (%)	Total N=1,050 n (%)
Baseline fibrosis stage defined by Applicant's algorithm				
F1B[1]	18 (5.2)	16 (4.5)	15 (4.3)	49 (4.7)
F2[2]	112 (32.1)	107 (30.4)	100 (28.7)	319 (30.4)
F3[3]	191 (54.7)	199 (56.5)	208 (59.6)	598 (57.0)
Other[4]	28 (8.0)	30 (8.5)	26 (7.4)	84 (8.0)
Baseline fibrosis stage defined by eligibility read				
F1A	9 (2.6)	8 (2.3)	4 (1.1)	21 (2.0)
F1B	40 (11.5)	34 (9.7)	36 (10.3)	110 (10.5)
F1C	6 (1.7)	12 (3.4)	13 (3.7)	31 (3.0)
F2	110 (31.5)	110 (31.2)	108 (30.9)	328 (31.2)
F3	184 (52.7)	188 (53.4)	188 (53.9)	560 (53.3)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt.
1. Participants where both pathologists rated as F1B at primary read.
2. Participants where one pathologist rated the screening liver biopsy as F2 and the other pathologist rated as F2 or lower at primary read.
3. Participants where at least one pathologist rated the screening liver biopsy as F3 at primary read, and those where both pathologists rated as F4 at primary read.
4. The Applicant's datasets were inconsistent on a single baseline score of these participants, but these participants were rated as some combination of F0, F1A, F1B and F1C fibrosis by the two pathologists at primary read.
Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; N, total number of subjects; n, number of subjects in subset

Unless otherwise specified, the remainder of the results presented in this section will focus on the analysis population used by the Agency, defined as all F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021.

Table 14 presents the baseline demographic characteristics for the analysis population used by the Agency for efficacy evaluation. The demographics were generally balanced across the treatment groups. Most participants are younger than 65 years old (74%), white (89%), not Hispanic or Latino (78%), and enrolled from the United States (66%).

Table 14. Baseline Demographics in All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Demographic Category Characteristic	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296	Total N=888
Sex, n (%)				
Female	161 (54.8)	166 (55.7)	170 (57.4)	497 (56.0)
Male	133 (45.2)	132 (44.3)	126 (42.6)	391 (44.0)
Age (years)				
Mean (SD)	57.2 (10.9)	55.8 (11.4)	57.6 (10.5)	56.9 (11.0)
Median	58.0	57.0	59.0	58.0
Min, Max	22.0, 83.0	18.0, 81.0	22.0, 81.0	18.0, 83.0
Age category, n (%)				
<65 Years	215 (73.1)	231 (77.5)	214 (72.3)	660 (74.3)
≥65 Years	79 (26.9)	67 (22.5)	82 (27.7)	228 (25.7)
Race, n (%)				
American Indian or Alaska Native	3 (1.0)	4 (1.3)	1 (<1)	8 (<1)
Asian	9 (3.1)	9 (3.0)	8 (2.7)	26 (2.9)
Black or African American	9 (3.1)	5 (1.7)	5 (1.7)	19 (2.1)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	0	1 (<1)
White	255 (86.7)	268 (89.9)	267 (90.2)	790 (89.0)
Not Able to Collect	4 (1.4)	4 (1.3)	7 (2.4)	15 (1.7)
Not Reported	2 (<1)	0	3 (1.0)	5 (<1)
Other[1]	11 (3.7)	8 (2.7)	5 (1.7)	24 (2.7)
Ethnicity, n (%)				
Hispanic or Latino	46 (15.6)	64 (21.5)	76 (25.7)	186 (20.9)
Non-Hispanic or Latino	244 (83.0)	231 (77.5)	215 (72.6)	690 (77.7)
Not reported	2 (<1)	1 (<1)	1 (<1)	4 (<1)
Unknown	0	1 (<1)	2 (<1)	3 (<1)
Not able to collect	2 (<1)	1 (<1)	2 (<1)	5 (<1)
Region, n (%)				
United States (US)	192 (65.3)	190 (63.8)	205 (69.3)	587 (66.1)
Non-US	102 (34.7)	108 (36.2)	91 (30.7)	301 (33.9)

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
[1.] Specified race includes 1/2 African, 1/2 Switzerland; Caucasian and American Indian; Hispanic; Indian; Indian-Subcontinent; Italian; Mexican American Chicano/a; Middle East; Native/White; Mexican American; South American; White/Japanese.
Abbreviations: N, total number of subjects; SD, standard deviation

Table 15 presents the baseline disease characteristics for the analysis population used by the Agency for efficacy evaluation. The baseline disease characteristics were generally balanced across the treatment groups. Most participants have type 2 diabetes (69%), hypertension (79%), dyslipidemia (71%), and did not use thyroxine (86%) at baseline. Mean (SD) body mass index (BMI) was 36 (7) kg/m^2 and mean (SD) BW was 101 (23) kg. There were high amounts of missing data for baseline MRI-PDFF and magnetic resonance elastography, so descriptive

summaries of the observed data for these variables may not accurately represent the patient population enrolled in the study.

Table 15. Baseline Disease Characteristics in All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Baseline Characteristic Statistic	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296	Total N=888
BMI (kg/m^2)				
Mean (SD)	35.5 (6.4)	35.4 (6.5)	36.1 (7.3)	35.7 (6.8)
Median	34.4	34.6	34.9	34.7
Min, max	22.4, 58.2	21.8, 61.5	22.2, 67.8	21.8, 67.8
Weight (kg)				
Mean (SD)	100.3 (22.6)	99.9 (22.1)	101.7 (22.9)	100.6 (22.5)
Median	99.0	96.6	99.6	98.8
Min, max	57.4, 184.4	55.4, 185.1	52.0, 173.3	52.0, 185.1
Type 2 diabetes, n (%)				
Yes	198 (67.3)	208 (69.8)	202 (68.2)	608 (68.5)
No	96 (32.7)	90 (30.2)	94 (31.8)	280 (31.5)
Hypertension, n (%)				
Yes	237 (80.6)	225 (75.5)	238 (80.4)	700 (78.8)
No	57 (19.4)	73 (24.5)	58 (19.6)	188 (21.2)
Dyslipidemia, n (%)				
Yes	205 (69.7)	211 (70.8)	217 (73.3)	633 (71.3)
No	89 (30.3)	87 (29.2)	79 (26.7)	255 (28.7)
LDL-C (mg/DL)				
Mean (SD)	106.3 (41.4)	106.6 (37.6)	102.4 (37.0)	105.1 (38.7)
Median	102.0	103.5	100.0	101.0
Min, max	25.0, 288.0	20.0, 224.0	22.0, 282.0	20.0, 288.0
Missing	0	0	1	1
Statin use, n (%)				
Yes	145 (49.3)	139 (46.6)	150 (50.7)	434 (48.9)
No	149 (50.7)	159 (53.4)	146 (49.3)	454 (51.1)
Thyroxine use, n (%)				
Yes	44 (15.0)	37 (12.4)	43 (14.5)	124 (14.0)
No	250 (85.0)	261 (87.6)	253 (85.5)	764 (86.0)
VCTE (kPa)				
Mean (SD)	13.1 (5.6)	13.3 (5.9)	13.8 (7.3)	13.4 (6.3)
Median	11.8	11.6	12.0	11.8
Min, max	4.8, 53.6	4.6, 42.8	4.3, 75.0	4.3, 75.0
Missing	12	11	9	32
CAP (db/M				
Mean (SD)	347.6 (36.6)	345.4 (37.1)	349.3 (39.2)	347.4 (37.7)
Median	350.0	348.0	350.0	349.0
Min, max	222.0, 400.0	203.0, 400.0	154.0, 400.0	154.0, 400.0
Missing	13	14	10	37
MRI-PDFF (%)[1]				
Mean (SD)	17.9 (6.7)	18.0 (6.7)	17.2 (6.7)	17.7 (6.7)
Median	17.0	17.0	16.4	16.6
Min, max	4.6, 36.3	2.5, 35.3	2.8, 35.9	2.5, 36.3
Missing	52	44	39	135

Baseline Characteristic Statistic	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296	Total N=888
MRE (kPa)				
Mean (SD)	3.5 (1.0)	3.6 (0.9)	3.8 (1.1)	3.6 (1.0)
Median	3.4	3.4	3.6	3.5
Min, max	2.0, 9.2	1.8, 7.9	2.0, 9.9	1.8, 9.9
Missing	124	138	122	384
FIB-4				
Mean (SD)	1.4 (0.7)	1.4 (0.7)	1.5 (0.8)	1.4 (0.7)
Median	1.3	1.3	1.4	1.3
Min, max	0.4, 4.6	0.2, 4.5	0.3, 5.7	0.2, 5.7
Missing	0	2	0	2
ELF				
Mean (SD)	9.8 (0.9)	9.8 (0.9)	9.9 (0.9)	9.8 (0.9)
Median	9.7	9.7	9.8	9.7
Min, max	7.8, 12.3	6.9, 13.1	8.0, 12.1	6.9, 13.1
Missing	6	3	3	12

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
[1.] According to the Applicant, the high amount of missing data in MRI-PDFF, which is one of the inclusion criterion, is due to "Patients with contraindications to an MRI-PDFF (e.g., metal prosthetics or uncontrolled claustrophobia) examination, or [who were] 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," as stated in the protocols for this inclusion criterion.
Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; FIB-4, fibrosis index based on 4 factors; LDL-C, low-density lipoprotein-cholesterol; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; N, total number of subjects; PDFF, proton density fat fraction; SD, standard deviation; VCTE, vibration-controlled transient elastography

Table 16 presents the baseline fibrosis stage by different histopathology readings. There were participants included in the analysis population of the Week 52 primary endpoints who had fibrosis stage 2 or 3 based on eligibility read but did not have fibrosis stage 2 or 3 based on consensus read. Refer to Section 6.3.2 for details of the different histopathology readings and concerns with the consensus read process in Trial MGL-3196-11.

Table 16. Baseline Fibrosis Stage by Different Histopathology Readings in All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Histopathology Read Method Fibrosis Stage	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296	Total N=888
Eligibility read, n (%)				
Stage 2	110 (37.4)	110 (36.9)	108 (36.5)	328 (36.9)
Stage 3	184 (62.6)	188 (63.1)	188 (63.5)	560 (63.1)
Primary read by pathologist A, n (%)				
Stage 1A/1B/1C	30 (10.2)	33 (11.1)	28 (9.5)	91 (10.2)
Stage 2	91 (31.0)	90 (30.2)	91 (30.7)	272 (30.6)
Stage 3	168 (57.1)	171 (57.4)	171 (57.8)	510 (57.4)
Stage 4	3 (1.0)	3 (1.0)	4 (1.4)	10 (1.1)
Missing	2 (<1)	1 (<1)	2 (<1)	5 (<1)

Histopathology Read Method Fibrosis Stage	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296	Total N=888
Primary read by pathologist B, n (%)				
Stage 0	5 (1.7)	4 (1.3)	1 (<1)	10 (1.1)
Stage 1A/1B/1C	33 (11.2)	26 (8.7)	30 (10.1)	89 (10.0)
Stage 2	87 (29.6)	105 (35.2)	82 (27.7)	274 (30.9)
Stage 3	167 (56.8)	159 (53.4)	179 (60.5)	505 (56.9)
Stage 4	2 (<1)	3 (1.0)	1 (<1)	6 (<1)
Missing	0	1 (<1)	3 (1.0)	4 (<1)
Consensus read, n (%)				
Stage 1A/1B/1C	20 (6.8)	20 (6.7)	5 (1.7)	45 (5.1)
Stage 2	95 (32.3)	102 (34.2)	98 (33.1)	295 (33.2)
Stage 3	170 (57.8)	170 (57.0)	183 (61.8)	523 (58.9)
Missing	9 (3.1)	6 (2.0)	10 (3.4)	25 (2.8)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Abbreviations: N, total number of subjects

Table 17 presents the disposition at Week 52 for the analysis population used by Agency for efficacy evaluation. During the trial, the percentage of participants who discontinued study drug was higher in the higher-dose resmetirom group (13% for placebo, 16% for 80 mg, and 21% for 100 mg). A similar trend was observed for study discontinuation rates. The percentage of participants who discontinued study drug due to AE or discontinued study due to AE was higher in the resmetirom 100 mg group than the other two treatment groups.

Table 17. Subject Disposition at Week 52 for All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Disposition Reason	Placebo N=294 n (%)	Resmetirom 80 mg N=298 n (%)	Resmetirom 100 mg N=296 n (%)	Total N=888 n (%)
Discontinued study drug	38 (12.9)	48 (16.1)	62 (20.9)	148 (16.7)
Adverse event	11 (3.7)	15 (5.0)	26 (8.8)	52 (5.9)
Investigators discretion	2 (<1)	1 (<1)	3 (1.0)	6 (<1)
Lost to follow-up	6 (2.0)	14 (4.7)	9 (3.0)	29 (3.3)
Protocol deviation	1 (<1)	0	1 (<1)	2 (<1)
Withdrawal by subject	17 (5.8)	17 (5.7)	20 (6.8)	54 (6.1)
Other	1 (<1)	1 (<1)	3 (1.0)	5 (1.0)
Discontinued study	27 (9.2)	37 (12.4)	52 (17.6)	116 (13.1)
Adverse event	6 (2.0)	6 (2.0)	20 (6.8)	32 (3.6)
Investigators discretion	0	0	2 (<1)	2 (<1)
Lost to follow-up	4 (1.4)	12 (4.0)	7 (2.4)	23 (2.6)
Protocol deviation	1 (<1)	0	2 (<1)	3 (<1)
Withdrawal by subject	15 (5.1)	18 (6.0)	20 (6.8)	53 (6.0)
Other	1 (<1)	1 (<1)	1 (<1)	3 (<1)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Abbreviations: N, number of subjects in treatment arm; n, number of subjects in subset

Efficacy Results

Main Analyses of the Primary Endpoints and Interpretation of Statistical Significance

Table 18 presents the Agency's primary analysis of the primary endpoints for the Week 52 interim analysis.

For ease of interpretation, the Agency's primary analysis uses the eligibility read to define the analysis population and the baseline fibrosis stage for the stratification factor used in analysis. The Agency's primary analysis uses the primary reads to evaluate the primary endpoints defined according to the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018). Refer to Section 6.3.2 for detailed rationale for these Agency choices for the main efficacy results and results of analyses using different histopathologic readings and definition of endpoints, including the primary analyses as specified by the Applicant. The statistical methodology for the Agency's primary analysis is aligned with the Applicant's pre-specified primary analysis methodology.

The asterisks in Table 18 denote the statistically significant results. Given the method for controlling the overall type I error rate across the interim and final analyses, two doses, and two primary endpoints, the p-values are compared to 0.037 instead of the standard 0.05 threshold, and the 95% CIs cannot be used to interpret whether an endpoint has achieved statistical significance.

Both resmetirom 80 mg and 100 mg arms demonstrated superiority to placebo on both histologic surrogate endpoints. The estimated risk difference (95% CI) on resolution of NASH and no worsening of liver fibrosis was 15% (10%, 21%) comparing resmetirom 80 mg to placebo, and was 19% (13%, 25%) comparing resmetirom 100 mg to placebo. The estimated risk difference (95% CI) on improvement of fibrosis and no worsening of NASH was 9% (4%, 15%) comparing resmetirom 80 mg to placebo, and was 12% (7%, 18%) comparing resmetirom 100 mg to placebo. There was an increase in the percentage of subjects for which the two pathologists disagreed about their responder status as the dose of resmetirom increased.

Table 18. Agency's Primary Analysis, Week 52 Interim Analysis Primary Endpoint Results, All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads and FDA Draft Guidance for Industry)[1], Trial MGL-3196-11

Endpoint Statistic Pathologist Read	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296
Resolution of NASH and no worsening of liver fibrosis			
Model-based response rate (%)[1]	11	26	30
Responder; two pathologists agree, n (%)	18 (6)	60 (20)	55 (19)
Two pathologists disagree, n (%)	29 (10)	37 (12)	68 (23)
Nonresponder; two pathologists agree, n (%)	247 (84)	201 (67)	173 (58)
Difference in response rate vs. placebo[1] (95% CI)[2]		15 (10, 21)	19 (13, 25)
p-value[3]		<0.0001*	<0.0001*

Endpoint Statistic Pathologist Read	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296
Improvement of fibrosis and no worsening of NASH[4]			
Model-based response rate (%)[1]	14	23	26
Responder; two pathologists agree, n (%)	25 (9)	46 (15)	51 (17)
Two pathologists disagree, n (%)	32 (11)	47 (16)	52 (18)
Nonresponder; two pathologists agree, n (%)	237 (81)	205 (69)	193 (65)
Difference in response rate vs. placebo[1] (95% CI)[2]		9 (4, 15)	12 (7, 18)
p-value[3]		0.0009*	<0.0001*

Source: Statistical reviewer analysis of adsl.xpt and admi.xpt datasets; results verified by the Applicant's response to Information Request (IR) dated November 20, 2023 and December 15, 2023
Note: The response value for a subject is 1 if the two pathologists agree that the subject is a responder, 0.5 if the two pathologists disagree, and 0 if the two pathologists agree that the subject is a nonresponder. Participants without a liver biopsy or with a liver biopsy outside of the target analysis window were considered nonresponders. Participants with a missing histopathology reading by a pathologist were considered rated as nonresponder by the pathologist.
Note: FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018).
1. Calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The response rate in the placebo group can be calculated from the comparison with the resmetirom 80 mg or 100 mg group and the results are similar. The presented results for the placebo group are based on the comparison with the resmetirom 100 mg group.
2. 95% Wald CIs based on Mantel-Haenszel mean score statistics. 95% CIs cannot be used to determine statistical significance.
3. Calculated using CMH test stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3).
* denotes statistical significance.
4. The participant is considered nonresponder if the fibrosis stage based on the primary read of the screening liver biopsy is stage 0. There were ten affected participants (5 in placebo, 4 in resmetirom 80 mg group, and 1 in resmetirom 100 mg group) whose screening liver biopsies were rated fibrosis stage 0 by pathologist B at primary read.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel (test); FDA, U.S. Food and Drug Administration; N, number of subjects in treatment arm; n, number of subjects in subset; NASH, nonalcoholic hepatitis

The main efficacy results used treatment policy strategy to handle intercurrent events of treatment discontinuation. Table 273 in Section 16.2.4 presents additional efficacy results that use composite strategy to handle intercurrent events of treatment discontinuation. There is only one participant affected for the primary endpoint of resolution of NASH and no worsening of liver fibrosis. The results support the beneficial treatment effect of resmetirom 80 mg and resmetirom 100 mg compared to placebo on the histologic surrogate endpoint.

Following the prespecified method to control the overall type I error rate described in Section 6.2.1.3:

- All four p-values for the comparisons of resmetirom 80 mg and 100 mg groups to placebo group on the primary endpoints were less than 0.037. Therefore, both the resmetirom 80 mg and 100 mg arms demonstrated superiority to placebo on both primary endpoints.
- Given the statistical significance of all four hypotheses on the primary endpoints, an alpha of 0.04 was passed on to testing the key secondary endpoint for the comparisons of resmetirom 80 mg and 100 mg to placebo.
- Both p-values for the comparisons of resmetirom 80 mg and 100 mg groups to placebo group on the key secondary endpoint were less than 0.02, demonstrating statistical significance.
- An alpha of 0.05 will be available to test the primary composite clinical benefit endpoint upon trial completion.

Missing Data for the Primary Endpoints

Table 19 presents the number and percentage of participants who had missing data for the Week 52 primary endpoints and for the primary read of the screening and Week 52 liver biopsies by each pathologist which was to define the primary endpoints. The percentages of missing data are higher in the resmetirom groups than the placebo group.

Table 19. Missing Data Summary, Week 52 Interim Analysis Primary Endpoints, All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Assessment	Placebo N=294 n (%)	Resmetirom 80 mg N=298 n (%)	Resmetirom 100 mg N=296 n (%)
Primary read for screening liver biopsy			
Pathologist A[1]	2 (0.7)	1 (0.3)	2 (0.7)
Pathologist B[2]	0 (0)	1 (0.3)	3 (1.0)
Primary read for Week 52 liver biopsy			
Due to study discontinuation	26 (8.8)	36 (12.1)	51 (17.2)
Due to missing Week 52 liver biopsy or other reasons[1]			
Pathologist A	16 (5.4)	27 (9.1)	26 (8.8)
Pathologist B	15 (5.1)	25 (8.4)	23 (7.8)
Primary endpoints[3]			
Pathologist A	44 (15.0)	63 (21.1)	77 (26.0)
Pathologist B	41 (13.9)	61 (20.5)	74 (25.0)

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt datasets
1. The additional missingness by pathologist A was because the liver biopsies were “deemed not adequate for evaluation by pathologist A secondary to poor quality” as stated in the Applicant response to information request dated November 20, 2023.
2. The additional missingness by pathologist B was because the Trichrome slides for the participant were not provided and pathologist B was not able to read the fibrosis stage for the participant due to the missing Trichrome slides as stated in the Applicant response to information request dated November 20, 2023.
3. The missingness in the primary read for either the screening liver biopsy and/or for the Week 52 liver biopsy led to the missingness in the Week 52 primary endpoints.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects in subset

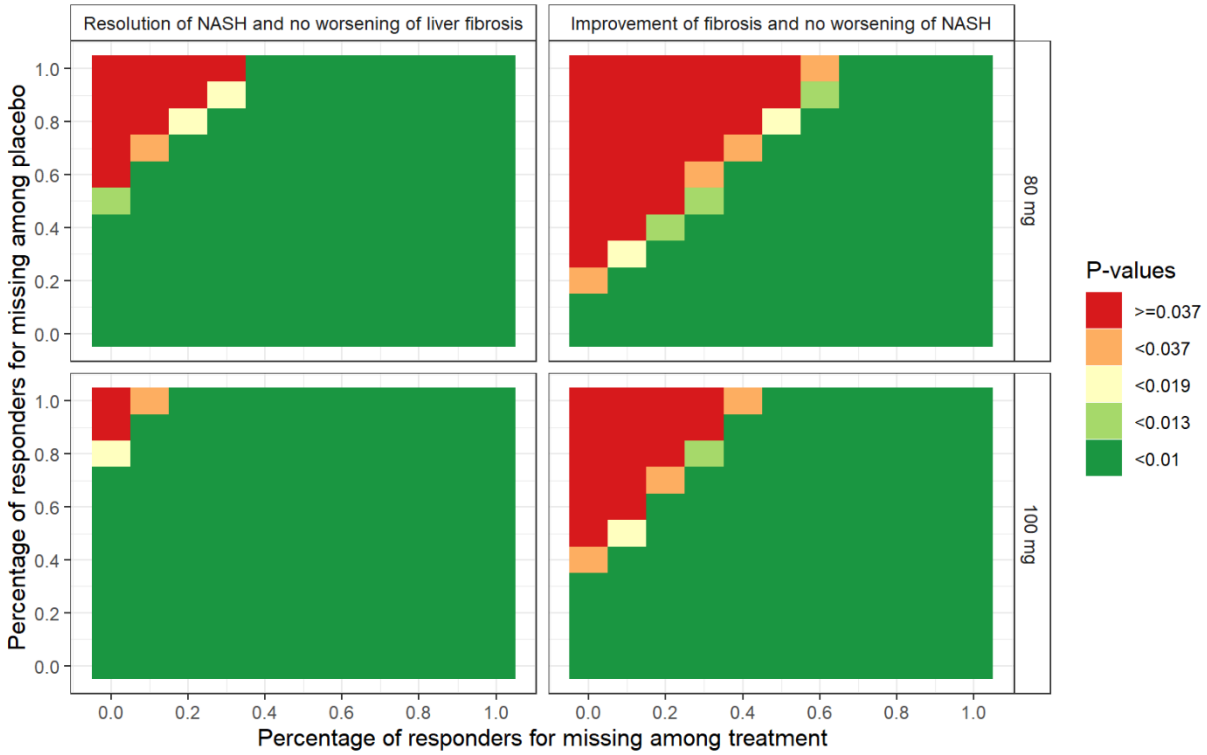
Sensitivity Analysis Results for the Primary Endpoint

In the primary analysis of the Week 52 primary endpoints, missing data were considered nonresponders. Sensitivity analyses were performed using MI to handle the missing data under a missing-at-random assumption. The conclusions of these sensitivity analyses were consistent with that of the primary analyses and support the beneficial treatment effect of resmetirom 80 mg and resmetirom 100 mg compared to placebo. Results from sensitivity analyses are presented in Section 16.2.1.

Figure 5 presents the results for the Agency’s tipping point analyses for the two dose groups of resmetirom and the two Week 52 primary endpoints (i.e., four hypotheses). In the comparison of resmetirom 80 mg group to the placebo group, the results start to tip to nonsignificant results (p-value ≥0.037) in scenarios where there were 20% or more responders assumed for the missing values in the placebo group than in the resmetirom 80 mg group and 60% or less responders were assumed for the missing values in the resmetirom 80 mg group. Given that the percentage of responders in the placebo group is about 10% less than the resmetirom 80 mg group among participants who have complete data, it is unlikely that there are 20% or more responders in the placebo group than the resmetirom 80 mg group among missing values. Similar rationale can be

applied to other Week 52 primary endpoint hypotheses. Therefore, the tipping point scenarios are considered extremely unlikely or implausible. Refer to Section 16.3 for additional results from the tipping point analyses.

Figure 5. Tipping Point Analysis Results, Week 52 Interim Analysis Primary Endpoint, All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads and FDA Draft Guidance for Industry), Trial MGL-3196-11



Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt datasets
Note: p-values from the CMH test were transformed using the Wilson & Hilferty transformation and pooled across 100 imputed datasets using Rubin's rule.
Note: FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018).
Abbreviations: CMH, Cochran-Mantel-Haenszel; FDA, U.S. Food and Drug Administration; NASH, nonalcoholic hepatitis

Results of Additional Histologic Endpoints

Table 20 presents results for Applicant prespecified secondary and Agency specified exploratory endpoints which are components of, or related to, the prespecified Week 52 primary endpoints. The results do not substantively change the conclusions about efficacy.

Table 20. Additional Histologic Endpoint Results, Week 52 Interim Analysis, All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Endpoints	Placebo N=294 (%)[1]	80 mg N=298 (%)[1]	100 mg N=296 (%)[1]	Risk Difference 80 mg-Placebo[1] (95% CI)[2]	Risk Difference 100 mg-Placebo[1] (95% CI)[2]
Resolution of NASH and improvement of fibrosis[3]					
With no additional requirement	6	15	17	8 (4, 13)	11 (7, 16)
With 2-point reduction in NAS	5	14	16	9 (4, 13)	11 (7, 15)
2-stage improvement of fibrosis[4] and					
No worsening in total NAS	5	10	11	5 (2, 9)	6 (3, 10)
No worsening in any NAS component	4	9	11	5 (2, 8)	7 (3, 10)
Resolution of NASH	12	29	33	17 (11, 23)	21 (15, 27)
2-point reduction in NAS	25	45	49	20 (13, 27)	23 (16, 30)
Improvement in ballooning	27	46	48	19 (13, 26)	22 (15, 29)
Improvement in inflammation	27	35	36	9 (2, 15)	9 (3, 16)
Improvement in steatosis	27	48	51	21 (14, 28)	24 (17, 31)
Fibrosis reduced to stage 0	2	6	5	4 (1, 6)	3 (1, 6)
2-stage improvement of fibrosis[4]	5	10	11	5 (2, 9)	7 (3, 10)
1-stage improvement of fibrosis[3]	17	25	27	9 (3, 14)	11 (5, 17)

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt datasets
[1.] Calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The response rate in the placebo group can be calculated from the comparison with the resmetirom 80 mg or 100 mg group and the results are similar. The presented results for the placebo group are based on the comparison with the resmetirom 100 mg group.
[2.] 95% Wald CIs based on Mantel-Haenszel mean score statistics.
[3.] The response value for a participant is 0 if the fibrosis stage based on the primary read of the screening liver biopsy is stage 0.
[4.] The response value for a participant is 0 if the fibrosis stage based on the primary read of the screening liver biopsy is stage 0 or stage 1.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects in subset; NAS, nonalcoholic fatty liver disease (NAFLD) activity score; NASH, nonalcoholic hepatitis

Subgroup Results of the Primary Endpoints

Table 21 and Table 22 present key subgroup results comparing resmetirom 80 mg and 100 mg to placebo for Agency's primary analyses of the Week 52 primary endpoint of resolution of NASH and no worsening of liver fibrosis and the endpoint of improvement of fibrosis and no worsening of NASH, respectively, as performed in Table 18 for the Week 52 interim analysis.

There were no clear differential results by subgroup comparing resmetirom 80 mg or 100 mg to placebo, except for a few of the racial subgroups with small sample sizes. These findings are not always consistent across endpoints and dose groups, and therefore, may be due to the small sample sizes and chance by examining many subgroups. Section 16.2.6 presents additional subgroup analysis results by different weight cutoffs.

Table 21. Subgroup Analyses for Resolution of NASH and No Worsening of Liver Fibrosis in All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Subgroup Type Characteristic	N	Placebo N=294 (%)	80 mg N=298 (%)	100 mg N=296 (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Overall	888	11	26	30	15 (10, 21)	19 (13, 25)
Sex						
Male	391	11	30	33	19 (10, 28)	23 (14, 31)
Female	497	11	24	28	13 (5, 20)	16 (9, 24)
Age						
<65 years	660	12	24	31	12 (6, 19)	19 (12, 26)
≥65 years	228	8	34	28	25 (13, 38)	20 (10, 30)
Race[1, 2]						
American Indian or Alaska Native	8	21	43	-	21 (-, -)	- (-, -)
Asian	26	12	56	31	37 (-14, 87)	19 (-, -)
Black or African American	19	17	41	22	30 (-, -)	6 (-, -)
Native Hawaiian or other Pacific Islander	1	-	-	-	- (-, -)	- (-, -)
White	790	10	26	31	16 (10, 22)	21 (15, 27)
Not able to collect	15	13	0	16	-17 (-, -)	3 (-, -)
Not reported	5	50	-	0	- (-, -)	-50 (-, -)
Other	24	17	11	0	-4 (-35, 27)	-17 (-47, 13)
Ethnicity[1, 2]						
Hispanic or Latino	186	14	21	36	7 (-6, 20)	22 (7, 37)
Non-Hispanic or Latino	690	11	28	28	17 (11, 23)	17 (11, 23)
Not reported	4	0	-	0	- (-, -)	0 (0, 0)
Unknown	3	-	-	-	- (-, -)	- (-, -)
Not able to collect	5	0	0	0	0 (-, -)	0 (-, -)
Region						
United States (US)	587	12	27	30	15 (7, 22)	17 (10, 24)
Non-US	301	9	27	31	18 (9, 28)	22 (13, 32)
Diabetes status						
No	280	11	27	30	16 (6, 26)	19 (9, 29)
Yes	608	11	26	30	15 (8, 22)	19 (12, 26)
Baseline fibrosis stage						
Stage 2	328	15	33	34	19 (9, 29)	20 (10, 29)
Stage 3	560	9	22	28	13 (7, 20)	19 (12, 26)

Subgroup Type Characteristic	N	Placebo N=294 (%)	80 mg N=298 (%)	100 mg N=296 (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Weight						
<90 kg	306	15	30	32	16 (5, 26)	18 (8, 28)
≥90 kg	582	9	24	29	15 (9, 22)	20 (13, 27)
BMI						
<35	462	13	34	33	21 (13, 30)	20 (12, 28)
≥35	426	9	19	27	10 (2, 17)	18 (10, 26)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt
Note: Response rates and differences in response rates were calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The 95% CIs are Wald CIs based on Mantel-Haenszel mean score statistics.
[1.] Unable to calculate the response rate using weights by stratum when there was no participant in one of the treatment arms of comparison across all observed strata.
[2.] Unable to calculate the standard error to construct the 95% CIs when there was no participant in one of the treatment arms of comparison in any observed stratum.
Abbreviations: BMI, body mass index; CI, confidence interval; N, number of subjects in treatment arm; NASH, nonalcoholic hepatitis

Table 22. Subgroup Analyses for Improvement of Fibrosis and No Worsening of NASH in All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Subgroup Type Characteristic	N	Placebo N=294 (%)	80 mg N=298 (%)	100 mg N=296 (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Overall	888	14	23	26	9 (4, 15)	12 (7, 18)
Sex						
Male	391	10	22	26	11 (3, 19)	16 (7, 24)
Female	497	17	25	27	8 (0, 16)	10 (2, 18)
Age						
<65 years	660	15	23	30	7 (1, 14)	15 (8, 22)
≥65 years	228	10	26	15	16 (5, 28)	5 (-4, 14)
Race[1, 2]						
American Indian or Alaska Native	8	43	0	-	-43 (-, -)	- (-, -)
Asian	26	19	47	25	28 (-13, 70)	6 (-, -)
Black or African American	19	33	9	0	-14 (-, -)	-33 (-, -)
Native Hawaiian or other Pacific Islander	1	-	-	-	- (-, -)	- (-, -)
White	790	13	23	27	10 (4, 16)	13 (7, 19)
Not able to collect	15	13	0	37	-17 (-, -)	24 (-, -)
Not reported	5	0	-	0	- (-, -)	0 (-, -)
Other	24	9	23	19	14 (-20, 47)	10 (-20, 41)

Subgroup Type Characteristic	N	Placebo N=294 (%)	80 mg N=298 (%)	100 mg N=296 (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Ethnicity[1, 2]						
Hispanic or Latino	186	16	24	37	8 (-6, 21)	21 (6, 36)
Non-Hispanic or Latino	690	13	24	22	10 (4, 16)	9 (3, 15)
Not reported	4	50	-	0	- (-, -)	-50 (-119, 19)
Unknown	3	-	-	-	- (-, -)	- (-, -)
Not able to collect	5	0	0	0	0 (-, -)	0 (-, -)
Region						
United States (US)	587	15	23	26	8 (1, 15)	11 (4, 18)
Non-US	301	12	24	26	12 (3, 21)	14 (4, 23)
Diabetes status						
No	280	17	24	34	7 (-3, 17)	16 (5, 27)
Yes	608	12	23	23	11 (4, 17)	10 (4, 17)
Baseline fibrosis stage						
Stage 2	328	16	26	35	10 (1, 19)	19 (9, 29)
Stage 3	560	12	22	21	9 (2, 16)	8 (1, 15)
Weight 90 kg						
<90 kg	306	15	28	29	14 (4, 24)	15 (4, 25)
≥90 kg	582	14	21	25	7 (0, 13)	11 (4, 18)
BMI						
<35	462	14	27	26	13 (5, 21)	12 (4, 20)
≥35	426	14	20	26	6 (-2, 14)	12 (4, 20)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt.
Note: Response rates and differences in response rates were calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The 95% CIs are Wald CIs based on Mantel-Haenszel mean score statistics.
[1.] Unable to calculate the response rate using weights by stratum when there was no participant in one of the treatment arms of comparison across all observed strata.
[2.] Unable to calculate the standard error to construct the 95% CIs when there was no participant in one of the treatment arms of comparison in any observed stratum.
Abbreviations: BMI, body mass index; CI, confidence interval; N, number of subjects in treatment arm; NASH, nonalcoholic hepatitis

Key Secondary Endpoint Results

Table 280 in Section 16.3.4 presents the results for the key secondary endpoint evaluating the percent change in LDL-C from baseline to Week 24. Regardless of the analysis method, the comparisons of both resmetirom 80 mg and 100 mg groups to placebo group meet statistical significance on the key secondary endpoint.

Liver Enzyme Results

Section 16.4 presents the summary of ALT and AST by treatment groups from baseline to Week 52. ALT and AST in the resmetirom groups increased to Week 4 while a similar increase was not seen in the placebo group. There was a trend of lower ALT and AST in resmetirom groups as compared to the placebo group starting after Week 12 through Week 52.

6.3. Key Efficacy Review Issues

6.3.1. Efficacy Analysis Includes Subjects With Stage F2 and F3 Fibrosis

Issue

The Agency issued draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018), providing a framework for phase 2 and 3 trial design. Among the inclusion criteria for phase 3 NASH trials is that patients have more than stage 1 and less than stage 4 fibrosis at enrollment, to ensure that patients have clear evidence of steatohepatitis without cirrhosis. Because the progression of NASH from one stage to the next is generally slow, enrolling patients with stage 1 fibrosis would mean that few if any would be expected to progress to clinically relevant outcomes during the course of a 1- or 5-year clinical trial, whether they receive active drug or placebo.

From the first version of the MGL-3196-11 protocol submitted in 2019, the explicit intention was to include only patients with NASH and F2 and F3 fibrosis in the primary efficacy analyses. Patients who had F1 fibrosis could be enrolled in the trial but analyses of this population were intended to be exploratory. This was affirmed with the Applicant in subsequent official communications.

Despite clear communications, the Applicant included subjects with F1B fibrosis in their primary efficacy analysis. There were 49 patients out of 1,050 in the overall patient population enrolled in MGL-3196-11 who had F1B fibrosis at baseline using the baseline fibrosis stage specified by the Applicant. However, patients with F1B fibrosis were excluded from the Agency's analysis given insufficient data to support that F1B is sufficiently different from other stage 1 substages (and sufficiently similar to F2 or F3 stages), with regard to either risk of fibrosis progression, or risk of development of cirrhosis and liver decompensation events, to warrant inclusion in the primary analysis. The Applicant also stated that subjects with FA/C fibrosis would be exploratory. Therefore, the primary analysis, in contrast with published reports of MGL-3196-11 trial results (Harrison et al. 2024), included only subjects with F2 or F3 fibrosis.

Background

NASH with no fibrosis, or with mild or moderate fibrosis, (stages F0 to F2) is associated with low rates of liver-related events and deaths, with substantively increased risks of worsening liver disease in patients with NASH and F3 fibrosis or cirrhosis (F4) (Angulo et al. 2015; Ekstedt et al. 2015). In the population of NASH patients with F0 to F2 fibrosis, the most common causes of morbidity and mortality are related to cardiovascular diseases, diabetes, and nonhepatic cancers (Ekstedt et al. 2015; Sanyal et al. 2021). The progression of disease in patients with lower fibrosis stages (F0 to F1) is slower than those patients with more advanced stages (Singh et al. 2015). In patients without advanced fibrosis, the probability of a liver-related event was shown to be higher for stage F2 fibrosis compared to reference, whereas the probability of a liver-related event for stage F1 fibrosis was no different from reference (Angulo et al. 2015). Because of the indolent nature of NASH, the Agency has accepted as critical inclusion criteria that NASH patients have a NASH activity score (NAS) of greater than or equal to 4, with at least 1 point each in inflammation and ballooning, as well as a NASH CRN fibrosis score of greater than stage 1 and less than stage 4 fibrosis (see the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018). These enrollment criteria were chosen to ensure that phase 3 trial participants, and, ultimately persons taking an approved drug, would have the potential to derive clinical benefit. The American Association for the Study of Liver Diseases (AASLD) affirms in their practice guidance that "patients with 'at risk' NASH (NASH with at least stage 2 fibrosis) are at increased risk of developing cirrhosis and liver-related complications" (Rinella et al. 2023b)."

Assessment

Enrollment criteria as specified by the FDA guidance for industry referenced above, and the aim of developing treatments targeted to F2 and F3 fibrosis patients were communicated to the Applicant on multiple occasions during the development program.

The Applicant opted to include patients with stage F1B fibrosis in their primary analysis. The Applicant provided a literature reference to support the claim that stage F1B fibrosis is associated with a higher risk of progression.

This analysis was based on a post hoc, subgroup analysis with few subjects (1A n=57, 1B n=56, 1C n=15), in which the rate of fibrosis progression (defined as progressing to stage F2 or higher) was similar for both 1A (36%) and 1B (43%) as compared with 1C (20%). The authors, in fact, conclude in their discussion of factors associated with fibrosis progression and regression, "Considering all substages of fibrosis stage 1 as a single stage did not significantly alter the results of the analysis." (Kleiner et al. 2019). These data were insufficient to warrant inclusion of patients with F1B fibrosis in the efficacy population. In addition, the Applicant did not provide data that patients with F1B fibrosis were at greater risk of developing liver-related complications as compared with other F1 subgroups.

The Agency's assessment is that the natural history of NASH with stage F1B fibrosis is similar to that of stage F1A and stage F1C, and not sufficiently similar to F2 or F3 stages, either with regard to risk of fibrosis progression, or, more importantly, with regard to risk of development of cirrhosis and liver decompensation events. Given that patients with F1 fibrosis are at lower risk of disease progression to cirrhosis and liver decompensation events, the Agency would accept fewer treatment-related risks in patients with F1 fibrosis than it might in those with more

advanced stages of fibrosis. In other words, a favorable benefit-risk assessment in early-stage fibrosis would require a treatment to have demonstrated a low risk of adverse events (AEs) with long-term (years) of use.

Conclusion

Additional clinical and histologic data from the placebo and treatment arms of Trial MGL-3196-11 through 54 months may help to further elucidate natural history and determine if there is a potential for treatment benefit in the enrolled population with lower stages of fibrosis that outweighs potential AEs with long-term use. However, at this time, the Agency affirms its prespecified primary efficacy analysis of patients with NASH and F2 to F3 fibrosis, as the currently available natural history data indicate these are the patients at increased risk of development of cirrhosis and liver decompensation events.

6.3.2. Definition and Analysis of Histologic Primary Endpoints

Issue

Primary analyses of the histologic surrogate endpoints (primary endpoints) for Week 52 interim analyses were not agreed upon with the Agency during the IND development program. Primary histologic endpoints as defined by the Applicant differ from those defined in the FDA guidance for industry.

Background

The following are topics of concern with the Applicant's prespecified primary analyses of the histologic surrogate endpoints for Week 52 interim analyses:

- Choice of histopathology readings to:
  - Define the analysis population with stage 2 (F2) or stage 3 (F3) fibrosis
  - Define the histologic surrogate endpoints
  - Define the baseline fibrosis stage for stratification factor in the analysis
- Definition of the histologic surrogate endpoints

There was discussion during the IND development program about the histopathology readings to define the histologic surrogate endpoints and the primary analysis methodology. Table 23 provides the timing of submissions to the Agency by the Applicant regarding the SAP in relation to data cutoff and unblinding. As unblinding occurred on December 2, 2022, the Agency was not able to provide feedback on the last version (3.0) of the SAP submitted on December 15, 2022. Table 23 does not include earlier versions of the SAP incorporated in meeting packages submitted to the IND, and these versions of the SAP specified a different primary analysis from the later submissions depicted in the table.

Table 23. Milestone Dates Relevant to SAP and Consensus Read for Week 52 Interim Analysis, Trial MGL-3196-11

Time	Action
July 31, 2022	Interim data cutoff
October 20, 2022	SAP Version 1.0, signed on October 18, 2022, was submitted to the Agency under the IND.
November 18, 2022	Interim database lock
December 1, 2022	Consensus read session #1
December 2, 2022	Consensus read session #2; Statistical CRO unblinded
December 5, 2022	Consensus read session #3
December 15, 2022	The following documents were submitted to the Agency under the IND. • SAP Version 3.0, signed on December 5, 2022 • First SAP Addendum • Liver Biopsy Analysis Manual Amendment 2, dated December 13, 2022, which documented an overview of the consensus read process • Consensus process for biopsy scoring (no internal finalization date by the Applicant) Applicant unblinded after submitting SAP Version 3.0
December 19, 2022	Consensus read session #4; press release
May 2023	Post-hoc consensus of baseline fibrosis stage among unaligned cases
September 7, 2023	The second SAP Addendum, dated May 26, 2023, was submitted to the NDA

Source: Summarized by statistical reviewer based on responses to information request, dated September 7, 2023 and November 20, 2023
Note: SAP Version 2.0 was not submitted to the Agency
Abbreviations: CRO, contract research organization; IND, investigational new drug; NDA, new drug application; SAP, statistical analysis plan

The specific histopathology readings to define the analysis population were first specified in Protocol Version 5.0, submitted on September 20, 2022, clarified in the SAP Version 1.0, which was submitted on October 20, 2022, and further clarified in the SAP Version 3.0, submitted on December 15, 2022, under the IND.

Although the Agency recommended a consensus read process during the IND development program, the Agency identified deficiencies in the consensus read performed by the Applicant during the NDA review. Table 23 presents the milestone dates relevant to the SAP and the consensus read; given the short time between the consensus reads, unblinding, and subsequent SAP addenda, it is not clear whether the consensus read process was adequately prespecified.

Baseline fibrosis stage for stratification factor was first specified in the SAP Version 1.0 as the final assignment in the electronic case report form, if differing from the randomization stratification factor, and was modified in the SAP Version 3.0 as the baseline fibrosis stage by the specified histopathology readings to define the Applicant's primary analysis population.

The Agency agreed with the definitions of the histologic surrogate endpoints earlier in the IND development program in the meeting minutes dated November 15, 2018; however, the definitions of the histologic surrogate endpoints differ from the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018).

Assessment

Choice of Read to Define Analysis Population

For the analysis population defined in SAP Version 3.0, participants with F3 fibrosis were defined as those participants where at least one pathologist rated the screening liver biopsy as F3 at primary read, and those where both pathologists rated as F4 at primary read; participants with F2 fibrosis were defined as those where one pathologist rated the screening liver biopsy as F2 and the other pathologist rated as F2 or lower at primary read. Participants with F1B fibrosis were defined as those where both pathologists rated the screening liver biopsy as F1B at primary read.

There are concerns with the interpretability of this algorithm to define the analysis population and with the fact that this algorithm was specified close to unblinding. Given these concerns, the Agency considered the advantages and disadvantages of different available options to define the analysis population with F2 and F3 fibrosis, as summarized in Table 24.

Table 24. Advantages and Disadvantages of Different Reads to Define the Analysis Population, Week 52 Interim Analysis, Trial MGL-3196-11

Read	Advantages	Disadvantages
Primary reads, as specified in SAP Version 3.0	• Prespecified by Applicant	• Complex algorithm and difficult interpretation • May not as accurately define fibrosis stage compared to an adequate consensus process (e.g., F4 fibrosis on both primary reads was defined as F3 for purposes of inclusion in analysis population) • Does not reflect how participants will be diagnosed in practice if biopsy is used
Consensus read	• May more accurately reflect F2 or F3 fibrosis than reading by individual pathologist, depending on adequacy of process • Straightforward interpretation	• Applicant's consensus process was not used to determine eligibility into the trial • Performed close to unblinding and not clear whether the process was prespecified • Performed post hoc for about 18% of the participants
Eligibility read	• Defines an analysis population close to how participants will be diagnosed in practice if biopsy is used • Straightforward interpretation	• Not prespecified for use in the analysis • May not as accurately define fibrosis stage compared to an adequate consensus process

Source: Statistical reviewer
Abbreviations: F2, fibrosis stage 2; F3, fibrosis stage 3; SAP, statistical analysis plan

Considering these advantages and disadvantages, the Agency considers eligibility read to be the most appropriate option to define the analysis population with F2 or F3 fibrosis in Trial MGL-3196-11, and this analysis population was used in the Agency's primary analysis results

presented in Section 6.2.1.4, and in Table 26 in this section. Results from the Applicant's primary analysis using the analysis population as specified in Version 3.0 of the SAP are also presented in Table 26 in this section. The overall results from the Agency's and the Applicant's primary analysis are consistent.

Baseline Fibrosis Stage for Stratification Factor

The SAP prespecified using the baseline fibrosis stage used to define the analysis population to define the baseline fibrosis stage for the stratification factor. Using the same the rationale provided for the choice of histopathology readings to define analysis population, the Agency used eligibility read to define the baseline fibrosis stage for the stratification factor for the analyses presented in Section 6.2.1.4 and in Table 26 in this section. Results from analyses using the Applicant's specified stratification factor in Version 3.0 of the SAP are also presented in Table 26 in this section for completeness. The overall results from the Agency's and the Applicant's primary analysis are consistent.

Histopathology Readings and Definition of the Histologic Surrogate Endpoints

The SAP prespecified using the primary read by two independent pathologists to define the histologic surrogate endpoints; however, during the IND development program, the Agency recommended using consensus read to define the histologic surrogate endpoints.

The histologic surrogate endpoints for Week 52 interim analyses prespecified by the Applicant were defined as:

- Resolution of NASH (0 for ballooning, 0 to 1 for inflammation) with an at least 2-point reduction in NAS and no worsening of fibrosis.
- At least a 1-point improvement in fibrosis stage and no worsening of NAS, where no worsening of NAS was defined as no worsening in the total of three NAS components (ballooning, inflammation, and steatosis).

Additionally, the SAP also specified among the fibrosis stages that a change from stage 1B (F1B) to F2 is not considered a worsening of fibrosis, and that a change from F2 to F1B is not considered an improvement in fibrosis.

The definitions of the endpoints are different from those in the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018):

- Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis, and a NAS score of 0 to 1 for inflammation, 0 for ballooning, and any value for steatosis.
- Improvement in liver fibrosis greater than or equal to 1 stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

The following are the key differences between the endpoints specified by the Applicant and the guidance:

- For the definition of the resolution of NASH and no worsening of fibrosis, the guidance does not require "at least 2-point reduction in NAS." The value of this additional criterion in the definition of the endpoint is unclear.
- For "no worsening of NAS," the guidance requires no increase in NAS for each component (ballooning, inflammation, and steatosis) instead of the Applicant's definition requiring no increase in total NAS.

Additionally, the Agency considers a change from any stage 1 (i.e., 1A, 1B, or 1C) to stage 2 of fibrosis a worsening of fibrosis, and a change from stage 2 to any stage 1 an improvement in fibrosis.

Ideally, the data would allow for an evaluation of the histologic surrogate endpoints based on consensus read and guidance definition of the endpoints. However, the lack of consensus on the individual histological features in the consensus read process made it impossible to perform the analyses of the endpoints as defined in the guidance based on consensus read. Table 25 presents the advantages and disadvantages of analyses with different available histopathology readings and different definitions of the endpoints.

Table 25. Advantages and Disadvantages of Different Histopathologic Readings and Different Endpoint Definitions for Week 52 Interim Analysis, Trial MGL-3196-11

Histopathology Read and Endpoint Definition	Advantages	Disadvantages
Histopathology reading: primary reads Endpoint definition: as specified in SAP	• Prespecified histopathology reading and endpoint definition	• No clear interpretation for a participant when there is disagreement on responder status between the pathologists • Endpoint definition deviates from guidance
Histopathology reading: consensus read Endpoint definition: as specified in SAP	• Consensus across two pathologists • Prespecified endpoint definition	• Consensus process performed close to unblinding and not clear whether the process was prespecified • Endpoint definition deviates from guidance
Histopathology reading: primary reads Endpoint definition: as specified in guidance	• Prespecified histopathology reading • Endpoint definition consistent with guidance	• Endpoint definition not prespecified • No clear interpretation for a participant when there is disagreement on responder status between the pathologists

Source: Statistical reviewer
Abbreviations: SAP, statistical analysis plan

Considering these advantages and disadvantages, the Agency considers the primary analysis to be based on primary reads and guidance definition of the endpoints, and these results are presented in Section 6.2.1.4 and Table 26 below.

In addition to the Agency's primary analysis choices discussed above, the Agency also evaluated the following analyses for the two histologic surrogate endpoints to evaluate the robustness of the efficacy results:

- Endpoints based on primary reads and the endpoint definitions as specified in SAP
- Endpoints based on consensus read and the endpoint definitions as specified in SAP
- Endpoints based on primary read by pathologist A and the endpoint definitions as specified in guidance
- Endpoints based on primary read by pathologist B and the endpoint definitions as specified in guidance

Summary of Primary Analysis Specified by Agency

The primary analysis by the Agency uses (1) the eligibility read to define the analysis population and the baseline fibrosis stage for the stratification factor used in analysis, and (2) the primary reads to evaluate the primary endpoints defined according to the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018).

Results of Analyses

Table 26 presents analysis results of the primary endpoints for the Week 52 interim analysis as specified by the Agency and by the Applicant, and results from analyses with alternative histopathologic readings and definitions for endpoints. Table 18 in Section 6.2.1.4 presents additional details for the primary analysis by the Agency, and Section 16.2.1 presents the analysis based on primary reads and the endpoint definitions as specified in the SAP. Both resmetirom 80 mg and 100 mg arms demonstrated superiority to placebo on both histologic surrogate endpoints and the conclusions about the statistical significance are the same, regardless of different analysis populations, different histopathology readings, and different endpoint definitions.

The Applicant's primary analysis in Table 26 utilizes the analysis population as specified in SAP Version 3.0. All other analyses in Table 26 present results for the analysis population defined by the Agency based on eligibility reads. For all analyses, the fibrosis stage used to define the analysis population was used to define the baseline fibrosis stage for the stratification factor.

Table 26. Additional Analyses of Week 52 Interim Analysis Primary Endpoints Based on Different Histopathologic Readings and Definitions for Endpoints, Trial MGL-3196-11

Response Rates	Placebo (%)	80 mg (%)	100 mg (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Resolution of NASH and no worsening of liver fibrosis					
Primary read and SAP endpoint including F1B (Applicant's primary analysis)[1]	N=318	N=316	N=321		
	10	26	30	16 (11, 22)	21 (15, 26)
Different histopathologic readings and definitions for endpoints[2]	N=294	N=298	N=296		
Primary read and guidance endpoint (Agency primary analysis)[3]	11	26	30	15 (10, 21)	19 (13, 25)
Primary read and SAP endpoint[3]	9	24	28	15 (10, 21)	19 (14, 25)
Consensus read and SAP endpoint[4]	7	24	26	17 (11, 22)	19 (13, 25)
Pathologist A and guidance endpoint[4]	13	27	36	14 (8, 20)	23 (16, 30)
Pathologist B and guidance endpoint[4]	9	26	24	17 (11, 23)	15 (9, 21)
Improvement of fibrosis and no worsening of NASH					
Primary read and SAP endpoint including F1B (Applicant's primary analysis)[1]	N=318	N=316	N=321		
	14	24	26	10 (5, 16)	12 (6, 17)
Different histopathologic readings and definitions for endpoints[2]	N=294	N=298	N=296		
Primary read and guidance endpoint (Agency primary analysis)[3]	14	23	26	9 (4, 15)	12 (7, 18)
Primary read and SAP endpoint[3]	14	24	24	10 (4, 16)	11 (5, 16)
Consensus read and SAP endpoint[4]	12	23	24	11 (5, 17)	12 (6, 18)
Pathologist A and guidance endpoint[4]	15	23	28	8 (2, 14)	13 (7, 20)
Pathologist B and guidance endpoint[4]	13	23	24	11 (5, 17)	11 (5, 17)

Source: Statistical reviewer's analysis of adsl.xpt, adcn3.xpt and admi.xpt datasets. Primary analysis as specified by the Applicant like interim Clinical Study Report MGL-3196-11 Table 15 (page 80), Table 14.2.1.1 and Table 14.2.1.2.

Note: The Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3) was used to calculate the response rates and risk differences.

[1] Analysis population specified by the Applicant includes all F1B, F2, and F3 participants (as defined by Applicant's algorithm) who were randomized on or before July 31, 2021, excluding participants who were missing a Week 52 biopsy due to the COVID-19 pandemic.

[2] Analysis population includes all F2 and F3 participants (based on eligibility read) who were randomized on or before July 31, 2021

[3] 95% Wald CIs based on Mantel-Haenszel mean score statistics are provided.

[4] 95% stratified Newcombe CIs are provided.

Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; CI, confidence interval; NASH, nonalcoholic hepatitis; SAP, statistical analysis plan

Conclusion

Regardless of the choice of histopathology reading and endpoint definition, both the resmetirom 80 mg and 100 mg arms demonstrated superiority to placebo on both reasonably likely surrogate endpoints: (1) resolution of NASH and no worsening of liver fibrosis, and (2) improvement of fibrosis and no worsening of NASH, evaluated at the Week 52 interim analysis.

The estimated risk difference (95% CI) on resolution of NASH and no worsening of liver fibrosis ranged from:

- 14% (8%, 20%) to 17% (11%, 23%) comparing resmetirom 80 mg to placebo
- 15% (9%, 21%) to 23% (16%, 30%) comparing resmetirom 100 mg to placebo

The estimated risk difference (95% CI) on improvement of fibrosis and no worsening of NASH ranged from:

- 8% (2%, 14%) to 11% (5%, 17%) comparing resmetirom 80 mg to placebo
- 11% (5%, 16%) to 13% (7%, 20%) comparing resmetirom 100 mg to placebo

6.3.3. Liver Histology as a Reasonably Likely Surrogate Endpoint

Issue

The Applicant is seeking accelerated approval under 21 CFR part 314, subpart H based on demonstrating an effect on surrogate endpoints.

Background

The histological endpoints described in the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment* (December 2018) are considered by the Agency to be surrogate endpoints that are reasonably likely to predict clinical benefit. Use of these endpoints was supported by retrospective and prospective published data that show F2 and F3 fibrosis is associated with higher mortality (Angulo et al. 2015; Ekstedt et al. 2015; Sanyal et al. 2021).

Accelerated approval can provide patients with serious and life-threatening diseases access to new therapy sooner for conditions for which there is an unmet need for treatment. Because accelerated approval is based on the drug's effect on a surrogate endpoint, it accepts some additional uncertainty as a tradeoff in providing earlier access to treatment. As a condition of the accelerated approval, FDA has required postapproval studies to verify and describe the drug's clinical benefit.

Assessment

Results of the prespecified primary endpoints are consistent with results of the surrogate endpoints considered reasonably likely to predict clinical benefit described in the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment* (December 2018) (refer to Section 6.3.2). As with any surrogate endpoint, there is uncertainty about how effects on the surrogate endpoints may

translate into a meaningful effect on clinical efficacy endpoints. Trial MGL-3196-11 is ongoing to verify and describe the drug's clinical benefit.

Conclusion

The results of the histological surrogate endpoints considered to be reasonably likely to predict clinical benefit support demonstration of effectiveness for an accelerated approval action. Trial MGL-3196-11 is ongoing to verify and describe the drug's clinical benefit.

6.3.4. Framework for Demonstrating Substantial Evidence of Effectiveness

Issue

SEE for resmetirom is based on a single adequate and well-controlled investigation (Trial MGL-3196-11) together with confirmatory evidence.

Background

Under section 505(d) of the FD&C Act, for a new drug to be approved for marketing in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling. The demonstration of effectiveness under this standard requires substantial evidence that the drug will have the effect it purports or is represented to have. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

SEE, which is the regulatory requirement for approval, generally consists of evidence from at least two adequate and well-controlled trials. However, for this NDA, SEE comes from a single adequate and well-controlled investigation (Trial MGL-3196-11) together with confirmatory evidence.

In certain circumstances, a single adequate and well-controlled investigation demonstrating efficacy together with appropriate confirmatory evidence may be sufficient to generate SEE. Such circumstances are described in the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), and include the persuasiveness of the single investigation; the robustness of the confirmatory evidence; the seriousness of the disease, particularly when there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled investigation.

Assessment

Trial MGL-3196-11 is the single adequate and well-controlled investigation supporting the effectiveness of resmetirom. Results demonstrated statistical significance on prespecified endpoints on a surrogate endpoint to support an accelerated approval. These results were persuasive.

There are currently no approved pharmacological treatments for NASH. Lifestyle management with reduced calorie diet and increased exercise is currently considered the standard of care, but most individuals are unable to achieve permanent weight loss (Anderson et al. 2001; Kenneally

et al. 2017). Bariatric surgery can be considered in patients who meet criteria for metabolic weight loss surgery as it may lead to resolution of NASH (Verrastro et al. 2023) and potentially improve long-term outcomes (Aminian et al. 2021). However, this is an invasive procedure with a significant risk of surgical complications.

Untreated NASH is a serious condition, which can lead to cirrhosis, liver failure/need for transplantation, HCC, and death (refer to Section 3: Introduction, "Analysis of Condition"), with an unmet need for pharmacological treatment. The persuasive results of Trial MGL-3196-11 along with data from earlier-phase trials will constitute SEE.

Confirmatory evidence includes:

MGL-3196-05, a phase 2, double-blind, placebo-controlled trial that enrolled adult patients with noncirrhotic biopsy-proven NASH, who were randomized 2:1 to resmetirom 80 mg (n=84) or placebo (n=41). The primary endpoint was the percent change in hepatic fat fraction by MRI-PDFF at 12 weeks, with 36-week liver biopsy and MRI-PDFF as secondary endpoints. Treatment with resmetirom reduced hepatic fat fraction at 12 and 36 weeks and was associated with improved NASH activity scores, higher rates of NASH resolution, and reduction of fibrosis stage compared to treatment with placebo. The impact on PD biomarkers is provided in Section 6.1.

Conclusion

SEE to support accelerated approval has been demonstrated for resmetirom, in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), based on one adequate and well-controlled investigation (Trial MGL-3196-11) and confirmatory evidence.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The overall documentation of the nonclinical program to support the safe use of resmetirom in clinical development and as an approved drug is summarized here. The nonclinical safety profile of resmetirom was evaluated in safety pharmacology studies, repeat-dose oral toxicology studies (mouse studies of up to 3 months, rat studies of up to 6 months, and dog studies of up to 9 months), reproductive and developmental studies in rats and rabbits, genetic toxicology studies (Ames test, in vitro chromosomal aberration assay, and in vivo rat micronucleus assay), and carcinogenicity studies in mice and rats. The nonclinical safety profile of the major human metabolite of resmetirom, MGL-3623 (also known as MGL-3196-M1 or M1), was evaluated in a 3-month mouse toxicology study, genetic toxicology studies (Ames test, in vitro micronucleus assay in TK6 human lymphoblast cells, and in vivo rat micronucleus assay), an embryo-fetal development (EFD) study in rats, and a 6-month carcinogenicity study in transgenic mice. The data from these studies are summarized below.

Safety Pharmacology

Resmetirom administered as a single oral dose of 50 or 120 mg/kg in dogs produced mild to moderate decreases in systolic and diastolic blood pressure, slight to mild increase in heart rate, and slight to mild decreases in QRS, RR, and PR intervals at 5 to 7, 2 to 8, or 4-hours postdose, respectively. A single oral administration of resmetirom at doses up to 300 mg/kg in rats had no significant effect on neurobehavioral or respiratory functions. Resmetirom at concentrations up to 30 µmol/L produced 18.2% inhibition of human Ether-à-go-go-related gene current.

General Toxicology

The most frequently observed effects were decreases in T4 (total and free), T3 (total and free), and TSH. These effects were observed in all general toxicology studies in rats, mice, and dogs and were likely related to the pharmacological activity of resmetirom. The effects varied across species. In general, the reductions in T4 were moderate to marked (e.g., up to ↓100% in rats), whereas T3 and TSH showed minimal to moderate reductions (e.g., up to ↓50% for total T3 (TT3) in dogs and up to ↓87% for TSH in rats), or were unaffected. The effects on T4, T3, and TSH were reversible following the end of treatment.

In the 6-month oral toxicity study in rats, adverse effects were observed in hematology and clinical chemistry, including increases in white blood cells and its differential counts, reticulocytes, ALT, AST, and total and bone alkaline phosphatase (ALP) at ≥30 mg/kg/day (6.1 times the maximum recommended dose based on AUC). Resmetirom at ≥ 30 mg/kg/day produced an increased incidence of mononuclear cell infiltrates in liver, nonspecific hepatocellular cytoplasmic alteration, and subcapsular/interlobular fibrosis (200 mg/kg/day only; 57 times the maximum recommended dose based on AUC). In skeletal muscle, degeneration/regeneration of individual myofibers occurred at ≥30 mg/kg/day. Resmetirom at ≥30 mg/kg/day produced a dose-dependent decrease in T4 (total and free), T3 (total and free), and TSH. The changes in TH were likely related to the pharmacologic activity of resmetirom.

In the 9-month oral toxicity study in beagle dogs, resmetirom at ≥45 mg/kg/day (7 times the maximum recommended dose based on AUC) produced a significant increase in ALT, AST, total ALP, liver ALP, and bone ALP. Resmetirom produced significant decreases in TT3, total T4, and free T4 in a dose-dependent manner at ≥5 mg/kg/day (0.3 times the maximum recommended dose based on AUC). Bile duct hyperplasia and bile stasis occurred in liver at 100 mg/kg/day (25 times the maximum recommended dose based on AUC), and epithelial thickening of tongue associated with epithelial inflammation were observed at ≥15 mg/kg/day in females (1.3 times the maximum recommended dose based on AUC).

MGL-3623, a major (disproportionate) human metabolite of resmetirom, was tested in a 3-month oral toxicity study in CD-1 mice at doses up to 100 mg/kg/day (6 times the maximum recommended dose based on AUC for MGL-3623). All doses produced a dose-dependent decrease in TSH levels, an increase in TT3 levels, and a decrease in total T4 levels (significant in males only). The no-observed-adverse-effect-level was considered to be 30 mg/kg/day in males, based on liver necrosis (2/10 males) and decreased bodyweight at 100 mg/kg/day. The-no-observed-adverse-effect-level in females was 100 mg/kg/day.

Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies of resmetirom included a fertility study in male and female rats, EFD studies in rats and rabbits, and a pre- and postnatal development study in rats. No effects on fertility and early embryonic development were observed at 30 mg/kg/day (6.9 times and 2.6 times the maximum recommended dose in male and female rats, respectively, based on AUC).

In pregnant rabbits, resmetirom at 75 mg/kg/day (3.5 times the maximum recommended dose based on AUC) produced an increase in postimplantation loss and decreases in viable fetuses and fetal weight. These effects were likely due to maternal toxicity (i.e., marked reductions in weight gain and food consumption). In both EFD studies (rats and rabbits), resmetirom produced marked, dose-dependent reductions in T4 and T3, and moderate reductions in TSH. These effects were attributed to the pharmacological activity of resmetirom.

In a pre- and postnatal development study in rats, resmetirom at 100 mg/kg/day (37 times the maximum recommended dose based on AUC) produced a 10% decrease in birthweight, increases in number of stillborn, pup deaths during postnatal days 1 to 4, and pups with absence of milk in stomach. Birthweight was recovered to normal BW during the lactation period. A significant decrease in BW and BW gain in offspring occurred at 100 mg/kg/day after the lactation period. There were marked, dose-dependent reductions in maternal plasma levels of total T4, free T4, TT3, free T3, and TSH at 100 mg/kg/day.

In pregnant rats, oral administration of the metabolite MGL-3623 at doses up to 100 mg/kg/day (4.7 times the maximum recommended dose based on AUC for MGL-3623) had no effects on EFD.

Genetic Toxicology

Resmetirom was not mutagenic or clastogenic in the Ames test, the in vitro chromosomal aberration test using cultured human peripheral blood lymphocytes, the in vitro micronucleus test using L5178Y tk+/- mouse lymphoma cells, or the in vivo rat micronucleus assay.

The metabolite M1 (MGL-3623) was considered positive for induction of micronuclei in TK6 human lymphoblast cells with metabolic activation. However, the relevance of the positive finding is uncertain because the increase in micronuclei was limited to a single concentration with cytotoxicity exceeding 50% (i.e., 59% growth inhibition was observed). In addition, MGL-3623 was not mutagenic in the Ames test or in the in vivo rat micronucleus assay. Thus, there is no safety concern of MGL-3623.

Carcinogenicity

In a 2-year carcinogenicity study in mice, resmetirom at 100 mg/kg/day (51 times the maximum recommended dose based on AUC) produced a statistically significant increase in combined incidence of leiomyoma (benign) and leiomyosarcoma (malignant) in uterus and in uterus and cervix combined in females. No tumorigenic effects were observed in male mice at doses of up to 100 mg/kg/day (35 times the maximum recommended dose based on AUC) or in female mice at doses of up to 30 mg/kg/day (14 times the maximum recommended dose based on AUC).

In a 2-year carcinogenicity study in rats, resmetirom at 30 mg/kg/day (6.5 times the maximum recommended dose based on AUC) produced a statistically significant increase in benign

fibroadenoma in mammary gland in males. No tumorigenic effects were observed in male rats at doses of up to 6 mg/kg/day (3.7 times the maximum recommended dose based on AUC) or in female rats at doses of up to 30 mg/kg/day (3.4 times the maximum recommended dose based on AUC).

In a 6-month carcinogenicity study in transgenic mice (RasH2), metabolite MGL-3623 was not tumorigenic at oral doses up to 1500 mg/kg/day.

Animal-to-Human Exposure Multiples in Labeling

Sections 8.1 and 13.1 of the label (full prescribing information) include animal-to-human drug exposure multiples that are based on AUC. Table 27 provides the animal and human AUC values that were used to calculate the AUC multiples.

Table 27. AUC Values for Animals and Humans Used to Calculate AUC Multiples

Study Type	**Dose (mg/kg/day) and AUC (ng•h/mL)**			
Rat fertility and early embryonic development (Study # 3196-12-018)	Dose: 3 AUC: ND	Dose: 10 AUC: ND	Dose: 30 M/F AUC: 53600* / 20600*	
Rat embryo-fetal development (Study # 3196-12-016)	Dose: 3 AUC: 6290**	Dose: 10 AUC: 15700**	Dose: 30 AUC: 48500**	Dose: 100 AUC: 162000**
Rabbit embryo-fetal development (Study # 3196-12-017)	Dose: 10 AUC: 7760**	Dose: 30 AUC: 21800**	Dose: 75 AUC: 27100**	
Rat pre- and postnatal development (Study # 3196-17-010)	Dose: 3 AUC: 6355***	Dose: 30 AUC: 55650***	Dose: 100 AUC: 287000***	
Rat embryo-fetal development with MGL-3623 (metabolite) (Study # 3196-17-019)	Dose: 3 AUC: 1910**	Dose: 30 AUC: 5320**	Dose: 100 AUC: 10100**	
Rat 2-year carcinogenicity (Study # 3196-18-005)	Dose: 1 M/F AUC: 5530/2000	Dose: 6 M/F AUC: 28500/8880	Dose: 30 M/F AUC: 50500/26300	
Mouse 2-year carcinogenicity (Study # 3196-18-006)	Dose: 3 M/F AUC: 12500/8870	Dose: 30 M/F AUC: 81700/111000	Dose: 100 M/F AUC: 276000/399000	
Human AUC Values	**AUC (ng•h/mL)**			
Human AUC (ng•h/mL) for resmetirom (100 mg/day)	7780			
Human AUC (ng•h/mL) for MGL-3623 (100 mg/day resmetirom)	2170			

Source: Prepared by nonclinical reviewer.
* Values were generated in a 3-month toxicology study in rats on day 91 (Study # 3196-12-006); toxicokinetic parameters were not determined in the fertility and early embryonic development study in rats.
** Determined on the final day of dosing.
*** Mean value of AUCs on gestation days 17 and 20
Abbreviations: AUC, area under the concentration-time curve; M/F, males/females; ND, not determined

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

This is an NME and will be the first drug in its class.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Resmetirom is not approved in the U.S. market or in any foreign market; therefore, no postmarketing safety data is available for resmetirom.

7.3.1. Adverse Events Identified in Postmarket Experiences

Resmetirom has not been marketed in any country, and there are no postmarketing safety data available.

7.3.2. Expectations on Safety

There are no safety concerns that are expected to change the favorable benefit/risk assessment or lead to increased risk with administration of resmetirom in the postmarket setting.

7.3.3. Additional Safety Issues From Other Disciplines

Nonclinical

The pre- and postnatal developmental (PPND) study in rats is deficient based on current International Council for Harmonisation (ICH) standards. This is discussed in Section 7.7.1.

7.4. FDA Approach to the Safety Review

During the safety review, (b) (4) services were used, and the clinical data scientist team helped in generating the safety tables and figures. Deficiencies in the initial data submitted to the NDA were adequately addressed through Applicant responses to information requests. The data quality was adequate to assess the safety of resmetirom.

Analysis Population

The Applicant submitted data from three phase 3 trials, including MGL-3196-11, MGL-3196-14, and MGL-3196-18, in the summary of clinical safety in module 2.7.4. Additional safety data was derived from two phase 2 trials, MGL-3196-05 and MGL-3196-06. The safety population, as described by the Applicant, included any patient who was randomized into a trial and received at least 1 dose of study drug. For Trial MGL-3196-11, the safety population for the Week 52 Primary Analysis included all F1B, F2, and F3 subjects in the intent-to-treat population who were randomized on or before July 31, 2021, and received at least 1 dose of study drug. The safety for F1 A/C subjects was summarized separately as an exploratory analysis by the Applicant.

During this review, for assessing the safety of resmetirom, the review team focused on the safety data from two phase 3, randomized, placebo-controlled trials, MGL-3196-11 and MGL-3196-14.

Rationale for the review team's review strategy:

- The primary safety analysis focused on subjects with NASH with stage F2 and F3 fibrosis in Trial MGL-3196-11 (the pivotal trial) because subjects with F2 and F3 fibrosis will be the intended use population. Refer to Section 6 for discussion regarding the selection of the F2/F3 population for the primary efficacy analysis.
- A pooled safety analysis was also conducted where the review team combined noncirrhotic NASH and NAFLD subjects from two trials, MGL-3196-11 and MGL-3196-14, respectively, as these were two similarly designed trials with a placebo comparator. NAFLD subjects were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH." This pooled population included subjects with all fibrosis stages from Trial MGL-3196-11. Subjects in the open-label noncirrhotic arm in Trial MGL-3196-14 were excluded from this pooled analysis due to lack of a comparator. This was different from the Applicant's pooling strategy.
- Because Trial MGL-3196-18 was primarily a continuation study for subjects from MGL-3196-14 and had no comparator arm, safety data from MGL-3196-18 were considered supportive to assess long-term safety of resmetirom. Data from MGL-3196-18 were reviewed separately and were excluded from the pooled safety analyses for the following reasons:
  - Disease progression: subjects who switched from placebo to treatment in Trial MGL-3196-18 may have had different underlying disease status compared to subjects who started on treatment in Trials MGL-3196-11 and MGL-3196-14.
  - MGL-3196-18 had a different trial design than the other trials—it was randomized and double-blind for the first 12 weeks, followed by an OLE.
  - MGL-3196-18 had different dosing regimens compared to the other trials.
- Safety data from MGL-3196-05 was also considered supportive and was excluded from the pooled analyses for the following reasons:
  - MGL-3196-05 had different dosing regimens compared to the other trials.
  - The duration of treatment (36 weeks) in MGL-3196-05 was different from the two included trials.
- Safety data from MGL-3196-06 was not included in this review as the trial evaluated the effect of resmetirom in a difference population (heterozygous familial hypercholesterolemia).

Treatment-Emergent Adverse Event Definitions

- Trial MGL-3196-11: Defined as any AE with onset or worsening of an existing event (increase in severity or becoming serious from nonserious criteria) after the first dose of study medication and within 30 days of the last dose of study medication (and, if applicable, prior to the first dose of open-label treatment).
- Trial MGL-3196-14: Defined as any AE with onset or postdose worsening of any pre-existing AE (existing prior to the first dose), either by severity or by study drug relationship, on or after the date of the first dose of study medication, up to 30 days after the date of the last dose of study medication.

- Trial MGL-3196-18: Defined as AEs that were new or worsened after the first dose of study drug up to 30 days after the date of last dose of study drug.

Adverse Event Grouping

The Applicant submitted the AE codes using Medical Dictionary for Regulatory Activities (Version 25.0). All the tables and data in this review are based on the original preferred terms (PTs) provided by the Applicant. Minimal recoding of the Applicant's submitted PTs was needed.

Laboratory and Vital Signs Approach

The review team used U.S. conventional units for all laboratory and vital signs analyses.

7.5. Adequacy of the Clinical Safety Database

7.5.1. Extent of Exposure

Exposure in Drug Development Program

A total of 2,858 subjects were exposed to the drug across all studies (Table 28). A total of 364 subjects were exposed during phase 1 development, 162 during phase 2 development, and 2,332 during phase 3 development.

Table 28. Subjects Exposed to Resmetirom by Studies

Study Number	Description	Resmetirom Dose (s)	Placebo n	Resmetirom n
Phase 1				
MGL-3196-08	Open-label, single dose, sequential crossover, bioavailability study in healthy subjects	40, 60 mg	n/a	16
VIA-3196-01	Randomized, double-blind, placebo-controlled, SAD, PK, PD, food effects study in healthy subjects	0.25, 1, 2.5, 5, 10, 20, 50, 100 and 200 mg	18	54
VIA-3196-02	Randomized, double-blind, placebo-controlled, MAD, PK, PD, safety, lipid changes, and biomarkers study in healthy subjects	5, 20, 50, 80, 100 and 200 mg	12	36
MGL-3196-07	Open-label PK and mass balance of 14C mgL-3196 in healthy subjects	40, 60, 100 mg	n/a	8
MGL-3196-10	Open-label, matched control, PK of resmetirom and MGL-3623 in subjects with HI and with NASH compared to healthy matched-control patients with normal hepatic function	40, 60, 80, or 100 mg	n/a	87

Study Number	Description	Resmetirom Dose (s)	Placebo n	Resmetirom n
MGL-3196-03	Open-label, sequential crossover DDI (simvastatin and rosuvastatin) study in healthy subjects	200 mg	n/a	25
MGL-3196-04	Open-label, DDI (atorvastatin) study in healthy Subjects	100 mg	n/a	14
MGL-3196-09	Open-label, DDI (pioglitazone) study in healthy subjects	100 mg	n/a	16
MGL-3196-12	Open-label, DDI (clopidogrel) study in healthy subjects	100 mg	n/a	20
MGL-3196-15	Open-label, DDI (pravastatin, simvastatin) study in healthy subjects	100 mg	n/a	25
MGL-3196-16	Open-label, DDI (warfarin) study in healthy subjects	100 mg	n/a	27
MGL-3196-17	Randomized, double-blind, placebo- and positive-controlled, cross-over QT study in healthy subjects	200 mg	n/a	36
Phase 2				
MGL-3196-05	Randomized, double-blind, placebo-controlled trial in subjects with biopsy-proven NASH	40, 60, 80, or 120 mg	41	84
MGL-3196-06	Randomized, double-blind, placebo-controlled trial in subjects with HeFH	60, 100 mg	38	78
Phase 3				
MGL-3196-11	Randomized, double-blind, placebo-controlled trial in subjects with biopsy-proven NASH	60, 80, 100 mg	349	701
MGL-3196-14	Randomized, double-blind, placebo-controlled trial in subjects with NAFLD	60, 80, 100 mg	318	822
MGL-3196- 14 (addendum)	Addendum to Trial MGL-3196-14, which included an open-label arm of subjects with compensated cirrhosis due to NASH and moderate renal impairment	60, 80, 100 mg	n/a	194
MGL-3196-18	Active treatment study including rollover subjects who completed Trial MGL-3196-14, subjects who failed screening for Trial MGL-3196-11 and MGL-3196-19, and de novo subjects meeting eligibility criteria	60, 80, 100 mg	n/a	615

Source: Clinical reviewer generated from synopses of individual clinical studies of resmetirom submitted by Applicant; module 2.7.6
Abbreviations: n/a, not applicable; DDI, drug-drug interaction; HeFH, familial hypercholesterolemia; HI, hepatic impairment; MAD, multiple dose ascending; n, number of subjects in subset; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PD, pharmacodynamic; PK, pharmacokinetic; SAD, single ascending dose

Trial MGL-3196-11, Pivotal Phase 3 Trial (Including F2 and F3 Fibrosis Stages)

The primary safety analysis was conducted on data from subjects with F2 and F3 fibrosis enrolled in Trial MGL-3196-11. For discussion on the methodology of selection of F2 and F3

subjects, refer to Section 6.2.1 and Section 6.3.2. A total of 888 subjects with F2 and F3 fibrosis were randomized 1:1:1 to receive placebo (n=294), 80 mg (n=298), or 100 mg (n=296) in Trial MGL-3196-11.

For demographics and clinical characteristics of subjects with F2 and F3 fibrosis enrolled in Trial MGL-3196-11, see Table 14 and Table 15 in Section 6.2.1.4. Participant disposition for this population is displayed in Table 17 in Section 6.2.1.4. A higher proportion of subjects in the resmetirom arms discontinued study drug (13%, placebo, 16% 80 mg, 21%, 100 mg) or discontinued the study (9%, placebo, 12% 80 mg, 18% 100 mg) compared with placebo.

Despite the numerical differences in drug or study discontinuation rates between placebo and resmetirom arms, total person years (PY) of exposure was similar across study arms. As noted in Table 29, over 75% of subjects across dose arms were treated for at least 52 weeks. The median duration of exposure was approximately 68 weeks, 66 weeks, and 74 weeks for the placebo, 80 mg, and the 100 mg arms, respectively.

Table 29. Duration of Exposure, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Parameter	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296
Duration of treatment, weeks			
Mean (SD)	77.1 (33.5)	76.1 (36.3)	71.7 (37.4)
Median (Q1, Q3)	67.7 (52.5, 102)	73.7 (52.1, 103.9)	65.6 (52, 91.9)
Min, max	0.1, 157.3	1.1, 156.6	0.1, 156.6
Total exposure (person years)	435	435	407
Subjects treated, by duration, n (%)			
<4 weeks	4 (1.4)	4 (1.3)	10 (3.4)
≥4 to <8 weeks	2 (0.7)	6 (2.0)	9 (3.0)
≥8 to <12 weeks	3 (1.0)	5 (1.7)	9 (3.0)
≥12 to <24 weeks	8 (2.7)	14 (4.7)	12 (4.1)
≥24 to <36 weeks	7 (2.4)	8 (2.7)	7 (2.4)
≥36 to <52 weeks	16 (5.4)	20 (6.7)	26 (8.8)
≥52 to <60 weeks	54 (18.4)	44 (14.8)	43 (14.5)
≥60 weeks	200 (68.0)	197 (66.1)	180 (60.8)

Source: adex.xpt and adsl.xpt; Software: R. Generated by clinical data scientist.
Note: The F2/F3 Population includes fibrosis stage 2 and 3 patients, based on the eligibility read by the central pathologist (see Methods section for more details).
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Abbreviations: F2, fibrosis stage 2; F3, fibrosis stage 3; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Trial MGL-3196-11, Pivotal Phase 3 Trial (Including All Fibrosis Stages)

In Trial MGL-3196-11, 2,983 subjects were screened, with 1,933 subjects failing screening and 1,050 subjects enrolled. Table 30 displays baseline demographics and clinical characteristics of the enrolled subjects. Overall, across the trial arms, approximately 56% of subjects were female, the median age was 57 to 58 years (range 18 to 83), with 24 to 27% of subjects over 65 years in age. Only 1 to 3% of subjects across the trial arms were older than 75 years. Over 88% of subjects enrolled were white, and 16% to 26% of subjects were of Hispanic or Latino ethnicity across trial arms. Over 64% of subjects were from the United States.

Table 30. Baseline Demographic and Clinical Characteristics, Safety Population, Trial MGL-3196-11

Characteristic	Placebo N=349	Resmetirom 80 mg N=352	Resmetirom 100 mg N=349
Sex, n (%)			
Female	192 (55.0)	198 (56.2)	197 (56.4)
Male	157 (45.0)	154 (43.8)	152 (43.6)
Age, years			
Mean (SD)	57.2 (10.8)	55.9 (11.6)	57 (11)
Median (min, max)	58 (22, 83)	57 (18, 81)	58 (22, 81)
Age group, years, n (%)			
≥18 to <40	27 (7.7)	32 (9.1)	27 (7.7)
≥40 to <65	230 (65.9)	237 (67.3)	229 (65.6)
≥65	92 (26.4)	83 (23.6)	93 (26.6)
Age group ≥75, years, n (%)			
≥75	9 (2.6)	5 (1.4)	10 (2.9)
Race, n (%)			
American Indian or Alaska Native	3 (0.9)	4 (1.1)	1 (0.3)
Asian	9 (2.6)	10 (2.8)	9 (2.6)
Black or African American	10 (2.9)	6 (1.7)	5 (1.4)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.3)
Not able to collect	4 (1.1)	4 (1.1)	9 (2.6)
Other	14 (4.0)	9 (2.6)	10 (2.9)
White	308 (88.3)	319 (90.6)	314 (90.0)
Ethnicity, n (%)			
Hispanic or Latino	54 (15.5)	79 (22.4)	89 (25.5)
Not able to collect	4 (1.1)	3 (0.9)	2 (0.6)
Non-Hispanic or Latino	289 (82.8)	267 (75.9)	255 (73.1)
Not reported	2 (0.6)	2 (0.6)	1 (0.3)
Unknown	0	1 (0.3)	2 (0.6)
Country of participation, n (%)			
Australia	15 (4.3)	16 (4.5)	11 (3.2)
Austria	2 (0.6)	1 (0.3)	1 (0.3)
Belgium	13 (3.7)	14 (4.0)	4 (1.1)
Canada	11 (3.2)	6 (1.7)	11 (3.2)
Switzerland	2 (0.6)	3 (0.9)	0
Germany	10 (2.9)	11 (3.1)	12 (3.4)
Spain	6 (1.7)	10 (2.8)	9 (2.6)
France	21 (6.0)	22 (6.2)	27 (7.7)
Great Britain	8 (2.3)	7 (2.0)	5 (1.4)
Hungary	10 (2.9)	11 (3.1)	4 (1.1)
Israel	10 (2.9)	14 (4.0)	16 (4.6)
Italy	6 (1.7)	9 (2.6)	7 (2.0)
Poland	1 (0.3)	2 (0.6)	1 (0.3)
United States	234 (67.0)	226 (64.2)	241 (69.1)
Region of participation, n (%)			
Non-United States	115 (33.0)	126 (35.8)	108 (30.9)
United States	234 (67.0)	226 (64.2)	241 (69.1)

Source: adsl.xpt; Software: R. Generated by clinical data scientist.
Abbreviations: N, number of participants in treatment group; n, number of participants with given characteristic; SD, standard deviation

Of the 1,050 subjects randomized in Trial MGL-3196-11, a higher proportion discontinued study drug (34%) and discontinued study (28%) in the 100 mg arm, compared to both 80 mg and placebo arms. For 80 mg and placebo, a similar proportion of subjects discontinued study drug

and study. A higher proportion of subjects in the 100 mg-dose arm discontinued the trial due to an AE as compared to placebo (~8% versus 3%, respectively), whereas the proportion discontinuing the trial due to an AE in the 80 mg-dose arm was similar to placebo (Table 31).

Table 31. Subject Disposition, Safety Population, Trial MGL-3196-11

Disposition Outcome	Placebo N=349 n (%)	Resmetirom 80 mg N=352 n (%)	Resmetirom 100 mg N=349 n (%)
Randomized	349 (100)	352 (100)	349 (100)
Safety population	349 (100)	352 (100)	349 (100)
Discontinued study drug	104 (29.8)	98 (27.8)	119 (34.1)
Adverse event	16 (4.6)	22 (6.2)	35 (10)
Composite clinical outcome event adjudicated by EAC	22 (6.3)	18 (5.1)	16 (4.6)
Investigators discretion	5 (1.4)	2 (0.6)	3 (0.9)
Lost to follow-up	16 (4.6)	18 (5.1)	15 (4.3)
Other	0 (0)	2 (0.6)	2 (0.6)
Protocol deviation	1 (0.3)	0 (0)	1 (0.3)
Withdrawal by subject	44 (12.6)	36 (10.2)	47 (13.5)
Discontinued study	73 (20.9)	73 (20.7)	98 (28.1)
Adverse event	9 (2.6)	12 (3.4)	27 (7.7)
Investigators discretion	2 (0.6)	2 (0.6)	3 (0.9)
Lost to follow-up	15 (4.3)	19 (5.4)	16 (4.6)
Other	1 (0.3)	1 (0.3)	2 (0.6)
Protocol deviation	1 (0.3)	0 (0)	2 (0.6)
Withdrawal by subject	45 (12.9)	39 (11.1)	48 (13.8)

Source: ds.xpt and adsl.xpt; Software: R, Generated by clinical data scientist.
Note: Median analysis duration is 71.8 weeks (Resmetirom 80 mg), 66.1 weeks (Resmetirom 100 mg), and 69.6 weeks (Placebo).
Abbreviations: CI, confidence interval; EAC, event adjudication committee; n, number of subjects in specified population or group; N, number of subjects in treatment arm

Table 32 below provides a summary of the overall duration of exposure by treatment arm, as well as the proportion of subjects with increasing increments of duration of exposure (bottom half of Table 32). Over 63% of subjects across dose arms were treated for at least 60 weeks. The median duration of exposure was approximately 72 weeks for the resmetirom 80 mg arm, 66 weeks for the resmetirom 100 mg arm, and 70 weeks for placebo. The total PY of exposure was similar across study arms.

Table 32. Duration of Exposure, Safety Population, Trial MGL-3196-11

Parameter	Placebo N=349	Resmetirom 80 mg N=352	Resmetirom 100 mg N=349
Duration of treatment, weeks			
Mean (SD)	77.2 (33.8)	75.7 (36.3)	72.9 (37.5)
Median (Q1, Q3)	69.6 (52.6, 102.6)	71.8 (52.1, 104)	66.1 (52.1, 93)
Min, max	0.1, 157.3	1.1, 156.6	0.1, 157.1
Total exposure (person-years)	517	511	488

Parameter	Placebo N=349	Resmetirom 80 mg N=352	Resmetirom 100 mg N=349
Patients treated, by duration, n (%)			
<4 weeks	5 (1.4)	4 (1.1)	11 (3.2)
≥4 to <8 weeks	3 (0.9)	8 (2.3)	11 (3.2)
≥8 to <12 weeks	4 (1.1)	6 (1.7)	9 (2.6)
≥12 to <24 weeks	9 (2.6)	17 (4.8)	14 (4.0)
≥24 to <36 weeks	9 (2.6)	9 (2.6)	7 (2.0)
≥36 to <52 weeks	17 (4.9)	24 (6.8)	29 (8.3)
≥52 to <60 weeks	65 (18.6)	55 (15.6)	49 (14.0)
≥60 weeks	237 (67.9)	229 (65.1)	219 (62.8)

Source: adex.xpt and adsl.xpt; Software: R, Generated by clinical data scientist.
Note: Median analysis duration is 71.8 weeks (resmetirom 80 mg), 66.1 weeks (resmetirom 100 mg), and 69.6 weeks (Placebo).
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Pooled Analysis (Trials MGL-3196-11 and MGL-3196-14)

The pooled analysis (n=2,019) included Trials MGL-3196-11 (n=1,050) and MGL-3196-14 (n=969).

- Refer to Table 30, Table 31, and Table 32 above for a description of the 1,050 subjects in Trial MGL-3196-11.
- In Trial MGL-3196-14, 969 subjects were enrolled in a 1:1:1 ratio of placebo (n=318), 80 mg (n=327), and 100 mg (n=324) dose arms.

Therefore, the pooled analysis comprised of Trials MGL-3196-11 and MGL-3196-14 included 667 subjects exposed to placebo, 679 subjects exposed to resmetirom 80 mg, and 673 subjects exposed to 100 mg.

Table 33 displays baseline demographic characteristics of the pooled population. Separated by treatment arm, the baseline demographics were similar across treatment arms. Across the trial arms, approximately 55% of subjects were female, the median age was 58 years (range 18 to 83), with 24 to 27% of subjects over 65 years in age. Only 2 to 3% of subjects across the trial arms were older than 75 years. Over 88% of subjects enrolled were white, and 26% to 29% of subjects were of Hispanic or Latino ethnicity across trial arms. Over 81% of subjects were from the United States.

Table 33. Baseline Demographic and Clinical Characteristics, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Characteristic	Placebo N=667	Resmetirom 80 mg N=679	Resmetirom 100 mg N=673
Sex, n (%)			
Female	360 (54.0)	380 (56.0)	374 (55.6)
Male	307 (46.0)	299 (44.0)	299 (44.4)
Age, years			
Mean (SD)	56.5 (11.4)	56 (11.6)	56.5 (11.3)
Median (min, max)	58 (20, 83)	58 (18, 82)	58 (20, 83)

Characteristic	Placebo N=667	Resmetirom 80 mg N=679	Resmetirom 100 mg N=673
Age group, years, n (%)			
≥18 to <40	62 (9.3)	65 (9.6)	59 (8.8)
≥40 to <65	427 (64.0)	449 (66.1)	447 (66.4)
≥65	178 (26.7)	165 (24.3)	167 (24.8)
Age group ≥75, years, n (%)			
≥75	16 (2.4)	16 (2.4)	23 (3.4)
Race, n (%)			
White	590 (88.5)	609 (89.7)	601 (89.3)
American Indian or Alaska Native	4 (0.6)	7 (1.0)	2 (0.3)
Asian	16 (2.4)	16 (2.4)	14 (2.1)
Black or African American	30 (4.5)	27 (4.0)	27 (4.0)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.1)	3 (0.4)
Not able to collect	6 (0.9)	6 (0.9)	11 (1.6)
Other	19 (2.8)	13 (1.9)	15 (2.2)
Ethnicity, n (%)			
Hispanic or Latino	175 (26.2)	188 (27.7)	197 (29.3)
Non-Hispanic or Latino	480 (72.0)	482 (71.0)	469 (69.7)
Not reported	5 (0.7)	4 (0.6)	3 (0.4)
Not able to collect	5 (0.7)	3 (0.4)	2 (0.3)
Unknown	2 (0.3)	2 (0.3)	2 (0.3)
Country of participation, n (%)			
Australia	15 (2.2)	16 (2.4)	11 (1.6)
Austria	2 (0.3)	1 (0.1)	1 (0.1)
Belgium	13 (1.9)	14 (2.1)	4 (0.6)
Canada	11 (1.6)	6 (0.9)	11 (1.6)
Switzerland	2 (0.3)	3 (0.4)	0
Germany	10 (1.5)	11 (1.6)	12 (1.8)
Spain	6 (0.9)	10 (1.5)	9 (1.3)
France	21 (3.1)	22 (3.2)	27 (4.0)
Great Britain	8 (1.2)	7 (1.0)	5 (0.7)
Hungary	10 (1.5)	11 (1.6)	4 (0.6)
Israel	10 (1.5)	14 (2.1)	16 (2.4)
Italy	6 (0.9)	9 (1.3)	7 (1.0)
Poland	1 (0.1)	2 (0.3)	1 (0.1)
United States	552 (82.8)	553 (81.4)	565 (84.0)
Is in United States, n (%)			
United States	552 (82.8)	553 (81.4)	565 (84.0)
Non-United States	115 (17.2)	126 (18.6)	108 (16.0)

Source: MGL-3196-11 adsl.xpt, MGL-3196-14 adsl.xpt; Software: R Generated by clinical data scientist.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 34 displays the disposition of the subjects in the pooled analysis. Overall, a similar proportion of subjects discontinued study drug or discontinued the study across treatment arms and placebo. However, a higher proportion of subjects in the resmetirom arms discontinued study drug due to an AE compared to placebo (7% for 100 mg, and 6% for 80 mg, versus 4% for placebo).

Table 34. Subject Disposition, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Disposition Event	Placebo N=669 n (%)	Resmetirom 80 mg N=679 n (%)	Resmetirom 100 mg N=674 n (%)
Randomized	669 (100)	679 (100)	674 (100)
Safety population	667 (99.7)	679 (100)	673 (99.9)
Discontinued study drug	177 (26.5)	192 (28.3)	188 (27.9)
Adverse event	27 (4)	43 (6.3)	50 (7.4)
Composite clinical outcome event adjudicated by EAC	22 (3.3)	18 (2.7)	16 (2.4)
Investigators discretion	8 (1.2)	5 (0.7)	3 (0.4)
Lost to follow-up	31 (4.6)	36 (5.3)	37 (5.5)
Protocol deviation	1 (0.1)	0 (0)	1 (0.1)
Study terminated by Applicant	1 (0.1)	0 (0)	1 (0.1)
Withdrawal by subject	82 (12.3)	81 (11.9)	76 (11.3)
Other	5 (0.7)	9 (1.3)	4 (0.6)
Discontinued study	140 (20.9)	156 (23)	167 (24.8)
Adverse event	13 (1.9)	21 (3.1)	37 (5.5)
Investigators' discretion	5 (0.7)	5 (0.7)	4 (0.6)
Lost to follow-up	32 (4.8)	42 (6.2)	39 (5.8)
Protocol deviation	1 (0.1)	0 (0)	3 (0.4)
Study terminated by Applicant	1 (0.1)	0 (0)	0 (0)
Withdrawal by subject	84 (12.6)	87 (12.8)	80 (11.9)
Other	4 (0.6)	1 (0.1)	4 (0.6)

Source: MGL-3196-11 adsl.xpt, MGL-3196-14 adsl.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: CI, confidence interval; EAC, endpoint adjudication committee; ITT, intent-to-treat; mITT, modified intent-to-treat; N, number of patients in treatment arm; n, number of subjects in specified population or group; N, number of subjects in treatment arm

Over 66% of subjects across dose arms were treated for at least 52 weeks. The median duration of exposure was approximately 52 weeks for all three dose arms. The total PY of exposure was similar across study arms (Table 35).

Table 35. Duration of Exposure, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Parameter	Placebo N=667	Resmetirom 80 mg N=679	Resmetirom 100 mg N=673
Duration of treatment, weeks			
Mean (SD)	62 (30.8)	59.7 (33)	59.5 (32.2)
Median (Q1, Q3)	52.3 (51.9, 77.5)	52.1 (51.6, 77.2)	52.1 (51.7, 76.9)
Min, max	0.1, 157.3	0.1, 156.6	0.1, 157.1
Total exposure (person-years)	793	777	767

Parameter	Placebo N=667	Resmetirom 80 mg N=679	Resmetirom 100 mg N=673
Patients treated, by duration, n (%)			
<4 weeks	16 (2.4)	14 (2.1)	28 (4.2)
≥4 to <8 weeks	9 (1.3)	18 (2.7)	14 (2.1)
≥8 to <12 weeks	6 (0.9)	23 (3.4)	15 (2.2)
≥12 to <24 weeks	28 (4.2)	38 (5.6)	32 (4.8)
≥24 to <36 weeks	26 (3.9)	32 (4.7)	19 (2.8)
≥36 to <52 weeks	104 (15.6)	103 (15.2)	108 (16.0)
≥52 to <60 weeks	241 (36.1)	221 (32.5)	238 (35.4)
≥60 weeks	237 (35.5)	230 (33.9)	219 (32.5)

Source: MGL-3196-11 adsl.xpt, MGL-3196-14 adsl.xpt; Software: R. Generated by clinical data scientist.
Note: This pooled analysis includes patients from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.5.2. Discussion

The safety database meets the minimum required sample size per the ICH guidance for industry, *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995). The potential U.S. population that has NASH with stage 2 and 3 hepatic fibrosis is estimated to be approximately 5.7 million people and is expected to increase over time (Estes et al. 2018). This available safety database is reasonable for a premarketing safety assessment of resmetirom for the proposed indication, patient population, dosage regimen, and duration. A total of 2858 subjects received resmetirom in the development program, and 1352 subjects received the proposed marketed dosages in the safety database.

7.6. Safety Results

In the following sections, safety assessments are summarized for:

- MGL-3196-11 efficacy population (NASH with F2 and F3 fibrosis)
- Pooled data from all subjects enrolled in MGL-3196-11 and MGL-3196-14

The subjects enrolled were appropriate to evaluate safety. The safety evaluation of resmetirom was adequate, and the demonstrated safety profile of resmetirom is acceptable for the indicated doses and population studied. Unless otherwise stated, analyses are generally presented using exposure-adjusted incidence rates (EAIRs) with the denominator of person years to adjust for any potential differences in exposure-time between treatment arms. Analysis of safety data was done by assessing PTs for AEs and also by carrying out narrow FDA Medical Queries (FMQs). FMQs are standardized groupings of similar AE terms intended to assist with the identification of potential safety issues during the review of clinical trial safety data. Each FMQ is aligned to a single system organ class (SOC) based on clinical judgment. Some FMQs may contain PTs from more than one SOC. Not all PTs are captured in FMQs. FMQ version 2.1 is publicly available on the federal docket (FDA 2022).

Briefly, the most common adverse drug reactions observed were diarrhea, nausea, pruritus, abdominal pain, vomiting, constipation, and dizziness, where diarrhea and nausea were the most common cause of treatment discontinuation. Deaths reported during the trials were not related. Serious adverse events (SAEs) were rare. A safety signal of drug-induced hepatotoxicity was noted during the review (Section 7.7.1).

The Applicant submitted Trials MGL-3196-18 and MGL-3196-05 in support of safety; these were not included in the pooled analysis (see Section 7.4 for rationale). These were reviewed separately and did not reveal any new safety signals. Safety data from phase 1 and open-label arms of Trials MGL-3196-14 and MGL-3196-18 was also reviewed with no new safety signals uncovered, except for a possible DILI case (Subject (b) (6)) in the open-label cirrhotic population in Trial MGL-3196-14. This case is discussed in Section 7.7.1. Applicant submitted a 120-day safety update on November 8, 2023, where no new safety signals were noted.

In summary, the overall assessment of safety of resmetirom does not preclude a conclusion of a favorable benefit-risk profile for the intended population.

7.6.1. Safety Results, Trial MGL-3196-11 (F2/F3 Population)

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial MGL-3196-11 (F2/F3 Population)

Table 36 displays an overview of AEs in the F2 and F3 population.

- The 100 mg-dose arm had a higher incidence of SAEs compared to placebo (EAIR per 100 PY of 10.5 versus EAIR per 100 PY of 8.3, respectively), whereas the 80 mg arm had a lower EAIR per 100 PY of SAE compared to placebo (7.7 versus 8.3, respectively). There were two SAEs with fatal outcomes in the 100 mg arm, none in the 80 mg arm, and one in the placebo arm. SAEs requiring hospitalization were also slightly higher in the 100 mg arm.
- Compared to placebo, the 100 mg arm had a higher EAIR of subjects with an AE leading to permanent discontinuation and dose interruption of study drug.

Table 36. Overview of Adverse Events, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Event Category	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
SAE	34/407.4 (8.3)	32/416 (7.7)	40/379.9 (10.5)	-0.7 (-4.7, 3.3)	2.2 (-2.1, 6.7)
SAEs with fatal outcome	1/434.6 (0.2)	0/434.8 (0)	2/406.7 (0.5)	-0.2 (-1.3, 0.7)	0.3 (-0.9, 1.6)
Life-threatening SAEs	4/431 (0.9)	1/434.8 (0.2)	2/406.3 (0.5)	-0.7 (-2.2, 0.5)	-0.4 (-2.0, 1.0)
SAEs requiring hospitalization	30/408.9 (7.3)	31/416.8 (7.4)	35/383.7 (9.1)	0.1 (-3.7, 3.9)	1.8 (-2.3, 6.0)
SAEs resulting in substantial disruption of normal life functions	3/432 (0.7)	1/434.8 (0.2)	2/406.3 (0.5)	-0.5 (-1.8, 0.7)	-0.2 (-1.6, 1.2)
Other	9/430.7 (2.1)	6/430.9 (1.4)	13/395.2 (3.3)	-0.7 (-2.7, 1.2)	1.2 (-1.1, 3.8)
AE leading to permanent discontinuation of study drug	18/433.7 (4.2)	22/431.9 (5.1)	33/403.5 (8.2)	0.9 (-2.0, 4.0)	4.0 (0.7, 7.7) *
AE leading to dose modification of study drug	29/407.5 (7.1)	33/405.5 (8.1)	41/382.8 (10.7)	1.0 (-2.9, 5.0)	3.6 (-0.6, 8.0)
AE leading to interruption of study drug	29/407.5 (7.1)	32/405.8 (7.9)	41/382.8 (10.7)	0.8 (-3.1, 4.7)	3.6 (-0.6, 8.0)
AE leading to reduction of study drug	0/434.6 (0)	1/434.5 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
AE leading to dose delay of study drug	0/434.6 (0)	0/434.8 (0)	0/406.6 (0)	0.0 (-0.9, 0.9)	0.0 (-0.9, 0.9)
Any AE	271/88.2 (307.3)	273/97.8 (279.2)	271/76.3 (355.2)	-28.1 (-78.0, 21.1)	47.9 (-7.7, 104.5)
Severe and worse	44/405.9 (10.8)	41/409.8 (10.0)	44/374.3 (11.8)	-0.8 (-5.4, 3.7)	0.9 (-3.9, 5.8)
Moderate	157/264.3 (59.4)	168/245.6 (68.4)	171/233.1 (73.4)	9.0 (-4.9, 23.1)	14.0 (-0.3, 28.6)
Mild	70/355.1 (19.7)	64/373 (17.2)	56/351 (16.0)	-2.6 (-8.9, 3.7)	-3.8 (-10.1, 2.5)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; py, person-years (at risk); PY, person-years

7.6.1.2. Deaths, Trial MGL-3196-11 (F2/F3 Population)

There were two deaths reported in the 100 mg arm for the F2 and F3 population, with no deaths in the 80 mg arm and one in the placebo arm. See Table 37.

Table 37. Deaths, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Preferred Term	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR[1] Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR[1] Difference (95% CI)
Any AE leading to death	1/434.6 (0.2)	0/434.8 (0)	2/406.7 (0.5)	-0.2 (-1.3, 0.7)	0.3 (-0.9, 1.6)
Cholestasis	0/434.6 (0)	0/434.8 (0)	1/406.7 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Hodgkin's disease	0/434.6 (0)	0/434.8 (0)	1/406.7 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Intracardiac thrombus	0/434.6 (0)	0/434.8 (0)	1/406.7 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Prosthetic cardiac valve thrombosis	0/434.6 (0)	0/434.8 (0)	1/406.7 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Death	1/434.6 (0.2)	0/434.8 (0)	0/406.6 (0)	-0.2 (-1.3, 0.7)	-0.2 (-1.3, 0.7)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
[1] EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of patients in treatment arm; n, number of patients with at least one event; py, person-years (at risk); PY, person-years (total exposure)

Table 38 displays the listing of all individual subjects who died in the F2 and F3 population in Trial MGL-3196-11, with PT for cause of death. It also displays a summary narrative and assessment of relatedness for the deaths. In summary, the two deaths reported in the 100 mg arm are likely unrelated to resmetirom.

Table 38. Listing of All Individual Subject Deaths, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Dose Arm	Subject ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death Preferred Term	Relatedness	Review Findings
100 mg	(b) (6)	69	M	793	933	Cholestasis Hodgkin's disease	Unrelated	Case discussed in detail in Section 7.7.2 as this was also a potential Hy's law case. This subject had a recurrence of Hodgkin's lymphoma.
100 mg	(b) (6)	64	M	197	213	Intracardiac thrombus Prosthetic cardiac valve thrombosis	Unrelated	Subject with history of aortic valve (AV) stenosis and AV replacement, atrial fibrillation, atrial flutter, carotid artery disease, coronary artery disease, and myocardial infarction. On Study Day 180, subject was hospitalized with a diagnosis of acute left ventricular failure, acute myocardial infarction, and prosthetic cardiac valve thrombosis. He was discharged on Study Day 183. Study drug dose was not changed. On Study Day 213, while on a cruise, subject called the ship's medical team because he was not feeling well. On arrival to the room, the team found the subject already deceased. No autopsy was performed. Case was adjudicated by the cardiac and hepatic committees and found to be not related to the drug.
Placebo	(b) (6)	52	M	264	263	Death	Unrelated	On Study Day 263 the subject's family informed the Applicant that the subject had died. No cause of death was provided, and no autopsy was performed. The Applicant assessed this to be not related.

Source: adae.xpt and Clinical Study Report for Trial MGL-3196-11; Software: R Generated by clinical data scientist and clinical reviewer.
Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Abbreviations: AE, adverse event; AV, aortic valve; F2, fibrosis stage 2; F3, fibrosis stage 3; ID, identifier; M, male; NA, not applicable

7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial MGL-3196-11 (F2/F3 Population)

The Applicant defined SAEs as below in the trial protocol (V 6.0).

An AE or adverse reaction (AR) is considered serious if, in the view of either the investigator or Applicant, it results in any of the following outcomes:

- Death.
- A life-threatening AE.
- Required hospitalization or prolongation of existing hospitalizations.
  - Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital will not be considered inpatient hospitalizations).
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Table 39 displays the SAEs reported in Trial MGL-3196-11 (F2 and F3 population) by SOC where the EAIR is greater than 0.2 per 100 PY in either drug dose-arms. This corresponds to SAEs reported by at least one subject in the trial arms. SAEs with incidence rates less than placebo are not displayed.

The incidence of SAEs was similar between the 80mg-arm and placebo, but higher in the resmetirom 100 mg group with an EAIR difference of 2.2 events per 100 PY (95% CI -2.1, 6.7) relative to placebo.

A higher incidence of malignancies was reported in the 100 mg arm compared to placebo, however, reported malignancies were not specific to any organ or body system. Malignancies are discussed in greater detail in Section 7.7.10.

Within the SOC musculoskeletal and connective tissue disorders, osteoarthritis was the most observed SAE, but this was not considered related to the drug. Arthralgia and myalgia were other SAEs present in the same SOC but were considered possibly related, given that these AEs are common in the disease also.

Renal and urinary disorders were reported in higher incidence in the 80 mg arm compared to placebo. SAEs reported under this SOC included nephro-and ureterolithiasis, acute kidney injury and pelvi-ureteric obstruction. Based on the MOA of resmetirom, and the fact that NAFLD may be associated with an increased risk of urolithiasis (Nam 2016; Qin et al. 2018), it is difficult to ascribe causality for these events to resmetirom.

An increased incidence of gall bladder-related SAEs was reported in the hepatobiliary SOC. This is discussed in more detail in Section 7.7.3.

EAIR for obstructive pancreatitis in the GI SOC, was higher in the drug arms (0.2 per 100 PY in 100 mg arm and 0.5 per 100 PY in 80 mg) compared to placebo, likely sequalae of gallbladder AEs (e.g., gallstones). The SOC of GI disorders is not displayed in Table 39, as overall the incidence of GI SAEs was similar to or lower in the drug arms compared to placebo. (1.5 per 100 PY in 100 mg arm and 0.7 per 100 PY in 80 mg, versus 1.6 per 100 PY in placebo). Obstructive pancreatitis is discussed further in Section 7.7.3.

Related SOCs (SAEs) were injury, poisoning and procedural complications (humerus, cervical vertebrae, and ankle fractures), blood and lymphatic system disorders (anemia), metabolism and nutrition disorders (hyper-and hypoglycemia), ear and labyrinth disorders (vertigo), skin and subcutaneous tissue disorders(urticaria), and investigations (increased creatinine phosphokinase). No SAEs in the SOCs of reproductive system and breast disorders, general disorders, and administration site conditions were considered related.

Analysis of AEs was also performed using FMQs (results displayed in Table 283 in Section 17.1), which provided consistent results as summarized above, except for two additional observed AEs occurring at a higher frequency in the resmetirom arms versus placebo—tendinopathy and rash.

Table 39. Subjects With Serious Adverse Events by System Organ Class (Occurring at EAIR ≥0.2 Per 100 PY in Either Drug Dose-Arm), Safety Population, Trial MGL-3196-11 (F2/F3 Population)

System Organ Class	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR[1] Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any SAE	34/407.4 (8.3)	32/416 (7.7)	40/379.9 (10.5)	-0.7 (-4.7, 3.3)	2.2 (-2.1, 6.7)
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	3/433.1 (0.7)	2/434.1 (0.5)	8/402.6 (2.0)	-0.2 (-1.6, 1.1)	1.3 (-0.3, 3.3)
Injury, poisoning, and procedural complications	4/430.7 (0.9)	3/432.1 (0.7)	7/401.1 (1.7)	-0.2 (-1.8, 1.2)	0.8 (-0.9, 2.8)
Musculoskeletal and connective tissue disorders	3/432 (0.7)	6/431.8 (1.4)	1/405.6 (0.2)	0.7 (-0.8, 2.4)	-0.4 (-1.8, 0.8)
Renal and urinary disorders	0/434.6 (0)	5/432.6 (1.2)	2/405 (0.5)	1.2 (0.3, 2.7) *	0.5 (-0.4, 1.8)
General disorders and administration site conditions	3/432.6 (0.7)	2/433.5 (0.5)	4/405.6 (1.0)	-0.2 (-1.6, 1.1)	0.3 (-1.2, 1.9)
Hepatobiliary disorders	0/434.6 (0)	2/434.2 (0.5)	3/405 (0.7)	0.5 (-0.4, 1.7)	0.7 (-0.1, 2.2)
Metabolism and nutrition disorders	0/434.6 (0)	1/433.7 (0.2)	3/404.1 (0.7)	0.2 (-0.7, 1.3)	0.7 (-0.1, 2.2)
Ear and labyrinth disorders	0/434.6 (0)	0/434.8 (0)	2/405.3 (0.5)	0.0 (-0.9, 0.9)	0.5 (-0.4, 1.8)
Reproductive system and breast disorders	0/434.6 (0)	0/434.8 (0)	2/404.2 (0.5)	0.0 (-0.9, 0.9)	0.5 (-0.4, 1.8)
Skin and subcutaneous tissue disorders	0/434.6 (0)	1/433.9 (0.2)	1/406.2 (0.2)	0.2 (-0.7, 1.3)	0.2 (-0.6, 1.4)
Blood and lymphatic system disorders	0/434.6 (0)	1/434.5 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Investigations	0/434.6 (0)	1/434.6 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; F2, fibrosis stage 2; F3, fibrosis stage 3; N, number of subjects in treatment arm; n, number of subjects with adverse event; py, person-years (at risk); PY, person-years (total exposure); SAE, serious adverse event; SOC, system organ class

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial MGL-3196-11 (F2/F3 Population)

Table 40 displays the AEs reported in Trial MGL-3196-11 (F2 and F3 population) by SOC leading to treatment discontinuation. Table 41 displays treatment discontinuations by narrow FMQ. AEs presented are where the EAIR is greater than equal to 0.2 per 100 PY in either drug dose arm. This corresponds to an AE leading to treatment discontinuation reported by at least one subject in the trial arms. AEs with incidence rates less than placebo or implausibly related to study drug are not displayed.

Incidence of AEs leading to treatment discontinuation was higher in the resmetirom 100 mg group with an EAIR difference of 4 per 100 PY (95% CI:-2.1, 6.7) relative to placebo, and in the 80 mg arm with an EAIR difference of 0.9 per 100 PY (95% CI: -2.0, 4.0) relative to placebo.

GI disorders were the most common AEs leading to treatment discontinuation. Among GI disorders, diarrhea and nausea were the most frequent causes of treatment discontinuation. Abdominal pain, vomiting, dyspepsia and obstructive pancreatitis were other AEs leading to treatment discontinuation in the GI disorders SOC.

The SOC of skin and subcutaneous tissue disorders was the next common cause of treatment discontinuation, with pruritus, urticaria and rash being the AEs leading to treatment discontinuation.

Relevant SOC and AEs leading to treatment discontinuation in the SOCs were investigations (elevated transaminases, discussed further in Section 7.6.1.6); metabolism and nutrition disorders (decreased appetite); cardiac disorders (palpitations, discussed further in Section 7.7.9); endocrine disorders (hypothyroidism, discussed in Section 7.7.2); and Injury, poisoning and procedural complications (cervical vertebral fracture).

AEs analyzed by FMQs in Table 41 yielded similar results. Diarrhea, nausea, and abdominal pain were the most common AEs leading to treatment discontinuation, followed by pruritus, rash, urticaria, and vomiting.

Within the SOC of hepatobiliary disorders, the most common cause for treatment discontinuation reported was hepatic cirrhosis. Other relevant AEs in this SOC were hyperbilirubinemia, jaundice, cholestasis, and bile duct stone. Hepatobiliary events are discussed in Section 7.7.3.

Hepatic injury, as assessed by FMQs and included in Table 41, is a grouped term, where the primary component term was hepatic cirrhosis. Hepatic cirrhosis is a clinical outcome of the disease and not considered a safety signal, and therefore, the term hepatic injury was not included in the label. The incidence of hepatic injury was also not substantively different in the drug arms compared to placebo. Drug-induced hepatotoxicity is discussed in greater detail in Section 7.7.1.

Table 40. Subjects With Adverse Events Leading to Treatment Discontinuation (Occurring at EAIR ≥0.2 Per 100 PY in Either Drug Dose Arm and Greater Than Placebo), by System Organ Class, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

System Organ Class	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any AE leading to discontinuation	18/433.7 (4.2)	22/431.9 (5.1)	33/403.5 (8.2)	0.9 (-2.0, 4.0)	4.0 (0.7, 7.7) *
Gastrointestinal disorders	3/434.5 (0.7)	9/434 (2.1)	15/404.1 (3.7)	1.4 (-0.2, 3.3)	3.0 (1.2, 5.5) *
Skin and subcutaneous tissue disorders	1/434.5 (0.2)	0/434.8 (0)	6/406.4 (1.5)	-0.2 (-1.3, 0.7)	1.2 (0.0, 3.0) *
Hepatobiliary disorders	3/434.4 (0.7)	5/434.7 (1.2)	6/406.4 (1.5)	0.5 (-1.0, 2.1)	0.8 (-0.7, 2.6)
Investigations	1/434.5 (0.2)	3/434.7 (0.7)	0/406.6 (0)	0.5 (-0.7, 1.8)	-0.2 (-1.3, 0.7)
Metabolism and nutrition disorders	0/434.6 (0)	0/434.8 (0)	2/406.6 (0.5)	0.0 (-0.9, 0.9)	0.5 (-0.4, 1.8)
Cardiac disorders	1/434.6 (0.2)	0/434.8 (0)	2/406.7 (0.5)	-0.2 (-1.3, 0.7)	0.3 (-0.9, 1.6)
Endocrine disorders	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Injury, poisoning, and procedural complications	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; py, person-years (at risk); PY, person-years (total exposure); SOC, system organ class

Table 41. Subjects With Adverse Events Leading to Treatment Discontinuation (Occurring at EAIR ≥0.2 Per 100 PY in Either Dose Arm and Greater Than Placebo) by FDA Medical Query (Narrow), Safety Population, Trial MGL-3196-11 (F2/F3 Population)*

FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Diarrhea	1/434.6 (0.2)	2/434.7 (0.5)	11/404.4 (2.7)	0.2 (-0.9, 1.5)	2.5 (1.0, 4.7) **
Hepatic injury	3/434.4 (0.7)	6/434.6 (1.4)	5/406.4 (1.2)	0.7 (-0.8, 2.4)	0.5 (-0.9, 2.3)
Abdominal pain	2/434.5 (0.5)	5/434.2 (1.2)	3/406.5 (0.7)	0.7 (-0.7, 2.3)	0.3 (-1.0, 1.8)
Nausea	0/434.6 (0)	3/434.8 (0.7)	4/406.3 (1.0)	0.7 (-0.2, 2.0)	1.0 (0.1, 2.5) *
Pruritus	0/434.6 (0)	0/434.8 (0)	3/406.4 (0.7)	0.0 (-0.9, 0.9)	0.7 (-0.1, 2.2)
Rash	0/434.6 (0)	0/434.8 (0)	3/406.6 (0.7)	0.0 (-0.9, 0.9)	0.7 (-0.1, 2.2)
Dyspepsia	2/434.5 (0.5)	3/434.3 (0.7)	1/406.5 (0.2)	0.2 (-1.1, 1.6)	-0.2 (-1.5, 1.0)
Vomiting	1/434.6 (0.2)	2/434.8 (0.5)	2/406.6 (0.5)	0.2 (-0.9, 1.5)	0.3 (-0.9, 1.6)
Fatigue	1/434.6 (0.2)	2/434.7 (0.5)	1/406.6 (0.2)	0.2 (-0.9, 1.5)	0.0 (-1.1, 1.2)

FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Urticaria	0/434.6 (0)	0/434.8 (0)	2/406.6 (0.5)	0.0 (-0.9, 0.9)	0.5 (-0.4, 1.8)
Headache	1/434.6 (0.2)	2/433 (0.5)	0/406.6 (0)	0.2 (-0.9, 1.5)	-0.2 (-1.3, 0.7)
Pancreatitis	0/434.6 (0)	1/434.8 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Dizziness	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Decreased appetite	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Fall	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Fracture	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Arthralgia	0/434.6 (0)	1/434.7 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Thrombosis	0/434.6 (0)	0/434.8 (0)	1/406.7 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Palpitations	0/434.6 (0)	0/434.8 (0)	1/406.6 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Subjects with at least one AE leading to discontinuation are presented
** Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); F2, fibrosis stage 2; F3, fibrosis stage 3; FMQ, FDA medical query; incl, including; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term; py, person-years (at risk); PY, person-years (total exposure); SOC, system organ class

There were significantly higher treatment discontinuations noted in the 100 mg dose arm compared to placebo. Treatment discontinuations were similar in the 80 mg-dose arm and placebo. Diarrhea and nausea were the most common cause of treatment discontinuations. These can be adequately managed through labeling.

7.6.1.5. Treatment-Emergent Adverse Events, Trial MGL-3196-11 (F2/F3 Population)

Table 42 displays the TEAEs reported in the F2 and F3 population in Trial MGL-3196-11 by SOC, occurring at an EAIR greater than equal to 1 per 100 PY in either dose arm.

Table 42. Subjects With Common Treatment-Emergent Adverse Events by System Organ Class (Occurring at EAIR ≥1 Per 100 PY in Either Dose Arm) Safety Population, Trial MGL-3196-11 (F2/F3 Population)

System Organ Class	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any AE	271/88.2 (307.3)	273/97.8 (279.2)	271/76.3 (355.2)	-28.1 (-78.0, 21.1)	47.9 (-7.7, 104.5)
Gastrointestinal disorders	154/269.8 (57.1)	169/230.2 (73.4)	182/204.4 (89.0)	16.3 (2.2, 30.9) *	31.9 (16.5, 48.2) *
Musculoskeletal and connective tissue disorders	110/313.3 (35.1)	115/317.7 (36.2)	123/281.8 (43.6)	1.1 (-8.3, 10.5)	8.5 (-1.5, 18.9)
Skin and subcutaneous tissue disorder	68/356.3 (19.1)	62/364.3 (17.0)	83/317.0 (26.2)	-2.1 (-8.4, 4.2)	7.1 (-0.1, 14.6)
Metabolism and nutrition disorders	71/377.8 (18.8)	61/381.0 (16.0)	75/333.1 (22.5)	-2.8 (-8.9, 3.2)	3.7 (-3.0, 10.6)
Nervous system disorders	72/360.8 (20.0)	77/358.4 (21.5)	68/341.2 (19.9)	1.5 (-5.2, 8.3)	-0.0 (-6.7, 6.7)
Respiratory, thoracic, and mediastinal disorders	41/396.8 (10.3)	39/397.7 (9.8)	47/373.4 (12.6)	-0.5 (-5.1, 4.0)	2.3 (-2.6, 7.2)
Renal and urinary disorders	28/407.1 (6.9)	19/420.3 (4.5)	33/380.2 (8.7)	-2.4 (-5.8, 0.9)	1.8 (-2.1, 5.9)
Reproductive system and breast disorders	15/418.7 (3.6)	19/419.6 (4.5)	22/385.3 (5.7)	0.9 (-1.9, 3.9)	2.1 (-0.9, 5.4)
Immune system disorders	16/419.6 (3.8)	19/416.4 (4.6)	22/387.8 (5.7)	0.7 (-2.1, 3.7)	1.9 (-1.2, 5.1)
Neoplasms—benign, malignant and unspecified (including cysts and polyps)	18/417.6 (4.3)	14/424.1 (3.3)	22/392.6 (5.6)	-1.0 (-3.9, 1.7)	1.3 (-1.8, 4.6)
Cardiac disorders	14/424.3 (3.3)	16/423.4 (3.8)	20/394.8 (5.1)	0.5 (-2.2, 3.2)	1.8 (-1.1, 4.8)
Ear and labyrinth disorders	10/424.2 (2.4)	16/420.8 (3.8)	12/396 (3.0)	1.4 (-1.0, 4.1)	0.7 (-1.7, 3.2)
Endocrine disorders	5/430.8 (1.2)	5/431.3 (1.2)	14/392.2 (3.6)	-0.0 (-1.7, 1.7)	2.4 (0.4, 4.9) *

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; F2, fibrosis stage 2; F3, fibrosis stage 3; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Table 43 displays the most common AEs by PTs and Table 44 displays the most common TEAEs by SOC and FMQ (narrow). The data presented in Table 43 and Table 44 are truncated at EAIR greater than or equal to 5 per 100 PY in either dose arms. If there is

little to no plausibility of relatedness for the AE, the SOC is not displayed. Table 284 and Table 285, in Section 17.1.2, provide a more extensive list of TEAEs by PT and FMQ (narrow), regardless of relatedness or severity.

Table 43. Subjects With Adverse Events (Occurring at EAIR ≥5 Per 100 PY in Either Dose Arm), Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Preferred Term	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Diarrhea	52/377.6 (13.8)	78/346 (22.5)	98/299.4 (32.7)	8.8 (2.6, 15.3) *	19.0 (11.7, 26.9)*
Nausea	36/400.4 (9.0)	65/359.2 (18.1)	51/351.6 (14.5)	9.1 (3.9, 14.7) *	5.5 (0.6, 10.7)*
Arthralgia	36/395.7 (9.1)	45/389.4 (11.6)	33/377.8 (8.7)	2.5 (-2.1, 7.1)	-0.4 (-4.7, 4.0)
Pruritus	18/412.4 (4.4)	24/402 (6.0)	36/369.3 (9.7)	1.6 (-1.6, 4.9)	5.4 (1.7, 9.5)*
Abdominal pain	18/414.5 (4.3)	27/409.9 (6.6)	32/373.1 (8.6)	2.2 (-1.0, 5.7)	4.2 (0.7, 8.1)*
Vomiting	15/423.5 (3.5)	27/409.5 (6.6)	30/378.9 (7.9)	3.1 (0.0, 6.4) *	4.4 (1.1, 8.1)*
Headache	28/402.5 (7.0)	31/400.5 (7.7)	21/381.6 (5.5)	0.8 (-3.1, 4.7)	-1.5 (-5.1, 2.1)
Fatigue	27/401.5 (6.7)	31/405.2 (7.7)	25/383.8 (6.5)	0.9 (-2.9, 4.8)	-0.2 (-3.9, 3.5)
Constipation	18/416.3 (4.3)	20/415.3 (4.8)	28/372.3 (7.5)	0.5 (-2.5, 3.6)	3.2 (-0.2, 6.9)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Note Median analysis duration is 73.7 weeks (Resmetirom 80 mg), 65.6 weeks (Resmetirom 100 mg), and 67.7 weeks (Placebo).
Note: Coded as MedDRA preferred terms (version 25.0)
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); F2, fibrosis stage 2; F3, fibrosis stage 3; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

Table 44. Subjects With Adverse Events (Occurring at EAIR of ≥5 Per 100 PY in Either Dose Arm), by System Organ Class, FDA Medical Query (Narrow), Safety Population Trial MGL-3196-11 (F2/F3 Population)

System Organ Class FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Gastrointestinal disorders					
Diarrhea	52/377.6 (13.8)	79/345.1 (22.9)	98/299.4 (32.7)	9.1 (2.9, 15.7) *	19.0 (11.7, 26.9) *
Nausea	36/400.4 (9.0)	66/357.5 (18.5)	51/351.6 (14.5)	9.5 (4.3, 15.1) *	5.5 (0.6, 10.7) *
Abdominal pain	53/383.5 (13.8)	47/387.8 (12.1)	58/353.2 (16.4)	-1.7 (-6.9, 3.4)	2.6 (-3.0, 8.4)
Vomiting	16/423.5 (3.8)	28/407.8 (6.9)	30/378.9 (7.9)	3.1 (-0.0, 6.5)	4.1 (0.8, 7.9) *
Constipation	18/416.3 (4.3)	20/415.3 (4.8)	28/372.3 (7.5)	0.5 (-2.5, 3.6)	3.2 (-0.2, 6.9)
Musculoskeletal and connective tissue disorders					
Arthralgia	36/395.7 (9.1)	45/389.4 (11.6)	33/377.8 (8.7)	2.5 (-2.1, 7.1)	-0.4 (-4.7, 4.0)
Arthritis	17/421.7 (4.0)	22/422.6 (5.2)	21/386.9 (5.4)	1.2 (-1.8, 4.3)	1.4 (-1.7, 4.7)
Skin and subcutaneous tissue disorders					
Pruritus	20/409.8 (4.9)	25/401.9 (6.2)	40/365.2 (11.0)	1.3 (-2.0, 4.8)	6.1 (2.2, 10.4) *
Rash	21/410.5 (5.1)	18/415.8 (4.3)	37/371.1 (10.0)	-0.8 (-3.9, 2.3)	4.9 (1.1, 9.1) *
General disorders and administration site condition					
Fatigue	35/394.2 (8.9)	36/401.4 (9.0)	33/375.9 (8.8)	0.1 (-4.2, 4.3)	-0.1 (-4.4, 4.2)
Dizziness	11/425.7 (2.6)	26/411.7 (6.3)	30/382.9 (7.8)	3.7 (0.9, 6.9) *	5.3 (2.2, 8.8) *
Nervous system disorders					
Headache	32/396.6 (8.1)	34/396.5 (8.6)	24/379 (6.3)	0.5 (-3.6, 4.7)	-1.7 (-5.7, 2.1)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); F2, fibrosis stage 2; F3, fibrosis stage 3; FDA, U.S. Food and Drug Administration; FMQ, FDA Medical Query; N, number of subjects in treatment arm; n, number of subjects with at least one event; PY, person-years (total exposure); py, person-years (at risk)

Incidence of GI TEAEs was higher in the resmetirom 100 mg group with an EAIR difference of 32 events per 100PY (95% CI: 16.5, 48.2) relative to placebo, and in the 80 mg arm with an EAIR difference of 16 events per 100 PY (95% CI: 2.2, 30.9) relative to placebo.

Among GI disorders, the most common TEAE reported in the F2 and F3 population was diarrhea. The incidence of diarrhea was highest in the 100 mg arm (33 per 100 PY), followed by 80 mg arm (23 per 100 PY) as compared to placebo (14 per 100 PY) (Table 41).This implies that for every 100 patients treated for a year with 100 mg or 80 mg dose, one would expect 33 or 23 cases of diarrhea, respectively. Diarrhea typically occurred at treatment initiation. The median time (25^{th}-75^{th} percentile) to a diarrheal event was 39 (2 to 195) days, 17 (3 to 70) days, and 6 (2 to 54) days in the placebo, 80 mg QD, and 100 mg QD arms, respectively. The severity of diarrhea was mild to moderate. Median duration of diarrhea was 9 days for placebo compared to 20 days for both 80 and 100 mg dosage arms.

The incidence of nausea was higher in the 80 mg arm (18 per 100 PY) and 100 mg arm (15 per 100 PY) compared to placebo (9 per 100 PY). Nausea occurred at treatment initiation. Among subjects with nausea, the median time (25^{th}-75^{th} percentile) to a nausea event was 85 (24 to 347) days, 28 (2 to 162), and 5 (2 to 40) in the placebo, 80 mg QD, and 100 mg QD arms, respectively. The severity of nausea was mild to moderate. Median duration of nausea was 17 days, 26 days, and 28 days for subjects in the placebo, 80 mg QD, and 100 mg QD arms, respectively.

The incidence of other GI AEs, vomiting, abdominal pain, and constipation were also higher in the 100 mg arm.

Vomiting episodes were mild to moderate in severity, and the median duration of these episodes was 2 days, 4 days, and 3 days in the placebo, 80 mg QD, and 100 mg QD arms, respectively.

Severity of abdominal pain was mild to moderate, with one case in the placebo arm compared to two cases in the 100 mg arm classified as severe. Median duration of abdominal pain was 8 days, 5 days, and 17 days in the placebo, 80 mg QD, and 100 mg QD arms, respectively.

Pruritus was the next common AE after nausea, with the highest incidence in the 100 mg arm (~10 per 100 PY), followed by the 80 mg arm (6 per 100 PY), as compared to that of placebo (~4 per 100 PY).

Dizziness was the third most common after GI AEs and pruritus, (~4 per 100 PY in both the dose arms, compared to ~1 per 100 PY in the placebo).

Some PTs had an EAIR per 100 PY of greater than equal to 5 in either dose arm but were considered unrelated. These included: Covid-19, type 2 diabetes, urinary tract infection, and upper respiratory tract infection.

Analyses of FMQs (Table 42) demonstrated similar results as the analysis of PTs, with GI AEs being more common than others.

Some FMQs with an EAIR per 100 PY of greater than equal to 5 in either dose arm were considered unrelated; these include: bacterial infection, nasopharyngitis, and renal and urinary tract infection. The primary term contributing to the FMQ of arthritis was osteoarthritis (OA), and was therefore not considered related as OA is an age-related condition and likely not drug-related. The primary term contributing to the FMQ hyperglycemia was type 2 diabetes, which is a common comorbidity in the NASH population, and for which resmetirom does not have an

apparent mechanism of inducing hyperglycemia; therefore, the hyperglycemia was also considered unrelated.

After reviewing PTs and FMQs, diarrhea, nausea, pruritus, abdominal pain, vomiting, dizziness, and constipation were included in Section 6 of the label. The PTs and FMQs of arthralgia, fatigue, and headache were not included in the label because the incidence of these AEs in the resmetirom arms was similar to placebo.

Other less common, but related AEs (FMQs and PTs)—where the EAIR was greater than at least 1 but less than 4 per 100 PY in either dose arms—included: decreased appetite, tendinopathy, depression, arrythmia, erythema, dysgeusia, abnormal uterine bleeding, palpitations, cardiac conduction disturbance, cholelithiasis, acute cholecystitis, and hypoglycemia. Hepatobiliary events (cholelithiasis, cholecystitis and obstructive pancreatitis) are discussed in Section 7.7.3.

Reactions such as rash and urticaria, that may reflect drug hypersensitivity, have been observed in the F2/F3 population. Rash was observed at an EAIR of 3 per 100 PY in those treated with placebo and 80 mg arm, each, and 5 per 100 PY in those treated with 100 mg. Urticaria was observed at an EAIR of 0.2 per 100 PY in those treated with placebo, 0.7 per 100 PY in those treated with 80 mg arm, and 1.5 per 100 PY in those treated with 100 mg arm. Rash and urticaria were causes of treatment discontinuations in a small number of subjects on treatment. Rash and urticaria were included in Section 6 of the prescribing information.

The Applicant has listed type 2 diabetes as an AESI. However, the incidence of type 2 diabetes in the F2/F3 population was similar across the trial arms, with EAIRs per 100 PY of 21, 23, and 21 in the placebo, 80 mg, and 100 mg arms, respectively. Similarly, the incidence of hyperglycemia was the same between 80 mg (45 per 100 PY) and placebo (45 per 100 PY), whereas the incidence was lower in the 100 mg arm compared to placebo (Table 284 and Table 285 in Section 17).

Other possibly related AEs (FMQs and PTs) with EAIR per 100 PY greater than 1 but less than 4 included hypothyroidism, frequent bowel movements, hypoglycemia, headache, palpitations, fatigue, nephrolithiasis and ureterolithiasis, and cough, As explained in Section 7.6.1.3, it is difficult to ascribe causality for nephrolithiasis and ureterolithiasis events to resmetirom at this time.

After reviewing the PTs and FMQs, diarrhea, nausea, pruritus, abdominal pain, vomiting, dizziness, and constipation were the most common AEs of concern that were higher in the treatment arms compared to placebo, and included in labeling. Rash and urticaria were also included in the label.

7.6.1.6. Laboratory Findings, Trial MGL-3196-11 (F2/F3 Population)

No clinically significant abnormalities were noted on analysis of laboratory findings for general chemistry, hematology, and renal function values at 52 weeks.

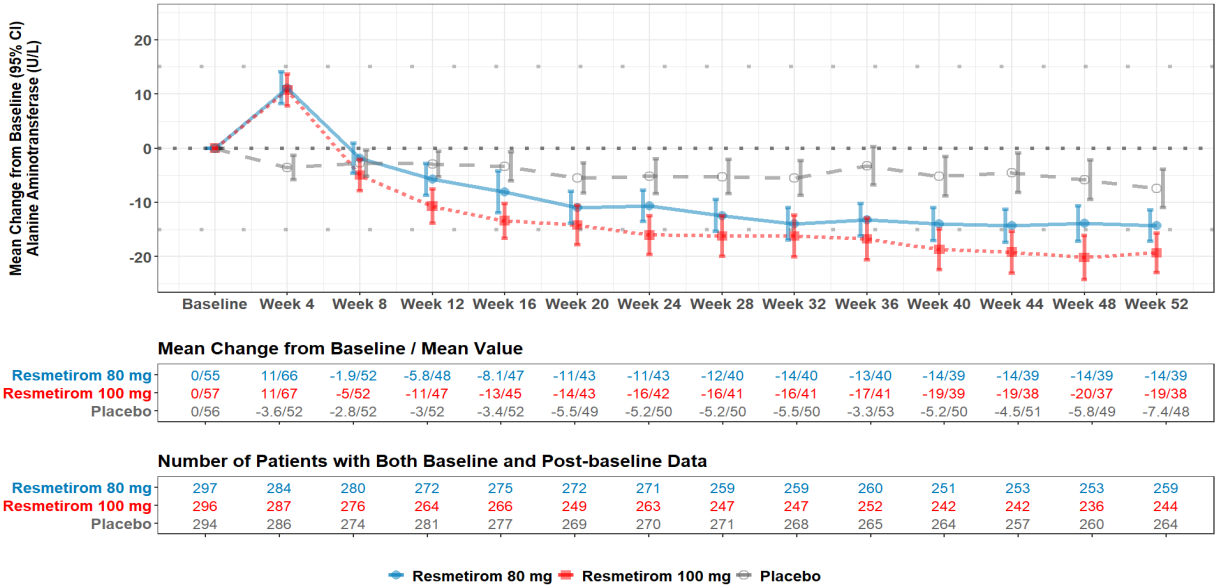
Liver Biochemistry

A discussion of common liver biochemistry tests in Trial MGL-3196-11, F2, and F3 populations is provided in this section.

Figure 6 displays the mean changes in ALT and AST values. Mean ALT and AST values increased in the first 4 weeks after initiating treatment with resmetirom to less than 1.5 times baseline. Values returned to baseline around 8 weeks after initiating treatment and continued to decrease with mean values of ALT and AST lower than placebo starting at 12 to 16 weeks and through Week 52.

Figure 67 in Section 17.1.3 displays the mean changes in values for total bilirubin (TB), direct bilirubin (DB), ALP, and gamma glutamyl transferase (GGT). No clinically significant changes were noted in mean TB. Observed increases in the mean values of DB (up to 0.03 mg/dL) and ALP (up to 5 U/L) in resmetirom dose arms compared to placebo were small, without associated symptoms, and of uncertain clinical significance. GGT values decreased during the course of treatment and remained low compared to placebo at 52 weeks.

Figure 6. Mean Change in ALT and AST Values From Baseline Over Time, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

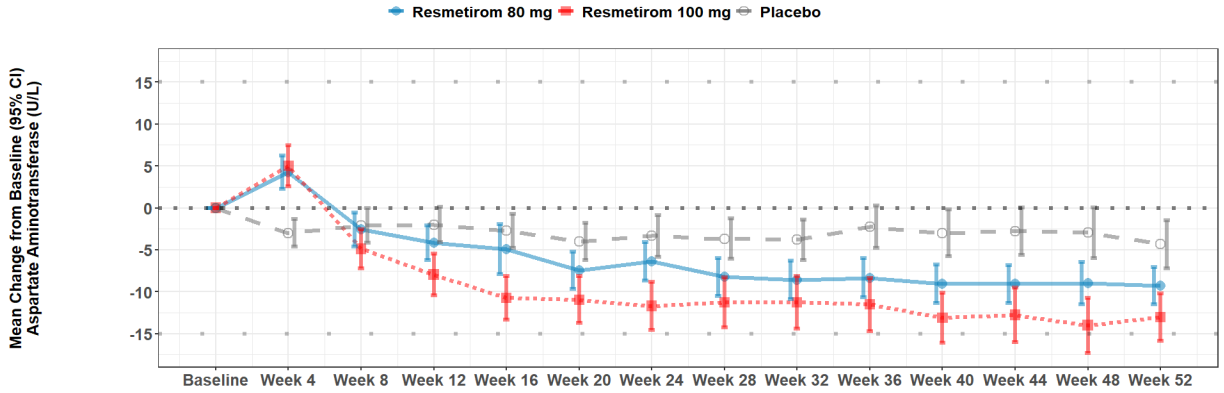


Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/55	11/66	-1.9/52	-5.8/48	-8.1/47	-11/43	-11/43	-12/40	-14/40	-13/40	-14/39	-14/39	-14/39	-14/39
Resmetirom 100 mg	0/57	11/67	-5/52	-11/47	-13/45	-14/43	-16/42	-16/41	-16/41	-17/41	-19/39	-19/38	-20/37	-19/38
Placebo	0/56	-3.6/52	-2.8/52	-3/52	-3.4/52	-5.5/49	-5.2/50	-5.2/50	-5.5/50	-3.3/53	-5.2/50	-4.5/51	-5.8/49	-7.4/48

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	297	284	280	272	275	272	271	259	259	260	251	253	253	259
Resmetirom 100 mg	296	287	276	264	266	249	263	247	247	252	242	242	236	244
Placebo	294	286	274	281	277	269	270	271	268	265	264	257	260	264



Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/40	4.3/44	-2.6/36	-4.2/35	-5/34	-7.4/32	-6.4/32	-8.2/30	-8.6/30	-8.4/30	-9.1/29	-9.1/30	-9/29	-9.3/29
Resmetirom 100 mg	0/44	5/49	-4.9/39	-8/36	-11/34	-11/32	-12/33	-11/32	-11/32	-12/33	-13/31	-13/31	-14/30	-13/31
Placebo	0/41	-3/38	-2.1/39	-2/39	-2.7/38	-4/37	-3.3/37	-3.7/37	-3.8/37	-2.3/39	-3/38	-2.8/38	-3/37	-4.4/36

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	297	284	280	272	275	272	271	258	259	260	252	253	253	258
Resmetirom 100 mg	296	287	276	264	266	249	263	247	247	252	242	242	236	244
Placebo	294	286	274	281	277	269	270	272	268	265	264	257	260	264

Source: adlbc2.xpt; Software: R, Generated by clinical data scientist.
Note: Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Note: Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; Intl., international; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 45 displays liver biochemistry analyte values exceeding specified thresholds (multiples of ULN). The FDA used the Applicant-provided ULNs for all analytes.

Table 45. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Laboratory Parameter Level	Placebo N=294 n/N_w (%)	Resmetirom 80 mg N=298 n/N_w (%)	Resmetirom 100 mg N=296 n/N_w (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
Alanine aminotransferase, high (U/L)					
Level 1 (>3× ULN)	28/293 (9.6)	32/294 (10.9)	39/293 (13.3)	1.3 (-3.6, 6.3)	3.8 (-1.4, 9.0)
Level 2 (>5× ULN)	7/293 (2.4)	5/294 (1.7)	5/293 (1.7)	-0.7 (-3.4, 1.8)	-0.7 (-3.4, 1.8)
Level 3 (>10× ULN)	0/293 (0)	1/294 (0.3)	0/293 (0)	0.3 (-1.0, 1.9)	0.0 (-1.3, 1.3)
Aspartate aminotransferase, high (U/L)					
Level 1 (>3× ULN)	29/293 (9.9)	25/294 (8.5)	35/293 (11.9)	-1.4 (-6.2, 3.4)	2.0 (-3.1, 7.2)
Level 2 (>5× ULN)	7/293 (2.4)	4/294 (1.4)	11/293 (3.8)	-1.0 (-3.7, 1.4)	1.4 (-1.6, 4.5)
Level 3 (>10× ULN)	0/293 (0)	1/294 (0.3)	0/293 (0)	0.3 (-1.0, 1.9)	0.0 (-1.3, 1.3)
Bilirubin, total, high (mg/dL)					
Level 1 (>1.5× ULN)	14/293 (4.8)	11/294 (3.7)	21/293 (7.2)	-1.0 (-4.6, 2.4)	2.4 (-1.5, 6.5)
Level 2 (>2× ULN)	5/293 (1.7)	3/294 (1.0)	10/293 (3.4)	-0.7 (-3.0, 1.5)	1.7 (-1.0, 4.7)
Level 3 (>3× ULN)	1/293 (0.3)	1/294 (0.3)	3/293 (1.0)	-0.0 (-1.6, 1.6)	0.7 (-1.0, 2.7)
Alkaline phosphatase, high (U/L)					
Level 1 (>1.5× ULN)	3/293 (1.0)	7/294 (2.4)	10/293 (3.4)	1.4 (-0.9, 3.9)	2.4 (0.0, 5.3) *
Level 2 (>2× ULN)	1/293 (0.3)	2/294 (0.7)	3/293 (1.0)	0.3 (-1.3, 2.1)	0.7 (-1.0, 2.7)
Level 3 (>3× ULN)	1/293 (0.3)	0/294 (0)	1/293 (0.3)	-0.3 (-1.9, 1.0)	-0.0 (-1.6, 1.6)

Source: adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Risk difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Only central laboratory data is included in the analysis, as local laboratory data was not included in the submitted datasets.
*Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F2, fibrosis stage 2; F3, fibrosis stage 3; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w number of subjects with data; ULN, upper limit of normal

ALT values greater than 3× ULN and greater than 5× ULN were seen in similar proportions across study arms. One subject had ALT values greater than 10× ULN in the 80 mg dose arm. AST values greater than 3× ULN and greater than 5× ULN were seen in similar proportions across study arms, with one subject in the 80 mg arm who had AST values greater than 10× ULN.

TB values greater than 2× ULN were noted in similar proportions across study arms. One percent of subjects in the 100 mg arm had TB values greater than 3× ULN compared to placebo (0.3%) and 80 mg QD (0.3%) arms, with one subject in the 80 mg arm and three subjects in the 100 mg arm who had TB values greater than 3× ULN.

An increase of ALP greater than 1.5× ULN was observed in 3% of subjects in the 100 mg arm compared to 2% in the 80 mg arm, and 1% in placebo. Two subjects in the 80 mg arm and three subjects in the 100 mg arm had ALP values greater than 2× ULN, and one subject in the 100 mg arm had ALP value greater than 3× ULN.

Although subjects receiving resmetirom had reductions in ALT, AST, and GGT at the end of 52 weeks, values greater than 3× the ULN for ALT and AST were noted in the trial in 9 to 13% of subjects across all study arms. The FDA also analyzed liver biochemistry data by baseline

elevations as NASH patients commonly have elevated liver analytes. Analysis of liver enzyme elevations by baseline status was similar to the analysis done using ULN thresholds. Therefore, some of these elevations could be capturing an increase in baseline liver transaminases and may not be clinically significant.

The increases in TB were attributed by the Applicant to Gilbert's syndrome, however, mean change in DB was also higher in the drug arms at the end of the treatment period. The magnitude of this increase was small and the clinical significance unclear. Similarly, the small increase in ALP observed is not specific, and could be due to liver disease, vitamin D deficiency, increased bone turnover, or other reasons.

In summary, no clinically significant changes in laboratory values related to chemistry, hematology, and kidney function were observed in the trial. Excursions in liver biochemistries that were observed have been included in labeling to alert the prescriber.

7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial MGL-3196-11 (F2/F3 Population)

DILI is a key safety issue and is discussed in detail in Section 7.7.1. Assessment of DILI in the F2/F3 population was not considered separately, but as part of the pooled safety database of Trials MGL-3196-11 and MGL-3196-14.

7.6.1.8. Vital Signs, Trial MGL-3196-11 (F2/F3 Population)

Overall, a minimal (3 mmHg) mean decrease in systolic blood pressure was observed in the resmetirom arms relative to placebo. There were no clinically significant changes observed for pulse rate, respiratory rate, or body temperature across treatment arms.

7.6.1.9. Subgroups, Trial MGL-3196-11 (F2/F3 Population)

Table 46 displays the incidence of AEs by subgroups. The incidence of AEs was similar across treatment arms in both male and female subjects. Given that approximately 87% of subjects across the treatment arms were white, subgroup analysis by race was not feasible.

The majority of subjects were less than 65 years of age. Among subjects older than 65 years, the incidence of AE was higher for both arms compared with placebo, with AEs in the 80 mg arm being the highest. (b) (4)

Table 46. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Characteristic	Placebo N=294 n/N_s (%)	Resmetirom 80 mg N=298 n/N_s (%)	Resmetirom 100 mg N=296 n/N_s (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
Sex, n (%)					
Female	152/161 (94.4)	156/166 (94.0)	159/170 (93.5)	-0.4 (-5.9, 5.0)	-0.9 (-6.4, 4.6)
Male	119/133 (89.5)	117/132 (88.6)	112/126 (88.9)	-0.8 (-8.7, 6.9)	-0.6 (-8.5, 7.2)
Age group, years, n (%)					
≥18 to <40	21/23 (91.3)	24/28 (85.7)	16/19 (84.2)	-5.6 (-24.8, 14.9)	-7.1 (-30.8, 14.3)
≥40 to <65	181/192 (94.3)	184/203 (90.6)	179/195 (91.8)	-3.6 (-9.1, 1.7)	-2.5 (-7.9, 2.8)
≥65	69/79 (87.3)	65/67 (97.0)	76/82 (92.7)	9.7 (0.8, 19.3) *	5.3 (-4.2, 15.5)
Age group ≥75, years, n (%)					
≥75	6/8 (75.0)	¾ (75.0)	9/9 (100)	-0.0 (-54.0, 45.6)	25.0 (-10.6, 60.0)
Race, n (%)					
American Indian or Alaska Native	3/3 (100)	4/4 (100)	1/1 (100)	0.0 (-52.8, 59.9)	0.0 (-83.7, 63.1)
Asian	8/9 (88.9)	7/9 (77.8)	7/8 (87.5)	-11.1 (-47.8, 27.8)	-1.4 (-40.0, 35.4)
Black or African American	8/9 (88.9)	2/5 (40.0)	4/5 (80.0)	-48.9 (-82.5, 2.3)	-8.9 (-55.9, 31.3)
Native Hawaiian or other Pacific Islander	0/1 (0)	0/0 (NA)	0/0 (NA)	NA	NA
White	236/255 (92.5)	248/268 (92.5)	247/267 (92.5)	-0.0 (-4.6, 4.7)	-0.0 (-4.7, 4.7)
Not able to collect	4/4 (100)	4/4 (100)	6/7 (85.7)	0.0 (-52.3, 52.3)	-14.3 (-53.1, 40.8)
Other	12/13 (92.3)	8/8 (100)	6/8 (75.0)	7.7 (-27.0, 34.1)	-17.3 (-54.1, 15.4)
Ethnicity, n (%)					
Hispanic or Latino	45/46 (97.8)	61/64 (95.3)	70/76 (92.1)	-2.5 (-11.1, 7.2)	-5.7 (-14.5, 4.2)
Not able to collect	½ (50.0)	1/1 (100)	2/2 (100)	50.0 (-64.2, 93.1)	50.0 (-46.8, 92.4)
Non-Hispanic or Latino	223/244 (91.4)	209/231 (90.5)	197/215 (91.6)	-0.9 (-6.3, 4.3)	0.2 (-5.1, 5.4)
Not reported	2/2 (100)	1/1 (100)	0/1 (0)	0.0 (-85.2, 74.2)	-100.0 (-100.0, 31.5)
Unknown	0/0 (NA)	1/1 (100)	2/2 (100)	NA	NA
Is in United States, n (%)					
United States	180/192 (93.8)	174/190 (91.6)	186/205 (90.7)	-2.2 (-7.7, 3.2)	-3.0 (-8.5, 2.4)
Non-United States	91/102 (89.2)	99/108 (91.7)	85/91 (93.4)	2.5 (-5.8, 11.0)	4.2 (-4.2, 12.7)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: The F2/F3 population includes fibrosis stage 2 and 3 subjects, based on the eligibility read by the central pathologist (see Methods section for more details).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with adverse event;n, number of patients subjects with at least one event; NA, not applicable; N_s, total number of patients for each specific subgroup who were assigned to that specific arm

7.6.2. Safety Results, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Table 47 displays an overview of AEs in the pooled population.

- Overall, the 100 mg dose arm had a higher incidence of SAEs compared to placebo (EAIR per 100 PY of 9.7 versus EAIR per 100 PY of 8.1, respectively), whereas the 80 mg arm had a similar incidence of SAEs compared to placebo. There were three SAEs with fatal outcomes in the 100 mg arm, two in the 80 mg arm and one in the placebo arm, all considered as unrelated to study drug. SAEs requiring hospitalization were marginally higher in the 100 mg arm.
- Compared to placebo, both the 80 mg and 100 mg arm had a significantly higher incidence of subjects with an AE leading to permanent discontinuation. A higher incidence of study drug dose-interruption was seen in the 100 mg arm.

Table 47. Overview of Adverse Events, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Event Category	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
SAE	60/747 (8.0)	70/724.1 (9.7)	61/752.1 (8.1)	-0.1 (-3.0, 2.8)	1.6 (-1.5, 4.7)
SAEs with fatal outcome	2/777.2 (0.3)	3/767.2 (0.4)	1/792.8 (0.1)	0.1 (-0.5, 0.8)	0.3 (-0.4, 1.0)
Life-threatening SAEs	2/776.5 (0.3)	5/765.6 (0.7)	6/787.2 (0.8)	-0.5 (-1.4, 0.3)	-0.1 (-1.1, 0.9)
SAEs requiring hospitalization	56/748.5 (7.5)	62/729.2 (8.5)	52/756 (6.9)	0.6 (-2.1, 3.4)	1.6 (-1.2, 4.5)
SAEs resulting in substantial disruption of normal life functions	4/775.6 (0.5)	7/765.6 (0.9)	6/788.3 (0.8)	-0.2 (-1.2, 0.7)	0.2 (-0.9, 1.2)
Other	13/769.9 (1.7)	22/749.5 (2.9)	17/784 (2.2)	-0.5 (-2.0, 1.0)	0.8 (-0.9, 2.5)
AE leading to permanent discontinuation of study drug	52/770.3 (6.8)	56/761.7 (7.4)	31/791.5 (3.9)	2.8 (0.6, 5.2) *	3.4 (1.1, 5.9) *
AE leading to dose modification of study drug	64/730.1 (8.8)	75/721.5 (10.4)	60/746.4 (8.0)	0.7 (-2.3, 3.7)	2.4 (-0.8, 5.6)
AE leading to interruption of study drug	63/730.3 (8.6)	75/721.5 (10.4)	60/746.4 (8.0)	0.6 (-2.4, 3.6)	2.4 (-0.8, 5.6)
AE leading to reduction of study drug	1/776.9 (0.1)	0/767.1 (0)	0/792.8 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
AE leading to dose delay of study drug	0/777.2 (0)	0/767.1 (0)	0/792.8 (0)	0.0 (-0.5, 0.5)	0.0 (-0.5, 0.5)
AE action taken unknown	6/771.3 (0.8)	9/755.7 (1.2)	5/789.5 (0.6)	0.1 (-0.8, 1.1)	0.6 (-0.4, 1.7)
Any AE	613/190 (322.6)	596/164.7 (362.0)	584/200.7 (291.0)	31.6 (-3.1, 66.5)	70.9 (33.8, 108.8) *
Severe and worse	74/737.1 (10.0)	79/715.9 (11.0)	84/743.5 (11.3)	-1.3 (-4.6, 2.1)	-0.3 (-3.7, 3.2)
Moderate	361/466.4 (77.4)	346/466 (74.2)	327/514.4 (63.6)	13.8 (3.3, 24.5) *	10.7 (0.3, 21.2) *
Mild	178/643.9 (27.6)	171/626.7 (27.3)	173/647.5 (26.7)	0.9 (-4.8, 6.7)	0.6 (-5.2, 6.3)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: Severity as assessed by the Applicant.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); SAE, serious adverse events;); py, person-years (at risk)

7.6.2.2. Deaths, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

There were three deaths reported in the 100 mg arm in the pooled population, with two deaths in the 80 arm and one in the placebo arm. See Table 48.

Table 48. Deaths: Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Preferred Term	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any AE leading to death	2/777.2 (0.3)	3/767.2 (0.4)	1/792.8 (0.1)	0.1 (-0.5, 0.8)	0.3 (-0.4, 1.0)
Myocardial infarction	0/777.2 (0)	1/767.1 (0.1)	0/792.8 (0)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Cholestasis	0/777.2 (0)	1/767.2 (0.1)	0/792.8 (0)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Hodgkin's disease	0/777.2 (0)	1/767.2 (0.1)	0/792.8 (0)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Intracardiac thrombus	0/777.2 (0)	1/767.2 (0.1)	0/792.8 (0)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Prosthetic cardiac valve thrombosis	0/777.2 (0)	1/767.2 (0.1)	0/792.8 (0)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Cardiac arrest	1/777.2 (0.1)	0/767.1 (0)	0/792.8 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
COVID-19	1/777.2 (0.1)	0/767.1 (0)	0/792.8 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Road traffic accident	1/777.2 (0.1)	0/767.1 (0)	0/792.8 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Death	0/777.2 (0)	0/767.1 (0)	1/792.8 (0.1)	-0.1 (-0.7, 0.4)	-0.1 (-0.7, 0.4)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

Table 286 in Section 17.2.1 displays the listing of all individual subjects who died in the pooled population. Only one death (0172-4059) was reported in Trial MGL-3196-14, with the rest reported in Trial MGL-3196-11(see Section 7.6.1.2). The deaths reported in the pooled safety population are likely unrelated to resmetirom.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

See Section 7.6.1.3 for definition of SAE used by the Applicant. Table 49 displays the SAEs reported in the pooled population by SOC. SOCs where the EAIR is greater than equal to 0.2 per 100 PY in either dose arms are displayed, cutoff is same as the F2/F3

population. SOCs with incidence rates less than placebo are not presented. If there is little to no plausibility of relatedness for the SAE, the SOC is not displayed.

Findings in the pooled analysis were similar to the F2/F3 population (Section 7.6.1.3). Subjects with SAEs by SOC and narrow FMQ, occurring at an EAIR difference greater than or equal to 0.2 per 100 PY in either dose arm in the pooled population, are displayed in Table 287, in Section 17.2.2.The FMQs noted in Table 287 do not differ substantively from the PTs already discussed in Section 7.6.1.3, except that the SOC of cardiac disorders is now included for the pooled population. Major adverse cardiovascular events (MACE) are discussed further in Section 7.7.9.

Table 49. Patients With Serious Adverse Events by System Organ Class (Occurring at EAIR Difference ≥0.2 Per 100 PY in Either Dose Arm), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any SAE	61/752.1 (8.1)	60/747 (8.0)	70/724.1 (9.7)	-0.1 (-3.0, 2.8)	1.6 (-1.5, 4.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9/789 (1.1)	3/776.5 (0.4)	14/760.7 (1.8)	-0.8 (-1.8, 0.1)	0.7 (-0.6, 2.1)
Injury, poisoning and procedural complications	4/788.8 (0.5)	6/774.1 (0.8)	9/759.2 (1.2)	0.3 (-0.6, 1.2)	0.7 (-0.3, 1.8)
Musculoskeletal and connective tissue disorders	6/788.9 (0.8)	9/771.3 (1.2)	4/763.6 (0.5)	0.4 (-0.6, 1.5)	-0.2 (-1.2, 0.7)
General disorders and administration site conditions	4/789.8 (0.5)	4/774.9 (0.5)	7/765.2 (0.9)	0.0 (-0.8, 0.9)	0.4 (-0.5, 1.4)
Renal and urinary disorders	1/792.7 (0.1)	6/774.9 (0.8)	2/765.5 (0.3)	0.6 (-0.0, 1.6)	0.1 (-0.5, 0.8)
Hepatobiliary disorders	0/792.8 (0)	3/776.5 (0.4)	4/764.5 (0.5)	0.4 (-0.1, 1.1)	0.5 (0.0, 1.3) *
Metabolism and nutrition disorders	1/792.3 (0.1)	1/776.1 (0.1)	4/764.6 (0.5)	0.0 (-0.6, 0.6)	0.4 (-0.2, 1.2)
Reproductive system and breast disorders	0/792.8 (0)	3/776.7 (0.4)	2/764.7 (0.3)	0.4 (-0.1, 1.1)	0.3 (-0.2, 1.0)
Investigations	0/792.8 (0)	3/775.6 (0.4)	0/767.1 (0)	0.4 (-0.1, 1.1)	0.0 (-0.5, 0.5)
Blood and lymphatic system disorders	0/792.8 (0)	1/776.9 (0.1)	2/766 (0.3)	0.1 (-0.4, 0.7)	0.3 (-0.2, 1.0)
Ear and labyrinth disorders	0/792.8 (0)	1/777 (0.1)	2/765.8 (0.3)	0.1 (-0.4, 0.7)	0.3 (-0.2, 1.0)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Table 50 displays the AEs observed in the pooled population leading to treatment discontinuation. AEs presented include those where the EAIR is greater than or equal to 0.3 per 100 PY in either dose arm. Table 288 in Section 17.2.3 displays the AEs observed in the pooled population by SOC for those AEs with EAIRs greater than or equal to 0.2 per 100 PY. If there is little to no plausibility of relatedness for the AE, the SOC is not displayed.

Table 289 in Section 17.2.3 is an expanded table with FMQs occurring at EAIR ≥0.1 per 100 PY in either drug dose arm leading to treatment discontinuation in the pooled population, irrespective of relatedness or severity. This corresponds to AE leading to treatment discontinuation reported by at least one subject in the trial arms.

Similar to the F2/F3 population, the incidence of AEs leading to treatment discontinuation was higher in the drug arms compared to placebo. The SOC of GI disorders was the most common SOC leading to treatment discontinuation, followed by skin and subcutaneous tissue disorders. Among GI disorders, diarrhea was the most common cause for treatment discontinuation, followed by nausea. In contrast to the F2/F3 population, headache was reported as a leading cause for treatment discontinuation in the pooled population. Other less common causes of treatment discontinuations were similar to those in the F2/F3 population. Hepatic cirrhosis, including the FMQ of hepatic injury, was an AE leading to treatment discontinuation, but it is considered a clinical outcome and not a safety event.

Table 50. Subjects With Adverse Events Leading to Treatment Discontinuation (Occurring at an EAIR ≥0.3 Per 100 PY in Either Dose Arm), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Preferred Term	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any AE leading to discontinuation	31/791.5 (3.9)	52/770.3 (6.8)	56/761.7 (7.4)	2.8 (0.6, 5.2) *	3.4 (1.1, 5.9) *
Diarrhea	1/792.8 (0.1)	15/775.5 (1.9)	20/764.5 (2.6)	1.8 (0.9, 3.1) *	2.5 (1.5, 3.9) *
Nausea	4/792.8 (0.5)	7/775.9 (0.9)	9/766.6 (1.2)	0.4 (-0.5, 1.4)	0.7 (-0.3, 1.8)
Vomiting	2/792.8 (0.3)	3/777.1 (0.4)	6/766.8 (0.8)	0.1 (-0.6, 0.9)	0.5 (-0.2, 1.5)
Pruritus	1/792.7 (0.1)	1/777.2 (0.1)	6/766.9 (0.8)	0.0 (-0.6, 0.6)	0.7 (-0.0, 1.6)
Headache	1/792.8 (0.1)	6/775.3 (0.8)	0/767.1 (0)	0.6 (-0.0, 1.6)	-0.1 (-0.7, 0.4)
Abdominal pain	0/792.8 (0)	3/777.1 (0.4)	1/767.1 (0.1)	0.4 (-0.1, 1.1)	0.1 (-0.4, 0.7)
Abdominal pain upper	2/792.6 (0.3)	2/776.7 (0.3)	3/767 (0.4)	0.0 (-0.7, 0.7)	0.1 (-0.6, 0.9)
Urticaria	0/792.8 (0)	0/777.2 (0)	3/767.1 (0.4)	0.0 (-0.5, 0.5)	0.4 (-0.1, 1.1)
Abdominal discomfort	0/792.8 (0)	1/776.3 (0.1)	2/767.1 (0.3)	0.1 (-0.4, 0.7)	0.3 (-0.2, 1.0)
Constipation	1/792.7 (0.1)	0/777.2 (0)	2/767 (0.3)	-0.1 (-0.7, 0.4)	0.1 (-0.5, 0.8)
Fatigue	1/792.7 (0.1)	2/777.1 (0.3)	1/767.1 (0.1)	0.1 (-0.5, 0.8)	0.0 (-0.6, 0.6)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R. Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

7.6.2.5. Treatment-Emergent Adverse Events, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Table 290, in Section 17.2.4, displays TEAEs by SOC reported in the pooled population.

Table 51 displays the most common considered-related AEs by PTs, that are truncated at EAIR greater than equal to 5 per 100 PY in either dose arms. A more extensive list of TEAEs by PTs and FMQs (narrow) is in Table 291 and Table 292 in Section 17.2.4, respectively, regardless of relatedness or severity. Some FMQs with an EAIR per 100 PY of greater than or equal to 5 in either dose arm were not considered related. These were bacterial infection, nasopharyngitis, renal and urinary tract infection, and are not displayed.

Assessment of TEAEs in the pooled population is similar to that of the F2/F3 population. GI disorders were the most common SOC for TEAEs in the pooled population, with diarrhea and nausea being the most common TEAEs in the pooled population. Other TEAEs, including the less common ones were similar to the F2/F3 population.

The Applicant has listed type 2 diabetes as an AESI. However, similar to the F2/F3 population, the incidence of type 2 diabetes in the pooled population was similar across the trial arms (Table 291, Section 17.2.4).

Table 51. Subjects With Common Adverse Events (Occurring at EAIR ≥5 Per 100 PY in Either Dose Arm), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Preferred Term	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Diarrhea	102/701.9 (14.5)	172/622.4 (27.6)	215/561.1 (38.3)	13.1 (8.2, 18.3) *	23.8 (18.1, 29.9) *
Nausea	67/739 (9.1)	114/666.4 (17.1)	122/653.9 (18.7)	8.0 (4.3, 12.0) *	9.6 (5.7, 13.7) *
Arthralgia	67/732 (9.2)	78/711.7 (11.0)	64/712.9 (9.0)	1.8 (-1.5, 5.2)	-0.2 (-3.3, 3.0)
Abdominal pain	33/762.3 (4.3)	47/737 (6.4)	61/709.1 (8.6)	2.0 (-0.3, 4.5)	4.3 (1.7, 7.0) *
Vomiting	31/771.4 (4.0)	38/743.2 (5.1)	58/725 (8.0)	1.1 (-1.1, 3.3)	4.0 (1.5, 6.6) *
Pruritus	31/763.2 (4.1)	44/732.9 (6.0)	57/715.1 (8.0)	1.9 (-0.3, 4.3)	3.9 (1.4, 6.6) *
Fatigue	43/747.2 (5.8)	57/730.7 (7.8)	43/730.8 (5.9)	2.0 (-0.6, 4.8)	0.1 (-2.4, 2.7)
Headache	54/742.9 (7.3)	56/730.9 (7.7)	52/724 (7.2)	0.4 (-2.4, 3.2)	-0.1 (-2.9, 2.7)
Constipation	34/767.3 (4.4)	41/739.2 (5.5)	44/723.2 (6.1)	1.1 (-1.2, 3.5)	1.7 (-0.7, 4.1)
Dizziness	22/775.6 (2.8)	41/744.6 (5.5)	37/742.8 (5.0)	2.7 (0.6, 4.9) *	2.1 (0.2, 4.3) *

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: Coded as MedDRA preferred terms (version 25.1)
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

7.6.2.6. Laboratory Findings, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

No clinically significant abnormalities were noted during analysis of laboratory findings for chemistry, hematology, and kidney function laboratory values at 52 weeks for the pooled population. Observed changes in analytes were consistent with changes observed in the MGL-3196-11 F2/F3 population.

Liver Biochemistry

Mean changes in liver biochemistries are displayed in Figure 68 in Section 17.2.5. Similar to the F2/F3 population, mean ALT and AST values increased in the first 4 weeks after initiating treatment with resmetirom in the pooled population, to less than 1.5 times baseline. As in the F2/F3 population, mean values returned to baseline around 8 weeks after initiating treatment and with mean values of ALT, AST, and GGT lower than placebo starting at 12 to 16 weeks and through week 52. No significant change was noted in values of total TB. No change was noted in mean TB. Observed increases in the mean values of DB (up to 0.02 mg/dL) and ALP (up to 4 U/L) in resmetirom dose arms compared to placebo were small, without associated symptoms and of uncertain clinical significance.

Table 52 displays liver biochemistry analyte values exceeding specified levels. The FDA used the upper limit of normal (ULN) thresholds submitted by the Applicant. DILI is discussed in greater detail in Section 7.7.1.

In the pooled population, a lower proportion of subjects had ALT values greater than 3× ULN compared to the F2/F3 population. ALT values greater than 3 times and greater than 5× ULN were observed in similar proportions in all three study arms. AST values greater than 3×three ULN were lower in the drug arms compared to placebo, in contrast to the F2/F3 population. The proportion of subjects who had AST values greater than 5× ULN was lower in the 80 mg arm compared to placebo, and similar in the 100 mg and placebo arms. The proportion of subjects with elevated TB and ALP values was similar across dose arms.

Overall, the trends noted in the pooled populations are similar to the F2/F3 population.

Table 52. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Laboratory Parameter Level	Placebo N=667 n/N_w (%)	Resmetirom 80 mg N=679 n/N_w (%)	Resmetirom 100 mg N=673 n/N_w (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
Alanine aminotransferase, high (U/L)					
Level 1 (>3× ULN)	61/658 (9.3)	55/671 (8.2)	63/662 (9.5)	-1.1 (-4.2, 2.0)	0.2 (-2.9, 3.4)
Level 2 (>5× ULN)	15/658 (2.3)	9/671 (1.3)	8/662 (1.2)	-0.9 (-2.5, 0.5)	-1.1 (-2.7, 0.4)
Level 3 (>10× ULN)	0/658 (0)	2/671 (0.3)	0/662 (0)	0.3 (-0.3, 1.1)	0.0 (-0.6, 0.6)
Aspartate aminotransferase, high (U/L)					
Level 1 (>3× ULN)	55/658 (8.4)	35/671 (5.2)	45/662 (6.8)	-3.1 (-5.9, -0.4) *	-1.6 (-4.5, 1.3)
Level 2 (>5× ULN)	11/658 (1.7)	5/671 (0.7)	13/662 (2.0)	-0.9 (-2.3, 0.3)	0.3 (-1.2, 1.9)
Level 3 (>10× ULN)	0/658 (0)	2/671 (0.3)	0/662 (0)	0.3 (-0.3, 1.1)	0.0 (-0.6, 0.6)
Bilirubin, total, high (mg/dL)					
Level 1 (>1.5× ULN)	25/658 (3.8)	20/671 (3.0)	29/662 (4.4)	-0.8 (-2.9, 1.2)	0.6 (-1.6, 2.8)
Level 2 (>2× ULN)	7/658 (1.1)	8/671 (1.2)	12/662 (1.8)	0.1 (-1.1, 1.4)	0.7 (-0.6, 2.2)
Level 3 (>3× ULN)	1/658 (0.2)	2/671 (0.3)	4/662 (0.6)	0.1 (-0.6, 0.9)	0.5 (-0.3, 1.4)
Alkaline phosphatase, high (U/L)					
Level 1 (>1.5× ULN)	5/658 (0.8)	10/671 (1.5)	16/662 (2.4)	0.7 (-0.5, 2.1)	1.7 (0.3, 3.2) *
Level 2 (>2× ULN)	2/658 (0.3)	3/671 (0.4)	4/662 (0.6)	0.1 (-0.7, 1.0)	0.3 (-0.6, 1.3)
Level 3 (>3× ULN)	1/658 (0.2)	0/671 (0)	1/662 (0.2)	-0.2 (-0.9, 0.4)	-0.0 (-0.7, 0.7)

Source: ISS adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: Only central laboratory data is included in the analysis, as local laboratory data was not included in the submitted datasets.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
*Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of patients subjects in treatment arm; n, number of patients subjects meeting criteria; N_w, number of patients subjects with data; ULN, upper limit of normal

7.6.2.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

DILI is a key safety issue and is discussed in Section 7.7.2.

7.6.2.8. Vital Signs' Analyses, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Overall, a minimal (<2 mmHg) mean decrease in systolic blood pressure was observed in the resmetirom arms relative to placebo. There were no clinically significant changes observed for pulse rate, respiratory rate, or body temperature across treatment arms for the pooled population.

7.6.2.9. Subgroup Analyses, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

The incidence of AEs by sex differed from the F2/F3 population, with the overall incidence of AEs higher for the drug arms compared to placebo among females and among older subjects (refer to Table 53), but similar among males. Given that more than 88% of subjects across the treatment arms were white, meaningful subgroup analysis by race was not feasible.

Table 53. Overview of Adverse Events by Demographic Subgroup, Safety Population, Pooled Trials, MGL-3196-11 and MGL-3196-14

Characteristic	Placebo N=667 n/N_s (%)	Resmetirom 80 mg N=679 n/N_s (%)	Resmetirom 100 mg N=673 n/N_s (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
Sex					
Female	316/360 (87.8)	351/380 (92.4)	341/374 (91.2)	4.6 (0.3, 9.0) *	3.4 (-1.1, 8.0)
Male	268/307 (87.3)	262/299 (87.6)	255/299 (85.3)	0.3 (-5.0, 5.7)	-2.0 (-7.6, 3.5)
Age group, years					
≥18 to <40	55/62 (88.7)	58/65 (89.2)	45/59 (76.3)	0.5 (-11.0, 12.3)	-12.4 (-26.4, 1.2)
≥40 to <65	376/427 (88.1)	402/449 (89.5)	399/447 (89.3)	1.5 (-2.7, 5.7)	1.2 (-3.0, 5.5)
≥65	153/178 (86.0)	153/165 (92.7)	152/167 (91.0)	6.8 (0.2, 13.5) *	5.1 (-1.8, 12.0)
Age group ≥75, years					
≥75	12/16 (75.0)	15/16 (93.8)	22/23 (95.7)	18.7 (-8.2, 45.2)	20.7 (-1.1, 46.3)
Race					
White	523/590 (88.6)	552/609 (90.6)	535/601 (89.0)	2.0 (-1.5, 5.5)	0.4 (-3.2, 4.0)
American Indian or Alaska Native	4/4 (100)	7/7 (100)	2/2 (100)	0.0 (-37.6, 51.4)	0.0 (-69.7, 53.5)
Asian	12/16 (75.0)	12/16 (75.0)	12/14 (85.7)	-0.0 (-30.4, 30.4)	10.7 (-20.3, 39.2)
Black or African American	21/30 (70.0)	22/27 (81.5)	22/27 (81.5)	11.5 (-11.6, 33.2)	11.5 (-11.6, 33.2)
Native Hawaiian or Other Pacific Islander	½ (50.0)	1/1 (100)	2/3 (66.7)	50.0 (-64.2, 93.1)	16.7 (-60.2, 78.7)
Not able to collect	5/6 (83.3)	6/6 (100)	10/11 (90.9)	16.7 (-28.5, 57.9)	7.6 (-26.9, 50.6)
Other	18/19 (94.7)	13/13 (100)	13/15 (86.7)	5.3 (-18.7, 25.1)	-8.1 (-34.1, 14.2)

Characteristic	Placebo N=667 n/N_s (%)	Resmetirom 80 mg N=679 n/N_s (%)	Resmetirom 100 mg N=673 n/N_s (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
Ethnicity					
Hispanic or Latino	149/175 (85.1)	169/188 (89.9)	168/197 (85.3)	4.8 (-2.1, 11.8)	0.1 (-7.1, 7.6)
Non-Hispanic or Latino	427/480 (89.0)	435/482 (90.2)	423/469 (90.2)	1.3 (-2.6, 5.2)	1.2 (-2.7, 5.2)
Not reported	4/5 (80.0)	4/4 (100)	1/3 (33.3)	20.0 (-37.9, 64.5)	-46.7 (-86.0, 24.4)
Not able to collect	3/5 (60.0)	3/3 (100)	2/2 (100)	40.0 (-31.2, 78.5)	40.0 (-41.9, 78.7)
Unknown	½ (50.0)	2/2 (100)	2/2 (100)	50.0 (-46.8, 92.4)	50.0 (-46.8, 92.4)
Is in United States					
United States	480/552 (87.0)	497/553 (89.9)	497/565 (88.0)	2.9 (-0.9, 6.7)	1.0 (-2.9, 4.9)
Non-United States	104/115 (90.4)	116/126 (92.1)	99/108 (91.7)	1.6 (-5.7, 9.4)	1.2 (-6.7, 9.1)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of patients with adverse event; N_s, total number of subjects for each specific subgroup who were assigned to that specific arm

7.7. Key Safety Review Issues

7.7.1. Hepatotoxicity: Drug-Induced Liver Injury

Issue

Resmetirom is a thyromimetic, partial agonist of THR-β, with actions on the hepatocyte purported to provide beneficial metabolic effects on reducing lipotoxicity, primarily through action at the THR-β, the predominant hepatocyte THR. However, resmetirom also has some action on THR-α (see Section 5.2). Thyromimetics are associated with safety signals related to the liver. In the pooled trial safety database (Trials MGL-3196-11 and MGL-3196-14), there were 10 potential Hy's law cases in both drug arms, but after detailed review, only one case of probable DILI was observed.

Background

Thyroid hormones (THs) regulate metabolic activity in the liver, thereby modulating hepatic function. The liver metabolizes THs and regulates their systemic effects. Therefore, thyroid dysfunction can affect liver function, wherein thyroid abnormalities can be seen in various liver conditions including NAFLD, cirrhosis, acute hepatitis, acute liver failure, and autoimmune liver disease.

Conversely, liver abnormalities can be associated with abnormalities in TH levels. Hypothyroidism has been associated with NAFLD (see Section 3) and elevation in liver enzymes. It has also been associated with cholestatic jaundice due to reduced bilirubin and bile excretion. In hyperthyroidism, liver injury can be both hepatocellular and cholestatic demonstrated by elevation in transaminases and ALP, respectively (Malik and Hodgson 2002). In addition, high doses of levothyroxine and other thyroid preparations can cause elevations in liver enzymes, which are generally of hepatocellular or mixed type. Levothyroxine use has been associated rarely with autoantibody-negative immunoallergic hepatitis, where eosinophilia was observed (NIDDK 2012).

Additionally, in preclinical studies in the resmetirom drug development program, elevation of transaminases and ALP levels, bile duct hyperplasia and bile stasis, and liver necrosis were observed (Section 7.1).

Assessment

DILI evaluation included the pooled safety population of MGL-3196-11 and MGL-3196-14. Additionally, cases of potential DILI were evaluated in the open label arms of Trial MGL-3196-14 and in Trial MGL-3196-18.

A general analysis of changes in liver biochemistry for the F2/F3 population and pooled population is discussed in Section 7.6.1.6 and 7.6.2.6.

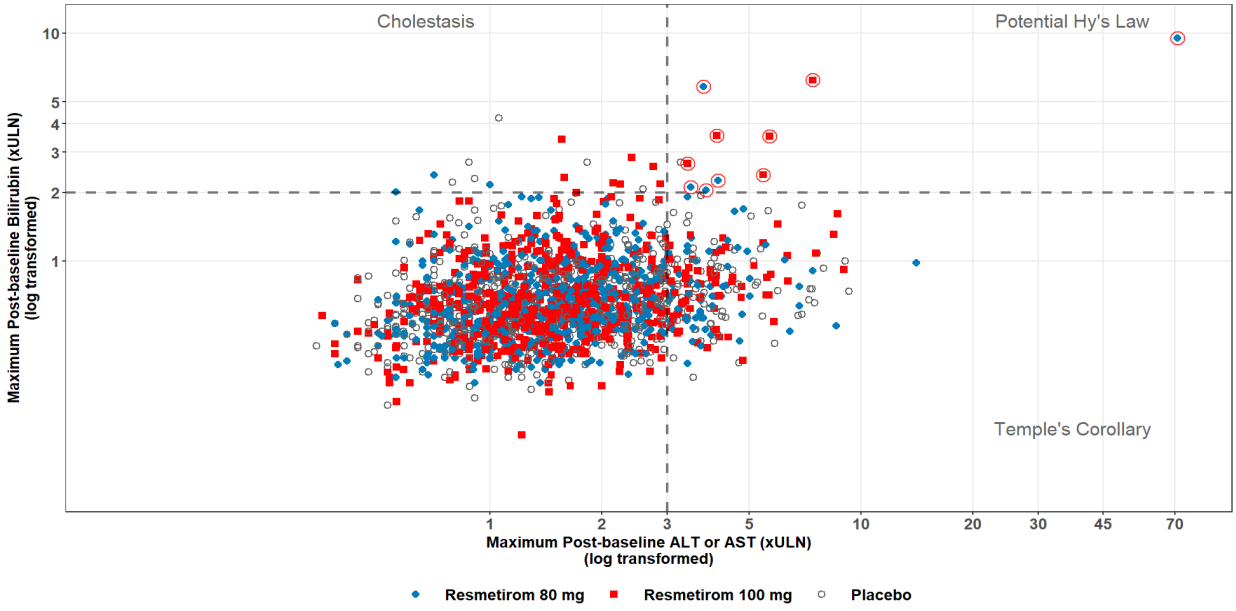
7.7.1.1. Assessment of Hepatocellular Injury, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Figure 7 displays the hepatocellular DILI screening plot for the pooled population. Table 54 displays the subjects in each quadrant of the screening plot for the pooled population. Each data point represents a subject plotted by their maximum ALT or AST versus their maximum TB values in the post-baseline period. A potential Hy's Law case (red circle in Figure 7) was defined as having any post-baseline TB equal to or exceeding 2× ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3× ULN. All subjects with at least one post-baseline ALT or AST and bilirubin are plotted. The within 30-day analysis window rule does not apply to cholestasis and Temple's corollary cases. The FDA used the ULN thresholds submitted by the Applicant.

To assist with detailed case review, DHN consulted the DILI Team to provide their assessment.

As seen in Figure 7 and Table 54, there were a total of 10 cases that qualified as potential Hy's law cases in both the drug arms across the two trials, compared to one case in the placebo arm. No substantive imbalance was observed in the cholestasis and Temple's corollary quadrants between the treatment arms.

Figure 7. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials, MGL-3196-11 and MGL-3196-14



Source: ISS adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Only central laboratory data is included in the analysis, as local laboratory data was not included in the submitted datasets.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ISS, integrated summary of safety; ULN, upper limit of normal

Table 54. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Quadrant	Placebo N=667 n/N_w (%)	Resmetirom 80 mg N=679 n/N_w (%)	Resmetirom 100 mg N=673 n/N_w (%)
Potential Hy's Law (right upper)	1/658 (0.2)	5/671 (0.7)	5/662 (0.8)
Cholestasis (left upper)	6/658 (0.9)	3/671 (0.4)	7/662 (1.1)
Temple's corollary (right lower)	85/658 (12.9)	60/671 (8.9)	72/662 (10.9)
Total	92/658 (14)	68/671 (10.1)	84/662 (12.7)

Source: ISS adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Only central laboratory data is included in the analysis, as local laboratory data was not included in the submitted datasets.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: DILI, drug-induced liver injury; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 55 lists the cases in the potential Hy's law quadrant that were included for case-level interrogation. This is followed by narratives of cases with reviewer assessment that were elevated for additional review by the DILI team. Of the 10 cases in the potential Hy's law quadrant, one case was assessed as probable DILI.

Table 55. Cases in the Potential Hy's Law Quadrant of Hepatocellular DILI Screening Plot, Pooled Population, Trials MGL-3196-11 and MGL-3196-14

Subject ID	Trial	Dose	Age	Sex	Race	Maximum ALT or AST Value (x ULN)	Maximum TB Value (x ULN)	Relatedness[1]	Reviewer Comments
(b) (6)	MGL-3196-14	80 mg	60	F	W	71.2	9.5	Probable	See narrative below
	MGL-3196-11	100 mg	69	M	W	7.4	6.2	Unlikely	See narrative below
	MGL-3196-11	100 mg	68	M	W	4.1	3.6	Unlikely	Elevated liver biochemistries most likely due to HCC and progression of underlying liver disease (advanced fibrosis at baseline). Laboratory values decreased after discontinuation of drug, but this decrease could also be attributed to HCC treatment.
	MGL-3196-11	100 mg	52	F	W	5.7	3.5	Unlikely	Liver biochemistries continued to worsen after discontinuation of drug. Multiple potential alternative causes: alcoholic hepatitis and subsequent decompensated cirrhosis, cholecystitis, bacteremia.
	MGL-3196-11	100 mg	37	M	W	5.4	2.4	Unlikely	Enzyme elevations occurred after drug discontinuation. Subject had significant alcohol intake and Gilbert's syndrome, which may have been the cause of elevated TB.
	MGL-3196-14	100 mg	60	M	W	3.4	2.7	Unlikely	Elevations were notable around 4 weeks after starting study drug (pattern consistent with resmetirom use, refer to Section 7.6.1.6 and 7.6.2.6). Enzymes returned to baseline without discontinuation of study drug. Elevation in TB could be explained by Gilbert's syndrome.
	MGL-3196-11	80 mg	62	F	W	3.5	2.1	Unlikely	Enzyme increased with alcohol use and improved when alcohol was discontinued. Enzymes improved without discontinuation of study drug.

Subject ID	Trial	Dose	Age	Sex	Race	Maximum ALT or AST Value (x ULN)	Maximum TB Value (x ULN)	Relatedness[1]	Reviewer Comments
(b) (6)	MGL-3196-11	80 mg	47	M	W	3.8	5.8	Unlikely	Enzyme elevations were acute and attributable to choledocholithiasis and obstructive pancreatitis.
	MGL-3196-14	80 mg	56	M	W	3.8	2.0	Unlikely	Elevation in liver enzymes likely due to alcohol intake, though enzymes reported as normal one month after discontinuing drug with elevated PEth values. Elevated TB likely due to Gilbert's syndrome. Limited information as subject was lost to follow-up.
	MGL-3196-14	80 mg	39	M	W	4.1	2.3	Unlikely	Elevations were noted off study drug. Could be disease-related or due to alcohol intake.

Source: clinical reviewer generated from clinical study reports, Trials MGL-3196-11 and MGl-3196-14

[1]. Based on Drug-Induced Liver Injury Network (DILIN) methodology to score liver injury events as definite, highly likely, probable, possible, or unlikely DILI

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; F, female; HCC, hepatocellular carcinoma; M, male; PEth, phosphtidylethanol; TB, total bilirubin; ULN, upper limit of normal; W, white

Case Narratives (Potential Hy's Law Cases)

Subjects [redacted] from Trial MGL-3196-14 and [redacted] from Trial MGL-3196-11 are described below. Subject [redacted] is also listed as a death in Section 7.6.1.2.

Case [redacted] (Trial MGL-3196-14)

Summary

This is a 60-year-old white female with NASH who developed elevated aminotransferases approximately 57 days after starting resmetirom (unblinded). Initial dose was 80 mg/day.

Baseline

At baseline, the subject's BMI was 44.8 kg/m^2. Relevant medical history, in addition to NASH, included hyperlipidemia, hypertension, and coronary atherosclerosis. Relevant medications included celecoxib and lisinopril. Alcohol consumption was reported as one to two beers per month.

- [redacted] (Study Day -482): Liver biopsy #1: Did not show significant steatosis but did show "portal hepatitis" without interface activity, and "forme fruste" of autoimmune hepatitis (AIH) or DILI were considered. Antinuclear antibody (ANA) and antimitochondrial antibody (AMA) were noted as "elevated", but titers were not provided. No note was made of concurrent medications with DILI risk.
- [redacted] (Study Day 48): Liver biopsy #2 (screening for Trial MGL-3196-11): Grade 1 steatosis, no ballooning, grade 1 lobular inflammation, grade 2 portal inflammation, fibrosis stage 1c, and "lymphocytic cholangitis (1 portal tract) or primary biliary cholangitis."
  - The subject failed screening for MGL-3196-11 but was enrolled in MGL-3196-14.

[redacted] (Study Day 1): Resmetirom 80 mg Started

- [redacted] (Study Day 1): Baseline ALT 35 U/L (ULN 41), AST 23 U/L (ULN 34), TB0.4 mg/dL (ULN 1.1), DB 0.05 (ULN 0.2). ALP was not provided but graphic suggests a level 100 U/L to 150 U/L (Figure 8 below).
- [redacted] (Study Day 57): ALT 236 U/L, AST 123 U/L, TB 0.6 mg/dL. ALP was not provided but Figure 8 indicates a level between 100 U/L to 150 U/L). No symptoms were mentioned. There was no mention of study drug change.
- [redacted] (Study Day 61): ALT 355, AST 176, TB 0.6 mg/dL ALP level not provided (~100 U/L based on provided chart). No symptoms were noted.

[redacted] (Study Day 64): Resmetirom Suspended

- [redacted] (Study Day 103): Liver enzymes increased to peak ALT 400 U/L, AST 212 U/L, and TB 0.6 mg/dL ALP not provided (~100 U/L based on Figure 8).
  - Lab workup as follows: ANA positive at >1:2560 (no baseline value provided other than comment of "elevated"). AMA titer 135 U (ULN≤20), however, retrospective testing of baseline serum was AMA positive at 120 U. Immunoglobulin G (IgG) was 1310 mg/dL compared to 1250 at baseline (ULN=1600). At the time of injury, anti-smooth muscle

antibody (ASMA) was indeterminate; anti-soluble liver antigen and anti- liver kidney microsomal were both negative. No viral serologies or imaging results were reported.

- (b) (6), (Study Day 124, 60 days off drug). Liver enzymes were ALT 204 U/L, AST 91 U/L, TB 0.52 mg/dL, and DB 0.09 mg/dL.
  - Liver biopsy #3: No NASH, mild portal inflammation with rare plasma cells. The findings were "not evocative of active autoimmune disease." There was "no interface hepatitis." Nevertheless, the biopsy did "not favor DILI but most probably an autoimmune disease."
- (b) (6) (Study Day 197, 133 days of drug): ALT and AST returned to baseline.

(b) (6) (Day 253, Day 1 for Rechallenge): Resmetirom Resumed (Delayed Due to COVID-19 Pandemic Delays).

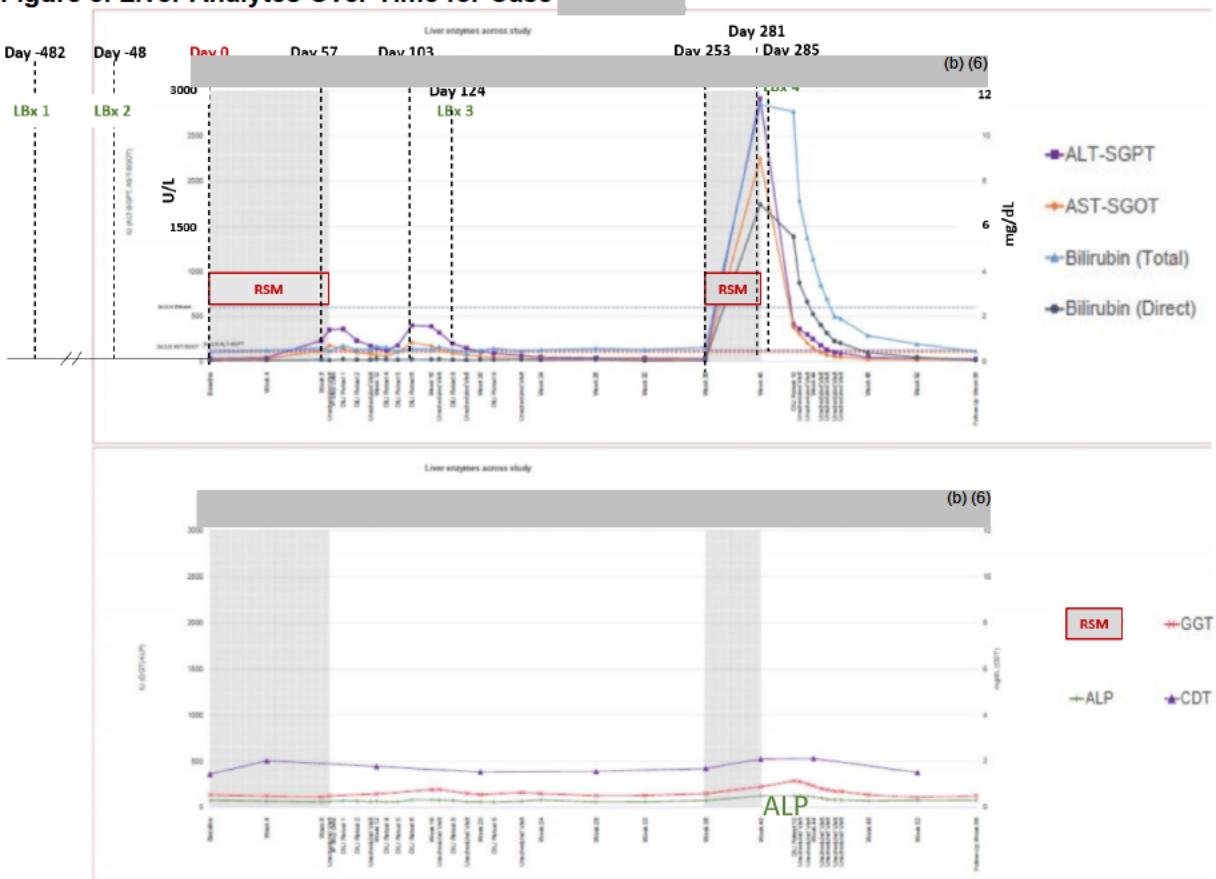
- (b) (6) (Day 265): Started CoQ-10 for "cardiac health"
- (b) (6) (Day 275): Developed nonserious dyspepsia, nausea, bloating, and fatigue after eating fried fish at a restaurant. CoQ-10 discontinued and began taking Zofran the next day for nausea.
- (b) (6): A negative Covid-19 test.
- (b) (6): Developed diarrhea and diagnosed with viral gastroenteritis at urgent care center. No liver analytes were checked.

(b) (6) (Day 281; Day 28 of rechallenge): Resmetirom Discontinued

- (b) (6) (Day 281; Day 28 for rechallenge): Fatigue and loss of appetite, but no fever, abdominal pain, or tenderness ("completely benign abdominal examination"). Noted to have mild scleral icterus. Labs drawn that day:
  - ALT 3226 U/L (ULN 56, local lab), AST 2429 U/L (ULN 37, local lab), ALP 140 U/L (ULN 149, local lab), and TB 10.9 mg/dL (ULN 1.3, local lab), DB 8 mg/dL (ULN 0.3, local lab).
  - White blood cells remained normal during liver injury.
  - Peak ALP during liver injury 1.1× ULN (127 U/L; ULN 116 central lab).
  - Testing for liver injury: negative acute serologies for hepatitis A virus (HAV), hepatitis B virus, hepatitis E virus, cytomegalovirus, SARS-CoV2, and Epstein–Barr virus (EBV). Hepatitis C virus antibody and hepatitis C virus ribonucleic acid negative. Autoimmune markers were positive for ANA (>1:1250) and positive for AMA. IgG 1770 mg/dL (ULN=1600).
  - Abdominal CT with intravenous contrast revealed gallstones with GB wall thickening, pericholecystic fluid without duct dilation with "high suspicion of acute cholecystitis," however no mention of GB hyperenhancement or common bile duct dilation.
- (b) (6) (Study Day 283, Day 1 second dechallenge): ALT 2510 U/L and AST 1965 U/L. Inpatient gastroenterology consultant concluded that DILI was the most likely cause of acute liver injury.

- [redacted] (Day 283, Day 2 second dechallenge): A hepatobiliary iminodiacetic acid scan was positive for acute cholecystitis versus obstructive disease. The magnetic resonance imaging (MRI) showed “no intra or extrahepatic biliary duct dilatation. No filling defects. There was mild extrinsic compression onto the common bile duct in the porta hepatis and in the region of the pancreatic head related to edema and the inflammatory changes in the porta hepatis.” ALT 2367 U/L AST 1895 U/L.
- [redacted] (Day 285, Day 4 second dechallenge): Liver analytes values continued to decrease: ALT 1933 U/L and AST 1527 U/L.
  - Transjugular liver biopsy (liver biopsy #4) was small, showing mixed mild-to-moderate portal inflammation with occasionally plasma cells and rare eosinophils, no steatosis or fibrosis (Stage 0 of 4). Narrative read the following: “Obviously it is very difficult and hazardous to propose a diagnosis given the small size and the poor quality of the material … obviously a marked and active inflammatory liver disease (autoimmune/AIH, drug-induced, other?).” There was no mention of concerns for duct obstruction on histology.
- [redacted] (Day 292, Day 11 of second dechallenge): Transferred to a liver transplant center for evaluation of liver transplant.
  - ALT 834 U/L, AST 781 U/L, TB 16.2 mg/dL. ALP not reported.
  - Ultrasound revealed gallbladder wall thickened, likely due to non-distended state. No pericholecystic fluid. Gallbladder contents sludge and small stones. There was no mention of bile duct dilation or cholecystitis.
- [redacted] (Day 293, Day 12 of second dechallenge): Hepatology consult impression was “elevated liver enzymes–likely severe DILI as supported by outside liver biopsy.” No transplant was needed.
- [redacted] (Day 294, Day 13 of second dechallenge): Magnetic resonance cholangiopancreatography was performed with no abnormal findings.
- [redacted] (Day 295, Day 14 of second dechallenge): Subject was discharged from hospital. No immunosuppression was administered.
  - Overall, ALT and AST fell by 50% in about 5 days, TB remained elevated in the 15 to 16 mg/dL range until it began to fall several days after the initial decline in ALT and AST.
- [redacted] (Day 341; Day 60 after second dechallenge): Liver analytes returned to normal.

Figure 8. Liver Analytes Over Time for Case (b) (6)



Source: modified by DILI Team member from clinical study report provided by Applicant for Trial MGL-3196-14 in module 5.3.5
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CDT, carbohydrate deficient transferrin; GGT, gamma glutamyl transferase, RSM, resmetirom; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transferase

Follow-Up

The subject had normal liver analytes as of (b) (6) (Study Day 391, Day 110 after second dechallenge): ALT 33 U/L, AST 23 U/L, AP 64 U/L, TB 0.46 mg/dL.

Pretreatment ANA titer was not available and stored serum was out of stability window for titer determination. The screening biopsy that disqualified the subject from Trial MGL-3196-11 was read by a second pathologist (Path B) who concurred with the initial read (Path A). The two biopsies performed during evaluation of treatment-emergent liver injury evaluations (biopsy #3, (b) (6), and biopsy #4, (b) (6)) were not available for trial pathologist rereading at the time of this review.

Assessment

The review team considered case (b) (6) as a case of *probable* DILI due to resmetirom that meets Hy's law criteria. However, the DILI phenotype best fits drug-induced autoimmune-like hepatitis (DI-ALH). A diagnosis of DILI is supported by the relatively short latencies for both exposures, with the second being shorter by half, consistent with a more rapid positive rechallenge. DI-ALH occurring in a background of subclinical AIH is supported by the subject's sex, age, pretreatment histology, pretreatment *reactive* autoimmune markers, followed by very

high ANA and high IgG during the liver injury, and lack of immunosuppression need (i.e., positive dechallenge unaided by corticosteroids) (Bjornsson et al. 2010; Andrade et al. 2023). While the biopsy on the second bout only hinted at DI-ALH, the sample was suboptimal.

The main competing diagnosis is AIH with de novo flares unrelated to resmetirom. Supporting AIH in isolation is the middle episode of enzyme elevations, occurring right on the heels of the first, when resmetirom was held (Figure 8). However, the severe and more rapid injury with resmetirom rechallenge is difficult to dismiss as coincidence, and rapid resolution of an ALT >3000 U/L and TB >15 mg/dL without need of immunosuppression is atypical for de novo AIH.

Bile duct obstruction and gallstone disease was considered, but the very high ALT, lack of ALP elevation, lack of symptoms (fever, abdominal tenderness, or pain), and lack of duct dilation do not support this liver injury explanation. A hepatobiliary iminodiacetic acid scan reported acute cholecystitis versus obstructive disease, but hepatobiliary iminodiacetic acid scans are known to perform poorly with high false positive rate in the setting of severe liver dysfunction (Ziessman 2014).

Celecoxib was also considered as a cause of the liver injury (Mukthinuthalapati et al. 2018), but according to the narrative, celecoxib was discontinued on (b) (6) (Day 78), which at most may be a cause of the first episode of liver analyte elevation, not the second episode, which was reported on day 282 of the trial, and 28 days after rechallenge with resmetirom.

Case (b) (6) (Trial MGL-3196-11)

Summary

This is a 69-year-old white male who developed elevated liver enzymes and bilirubin approximately 765 days after starting resmetirom 100 mg/day in the setting of Hodgkin's lymphoma.

Baseline

Relevant medical history included diabetes, hypertension, hyperlipidemia, aortic atherosclerosis, history of Hodgkin's lymphoma (6 years prior to study entry), and splenomegaly. Alcohol history was not provided. Concurrent medications relevant to DILI risk included atorvastatin (no dates given).

(b) (6) Resmetirom 100 mg Started

- (b) (6) (Day 1): started study drug (100mg). Baseline ALT, AST, AP, and TB were not provided.
- (b) (6) (Day 730): ALT, AST, ALP, and TB were 22 U/L (ULN 46), 18 U/L (ULN 35), 61 U/L (ULN 116) ,), and 0.6 mg/dL (ULN 1.1), respectively.
- (b) (6) (Day 765), ALT, AST, AP, and TB were mildly elevated at 66 U/L, 115 U/L, 119 U/L and 0.7 mg/dL, respectively. No liver-related symptoms and no change in study drug.
- (b) (6) (Day 792): presented to his PCP with jaundice; ALT, AST, ALP, and TB were 204 U/L, 291 U/L, 1255 U/L, and 16.4 mg/dL, respectively. The international

normalized ratio was 1.5. In retrospect he had had an over 2-week period of fatigue and weight loss, and dark urine for about a month, but no fever.

[redacted] **Resmetirom Discontinued**

- [redacted] (Day 793, Day 1 dechallenge): Subject was evaluated in ER and admitted to the hospital. TB was 16.7 mg/dL. Further workup included CT scan of abdomen and pelvis, neck, chest, along with MRI of the abdomen. These demonstrated diffuse enlargement of lymph nodes (periportal, peritoneal, retroperitoneal, mediastinal, right hilar). He was diagnosed with Hodgkin's lymphoma. MRI of the abdomen suggested common hepatic duct stricture, however, there was no intrahepatic biliary ductal dilation.
  - Liver analytes were followed, and they continued to be elevated, with TB values between 15 and 18 mg/dL, and with elevated ALT (166 to 187), AST (203 to 235) and ALP (940 to 1093). DB values were also elevated, at 8.8 mg/dL. ANA was reported as positive. AMA was also positive. No viral tests were provided and IgG level was not checked.
- [redacted] (Day 799, Day 7 dechallenge): Subject had ongoing jaundice and scleral icterus. Laboratory results: ALT 155 IU/L, AST 200 IU/L, TB, 16.8 mg/dL, DB, 8.8 mg/dL. The next day ([redacted] Day 800), he underwent lymph node biopsy which confirmed the diagnosis of Hodgkin's lymphoma. ERCP was done, which showed no ductal dilation or obstruction.
- [redacted] (Day 802, Day 10 dechallenge): Liver biopsy was done and showed "rare portal areas identified which did not show any evidence of inflammation; the intervening stroma in the biliary duct showed evidence of fibrosis; the liver parenchyma cells showed mild reactive changes; there was 1+ steatosis, no evidence of malignancy, iron stains were negative, trichrome stains showed septal and bridging fibrosis (cirrhosis), metavir score IV, and no evidence of lymphoma."
  - His liver analytes did not improve thereafter; none of them fell by more than 50% of peak values. He was thereafter followed by oncology. A PET scan was done which showed no obvious etiology for liver injury. Unclear which, if any, chemotherapy was rendered.
- [redacted] (Day 887, Day 95 dechallenge): a hepatology consult concluded that etiology for the cholestatic liver injury remained unclear.
- [redacted] (day 906, Day 114 dechallenge): subject hospitalized with a GI bleed and hypotension, and subsequently died on [redacted] (Day 933).

Assessment

This case was assessed as *unlikely* DILI due to resmetirom. The long latency (765 days) would be atypical, and the completely normal liver analytes (ALT 22 U/L, AST 18 U/L, AP 61 U/L, TB 0.6 mg/dL) just 35 days prior to injury onset argue against a chronic DILI while on resmetirom. Liver enzyme rise was documented to coincide with the Hodgkin's recurrence. Also, there was no dechallenge washout. Though rare, severe cholestasis with or without vanishing bile duct syndrome is described with Hodgkin's lymphoma (Lieberman 1986; Hubscher et al. 1993; Yalcin et al. 1999; Deacon et al. 2023). Liver biopsy may be indicative of a bile duct injury and

impending vanishing bile duct syndrome with “intervening stroma” or fibrosis of the bile ducts. Also, the biopsy had only “rare portal areas identified,” and therefore, the sample may have been inadequate. Hodgkin’s with a paraneoplastic cholestatic injury would be a unifying diagnosis.

Assessment of Cases in the Temple’s Corollary Quadrant

To further interrogate DILI, subjects in the Temple’s corollary quadrant (ALT or AST ≥3× ULN and TB <2× ULN) were assessed. Table 56 displays the number of subjects with ALT or AST elevation ≥3, 5 or 10× ULN. The table also displays the number of subjects who had elevations in ALT or AST with elevations in TB. Case narratives for subjects with ALT or AST values ≥5× ULN were reviewed.

Table 56. Subjects in the Temple’s Corollary Quadrant of the Hepatocellular DILI Screen, Pooled Analyses, MGL-3196-11, MGL-3196-14

Liver Analytes	Placebo N_w=658 n (%)	Resmetirom 80 mg N_w=671 n (%)	Resmetirom 100 mg N_w=662 n (%)
AST or ALT ≥3× ULN	85 (12.9)	60 (8.9)	72(10.9)
AST or ALT ≥5× ULN	20 (3.0)	10 (1.5)	14 (2.1)
AST or ALT ≥10× ULN	0 (0)	1 (0.1)	0 (0)
AST or ALT ≥3× ULN and TB ≥ULN	22 (3.3)	15(2.2)	16 (2.4)
AST or ALT ≥5× ULN and TB ≥ULN	7 (1.1)	2(0.3)	6(0.9)
AST or ALT ≥10× ULN and TB ≥ULN	0	0	0

Source: Reviewer generated from clinical data scientist provided tables from hepatocellular DILI screening analysis of ISS adlbc2.xpt.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ISS, integrated summary of safety; n, number of subjects meeting criteria; N_w, number of subjects with data; TB, total bilirubin; ULN, upper limit of normal

Evaluation of case narratives provided alternative explanations for elevation in liver chemistries in all cases, except for subject (b) (6) (discussed below). Alternative explanations for liver enzyme elevations included disease fluctuations in the setting of elevated baseline values, liver adaptation to resmetirom, alcohol use, concomitant drug use (e.g., statin), other disease processes (e.g., hypothyroidism, urinary tract infection, cholecystitis), and chemical use (hair dye). One case in the Temple’s corollary quadrant in Trial MGL-3196-11 ((b) (6)) was further evaluated by DHN’s DILI team.

Case (b) (6) (Trial MGL-3196-11)

Summary

This is a 46-year-old white female with NASH who developed elevated aminotransferases starting approximately 111 days after starting resmetirom (unblinded). Initial dose was 80 mg/day.

Baseline

At baseline, the subject’s BMI was 27.2 kg/m^2. Relevant medical history, in addition to NASH, included type 2 diabetes mellitus. Relevant medications included dapagliflozin and sitagliptin. Alcohol consumption history not provided.

[redacted] **(Study Day 1): Resmetirom 80 mg Started**

- [redacted] (Study Day 1): Baseline liver analytes were normal except for GGT: ALT 39 U/L, AST 26 U/L, ALP, 62 U/L, TB, 0.42 mg/dL, DB, 0.08 mg/dL, and GGT, 58 U/L (ULN 38).
- [redacted] (Study Day 56): diagnosed with concurrent stage 1 indolent multiple myeloma (MM)
- [redacted] (Study Day 111): Elevation in transaminases and GGT: ALT 578 U/L, AST 448 U/L, GGT 132 U/L. Other liver related analytes were normal: ALP 64 U/L, TB 1.1 mg/dL, DB 0.5 mg/dL.
- Additional laboratory workup: mitochondrial M2 antibody IgG 5.4 negative (ULN 0 to 20), SMA IgG titer 1:20 (normal <1:20), IgG 26.4 g/L (normal range 7 to 16), IgA 4.0 g/L (normal range 0.7 to 4.0), immunoglobulin M (IgM) 1.6 g/L (normal range 0.4 to 2.3), IgE 7 U/mL (normal <100), IgD 1.42 mg/dL (normal range 0.20 to 15.27), phosphatidylethanol (PETH) not detected.
- [redacted] (Study Day 113): ALT 813 U/L, AST 777 U/L, ALP 80 U/L, and TB 1.04 mg/dL.
  - Additional laboratory workup:
    - Anti-cytomegalovirus IgG 14000 (positive; signifies past infection), anti-CMV IgM 0.513 (negative).
    - Anti-HAV 21.7 (inconclusive). Although not clear, it is possible that the inconclusive value was repeated, as the narrative also reports a negative anti-HAV IgM (0.03) test.
    - Hepatitis B surface antigen <0.10 (negative), anti-hepatitis B core antibody total 0.08 (negative), anti-hepatitis B surface antibody 764 (positive; signifies vaccination against hepatitis B virus).
    - Anti-hepatitis C virus (negative).
    - Epstein-Barr serology showed anti-viral capsid antigen (VCA) IgG 202 (positive; interpreted as Positive; isolated presence of anti-VCA IgG). There are no reports of Epstein-Barr virus nuclear antigen, anti-VCA IgM or other EBV serology in the narrative, but the narrative mentions the serological profile is atypical and corresponds to past EBV infection with loss of anti-Epstein-Barr virus nuclear antigen IgG or recent infection without detection of anti-VCA IgM.
  - The subject did not experience any symptoms and confirmed she made no changes in concomitant medications or lifestyle.

[redacted] **(Study Day 113): Resmetirom Discontinued**

- [redacted] (Study Day 117, Day 4 dechallenge): ALT 444, AST 359, ALP 62, TB, 0.85
- [redacted] (Study Day 118, Day 5 dechallenge): the subject was under investigation for IgG lambda monoclonal dysglobulinemia. Last total IgG was 26 g/L with a peak of monoclonal IgG lambda of 12 g/L.

- [redacted] (Study Day 125, Day 12 dechallenge): ALT 167, AST 92, ALP 57, TB 0.41, DB 0.10.
- [redacted] (Study Day 141, Day 28 dechallenge): Liver enzymes normalized: ALT 28, AST 20, ALP 64, TB 0.36, DB 0.13.

[redacted] **(Study Day 141, Day 28 Dechallenge**): **Subject Withdrawn From Study**

Assessment

The division has assessed this event as a *possible* DILI. The subject had acute transaminase elevations around 2 months after diagnosis of multiple myeloma. Liver enzymes started to decrease after the study drug was discontinued, demonstrating an impressive positive dechallenge. HAV is unlikely to be the cause of this increase, as the anti-HAV IgM was negative. We considered EBV infection less likely with no symptoms and "atypical serological profile" (loss of anti-EBNA and lack of anti-VCA IgM). There were no compelling data for DI-ALH (ASMA negative, IgG normal), but ANA results were not provided. There are isolated case reports of liver involvement in MM, but liver enzymes resolve only after starting treatment. There is no mention of the subject initiating treatment for MM. Therefore, a positive de-challenge without myeloma treatment makes liver involvement of the myeloma unlikely.

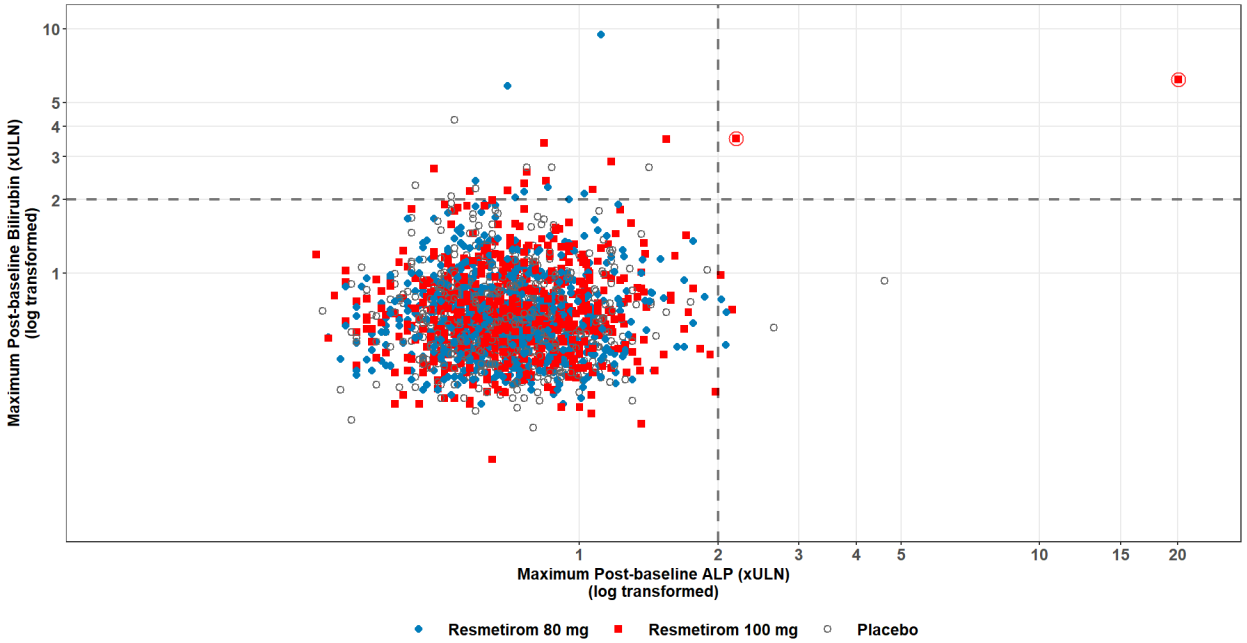
Assessment of Cases in the Cholestatic Quadrant of the Hepatocellular DILI Screen

In addition to evaluation of cases in the potential Hy's law cases and Temple's corollary, narratives for cases in the cholestatic quadrant of the hepatocellular DILI screen were reviewed. The majority of elevations of TB in this quadrant were attributable to Gilbert's syndrome. None of the cases were considered likely related to resmetirom.

7.7.1.2. Assessment of Cholestatic Injury, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Figure 9 displays the cholestatic DILI screening plot for the pooled population. Table 57 displays the subjects in each quadrant of the screening plot for the pooled population. Each data point represents a subject plotted by their maximum ALP versus their maximum TB values in the postbaseline period. A potential cholestatic DILI case (red circled in Figure 9) was defined as having a maximum postbaseline TB equal to or greater than 2×x ULN within 30 days after postbaseline ALP became equal to or exceeding 2× ULN.

Figure 9. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Trials, MGL-3196-11 and MGL-3196-14



Source: ISS adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Only central laboratory data is included in the analysis, as local laboratory data was not included in the submitted datasets.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: ALP, alkaline phosphatase; ISS, integrated summary of safety; ULN, upper limit of normal

Table 57. Patients in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, Pooled Trials, MGL-3196-11 and MGL-3196-14

Quadrant	Placebo N=667 n/N_w (%)	Resmetirom 80 mg N=679 n/N_w (%)	Resmetirom 100 mg N=673 n/N_w (%)
TB ≥2× ULN and ALP ≥2× ULN (right upper)	0/658 (0)	0/671 (0)	2/662 (0.3)
TB ≥2× ULN and ALP <2× ULN (left upper)	7/658 (1.1)	8/671 (1.2)	10/662 (1.5)
TB <2× ULN and ALP ≥2× ULN (right lower)	2/658 (0.3)	3/671 (0.4)	2/662 (0.3)
Total	9/658 (1.4)	11/671 (1.6)	14/662 (2.1)

Source: ISS adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Only central laboratory data is included in the analysis, as local laboratory data was not included in the submitted datasets.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; TB, total bilirubin; ULN, upper limit of normal

Narratives for all subjects in each quadrant of the cholestatic DILI screening plot were reviewed. Twenty subjects in the right-upper (TB ≥2× ULN and ALP ≥2× ULN) and left-upper quadrants (TB ≥2× ULN and ALP <2× ULN) were captured in the hepatocellular DILI screening plot and have been discussed in Section 7.7.1.1. For five subjects in the right-lower quadrant (TB <2× ULN and ALP ≥2× ULN) that were not captured, the elevation in ALP was not considered likely due to the drug. Alternative explanations for elevations in liver tests included disease-related fluctuations in the setting of elevated baseline, bone turnover due to fracture, and Paget's disease.

7.7.1.3. Additional Cases Reviewed

Open-label arms of Trial MGL-3196-14 were also reviewed for potential DILI cases. One additional case, (b) (6) was reviewed by the DILI team. This case was reported in the open-label NASH cirrhosis arm of Trial MGL-3196-14 in the clinical study report (CSR). In contrast to the Applicant's assessment, the Agency considered this case to be *possibly* related to study drug.

Case (b) (6) (Trial MGL-3196-14)

This is a 78-year-old white female with compensated cirrhosis who developed elevated aminotransferases approximately 140 days after starting resmetirom.

Baseline

Subject's relevant medical history included compensated cirrhosis (Child-Pugh A, model of end-stage liver disease 8) and hypothyroidism on levothyroxine. Alcohol history was not provided.

- (b) (6) (Day -20): At screening, ALT 55 U/L (ULN 41), AST 63 U/L (ULN 34), ALP 91 U/L (ULN 116), and TB 0.73 mg/dL (ULN 1.1).

(b) (6) Resmetirom 80 mg Started

- (b) (6) (Day 1): Baseline BMI not provided. The subject's ALT 48 U/L, AST 51 U/L, ALP 85 U/L, and TB 0.73 mg/d.

  Her IgG level was mildly elevated at 1730 mg/dL (ULN 1600); other immunoglobulin levels were normal; and AMA, ASMA, Anti-LKM1, and anti-LSA were negative.

  No ANA data were provided.
- (b) (6) (Day 83): Subject's dosage was decreased to 60 mg daily. No reason for the dose decrease was provided.
- (b) (6) (Day 141): ALT 148 U/L, AST 193 U/L, ALP 143 U/L, and TB 1.39 mg/dL, respectively. No symptoms were reported.

(b) (6) Resmetirom Discontinued

- (b) (6) (Day166): US showed cirrhosis with no focal lesion.
- (b) (6) (Day 196): Liver chemistries reached peak elevations with ALT 178 U/L, AST 214 U/L, ALP 183 U/L, TB 1.05 mg/dL, DB 0.31 mg/dL.
  - On May 18, 2021, additional labs were repeated, and ASMA was now weakly positive at 1:40 and IgG was up to 2610 mg/dL (ULN 1600). Other autoantibodies which were checked at baseline were still negative. ANA result was not provided.
  - Liver enzymes and TB remained elevated for approximately 4 months before demonstrating gradual improvement (Figure 10).
- (b) (6) (Day 230): A diagnosis of AIH was made, without mention of a liver biopsy. No symptoms were documented, and no treatment was immediately rendered.

- [redacted] (b) (6) (Day 250): Immunosuppression started with azathioprine 50 mg daily for 2 weeks, followed by mycophenolate mofetil 500 mg twice daily, which is "ongoing."

  At the time of initiating immunosuppression, liver enzymes had already fallen by approximately 60 to 70% of peak levels (Figure 10).

  Thereafter, liver enzymes and TB decreased back to baseline by [redacted] (b) (6) (Day 281). No other evaluation information was provided. Liver imaging was not mentioned. It is unclear if the subject is still on immunosuppressive medications.

Figure 10. Liver Analytes Over Time for Case [redacted] (b) (6)

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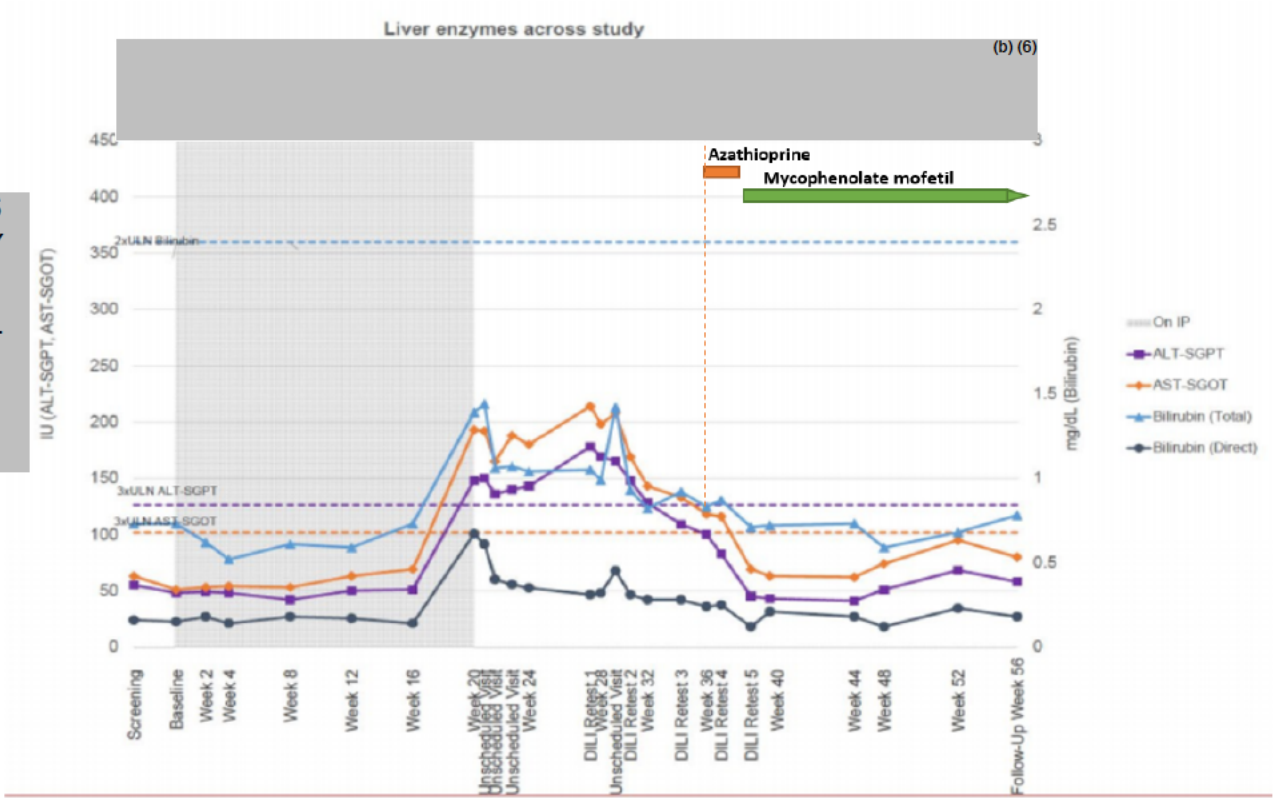


Source: modified by DILI Team member from clinical study report provided by Applicant for Trial MGL-3196-14 in module 5.3.5.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; IU, international unit; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transferase

Assessment

The review team considered this case to be at least *possible,* if not probable, DILI due to resmetirom; this case might also fit with DI-ALH. Whereas IgG levels can be elevated in cirrhosis, the 50% increase in IgG, seroconversion to a positive ASMA (albeit low titer) and decline in liver analytes even before immunosuppression are suggestive of a mild DILI with AIH features rather than de novo AIH. Indeed, the subject may not have required immunosuppression as her liver enzymes had improved substantially before it was initiated (Figure 10). A liver biopsy would have been helpful but was not performed. The local provider initially chose azathioprine for immunosuppression, and subsequently switched to mycophenolate without explanation.

7.7.1.4. Conclusion

Assessment of DILI in the pooled (placebo-controlled) population revealed three potential DILI cases, and one additional case in the open-label NASH cirrhosis arm of Trial MGL-3196-14. These cases were reviewed by DHN's DILI team, and of these four, three were concerning for probable or possible DILI attributable to resmetirom.

One case, (b) (6), was independently adjudicated by four Agency hepatologists and considered *probable* by all, as resmetirom-related DILI, meeting Hy's Law criteria, but with a drug-induced, autoimmune-like hepatitis (DI-ALH phenotype for the liver injury. The simplified AIH score for this subject was 6 to 7 (probable AIH) (Hennes et al. 2008), and DI-ALH cases often have high AIH scores. The review team favored DI-ALH over AIH because of the positive resmetirom rechallenge and normalization of liver analytes without immunosuppressive therapy. This subject had two pre-enrollment liver biopsies suggesting a subclinical autoimmune liver disorder. The review team speculates that resmetirom caused a DI-ALH in a subject predisposed to such an injury. Such predisposition is a common hypothesis for DI-ALH pathophysiology.

The second case is a cirrhotic NASH subject (Subject (b) (6)) who was assessed as *possible* DILI due to resmetirom, also accompanied by autoimmune features. The injury was mild. The narrative suggests that AIH was diagnosed, but no biopsy was documented. While this subject received immunosuppression, it is not clear that such treatment was needed. The enzymes had fallen 60 to 70% before immunosuppression, and it is unknown if the subject was able to taper off therapy. A successful taper of immunosuppression would be unusual for de novo AIH but typical of DI-ALH.

The third case ((b) (6)) in the intended use (F2/F3) population was assessed as *possible* DILI This case was confounded by concurrent indolent MM. Given the impressive positive de-challenge in the setting of untreated MM makes liver involvement of the myeloma unlikely. Potential other causes considered by the Applicant, HAV and EBV, are unlikely.

While one Hy's Law case out of 3,000 subjects exposed typically raises a concern for postmarket risk of significant DILI, the phenotype of DI-ALH makes applicability of Hy's Law less clear. It is unclear whether DI-ALH carries a 10% mortality risk, particularly because a therapy (corticosteroids) may be available. If DI-ALH is recognized early and temporary immunosuppression applied, the mortality risk could be lower.

Given that there is an overall favorable benefit-risk profile for resmetirom, these three liver injury cases do not preclude approval of resmetirom. The following actions will be recommended:

- Description of Case (b) (6) will be included in the *Warnings and Precautions* section, with instructions to the provider on monitoring for drug induced hepatotoxicity.
- Instructions to the provider to consider an evaluation for DI-ALH if liver enzyme elevations do not resolve with dechallenge.
- Enhanced pharmacovigilance for DILI for 2 years, to ensure the Agency receives timely postmarket hepatic safety information.

7.7.2. Treatment-Related Changes in Thyroid Hormones

Issue

Resmetirom is a THR-ß agonist. THR-ß is the predominant receptor subtype in the liver and resmetirom is intended to act in the liver, avoiding unwanted systemic actions of TH in heart and bone, mediated through THR-α. Although a THR-ß agonist, resmetirom does have some agonist activity on THR-α receptors (see Section 5.2), and therefore, may have potential effects on the TH axis.

Background

Refer to Section 3 for description of THR subtypes and their role, and discussion of population studies in NAFLD and NASH with respect to thyroid dysfunction.

The Applicant's hypothesis is that deficiency in THR-β activity in the livers in subjects affected by NASH cannot be corrected by treatment with TH because TH is rapidly metabolized due to the action of deiodinases. This progressive hepatic hypothyroidism may play a role in the pathophysiology of NASH due to reduced hepatic conversion of T4 to T3, which is mediated by deiodinase 1 (DIO1), a THR-ß target gene in the liver (Nomura et al. 1975).

Preclinical studies of resmetirom identified effects on TH axis function, such as decreases in T4 (total and free), T3 (total and free), and TSH. These effects were observed in all general toxicology studies in rats, mice, and dogs, and varied across species. In general, the reductions in T4 were moderate to marked, whereas effects on T3 and TSH ranged from no change to moderate reductions. The effects on T4, T3, and TSH were reversible following the end of treatment (for more detail, refer to Section 7.1).

In the phase 2 trial, resmetirom treatment was associated with reduced levels of free thyroxine (FT4) from baseline to week 36 ($p<0.0001$), with no changes in other thyroid axis hormones (free triiodothyronine (FT3), TSH, or thyroxine-binding globulin.

In the pivotal trial, the Applicant specified a dose-reduction regimen based on FT4 levels. Exclusion and monitoring criteria pertaining to thyroid function were specified in the protocol for both trials (see Section 15).

Assessment

Analysis of effects on thyroid function was undertaken with help from FDA endocrinologists. Pertinent results from their assessment are presented in this section with supplementary analyses presented in Section 17.

Changes in Thyroid Hormone Levels

Potential effects on TH levels were assessed according to baseline use of exogenous thyroxine products, given exogenous thyroxine and underlying hypothyroidism may confound the interpretation of results.

Free T4

In Trial MGL-3196-11, a small reduction in FT4 levels from baseline to Week 52 was noted for both the resmetirom 80 mg and 100 mg arms compared to placebo, in both thyroxine-treated and thyroxine- untreated subjects.

In subjects not on thyroxine, FT4 levels decreased by approximately 14% and 18% from baseline in the 80 mg arm and 100 mg arm, respectively. The reductions in FT4 levels compared to placebo was statistically significant for both resmetirom doses, but FT4 values remained within normal ranges. Similar changes in FT4 levels were observed in subjects who were on thyroxine therapy at baseline. The small declines in the mean FT4 levels occurred early in the study (i.e., weeks 4 to 8), with FT4 remaining relatively stable throughout the remainder of the study (refer to Table 293 in Section 17.3).

Similar decreases in FT4 levels were noted in the intended use population, subjects with F2/F3 fibrosis, where mean change in FT4 values from baseline were noted to be lower in both dose arms, compared to placebo, in the whole population, irrespective of exogenous thyroxine-use status (Figure 69, Section 17.3.1).

TSH

In subjects not on thyroxine, a small reduction in mean TSH values was seen in both resmetirom treatment arms compared to placebo at Week 52, in Trial MGL-3196-11. The absolute mean numerical changes were small and TSH remained within normal ranges. Similar modest reductions in mean TSH levels were seen in subjects on thyroxine at baseline (refer to Table 293 in Section 17.3.1).

When assessing effects only in subjects with F2/F3 fibrosis, mean changes in the TSH values were similar to the ones seen in the full analysis population (Figure 70, Section 17.3.1).

Free Triiodothyronine and TT3

In Trial MGL-3196-11, no meaningful changes in the active THs, T3 (both total and free T3) were observed. Interpretation of FT3 and TT3 results should be made with caution, because FT3 has a very short half-life, and TT3 may be affected by increases in SHBG levels, which are seen with resmetirom.

Similar changes from baseline to Week 52 in mean FT4, TSH, and T3 levels were observed in Trial MGL-3196-14 (Table 294, Section 17.3).

Treatment-Emergent Abnormalities in Thyroid Hormones

The shifts in the thyroid axis hormones from baseline through Week 52 to any abnormal occurrence postbaseline by exogenous thyroxine-use status at baseline were also evaluated. Refer to Table 58 and Table 59 below.

Table 58. Thyroid Hormone Abnormalities in Subjects Not on Thyroxine at Baseline, Trial MGL-3196-11 (Non-Cirrhotic NASH Safety Population – F1B, F2, F3)

Abnormality Free T4 and TSH Value	Placebo (N=276)	Resmetirom 80 mg (N=283)	Resmetirom 100 mg (N=277)
Subjects with abnormality at any postbaseline assessment, but not at baseline[1], n (%)			
Free T4 <0.7 ng/dL	7 (2.5)	46 (16.3)	82 (29.6)
TSH <0.3 mIU/L	3 (1.1)	10 (3.5)	9 (3.2)
TSH >4.5 mIU/L	31 (11.2)	22 (7.8)	23 (8.3)
Subjects with abnormality at two or more consecutive postbaseline assessments, but not at baseline[1], n (%)			
Free T4 <0.7 ng/dL	2 (0.7)	29 (10.2)	52 (18.8)
TSH <0.3 mIU/L	0	2 (0.7)	3 (1.1)
TSH >4.5 mIU/L	5 (1.8)	4 (1.4)	8 (2.9)

Source: Table 3, Applicant Response to IR dated November 17, 2023

[1] Subjects with missing baseline data are counted as not having an abnormality at baseline.

Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; IR, information request; N, number of subjects in treatment arm; n, number of subjects in subset; NASH, nonalcoholic steatohepatitis; T4, tetraiodothyronine; TSH, thyroid stimulating hormone

In subjects not on thyroxine (Table 58 above):

- FT4: a higher proportion of subjects in the resmetirom 80 mg and 100 mg treatment groups compared with placebo had a shift from Baseline levels ≥0.7 ng/dL to at least one measurement below 0.7 ng/dL (i.e., the lower normal limit) postbaseline. Declines in FT4 on at least two consecutive occasions were also higher in the treatment arms compared to placebo, but these were transient in most subjects.
- TSH: a higher proportion of subjects in the resmetirom 80 mg and 100 mg treatment groups compared with placebo had a shift in TSH from a baseline of ≥0.3 mIU/L to at least one occurrence of TSH <0.3 mIU/L postbaseline, but this was seen in lower numbers compared to FT4. Declines in TSH on at least two consecutive occasions were marginally higher in the treatment arms, but these changes were also transient.
- A shift in TSH level from a baseline TSH ≤4.5 mIU/L to TSH >4.5mIU/L at any time during the study was seen in a higher proportion of subjects in the placebo arm compared to drug arms for any postbaseline assessment and was similar in all arms for two or more consecutive postbaseline assessments.

Table 59. Thyroid Abnormalities in Subjects on Thyroxine at Baseline, Trial MGL-3196-11 (Non-Cirrhotic NASH Safety Population – F1B, F2, F3)

Abnormality Free T4 and TSH Value	Placebo (N=45)	Resmetirom 80 mg (N=39)	Resmetirom 100 mg (N=46)
Subjects with abnormality at any postbaseline assessment, but not at Baseline[1], n (%)			
Free T4 <0.7 ng/dL	0	6 (15.4)	15 (32.6)
TSH <0.3 mIU/L	4 (8.9)	9 (23.1)	15 (32.6)
TSH >4.5 mIU/L	9 (20.0)	7 (17.9)	14 (30.4)

Subjects with abnormality at two or more consecutive postbaseline assessments, but not at Baseline[1], n (%)			
Free T4 <0.7 ng/dL	0	2 (5.1)	11 (23.9)
TSH <0.3 mIU/L	1 (2.2)	4 (10.3)	8 (17.4)
TSH >4.5 mIU/L	3 (6.7)	2 (5.1)	5 (10.9)

Source: Table 6, Applicant Response to IR, dated November 17, 2023

[1] Subjects with missing baseline data are counted as not having an abnormality at Baseline.

Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; IR, information request; N, number of subjects in treatment arm; n, number of subjects in subset; NASH, nonalcoholic steatohepatitis; T4, tetraiodothyronine; TSH, thyroid stimulating hormone

In subjects on thyroxine:

- FT4: Similar to subjects who were not on thyroxine, a higher proportion of subjects in the resmetirom 80 mg and 100 mg treatment groups compared with placebo had a shift from baseline levels ≥0.7 ng/dLto at least one measurement below 0.7 ng/dL postbaseline. Declines in FT4 on at least two consecutive occasions were also higher in the treatment arms compared to placebo. A small number of subjects (6%) had persistently low FT4, however, all subjects maintained normal TSH.
- TSH: A higher proportion of subjects in the resmetirom 80 mg and 100 mg treatment groups compared with placebo had a shift in TSH from a baseline of ≥0.3 mIU/L to at least one occurrence of TSH <0.3 mIU/L postbaseline, but in contrast to those not on thyroxine, this was seen in similar numbers as those who had a decline in FT4. Declines in TSH on at least two consecutive occasions were also higher in the treatment arms. These decreases in TSH were typically not associated with abnormalities in other THs (FT4, TT3), and were transient.
- A shift in TSH level from a baseline TSH ≤4.5 mIU/L to TSH >4.5 mIU/L was seen in higher proportion only in the 100 mg arm compared to placebo. These increases were transient and were not associated with FT4 abnormalities.

Assessment

- Declines in FT4 below normal occurred in a higher proportion of subjects in the treatment arms compared to placebo but TSH remained normal in these subjects. TSH, the most reliable and sensitive marker of thyroid function, remained within normal limits throughout the trial in subjects with transient or persistent declines in FT4. The TH changes in the few subjects with declines in TSH below normal suggest that any TSH-lowering effect of resmetirom is transient and is likely not clinically meaningful.
- These findings are suggestive of preservation of hypothalamic-pituitary-thyroid axis function.
- Subjects on thyroxine at baseline had an overall higher incidence of thyroid function abnormalities (i.e., low FT4, TSH decrease, and TSH increase) compared to subjects who were not on thyroxine therapy at baseline, suggesting that individuals with underlying thyroid disease may be more susceptible to resmetirom-induced effects on the hypothalamic-pituitary-thyroid axis.
- A few subjects were started on low-dose levothyroxine therapy based on the low FT4 levels. However, the clinical utility of initiation of TH replacement therapy in this clinical scenario of transiently low FT4 with normal TSH is unclear.

Analysis of Thyroid Status Related Preferred Terms

Table 60 displays the AEs related to thyroid status in the pooled population, Trials MGL-3196-11 and MGL-3196-14. The incidence of AEs related to thyroid function abnormalities (e.g., hypothyroidism, hyperthyroidism, and blood TSH decreased) was overall low during Trials MGL-3196-11 and MGL-3196-14. However, a higher proportion of subjects in the drug arms were noted to have thyroid-related AEs compared to placebo.

Table 60. Adverse Events AE Related to Thyroid Status, Pooled Population, Trials MGL-3196-11 and Trial MGL-3196-14

AE Related to Thyroid Status	Placebo PY=792.8 N=667 n/py (EAIR	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Hypothyroidism	3/790.5 (0.4)	7/772.1 (0.9)	13/757.7 (1.7)	0.5 (-0.3, 1.5)	1.3 (0.4, 2.6) *
Blood thyroid-stimulating hormone decreased	0/792.8 (0)	3/773.1 (0.4)	4/762 (0.5)	0.4 (-0.1, 1.1)	0.5 (0.0, 1.3) *
Hyperthyroidism	0/792.8 (0)	1/776.9 (0.1)	1/765.5 (0.1)	0.1 (-0.4, 0.7)	0.1 (-0.4, 0.7)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Coded as MedDRA preferred terms (25.0)
Note: EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; PY, person-years (total exposure); py, person-years (at risk)

Further review of laboratory data by FDA endocrinologists concluded:

- In Trial MGL-3196-11, a small proportion (1.8%) of subjects with the AE of hypothyroidism(based on slightly high TSH, or low FT4) were started on low-dose levothyroxine, with subsequent normalization of TSH, or decline in TSH to below normal, questioning the clinical utility of levothyroxine treatment. In Trial MGL-3196-14, the majority of subjects who had an AE of hypothyroidism during the trial were on thyroxine therapy at baseline (i.e., had a diagnosis of hypothyroidism prior to resmetirom initiation). In these subjects on thyroxine at baseline, transient TSH elevations after starting resmetirom, without changes in FT4 or TT3, did not require thyroxine dose adjustment.
- In Trial MGL-3196-11, a small proportion of subjects in the resmetirom arm had AEs of TSH decreased, most of whom were on thyroxine at baseline. The AE of “TSH decrease” was transient and not clinically meaningful.
- The AE of hyperthyroidism was reported in a very small number of subjects who were being treated with TH replacement at baseline. The AE was reported based on mild TSH decline with normal FT4 and T3, which improved with thyroxine dose reduction.

Analysis of AEs Signs/Symptoms Potentially Related to Thyroid Status

To further examine the possible clinical significance of shifts in THs, particularly the reduction in FT4, AEs potentially suggestive of hyperthyroidism and hypothyroidism were evaluated in the pooled safety data of noncirrhotic NASH/NALFD subjects from Trials MGL-3196-11 and MGL-3196-14 (Table 61). Tremor, tachycardia, and constipation were observed at a higher rate in

resmetirom-treated arms compared to placebo, although these AEs were overall uncommon (tremor and tachycardia) or observed at a modestly higher rate compared to placebo (constipation).

Table 61. Subjects With Adverse Events Potentially Related to Hyperthyroidism and Hypothyroidism by FDA Medical Query (Narrow), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Preferred Term	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
AEs possibly related to hyperthyroidism					
Fatigue	53/739.4 (7.2)	66/725.8 (9.1)	53/721.4 (7.3)	1.9 (-1.0, 4.9)	0.2 (-2.6, 3.0)
Tachycardia	5/789.3 (0.6)	7/773.8 (0.9)	8/763.1 (1.0)	0.3 (-0.7, 1.3)	0.4 (-0.6, 1.5)
Tremor	1/791.8 (0.1)	7/772.2 (0.9)	5/765 (0.7)	0.8 (0.1, 1.8) *	0.5 (-0.1, 1.4)
Irritability	4/788.4 (0.5)	1/776.3 (0.1)	3/765.8 (0.4)	-0.4 (-1.2, 0.3)	-0.1 (-1.0, 0.7)
Anxiety	22/776.9 (2.8)	21/763.1 (2.8)	20/752.7 (2.7)	-0.1 (-1.8, 1.7)	-0.2 (-1.9, 1.6)
Insomnia	21/771.7 (2.7)	16/764.7 (2.1)	18/756.8 (2.4)	-0.6 (-2.3, 1.0)	-0.3 (-2.0, 1.3)
AEs possibly related to hypothyroidism					
Fatigue	53/739.4 (7.2)	66/725.8 (9.1)	53/721.4 (7.3)	1.9 (-1.0, 4.9)	0.2 (-2.6, 3.0)
Constipation	34/767.3 (4.4)	41/739.2 (5.5)	44/723.2 (6.1)	1.1 (-1.2, 3.5)	1.7 (-0.7, 4.1)
Arthralgia	67/732 (9.2)	78/711.7 (11.0)	64/712.9 (9.0)	1.8 (-1.5, 5.2)	-0.2 (-3.3, 3.0)
Myalgia	19/777.1 (2.4)	16/763.5 (2.1)	19/750.1 (2.5)	-0.3 (-1.9, 1.2)	0.1 (-1.6, 1.8)

Source: Clinical Data Scientist: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FDA, U.S. Food and Drug Administration; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk).

Resmetirom Dose Reduction Based on FT4 Levels

In Trial MGL-3196-11, 12 subjects (1.9%), (10 [3.1%] in resmetirom 100 mg arm and 2 [0.6%] subjects in resmetirom 80 mg arm) underwent resmetirom dose reduction at week 12 because they met the protocol-specified FT4 criteria of ≥30% decrease from baseline in FT4 to <0.7 ng/dL at Weeks 4 and 8. The changes in thyroid function tests after dose reduction show a subsequent increase in mean FT4 levels back to normal reference ranges. Slight changes in mean FT3, T3, and TSH levels were also noted, but were within normal reference ranges both before and after dose adjustment.

A similar proportion of subjects required resmetirom dose adjustment during Trial MGL-3196-14: 12 (2.4%) subjects underwent dose reduction from 100 mg resmetirom to 80 mg and 2 (0.6%) subjects underwent dose reduction from 80 mg resmetirom to 60 mg. Second dose-reductions for low FT4 in the phase 3 studies were rare (6 subjects total in both studies combined)

The clinical relevance of FT4 level decreasing below 0.7 ng/dL while TSH and T3 levels remained within normal ranges is not clear. As such, the clinical utility of resmetirom dose reduction in subjects who develop isolated FT4 levels (with normal TSH and T3 levels) remains unknown.

Conclusion

Small fluctuations in FT4 were seen in resmetirom-treated subjects during the trial, which rarely led to FT4 levels outside of the normal range. Nonsignificant small fluctuations in TSH and T3 levels were also occasionally seen, again with levels remaining within normal limits. The fluctuations in thyroid function tests (TFTs) were transient in nature and not associated with thyroid-related symptoms in the subjects who developed these TFT fluctuations Changes of similar magnitude in TFTs were seen in subjects who were euthyroid at baseline compared to those who were hypothyroid receiving TH replacement therapy.

Overall, the function of the hypothalamic-pituitary-thyroid axis was maintained during resmetirom treatment despite small, transient fluctuations in TH levels seen in some subjects during the trial. The review team determined that no additional measures beyond routine clinical monitoring, individualized based on baseline thyroid function and non-resmetirom related risk of thyroid abnormalities, were indicated in subjects with NASH taking this product.

7.7.3. Treatment-Related Gallstone Adverse Events

Issue

There is a strong association between gallstone disease and NAFLD/NASH (Kichloo et al. 2021), both of which occur more commonly in patients with obesity and diabetes. In addition, weight loss and drugs that promote weight loss are associated with increased gallstone formation (Everhart 1993; May 1998; He et al. 2022). Thyroid hormones increase hepatic fatty acid beta-oxidation and the excretion of cholesterol and phospholipids into bile (Sinha et al. 2018). Because resmetirom is a thyromimetic compound targeting hepatic THR-ß, it is expected to promote bile formation and secretion, increase cholesterol metabolism and formation of bile acids, and increase secretion of cholesterol, increasing the potential for gallstone formation.

Background

Although most gallstones are asymptomatic, a minority of patients with gallstones can develop serious complications, including acute cholecystitis and pancreatitis. Cystic duct obstruction due to gallstones is responsible for greater than 90% of acute cholecystitis (Gallaher and Charles 2022). Gallstones are the most common cause of acute pancreatitis, accounting for 40 to 70% of cases (Forsmark et al. 2007).

There is an association between thyroid dysfunction and gallbladder events. Hypothyroidism increases the incidence of cholelithiasis and acute cholecystitis (Laukkarinen et al. 2012). There is limited population-based data on the association between hyperthyroidism and gallstone formation. But, in hyperthyroidism there is enhanced excretion of cholesterol and an increased turnover of LDL-C (Duntas 2002),which could be contributory in the pathogenesis of gallstones. Hyperthyroidism is also associated with rapid weight loss, which can contribute to the pathophysiology of gallstone formation.

In the phase 2 trial, MGL-3196-05, which was 36 weeks in duration, there was one event of bile duct stones in the placebo group. Because there is a known risk in the condition and because the MOA of resmetirom theoretically could increase the risk of gallstone-related AEs, these were analyzed in Trials MGL-3196-11 and MGL-3196-14.

Assessment

Gallstone-related PTs were assessed in the pooled population, Trials MGL-3196-11, and MGL-3196-14. Table 62 displays the PTs of gallstone-related events in the pooled population, which were bile duct stone, cholelithiasis, acute cholecystitis, and obstructive pancreatitis.

Given that most gallstones are asymptomatic, it is possible that the gallstones detected during screening and monitoring during the trial could have been present prior to the initiation of resmetirom therapy, however, cholelithiasis was reported more frequently in the resmetirom-treated groups, although still rare (<1 per 100 PY).

The events of obstructive pancreatitis (gallstone) were SAEs. Although obstructive pancreatitis (gallstone) was rare in both the drug arms, it occurred at a higher rate compared to placebo, where no cases were observed. The incidence of gallstones was also low in the pooled population but was higher for the drug arms (0.9 per 100 PY for 80 mg arm and 0.8 per 100 PY for the 100 mg arm). Similarly, there were few events of acute cholecystitis observed, and these were marginally higher in the drug arms compared to placebo.

Table 62. Adverse Events of Special Interest Assessment, Gallstone-Related, Pooled Population, Trials MGL-3196-11 and MGL-3196-14

Preferred Term	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Cholelithiasis	2/790.4 (0.3)	7/770.8 (0.9)	6/764.1 (0.8)	0.7 (-0.1, 1.6)	0.5 (-0.2, 1.5)
Bile duct stone	0/792.8 (0)	1/777.2 (0.1)	1/766.2 (0.1)	0.1 (-0.4, 0.7)	0.1 (-0.4, 0.7)
Cholecystitis*	1/792.7 (0.1)	2/776.5 (0.3)	3/764.2 (0.4)	0.1 (-0.5, 0.8)	0.3 (-0.4, 1.0)
Obstructive pancreatitis (gallstone)	0/792.8 (0)	2/777.2 (0.3)	2/765.8 (0.3)	0.3 (-0.2, 0.9)	0.3 (-0.2, 1.0)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
* cholecystitis is an FMQ (narrow) comprised of the PTs, cholecystitis and cholecystitis, acute.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); FMQ, FDA medical query; PT, preferred term

Conclusion

Treatment-related gallstone AEs were uncommon in the safety database including MGL-3196-11 and MGL-3196-14 but were higher in the resmetirom treatment groups than in the placebo groups.

Given the MOA of resmetirom, it is possible that as the drug is given to a large population, the incidence of gallstone events may increase. Therefore, the adverse drug reaction of gallstone-related events is included in the Warnings and Precautions section of labeling to alert prescribers. Additional data will be collected during the confirmatory clinical benefit Trial MGL-3196-011 and during routine postmarket reporting.

7.7.4. Treatment-Related Gastrointestinal Adverse Events

Issue

GI AEs were the most common TEAE reported during the development program. For example, in the phase 2 clinical trial, MGL-3196-05, diarrhea was the most common AE, reported within 36 weeks of treatment in 37% of subjects receiving resmetirom, compared to 10% of those in the placebo group. Most experienced the event within the first 12 weeks of treatment. By the end of the 36-week treatment period, nausea and upper abdominal pain were also more common in the resmetirom groups than in placebo group subjects. In MGL-3196-05, diarrhea and nausea were mostly mild or moderate, but one subject reported severe abdominal pain. Drug was withdrawn for two subjects in the phase 2 trial due to diarrhea.

Background

Although none of the reported GI AEs in phase 2 development were described as severe, further characterization was needed in larger, longer-duration phase 3 trials. It was important to understand whether the GI AEs could lead to treatment interruption or discontinuation that would limit the potential for long-term adherence to therapy. The GI AEs in MGL-3196-11 and MGL-3196-14 were also analyzed by subgroups, to determine whether specific groups were more likely to experience these AEs.

Assessment

GI AEs are described for the F2/F3 population in Section 7.6.1.5, and for the pooled population in Section 7.6.2.5. Because these were AESIs, in-depth analysis of the most common GI AEs was conducted. Refer to Section 7.6.1.5 for discussion regarding EAIRs, time to onset and severity, and Section 7.6.1.4 for EAIRs related to treatment discontinuation secondary to GI AEs in the F2/F3 population.

In this section, further discussion of the GI AEs in the pooled population is described. GI AEs were a common cause of treatment discontinuation (Table 289 in Section 17.2.3), where 29 (4 per 100 PY) and 28 (4 per 100 PY) subjects discontinued treatment in the 100 mg and 80 mg arms, respectively, compared to 9 (1 per 100 PY) in placebo. AEs leading to treatment discontinuations in the pooled population are discussed in Section 7.6.2.4. GI events were also the most common TEAEs observed in the pooled population (Table 51, Section7.6.2.5). However, only one SAE of abdominal pain was reported in the pooled population. Among GI events, diarrhea and nausea were the most common TEAEs and causes of treatment discontinuation (Table 50 in Section 7.6.2.4).

This section will focus on the four most common GI AEs: diarrhea, nausea, abdominal pain, and vomiting .

Diarrhea

The severity of diarrhea (narrow FMQ) was mostly mild to moderate in the drug arms with only one subject each in the drug arms reporting episodes as severe. Diarrheal episodes started at study initiation. Among subjects with diarrhea, 76% of subjects in the 80 mg arm (132 out of

173) and 84% of subjects in the 100 mg arm (181 out of 215) had reported diarrhea in the first 100 days of drug use. The median duration of diarrhea was 8 days, 16 days, and 18 days in the placebo, 80 mg dose arm, and 100 mg dose arm, respectively. EAIRs for treatment discontinuation due to diarrhea were 0.1 per 100 PY, 2 per 100 PY, 3 per 100 PY for placebo, 80 mg dose arm, and 100 mg dose arm, respectively.

Nausea

The severity of nausea (narrow FMQ) was mild to moderate in the drug arms, with no subjects reporting the event as severe in the drug arms. Nausea episodes started at study initiation. Among subjects with nausea, 68% of subjects (78 out of 115) in the 80 mg arm and 82% of subjects (100 out of 122) in the 100 mg arm had reported nausea in the first 100 days of drug use. The median duration of nausea was 17 days, 20 days, and 19 days in the placebo, 80 mg dose arm, and 100 mg dose arm, respectively. EAIRs for treatment discontinuation due to nausea were 1 per 100 PY for both the 80 mg and 100 mg dose arm, compared to 0.5 per 100 PY for placebo.

Abdominal Pain

The severity of abdominal pain was mostly mild to moderate in the drug arms, with only two subjects in the 100 mg dose arm reporting the event as severe. Abdominal pain episodes started at study initiation. Among subjects with abdominal pain, 53% of subjects (25 out of 47) in the 80 mg arm and 77% of subjects (47 out of 61) in the 100 mg arm had reported abdominal pain within the first 100 days of drug use, with majority (>83% across drug arms) reporting by 300 days of drug use. The median duration of abdominal pain was 8 days, 15 days, and 15 days in the placebo, 80 mg dose arm, and 100 mg dose arm, respectively.

Vomiting

The severity of vomiting (narrow FMQ) was also mild to moderate in the drug arms. Vomiting episodes started at study initiation, but among subjects with vomiting, about 51% of subjects (20 out of 39) in the 80 mg arm and 58% of subjects (34 out of 59) in the 100 mg arm had reported vomiting within the first 100 days of drug use, with majority (>80% across drug arms) reporting by 300 days of drug use. The median duration of vomiting was 3 days, 3 days, and 2 days in the placebo, 80 mg dose arm, and 100 mg dose arm, respectively. Six (0.8 per 100 PY) subjects in the 100 mg dose arm, 3 (0.4 per 100 PY) subjects in the 80 mg dose arm discontinued treatment due to vomiting, compared to 2 (0.3 per 100 PY) subjects in the placebo arm.

Conclusion

Diarrhea and nausea were the most common TEAEs reported across Trials MGL-3196-11 and MGL-3196-14 in the pooled analysis. GI events started with initiation of treatment, and generally resolved within a median 20 days in the pooled population. Even though most GI events were mild to moderate in severity, they were the most common cause of treatment discontinuations, which may have an impact on treatment adherence for a small proportion of patients. For every 100 patients treated for a year with the 80 mg dose of resmetirom, 23 events of diarrhea and 18 events of nausea would be expected. GI events in the F2/F3 population are described in Section 6 of the label to alert the prescriber.

7.7.5. Treatment-Related Pruritus

Issue

Although pruritus has not been considered a common problem for patients with NASH, NASH with advanced fibrosis (F3/F4) can be associated with clinically significant pruritus (Younossi et al. 2020; Boehlig et al. 2022). Pruritus has been found to be a TEAE in clinical trials evaluating other potential therapies for NASH, such as FXR agonists (Panzitt et al. 2022).

Background

The Applicant considered pruritus as an AESI. But, as pruritus was not considered a common or severe event in patients with NASH, specific PROs for pruritus were not administered during Trials MGL-3196-11 or MGL-3196-14. Safety information on pruritus was collected as part of standard AE reporting in the trials.

Assessment

For EAIRs for pruritus-related treatment discontinuation and TEAEs, see Sections 7.6.1.4 and 7.6.1.5 for the F2/F3 population, and 7.6.2.4 and 7.6.2.5 for the pooled population. This section will further discuss pruritus in the pooled population. The severity of pruritus was mild to moderate. Among subjects who developed pruritus, symptoms began within the first 100 days of treatment for about 60% (26 out of 44 in the 80 mg arm and 39 out of 64 in the 100 mg arm, respectively). Most (>86% across drug arms) developed symptoms within the first 300 days of treatment. The median duration of pruritus was 28 days, 33 days, and 42 days in the placebo, 80 mg dose arm, and 100 mg dose arm, respectively.

Conclusion

Subjects who received resmetirom had a higher incidence of pruritus than those who received placebo. In the pooled safety population, pruritus was a cause of treatment discontinuation in one subject in the 80 mg group and six patients in the 100 mg group, compared to one in the placebo. Episodes of pruritus were mild to moderate in severity but lasted for a median of >30 days across dose arms. Given pruritus was also observed in the placebo-treated group, underlying liver disease may also be a potential contributor of pruritus in this population. Pruritus will be included in the label to inform prescribers and patients of this AR. This AE can be further evaluated in ongoing resmetirom studies and in postmarket safety monitoring.

7.7.6. Deficiencies in the Pre- and Postnatal Developmental Study in Rats

Issue

The PPND study in rats is deficient based on current ICH standards.

Background

The PPND study in rats is incomplete due to the absence of testing for behavior, motor activity, sensory or sensorimotor functions, and reflex development, and the absence of observations of

early landmarks of physical development. These parameters are recommended for evaluation of the F1 generation during the preweaning period (postnatal Days 0 to 20) in PPND studies (ICH guidance for industry, *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021)). However, the only developmental parameter that was monitored during the preweaning period was bodyweight. Although the completed tests in the F1 generation rats (passive avoidance and M-water maze during the postweaning period) are adequate for the evaluation of learning and memory, these tests alone are insufficient for providing a comprehensive assessment of the developmental effects from maternal exposure to resmetirom. Therefore, the PPND study in rats is deficient based on the testing standards for evaluation of development during the preweaning phase in PPND studies, as indicated in the following statement in (ICH S5(R3) 2021): "The best indicator of physical development is bodyweight, however, measurement of BW alone is not an acceptable substitute for the evaluation of other developmental parameters."

Assessment

For evaluation of the acceptability of the PPND study in rats, it should be noted that this study was initiated prior to publication of (ICH S5(R3) 2021) (Step 4), and therefore the relevant ICH guidance at the time of study initiation was ICH guidance for industry, *S5(R2) Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility* (November 2005). (ICH S5(R2) 2005) contains text that can be interpreted as being supportive of the Applicant's design of the PPND study in rats, specifically the evaluation of development during the preweaning period based solely on frequent BW measurement. However, we are unaware of any data that can justify this approach. The PPND study included BW measurements on postnatal days 1, 4, 7, 10, 14, 18, and 21, which is in accordance with the recommendation in (ICH S5(R3) 2021) for frequent bodyweight measurement during this period, in addition to other recommended developmental parameters as stated above. Based on these considerations, the PPND study is deemed acceptable, although it is deficient based on current ICH standards.

Conclusion

To address the deficiencies in the PPND study, a statement has been added to Section 8.1 (*Pregnancy*) of the label under the *Data* subheading.

7.7.7. Treatment-Related Changes in Sex Hormones

Issue

Observational studies have demonstrated that progression of NAFLD and NASH is associated with decreased SHBG levels, and regression of NAFLD is associated with increased SHBG levels (Wang et al. 2020; Zhang et al. 2022). The impact of changes in SHBG and associated sex hormones (including estradiol, testosterone, follicle-stimulating hormone, and luteinizing hormone) in the setting of pharmacological intervention for NASH was unknown. (b) (4) .

Background

Thyroid hormones increase the levels of plasma SHBG (Anderson 1974). Levels of SHBG are lower in the hypothyroid state and these levels increase with levothyroxine therapy (Dumoulin et al. 1995). The effects of THs on SHBG are likely an indirect effect via increasing hepatocyte nuclear factor-4α (HNF-4α) gene expression, and by reducing cellular palmitate levels, which increase HNF-4α levels in hepatocytes (Selva and Hammond 2009).

The phase 2 trial for resmetirom included dose adjustment based on SHBG and demonstrated that the percent change in hepatic fat fraction from baseline at Week 12 was greater in the higher SHBG response group ((38.7%), compared to the lower SHBG response group (23.7%). Overall, SHBG levels increases from Baseline in the drug arm were higher compared to placebo. All sex hormones also increased with treatment except for free testosterone.

Subjects in Trials MGL-3196-11 and MGL-3196-14 had Baseline and 52-Week levels of sex hormones and SHBG evaluated, and results were stratified by sex. ARs were collected, including reproductive system events to assess clinical safety.

Assessment

The change from baseline to Week 52 in hypothalamic-pituitary-gonadal axis hormones, including sex hormones binding to SHBG, was assessed during Trial MGL-3196-11. As expected, increases in all sex hormones were noted in both sexes treated with resmetirom (Table 295 in Section 17.3.2). Statistically significant changes were notable for estradiol, total testosterone, follicle-stimulating hormone, and luteinizing hormone in males, and for total testosterone in females. No changes in free testosterone levels, the active form of testosterone hormone, were seen in either sex. Similar findings of changes in sex hormones and SHBG were noted in Trial MGL-3196-14.

To further examine whether the observed changes in the sex hormones were of clinical significance, the AEs reporting in the SOC reproductive system and breast disorders in the pooled safety analyses of Trials MGL-3196-11 and MGL-3196-14 were reviewed. In males, there was a very low incidence of AEs of erectile dysfunction (1.2% resmetirom 80 mg versus 0.6% resmetirom 100 mg, versus 1.1% placebo) and gynecomastia (0.3% placebo, and no subjects in resmetirom arms), with no differences between resmetirom arms and placebo (Table 63).

Table 63. Subjects With Adverse Events by Male-Specific FDA Medical Query (Narrow) and Preferred Term, Male Safety Population, Pooled Trials, MGL-3196-11 and MGL-3196-14

System Organ Class FMQ (Narrow)	Placebo PY=364.6 N=307 n/py (EAIR)	Resmetirom 80 mg PY=335.5 N=299 n/py (EAIR)	Resmetirom 100 mg PY=347.4 N=299 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Reproductive system and breast disorders					
Gynecomastia	1/364.4 (0.3)	0/335.5 (0)	0/347.4 (0)	-0.3 (-1.6, 0.9)	-0.3 (-1.6, 0.8)
Erectile dysfunction	4/361.6 (1.1)	4/332.6 (1.2)	2/346.5 (0.6)	0.1 (-1.8, 2.1)	-0.5 (-2.3, 1.1)

Source: Clinical Data Scientist, MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

Likewise, in females, a low incidence (<1.5%) of AEs of the reproductive system was seen (Table 64).

Table 64. Subjects With Adverse Events by Female-Specific FDA Medical Query (Narrow) and Preferred Term, Female Safety Population, Pooled Trials, MGL-3196-11 and MGL-3196-14

System Organ Class FMQ (Narrow) Preferred Term	Placebo PY=428.2 N=360 n/py (EAIR)	Resmetirom 80 mg PY=441.7 N=380 n/py (EAIR)	Resmetirom 100 mg PY=419.7 N=374 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Reproductive system and breast disorders (SOC)					
Abnormal uterine bleeding (FMQ)	1/427.5 (0.2)	3/440.8 (0.7)	6/414.6 (1.4)	0.4 (-0.7, 1.8)	1.2 (-0.0, 2.9)
Menstruation irregular	0/428.2 (0)	0/441.7 (0)	2/416.9 (0.5)	0.0 (-0.9, 0.9)	0.5 (-0.4, 1.7)
Vaginal hemorrhage	0/428.2 (0)	1/441.5 (0.2)	2/419.2 (0.5)	0.2 (-0.7, 1.3)	0.5 (-0.4, 1.7)
Heavy menstrual bleeding	0/428.2 (0)	1/441.1 (0.2)	1/418.7 (0.2)	0.2 (-0.7, 1.3)	0.2 (-0.7, 1.4)
Postmenopausal hemorrhage	1/427.5 (0.2)	0/441.7 (0)	1/419 (0.2)	-0.2 (-1.3, 0.6)	0.0 (-1.1, 1.1)
Abnormal uterine bleeding	0/428.2 (0)	1/441.7 (0.2)	0/419.7 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)

Source: Clinical Data Scientist, MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Conclusion

In conclusion, given the small number of events, their transient nature and low severity, as well as the presence of confounding factors, a causal relationship between resmetirom and reproductive-related AEs is unlikely. Rather, the observed effects on reproductive hormone levels (total testosterone, estradiol) in both males and females are expected changes associated with the increases in SHBG and are unlikely of clinical significance. No sex-hormone-related monitoring is included in the prescribing information for resmetirom.

7.7.8. Treatment-Related Changes in Bone Metabolism

Issue

Resmetirom is a THR-ß partial agonist with high selectivity for hepatic THR-ß. However, potential off-target adverse effects of resmetirom via THR-α gonism may affect bone metabolism. TSH also has direct action on bone (Abe et al. 2003; Williams and Bassett 2018).

Background

In the phase 2 trial during the 36-Week, double-blind treatment period, no appreciable differences in bone mineral density (BMD) were observed between the resmetirom arm and placebo.

Because of the known effects of THR-α agonism and the potential for bone loss and fractures in patients treated with resmetirom, Trials MGL-3196-11 and MGL-3196-14 included BMD measurements via dual X-ray absorptiometry (DXA) scan, bone biomarkers, as well as collection of AEs of fractures (an AESI).

Assessment

In Trial MGL-3196-11, serial DXA scans of the femoral neck, femoral total (hip), and spine were collected at baseline and Week 52. Data for the observed BMD T-scores and Z-score values at baseline, Week 52, as well as the change from baseline to Week 52, were evaluated in the entire study population, as well as in various subgroups (i.e., female subjects with estradiol greater than or equal to 30 ng/L versus. less than 30 ng/L at baseline; subjects taking thyroxine versus not taking thyroxine; subjects with weight loss greater than or equal to 5% versus less than 5% at Week 52).

Evaluation of the T-score changes in the female subjects with estradiol less than 30 ng/L (i.e., postmenopausal), in whom T-score values are most reliable, revealed no notable differences between resmetirom and placebo arms in femoral neck and lumbar spine T-scores. Similarly, there were no notable differences observed between resmetirom and placebo arms when evaluating the Z-score changes in the female subjects with estradiol greater than 30 ng/L (i.e., premenopausal), in whom Z-score values are most reliable. No clinically significant differences in T-score and Z-score changes between resmetirom and placebo arm were noted in any of the other subgroups.

The Applicant also evaluated the BMD data using shift tables of BMD T-score risk category for fracture. The Applicant defined the subgroup with the highest potential risk for fractures as the

females with estradiol less than 30 (postmenopausal), who were not taking thyroxine at Baseline, and who had weight loss less than 5% at Week 52. In this and other subgroups evaluated, there were few subjects that progressed from a lower to a higher risk category of fracture based on T-score, and the number of subjects who shifted from lower to higher risk was similar between resmetirom arms and placebo.

Evaluation of bone turnover markers in the subgroup of subjects with the Applicant-defined highest potential risk for fractures revealed small increases in both procollagen type 1 N-terminal propeptide (a bone formation marker) and beta-C-terminal telopeptide (a bone resorption marker) in resmetirom-treated subjects compared to placebo at Week 52. The clinical significance of these changes in the absence of BMD changes observed by DXA remains unknown.

The incidence of AEs of fracture, osteopenia, and osteoporosis was similar between resmetirom and placebo treatment arms in MGL-3196-11 and MGL-3196-14, and in Trial MGL-3196-18 (refer to Section 3.2), which allowed an assessment of long-term exposure on bone (approximately 2 years), indicating no increase in fracture risk due to resmetirom therapy.

There were five SAEs of fractures in four subjects in Trial MGL-3196-11: two subjects in the resmetirom 80 mg arm (ankle fracture, pelvic fracture, spinal fracture) and two subjects in the resmetirom 100 mg arm (humerus fracture, cervical vertebral fracture). The SAE of cervical vertebral fracture led to study-drug discontinuation. Upon review of the case narratives of the four subjects with SAEs of fractures, FDA staff concluded that none of the fractures were likely related to the study drug. All events were traumatic fractures and were deemed serious due to requirement for hospitalization and surgical intervention; all events were recovered or resolved.

Evaluation of the AEs of fractures and osteoporosis in Trial MGL-3196-18, which was a 52-week extension study of Trial MGL-3196-14 evaluating the safety of resmetirom in subjects with NAFLD, showed no increase in events with 2 years of exposure to resmetirom.

Conclusion

In summary, after 1 year of treatment with resmetirom, there was no evidence of drug-induced adverse effects on bone metabolism based on clinical AEs and BMD assessments by DXA. However, the long-term impact of the drug on bone metabolism remains unknown. Completion of MGL-3196-11 with 54 months of follow-up for efficacy and safety will provide additional understanding of this safety concern, and postmarket AE reporting will be carefully monitored.

7.7.9. Major Adverse Cardiovascular Events

Issue/Background

Patients with NASH and other metabolic dysfunction-related conditions, such as type 2 diabetes, are at increased risk for MACE, and therefore, new drugs being developed for NASH should assess whether the drug may be associated with increased risk of MACE. MACE was an AESI specified by the Applicant.

THs can have various effects on the heart, which include elevating heart rate, increasing cardiac contractility, improving the systolic and diastolic function of the heart, and decreasing systemic vascular resistance. There are significant cardiovascular clinical manifestations of thyroid

dysfunction. For example, hyperthyroidism is commonly associated with palpitations, anginal chest pain, systolic hypertension, atrial fibrillation, and heart failure. On the other hand, hypothyroidism is associated with bradycardia, fatigue, and impaired cardiac contractility (Klein and Danzi 2016).

Even though resmetirom is a partial THR-ß agonist, no thyromimetic is a pure THR-β or THR-α agonist. Therefore, there is a possibility of off-target effects, which include cardiotoxicity as the effect of THs on the heart is mediated by THR-α.

Assessment

Adjudicated MACE was assessed in both trials, MGL-3196-11 and MGL-3196-14.

Table 65 displays the grouping of adjudicated MACE in Trial MGL-3196-11. Overall, the EAIR per 100 PY of a MACE event was the same for the drug arms compared to placebo.

Table 65. Adjudicated MACE Event, Safety Population, Trial MGL-3196-11

Adjudicated MACE Event	Placebo PY=516.7 N=349 n/py (EAIR)	Resmetirom 80 mg PY=510.9 N=352 n/py (EAIR)	Resmetirom 100 mg PY=487.8 N=349 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
AE grouping	1/514.5 (0.2)	1/510.6 (0.2)	1/487.9 (0.2)	0.0 (-0.9, 0.9)	0.0 (-0.9, 1.0)
Intracardiac thrombus	0/516.7 (0)	0/510.9 (0)	1/487.9 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Prosthetic cardiac valve thrombosis	0/516.7 (0)	0/510.9 (0)	1/487.9 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Acute myocardial infarction	1/514.5 (0.2)	1/510.6 (0.2)	0/487.8 (0)	0.0 (-0.9, 0.9)	-0.2 (-1.1, 0.6)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 71.8 weeks (resmetirom 80 mg), 66.1 weeks (resmetirom 100 mg), and 69.6 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); MACE, major adverse cardiovascular events; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

Table 66 displays the grouping of adjudicated MACE in Trial MGL-3196-14. Overall, the incidence of MACE was minimally higher in the 100 mg arm (0.6%) compared to placebo (0.3%).

Table 66. Adjudicated MACE Event, Safety Population, Trial MGL-3196-14

Adjudicated MACE Event	Placebo N=318 n (%)	Resmetirom 80 mg N=327 n (%)	Resmetirom 100 mg N=324 n (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
AE grouping related to AESI	1 (0.3)	0	2 (0.6)	-0.3 (-1.8, 0.9)	0.3 (-1.2, 1.9)
Acute myocardial infarction	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Cerebrovascular accident	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Myocardial infarction	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Duration is 52 weeks.
Note: Risk difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; MACE, major adverse cardiovascular events; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 67 displays other adjudicated cardiovascular events in Trial MGL-3196-11, where events were higher in placebo compared to the drug arms.

Table 67. Adjudicated Other CV Events, Safety Population, Trial MGL-3196-11

Adjudicated Other CV Event	Placebo PY=516.7 N=349 n/py (EAIR)	Resmetirom 80 mg PY=510.9 N=352 n/py (EAIR)	Resmetirom 100 mg PY=487.8 N=349 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
AE grouping related to AESI	3/515.6 (0.6)	0/510.9 (0)	2/486.6 (0.4)	-0.6 (-1.7, 0.2)	-0.2 (-1.3, 1.0)
Cardiac failure	1/516.6 (0.2)	0/510.9 (0)	1/486.6 (0.2)	-0.2 (-1.1, 0.6)	0.0 (-0.9, 1.0)
Acute myocardial infarction	1/516.6 (0.2)	0/510.9 (0)	1/487.8 (0.2)	-0.2 (-1.1, 0.6)	0.0 (-0.9, 1.0)
Acute left ventricular failure	1/516.3 (0.2)	0/510.9 (0)	1/487.8 (0.2)	-0.2 (-1.1, 0.6)	0.0 (-0.9, 1.0)
Myocardial ischemia	1/516 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Angina pectoris	1/516 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 71.8 weeks (resmetirom 80 mg), 66.1 weeks (resmetirom 100 mg), and 69.6 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; CV, cardiovascular; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

Cardiac disorders were also interrogated in the pooled population, Trials MGL-3196-11 and MGL-3196-14. Overall, the EAIR for SAEs in SOC of cardiac disorders were lower in the drug arms compared to placebo. EAIRs for cardiac disorders leading to treatment discontinuation were marginally higher in the drug arms compared to placebo (0.1 per 100 PY in placebo, 0.3 per 100 PY in 80 mg arm, and 0.3 per 100 PY in 100 mg arm).

For TEAEs, the EAIR per 100 PY of SOC of cardiac disorders were also marginally higher in the drug arms (5.9 per 100PY in 100 mg and 80 mg arms), compared to placebo (4.5 per 100 PY). The FMQ's within the SOC of cardiac disorders that were higher than placebo in either arm are displayed in Table 68. EAIRs for arrythmia, palpitations, tachycardia, and cardiac conduction disturbances were higher in the treatment arms compared to placebo.

Table 68. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Cardiac disorders (SOC)					
Arrhythmia	10/787 (1.3)	16/766.8 (2.1)	18/757.6 (2.4)	0.8 (-0.5, 2.3)	1.1 (-0.3, 2.6)
Palpitations	6/789.6 (0.8)	10/772.2 (1.3)	8/759.7 (1.1)	0.5 (-0.5, 1.7)	0.3 (-0.7, 1.4)
Tachycardia	5/789.3 (0.6)	7/773.8 (0.9)	8/763.1 (1.0)	0.3 (-0.7, 1.3)	0.4 (-0.6, 1.5)
Cardiac conduction disturbance	5/789.1 (0.6)	6/773.2 (0.8)	6/763.7 (0.8)	0.1 (-0.8, 1.1)	0.2 (-0.8, 1.2)
Heart failure	2/792.4 (0.3)	2/776 (0.3)	5/765.2 (0.7)	0.0 (-0.7, 0.7)	0.4 (-0.3, 1.3)
Myocardial infarction	3/789.6 (0.4)	2/776.4 (0.3)	5/765.2 (0.7)	-0.1 (-0.9, 0.6)	0.3 (-0.5, 1.2)
Acute coronary syndrome	4/789.6 (0.5)	3/775.4 (0.4)	5/765.2 (0.7)	-0.1 (-1.0, 0.7)	0.1 (-0.7, 1.1)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Conclusion

The incidence of MACE in Trials MGL-3196-11 and MGL-3196-14 was low and not substantively different from placebo. Similarly, the incidences for adjudicated other cardiovascular events were also low. Overall, the incidence of cardiac disorders was quite low in both the trials. The 54-month follow-up in MGL-3196-11 will provide important data to assess whether longer-term treatment is associated with a different rate of MACE compared to placebo.

7.7.10. Malignancy

Issue

Patients with NASH are at increased risk of malignancies, including HCC. Comorbid obesity also increases malignancy risk. Thyroid hormones and THRs have been linked to various malignancies. Given resmetirom is a thyromimetic, malignancy was considered an AESI and incidence of malignancy was assessed in the resmetirom-treated subjects in comparison to placebo.

Background

THs play an important role in cell growth, differentiation, and metabolism, Circulating THs interact with THRs to promote downstream signaling pathways and activate transcription factors. THs can influence many pathways that influence tumorigenesis.

Experimental data demonstrates that under physiological conditions, THRs are reported to suppress tumor effects, but abnormal expression of THR-β has been shown to promote carcinogenesis. THR-β1 expression can extend the overall survival curve in B*RCA1*-associated

breast cancer, whereas THR-α was associated with reduced 5-year overall survival (Heublein et al. 2015). THR-α binding to T3 also promotes GI cancer development. Both in vitro and in vivo, colorectal cancer proliferation is induced by T4 and thyroxine. Mutations or decreased expression of THR-β have been noted in thyroid cancer and lung cancer. In human astrocytomas, there is decreased expression of THR-α1 and THR-α2, with increases in THR-β1 expression (Liu et al. 2019).

Associations between THs and THRs, and development of HCC have also been reported. Experimental data suggests that the increased risk of HCC is related to induction of TSH in a hypothyroid state. In HCC tissue, TSH receptor is overexpressed, and both THR-α and THR-β display high dominance of truncating and point mutations (Liu et al. 2019; Lin et al. 2020).

Population-based studies have also identified a link between thyroid dysfunction and various types of cancer. Prospective analyses have reported associations between increased cancer risk and low TSH levels, high FT4 levels, and hyperthyroidism, with an increased risk for solid cancers, especially lung, breast, thyroid cancer, and prostate cancer (Hellevik et al. 2009; Yeh et al. 2013; Khan et al. 2016). Hypothyroid state has been linked to a lower risk of prostate cancer and breast cancer (Kuijpens et al. 2005; Mondul et al. 2012; Sogaard et al. 2016). Hypothyroidism has also been associated with an elevated risk of HCC (Reddy et al. 2007; Hassan et al. 2009). TSH and FT4 have been correlated with prognostic factors such as tumor size, with higher FT4 correlated with a worse prognosis in HCC.

Despite these theoretical risks, nonclinical studies of resmetirom have not suggested an increased risk of malignancy in humans. In a 2-year study in CD-1 mice, resmetirom produced leiomyoma or leiomyosarcoma in the uterus at a dose of 100 mg/kg/day (51 times the maximum recommended dose based on AUC). No tumorigenic effects were observed in female mice at doses of up to 30 mg/kg/day (14 times the maximum recommended dose based on AUC) or in male mice at doses of up to 100 mg/kg/day (35 times the maximum recommended dose based on AUC).

In a 2-year study in Sprague-Dawley rats, resmetirom produced benign fibroadenoma in the mammary gland of males at a dose of 30 mg/kg/day (6.5× the maximum recommended dose based on AUC). No tumorigenic effects were observed in male rats at doses of up to 6 mg/kg/day (3.7× the maximum recommended dose based on AUC) or in female rats at doses of up to 30 mg/kg/day (3.4× the maximum recommended dose based on AUC).

Assessment

The incidence of neoplasms was assessed in both, Trials MGL-3196-11 and MGL-3196-14.

In the phase 3 development program, two cases of HCC were detected in the pooled safety analysis of MGL-3196-11 and MGL-3196-14. One subject receiving resmetirom 100 mg in Trial MGL-3196-11 was diagnosed on Study Day 58, after he was noted to have elevated bilirubin and transaminases. MRI showed extensive liver fibrosis, splenomegaly and varices, consistent with advanced liver disease and portal hypertension. The subject discontinued study drug and was withdrawn from the study. The Investigator and Applicant considered the HCC not related to study drug. A subject in Trial MGL-3196-14 was found to have a 2.9-centimeter liver lesion, prior to signing informed consent. It is unclear from the narrative whether he received any doses

of study drug, but liver biopsy confirmed the diagnosis of HCC on Study Day 54. This event was not related to study drug.

Overall, the incidence of non-HCC neoplasms was low in both Trials MGL-3196-11 and MGL-3196-14, and the incidence in the resmetirom arms were not substantively different from placebo (see tables Table 296 and Table 297 in Section 17.3.3).

Conclusion

In Trials MGL-3196-11 and MGL-3196-14, two cases of HCC were detected, neither of which was considered related to the study drug. Non-HCC malignancies were uncommon, and there was no discernable imbalance between treatment and placebo arms. The 54-month follow-up in MGL-3196-11 will provide important data to assess whether longer-term treatment is associated with any differences in the risk of malignancies.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Age

No dosage adjustment for age (patients aged 65 years and older) is necessary.

(b) (4)

- Subjects aged 65 years and older had numerically higher incidences of TEAEs (e.g., diarrhea, pruritus, urinary tract infections) relative to subjects aged less than 65 years.
- Within the age 65 years and older subgroup, numerically higher incidences of these TEAEs were observed in subjects treated with 100 mg relative to those subjects treated with 80 mg.

However, the overall higher incidence of TEAEs was observed with 100 mg regardless of age. Refer to Section 6.2.1.4 for additional details.

In addition, in population PK (PopPK) analysis, age (range: 18 to 83 years) was not identified as a significant covariate impacting the PK of resmetirom after accounting for BW. The median [Q5%; Q95%] weight-normalized apparent clearance is 0.165 [0.0687; 0.287] L/h/kg for patients aged <65 and 0.164 [0.0647; 0.290] L/h/kg for patients aged ≥65 years, respectively. Refer to Section 14.5 for more details. (Table 10 of PopPK report). Thus, a dosage adjustment based on age is unlikely to mitigate PK-related AEs, if any.

8.1.2. Body Weight

A weight-based dosing, i.e., 80 mg for patients weighing ≤100 kg and 100 mg for patients weighing ≥100 kg, is recommended based on a significant effect of BW on PK and a decreasing trend of efficacy in higher BW groups.

(b) (4)

- Among subjects weighing ≤80 kg, a higher proportion randomized to 100 mg discontinued prior to Week 52 in MGL-3196-11 relative to subjects randomized to 80 mg, while the efficacy was comparable between 80 mg and 100 mg (Table 69).

Table 69. Applicant's Post -Hoc Analysis of Week 52 Outcomes by Dose and Baseline Body Weight, Trial MGL-3196-11

	Resmetirom 80 mg		Resmetirom 100 mg	
	≤80 kg	>80 kg	≤80 kg	>80 kg
≥120% Increase in SHBG at Week 52	40 (71.4)	92 (41.8)	30 (66.7)	127 (58.3)
≥30% reduction in MRI-PDFF at Week 52	34 (72.3)	112 (60.2)	25 (65.8)	135 (73.4)
Week 52 MITT*				
Consensus Fibrosis Improvement Responder	18 (29.0)	59 (22.7)	16 (28.1)	66 (24.8)
Consensus NASH Resolution Responder	16 (25.8)	61 (23.5)	15 (26.3)	74 (27.8)
Week 52 Paired Biopsies				
Consensus Fibrosis Improvement Responder	18 (35.3)	59 (28.5)	16 (39.0)	66 (31.9)
Consensus NASH Resolution Responder	16 (31.4)	61 (29.5)	15 (36.6)	74 (35.7)
Discontinued Study Prior to Week 52	6 (9.7)	34 (13.1)	12 (21.1)	46 (17.3)

Source: Table 34, page 97, Module 2.7.3 Summary of Clinical Efficacy
Note that the Applicant's analysis included subjects with fibrosis stages F1B, F2, and F3.
* For NASH resolution and fibrosis responder status, subjects with composite clinical endpoints, missing responses, and Week 52 biopsies out of window are considered nonresponders.
Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; MITT, modified intent-to-treat; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; SHBG, sex hormone binding globulin

While the BW significantly affected the PK, the (b) (4) 80 kg BW cutoff was not well supported. In addition, the proportion of discontinuations prior to Week 52 was generally higher in the 100 mg dose cohort compared to the 80 mg cohort regardless of BW. It is also noted that a BW cutoff of 90 kg was used for subgroup analyses for efficacy. Refer to Section 6.2.1.4.

In response to the Agency's inquiry, the Applicant conducted a subgroup analysis of the response rate in MGL-3196-11 across five BW subgroups (i.e., <80 kg, 80 to <90 kg, 90 to <100 kg, 100 to <110 kg, and ≥110 kg) (Table 70). In the 80 mg dose group, a numerically lower proportion of subjects with BW ≥100 kg achieved NASH resolution or fibrosis response relative to subjects with BW <100 kg.

Table 70. Applicant's Post -Hoc Analysis of Week 52 Outcomes by Dose and Baseline Body Weight, Trial MGL-3196-11

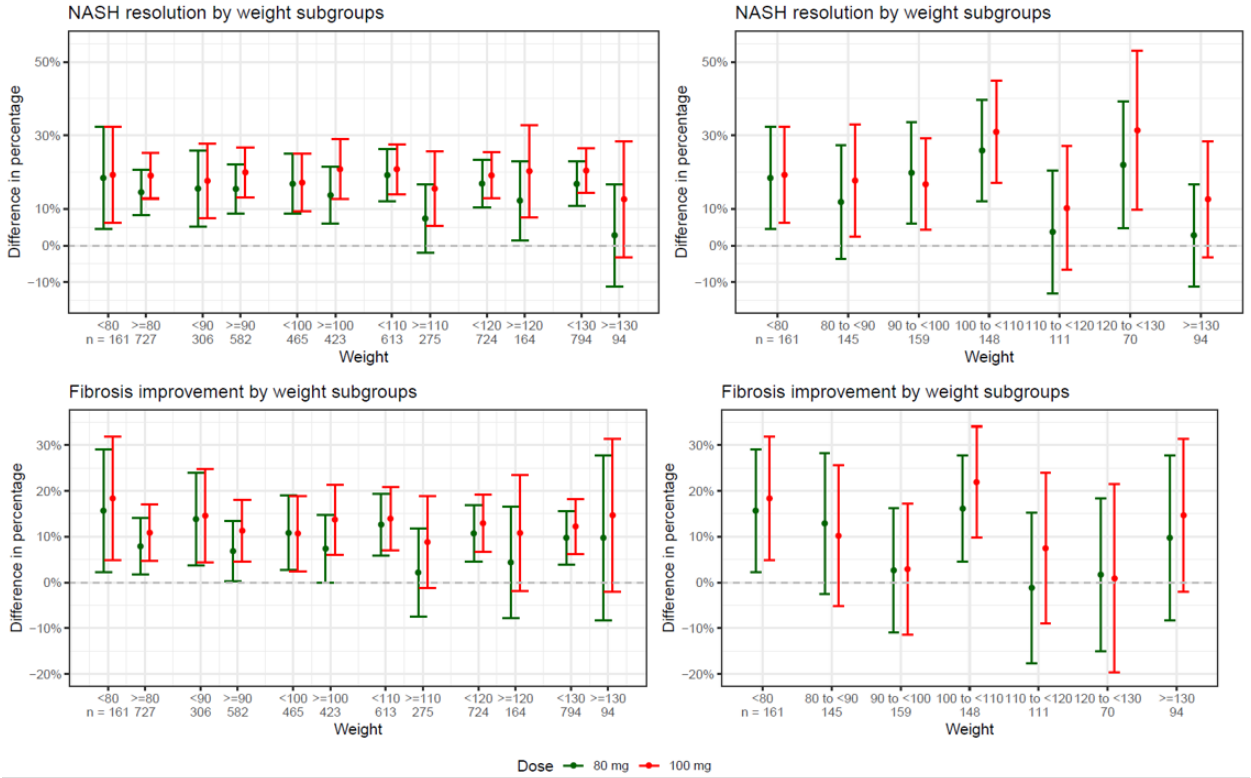
Assessment	Resmetirom 80 mg					Resmetirom 100 mg				
	<80 kg	80 - <90 kg	90 - <100 kg	100 - <110 kg	≥110 kg	<80 kg	80 - <90 kg	90 - <100 kg	100 - <110 kg	≥110 kg
≥120% increase in SHBG at Week 52	39 (72.2)	30 (56.6)	28 (52.8)	14 (34.1)	21 (28.0)	30 (68.2)	27 (62.8)	28 (63.6)	27 (62.8)	45 (50.6)
≥30% 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, subjects with composite clinical endpoints, missing responses and week 52 biopsies out of window are considered non-responders.

Source: Table 2, Module 1.11.3, Response to IR, November 15, 2023
Note that the Applicant's analysis included subjects with fibrosis stages F1B, F2, and F3.
Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; IR, information request; MITT, modified intent-to-treat; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; SHBG, sex hormone binding globulin

FDA conducted subgroup analyses by BW subgroups of NASH resolution and fibrosis response in all subjects with NASH and fibrosis stage F2-F3 in Trial MGL-3196-11 (Figure 11). Although the data do not show a significant difference in efficacy between doses of 80 and 100 mg, data indicate a trend in decreasing NASH resolution and fibrosis response for both 80 and 100 mg doses in higher BW subgroups (i.e., BW ≥110 kg). The trend appears more pronounced at the 80 mg dose relative to the 100 mg dose. In addition, when the data are analyzed using different BW cutoffs (Figure 11, left plots), the difference in efficacy between doses of 80 and 100 mg is more pronounced for higher BW subgroups (i.e., BW ≥100 kg).

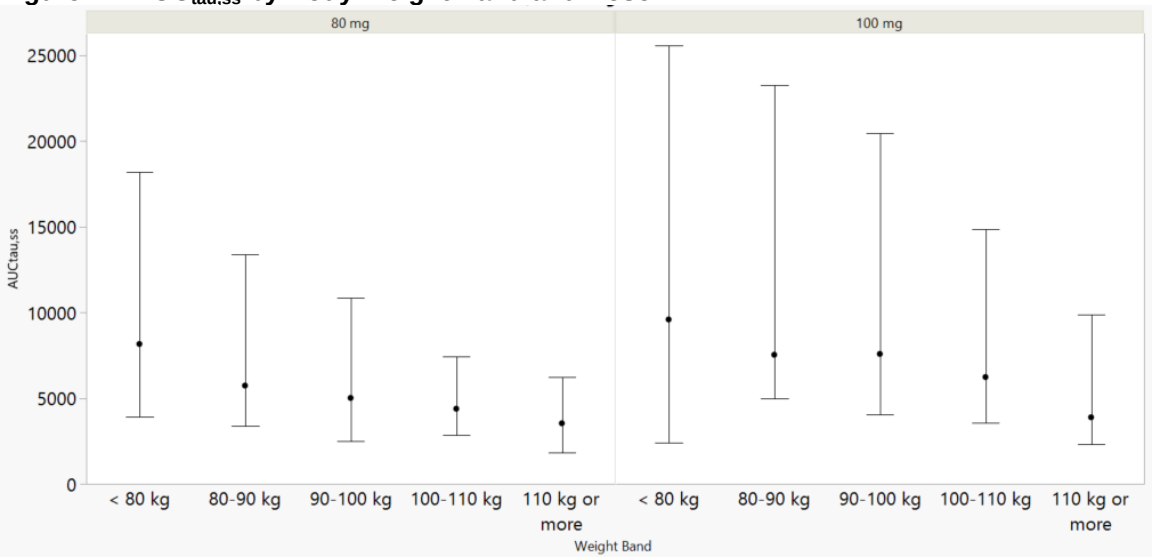
Figure 11. NASH Resolution and Fibrosis Response by Body Weight Subgroups by Weight Cutoff and Weight Band in Subjects with NASH and Fibrosis Stage F2-F3, Trial MGL-3196-11



Source: Statistics reviewer's analysis
Note: Difference in percentage refers to the risk difference relative to placebo. Points represent the risk difference while error bars show the 95% confidence interval.
Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; NASH, nonalcoholic steatohepatitis

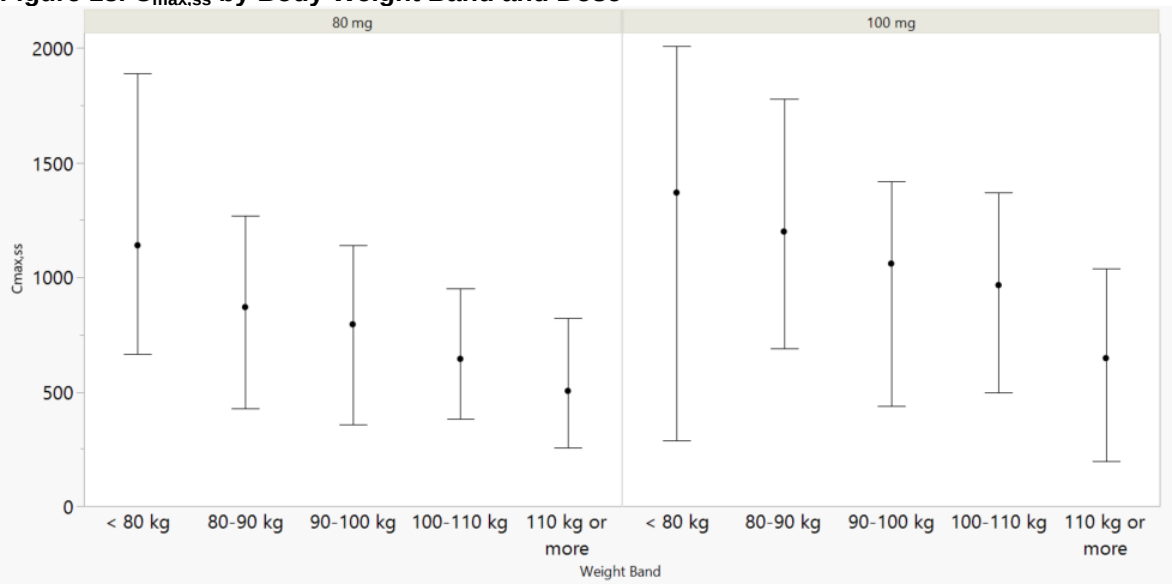
In the population PK analysis, BW was identified as a significant covariate impacting the clearance and volume of distribution of resmetirom. Patients with higher BW have higher clearance and, therefore, lower exposure to resmetirom. The median area under the curve over the dosing interval at steady state ($AUC_{tau,ss}$) and C_{max} in the low BW patients (weight <80 kg) was 1.9- to 2.3-fold greater and 1.8- to 2.3-fold greater, respectively, than that in the highest weight patients, those with BW of ≥100 kg (refer to Section 14.5).

Figure 12. $AUC_{tau,ss}$ by Body Weight Band and Dose



Source: Reviewer-generated plot using data from Table 1, Module 1.11.3, Response to IR, November 15, 2023
Note: Points represent the median. The lower and upper whiskers represent Q5 and Q95, respectively.
Note: For the 80 mg group, N in each weight band is as follows: <80 kg, N=56; 80-90 kg, N=56; 90-100 kg, N=59; 100-110 kg, N=45; 110 kg or more, N=97
Note: For the 100 mg group, N in each weight band is as follows: <80 kg, N=50; 80-90 kg, N=48; 90-100 kg, N=56; 100-110 kg, N=45; 110 kg or more, N=105
Abbreviations: $AUC_{tau,ss}$, area under the curve over the dosing interval at steady state; IR, information request; N, number of subjects in treatment arm; Q, quartile

Figure 13. $C_{max,ss}$ by Body Weight Band and Dose



Source: Reviewer-generated plot using data from Table 1, Module 1.11.3, Response to IR, November 15, 2023
Note: Points represent the median. The lower and upper whiskers represent Q5 and Q95, respectively.
Note: For the 80 mg group, N in each weight band is as follows: <80 kg, N=56; 80-90 kg, N=56; 90-100 kg, N=59; 100-110 kg, N=45; 110 kg or more, N=97
Note: For the 100 mg group, N in each weight band is as follows: <80 kg, N=50; 80-90 kg, N=48; 90-100 kg, N=56; 100-110 kg, N=45; 110 kg or more, N=105
Abbreviations: $C_{max,ss}$, maximum concentration at steady state; IR, information request; N, number of subjects in treatment arm; Q, quartile

To evaluate the effect of BW on PK, a request was sent to the Applicant to estimate resmetirom PK using different BW cutoffs (i.e., <80 kg, 80 to <90 kg, 90 to <100 kg, 100 to <110 kg, and ≥110 kg) (Table 71). The data for $AUC_{tau,ss}$ and maximum concentration at steady state were adapted into a graphic presentation in Figure 12 and Figure 13, respectively. Similar to $AUC_{tau,ss}$ and C_{max}, at a dose of 80 mg, median $C_{ave,ss}$ in subjects weighing <80 kg was 1.9- and 2.3-fold greater than that subjects with BW of 100 to <110 kg or ≥110 kg, respectively. For subjects with BW of 80 to <90 kg or 90 to <100 kg, ratios of exposure ($AUC_{tau,ss}$ and $C_{ave,ss}$) are ≤1.6-fold relative to subjects with BW <80 kg.

E-R analyses for efficacy using the primary endpoints in Trial MGL-3196-11 (i.e., NASH resolution or fibrosis response) indicated that the probability of achieving efficacy increased with increasing $C_{ave,ss}$. Subjects in all exposure quartiles had greater probability of achieving efficacy over placebo. However, the observed response was approximately comparable between the 1st, 2nd, and 3rd exposure quartiles ($C_{ave,ss}$ <321 ng/mL), while the probability of achieving efficacy was greatest for subjects falling in the highest exposure quartile ($C_{ave,ss}$ ≥321 ng/mL) (refer to Section 6.1). Per Table 71, at a dose of 80 mg, the 95th percentile $C_{ave,ss}$ values in patients with BW of 100 to <110 kg or ≥110 kg (310 ng/mL and 259 ng/mL, respectively) are lower than the threshold of 321 ng/mL separating the 3rd and 4th exposure quartiles in E-R efficacy analyses. Thus, at a dose of 80 mg, it is likely that little to no patients with BW ≥100 kg fell within the highest exposure quartile. At a dose of 100 mg, a greater proportion of patients with BW of 100 to <110 kg or ≥110 kg are likely to have fallen in the highest exposure quartile (95th percentile $C_{ave,ss}$ of 622 and 412 ng/mL, respectively), associated with the greatest probability of achieving NASH resolution or fibrosis response in MGL-3196-11.

Table 71. Descriptive Statistics of Resmetirom PK Parameters at 80 mg and 100 mg by Body Weight Group

	Resmetirom 80 mg					Resmetirom 100 mg				
Assessment	<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	8180	5750	5030	4400	3550	9610	7550	7600	6250	3900
[Q05;Q95]	[3950;18200]	[3400;13400]	[2530;10900]	[2860;7440]	[1840;6230]	[2440;25600]	[5000;23300]	[4050;20500]	[3590;14900]	[2330;9890]
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	1140	870	795	644	504	1370	1200	1060	966	647
[Q05;Q95]	[664;1890]	[428;1270]	[358;1140]	[381;951]	[255;821]	[288;2010]	[689;1780]	[437;1420]	[499;1370]	[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	341	240	210	183	148	400	315	316	261	163
[Q05;Q95]	[165;759]	[142;560]	[105;455]	[119;310]	[76.5;259]	[102;1070]	[208;970]	[169;856]	[150;622]	[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	25.5	18.4	12.0	14.1	9.77	29.7	22.2	51.0	22.1	12.8
[Q05;Q95]	[4.23;336]	[3.36;277]	[3.13;270]	[2.93;104]	[1.91;107]	[4.32;686]	[5.57;502]	[4.23;604]	[4.06;291]	[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
$t_{1/2\alpha}$ (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	1.15	1.24	1.02	1.12	1.11	1.44	1.08	1.37	1.34	1.30
[Q05;Q95]	[0.610;2.24]	[0.599;2.41]	[0.607;2.48]	[0.567;2.56]	[0.575;2.51]	[0.570;2.49]	[0.601;2.55]	[0.655;2.72]	[0.517;2.35]	[0.655;2.73]
Geometric Mean	1.13	1.21	1.10	1.12	1.16	1.26	1.16	1.39	1.14	1.24
$t_{1/2\beta}$ (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	4.53	4.41	4.29	4.50	4.45	4.41	4.43	5.29	4.65	4.50
[Q05;Q95]	[3.68;11.1]	[3.68;13.4]	[3.69;14.2]	[3.73;15.8]	[3.63;10.0]	[3.52;15.8]	[3.78;15.1]	[3.75;27.3]	[3.77;11.6]	[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; $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$ = elimination half-life; CV = coefficient of variation; Q05 = 5th quantile; Q95 = 95th quantile

Source: Table 1, Module 1.11.3, Response to IR, November 15, 2023
Abbreviations:

The data suggest that patients with higher BW may benefit from receiving a higher dosage of resmetirom. Relative to a dosage of 80 mg QD for the general patient population, the recommended dosage for patients with body weight ≥100 kg is 100 mg QD. The rationale for recommending a higher dosage in patients with BW ≥100 kg includes the following:

- A higher dosage in higher BW patients will yield comparable PK across patients of all BWs.
- Increased resmetirom exposure in higher BW patients is associated with a higher probability of achieving efficacy (i.e., NASH resolution and/or fibrosis response).
- Analysis of NASH resolution and fibrosis response by BW subgroups indicate a trend towards decreased efficacy at doses of 80 and 100 mg in higher BW subgroups, with a more pronounced effect at 80 mg.
- Dosage adjustments based on BMI are not recommended as BMI was not found to impact the PK of resmetirom after accounting for BW.

8.1.3. FT4

No dosage adjustments based on levels of FT4 are recommended.

In MGL-3196-11 and MGL-3196-14, dose adjustments at Weeks 12 and 24 based on levels of FT4 were prespecified in the protocol, as follows. Note that no dose reductions were made later than Week 24 and doses were not reduced to less than 60 mg.

- If subjects present with ≥30% decrease from baseline in free T4 to < 0.7 ng/dL at Weeks 4 and 8, doses were reduced by 20 mg at Week 12.
  - Subjects randomized to 100 mg received 80 mg.
  - Subjects randomized to 80 mg receive 60 mg.
- If subjects continued to present with ≥30% decrease from baseline in free T4 to <0.7 ng/dL at Weeks 16 and 20, doses were reduced by another 20 mg at Week 24.
  - Only applicable to subjects who initially received 100 mg. (In which case, doses would be reduced to 60 mg at Week 24).

Across Trials MGL-3196-11 and MGL-3196-14, a total of 22 subjects (double-blind arms only) had doses adjusted per protocol based on free T4. This included 18 subjects randomized to 100 mg (10 subjects in MGL-3196-11 and 8 subjects in MGL-3196-14) and 4 subjects randomized to 80 mg (2 subjects each in MGL-3196-11 and MGL-3196-14).

Overall, very few subjects had their dose of resmetirom adjusted based on levels of FT4. In addition, there were no clinical findings associated with decreases in FT4 (refer to Section 7.7.2).

8.1.4. Hepatic Impairment

Patients with precirrhotic NASH may progress to cirrhosis (fibrosis stage F4) during treatment.

Based on data from a dedicated hepatic impairment (HI) study, no dosage adjustment is recommended in patients with mild HI (Child-Pugh A).

Resmetirom is not recommended for patients with moderate to severe HI (Child-Pugh B and C).

Notably, subjects with cirrhosis were not enrolled in Trial MGL-3196-11 or in the placebo-controlled cohorts of Trial MGL-3196-14. A separate clinical study is ongoing to evaluate the efficacy and safety of resmetirom in patients with compensated NASH cirrhosis (MGL-3196-19). Thus, the safety and effectiveness of resmetirom have not been established in NASH cirrhosis patients.

The Applicant proposed the following dosage recommendations for patients with HI, defined using Child-Pugh criteria:

- No dosage adjustment in patients with mild HI (Child-Pugh A)
- (b) (4)
-

The Applicant conducted a PK study in non-NASH and NASH subjects with HI (MGL-3196-10) (refer to Section 14.2.9). In the HI study, PK parameters were evaluated in subjects with normal hepatic function and subjects with HI. The subjects with HI were diagnosed with alcohol-related liver disease or hepatitis C.

Following QD dosing of 80 mg for 6 days, resmetirom area under the concentration-time curve over one dosing interval was 1.3-fold, 2.7-fold and 19-fold higher in subjects with mild, moderate and severe HI (Child-Pugh A, B and C), respectively compared to subjects with normal hepatic function. Resmetirom C_{max} was 1.2-fold, 1.7-fold, and 8.1-fold higher in subjects with mild, moderate, and severe HI, respectively compared to subjects with normal hepatic function. Following QD dosing with 80 mg, 1.2- to 2.8-fold accumulation in resmetirom area under the concentration-time curve over one dosing interval was observed among subjects with HI.

Table 72. Mean (CV%) PK Parameters of Resmetirom and Major Metabolite in Subjects With Normal Hepatic Function and Patients With Hepatic Impairment Following 80 mg Once Daily for 6 Days

Drug or Metabolite Parameter	Normal Hepatic Function (N=7)	Mild HI (Child-Pugh A) (N=10)	Moderate HI (Child-Pugh B) (N=9)	Severe HI (Child-Pugh C) (N=3)
Resmetirom				
$C_{max,ss}$ (ng/mL)	1070 (51.0)	1390 (67.8)	1830 (47.5)	7730 (17.4)
$AUC_{tau,ss}$ (ng*h/mL)	5100 (51.5)	5570 (66.4)	15100 (65.8)	97600 (39.0)
$AUC_{last,ss}$ (ng*h/mL)	5090(51.8)	5560 (66.5)	14600 (82.1)	148000 (51.8)
MGL-3623				
$C_{max,ss}$ (ng/mL)	420 (38)	635 (47.5)	566 (18)	826 (26)
$AUC_{tau,ss}$ (ng*h/mL)	2490 (35.5)	3210 (39.7)	4900 (57)	14500 (38.8)
$AUC_{last,ss}$ (ng*h/mL)	2480(35.7)	3210 (39.7)	5510 (65.4)	25200 (47.8)

Source: Table 3, Report MC19R-0032 for Trial MGL-3196-10

Abbreviations: $AUC_{tau,ss}$, area under the curve over the dosing interval at steady state; $AUC_{last,ss}$, area under the plasma concentration curve from time 0 to the last detectable time point at a steady state; $C_{max,ss}$, maximum concentration at steady state; CV, coefficient of variation; HI, hepatic impairment; N, number of subjects in treatment arm

The PK of resmetirom was also compared in noncirrhotic NASH subjects (n=8) and in subjects with NASH cirrhosis with mild HI (Child-Pugh A) (n=20). NASH was confirmed by biopsy. Geometric mean AUC and C_{max} in NASH cirrhosis subjects with mild HI (Child-Pugh Class A; n=20) were 6% higher and 10% lower, respectively, compared to noncirrhotic NASH subjects (n=8) following 100 mg QD dosing of resmetirom for 6 days.

PopPK analyses of MGL-3196-14 and MGL-3196-11, which included an open-label treatment arm for subjects with histologic conversion to cirrhosis at Week 52, predicted about 1.3 to 1.6-fold higher $AUC_{tau,ss}$ in NASH subjects with F4 fibrosis compared to precirrhotic NASH subjects with similar BW (Table 73). PopPK analyses of MGL-3196-14 and MGL-3196-11, which included an open-label treatment arm for subjects with histologic conversion to cirrhosis at Week 52, predicted about 1.3 to 1.6-fold higher $AUC_{tau,ss}$ in NASH subjects with F4 fibrosis compared to precirrhotic NASH subjects with similar BW (Table 73). Both 60 mg and 80 mg are being studied in NASH patients with compensated cirrhosis.

The safety and effectiveness of resmetirom have not been established in NASH cirrhosis patients. Therefore, given the increased systemic exposure, it is recommended to avoid use of resmetirom in patients with decompensated cirrhosis or moderate or severe hepatic impairment (i.e., Child-Pugh Class B or C).

Table 73. PK Parameters of Resmetirom at Steady-State After 80 mg Once-Daily Dosing – By Fibrosis Stage and Body Weight Tertiles, Trials MGL-3196-11 and MGL-3196-14

Fibrosis Stage PK Parameter	Body Weight Tertiles		
F1-3	**<89.1 kg (N=220)**	**89.1 to <108 kg (N=211)**	**≥108 kg (N=222)**
$AUC_{tau,ss}$ (ng*h/mL)			
Mean (CV%)	7700 (50.2%)	5690 (58.8%)	4170 (57.0%)
Median[Q05; Q95]	6650 [3820;16700]	4940[2840;12100]	3730[2020;6960]
$C_{max,ss}$ (ng/mL)			
Mean (CV%)	1030 (33.3%)	748 (29.0%)	554 (31.2%)
Median [Q05; Q95]	1000 [462;1750]	734 [382;1100]	540 [295;858]
$C_{min,ss}$ (ng/mL)			
Mean (CV%)	55.1 (176.2%)	49.4 (228.4%)	33.5 (237.3%)
Median [Q05; Q95]	20.3 [3.64;237]	15.3 [3.10;274]	11.4 [2.21;130]
F4	**<89.1 kg (N=64)**	**89.1 to <108 kg (N=50)**	**≥108 kg (N=51)**
$AUC_{tau,ss}$ (ng*h/mL)			
Mean (CV%)	12500 (82.5%)	7550 (62.8%)	5960 (71.3%)
Median[Q05; Q95]	9130[4340;28900]	6400[3660;17600]	5140[2540;13100]
$C_{max,ss}$ (ng/mL)			
Mean (CV%)	1310 (41.1%)	840 (25.9%)	677 (32.2%)
Median[Q05; Q95]	1240 [754;2270]	804 [523;1240]	652 [392;1070]
$C_{min,ss}$ (ng/mL)			
Mean (CV%)	174 (199.5%)	95.8 (176.5%)	69.9 (206.0%)
Median[Q05; Q95]	50.5 [4.88;812]	35.6 [5.02;471]	28.9 [3.59;308]

Source: Tables 8-9, Population PK Analysis report.
Note: NASH subjects with F4 fibrosis enrolled in MGL-3196-11 (N=10) and MGL-3196-14 (N=161).
Abbreviations: $AUC_{tau,ss}$, area under the curve over the dosing interval at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CV, coefficient of variation; F1, fibrosis stage 1; F3, fibrosis stage 3; F4, fibrosis stage 4; N, number of subjects in treatment arm; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic; Q, quartile

8.1.5. Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. Resmetirom has not been studied in patients with severe renal impairment (b) (4)

Subjects with mild and moderate renal impairment were enrolled in phase 3 trials, MGL-3196-11 and MGL-3196-14 (eGFR ≥ 45 mL/min/1.73 m^2). In Trial MGL-3196-14, subjects with eGFR ≥30 and <45 mL/min/1.73 m^2 were also enrolled directly into an open-label treatment arm. Data were not provided in the CSR from the open-label arm, including from subjects with eGFR ≥30 and <45 mL/min/1.73 m^2.

Based on PopPK analysis, there were no clinically significant differences in the PK of resmetirom based on mild or moderate renal impairment (i.e., eGFR 30 to 89 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation) (refer to Section 14.5).

No significant impact of mild or moderate renal impairment on PK is consistent with renal excretion being a minor elimination pathway for resmetirom. In a mass balance study, 24% of orally administered total radioactive dose was recovered in the urine, including 1% of the total dose as unchanged resmetirom, and 16% of the total dose as metabolite MGL-3623 (refer to Section 14.2.2).

Subjects with severe renal impairment (i.e., eGFR <30 mL/min/1.73 m^2) were not enrolled in either study. A dedicated PK study was not conducted in subjects with severe renal impairment. As such there is insufficient data to inform dosage for patients with severe renal impairment.

A postmarketing study to evaluate the effects of severe RI on the PK of resmetirom and its major metabolites will be conducted.

A protocol for this study was submitted to IND 122865 on November 13, 2023.

8.1.6. ABC*G2* Genotype

Resmetirom is a substrate of breast cancer resistance protein (BCRP) transporter in vitro. The Applicant evaluated effects of variants in PK-related genes (adenosine triphosphate binding cassette subfamily G member 2 [ABCG2, which encodes BCRP], CYP2C8, and solute carrier organic anion transporter family member 1B1) on resmetirom and metabolite MGL-3623 PK. Compared to ABCG2 reference SNP (single nucleotide polymorphism) cluster ID (rs)2231142 G/G, T allele carriers (G/T+T/T, T allele is associated with reduced function of BCRP (reviewed in (Fohner et al. 2017)) had significantly higher resmetirom (~1.8-fold) and MGL-3623 (~1.6-fold) $AUC_{0\text{-}8hr}$[3] in analyses from Phase 2 study, Study 05. ABCG2 genotype was further evaluated in multivariable analyses which included BW in Phase 2 and 3 studies. The model with BW and genotype (no interaction term) was deemed most appropriate by the reviewer and based on results, ABCG2 rs2231142 T allele carriers had significantly higher AUC for resmetirom. Although statistically significant, ratios of least square mean estimates support that ABCG2 genotype does not have a clinically significant impact on resmetirom PK (estimated 1-17% higher AUC for T allele carriers). Furthermore, the reviewer did not find any trends in TEAEs by ABCG2 rs2231142 genotype. Overall, given resmetirom is a BCRP substrate, ABCG2 genotype was studied throughout drug development with similar results across studies in patients with NASH, and there are no clinical drug-drug interaction (DDI) studies with BCRP inhibitors, we

[3] In phase 2 trial, a dosage adjustment was allowed based on AUC at Week 2. The $AUC_{0\text{-}8hr}$ was based on dense PK sampling. Refer to Section 14.6 for more details.

recommend including ABCG2 genotype in the list of specific populations with no clinically significant PK changes in Section 12.3 of the label. Refer to Section 14.6 for additional details.

8.2. Extrinsic Factors

8.2.1. Food Effect

The Applicant proposed that resmetirom can be taken with or without food. An assessment of the effect of food was conducted in healthy subjects at steady state at a dosage of 100 mg QD as part of Trial MGL-3196-09 (refer to Section 14.2.3). Relative to the fasted state, in the fed state, resmetirom C_{max} and area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule were decreased by 33% and 11%, respectively. The median time to maximum concentration was delayed by about 2 hours in the presence of food. These changes are not considered to be clinically relevant. Thus, resmetirom may be taken without regard to food. In phase 3 trial, MGL-3196-11, no specific dosing instructions with regard to food were provided.

8.2.2. Effect of Resmetirom on Other Drugs

In vitro studies were conducted to evaluate the potential of resmetirom to inhibit drug metabolizing enzymes and transporters. In vitro data predict that resmetirom may mediate DDIs via inhibition of CYP2C8 and BCRP as shown in Table 74.

Resmetirom also inhibited uridine 5'-diphospho (UDP) glucuronosyltransferase (UGT)1A4 and UGT1A9 with half maximal inhibitory concentration (IC_{50}) values of 0.56µM and 1.14µM, respectively. Although the observed steady state C_{max} of resmetirom in NASH subjects following a dose of 80 mg (i.e., 778 ng/mL or 1.8µM) exceeds the IC_{50} values for UGT1A4 and UGT1A9, resmetirom is >99% protein bound. The unbound C_{max} is therefore lower than the observed in vitro IC_{50} values. Thus, drug interactions mediated via inhibition of UGT1A4 and UGT1A9 are not expected. Refer to Section 14.1 for details.

Table 74. Resmetirom Inhibition of Cytochrome P450 (CYP) Enzymes and Transporters

Drug Metabolizing Enzyme or Transporter	IC_{50} (µM)	R Value[a]	R Value Threshold[a]
CYP Enzymes			
1A2	> 50	1.00[b]	1.02
2B6	No inhibition observed	ND	1.02
2C8	0.90	1.04	1.02
2C9	22	1.00	1.02
2C19	> 50	1.00 [b]	1.02
2D6	> 50	1.00 [b]	1.02
3A4	≥ 215	1.00	1.02

Transporters			
P-gp	99.6	7.38[c]	10
BCRP	0.96	766[c]	10
OATP1B1	3.72	1.01	1.1
OATP1B3	10[d]	1.00	1.1
OAT1	> 100	0[b]	0.1
OAT3	4.53	0	0.1
OCT2	No inhibition observed	ND	0.1
MATE1	> 100	0[b]	0.1
MATE2-K	> 100	0[b]	0.1
BSEP	34.7	ND	N/A
UGT Enzymes			
UGT1A4	0.56	--	
UGT1A9	1.14	--	

Source: Study reports for 3196-12-022, 10315, 3196-15-001, 10315, 3196-16-001, 3196-23-001, 3196-16-006, 09769
Note: Rows in gray indicate a DDI risk when the calculated value exceeds its threshold.
[a.] R value equations and thresholds derived from the FDA guidance for industry, *In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020b). Calculations are based on a resmetirom oral dose of 80 mg yielding a steady state C_{max} of 778 ng/mL (1.8µM).
[b.] Although no IC_{50} value was determined, R value was calculated assuming IC_{50} of 50 or 100µM.
[c.] Values and thresholds correspond to DDI potential in the gut.
[d.] No IC_{50} value was determined. In Study 09769, resmetirom inhibited OATP1B3 by 60 to 70% at a concentration of 10µM. Thus, 10µM was used for calculation of the R value.
Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DDI, drug-drug interaction; FDA, U.S. Food and Drug Administration; IC_{50}, half-maximal inhibitory concentration; MATE, multidrug and toxin extrusion; ND, not determined; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; UGT, uridine 5'-diphospho (UDP) glucuronosyltransferase

8.2.2.1. Statins

The Applicant proposed the following dosages of certain statins when resmetirom is co-administered for labeling:

- Atorvastatin and pravastatin: up to 40 mg/day
- Simvastatin and rosuvastatin: up to 20 mg/day

The proposed dosage limit for statins is supported by in vivo DDI study results and the DDI-based dosage adjustment per respective labeling. Of note, in phase 3 trials, the same dosage limits for respective statins were implemented. In phase 3 studies, dosage limits were also implemented for lovastatin (up to 40 mg/day) and pitavastatin (up to 2 mg/day). However, no recommendations were proposed in labeling for lovastatin or pitavastatin.

Briefly, statins are commonly used in patients with NASH and with dyslipidemia. In in vitro studies, resmetirom was found to inhibit organic anion transporting polypeptide (OATP)1B1, OATP1B3, and BCRP (refer to Section 14.1). The potential DDI liability resulting from co-administration of resmetirom and statins, OATP1B substrates, is shown in Table 75.

Table 75. Drug-Drug Interaction Liability Between Resmetirom and Statins

Drug	CYP-Mediated DDIs	Transporter-Mediated DDIs
Rosuvastatin	None	BCRP substrate OATP1B1/1B3 substrate
Atorvastatin	3A4 moderate sensitive substrate	OATP1B1/1B3 substrate
Pravastatin	None	OATP1B1/1B3 substrate
Simvastatin	3A4 sensitive substrate	OATP1B1/1B3 substrate

Drug	CYP-Mediated DDIs	Transporter-Mediated DDIs
Lovastatin	3A4 sensitive substrate	OATP1B1 substrate
Pitavastatin	None	OATP1B1/1B3 substrate
Resmetirom[a]	2C8 inhibitor	BCRP inhibitor OATP1B1/1B3 inhibitor

Source: For Healthcare Professionals – FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems (FDA 2024); resmetirom in vitro studies 09769, 3196-12-022, 10315, 3196-15-001.
[a] Only inhibition of CYP enzymes and transporters are shown. Resmetirom is also a substrate for CYP2C8, BCRP, and OATP1B1/3.
Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; DDI, drug-drug interaction; OATP1B1/3, organic anion-transporting polypeptide 1B1/3

In clinical DDI studies, an increase of AUC for various statins by 1.4 to 1.8-fold was observed with resmetirom co-administration (Table 76). Refer to Sections 14.2.5, 14.2.6, and 14.2.7 for details.

Table 76. Impact of Resmetirom Coadministration on the PK of Statins

Study	Statin	Statin Dose	Resmetirom QD Dosage	C_{max}	AUC
MGL-3196-03	Rosuvastatin	10 mg	200 mg	↑ 2.9-fold	↑ 1.8-fold
MGL-3196-04	Atorvastatin	20 mg	100 mg	↔ No change	↑ 1.4-fold
MGL-3196-15	Pravastatin	40 mg	100 mg	↑ 1.3-fold	↑ 1.4-fold
MGL-3196-15	Simvastatin	20 mg	100 mg	↑ 1.4-fold	↑ 1.7-fold
	Simvastatin acid[a]			↑ 2.0-fold	↑ 1.6-fold

Source: Clinical Study Reports for MGL-3196-03, MGL-3196-04, and MGL-3196-15
[a] Simvastatin acid is included as it is a major active metabolite for simvastatin.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; QD, once daily

The data suggest that resmetirom may be an inhibitor of OATP1B1/3 based on a less than 2-fold increase in the AUC of the statins evaluated. Nevertheless, based on the known safety profile of statins, a dosage adjustment of concomitant statins may be needed. It is recommended to limit the daily dosage of statins as follows:

- Simvastatin and rosuvastatin: limit the statin dosage to 20 mg/day
- Atorvastatin and pravastatin: limit the statin dosage to 40 mg/day

Note that rosuvastatin is the only statin studied with resmetirom at a dosage of 200 mg QD, a dosage 2 times higher than the highest proposed dosage of 100 mg QD. The effects on rosuvastatin when co-administered with resmetirom at 200 mg QD may thus be greater than what may be observed when co-administered with resmetirom at 80 or 100 mg QD. In addition, rosuvastatin is the only statin evaluated that is also a substrate of BCRP. In vitro studies predict that resmetirom is an inhibitor of BCRP. BCRP inhibition may thus have contributed to the increase in C_{max} with co-administration.

Rosuvastatin is approved at daily dosages ranging from 5 to 40 mg. The approved labeling for rosuvastatin (Crestor) describes several DDIs. Rosuvastatin AUC increased by 1.9- to 2.0-fold when co-administered with fostamatinib, febuxostat, and tafamidis. In all cases, the total daily dosage of rosuvastatin is limited to 20 mg when co-administered with either drug. Meanwhile, a 2.4-fold increase in rosuvastatin C_{max} following co-administration with darunavir/ritonavir was not considered clinically significant and no dosage adjustments are recommended. Thus, it is recommended to limit the total daily dosage of rosuvastatin to 20 mg when co-administered with resmetirom.

Atorvastatin is approved at daily dosages ranging from 10 to 80 mg. Per the approved labeling for atorvastatin calcium (LIPITOR), the total daily dosage of atorvastatin is limited to 40 mg when co-administered with nelfinavir based on a 1.7-fold increase in atorvastatin AUC. Thus, it is recommended to limit the total daily dosage of atorvastatin to 40 mg when co-administered with resmetirom.

Pravastatin is approved at daily dosages ranging from 10 to 80 mg. Per the approved labeling for pravastatin sodium (PRAVACHOL), the total daily dosage of pravastatin is limited to 40 mg when co-administered with macrolide antibiotics (e.g., erythromycin, clarithromycin). Co-administration of pravastatin and clarithromycin resulted in a 1.1-fold and 1.3-fold increase in pravastatin AUC and C_{max}, respectively. The pravastatin daily dosage is limited to 20 mg when co-administered with cyclosporine, co-administration of which yielded a 2.8-fold increase in pravastatin AUC. Thus, it is recommended to limit the total daily dosage of pravastatin to 40 mg when co-administered with resmetirom.

Simvastatin is approved at daily dosages ranging from 5 to 40 mg. Per the approved labeling for simvastatin (ZOCOR), the total daily dosage of simvastatin is limited to 20 mg when co-administered with amiodarone, amlodipine, ranolazine, or lomitapide. Co-administration of simvastatin with each of these medications resulted in up to a 2-fold increase in simvastatin AUC and C_{max}, and up to a 2.3-fold increase in simvastatin acid AUC and C_{max}. Thus, it is recommended to limit the total daily dosage of simvastatin to 20 mg when co-administered with resmetirom.

No clinical studies were conducted with lovastatin or pitavastatin. Thus, there are no data to inform dosage recommendations for lovastatin or pitavastatin.

8.2.2.2. CYP2C8 Substrates

In in vitro studies, resmetirom was determined to be an inhibitor of CYP2C8. The Applicant conducted a clinical DDI study, MGL-3196-09, to evaluate the impact of resmetirom on the PK of pioglitazone, an anti-diabetic drug commonly used in patients with NASH and a moderate sensitive substrate of CYP2C8. In MGL-3196-09, a single 15 mg dose of pioglitazone was co-administered with resmetirom 100 mg QD at steady state. Co-administration resulted in an increase in pioglitazone C_{max} and AUC by 1.1-fold and 1.4-fold, respectively (refer to Section 14.2.3). Resmetirom may thus be characterized as a weak inhibitor of CYP2C8.

Per the approved labeling for pioglitazone hydrochloride (Actos), this extent of exposure change does not require dosage adjustment: no dosage adjustment for a 34% increase in pioglitazone AUC and a 14% increase in C_{max} by concomitant ketoconazole. However, it will be important to inform healthcare providers that resmetirom is a weak inhibitor of CYP2C8. Thus, the recommended intervention is to monitor patients more frequently for Ars if resmetirom is co-administered with CYP2C8 substrates for which minimal concentration changes may lead to clinically significant differences in safety.

8.2.2.3. Warfarin

The Applicant conducted a clinical study to evaluate the impact of resmetirom on the PK of warfarin (MGL-3196-16). *S*-warfarin is a moderate sensitive substrate of CYP2C9. In in vitro

studies, resmetirom was found to weakly inhibit CYP2C9. In MGL-3196-16, all subjects received a titrated dose of warfarin to achieve a stable international normalized ratio value. Warfarin PK was assessed following co-administration with 100 mg QD resmetirom at steady state. Results demonstrated that resmetirom had no impact on the PK of *S*-warfarin (refer to Section 14.2.8). Thus, no dosage adjustments are recommended for warfarin.

8.2.2.4. BCRP Substrates

Based on data from in vitro studies, resmetirom is an inhibitor of BCRP. The Applicant conducted a clinical study evaluating the impact of steady state resmetirom (200 mg QD) on the PK of rosuvastatin. Following co-administration with resmetirom, rosuvastatin C_{max} increased 2.9-fold relative to administration alone. This increase in C_{max} is greater than was observed with other statins (i.e., atorvastatin, simvastatin, pravastatin) and this may have been due to resmetirom inhibition of BCRP. Notably, rosuvastatin is the only statin evaluated that is known to be sensitive to BCRP inhibition. However, clinical data evaluating the impact of resmetirom on atorvastatin, simvastatin, or pravastatin indicate that resmetirom may also be a weak inhibitor of OATP1B. As rosuvastatin is also an OATP1B substrate, the magnitude of impact following co-administration with resmetirom is likely due to inhibition of both BCRP and OATP1B.

Clinical data evaluating the impact of resmetirom on the PK of specific BCRP substrates are not available. In phase 3 trials, MGL-3196-11 and MGL-3196-14, use of BCRP substrates was not prohibited or restricted.

A postmarketing commitment study evaluating the impact of resmetirom on the PK of a BCRP substrate is recommended to further inform a possible DDI risk management strategy for BCRP substrates.

8.2.2.5. UGT1A4 and UGT1A9 Substrates

Based on data from in vitro studies, resmetirom may inhibit UGT1A4 and UGT1A9 at clinically relevant concentrations. Clinical data evaluating the impact of resmetirom on the PK of UGT1A4 or UGT1A9 substrates are not available. In phase 3 trials, MGL-3196-11 and MGL-3196-14, use of substrates of UGT1A4 and UGT1A9 was prohibited. However, as resmetirom is >99% protein bound, the unbound C_{max} (resmetirom unbound C_{max} following a dose of 80 mg=1.8µM × 0.01=0.018µM) is lower than the observed in vitro IC_{50} values for UGT1A4 and UGT1A9 (0.56µM and 1.14µM, respectively). Thus, drug interactions mediated via inhibition of UGT1A4 and UGT1A9 are not expected.

8.2.3. Effect of Other Drugs on Resmetirom

8.2.3.1. CYP2C8 Inhibitors

In in vitro studies, resmetirom was determined to be a substrate of CYP2C8, but not other cytochrome P450 enzymes. The Applicant conducted a clinical DDI study to evaluate the impact of steady state clopidogrel, a moderate inhibitor of CYP2C8, on the PK of resmetirom (MGL-3196-12). In MGL-3196-12, subjects received clopidogrel at the approved dosing regimen (i.e.,

300 mg loading dose followed by 75 mg QD) and resmetirom at a dosage of 100 mg QD. At steady state, co-administration of clopidogrel and resmetirom yielded an increase in resmetirom C_{max} and AUC by 1.3-fold and 1.7-fold, respectively. In addition, the C_{max} and AUC of metabolite MGL-3623 decreased by 69% and 50%, respectively (refer to Section 14.2.4). Results are consistent with inhibition of CYP2C8-mediated metabolism of resmetirom to MGL-3623 in vitro.

As doses higher than 100 mg have not been studied in patients with NASH, a dose reduction by 20 mg is recommended to minimize substantial exposure increase when clopidogrel or other moderate CYP2C8 inhibitors are co-administered.

For patients weighing <100 kg, the dose should be reduced to 60 mg QD when administered concomitantly with clopidogrel or other moderate CYP2C8 inhibitors.

For patients weighing ≥100 kg, the dose should be reduced to 80 mg QD when administered concomitantly with clopidogrel or other moderate CYP2C8 inhibitors.

Data evaluating the impact of strong CYP2C8 inhibitors on the PK of resmetirom are not available. Thus, concomitant use of resmetirom is not recommended with strong inhibitors of CYP2C8.

8.2.3.2. Inhibitors of OATP1B1, OATP1B3, and/or BCRP

In in vitro studies, resmetirom was determined to be a substrate of the transporters OATP1B1, OATP1B3, and BCRP. Thus, co-administration of resmetirom with inhibitors of these transporters may increase plasma concentrations of resmetirom, which may increase the risk of Ars. However, clinical studies were not conducted evaluating the impacts of inhibitors of these transporters on the PK of resmetirom. The Applicant proposed that inhibitors of OATP1B1, OATP1B3, (b) (4) should not be used concomitantly with resmetirom. Given the theoretical risk of increased Ars and the unknown impacts of OATP1B inhibition on resmetirom PK, the Applicant's proposal is reasonable. Thus, concomitant use of resmetirom is not recommended with inhibitors of OATP1B1 and OATP1B3.

Although resmetirom is a substrate of BCRP in vitro, the available data suggest that BCRP inhibitors may not impact the PK of resmetirom. In mass balance study, Trial MGL-3196-07, the mean total percent recovery of radiolabeled resmetirom was approximately 91%. In addition, about 67% of the administered radioactive dose was detected in feces as metabolites with little unchanged parent drug detected. (refer to Section 14.2.2). As additional supportive evidence, an analysis of resmetirom PK by ABCG2 genotype indicated that there is no clinically significant impact of ABCG2 genotype on resmetirom PK, specifically for carriers of the T allele, associated with reduction function of BCRP (refer to Section 8.1.5). Thus, drug interactions with resmetirom mediated via inhibition of BCRP are not expected.

8.3. Plans for Pediatric Drug Development

In the toxicology written summary, the Applicant stated that juvenile rat toxicity studies are in progress, however, the final report for the definitive study was submitted late in the review cycle

(February 5, 2024). Results of this study are not required to initiate studies in postpubertal adolescents, however, these data will be reviewed to support dosing in the prepubertal pediatric population.

The initial agreed iPSP from July 2021 explained that Madrigal would request a partial waiver of pediatric studies in pediatric patients younger than age 6, and deferral of pediatric studies in patients 6 to 17. Initial studies would begin in postpubertal adolescents 12 to 17 years of age, followed by studies in the 6-to-12-year-old cohort.

The prevalence of NAFLD in pediatrics has been estimated at approximately 9.6%, increasing with age and comorbid obesity (Schwimmer et al. 2006). The histopathological features of pediatric NASH are similar to that of adults, but studies have suggested key differences in pediatric NASH exist, including less ballooning and more portal inflammation and/or fibrosis. A recent study demonstrated the existence of two sub-phenotypes of pediatric NAFLD characterized by zone 1 and zone 3 steatosis, with older-aged children, 12 years and older, having more zone 3 steatosis, similar to adult NASH (Africa et al. 2018). Pediatric NAFLD/NASH can be progressive and severe, with several retrospective studies reporting incidence rates of stage 3 fibrosis as high as 10 to 25% among children with NAFLD (Alkhouri et al. 2019).

Pursuant to the Pediatric Research Equity Act, postmarketing requirements will be issued for studies in the two aforementioned pediatric cohorts. The postpubertal adolescent draft study protocol will need to be submitted within 1 year, in an effort to expedite gathering important clinical data to support access to NASH treatment for pediatric and adolescent patients.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Animal Data

The nonclinical information in Table 77 was used in support of the indicated labeling sections. Additional nonclinical data are located in Section 13.1.9 and the final labeling is discussed in Section 23.

Table 77. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	No embryo-fetal developmental effects occurred in pregnant rats treated orally with resmetirom at doses ≤100 mg/kg/day (21 times the maximum recommended dose based on AUC) or in pregnant rabbits treated orally with up to 30 mg/kg/day (2.8 times the maximum recommended dose based on AUC) during the period of organogenesis. In pregnant rabbits treated orally with 75 mg/kg/day (3.5 times the maximum recommended dose based on AUC), an increase in postimplantation loss and decreases in viable fetuses and fetal weight were observed. These effects were likely due to maternal toxicity (i.e., marked reductions in weight gain and food consumption). In both embryo-fetal developmental studies (rats and rabbits), resmetirom produced marked, dose-dependent reductions in T4 and T3, and moderate

Labeling Section	Nonclinical Data
	reductions in TSH. These effects were attributed to the pharmacological activity of resmetirom (activation of THR-β). In a pre- and postnatal development study, rats were treated orally with resmetirom doses of 3, 30, or 100 mg/kg/day during organogenesis through lactation. Resmetirom at 100 mg/kg/day (37 times the maximum recommended dose based on AUC) produced a 10% decrease in birthweight, increases in number of stillborn, pup deaths during postnatal Days 1 to 4, and pups with absence of milk in stomach. Birthweight was recovered to normal body weight during the lactation period. A significant decrease in body weight (up to 11.2%) and body weight gain (16.6%) in offspring occurred at 100 mg/kg/day after the lactation period. There were marked reductions in maternal plasma levels of total T4 (88%), free T4 (66%), total T3 (79%), free T3 (50%), and TSH (44%) at 100 mg/kg/day. This study did not evaluate early landmarks of physical and neurobehavioral development (e.g., eye opening, pinna unfolding, surface righting, auditory startle, air righting, and response to light), sensory functions, or motor activity, prior to weaning, in offspring. However, resmetirom at 100 mg/kg/day had no effects on learning and memory as evaluated by passive avoidance and water maze tests. The rationale for accepting the study is presented in Section 7.7.6. (Key Safety Review Issues). In pregnant rats, oral administration of the metabolite MGL-3623 at doses ≤100 mg/kg/day (4.7 times the maximum recommended dose based on AUC for MGL-3623) during organogenesis had no effects on embryo-fetal development.
8.2 Lactation	The Applicant did not measure resmetirom in milk in the pre- and postnatal developmental study in rats.

Source: Prepared by the nonclinical reviewer
Abbreviation: AUC, area under the plasma concentration-time curve; T3, triiodothyronine; T4, thyroxine; THR-β, thyroid hormone receptor β; TSH, thyroid stimulating hormone

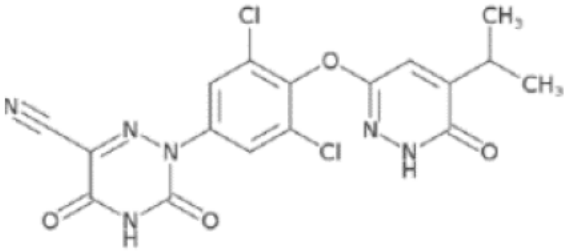
9. Product Quality

Drug Substance

Resmetirom (MGL-3196) is a THR-ß agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). Resmetirom has not been previously marketed or approved in the United States and therefore, it is classified as an NME.

Resmetirom is a white to brownish-orange (b) (4) crystalline powder with low aqueous solubility below pH 6 and greatly improved solubility above pH 7 (0.44 mg/mL at pH 7.04). It is nonhygroscopic with pKa of 3.82 and 10.2 in 0.15M KCl. Crystal (b) (4) for resmetirom was identified as the (b) (4) stable form, (b) (4) and has been used for drug development. Prior to use in the composition of the drug product, resmetirom (b) (4). The chemical name for resmetirom is 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. It has a molecular formula of $C_{17}H_{12}Cl_2N_6O_4$, a molecular weight of 435.22 g/mol; the chemical structure can be found in Figure 14.

Figure 14. Chemical Structure of Resmetirom



Source: Generated by the FDA review team.
Abbreviation: FDA, U.S. Food and Drug Administration

The drug substance for this application is manufactured in accordance with Current Good Manufacturing Practice requirements by [redacted]. Resmetirom is packaged in [redacted]. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date of [redacted] months. Sufficient stability data is provided in the application that supports retest date of [redacted] months when stored at a condition of [redacted] in the proposed container closure.

Drug Product

REZDIFFRA (resmetirom) tablets are film-coated, immediate release tablets containing 60 mg, 80 mg, or 100 mg of resmetirom as the active ingredient, and the following: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. Opadry film coating consists of polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, red iron oxide (100 mg tablets), and yellow iron oxide (80 mg and 100 mg tablets). Components used in the composition of the drug product are all compendial materials and/or composed from compendial materials.

The 60 mg tablets are white, oval-shaped, film-coated tablets that are debossed with "P60" on one side and are plain on the other side. The 80 mg tablets are yellow oval-shaped film-coated tablets debossed with "P80" on one side and plain on the other side. The 100 mg tablets are beige to pinkish, oval-shaped, film-coated tablets that are debossed with "P100" on one side and are plain on the other side.

REZDIFFRA (resmetirom) tablets are manufactured in accordance with Current Good Manufacturing Practice requirements by [redacted] UPM Pharmaceuticals for Madrigal Pharmaceuticals, Inc. They are tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout the proposed expiration dating period of 36 months for 30-count bottles, 24 months for 90-count bottles, and 18 months for 7-count bottles (physician samples).

Sufficient stability data that support the proposed expiration dating periods and the long-term storage (shelf-life storage) condition of 20 to 25°C (68 to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F), has been provided in the application.

Office of Pharmaceutical Quality Recommendation

- The Applicant of this 505(b)(1) NDA has provided sufficient chemistry, manufacturing, and controls information to assure the identity, strength, purity, and quality of the drug substance, resmetirom, and drug product, REZDIFFRA (resmetirom) tablets 60 mg, 80 mg, and 100 mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The chemistry, manufacturing, and controls revisions on labels/labeling have been communicated to the Applicant and the recommended chemistry, manufacturing, and controls revisions have been accepted by the Applicant.
- The Applicant's current environmental assessment report submitted to the application has been reviewed and accepted by the Office of Pharmaceutical Quality (OPQ) environmental assessment team for the approval of the application. However, the OPQ environmental assessment team concluded that the Applicant should provide additional environmental assessment information postapproval (refer to Chapter III of the OPQ Integrated Quality Assessment). A postmarketing commitment to continue providing the required environmental assessment report postapproval will be included in the approval recommendation for this application.

Therefore, this application is recommended for approval from the OPQ perspective with following expiration dating periods:

- 36 months for the drug products 60 mg, 80 mg, and 100 mg packaged in 30-count bottles.
- 24 months for the drug products 80 mg and 100 mg packaged in 90-count bottles.
- 18 months for the drug products 80 mg and 100 mg packaged in 7-count bottles (physician samples).

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Human Subjects Protections

The Applicant states that the clinical trials (MGL-3196-05, MGL-3196-11, MGL-3196-14, and MGL-3196-18) were designed and conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH E6 and Title 21, Part 56 of the US CFR relating to Institutional Review Boards and Independent Ethics Committees.

Protocols, protocol amendments, informed consent forms, investigator brochures, and other study documents were reviewed and approved by an Institutional Review Board/Independent Ethics Committees before the study was initiated. Participants or their legally authorized representatives were required to sign a statement of informed consent, that met the requirements of 21 CFR 50, ICH guidelines, the Institutional Review Board or study center, and local regulations, where applicable.

Clinical Site Inspections

Two clinical investigators (Drs. Moussa and Neff) and the Applicant (Madrigal Pharmaceuticals, Inc., Conshohocken, PA) were inspected for Trials MGL-3196-11, MGL-3196-14, and MGL-3196-18. Based on the inspection results, the studies appear to have been conducted adequately and the clinical data generated by these sites and submitted by the Applicant appear acceptable in support of this NDA. Refer to Section 22.

Financial Disclosures

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the FDA guidance for industry, *Financial Disclosure by Clinical Investigators* (February 2013), and by 21 CFR 54.4. Refer to Section 25.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint is based on independent pathologists' histology readings. Pathologists were blinded to treatment arm.

In conclusion, the likelihood that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not convened for the review of this NDA, because the team has determined that no external input was needed for the review of this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

On June 6, 2014, Madrigal Pharmaceuticals, Inc. requested a pre-IND application meeting to discuss the clinical development of resmetirom (MGL-3196) in subjects with nonalcoholic steatohepatitis (NASH) in the context of a phase 2a protocol. Written responses were provided on August 8, 2014. The Agency provided comments regarding the drug product specifications and stability plan to be used in the phase 2a study, the planned nonclinical studies and timing of the submission of the chronic toxicology study results, the study design, endpoints, and key data analyses to assess efficacy and safety in the planned phase 2 a study, and the general outline of the phase 2b/3 clinical plan.

On October 23, 2014, the Applicant requested further clarification regarding the genotoxicity evaluation that should be provided for all impurities and sought clarification with respect to the submission of "full study reports" of planned chronic toxicity studies in rats and dogs before the first subject exceeds 12 weeks of treatment in the phase 2a study. In the Advice/information request (IR) letter dated November 21, 2014, the Division disagreed with the timing of the Applicant's planned genotoxicity evaluation of resmetirom (MGL-3196) active pharmaceutical ingredient and disagreed with the Applicant's statement that no additional genotoxicity evaluation would be needed to support the use of resmetirom (MGL-3196) 40 mg and 60 mg capsules in phase 2a clinical studies. The Division agreed to the proposed approach for full study reports and provided further guidance regarding what would be an acceptable genotoxicity evaluation to support the use of MGL-3196 40 mg and 60 mg capsules in phase 2a clinical studies.

On July 25, 2016, IND 122865 for resmetirom for the treatment of NASH was submitted, with a phase 2 randomized, placebo-controlled study protocol. A Study May Proceed letter was issued on August 24, 2016.

Madrigal submitted a Fast Track Designation request on May 4, 2017, which was denied on June 23, 2017, due to lack of adequate evidence to demonstrate the product had the potential to address this medical need.

On April 26, 2018, the Applicant requested a type B, end-of-phase 2 meeting, which was held on November 7, 2018. During the meeting the clinical study development plan, proposed phase ¾ clinical protocol, and statistical analysis plan (SAP) intended to support the New Drug Application (NDA) submission were discussed. The Applicant indicated their intent to seek accelerated approval under 21 CFR § 314, Subpart H.

The Applicant requested a type B Written Response Only meeting on May 9, 2018, to discuss the continuing development of MGL-3196 and to obtain feedback on the proposed nonclinical and clinical study development plan, and the proposed phase ¾ clinical protocol and SAP. The Division issued a Final Written Response letter on September 27, 2018, agreeing that the nonclinical data package was adequate to support the proposed phase ¾ study and provided recommendations regarding the Applicant's clinical pharmacology program.

A type C guidance meeting request was submitted on November 9, 2018. This meeting was held as a face-to-face meeting on February 5, 2019, to discuss the revised proposed phase ¾ clinical protocol and SAP.

The Applicant submitted a second request for Fast Track Designation on August 16, 2019, which was granted on October 18, 2019.

(b) (4)

(b) (4) DHN provided additional comments to assist the Applicant in redesigning their clinical trial and drug development.

The Agency received a type C meeting request on August 7, 2020, to discuss the updated proposed SAP for the phase 3 MAESTRO-NASH study, the proposed process for evaluation of liver biopsy endpoints and central liver biopsy review of baseline and Week 52 biopsies from MAESTRO-NASH. DHN had no objections to the Applicant's plans to conduct two trials, namely, MAESTRO-NASH and MAESTRO-NAFLD-1, but expressed concerns about the size of the safety database. DHN stated the expectation that patient exposure to resmetirom should be at relevant doses and durations in the population of interest (i.e., NASH with liver fibrosis) to adequately assess safety. Furthermore, DHN noted that the development plan had changed considerably since the end-of-phase 2 meeting and expressed significant concerns about the drug development plan, including concerns that the trial duration and drug exposures may not be adequate to assess the long-term safety of resmetirom for chronic use. Furthermore, DHN noted that a single phase 3 study may not be adequate to support the planned NDA for evaluation of efficacy and that, generally, two adequate and well-controlled trials are needed to provide substantial evidence of efficacy.

The Applicant submitted their initial pediatric study plan (iPSP) to IND 122865 on February 2, 2021, and submitted amendments to their iPSP dated July 8, and July 14, 2021. An Agreed iPSP letter was issued on July 28, 2021.

The Applicant engaged DHN in several meetings between August 2020 and July 2022. During a type C teleconference meeting held on February 16, 2022, DHN agreed with the Applicant's proposed inclusion criteria for defining cirrhosis due to NASH. DHN also found the Applicant's proposed enrichment strategy acceptable. DHN requested clarification regarding the dose assignment strategy for a potential 3-arm study and stated that the Applicant should ensure blinding measures are specified to maintain study integrity. It was noted that no consensus was reached between the Applicant and DHN for dose adjustment based on changes in free thyroxine (FT4). Additionally, the Applicant stated their intent to submit a type C meeting request to provide data on inter- and intraindividual variability of FT4 in euthyroid and hypothyroid subjects, as well as FT4 and sex hormone binding globulin (SHBG) pharmacokinetic (PK)/pharmacodynamic (PD) data from their previously conducted clinical trials. DHN emphasized that having successful clinical endpoint results from two adequate and well-controlled trials (i.e., MGL-3196-11 and MGL-3196-19) would provide the greatest assurance of efficacy and safety to support a full traditional approval in a NASH patient population. Meeting minutes were issued on March 2, 2022.

The Applicant requested a type C meeting on March 25, 2022, but withdrew the meeting request on April 4, 2022, based on advice provided by the DHN to resubmit the meeting request as a formal pre-NDA meeting request.

Another type C meeting request was submitted by the Applicant on May 26, 2022, to (1) gain concurrence on the resmetirom dosing plan for cirrhotic NASH patients and statin dosing plan; (2) discuss the MAESTRO-NASH study SAP, including the updated approach to controlling Type 1 error and liver biopsy review; (3) seek alignment on the conformance of biospecimen data collection, handling, recording, and microscopic examinations that will be the basis for data analysis of histology-based primary endpoints; and (4) obtain additional clarity about the response provided during the type C meeting held February 16, 2022, and to comments provided

in an Advice/IR letter dated May 5, 2022, which included recommendations from the Center for Devices and Radiological Health regarding the proposed assays for free FT4 and SHBG and maintaining the blind-to-treatment arm assignment. In the Final Written Responses letter, dated August 22, 2022, DHN provided additional guidance on the Applicant's proposal to use FT4 and SHBG to support dose adjustments in cirrhotic NASH patients, the proposed statin dose plan, the statistical analysis approach, and revised SAP. The Center for Devices and Radiological Health also provided guidance regarding the use and development of biomarker assays for SHBG and FT4 if they are determined to be essential for the safe and effective therapeutic use of the drug product.

On July 26, 2022, the Applicant submitted a type C meeting request seeking alignment on the (1) approach for the pooling strategy for safety and summary of clinical safety and integrated summary of safety, (2) approach for submission of the summary of clinical efficacy and integrated summary of effectiveness, and (3) categorical exclusion for the environmental assessment for resmetirom for treatment of NASH patients. In the Final Written Responses letter, dated November 8, 2022, DHN stated that it was premature to agree to the Applicant's proposed plans for the summary of clinical safety without review of the integrated summary of safety SAP, and requested that the Applicant submit the integrated summary of safety SAP for DHN's review. DHN also stated that it was premature to agree to the clinical efficacy/integrated summary of effectiveness without a review of the SAP for the summary of clinical efficacy / integrated summary of effectiveness. DHN also provided guidance on electronic common technical document module organization and the required environmental assessment.

On November 30, 2022, the Applicant submitted a request for a type B, pre-NDA meeting to discuss the development of resmetirom for the treatment of NASH. A teleconference was held on February 27, 2023. In the meeting minutes, dated March 24, 2023, DHN provided guidance on the continued development of resmetirom for the treatment of NASH in preparation for an NDA submission.

A breakthrough therapy designation request was submitted on February 17, 2023, and granted on April 11, 2023, for resmetirom for the treatment of NASH with liver fibrosis. The Applicant's subsequent request for a rolling review of their NDA was granted on May 22, 2023.

Pursuant to Section 505(b)(1) in the Federal Food, Drug, and Cosmetic Act, Madrigal submitted the first part of NDA 217785 for resmetirom for the treatment of NASH with liver fibrosis. The submission, received on June 6, 2023, included nonclinical module 2 sections and nonclinical module 4 study reports and dataset. The submission submitted on June 28, 2023, included chemistry, manufacturing, and controls module 3 and related documents, in addition to the corrected, updated form FDA 356h, to reflect the indication granted breakthrough therapy designation. On July 14, 2023, Madigral submitted the final portion of the original NDA for resmetirom, which included the clinical section in module 2 and clinical module 5 study reports and datasets. Madrigal requested priority review, which was granted on September 12, 2023.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Primary Pharmacology

Resmetirom (also known as MGL-3196, VIA-3196, or RO4923659) is a partial agonist at the thyroid hormone receptor β (THR-β). In an in vitro functional assay for THR-β activation, resmetirom produced 83.8% of the maximum response compared to triiodothyronine (T3), with an half maximal effective concentration (EC_{50}) of 0.21µM (Kelly et al. 2014). The same functional assay for thyroid hormone receptor α (THR-α) agonism showed 48.6% efficacy for resmetirom relative to T3, with an EC_{50} of 3.74µM. Details of the functional response detected by this assay, in a separate study performed by the Applicant, are provided in Section 13.2.2. THR-β is the predominant thyroid hormone receptor (THR) in the liver. Activation of THR-β by T3 impacts the metabolism of cholesterol and triglycerides.

A tabulated summary of the relevant in vitro and in vivo pharmacology studies in animals conducted in support of the mechanism of action are listed below. Resmetirom was coded as RO4923659 in the pharmacology study reports.

Table 78. Primary Pharmacology Studies

Study/Study No.	Findings
24-Day Study of RO4923659 and Rosiglitazone in Male Diet-Induced Obese C57Bl/6J Mice, for Glycemic and Lipemic Endpoints (Study THR-75) • 0.3, 1.0, and 3.0 mg/kg, Oral QD RO4923659 • 10 mg/kg, Oral QD rosiglitazone	C57BL/6J mice were fed a 60% high-fat diet for 14 weeks prior to the initiation of dosing. Subsequently, RO4923659 (0.3, 1, 3, and 10 mg/kg) was administered orally by gavage, once daily for 24 days while the mice continued on the high-fat diet. After 21 days of dosing, there was a significant decrease in plasma total T3 at ≥1 mg/kg and T4 at 0.3 mg/kg compared to vehicle control animals. Plasma cholesterol, relative liver weight, and hepatic triglycerides were significantly reduced at ≥0.3 mg/kg. Expression of some thyroid hormone-receptor regulated genes in liver showed the effect expected by RO4923659 (↑CYP7A1, ↑malic enzyme, ↑SREBP2). Overall, there was a down-regulation of genes involved in fatty acid oxidation (↓PPARA, ↓CPT1B, ↓ACADM, ↓ACCA1, ↓ACOX). Gene expression of nearly half of the cytochrome P450 proteins (CYP) was significantly changed. Many of these changes reflect the effects of the compound on cholesterol and bile acid metabolism (↑CYP7A1, ↑CYP27A1, ↑ABCB11). Several of the CYPs that were up- or downregulated are known to metabolize many prescribed drugs.
25-Week Study of RO4923659 and Rosiglitazone Given as Food Admixtures to Diet-Induced Obese Male C57Bl/6J Mice (Study THR-74) • 0.1, 0.3, 1.0, and 3.0 mg/kg/day RO4923659 • 3 mg/kg/day rosiglitazone	RO4923659 (0.1, 0.3, 1, 3 mg/kg) was administered orally to mice in a high-fat diet admixture for 25 weeks. The placebo control group was administered the high-fat diet placebo admixture. The normal control group was administered the standard diet. After 25 weeks of RO4923659 administration, absolute and relative liver weight were decreased up to -44% and -24%, respectively, at 3 mg/kg. Energy expenditure was increased at ≥0.3 mg/kg. Plasma cholesterol was decreased at ≥0.1 mg/kg and plasma triglycerides were decreased at 3 mg/kg. Liver histology showed a decrease in the degree of hepatocyte vacuolation (minimal at 3 mg/kg and slight-to-moderate at 0.3 mg/kg vs. moderate-to-severe in placebo admixture-fed control animals). Bone density was significantly decreased at ≥1 mg/kg (up to -8.5%). Lean mass and % fat were significantly decreased at 3 mg/kg. In liver, transcripts for some inflammatory genes and major fibrosis-associated genes were downregulated to near the level of the normal control animals. Genes that are rate-limiting steps in cholesterol metabolism, bile acid synthesis, and clearance were dramatically upregulated in liver; however, genes involved in cholesterol biosynthesis were also significantly upregulated. Downregulation of PPARγ, and upregulation of cyclin D11 and ABCB11 (bile salt export pump) was observed. A substantial number of cytochrome P450 gene changes were observed (↑CYP7A1 [catalyzes first and rate limiting step in cholesterol metabolism in liver], ↑CYP7B1 [catalyzes first reaction in conversion of cholesterol to bile acid], ↓CYP3A11 [CYP3A4]). Thyroid hormone-receptor regulated genes were regulated as expected by RO4923659 (↑mitochondrial glycerol-3-phosphate dehydrogenase, ↑malic enzyme, ↑deiodinase 1, ↓thyroid binding globulin).

Source: Prepared by nonclinical reviewer.

Abbreviations: ABCB11, ATP (adenosine triphosphate) binding cassette subfamily B member 11/ bile salt export pump; ACADM, medium-chain acyl-CoA dehydrogenase; ACCA1, acetyl-coenzyme A carboxylase carboxyl transferase subunit alpha; ACOX1, peroxisomal acyl-coenzyme A oxidase 1; CPT1B, carnitine palmitoyltransferase 1, CYP, cytochrome P450; PPARA, peroxisome proliferator activated receptor α; PPARγ, peroxisome proliferator activated receptor γ; QD, once daily; SREBP2, sterol regulatory element-binding protein 2; THR, thyroid hormone receptor

13.1.2. Secondary Pharmacology

Table 79. Secondary Pharmacology Studies

Study/Study No.	Findings
Cardiac-specific nuclear effects of RO4923659 (Study 01154-04)	A single injection of RO4923659 (5, 20, and 40 mg/kg) in thyroidectomized rats had no significant effect on transcription of alpha myosin heavy chain (α-MHC, a cardiac myocyte specific gene regulated by thyroid hormone) at 6 hours postinjection. Exposure levels of RO4923659 at 6 hours were 15.4μM, 57μM, and 94μM at the 5, 20, and 37.5 mg/kg doses, respectively.
In vitro binding assays (Study 01125-06 and 01126-06)	In an in vitro receptor binding assay screen, there was >50% inhibition of binding with benzodiazepine and VitD3, indicating a possibility of off-target effects at these receptor sites. Additional characterization of the interaction with the BZD and VitD3 receptors led to the calculation of an IC_{50} of 10μM for BZD and 7.1μM for VitD3.

Source: Prepared by nonclinical reviewer. BZD, benzodiazepine; $VitD_3$, Vitamin D3.
Abbreviation: BZD, benzodiazepine; IC_{50}, half maximal inhibitory concentration; MHC, myosin heavy chain, α isoform; VitD3, vitamin 3

13.1.3. Safety Pharmacology

Table 80. Safety Pharmacology Studies

Study/Study No.	Findings
RO4923659-000-002 (THRA): In Vitro Effect on hERG Current (Ikr) Expressed in Human Embryonic Kidney (HEK) Cells (Study 08757)	Dose-dependent blockage of hERG current by RO4923659 was observed, with a maximum of 18.2% inhibition at 30μM.
RO4923659-000 (THRA): Cardiovascular Assessment in Conscious Radiotelemetry-Implanted Beagle Dogs Following Oral Gavage Administration (Study 09979) • Dog (4/sex) • 10, 50, and 120 mg/kg, single oral dose (gavage)	Dogs (4/sex) were administered a single oral dose of RO4923659 at 0, 10, 50, and 120 mg/kg with a minimum 6-day washout period between doses. Hemodynamic and ECG parameters were monitored. There were mild to moderate decreases in systolic and diastolic blood pressure between 5 to 7 hours postdose at 50 and 120 mg/kg. Slight to mild increase in heart rate was observed between 2 to 8 hours postdose at 50 and 120 mg/kg. Slight to mild decreases in QRS, RR, and PR intervals that were maximal at 4 hours postdose were noted at 50 and 120 mg/kg. Clinical signs included emesis and diarrhea within 4 hours postdose at 50 and 120 mg/kg.
The Acute Central Nervous System Pharmacological Study of RO4923659-000 Following Oral Administration in Han (Crl:WI) Rats Using a Modified Functional Observational Battery (Study 10348) • Rat (6 males/group) • 30, 100, and 300 mg/kg, single oral dose	In a modified functional observational battery (FOB) and qualitative activity assessment, there were no effects on central nervous system function that were considered as test article-related following a single oral dose of 0, 30, 100, or 300 mg/kg. RO4923659-000 was administered in male Crl:WI(Han) rats. Catalepsy (muscular rigidity, inactivity, decrease response to stimuli) was observed in one male rat at 300 mg/kg at the 6- and 24-hour time points. This finding is of interest as RO4923659 in studies # 01125-06 and 01126-06 has been shown to interact with the benzodiazepine receptor; this off-target activity could account for this response. The IC_{50}

Study/Study No.	Findings
	for benzodiazepine receptor binding was 7μM, and the drug concentration in rats at 300 mg/kg is calculated to be ~84μM based on C_{max} (male rats with single oral dose at 300 mg/kg), thereby making this interaction plausible. However, given that catalepsy was only observed in one animal, this finding could not be definitively attributed to drug administration. In the 26-week general toxicity study in rats, catalepsy was not observed at doses ≤200 mg/kg/day (56 times the exposure at the maximum proposed human dose based on AUC).
RO4923659-000: Respiratory Assessment of Orally Administered RO4923659-000 to Plethysmograph- Restrained Male Wistar Rats (Study 10349) • Rat (2 males/group) • 30, 100, and 300 mg/kg, single oral dose	Administration of 0, 30, 100, or 300 mg/kg RO4923659 resulted in no notable effects on respiratory frequency, tidal volume, or minute volume.

Source: Prepared by nonclinical reviewer.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; ECG, electrocardiogram; FOB, functional observational battery; HEK, human embryonic kidney; hERG, human Ether-à-go-go-related gene; IC_{50}, half maximal inhibitory concentration; Ikr, rapid delayed rectifier channel; THRA, THR (thyroid hormone receptor) gene

13.1.4. Absorption, Distribution, Metabolism, and Excretion/Pharmacokinetics

Table 81. ADME/PK Studies

Study/Study No.	Findings
Single Oral Dose PK Study in Wistar Han Rats (Study 09944) • Rat (3 males/group) • 500, 1000, and 2000 mg/kg, single oral dose	After a single oral dose in rats, a dose proportional increase in exposure was observed from 500 to 1000 mg/kg, but there was no further increase at 2000 mg/kg, which may be attributed to saturation of absorption. One rat at 1000 mg/kg was found dead at 10 hours postdose (at 6 hours postdose, AUC=215,000 ng·hr/mL; C_{max}=64,300 ng/mL). One rat at 2000 mg/kg was cool to the touch at 24 hours and found dead by 48 hours (AUC=4,960,000 ng·hr/mL; C_{max}=413,000 ng/mL; T_{max}=24 hours). Based on this study, the minimum lethal dose from a single oral administration of RO4923659 is 1000 mg/kg in the rat. **Table 82. PK Parameters After a Single Oral Dose in Rats** **Dose (mg/kg)** / **AUC (ng·hr/mL)** / **C_{max} (ng/mL)** / **T_{max} (hr)** 500 / 1,710,000 / 92,600 / 10.7 1000 / 3,040,000 / 195,000 / 13 2000 / 3,100,000 / 222,000 / 16.7 Source: Prepared by the nonclinical reviewer from data in study report 09944 pages 4-5. Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{max}, median time to maximum concentration

<table>
<tr><th>Study/Study No.</th><th>Findings</th></tr>
<tr><td>Single-Dose IV and PO PK in Wistar Han Rats (Study 09707)
Rat (3 males/group)
5 mg/kg, Single IV bolus and single oral dose</td><td>RO4923659 had low volume of distribution (0.42 L/kg) and low clearance (2.35 ml/min/kg) following administration of 5 mg/kg IV in rats. $T_{1/2}$ was 3.4 hours. After oral dosing with 5 mg/kg in Klucel suspension, absorption was slow, with T_{max} observed at 6 hours.</td></tr>
<tr><td>Single-Dose PK of MGL-3623 in Sprague-Dawley Rats (Study 3196-16-13)
Rat (21 males/group)
10 mg/kg, single oral dose
1 mg/kg, IV
1 mg/kg, subcutaneous</td><td>The bioavailability of MGL-3623 (major metabolite in humans, also referred to as M1 or MGL-3196-M1) was 6.6% in rats following a single oral dose of MGL-3623. Systemic exposure (C_{max} and AUC) to M1 in rats increased with dose in a less than dose-proportional manner.</td></tr>
<tr><td>PK Study in Zucker Rats (Study THR-34)
Rat (3 males)
10 mg/kg, single oral dose</td><td>Table 83. Concentration of RO4923659 in Plasma, Heart, and Liver of Zucker Rats<table><tr><th>Sample</th><th>Concentration (ng/mL)</th><th>C_{max} (µM)</th><th>Tissue/Plasma Ratio</th></tr><tr><td>Plasma</td><td>3200</td><td>7</td><td>NA</td></tr><tr><td>Heart</td><td>400</td><td>0.9</td><td>0.1</td></tr><tr><td>Liver</td><td>14000</td><td>32</td><td>4.5</td></tr></table>Source: Prepared by the nonclinical reviewer from data in study report THR-34 pages 2-4.
Abbreviations: NA, not applicable; THR, thyroid hormone receptor</td></tr>
<tr><td>Single Dose IV and PO PK in Female Beagle Dogs (Study 08958)
Dog (4 females/group)
5 mg/kg, single IV bolus
10 mg/kg, single oral dose</td><td>RO4923659 had a low volume of distribution (0.4 L/kg) and low clearance (7.7 mL/min/kg) after IV dosing with 5 mg/kg dose in dogs. Absorption following oral dosing with 10 mg/kg was slow, with a bioavailability of 10%. Low absorption in Caco2 cells was also observed.</td></tr>
<tr><td>A Single Dose PO PK in Dogs (Study 09877)
Dog (3 males/group)
10 and 60 mg/kg, single oral dose</td><td>In dogs given a single oral dose of RO4923659, the increase in exposure from 10 to 60 mg/kg was markedly higher than dose proportional (26-fold increase). Clinical signs included emesis and loose stool at 4 hours postdose and diarrhea at 8 hours postdose.
Table 84. PK Parameters in Dogs After a Single Oral Dose<table><tr><th>Dose (mg/kg)</th><th>AUC (ng·hr/mL)</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>Bioavailability</th></tr><tr><td>10</td><td>7961</td><td>630</td><td>4</td><td>36%</td></tr><tr><td>60</td><td>204450</td><td>21833</td><td>5</td><td>100%</td></tr></table>Source: Prepared by the nonclinical reviewer from data in study report 09877 page 4.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{max}, median time to maximum concentration</td></tr>
<tr><td>High Dose PK in Fed Dogs (Study 10006)
Dog (3 males/group)
180 mg/kg, single oral dose</td><td>In fed dogs, the AUC for RO4923659 was 1,845,590 ng·hr/mL and C_{max} was 158,333 ng/mL. T_{max} was 8 hours. Bioavailability was >100%. Clinical signs included diarrhea (2 hours postdose) and emesis (6 hours postdose).</td></tr>
</table>

Study/Study No.	Findings
High Dose PK in Fasted Dogs (Study 10059) • Dog (3 males/group) • 180 mg/kg, single oral dose	In fasted dogs, the AUC for RO4923659 was 3,919,300 ng·hr/mL and C_{max} was 273,333 ng/mL. T_{max} was 5 hours. Bioavailability was >100%. Clinical signs included emesis at 2 and 8 hours postdose. One dog had diarrhea at 24 hours postdose and kidney failure and was sacrificed due to poor condition. The AUC and C_{max} in the fasted state were approximately 1.5- to 3.0-fold higher than in the fed state.
A Single Dose IV Study in C57 Mice (Study 09984) • Mouse (20 males/group) • 5 mg/kg, single IV bolus	RO4923659 had low volume of distribution (0.51 L/kg) and low clearance (1.45 mL/min/kg) after IV administration of 5 mg/kg in the mice.
Exposure From 24 Day Efficacy Study in DIO Mice (Study THR-75) • Mouse (9 males/group) • 0.3, 1, and 3 mg/kg/day, oral QD	The exposure (C_{max} and AUC) of RO4923659 in DIO mice increased dose-proportionally from 0.3 to 1.0 mg/kg on Days 1 and 21. The increase in exposure from 1.0 to 3.0 mg/kg was less than dose proportional on Day 1 but was dose proportional from 1.0 to 3.0 mg/kg on Day 21. **Table 85. PK Parameters in DIO Mice After Repeat Dosing** Day | Dose (mg/kg) | AUC (ng·hr/mL) | C_{max} (ng/mL) | T_{max} (hr) 1 | 0.3 | 4269.2 | 275 | 8 1 | 12,590 | 927 | 2 3 | 15,414 | 1700 | 2 21 | 0.3 | 2927.9 | 368 | 2 1 | 9613.3 | 794 | 2 3 | 26,784.5 | 2690 | 2 Source: Prepared by the nonclinical reviewer from data in study report THR-75 page 4 (corrected version). Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; DIO, diet induced obese; PK, pharmacokinetic; T_{max}, median time to maximum concentration
DIO Mice Plasma and Liver Exposure (Study THR-76) • Mouse (12 males) • 1 mg/kg, single oral dose	In DIO mice, AUC and C_{max} for RO4923659 in liver were ~7-fold higher than those parameters in plasma, based on drug level measurements taken from 0.5 to 24 hours postdose.
23-Day Study in DIO Mice (Study THR-28) • Mouse (9 males/group) • 0.3, 1, 3, and 10 mg/kg, oral QD	RO4923659 was detectable in the heart only in the 0.3 and 10 mg/kg dose groups. The level of RO4923659 in the liver increased with dose. **Table 86. Mean Concentration of RO4923659 in Plasma, Heart, and Liver of DIO Mice on Day 21** Sample | Concentration (ng/mL): 0.3 mg/kg | 1 mg/kg | 3 mg/kg | 10 mg/kg Plasma | 680 | 1600 | 6900 | 17000 Heart | 300 | BLQ <300 | BLQ <300 | 355 Liver | 1850 | 4000 | 8266 | 16000 Source: Prepared by the nonclinical reviewer from data in study report THR-28 pages 10-11. Abbreviations: BLQ, below the limit of quantification; DIO, diet induced obese; THR, thyroid hormone receptor

Study/Study No.	Findings
Pharmacokinetics of MGL-3196, MGL-3196-M1, and MGL-3196-M2 in Mice Following a Single Dose of MGL-3196 (Study 3196-016-003) • Mouse (21 males/group) • 10, 30, and 100 mg/kg, single oral dose	In mice given a single oral administration of 100 mg/kg MGL-3196, systemic exposure (AUC_{0-24}) to M1 and M2 was 0.1% and 1.3% of the parent drug (MGL-3196), respectively. AUC and C_{max} for M1 and M2 increased with dose of MGL-3196.
Single-Dose Pharmacokinetics of MGL-3623 in Mice (Study 3196-16-14) • Mouse (21 males/group) • 10 mg/kg, single oral dose • 0.2 mg/kg, IV • 0.2 mg/kg, subcutaneous	The bioavailability of MGL-3623 (M1) was 25% in mice following a single oral dose of M1. Systemic exposure (C_{max} and AUC) to M1 in mice increased with dose in a less-than-dose-proportional manner following a single dose of MGL-3623.
Single IV and Oral Dose PK Study in Female Cynomolgus Monkeys (Study 08959) • Monkey (2 females/group) • 2.5 mg/kg, IV bolus, single • 10 mg/kg, single oral dose	RO4923659 had a low volume of distribution (0.23 L/kg) and low clearance (7.9 mL/min/kg) after a 2.5 mg/kg IV dose. After oral dosing with 10 mg/kg, absorption was very low (most of the samples had drug levels less than the detection limit of 10 ng/ml). RO4923659 showed low permeability and high efflux ratio in an experiment with Caco2 cells. The compound had good microsomal stability, and high protein binding.
Single Dose PO PK in Female Monkeys (Study 09878) • Monkey (3 females/group) • 10 and 60 mg/kg, single oral dose (Intubation)	The exposure (AUC) to RO4923659 increased in a dose-proportional manner from 10 to 60 mg/kg. At 60 mg/kg, the exposure in monkeys was 3-fold lower than the minimum efficacious exposure (11 µg·hr/ml at 1 mg/kg in DIO mice). Due to insufficient exposure, monkeys were not recommended for use in general toxicology studies. Clinical signs included emesis and loose stool at 4 hours postdose and diarrhea and emesis at 8 hours postdose.
Evaluation of the Covalent Protein Binding in Rat, Dog, Monkey and Human Liver Microsomal Incubations Using [^{14}C]RO4923659-001 (Study 09757)	10µM [^{14}C]RO4923659-001 was incubated with microsomes (1 mg/mL) prepared from male Wistar rat, male Beagle dog, male Cynomolgus monkey, and gender-pooled human liver tissues. No significant covalent protein binding of RO4923659 was observed following microsomal incubation.
RO4923659: In Vitro Plasma Protein Binding, Blood to Plasma Ratios and Partitioning to Red Blood Cells in Human and Various Animal Species (Study 10018)	[^{14}C]RO4923659 was highly bound to plasma proteins from all species (98.6 to 99.6%). Protein binding was independent of concentration. [^{14}C]RO4923659 was highly bound to human serum albumin (99.6%). Association of [^{14}C]RO4923659 with red blood cells was similar in four of the five species.
Identification, Profiling, and Quantitation of the Metabolites of [^{14}C]MGL-3196 in Plasma, Urine, and Feces from Sprague Dawley Rats (Study 3196-16-010)	Approximately 85% of administered radioactivity from [^{14}C]MGL-3196 was eliminated within 72 hours after dosing, mainly via feces (68.6%) and urine (16.2%). Radioactivity was detected in all tissues. At 1392 hours (58 days) postdose, radioactivity concentrations at >7.9 ng equiv/g were present in 7 of 40 tissues (blood, liver, Harderian gland, pancreas, pigmented skin, lung, eye lens), whereas radioactivity levels in other tissues were approaching the lower limit of quantitation (7.66 ng equiv/g), suggesting that elimination of the parent drug and its radiolabeled metabolites was nearly completed.

Study/Study No.	Findings
Identification, Profiling, and Quantitation of the Metabolites of [^{14}C]MGL-3196 in Plasma, Urine, and Feces from Beagle Dogs (Study 3196-16-012)	MGL-3196 was the only radioactive component which was both detected and quantified in plasma. The radioactive oxidation metabolites M1 and M2 were also detected in plasma by mass spectrometry, but the levels were below quantitation limits of the radio flow-through detector (RFD). [^{14}C]MGL-3196-derived material in urine accounted for 2.51% of administered dose through 120 hours postdose. MGL-3196 was the major radioactive component in urine and accounted for 2.23% of administered dose. Metabolites M471-1, M1, and M2 were detected by mass spectrometry, but the levels were below quantitation limits of the RFD. [^{14}C]MGL-3196-derived material in feces accounted for 75.05% of administered dose through 120 hours postdose. MGL-3196 was the primary radioactive component in feces, which accounted for 67.54% of administered dose. M1 and M2 accounted for 3.05 and 1.93% of administered dose, respectively. M453, M469, and an unknown metabolite each presented as ~1% of administered dose. Total metabolites in feces accounted for approximately 7.5% of the total [^{14}C]MGL-3196-derived radioactivity that was administered.
In vitro Metabolite Profiles of [^{14}C]RO4923659 (THR) in Liver Microsomes and Hepatocytes (Study 10930)	Metabolite M1 (a mono-oxygenation product) was primarily produced in monkeys and humans (microsomes and hepatocytes) but was also observed at low levels in microsomes from dogs following incubation. A second metabolite, M2, was observed in all species in hepatocytes (highest in the rat).
Prediction of In Vitro Clearance of THR Compound RO4923659 in Cryopreserved Dog and Mouse Hepatocytes (Study 01078-06)	The intrinsic clearance (CL_{int}) of RO4923659 was determined using cryopreserved dog and mouse CD1 hepatocytes. RO4923659 had low clearance (high stability) in dog and mouse hepatocytes.
Prediction of In Vivo Clearance of THR Compound RO4923659 in Cryopreserved Rat, Monkey, and Human Hepatocytes (Study 01079-06)	The intrinsic clearance (CL_{int}) of RO4923659 was determined using cryopreserved rat, monkey, and human hepatocytes. RO4923659 had low clearance (high stability) in rat, monkey, and human hepatocytes.
Pharmacokinetic and Urinary Excretion Study in Dogs with Oral Dose Administration of MGL-3196 (non-GLP) (Study 3196-016-005) • Dog (3 males) • 100 mg/kg, single oral dose	MGL-3196 was detected at 8, 16, and 24 hours postdose in urine, with the highest average concentration of 109600 ng/mL at 8 hours postdose. The mean amount recovered in urine was 16.8 mg, which represented 1.84% of the total administered dose of MGL-3196. M1 was detected at 8, 16, and 24 hours postdose in urine, with the highest average concentration of 26140 ng/mL at 16 hours postdose. The mean amount recovered in urine was 2.55 mg, which represented 0.29% of the total administered dose of MGL-3196. M2 was detected in all plasma samples from the three animals at 4 and 8 hours postdose. The highest average concentration was 3.2 ng/mL.
Mass Balance and Pharmacokinetic Study in Male Beagle Dogs Following Repeat Oral Doses of MGL-3196 and [^{14}C]MGL-3196 (Study 3196-17-001)	The primary route of elimination of radioactivity after a single oral dose of [^{14}C]MGL-3196 in dogs was feces, which accounted for 76.3% of administered dose at 168 hours postdose. An average of 2.57% of administered dose was recovered in urine at 168 hours postdose. An average of 54.2% of administered dose was recovered in feces at 0 to 24 hours postdose; 2.34% (average) of administered dose was recovered in urine at 8 to 24 hours postdose. [^{14}C]MGL-3196-derived radioactivity was quantifiable in blood and plasma of male dogs through 48 hours (the last timepoint for blood sampling). $T_{1/2}$ of radioactivity was 17.6 hours in blood and 12.5 hours in plasma. The mean blood to

Study/Study No.	Findings
	plasma $AUC_{inf\text{-}obs}$ ratio for dogs was 0.52. Both MGL-3196 and M1 reached maximum levels at 6 hours postdose. The level of M1 in plasma was approximately 1% of the MGL-3196 level. At 4 hours postdose on Day 17, MGL-3196 was the major component in liver, bile duct, blood, bile, and plasma. The concentrations of M1 in the same tissue or organ samples were much lower than the levels of MGL-3196. MGL-3196 was present at high concentrations in liver, bile duct, and bile. The mean concentrations of M1 in bile and liver were approximately 4% of the levels of MGL-3196. The biliary concentrations of M1 and MGL-3196 were 1035- and 245 times the plasma levels of M1 and MGL-3196, respectively, indicating that both compounds can undergo biliary excretion.
Excretion Mass Balance, Pharmacokinetics, and Tissue Distribution by Quantitative Whole-Body Autoradiography in Rats Following a Single Oral Administration of [^{14}C]MGL-3196 (Study 3196-16-009)	The primary route of elimination of radioactivity after a single oral dose of [^{14}C]MGL-3196 in Sprague Dawley (SD) rats was feces, which accounted for 68.6% of the administered dose. An average of 16.2% of the administered dose was recovered in urine. No radioactivity was detected at 96 to 120 hours in feces or at 120 to 144 hours in urine. [^{14}C]MGL-3196-derived radioactivity was quantifiable in plasma of male SD rats through 48 hours (the last timepoint for this group). Radioactivity was detected in plasma at 1 hour after dosing, with T_{max} observed at 4 hours postdose. $T_{1/2}$ was 9.6 hours. In Long Evans (LE) rats, [^{14}C]MGL-3196-derived radioactivity was quantifiable in blood through 768 hours (32 days). Radioactivity was detected in blood and plasma at 1 hour after dosing, with T_{max} observed at 4 and 8 hours postdose. Radioactivity concentrations decreased slowly over time with a $t_{1/2}$ of 447.6 hours in blood and 54.6 hours in plasma. The longer $t_{1/2}$ value obtained for LE rats is attributed to prolonged release of radioactivity from tissues. Orally administered [^{14}C]MGL-3196 was rapidly absorbed and widely distributed throughout the body in male LE rats, with quantifiable concentrations present in many tissues through 768 hours postdose (17 of 40 tissues). The highest concentrations of radioactivity were found in alimentary canal contents, bile, and urinary bladder contents. Overall, concentrations of radioactivity in most tissues of LE rats (pigmented) were lower than or similar to that present in cardiac blood. C_{max} in most tissues (34 of 40 tissues) was observed at 8 hours postdose (T_{max}). Tissues with C_{max} greater than 700 ng equivalents of MGL-3196 per gram of sample (ng equiv/g) included the following: liver, renal cortex, cecum, urinary bladder, renal medulla, small intestine, esophagus, cardiac blood, pigmented skin, and nonpigmented skin. Tissues with C_{max} <100 ng equiv/g included the brain (medulla, cerebellum, cerebrum), eye lens, spinal cord, and bone. At 1392 hours (58 days) postdose, radioactivity concentrations at >7.9 ng equiv/g were present in 7 of 40 tissues (blood, liver, Harderian gland, pancreas, pigmented skin, lung, and eye lens). Liver AUC and renal cortex AUC for total radioactivity after dosing with [^{14}C]MGL-3196 were approximately 10 times and 3 times the plasma AUC value, respectively. [^{14}C]MGL-3196-related radioactivity was not specifically associated with the melanin-containing tissues in the pigmented LE rats.
RO4923659: Evaluation of Thyroid Hormone Agonist for In Vitro Induction Potential in Primary Human Hepatocyte Cultures (Study 10182)	RO4923659 demonstrated weak potential to induce CYP3A4 mRNA and CYP3A4/5 catalyzed midazolam 1'-hydroxylation activity in primary human hepatocytes from two donors; however, CYP3A4 mRNA was slightly suppressed in the remaining four donors. CYP1A2 mRNA was weakly suppressed in all six donors, which resulted in weak suppression of CYP1A2 enzyme activity for three of the donors. Enzyme activity was

Study/Study No.	Findings
	not suppressed below 50% of control levels. RO4923659 had minimal effect on CYP2B6 and CYP2C9. RO4923659 does not have the potential to induce mRNA levels for MDR-1 or MRP2 in primary human hepatocytes.
RO4923659-000 [THR Agonist]: Evaluation of the Cytochrome P450 Inhibition and Time-Dependent Inactivation by RO4923659-000 Using Human Liver Microsomal Incubations (Study 10315)	The clinical drug-drug interaction potential of RO4923659 was evaluated at concentrations of 1, 10, 25, and 50μM in human liver microsomes (HLM). Weak inhibition was observed for CYP2C9 (IC_{50}=22μM). No inhibition was observed for CYP1A2, CYP1A6, CYP2C19, CYP2D6, or CYP3A4/5 at concentrations up to 50μM. The time-dependent inactivation of CYP2C9 and CYP3A4/5 was evaluated by preincubation of RO4923659 at 10μM with pooled HLM. After 24 minutes of pre-incubation, no significant loss of CYP2C9 or CYP3A4/5 activities in HLM were observed.
RO4923659 (THR): Evaluation of the Interaction between Drug Efflux Transporters and RO4923659 (Study 09989)	The effect of RO4923659 on in vitro bidirectional transport was evaluated in Caco2, MDCKII-MDR1, MDCKII (wild-type) cells, and breast cancer resistance protein (BCRP) membrane vesicle transport systems. The results indicated that RO4923659 is a weak P-gp substrate and is not a P-gp inhibitor. The results also suggested that the transport of RO4923659 is mediated by other transporters such as BCRP and is ATP-dependent. The permeability of RO4923659 in either direction of cell transport was not affected by pH values in the range of 5.5 to 7.4.
Evaluation of the Interaction between RO4923659 and OATP1B1 and OATP1B3 (Study 09769)	Active uptake of RO4923659 was observed in rat, dog, and human hepatocytes. RO4923659 is a substrate for OATP1B1 and OATP1B3 and is a mild/moderate inhibitor of OATP1B1 and OATP1B3 transporters. RO4923659 reduced the uptake of pravastatin in a fibroblast cell line transfected with OATP1B1 (mild inhibition) or OATP1B3 (moderate inhibition).
Study to Investigate Whether the Test Compound, MGL-3196-M1, is a Substrate of the Transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, and an Inhibitor of P-gp (Study 3196-16-004)	The data indicates that MGL-3196-M1 (MGL-3623) is not a substrate of P-gp. However, MGL-3196-M1 was shown to be a substrate of the human BCRP transporter and the human OATP1B1 and OATP1B3 transporters, based on the study criteria. MGL-3196-M1 was also a substrate of the human OAT3 transporter but was not a substrate of the human OAT1 or OCT2.
Study to Investigate Whether the Test Compounds, MGL-3196 and MGL-3196-M1, are Inhibitors of Human BSEP and MRP2 and Substrates of MRP2 (Study 3196-16-006)	MGL-3196 inhibited BSEP-mediated transport of TCA with an IC_{50} value of 34.7μM. MGL-3196-M1 at 0.3 to 30μM did not inhibit BSEP-mediated transport of TCA. However, MGL-3196-M1 at 100μM inhibited BSEP-mediated transport by 48.6%. MGL-3196 and MGL-3196-M1 did not inhibit MRP2-mediated E17G transport. MGL-3196 and MGL-3196-M1 were not substrates of the human MRP2 transporter.
Study to Investigate UGT Inhibition of MGL-3196 (Study 3196-17-014)	MGL-3196 produced inhibition of all UGT isoforms, with IC_{50} values of 3.22, 16.7, 0.557, 44.2, 1.14, and 32.6μM for UGT1A, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, respectively.

Source: Prepared by the nonclinical reviewer.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; ATP, adenosine triphosphate; AUC, area under the concentration-time curve; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; $AUC_{inf\ obs}$, AUC from time of dosing extrapolated to infinity, based on the last observed concentration; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CL_{inf}, intrinsic clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DIO, diet induced dose; E17G, estradiol 17β-D-glucuronide; IC_{50}, half-maximal inhibitory concentration; HLM, human liver microsomes; IV, intravenous; M1, metabolite 1; M2, metabolite 2; LE, Long Evans; MDCK, Madin-Darby Canine Kidney; MDR1, multidrug resistance gene 1; MRP2, multidrug resistance protein 2; OAT, organic anion transporter; OAT3, organic anion transporter 3; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetic; PO, by mouth; QD, once daily; SD, Sprague Dawley; TCA, taurocholic acid; $T_{1/2}$, elimination half-life; THR, thyroid hormone receptor; T_{max}, median time to maximum concentration; UGT, uridine 5'diphosphoglucuronosyltransferease

Table 87. Comparison of Pharmacokinetic Parameters Across Species

	Intravenous				Oral Gavage				
Species	**Rat**	**Mouse**	**Dog**	**Monkey**	**Rat**	**Mouse**	**Dog**	**Monkey**	**Rabbit**
Study No.	9707	9884	8958	8959	9774	3196-16-003	9928	3196-12-014	10040
Feeding condition	UN	UN	UN	UN	UN	Fasted	UN	Fed	UN
Dose (mg/kg)	5	5	5	2.5	10	10	10	10	10
$t_{1/2}$ (hr)	3.40	4.47	2.10	1.67	4.05	4.53	4.17	3.2	2.19
C_{max} (ng/mL)	-	-	-	-	3,447	2,650	364	524	2,717
T_{max} (hr)	-	-	-	-	5	4	3	1	1
$AUC_{0\text{-}inf}$ (ng·hr/mL)	38,149	57,476	11,220	5,313	40,545	35,300	2,936	1,528	12,196
AUC (ng·hr/mL)	-	-	-	-	-	33,900		-	-
F_{rel} (%)	-	-	-	-	53	31	13.1	7.2	-

Source: Prepared by the nonclinical reviewer.
Note: Relative bioavailability calculated based on exposure (AUC) after IV administration.
Abbreviations: AUC, area under the plasma concentration versus time curve; $AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximal plasma concentration; F, female; F_{rel}, relative bioavailability; hr, hour; IV, intravenous; M, male; $t_{1/2}$, elimination half-life; T_{max}, median time to maximum concentration; UN, unknown

13.1.5. General Toxicology

13.1.5.1. A 90-Day Repeat-Dose Oral Range-Finding Toxicity Study of MGL-3196 in Mice With a 4-Week Recovery, Study 3196-17-020; 0470MM72.004

Key Study Findings

- MGL-3196 had no significant effects on body weight (BW) or BW gain, except for the 100 mg/kg/day female group which showed a significant increase in BW (↑6.5%).
- In general, MGL-3196 at ≥30 mg/kg/day caused a significant and dose-dependent increase in food consumption (up to 42.3% in males and 21% in females), which was likely related to the pharmacologic activity of MGL-3196.
- MGL-3196 at 200 mg/kg/day produced statistically significant hematology changes, including decreases in erythrocytes (↓19%), hemoglobin (HGB) (↓19%), and hematocrit (↓19%), and an increase in platelets (↑91%).
- Alanine aminotransferase (ALT) was significantly increased in females at 3 and 100 mg/kg/day (↑230% and ↑574%, respectively). Males in the 100 mg/kg/day group had a significant increase in alkaline phosphatase (ALP) (↑191%), however, the 200 mg/kg/day males showed no change in ALP.
- MGL-3196 produced a dose-dependent decrease in total and free tetraiodothyronine (T4), which was likely related to the pharmacologic activity of MGL-3196.
- MGL-3196 at all doses produced depletion of hepatocellular glycogen, hepatocellular hypertrophy with formation of multinucleated hepatocytes, and single cell necrosis (multifocal single cell necrosis in 3/10 males at 200 mg/kg/day). In females, the effects on hepatocytes were dose dependent. The changes in hepatocytes in males were partially reversible. Mixed cell infiltrate in liver was observed in the 100 mg/kg/day group (both sexes) and 200 mg/kg/day males; the incidence was dose dependent, but not severity.

- The no observed adverse effect level (NOAEL) was not identified due to changes in hepatocytes (glycogen depletion and multinucleated hepatocytes) at all doses. The maximum tolerated dose was considered to be 100 mg/kg/day based on the decrease in red blood cell (RBC) parameters at 200 mg/kg/day and multifocal single hepatocyte necrosis in males at 200 mg/kg/day.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 88. Information, Study 3196-17-020; 0470MM72.004

Methods	Details
Dose and frequency of dosing	• 3, 30, 100, 200 mg/kg QD for males • 3, 30, 100 mg/kg QD for females
Route of administration	Oral
Formulation/vehicle	MGL-3196 was dissolved in 2% klucel LF, 0.1% tween 80, 0.09% methylparaben, and 0.01% propylparaben in purified water at concentrations of 0.3, 3, 10, or 20 mg/mL.
Species/strain	Mouse/CD1(ICR)
Number/sex/group	• 16 (main study groups) for male groups 1 to 5 and female groups 1 to 4 • 16 (4-week recovery groups) for male groups 1 to 5 and female groups 1 to 4
Age	6-9 weeks
Satellite groups/unique design	• 48/sex/group for toxicokinetics (TK) for male groups 1 to 5 and female groups 1 to 4 • There were no females in the high-dose group (200 mg/kg/day) in main study, recovery, and TK groups. No rationale was provided by the Applicant.
Dosing solution analysis	All formulations were homogenous. The concentrations of all the formulations met the acceptance criteria (85-115% of target concentration) except for the 3 mg/kg formulation (0.3 mg/mL) for the initial week of dosing, which was 82.5% of target concentration.

Source: Prepared by the nonclinical reviewer
Abbreviations: GLP, good laboratory practice; ICR, Institute of Cancer Research; QD, once daily; TK, toxicokinetics

Table 89. Observations and Results, Study 3196-17-020; 0470MM72.004

Parameter	Major Findings
Mortality	A total of eight premature deaths occurred. The cause of death for one control mouse was accidental, and another female in the control group was euthanized due to suspected pregnancy. One mouse in the 3 mg/kg/day group was euthanized due to perforated esophagus. The causes of death for other mice were not provided (two animals in the 30 mg/kg/day groups [main study and TK groups], one each in the 100 mg/kg/day group and the 200 mg/kg/day [TK] group).

Parameter	Major Findings
	It is unclear whether some of the deaths were related to treatment since the Applicant did not indicate the cause of death for some animals in the study report.
Clinical signs	None
Body weight/food consumption	Overall, there were no treatment-related changes in body weight or body weight gain during the treatment and recovery periods. A significant and dose-dependent increase in food consumption (↑up to 42.3%) occurred in males at ≥30 mg/kg/day. A significant decrease in food consumption (↓5.9%) was observed in the 200 mg/kg/day males at the end of the recovery period. A significant increase in food consumption (↑up to 21%) occurred in females at 30 and 100 mg/kg/day. The change in food consumption was reversible. The changes in food consumption were likely related to pharmacologic activity of MGL-3196.
Ophthalmoscopy	No effects
Electrocardiogram	Not applicable
Hematology	In males, MGL-3196 at 200 mg/kg/day produced statistically significant changes, including decreases in erythrocytes (↓19%), hemoglobin (↓19%), and hematocrit (↓19%), and an increase in platelets (↑91%).
Clinical chemistry	A dose-dependent and significant decrease in cholesterol (↓31 to 74%) and triglycerides (↓48 to 71%) occurred at ≥3 mg/kg/day. These changes were considered to be related to the pharmacologic activity of MGL-3196. A significant decrease in total bilirubin in males was observed at 30 and 100 mg/kg/day (↓43% and ↓50%, respectively) and in females at 100 mg/kg/day (↓52%). A significant increase in ALT occurred in females at 3 and 100 mg/kg/day (↑230% and ↑574%, respectively). ALP was significantly increased in males at 100 mg/kg/day (↑191%). All the changes were reversible.
Urinalysis	Not applicable.
Gross pathology	Two males in the 200 mg/kg/day group had pale, enlarged liver that was associated with mild hepatocellular hypertrophy.
Organ weights	Statistically significant changes in absolute and relative organ weights (adrenal, liver, spleen, thyroid/parathyroid, kidney) was observed at all doses. The changes were sporadic and not dose dependent. None of these changes were drug related.
Histopathology Adequate battery: Yes	Overall, MGL-3196 at all doses produced widespread hepatocellular glycogen depletion and hepatocellular hypertrophy (centrilobular to midzonal hepatocytes with slight distortion of lobular architecture) in 9 to 10 of 10 males and 4 to 10 of 9 to 10 females in each dose group. Affected hepatocytes had enlarged nuclei and expanded, finely granular to stippled cytoplasm, with occasional multinucleated forms (three to five nuclei) coded separately. Single cell necrosis in liver was observed in all male treatment groups with a dose-dependent increase; this lesion was described as multifocal single cell necrosis in 5/10 males at 200 mg/kg/day. Mixed cell infiltrate in liver was observed in the 100 and 200 mg/kg/day males with dose-dependent incidence; severity was not dose dependent. Males were more affected than females. The incidence and severity of hepatocyte glycogen depletion, hepatocellular hypertrophy, and multinucleated hepatocytes in females was dose dependent. These changes were partially reversible in males. In females, these changes

Parameter	Major Findings
	were reversible since only 1 of 10 animals had decreased hepatocyte glycogen.
T4, T3, and TSH	Total T4 and free T4 were decreased by up to 61.5% to 46.8%, respectively. There was no apparent drug-related effect on total T3, free T3, or TSH. All changes were reversible.
Toxicokinetics (TK)	Blood samples were collected on Days 1 and 90 at 0, 0.5, 1, 2, 4, 6, and 24 hours postdose for analysis of MGL-3196 and its metabolite, MGL-3623. Exposure to MGL-3196 (C_{max} and AUC_{0-24}) was dose proportional. There was no accumulation of the parent drug following repeated doses, with the exception of males in the 200 mg/kg/day group. On Day 90, exposure to parent drug in females at 30 and/or 100 mg/kg/day was slightly higher than that of males (C_{max} was 1.6 times higher at 100 mg/kg/day, AUC_{0-24} was 1.4 times higher at 30 mg/kg/day and 1.2 times higher at 100 mg/kg/day). Systemic exposure to the metabolite MGL-3623 was <0.125% of the exposure to the parent compound in both sexes. At 100 mg/kg/day, there was a sex-related difference in the formation of MGL-3623, with a 2-fold difference in AUC_{0-24} and C_{max} and notably higher exposures in males than females. Exposure was generally lower on Day 90 compared to Day 1. The toxicokinetic data are summarized in Table 90 and Table 91.

Source: Prepared by the nonclinical reviewer.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hr) using the linear trapezoidal rule; ALP, alkaline phosphatase; ALT, alanine aminotransferase; C_{max}, maximum plasma concentration; MGL-3196, resmetirom; T3, triiodothyronine; T4, thyroxine; TK, toxicokinetics; TSH, thyroid stimulating hormone

Table 90. Summary of Plasma TK Parameters of MGL-3196 (Parent Drug) in Male and Female Mice on Days 1 and 90

	Male MGL-3196 Dose, mg/kg/Day				Female MGL-3196 Dose, mg/kg/Day		
TK Parameters	**3**	**30**	**100**	**200**	**3**	**30**	**100**
Day 1							
T_{max}, h	4.00	2.00	8.00	2.00	1.00	8.00	4.00
C_{max}, ng/mL	1,140	9,690	34,000	25,000	1,390	10,100	28,500
$AUC_{(0-24)}$, ng*h/mL	14,700	80,300	403,000	222,000	18,200	148,000	376,000
$AUC_{(0-T)}$, ng*h/mL	14,700	80,300	403,000	222,000	18,200	148,000	376,000
$T_{1/2}$, h	6.15	5.68	NC	11.6	3.75	NC	5.09
C_{max} (Male/Female)	0.820	0.959	1.19	-	-	-	-
$AUC_{(0-24)}$ (Male/Female)	0.808	0.543	1.07	-	-	-	-

	Male MGL-3196 Dose, mg/kg/Day				Female MGL-3196 Dose, mg/kg/Day		
TK Parameters	**3**	**30**	**100**	**200**	**3**	**30**	**100**
Day 90							
T_{max}, h	2.00	4.00	2.00	6.00	2.00	2.00	4.00
C_{max}, ng/mL	1,170	6,850	19,500	74,300	1,610	8,860	31,700
$AUC_{(0-24)}$, ng*h/mL	12,400	67,300	258,000	757,000	15,200	94,200	318,000
$AUC_{(0-T)}$, ng*h/mL	12,400	67,300	258,000	757,000	15,200	94,200	318,000
$T_{1/2}$, h	4.05	3.14	8.53	NC	2.47	2.29	2.44
C_{max} (Male/Female)	0.727	0.773	0.615	-	-	-	-
$AUC_{(0-24)}$ (Male/Female)	0.816	0.714	0.811	-	-	-	-
C_{max} Ratio (Day 90/Day 1)	1.03	0.707	0.574	2.97	1.16	0.877	1.11
$AUC_{(0-24)}$ Ratio (Day 91/Day 1)	0.844	0.838	0.640	3.41	0.835	0.636	0.846

Source: Applicant's report 3196-17-020; 0470MM72.004.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; C_{max}, maximum plasma concentration; F, female; M, male; MGL-3196, resmetirom; NC, not calculated; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%

Table 91. Summary of Plasma TK Parameters of MGL-3623 (Metabolite) in Male and Female Mice on Days 1 and 90

	Male MGL-3196 Dose, mg/kg/Day				Female MGL-3196 Dose, mg/kg/Day		
TK Parameters	**3**	**30**	**100**	**200**	**3**	**30**	**100**
Day 1							
T_{max}, h	8.00	8.00	8.00	4.00	6.00	6.00	4.00
C_{max}, ng/mL	0.825	3.81	42.0	15.3	1.42	7.71	17.8
$AUC_{(0-24)}$, ng*h/mL	9.02	59.8	425	140	12.7	79.3	181
$AUC_{(0-T)}$, ng*h/mL	2.42	59.8	425	140	6.77	40.4	181
$T_{1/2}$, h	NC	NC	NC	NC	NC	NC	6.90
C_{max} (Male/Female)	0.581	0.494	2.36	-	-	-	-
$AUC_{(0-24)}$ (Male/Female)	0.710	0.754	2.35	-	-	-	-
$\%C_{max}$ (metabolite/parent)	0.0724	0.0393	0.124	0.0612	0.102	0.0763	0.0625
$\%AUC_{(0-24)}$ (metabolite/parent)	0.0614	0.0745	0.105	0.0631	0.0698	0.0536	0.0481
Day 90							
T_{max}, h	6.00	8.00	0.00	6.00	NC	6.00	4.00
C_{max}, ng/mL	0.245	1.72	6.97	90.7	0.00	1.28	3.76
$AUC_{(0-24)}$, ng*h/mL	0.490	22.7	69.7	617	NC	14.4	40.3
$AUC_{(0-T)}$, ng*h/mL	0.245	8.94	69.7	617	0.00	7.60	20.7
$T_{1/2}$, h	NC	NC	NC	NC	NC	NC	NC
C_{max} (Male/Female)	NC	1.34	1.85	-	-	-	-
$AUC_{(0-24)}$ (Male/Female)	NC	1.58	1.73	-	-	-	-
$\%C_{max}$ (metabolite/parent)	0.0209	0.0251	0.0357	0.122	NC	0.0144	0.0119
$\%AUC_{(0-24)}$ (metabolite/parent)	3.95E-03	0.0337	0.0270	0.0815	NC	0.0153	0.0127
C_{max} Ratio (Day 90/Day 1)	0.297	0.451	0.166	5.93	NC	0.166	0.211
$AUC_{(0-24)}$ Ratio (Day 91/Day 1)	0.0543	0.380	0.164	4.41	NC	0.182	0.223

Source: Applicant's report 3196-17-020; 0470MM72.004.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; C_{max}, maximum plasma concentration; F, female; M, male; MGL-3196, resmetirom; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half of life), the time required for plasma concentration of a drug to decrease by 50%

13.1.5.2. A 3-Month Oral Toxicity Study With VIA-3196 in Rats With a 4-Week Recovery Period, Studies 3196-12-006 and 3196-12-025

The Applicant conducted two 13-week oral toxicity studies in rats. The doses tested were 0, 1, 3, and 30 mg/kg/day in the first study (Study 3196-12-006), and 0 and 150/200 mg/kg/day in the second study (Study#: 3196-12-025). The rationale for conducting two 13-week studies was not provided. Beginning on Day 15 of Study 3196-12-025, animals in the 150 mg/kg/day group were treated with 200 mg/kg/day until the end of the treatment period. The combined results from these two studies are presented below.

Key Study Findings

- VIA-3196 at ≥30 mg/kg in males and 150/200 mg/kg in females had significant effects on BW (↑up to 17%) and BW gain (↑up to 6-fold on Day 91). The increase in BW in females was not reversible.
- VIA-3196 at ≥30 mg/kg/day caused a significant and dose-dependent increase in food consumption (up to 41% in males and 22% in females), which was likely related to the pharmacologic activity of VIA-3196. The increase in food consumption was not reversible.
- VIA-3196 at 150/200 mg/kg/day produced significant changes in hematology, including increases in white blood cells (↑up to 55% in females) and its differential counts, and reticulocytes (↑up to 45%). Decreases in RBC (↓up to 7%) and HGB (↓up to 6%) also occurred at 150/200 mg/kg/day. Platelet counts were increased by up to 47% at ≥30 mg/kg/day.
- At 150/200 mg/kg/day, VIA-3196 produced significant increases in plasma phosphorus (↑up to 35%), potassium (↑up to 21%), total bilirubin (↑up to 107%), ALT (↑up to 56% in males), aspartate aminotransferase (AST) (↑up to 67% in males), bone ALP (↑220% in males), intestinal ALP (↑32% in males), and liver ALP (↑50% in females).
- VIA-3196 produced a dose-dependent decrease in total and free T4 and thyroid stimulating hormone (TSH), which was likely related to the pharmacologic activity of VIA-3196. A significant increase in total and free T3 was observed in males at 150/200 mg/kg/day. These changes were reversible.
- VIA-3196 at ≥30 mg/kg/day produced significant increases in absolute and relative weights of the heart, kidney, and spleen, whereas thyroid/parathyroid weight was decreased. No microscopic changes were observed in these organs.
- There were no treatment-related histopathological changes. However, it appeared that VIA-3196 at ≥30 mg/kg/day increased the incidence and severity of chronic progressive nephropathy, a spontaneous kidney disease in rats.
- No target organs of toxicity were identified. The NOAEL was considered to be 30 mg/kg/day due to significant changes in clinical chemistry, hematology, and total/free T4 and TSH at 150/200 mg/kg/day.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 92. Information, Study 3196-12-006 and 3196-12-025

Methods	Details
Dose and frequency of dosing	0, 1, 3, 30, 150, and 200 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	VIA-3196 was dissolved in 2% klucel LF, 0.1% tween 80, 0.09% methylparaben, 0.01% propylparaben in purified water at concentrations of 0.2, 0.6, 6, 30, or 40 mg/mL.
Species/strain	Rats/Sprague-Dawley
Number/sex/group	• 10 (main study groups) • 5 (4-week recovery groups)
Age	6 to 7 weeks
Satellite groups/ unique design	9 to 10/sex/group for toxicokinetics (TK)
Dosing solution analysis	All formulations were homogenous. The concentrations of all the formulations met the acceptance criteria (85 to 115% of target concentration).

Source: Prepared by the nonclinical reviewer.
Abbreviations: GLP, good laboratory practice; QD, once daily; TK, toxicokinetics

Table 93. Observations and Results, Study 3196-12-006 and Study 3196-12-025

Parameter	Major Findings
Mortality	There was a total of six premature deaths, and the causes of death included injury (one control animal) and gavage errors (three animals). Two animals (one in the 3 mg/kg/day TK group and one vehicle control animal) were found dead and the cause of the death was not determined.
Clinical signs	None
Body weight/food consumption	Statistically significant increases in body weight (17%) and body weight gain (40) occurred in the 30 and 150/200 mg/kg/day groups on Day 91. The changes in male body weight and body weight gain were reversible. Significant increases in food consumption occurred at 30 mg/kg/day (↑up to 15%) and at 150/200 mg/kg/day (↑up to 41%). The changes in food consumption were likely related to pharmacologic activity of VIA-3196. All changes in body weight and food consumption were dose dependent.
Ophthalmoscopy	No effects
Electrocardiogram	Not applicable

Parameter	Major Findings
Hematology	Statistically significant increases in platelet count (11 to 58%) were observed in the 30 and 150/200 mg/kg/day groups. This effect was partially reversible in the 150/200 mg/kg/day group. Statistically significant changes in hematology, including increases in absolute and relative monocytes counts (72 to 170%), WBC (55% in females), absolute lymphocytes (43% in females), absolute and relative neutrophils (34 to 112% in females), MCV (3 to 4%), MCH (1 to 2%), and absolute reticulocyte counts (11 to 45%) were observed. Decreases in RBC (4 to 7%), MCHC (2%), and HGB (2 to 6%) were also observed at 150/200 mg/kg/day. These changes were reversible except for the increase in relative neutrophil count in males, and decrease in red blood cell indices (HGB, HCT, MCV, MCH) in females.
Clinical chemistry	VIA-3196 at ≥3 mg/kg/day caused dose-dependent and significant changes, including decreases in total protein (up to 10%), globulin (up to 23%), cholesterol (males only, up to 41%), blood urea nitrogen (at 150/200 mg/kg only, 12 to 31%), triglycerides (at 150/200 mg/kg only, 31 to 46%), and albumin (11% in females only at 150/200 mg/kg). These changes were reversible. Statistically significant increases in triglycerides (34 to 43%) and cholesterol (11 to 26%) were observed at the end of the recovery period. Changes related to cholesterol and triglycerides were attributed to the pharmacologic activity of VIA-3196. Statistically significant increases in phosphorus (35% at 150/200 mg/kg), potassium (21% at 150/200 mg/kg), total bilirubin (dose-dependent effect in males at ≥30 mg/kg, up to 107%; 18% in females at 150/200 mg/kg), ALT (56% in males at 150/200 mg/kg), AST (67% in males at 150/200 mg/kg), and cholesterol (28% in females at 150/200 mg/kg) were observed. ALP isoenzymes were analyzed in animals treated with 150/200 mg/kg/day. Statistically significant increases were observed for bone ALP (220%) and intestinal ALP (32%) in males, and liver ALP (50%) in females. Statistically significant decreases were observed for bone ALP (40 to 61%) and total ALP isoenzymes (21 to 51%) at the end of the recovery period.
Urinalysis	No effects
Gross pathology	No effects
Organ weights	Significant increases in absolute and relative kidney weights occurred at 30 mg/kg/day (≤20% in males; ≤12% in females). Significant increases in absolute and relative heart (13 to 14%) and spleen (21 to 31%) weights occurred at 30 mg/kg/day. Changes in males were not reversible. Significant changes in absolute and relative organ weights occurred at 150/200 mg/kg/day, including adrenal gland (↑up to 12% in absolute weight; ↓up to 5% in relative to body weight), heart (↑up to 37%), kidney (↑up to 51%), liver (↑up to 55%), ovaries (↑up to 39%), spleen (↑up to 73%), testes (↑up to 13% in absolute weight, but ↓3% in relative to body weight), and thyroid/parathyroid (↓up to 28%). These changes were not reversible.
Histopathology Adequate battery: Yes	Incidence and severity of chronic progressive nephropathy (CPN) was increased at ≥30 mg/kg/day.

Parameter	Major Findings
T4, T3, and TSH	Dose-dependent and significant reductions in total T4 (up to 100% in males and 94% in females) occurred at ≥3 mg/kg/day. Free T4 was decreased by up to 97% in males at ≥3 mg/kg/day and by up to 86% in females at all doses (≥1 mg/kg/day). Significant increases in total T3 were observed in males at 1, 3, and 30 mg/kg/day (up to 27.7%). Free T3 was increased in males at 30 and 150/200 mg/kg/day (up to 64.6%). Total T3 was significantly decreased in both sexes at 150/200 mg/kg/day. At 150/200 mg/kg, VIA-3196 produced a significant reduction in TSH (73.8% in males and 56.2% in females).
Toxicokinetics (TK)	Blood samples were collected on Days 1 and 91 at 0, 0.5, 1, 2, 4, 6, 10, and 12 hours postdose for analysis of parent drug (VIA-3196) and metabolites M1 and M2. VIA-3196 at doses in the range of 1 to 30 mg/kg/day exhibited slight accumulation following 91 days of treatment. Following dosing of 150 mg/kg for 14 days and 200 mg/kg for 77 days, there was modest accumulation of VIA-3196 ranging from 2.2 to 3.7-fold, compared to plasma exposure on Day 1. The change in dose level on Day 15 from 150 to 200 mg/kg/day may have contributed to the accumulation of VIA-3196. Plasma exposure (AUC) to VIA-3196-M1 and VIA-3196-M2 was much lower than that of the parent drug, VIA-3196 (<1% on days 16 and 91). Systemic exposure (C_{max} and AUC) to VIA-3196-M1 was approximately 6-fold greater in males compared to females on Day 16. C_{max} and AUC_{0-24} increased by 6-fold and 19-fold, respectively, on Day 91 as compared to Day 16 in the 200 mg/kg/day group. Exposure in both sexes was generally higher on day 91 than Day 16 (2-fold increase in C_{max} and 2- to 8-fold increase in AUC). The estimated systemic exposure to VIA-3196-M2 was greater than the exposure to M1 by approximately 2- to 4-fold in males, and 15- to 24-fold in females. The toxicokinetic data are summarized in Table 94, Table 95, and Table 96.

Source: Prepared by the nonclinical reviewer.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CPN, chronic progressive nephropathy; HCT, hematocrit; HGB, hemoglobin; M1, metabolite 1; M2, metabolite 2; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TK, toxicokinetics; TSH, thyroid stimulating hormone; VIA-3196, resmetirom; WBC, white blood cell

Table 94. Summary of Plasma TK Parameters for VIA-3196 (Parent Drug) on Days 1 and 90 in Rats Treated With 1, 3, or 30 mg/kg/day

Day	Parameter	VIA-3196 Dosage mg/kg/day					
		Male			Female		
		1	3	30	1	3	30
1	Cmax, ng/mL	306	774	3,780	173	580	4,250
	Tmax, h	4.00	4.00	4.00	2.00	4.00	2.00
	AUC(0- T), ng·h/mL	2,930	8,610	51,900	1,080	6,070	28,100
	AUC(0-24), ng·h/mL	2,930	8,610	51,900	1,430	6,070	28,100
	AUC(0-inf), ng·h/mL	2,940	8,640	52,000	1,340	6,090	28,100
	$T_{1/2}$, h	2.41	2.60	2.47	3.64	2.64	2.41
	kel (λ), 1/h	0.287	0.267	0.281	0.190	0.263	0.287
	Cmax Ratio (M/F)	1.77	1.33	0.889	-	-	-
	AUC(0-24) Ratio (M/F)	2.05	1.42	1.85	-	-	-
91	Cmax, ng/mL	454	1,110	5,260	305	962	3,100
	Tmax, h	4.00	6.00	6.00	2.00	2.00	2.00
	AUC(0- T), ng·h/mL	4,900	12,200	53,600	2,460	6,460	20,600
	AUC(0-24), ng·h/mL	4,900	12,200	53,600	2,460	6,460	20,600
	$T_{1/2}$, h	5.04	-	-	2.48	3.29	2.86
	kel (λ), 1/h	0.137	NC	NC	0.280	0.210	0.242
	Cmax Ratio (M/F)	1.49	1.15	1.70	-	-	-
	AUC(0-24) Ratio (M/F)	1.99	1.89	2.60	-	-	-
	Cmax Ratio (Day 91/Day 1)	1.48	1.43	1.39	1.76	1.66	0.729
	AUC(0-24) Ratio (Day 91/Day 1)	1.67	1.42	1.03	1.72	1.06	0.733

Source: Applicant's report 3196-12-006.
Abbreviations: AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; NC, not calculated; TK, toxicokinetic; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196, resmetirom

Table 95. Summary of Plasma TK Parameters for VIA-3196 (Parent Drug) on Days 1, 16, and 90 in Rats Treated With 150/200 mg/kg/day

Sex	Male			Female		
Day	1	16	91	1	16	91
VIA-3196 Dose, mg/kg/day*	150	200	200	150	200	200
Cmax, ng/mL	10,000	15,200	34,000	6,310	22,300	28,400
Tmax, h	6.00	4.00	10.0	4.00	2.00	2.00
AUC(0-T), ng·h/mL	139,000	119,000	509,000	88,800	121,000	191,000
AUC(0-24), ng·h/mL	139,000	119,000	509,000**	88,800	121,000	191,000
AUC(0-inf), ng·h/mL	NC	NC	NC	92,500	NC	NC
$T_{1/2}$, h	NC	6.87	NC	4.81	6.57	7.12
Kel, $^1/_h$	NC	0.101	NC	0.144	0.106	0.0973
Cmax Ratio (M/F)	1.58	0.682	1.20	-	-	-
AUC(0-24) Ratio (M/F)	1.57	0.983	2.66	-	-	-

Source: Applicant's report 3196-12-025.
* VIA-3196 was dosed at 150 mg/kg/day on Days 1 through 14 and 200 mg/kg/day on Days 15 through 91.
** The AUC in male rats given 200 mg/kg/day (Group 4) calculated for Day 91 is influenced by the group mean concentration at 10 hours postdose, and this group mean concentration is influenced by the value determined for one of three animals (Rat 2579).
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; NC, not calculated due to insufficient data points in the post distribution phase; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half of life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196, resmetirom

Table 96. Summary of Plasma TK Parameters for Metabolites VIA-3196-M1 and VIA-3196-M2 on Days 16 and 91 in Rats Treated With 150/200 mg/kg/day VIA-3196

Day	Analyte	Sex	Cmax (ng/mL)	Tmax (h)	$AUC_{(0-T)}$ (ng·h/mL)	$AUC_{(0-24)}$ (ng·h/mL)	λ (1/h)	$T_{1/2}$ (h)
16	VIA-3196-M1	Male	14.4	4.00	55.3	55.3	0.100	6.91
		Female	2.57	2.00	5.68	9.11	NC	NC
	VIA-3196-M2	Male	36.8	4.00	240	240	0.0831	8.34
		Female	38.8	2.00	86.9	156	NC	NC
91	VIA-3196-M1	Male	35.9	10.0	448	448*	NC	NC
		Female	5.80	2.00	20.0	23.5	0.261	2.66
	VIA-3196-M2	Male	116	4.00	1,780	1,780*	0.110	6.33
		Female	104	2.00	447	556	0.212	3.27

Source: Applicant's report 3196-12-025.
Note: VIA-3196 was dosed at 150 mg/kg/day for 14 days, then the dose was increased to 200 mg/kg/day from Day 15 through Day 91 in order to achieve higher exposure (Protocol Amendment 1).
* The AUC in male rats given 200 mg/kg/day (Group 4) calculated for Day 91 is influenced by the group mean concentration at 10 hours postdose, and this group mean concentration is influenced by the value determined for one of 3 animals (Rat 2579)
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; M1, metabolite 1; M2, metabolite 2; NC, not calculated; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; λ, elimination rate constant; VIA-3196, resmetirom

13.1.5.3. A 6-Month Oral Toxicity Study With MGL-3196 in Rats With an 8-Week Recovery Period, Study 3196-13-003

Key Study Findings

- MGL-3196 at ≥3 mg/kg/day in males and ≥30 mg/kg/day in females had significant effects on BW (↑up to 19.7% in males and 32% in females) and BW gain. Increased BW in animals at 200 mg/kg/day was not reversible.
- MGL-3196 at ≥30 mg/kg/day caused a significant and dose-dependent increase in food consumption (up to 64% in males and 45% in females), which was likely related to the pharmacologic activity of MGL-3196. The increase in food consumption was not reversible.
- MGL-3196 at ≥30 mg/kg/day produced significant changes in hematology, including increases in white blood cells (↑up to 41%) and its differential counts, and reticulocytes (↑up to 53%). Decreases in RBC (↓up to 13%) and HGB (↓up to 12%) mainly occurred at 200 mg/kg/day. Platelet counts were increased by up to 108% at ≥3 mg/kg/day.
- At ≥30 mg/kg/day, MGL-3196 resulted in significant increases in plasma phosphorus (↑up to 45%), potassium (↑up to 23%), total bilirubin (↑up to 82%), ALT (↑up to 31%), AST (↑up to 129%), total ALP (↑up to 73%), and bone ALP (↑681%).
- MGL-3196 produced a dose-dependent decrease in total and free T4, total and free T3, and TSH, which was likely related to the pharmacologic activity. These changes were not reversible at 200 mg/kg/day.
- MGL-3196 at ≥30 mg/kg/day produced significant increases in absolute and relative weights of the heart, kidney, and spleen, and a significant decrease in thyroid/parathyroid weights at 200 mg/kg/day. No histopathological changes were observed in these organs.
- Treatment-related changes were observed in liver at ≥30 mg/kg/day, which included increased incidence of mononuclear cell infiltrates, non-specific hepatocellular cytoplasmic alteration, and subcapsular/interlobular fibrosis (200 mg/kg/day only). In skeletal muscle, degeneration/regeneration of individual myofibers occurred at ≥30 mg/kg/day.
- The target organs of toxicity were liver and skeletal muscle. The NOAEL was considered to be 3 mg/kg/day based on the significant changes in clinical chemistry, hematology, T4, T3, TSH, and the histopathological changes in liver and skeletal muscle at 30 and/or 200 mg/kg/day.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 97. Information, Study 3196-14-003

Methods	Details
Dose and frequency of dosing	3, 30, 200 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	MGL-3196 was dissolved in 2% klucel, 0.1% tween 80, 0.09% methylparaben, and 0.01% propylparaben in purified water at concentrations of 0.6, 6, or 40 mg/mL.
Species/strain	Rats/Sprague-Dawley
Number/sex/group	• 15 (main study groups) • 5 (8-week recovery groups)
Age	6 to 7 weeks
Satellite groups/ unique design	4 to 10/sex/group for toxicokinetics (TK)
Dosing solution analysis	All formulations were homogenous. The concentrations of the formulations at 6 and 40 mg/mL met the acceptance criteria (85 to 115% of target concentration). However, the concentrations of the formulation at 0.6 mg/mL did not meet the acceptance criteria; the concentration was 81.3% of the nominal concentration. Thus, the formulation of 0.6 mg/mL was 0.455 mg/ml.

Source: Prepared by the nonclinical reviewer.
Abbreviations: GLP, good laboratory practice; MGL-3196, resmetirom; QD, once daily; TK, toxicokinetics

Table 98. Observations and Results, Study 3196-14-003

Parameter	Major Findings
Mortality	A total of six premature deaths occurred. Two male rats in the main study (# 0489 and 0529) were found dead. At necropsy, dark kidneys, liver, and lungs were observed for # 0489 (30 mg/kg), and enlarged kidneys and liver were observed for # 0529 (200 mg/kg). The exact cause of death could not be determined for these animals. Three animals in the main study (control male # 0410, high-dose male # 0521, and high-dose female # 0551), and one TK low-dose male (# 0592) were euthanized for humane reasons on Days 146, 4, 181, and 8, respectively.
Clinical signs	None
Body weight/food consumption	Statistically significant increases in body weight occurred in males (all treatment groups, up to 19.7%) and females (mid- and high-dose groups, up to 32%). The change in body weight in the high-dose group was not reversible. Significant increases in food consumption were observed (↑up to 28% at 30 mg/kg/day; ↑up to 64% at 200 mg/kg/day). The change in food consumption was not reversible. All changes in body weight and food consumption were dose dependent. The changes in food consumption were likely related to pharmacologic activity of VIA-3196.
Ophthalmoscopy	No effects
Electrocardiogram	Not applicable

Parameter	Major Findings
Hematology	Effects included significant increases in platelet count (up to 108%), WBC (up to 41%), WBC differential, and reticulocytes (up to 53%), which occurred mainly in the mid- and high-dose groups with dose dependency. Small but statistically significant changes occurred mainly in the high-dose group, including decreases in RBC (up to 13%), HGB (up to 12%), and HCT (10.3%), and an increase in HCT (3.8%) and MCV (up to 4.5%) in mid-dose males. The increases in platelets and reticulocytes were not reversible. Slight but statistically significant decreases (<10%) in prothrombin time (PT) were observed at all doses. This change was reversible.
Clinical chemistry	Significant increases in total bilirubin (up to 82% at ≥30 mg/kg/day), ALT (up to 31% at 200 mg/kg/day), AST (up to 129% at 200 mg/kg/day), phosphorus (up to 45% in males at ≥3 mg/kg/day and females at ≥30 mg/kg/day), and potassium (up to 23% in males at ≥30 mg/kg/day and females at 200 mg/kg/day). Significant decreases in total protein (up to 14%), globulin (up to 23%), albumin (up to 19%), blood urea nitrogen (up to 44%), and creatinine (up to 18%) occurred at ≥30 mg/kg/day or at 200 mg/kg/day. Other effects included decreases in glucose for females at ≥3 mg/kg/day and males at ≥30 mg/kg/day (up to 18%) and decreases in triglycerides (up to 65%) and cholesterol (up to 41%) at ≥30 mg/kg/day. These changes were likely related to the pharmacologic activity of MGL-3196. MGL-3196 produced a dose-dependent and significant increase in total ALP at ≥30 mg/kg (up to 73%), and in bone ALP in males at ≥3 mg/kg (up to 681%) and females at ≥30 mg/kg (up to 73%). All changes except for increased triglycerides and decreased globulin in the high-dose females were reversible.
Urinalysis	No effects
Gross pathology	No effects
Organ weights	A dose-dependent and significant increase in absolute and/or relative weight of heart (up to 58% in absolute weight and up to 33% relative to body weight), kidney (up to 80% in absolute weight and up to 46% relative to body weight), and spleen (up to 116% in absolute weight and up to 73% relative to body weight) was observed at ≥3 mg/kg. Significant increases in absolute and relative organ weights in adrenal glands, liver, lung, pituitary, testes, and ovaries occurred at 200 mg/kg. A significant decrease in absolute (up to 24% in males only) and relative thyroid/parathyroid weight (up to 36%) was observed at 200 mg/kg. Organ weight changes were not reversible in the following organs at 200 mg/kg: adrenal gland, heart, kidney (at ≥30 mg/kg), liver, and spleen.

Parameter	Major Findings
Histopathology Adequate battery: Yes	Drug-related histopathological changes were observed in liver at 30 and 200 mg/kg/day, which included the following: an increased incidence of mononuclear cell infiltrates (primary macrophages); a non-specific hepatocellular cytoplasmic alteration characterized by a homogenous, eosinophilic, granular to “ground glass” appearance with uncertain etiology; and minimal focal to multifocal subcapsular/interlobular fibrosis at 200 mg/kg/day only. Among the rats that died prematurely, the 30 mg/kg/day male and two females in the 200 mg/kg/day group had focal to multifocal random areas of mild mixed cell inflammation surrounding several necrotic hepatocytes, with or without reactive fibroplasia. A dose-dependent increased incidence of focal or multifocal degeneration/regeneration (minimal to mild) of individual myofibers was observed in the skeletal muscle of the thigh, panniculus muscle of the skin, and the muscular tunic of the esophagus at ≥30 mg/kg/day. In the recovery groups (200 mg/kg/day), mononuclear cell infiltrate (1/5 males and 1/5 females), and subcapsular fibrosis (2/5 males) in liver were observed; therefore, these effects were not completely reversible from the main study.
T4, T3 and TSH	MGL-3196 produced significant, dose-dependent reductions in total T4 and free T4 (up to 86.9% and 84.7%, respectively), total T3 and free T3 (up to 29.9% and 44.7%, respectively), and TSH (up to 87.2%). Decreases in total T4/T3 and free T4/T3 in males at 200 mg/kg and in females at ≥30 mg/kg were not reversible at the end of the 8-week recovery period. The change in TSH was reversible.
Toxicokinetics (TK)	Blood samples were collected on Days 1, 92, and 178 at 0, 0.5, 1, 2, 4, 6, 10, and 24 hours postdose for analysis of MGL-3196. Overall, systemic exposure to MGL-3196 (C_{max} and AUC_{0-24}) was dose proportional. No consistent sex-related differences were observed, although systemic exposure was slightly higher in males (less than 2-fold in most cases as shown in the tables below). MGL-3196 exhibited accumulation following repeated doses in both sexes. The accumulation was greatest at the highest dose (3.25-fold in males based on AUC on Day 178 and Day 1). The toxicokinetic data are summarized in Table 99.

Source: Prepared by the nonclinical reviewer.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; HCT, hematocrit; HGB, hemoglobin; MCV, mean corpuscular volume; MGL-3196, resmetirom; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; VIA-3196, resmetirom; WBC, white blood cell

Table 99. Summary of Plasma TK Parameters of MGL-3196 on Days 1, 92, and 178 in Rats Treated With 3, 30, or 200 mg/kg/day

TK Parameter	MGL-3196 Dose, mg/kg/day					
	Male			Female		
	3	30	200	3	30	200
Day 1						
C_{max}, ng/mL	953	4,560	11,000	635	4,220	17,300
T_{max}, h	2.00	4.00	6.00	2.00	2.00	2.00
$AUC_{(0-T)}$, ng·h/mL	7,140	44,400	151,000	4,250	28,500	140,000
$AUC_{(0-24)}$, ng·h/mL	7,140	44,400	151,000	4,250	28,500	140,000
$AUC_{(0-inf)}$, ng·h/mL	7,160	44,600	NC	4,270	28,600	151,000
$T_{1/2}$, h	2.64	2.82	NC	3.06	2.79	6.29
K_{el}, 1/ h	0.263	0.246	NC	0.226	0.249	0.110
C_{max} Ratio (M/F)	1.50	1.08	0.636	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	1.68	1.56	1.08	-	-	-
Day 92						
C_{max}, ng/mL	1,120	7,080	70,700	869	4,930	59,400
T_{max}, h	4.00	2.00	2.00	4.00	2.00	2.00
$AUC_{(0-T)}$, ng·h/mL	10,800	64,900	392,000	6,740	30,000	362,000
$AUC_{(0-24)}$, ng·h/mL	10,800	64,900	392,000	6,740	30,000	362,000
$T_{1/2}$, h	4.58	3.70	10.1	3.22	3.14	12.4
K_{el}, 1/ h	0.151	0.187	0.0683	0.215	0.221	0.0558
C_{max} Ratio (M/F)	1.29	1.44	1.19	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	1.60	2.16	1.08	-	-	-
C_{max} Ratio (Day 92/Day 1)	1.18	1.55	6.43	1.37	1.17	3.43
$AUC_{(0-24)}$ Ratio (Day 92/Day 1)	1.51	1.46	2.60	1.59	1.05	2.59
Day 178						
C_{max}, ng/mL	946	4,720	76,800	1,170	4,770	60,400
T_{max}, h	4.00	2.00	4.00	2.00	2.00	2.00
$AUC_{(0-T)}$, ng·h/mL	9,220	54,400	490,000	8,140	40,300	390,000
$AUC_{(0-24)}$, ng·h/mL	9,220	54,400	490,000	8,140	40,300	390,000
$T_{1/2}$, h	4.18	3.39	7.26	3.34	3.34	10.8
K_{el}, 1/ h	0.166	0.205	0.0955	0.208	0.208	0.0640
C_{max} Ratio (M/F)	0.809	0.990	1.27	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	1.13	1.35	1.26	-	-	-
C_{max} Ratio (Day 178/Day 1)	0.993	1.04	6.98	1.84	1.13	3.49
$AUC_{(0-24)}$ Ratio (Day 178/Day 1)	1.29	1.23	3.25	1.92	1.41	2.79
C_{max} Ratio (Day 178/Day 92)	0.845	0.667	1.09	1.35	0.968	1.02
$AUC_{(0-24)}$ Ratio (Day 178/Day 92)	0.854	0.838	1.25	1.21	1.34	1.08

Source: Applicant's report 3196-14-003.
Abbreviations: AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; MGL-3196, resmetirom; NC, not calculated; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half of life), the time required for plasma concentration of a drug to decrease by 50%

13.1.5.4. A 3-Month Oral Toxicity Study With VIA-3196 in Dogs With a 4-Week Recovery Period, Study 0470DM72.001

Key Study Findings

- VIA-3196 at doses up to 45 mg/kg/day had no effects on BW, BW gain, food consumption, ophthalmology, electrocardiogram (ECG), hematology, plasma troponin, or ALP (including individual ALP isozymes).
- VIA-3196 at all doses produced a significant and dose-dependent decrease in cholesterol levels in both sexes. VIA-3196 at 15 and 45 mg/kg/day in males and at 15 mg/kg/day in females produced a significant decrease in triglycerides. The decreases in cholesterol and triglycerides are attributed to the pharmacological activity of the drug.
- There were no drug-related findings in organ weights, macroscopic examination, or microscopic examination.
- VIA-3196 at 15 and 45 mg/kg/day produced significant decreases in total and free T4 in males.
- Exposure to VIA-3196 (maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC)) increased with dose in a greater than dose-proportional manner.
- The plasma concentrations of the metabolite VIA-3196-M1 were substantially lower than the parent compound. VIA-3196-M1 did not accumulate after repeated doses of VIA-3196 for 91 days.
- The target organ of toxicity was thyroid gland.
- The NOAEL in males for thyroid gland changes was considered to be 5 mg/kg/day due to significant decreases in total and free T4 at 15 and 45 mg/kg/day.
- The NOAEL in females was considered to be 45 mg/kg/day.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 100. Information, Study 0470DM72.001

Methods	Details
Dose and frequency of dosing	2.5, 5, 15, 45 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	VIA-3196 was dissolved in 2% klucel, 0.1% tween 80, 0.09% methylparaben, 0.01% propylparaben in purified water at concentrations of 0.5, 1, 3, or 9 mg/mL.
Species/strain	Dog/beagle
Number/sex/group	• 4 (main study groups) • 2 (4-week recovery groups)

Methods	Details
Age	6.5 to 7.5 months
Satellite groups/ unique design	For groups 1 to 4, the first day of dosing was in March 2012. Thereafter, the Applicant added group 5 (45 mg/kg/day) to the study with the first day of dosing in June 2012. The delayed addition of group 5 to the study created bias in the body weight data, because the mean body weight in group 5 on Day 1 of dosing was lower than in group 1 (control) on Day 1 of dosing.
Dosing solution analysis	All formulations met the acceptance criteria.

Source: Prepared by the nonclinical reviewer
Abbreviation: GLP, good laboratory practice; QD, once daily; VIA-3196, resmetirom

Table 101. Observations and Results, Study 0470DM72.001

Parameter	Major Findings
Mortality	None
Clinical signs	None
Body weight/food consumption	None
Ophthalmoscopy	None
Electrocardiogram	None
Hematology	A statistically significant decrease in proportional and absolute counts for large unstained cells (LUC) (up to 56.5% in females and 48.5% in males) occurred at all doses in females and at 2.5 and 45 mg/kg/day in males. This change was reversible.
Clinical chemistry	A significant and dose-dependent decrease in cholesterol levels was observed in both sexes (up to 54% in males and 50% in females) at all doses. A significant decrease in triglycerides (up to 47% in males and 46% in females) occurred at 15 and 45 mg/kg/day in males and at 15 mg/kg/day in females. The reductions in cholesterol and triglycerides were reversible and were attributed to the pharmacologic activity of the drug. VIA-3196 had no effects on total ALP or its isoforms.
Urinalysis	None
Gross pathology	None
Organ weights	None
Histopathology Adequate battery: Yes	None
T4, T3, and TSH	A significant decrease in total T4 (67.3%) occurred in males at 45 mg/kg/day. Free T4 was decreased in the 15 and 45 mg/kg/day males (59.9% and 73.1%, respectively). In females, nonsignificant decreases in total and free T4 occurred at 15 and 45 mg/kg/day. The decrease in total and free T4 was dose dependent and considered as drug related. No changes in TSH were observed.
Cardiac troponin I	None

Parameter	Major Findings
Toxicokinetics (TK)	Blood samples were collected on Days 1 and 91 at 0, 1, 2, 4, 8, 12, 16, and 24 hours postdose for analysis of VIA-3196 and the metabolites VIA-3196-M1 and VIA-3196-M2. Exposure to VIA-3196 (C_{max} and AUC) increased in a greater than dose-proportional manner on Days 1 and 91, with no sex-related difference in the TK parameters. Overall, no accumulation occurred after repeated doses, except in the 2.5 mg/kg/day females and the 5 mg/kg/day males. The plasma concentrations of the metabolite VIA-3196-M1 were substantially lower than the parent compound. VIA-3196-M1 did not accumulate with repeated dosing of VIA-3196 for 91 days. Toxicokinetic parameters were not assessed for VIA-3196-M2 due to very low and variable plasma concentrations after a single dose (Day 1) or repeated dosing (Day 91) of 45 mg/kg/day VIA-3196. No sex-related differences or apparent accumulation were noted. The toxicokinetic data are summarized in Table 102, Table 103, and Table 104.

Source: Prepared by the nonclinical reviewer
Abbreviations: AUC, area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; ALP, alkaline phosphatase; C_{max}, maximum plasma concentration; LUC, large unstained cells; M1, metabolite 1; M2, metabolite 2; T3, triiodothyronine; T4, thyroxine; TK, toxicokinetics; TSH, thyroid stimulating hormone; VIA-3196, resmetirom

Table 102. VIA-3196 (Parent Drug) TK Parameters in Male Dogs on Days 1 and 91 in a 3-Month Oral Toxicity Study

Day	Parameters	VIA-3196 Dosage mg/kg/day							
		Male							
		2.5		5		15		45	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	C_{max}, ng/mL	85.2	31.6	198	95.6	1,310	801	8,150	8,640
	T_{max}, h*	2.50 (1-4)	1.22	2.33 (2-4)	0.816	3.67 (2-8)	2.34	4.67 (4-8)	1.63
	$AUC_{(0-T)}$, ng·h/mL	469	101	1,230	690	8,870	6,800	46,600	42,100
	$AUC_{(0-24)}$, ng·h/mL	472	103	1,230	684	8,870	6,800	46,600	42,100
	$AUC_{(0-inf)}$, ng·h/mL	477	102	1,250	691	7,740	6,890	47,000	42,000
	$T_{1/2}$, h	3.51	0.843	3.29	1.60	3.19	0.728	3.77	1.63
	Kel (λ), 1/h	0.209	0.0601	0.245	0.0866	0.227	0.0524	0.208	0.0718
	C_{max} Ratio (M/F)	0.819	-	1.01	-	2.90	-	0.685	-
	$AUC_{(0-24)}$ Ratio (M/F)	0.935	-	0.939	-	2.55	-	0.690	-
91	C_{max}, ng/mL	139	78.2	650	611	2,460	2,770	8,720	10,600
	T_{max}, h*	2.00 (2-2)	0.00	2.00 (2-2)	0.00	1.83 (1-2)	0.408	3.50 (1-8)	2.51
	$AUC_{(0-T)}$, ng·h/mL	702	403	2,450	1,990	8,000	4,810	39,900	46,700
	$AUC_{(0-24)}$, ng·h/mL	702	403	2,450	1,990	8,000	4,810	39,900	46,700
	$T_{1/2}$, h	4.41	0.974	3.16	0.830	3.50	0.492	4.54	1.47
	Kel (λ), 1/h	0.164	0.0376	0.232	0.0610	0.202	0.0308	0.164	0.0423
	C_{max} Ratio (M/F)	0.545	-	1.98	-	1.81	-	0.661	-
	$AUC_{(0-24)}$ Ratio (M/F)	0.548	-	1.59	-	1.27	-	0.742	-
	C_{max} Ratio (Day 91/Day 1)	1.63	-	3.28	-	1.88	-	1.07	-
	$AUC_{(0-24)}$ Ratio (Day 91/Day 1)	1.49	-	1.99	-	0.902	-	0.856	-

Source: Applicant's report 0470DM72.001.
Abbreviations: AUC, area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel (λ), elimination rate constant; M, male; SD, standard deviation; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196, resmetirom

Table 103. VIA-3196 (Parent Drug) TK Parameters in Female Dogs on Days 1 and 91 in a 3-Month Oral Toxicity Study

Day	Parameters	VIA-3196 Dosage mg/kg/day							
		Female							
		2.5		5		15		45	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	C_{max}, ng/mL	104	60.3	197	73.5	452	104	11,900	13,300
	T_{max}, h*	1.67 (1-2)	0.516	6.00 (1-16)	6.42	2.50 (1-4)	1.22	4.33 (2-8)	1.97
	$AUC_{(0-T)}$, ng·h/mL	500	173	1,300	511	3,480	972	67,500	72,100
	$AUC_{(0-24)}$, ng·h/mL	505	169	1,310	506	3,480	972	67,500	72,100
	$AUC_{(0-inf)}$, ng·h/mL	519	173	1,580	742	3,560	993	68,000	72,300
	$T_{1/2}$, h	4.58	1.13	4.73	1.01	3.90	1.31	5.14	2.48
	Kel (λ), 1/h	0.161	0.0507	0.151	0.0349	0.196	0.0701	0.162	0.0706
	C_{max} Ratio (M/F)	-	-	-	-	-	-	-	-
	$AUC_{(0-24)}$ Ratio (M/F)	-	-	-	-	-	-	-	-
91	C_{max}, ng/mL	255	109	328	185	1,360	789	13,200	9,690
	T_{max}, h*	2.00 (2-2)	0.00	1.00 (1-2)	0.516	2.00 (1-4)	0.983	2.67 (2-4)	1.03
	$AUC_{(0-T)}$, ng·h/mL	1,280	476	1,540	576	6,280	4,470	53,800	39,000
	$AUC_{(0-24)}$, ng·h/mL	1,280	476	1,540	576	6,280	4,470	53,800	39,000
	$T_{1/2}$, h	5.08	2.91	3.34	0.649	5.52	2.33	5.16	3.47
	Kel (λ), 1/h	0.166	0.0660	0.215	0.0456	0.153	0.0795	0.185	0.0973
	C_{max} Ratio (M/F)	-	-	-	-	-	-	-	-
	$AUC_{(0-24)}$ Ratio (M/F)	-	-	-	-	-	-	-	-
			-		-		-		
	C_{max} Ratio (Day 91/Day 1)	2.45	-	1.66	-	3.01	-	1.11	-
	$AUC_{(0-24)}$ Ratio (Day 91/Day 1)	2.53	-	1.18	-	1.80	-	0.797	-

Source: Applicant's report 0470DM72.001.
* Expressed as median and range.
Abbreviations: AUC, area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel (λ), elimination rate constant; M, male; SD, standard deviation; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196, resmetirom

Table 104. VIA-3196-M1 (Metabolite) TK Parameters in Dogs on Days 1 and 91 in a 3-Month Oral Toxicity Study

Day	Parameters	VIA-3196-M1 Dosage mg/kg/day			
		45		45	
		Male		Female	
		Mean	SD	Mean	SD
1	C_{max}, ng/mL	83.6	98.0	118	132
	T_{max}, h*	6.00 (4-12)	3.35	5.67 (2-12)	3.67
	$AUC_{(0-T)}$, ng·h/mL	417	453	752	887
	$AUC_{(0-24)}$, ng·h/mL	552	519	893	914
	$AUC_{(0-inf)}$, ng·h/mL	350	380	1,120	1,200
	$T_{1/2}$, h	4.69	1.59	2.29	1.10
	Kel (λ), 1/h	0.163	0.0673	0.374	0.227
	C_{max} Ratio (M/F)	0.708		-	
	$AUC_{(0-24)}$ Ratio (M/F)	0.618		-	
91	C_{max}, ng/mL	71.0	112	105	83.8
	T_{max}, h*	3.67 (2-8)	2.34	3.67 (2-8)	2.34
	$AUC_{(0-T)}$, ng·h/mL	308	455	451	326
	$AUC_{(0-24)}$, ng·h/mL	313	453	453	326
	$T_{1/2}$, h	5.98	1.98	2.96	2.14
	Kel (λ), 1/h	0.125	0.0361	0.320	0.166
	C_{max} Ratio (M/F)	0.676	-	-	-
	$AUC_{(0-24)}$ Ratio (M/F)	0.691	-	-	-
	C_{max} Ratio (Day 91/Day 1)	0.849	-	0.890	-
	$AUC_{(0-24)}$ Ratio (Day 91/Day 1)	0.567	-	0.507	-

Source: Applicant's report 0470DM72.001.
* Expressed as median and range.
Abbreviations: AUC, area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel (λ), elimination rate constant; M, male; M1, metabolite 1; SD, standard deviation; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196, resmetirom

13.1.5.5. A 9-Month Oral Toxicity Study With MGL-3196 in Dogs With a 4-Week Recovery Period, Study 0472DM72.001

Key Study Findings

- MGL-3196 produced significant decreases in cholesterol at all doses (5 to 100 mg/kg/day) and in triglycerides at ≥15 mg/kg/day. These changes were attributed to the pharmacological activity of MLG-3196.
- MGL-3196 at 45 and 100 mg/kg/day produced a significant increase in ALT, with a significant increase in AST at 100 mg/kg/day.
- In males, MGL-3196 at 100 mg/kg/day produced significant increases in total ALP, liver ALP, and bone ALP.

- In females, MGL-3196 at 45 and 100 mg/kg/day produced significant increases in total ALP and liver ALP. There was a significant increase in bone ALP at ≥15 mg/kg/day.
- MGL-3196 produced significant decreases in total T3 (TT3), T4, and free T4 in a dose-dependent manner.
- The changes in clinical chemistry parameters and thyroid hormones (THs) were reversible.
- Drug-related histopathological findings included increased extramedullary hematopoiesis in liver at all doses, bile duct hyperplasia and bile stasis in liver at 100 mg/kg/day, and epithelial thickening of tongue associated with epithelial inflammation at ≥15 mg/kg/day (females). These changes were not reversible, with the exception of extramedullary hematopoiesis in liver.
- Systemic exposure to MGL-3196 and its metabolite (MGL-3196-M1) increased with dose level. Overall, the area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule (AUC_{0-24}) for MGL-3196-M1 was 0.4 to 2% of AUC_{0-24} values for MGL-3196.
- The target organs of toxicity were liver (bile duct), thyroid gland (based on changes in T3 and T4), and tongue.
- The NOAEL for thyroid was not identified due to the reduction in plasma levels of total and free T3 and T4 at all doses. The NOAEL for liver was considered to be 15 mg/kg/day due to the increase in ALT and ALP at ≥45 mg/kg/day and bile duct hyperplasia and bile stasis at 100 mg/kg/day. The NOAEL for the effects in tongue in females was considered to be 5 mg/kg/day, based on epithelia thickening at ≥15 mg/kg/day.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 105. Information, Study 0472DM72.001

Methods	Details
Dose and frequency of dosing	5, 15, 45, 100 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	MGL-3196 was dissolved in 2% klucel, 0.1% tween 80, 0.09% methylparaben, and 0.01% propylparaben in purified water at concentrations of 1, 3, 9, and 20 mg/mL.
Species/strain	Dog/beagle
Number/sex/group	• 4 (main study groups) • 2 (4-week recovery groups)

Methods	Details
Age	5.75 to 6.75 months
Satellite groups/ unique design	None
Dosing solution analysis	All formulations met the acceptance criteria, with the exception of formulations with nominal concentrations of 9 and 20 mg/mL used on Day 1 (actual concentrations were 82.4% and 83.9% of the nominal concentrations, respectively, which were below the acceptance criteria of 85 to 115%).

Source: Prepared by the nonclinical reviewer
Abbreviation: GLP, good laboratory practice; MGL-3196, resmetirom; QD, once daily

Table 106. Observations and Results, Study 0472DM72.001

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weight/food consumption	None
Ophthalmoscopy	None
Electrocardiogram	None
Hematology	None
Clinical chemistry	A significant and dose-dependent decrease in cholesterol levels (up to 57%) occurred at all doses was observed. A significant decrease in triglycerides (up to 46.1% in males and 53.9% in females) was observed at 15 mg/kg/day in males, and at 45 and 100 mg/kg/day in females. The reductions in cholesterol and triglycerides were reversible and were attributed to the pharmacologic activity of the drug. ALT was increased by up to 3.5-fold and 9.1-fold at 45 and 100 mg/kg/day, respectively. The increases in ALT were generally more pronounced in male dogs. In males at 100 mg/kg/day, significant increases in AST (49.1% to 53.2%) with no significant change in bilirubin occurred on Days 85 and 176. A mild increase in bilirubin (48%) with no significant change in AST was observed on Day 274. In males, significant increases in total ALP (up to 121%), liver ALP (up to 7.4-fold), and bone ALP (81%) were observed at 100 mg/kg/day. In females, significant increases in total ALP (up to 3.4-fold) and liver ALP (up to 22.6-fold) occurred at 45 and 100 mg/kg/day. A significant increase in bone ALP was observed at 15, 45, and 100 mg/kg/day (up to 3.9-fold). Overall, the changes in ALP were dose- and duration-dependent. No changes in intestinal ALP were observed. The changes in ALT, AST, and ALP were drug related and were completely reversible. Significant increases (14 to 19%) in globulin, associated with significant decreases (16 to 18%) in albumin/globulin ratio (A/G) occurred in the 100 mg/kg/day males. The changes in globulin and albumin/globulin ratio were reversible.
Urinalysis	A statistically significant reduction in specific gravity (1.02, as compared to 1.04 in the control group) occurred in females in the 100 mg/kg/day group. The change was reversible.

Parameters	Major Findings
Gross pathology	Multiple adhesions of the lungs to the diaphragm, a firm liver surface, and discolored multiple areas on all liver lobes were observed in one male in the 100 mg/kg/day recovery group. The gross changes in liver were correlated with bile duct hyperplasia and bile stasis. This dog had the highest level of liver ALP during the treatment period. Liver ALP in this animal was 5 times the control value at the end of the recovery period. In addition, this dog had the highest exposure to MGL-3196 among all animals on Days 89 and 272, and the second highest exposure on Day 180.
Organ weights	A significant decrease in thyroid/parathyroid weight relative to body weight was observed at 45 and 100 mg/kg/day (35.2% and 28.6%, respectively). The change was not reversible.
Histopathology Adequate battery: Yes	Drug-related microscopic findings were observed in liver in both sexes, including increased extramedullary hematopoiesis at all doses, bile duct hyperplasia, and bile stasis at 100 mg/kg/day (three of four males and two out of four females). Minimal to mild dorsal and ventral epithelial thickening of tongue associated with minimal neutrophilic inflammation in females occurred at ≥15 mg/kg/day.
Cardiac troponin I	None
T3, T4, TSH	A significant decrease in free T3 (up to 26.6% in males and 40.5% in females) occurred at 45 and 100 mg/kg/day on Day 176. Significant decreases in total T3 (up to 50.3%), total T4 (up to 80%), and free T4 (up to 90.9%) occurred in males at all doses. A significant decrease in total T4 (up to 76%) was observed at ≥45 mg/kg/day, with a significant decrease in free T4 (up to 80.4%) at ≥15 mg/kg/day in females. MGL-3196 had no effects on TSH. All changes were reversible.
Toxicokinetics (TK)	Blood samples were collected on Days 1, 89, 180, and 272 at 0, 1, 2, 4, 8, 12, 16, and 24 hours postdose for analysis of MGL-3196 and its metabolite MGL-3196-M1. Systemic exposure (mean C_{max} and AUC_{0-24}) to MGL-3196 increased with dose level. The increase in systemic exposure (mean AUC_{0-24}) was greater than dose-proportional from 5 to 100 mg/kg/day. The TK data for MGL-3916-M1 is limited to the 45 and 100 mg/kg/day groups due to extremely low plasma concentrations of this metabolite. The AUC_{0-24} of MGL-3196-M1 was 0.4% to 2% of the AUC_{0-24} values for MGL-3196. No sex-related differences in MGL-3196 and MGL-3196-M1 exposure were observed. No accumulation of either the parent drug or the metabolite occurred after repeated dosing. TK data for MGL-3196 and MGL-3196-M1 are summarized in the Table 107, Table 108, Table 109, and Table 110.

Source: Prepared by the nonclinical reviewer
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hr) using the linear trapezoidal rule; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C_{max}, maximum plasma concentration; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; MGL-3196, resmetirom; M1, metabolite 1; TK, toxicokinetics

Table 107. Toxicokinetic Parameters of MGL-3196 (Parent Drug) in Dogs on Days 1, 89, and 180 in a 9-Month Oral Toxicity Study

TK Parameter	MGL-3196 Dose, mg/kg/day							
	Male				Female			
	5	15	45	100	5	15	45	100
Day 1								
C_{max}, ng/mL	267	1,520	2,920	31,100	327	782	14,400	19,900
T_{max}, h	1.50	3.33	5.67	5.33	2.00	2.67	5.67	5.33
$AUC_{(0-T)}$, ng·h/mL	1,940	8,190	22,300	212,000	2,010	6,020	129,000	136,000
$AUC_{(0-24)}$, ng·h/mL	1,940	8,190	22,300	212,000	2,010	6,020	129,000	136,000
$AUC_{(0-inf)}$, ng·h/mL	1,960	8,300	16,800	212,000	1,340	6,070	129,000	119,000
$T_{1/2}$, h	2.83	4.64	3.69	2.21	3.14	2.69	3.04	2.48
K_{el}, 1/h	0.252	0.186	0.235	0.349	0.233	0.274	0.259	0.323
C_{max} Ratio (M/F)	0.817	1.94	0.203	1.56	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	0.965	1.36	0.173	1.56	-	-	-	-
Day 89								
C_{max}, ng/mL	557	1,670	9,400	50,000	601	2,950	10,500	39,900
T_{max}, h	1.83	2.33	2.67	2.67	1.33	2.00	2.33	3.33
$AUC_{(0-T)}$, ng·h/mL	2,260	7,840	38,000	338,000	2,690	12,900	42,500	191,000
$AUC_{(0-24)}$, ng·h/mL	2,270	7,840	38,000	338,000	2,700	12,900	42,500	191,000
$T_{1/2}$, h	3.65	3.19	3.41	4.59	3.45	4.27	3.26	3.21
K_{el}, 1/h	0.283	0.227	0.217	0.167	0.217	0.175	0.218	0.239
C_{max} Ratio (M/F)	0.927	0.566	0.895	1.25	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	0.841	0.608	0.894	1.77	-	-	-	-
C_{max} Ratio (Day 89/Day 1)	2.09	1.10	3.22	1.61	1.84	3.77	0.729	2.01
$AUC_{(0-24)}$ Ratio (Day 89/Day 1)	1.17	0.957	1.70	1.59	1.34	2.14	0.329	1.40
Day 180								
C_{max}, ng/mL	526	1,710	15,400	32,500	828	1,780	9,230	46,900
T_{max}, h	2.00	2.33	3.00	2.67	1.83	2.17	2.33	2.67
$AUC_{(0-T)}$, ng·h/mL	2,350	7,350	63,300	168,000	2,960	9,920	46,000	226,000
$AUC_{(0-24)}$, ng·h/mL	2,350	7,350	63,300	168,000	2,960	9,920	46,000	226,000
$T_{1/2}$, h	3.28	3.29	4.40	3.67	3.18	5.54	4.02	3.78
K_{el}, 1/h	0.276	0.221	0.182	0.239	0.236	0.207	0.177	0.205
C_{max} Ratio (M/F)	0.635	0.961	1.67	0.693	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	0.794	0.741	1.38	0.743	-	-	-	-
C_{max} Ratio (Day 180/Day 1)	1.97	1.13	5.27	1.05	2.53	2.28	0.641	2.36
$AUC_{(0-24)}$ Ratio (Day 180/Day 1)	1.21	0.897	2.84	0.792	1.47	1.65	0.357	1.66
C_{max} Ratio (Day 180/Day 89)	0.944	1.02	1.64	0.650	1.38	0.603	0.879	1.18
$AUC_{(0-24)}$ Ratio (Day 180/Day 89)	1.04	0.938	1.67	0.497	1.10	0.769	1.08	1.18

Source: Applicant's report 0472DM72.001.

Abbreviations: AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; MGL-3196, resmetirom; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%

Table 108. Toxicokinetic Parameters of MGL-3196 (Parent Drug) in Dogs on Day 272 in a 9-Month Oral Toxicity Study

TK Parameter	MGL-3196 Dose, mg/kg/day							
	Male				Female			
	5	15	45	100	5	15	45	100
Day 272								
C_{max}, ng/mL	320	3,280	9,130	64,500	722	3,490	20,200	49,400
T_{max}, h	1.50	2.33	2.33	3.67	2.00	2.00	2.83	3.67
$AUC_{(0-T)}$, ng·h/mL	1,540	11,000	31,300	330,000	3,020	11,600	77,600	195,000
$AUC_{(0-24)}$, ng·h/mL	1,540	11,000	31,300	330,000	3,020	11,600	77,600	195,000
$T_{1/2}$, h	4.64	3.76	4.42	3.38	3.69	4.83	2.99	3.92
K_{el}, 1/h	0.173	0.194	0.197	0.234	0.204	0.149	0.233	0.199
C_{max} Ratio (M/F)	0.443	0.940	0.452	1.31	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)	0.510	0.948	0.403	1.69	-	-	-	-
C_{max} Ratio (Day 272/Day 1)	1.20	2.16	3.13	2.07	2.21	4.46	1.40	2.48
$AUC_{(0-24)}$ Ratio (Day 272/Day 1)	0.794	1.34	1.40	1.56	1.50	1.93	0.157	0.363
C_{max} Ratio (Day 272/Day 180)	0.608	1.92	0.593	1.98	0.872	1.96	2.19	1.05
$AUC_{(0-24)}$ Ratio (Day 272/Day 180)	0.655	1.50	0.494	1.96	1.02	1.17	1.69	0.863

Source: Applicant's report 0472DM72.001.
Abbreviations: AUC_{0-T} (AUC_{0-24}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; MGL-3196, resmetirom; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%

Table 109. Toxicokinetic Parameters of MGL-3196-M1 (Metabolite) in Dogs

TK Parameter	MGL-3196 Dose, mg/kg/day							
	Male				Female			
	5	15	45	100	5	15	45	100
Day 1								
C_{max}, ng/mL	0.882	12.4	36.4	560	1.56	4.64	243	315
$\%C_{max}$ MGL-3196	0.296	0.624	1.02	1.64	0.460	0.624	1.40	1.46
T_{max}, h	4.25	3.33	6.33	5.33	4.67	4.33	5.67	5.33
$AUC_{(0-T)}$, ng·h/mL	5.09	60.0	233	3,810	12.4	36.4	2,180	2,150
$AUC_{(0-24)}$, ng·h/mL*	NC	183	223	3,490	60.7	73.7	2,580	2,570
$\%AUC_{(0-24)}$ MGL-3196*	NC	1.02	0.968	1.61	1.12	1.84	1.52	1.53
$AUC_{(0-inf)}$, ng·h/mL	NC	183	294	3,500	NC	74.7	2,590	2,570
$T_{1/2}$, h	NC	2.03	1.50	2.47	NC	3.58	2.94	1.65
K_{el}, 1/h	NC	0.341	0.462	0.352	NC	0.194	0.315	0.442
C_{max} Ratio (M/F)	0.565	2.67	0.150	1.78	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)*	NC	NC	0.0864	1.36	-	-	-	-
Day 89								
C_{max}, ng/mL	1.93	8.69	48.1	473	2.37	24.1	54.3	204
$\%C_{max}$ MGL-3196	0.334	0.482	0.509	0.704	0.462	0.438	0.511	0.445
T_{max}, h	2.50	3.33	3.00	2.67	2.83	2.00	3.50	3.67
$AUC_{(0-T)}$, ng·h/mL	5.42	39.5	219	3,560	10.9	174	256	1,040
$AUC_{(0-24)}$, ng·h/mL*	NC	48.9	253	3,560	NC	219	299	1,250
$\%AUC_{(0-24)}$ MGL-3196*	NC	0.591	0.623	0.826	NC	0.758	0.668	0.509
$T_{1/2}$, h	NC	8.02	4.42	4.72	NC	4.06	3.82	5.64
K_{el}, 1/h	NC	0.0864	0.168	0.170	NC	0.180	0.209	0.137
C_{max} Ratio (M/F)	0.814	0.361	0.886	2.32	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)*	NC	NC	0.846	2.85	-	-	-	-
C_{max} Ratio (Day 89/Day 1)	2.19	0.701	1.32	0.845	1.52	5.19	0.223	0.648
$AUC_{(0-24)}$ Ratio (Day 89/Day 1)*	NC	NC	1.13	1.02	NC	NC	0.116	0.486
Day 180								
C_{max}, ng/mL	1.88	6.91	104	207	4.40	13.6	65.7	270
$\%C_{max}$ MGL-3196	0.371	0.395	0.632	0.702	0.404	0.610	0.637	0.537
T_{max}, h	2.17	2.67	2.67	3.00	3.17	6.17	2.33	3.00
$AUC_{(0-T)}$, ng·h/mL	7.18	32.6	438	1,260	20.0	76.3	320	1,450
$AUC_{(0-24)}$, ng·h/mL*	NC	44.0	439	1,260	83.5	72.9	322	1,450
$\%AUC_{(0-24)}$ MGL-3196*	NC	0.603	0.639	0.822	1.37	0.760	0.672	0.598
$T_{1/2}$, h	NC	4.59	4.47	4.25	6.29	11.9	4.42	3.21
K_{el}, 1/h	NC	0.179	0.204	0.200	0.110	0.0587	0.163	0.285
C_{max} Ratio (M/F)	0.427	0.508	1.58	0.767	-	-	-	-
$AUC_{(0-24)}$ Ratio (M/F)*	NC	NC	1.36	0.869	-	-	-	-
C_{max} Ratio (Day 180/Day 1)	2.13	0.557	2.86	0.370	2.82	2.93	0.270	0.857
$AUC_{(0-24)}$ Ratio (Day 180/Day 1)*	NC	NC	1.97	0.361	NC	NC	0.125	0.564
C_{max} Ratio (Day 180/Day 89)	0.974	0.795	2.16	0.438	1.86	0.564	1.21	1.32
$AUC_{(0-24)}$ Ratio (Day 180/Day 89)*	NC	NC	1.74	0.354	NC	NC	1.08	1.16

Source: Applicant's report 0472DM72.001.

* For the 5 and 15 mg/kg/day doses of MGL-3196, the concentration of MGL-3196-M1 was low and many $AUC_{(0-24)}$ of MGL-3196-M1 could not be calculated. As a result, many of the $AUC_{(0-24)}$ values reported in this table are based on values for only 1 or a few animals. For this reason, the MGL-3196-M1 $AUC_{(0-24)}$ discussion is limited to a discussion of the 45 and 100 mg/kg/day doses of MGL-3196.

Abbreviations: AUC_{0-T} (AUC_{0-24}; AUC_{0-inf}), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; MGL-3196, resmetirom; M1, metabolite 1; NC, not calculated; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%

Table 110. Toxicokinetic Parameters of MGL-3196-M1 (Metabolite) in Dogs (Continued)

TK Parameter	MGL-3196 Dose, mg/kg/day							
	Male				Female			
	5	15	45	100	5	15	45	100
Day 272								
C_{max}, ng/mL	1.05	27.7	58.5	527	3.09	36.0	170	334
%C_{max} MGL-3196	0.372	0.658	0.597	0.758	0.429	0.619	0.743	0.693
T_{max}, h	4.83	2.67	2.33	4.00	2.50	2.33	3.33	3.67
$AUC_{(0\text{-}T)}$, ng·h/mL	4.59	80.9	215	2,970	17.0	132	769	1,330
$AUC_{(0\text{-}24)}$, ng·h/mL*	NC	108	280	2,970	52.1	134	912	1,330
%$AUC_{(0\text{-}24)}$ MGL-3196*	NC	0.836	0.747	0.827	0.684	0.856	0.934	0.691
$T_{1/2}$, h	NC	4.22	5.27	4.20	NC	5.43	2.95	4.59
K_{el}, 1/h	NC	0.178	0.176	0.168	NC	0.133	0.241	0.181
C_{max} Ratio (M/F)	0.340	0.769	0.344	1.58	-	-	-	-
$AUC_{(0\text{-}24)}$ Ratio (M/F)*	NC	NC	0.307	2.23	-	-	-	-
C_{max} Ratio (Day 272/Day 1)	1.19	2.23	1.61	0.941	1.98	7.76	0.700	1.06
$AUC_{(0\text{-}24)}$ Ratio (Day 272/Day 1)*	NC	NC	1.26	0.851	NC	NC	0.353	0.518
C_{max} Ratio (Day 272/Day 180)	0.559	4.01	0.563	2.55	0.702	2.65	2.59	1.24
$AUC_{(0\text{-}24)}$ Ratio (Day 272/Day 180)*	NC	NC	0.638	2.36	NC	NC	2.83	0.917

Source: Applicant's report 0472DM72.001.

* For the 5 and 15 mg/kg/day doses of MGL-3196, the concentration of MGL-3196-M1 was low and many $AUC_{(0\text{-}24)}$ of MGL-3196-M1 could not be calculated. As a result, many of the $AUC_{(0\text{-}24)}$ values reported in this table are based on values for only one or a few animals. For this reason, the MGL-3196-M1 $AUC_{(0\text{-}24)}$ discussion is limited to a discussion of the 45 and 100 mg/kg/day doses of MGL-3196

Abbreviations: $AUC_{0\text{-}T}$ ($AUC_{0\text{-}24}$), area under the curve from time 0 to the last measurable concentration using the linear trapezoidal rule; C_{max}, maximum plasma concentration; F, female; Kel, elimination rate constant; M, male; MGL-3196, resmetirom; NC, not calculated since the $AUC_{(0\text{ to }24)}$ was not calculated for Days 1, 180, and 272; TK, toxicokinetics; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%

13.1.6. General Toxicology: Additional Studies

13.1.6.1. MGL-3623: A 28-Day Oral Range Finding Toxicity Study in CbyB6F1-Tg(HRAS)2Jic Wild Type [rasH2] Transgenic Mice, Study 3196-18-009 ((b) (4) No. 2835-001)

In the 28-day range-finding study in RasH2 mice, MGL-3623 (disproportionate human metabolite of resmetirom) was tested at oral doses of 20, 100, 500, and 1500 mg/kg/day, administered by gavage. No deaths, clinical signs, or significant adverse effects on weight gain were observed. A test article-related decrease in leukocyte count, platelets, and lymphocytes was noted in males at 500 and 1500 mg/kg/day, with statistically significant decreases in leukocytes and lymphocytes at 1500 mg/kg/day. An increase in red cell distribution width percent occurred at all doses in males. Spleen weights were decreased in both sexes at 100, 500, and 1500 mg/kg/day. Test article-related increases in ALP, AST, and ALT were noted in males at 100, 500, and 1500 mg/kg/day. In females, a treatment-related decrease in ALP occurred at 500 and 1500 mg/kg, and an increase in ALT was noted at 100, 500, and 1500 mg/kg. Moderate centrilobular hepatocellular hypertrophy occurred in 5 out of 10 males at 500 mg/kg and 7 out of 10 males at 1500 mg/kg, and minimal centrilobular hypertrophy occurred in 2 out of 10 females at 1500 mg/kg. The maximum tolerated dose was considered to be 1500 mg/kg/day.

13.1.6.2. A 90-Day Repeat-Dose Oral Range-Finding Toxicity Study of MGL-3196 M1 in Mice With a 4-Week Recovery, Study 3196-18-001

In the 90-day oral dose range-finding study, CD-1 mice were treated with 0, 3, 30, or 100 mg/kg/day MGL-3623 (disproportionate human metabolite of resmetirom). Statistically significant decreases in BW were observed in males in all treatment groups from Day 15 through study termination. A statistically significant decrease in absolute liver weight was noted in males at 3 and 100 mg/kg/day, which was considered as test article related. All doses produced a dose-dependent decrease in TSH levels, an increase in TT3 levels, and a decrease in total T4 levels (significant in males only). The NOAEL was considered to be 30 mg/kg/day in males, based on liver necrosis (2 out of 10 males) and decreased BW at 100 mg/kg/day. The NOAEL in females was 100 mg/kg/day.

13.1.6.3. RO4923659-000 (THRA): A 4-Week Oral Toxicity and Toxicokinetic Study in Rats Followed by a 4-Week Recovery Period, Studies 10234 or 1026085

In this 4-week oral dosing study, Sprague Dawley rats were treated with 0, 3, 30, 100, or 300 mg/kg/day RO4923659-000 (resmetirom). The test-article at doses ≥30 mg/kg produced increases in mean BW in both sexes, bone formation in the sternum and femur (not reversible at ≥100 mg/kg), heart weight (not reversible), platelets, reticulocytes, and liver enzymes, with increased liver weight and necrosis/apoptosis, hypertrophy, and infiltration at ≥100 mg/kg. There were decreases in total protein, albumin, globulin, HGB, and RBCs, and increases in phosphorus and potassium. Kidney weight was increased, with corresponding pathology of hyaline droplets, dilatation, or mineralization at ≥30 mg/kg/day. These changes were not completely reversible.

The test-article produced a dose-dependent decrease in T4/T3/TSH associated with thyroid atrophy of follicular epithelium at ≥30 mg/kg. Systemic exposure to the test-article (AUC and C_{max}) increased in a less than dose-proportional manner between doses of 3 to 30 mg/kg and was approximately dose-proportional from 30 to 300 mg/kg. The low observed adverse effect level was close to 3 mg/kg/day due to the significant toxicity observed at 30 mg/kg/day and the less than dose-proportional increase in exposure observed between 3 and 30 mg/kg (3 to 5 times AUC and 4 to 5 times C_{max}).

13.1.6.4. RO4923659-000 (THRA): A 4-Week Oral (Intubation) Toxicity and Toxicokinetic Study in Dogs Followed by a 4-Week Recovery Period, Studies 10339 or 1028363

In the 4-week oral dose study, beagle dogs were treated with 0, 5, 20, or 50 mg/kg/day RO4923659-000 (resmetirom). During the first week of treatment, emesis was observed at all doses in males and at 20 and 50 mg/kg/day in females. Soft feces, mucoid feces, and diarrhea were noted in the 20 and 50 mg/kg/day animals during the first few days. Inconsistent and non-dose dependent changes in ECG parameters were observed, such as a decrease in heart rate and an increase in RR interval. There was a non-dose dependent increase in heart weight (19 to 32% relative to brain weight) following recovery, but it was also noted that heart weight in the

recovery control animals was slightly lower than that observed for the main study controls at Day 28. No microscopic changes were correlated with the increase in heart weight. ALT was increased at ≥5 mg/kg in males and 50 mg/kg in females. ALP was increased at 50 mg/kg. Histopathologic examination showed bile duct proliferation and capsular fibrosis in 2 out of 3 males at 50 mg/kg/day and pigment deposits at doses ≥5 mg/kg. Decreases in TSH and T4 (total and free) occurred at ≥5 mg/kg. TT3 was reduced at 50 mg/kg. During recovery, mononuclear inflammation was present in the kidney. Mononuclear infiltration was also present in the brain in 1 out of 3 high-dose males and in 1 out of 2 recovery males. Gliosis was noted in 1 out of 2 recovery males at ≥20 mg/kg. Exposure increased with dose in a greater than dose-proportional manner in both sexes between 5 and 50 mg/kg. The NOAEL was 5 mg/kg/day based on moderate reductions in T4 and TSH as well as ALT increases in males.

13.1.7. Genetic Toxicology

Table 111. Genetic Toxicology

Study/Study No.	Key Study Findings
Bacterial Reverse Mutation Test (Ames test) (Study 2363M07) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *S. Typhimurium* TA1535, TA97, TA98, TA100, TA102. Concentrations: 0 (DMSO), 50, 158, 500, 1580, and 5000 µg/plate ±S9. Treatment duration: 2 days at 37º C. Result: RO4923659 did not induce any dose-related increase in the number of revertant colonies/plate in any of the five tester strains, in the presence or absence of S9. RO4923659 was not mutagenic at doses up to 5000 µg.
Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes (Study 2346M07) • GLP compliance: Yes • Study is valid: Yes	Maximum concentrations tested: 350 µg/mL for 3 hours ± S9 metabolic activation and 50 µg/mL for 20 hours (-S9). Result: RO4923659 did not induce chromosome aberrations in cultured human peripheral blood lymphocytes under these assay conditions.
Results of the In Vitro Micronucleus Test (MNT) With RO4923659-000 Using a Microscale Screening Protocol With L5178Y tk+/- Mouse Lymphoma Cells (Study 2057M04) • GLP compliance: No • Study is valid: Yes	Maximum concentrations tested: 110 µg/mL for 24 hours without S9 metabolic activation and 250 µg/mL for 3 hours with S9 metabolic activation. Result: RO4923659 did not produce clastogenic or aneugenic activity in the presence or absence of metabolic activation with S9.
In Vivo Rat Bone Marrow Micronucleus Assay With MGL-3196 (Study (b) (4)-891007) • GLP compliance: Yes • Study is valid: Yes	Species/Strain: Rats/Crl:CD(SD). Doses: 250, 600, and 2000 mg/kg/day for 3 days. Results: MGL-3196 did not produce an increase in the proportion of micronucleated polychromatic erythrocytes (%MN-PCEs). MGL-3196 had no effect on the ratio of polychromatic to total erythrocytes (PCE:TE ratio). Therefore, MGL-3196 was not clastogenic under the testing conditions.

Study/Study No.	Key Study Findings
Genetic Toxicology of Impurities	
(b) (4) Bacterial Reverse Mutation Assay (Study 3196-18-002) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and *Escherichia coli* strain (WP2 uvrA). Concentrations: 2.5, 5.0, 10, 25, 50, 100, 250, and 500 µg/plate ± S9. Treatment duration: 2 days at 36 to 38°C. Result: The (b) (4) was negative for mutagenicity under the test conditions.
(b) (4) Bacterial Reverse Mutation Assay (Study 3196-18-007) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and *Escherichia coli* strain (WP2 uvrA). Concentrations: 100, 250, 500, 1000, 2500, and 5000 µg/plate±S9. Treatment duration: 2 days at 36 to 38°C. Result: The impurity (b) (4) was negative for mutagenicity under the test conditions.
(b) (4) Bacterial Reverse Mutation Assay (Study 3196-18-008) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and *Escherichia coli* strain (WP2 uvrA). Concentrations: 25, 50, 100, 250, 500, 1000, and 2500 µg/plate±S9. Treatment duration: 2 days at 36 to 38°C. Result: The impurity (b) (4) was negative for mutagenicity under the test conditions.
(b) (4) Bacterial Reverse Mutation Assay (Study 3196-21-005) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and *Escherichia coli* strain (WP2 uvrA). Concentrations: 2.3, 6.9, 20.6, 61.7, 185, 556, 1667, and 5000 µg/plate±S9. Treatment duration: 2 days at 36 to 38°C Result: The impurity (b) (4) was negative for mutagenicity under the test conditions.
(b) (4) Bacterial Reverse Mutation Assay (Study 3196-21-001) • GLP compliance: Yes • Study is valid: Yes • (b) (4)	Tester strains: *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and *Escherichia coli* strain (WP2 uvrA). Concentrations: 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate±S9. Treatment duration: 2 days at 36 to 38°C. Result: (b) (4) produced increases in the number of revertant colonies in the *S. typhimurium* strain TA1535, with and without metabolic activation. Therefore, (b) (4) was positive for mutagenicity. (b) (4) is not a specified impurity in the drug substance or drug product. However, the CMC review team for drug substance agrees with the Applicant's justification for not specifying (b) (4) (i.e., (b) (4) was not detected at (b) (4) ppm in six resmetirom batches using UPLC-MS; (b) (4) ppm is below (b) (4) % of the TTC [15 ppm]).
3196-16-007: (b) (4) Bacterial Reverse Mutation Assay in Salmonella typhimurium (Study 3196-16-007) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *S. Typhimurium* strains TA1537, TA98, TA100, and TA1535. Concentrations: 2.5, 5, 10, 25, 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate±S9. Treatment duration: 2 days at 36 to 38°C. Result: (b) (4) was not mutagenic under the testing conditions.

Study/Study No.	Key Study Findings
Genetic Toxicology of Metabolite	
M1 Metabolite Bacterial Reverse Mutation Assay in Salmonella typhimurium (Study 3196-16-008) • GLP compliance: Yes • Study is valid: Yes	Tester strains: *Salmonella typhimurium* TA1537, TA98, TA100, TA1535, and TA102. Concentrations: 100, 250, 500, 1000, 2500, and 5000 µg/plate±S9. Treatment duration: 2 days at 36 to 38°C. Result: The M1 metabolite (MGL-3623) was not mutagenic under the testing conditions.
M1 Metabolite In Vitro Micronucleus Assay in TK6 Cells (Study 3196-17-004) • GLP compliance: Yes • Study is valid: Yes	Maximum concentrations tested: 350 µg/mL for 27 hours without S9 metabolic activation and 460 µg/mL for 4 hours with and without S9 metabolic activation. Result: The metabolite M1 (MGL-3623) was considered positive for inducing micronuclei in TK6 cells in the 4-hr treatment with metabolic activation. Therefore, the potential clastogenicity of M1 was further evaluated in an in vivo micronucleus study (Study 3196-17-006). However, based on comments in ICH guidance S2(R1) (Note 9) for in vitro cytogenetic assays, the relevance of the positive finding in the current study is uncertain because the increase in micronuclei was limited to a single concentration with cytotoxicity exceeding 50% (i.e., 59% growth inhibition was observed).
An In Vivo Micronucleus Assay of MGL-3623 by Oral Gavage in Sprague Dawley Rats (Study 3196-17-006) • GLP compliance: Yes • Study is valid: Yes	Species/strain: Rats/Crl:CD(SD). Doses: 250, 800, 2000 mg/kg/day for 2 days. Results: MGL-3623 did not produce statistically significant or dose-dependent increases in the proportion of micronucleated polychromatic erythrocytes (%MN-PCEs) in male rats. No bone marrow cytotoxicity was observed at any dose level. Therefore, MGL-3623 was negative for clastogenic activity and/or disruption of the mitotic apparatus under the conditions of this assay.

Source: Prepared by nonclinical reviewer
Abbreviations: Crl:CD(SD), Charles River Laboratories caesarean-derived Sprague Dawley rat; (b) (4); DMSO, dimethyl sulfoxide; GLP, good laboratory practice; ICH, International Council for Harmonisation; MN-PCEs, micronucleated polychromatic erythrocytes; MNT, micronucleus test; M1, metabolite 1; RO4923659, resmetirom; TK6, thymidine kinase 6; TTC, threshold of toxicological concern; UPLC-MS, ultra-performance liquid chromatography-mass spectrometry

13.1.8. Carcinogenicity

13.1.8.1. A 2-Year Oral Carcinogenicity Study of MGL-3196 in Sprague-Dawley Rats, Study 3196-18-005

In the 2-year oral carcinogenicity study in Sprague-Dawley rats, animals (65/sex/group) were administered MGL-3196 via oral gavage at dose levels of 0 (vehicle), 0 (0.9% NaCl), 1, 6, or 30 mg/kg/day. The vehicle was 2% Klucel LF, 0.1% tween 80, 0.09% methylparaben, 0.01% propylparaben in purified water. Statistical analysis was based on comparison of the treatment groups to the vehicle control group. Males and females at 30 mg/kg/day were sacrificed prior to the scheduled sacrifice date on Day 604/605 (Week 86) and Day 647/648 (Week 92), respectively, due to the decline in group survival to <25%. Death rates in males and females at 30 mg/kg/day were significantly higher compared to the vehicle control group, and there was a significant dose-response relationship for mortality in both sexes compared to the vehicle control group. BWs were increased in a dose-dependent manner in both sexes, compared to the vehicle control group. The male groups showed a positive dose response for benign fibroadenoma in the mammary gland that was statistically significant at the adjusted level of significance for rare tumors, compared to the vehicle control group. The pairwise comparison of the incidence rate of benign fibroadenoma in the mammary gland was statistically significant in males at 30 mg/kg/day, as shown in Table 112.

Executive Carcinogenicity Assessment Committee conclusions:

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee also concluded that the benign fibroadenoma in the mammary gland was statistically significant and drug related in males at the high dose of 30 mg/kg/day.

Table 112. Statistical Analysis of Benign Fibroadenoma in Rats

Sex	Organ Name	Tumor Name	0 mg/kg/Day V Control P-Trend	1 mg/kg/Day Low (L) P-VC vs. L	6 mg/kg/Day Mid (M) P-VC vs. M	30 mg/kg/Day High (H) P-VC vs. H	0 mg/kg/Day Saline C (SC) P-VC vs. SC
Male	Gland, mammary	Fibroadenoma, benign	0/63 (39) 0.0021*	0/60 (38) NC	2/62 (38) 0.2403	4/61 (27) 0.0244**	0/62 (36) NC

Source: FDA statistical reviewer.
Note: Tumor incidence shown as X/ZZ (YY): X=number of tumor-bearing animals; ZZ=unweighted total number of animals observed; YY=mortality weighted total number of animals.
* Indicates statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.
** Indicates statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.
Abbreviations: P, p value; VC, vehicle control; SC, saline control, NC, not calculable

13.1.8.2. CD-1 Mouse Carcinogenicity Study

In the 2-year oral carcinogenicity study in CD-1 mice, animals (65/sex/group) were administered MGL-3196 by oral gavage at dose levels of 0 (vehicle), 0 (0.9% NaCl), 3, 30, or 100 mg/kg/day. The vehicle was 2% Klucel LF, 0.1% tween 80, 0.09% methylparaben, and 0.01% propylparaben in purified water. Statistical analysis was based on comparison of the treatment groups to the vehicle control group. Males at 100 mg/kg/day were sacrificed prior to the scheduled sacrifice date on Day 685/686 (Week 98), when group survival declined to <25%. Terminal sacrifice of females in all groups occurred on Days 699/700 (Week 100) due to decline of survival to <25%

in the vehicle control females. A statistically significant dose-response relationship in mortality was observed in males compared to the vehicle control group, and the mortality rate was significantly higher in males at 100 mg/kg/day. Increase in BW was observed in males at all doses and in females at 100 mg/kg/day, compared to the vehicle control group. A statistically significant positive dose response was observed for leiomyoma (rare tumor, benign) or the combination of leiomyoma and leiomyosarcoma (malignant) in the uterus alone and in the uterus and cervix combined, compared to the vehicle control group. The incident rates of the combination of leiomyoma and leiomyosarcoma in the uterus and in uterus plus cervix were significantly higher, at 100 mg/kg/day, compared to the vehicle control group. However, the tumor findings in the cervix were limited to a single incidence of leiomyosarcoma at 3 mg/kg/day (1 out of 65 females).

Executive Carcinogenicity Assessment Committee conclusions:

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that the combined incidence of leiomyoma (benign) and leiomyosarcoma (malignant) in uterus and in uterus and cervix combined was statistically significant and drug-related in females at the high dose of 100 mg/kg/day.

Table 113. Statistical Analysis of Leiomyoma and Leiomyosarcoma in Mice

Sex	Organ Name	Tumor Name	0 mg/kg/Day Vehicle C P-Trend	3 mg/kg/Day Low (L) P-VC vs. L	30 mg/kg/Day Mid (M) P-VC vs. M	100 mg/kg/Day High (H) P-VC vs. H	0 mg/kg/Day Saline (SC) P-VC vs. SC
Female	Uterus	Leiomyoma, benign	0/65 (38)	2/65 (45)	0/65 (40)	4/65 (41)	0/65 (41)
			0.0248*	0.2909	NC	0.0674	NC
		C_leiomyoma/ Leiomyosarcoma	0/65 (38)	2/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
			0.0086*	0.2909	NC	0.0354**	NC
	Uterus/ Cervix	C_leiomyoma/ Leiomyosarcoma	0/65 (38)	3/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
			0.0213*	0.1544	NC	0.0354**	NC

Source: FDA statistical reviewer.
Note: Tumor incidence shown as X/ZZ (YY): X=number of tumor-bearing animals; ZZ=unweighted total number of animals observed; YY=mortality weighted total number of animals.
* Indicates statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.
** Indicates statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.
Abbreviations: P, p value; VC, vehicle control; SC, saline control, NC, not calculable

13.1.8.3. A GLP 26-Week Study of MGL-3623 by Oral Gavage in CbyB6F1-Tg(HRAS)2Jic Mice, Study 3196-19-002

In the 26-week oral carcinogenicity study of metabolite MGL-3623 in CbyB6F1-Tg(HRAS)2Jic mice (25/sex/group), the test article was administered by oral gavage at dose levels of 0 (vehicle), 0 (0.9% NaCl), 15, 300, or 1500 mg/kg/day. The vehicle was 2% Klucel LF, 0.1% tween 80, 0.09% methylparaben, 0.01% propylparaben in purified water. Statistical analysis was based on comparison of the treatment groups to the vehicle control group. The positive control group was administered N-nitroso-N-methylurea (75 mg/kg/day) via intraperitoneal injection. There was no statistically significant dose-response relationship for mortality in MGL-3623-treated groups compared to the vehicle control group. The mortality rates for both sexes in the positive control group (N-nitroso-N-methylurea) were statistically higher than the vehicle control group. The MGL-3623 treatment groups showed no statistically significant positive dose-response relationships for tumor incidence or increase in tumor incidence rates compared to the vehicle control group. The tumor incidence for papilloma (benign) in skin and stomach and lymphoma (malignant) in the whole body was significantly higher in the positive control group compared to the vehicle control group.

Executive Carcinogenicity Assessment Committee conclusions:

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that there was no evidence of drug-related neoplasms in male and female mice for the 26-week study.

13.1.9. Reproductive and Developmental Toxicology

13.1.9.1. Fertility and Early Embryonic Development

13.1.9.1.1. An Oral (Gavage) Study of Fertility and Early Embryonic Development to Implantation of VIA-3196 in Rats (Study (b) (4)-891006)

Key Study Findings

- Significant increases in BW gain and food consumption occurred in males at 10 and 30 mg/kg/day (mid and high dose) and in females at 30 mg/kg/day, generally throughout the premating period in females and the entire treatment period in males. Increased BW gain was associated with increased food consumption. The effects were not considered to be adverse.
- A slight and statistically significant increase in pituitary weight (absolute and relative to brain weight) occurred in the 30 mg/kg/day males. This effect was considered as drug-related but not adverse due to the small magnitude.
- A slight and statistically significant increase in ovary weight (absolute and relative to brain weight) occurred in the 10 and 30 mg/kg/day females. This effect was considered as drug-related but not adverse due to the small magnitude.

- VIA-3196 had no adverse effects on reproductive function in either sex and no effects on embryonic survival.
- The NOAEL for maternal/paternal toxicity, fertility, and early embryonic development was 30 mg/kg/day in males and females.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 114. Rat Oral Fertility and Early Embryonic Developmental Study Methods, Study (b) (4)-891006

Parameter	Method Details
Dose and frequency of dosing	Males and females: 3, 10, 30 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	VIA-3196 was formulated in 2% Klucel, 0.1% tween 80, 0.09% methylparaben, and 0.01% propylparaben in deionized water at concentrations of 0.6, 2, and 6 mg/mL.
Species/strain	Sprague-Dawley rats (Crl:CD SD, IGS, BR)
Number/sex/group	25
Satellite groups	None
Study design	Males received 28 daily doses prior to cohabitation. Males were dosed throughout the mating period through 1 day prior to euthanasia for a total of 63 to 64 doses. Females received 14 daily doses prior to cohabitation and were dosed through gestation day (GD) 7 for a total of 22 to 34 doses.
Deviation from study protocol affecting interpretation of results	None

Source: Prepared by the nonclinical reviewer.
Abbreviations: Crl:CD SD, Charles River Laboratories caesarean-derived Sprague Dawley rat; GD, gestation day; IGS, International Genetic Standard; QD, once daily

Table 115. Observations and Results

Parameter	Results
Mortality	One male in the 30 mg/kg/day group was found dead on Day 34. The cause of death could not be determined due to the absence of adverse clinical signs and macroscopic findings. No deaths occurred in females.
Clinical signs	None
Body weight/food consumption	No significant effects on bodyweight were observed. In the 10 mg/kg/day males, a significant increase in body weight gain occurred during Days 3 to 7 (23.8%), and Days 10 to 14 (25%). In the 30 mg/kg/day males, a significant increase in body weight gain occurred throughout the treatment period (Days 0 to 63, 12.7%). In 30 mg/kg/day females, a significant increase in body weight gain occurred during the premating period (50%). In the 10 and 30 mg/kg/day males, a significant increase (up to 14.8%) in food consumption was observed throughout the treatment period.

Parameter	Results
	In 10 and 30 mg/kg/day females, a significant increase (up to 8.7%) in food consumption was observed during Days 7 to 10, 10 to 13, and 13 to 15 of the premating period. The increases in body weight gain and food consumption were drug-related, but not adverse.
Mating and fertility indices	No effects occurred in males or females.
Organ weights	In the 30 mg/kg/day males, a significant increase in pituitary weight was observed (absolute [10.5%] and relative to brain weight [10.7%]). A significant increase in ovary weight occurred in the 10 and 30 mg/kg/day females (9.5% for absolute weight; 8.7% and 10.3% for ovary/brain weight ratio at 10 and 30 mg/kg/day, respectively). Both changes were likely drug-related but were not considered to be adverse due to the small magnitude.
Necropsy findings, Cesarean section data	In the 30 mg/kg/day group, significant increases were observed in the number of corpora lutea (16.8 per dam vs. 15.1 per dam in controls) and implantation sites (15.9 per dam vs. 14.4 per dam in controls). However, these changes were not considered as drug-related because the values at 30 mg/kg/day were within the range of mean values in the (b) (4) historical control data for both the mean number of corpora lutea and the mean number of implantation sites. An increase in postimplantation loss (9.0% early resorptions per litter as compared to 4.6% per litter in controls) in the 30 mg/kg/day group was not considered as drug related because the increase was mostly due to a single female with 50% postimplantation loss, and the value at 30 mg/kg/day was within the range of mean values in the (b) (4) historical control data. VIA-3196 had no effect on the number of viable embryos.
NOAEL	The NOAEL for maternal/paternal toxicity, fertility, and early embryonic development was 30 mg/kg/day in males and females.

Source: Prepared by the nonclinical reviewer.
Abbreviations: NOAEL, no observed adverse effect level; VIA-3196, resmetirom

13.1.9.2. Embryofetal Development

13.1.9.2.1. An Oral (Gavage) Study of the Effects of VIA-3196 on Embryo/Fetal Development in Rats, Study (b) (4)-891005; 3196-12-016

Key Study Findings

- VIA-3196 (3 to 100 mg/kg/day) had no effects on mean maternal BW, net BW, net BW gain, or gravid uterine weights.
- A dose-dependent, significant increase in BW gain occurred during gestation days (GD) 9 to 18. VIA-3196 at 100 mg/kg/day produced a significant increase in BW gain during GD 6 to 18.
- VIA-3196 at 30 and 100 mg/kg/day produced a dose-dependent and significant decrease in food consumption during GD 6 to 9.

- No drug-related malformations or variations were found in the visceral examination of fetuses.
- No drug-related skeletal malformations were observed. Fetuses in the 100 mg/kg/day group showed increases in skeletal variations, including delayed ossification of sternebrae and hyoid (both unossified), and reduced ossification of the vertebral arches. However, these changes were not considered as drug related.
- VIA-3196 at all doses produced a dose-dependent and significant decrease in maternal concentrations of free T4 and total T4.
- VIA-3196 at 10, 30, and 100 mg/kg/day produced a dose-dependent decrease in TSH (not statistically significant).
- Systemic exposure to VIA-3196 (AUC_{0-24} and C_{max}) on GD 6 and 17 increased with dose in a dose-proportional manner.
- The NOAEL for maternal toxicity was 30 mg/kg/day, based on the decreases in food consumption (17%), total T4 (86.3%), free T4 (65.2%), and TSH (34.2%) at 100 mg/kg/day.
- The NOAEL for embryo-fetal developmental toxicity was considered to be 100 mg/kg/day based on the absence of adverse effects on embryo/fetal development.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 116. Methods of Oral Embryo-Fetal Developmental Study in Rats, Study (b) (4)-891005; 3196-12-016

Parameter	Method Details
Dose and frequency of dosing	3, 10, 30, 100 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	2.0% Klucel, 0.1% Tween 80, 0.09% methylparaben, and 0.01% propylparaben in deionized water
Species/strain	Rat/Crl:CD(SD)
Number/sex/group	25 females
Satellite groups	None
Study design	Mated females were administered VIA-3196 once daily during gestation days (GD) 6 to 17.
Deviation from study protocol affecting interpretation of results	None

Source: Prepared by the nonclinical reviewer.
Abbreviation: Crl:CD(SD), Charles River Laboratories caesarean-derived Sprague Dawley rat; GD, gestation day; QD, once daily; VIA-3196, resmetirom

Table 117. Observations and Results, Study (b) (4)-891005; 3196-12-016

Parameter	Results
Mortality	None
Clinical signs	None

Parameter	Results
Body weight/ food consumption	No effects on maternal body weight, net body weight, net body weight gain, or gravid uterine weight. Significant decrease in body weight gain in the 30 and 100 mg/kg/day groups (53.8% and 46.2%, respectively) during GD 6-9. Significant, dose-dependent increase in weight gain during GD 9-12 (29.4%, 41.2%, and 47% at 10, 30 and 100 mg/kg/day, respectively) and during GD 12-18 (12.5% and 15.6% at 30 and 100 mg/kg/day, respectively). Significant increase in overall body weight gain during GD 6-18 (12.9%) at 100 mg/kg/day. Dose-dependent and significant decrease in food consumption during GD 6-9 (up to -17%) at 30 and 100 mg/kg/day. Changes in body weight gain and food consumption were drug-related and were reversible.
Cesarean section data	No effects on corpora lutea, implantation sites, preimplantation loss, postimplantation loss, or live litter size.
Organ weight	No effects on brain and thyroid weights (absolute, relative to net body weight, and/or relative to brain weight).
Necropsy findings, offspring	No drug-related changes in mean fetal body weight or fetal sex ratio. No drug-related malformations (external, visceral, and skeletal).
T4, T3, TSH	Significant, dose-dependent reductions in maternal levels of free T4 (26.3 to 65.2%) and total T4 (48.3 to 86.3%) at all doses. Total T3 decreased by 52.2% at 100 mg/kg/day (not statistically significant). Dose-dependent increase in free T3 (36.7 to 52.2%) at 30 and 100 mg/kg/day (not significant). Dose-dependent decrease in mean TSH serum levels (24.6 to 34.2%) in the 10, 30, and 100 mg/kg/day groups (not significant).
NOAEL	The NOAEL for maternal toxicity was 30 mg/kg/day, based on the reductions in food consumption, T4 (total and free), and TSH at 100 mg/kg/day. The NOAEL for embryo-fetal developmental toxicity was considered to be 100 mg/kg/day based on the absence of adverse effects on embryo-fetal development.
Toxicokinetics (TK)	Blood samples were collected at 0 (predose), 1, 2, 4, 8, and 24 hours after dose administration on GD 6 and 17 for analysis of VIA-3196. Systemic exposure to VIA-3196 (AUC_{0-24} and C_{max}) on GD 6 and 17 increased with dose in a dose-proportional manner. On GD 17 (final day of dosing), slight accumulation was observed in the 100 mg/kg/day group, whereas no accumulation occurred at the lower doses. TK data is summarized in Table 118.

Source: Prepared by the nonclinical reviewer.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; GD, gestation day; NOAEL, no observed adverse effect level; TK, toxicokinetics; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; VIA-3196, resmetirom

Table 118. Summary of Toxicokinetic Parameters of VIA-3196 in Pregnant Rats

	Group 2 (3 mg/kg/day)	Group 3 (10 mg/kg/day)	Group 4 (30 mg/kg/day)	Group 5 (100 mg/kg/day)
		Gestation Day 6		
C_{max} (ng/mL)	555	2150	3150	9100
T_{max} (hr)	4.00	4.00	4.00	4.00
$AUC_{(0-24)}$ (ng*hr/mL)	7280	22,900	43,400	128,000
		Gestation Day 17		
C_{max} (ng/mL)	644	1560	3920	11,300
T_{max} (hr)	4.00	4.00	8.00	8.00
$AUC_{(0-24)}$ (ng*hr/mL)	6290	15,700	48,500	162,000

Source: Applicant's report (b) (4)-891005; 3196-12-016.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; T_{max}, median time to maximum concentration; VIA-3196, resmetirom

13.1.9.2.2. An Oral (Gavage) Study of the Effects of VIA-3196 on Embryo/Fetal Development in Rabbits, Study (b) (4)-891004

Key Study Findings

- VIA-3196 at 30 and 75 mg/kg/day produced reductions in defecation, BW (75 mg/kg/day), and BW gain (96.8% at 75 mg/kg during treatment), which were associated with a significant decrease in food consumption.
- VIA-3196 at 75 mg/kg/day produced abortion, an increase in postimplantation loss, and a decrease in viable fetuses.
- VIA-3196 at 75 mg/kg/day produced a 9.3% decrease in fetal BW.
- No drug-related malformations or variations were observed in the visceral and skeletal examinations.
- VIA-3196 at 75 mg/kg/day produced a significant decrease in TT3 and free T4.
- Systemic exposure to VIA-3196 increased with dose level.
- Systemic exposure to the metabolites VIA-3196-M1 and VIA-3196-M2 was low and highly variable after repeated doses of 75 mg/kg/day VIA-3196.
- The NOAEL for maternal toxicity was 10 mg/kg/day.
- The NOAEL for embryo-fetal development was 30 mg/kg/day, based on the incidence of abortion, increase in postimplantation loss, decrease in viable fetuses, and decrease in fetal weight at 75 mg/kg/day. However, each of these effects likely resulted from severe maternal toxicity.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 119. Rabbit Oral Embryo-Fetal Developmental Study Methods, Study (b) (4)-891004; 3196-12-17

Parameter	Method Details
Dose and frequency of dosing	10, 30, 75 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	VIA-3196 was formulated in 2.0% Klucel, 0.1% Tween 80, 0.09% methylparaben, and 0.01% propylparaben in deionized water at concentrations of 2, 6, and 15 mg/mL.
Species/strain	New Zealand White (Hra:(NZW)SPF)
Number/sex/group	22 mated females
Satellite groups	4 mated females/group in toxicokinetic groups
Study design	Mated females were administered VIA-3196 once daily during gestation days (GD) 7 to 20.
Deviation from study protocol affecting interpretation of result	None

Source: Prepared by the nonclinical reviewer.
Abbreviations: GD, gestation day; (NZW)SPF, New Zeeland White specific-pathogen free (rats); QD, once daily; VIA-3196, resmetirom

Table 120. Observations and Results, Study (b) (4)-891004; 3196-12-17

Parameter	Results
Mortality	One control female was found dead on GD 18, and the cause of death was undetermined. One control female was euthanized in extremis on GD 19 due to a missing upper incisor, reduced food consumption, and body weight loss. One female with misshapen heart in the main study animals and one female with gavage-related injury in the TK animals were found dead on GD 16 and 15, respectively. None of the deaths were test-article-related.
Clinical signs	Two females in the 75 mg/kg/day group (main study) aborted on GD 26 (2 and 9 dead fetuses). Abortion was preceded by reduced food consumption and body weight loss. Other adverse clinical signs included decreased defecation, small feces, and/or soft stool. The abortions were secondary to the maternal toxicity of VIA-3196. A higher incidence of decreased defecation occurred at 30 and 75 mg/kg/day.
Body weight/food consumption	At 30 mg/kg/day, a significant decrease in body weight gain occurred during GD 7 to 21 (-46.5%), with a reduction of -122.9% in weight gain during GD 14 to 15. Body weight and body weight gain in the 30 mg/kg/day group were comparable to the control group after the end of dosing (GD 21 to 29). A significant decrease in mean net body weight gain (-83%) was observed on GD 29.

Parameter	Results
	At 75 mg/kg/day, a significant decrease in body weight occurred during GD 12 to 24 (7.2-10%). Body weight gain was reduced during GD 7 to 21 (96.8%), with a decrease of 68.6 to 241.7% body weight gain during GD 9 to 14. A significant increase in body weight gain occurred at 75 mg/kg/day after the cessation of treatment (81.1%). Significant decreases in mean net body weight and net body weight gain were observed in the 75 mg/kg/day group on GD 29 (-6.9% and -93.2%, respectively). Food consumption was significantly reduced by up to 42.3% at 30 mg/kg/day and up to 42.4% at 75 mg/kg/day. Following the cessation of dosing (GD 21 to 29), food consumption in the 75 mg/kg/day group was significantly higher (15.9%) than the control group. Changes in body weight, body weight gain, and food consumption were drug related.
Cesarean section data	As described above (in the "Clinical signs" section of this table), abortion occurred in females # 67184 and # 67189 in the 75 mg/kg/day group on GD 26. Female # 67184 had one early resorption and seven live fetuses with no apparent malformations. Females treated with 75 mg/kg/day showed an increase (nonsignificant) in postimplantation loss (12.4% per litter vs. 8.4% in control group) and a decrease in viable fetuses (87.6% per litter vs. 91.6% in control group). The incidence of postimplantation loss and the proportion of viable fetuses in the 75 mg/kg/day group were not within the respective (b) (4) historical data ranges. Therefore, the increase in postimplantation loss and the decrease in viable fetuses are considered to be drug related, however these effects are also considered as secondary to maternal toxicity, as with the incidence of abortion in this dose group.
Organ weight	No changes in mean brain or thyroid weights were observed (absolute, relative to net body weight and/or relative to brain weight).
Necropsy findings, offspring	Macroscopic findings were found in dead or euthanized females. None of the findings were drug related. No drug-related changes in live litter size or fetal sex ratios were observed. A dose-dependent decrease in fetal body weight occurred (up to 9.3% at 75 mg/kg/day). The reduction in fetal weight at 75 mg/kg/day is considered to be adverse based on the magnitude of change, which was likely due to maternal toxicity. No drug-related malformations (external, visceral, and skeletal) were found.
T4, T3, TSH	F0 Dams A dose-dependent reduction in maternal levels of total T4 (42.5 to 70.6%), free T4 (41.7 to 75%), total T3 (14.1 to 41.7%), and free T3 (15.5 to 34.5%) occurred at all doses as measured on GD 21. The changes reached statistical significance at 75 mg/kg/day. TSH was unaffected. The changes in T4 and T3 were drug related.

Parameter	Results
Toxicokinetics (TK)	Blood samples were collected at 0 (predose), 1, 2, 4, 8, and 24 hours after dose administration on GD 7 and 20 for analysis of VIA-3196 and its metabolites VIA-3196-M1 and VIA-3196-M2. The concentrations of VIA-3196-M2 were estimated based on the VIA-3196-M1 levels and were not directly measured. Systemic exposure to VIA-3196 (AUC_{0-24} and C_{max}) increased with dose in a dose-proportional manner at the increment of 10 to 30 mg/kg/day. VIA-3196 accumulated in plasma following repeated administration of 10 and 30 mg/kg/day. Systemic exposure (C_{max} and AUC_{0-24}) to VIA-3196-M1 after repeated dosing with 75 mg/kg/day VIA-3196 was low and highly variable on both GD 7 and GD 20. Plasma concentrations and systemic exposure were apparently greater for VIA-3196-M2 than for VIA-3196-M1. Systemic exposure (C_{max} and AUC_{0-24}) to VIA-3196-M2 after repeated dosing with 75 mg/kg/day VIA-3196 was highly variable on GD 20, although the mean C_{max} and AUC_{0-24} were similar on GD 7 and GD 20. The TK data for VIA-3196, VIA-3196-M1, and VIA-3196-M2 is summarized in Table 121 and Table 122.
NOAEL	The NOAEL for maternal toxicity was 10 mg/kg/day. The NOAEL for embryo-fetal development was 30 mg/kg/day, based on the incidence of abortion, increase in postimplantation loss, decrease in viable fetuses, and decrease in fetal weight at 75 mg/kg/day. However, each of these effects likely resulted from severe maternal toxicity.

Source: Prepared by the nonclinical reviewer.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; GD, gestation day; M1, metabolite 1; M2, metabolite 2; NOAEL, no observed adverse effect level; T3, triiodothyronine; T4, thyroxine; TK, toxicokinetics; TSH, thyroid stimulating hormone; VIA-3196, resmetirom

Table 121. Summary of Toxicokinetic Parameters of VIA-3196 (Parent Drug) in Pregnant Rabbits

	Group 2 (10 mg/kg/day)	Group 3 (30 mg/kg/day)	Group 4 (75 mg/kg/day)
		Gestation Day 7	
C_{max} (ng/mL)	1,070	2,750	5,390
SD	413	979	2,370
T_{max} (h)	1.50	1.00	2.00
SD	0.577	0.00	1.41
$T_{1/2}$ (h)	2.86	3.07	4.17
SD	0.493	0.114	1.11
$AUC_{(0-24)}$ (ng*h/mL)	5,350	12,300	29,800
SD	2,460	3,240	12,700
		Gestation Day 20	
C_{max} (ng/mL)	2,080	5,940	5,520
SD	480	1,330	5,530
T_{max} (h)	1.00	1.00	1.33
SD	0.00	0.00	0.577
$T_{1/2}$ (h)	2.80	3.45	8.00
SD	0.0670	0.124	4.59
$AUC_{(0-24)}$ (ng*h/mL)	7,760	21,800	27,100
SD	3,240	3,500	20,200

Source: Applicant's report (b) (4)-891004; 3196-12-17.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196, resmetirom

Table 122. Summary of Toxicokinetic Parameters for Metabolites VIA-3196-M1 and VIA-3196-M2 in Pregnant Rabbits

	VIA-3196-M1	VIA-3196-M2
	Group 4 (75 mg/kg/day)	Group 4 (75 mg/kg/day)
	Gestation Day 7	
C_{max} (ng/mL)	64.0	748
SD	61.1	435
T_{max} (h)	2.0	2.0
SD	1.41	1.41
$T_{1/2}$ (h)	NC	4.23
SD	NC	1.24
$AUC_{(0-24)}$ (ng*h/mL)	345	3,780
SD	388	2,020
	Gestation Day 20	
C_{max} (ng/mL)	NC[a]	838
SD	NC[a]	1,230
T_{max} (h)	NC[a]	1.67
SD	NC[a]	0.577
$T_{1/2}$ (h)	NC[a]	6.76
SD	NC[a]	4.09
$AUC_{(0-24)}$ (ng*h/mL)	NC[a]	3,510
SD	NC[a]	4,730

Source: Applicant's report (b) (4)-891004; 3196-12-17.

[a] Only 1 rabbit had a measurable plasma concentration on Gestation Day 20.

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; NC, not calculated; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$ (half-life), the time required for plasma concentration of a drug to decrease by 50%; VIA-3196-M1 and VIA-3196-M2, metabolites of VIA-3196 (resmetirom)

13.1.9.2.3. An Oral (Gavage) Study of the Effects of MGL-3623 on Embryo/Fetal Development With a Toxicokinetic Phase in Rats, Study 3196-17-019

Key Study Findings

- Administration of MGL-3623 (a major metabolite in humans, also referred to as MGL-3196-M1, VIA-3196-M1, or M1) had no effects on BW, BW gain, or food consumption.
- MGL-3623 had no effects on post-implantation loss, number or percentage of viable fetuses, mean fetal BW, or fetal sex ratio.
- No test article-related malformations or variations were observed in the visceral and skeletal examinations.
- MGL-3623 at 3 and 100 mg/kg/day produced a significant decrease in free T3 (-10.5% for both doses), with no dose-dependent effect. A significant decrease in TSH occurred at 3 mg/kg/day (-28.8%).
- Systemic exposure to MGL-3623 increased with dose level. There was no accumulation in plasma following repeated doses.

- The NOAEL for maternal and embryo-fetal developmental toxicity was 100 mg/kg/day, the highest dose tested.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 123. Rat Oral Embryo-Fetal Developmental Study Methods, Study 3196-17-019

Parameter	Method Details
Dose and frequency of dosing	3, 30, 100 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	MGL-3623 (also known as MGL-3196-M1, VIA-3196-M1, or M1) was formulated in 2% Klucel, 0.1% Tween 80, 0.09% methylparaben, and 0.01% propylparaben in deionized water at concentrations of 0.3, 3, and 10 mg/mL.
Species/strain	Rats/ Crl:CD(SD)
Number/sex/group	25 pregnant females in main study groups
Satellite groups	8 pregnant females in toxicokinetic groups
Study design	Mated females were administered MGL-3623 once daily during gestation days (GD) 6 to 17.
Deviation from study protocol affecting interpretation of results	None

Source: Prepared by the nonclinical reviewer.
Abbreviations: GD, gestation day; M1, metabolite 1, M2, metabolite 2; QD, once daily; VIA-3196, resmetirom

Table 124. Observations and Results, Study 3196-17-019

Parameter	Results
Mortality	One control female in the TK group was found dead on GD 18. The cause of death was skeletal muscle trauma of the ventral neck from the blood collection procedures.
Clinical signs	None
Body weight/food consumption	No effects.
Cesarean section data	MGL-3623 had no effects on corpora lutea, implantation sites, or preimplantation loss, postimplantation loss, number and percentage of viable fetuses, mean fetal body weight, or fetal sex ratio.
Organ weight	No changes in mean brain or thyroid weights (absolute, relative to net body weight and/or relative to brain weight) were observed.
Necropsy findings, offspring	No test article-related malformations (external, visceral, and skeletal) were found.
T4, T3, TSH	MGL-3623 had no effects on the maternal levels of total T4, free T4, or total T3 on GD 17. MGL-3623 at 3 and 100 mg/kg/day produced a significant decrease in free T3 (-10.5% at both doses). However, the effect was small and not dose dependent. A significant decrease in TSH occurred at 3 mg/kg/day (-28.8%), with no changes observed at 30 or 100 mg/kg/day.

Parameter	Results
Toxicokinetics (TK)	Blood samples were collected at 0 (predose), 1, 2, 4, 8, and 24 hours after dose administration on GD 6 and 17. Systemic exposure to MGL-3623 (C_{max} and AUC_{0-24}) increased with dose level. No accumulation of MGL-3623 occurred after dosing for 12 days. The TK data is summarized in Table 125.
NOAEL	The NOAEL for maternal and embryo-fetal developmental toxicity was 100 mg/kg/day, the highest dose tested.

Source: Prepared by the nonclinical reviewer.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; GD, gestation day; NOAEL, no observed adverse effect level; T3, triiodothyronine; T4, thyroxine; TK, toxicokinetics; TSH, thyroid stimulating hormone; T_{max}, median time to maximum concentration; TSH, thyroid stimulating hormone

Table 125. Summary of Toxicokinetic Parameters of MGL-3623 in Rats

Parameter	3 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Gestation Day 6			
Cmax (ng/mL)	344	1240	1570
AUC(0-24) (ng•h/mL)	2520	7070	16,200
Tmax (h)	4.00	4.00	4.00
Gestation Day 17			
Cmax (ng/mL)	189	862	1080
AUC(0-24) (ng•h/mL)	1910	5320	10,100
Tmax (h)	4.00	4.00	4.00

Source: Applicant's report # 3196-17-019.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule C_{max}, maximum plasma concentration; T_{max}, median time to maximum concentration

13.1.9.3. Pre- and Postnatal Development

13.1.9.3.1. A Developmental and Perinatal/Postnatal Reproduction Study of MGL-3196 by Oral (Gavage) in Rats, Including a Postnatal Behavioral/Functional Evaluation, Study 3196-17-010

Key Study Findings

F0 Generation

- MGL-3196 or the vehicle control article was administered orally from GD 6 through Day 20 postpartum. All doses (3, 30, 100 mg/kg/day) produced a significant dose-dependent increase in BW gain during GD 9-12. During the lactation period, MGL-3196 at all doses produced a significant increase in BW or BW gain. These changes were not adverse.
- MGL-3196 at 100 mg/kg/day produced a statistically significant increase in the number of pups found dead or presumed cannibalized on postnatal day (PND) 1 and during PND 2 to 4.
- At 100 mg/kg/day, MGL-3196 produced a statistically significant decrease in viability index, the number of surviving pups per litter on PND 10, 14, 18, and 21, and the percentage of liveborn pups. Dosing with 100 mg/kg/day also produced an increase in the number of dams with stillborn.

- MGL-3196 at 100 mg/kg/day produced substantial decreases in mean TH concentrations (total and free T4 and T3, TSH). The decrease in TH levels was most likely related to pharmacological activity of MGL-3196.
- Exposure to MGL-3196 (C_{max} and AUC_{0-24}) increased with dose level during the gestation period.
- The NOAEL for maternal toxicity was 30 mg/kg/day, based on the effects on TH levels at 100 mg/kg/day.

F1 Generation

- MGL-3196 at 100 mg/kg/day (maternal dosing only) produced increases in the total number of stillborn pups, number of pups that were found dead, and number of pups with no milk present in the stomach.
- MGL-3196 at 100 mg/kg/day produced a 10% decrease in pup weight per litter on PND 1. Thereafter, significant increases in pup weight were observed in the 30 mg/kg/day group on PND 14, 18, and 21, and in the 100 mg/kg/day group on PND 18.
- After weaning (PND 20), pups from the 100 mg/kg/day group showed significant decreases in BW and food consumption.
- A significant delay in the onset of vaginal patency occurred in the offspring of the 100 mg/kg/day females. This delay was likely due to the decrease in BW in the F1 females.
- MGL-3196 at 100 mg/kg/day had no adverse effects on learning (including short-term and long-term retention), mating, or fertility in F1 rats.
- Maternal dosing with MGL-3196 in F0 rats had no effects on the number of corpora lutea, preimplantation and post-implantation loss, number of viable embryos, number of dams with any nonviable embryos, or placentae appearance in F1 rats.
- The NOAEL in the F1 generation was 30 mg/kg/day based on the increases in total number of stillborn pups, number of pups that were found dead, and number of pups with no milk present in the stomach at 100 mg/kg/day.
- This study is deficient based on the current International Council for Harmonisation (ICH) standards for the conduct of pre- and postnatal developmental studies (refer to Section 7.7.6 for details).

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 126. Methods of Oral Pre-and Postnatal Developmental Study in Rats, Study 3196-17-010

Parameter	Method Details
Dose and frequency of dosing	3, 30, 100 mg/kg QD
Route of administration	Oral gavage
Formulation/vehicle	2.0% Klucel, 0.1% Tween 80, 0.09% methylparaben, and 0.01% propylparaben in deionized water
Species/strain	Rat/ Sprague Dawley CD (Crl:CD[SD])
Number/sex/group	22 females/group for main study
Satellite groups	Toxicokinetic groups (4 to 8 females/group)
Study design	MGL-3196 or the vehicle control article was administered orally from gestation day (GD) 6 through Day 20 postpartum. The study did not evaluate early landmarks of development and reflex ontogeny (e.g., eye opening, pinna unfolding, surface righting, auditory startle, air righting, and response to light), sensory functions, or motor activity prior to weaning.
Deviation from study protocol affecting interpretation of results	None

Source: Prepared by the nonclinical reviewer.
Abbreviations: Crl:CD(SD), GD, gestation day; Charles River Laboratories caesarean-derived Sprague Dawley rat; MGL-3196, resmetirom; QD, once daily

Table 127. Observations and Results, Study 3196-17-010

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weights/Food consumption	A significant increase in body weight gain occurred in all treatment groups during GD 9 to 12 (16.7%, 26.3%, and 34.1% at 3, 30, and 100 mg/kg/day, respectively). A significant increase in body weight (4.8% to 6.9%) occurred at 100 mg/kg/day during lactation days (LD) 9 to 21. A significant increase in body weight gain at 30 and 100 mg/kg/day was observed during LD 7 to 14 (50% and 58.6%, respectively). This increase was considered as treatment-related, but not adverse. The increase in body weight gain can be attributed to the pharmacologic activity of MGL-3196. No changes in food consumption were observed during gestation or lactation.
Necropsy findings, Cesarean section data	MGL-3196 had no effects on the number of dams delivering litters, duration of gestation, implantation sites per delivered litter, gestation index, dams with all pups dying, litter sizes, or pup sex ratio. However, treatment with 100 mg/kg/day produced an increase in the number of dams with stillborn. MGL-3196 at 100 mg/kg/day produced a statistically significant increase in the number of pups found dead or presumed cannibalized on post-neonatal day (PND) 1 and during PND 2 to 4, including two dams with total litter loss during the preweaning (lactation) period. Effects in the 100 mg/kg/day group included a statistically significant decrease in viability index (84.7% as compared to 99.2% in controls), reductions in the number of surviving pups per litter on PND 10, 14, 18, and 21, and a decrease in percentage of liveborn pups (95.8% as compared to 99.6% in controls) at 100 mg/kg/day.

Parameters	Major Findings
Necropsy findings, offspring	Maternal dosing with 100 mg/kg/day produced an increase in the total number of stillborn pups, number of pups that were found dead, and the number of pups with no milk present in the stomach. In the 100 mg/kg/day maternal group, a statistically significant increase in the number of litters with coldness to touch and pups with umbilical hernias (six litters) was observed. A significant decrease in pup weight per litter (-10%) occurred on PND 1 at the maternal dose of 100 mg/kg/day. Significant increases in pup weight per litter occurred during PND 4 to 21 at all doses (up to 19.7%, 16.7%, and 11.9% at maternal doses of 3, 30, and 100 mg/kg/day, respectively). This effect was considered as drug related but was not adverse. A significant decrease in body weight occurred during PND 29 to 57 in F1 males and during PND 29 to 36 in F1 females (up to 11.2% in both sexes) at the maternal dose of 100 mg/kg/day. Reductions in body weight gain occurred during PND 22 to 36 in males (up to 16.6%) and during PND 22 to 43 in females (up to 15%) at the maternal dose of 100 mg/kg/day. The reductions in body weight and body weight gain were drug-related at 100 mg/kg/day. Significant decreases in food consumption were observed in F1 males (up to 34.2%) during PND 22 to 43, in F1 females (up to 23.3%) during PND 22 to 36, and in pregnant F1 females (9.1%) during GD 0 to 7 at the maternal dose of 100 mg/kg/day group. The changes in food consumption were considered to be drug related. A significant delay in the onset of vaginal patency was observed at the maternal dose of 100 mg/kg/day (mean of 33.7 days as compared to 30.9 days in control females), which was likely due to the decrease in body weight. MGL-3196 had no effects on learning, short-term retention, long-term retention, or response inhibition in the F1 generation, as evaluated by performance in the passive avoidance and water maze tests. MGL-3196 had no effects on mating, fertility index, number of corpora lutea, preimplantation and post-implantation loss, number of viable embryos, number of dams with any nonviable embryos, or placentae appearance in the F1 generation. A significant increase in absolute and relative weight of left and right testis (up to 20% and 21%, respectively) occurred in the F1 generation from the maternal dose group of 100 mg/kg/day.

Parameters	Major Findings
Toxicokinetics (TK)	Blood samples were collected from dams at 0 (predose), 1, 2, 4, 8, and 24 hours on GD 6, 17, and 20 after dosing for analysis of MGL-3196 and MGL-3623. Exposure to MGL-3196 (C_{max} and AUC_{0-24}) increased with dose level. There was no accumulation of MGL-3196 following dosing for 15 days. The metabolite MGL-3623 was detected at markedly low levels in the systemic circulation on GD 6, 17, and 20 in the F0 females. The plasma exposure to MGL-3623 was <0.04% of the parent compound MGL-3196 on GD 6, and was <0.02% of the parent compound on GD 17 and 20. TK data for MGL-3196 and MGL-3623 is presented in Table 128.
T3, T4, TSH	Blood samples were collected from dams on GD 20 at 2 hr postdose. Blood samples were collected at 24 hr postdose for analysis of thyroid hormone among drug-treated animals terminated on GD 21. MGL-3196 at all doses produced a dose-dependent decrease in thyroid hormones. Administration of 100 mg/kg/day produced substantial decreases in mean thyroid hormone concentrations (TSH: -43.7%; total T4: -87.7%; free T4: -66.1%; total T3: -79.1%; free T3: -50.4%) compared to the control values. The decrease in thyroid hormone levels is attributed to the pharmacological activity of MGL-3196.
NOAEL	The NOAEL for maternal toxicity was 30 mg/kg/day, based on the effects on thyroid hormone levels at 100 mg/kg/day. The NOAEL in the F1 generation was 30 mg/kg/day based on the increases in total number of stillborn pups, number of pups that were found dead, and number of pups with no milk present in the stomach at 100 mg/kg/day.

Source: Prepared by the nonclinical reviewer.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; GD, gestation day, LD, lactation day; MGL-3196, resmetirom; NOAEL, no observed adverse effect level; PND, post-natal day; T3, triiodothyronine; T4, thyroxine; TK, toxicokinetics; TSH, thyroid stimulating hormone

Table 128. TK Parameters for MGL-3196 (Parent Drug) and MGL-3623 (Metabolite) in F0 Female Rats on Gestation Days 6, 17, and 20 Following Oral Doses of MGL-3196

Gestation Day	MGL-3196 Dose, mg/kg/day	MGL-3196 3	MGL-3196 30	MGL-3196 100	MGL-3623 3	MGL-3623 30	MGL-3623 100
6	T_{max}, h	4.00	4.00	4.00	NC	8.00	4.00
	C_{max}, ng/mL	1,320	6,710	13,600	0.00	2.03	2.32
	$AUC_{(0-T)}$, ng·h/mL	14,500	88,600	181,000	0.00	7.19	39.3
	$AUC_{(0-24)}$, ng·h/mL	14,500	88,600	181,000	NC	23.5	39.3
	$T_{1/2}$, h	NC	NC	NC	NC	NC	NC
	$\%C_{max}$ (Metabolite/Parent)	-	-	-	0.00	0.0303	0.0171
	$\%AUC_{(0-24)}$ (Metabolite/Parent)	-	-	-	NC	0.0265	0.0217
17	T_{max}, h	4.00	2.00	8.00	NC	8.00	0.00
	C_{max}, ng/mL	829	5,470	20,900	0.00	0.964	2.48
	$AUC_{(0-T)}$, ng·h/mL	7,480	73,500	341,000	0.00	13.1	37.3
	$AUC_{(0-24)}$, ng·h/mL	7,480	73,500	341,000	NC	13.1	37.3
	$T_{1/2}$, h	NC	5.71	NC	NC	NC	NC
	$\%C_{max}$ (Metabolite/Parent)	-	-	-	0.00	0.0176	0.0119
	$\%AUC_{(0-24)}$ (Metabolite/Parent)	-	-	-	NC	0.0178	0.0109
	C_{max} Ratio (Day 17/Day 6)	0.628	0.815	1.54	NC	0.475	1.07
	$AUC_{(0-24)}$ Ratio (Day 17/Day 6)	0.516	0.830	1.88	NC	0.557	0.949
20	T_{max}, h	2.00	2.00	4.00	NC	8.00	0.00
	C_{max}, ng/mL	481	2,710	13,600	0.00	0.453	1.07
	$AUC_{(0-T)}$, ng·h/mL	5,230	37,800	233,000	0.00	1.26	18.4
	$AUC_{(0-24)}$, ng·h/mL	5,230	37,800	233,000	NC	4.88	18.4
	$T_{1/2}$, h	2.58	3.14	NC	NC	NC	NC
	$\%C_{max}$ (Metabolite/Parent)	-	-	-	0.00	0.0167	7.87E-03
	$\%AUC_{(0-24)}$ (Metabolite/Parent)	-	-	-	NC	0.0129	7.90E-03
	C_{max} Ratio (Day 20/Day 6)	0.364	0.404	1.00	NC	0.223	0.461
	$AUC_{(0-24)}$ Ratio (Day 20/Day 6)	0.361	0.427	1.29	NC	0.208	0.468

Source: Applicant's report # 3196-17-010.
Abbreviations: AUC_{0-24} $AUC_{0-T,}$ area under the curve from time 0 to the last measurable concentration (e.g. 24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; MGL-3196, resmetirom; NC, not calculated; TK, toxicokinetics; T_{max}, median time to maximum concentration

13.1.10. Other Toxicology/Specialized Studies

13.1.10.1. Impurities/Degradants

The starting material [redacted] (b) (4) is specified at ≤ [redacted] (b) (4) ppm in the drug substance, which assures that the maximum daily exposure cannot exceed [redacted] (b) (4) µg (acceptable intake for lifetime exposure to genotoxic impurities as stated in (ICH M7(R2) 2023)). The Applicant is controlling [redacted] (b) (4) as a genotoxic impurity in the drug substance, based on findings from a literature search that included the induction of pulmonary tumors following intraperitoneal injection in mice and the positive prediction of mutagenicity from *in silico* methods.

The Applicant used quantitative structure-activity relationship ((Q)SAR) analysis to evaluate the potential mutagenicity of process impurities that were detected in drug process, drug substance, or drug product. Derek Nexus (expert-based) and/or Leadscope Model Applier Systems (LSMA, statistical-based or expert-based) (Q)SAR tools were used in the analysis in accordance with (ICH M7(R2) 2023). All study reports are summarized in Table 129.

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13.1.10.1.1. Toxicology Qualification for [redacted] and [redacted] Study 3196-21-008)

The impurities [redacted] and [redacted] were designated as non-mutagenic (Class 4) based on (ICH M7(R2) 2023) in Study # 3196-21-007 (reviewed in Table 130). Qualified levels of [redacted] were calculated in accordance with ICH guidelines, based on the NOAEL in the 6-month-old rat and 9-month-old dog toxicology studies (Study # 3196-14-003 and 3196-14-002, respectively). The maximum recommended dose of 100 mg MGL-3196 per day was used to calculate the qualified levels for these nonmutagenic impurities. However, the Applicant stated the following: "Historically, the qualification level for these non-mutagenic impurities was also calculated based on a maximum dose of 200 mg MGL-3196 per day." Thus, the assumed doses of 100 mg/day and 200 mg/day were used in the Applicant's qualification of the two impurities, as presented in Table 131.

Table 131. Qualification Calculations for [redacted] and [redacted]

Step No.	Step	Value (based on maximum daily dose of 200 mg/day)	Value (based on maximum daily dose of 100 mg/day)
1	NOAEL, species	45 mg/kg; dogs	45 mg/kg; dogs
2	Body-surface area-based factor to convert dog dose to human, (dividing, from table 1 of guidance)	1.8	1.8
3	Human Equivalent Dose (HED)	25 mg/kg	25 mg/kg
4	Maximum clinical dose/day	200 mg	100 mg
5	Maximum human clinical dose mg/kg/day (60 kg human)	3.333 mg/kg/day	1.667 mg/kg/day
6	Impurity	[redacted]	
7	Level of impurity in MGL-3196 lot 02130033 used in six-month rat and nine-month dog studies (COA, release date 3/29/2013)		
8	HED of impurity (step 7 x step 3)		
9	Equivalent % (HPLC AUC) in maximum human clinical dose ((step 8 ÷ step 5) x 100%)		
10	Qualified level		

Source: Applicant's report # 3196-21-008
Abbreviations: AUC, area under the concentration-time curve; COA,, certificate of analysis; HED, human equivalent dose; HPLC, high-performance liquid chromatography; MGL-3196, resmetirom

As shown in Table 131, the Applicant's calculation method produced a qualified level of ≤ (b) (4)% for (b) (4) and ≤ (b) (4)% for (b) (4), based on the maximum daily dose of 100 mg MGL-3196. However, the Applicant used a safety factor of 2 to set the limits for (b) (4) and (b) (4) at ≤ (b) (4)% and ≤ (b) (4)%, respectively, as a conservative measure (e.g., (b) (4)

Although we do not agree with the Applicant's designation of 45 mg/kg/day as the NOAEL in the 9-month-old dog toxicity study, the Applicant's use of 45 mg/kg/day as the basis for calculation of acceptance criteria (qualified levels) of (b) (4) is acceptable. Our acceptance is based on the absence of clinical signs of toxicity and the minimal histological changes in liver (increased extramedullary hematopoiesis) and other organs (epithelial inflammation and thickening in tongue) in the group treated with 45 mg/kg/day. We also concur with the Applicant's use of an additional safety factor (2) for calculation of the acceptance criteria for the drug substance impurities. Therefore, the Applicant's proposed acceptance criteria, ≤ (b) (4)% for (b) (4) and ≤ (b) (4)% for (b) (4), are acceptable.

13.1.11. Referenced NDAs, BLAs, DMFs

There were no NDAs, BLAs, or DMFs referenced for the pharmacology/toxicology review of this application.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Primary Pharmacology

13.2.1.1. Data Report for Pharmacology Services, Study TW04-0015410)

Key Study Findings

- MGL-3196 was 28 times more potent than MGL-3623 in the THRβ-RXRα heterodimer coactivator recruitment assay.
- MGL-3196 was 20 times more potent than MGL-3623 in the THRα-RXRα heterodimer coactivator recruitment assay.
- Both MGL-3196 and MGL-3623 were more potent in the THRβ-RXRα heterodimer coactivator recruitment assay than in the THRα-RXRα heterodimer coactivator recruitment assay.

Methods

MGL-3196 and the major human metabolite MGL-3623 were evaluated in two functional assays: (1) THRβ-RXRα heterodimer coactivator recruitment assay, and (2) THRα-RXRα heterodimer

coactivator recruitment assay. According to the study report, the methods for this functional assay were based on the publication by (Kelly et al. 2014). This publication provided a detailed methodology which was not included in the study report. In this cell-free in vitro assay, MGL-3196, MGL-3623, or T3 (reference compound) was allowed to bind to his-tagged THR in the presence of the retinoid X receptor (RXR). The ability of this liganded heterodimeric complex to recruit the biotin-linked coactivator peptide, glucocorticoid receptor interacting protein 1, was measured with time-resolved fluorescence resonance energy transfer. The criterion for a significant response was ≥50% increase in fluorescence relative to T3 response.

Results

In the in vitro functional assay for THRβ-RXRα heterodimer activation, MGL-3196 produced 81% of the maximum response compared to T3, with an EC_{50} of 0.70µM. The metabolite MGL-3623 produced 67% of the maximum response compared to T3 for THRβ-RXRα heterodimer activation, with an EC_{50} of 19.3µM. The same functional assay for THRα-RXRα heterodimer activation showed 85% efficacy for MGL-3196 relative to T3, with an EC_{50} of 3.83µM. MGL-3623 produced 59% of the maximum response compared to T3 for THRα-RXRα heterodimer activation, with an EC_{50} of 75.9µM. The concurrent EC_{50} values for the reference compound, T3, were consistent with the historical values (concurrent THRβ-RXRα heterodimer activation EC_{50}=6.14 nM and THRα-RXRα heterodimer activation EC_{50}=3.88 nM). It was noted in the study report that MGL-3196 and MGL-3623 showed fluorescence interference when reading time-resolved fluorescence resonance energy transfer in agonist mode in the THRβ-RXRα and THRα-RXRα heterodimer coactivator recruitment assays and therefore the results might be "spurious." However, the EC_{50} values for MG-3196 are generally similar to the values published in Kelly MJ et al (THRβ-RXRα heterodimer activation EC_{50}=0.21µM and THRα-RXRα heterodimer activation EC_{50}=3.74µM).

Table 132. Summary of Thyroid Hormone Receptor/RXR Heterodimer Coactivator Recruitment Assay

Assay	Test Compound	EC_{50}	Minimum Significant Response**		Maximum Significant Response**		Concentration Range Tested
			Concentration	% Response*	Concentration	% Response*	
THRα-RXRα heterodimer coactivator recruitment	MG-3196	3.83µM	10µM	69%	100µM	85%	1 nM-100 µM
THRβ-RXRα heterodimer coactivator recruitment	MG-3196	0.70µM	1µM	58%	100µM	81%	1 nM-100 µM
THRα-RXRα heterodimer coactivator recruitment	MGL-3623	75.9µM	100µM	59%	100µM	59%	10 nM-1 mM
THRβ-RXRα heterodimer coactivator recruitment	MGL-3623	19.3µM	10µM	51%	100µM	67%	10 nM-1 mM

Source: Prepared by the nonclinical reviewer from study report TW04-0015410 pages 5-7
* Relative to T3 response.
** Criteria was ≥50% increase in fluorescence relative to T3 response.
Abbreviations: EC_{50}, half maximal effective concentration; THRα-RXRα, thyroid hormone receptor alpha-retinoid X receptor alpha; THRβ-RXRα, thyroid hormone receptor beta-retinoid X receptor alpha

13.2.1.2. In Vitro Pharmacology Study of Compounds 3196-M1 and MGL-3196, Study 100004698

MGL-3196 and 3196-M1 (MGL-3623) were evaluated in a THR radioligand assay. T3 was used as a reference compound. Rat liver tissue was the source of the THRs used in the binding determination. Equivalent mRNA concentrations for THR-α2 and THR-β1, but negligible concentrations of THR-α1 have been measured in adult rat liver (Keijzer et al. 2007). Since THR-α2 lacks the ligand binding domain and does not bind to T3 (Paisdzior et al. 2022), THR-β1 is assumed to be the receptor tested in this assay. The reported K_i values were 4.3×10^{-6} M and 1.3×10^{-7} M for MGL-3623 and MGL-3196, respectively. This demonstrates a 33-fold lower binding affinity for MGL-3623 compared to MGL-3196. The reported K_i for the reference compound T3 was 6.8×10^{-11}M. The K_d value for radiolabeled T3 was 0.24 nM.

13.2.2. Other Toxicology/Specialized Studies

13.2.2.1. Neutral Red Uptake Phototoxicity Assay of MGL-3196 in BALB/c 3T3 Mouse Fibroblasts, Study 3196-19-001

The phototoxic effects of MGL-3196 was evaluated in BALB/c 3T3 mouse fibroblasts. Cells were treated with MGL-3196 at concentrations ranging from 1.78 to 100 µg/mL, and viability was measured in the presence or absence of 5 J/cm^2 of UV-A and 21 to 22 mJ/cm^2 of UV-B radiation. Promethazine was used as the positive control. MGL-3196 did not show phototoxic potential in this assay.

13.2.3. Impurities/Degradants

13.2.3.1. [(b) (4)]: A Bacterial Reverse Mutation Test in Salmonella Typhimurium and Escherichia Coli, Study 3196-22-008

Background Information

The potential mutagenicity of the impurity [(b) (4)] (also known as [(b) (4)] was evaluated using both Derek 6.1.1 Nexus 2.4.0 (mutagenicity only) and LSMA Version 3.0.2-4 (mutagenicity suite) (Q)SAR tools, as described in the study report *ICH M7 Assessment of* [(b) (4)] (Study 3196-22-007). In the Derek model, mutagenicity of this impurity was predicated to be plausible due to the presence of an [(b) (4)]. The LMSA model provided a positive prediction for bacterial mutagenicity for [(b) (4)] based on two structural features ([(b) (4)] functional groups) that provided the strongest positive contributions to the mutagenic potential of the compound. Thus, [(b) (4)] was designated as Class 3 in accordance with (ICH M7(R2) 2023).

The Applicant conducted the current study (Ames test) for [(b) (4)] to confirm the positive mutagenicity prediction from the (Q)SAR methods.

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Table 133. Information, Study 3196-22-008

Study Features and Methods	Details
Study no.	3196-22-008
Study report location	Module 4.2.3.7.6
Drug lot #, % purity	2333-112, 99.9%
Strains	*Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) and *Escherichia coli* strain (WP2 uvrA)
Concentrations in definitive study	1.58, 5, 15.8, 50, 158, 500, 1581, and 5000 µg/plate
Basis of concentration selection	No dose range-finding study was conducted. The Applicant provided the following rationale for dose selection: "Typically, the test item is dosed at a range of concentrations but is only assessed at the five highest concentrations below the toxic concentration or, if non-toxic, at five concentrations up to the standard limit of 5000 µg/plate."
Negative control	Dimethyl sulfoxide (DMSO)
Positive control	**Table 134. Positive Controls With or Without Metabolic Activation** **Positive Controls (Concentrations) / Strains** Without Metabolic Activation (b) (4) — TA1537, TA98, TA100 and TA1535, WP2 uvrA TA1537, TA1535, WP2 uvrA, TA 98, TA 100 Source: Generated by FDA nonclinical reviewer. Note on Strains: • *Salmonella typhimurium* (TA1537, TA98, TA100, and TA1535) • *Escherichia coli* strain (WP2 uvrA)
Formulation/vehicle	(b) (4) was prepared in DMSO at 15.8, 50, 158, 500, 1581, 5000, 15811, and 50000 mcg/mL.
Incubation and sampling time	Plate incorporation method was used, and plates with or without addition of phenobarbital/5,6-benzoflavone induced male rat liver S9 mixture were incubated at 37°C for approximately 72 hours.
Comment on study validity	Valid.

Source: Generated by FDA nonclinical reviewer
Abbreviations: DMSO, dimethyl sulfoxide; FDA, U.S. Food and Drug Administration

Results

Cytotoxicity was observed at 5000 µg/plate in strains TA1537, TA98, and WP2 uvrA, and at ≥1581 µg/plate in strain TA100 in the absence of S9 mix.

(b) (4) did not produce an increase in number of revertant colonies in any of the tested *S. typhimurium* strains or in *E. coli* WP2 uvrA, with or without metabolic activation. Therefore, (b) (4) was negative for mutagenicity under the test conditions.

13.2.3.2. Leadscope Model Applier Assessments to Meet the Requirement of ICH M7 for MGL-3196, Study 3196-19-004

A total of thirteen compounds associated with the active pharmaceutical ingredient (MGL-3196) were assessed for potential mutagenicity using (Q)SAR or literature-based assessments. Eleven MGL-3196 impurities, and MGL-3196, were evaluated using LSMA version 2.3.7-1 (mutagenicity suite), a (Q)SAR prediction software package with both expert and statistical models.

The mutagenicity for (b) (4) (CAS # (b) (4)) and (b) (4) (CAS # (b) (4)) was assessed based on available literature in the public domain.

The genotoxicity potential of MGL-3196, the active pharmaceutical ingredient, was evaluated in two Ames assays (Study 2060M04 and Study 2363M07), in vitro micronucleus assay (Study 2057M04), in vitro chromosomal aberration assay (Study 2346M07), and in vivo micronucleus study in rats (Study 891007). MGL-3196 was negative for mutagenicity or genotoxicity in these studies under the test conditions (see Section 13.1.7).

LSMA results, conclusions, and proposed classifications based on (ICH M7(R2) 2023) are presented in Table 135.

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

The Applicant provided mutagenic information for [redacted] and [redacted] based on a literature search. However, the studies cited by the Applicant are either inadequate or unavailable online. This includes the following citations:

- National Library of Medicine / National Institutes of Health 2004. TOXNET, Hazardous Substances Database, United States National Library of Medicine/National Institutes of Health.
- [redacted]

Therefore, the nonclinical reviewer conducted a thorough literature search to obtain adequate mutagenicity information for [redacted] and [redacted] as shown in Table 136. Based on available mutagenicity data in the public domain, [redacted] and [redacted] were considered to be Class 5 impurities in accordance with (ICH M7(R2) 2023).

Table 136. Genotoxic Risk Assessment for [redacted] and [redacted]

Structures	Mutagenicity	Proposed ICH M7 Class
[redacted]	[redacted] was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA97, and TA98 at 100 to 10000 µg/plate, with and without the presence of metabolic activation [redacted] This compound was found to cause an increase in sister chromatid exchanges in Chinese hamster ovary cells but not in bone marrow cells of mice orally administered with doses ranging from [redacted]	5
	[redacted] was not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 at 4 to 5000 µg/plate, with and without the presence of metabolic activation [redacted]	5

Source: Prepared by the nonclinical reviewer
Abbreviation: ICH, International Council on Harmonisation

13.2.3.3. Computational Toxicity Assessment of [redacted], [redacted], and [redacted] Using the Leadscope Model Applier

The Applicant evaluated the potential mutagenicity of [redacted], [redacted], and [redacted] using both statistical-based ((Q)SAR) model (*E Coli-Sal 102 A-T Mut*, and *salmonella*

mutagenicity Genetox test) and Genetox Expert Alerts (Bacterial Mutation). The study results are reported in the following three study reports:

- Computational Toxicity Assessment Using the Leadscope Model Applier of (b) (4) (Study 3196-23-003)
- Computational Toxicity Assessment Using the Leadscope Model Applier of (b) (4) (Study 3196-23-004)
- Computational Toxicity Assessment Using the Leadscope Model Applier for (b) (4) (Study 3196-23-005)

The (Q)SAR results are reviewed and presented in Table 137.

Table 137. (Q)SAR Results for (b) (4)

	Leadscope Results for Impurities/Structures		
	Study 3196-23-003	**Study 3196-23-004**	**Study 3196-23-005**
	(b) (4)		
Parameters			
Genetox Suite:* E Coli – Sal 102 A-T Mut v1	Not in Domain	Negative	
Genetox Suite:** Salmonella Mut v3	Negative		
Genetox Expert Alerts: Bacterial Mutation v3	Negative		
Applicant's conclusions	(b) (4) were negative for mutagenicity based on the (Q)SAR analysis.		
FDA's conclusions	(b) (4) should be designated as Class 5 based on (ICH M7(R2) 2023).		

Source: Generated by FDA nonclinical reviewer.
* This is the statistical-based ((Q)SAR) model that predicts the results of either the *E. coli* or *Salmonella* TA102 strain mutagenicity (Ames) test.
** This is the statistical-based ((Q)SAR) model that predicts the results of the *Salmonella* mutagenicity (Ames) test.
Abbreviations: FDA, U.S. Food and Drug Administration; ICH, International Council on Harmonisation; (Q)SAR, quantitative structure-activity relationship

13.2.3.4. Comments on Inactive Ingredients

The inactive ingredients in the drug product (tablets containing 60, 80, or 100 mg resmetirom) include colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. In addition, the tablets are coated with Opadry II (white, yellow, or beige for the 60, 80, and 100 mg strengths, respectively). Based on the recommended doses, only one tablet among the available strengths will be ingested per day. There is no safety concern for the amount of daily exposure to the inactive ingredients or the expected chronic duration of use, based on the acceptance of these ingredients in FDA-approved drugs.

The coating for the 80 mg tablets contains yellow iron oxide, and the coating for the 100 mg tablets contains yellow iron oxide and red iron oxide. The maximum daily intake of elemental iron from these products will be less than 5 mg. Therefore, the drug product is compliant with 21 CFR 73.1200, which states that the maximum daily intake of the color additive synthetic iron oxide from drugs ingested by humans shall not exceed 5 mg, calculated as elemental iron per day.

14. Clinical Pharmacology

14.1. In Vitro Studies

At a dosage of 100 mg once daily (QD), the estimated mean (coefficient of variation (CV)%) C_{max} for resmetirom and MGL-3623 at steady state in patients with NASH is 971 (40.9%) ng/mL and 235 (27.5%) ng/mL, respectively. To interpret data from in vitro studies in the context of clinically relevant concentrations of resmetirom and MGL-3623, these C_{max} values translate to concentrations of 2.2µM and 0.5µM for resmetirom and MGL-3623, respectively.

14.1.1. In Vitro Absorption of Resmetirom, Study 09989

In Madin-Darby Canine Kidney (MDCK)II- multidrug resistance gene 1 (MDR1) cells, elacridar, an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) (FDA 2023), decreased the permeability of resmetirom in the basolateral to apical direction. Permeability of resmetirom was also assessed in Caco-2 cell monolayers. In Caco-2 cell monolayers resmetirom had an efflux ratio of 43.6 indicating efflux transport from the basolateral to apical direction. Nevertheless elacridar did not affect the efflux ratio. Discordant results were observed in Caco-2 cells in which elacridar did not impact resmetirom basolateral to apical permeability. The reason for this discrepancy may be because the Madin-Darby Canine Kidney II- multidrug resistance gene 1 cell line over-expresses P-gp. The results suggest that resmetirom undergoes transporter-mediated efflux. P-gp and other transporters likely contribute to resmetirom efflux. Notably, permeability and efflux were not affected by varying pH values between 5.5 and 7.4.

A membrane vesicle system was used to determine whether resmetirom is a substrate of BCRP. Addition of sulfasalazine, a BCRP substrate (FDA 2023), was found to decrease transport of radiolabeled resmetirom by 43%, suggesting that resmetirom is a substrate of BCRP.

Resmetirom was investigated as an inhibitor of transporter-mediated efflux of quinidine and loperamide in Madin-Darby Canine Kidney II- multidrug resistance gene 1 cells. Quinidine and loperamide are both substrates of P-gp and are acceptable for this evaluation (FDA 2023). Resmetirom did not inhibit the transport of either substrate in either direction. The data suggest that resmetirom is not an inhibitor of P-gp.

14.1.2. Plasma Protein Binding of Resmetirom and MGL-3623, Studies 10018, 3196-18-010

Plasma protein binding of resmetirom was determined via equilibrium dialysis at concentrations ranging from 250 to 20,000 ng/mL following incubation at 37 °C for 4 hours (Study 10018). The blood to plasma partitioning ratio was also determined at resmetirom concentrations ranging from 250 to 10,000 ng/mL. In human plasma, resmetirom was 99.39% bound to plasma proteins and the blood to plasma ratio was 0.55. Protein binding was independent of concentration.

Plasma protein binding of metabolite MGL-3623 was determined via equilibrium dialysis at concentrations ranging from 1 to 30µM following incubation at 37 °C for 6 hours (Study 3196-18-010). In human plasma, MGL-3623 was 98.81% bound to plasma proteins. Protein binding was independent of concentration.

14.1.3. Hepatobiliary Distribution of Resmetirom, Study 3196-16-011

The hepatobiliary distribution of resmetirom and metabolite MGL-3623 (M1) were evaluated in vitro using sandwich-cultured human hepatocytes (proprietary B-CLEAR® technology with Transporter Certified™ hepatocytes [QTS, Durham, NC]). The effects of temperature (4 and 37 °C) and concentration (3, 10, 30, and 100µM) on total (hepatic and bile) accumulation were also determined. Accumulation was found to be concentration- and temperature-dependent with total accumulation of both resmetirom and MGL-3623 increasing with increasing concentration from 3 to 100µM and increasing temperature from 4 to 37 °C. The data suggest that hepatic uptake of resmetirom is an active process. The temperature-dependent accumulation and formation of MGL-3623 is consistent with a metabolism-dependent mechanism.

The Biliary Excretion Index, which quantifies the biliary efflux potential as a fraction of total accumulation excreted into the bile pocket, was determined to be 33.7% and 30.4% for resmetirom and MGL-3623, respectively. The data suggest that both resmetirom and MGL-3623 can be eliminated in bile.

14.1.4. Resmetirom as a Substrate of Intestinal and Hepatic Uptake Transporter **OSTα/β** (Study 3196-20-004)

This in vitro study evaluated whether resmetirom is a substrate of the human organic solute transporter- α/β (OSTα/β), an uptake transporter located on the intestine and liver. Resmetirom at concentrations of 1, 10, and 100µM was incubated with MDCKII cells expressing human OSTα/β. Cellular uptake was compared to control MDCKII cells that did not express OSTα/β. At the lowest tested concentration of 1µM, the uptake ratio was 1.35. At concentrations of 10 and 100µM, the uptake ratios were 1.94 and 2.79, respectively. The uptake ratio for probe substrate rosuvastatin was ≤1.55 at concentrations up to 10µM. The data suggest that resmetirom is a substrate of human OSTα/β and this transporter is at least partially responsible for active uptake in the intestine and liver.

14.1.5. Resmetirom as a Substrate and Inhibitor of OATP1B1 and OATP1B3 (Study 09769)

The substrate and inhibitory potential of resmetirom was evaluated for transporters organic anion transporting polypeptide (OATP)1B1 and OATP1B3 using Chinese hamster ovary fibroblasts stably transfected with the human transporters. Uptake of ^{14}C-resmetirom were approximately 5- and 3-fold higher in Chinese hamster ovary cells expressing OATP1B1 and OATP1B3, respectively, relative to cells not expressing OATP transporters. Uptake was determined to be concentration-dependent and saturable across resmetirom concentrations of 1 to 40µM. Uptake in OATP transporter-expressing cells in the presence of 10µM cyclosporine A or ritonavir was decreased by 78 to 83% and 20 to 67%, respectively. Uptake of radiolabeled estradiol 17β-glucuronide (2µM) and pravastatin (1µM) was assayed in the presence of resmetirom. Both estradiol 17β-glucuronide and pravastatin are substrates of OATP1B1 and OATP1B3 and are acceptable for this evaluation (FDA 2023). In the presence of 10µM resmetirom, estradiol glucuronide uptake was decreased by about 60 to 70%, while pravastatin uptake was decreased by 29 to 57%.

The data indicate that resmetirom is a substrate of transporters OATP1B1 and OATP1B3. Resmetirom also demonstrated inhibitory potential of OATP-mediated uptake.

14.1.6. Resmetirom Metabolism and Evaluation as a CYP Substrate (Studies 3196-20-006, 01079-06, 10930, 3196-12-019)

Metabolic stability of resmetirom and formation of metabolite MGL-3623 was evaluated in human intestinal microsomes (Study 3196-20-006). Hepatic stability was assessed in cryopreserved human hepatocytes (Study 01079-06). After a 120-minute incubation with 100µM resmetirom in human intestinal microsomes, 76.5% of resmetirom remained and M1 was detectable after incubation. In cryopreserved human hepatocytes, resmetirom was found to have low clearance and high stability.

The metabolite profile of ^{14}C-radiolabeled resmetirom (20µM) was evaluated in human liver microsomes (HLM) and cryopreserved hepatocytes (Study 10930). Resmetirom was the major species remaining following 30-minute incubation in microsomes and hepatocytes, with 99.2% and 98.7% resmetirom remaining, respectively. A mono-oxygenated metabolite MGL-3623 was formed in both cell types. A second metabolite M2 with unknown structure was formed only in hepatocytes.

The cytochrome P450 (CYP) enzymes responsible for generation of metabolite MGL-3623 were determined following incubation of 10µM resmetirom in HLM and with cDNA-expressed human CYP isozymes (Study 3196-12-019). When incubated with HLM, MGL-3623 was the primary metabolite formed. With cDNA-expressed human CYP enzymes, MGL-3623 was only observed after incubation with CYP2C8. Formation of MGL-3623 was inhibited (~70%) in the presence of quercetin, a CYP2C8 inhibitor. The data indicate that CYP2C8 is the primary enzyme responsible for metabolizing resmetirom to MGL-3623.

14.1.7. Drug-Drug Interaction Potential of Resmetirom (Studies 3196-12-022, 3196-13-004, 3196-15-001, 3196-16-001, 3196-16-006, 3196-17-014, 3196-18-004, 3196-20-005, 3196-23-001, 09769, 09989, 10182, 10315)

As described above, resmetirom was identified as a substrate of CYP2C8, but not other CYP enzymes (Study 3196-12-019). Resmetirom was found to be a substrate of BCRP, OATP1B1, and OATP1B3, (Studies 3196-23-001, 09989, 09769). Resmetirom is not a substrate of P-gp (Studies 3196-23-001, 09989) or multidrug resistance protein 2 (MRP2) (Study 3196-16-006).

Inhibition

Inhibition of the CYP enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 was evaluated in pooled HLM at resmetirom concentrations up to 50µM (Studies 3196-12-022, 10315). Inhibition of CYP3A4 was assessed in HLM at concentrations up to 300µM (Studies 3196-15-001, 10315). Resmetirom inhibited CYP2C8 and CYP2C9 with half maximal inhibitory concentration (IC_{50}) values of 0.90µM and 22µM, respectively. No inhibition was observed for CYP2B6, while estimated IC_{50} values for CYP1A2, CYP2A6, CYP2C19, and CYP2D6 were ≥50µM. The average IC_{50} values for CYP3A4 were 215 µM (midazolam as a substrate) and >300µM (testosterone as a substrate). Time-dependent inhibition was not observed for any CYP enzyme.

Inhibition of uridine 5'-diphospho (UDP) glucuronosyltransferase (UGT) enzymes was assessed in UGT-expressed Supersomes™ at resmetirom concentrations up to 100µM (Study 3196-17-014). Resmetirom was found to inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, with IC_{50} values of 3.22µM, 16.7µM, 0.56µM, 44.2µM, 1.14µM, and 32.6µM, respectively.

Induction

Induction of CYP1A2, CYP2B6, and CYP3A4 was assessed in cryopreserved human hepatocytes at resmetirom concentrations up to 100µM (Study 3196-18-004). No induction was observed for CYP1A2. Induction was observed for CYP2B6 and CYP3A4, with EC_{50} values ranging from 37 to 50µM. Induction of CYP2C9, P-gp, and MRP2 was not observed in human hepatocytes at resmetirom concentrations up to 10µM (Study 10182).

The potential of resmetirom to induce UGT enzymes was determined In cryopreserved human hepatocytes at concentrations up to 100µM (Study 3196-20-005). Variability in UGT induction was observed across donors. Resmetirominduced UGT1A1 with EC_{50} values ranging from 14.3 to 97.4µM across two donors, while induction was incomplete for the third donor. Induction of UGT1A3 was also observed in two out of three donors with an EC_{50} of 1.67µM determined from a single donor. No induction was observed for UGT1A6 or UGT2B7. Given the observed inter-donor variability, it is difficult to make definitive conclusions on the ability of resmetirom to induce UGT enzymes.

Transporter Inhibition

Resmetirom inhibition of OATP1B1 and organic anion transporter (OAT)3 was assessed in transporter-expressing human embryonic kidney cells at concentrations up to 100µM (Study 3196-15-001). Inhibition of transporters OAT1, organic cation transporter 2, MATE1, and MATE2-K was assessed in transfected (human embryonic kidney)293 cells at concentrations up to 100µM (Study 3196-16-001). Inhibition of P-gp, bile salt export pump, and MRP2 was determined in vesicular transport inhibition assays (Studies 3196-23-001, 3196-16-006). The IC_{50} values for P-gp, OATP1B1, OAT3, and bile salt export pump were 99.6µM, 3.72µM, 4.53µM, and 34.7µM, respectively. The IC_{50} values for OAT1, MATE1, and MATE2-K were all >100µM. No inhibition of organic cation transporter 2 or MRP2 was observed. As previously described, resmetirom inhibited OATP1B3 by 60 to 70% at a concentration of 10µM (Study 09769).

Discordant results were observed for resmetirom inhibition of BCRP, which was evaluated in two in vitro studies. The first assessed inhibition in Caco-2 cells at resmetirom concentrations up to 300µM (Study 3196-15-001). The IC_{50} was 27.4µM. The second assessed inhibition in vesicular transport inhibition assays at resmetirom concentrations up to 300µM (Study 3196-23-001). The IC_{50} was 0.96µM. The reason for this discrepancy may be because assay conditions in the vesicular transport assay favor inhibition of BCRP by resmetirom:

- In vesicular transport assays (3196-23-001), membrane vesicles were pre-incubated with resmetirom for 15 minutes prior to initiation of the reaction. In the assay using Caco-2 cells (3196-15-001), there was no pre-incubation with cell monolayers.
- Both assays used estrone 3-sulfate, a known BCRP substrate,**Error! Bookmark not defined.** as the probe substrate. The concentration of estrone-3-sulfate used in the vesicular transport and Caco-2 cell assays was 1µM and 10µM, respectively.
  - In a literature report, the Michaelis constant (K_m) of estrone-3-sulfate for BCRP is reported to be 7.4µM (Elsby et al. 2023). Thus, Caco-2 cell assays used a substrate concentration around or greater than the K_m.

The IC_{50} of BCRP will be considered as the more conservative value of 0.96µM. Note that regardless of which value is used (i.e., 27.4 or 0.96µM), a potential drug-drug interaction (DDI) mediated via inhibition of BCRP is predicted.

14.1.8. Metabolite MGL-3623 as a Substrate of Transporters (Studies 3196-16-004, 3196-16-006)

MGL-3623 was evaluated as a substrate of transporters in MDR1-MDCK cells (P-gp), Caco-2 cells (BCRP), and transfected human embryonic kidney cells (solute carrier transporters) (Study 3196-16-004). MGL-3623 was evaluated as a substrate of MRP2 in vesicular transport assays (3196-16-006). MGL-3623 was determined to be a substrate of BCRP, OATP1B1, OATP1B3, and OAT3. MGL-3623 was not a substrate of P-gp, OAT1, organic cation transporter 2, or MRP2.

14.1.9. Metabolite MGL-3623 as an Inhibitor or Inducer of CYP Enzymes and Transporters (Studies 3196-13-002, 3196-13-004, 3196-16-004, 3196-16-006)

Inhibition of CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 by metabolite MGL-3623 was determined in pooled HLM at concentrations up to 50µM (Study 3196-13-002). MGL-3623 inhibited CYP2C8 with an IC_{50} of 6.10µM. MGL-3623 weakly inhibited CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 with IC_{50} values of >50µM, 27µM, 24µM, 33µM, and 35µM (both midazolam and testosterone as substrates). No inhibition of CYP2D6 was observed. MGL-3623 is not a time-dependent inhibitor of CYP3A4/5

MGL-3623 inhibited OATP1B3 with an IC_{50} of 22.6µM (Study 3196-13-004) and bile salt export pump with an IC_{50} >100µM (3196-16-006). MGL-3623 inhibited BCRP and OATP1B1 with IC_{50} values >10µM. MGL-3623 did not inhibit MRP2 or P-gp at concentrations up to 100µM.

14.2. In Vivo Studies

Formulations Used in Clinical Pharmacology Studies

The proposed to-be-marketed (TBM) formulation for resmetirom are oral immediate-release tablets available at strengths of 60, 80, or 100 mg. Several clinical pharmacology studies and the phase 3 studies (MGL-3196-11 and MGL-3196-14) were conducted using the oral tablets. However, the Applicant has noted that the proposed TBM tablet formulation differs from that used in the phase 3 studies via implementation of a tablet color-change for differentiation of tablet strengths. The Applicant provided comparative dissolution data to compare the phase 3 tablet formulation (Formulation 8) to the TBM tablet formulation (Formulation 8A). The biopharmaceutics review found that formulation 8 and formulation 8A had similar dissolution profiles. Refer to the Integrated Quality Review in DARRTS, dated January 29, 2024 (reference ID: 5318570). The data support bridging of the TBM tablet and the phase 3 tablet formulation.

The remaining clinical pharmacology studies and the phase 2 trial, MGL-3196-05 were conducted with prior oral capsule formulations. Six capsule formulations were used in Trials VIA-3196-01, VIA-3196-02, MGL-3196-03, MGL-3196-04, MGL-3196-05, and MGL-3196-07. A relative bioavailability (BA) study, Trial MGL-3196-08, was conducted to bridge the capsule formulations used in phase 2 trial, MGL-3196-05 and the mass balance study, Trial MGL-3196-07 (Formulations 5 [40 mg strength] and 6 [60 mg strength]) and a prototype tablet formulation (Formulation 7 [40 mg and 60 mg strengths]) that differed from the tablet formulation used in phase 3 studies (Formulation 8). Prototype tablet Formulation 7 was used in Trials MGL-3196-08, MGL-3196-09, and MGL-3196-10, in which a 100 mg dose of resmetirom was administered as 1 x 40 mg + 1 x 60 mg. Comparative dissolution data was provided comparing capsule Formulation 6 (60 mg capsule), tablet Formulation 7 (40 or 60 mg tablets), and tablet Formulation 8 (phase 3 formulation). The total excipient change between Formulation 7 and Formulation 8 is within 10% and similar dissolution profiles were observed. Refer to the Integrated Quality Review in DARRTS dated January 29, 2024 (reference ID: 5318570).

Clinical studies supporting clinical pharmacology information of resmetirom are summarized in Table 138.

Table 138. Summary of Clinical Pharmacology Studies

Study	Formulation[a]	Dose and Regimen
VIA-3196-01 (SAD in healthy adults)	Capsules (Formulations 1 to 4)	0.25, 1, 2.5, 5, 10, 20, 50, 100, 200 mg, single dose
VIA-3196-02 (MAD in healthy adults)	Capsules (Formulations 2 to 4)	5, 20, 50, 80, 100, and 200 mg QD for 14 days
MGL-3196-20 (SAD/MAD in healthy adults)	Tablets[b]	40, 60, 80, 100, or 200 mg as a single dose or QD for 6 days
MGL-3196-07 (Mass balance)	Capsules (Formulations 5 and 6)	100 mg (1 × 40 and 1 × 60 mg) QD for 6 days; 100 mg oral solution containing 100 µCi ^{14}C-resmetirom on Day 7
MGL-3196-03 (DDI: Effects on rosuvastatin and simvastatin)	Capsules (Formulation 4)	200 mg (4 × 50 mg) resmetirom QD for 11 days 20 mg simvastatin 10 mg rosuvastatin
MGL-3196-04 (DDI: Effects on atorvastatin)	Capsules (Formulation 4)	100 mg resmetirom (2 × 50 mg) QD for 9 days 20 mg atorvastatin
MGL-3196-09 (DDI: Effects on pioglitazone; food effect)	Tablets (Formulation 7)	100 mg (1 × 40 and 1 × 60 mg) resmetirom QD for 13 days 15 mg pioglitazone
MGL-3196-15 (DDI: Effects on pravastatin and simvastatin)	Tablets (Formulation 8)	100 mg (1 × 100 mg) resmetirom QD for 10 days 40 mg pravastatin 20 mg simvastatin
MGL-3196-16 (DDI: Effects on warfarin)	Tablets (Formulation 8)	100 mg (1 × 100 mg) resmetirom QD for 8 days Up to 5 mg warfarin (titrated) QD for 21 days
MGL-3196-12 (DDI: Effects of clopidogrel on resmetirom)	Tablets (Formulation 8)	100 mg (1 × 100 mg) resmetirom on Day 1, then QD on Days 6 to 14 300 mg (4 × 75 mg) clopidogrel on Day 3, then 75 mg QD on Days 4 to 11
MGL-3196-17 (Thorough QT)	Tablets (Formulation 8)	200 mg (2 × 100 mg) resmetirom QD for 6 days 400 mg moxifloxacin Placebo
MGL-3196-10 (Hepatic impairment)	Tablets (Formulation 7)	40, 60, 80, or 100 mg QD for 6 days (all dosed as 40 or 60 mg tablets)
MGL-3196-08 (Relative BA)	Capsules (Formulations 5 and 6), Tablets (Formulation 7)	100 mg (1 × 40 and 1 × 60 mg) Comparing the capsule formulations used in phase 2 trial and tablet formulation used in the HI study.
MGL-3196-05 (Phase 2 in subjects with NASH)	Capsules (Formulations 5 and 6)	80 mg (2 × 40 mg) QD for 4 weeks with exposure-based dose adjustment to

Study	Formulation[a]	Dose and Regimen
		either 40, 60, 80, or 120 mg (all dosed as 40 or 60 mg capsules) at Week 4 (total study duration of 36 weeks)
MGL-3196-11 (Phase 3 in subjects with NASH)	Tablets (Formulation 8)	80 or 100 mg QD for 12 months with possible dose reduction to 60 mg (1 × 60, 1 × 80, or 1 × 100 mg) Open-label arm: 80 mg QD with exposure- or safety-based dose adjustment to 100, 60 mg, or 40 mg at Week 4
MGL-3196-14 (Phase 3 in subjects with NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH")	Tablets (Formulation 8)	80 or 100 mg QD for 12 months with possible dose reduction to 60 mg (1 × 60, 1 × 80, or 1 × 100 mg) Open-label arm (subjects with compensated NASH cirrhosis): 80 mg QD with exposure- or safety-based dose adjustment to 100, 60 mg, or 40 mg at Week 4

Source: Reviewer-generated table derived from Applicant's Summary of Clinical Pharmacology, Module 2.3.P (Drug Product), and MGL-3196-20 Pharmacokinetics Report (IND 122865).
[a] All drug product formulations are for oral administration. The tablets used in phase 3 studies (formulation 8) differ from the proposed to-be-marketed tablet formulation by a color change (formulation 8A).
[b] The pharmacokinetics report for Trial MGL-3196-20 was submitted to IND 122865 on January 19, 2024. The protocol for this study indicates a tablet formulation manufactured by UPM Pharmaceuticals was used. It is unclear whether Formulation 7 or 8 was used.
Abbreviations: DDI, drug-drug interaction; MAD, multiple ascending dose; MGL-3196, resmetirom; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; QD, once daily; SAD, single ascending dose

14.2.1. Relative BA Study, Trial MGL-3196-08

Title

A single center, open-label, single-dose crossover, BA study of MGL-3196 tablets compared to capsules in healthy subjects.

Objectives

To assess the relative BA of a 100 mg MGL-3196 dose in tablet form compared to the corresponding capsule form.

Study Design

A total of 16 subjects were enrolled and completed the study.

- 100 mg resmetirom tablets on Day 1 followed by 100 mg resmetirom capsules on Day 5
- 100 mg resmetirom capsules on Day 1 followed by 100 mg resmetirom tablets on Day 5

The capsule formulation (formulations 5 and 6) and prototype tablet formulation (formulation 7) were both administered as 1 × 40 mg and 1 × 60 mg to make up 100 mg, and there were 4 days of washout period between the two treatments. All doses were administered following a 10-hour fasting period.

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a body mass index (BMI) between 18 and 32 kg/m^2. All

prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to receiving the first dose of drug. Concomitant medications were not permitted.

PK samples for resmetirom and metabolite MGL-3623 were collected on Days 1 and 5 predose, and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48.

PD samples for fasting lipids (high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, apolipoprotein B (ApoB), apolipoprotein A1 (ApoA1) were collected at Screening, predose on Days 1 and 5, and on Day 7. Reverse T3, thyroid binding globulin, SHBG, and lipoprotein A were collected predose on Days 1 and 5, and on Day 7. Samples for assessment of TSH, free and TT3, and free and total T4 were collected at Screening, predose on Days 1 and 5, Day 7, and additional samples were collected on Days 12-14.

PK Results

PK parameters for resmetirom and metabolite MGL-3623 following administration of the capsule and prototype tablet formulations are shown in Table 139 and Table 140, respectively.

Overall, bioequivalence between the capsule and prototype table formulations was not established based on the PK of resmetirom and MGL-3623. When administered as the prototype tablet, resmetirom and MGL-3623 exposures were approximately 12% and 22-23% greater, respectively, relative to that observed following administration of the capsule.

Table 139. Summary of Mean Plasma PK Parameters for Resmetirom Following a 100 mg Dose of Capsule or Tablet

PK Parameter	MGL-3196 in Capsule					MGL-3196 in Tablet			
	N	Mean	SD	%CV		N	Mean	SD	%CV
C_{max}, ng/mL	16	1,090	568	52.1		16	1,080	628	58.1
T_{max}, h*	16	4.00	2-6	-		16	4.00	2-6	-
AUC_{0-T}, ng·h/mL	16	3,690	1,760	47.6		16	4,070	2,170	53.4
AUC_{0-inf}, ng·h/mL	16	3,710	1,760	47.4		16	4,080	2,180	53.3
% AUC_{extr}	15	0.500	0.499	99.8		14	0.371	0.345	92.9
λ, h^{-1}	15	0.388	0.134	34.6		14	0.378	0.122	32.2
$T_{1/2}$, h	15	2.03	0.805	39.7		14	2.05	0.729	35.7
CL/F, L/h	15	36.4	20.5	56.3		14	27.6	10.4	37.7
Vd/F, L	15	92.9	34.0	36.6		14	72.4	14.1	19.5

Source: Table 13, page 39, CSR for MGL-3196-08
* Expressed as median and range
Abbreviations: AUC, area under the concentration-time curve; AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, (half-life), the time required for plasma concentration of a drug to decrease by 50%; λ, elimination rate constant

Table 140. Summary of Mean Plasma PK Parameters for MGL-3623 Following a 100 mg Dose of Capsule or Tablet

PK Parameter	MGL-3196 in Capsule					MGL-3196 in Tablet			
	N	Mean	SD	%CV		N	Mean	SD	%CV
C_{max}, ng/mL	16	576	295	51.1		16	674	304	45.2
T_{max}, h*	16	4.00	3-6	-		16	4.00	3-4	-
AUC_{0-T}, ng·h/mL	16	2,540	1,080	42.3		16	3,020	1,050	34.7
AUC_{0-inf}, ng·h/mL	16	2,560	1,080	42.0		16	3,040	1,060	34.8
% AUC_{extr}	15	0.858	0.796	92.8		16	0.532	0.380	71.6
λ, h^{-1}	15	0.282	0.103	36.6		16	0.272	0.0824	30.2
$T_{1/2}$, h	15	2.75	0.923	33.6		16	2.74	0.753	27.5

Source: Table 14, page 40, CSR for MGL-3196-08
* Expressed as median and range
Abbreviations: AUC, area under the concentration-time curve; AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, (half-life), the time required for plasma concentration of a drug to decrease by 50%; λ, elimination rate constant

Statistical analyses to compare the geometric means for the capsule and prototype tablet formulations for resmetirom and MGL-3623 are shown in Table 141 and Table 142, respectively. Bioequivalence criteria (i.e., geometric mean ratio falling within the 80 to 125% interval) was met for resmetirom C_{max} between the capsule and prototype tablet formulation. Both the area under the concentration-time curve from dosing (time 0) to time t and area under the plasma concentration versus time curve from time zero extrapolated to infinity (AUC_{0-inf}) were about 12% higher when resmetirom was administered as the prototype tablets relative to the capsules. For metabolite MGL-3623, bioequivalence criteria were not met for any PK parameter. Following administration of resmetirom tablets, MGL-3623 exposure was approximately 22 to 23% greater than that following administration of resmetirom capsules. As only 16 subjects were enrolled in MGL-3196-08, the Applicant hypothesizes that this may be due to high intersubject variability. The %CV for most PK parameters was >30% for both resmetirom and MGL-3623.

Table 141. Comparison of Geometric Mean PK Parameters for Resmetirom Following Administration of Capsules or Tablets

PK Parameter	MGL-3196		%Ratio[a]	Lower 90% CI[b]	Upper 90% CI[c]
	Capsule GLSM	Tablet GLSM			
C_{max} (ng/mL)	935	940	100.49	82.99	121.67
AUC_{0-T} (ng•h/mL)	3,260	3,670	112.48	95.80	132.07
AUC_{0-inf} (ng•h/mL)	3,280	3,680	112.32	95.80	131.69

Source: Table 15, page 41, CSR for MGL-3196-08
[a.] % ratio of MGL-3196 geometric means following MGL-3196 in tablet to capsule
[b.] Lower levels of the 90.00% CI
[c.] Upper levels of the 90.00% CI
Abbreviations: AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CSR, clinical study report; GLSM, geometric least-squares mean; MGL-3196, resmetirom; PK, pharmacokinetic

Table 142. Comparison of Geometric Mean PK Parameters for MGL-3623 Following Administration of Capsules or Tablets

PK Parameter	MGL-3196		%Ratio[a]	Lower 90% CI[b]	Upper 90% CI[c]
	Capsule GLSM	Tablet GLSM			
C_{max} (ng/mL)	504	613	121.78	105.56	140.51
AUC_{0-T} (ng•h/mL)	2,330	2,870	123.06	109.10	138.80
AUC_{0-inf} (ng•h/mL)	2,350	2,880	122.72	108.95	138.23

Source: Table 16, page 41, CSR for MGL-3196-08
[a.] % ratio of MGL-3623 geometric means following MGL-3196 in tablet to capsule
[b.] Lower levels of the 90.00% CI
[c.] Upper levels of the 90.00% CI
Abbreviations: AUC_{0-t}, area under the concentration-time curve from dosing (time 0) to time t; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CSR, clinical study report; GLSM, geometric least-squares mean MGL-3196, resmetirom; PK, pharmacokinetic

PD Results

Mean change from baseline to Day 7 or Day 12 in PD biomarkers was assessed. Changes from baseline to Day 12 in TSH, free and TT3, and free and total T4 are shown in Table 143. Changes from baseline to Day 7 in fasting lipids are shown in Table 144. Changes from baseline to Day 8 in cardiac biomarkers and other biomarkers including SHBG are shown in Table 145. Little to no changes in PD biomarkers were observed. As subjects only received two doses of resmetirom administered 5 days apart, significant changes in PD biomarkers are not expected.

Table 143. Summary Statistics for Changes in TSH, Free and Total T3, and Free and Total T4

		T3		T4	
	TSH (uIU/mL)	Free (pg/mL)	Total (ng/dL)	Free (ng/dL)	Total (ug/dL)
	n=16	n=16	n=16	n=16	n=16
Baseline (Mean (SD))	2.41 (1.814)	3.23 (0.359)	111.4 (12.69)	1.16 (0.115)	6.56 (0.777)
ΔBaseline[a] (Mean (SD))	0.08 (1.649)	0.58 (0.458)	15.6 (16.12)	0.08 (0.124)	0.18 (0.673)

Source: Table 21, page 49, CSR for MGL-3196-08
[a] Change from baseline at Day 12 relative to the first dose of MGL-3196
Abbreviations: SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone

Table 144. Summary Statistics for Changes in Fasting Lipids

	Total Cholesterol (mg/mL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)	ApoB (mg/dL)	ApoA1 (mg/dL)
	n=16	n=16	n=16	n=16	n=16	n=16
Baseline (Mean (SD))	200.0 (43.66)	130.2 (37.88)	47.3 (11.75)	161.3 (90.35)	101.4 (25.42)	141.6 (17.15)
ΔBaseline[a] (Mean (SD))	-10.7 (17.94)	-4.8 (15.54)	-3.3 (5.82)	-14.4 (58.12)	-12.8 (10.32)	-14.3 (11.58)

Source: Table 22, page 49, CSR for MGL-3196-08
[a] Change from baseline at Day 7 relative to the first dose of MGL-3196
Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CSR, clinical study report; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density n, number of subjects in subset; SD, standard deviation

Table 145. Summary Statistics for Changes in Cardiac Biomarkers, rT3, Lp(a), SHBG, and TBG

	Cardiac Biomarkers		Other Biomarkers			
	BNP (pg/mL)	CK-MB (ng/mL)	rT3 (ng/dL)	Lp(a) (mg/dL)	SHBG (nmol/L)	TBG (ug/mL)
	n=16	n=16	n=16	n=16	n=16	n=16
Baseline Mean (SD)	20.6 (12.72)	1.094 (1.0681)	16.88 (4.343)	24.7 (22.56)	35.4 (14.08)	18.28 (2.801)
ΔBaseline[a] Mean (SD)	-5.0 (8.87)	-0.293 (0.8307)	-1.01 (2.749)	3.9 (3.56)	0.1 (5.03)	0.20 (1.500)

Source: Table 23, page 50, CSR for MGL-3196-08
[a] Change from baseline at Day 7 relative to the first dose of MGL-3196.
Abbreviations: BNP, brain natriuretic peptide; CK-MB, creatine kinase MB; Lp(a), lipoprotein a; rT3, reverse triiodotronine; SHBG, sex hormone binding globule; TBH, thyroxine binding globule

14.2.2. Mass Balance Study, Trial MGL-3196-07

Title

An open-label, single radiolabeled dose, nonrandomized study to determine the mass balance of ^{14}C mgL-3196.

Objectives

- To determine the plasma PK and mass balance of ^{14}C-resmetirom total radioactivity in male human subjects after multiple oral doses
- To provide samples of whole blood, plasma, urine, and feces for metabolite identification and profiling

Study Design

A total of eight subjects were enrolled in the study. In the prestudy phase, subjects received a single 100 mg oral dose of resmetirom, administered as 100 mL of a 1 mg/mL suspension formulation. During the study phase, subjects received 100 mg resmetirom QD on Days 1 to 6. Doses were administered using the capsule formulation as 1 × 40 mg and 1 × 60 mg (formulations 5 and 6). On Day 7, subjects received 100 mg of a 1 mg/mL oral suspension formulation of resmetirom containing 100 µCi of ^{14}C-radiolabeled resmetirom. All doses were administered following a fasting period of at least 10 hours.

The study enrolled healthy male subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 14 or 7 days prior to receiving the first dose of drug. Subjects were excluded if they were treated with any known drugs that are moderate or strong inhibitors or inducers of CYP enzymes within 30 days prior to the first dose of study drug. Concomitant medications were not permitted.

Whole blood and plasma samples for radioanalysis were collected predose on Day 7, and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and at 24-hour intervals until discharge criteria were met (i.e., >90% of the administered radioactivity was excreted or sample collections contained <1% of administered radioactivity for 2 consecutive days).

Blood and plasma samples for metabolite identification and PK analysis were collected postdose during the prestudy phase at hours 2, 4, 6, and 8. During the study phase, samples were collected at predose on Days 2 through 7, 4 hours postdose on Day 6, and postdose on Day 7 at hours 0.5 ,1, 2, 3, 4, 6, 8, 12, 24, and at 24-hour intervals until discharge criteria were met.

Urine samples were collected predose on Day 7, then postdose at the following intervals: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, and then in 24-hour intervals until one of the discharge criteria were met. Fecal samples were collected predose on Day 7, and postdose at 0 to 24 hours, and then in 24-hour intervals until one of the discharge criteria were met.

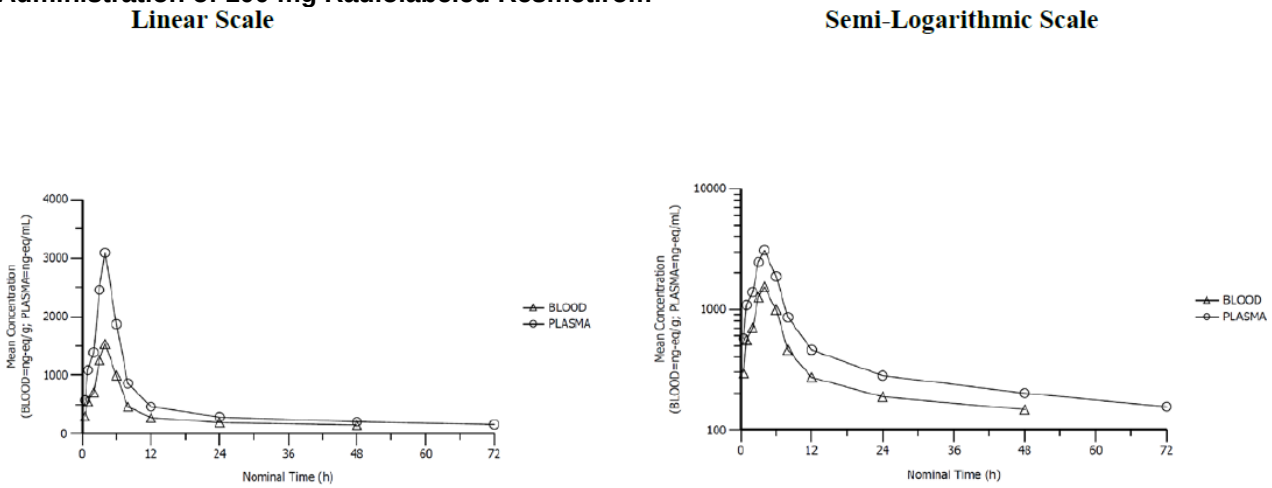
Radioactivity Results

Across all subjects, the mean (SD) total percent recovery of radiolabeled resmetirom in urine and feces was 91.01% (2.15). The major route of elimination was in the feces, which accounted for a

mean (SD) of 67.37% (3.98) of the administered radioactive dose. Renal excretion was a minor route of elimination, with a mean (SD) of 23.64% (4.01) of the radioactive dose recovered in the urine.

The mean concentration-time profile for ^{14}C-radiolabeled resmetirom in plasma and whole blood is shown in Figure 15. The time profiles indicate that radiolabeled resmetirom concentrations were higher in plasma relative to whole blood. PK parameters of total radioactivity are shown in Table 146. Based on C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$, radioactivity exposure in plasma was approximately 1.7- to 2.0-fold greater than in whole blood.

Figure 15. Mean Total Radioactivity Plasma and Blood Concentration-Time Profiles Following Administration of 100 mg Radiolabeled Resmetirom



Source: Figure 1, page 44, CSR for MGL-3196-07

Table 146. Plasma and Blood PK Parameters of Total Radioactivity Following Administration of 100 mg Radiolabeled Resmetirom

PK Parameter	Plasma				Blood			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng-eq/mL)	8	3,430	2,200	64.22	8	1,740	1,100	63.43
T_{max} (h)[a]	8	4.00 (1.00–6.00)	1.55	37.64	8	4.00 (1.00–6.00)	1.55	37.64
AUC_{last} (ng-eq•h/mL)	8	26,210	10,460	39.90	8	13,590	6,394	47.04
AUC_{0-inf} (ng-eq•h/mL)	8	35,720	9,446	26.45	6	21,490	7,778	36.19
$T_{1/2}$ (h)	8	34.39	27.23	79.20	6	26.16	27.76	106.15
CL/F (L/h)	8	3.004	0.9258	30.81	-	-	-	-
V_z/F (L)	8	141.0	108.1	76.66	-	-	-	-

Source: Table 16, page 56, Summary of Clinical Pharmacology
[a] Expressed as median and range.
Abbreviations: AUC_{last}, area under the concentration-time curve from dosing to the time of the last measured concentration; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects in treatment arm; SD, standard deviation; PK, pharmacokinetic; T_{max}, median time to maximum concentration; $T_{1/2}$, (half-life), the time required for plasma concentration of a drug to decrease by 50%, Vz/F, apparent volume of distribution during terminal phase

Radio-quantitation of resmetirom and its metabolites in plasma is shown in Table 147. Results indicate that resmetirom was the major radioactive component observed in plasma, accounting for about 55.22% of the total AUC_{0-24}. Metabolite MGL-3623, a mono-oxidation metabolite, is the second most abundant species, accounting for 15.91% of total AUC_{0-24}.

Oxalic acid was also formed as a metabolite, accounting for 14.46% of total AUC_{0-24}. The Applicant proposes that oxalic acid may be an artifact and/or degradation product of metabolites. All other metabolites accounted for <10% of total AUC_{0-24}, including M2 (mono-oxidation), M467_2 (double oxidation), and M611 (glucuronidation).

Table 147. Radio-Quantitation of Resmetirom and Metabolites in Plasma Following Administration of a 100 mg Radiolabeled Dose

Item	Oxalic Acid	M467_2	M1 (MGL-3623)	M2	M611	Resmetirom	Sum
AUC_{0-24} (ng-eq•h/mL)	3,047.04	961.6025	3,353.81	1,573.158	502.64	11,637.38	21,075.62
AUC%	14.46	4.56	15.91	7.46	2.38	55.22	100.00

Source: Table 17, page 56, Summary of Clinical Pharmacology
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; M1, metabolite 1, M2, metabolite 2

Notably, although oxalic acid was detected as a major metabolite in plasma, oxalic acid was not detected in urine. The Applicant hypothesizes that this may be due to possible precipitation of calcium oxalate that could have occurred during sample processing, and/or another biological excretion process. The Applicant indicated that oxalic acid was not measured in other clinical PK studies of resmetirom. Oxalic acid is present in certain foods and is also produced endogenously

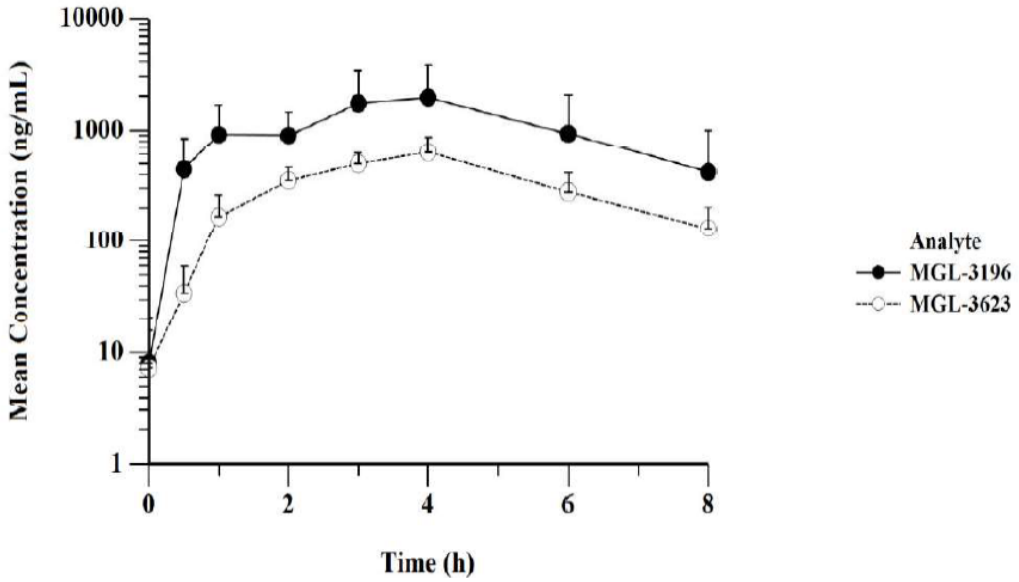
in humans. Given that oxalic acid concentrations in humans may depend on diet, it would be difficult to attribute the measured quantity of oxalic acid to resmetirom dosing. In addition, per the Applicant, endogenous plasma levels of oxalic acid are approximately twice as high as those formed from a 100 mg dose of resmetirom.

In urine, resmetirom accounted for 1.02% of the administered radiolabeled dose, and 5.12% of the total radiolabeled material in urine. Metabolite MGL-3623 was the primary species in urine, accounting for 15.71% of the dose, and 78.43% of the total radiolabeled material in urine. In feces, resmetirom was not detected, while MGL-3623 accounted for 3.30% of the dose.

Non-Radiolabeled PK Results

The concentration-time profiles of resmetirom and MGL-3623 in plasma after dosing on Day 7 is shown in Figure 16. PK parameters are shown in Table 148. Following multiple doses of resmetirom the mean C_{max} and AUC_{0-24} of MGL-3623 were approximately 47.2% and 51.4% those of resmetirom. As the PK parameters shown are those following administration of an oral solution formulation, differences from the capsule and tablet formulations evaluated in other studies are expected.

Figure 16. Plasma Concentration-Time Profiles of Resmetirom (MGL-3196) and MGL-3623 on Day 7



Source: Figure 10, page 58, Summary of Clinical Pharmacology.

Table 148. Summary of Plasma PK Parameters of Resmetirom (MGL-3196) and MGL-3623 on Day 7 Following Administration of 100 mg of an Aqueous Oral Formulation

	MGL-3196				MGL-3623			
PK Parameter	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	8	2250	1770	78.5	8	644	233	36.1
T_{max}, h[a]	8	3.00	(1.00-6.00)		8	4.00	(3.00-4.00)	
AUC_{0-24}, ng·h/mL	8	10800	9850	91.6	8	3350	1,110	33.2
AUC_{last}, ng·h/mL	8	10700	9870	91.9	8	3350	1,110	33.2
C_{avg}, ng/mL	8	448	410	91.6	8	140	46.3	33.2
C_{min}, ng/mL	8	7.21	11.9	165	8	6.86	8.73	127
T_{min}, h	8	15.0	12.4	82.8	8	12.0	12.8	107
C_{last}, ng/mL	8	11.6	11.7	100	8	7.55	9.46	125
T_{last}, h	8	21.0	5.55	26.5	8	24.0	0.00	0.00
C_{trough}, ng/mL	8	8.04	12.7	158	8	7.25	8.48	117
λ, h^{-1}	8	0.300	0.116	38.6	8	0.204	0.0458	22.5
$T_{1/2}$, h	8	2.55	0.730	28.6	8	3.61	1.11	30.6
%MGL-3196 C_{max}[b]	8	47.2	32.7	69.3	-	-	-	-
%MGL-3196 $AUC_{(0-24)}$ [b]	8	51.4	31.3	60.9	-	-	-	-

Source: Table 14, page 51, CSR for MGL-3196-07

[a] Expressed as median and range

[b] % PK parameter of the metabolite (MGL-3623) compared to that of the parent compound (MGL-3196)

Abbreviations: AUC_{last}, area under the plasma concentration curve from time 0 to the last detectable time point at a steady state; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{avg}, average concentration during a dosing interval in steady state; C_{last}, last measured concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, concentration immediately prior to administration of the next dose; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; T_{min}, time of minimal plasma concentration; T_{last}, area under the concentration-time curve from the time of dosing through time t; λ, elimination rate constant

14.2.3. DDI Study With Pioglitazone and Food-Effect Study, Trial MGL-3196-09

Title

A single-center, open-label, drug interaction study of resmetirom with pioglitazone, and to assess food effect in healthy subjects.

Objectives

Primary

- To determine whether the single-dose PK (i.e., AUC) of pioglitazone is affected by chronic dosing with resmetirom 100 mg/day in healthy subjects.

Secondary

- Describe the effect, if any, of resmetirom on the C_{max} of pioglitazone and on the PK of pioglitazone metabolite M-IV (hydroxy-pioglitazone).
- Assess the effect of food on the PK of MGL-3196 and its metabolite MGL-3623 after a single dose of resmetirom.
- To assess the PK of resmetirom and its metabolite MGL-3623 under fasting conditions after a single dose of resmetirom and after six daily AM doses of 100 mg resmetirom in healthy subjects.

Exploratory

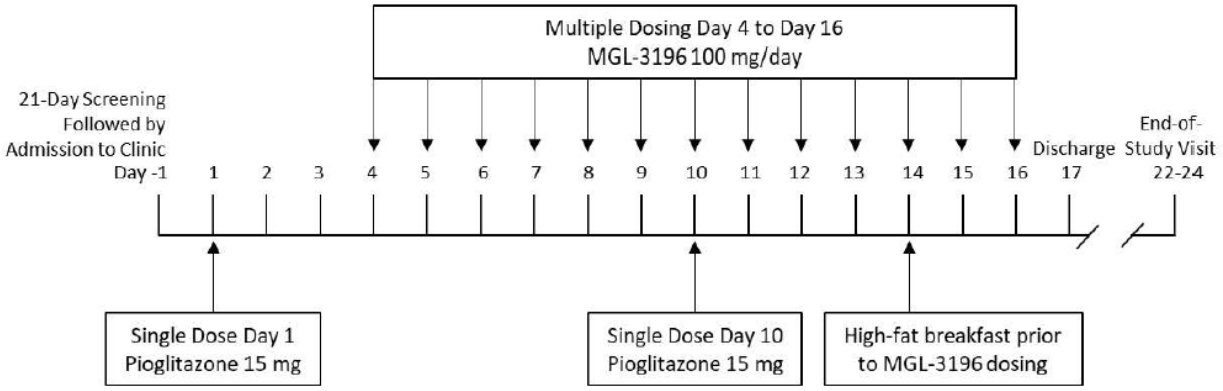
- To describe the thyroid hormone parameters after dosing with resmetirom 100 mg for 13 days in healthy subjects.
- To describe the lipid parameters after dosing with resmetirom 100 mg for 13 days in healthy subjects.

Study Design

This study was designed as an open-label, DDI study to determine whether resmetirom altered the PK of pioglitazone in healthy subjects. The effect of food on the PK of resmetirom was also assessed after repeated doses of resmetirom.

All subjects received resmetirom at a dose of 100 mg in the morning on Days 4 to 16. Pioglitazone 15 mg was orally administered under fasting conditions alone on Day 1, and concomitantly with resmetirom on Day 10, following administration of 7 daily doses of resmetirom. To assess food effect, all subjects received a high-fat breakfast on Day 14, approximately 30 minutes before resmetirom dosing.

Figure 17. Study Design, MGL-3196-06



Source: Figure 11, page 62, Summary of Clinical Pharmacology
Abbreviation: MGL-3196, resmetirom

All doses of resmetirom were administered using a tablet formulation as 1 × 40 mg and 1 × 60 mg (prototype formulation 7). Pioglitazone was supplied as 15 mg tablets as a commercially available generic product. On days when PK profiles were being collected (Days 1, 4, 9, 10, and 14), doses were administered following a fasting period of at least 10 hours. Subjects were

required to fast prior to Day 14, during which subjects received a high-fat breakfast prior to the dose of resmetirom.

The study enrolled healthy male and female subjects between the ages of 19 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to Day 1. Concomitant medications were not permitted.

Blood PK samples for pioglitazone were collected on Days 1 and 10 at predose and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96.

Blood PK samples for resmetirom and metabolite MGL-3623 were collected on Days 4, 9, 10, and 14 at predose and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 (Days 5, 10, 11, and 15). Additional trough PK samples were collected on Days 6, 7, 8, 12, 13, 16, and 17.

PD samples for fasting lipids (HDL, LDL, triglycerides, ApoB, ApoA1) were collected on Days -1, 4, and 17. Samples for SHBG were collected on Days 4 and 17. Samples for assessment of TSH, free and TT3, and free and total T4 were collected at screening, and on Days -1, 4, 9, 14, 17, and at the final visit (Days 22 to 24).

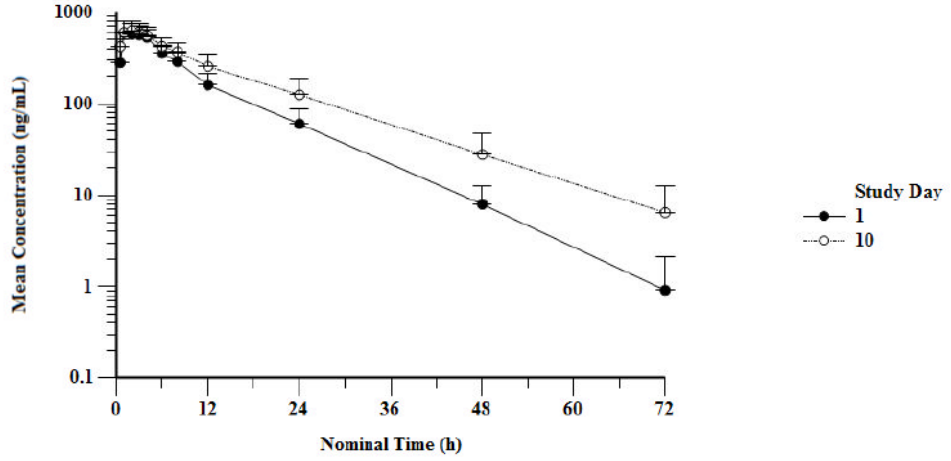
PK Results

A total of 16 subjects were enrolled in the study, and 15 completed the study, with 1 subject withdrawing on Day 6.

The data indicate that pioglitazone exposure increases when administered concomitantly with 100 mg/day resmetirom relative to administration of pioglitazone alone. Although little change in C_{max} was observed (6% increase), AUC_{inf} was increased by 45%. The concentration-time profiles suggests that clearance is slower following co-administration with resmetirom, which is corroborated by the longer observed half-life. When pioglitazone was co-administered with resmetirom, hydroxy-pioglitazone C_{max} and AUC_{last} decreased by 20% and 15%, respectively. Changes in pioglitazone clearance and decreases in the exposure of metabolite hydroxy-pioglitazone are consistent with the proposed mechanism of CYP2C8 inhibition.

The concentration-time profiles and PK parameters of pioglitazone when administered alone (Day 1) and when administered concomitantly with resmetirom (Day 10) are shown in Figure 18 and Table 149, respectively. The geometric mean ratio and associated 90% CI for C_{max} and AUC_{last} for both pioglitazone and metabolite hydroxy-pioglitazone are shown in Table 150.

Figure 18. Mean (SD) Plasma Concentration-Time Profiles Following a 15 mg Dose of Pioglitazone With (Day 10) or Without (Day 1) 100 mg/Day Resmetirom



Source: Figure 1, page 127, CSR for MGL-3196-09 Appendix 16.2.5.8
Note: The plot is shown on the semi-logarithmic scale.
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; SD, standard deviation

Table 149. Summary of Pioglitazone PK Parameters Following a 15 mg Dose of Pioglitazone With (Day 10) or Without (Day 1) 100 mg/Day Resmetirom

PK Parameter	Absence of MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	16	654	169	25.8	15	686	188	27.4
T_{max}, h	16	1.68	0.947	56.3	15	1.64	0.764	46.7
$AUC_{(0-72)}$, ng·h/mL	16	6,680	1,810	27.1	15	9,730	3,060	31.4
AUC_{last}, ng·h/mL	16	6,640	1,830	27.5	15	9,720	3,060	31.5
AUC_{inf}, ng·h/mL	16	6,680	1,820	27.2	15	9,840	3,140	31.9
% AUC_{extr}	16	0.784	0.645	82.2	15	1.05	0.888	84.2
λ, h^{-1}	16	0.0919	0.0261	28.4	15	0.0716	0.0202	28.2
$T_{1/2}$, h	16	8.01	1.84	23.0	15	10.3	2.53	24.5

Source: Table 1, page 118, CSR for MGL-3196-09 Appendix 16.2.5.8
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from dosing to the time of the last measured concentration; AUC_{0-72}, area under the curve from time 0 to the last measurable concentration (72 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CV, coefficient of variation; MGL-3196, resmetirom; N, total number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation $T_{1/2}$, (half-life), the time required for plasma concentration of a drug to decrease by 50%; λ, elimination rate constant

Table 150. GMRs and 90% CIs for Pioglitazone and Hydroxy-Pioglitazone PK Parameters Following a 15 mg Dose of Pioglitazone With (Day 10) or Without (Day 1) 100 mg/Day Resmetirom

PK Parameter	Pioglitazone GLSM		GMR[a] (%)	90% CI[b]
	Absence of Resmetirom	Presence of Resmetirom		
Pioglitazone				
C_{max} (ng/mL)	624	659	105.76	88.94–125.75
AUC_{last} (ng•h/mL)	6,390	9,250	144.69	124.38–168.33
Hydroxy-pioglitazone				
C_{max} (ng/mL)	257	206	79.93	73.16–87.34
AUC_{last} (ng•h/mL)	11,900	10,100	84.77	78.62–91.41

Source: Table 25, page 64, Summary of Clinical Pharmacology

[a.] GMR=geometric mean ratio (%) of pioglitazone (or its metabolite) with MGL-3196 to without MGL-3196.

[b.] CI=confidence interval around the geometric mean ratio.

Abbreviations: AUC_{last}, area under the concentration-time curve from dosing to the time of the last measured concentration; C_{max}, maximum plasma concentration; GLSM, geometric least squares mean; PK, pharmacokinetic

PK parameters of resmetirom and metabolite MGL-3623 measured on Days 4 (single dose), 9 (multiple dose), 10 (multiple dose plus pioglitazone), and 14 (multiple dose following a high-fat breakfast) are shown in Table 151. Following single and multiple doses of resmetirom, the median time to maximum concentration (T_{max}) ranged from 3.5 to 4 hours and the mean half-life ranged from 1.8 to 2.5 hours. Following 6 days of QD dosing, resmetirom C_{max} and AUC_{0-24} accumulated with a ratio of 2.4 and 2.9, respectively. MGL-3623 exhibits little accumulation as compared to parent drug. Little change in the PK of resmetirom and MGL-3623 was observed on Day 10 when resmetirom was co-administered with pioglitazone.

Table 151. PK Parameters of Resmetirom and MGL-3623 Following Single and Repeated Doses of 100 mg/Day Resmetirom

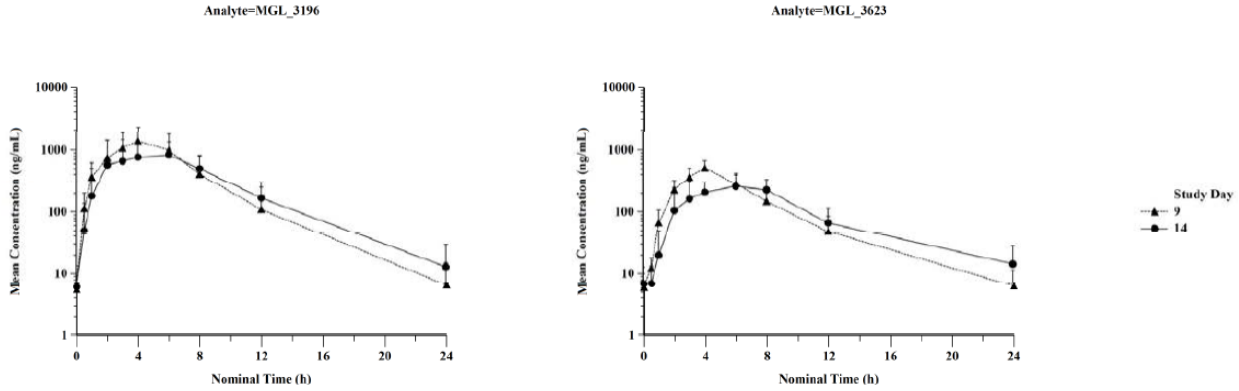
PK Parameter	Resmetirom				MGL-3623			
	N	Mean	SD	%CV	N	Mean	SD	%CV
Day 4 (Single Dose)								
C_{max} (ng/mL)	16	730	404	55.3	16	560	205	36.6
T_{max} (h)	16	3.48	(2.00-6.00)	34.1	16	3.98	(2.98-6.00)	22.1
AUC_{0-24} (ng•h/mL)	15	2,790	1,210	43.4	15	2,490	761	30.5
$T_{1/2}$ (h)	14	1.84	1.00	54.2	15	2.63	0.725	27.6
Day 9 (Multiple Dose)								
C_{max} (ng/mL)	15	1,650	1,030	62.4	15	522	154	29.5
T_{max} (h)	15	3.98	(2.98-6.02)	24.4	15	3.98	(2.98-6.00)	14.7
AUC_{0-24} (ng•h/mL)	14	8,780	5,490	62.5	15	2,860	884	31.0
$T_{1/2}$ (h)	14	2.48	0.558	22.5	15	3.57	0.980	27.5
C_{max} Ratio (Day 9/Day 4)	15	2.42	1.73	71.5	15	0.979	0.390	39.8
AUC_{0-24} Accumulation ratio (Day 9/Day 4)	15	2.86	1.49	52.1	15	1.15	0.323	28.1
Day 10 (Multiple Dose + Pioglitazone)								
C_{max} (ng/mL)	15	1,640	829	50.4	15	554	187	33.8
T_{max} (h)	15	4.00	(3.00-6.00)	25.5	15	4.00	(3.02-6.00)	14.5
AUC_{0-24} (ng•h/mL)	15	8,310	5,100	61.4	15	2,900	981	33.9
$T_{1/2}$ (h)	15	2.45	0.581	23.7	15	3.34	0.993	29.7
C_{max} Ratio (Day 10/Day 9)	15	1.10	0.351	31.9	15	1.08	0.268	24.8
AUC_{0-24} Ratio (Day 10/Day 9)	15	1.03	0.312	30.3	15	1.03	0.261	25.3
Day 14 (Multiple Dose Following a High-fat Breakfast)								
C_{max} (ng/mL)	15	1,110	819	73.8	15	319	151	47.4
T_{max} (h)	15	5.98	(2.00-8.20)	34.2	15	6.00	(2.00-8.20)	34.2
AUC_{0-24} (ng•h/mL)	13	7,550	4,780	63.3	11	2,390	1,040	43.7
$T_{1/2}$ (h)	13	2.80	0.663	23.7	11	4.12	1.48	36.0
C_{max} Ratio (Day 14/Day 9)	15	0.847	0.812	95.9	15	0.680	0.433	63.7
AUC_{0-24} Ratio (Day 14/Day 9)	15	0.925	0.263	28.4	15	0.849	0.187	22.0

Source: Table 26, page 64-65, Summary of Clinical Pharmacology
Note: For T_{max}, median is presented instead of mean and min-max are presented instead of SD.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, total number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, (half-life), the time required for plasma concentration of a drug to decrease by 50%

Concentration-time profiles and statistical analyses of resmetirom and MGL-3623 PK in the fasted (Day 9) and fed (Day 14) states are shown in Figure 19 and Table 152, respectively. When resmetirom is administered following a high-fat breakfast, the median T_{max} values of resmetirom and MGL-3623 are delayed by 2 hours to approximately 6 hours postdose. In the fed state, resmetirom C_{max} and AUC_{0-24} decreased by 33% and 11%, respectively, while MGL-3623 C_{max} and AUC_{0-24} decreased by 42% and 17%, respectively. Note that a 100 mg dose was

administered as 1 × 40 mg and 1 × 60 mg, which differs from the TBM tablets, which are available at strengths of 80 or 100 mg.

Figure 19. Mean (SD) Plasma Concentration-Time Profiles of Resmetirom and MGL-3623 Following 100 mg/Day in the Fasted (Day 9) and Fed (Day 14) States



Source: Figure 5, page 135, CSR for MGL-3196-09 Appendix 16.2.5.8
Note: The plots are shown on the semi-logarithmic scale.
Abbreviation: CSR, clinical study report; SD, standard deviation

Table 152. GMRs and 90% CIs for Resmetirom and MGL-3623 PK Parameters Following 100 mg/Day Resmetirom in the Fasted (Day 9) and Fed (Day 14) States

PK Parameter	Geometric Mean		GMR[a] (%)	90% CI[b]
	Fed (Test) (N = 15)	Fasted (Reference) (N = 15)		
Resmetirom				
C_{max} (ng/mL)	916	1,360	67.12	50.47–89.24
$AUC_{(0-24)}$ (ng•h/mL)	6,100	6,830	89.29	78.72–101.27
MGL-3623				
C_{max} (ng/mL)	291	496	58.61	45.91–74.81
$AUC_{(0-24)}$ (ng•h/mL)	2,260	2,720	83.04	75.19–91.70

Source: Table 27, page 66, Summary of Clinical Pharmacology
Note: Fed state=Day 14, fasting state=Day 9
[a] GMR=geometric mean ratio (%) of resmetirom (or its metabolite) under fed conditions to fasting conditions
[b] CI=confidence interval around the geometric mean ratio
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; N, number of subjects in treatment arm

PD Results

Little change in thyroid hormones was observed following resmetirom treatment in healthy subjects. Thyroid hormones including free and TT3, total T4, and TSH all remained within normal limits at baseline and throughout the study period. Free T4 was found to decrease below the reference range (1 to 1.8 ng/dL) on Days 17 and 22 with mean (SD) values of 0.93 (0.11) and 0.97 (0.15) ng/dL, respectively. Resmetirom treatment beginning on Day 4 was also found to

reduce lipoprotein(a) (mean change [SD]=10.2 [12.2]) and increase SHBG (mean change [SD] =42.8 [34.7]).

The impact of resmetirom on lipids are shown in Table 153. Following resmetirom dosing at 100 mg/day on Days 4 to 16, several lipid markers were found to decrease on Day 17, including cholesterol (LDL cholesterol), triglycerides, and ApoB.

Table 153. Change From Baseline in Lipid Markers Following 100 mg/Day Resmetirom from Days 4 to 16

	n	Mean (SD)	Change from Baseline Mean (SD)
Cholesterol (mg/dL)			
Baseline[a]	16	198.5 (31.27)	
Day 17	15	154.1 (24.42)	-43.3 (26.55)
HDL Cholesterol (mg/dL)			
Baseline[a]	16	55.1 (17.08)	-
Day 17	15	50.5 (14.19)	-3.5 (8.52)
LDL Cholesterol (mg/dL)			
Baseline[a]	16	140.0 (29.00)	-
Day 17	15	101.1 (21.72)	-38.5 (23.65)
Triglycerides (mg/dL)			
Baseline[a]	16	100.3 (54.89)	
Day 17	15	77.5 (40.31)	-23.9 (22.97)
Apolipoprotein A1 (mg/dL)			
Baseline[a]	16	155.1 (33.79)	-
Day 17	15	137.1 (29.02)	-15.7 (17.91)

	n	Mean (SD)	Change from Baseline Mean (SD)
Apolipoprotein B (mg/dL)			
Baseline[a]	16	99.6 (18.88)	
Day 17	15	76.8 (16.29)	-22.8 (15.12)

Source: Table 20, page 51-52, CSR for MGL-3196-09
Note: Reference ranges: cholesterol, 93 to 282 mg/dL; HDL cholesterol, 34 to 96 mg/dL; LDL cholesterol, 65 to 198 mg/dL; triglycerides, 38 to 269 mg/dL; apolipoprotein A1, 101 to 199 mg/dL (female) and 94 to 178 mg/dL (male); apolipoprotein B, 55 to 125 mg/dL (female) and 55 to 140 mg/DL (male).
[a] Baseline is defined as the result closest and prior to dosing on Day 4.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation

14.2.4. DDI Study With Clopidogrel, Trial MGL-3196-12

Title

A single-center, open-label, drug interaction study of resmetirom with clopidogrel in healthy subjects.

Objectives

Primary

- To determine whether the single- and multiple-dose PK of resmetirom is affected by coadministration with clopidogrel in healthy subjects.

Secondary

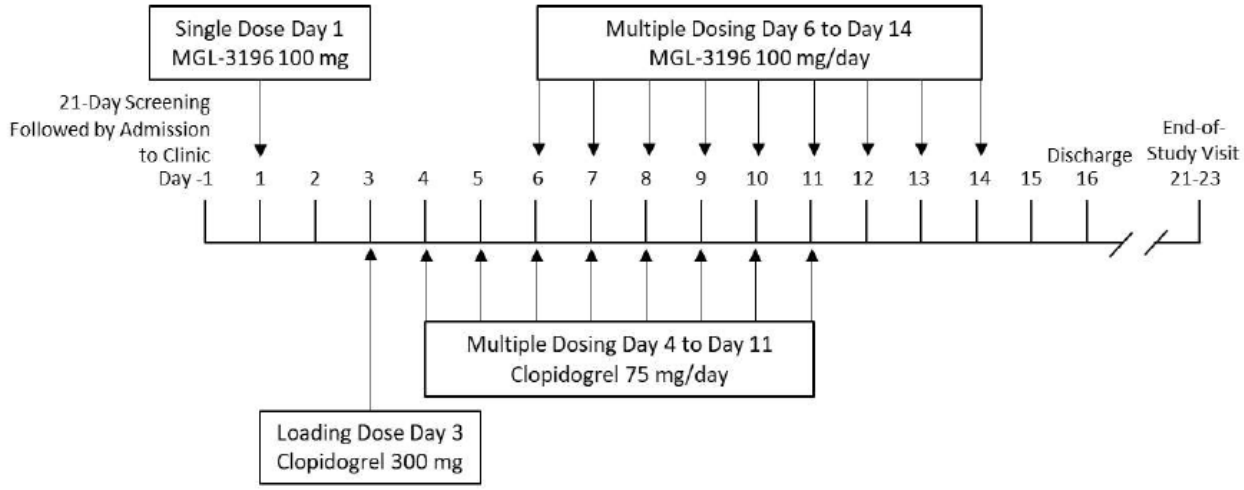
- To describe the effect, if any, of clopidogrel on the PK of resmetirom.
- To assess the safety and tolerability of 6 daily doses of 100 mg resmetirom in combination with 75 mg daily doses of clopidogrel in healthy subjects.

Study Design

This study was designed as an open-label DDI study to determine whether clopidogrel alters the PK of resmetirom as a CYP2C8 inhibitor.

All subjects received resmetirom at a dose of 100 mg in the morning on Day 1. Clopidogrel was administered beginning on Day 3, starting with a 300 mg oral loading dose, followed by 75 mg oral doses administered QD on Days 4 through 11. Resmetirom was administered at a dosage of 100 mg QD beginning on Day 6 through Day 14. Note that the dosage regimen for clopidogrel used in this study is the same as that recommended for the treatment of patients with acute coronary syndrome.

Figure 20. Study Design, Trial MGL-3196-12



Source: Figure 12, page 74, Summary of Clinical Pharmacology
Abbreviations: MGL-3196, resmetirom

All doses of resmetirom were administered using a tablet formulation as 1 × 100 mg (Formulation 8). Clopidogrel was supplied as 300 mg and 75 mg tablets as commercially available Plavix. On days when PK profiles were being collected, doses were administered following a fasting period of at least 8 hours.

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. All prescription or non-prescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to Day 1. Concomitant medications were not permitted.

Blood PK samples for resmetirom and metabolite MGL-3623 were collected predose on Days 1, 6, 7, 8, 9, 10, 11, 12, 13, and 14. Additional samples were collected postdose on Days 1, 6, 11, and 14 at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24.

Blood PK samples for clopidogrel and its metabolites were collected predose on Days 3, 5, 7, 11, and 13. Samples were also collected postdose on Days 5 and 11 at hours 0.5, 1, 2, 3, 4, 6, 12, and 24.

Urine PK samples for resmetirom were collected on Days 1, 6, 11, and 14 at predose, and the following intervals: 0-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, and 24-48 hours. On Days 9 and 10, urine PK samples were collected over an interval of 0-24 hours.

PD samples for fasting lipids (HDL, LDL, triglycerides, ApoB, ApoA1) were collected on Days -1, 6, and 14. Samples for TSH, free and TT3 and T4 were collected on Days -1, 6, 11, and 14. Samples for reverse T3 and SHBG were collected on Days 6 and 14.

PK Results

A total of 20 subjects were enrolled in the study. All 20 subjects completed the study.

The PK of resmetirom and MGL-3623 after a single dose was evaluated in the presence and absence of clopidogrel. A single 100 mg dose of resmetirom was administered on Day 1. PK data from Day 1 were compared to data on Day 6, when a single 100 mg dose of resmetirom was administered following administration of clopidogrel including a 300 mg loading dose and three 75 mg doses given QD. The summary of single-dose PK parameters for resmetirom and MGL-3623 in the presence and absence of clopidogrel is shown in Table 154 and Table 155. Statistical analyses, including calculation of geometric mean ratios and associated 90% CIs are shown in Table 156.

When resmetirom was co-administered with clopidogrel on Day 6, C_{max} and AUC increased by 1.9-fold and about 2.6-fold, respectively. No change in T_{max} was observed, while resmetirom exhibited a longer half-life of 3.2 hours (up from 2.0 hours) in the presence of clopidogrel. Exposure to MGL-3623 was reduced when resmetirom was co-administered with clopidogrel. The C_{max} and AUC of MGL-3623 decreased by 69% and 56 to 57%, respectively. The ratio of MGL-3623 exposure to resmetirom exposure also decreased when resmetirom was co-administered with clopidogrel. Taken together, the data are consistent with inhibition of resmetirom metabolism to MGL-3623 by clopidogrel and/or its metabolites.

Table 154. Summary of PK Parameters for Resmetirom Following a Single 100 mg Dose in the Absence (Day 1) and Presence (Day 6) of Clopidogrel

PK Parameter	Absence of Clopidogrel				Presence of Clopidogrel			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	20	1180	607	51.4	20	2130	754	35.4
T_{max} (h)[a]	20	4.00 (2-6)	-	-	20	4.00 (1-6)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	19	4600	1850	40.2	20	12,300	5570	45.5
$AUC_{(last)}$ (ng·h/mL)	20	4490	1840	40.9	20	12,300	5570	45.5
$AUC_{(0-inf)}$ (ng·h/mL)	19	4600	1850	40.2	20	12,400	5670	45.8
$\%AUC_{extr}$	19	0.497	0.352	70.9	20	0.954	0.633	66.4
λ (h^{-1})	19	0.392	0.129	32.9	20	0.220	0.0355	16.2
$T_{1/2}$ (h)	19	1.99	0.749	37.5	20	3.23	0.511	15.8

Source: Table 8, page 43, CSR for MGL-3196-12

[a] Expressed as median and range (min-max)

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, terminal elimination rate constant

Table 155. Summary of PK Parameters for MGL-3623 Following a Single 100 mg Dose of Resmetirom in the Absence (Day 1) and Presence (Day 6) of Clopidogrel

PK Parameter	Absence of Clopidogrel				Presence of Clopidogrel			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	20	705	248	35.2	20	229	111	48.7
T_{max} (h)[a]	20	4.00 (2-6)	-	-	20	4.00 (3-8)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	20	3400	1070	31.3	20	1510	597	39.6
$AUC_{(last)}$ (ng·h/mL)	20	3400	1070	31.3	20	1510	597	39.6
$AUC_{(0-inf)}$ (ng·h/mL)	20	3420	1070	31.3	17	1630	703	43.2
$\%AUC_{extr}$	20	0.536	0.327	61.0	17	8.98	5.83	64.9
λ (h^{-1})	20	0.231	0.0252	10.9	17	0.116	0.0338	29.0
$T_{1/2}$ (h)	20	3.04	0.424	13.9	17	6.45	1.88	29.1
% MGL-3196 C_{max}[b]	20	68.6	30.8	45.0	20	12.0	7.83	65.2
% MGL-3196 $AUC_{(0-24)}$[b]	19	85.2	36.9	43.4	20	14.4	8.90	61.8

Source: Table 9, page 44, CSR for MGL-3196-12

[a.] Expressed as median and range (min-max)

[b.] % PK parameter of the metabolite (MGL-3623) to that of the parent compound (MGL-3196)

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, terminal elimination rate constant

Table 156. Statistical Analyses for Resmetirom and MGL-3623 PK Following a Single 100 mg Dose of Resmetirom in the Absence (Day 1) and Presence (Day 6) of Clopidogrel

PK Parameter	No Clopidogrel Day 1 (Reference)	With Clopidogrel Day 6[a] (Test)	GMR(%)[b]	90% CI[c]
Resmetirom				
C_{max} (ng/mL)	1,040	1,990	190.62	160.44–226.47
AUC_{0-24} (ng•h/mL)	4,280	11,100	258.64	220.84–302.92
AUC_{0-inf} (ng•h/mL)	4,290	11,200	260.86	222.70–305.55
MGL-3623				
C_{max} (ng/mL)	658	205	31.10	26.36–36.69
AUC_{0-24} (ng•h/mL)	3,260	1,390	42.64	37.19–48.89
AUC_{0-inf} (ng•h/mL)	3,280	1,450	44.35	38.55–51.03

Source: Table 34, page 76, Summary of Clinical Pharmacology

[a] Clopidogrel: three consecutive doses of 75 mg/day from Days 4 to 6 (including a 300 mg loading dose on Day 3).

[b] GMR=geometric mean ratio (%) of resmetirom (or its metabolite) with clopidogrel to without clopidogrel.

[c] CI=confidence interval around the geometric mean ratio.

Abbreviations: AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

The PK of resmetirom and MGL-3623 following multiple doses of resmetirom was also evaluated in the presence and absence of clopidogrel. Resmetirom and MGL-3623 PK was assessed at steady state on Day 11 following six QD doses of 100 mg in the presence of clopidogrel (300 mg loading dose on Day 3, followed by 75 mg QD on Days 4 to 11). Resmetirom was dosed at 100 mg QD through Day 14, three additional days after clopidogrel dosing was halted. Note that per the labeling for Plavix, the half-life of clopidogrel is about 6 hours, while the half-life of its active metabolite is about 30 minutes.

The summary of multiple-dose PK parameters for resmetirom and MGL-3623 in the presence (Day 11) and absence (Day 14) of clopidogrel is shown in Table 157 and Table 158. Statistical analyses are shown in Table 159.

Relative to resmetirom administration alone on Day 14, when resmetirom was co-administered with clopidogrel on Day 11, C_{max} and AUC_{0-24} increased by 1.3-fold and 1.7-fold, respectively. As observed following a single dose, resmetirom exhibited a longer half-life of about 3.5 hours (up from 2.6 hours) in the presence of clopidogrel. At steady state, exposure to MGL-3623 was reduced when resmetirom was co-administered with clopidogrel, with C_{max} and AUC_{0-24} decreasing by 69% and 50%, respectively. As observed following a single dose, the ratio of MGL-3623 exposure to resmetirom exposure decreased when resmetirom was co-administered with clopidogrel. These data are consistent with inhibition of resmetirom metabolism to MGL-3623 by clopidogrel and/or its metabolites, although the effect of clopidogrel co-administration on resmetirom PK is less pronounced when resmetirom is dosed to steady state.

Table 157. Summary of PK Parameters for Resmetirom Following Multiple 100 mg Doses in the Absence (Day 14) and Presence (Day 11) of Clopidogrel

PK Parameter	Absence of Clopidogrel				Presence of Clopidogrel			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	20	2570	1910	74.6	20	2810	1370	48.8
T_{max} (h)[a]	20	4.00 (3-6)	-	-	20	4.00 (2-6)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	20	13,400	12,200	91.0	20	18,700	12,300	65.7
$AUC_{(last)}$ (ng·h/mL)	20	13,400	12,200	91.0	20	18,700	12,300	65.7
λ (h^{-1})	20	0.288	0.104	36.1	20	0.207	0.0437	21.1
$T_{1/2}$ (h)	20	2.61	0.634	24.2	20	3.49	0.772	22.1
C_{min} (ng/mL)	20	10.8	16.8	155	20	49.0	54.7	112
C_{av} (ng/mL)	20	558	508	91.0	20	781	513	65.7
C_{max} ratio (Day 14/Day 1)	20	2.17	1.29	59.3	-	-	-	-
$AUC_{(0-24)}$ ratio (Day 14/Day 1)	19	2.82	2.06	73.0	-	-	-	-

Source: Table 11, page 46, CSR for MGL-3196-12.
[a] Expressed as median and range (min-max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; C_{av}, average concentration during a dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration over a dosing interval; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, terminal elimination rate constant

Table 158. Summary of PK Parameters for MGL-3623 Following Multiple 100 mg Doses of Resmetirom in the Absence (Day 14) and Presence (Day 11) of Clopidogrel

PK Parameter	Absence of Clopidogrel				Presence of Clopidogrel			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	20	565	237	42.0	20	181	81.5	45.1
T_{max} (h)[a]	20	4.00 (3-6)	-	-	20	4.00 (3-8)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	20	3070	1440	46.9	20	1580	754	47.7
$AUC_{(last)}$ (ng·h/mL)	20	3070	1440	47.0	20	1580	754	47.7
λ (h^{-1})	20	0.189	0.0874	46.2	17	0.117	0.0355	30.3
$T_{1/2}$ (h)	20	4.35	1.85	42.5	17	6.53	2.28	34.9
C_{min} (ng/mL)	20	8.95	9.70	108	20	19.0	18.1	95.5
C_{av} (ng/mL)	20	128	60.0	46.9	20	65.9	31.4	47.7
C_{max} ratio (Day 14/Day 1)	20	0.846	0.277	32.8	-	-	-	-
$AUC_{(0-24)}$ ratio (Day 14/Day 1)	20	0.910	0.272	29.9	-	-	-	-
% MGL-3196 C_{max}[b]	20	31.9	17.9	56.1	20	7.67	5.22	68.1
% MGL-3196 $AUC_{(0-24)}$[b]	20	37.3	22.8	61.0	20	10.0	5.36	53.4

Source: Table 12, page 47, CSR for MGL-3196-12.
[a.] Expressed as median and range (min-max).
[b.] % PK parameter of the metabolite (MGL-3623) to that of the parent compound (MGL-3196).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; C_{av}, average concentration during a dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration over a dosing interval; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, terminal elimination rate constant

Table 159. Statistical Analyses for Resmetirom and MGL-3623 PK Following Multiple 100 mg Doses of Resmetirom in the Absence (Day 14) and Presence (Day 11) of Clopidogrel

PK Parameter	No Clopidogrel Day 14[a] (Reference)	With Clopidogrel Day 11[b] (Test)	GMR(%)[c]	90% CI[d]
Resmetirom				
C_{max} (ng/mL)	1,920	2,530	131.89	100.50–173.06
AUC_{0-24} (ng•h/mL)	9,090	15,900	174.95	133.47–229.33
MGL-3623				
C_{max} (ng/mL)	525	163	31.06	24.29–39.72
AUC_{0-24} (ng•h/mL)	2,830	1,420	50.38	41.74–60.80

Source: Table 34, page 77, Summary of Clinical Pharmacology
[a.] Resmetirom: multiple doses of 100 mg/day (9 consecutive days of resmetirom, 6 with clopidogrel Days 6 to 11, and 3 without clopidogrel, from Days 12 to 14).
[b.] Clopidogrel: 8 consecutive doses of 75 mg/day from Days 4 through 11 (including a 300 mg loading dose on Day 3).
[c.] GMR=geometric mean ration (%) of resmetirom (or its metabolite) with clopidogrel to without clopidogrel.
[d.] CI=confidence interval around the geometric mean ratio.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

The percent of resmetirom excreted in urine following single and multiple doses is shown in Table 160. Although excretion of resmetirom in urine remained low throughout the treatment period, the fraction of the dose excreted in urine increased when measured during clopidogrel co-administration. The percent MGL-3623 excreted in urine was found to decrease when measured during clopidogrel co-administration (11.8 to 14.6% in the absence of clopidogrel to 6.8 to 7.4% in the presence of clopidogrel). The increase in resmetirom urine excretion may therefore be due to a reduction in resmetirom metabolism.

Table 160. Summary of Percent Resmetirom Excreted in Urine Following 100 mg Doses in the Absence and Presence of Clopidogrel

Day	Clopidogrel	PK Parameter	N	Mean (%)	SD (%)	%CV
1	Absence	%Excreted	20	0.704	0.627	89.2
6	Presence	%Excreted	20	1.87	1.23	65.8
10	Presence	%Excreted	20	3.16	2.84	89.6
11	Presence	%Excreted	20	2.17	1.37	63.3
14	Absence	%Excreted	20	1.19	0.933	78.2

Source: Table 36, page 77, Summary of Clinical Pharmacology
Abbreviations: CV, coefficient of variation; N, number of subjects in each treatment arm; PK, pharmacokinetic; SD< standard deviation

The PK of clopidogrel and two metabolites was assessed in the presence and absence of resmetirom. Clopidogrel PK on Day 5 (300 mg loading dose on Day 3 followed by 75 mg QD) was compared to that on Day 11 (co-administration with resmetirom dosed to steady state). Statistical analyses for clopidogrel and two metabolites (an active thiol metabolite [AM-MPB] and an inactive carboxylic acid metabolite [CLPA]) are shown in Table 161.

Little change in the PK parameters of clopidogrel and its metabolites were observed in the presence of resmetirom. Clopidogrel C_{max} was unchanged, while AUC increased by 1.1- to 1.2-fold. The active thiol metabolite, AM-MPB, showed increases in C_{max} and AUC by 1.2-fold, and 1.3-fold, respectively. The inactive carboxylic acid metabolite, CLPA, showed a reduced C_{max} by about 17% with no change in AUC. Overall, resmetirom was not found to impact the PK of clopidogrel and its two major metabolites.

Table 161. Statistical Analyses for PK of Clopidogrel and Metabolites in the Absence (Day 5) and Presence (Day 11) of Resmetirom

PK Parameter	Clopidogrel Geometric Mean		% Ratio[a]	CI 90% Lower[b]	CI 90% Higher[c]
	Absence of MGL-3196	Presence of MGL-3196			
C_{max} (ng/mL)	0.890	0.911	102.30	85.00	123.11
$AUC_{(0-24)}$ (ng·h/mL)	1.91	2.29	119.98	91.75	156.90
$AUC_{(last)}$ (ng·h/mL)	1.53	1.72	112.73	90.68	140.14
$AUC_{(0-inf)}$ (ng·h/mL)	1.91	2.11	110.61	86.62	141.25
PK Parameter	**Clopidogrel AM-MPB Geometric Mean**		**% Ratio[a]**	**CI 90% Lower[b]**	**CI 90% Higher[c]**
	Absence of MGL-3196	**Presence of MGL-3196**			
C_{max} (ng/mL)	10.0	11.6	116.28	92.21	146.65
$AUC_{(0-24)}$ (ng·h/mL)	12.7	16.5	130.22	118.39	143.24
$AUC_{(last)}$ (ng·h/mL)	12.5	16.3	131.25	119.04	144.72
$AUC_{(0-inf)}$ (ng·h/mL)	12.7	16.6	130.32	118.25	143.62
PK Parameter	**CLPA Geometric Mean**		**% Ratio[a]**	**CI 90% Lower[b]**	**CI 90% Higher[c]**
	Absence of MGL-3196	**Presence of MGL-3196**			
C_{max} (ng/mL)	2400	1990	83.07	70.27	98.21
$AUC_{(0-24)}$ (ng·h/mL)	8570	8170	95.37	91.03	99.91
$AUC_{(last)}$ (ng·h/mL)	8570	8170	95.37	91.03	99.91
$AUC_{(0-inf)}$ (ng·h/mL)	9480	9110	96.03	90.69	101.68

Source: Table 17, page 52, CSR for MGL-3196-12

[a.] % Ratio of clopidogrel, clopidogrel AM-MPB, or CLPA geometric means with to with without MGL-3196.

[b.] Lower levels of the 90% CI

[c.] Upper levels of the 90% CI

Abbreviations: AM-MPB, derivatized active metabolite; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; CI, confidence interval; CLPA, inactive carboxylic acid metabolite; C_{max}, maximum plasma concentration; PK, pharmacokinetic

PD Results

Change from baseline in thyroid parameters and lipid parameters are shown in Table 162 and Table 163, respectively. Most thyroid parameters, including TSH, free and TT3, and total T4 remained within their respective reference ranges throughout the treatment period. Definitive changes in these parameters were not observed after resmetirom dosing. Free T4 was found to decrease with resmetirom dosing, with values below the lower limit of the reference range on Day 14.

Mean levels of lipid parameters were within the normal range at Baseline and Day 14. Decreases were observed for total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and ApoB. Although decreases were also observed for triglycerides, ApoA1, and lipoprotein (a), there was greater variability for these metrics.

Table 162. Change From Baseline Through Day 14 in Thyroid Hormone Parameters Following Resmetirom Dosing

	Mean (SD)	Change from Baseline Mean (SD)
	N=20	N=20
Thyrotropin (uIU/mL)		
Baseline	1.88 (0.798)	-
Day 6	2.12 (0.829)	0.24 (0.543)
Day 11	1.47 (0.706)	-0.41 (0.557)
Day 14	1.53 (0.863)	-0.35 (0.627)
Triiodothyronine Free (ng/L)		
Baseline	3.36 (0.268)	-
Day 6	3.07 (0.307)	-0.29 (0.364)
Day 11	2.93 (0.285)	-0.43 (0.261)
Day 14	2.85 (0.265)	-0.51 (0.311)
Triiodothyronine Total (ng/dL)		
Baseline	117.5 (14.00)	-
Day 6	122.0 (15.36)	4.5 (11.64)
Day 11	122.5 (15.72)	5.0 (11.63)
Day 14	118.4 (11.21)	1.0 (14.52)
Thyroxine Free (ng/dL)		
Baseline	1.25 (0.132)	-
Day 6	1.30 (0.154)	0.05 (0.147)
Day 11	1.04 (0.131)	-0.21 (0.128)
Day 14	0.91 (0.112)	-0.34 (0.099)
Thyroxine Total (µg/dL)		
Baseline	7.60 (0.904)	-
Day 6	7.76 (1.444)	0.17 (0.963)
Day 11	6.33 (1.130)	-1.27 (0.729)
Day 14	5.44 (0.956)	-2.16 (0.506)

Source: Table 19, page 56, CSR for MGL-3196-12.
Note: Baseline was defined as the result closest and prior to dosing on Day 1.
Note: Reference ranges: TSH, 0.4 to 4 mIU/L; T3 Free, 2.2 to 4.5 ng/L; T3 Total, 84 to 160 ng/dL; T4 free, 1 to 1.8 ng/dL; T4 total, 4.5 to 12 µg/dL.
Abbreviations: SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyroptropin (thyroid stimulating hormone)

Table 163. Change From Baseline to Day 14 in Lipid Parameters Following Resmetirom Dosing

	Mean (SD)	Change from Baseline Mean (SD)
	N=20	N=20
Total Cholesterol (mg/dL)		
Baseline[a]	188.0 (19.86)	-
Day 14	145.5 (26.32)	-42.6 (18.09)
HDL-C (mg/dL)		
Baseline[a]	48.7 (12.15)	-
Day 14	45.6 (9.48)	-3.1 (5.25)
LDL-C (mg/dL)		
Baseline[a]	126.2 (20.13)	-
Day 14	90.0 (24.98)	-36.2 (15.37)
Triglycerides (mg/dL)		
Baseline[a]	139.4 (62.03)	-
Day 14	115.0 (52.51)	-24.5 (34.47)
Apolipoprotein A1 (mg/dL)		
Baseline[a]	135.3 (19.95)	-
Day 14	121.6 (13.95)	-13.8 (13.33)
Apolipoprotein B (mg/dL)		
Baseline[a]	91.4 (14.71)	-
Day 14	69.4 (18.84)	-22.0 (9.33)
Lipoprotein(a) (nmol/L)		
Baseline[a]	66.4 (52.98)	-
Day 14	54.3 (53.61)	-12.1 (9.90)

Source: Table 20, page 57, CSR for MGL-3196-12
Note: Reference ranges: total cholesterol, 121 to 240 mg/dL; HDL-C, 31 to 85 mg/dL; LDL-C, 65 to 160 mg/dL; triglycerides, 37 to 228 mg/dL; ApoA1, >125 mg/dL (female) and >115 mg/dL (males); ApoB, 0 to 89 mg/dL; Lp(a), 0 to 74 nmol/L.
[a.] Baseline is defined as the results closest and prior to dosing on Day 6.
Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SD, standard deviation

Levels of SHBG were found to increase from Day 6 to Day 14 following multiple doses of resmetirom. Mean (SD) levels of SHBG increased from 45.4 (24.0) nmol/L on Day 6 to 99.2 (59.0) nmol/L on Day 14 (mean [SD] change from baseline of 54.0 [39.0] nmol/L).

14.2.5. DDI Study With Simvastatin and Pravastatin, Trial MGL-3196-15

Title

A single-center, open-label, drug interaction study of resmetirom with pravastatin and simvastatin in healthy subjects.

Objectives

Primary

- To determine whether the PK of pravastatin and its metabolite (3α-hydroxy isomer) are affected by chronic dosing with resmetirom in healthy subjects when given concomitantly or at approximately 12 hours after resmetirom.
- To determine whether the PK of simvastatin and simvastatin acid are affected by chronic dosing with resmetirom in healthy subjects when given concomitantly.

Secondary

- To assess the PK of resmetirom and its metabolite MGL-3623 after dosing with 100 mg resmetirom.
- To assess the safety and tolerability of resmetirom, pravastatin, and simvastatin administration in healthy subjects.

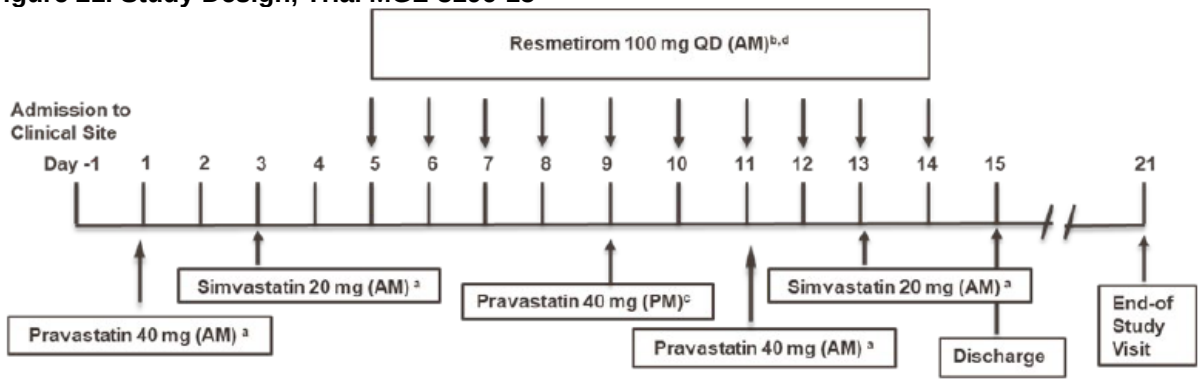
Study Design

This study was designed as an open-label DDI study to determine whether resmetirom alters the PK of pravastatin and/or simvastatin.

All subjects received pravastatin at a dose of 40 mg on the morning of Days 1 and 11. 40 mg pravastatin was also administered on the evening of Day 9 (approximately 10 p.m.). Simvastatin at a dose of 20 mg was administered on Days 3 and 13. Resmetirom at a dosage of 100 mg QD was administered on Days 5 through 14.

Note that the recommended starting dosage of pravastatin in adults is 40 to 80 mg QD and may be taken at any time of the day. The approved labeling for Pravachol (pravastatin sodium oral tablets) indicates that the systemic BA of pravastatin administered following a bedtime dose is decreased 60% compared to that following an AM dose. The recommended dosage of simvastatin in adults is 20 to 40 mg taken QD in the evening. In this study, simvastatin is administered only in the morning. Although this is not consistent with labeled recommendations, this design may increase the potential of observing an interaction relative to evening administration approximately 12 hours after resmetirom dosing (approx. 2-3 half-lives).

Figure 21. Study Design, Trial MGL-3196-15



Source: Figure 1, page 28, Protocol for MGL-3196-15
Abbreviations: QD, once daily

All doses of resmetirom were administered using a tablet formulation of 1 × 100 mg (formulation 8). Pravastatin was supplied as 40 mg tablets as a commercially available generic product. Simvastatin was supplied as 20 mg tablets as a commercially available generic product. On days when full PK profiles were being collected, doses were administered following a fasting period of at least 8 hours. Subjects were required to fast 4 hours prior to the evening dose of pravastatin administered on Day 9.

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 14 days prior to Day 1. Concomitant medications were not permitted.

Blood PK samples for simvastatin were collected on Days 3 and 13 at predose, and postdose at hours 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 16, 24, and 48.

Blood PK samples for pravastatin were collected following morning administration on Days 1 and 11 at predose, and postdose at hours 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 16, 24, and 48. Samples were also collected following evening administration on Day 9 at predose, and postdose at hours 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 16, and 24.

Blood PK samples for resmetirom and metabolite MGL-3623 were collected predose on Days 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14. Additional samples were collected postdose on Days 5, 11, and 13 at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24. PK blood samples for resmetirom and MGL-3623 were also collected on the evening of Day 9 at the same timepoints as for pravastatin.

PD samples for fasting lipids (HDL, LDL, triglycerides), TSH, and free and TT3 and T4 were collected at Screening, predose on Day 5 and on Day 15. Samples for SHBG were collected on Days 5 and 15.

PK Results

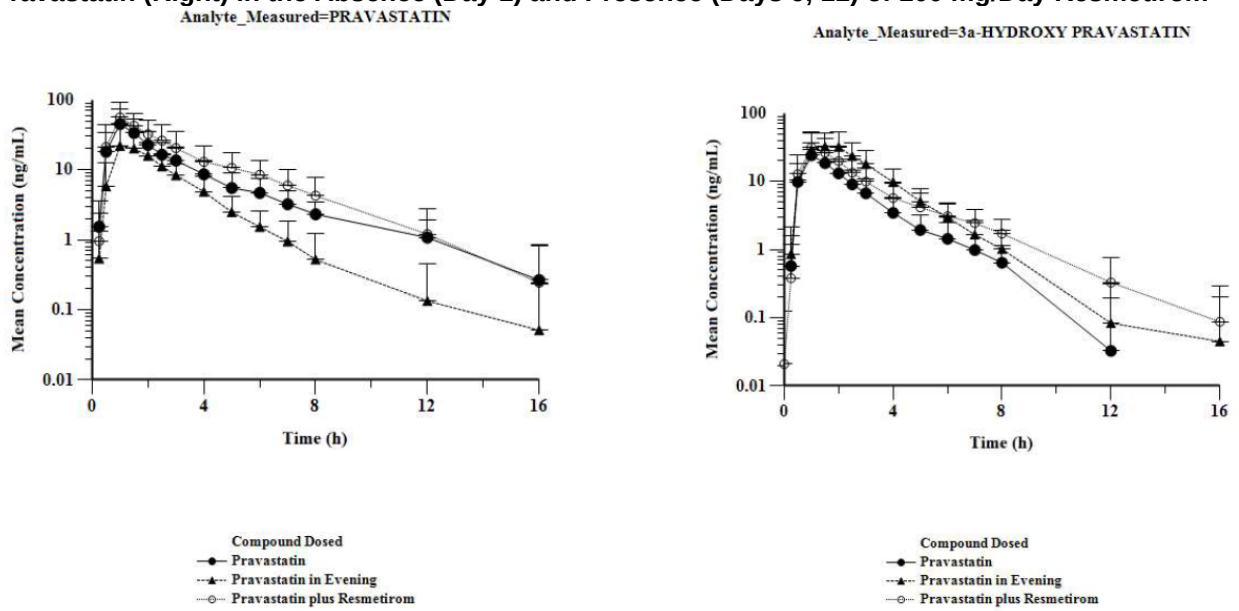
A total of 25 subjects were enrolled in the study and all 25 subjects completed the study.

Concentration-time profiles of pravastatin and metabolite 3α-hydroxy pravastatin in the absence and presence of resmetirom are shown in Figure 22. PK parameters for pravastatin and 3α-hydroxy pravastatin are shown in Table 164 and Table 165, respectively. Statistical analyses are

shown in Table 166. When a single 40 mg dose of pravastatin is co-administered with 100 mg/day resmetirom, the C_{max} and AUC_{0-24} of pravastatin increase 1.26- and 1.39-fold, respectively. The C_{max} and AUC_{0-24} of metabolite 3α-hydroxy pravastatin increase by 1.18- and 1.63-fold, respectively. Little change in T_{max} was observed for both species. The half-life of pravastatin did not change in the presence of resmetirom. However, the half-life of 3α-hydroxy pravastatin was slightly increased when pravastatin was co-administered with resmetirom.

C_{max} and AUC_{0-24} of pravastatin are decreased by about 54% and 65%, respectively, when pravastatin is administered in the evening, relative to in the morning (comparison of Day 9 to Day 11). This is consistent with effects noted in the approved labeling for pravastatin (Pravachol oral tablets) in which the systemic BA of pravastatin is decreased by about 60% when administered at bedtime compared to following a morning dose. C_{max} and AUC_{0-24} of 3α-hydroxy pravastatin were increased by 1.29- and 1.18-fold, respectively, when pravastatin is administered in the evening, relative to in the morning (comparison of Day 9 to Day 11).

Figure 22. Mean (SD) Plasma Concentration-Time Profiles of Pravastatin (Left) and 3a-Hydroxy Pravastatin (Right) in the Absence (Day 1) and Presence (Days 9, 11) of 100 mg/Day Resmetirom



Source: Figure 14, page 81, Summary of Clinical Pharmacology
Abbreviation: SD, standard deviation

Table 164. Summary of PK Parameters of Pravastatin in the Absence (Day 1) and Presence (Days 9, 11) of 100 mg/Day Resmetirom

Pharmacokinetic Parameter	Absence of Resmetirom (Day 1)				Presence of Resmetirom (Day 11)				Presence of Resmetirom (Day 9)			
	N	Mean	SD	%CV	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	25	46.1	28.0	60.7	25	58.3	32.8	56.2	25	26.6	20.4	76.8
T_{max} (h)[a]	25	1.00 (1-1.5)	-	-	25	1.00 (1-2)	-	-	25	1.50 (0.5-2.5)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	25	112	54.4	48.7	25	160	89.0	55.6	25	55.8	34.3	61.4
AUC_{last} (ng·h/mL)	25	108	54.2	50.4	25	155	87.1	56.4	25	54.2	34.1	62.9
AUC_{inf} (ng·h/mL)	25	112	54.6	48.6	25	161	90.0	55.9	25	56.2	34.5	61.4
$\%AUC_{extr}$	25	5.06	3.27	64.5	25	4.83	4.63	95.8	25	3.99	3.38	84.7
λ (h^{-1})	25	0.269	0.0946	35.1	25	0.288	0.0981	34.1	25	0.501	0.219	43.7
$T_{1/2}$ (h)	25	2.92	1.07	36.5	25	2.76	1.21	43.7	25	2.00	2.28	114

Source: Table 9, page 43, CSR for MGL-3196-15.
[a] Expressed as median and range (min-max).[a.] Expressed as median and range (min-max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{last}; AUC_{inf}, area under the concentration-time curve from the time of dosing extrapolated to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ , terminal elimination rate constant

Table 165. Summary of PK Parameters of 3a-Hydroxy Pravastatin in the Absence (Day 1) and Presence (Days 9, 11) of 100 mg/Day Resmetirom

Pharmacokinetic Parameter	Absence of Resmetirom (Day 1)				Presence of Resmetirom (Day 11)				Presence of Resmetirom (Day 9)			
	N	Mean	SD	%CV	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	25	25.7	12.4	48.5	25	33.6	19.8	59.0	25	43.3	22.7	52.3
T_{max} (h)[a]	25	1.00 (0.5-2)	-	-	25	1.00 (0.5-2)	-	-	25	1.50 (0.5-2.5)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	25	51.8	25.8	49.9	24	83.9	41.8	49.8	25	99.3	44.7	45.0
AUC_{last} (ng·h/mL)	25	49.5	24.9	50.3	25	78.1	43.1	55.2	25	97.5	44.7	45.9
AUC_{inf} (ng·h/mL)	25	51.8	25.9	50.0	24	84.2	41.8	49.6	25	99.3	44.8	45.1
$\%AUC_{extr}$	25	5.20	3.61	69.4	24	4.86	3.88	79.8	25	2.23	2.27	102
λ (h^{-1})	25	0.465	0.245	52.7	24	0.349	0.125	35.9	25	0.546	0.143	26.1
$T_{1/2}$ (h)	25	1.82	0.881	48.4	24	2.31	1.16	50.2	25	1.38	0.498	36.0
% Pravastatin C_{max}[b]	25	74.8	65.7	87.8	25	77.3	57.9	74.9	25	203	95.1	46.9
% Pravastatin $AUC_{(0-24)}$[b]	25	60.4	57.8	95.8	24	68.8	46.5	67.6	25	209	92.2	44.2

Source: Table 10, page 45, CSR for MGL-3196-15.
[a.] Expressed as median and range (min-max).
[b.] % PK parameter of the metabolite (3α-hydroxy pravastatin) to that of the parent compound (pravastatin).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{last}; AUC_{inf}, area under the concentration-time curve from the time of dosing extrapolated to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ , terminal elimination rate constant

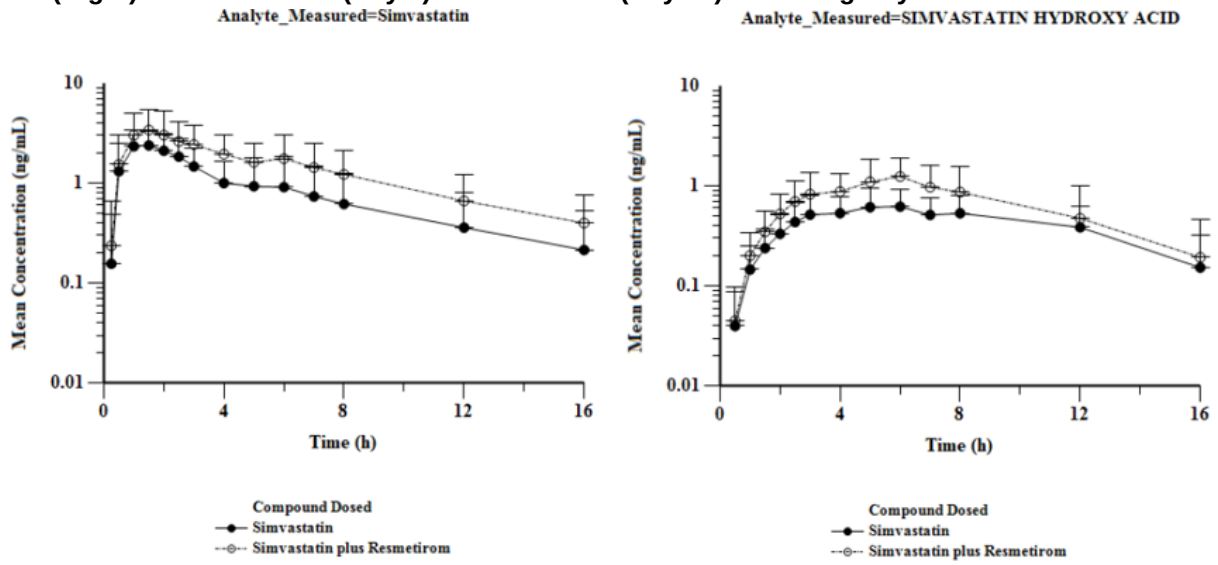
Table 166. Statistical Analyses of Pravastatin and 3a-Hydroxy Pravastatin PK in the Absence (Day 1) and Presence (Day 11) of 100 mg/Day Resmetirom

PK Parameter	Absence of Resmetirom (Day 1) Reference	Presence of Resmetirom[a] (Day 11) Test	GMR(%)[b] (90% CI)[c] Day 11/Day 1
Pravastatin			
C_{max} (ng/mL)	39.4	49.6	126.07 (107.79–147.44)
$AUC_{0\text{-}inf}$ (ng•h/mL)	99.6	138	139.04 (120.58–160.33)
3α-Hydroxy Pravastatin			
C_{max} (ng/mL)	22.5	26.6	118.27 (89.75–155.87)
$AUC_{0\text{-}inf}$ (ng•h/mL)	44.6	72.7	163.22 (133.26–199.91)

Source: Table 38, page 82, Summary of Clinical Pharmacology
[a.] Resmetirom was administered in the morning for 7 consecutive days with a single 40 mg dose of pravastatin.
[b.] GMR=geometric mean ratio (%) of pravastatin (or its metabolite) with resmetirom to without resmetirom.
[c.] CI=confidence interval around the geometric mean ratio.
Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

Concentration-time profiles of simvastatin and metabolite simvastatin acid in the absence and presence of resmetirom are shown in Figure 23. PK parameters for simvastatin and simvastatin acid are shown in Table 167 and Table 168, respectively. Statistical analyses are shown in Table 169. When a single 20 mg dose of simvastatin is coadministered with 100 mg/day resmetirom, the C_{max} and $AUC_{0\text{-}24}$ of simvastatin increase 1.39- and 1.75-fold, respectively. The C_{max} and $AUC_{0\text{-}24}$ of metabolite simvastatin acid increase by 2.01- and 1.57-fold, respectively. Little change in T_{max} was observed for both species. The half-life of simvastatin was slightly increased when co-administered with resmetirom. The half-life of simvastatin acid did not change in the presence of resmetirom.

Figure 23. Mean (SD) Plasma Concentration-Time Profiles of Simvastatin (Left) and Simvastatin Acid (Right) in the Absence (Day 3) and Presence (Day 13) of 100 mg/Day Resmetirom



Source: Figures 3 and 4, page 93-94, CSR for MGL-3196-15 Appendix 16.2.5.6
Abbreviations: MGL-3196, resmetirom; SD, standard deviation

Table 167. Summary of PK Parameters of Simvastatin in the Absence (Day 3) and Presence (Day 13) of 100 mg/Day Resmetirom

Pharmacokinetic Parameter	Absence of Resmetirom				Presence of Resmetirom			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	24	2.95	1.06	35.9	23	4.23	2.27	53.6
T_{max} (h)[a]	24	1.50 (0.5-6)	-	-	23	1.50 (1-6)	-	-
$AUC_{(0-16)}$ (ng·h/mL)	24	13.0	7.60	58.5	23	21.8	10.7	49.1
$AUC_{(0-24)}$ (ng·h/mL)	24	14.5	9.80	67.7	23	24.4	12.7	52.0
AUC_{last} (ng·h/mL)	24	14.3	9.87	69.0	23	24.4	12.8	52.4
AUC_{inf} (ng·h/mL)	22	13.5	6.97	51.6	21	26.2	15.7	59.9
$\%AUC_{extr}$	22	6.41	3.47	54.1	21	7.59	5.23	68.9
λ (h^{-1})	22	0.154	0.0639	41.5	21	0.130	0.0456	35.1
$T_{1/2}$ (h)	22	5.13	1.73	33.7	21	5.97	1.92	32.2

Source: Table 11, page 46, CSR for MGL-3196-15
[a] Expressed as median and range (min-max).
Abbreviations: $AUC_{(0-16)}$, area under the plasma concentration-time curve from time zero to 16 hours; $AUC_{(0-24)}$, area under the plasma concentration-time curve from time zero to 24 hours; AUC_{extr}, extrapolated area under the plasma concentration-time curve under the time of the last measurable concentration to infinity, expressed as percentage of AUC_{last}; AUC_{inf}, area under the plasma concentration-time curve from time to zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; SD, standard deviation; $T_{1/2}$, terminal half-life; T_{max}, median time to maximum concentration; λ , terminal elimination rate constant

Table 168. Summary of PK Parameters of Simvastatin Acid in the Absence (Day 3) and Presence (Day 13) of 100 mg/Day Resmetirom

Pharmacokinetic Parameter	Absence of Resmetirom				Presence of Resmetirom			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	24	0.718	0.321	44.7	23	1.54	0.903	58.7
T_{max} (h)[a]	24	5.50 (2.5-12)	-	-	23	6.00 (3-8)	-	-
$AUC_{(0-16)}$ (ng·h/mL)	19	7.17	3.23	45.1	22	10.4	5.96	57.1
$AUC_{(0-24)}$ (ng·h/mL)	18	8.43	4.08	48.4	22	11.8	7.52	63.5
AUC_{last} (ng·h/mL)	24	7.04	4.23	60.1	23	11.4	7.57	66.4
AUC_{inf} (ng·h/mL)	16	8.47	4.16	49.1	18	11.7	6.53	55.8
$\%AUC_{extr}$	16	7.89	4.71	59.7	18	7.68	4.61	60.0
λ (h^{-1})	16	0.170	0.0372	21.9	18	0.195	0.0935	48.0
$T_{1/2}$ (h)	16	4.33	1.29	29.9	18	4.39	2.02	46.0
% Simvastatin C_{max}[b]	24	28.0	21.9	78.4	23	42.4	32.0	75.5
% Simvastatin $AUC_{(0-24)}$[b]	18	61.6	35.6	57.9	22	53.7	46.6	86.8

Source: Table 12, page 47, CSR for MGL-3196-15.
[a.] Expressed as median and range (min-max).
[b.] % PK parameter of the metabolite (simvastatin hydroxy acid) to that of the parent compound (simvastatin).
Abbreviations: $AUC_{(0-16)}$, area under the plasma concentration-time curve from time zero to 16 hours; $AUC_{(0-24)}$, area under the plasma concentration-time curve from time zero to 24 hours; AUC_{extr}, extrapolated area under the plasma concentration-time curve under the time of the last measurable concentration to infinity, expressed as percentage of AUC_{last}; AUC_{inf}, area under the plasma concentration-time curve from time to zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal half-life; T_{max}, median time to maximum concentration; λ , terminal elimination rate constant

Table 169. Statistical Analyses of Simvastatin and Simvastatin Acid PK in the Absence (Day 3) and Presence (Day 13) of 100 mg/Day Resmetirom

PK Parameter	Absence of Resmetirom (Day 3) Reference	Presence of Resmetirom[a] (Day 13) Test	GMR(%)[b] (90% CI)[c] Day 13/Day 3
Simvastatin			
C_{max} (ng/mL)	2.71	3.75	138.54 (121.44–158.06)
AUC_{0-inf} (ng•h/mL)	12.9	22.5	174.62 (153.02–199.28)
Simvastatin Acid			
C_{max} (ng/mL)	0.646	1.30	201.45 (169.16–239.92)
AUC_{0-inf} (ng•h/mL)	6.33	9.93	156.72 (136.41–180.05)

Source: Table 39, page 84, Summary of Clinical Pharmacology
[a.] Resmetirom was administered in the morning for 9 consecutive days with a single 20 mg dose of simvastatin on Day 13.
[b.] GMR=geometric mean ratio (%) of simvastatin (or its metabolite) with resmetirom to without resmetirom.
[c.] CI=confidence interval around the geometric mean ratio.
Abbreviations: AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

PK of resmetirom and MGL-3623 following a single dose on Day 5 and multiple doses on Day 11 (in the presence of pravastatin) and Day 13 (in the presence of simvastatin) are shown in Table 170 and Table 171, respectively. Following multiple doses of resmetirom, C_{max} and AUC_{0-24} accumulated by 1.7- to 2.1-fold and 2.2- to 2.4-fold, respectively. No accumulation of C_{max} or AUC_{0-24} was observed for MGL-3623. This behavior is consistent with observations in other PK studies of resmetirom. Co-administration with pravastatin or simvastatin did not impact the PK of resmetirom. Although the C_{max} values of resmetirom and MGL-3623 appeared greater following co-administration with simvastatin, there was little difference in the AUC_{0-24} for both species.

Table 170. Summary of Resmetirom and MGL-3623 PK Following a Single 100 mg Dose (Day 5)

	Resmetirom Alone (Day 5)				MGL-3623 Alone (Day 5)			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	25	934	418	44.8	25	580	217	37.4
T_{max} (h)[a]	25	3.00 (1-6)	-	-	25	4.00 (2-6)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	21	3640	1600	43.9	25	4920	1500	51.4
AUC_{last} (ng·h/mL)	25	3460	1520	43.9	25	2920	1500	51.4
AUC_{inf} (ng·h/mL)	21	3650	1600	43.9	25	2940	1510	51.4
$\%AUC_{extr}$	21	0.409	0.253	61.8	25	0.677	0.424	62.7
λ (h^{-1})	21	0.414	0.148	35.8	25	0.254	0.101	39.6
$T_{1/2}$ (h)	21	1.93	0.801	41.5	25	3.02	0.857	28.4
% resmetirom C_{max}[b]	-	-	-	-	25	66.2	22.4	33.8
% resmetirom $AUC_{(0-24)}$[b]	-	-	-	-	21	89.3	36.4	40.8

Source: Table 15, page 50, CSR for MGL-3196-15/

[a] Expressed as median and range (min-max).

[b] % PK parameter of the metabolite (MGL-3623) to that of the parent compound (resmetirom).

Abbreviations: $AUC_{(0-24)}$, area under the plasma concentration-time curve from time zero to 24 hours; AUC_{extr}, extrapolated area under the plasma concentration-time curve under the time of the last measurable concentration to infinity, expressed as percentage of AUC_{last}; AUC_{inf}, area under the plasma concentration-time curve from time to zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal half-life; T_{max}, median time to maximum concentration; λ , apparent terminal elimination rate constant

Table 171. Summary of Resmetirom and MGL-3623 Steady State PK Following 100 mg/Day in the Presence of Pravastatin (Day 11) or Simvastatin (Day 13)

Pharmacokinetic Parameter	Resmetirom in Presence of Pravastatin (Day 11)				MGL-3623 in Presence of Pravastatin (Day 11)			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	24	1570	783	49.9	24	492	136	27.7
T_{max} (h)[a]	24	4.00 (2-6)	-	-	24	4.00 (2-6)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	23	7860	4120	52.4	24	2850	1360	47.7
AUC_{last} (ng·h/mL)	24	7700	4100	53.3	24	2850	1360	47.7
λ (h^{-1})	23	0.272	0.0578	21.3	24	0.212	0.0752	35.4
$T_{1/2}$ (h)	23	2.63	0.405	15.4	24	3.53	0.891	25.3
C_{min} (ng/mL)	24	3.64	4.41	121	24	5.04	6.50	129
C_{avg} (ng/mL)	23	327	171	52.4	24	119	56.6	47.7
% resmetirom C_{max}[b]	-	-	-	-	24	37.2	15.9	42.8
% resmetirom $AUC_{(0-24)}$[b]	-	-	-	-	23	42.7	18.6	43.6
Pharmacokinetic Parameter	**Resmetirom in Presence of Simvastatin (Day 13)**				**MGL-3623 in Presence of Simvastatin (Day 13)**			
	N	**Mean**	**SD**	**%CV**	**N**	**Mean**	**SD**	**%CV**
C_{max} (ng/mL)	25	1930	1810	93.4	25	669	907	136
T_{max} (h)[a]	25	4.00 (2-8)	-	-	25	4.00 (2-6)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	24	8690	5250	60.4	25	3070	1770	57.5
AUC_{last} (ng·h/mL)	25	8410	5320	63.3	25	3070	1770	57.5
λ (h^{-1})	23	0.277	0.0676	24.4	25	0.199	0.0784	39.3
$T_{1/2}$ (h)	23	2.60	0.463	17.8	25	3.88	1.36	34.9
C_{min} (ng/mL)	25	4.94	7.19	146	25	5.61	6.26	112
C_{avg} (ng/mL)	24	362	219	60.4	25	128	73.6	57.5
% resmetirom C_{max}[b]	-	-	-	-	25	36.8	15.9	43.3
% resmetirom $AUC_{(0-24)}$[b]	-	-	-	-	24	42.2	19.2	45.5

Source: Table 16, page 52, CSR for MGL-3196-15.

[a] Expressed as median and range (min-max).

[b] % PK parameter of the metabolite (MGL-3623) to that of the parent compound (resmetirom).

Abbreviations: $AUC_{(0-24)}$, area under the plasma concentration-time curve from time zero to 24 hours; AUC_{extr}, extrapolated area under the plasma concentration-time curve under the time of the last measurable concentration to infinity, expressed as percentage of AUC_{last}; AUC_{inf}, area under the plasma concentration-time curve from time to zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal half-life; T_{max}, median time to maximum concentration; λ , apparent terminal elimination rate constant

PD Results

Thyroid Parameters

Little changes in thyroid parameters were observed from Day 5 to Day 15 following dosing with 100 mg/day resmetirom. The mean (SD) change from Day 5 in TSH, total T4, free T4, TT3, and free T3 was -0.35 (0.72) mIU/L, -1.05 (0.61) µg/dL, -0.21 (0.12) ng/dL, 2.5 (11.9) ng/dL, and -0.01 (0.27) ng/L, respectively. It was noted that 9/25 subjects (36%) had shifts in free T4 from normal on Day 5 to low on Day 15. Increases in SHBG were observed from Day 5 to Day 15 with mean (SD) values of 42.6 (30.6) nmol/L and 71.7 (45.2) nmol/L.

Lipid Parameters

Following dosing with 100 mg/day resmetirom, the mean (SD) change from Day 5 to Day 15 in cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was -33.1 (17.0) mg/dL, -3.1 (4.6) mg/dL, -27.6 (18.6) mg/dL, and -38.8 (63.8) mg/dL, respectively. The data indicate that

there were reductions in total cholesterol and LDL cholesterol and triglycerides after dosing with resmetirom.

14.2.6. DDI Study With Simvastatin and Rosuvastatin, Trial MGL-3196-03

Title

A single-center, open-label, drug interaction study of resmetirom with rosuvastatin and simvastatin in healthy subjects.

Objectives

Primary

- To determine whether the single-dose PK of rosuvastatin is affected by chronic dosing with resmetirom 200 mg/day in healthy subjects.
- To determine whether the single-dose PK of simvastatin is affected by chronic dosing with resmetirom 200 mg/day in healthy subjects.

Secondary

- To assess the PK of resmetirom and its metabolite MGL-3623 after a single dose and after dosing with 200 mg every morning (qAM) for 11 days in healthy subjects.
- To assess the safety and tolerability of resmetirom, 200 mg qAM for 11 days in healthy subjects.
- To determine whether the C_{max} of rosuvastatin or simvastatin acid is affected by chronic dosing with resmetirom 200 mg/day in healthy subjects.
- To determine whether the $AUC_{0\text{-}inf}$ or C_{max} of simvastatin (prodrug, inactive lactone) is affected by chronic dosing with resmetirom 200 mg/day in healthy subjects.

Study Design

This study was designed as an open-label, sequential crossover DDI study to determine whether multiple doses of resmetirom alter the PK of rosuvastatin and simvastatin in healthy subjects.

All subjects received simvastatin at a dose of 20 mg on Days 1 and 12. Rosuvastatin at a dose of 10 mg was administered on Days 3 and 14. Resmetirom at a dosage of 200 mg QD was administered on Days 6 through 16. Thus, resmetirom and simvastatin were co-administered on Day 12, while resmetirom and rosuvastatin were co-administered on Day 14. All doses were administered in the morning.

The recommended dosage of simvastatin in adults is 20 to 40 mg taken QD in the evening. In this study, simvastatin is administered only in the morning. Although this is not consistent with labeled recommendations, this design may increase the potential of observing an interaction relative to evening administration approximately 12 hours after resmetirom dosing (approxx. 2-3 half-lives). The recommended starting dosage of rosuvastatin in adults is 5 to 40 mg QD and

may be taken at any time of the day. It is noted that the AUC of rosuvastatin does not differ following evening or morning drug administration.

All doses of resmetirom were administered using a capsule formulation of 4 × 50 mg (formulation 4). Simvastatin was supplied as 20 mg tablets as a commercially available generic product. Rosuvastatin was supplied as 10 mg tablets as commercially available Crestor. On days when full PK profiles were being collected, doses were administered following a fasting period of at least 8 hours.

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to Day 1. Concomitant medications were not permitted.

Blood PK samples for simvastatin and simvastatin acid were collected on Days 1 and 12 at predose, and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24.

Blood PK samples for rosuvastatin and N-desmethyl rosuvastatin were collected on Days 3 and 14 at predose, and postdose at hours 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, and 72.

Blood PK samples for resmetirom and metabolite MGL-3623 were collected predose on Days 5, 6, 10, 12, 13, and 14. Additional samples were collected postdose on Days 6 and 14 at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24.

PD samples for fasting lipids (HDL, LDL, triglycerides, ApoB, ApoA1) were collected predose on Days 1, 6, and 12, and on Day 17. Samples for TSH, and free and TT3 and T4 were collected at Screening, predose on Days 1, 6, and 12, and on Days 17and at the Endof Study Visit. Samples for SHBG were collected predose on Day 6 and on Day 17.

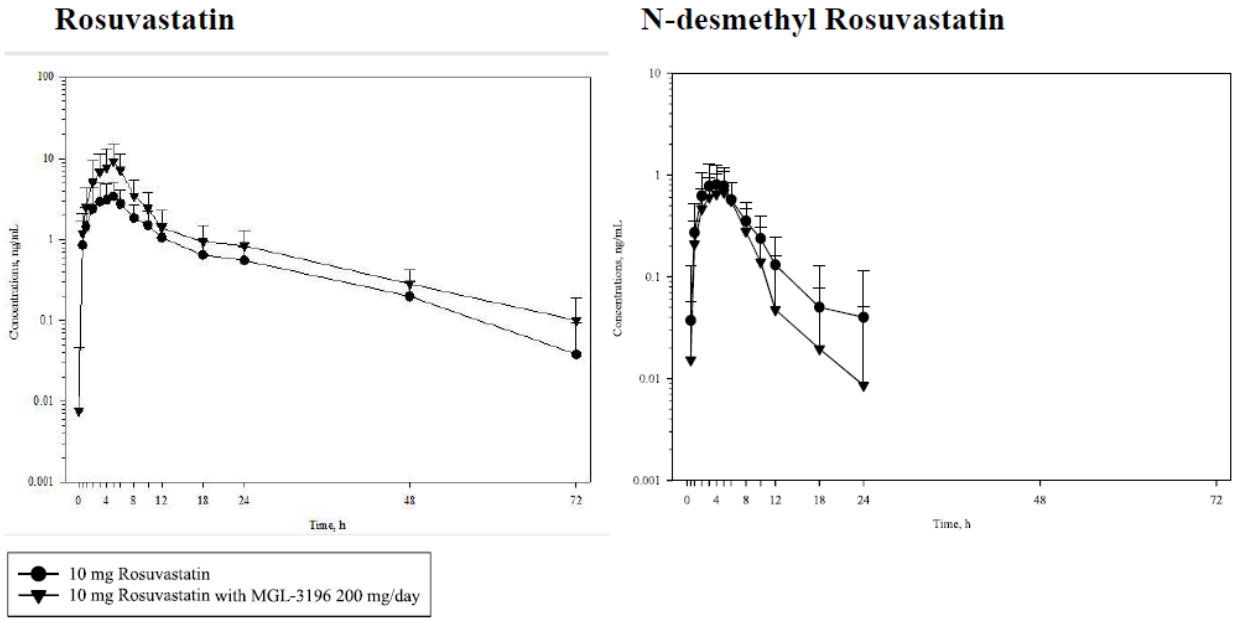
PK Results

A total of 25 subjects were enrolled in the study and all 25 subjects completed the study.

Concentration-time profiles of rosuvastatin and metabolite N-desmethyl rosuvastatin in the absence and presence of 200 mg/day resmetirom are shown in Figure 24. PK parameters for rosuvastatin and N-desmethyl rosuvastatin are shown in Table 172 and Table 173, respectively. Statistical analyses are shown in Table 174. When a single 10 mg dose of rosuvastatin is co-administered with 200 mg/day resmetirom, the C_{max} and AUC_{last} of rosuvastatin increase by 2.9- and 1.8-fold, respectively. For N-desmethyl rosuvastatin, AUC_{last} decreases by 23%, with no change in C_{max}. T_{max} did not change in the presence of resmetirom for both species. The half-life of rosuvastatin was also not different in the presence of resmetirom. The mean half-life of N-desmethyl rosuvastatin was shorter when rosuvastatin was co-administered with resmetirom.

Per the approved labeling for Crestor (rosuvastatin calcium oral tablets), N-desmethyl rosuvastatin is formed principally by CYP2C9. The small decrease observed on N-desmethyl rosuvastatin PK in the presence of resmetirom indicates that resmetirom may exhibit weak inhibitory activity towards CYP2C9. The larger increase in rosuvastatin exposure may therefore be driven by transporter inhibition (OATP1B1 and/or BCRP).

Figure 24. Mean (SD) Plasma Concentration-Time Profiles of Rosuvastatin (Left) and N-desmethyl Rosuvastatin (Right) Following a 10 mg Dose in the Absence (Day 3) and Presence (Day 14) of 200 mg/Day Resmetirom



Source: Figure 4, page 43, Summary of Clinical Pharmacology
Note: The plots are shown in the semi-logarithmic scale.
Abbreviations: MGL-3196, resmetirom; SD, standard deviation

Table 172. Summary of PK Parameters of Rosuvastatin Following a 10 mg Dose in the Absence (Day 3) and Presence (Day 14) of 200 mg/Day Resmetirom

PK Parameter	Rosuvastatin							
	Absence MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	25	3.62	2.04	56.5	25	10.6	6.19	58.2
T_{max}, h	25	4.56	0.821	18.0	25	4.60	1.22	26.6
AUC_{last}, ng·h/mL	25	44.5	22.9	51.3	25	85.2	48.0	56.3
AUC_{inf}, ng·h/mL	22	51.7	22.8	44.1	24	92.4	47.2	51.1
% AUC_{extr}	25	10.6	6.13	57.7	25	6.59	4.76	72.2
λ, h^{-1}	25	0.0414	0.0145	35.1	25	0.0398	0.0108	27.2
$T_{1/2}$, h	25	18.2	4.93	27.1	25	18.6	4.68	25.2

Source: Table 1, page 156, CSR for MGL-3196-03 Appendix 16.2.5.8
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of $AUC_{0\text{-}inf}$; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; $AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; N, number of subjects in treatment arm; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 173. Summary of PK Parameters of N-desmethyl Rosuvastatin Following a 10 mg Dose of Rosuvastatin in the Absence (Day 3) and Presence (Day 14) of 200 mg/Day Resmetirom

PK Parameter	N-desmethyl Rosuvastatin							
	Absence MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	25	0.862	0.487	56.5	25	0.795	0.401	50.5
T_{max}, h	25	4.12	0.781	18.9	24	4.46	1.10	24.7
AUC_{last}, ng·h/mL	25	5.97	3.95	66.1	25	4.38	2.98	68.0
AUC_{inf}, ng·h/mL	20	6.78	3.79	55.9	11	7.09	3.73	52.6
% AUC_{extr}	23	13.3	5.99	45.0	15	12.7	7.83	61.5
λ, h^{-1}	23	0.212	0.0909	42.9	15	0.275	0.104	37.8
$T_{1/2}$, h	23	4.18	2.73	65.4	15	3.15	2.20	69.6
% Rosuvastatin C_{max}*	25	25.8	11.7	45.3	24	8.76	4.41	50.3
% Rosuvastatin AUC_{last}*	25	14.3	9.27	64.8	24	5.83	3.46	59.2
% Rosuvastatin AUC_{inf}*	19	13.9	4.91	35.3	11	7.84	4.58	58.4

Source: Table 2, page 157, CSR for MGL-3196-03 Appendix 16.2.5.8
* % PK parameter of the metabolite (N-desmethyl rosuvastatin) to that of the parent compound (rosuvastatin).
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of $AUC_{0\text{-}inf}$; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; $AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 174. Statistical Analyses of Rosuvastatin and N-desmethyl Rosuvastatin PK in the Absence (Day 3) and Presence (Day 14) of 200 mg/Day Resmetirom

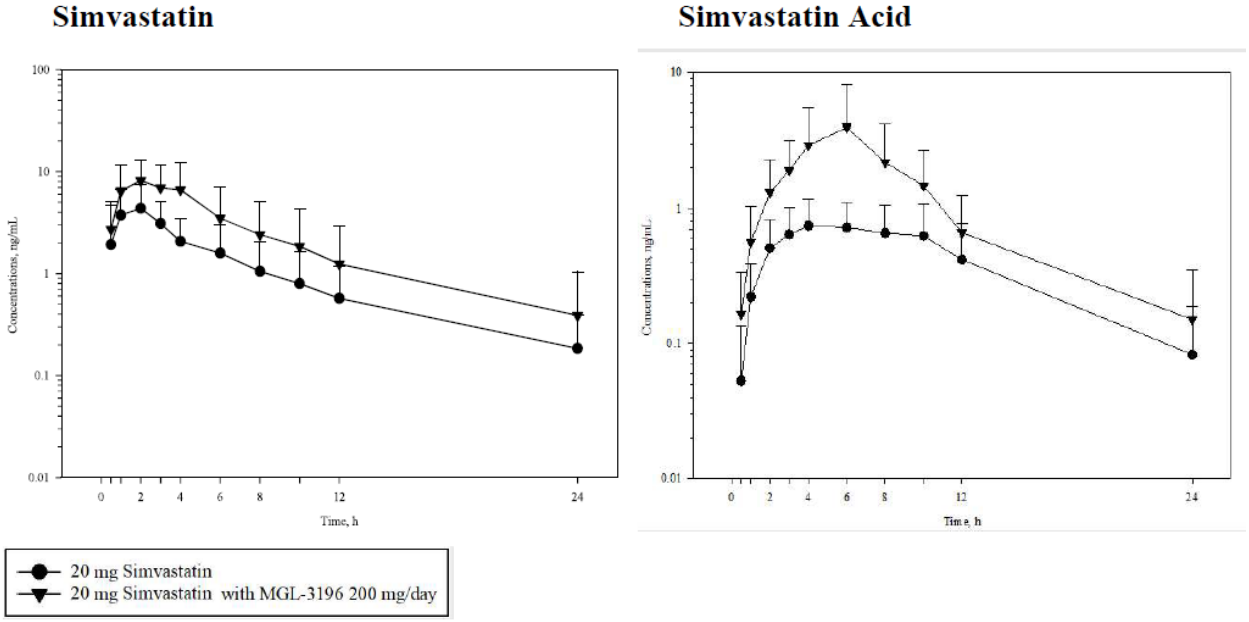
PK Parameter	Rosuvastatin Geometric Mean		GMR[a] (%)	90% CI
	Absence of Resmetirom	Presence of Resmetirom		
C_{max} (ng/mL)	3.11	9.09	292.20	247.43–345.07
AUC_{last} (ng•h/mL)	38.0	73.3	192.76	167.63–221.67
$AUC_{0\text{-}inf}$ (ng•h/mL)	46.6	85.1	182.41	161.41–206.15
PK Parameter	**N-desmethyl Rosuvastatin Geometric Mean**		**GMR (%)**	**90% CI**
	Absence of Resmetirom	**Presence of Resmetirom**		
C_{max} (ng/mL)	0.734	0.722	98.44	86.40–112.16
AUC_{last} (ng•h/mL)	4.73	3.64	77.01	65.93–89.94
$AUC_{0\text{-}inf}$ (ng•h/mL)	6.69	5.42	80.92	64.55–101.45

Source: Table 9, page 43, Summary of Clinical Pharmacology
[a] GMR = geometric mean ratio (%) of rosuvastatin (or its metabolite) with MGL-3196 to without MGL-3196.
Abbreviations: AUC_{last}, area under the concentration-time curve from the time of dosing through time t; $AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; MGL-3196, resmetirom; PK, pharmacokinetic

Concentration-time profiles of simvastatin and metabolite simvastatin acid in the absence and presence of 200 mg/day resmetirom are shown in Figure 25. PK parameters for simvastatin and simvastatin acid are shown in and , respectively. Statistical analyses are shown in .

When a single 20 mg dose of simvastatin is co-administered with 200 mg/day resmetirom, the C_{max} and $AUC_{0\text{-}inf}$ of simvastatin increase by 1.8- and 1.9-fold, respectively. For simvastatin acid, C_{max} and $AUC_{0\text{-}inf}$ increase by 3.9- and 2.4-fold, respectively. T_{max} and half-life did not change in the presence of resmetirom for both species. The approved labeling for Zocor (simvastatin oral tablets) indicates that simvastatin acid is a substrate of OATP1B1 and concomitant administration of inhibitors of OATP1B1 and/or CYP3A4 may lead to increased exposure of simvastatin acid. As resmetirom was not found to inhibit CYP3A4 *in vitro*, the increased exposure to simvastatin and simvastatin acid observed in the presence of resmetirom is consistent with OATP1B1 inhibition.

Figure 25. Mean (SD) Plasma Concentration-Time Profiles of Simvastatin (Left) and Simvastatin Acid (Right) Following a 20 mg Dose in the Absence (Day 1) and Presence (Day 12) of 200 mg/Day Resmetirom



Source: Figure 5, page 44, Summary of Clinical Pharmacology
Note: The plots are shown in the semi-logarithmic scale.
Abbreviations: MGL-3196, resmetirom; SD, standard deviation

Table 175. Summary of PK Parameters of Simvastatin Following a 20 mg Dose in the Absence (Day 1) and Presence (Day 12) of 200 mg/Day Resmetirom

PK Parameter	Simvastatin							
	Absence MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	25	5.92	3.30	55.7	25	11.4	6.15	53.9
T_{max}, h	25	1.98	1.46	73.7	25	2.44	1.08	44.4
$AUC_{(0-24)}$, ng·h/mL	25	26.2	14.2	54.3	25	57.8	44.5	76.9
AUC_{last}, ng·h/mL	25	26.1	14.3	54.7	25	57.7	44.5	77.0
AUC_{inf}, ng·h/mL	24	28.2	16.4	58.2	24	61.1	51.5	84.3
% AUC_{extr}	25	7.01	5.32	75.9	25	5.39	5.13	95.2
λ, h^{-1}	25	0.130	0.0712	54.9	25	0.138	0.0501	36.3
$T_{1/2}$, h	25	6.60	2.83	42.8	25	5.67	2.13	37.5

Source: Table 3, page 158, CSR for MGL-3196-03 Appendix 16.2.5.8
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 176. Summary of PK Parameters of Simvastatin Acid Following a 20 mg Dose of Simvastatin in the Absence (Day 1) and Presence (Day 12) of 200 mg/Day Resmetirom

PK Parameter	Simvastatin Hydroxy Acid							
	Absence MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	25	0.914	0.502	55.0	25	4.50	4.05	90.1
T_{max}, h	25	5.48	2.04	37.3	25	5.36	2.02	37.7
$AUC_{(0-24)}$, ng·h/mL	22	10.6	5.83	54.9	24	28.7	22.3	77.7
AUC_{last}, ng·h/mL	25	9.39	6.15	65.5	25	29.0	22.0	75.8
AUC_{inf}, ng·h/mL	18	11.3	6.47	57.3	24	29.9	23.1	77.3
% AUC_{extr}	20	12.3	10.8	87.6	24	4.97	4.65	93.5
λ, h^{-1}	20	0.164	0.0705	43.1	24	0.192	0.0862	44.8
$T_{1/2}$, h	20	4.96	1.93	39.0	24	4.35	2.03	46.7
% Simvastatin C_{max}*	25	19.1	12.7	66.5	25	48.4	40.3	83.3
% Simvastatin $AUC_{(0-24)}$*	22	40.4	18.6	46.0	24	55.1	31.1	56.4

Source: Table 4, page 159, CSR for MGL-3196-03 Appendix 16.2.5.8
* % PK parameter of the metabolite (simvastatin hydroxy acid) to that of the parent compound (simvastatin).
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 177. Statistical Analyses of Simvastatin and Simvastatin Acid PK in the Absence (Day 1) and Presence (Day 12) of 200 mg/Day Resmetirom

PK Parameter	Simvastatin Geometric Mean		GMR (%)	90% CI
	Absence of Resmetirom	Presence of Resmetirom		
C_{max} (ng/mL)	5.03	9.26	184.01	139.02–243.55
AUC_{0-inf} (ng•h/mL)	24.1	46.1	191.53	144.42–254.02
C_{max} (ng/mL)	0.798	3.11	390.25	296.84–513.06
AUC_{0-inf} (ng•h/mL)	9.42	22.4	237.91	167.18–338.56

Source: Table 10, page 45, Summary of Clinical Pharmacology.
Note: The top two rows show C_{max} and AUC_{0-inf} for simvastatin. The bottom two rows show the C_{max} and AUC_{0-inf} for simvastatin acid.
Note: GMR = geometric mean ratio (%) of simvastatin (or its metabolite) with resmetirom to without resmetirom.
Abbreviations: AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

PK of resmetirom and MGL-3623 following a single dose on Day 6 and multiple doses on Day 14 are shown in Table 178 and Table 179, respectively. Steady state was reached following 5 to 7 days of dosing. Following multiple doses of resmetirom, C_{max} and AUC_{0-24} accumulated by 4.0-fold and 5.5-fold, respectively. No accumulation of C_{max} or AUC_{0-24} was observed for MGL-3623. While the lack of accumulation for MGL-3623 is consistent with observations in other PK studies of resmetirom, the magnitude of accumulation for resmetirom is greater than what has previously been observed (approx. 2-3-fold). As a result, the ratio of MGL-3623 exposure to resmetirom exposure following multiple doses of resmetirom is lower than what has been observed in other studies. This may be because most PK studies evaluated a 100 mg dose of resmetirom, while 200 mg was studied in MGL-3196-03.

Table 178. Summary of Resmetirom and MGL-3623 PK Following a Single 200 mg Dose (Day 6)

PK Parameter	MGL-3196				MGL-3623			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	25	1,560	1,050	66.9	25	776	353	45.5
T_{max}, h	25	4.36	1.47	33.7	25	4.68	1.41	30.0
$AUC_{(0-24)}$, ng·h/mL	22	6,610	3,470	52.5	23	3,910	1,770	45.3
AUC_{last}, ng·h/mL	25	6,200	3,530	57.0	25	4,080	1,800	44.2
AUC_{inf}, ng·h/mL	22	6,620	3,480	52.5	23	3,930	1,780	45.3
% AUC_{extr}	22	0.458	0.557	122	23	0.645	0.445	69.0
λ, h^{-1}	22	0.273	0.0575	21.1	23	0.233	0.0298	12.8
$T_{1/2}$, h	22	2.63	0.468	17.8	23	3.02	0.389	12.9
% MGL-3196 C_{max}*	-	-	-	-	25	61.5	30.6	49.8
% MGL-3196 $AUC_{(0-24)}$*	-	-	-	-	21	75.6	38.4	50.8

Source: Table 5, page 160, CSR for MGL-3196-03 Appendix 16.2.5.8
* % PK parameter of the metabolite (simvastatin hydroxy acid) to that of the parent compound (simvastatin).
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 179. Summary of Resmetirom and MGL-3623 PK Following Multiple 200 mg Doses (Day 14)

PK Parameter	MGL-3196				MGL-3623			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	25	4,910	3,510	71.5	25	624	237	37.9
T_{max}, h	25	4.65	1.47	31.6	25	4.73	1.24	26.3
$AUC_{(0-24)}$, ng·h/mL	25	31,200	31,900	102	22	4,420	2,400	54.3
AUC_{last}, ng·h/mL	25	31,200	31,900	102	25	4,690	2,520	53.8
AUC_{inf}, ng·h/mL	-	-	-		-	-	-	-
% AUC_{extr}	-	-	-		-	-	-	-
λ_z, h^{-1}	25	0.226	0.0437	19.3	22	0.151	0.0471	31.2
$T_{1/2}$, h	25	3.21	0.787	24.5	22	5.28	2.49	47.1
C_{trough}, ng/mL	25	245	453	185	25	90.2	118	130
C_{min}, ng/mL	25	114	269	235	25	50.9	74.0	145
C_{av}, ng/mL	25	1,300	1,330	102	22	184	99.9	54.3
C_{max} Ratio (Day 14/Day 6)	25	3.98	3.06	76.9	25	0.919	0.428	46.6
$AUC_{(0-24)}$ Ratio (Day 14/Day 6)	22	5.46	5.04	92.3	20	1.24	0.565	45.6
% MGL-3196 C_{max}*	-	-	-	-	25	17.6	10.3	58.5
% MGL-3196 $AUC_{(0-24)}$*	-	-	-	-	22	25.0	14.1	56.4

Source: Table 6, page 161, CSR for MGL-3196-03 Appendix 16.2.5.8
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{av}, average concentration during a dosing interval in steady state; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CSR, clinical study report; C_{trough}, concentration immediately prior to administration of the next dose; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

PD Results

Thyroid Parameters

Mean free T4 was below the reference range (1 to 1.8 ng/dL) at Day 17 postdose, with a mean decrease of -0.33 ng/dL. Mean results for other thyroid evaluations (TSH, total T4, free and TT3) were generally within the reference ranges.

There were shifts in free T4 from normal at baseline to low at postdose for 17 subjects, including 5 subjects at Day 12, 17 subjects at Day 17, and 7 subjects at the follow-up visit (Day 22). The lowest value in these subjects was 0.7 ng/dL. Serum T4 was noted to be decreased from baseline for all subjects at the majority of these time points. Two subjects had TSH values that decreased below the reference range (0.4 to 4 mIU/L) during the study but reversed to within the normal range at the follow-up visit on Day 22.

Mean SHBG remained within the reference range (10 to 124 nmol/L) but increased from baseline to Day 17 with mean values of 29.4 nmol/L and 76.9 nmol/L. Thirteen subjects had SHBG values above the reference range on Day 17 (highest value of 198 nmol/L).

Lipid Parameters

Mean fasting lipids over time are shown in Table 180. From Day 6 (the first day of resmetirom dosing) to Day 17, the largest decreases were observed for LDL and triglycerides.

Table 180. Summary of Mean Fasting Lipids Over Time

Laboratory Test	Baseline* (SD)	Day 6 Predose (SD)	Day 12 Predose (SD)	Day 17 (SD)
HDL	51.8 mg/dL (16.74)	50.2 mg/dL (14.36)	45.4 mg/dL (12.19)	45.5 mg/dL (10.07)
LDL	124.8 mg/dL (42.92)	104.1 mg/dL (35.06)	86.9 mg/dL (33.23)	70.7 mg/dL (28.31)
Calculated LDL	107.6 mg/dL (41.83)	87.6 mg/dL (33.11)	74.9 mg/dL (31.03)	61.2 mg/dL (26.25)
Apolipoprotein A1	142.6 mg/dL (24.06)	140.2 mg/dL (19.95)	129.6 mg/dL (18.33)	120.0 mg/dL (15.6)
Apolipoprotein B	96.4 mg/dL (29.72)	84.4 mg/dL (26.43)	66.9 mg/dL (26.57)	58.2 mg/dL (22.27)
Triglycerides	145.0 mg/dL (92.03)	145.6 mg/dL (83.35)	131.7 mg/dL (67.12)	83.1 mg/dL (41.33)
Lipoprotein A	-	21.4 nmol/L (30.52)	-	14.8 nmol/L (25.19)

Source: Table 12-2, page 53, CSR for MGL-3196-03.
*Baseline is the last nonmissing observation collect closest and prior to Dat 1 dosing which is generally the result on Day 1; with the exception of baseline for lipoprotein A, which is Day 6 Predose.
Note: Dat 6 predose is after single doses of simvastatin on Day 1 and rosuvastatin on Day 3.
Note: Day 12 predose is after repeated doses of MGL-3196 alone starting on Day 6.
Note: Day 17 is after MGL-3196 + simvastatin on Day 12 and MGL-3196 + rosuvastatin on Day 14.
Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation

14.2.7. DDI Study With Atorvastatin Trial MGL-3196-04

Title

A single-center, open-label, drug interaction study of resmetirom with atorvastatin in healthy subjects.

Objectives

Primary

- To determine whether the single-dose PK of a 20 mg dose of atorvastatin is affected by chronic dosing with resmetirom 100 mg/day in healthy subjects.

Secondary

- To assess the PK of resmetirom and its metabolite MGL-3623 after a single dose and after dosing with 100 mg qAM for 9 days in healthy subjects.
- To assess the safety and tolerability of resmetirom 100 mg qAM for 9 days in healthy subjects.
- To determine whether the C_{max} of atorvastatin is affected by chronic dosing with resmetirom 100 mg/day in healthy subjects.

Study Design

This study was designed as an open-label, DDI study to determine whether multiple doses of resmetirom alter the PK of atorvastatin in healthy subjects.

All subjects received atorvastatin at a dose of 20 mg on Days 1 and 10. Resmetirom at a dosage of 100 mg QD was administered on Days 4 through 12. Thus, resmetirom and atorvastatin were co-administered on Day 10. All doses were administered in the morning.

The recommended dosage of atorvastatin in adults is 10 to 80 mg taken QD at any time of the day with or without food. Per the approved labeling for Lipitor (atorvastatin calcium oral tablets), the plasma exposures (C_{max} and AUC) are decreased by about 30% following evening drug administration compared with morning. In this study, atorvastatin is administered only in the morning.

All doses of resmetirom were administered using a capsule formulation as 2 × 50 mg (formulation 4). Atorvastatin was supplied as commercially available Lipitor (atorvastatin calcium) 20 mg tablets. On days with PK sample collection, doses were administered following a fasting period of at least 8 hours.

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to Day 1. Concomitant medications were not permitted.

Blood PK samples for atorvastatin and metabolites (atorvastatin lactone, ortho- and para-hydroxyatorvastatin) were collected on Days 1 and 10 at predose, and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 48, and 72.

Blood PK samples for resmetirom and metabolite MGL-3623 were collected predose on Days 4, 5, 6, 7, 9, 10, 11, 12, and 13. Additional samples were collected postdose on Days 4, 9, and 10 at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24.

PD samples for fasting lipids (HDL, LDL, triglycerides, ApoB, ApoA1) were collected on Day -1, predose on Day 4, and on Day 13. Samples for TSH, and free and TT3 and T4 were collected at screening, Day -1, predose on Days 4 and 9, and on Days 13 and 18 to 20. Samples for SHBG were collected predose on Day 4 and on Day 13.

PK Results

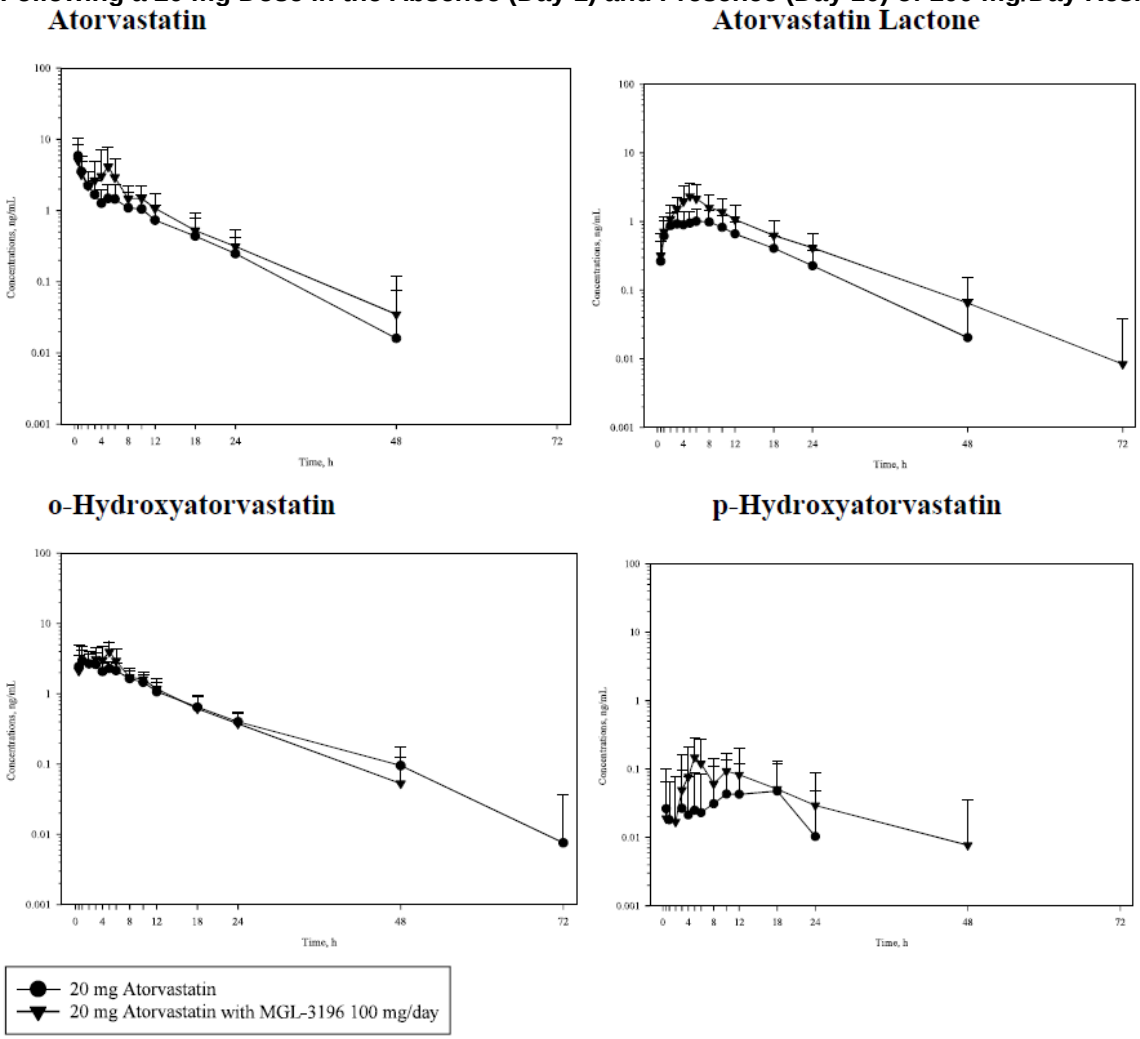
A total of 14 subjects were enrolled in the study, and 13 subjects completed the study. One subject withdrew due to a personal reason.

Concentration-time profiles of atorvastatin and metabolites atorvastatin lactone, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin in the absence and presence of 100 mg/day resmetirom are shown in Figure 26. PK parameters for atorvastatin, atorvastatin lactone, ortho-hydroxyatorvastatin and para-hydroxyatorvastatin are shown in Table 181, Table 182, Table 183, and Table 184, respectively. Statistical analyses are shown in Table 185. Note that statistical analyses for para-hydroxyatorvastatin were not conducted due to low exposure.

When a single 20 mg dose of atorvastatin is co-administered with 100 mg/day resmetirom, the AUC_{last} of atorvastatin increased by 1.4-fold with no change in C_{max}. For metabolite atorvastatin lactone, C_{max} and AUC_{last} increased by 2.0- and 1.8-fold, respectively. For ortho-hydroxyatorvastatin, C_{max} increased by 1.2-fold with no change in AUC. T_{max} values for all species were similar in the presence of resmetirom as in the absence of resmetirom. The half-life of atorvastatin and atorvastatin lactone were not different in the presence of resmetirom. The mean half-life of ortho-hydroxyatorvastatin was shorter when atorvastatin was co-administered with resmetirom.

Per the approved labeling for Lipitor (atorvastatin calcium oral tablets), atorvastatin and its metabolites are substrates of OATP1B1. Exposure to atorvastatin and atorvastatin lactone were increased when atorvastatin was co-administered with resmetirom at steady state, which may be due to OATP1B1 inhibition. Little impact was observed for ortho-hydroxyatorvastatin. However, it is not clear how much OATP1B1 contributes towards the elimination of ortho-hydroxyatorvastatin.

Figure 26. Mean (SD) Plasma Concentration-Time Profiles of Atorvastatin and Metabolites Following a 20 mg Dose in the Absence (Day 1) and Presence (Day 10) of 100 mg/Day Resmetirom



Source: Figure 7, page 49, Summary of Clinical Pharmacology
Note: All plots are shown in the semilogarithmic scale.
Abbreviations: MGL-3196, resmetirom; SD, standard deviation

Table 181. Summary of PK Parameters of Atorvastatin Following a 20 mg Dose in the Absence (Day 1) and Presence (Day 10) of 100 mg/Day Resmetirom

PK Parameter	Absence of MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	14	6.41	3.86	60.2	13	6.86	4.12	60.1
T_{max}, h	14	0.894	0.815	91.1	13	2.12	2.15	102
$AUC_{(0-72)}$, ng·h/mL	14	28.4	16.4	57.7	13	40.0	25.0	62.6
AUC_{last}, ng·h/mL	14	25.8	15.9	61.7	13	37.1	24.2	65.2
AUC_{inf}, ng·h/mL	14	28.2	16.5	58.6	13	39.7	25.5	64.3
% AUC_{extr}	14	8.91	4.19	47.0	13	6.53	3.02	46.2
λ, h^{-1}	14	0.0965	0.0260	26.9	13	0.114	0.0415	36.6
$T_{1/2}$, h	14	7.65	1.93	25.2	13	7.14	3.45	48.4

Source: Table 14.2.1.1, page 61, CSR for MGL-3196-04
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-72}, area under the curve from time 0 to the last measurable concentration (72 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 182. Summary of PK Parameters of Atorvastatin Lactone Following a 20 mg Dose of Atorvastatin in the Absence (Day 1) and Presence (Day 10) of 100 mg/Day Resmetirom

PK Parameter	Absence of MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	14	1.16	0.573	49.3	13	2.40	1.29	53.7
T_{max}, h	14	5.29	1.90	35.8	13	5.08	0.643	12.7
$AUC_{(0-72)}$, ng·h/mL	14	18.4	9.94	54.1	13	32.6	18.6	57.1
AUC_{last}, ng·h/mL	14	16.1	9.37	58.1	13	30.3	19.1	62.9
AUC_{inf}, ng·h/mL	14	18.5	9.93	53.6	13	32.7	19.3	58.9
% AUC_{extr}	14	14.0	4.62	33.0	13	9.05	3.88	42.9
λ, h^{-1}	14	0.0903	0.0239	26.5	13	0.0839	0.0244	29.1
$T_{1/2}$, h	14	8.26	2.51	30.3	13	9.08	3.13	34.4
% Atorvastatin C_{max}*	14	21.6	11.8	54.6	13	39.9	20.4	51.1
% Atorvastatin $AUC_{(0-72)}$*	14	65.5	15.7	24.0	13	83.1	20.7	24.9

Source: Table 14.2.1.2, page 62, CSR for MGL-3196-04
* % PK parameter of the metabolite (atorvastatin lactone) to that of the parent compound (atorvastatin).
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-72}, area under the curve from time 0 to the last measurable concentration (72 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 183. Summary of PK Parameters of Ortho-Hydroxyatorvastatin Following a 20 mg Dose of Atorvastatin in the Absence (Day 1) and Presence (Day 10) of 100 mg/Day Resmetirom

PK Parameter	Absence of MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	14	3.86	1.88	48.8	13	4.62	1.62	35.0
T_{max}, h	14	1.72	1.30	75.6	13	2.81	2.14	76.4
$AUC_{(0-72)}$, ng·h/mL	14	39.0	10.8	27.7	13	42.3	11.8	27.8
AUC_{last}, ng·h/mL	14	36.7	11.3	30.7	13	39.7	12.0	30.1
AUC_{inf}, ng·h/mL	14	39.4	11.1	28.1	13	41.8	12.1	29.0
% AUC_{extr}	14	7.36	4.37	59.4	13	5.42	1.96	36.1
λ, h^{-1}	14	0.0682	0.0215	31.5	13	0.100	0.0377	37.6
$T_{1/2}$, h	14	11.1	3.25	29.3	13	7.98	3.15	39.5
% Atorvastatin C_{max}*	14	70.5	32.0	45.4	13	82.6	40.1	48.5
% Atorvastatin $AUC_{(0-72)}$*	14	154	40.0	26.0	13	126	49.1	39.0

Source: Table 14.2.1.3, page 63, CSR for MGL-3196-04
* % PK parameter of the metabolite (o-hydroxyatorvastatin) to that of the parent compound (atorvastatin).
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-72}, area under the curve from time 0 to the last measurable concentration (72 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 184. Summary of PK Parameters of Para-Hydroxyatorvastatin Following a 20 mg Dose of Atorvastatin in the Absence (Day 1) and Presence (Day 10) of 100 mg/Day Resmetirom

PK Parameter	Absence of MGL-3196				Presence of MGL-3196			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max}, ng/mL	14	0.0830	0.103	125	13	0.215	0.145	67.4
T_{max}, h	7	9.87	7.22	73.2	12	8.42	4.34	51.5
$AUC_{(0-72)}$, ng·h/mL	0	NC	NC	NC	12	2.21	2.74	124
AUC_{last}, ng·h/mL	14	0.645	1.40	217	13	1.59	2.29	144
AUC_{inf}, ng·h/mL	0	NC	NC	NC	0	NC	NC	NC
% AUC_{extr}	0	NC	NC	NC	0	NC	NC	NC
λ, h^{-1}	0	NC	NC	NC	0	NC	NC	NC
$T_{1/2}$, h	0	NC	NC	NC	0	NC	NC	NC
% Atorvastatin C_{max}*	7	3.17	2.68	84.5	13	3.68	2.38	64.7
% Atorvastatin $AUC_{(0-72)}$*	0	NC	NC	NC	12	5.09	6.51	128

Source: Table 14.2.1.4, page 64, CSR for MGL-3196-04.
* % PK parameter of the metabolite (p-hydroxyatorvastatin) to that of the parent compound (atorvastatin).
Abbreviations: AUC_{extr}, extrapolated area under the concentration-time curve from the time of the last measurable concentration to infinity, expressed as a percentage of AUC_{0-inf}; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-72}, area under the curve from time 0 to the last measurable concentration (72 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; MGL-3196, resmetirom; N, number of subjects in treatment arm; NC, not calculated; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life; λ, elimination rate constant

Table 185. Statistical Analyses for PK of Atorvastatin and Metabolites in the Absence (Day 1) and Presence (Day 10) of 100 mg/Day Resmetirom

PK Parameter	Atorvastatin Geometric Mean		GMR[a] (%)	90% CI[b]
	Absence of Resmetirom	Presence of Resmetirom		
C_{max}, ng/mL	5.87	5.93	101.12	85.22–119.99
AUC_{last}, ng•h/mL	23.1	32.1	139.00	125.62–153.82
$AUC_{0–72}$, ng•h/mL	25.6	34.8	135.71	123.02–149.71
$AUC_{0–inf}$, ng•h/mL	25.4	34.3	135.09	121.75–149.89
PK Parameter	**Atorvastatin Lactone Geometric Mean**		**GMR[a] (%)**	**90% CI[b]**
	Absence of Resmetirom	**Presence of Resmetirom**		
C_{max}, ng/mL	1.06	2.11	198.53	165.19–238.61
AUC_{last}, ng•h/mL	14.4	25.3	176.19	149.64–207.97
$AUC_{0–72}$, ng•h/mL	16.4	28.1	170.91	146.49–200.23
$AUC_{0–inf}$, ng•h/mL	16.8	27.9	166.16	142.18–200.46
PK Parameter	**o-Hydroxyatorvastatin Geometric Mean**		**GMR[a] (%)**	**90% CI[b]**
	Absence of Resmetirom	**Presence of Resmetirom**		
C_{max}, ng/mL	3.62	4.37	120.68	102.50–142.07
AUC_{last}, ng•h/mL	34.7	38.0	109.62	101.84–118.00
$AUC_{0–72}$, ng•h/mL	37.2	40.8	109.71	103.14–116.70
$AUC_{0–inf}$, ng•h/mL	37.5	40.2	107.05	100.20–114.37

Source: Table 13, page 50, Summary of Clinical Pharmacology.

[a.] GMR=geometric mean ratio (%) of a drug with MGL-3196 to without MGL-3196.

[b.] CI=confidence interval around the geometric mean ratio.

Abbreviations: AUC_{last}, area under the concentration-time curve from the time of dosing through time t; AUC_{0-72}, area under the curve from time 0 to the last measurable concentration (72 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; MGL-3196, resmetirom; PK, pharmacokinetic

PK of resmetirom and MGL-3623 following a single dose on Day 4 and multiple doses on Day 9 (resmetirom alone) and 10 (in the presence of atorvastatin) are shown in Table 186. Steady state was reached following 4 to 6 days of dosing. Following multiple doses of resmetirom, C_{max} and AUC_{0-24} accumulated by 1.8- to 2.2-fold and 2.4- to 3.1-fold. No accumulation of C_{max} or AUC_{0-24} was observed for MGL-3623. This behavior is consistent with observations in other PK studies of resmetirom.

Exposure to resmetirom and MGL-3623 increased on Day 10 in the presence of atorvastatin relative to when resmetirom was administered alone on Day 9. Resmetirom C_{max} and AUC_{0-24} increased by 1.2- and 1.3-fold, respectively, while MGL-3623 C_{max} and AUC_{0-24} both increased by about 1.4-fold. There is high variability in the PK of resmetirom and MGL-3623 and this may have contributed to the modest differences observed between Days 9 and 10.

Table 186. Summary of PK Parameters for Resmetirom and MGL-3623 Following a Single 100 mg Dose (Day 4) and Multiple 100 mg Doses Alone (Day 9) and in the Presence of Atorvastatin (Day 10)

Dose / Regimen	C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	T_{max} (h)	$T_{1/2}$ (h)
Resmetirom				
100 mg / Single dose	812 (72.7)	2,490 (61.5)	4.00 (2.00, 6.03)	1.82 (0.521)
100 mg / Multiple dose	1,430 (78.7)	5,880 (77.5)	4.01 (3.00, 6.00)	2.67 (0.490)
100 mg / Multiple dose + atorvastatin (20 mg)	1,780 (60.8)	7,800 (80.5)	3.00(4.00,6.00)	2.63 (0.302)
MGL-3623 (Metabolite)				
100 mg / Single dose	458 (57.7)	2,050 (50.4)	4.00 (3.00-6.03)	2.50 (0.377)
100 mg / Multiple dose	322 (54.0)	1,610 (45.1)	4.01 (3.00,6.00)	3.84 (0.844)
100 mg / Multiple dose + atorvastatin (20 mg)	460 (43.6)	2,220 (35.0)	4.00 (3.00-6.00)	3.43 (0.334)

Source: Table 14, page 51, Summary of Clinical Pharmacology.
Note: Data are presented as arithmetic mean (%CV). T_{max} is presented as median (min, max). $T_{1/2}$ is presented as mean (SD).
Note: PK analysis of resmetirom was performed on Day 4, Day 9 (6 consecutive administration), and Day 10 (7 consecutive administration).
Abbreviations: C_{max}, maximum plasma concentration; CV, coefficient of variation; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; MGL-3623, resmetirom; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, terminal half-life

PD Results

Thyroid Parameters

Mean free T4 was below the reference range (1 to 1.8 ng/dL) at Day 13, with a mean value of 0.98 ng/dL and a decrease from baseline of -0.12 ng/dL. There were shifts in free T4 from normal at baseline to low at postdose for 6 subjects, including 2 subjects at Day 9, 5 subjects at Day 13, and 4 subjects at Day 18. The lowest value in these subjects was 0.8 ng/dL. Mean results for other thyroid evaluations (TSH, total T4, free and TT3) were within the reference ranges at all timepoints.

Mean SHBG remained within the reference range (10 to 124 nmol/L), but increased from baseline to Day 13, with mean values of 32.1 nmol/L and 50.2 nmol/L.

Lipid Parameters

Mean fasting lipids over time are shown in Table 187. From Day 4 (the first day of resmetirom dosing) to Day 13, the largest decreases were observed for triglycerides.

Table 187. Summary of Mean Fasting Lipids Over Time

Laboratory Test (Units)	Normal Range	Baseline[a] (SD) (n = 14)	Day 4 Predose (SD) (n = 14)	Day 13 (SD) (n = 13)
HDL (mg/dL)	31–85	50.8 (13.62)	46.7 (13.76)	44.6 (12.74)
LDL (mg/dL)	65–160	113.1 (31.22)	94.8 (26.53)	74.9 (24.26)
Calculated LDL (mg/dL)	65–160	106.1 (30.82)	87.0 (26.28)	67.6 (23.85)
ApoA1 (mg/dL)	101–176	146.8 (22.75)	137.7 (24.08)	127.2 (21.49)
ApoB (mg/dL)	49–109	84.6 (23.43)	73.4 (20.13)	59.8 (17.31)
TGs (mg/dL)	37–288	88.3 (39.60)	140.6 (54.33)	112.2 (36.47)
Lp(a) (nmol/L)	0–74	-	35.7 (36.52)	30.7 (40.21)

Source: Table 15, page 52, Summary of Clinical Pharmacology

[a] Baseline is the last nonmissing observation collected closest and prior to Day 1 dosing, which is generally the result on Day 1, with the exception of baseline Lp(a), which is Day 4 predose. Day 4 predose is after a single dose of atorvastatin on Day 1 and before starting treatment with resmetirom. Day 13 is after resmetirom alone from Days 4 to 9, atorvastatin + resmetirom on Day 10, and resmetirom alone on Days 11 and 12.

Abbreviations: ApoA1 apolipoprotein A-1; ApoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); SD, standard deviation; TG, triglycerides

14.2.8. DDI Study With Warfarin, Trial MGL-3196-16

Title

A single-center, open-label, drug interaction study to assess the effect of resmetirom on warfarin in healthy subjects.

Objectives

Primary

- Assess the effect of resmetirom on the PK of warfarin (*R*- and *S*-warfarin).
- Examine the effect of resmetirom on the PD of warfarin international normalized ratio (INR).

Secondary

- Examine the effect of resmetirom on the PD of warfarin prothrombin time and activated partial thromboplastin time (aPTT).
- Assess the PK of resmetirom and its metabolite MGL-3623.
- Examine the safety and tolerability of resmetirom and warfarin co-administration in healthy volunteers.

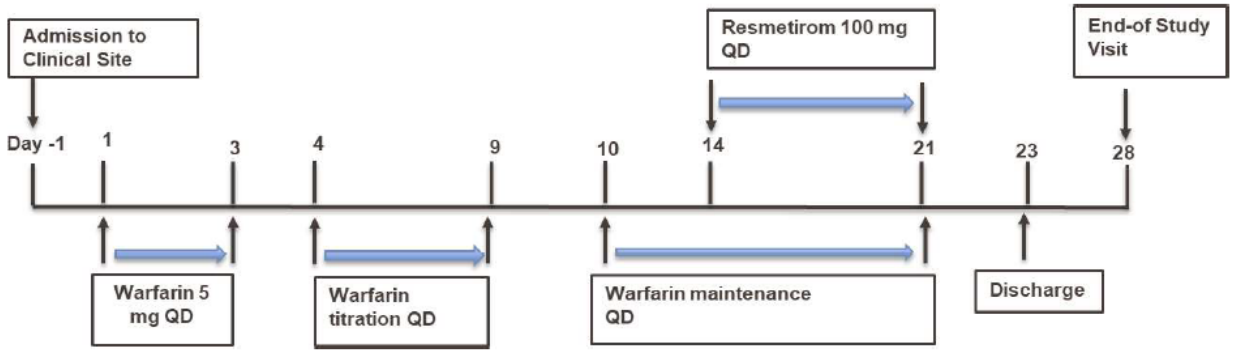
Study Design

This study was designed as an open-label DDI study to determine whether resmetirom altered the PK and PD of warfarin as a substrate of CYP2C9 (*S*-warfarin) in healthy subjects.

All subjects received warfarin at a dosage of 5 mg QD on Days 1 to 3. Each individual subject's dose of warfarin was titrated using commercially available warfarin tablets (strengths of 1, 2.5, and 5 mg) from Days 4 to 9 to achieve an INR value of 1.2 to 2.2. Once each subject's specific maintenance dose was determined, this maintenance dose was administered on Days 10 to 21. Resmetirom at a dosage of 100 mg QD was administered on Days 14 to 21. Note that the starting dosage of 5 mg QD and titration of the warfarin dosage based on INR response is consistent with the approved labeling for Coumadin (warfarin sodium oral tablets).

Note that across all indications (e.g., venous thrombosis, atrial fibrillation, reduction in myocardial infarction), warfarin labeling recommends a target INR range of 2.0 to 3.5. The Applicant used an INR reference range of 0.9 to 1.1, while elevations in INR are expected in patients taking warfarin. As this study is evaluating the potential for DDIs between resmetirom and warfarin in healthy subjects not normally on anticoagulant therapy, the proposed target INR range of 1.2 to 2.2 appears acceptable.

Figure 27. Study Design, Trial MGL-3196-16



Source: Figure 16, page 86, Summary of Clinical Pharmacology
Abbreviations: MGL-3196, resmetirom; QD, once daily

All doses of resmetirom were administered using a tablet formulation of 1 × 100 mg (formulation 8). Commercially available warfarin was supplied as 1, 2.5, and 5 mg tablets. Doses were administered following a fasting period of at least 8 hours.

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 32 kg/m^2. Subjects with prothrombin time, aPTT, INR, protein C, or protein S value that was clinically significant (value above the normal range) at screening were excluded, as were subjects deemed poor warfarin metabolizers based on CYP2C9 genotype. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to Day 1. Use of antibiotics 14 days prior to dosing was also prohibited as antibiotics may alter INR levels. Subjects were also excluded if they ingested large daily doses of vitamin K or consumed large quantities of foods containing high levels of vitamin K during the 2 months prior to Day 1. Concomitant medications were not permitted.

Blood PK samples for *R*- and *S*-warfarin were collected predose on Days 9 to 14, and 18 to 20. On Days 12 and 21, additional postdose samples were collected at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 (Day 21 only).

Blood PK samples for resmetirom and metabolite MGL-3623 were collected predose on Days 14, 16, 18, 20, and 31. Additional samples were collected postdose on Days 14 and 21 at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24.

Samples to assess warfarin PD (INR, prothrombin time, and aPTT) were collected at screening, and predose on Days 1 to 21. Additional samples were collected on Days 22, 23, and at the end-of- study visit.

PD samples for fasting lipids (HDL, LDL, triglycerides), TSH, and free and TT3 and T4 were collected at screening, predose on Day 14, and on Day 22. Samples for SHBG were collected predose on Day 14 and on Day 22.

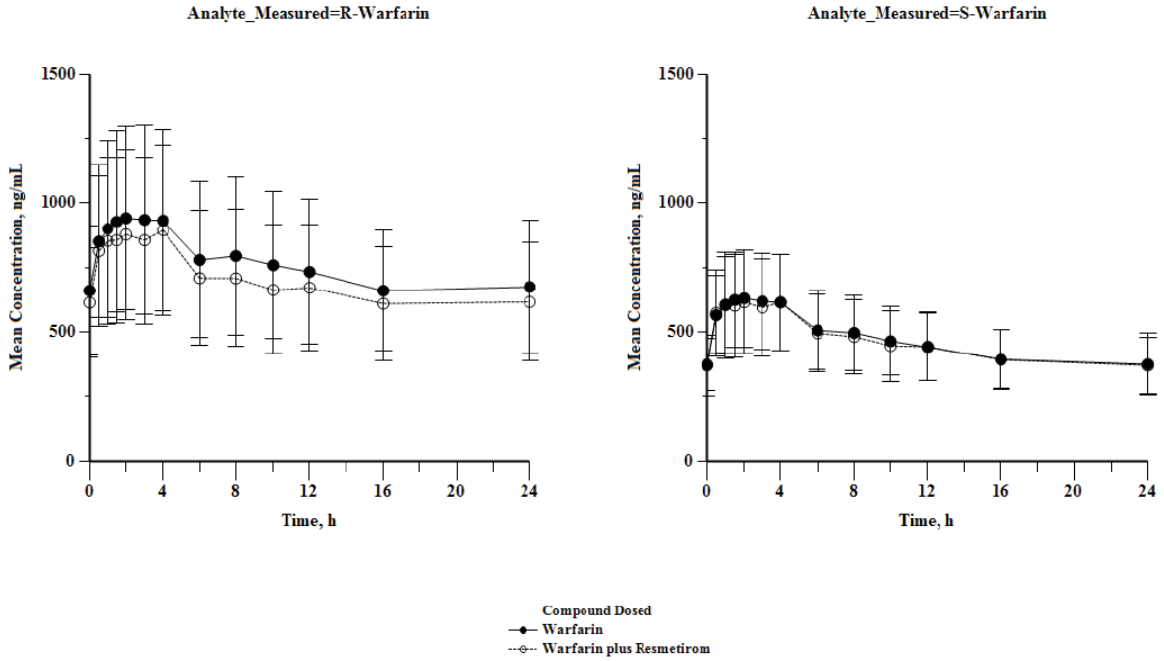
Subject Disposition

A total of 28 subjects were enrolled in the study, and 25 subjects (89.3%) completed the study. Two of these subjects discontinued due to treatment-emergent AEs of increased INR. One subject had increased INR on Day 15 after receiving warfarin alone from Days 1 to 13 and then warfarin plus resmetirom on Day 14. One subject had prolonged aPTT, prolonged prothrombin time, and increased INR on Days 14 and 15 after receiving warfarin alone from Days 1 to 13. Treatment-emergent AEs resolved after discontinuation of study drugs, receipt of 5 mg phytomenadione (vitamin K), and withdrawal from the study.

PK Results

Concentration-time profiles of *R*-warfarin and *S*-warfarin in the absence (Day 12) and presence of steady state resmetirom (Day 21) are shown in Figure 28. PK parameters for *R*-warfarin and *S*-warfarin are shown in Table 188 and Table 189, respectively. Statistical analyses of geometric mean ratios and 90% CIs are shown in Table 190. Resmetirom dosed at 100 mg/day did not impact the PK of *R*- or *S*-warfarin, with geometric mean ratios and associated 90% CIs for C_{max} and AUC_{0-24} falling within 80 to 125%.

Figure 28. Mean (SD) Plasma Concentration-Time Profiles of R-Warfarin (Left) and S-Warfarin (Right) in the Absence and Presence of 100 mg/Day Resmetirom



Source: Figure 1, page 121, CSR for MGL-3196-16 Appendix 16.2.5
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; SD, standard deviation

Table 188. Summary of PK Parameters of R-Warfarin in the Absence (Day 12) and Presence (Day 21) of 100 mg/Day Resmetirom

PK Parameter	Absence of Resmetirom (Day 12)				Presence of Resmetirom (Day 21)			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	27	983	365	37.1	25	917	344	37.5
T_{max} (h)[a]	27	2.00 (0.5-4)	-	-	25	2.00 (0.5-4)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	27	18,100	6760	37.3	25	16,500	6030	36.5

Source: Table 7, page 39, CSR for MGL-3196-16
[a.] Expressed as median and range (min-max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration

Table 189. Summary of PK Parameters of S-Warfarin in the Absence (Day 12) and Presence (Day 21) of 100 mg/Day Resmetirom

PK Parameter	Absence of Resmetirom (Day 12)				Presence of Resmetirom (Day 21)			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	27	676	197	29.1	25	657	214	32.6
T_{max} (h)[a]	27	2.00 (0.5-4)	-	-	25	2.00 (0.5-4)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	27	11,100	3210	28.9	25	10,900	3210	29.4

Source: Table 8, page 39, CSR for MGL-3196-16
[a.] Expressed as median and range (min-max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration

Table 190. Statistical Analyses of R- and S-Warfarin PK in the Absence (Day 12) and Presence (Day 21) of 100 mg/Day Resmetirom

PK Parameter	R-Warfarin Geometric Mean		% GMR[a]	CI 90% Lower[b]	CI 90% Upper[c]
	Absence of Resmetirom (Day 12)	Presence of Resmetirom (Day 21)			
C_{max} (ng/mL)	919	873	94.97	89.69	100.56
$AUC_{(0-24)}$ (ng·h/mL)	16,900	15,800	93.47	88.02	99.25
PK Parameter	**S-Warfarin Geometric Mean**		**% GMR[d]**	**CI 90% Lower[b]**	**CI 90% Upper[c]**
	Absence of Resmetirom (Day 12)	**Presence of Resmetirom (Day 21)**			
C_{max} (ng/mL)	648	633	97.62	90.70	105.07
$AUC_{(0-24)}$ (ng·h/mL)	10,700	10,600	99.41	91.99	107.42

Source: Table 9, page 40, CSR for MGL-3196-16.
[a.] % *R*-warfarin geometric means with resmetirom to without resmetirom
[b.] Lower levels of the 90% CIs.
[c.] Upper levels of the 90% CIs.
[d.] % *S*-warfarin geometric means with resmetirom and without resmetirom.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

Steady state PK parameters for resmetirom and metabolite MGL-3623 on Day 21 with warfarin co-administration are shown in Table 191. PK parameters of resmetirom and MGL-3623 are consistent with that measured in other studies, including a median T_{max} of about 4 hours and a

mean (SD) half-life of about 2.79 (0.43) hours. Relative to Day 14, resmetirom C_{max} and AUC_{0-24} accumulated about 2-fold on Day 21, while no accumulation was observed for MGL-3623.

Table 191. Summary of PK Parameters of Resmetirom and MGL-3623 on Day 21 Following Repeat Doses of 100 mg/Day Resmetirom

PK Parameter	Resmetirom				MGL-3623			
	N	Mean	SD	%CV	N	Mean	SD	%CV
C_{max} (ng/mL)	24	2010	1560	77.9	24	455	269	59.2
T_{max} (h)[a]	24	4.00 (2-6)	-	-	24	4.00 (2-6)	-	-
$AUC_{(0-24)}$ (ng·h/mL)	24	9730	7670	78.8	24	2320	1150	49.4
AUC_{last} (ng·h/mL)	24	9730	7670	78.8	24	2320	1150	49.4
λ (h^{-1})	24	0.253	0.0369	14.6	23	0.185	0.0460	24.8
$T_{1/2}$ (h)	24	2.79	0.432	15.5	23	4.01	1.17	29.2
C_{min} (ng/mL)	24	11.0	18.7	169	24	6.99	7.60	109
C_{av} (ng/mL)	24	405	320	78.8	24	96.6	47.8	49.4
C_{max} Ratio (D21/D14)	24	2.05	1.91	93.4	24	0.934	0.704	75.4
$AUC_{(0-24)}$ Ratio (D21/D14)	22	2.00	1.01	50.4	22	0.814	0.293	36.0
% Resmetirom C_{max}[b]	-	-	-	-	24	29.4	16.9	57.3
% Resmetirom $AUC_{(0-24)}$[b]	-	-	-	-	24	32.6	18.4	56.4

Source: Table 11, page 42, CSR for MGL-3196-16

[a.] Expressed as median and range (min-max).

[b.] %PK parameter of the metabolite (MGL-3623) to that of the parent compound (resmetirom).

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{last}, area under the curve from time zero to the last measurable plasma concentration; C_{av}, average concentration during a dosing interval for repeated dosing; C_{max}, maximum plasma concentration; C_{min}, minimum observed concentration over a dosing interval for repeated dosing; CV, coefficient of variation; D, day; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, apparent terminal elimination rate constant

PD Results

INR

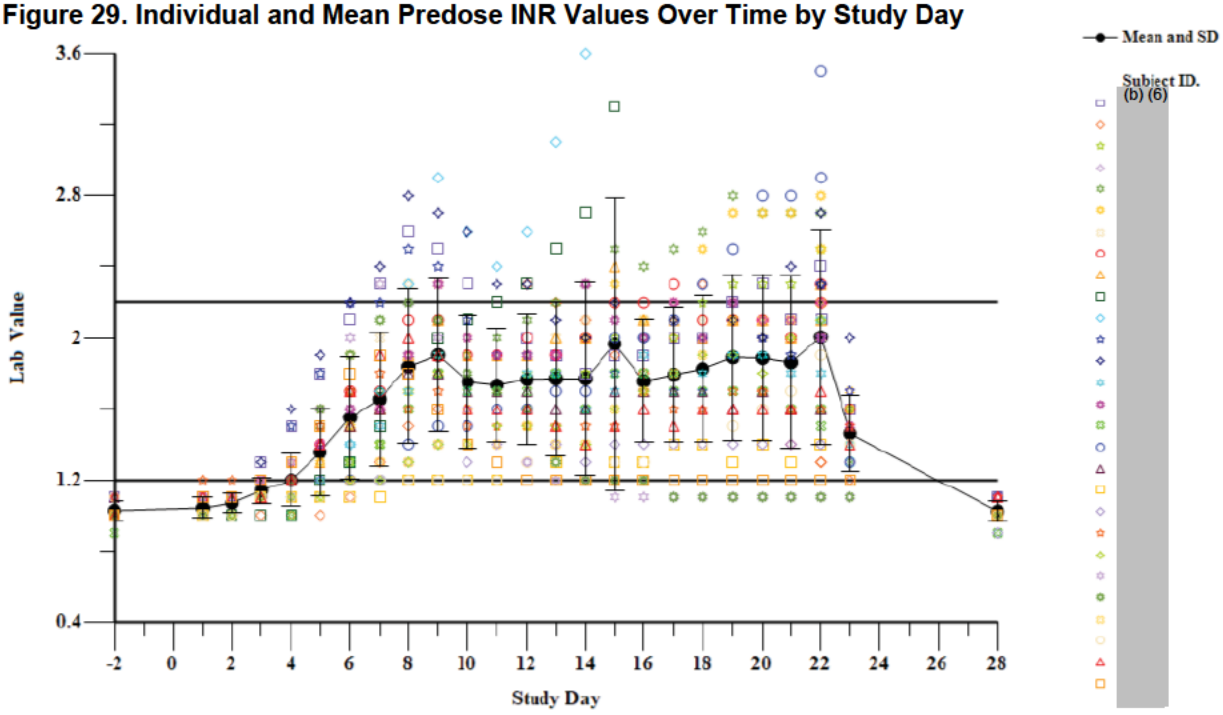
Descriptive statistics for INR following warfarin dosing in the absence (Day 14) and presence (Day 21) of 100 mg/day resmetirom are shown in Table 192. Individual and Mean INR by study day is shown in Figure 29. Descriptive statistics indicate little change in mean INR from Day 14 to Day 21 with mean (SD) INR of 1.77 (0.54) and 1.86 (0.49), respectively. The mean (SD) difference was 0.20 (0.37). When assessed by study day, mean INR remains approximately consistent beginning at Day 8 for the remainder of the study. There appears to be a trend of increasing INR between Days 15 and 22 after dosing with 100 mg/day resmetirom. However, the magnitude of the increase is small and INR levels were maintained within the target range of 1.2 to 2.2.

Table 192. Descriptive Statistics for INR Following Warfarin Dosing in the Absence (Day 14) and Presence (Day 21) of 100 mg/Day Resmetirom

Descriptive Statistics	Day 14	Day 21	Day 21 Minus Day 14
N	27	25	25
Mean	1.77	1.86	0.200
SD	0.543	0.486	0.366
%CV	30.7	26.1	183
Median	1.60	1.90	0.100
Minimum-Maximum	1.20-3.60	1.10-2.80	-0.700-1.10
Geometric Mean	1.70	1.80	N/A

Source: Table 13, page 43, CSR for MGL-3196-16
Abbreviations: CSR, clinical study report; CV, coefficient of variation; INR, international normalized ratio; MGL-3196, resmetirom; N, number of subjects; SD, standard deviation

Figure 29. Individual and Mean Predose INR Values Over Time by Study Day



Source: Figure 4, page 125, CSR for MGL-3196-16 Appendix 16.2.5
Note: Horizontal lines represent the lower and upper reference limits.
Abbreviations: CSR, clinical study report; INR, international normalized ratio; MGL-3196, resmetirom

Thyroid Parameters

Little changes in thyroid parameters were observed from Day 14 to Day 22 following dosing with 100 mg/day resmetirom. The mean (SD) change from Day 14 in TSH, total T4, free T4, TT3, and free T3 were -0.23 (0.34) IU/L, -1.35 (0.51) µg/dL, -0.12 (0.05) ng/dL, -0.02 (0.07) µg/L, and -0.03 (0.21) ng/L, respectively.

Lipid Parameters

Following dosing with 100 mg/day resmetirom, the mean (SD) change from Day 14 to Day 22 in cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was -35.4 (11.5) mg/dL, -5.2 (2.8) mg/dL, -22.4 (12.9) mg/dL, and -15.9 (17.8) mg/dL, respectively. The data indicate that there were reductions in total cholesterol and LDL cholesterol and triglycerides after dosing with resmetirom.

14.2.9. Hepatic Impairment Study, Trial MGL-3196-10

Title

A phase 1, open-label, nonrandomized study to evaluate the PK, safety, and tolerability of multiple oral doses of resmetirom in subjects with varying degrees of hepatic impairment (HI) and healthy matched control subjects with normal hepatic function.

Objectives

Primary

- To evaluate the PK profiles of resmetirom and major metabolite MGL-3623 following QD oral doses of MGL-3196 QD for 6 days in subjects with varying degrees of HI compared to healthy matched control subjects with normal hepatic function.

Secondary

- To assess the relationship between dose and/or plasma concentrations of resmetirom and MGL-3623 and safety biomarkers and PD parameters in subjects with varying degrees of hepatic function.
- To evaluate the PK profiles of resmetirom and major metabolite MGL-3623 following QD oral doses of MGL-3196 QD for 6 days in NASH subjects with NASH cirrhosis (generally well-compensated, mild HI) at 80 and 100 mg doses compared to noncirrhotic NASH (no HI) at a 100 mg dose.

Study Design

This study was designed as an open-label, nonrandomized, parallel-group study. Resmetirom oral doses of 80 mg were administered to normal matched subjects without HI (cohort 1), subjects with mild HI (Child-Pugh A, cohort 2), moderate HI (Child-Pugh B, cohort 3), and some subjects with severe HI (Child-Pugh C, cohort 4). An 80 mg dose was also evaluated in some NASH subjects with cirrhosis (cohort 6). Doses of 40 mg and 60 mg were evaluated in some subjects in cohort 4 (severe HI) and matched healthy subjects. Doses of 100 mg were administered to NASH subjects without cirrhosis (cohort 5) and subjects with NASH cirrhosis (cohort 6). All doses were administered QD for 6 days.

The starting dose in cohorts 1 to 4 was 80 mg. Doses could have been decreased to 40 or 60 mg or increased up to 100 mg based on review of PK and safety. Doses were administered using the tablet formulation as 1 × 40 mg and 1 × 60 mg (prototype formulation 7). All doses were administered following a fasting period of at least 10 hours.

The study enrolled male or female subjects between the ages of 18 and 85 years, with BW >50 kg. All participants must have had a BMI between 18 and 45 kg/m^2, except in patients with NASH (cohorts 5 and 6) for whom an upper BMI limit was not defined. Patients with moderate and severe renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) were excluded. NASH patients with moderate renal impairment (eGFR ≥45 mL/min/1.73 m^2) were permitted. Patients with NASH were required to have a liver biopsy-confirmed diagnosis of NASH, either from historical data (i.e., previous liver biopsy within the last 5 years), or with a liver biopsy performed at Screening.

Healthy control subjects without HI were matched to subjects with HI with respect to age, BMI, and gender. These subjects were required not to be taking any prescribed or nonprescribed medications, vitamins, and herbal and dietary supplements within 7 days prior to the first dose of study drug. Subjects with HI in cohorts 2 to 4 and 6 were allowed to take chronic medications unless excluded by the protocol (e.g., inhibitors of OATP transporters, and substrate or inhibitors of CYP2C8)

Blood PK samples for resmetirom and metabolite MGL-3623 were collected predose on Days 1 and 6. Postdose samples were collected on Days 1 and 6 at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Days 2 and 7), and 48 (Days 3 and 8). An additional sample was collected on Day 14.

Urine PK samples were collected predose on Days 1 and 6, and postdose at intervals of 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, and 24 to 48 hours.

PD samples for fasting lipids (HDL, LDL, triglycerides, ApoB, ApoA1) and SHBG were collected predose on Day 1 and on Days 7 and 14. Samples for assessment of TSH, free and TT3, and free and total T4 were collected at screening, predose on Day 1, and on Days 7 and 14.

Subject Disposition

The study enrolled the following cohorts with dosing as listed:

- Cohort 1: matched subjects with normal hepatic function (n=13)
  - 8 subjects received 80 mg
  - 3 subjects received 60 mg
  - 2 subjects received 40 mg
- Cohort 2: mild HI (Child-Pugh A) (n=10)
  - All 10 subjects received 80 mg
- Cohort 3: moderate HI (Child-Pugh B) (n=10)
  - All 10 subjects received 80 mg
- Cohort 4: severe HI (Child-Pugh C) (n=15)
  - 3 subjects received 80 mg
  - 6 subjects received 60 mg
  - 5 subjects received 40 mg
  - 1 subject erroneously received 80 mg on Day 1, but received 40 mg on subsequent days.

- Cohort 5: NASH subjects without cirrhosis (n=8)
  - All 8 subjects received 100 mg
- Cohort 6: NASH subjects with cirrhosis (n=31) including 30 subjects with mild HI (Child-Pugh A) and 1 subject with moderate HI (Child-Pugh B)
  - 20 subjects (mild HI) received 100 mg
  - 10 subjects (mild HI) and one subject (moderate HI) received 80 mg

Subjects with HI were diagnosed with hepatitis C or alcohol-related liver disease. The median (range) Child-Pugh scores at the screening visit were 5.5 (5, 6), 8 (7, 9), and 11 (10, 13) for non-NASH subjects with mild, moderate, and severe HI, respectively. The median (range) Child-Pugh score among subjects with NASH cirrhosis was 5 (5, 9). NASH cirrhotic subjects with mild HI had Child-Pugh scores of 5 to 6. As noted above, one subject with NASH cirrhosis presented with moderate HI. This subject had a Child-Pugh score of 9.

PK Results

Concentration-time profiles and key PK parameters in subjects who received a single 80 mg dose of resmetirom are shown in Figure 30 and Table 193. Profiles and PK parameters on Day 6 are shown in Figure 31 and Table 194.

PK After a Single-Dose Administration of 80 mg With HI

Resmetirom

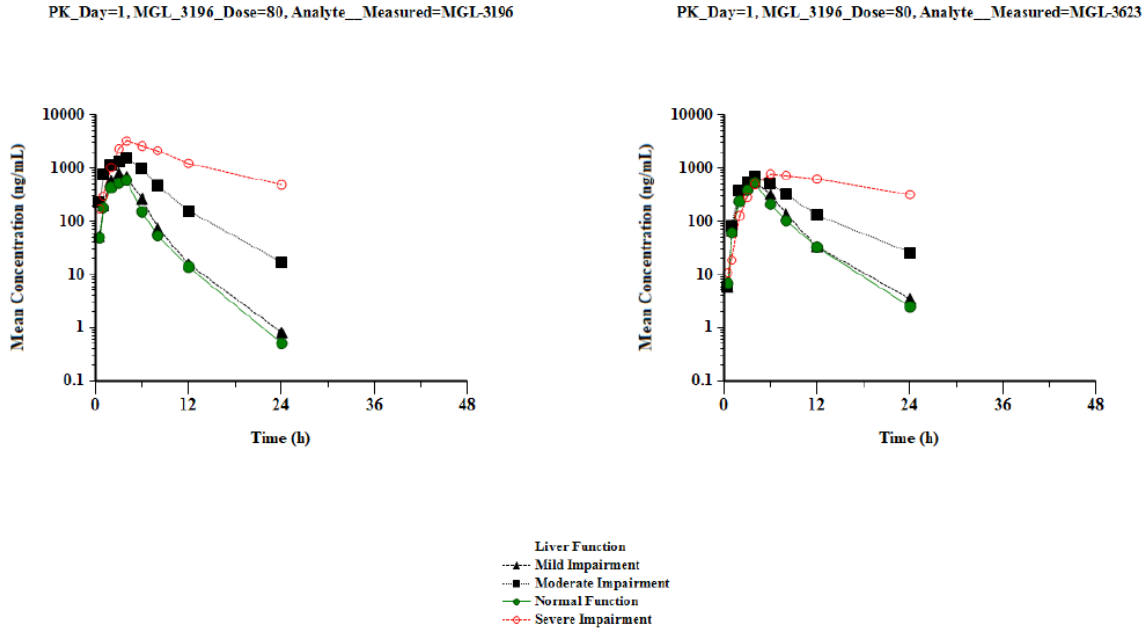
Following a single 80 mg dose of resmetirom, compared to subjects with normal hepatic function, AUC of resmetirom was higher by 25 to 26%, 244 to 246%, and 1051 to 1163% in subjects with mild, moderate, or severe HI, respectively. Compared to subjects with normal hepatic function, C_{max} of resmetirom was higher by 13%, 128%, and 414% in subjects with mild, moderate, or severe HI, respectively.

MGL-3623, Major Metabolite

After a single dose administration of 80 mg, AUC of MGL-3623 was higher by 22 to 23%, 115 to 121%, and 199 to 387%, in subjects with mild, moderate, or severe HI, respectively, compared to subjects with normal hepatic function. C_{max} of MGL-3623 was higher by 9%, 35%, and 43% in subjects with mild, moderate, or severe HI, respectively, compared to subjects with normal hepatic function.

The calculated clearance of resmetirom was progressively decreased in subjects with increasing severity of HI (38.0, 30.3, 13.7, and 3.21 L/h for normal, mild HI, moderate HI, and severe HI, respectively).

Figure 30. Mean Plasma Concentration-Time Profiles of Resmetirom (Left) and MGL-3623 (Right) on Day 1 Following an 80 mg Dose in Subjects With Varying Hepatic Function



Source: Figure 5, page 69, CSR for MGL-3196-10 Section 14
Note: Plots are shown in the semi-logarithmic scale
Abbreviations: CSR, clinical study report; MGL-3136, resmetirom

Table 193. PK Parameters and Statistical Analysis for Resmetirom and MGL-3623 in Subjects With Varying Hepatic Function Following a Single 80 mg Dose

PK Parameter	Resmetirom Geometric Mean				GMR(%)[a]	GMR(%)[b]	GMR(%)[c]
	Normal (N=8)	Mild (N=10)	Moderate (N=10)	Severe (N=4)*			
C_{max}, (ng/mL)	691	778	1,580	3,550	112.61	228.12	514.17
$AUC_{(0-24)}$, (ng·h/mL)	2,350	2,950	8,100	29,700	125.48	344.26	1263.12
$AUC_{(0-inf)}$, (ng·h/mL)	2,360	2,950	8,140	27,100	125.46	345.79	1150.70
PK Parameter	**MGL-3623 Geometric Mean**				**GMR(%)[a]**	**GMR(%)[b]**	**GMR(%)[c]**
	Normal (N=8)	**Mild (N=10)**	**Moderate (N=10)**	**Severe (N=4)****			
C_{max}, (ng/mL)	506	552	682	727	108.90	134.72	143.59
$AUC_{(0-24)}$, (ng·h/mL)	2,250	2,760	4,840	11,000	122.43	215.06	486.82
$AUC_{(0-inf)}$, (ng·h/mL)	2,260	2,770	4,990	6,770	122.66	220.51	299.26

Source: Table 29, page 70, Summary of Clinical Pharmacology
Note: GMR=geometric mean ratio (%) for hepatic impairment to normal liver function.
* N=3 for AUC_{0-inf}
** N=1 for AUC_{0-inf}
[a] Mild/normal
[b] Moderate/normal
[c] Severe/normal
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; N, number of subjects; PK, pharmacokinetic

PK After Repeated Administration of 80 mg QD for 7 Days by Severity of HI

Resmetirom

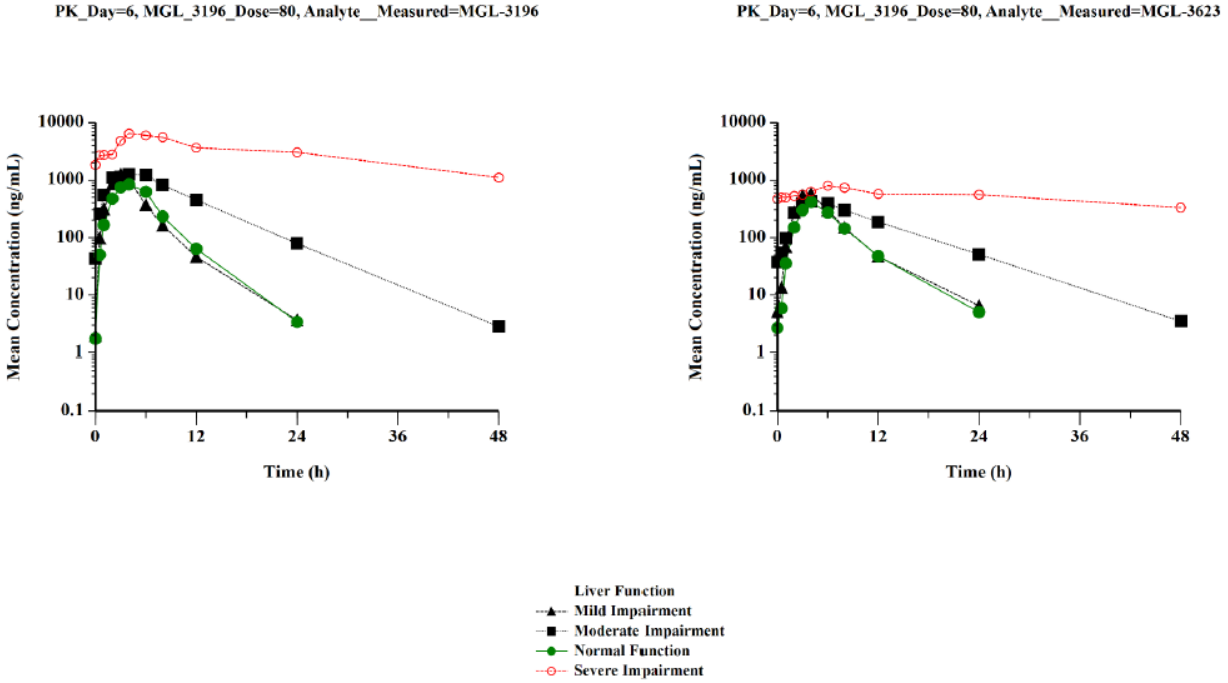
Following multiple doses of 80 mg for 7 days, AUC of resmetirom was 1.03-, 2.71-, and 21-fold higher in subjects with mild HI, moderate HI, or severe HI, respectively. C_{max} was 1.17-, 1.73-, and 8.12-fold higher in subjects with mild, moderate, or severe HI, respectively, compared to subjects with normal hepatic function.

MGL-3623

Following multiple doses of 80 mg for 7 days, AUC of MGL-3623 was 1.28-, 1.87-, and 5.9-fold higher in subjects with mild HI, moderate HI, or severe HI, respectively. C_{max} of MGL-3623 was 1.45-, 1.43-, and 2.07-fold higher in subjects with mild HI, moderate HI, or severe HI, respectively.

The ratio of MGL-3623 exposure to resmetirom exposure was decreased with increasing severity of HI, suggesting that metabolism of resmetirom to MGL-3623 decreased in HI.

Figure 31. Means Plasma Concentration-Time Profiles of Resmetirom (Left) and MGL-3623 (Right) on Day 6 Following Multiple 80 mg Doses in Subjects With Varying Hepatic Function



Source: Figure 6, page 71, CSR for MGL-3196-10 Section 14
Note: Plots are shown in the semi-logarithmic scale.
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom

Table 194. PK Parameters and Statistical Analysis for Resmetirom and MGL-3623 in Subjects With Varying Hepatic Function Following Multiple 80 mg Doses

PK Parameter	Resmetirom Geometric Mean				GMR(%) [a]	GMR(%) [b]	GMR(%) [c]
	Normal (N=7)	Mild (N=10)	Moderate (N=9)	Severe (N=3)			
C_{max} (ng/mL)	942	1,110	1,630	7,650	117.41	173.15	811.89
$AUC_{(0-24)}$ (ng•h/mL)	4,360	4,480	11,800	91,500	102.74	270.53	2,098.70
PK Parameter	**MGL-3623 Geometric Mean**				**GMR(%) [a]**	**GMR(%) [b]**	**GMR(%) [c]**
	Normal (N=7)	**Mild (N=10)**	**Moderate (N=9)**	**Severe (N=3)**			
C_{max} (ng/mL)	390	565	**558**	806	144.98	143.14	206.74
$AUC_{(0-24)}$ (ng•h/mL)	2,340	2,990	**4,380**	13,800	127.68	187.20	591.15

Source: Table 1, Response to Clinical Pharmacology IR, NDA 217785 SDN 23, October 17, 2023
Note: GMR=geometric mean ratio (%) for hepatic impairment to normal liver function.
[a.] Mild/normal
[b.] Moderate/normal
[c.] Severe/normal
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; N, number of subjects; PK, pharmacokinetic

Subjects with severe HI and matched control subjects also received resmetirom at doses of 40 and 60 mg. PK parameters are shown in Table 195. At 60 mg, subjects with severe HI had C_{max} and AUC_{0-24} values that were 3.8- and 17-fold higher, respectively, relative to subjects with normal hepatic function. At a dose of 40 mg, subjects with severe HI had C_{max} and AUC_{0-24} values that were 5.9- and 9.9-fold higher, respectively, relative to subjects with normal hepatic function.

After administration of 40 mg, 60 mg, or 80 mg QD for 7 days in subjects with severe HI, mean AUC_{0-24} of resmetirom was 17300 ng*h/mL, 51400 ng*h/mL, and 97600 ng*h/mL, respectively. Mean AUC_{0-24} on day 7 increased by 5.6-fold, with a 2-fold increase from 40 mg to 80 mg.

Table 195. PK Parameters of Resmetirom in Subjects With Normal Hepatic Function and Severe HI Following Single and Multiple Doses of 40 and 60 mg

	Normal Hepatic Function (n = 2)	Severe Hepatic Function (n = 5)	Normal Hepatic Function (n = 3)	Severe Hepatic Function (n = 6)
Dose Level	**40 mg**	**40 mg**	**60 mg**	**60 mg**
Day 1				
C_{max} (ng/mL)	316 (60.7)	1,850 (42.1)	852 (65.8)	3,250 (88.9)
T_{max} (h)	3.50 (3–4)	4.00 (3–6)	3.67 (3,4)	4.33 (3–6)
AUC_{0-24}	1,250 (67.3)	12,400 (35.7)	2,440 (57.2)	41,700 (74.3)
$T_{1/2}$ (h)	1.78 (45.5)	4.87 (19.6)	2.32 (63.1)	3.75 (24.7)
Day 6				
C_{max} (ng/mL)	527 (60.6)	2,310 (40.2)	1,050 (69.0)	3,860 (58.2)
T_{max} (h)	4.00 (4–4)	4.00 (3–4)	3.67 (3–4)	4.83 (1–8)
AUC_{0-24}	1,740 (59.4)	17,300 (64.5)	3,370 (63.8)	51,400 (84.4)
$T_{1/2}$ (h)	2.17 (40.7)	6.30 (21.3)	1.97 (47.6)	8.38 (61.7)

Source: Table 31, page 71, Summary of Clinical Pharmacology
Note: Data are presented as mean (%CV), except T_{max}, presented as median (min, max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; HI, hepatic impairment; n, number of subjects in subset; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, apparent terminal elimination rate constant

Noncirrhotic NASH Versus Cirrhotic NASH With Mild HI

Trial MGL-3196-10 also evaluated the PK of resmetirom in subjects with non-cirrhotic NASH and cirrhotic NASH at doses of 80 to 100 mg. PK parameters are shown in Table 196.

After a single dose of 100 mg, subjects with cirrhotic NASH (mild HI) had C_{max} and AUC_{0-24} values that were 1.29- and 1.15-fold higher, respectively, relative to subjects with noncirrhotic NASH. On Day 6, following multiple 100 mg doses, subjects with cirrhotic NASH (mild HI) had C_{max} and AUC_{0-24} values that were about 19% and 18% *lower*, respectively, relative to subjects with noncirrhotic NASH. The low impact of mild HI on the PK of resmetirom in subjects with NASH is consistent with observations in subjects without NASH.

After a single dose of 80 mg, subjects with cirrhotic NASH (mild HI) had C_{max} and AUC_{0-24} values that were 1.19-fold higher and about 6.3% lower, respectively, relative to cirrhotic NASH subjects who received a single dose of 100 mg. On Day 6, following multiple 80 mg doses, subjects with cirrhotic NASH (mild HI) had C_{max} and AUC_{0-24} values that were 6.4% and 26% lower, respectively, relative to cirrhotic NASH subjects who received multiple 80 mg doses.

One subject with NASH cirrhosis and moderate HI who received 80 mg QD for 6 days had C_{max} and AUC_{0-24} values that were 4.8- and 12-fold higher, respectively, relative to cirrhotic NASH subjects with mild HI who received 80 mg QD for 6 days. This subject presented with a Child-Pugh score of 9 (upper end of moderate severity). This effect of moderate HI is not consistent with observations in non-NASH subjects. The data are not sufficient to determine whether the cause was due to NASH etiology since the data are only available from a single subject. In addition, changes in PK in subjects with NASH cirrhosis and mild HI were consistent with observations in non-NASH subjects with mild HI.

Table 196. PK Parameters of Resmetirom in Subjects With Non-Cirrhotic and Cirrhotic NASH Following Single and Multiple Doses of 80 and 100 mg

	Cirrhotic NASH (n = 10)	Cirrhotic NASH (n = 1)	Cirrhotic NASH (n = 20)	Non-cirrhotic NASH (n = 8)
HI Classification From Child-Pugh Scoring system	**Mild HI**	**Moderate HI**	**Mild HI**	**Normal Liver Function**
Dose Level	**80 mg**	**80 mg**	**100 mg**	**100 mg**
Day 1				
C_{max} (ng/mL)	1,850 (55.9)	6,810	1,550 (64.8)	1,200 (45.6)
T_{max} (h)	3.70 (2,6)	4.00	4.20 (2,6)	4.75 (2,8)
AUC_{0-24}	7,330 (52.4)	73,100	7,820 (78.2)	6,820 (50.2)
$T_{1/2}$ (h)	2.91 (10.1)	6.76	2.88 (25.3)	2.78 (20.3)
Day 6				
C_{max} (ng/mL)	1,890 (54.4)	9,040	2,020 (77.8)	2,490 (94.7)
T_{max} (h)	3.70 (3,6)	6.00	3.90 (2,6)	4.00 (3,6)
AUC_{0-24}	9,780 (59.9)	114,000	13,200 (99.6)	16,000 (162)
$T_{1/2}$ (h)	3.27 (32.7)	11.3	3.39 (32.1)	3.25 (40.6)

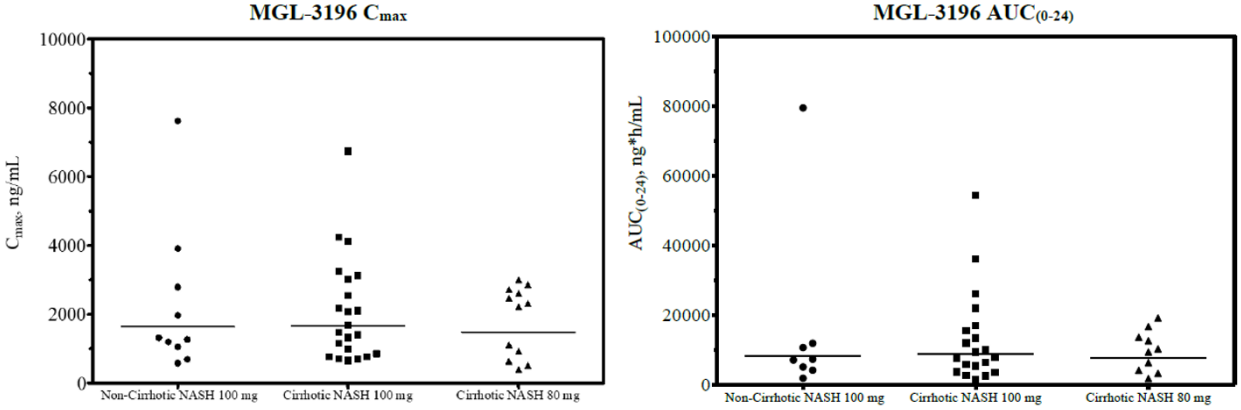
Source: Table 32, page 72, Summary of Clinical Pharmacology
Note: Data are presented as mean (%CV), except T_{max}, presented as median (min, max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; HI, hepatic impairment; n, number of subjects in subset; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, median time to maximum concentration; λ, apparent terminal elimination rate constant

In Table 196, mean C_{max} and AUC_{0-24} on Day 6 in noncirrhotic NASH subjects and cirrhotic NASH subjects with mild HI receiving 100 mg QD were noted to have high variability. The individual data show large variability in C_{max} and AUC_{0-24} values, with some subjects exhibiting large values (Figure 32). Notably, the variability in exposure is greater among subjects receiving

100 mg relative to subjects receiving 80 mg. Variability in exposure was also observed among non-NASH subjects with normal liver function or mild HI receiving a dose of 80 mg (Figure 33), although apparently lower than observations in subjects with NASH.

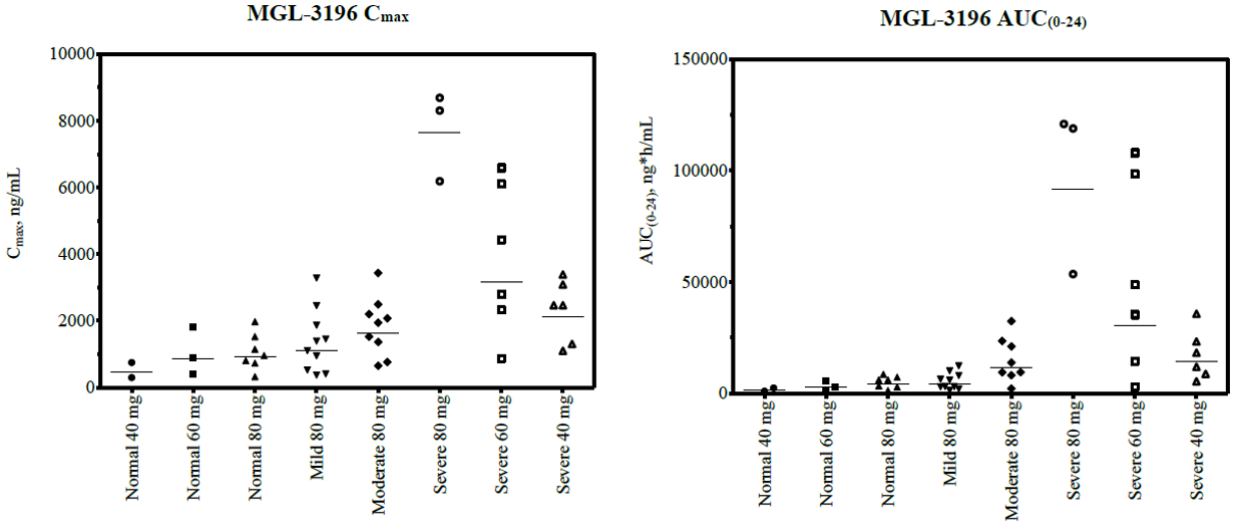
The high variability in exposure at 100 mg among subjects with NASH is driven by a few subjects and highlights the heterogeneity of this population. Notably, resmetirom is currently proposed for the treatment of patients with noncirrhotic NASH and fibrosis stage F2 to F3. A separate clinical study is ongoing to evaluate the efficacy and safety of resmetirom in patients with compensated NASH cirrhosis (MGL-3196-19). Thus, at the time of this review, the safety and effectiveness of resmetirom have not been established in NASH cirrhosis patients.

Figure 32. Individual and Geometric Mean Steady-State Resmetirom C_{max} and AUC_{0-24} in NASH Subjects Receiving 80 or 100 mg



Source: Figure 4, pages 66-67, CSR for MGL-3196-10 Section 14
Note: Cirrhotic NASH 100 mg refers to cirrhotic NASH subjects with mild hepatic impairment (Child-Pugh A) who received a dosage of 100 mg QD. Cirrhotic NASH 80 mg refers to cirrhotic NASH subjects with mild hepatic impairment who received a dosage of 80 mg QD.
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CSR, clinical study report; NASH, nonalcoholic steatohepatitis; QD, once daily

Figure 33. Individual and Geometric Mean Steady State Resmetirom C_{max} and AUC_{0-24} in Non-NASH Subjects Receiving 40, 60, or 80 mg by Hepatic Impairment



Source: Figure 2, pages 62-63, CSR for MGL-3196-10 Section 14
Note: Normal refers to normal liver function. Mild, moderate, and severe refer to varying degrees of hepatic impairment (Child-Pugh A, B, and C, respectively).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CSR, clinical study report; NASH, nonalcoholic steatohepatitis

Among subjects receiving 80 mg resmetirom QD, resmetirom excretion in urine was low throughout the dosing period with values ≤1.18%. The percent excretion of MGL-3623 was higher, ranging from 5.2 to 20% across all cohorts throughout the dosing period. This is consistent with results in urine from mass balance study, Trial MGL-3196-07, in which resmetirom accounted for 1.02% of the dose, while MGL-3623 accounted for 15.71% of the dose.

PD Results

Change from baseline in fasting lipids across cohorts are shown in Table 197. Change from baseline in thyroid hormones are shown in Table 198. Note that the data shown in Table 197 and Table 198 combine data from subjects receiving all doses (ranging from 40 to 100 mg). Most cohorts showed decreases in ApoB, high-density lipoprotein-cholesterol, LDL-C, and triglycerides. The magnitude of decrease for ApoB, LDL-C, and triglycerides were greatest in subjects with NASH relative to subjects without NASH. Changes in thyroid hormones including TSH (thyrotropin), T4 (thyroxine) and T3 were not consistent across subjects.

Table 197. Summary of Observed Values and Change From Baseline in Fasting Lipids

Assay Statistic	Normal (N=13)	Mild (N=10)	Moderate (N=10)	Severe (N=15)	NASH Non-cirrhosis (N=8)	NASH Cirrhosis (N=31)
ApoB (mg/dL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	101.5 (20.5)	102.4 (31.0)	71.8 (21.5)	66.1 (29.3)	116.3 (46.8)	75.7 (21.1)
Baseline Median	101.0	91.5	70.0	58.0	104.5	72.0
Baseline Min, Max	62, 133	72, 167	45, 109	28, 118	66, 204	49, 148
Day 7 Mean (SD)	97.8 (20.1)	92.0 (30.7)	71.9 (22.4)	64.7 (30.7)	94.9 (35.0)	64.9 (24.6)
Mean (SD) CFB at Day 7	-3.8 (8.5)	-10.4 (10.3)	0.1 (15.2)	-1.4 (8.7)	-21.4 (26.9)	-10.8 (15.4)
Mean (SD) %CFB at Day 7	-3.3% (9.0)	-10.4% (11.2)	2.2% (27.5)	-3.2% (13.4)	-16.0% (18.5)	-14.1% (19.1)
HDL-C (mg/dL)	N=12	N=10	N=9	N=14	N=8	N=31
Baseline Mean (SD)	50.9 (11.1)	47.6 (12.0)	46.2 (15.9)	44.6 (14.0)	39.9 (7.1)	49.2 (14.7)
Baseline Median	52.5	51.0	44.0	41.0	38.0	51.0
Baseline Min, Max	33, 67	28, 62	27, 78	23, 78	34, 56	20, 83
Day 7 Mean (SD)	50.9 (12.1)	42.9 (11.0)	39.2 (9.2)	40.9 (17.8)	40.6 (5.6)	43.3 (12.3)
Mean (SD) CFB at Day 7	0.0 (6.2)	-4.8 (5.8)	-7.0 (9.8)	-3.7 (7.1)	0.8 (8.5)	-6.0 (6.1)
Mean (SD) %CFB at Day 7	0.33% (11.4)	-9.1% (11.4)	-11.7% (14.8)	-10.0% (16.2)	4.1% (20.7)	-10.7% (11.7)
Direct LDL-C (mg/dL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	133.2 (24.2)	134.1 (42.0)	99.4 (36.2)	84.3 (47.6)	123.8 (73.1)	86.9 (22.0)
Baseline Median	138.0	119.5	83.0	67.0	100.0	87.0
Baseline Min, Max	87, 164	92, 220	58, 158	31, 207	65, 292	53, 153
Day 7 Mean (SD)	132.8 (27.9)	124.1 (40.2)	100.1 (41.3)	88.6 (53.8)	100.3 (49.4)	73.1 (25.0)
Mean (SD) CFB at Day 7	-0.3 (15.1)	-10.0 (11.1)	0.7 (16.1)	4.3 (12.5)	-23.5 (43.9)	-13.9 (22.3)
Mean (SD) %CFB at Day 7	-0.2% (11.3)	-7.4% (9.6)	-0.3% (16.3)	2.9% (16.0)	-14.1% (25.3)	-14.9% (24.2)
Triglycerides (mg/dL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	126.1 (61.9)	123.5 (64.1)	85.1 (30.3)	102.9 (59.2)	428.3 (548.3)	154.1 (130.9)
Baseline Median	117.5	110.5	83.0	79.0	199.0	116.0
Baseline Min, Max	64, 270	62, 278	43, 119	29, 244	97, 1726	70, 811
Day 7 Mean (SD)	96.6 (39.8)	107.8 (49.3)	67.7 (15.9)	80.9 (43.2)	261.9 (392.0)	107.5 (84.9)
Mean (SD) CFB at Day 7	-29.5 (41.9)	-15.7 (45.4)	-17.4 (21.5)	-22.0 (23.9)	-166.4 (198.2)	-46.6 (51.1)
Mean (SD) %CFB at Day 7	-19.0% (22.1)	-7.1% (35.6)	-14.5% (25.4)	-18.5% (16.3)	-37.2% (20.4)	-28.8% (14.2)

Source: Table 10, pages 64-65, CSR for MGL-3196-10
Abbreviations: ApoB, apolipoprotein B; CFB, change from baseline; %CFB, percentage change from baseline; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Max, maximum; Min, minimum; NASH, nonalcoholic steatohepatitis; SD, standard deviation

Table 198. Summary of Observed Values and Change From Baseline in Thyroid Hormones

Assay Statistic	Normal (N=13)	Mild (N=10)	Moderate (N=10)	Severe (N=15)	NASH Non-cirrhosis (N=8)	NASH Cirrhosis (N=31)
Thyrotropin (mIU/L)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	1.73 (0.57)	2.25 (1.36)	3.04 (2.92)	1.82 (0.80)	2.41 (1.53)	1.88 (0.87)
Baseline Median	1.60	1.96	2.16	1.70	2.11	1.73
Baseline Min, Max	0.78, 2.99	0.75, 5.53	0.97, 10.47	0.75, 3.20	0.02, 5.01	0.45, 4.19
Day 7 Mean (SD)	1.97 (0.70)	1.94 (0.88)	3.04 (2.71)	1.69 (0.87)	1.98 (1.34)	1.82 (0.95)
Mean (SD) CFB at Day 7	0.23 (0.61)	-0.30 (0.69)	0.01 (0.43)	-0.14 (0.85)	-0.43 (0.85)	-0.06 (0.73)
Mean (SD) %CFB at Day 7	17.1% (35.2)	-8.5% (23.4)	6.0% (19.8)	3.2% (63.7)	-14.9% (28.8)	3.4% (39.9)
Thyroxine, Free (ng/dL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	1.02 (0.12)	1.04 (0.23)	0.94 (0.18)	1.04 (0.13)	1.14 (0.14)	1.05 (0.17)
Baseline Median	1.03	1.06	0.92	1.05	1.15	1.02
Baseline Min, Max	0.85, 1.18	0.71, 1.37	0.73, 1.20	0.85, 1.29	0.84, 1.36	0.67, 1.41
Day 7 Mean (SD)	1.03 (0.07)	1.06 (0.21)	0.96 (0.24)	0.92 (0.19)	1.16 (0.23)	1.09 (0.23)
Mean (SD) CFB at Day 7	0.01 (0.12)	0.02 (0.10)	0.02 (0.12)	-0.12 (0.17)	0.03 (0.18)	0.04 (0.11)
Mean (SD) %CFB at Day 7	2.0% (11.7)	2.5% (9.0)	1.7% (12.7)	-11.6% (16.5)	2.2% (15.8)	3.5% (10.2)
Triiodothyronine, Free (pg/mL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	2.84 (0.32)	3.36 (0.45)	3.43 (0.67)	2.05 (0.29)	3.09 (0.57)	2.74 (0.49)
Baseline Median	2.90	3.45	3.40	2.00	3.00	2.70
Baseline Min, Max	2.3, 3.3	2.8, 4.3	2.6, 4.9	1.7, 2.7	2.4, 4.2	1.4, 3.9
Day 7 Mean (SD)	2.78 (0.26)	3.34 (0.46)	3.36 (0.66)	1.89 (0.33)	2.88 (0.38)	2.54 (0.41)
Mean (SD) CFB at Day 7	-0.06 (0.35)	-0.02 (0.20)	-0.08 (0.24)	-0.17 (0.26)	-0.21 (0.41)	-0.20 (0.24)
Mean (SD) %CFB at Day 7	-1.2% (12.5)	-0.6% (6.1)	-2.0% (6.9)	-7.9% (12.1)	-5.6% (12.6)	-6.4% (9.7)
Thyroxine (µg/dL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	5.94 (1.01)	7.97 (2.43)	6.30 (0.93)	5.79 (1.00)	6.93 (0.99)	6.99 (1.10)
Baseline Median	5.90	7.11	6.59	5.60	7.10	6.80
Baseline Min, Max	4.20, 7.60	5.70, 13.80	4.80, 7.78	4.30, 7.90	5.50, 8.30	5.20, 9.20
Day 7 Mean (SD)	6.06 (1.08)	8.00 (2.48)	6.31 (1.24)	5.22 (1.24)	7.11 (1.42)	7.19 (1.43)
Mean (SD) CFB at Day 7	0.12 (0.62)	0.03 (0.81)	0.01 (0.56)	-0.57 (0.96)	0.19 (0.95)	0.20 (0.69)
Mean (SD) %CFB at Day 7	2.4% (9.4)	1.0% (9.1)	-0.4% (10.1)	-9.6% (16.9)	2.7% (12.8)	2.7% (9.6)
Triiodothyronine (ng/mL)	N=12	N=10	N=9	N=15	N=8	N=31
Baseline Mean (SD)	0.98 (0.17)	1.22 (0.23)	1.16 (0.19)	0.77 (0.12)	1.16 (0.19)	1.12 (0.21)
Baseline Median	1.00	1.15	1.20	0.70	1.25	1.20
Baseline Min, Max	0.7, 1.3	1.0, 1.7	0.8, 1.4	0.6, 1.0	0.8, 1.3	0.6, 1.6
Day 7 Mean (SD)	1.01 (0.15)	1.18 (0.14)	1.14 (0.25)	0.75 (0.16)	1.15 (0.11)	1.08 (0.22)
Mean (SD) CFB at Day 7	0.03 (0.10)	-0.04 (0.17)	-0.01 (0.23)	-0.01 (0.14)	-0.01 (0.16)	-0.04 (0.13)
Mean (SD) %CFB at Day 7	4.3% (10.4)	-1.8% (12.9)	-0.1% (19.1)	-1.3% (16.8)	0.8% (15.7)	-3.4% (12.6)

Source: Table 11, pages 67-68, CSR for MGL-3196-10
Abbreviations: ApoB, apolipoprotein B; CFB, change from baseline; %CFB, percentage change from baseline; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Max, maximum; Min, minimum; NASH, nonalcoholic steatohepatitis; SD, standard deviation

Increases in SHBG were also assessed in all cohorts. Increases ≥ 26.3% and up to 60.8% (subjects with non-cirrhotic NASH) from baseline to Day 7 were observed.

14.2.10. Single Ascending-Dose Study, Trial VIA-3196-01

Title

A randomized, double-blind, placebo-controlled, single ascending-dose study to evaluate the safety, PK, and PD of resmetirom in healthy subjects.

Study Design

This study was designed as a single-center, randomized, double-blind, placebo-controlled, single ascending dose study of resmetirom in healthy subjects. Subjects were randomized 3:1 to receive resmetirom or placebo on the morning of Day 1 at doses of 0.25, 1, 2.5, 5, 10, 20, 50, 100, or 200 mg. Each cohort contained 8 subjects (total n=72), with 54 subjects planned to receive resmetirom and 18 subjects planned to receive placebo.

Note that the food effect was also assessed. Subjects enrolled in the 10 mg cohort returned approximately 7 days after dosing to receive another single dose of 10 mg under fed conditions (i.e., with a high-fat breakfast). However, in this study, the food effect was evaluated using an older formulation and different dose from that TBM. The food effect was assessed later in Trial MGL-3196-09 using a later formulation (Prototype Formulation 7) at the proposed TBM dose of 100 mg. Therefore, food-effect results from Trial VIA-3196-01 will not be discussed.

All doses were administered following a fasting period of at least 10 hours. Doses of resmetirom were administered using several capsule formulations (formulations 1 to 4). Each of the four capsule formulations were available at a single strength of 0.25, 2.5, 10, and 50 mg for formulations 1, 2, 3, and 4, respectively (note that although these formulations contained the same excipients, the % w/w differed). Dosing of resmetirom was as follows:

- 0.25 mg: 1 × 0.25 mg capsule
- 1 mg: 4 × 0.25 mg capsules
- 2.5 mg: 1 × 2.5 mg capsule
- 5 mg: 2 × 2.5 mg capsules
- 10 mg: 1 × 10 mg capsule
- 20 mg: 2 × 10 mg capsules
- 50 mg: 1 × 50 mg capsule
- 100 mg: 2 × 50 mg capsules
- 200 mg: 4 × 50 mg capsules

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 30 kg/m^2, and an LDL cholesterol >85 mg/dL. All prescription or non-prescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to the first dose of study drug. Concomitant medications were not permitted.

Blood PK samples for resmetirom were collected predose on Day 1, and postdose at minutes 15, 30, and 45, and hours 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48.

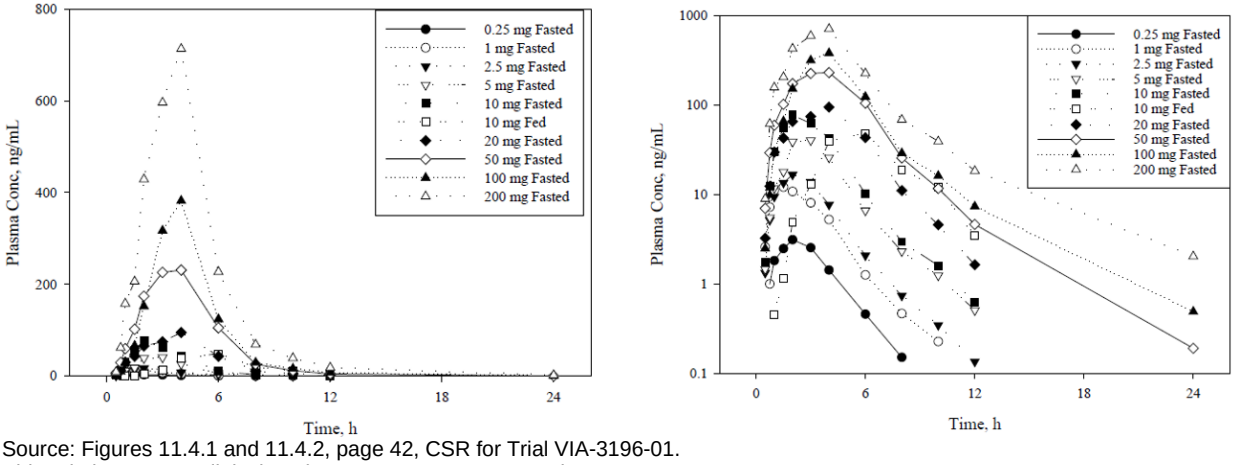
PD samples for fasting lipids were collected on Days -1, 2, 3, and 9 (day of the final visit). Samples for assessment of TSH were collected on Day -1, and postdose at hours 4, 8, 12, and 24, and Days 3 and 9. Samples to assess free and TT3 and T4 were collected on Days -1, 3, and 9.

PK Results

A total of 72 subjects were enrolled in the study across 9 dosing cohorts, including 54 subjects who received resmetirom and 18 subjects who received placebo. All 72 subjects completed the study.

Mean concentration-time profiles by dose cohort and PK parameters are shown in Figure 34 and Table 199, respectively. Across all fasted dose cohorts, the median T_{max} ranged from 1.8 to 4.2 hours. The geometric mean half-life ranged from 1.4 to 4.2 hours. There is a trend towards longer T_{max} and longer half-life with increasing dose. A trend towards higher clearance and higher volume at higher doses was also observed. However, it is difficult to draw definitive conclusions given that four different formulations were used across cohorts. It is unclear whether formulation effects may have contributed to these differences. Observations of longer half-life at higher doses may also be a factor of the bioanalytical assay detection limit (lower limit of quantitation (LLOQ)=0.05 ng/mL) such that complete concentration-time profiles may not have been detected at lower doses.

Figure 34. Mean Plasma Concentration-Time Profiles of Resmetirom Following Single Oral Doses in the Linear (Left) and Semi-Log (Right) Scales



Source: Figures 11.4.1 and 11.4.2, page 42, CSR for Trial VIA-3196-01.
Abbreviations: CSR, clinical study report; VIA-3196, resmetirom

Table 199. Geometric Mean Plasma PK Parameters of Resmetirom Following Single Oral Doses

Dose/Food Status	C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	T_{max} (h)	$T_{1/2}$ (h)	CL/F (L/h)	Vd/F (L)
0.25 mg/Fasted	3.73 (31.3)	12.0 (41.4)	2.17 (1.50–3.00)	1.36 (31.5)	20.9 (41.4)	41.2 (30.3)
1.0 mg/Fasted	15.2 (56.5)	48.2 (33.4)	1.83 (1.50–4.17)	1.73 (18.9)	20.7 (33.4)	51.7 (49.2)
2.5 mg/Fasted	20.2 (58.9)	65.9 (38.6)	2.58 (1.50–4.17)	1.88 (40.1)	37.9 (38.7)	103 (42.6)
5 mg/Fasted	47.8 (23.7)	164 (32.0)	2.59 (2.17–4.17)	1.90 (44.5)	30.5 (32.1)	83.8 (36.7)
10 mg/Fasted	103 (53.4)	301 (39.6)	2.17 (1.50–4.17)	2.39 (24.5)	33.2 (39.7)	114 (42.1)
10 mg/Fed	54.2 (21.3)	294 (28.3)	6.17 (4.17–6.17)	1.93 (48.3)	33.9 (28.2)	94.5 (50.5)
20 mg/Fasted	104 (61.8)	470 (57.3)	4.17 (3.00–6.17)	2.71 (7.04)	42.5 (57.3)	166 (54.3)
50 mg/Fasted	365 (69.9)	1,430 (52.6)	4.17 (2.17–6.17)	2.93 (20.9)	34.4 (56.4)	146 (40.3)
100 mg/Fasted	521 (70.8)	1,700 (62.4)	4.17 (1.50–4.17)	3.20 (27.4)	58.7 (62.4)	271 (68.7)
200 mg/Fasted	775 (50.5)	3,170 (51.4)	3.00 (3.00–4.17)	4.17 (17.7)	62.6 (51.5)	377 (57.8)

Source: Table 1, page 35, Summary of Clinical Pharmacology
Note: Data are presented as geometric mean (geometric %CV) except for T_{max} which is presented as median (min-max).
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; T_{max}, median time to maximum concentration; $T_{1/2}$, elimination half-life; Vd/F, apparent volume of distribution

Dose-proportionality was assessed across the dose range of 0.25 to 200 mg using a power-law model based on calculations of C_{max} and AUC_{0-inf} in each cohort. The mean (90% CI) slope determined for C_{max} and AUC_{0-inf} were 0.8053 (0.7500, 0.8605) and 0.8413 (0.7924, 0.8901), respectively. The data indicate that resmetirom C_{max} and AUC_{0-inf} increase in a less-than-dose proportional manner between doses of 0.25 and 200 mg. Capsule formulations 1 to 3 have not been bridged to formulations used in later studies. It is therefore possible that the use of different capsule formulations across dose cohorts could have impacted dose proportionality analyses.

PD Results

Following a single oral dose of resmetirom at dose levels ranging from 0.25 to 200 mg, no apparent effects on PD parameters were observed, including TSH, free and TT3 and T4, and fasting lipids (e.g., LDL cholesterol, triglycerides).

14.2.11. Multiple Ascending-Dose Study, Trial VIA-3196-02

Title

A randomized, double-blind, placebo-controlled, multiple ascending-dose study to evaluate the safety, PK, and PD of resmetirom in healthy subjects.

Study Design

This study was designed as a single-center, randomized, double-blind, placebo-controlled, multiple ascending dose study of resmetirom in healthy subjects. Subjects were randomized 3:1 to receive resmetirom or placebo. Resmetirom was administered at doses of 5, 20, 50, 80, 100, or 200 mg. Doses were administered QD for 14 days. Each cohort contained 8 subjects (total n =48), with 36 subjects planned to receive resmetirom and 12 subjects planned to receive placebo.

Dosing began with the 20 mg cohort. Following review of clinical safety data, dosing continued at the 5 mg and 50 mg cohorts, which were dosed concurrently. Following review of safety data from these cohorts, the three remaining cohorts proceeded at dose levels of 80 mg, 100 mg, and 200 mg.

All doses were administered following a fasting period of at least 12 hours. Doses of resmetirom were administered using three capsule formulations (formulations 2-4). Each of the three capsule formulations were available at a single strength of 2.5, 10, and 50 mg for formulations 2, 3, and 4, respectively (note that although these formulations contained the same excipients, the % w/w differed). Dosing of resmetirom was as follows:

- 5 mg: 2 × 2.5 mg capsules
- 20 mg: 2 × 10 mg capsules
- 50 mg: 1 × 50 mg capsule
- 80 mg: 1 × 50 mg and 3 × 10 mg capsules
- 100 mg: 2 × 50 mg capsules
- 200 mg: 4 × 50 mg capsules

The study enrolled healthy male and female subjects between the ages of 18 and 55 years, with BW >50 kg. All subjects must have had a BMI between 18 and 30 kg/m^2, and an LDL cholesterol ≥110 mg/dL. The latter criterion was hypothesized to maximize the chance of seeing a PD effect after 14 days of dosing. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 7 days prior to the first dose of study drug. Concomitant medications were not permitted.

Blood PK samples for resmetirom and MGL-3623 were collected predose on Days 1, 2, 3, 6, 9, 12, 14, and 15. Postdose samples were collected on Days 1 and 14 at hours 0.5, 1, 2, 3, 4, 6, 8, 10, and 12. An additional sample was collected on Day 16. Urine PK samples were collected on Days 1 and 14 predose, and postdose at intervals of 0 to 7, 7 to 14, and 14 to 24 hours. An additional urine sample was collected on Day 15.

PD samples for fasting lipids were collected at baseline and on Days 1, 3, 6, 9, 12, 14, 15, 16 and 21 (day of the end-of-study visit). Samples for assessment of TSH, and free and TT3 and T4 were collected at screening, and on Days 1, 3, 6, 9, 12, 14, 15, 16, and 21. An additional sample was collected at a follow-up visit on Days 27 to 32 for subjects enrolled in the 100 mg and 200 mg cohorts. Additional samples for TSH-only were collected postdose on Days 1 and 14 at hours 3, 6, and 12; and predose on Day 2. Samples to assess SHBG were collected on Days 1, 15, and 21.

PK Results

A total of 48 subjects were enrolled in the study across 6 dosing cohorts (N = 8/cohort), including 36 subjects who received resmetirom and 12 subjects who received placebo. 46 subjects completed the study, with two subjects discontinuing prematurely (one subject withdrew for personal reasons; one subject withdrew due to an adverse event (AE) of migraine).

Resmetirom

Mean concentration-time profiles by dose cohort and PK parameters of resmetirom and metabolite MGL-3623 are shown in Figure 35, Table 200 and Table 201, respectively. Following single oral doses of resmetirom, the median T_{max} ranged from 2.2 to 5.2 hours. The geometric mean half-life ranged from 1.7 to 3.1 hours. AUC and C_{max} at doses of 5, 20, and 50 mg were generally consistent with observations in single ascending dose study, Trial VIA-3196-01. AUC and C_{max} at 100 mg and 200 mg were higher and lower, respectively, than what was observed in Trial VIA-3196-01. Notably, exposure at the 100 mg dose was found to be higher than that at the 200 mg dose.

On Day 14, there was little change in the T_{max} and half-life; the median T_{max} ranged from 2.6 to 4.2 hours, while the geometric mean half-life ranged from 2.5 to 4.5 hours. Accumulation based on C_{max} and AUC_{0-24} was observed at doses ≥ 50mg, with no accumulation observed with QD dosing in the 5 and 20 mg cohorts. Accumulation ratios for C_{max} were 1.4, 1.7, 1.7, and 2.2 for the 50, 80, 100, and 200 mg cohorts, respectively. Accumulation ratios for AUC_{0-24} were 1.6, 1.8, 2.6, and 2.8 for the 50, 80, 100, and 200 mg cohorts, respectively. Based on predose concentrations measured for the dose cohorts receiving 100 and 200 mg, steady state for resmetirom was reached by Days 3 to 6.

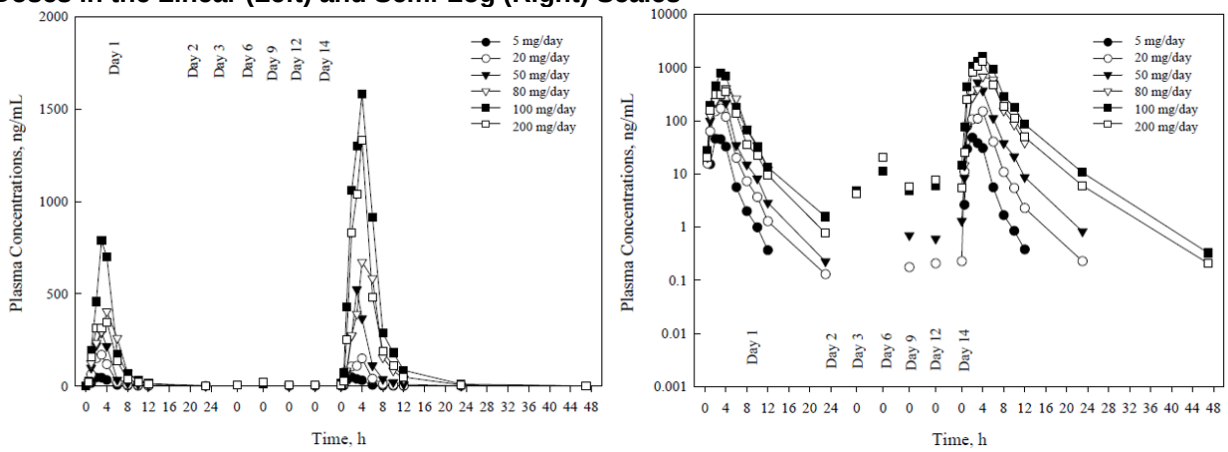
MGL-3623

The PK of MGL-3623 was measured in cohorts receiving doses of resmetirom ≥20 mg. Following a single dose of resmetirom, the median T_{max} ranged from 3.6 to 5.2 hours, and the geometric mean half-life ranged from 1.2 to 3.3 hours. Consistent with the PK of resmetirom, exposure to MGL-3623 following a 100 mg dose of resmetirom was greater than observations following administration of a 200 mg dose. The ratio of AUC_{0-inf} between MGL-3623 and resmetirom ranged from 0.8 to 1.2 across all cohorts.

On Day 14, there was little change in the T_{max} and half-life. The median T_{max} ranged from 4.2 to 6.2 hours, while the geometric mean half-life ranged from 2.1 to 4.8 hours. The T_{max} of MGL-3623 is delayed relative to resmetirom, suggesting formation of MGL-3623 following absorption of resmetirom. No accumulation of MGL-3623 was observed with QD dosing at any dose of resmetirom, with accumulation ratios for C_{max} and AUC_{0-24} all falling below 1 (C_{max}: 0.62 to

0.85; AUC_{0-24}: 0.72 to 0.98). As resmetirom AUC increased with repeat dosing, while no accumulation of MGL-3623 was observed, the AUC ratio between MGL-3623 and resmetirom decreased on Day 14 (range: 0.28 to 0.84). The AUC ratio tended to decrease with increasing dose. As resmetirom was identified to be both a substrate and inhibitor of CYP2C8, this observation may be in part due to inhibition of CYP2C8-mediated metabolism to MGL-3623. Based on predose concentrations measured for the dose cohorts receiving 100 and 200 mg, steady state for MGL-3623 was reached by Days 3 to 6.

Figure 35. Mean Plasma Concentration-Time Profiles of Resmetirom Following Multiple Oral Doses in the Linear (Left) and Semi-Log (Right) Scales



Source: Figures 11.4.4 and 11.4.5, page 65-66, CSR for Trial VIA-3196-02.
Abbreviations: CSR, clinical study report; VIA-3196, resmetirom

Table 200. Geometric Mean Plasma PK Parameters of Resmetirom on Days 1 and 14 Following Multiple Oral Doses

PK Parameters	VIA-3196 Dose, mg/day					
	5	20	50	80	100	200
Day 1						
T_{max}, h	3.00	3.00	3.00	5.17	3.00	2.18
(min, max)	*(2.17,4.17)*	*(2.17,4.17)*	*(2.17,4.17)*	*(3.00,6.17)*	*(2.17,4.17)*	*(1.17,4.23)*
C_{max}, ng/mL	64.4	190	420	611	991	578
CV%	*42.5*	*29.9*	*28.2*	*29.6*	*33.7*	*44.3*
$AUC_{(0-24)}$, ng·h/mL	194	655	1,230	2,510	3,570	2,340
CV%	41.5	30.1	23.6	35.4	59.5	33.2
$AUC_{(0-inf)}$, ng·h/mL	194	656	1,230	2,510	3,580	2,340
CV%	41.5	30.1	23.6	35.5	59.6	33.1
$T_{1/2}$, h	1.73	2.79	2.52	2.16	3.16	2.75
sd	*0.619*	*0.243*	*0.391*	*0.684*	*0.435*	*0.245*
Day 14						
T_{max}, h	2.59	4.17	3.00	4.17	4.17	4.17
(min, max)	*(2.17,4.17)*	*(2.17,4.17)*	*(3.00,4.17)*	*(4.17,6.17)*	*(2.17,6.17)*	*(3.00,6.17)*
C_{max}, ng/mL	56.2	162	581	990	1,720	1,490
CV%	*56.7*	*36.6*	*33.5*	*68.5*	*45.4*	*106*
$AUC_{(0-24)}$, ng·h/mL	186	665	1,990	4,250	9,430	7,100
CV%	*36.4*	*45.5*	*29.5*	*79.3*	*57.9*	*140*
$T_{1/2}$, h	2.71	3.18	3.18	2.45	4.47	4.46
sd	*1.09*	*0.692*	*0.689*	*0.675*	*0.521*	*0.201*
AI, C_{max}	0.873	0.854	1.38	1.71	1.73	2.24
CV%	*35.7*	*46.4*	*36.4*	*56.2*	*30.4*	*114*
AI, $AUC_{(0-24)}$	0.958	1.01	1.61	1.79	2.64	2.79
CV%	*34.8*	*32.9*	*36.6*	*48.1*	*47.1*	*131*

Source: Table 11.4.3, page 63, CSR for Trial VIA-3196-02.
Note: N=6 per cohort, except for the 80 and 200 mg dose cohorts on Day 14, where N=5.
Note: T_{max} is expressed as median; $T_{1/2}$ is arithmetic mean.
Note: AI=accumulation index calculated from ratio of AUC_{0-24}, Day 14/AUC_{0-24}, Day 1 and ratio of C_{max}, Day 14/C_{max}, Day 1.
Abbreviations: AI, accumulation index; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, elimination half-life; VIA-3196, resmetirom

Table 201. Geometric Mean Plasma PK Parameters of MGL-3623 on Days 1 and 14 Following Multiple Oral Doses of Resmetirom

PK Parameters	VIA-3196 Dose, mg/day					
	5[a]	20	50	80	100	200
Day 1						
T_{max}, h	-	3.59	3.59	5.17	4.17	3.60
(min, max)		(2.17, 4.17)	(3.00, 4.17)	(4.17, 6.17)	(3.00, 4.18)	(2.17, 6.17)
C_{max}, ng/mL	-	180	362	419	650	528
CV%		29.2	52.4	42.9	22.3	59.7
$AUC_{(0-24)}$, ng·h/mL	-	774	1,420	2,340	2,840	2,550
CV%		37.1	46.6	26.9	38.4	45.6
$AUC_{(0-inf)}$, ng·h/mL	-	775	1,420	2,360	2,850	2,560
CV%		37.2	46.9	27.1	38.9	45.5
$T_{1/2}$, h	-	1.82	2.83	3.21	3.30	2.77
sd		0.524	0.675	0.678	0.521	0.975
$AUC_{(0-inf)}$ Ratio (VIA-3196-M1/VIA-3196)	-	1.18	1.15	0.941	0.799	1.09
CV%		17.3	30.8	28.5	43.8	16.8
Day 14						
T_{max}, h	-	4.17	4.17	6.17	4.17	4.17
(min, max)		(4.17, 4.17)	(3.00, 4.17)	(4.17, 6.17)	(4.17, 4.17)	(3.00, 4.17)
C_{max}, ng/mL	-	111	308	345	446	511
CV%		23.6	41.7	38.2	18.2	48.2
$AUC_{(0-24)}$, ng·h/mL	-	558	1,390	2,050	2,660	2,500
CV%		33.1	29.1	34.6	33.0	57.1
$T_{1/2}$, h	-	2.11	3.08	3.69	4.81	4.45
sd		0653	0.971	0.706	1.78	1.77
$AUC_{(0-24)}$ Ratio (VIA-3196-M1/VIA-3196)	-	0.840	0.697	0.482	0.282	0.352
CV%		20.3	33.0	59.5	63.2	53.2
Estimated Exposure of VIA-3196-M1[b],%		41	38	30	21	25
AI, C_{max}	-	0.619	0.849	0.838	0.687	0.848
CV%		26.6	52.6	41.4	12.7	44.9
AI, $AUC_{(0-24)}$	-	0.721	0.979	0.891	0.937	0.903
CV%		15.1	44.5	23.0	14.3	53.4

Source: Table 11.4.4, page 64, CSR for Trial VIA-3196-02.

[a] Plasma was not analyzed for M1.

[b] Calculated from $AUC_{(0-24)}$ VIA-3196-M1 / [$AUC_{(0-24)}$ VIA-3196 + $AUC_{(0-24)}$ VIA-3196-M1 + estimated $AUC_{(0-24)}$ VIA-3196-M2]

Note: T_{max} is expressed as median; $T_{1/2}$ is arithmetic mean.

Note: Accumulation Index (AI) calculated from ratio of $AUC_{(0-24)}$, Day 14 / $AUC_{(0-24)}$, Day 1 and ratio of C_{max}, Day 14 / C_{max}, Day 1

Abbreviations: AI, accumulation index; AUC_{0-inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; M1, metabolite 1; M2, metabolite 2; PK, pharmacokinetic; SD, standard deviation; T_{max}, median time to maximum concentration; $T_{1/2}$, elimination half-life; VIA-3196, resmetirom

Dose-proportionality for resmetirom and MGL-3623 was assessed using a Power-Law model based on C_{max} and AUC values calculated on Day 1 and Day 14 across the dose range of 5 to 200 mg (resmetirom) or 20 to 200 mg (MGL-3623). Results are shown in Table 202. Results indicate that resmetirom C_{max} and $AUC_{0\text{-}inf}$ increase in a less-than-dose proportional manner following single doses of 5 to 200 mg. These results are consistent with those from single ascending dose study, Trial VIA-3196-01. At steady state, resmetirom C_{max} and $AUC_{0\text{-}24}$ were found to increase in a dose-proportional manner. MGL-3623 exposure increased in a less-than-dose proportional manner both after a single dose of resmetirom, and at steady state.

Although the Applicant concluded dose proportionality from 5 to 200 mg at steady state, summary PK parameters do not support this assertion. The following were observed:

- The geometric mean C_{max} and AUC were lower for the 200 mg cohort relative to the 100 mg cohort.
- Greater-than-dose-proportional increases in Day 14 $AUC_{0\text{-}24}$ at doses ≥50 mg, with a 2.1-fold increase observed with a 1.6-fold increase in dose between doses of 50 and 80 mg, and a 2.2-fold increase observed with a 1.25-fold increase in dose between doses of 80 and 100 mg.
- It is possible that the use of different capsule formulations and the number of dosage units for total dose across dose cohorts could have impacted dose proportionality analyses.

It was observed that the mean BW among subjects in the 100 mg cohort (i.e., 67.4 kg) was lower than that among subjects in other cohorts (78.6 to 84.1 kg). BW is a significant covariate affecting the clearance and volume of distribution of resmetirom such that subjects with lower BW had higher exposure to resmetirom (refer to Section 14.5). Lower BW may at least in part have contributed to the observed greater exposure in the 100 mg cohort relative to that in the 200 mg cohort.

When PK data from VIA-3196-02 were assessed excluding the 100 mg dose cohort, C_{max} and AUC increased dose-proportionally across the dose range of 5 to 200 mg.

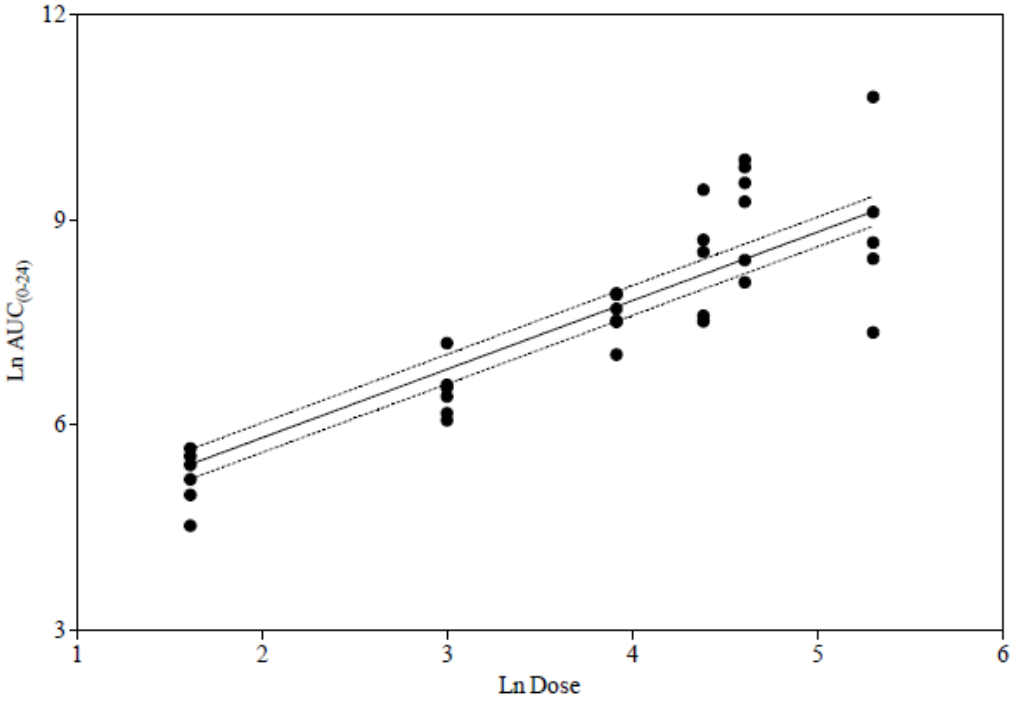
- C_{max} slope (standard error)=0.95 (0.10)
- AUC slope (standard error)=1.04 (0.10)

Table 202. Summary Statistics for Assessment of Dose-Proportionality of Resmetirom and MGL-3623

Analyte	Day	Parameter	Slope		
			Mean (SE)	90% CI	P-value (Slope = 1)
VIA-3916	1	Cmax	0.7059 (0.06808)	0.5907 to 0.8211	0.0001[a]
		AUC(0-inf)	0.7815 (0.06608)	0.6698 to 0.8933	0.0022[a]
	14	Cmax	1.016 (0.09602)	0.8533 to 1.179	0.8689
		AUC(0-24)	1.125 (0.1055)	0.9467 to 1.304	0.2434
VIA-3916-M1	1	Cmax	0.5131 (0.1065)	0.3320 to 0.6942	< 0.0001[a]
		AUC(0-inf)	0.5828 (0.09459)	0.4219 to 0.7437	0.0001[a]
	14	Cmax	0.6797 (0.1097)	0.4926 to 0.8669	0.0071[a]
		AUC(0-24)	0.7186 (0.1131)	0.5257 to 0.9115	0.0195[a]

Source: Table 11.4.5, page 67, CSR for Trial VIA-3196-02.
Note: In the table, VIA-3916 is resmetirom, while VIA-3916-M1 is MGL-3623.
Note: Dose-proportionality was assessed across the dose range of 5 to 200 mg for resmetirom, and 20 to 200 mg for MGL-3623.
Note: For resmetirom, N=36 on Day 1 and N=34 on Day 14.
* Reject null hypothesis (i.e., slope≠1).
Abbreviations: $AUC_{(0\text{-inf})}$, area under the plasma concentration versus time curve from time zero extrapolated to infinity; $AUC_{(0\text{-}24)}$, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule, CI, coefficient of variation; C_{max}, maximum plasma concentration; M1, metabolite 1; N, number of subjects in treatment arm; SE, standard error; VIA-3916, resmetirom

Figure 36. Resmetirom Ln(AUC) Vs. Ln(Dose) on Day 14 for Dose Proportionality Analysis



Source: Figure 11.4.9, page 69, CSR for Trial VIA-3196-02.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{(0\text{-}24)}$, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; CSR, clinical study report; Ln, natural logarithm; VIA-3196, resmetirom

In urine, the mean (CV%) percent of resmetirom recovered ranged from 0.21% (26.3%) to 0.95% (43.5%) following single doses of 20 and 200 mg. The mean (CV%) percent of MGL-3623 recovered ranged from 4.65% (33.7%) to 19.8% (21.6%) following single doses of 20 and 200 mg. Little change in the percent recovered in urine was observed following repeat oral doses between 20 and 200 mg. Across all cohorts, the mean (CV%) percent of resmetirom recovered ranged from 0.66% (70.4%) to 1.11% (111%), while the mean (CV%) percent of MGL-3623 recovered ranged from 4.65% (47.6%) to 16.0% (33.3%).

PD Results

Thyroid hormone levels at baseline and 24 hours after the last dose administered on Day 14 across dose cohorts are shown in Table 203. No changes from baseline were observed for free and TT3 in any dose cohort. Small reductions in free and total T4 were observed at doses ≥80 mg. Significant changes in TSH were not observed at any dose level.

Dose-dependent changes in SHBG were also observed with the greatest changes observed at doses ≥80 mg. In the 80, 100, and 200 mg cohorts, SHBG increased by 20 to 28.2% relative to baseline values. These changes in SHBG were associated with increases in total testosterone, with the largest changes from Baseline to Day 15 observed at the highest dose cohorts of 100 and 200 mg (mean change from baseline of 389 and 198 ng/dL for 100 and 200 mg cohorts, respectively).

Table 203. Thyroid Hormone Levels at Baseline and Following Repeat Doses of Resmetirom for 14 Days

Dose	Free T3 (mg/mL)		Free T4 (ng/dL)		Total T3 (ng/mL)		Total T4 (µg/dL)		TSH (µIU/mL)
	Baseline	Postdose	Baseline	Postdose	Baseline	Postdose	Baseline	Postdose	Difference[a]
Placebo	4.12 ± 0.7	4.04 ± 0.56	1.07 ± 0.16	1.09 ± 0.16	1.35 ± 0.27	1.33 ± 0.25	6.60 ± 0.92	6.88 ± 0.96	1.13 ± 1.09
5 mg	4.65 ± 0.88	4.33 ± 0.79	0.96 ± 0.17	0.88 ± 0.11	1.81 ± 1.02	1.66 ± 0.85	6.01 ± 0.73	6.17 ± 0.55	0.69 ± 1.03
20 mg	3.87 ± 0.27	4.03 ± 0.32	1.08 ± 0.13	1.02 ± 0.11	1.70 ± 0.70	1.55 ± 0.65	6.42 ± 1.04	5.76 ± 0.7	2.08 ± 1.65
50 mg	4.25 ± 0.19	4.02 ± 0.26	1.03 ± 0.15	0.96 ± 0.08	1.36 ± 0.11	1.30 ± 0.13	6.51 ± 0.5	6.47 ± 0.67	0.67 ± 0.47
80 mg	3.93 ± 0.47	4.16 ± 0.3	1.32 ± 0.15	1.03 ± 0.11	1.58 ± 0.25	1.35 ± 0.20	8.05 ± 1.18	6.6 ± 1.33	0.21 ± 0.85
100 mg	4.66 ± 0.42	4.01 ± 0.31	1.05 ± 0.22	0.94 ± 0.15	1.43 ± 0.20	1.27 ± 0.21	6.65 ± 1.31	4.82 ± 0.69	0.25 ± 0.53
200 mg	3.55 ± 0.32	3.95 ± 0.3	0.93 ± 0.07	0.78 ± 0.13	1.19 ± 0.07	1.14 ± 0.08	6.27 ± 0.34	4.48 ± 0.75	0.2 ± 0.39

Source: Table 6, page 40, Summary of Clinical Pharmacology
Note: Data are presented as arithmetic mean ± standard deviation. Thyroid hormone levels were measured after 14 once-daily doses of resmetirom. Thyroid hormones were assed 24 hours after Dose 14.
[a.] Difference from baseline.
Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone

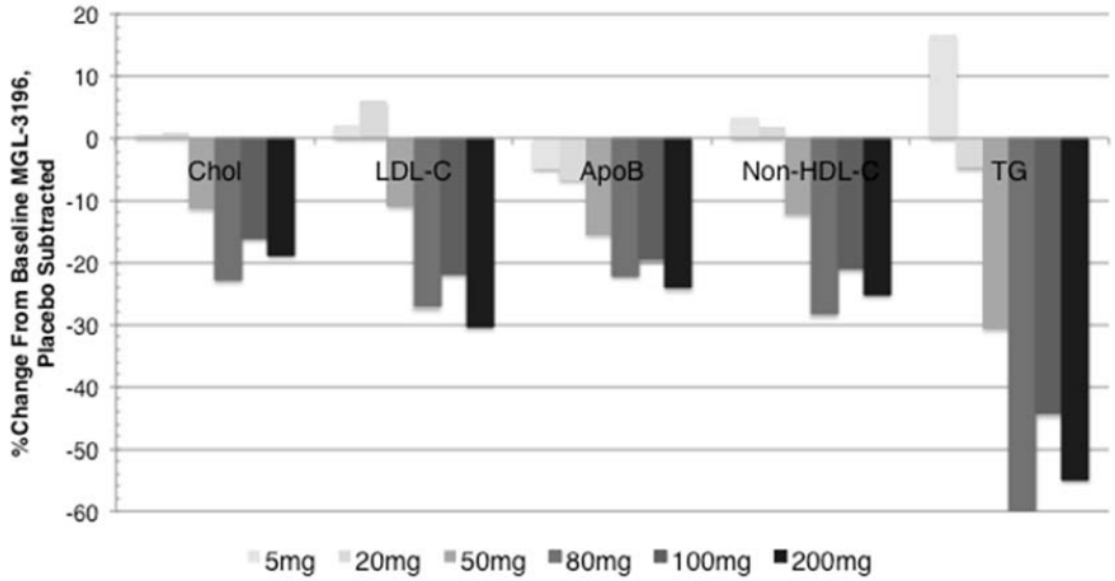
Subjects enrolled in VIA-3196-02 were required to have elevated LDL (≥110 mg/dL) to assess the impact of resmetirom on lipids. The impact on plasma lipid parameters is shown in Table 204 and Figure 37. Dose-dependent reductions in all lipid parameters, including total cholesterol, LDL cholesterol, ApoB, non-HDL cholesterol, and triglycerides (TGs) were observed beginning at doses ≥50 mg. The largest changes were observed at dose levels of 80, 100, and 200 mg.

Table 204. Percent Change From Baseline in Lipid Parameters Relative to Placebo Following 14 Days of Dosing With Resmetirom

Dose	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	ApoB (mg/dL)	Non-HDL Cholesterol (mg/dL)	TGs (mg/dL)
5 mg	0.7 ± 13.4	2.0 ± 14.3	-4.9 ± 11.7	3.3 ± 15.8	16.7 ± 17
20 mg	0.7 ± 10	6.1 ± 15.3	-6.6 ± 12.8	1.7 ± 11.6	-4.7 ± 47.2
50 mg	-11.3 ± 15.3	-10.9 ± 22	-15.4 ± 18.6	-12.2 ± 17.4	-30.6 ± 39.9
80 mg	-22.8 ± 8.7	-27.2 ± 9.9	-22.0 ± 11.1	-28.3 ± 10.7	-59.8 ± 11.7
100 mg	-16.0 ± 6.5	-21.8 ± 10.4	-19.5 ± 6.5	-21.0 ± 8.9	-44.4 ± 21.1
200 mg	-18.7 ± 10.3	-30.3 ± 10.8	-24.1 ± 11.7	-25.1 ± 13.6	-54.8 ± 44.8

Source: Table 7, page 40-41, Summary of Clinical Pharmacology
Abbreviations: ApoB, apolipoprotein B; non-HDL, non-high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides

Figure 37. Percent Change From Baseline in Lipid Parameters Relative to Placebo Following 14 Days of Dosing With Resmetirom



Source: Figure 11.4.1, page 53, CSR for Trial VIA-3196-02.
Note: Changes in lipids after 14 doses. The percent change from baseline (CFB) for each subject was determined, averaged by dose and corrected to placebo. The baseline determination was fasting, just prior to the first dose and the determination was made fasting 24 hours after the 14th dose.
Abbreviations: ApoB, apolipoprotein B; CFB, change from baseline; CSR, clinical study report; non-HDL, non-high-density lipoprotein; non-HDL-C, non high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MGL-3136, resmetirom; TG, triglycerides; VIA-3196, resmetirom

14.2.12. Single and Multiple Ascending Dose Study in Healthy Subjects, Trial MGL-3196-20

Title

A randomized, double-blind, single and multiple (6 days) ascending dose study to evaluate the PK, safety, and tolerability of resmetirom (40 mg, 60 mg, 80 mg, 100 mg, and 200 mg) in healthy Japanese and Caucasian subjects.

Study Design

A PK report for this study was submitted to IND 122865 on January 19, 2024 (Madrigal Pharmaceuticals 2023).[4] Note that the full clinical study report (CSR) for this study has not been submitted to this IND. This study provides information on dose proportionality using the tablet formulation of resmetirom and has thus been included in this review.

This study was designed as a single-center, randomized, double-blind, placebo-controlled, single and multiple ascending dose study of resmetirom in healthy Japanese and Caucasian subjects. Subjects were randomized 3:1 to receive resmetirom or placebo. Resmetirom was administered at doses of 40, 60, 80, 100, or 200 mg. Single doses were administered on Day 1. Multiple doses were administered QD on Days 3 to 8. Each cohort contained 16 subjects, including 8 Japanese subjects and 8 Caucasian subjects (total n=80). In each cohort, 12 subjects received resmetirom and 4 subjects received placebo.

All doses were administered following a fasting period of at least 8 hours. Doses of resmetirom were administered using the tablet formulation of resmetirom as follows:

- 40 mg: 1 × 40 mg tablet
- 60 mg: 1 × 60 mg tablet
- 80 mg: 1 × 80 mg tablet
- 100 mg: 1 × 100 mg tablet
- 200 mg: 2 × 100 mg tablets

The resmetirom tablets used in this study have the same excipients and are produced by the same manufacturer as the proposed TBM resmetirom tablets. Note that a 40 mg strength tablet was used in this study, while a 40 mg strength is not proposed for marketing.

The study enrolled healthy male and female Japanese and Caucasian subjects between the ages of 20 and 55 years, with BW >45 kg. All subjects must have had a BMI between 18 and 30 kg/m^2. Japanese and Caucasian subjects were matched within 15% of BMI. All prescription or nonprescription drugs, vitamins, and herbal and dietary supplements were prohibited within 14 days prior to the first dose of study drug. Concomitant medications were not permitted.

Blood PK samples for resmetirom and MGL-3623 were collected on Days 1 and 8 at predose and postdose at hours 0.5, 1, 2, 3, 4, 6, 8, and 12. Predose samples were collected on Days 1, 3, 4, 5,

[4] The Applicant is the owner of IND 122865.

6, 7, and 8. Additional samples were collected on Days 2, 9, 10, 11, and 12 (200 mg cohort only).

PK Results

PK results provided here focus on multiple dose PK and assessment of dose proportionality across the dose range. Note that the bioanalytical assay used to quantitate resmetirom plasma concentrations is the same as that used for Trials MGL-3196-05, MGL-3196-11, and MGL-3196-14.

Resmetirom C_{max} and AUC increase in an approximately doseproportional manner between doses of 40 and 100 mg. Both C_{max} and AUC increase in a greaterthandose proportional manner between doses of 100 and 200 mg. Between doses of 40 and 100 mg, geometric mean C_{max} increased 2.5-fold and AUC_{0-24} increased 2.9-fold for a 2.5-fold increase in dose. Between doses of 100 and 200 mg, geometric mean C_{max} increased 4.3-fold and AUC_{0-24} increased 5.6-fold for a 2-fold increase in dose. After multiple doses, resmetirom AUC_{0-24} ratio between Day 6 and Day 1 was 2.4-2.9 at 100 mg and 3.9-6 at 200 mg, across Caucasian and Japanese subjects. The AUC_{0-24} ratio between Day 6 and Day 1 for the metabolite, MGL-3623 was about 1 across doses.

Following QD dosing, the percent ratio of AUC_{0-24} for MGL-3623 to resmetirom decreased from 73.5% at 60 mg to 17.1% at 200 mg, suggesting a saturation of metabolism of resmetirom to MGL-3623 at higher doses.

Subjects with similar BWs were enrolled across all cohorts (Table 205). Per PopPK analysis, race/ethnicity is not a significant covariate affecting the PK of resmetirom after accounting for BW (refer to Section 14.5). In this study, the BWnormalized systemic exposure tended to be higher in Japanese than Caucasians although PK was similar between these populations. For the assessment of dose proportionality, PK results combined between Japanese and Caucasian subjects will be presented.

Table 205. Body Weight by Dose Cohort in MGL-3196-20

Variable/ Category	40 mg Resmetirom Jpn (N = 6)	40 mg Resmetirom Cau (N = 6)	60 mg Resmetirom Jpn (N = 6)	60 mg Resmetirom Cau (N = 7)	80 mg Resmetirom Jpn (N = 6)	80 mg Resmetirom Cau (N = 6)	100 mg Resmetirom Jpn (N = 6)	100 mg Resmetirom Cau (N = 6)	200 mg Resmetirom Jpn (N = 6)	200 mg Resmetirom Cau (N = 6)	Pooled Placebo Jpn (N = 10)	Pooled Placebo Cau (N = 10)	Overall (N = 81)
Weight (kg)													
n	6	6	6	7	6	6	6	6	6	6	10	10	81
Mean	62.02	64.98	66.43	72.01	64.60	77.33	66.90	78.32	68.23	74.57	67.22	70.75	69.43
(SD)	(10.383)	(7.247)	(11.701)	(6.638)	(10.935)	(12.178)	(6.546)	(9.085)	(8.731)	(11.341)	(10.484)	(12.461)	(10.569)
Median	62.65	64.30	70.70	72.40	66.70	77.85	65.75	80.35	68.15	72.70	67.30	67.70	68.00

Source: Adapted from Table 1, Applicant's IR Response dated February 8, 2024 under IND 122865
Abbreviations: Cau, Caucasian; IND, investigational new drug; Jpn, Japanese; MGL-3196, resmetirom; N, number of subjects in treatment arm; SD, standard deviation

C_{max} and AUC_{0-24} of resmetirom following QD dosing for 6 days combining data from Japanese and Caucasian subjects is shown in Table 206. Across all dose cohorts, the median T_{max} ranged from 3 to 5 hours, while the mean half-life ranged from 1.8 to 3.8 hours.

Between doses of 40 and 100 mg, geometric mean C_{max} increased 2.5-fold and AUC_{0-24} increased 2.9-fold for a 2.5-fold increase in dose. Between doses of 100 and 200 mg, geometric mean C_{max} increased 4.3-fold and AUC_{0-24} increased 5.6-fold for a 2-fold increase in dose. Thus, exposure increases in a dose proportional manner between doses of 40 and 100 mg, and in a greater-than-dose-proportional manner between doses of 100 and 200 mg.

Table 206. Summary Statistics for Resmetirom C_{max} and AUC_{0-24} by Dose Cohort Following QD Dosing for 6 Days

PK Parameter	40 mg (N = 12)	60 mg (N = 12[a])	80 mg (N = 12)	100 mg (N = 12)	200 mg (N = 11)
C_{max} (ng/mL)					
Mean (CV%)	726 (46)	1011 (42)	906 (47)	1908 (56)	7941 (50)
Median	797	891	828	1795	6920
Geometric Mean	641	931	826	1607	6947
AUC_{0-24} (ng*h/mL)					
Mean (CV%)	2591 (36)	3854 (57)	4046 (43)	8646 (68)	48300 (61)
Median	2570	3020	3865	6975	57100
Geometric Mean	2416	3325	3663	7020	39166

Source: Reviewer's analysis using PK parameters derived from Tables B-11, B-12, B-13, B-14, and B-15, Report MC22R-0019 for Trial MGL-3196-20

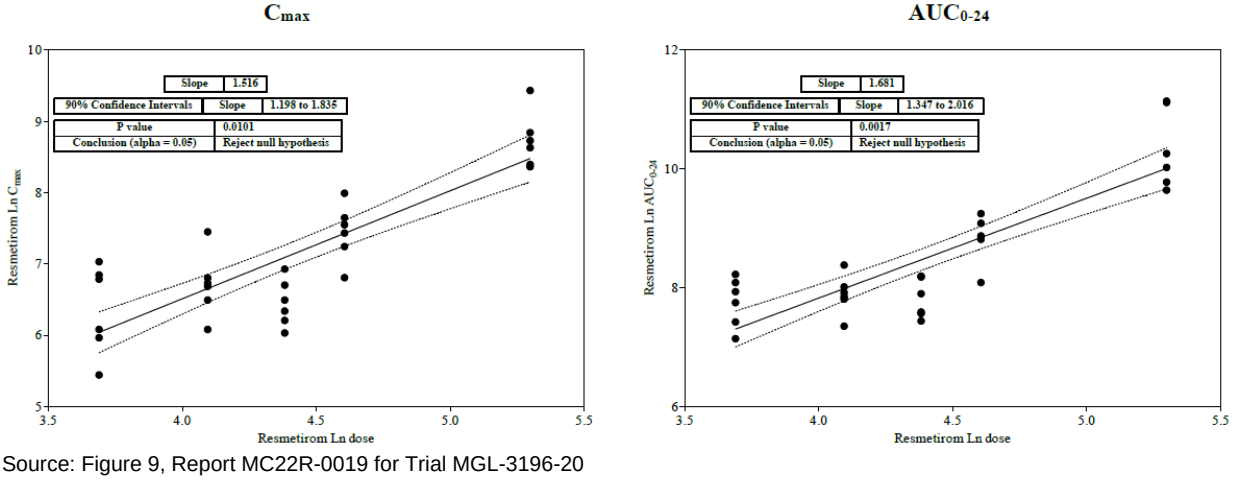
[a.] N=11 for AUC_{0-24}

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; CV, coefficient of variation

Notably C_{max} and AUC_{0-24} following administration of a 200 mg dose differ from what was observed in Trial VIA-3196-02 (geometric mean C_{max} and AUC_{0-24} at steady state following 200 mg QD of 1490 ng/mL and 7100 ng□h/mL, respectively). The reason for this discrepancy is unclear. C_{max} and AUC_{0-24} following a 200 mg dose in Trial MGL-3196-20 are consistent with those reported in Trials MGL-3196-03 (mean [CV%] C_{max} and AUC_{0-24} = 4910 [72%] ng/mL and 31,200 [102%] ng□h/mL, respectively) and MGL-3196-17 (mean [%CV] C_{max} and AUC_{0-24} = 5750 [65%] ng/mL and 35,800 [85%] ng□h/mL, respectively). Thus, results from Trial MGL-3196-20 are considered more relevantto understanding whether resmetirom PK is dose proportional.

The Applicant's assessment of dose proportionality divided by Japanese and Caucasian subjects is shown in Figure 38 and Figure 39. Results indicate that resmetirom C_{max} and AUC_{0-24} increase in a greater-than-dose-proportional manner between doses of 40 and 200 mg. Dose proportionality for C_{max} could not be rejected for Japanese subjects.

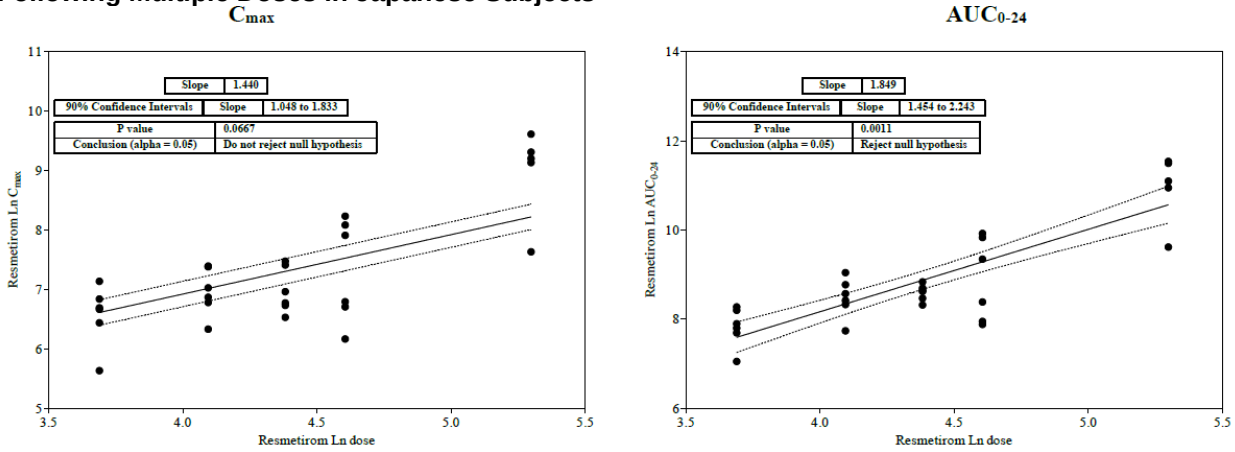
Figure 38. Assessment of Dose Proportionality for Resmetirom C_{max} (Left) and AUC_{0-24} (Right) Following Multiple Doses in Caucasian Subjects



Source: Figure 9, Report MC22R-0019 for Trial MGL-3196-20

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; Ln, natural logarithm; MGL-3196, resmetirom

Figure 39. Assessment of Dose Proportionality for Resmetirom C_{max} (Left) and AUC_{0-24} (Right) Following Multiple Doses in Japanese Subjects



Source: Figure 11, Report MC22R-0019 for Trial MGL-3196-20
Abbreviations: AUC_{0-24}, area under the curve from time 0 to the last measurable concentration (24 hours) using the linear trapezoidal rule; C_{max}, maximum plasma concentration; Ln, natural logarithm; MGL-3196, resmetirom

14.2.13. Phase 2 Study in NASH Patients, Trial MGL-3196-05

Title

A phase 2, multicenter, double-blind, randomized, placebo-controlled study of MGL-3196 in patients with NASH.

Objectives

Primary

- To determine the effect of once-daily oral MGL-3196 80 mg versus placebo (randomized 2:1) for 12 weeks on the percent change in hepatic fat fraction by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), from Baseline, in patients with biopsy-proven NASH.

There were numerous secondary objectives in the study, including looking at changes in thyroid axis hormones, lipid parameters (LDL-C, high-density lipoprotein-cholesterol, non-high-density lipoprotein-cholesterol, total cholesterol, triglycerides, apoB, and lipoprotein(a)), and NASH and fibrosis biomarkers (cytokeratin-18, fibrosis-4, and enhanced liver fibrosis test). Tertiary exploratory objectives included exploring the relationship between plasma MGL-3196 exposure and changes in efficacy and safety biomarkers; and exploring possible relationships between genomic markers of NASH and responses to MGL-3196.

Study Design

Main Study

This study was designed as a multicenter, randomized, double-blind, placebo-controlled study in subjects with biopsy-proven NASH. Subjects were randomized 2:1 to receive 80 mg resmetirom

or placebo QD for 36 weeks. Following 12 weeks of treatment, the primary endpoint, and percent change from baseline in hepatic fat fraction (MRI-PDFF) were measured. All subjects underwent a liver biopsy after 36 weeks.

Extension Study

Subjects who completed the main Study and met inclusion criterion for significant elevation in liver enzymes at Week 30 were eligible for the 36-week open-label extension study. At Weeks 12 and 36, subjects underwent MRI-PDFF. Subjects randomized to resmetirom during the main Study remained on the same dose of resmetirom or had a prespecified increase in dose (see dose adjustment scheme below).

In the main study and extension study, doses of resmetirom ranging from 40 to 120 mg were administered using two capsule formulations (formulations 5 and 6). Each capsule formulation was available at a single strength of 40 or 60 mg for formulations 5 and 6, respectively.

Inclusion/Exclusion Criteria

The study enrolled patients aged ≥18 years with biopsy-proven NASH and (nonalcoholic fatty liver disease [NAFLD] Activity Score [NAS] of at least 1 in steatosis, ballooning degeneration, and lobular inflammation) and fibrosis stage 1 to 3. This study enrolled subjects with eGFR ≥60 mL/min/1.73 m^2. Subjects presenting with cirrhosis on liver biopsy (stage 4 fibrosis), or clinical evidence of hepatic decompensation were excluded. Subjects with hyperthyroidism, on thyroid replacement therapy, or with untreated clinical or subclinical hypothyroidism were also excluded.

Subject Disposition

In the main study, a total of 125 subjects were enrolled, including 84 subjects who were randomized to receive resmetirom and 41 subjects who were randomized to receive placebo. Overall, about 93% (116/125) of subjects completed the 12-week treatment period, while 86.4% (108/125) of patients completed the 36-week treatment period. In the Extension Study, 31 subjects were enrolled (including 17 subjects initially randomized to resmetirom, and 14 subjects initially randomized to placebo). Twenty-nine subjects (94%) completed the 36-week treatment period.

Use of the following medications were excluded: T3, thyroxine, obeticholic acid, ursodeoxycholic acid, vitamin E (>400 IU/day), lipid modifying therapies, OATP transporter inhibitors (e.g., gemfibrozil, cyclosporine A, or protease inhibitors), drugs historically associated with NAFLD, repaglinide or a glitazone (CYP2C8 substrates), gemfibrozil (inhibitor of CYP2C8), oral corticosteroids, warfarin, or any medications with the potential to affect thyroid hormone production or that may interfere with thyroid function.

PK/PD Sample Collection

In the Main Study, blood PK samples for resmetirom and MGL-3623 were collected predose on Day 1 and Weeks 2, 4, 8, 16, 24, and 36. Additional postdose PK samples were collected at Week 2 at hours 2, 4, 6, and 8 postdose. In the extension study, blood PK samples for resmetirom and MGL-3623 were collected predose on Day 1 and Weeks 2, 4, 8, 16, 24, and 36. An additional postdose PK sample was collected 4 hours postdose at Week 2.

MRI-PDFF was conducted on Day 1, and Weeks 12 and 36 (main study and extension study).

In this review, the calibration of MRI-PDFF was not reviewed.

In both the main study and extension study, samples to assess thyroid axis hormones, SHBG, and fasting lipid parameters were measured on Day 1 and Weeks 2, 4, 8 12, 16, 20, 24, 30, and 36.

Dose Titration

All subjects initially received 80 mg and doses were adjusted at Week 4 based on PK assessments at Week 2 (samples collected at predose, and hours 2, 4, 6, and 8 postdose) and SHBG measurements as shown in Table 207. The Applicant indicated that a combined resmetirom and MGL-3623 exposure ≤5500 ng*h/mL did not demonstrate a drug-related decrease in free T4 to below the lower limit of normal in phase 1 studies.

Table 207. Dose Titration Scheme, Trial MGL-3196-05

Conditions at Week 2	Week 4 Dose
Combined AUC_{inf} (resmetirom+MGL-3623) >11000 ng*h/mL AND SHBG change from baseline > 150%	40 mg
Combined AUC_{inf} (resmetirom+MGL-3623) >11000 ng*h/mL with SHBG change from baseline < 150%	60 mg [a]
Combined AUC_{inf} (resmetirom+MGL-3623) >5500 ng*h/mL	60 mg
Combined AUC_{inf} (resmetirom+MGL-3623) ≤5500 ng*h/mL	80 mg
Combined AUC_{inf} (resmetirom+MGL-3623) ≤3000 ng*h/mL	100 mg

Source: Reviewer-generated table adapted from CSR for MGL-3196-05

[a] Under this condition predose concentrations and SHBG were measured at Week 4. At Week 4, if SHBG change from Baseline was >150% and predose concentrations were >40 ng/mL for both resmetirom and MGL-3623, then the dose was reduced to 40 mg at Week 8.

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; CSR, clinical study report; MGL-3196, resmetirom; SHBG, sex hormone binding globulin

In a protocol amendment, doses could be adjusted later than Week 4 in the main Study, or in the Extension Study as outlined in Table 208.

Table 208. Dose Adjustment Scheme in the Main or Extension Study,Trial MGL-3196-05

Current Dose	Main Study Week 2 PK (AUC, combined MGL-3196 plus M1 on 80 mg dose)	Main Study Predose at Week 2	Main Study Predose Week 8 (post dose adjustment)	Main Study SHBG <+75% CFB at Week 12 (post dose adjustment)	Action in Main and/or Extension Study
40 mg			<5 ng/mL	Yes	Increase to 60 mg/day
60 mg	≤5500 ng·hr/mL[a]		<1 ng/mL	Yes	Increase to 80 mg/day
80 mg	<4000 ng·hr/mL AND SHBG %CFB <90)			OR[b] Yes	Increase to 100 mg/day
100 mg	≤3000 ng·hr/mL	<5 ng/mL			Increase to 120 mg
120 mg					No change

Source: Table 2, CSR for MGL-3196-05
[a] Recalculated 80 mg AUC based on correct elimination rate constant for MGL-3196 and M1 in patients who demonstrated average predose levels <5 ng/mL at Week 2, 4, and 8 and had initial calculated AUC <7000 ng · hr/mL.
[b] Either exposure <4000 ng hr.mL with SHBG%CFB<+90 OR SHBG<+70%CFB qualifies for increase to 100mg.
Abbreviations: AUC, area under the plasma concentration-time curve; CFB, change from baseline; M1, MGL-3196-M1; PK, pharmacokinetic; SHBG, sex hormone-binding globulin

Dose adjustments were also made based on thyroid indices. At Week 8 or later, down-titration from 80 mg to 60 mg, or from 60 mg to 40 mg was permitted based on whether levels of free T4 fell between 0.55 and 0.7 ng/dL. The dose adjustment scheme for patients who were randomized to placebo in the Main Study is shown in Table 209.

Table 209. Dose Adjustment Scheme for Subjects Assigned to Placebo in the Main Study

Extension Study Week 2 MGL-3196 Concentration		Extension Study	Extension Study
Predose	**4 h Post Dose**	**Week 2 SHBG**	**Week 4 Action**
>35 ng/mL	>1350 ng/mL	>200% CFB[a]	Down-titrate to 40 mg
Patients not meeting criteria for 40, 80, 100, or 120 mg			Down-titrate to 60 mg
<15 ng/mL	<600 ng/mL	OR <75% CFB increase[b]	Remain on 80 mg or increase (see next rows)
<5 ng/mL	≤350 ng/mL	No rule	Increase to 100 mg
<2 ng/mL	≤150 ng/mL	No rule	Increase to 120 mg

Source: Table 3, CSR for MGL-3196-05
[a] Change from baseline, where baseline is Extension Study Day 1.
[b] Either predose <15 ng/mL plus 4h <600 ng/mL OR SHBG <+75%CFB.
Abbreviations: CFB, change from baseline; SHBG, sex hormone-binding globulin

Dosing by study visit in the main study is shown in Table 210. At Week 4, out of 84 subjects randomized to 80 mg, 38 (45%) subjects had their dose reduced to 60 mg, while 5 (6%) had their dose increased to 100 mg. One subject decreased to 40 mg while the rest continued at a dose of 80 mg. Throughout the treatment period, most subjects remained on 80 mg or 60 mg although a few subjects received doses of 40, 100, or 120 mg by the end of the main study.

Table 210. Resmetirom Doses Received by Study Visit, Trial MGL-3196-05 Main Study

		MGL-3196						
Visit	Placebo (N= 41) n (%)	40 mg n	60 mg n	80 mg n	100 mg n	120 mg n	Total (N= 84) n (%)	Overall (N=125) n (%)
Baseline	41 (100.0)	0	0	84	0	0	84 (100.0)	125 (100.0)
Week 4	39 (95.1)	1	38	35	5	0	79 (94.0)	118 (94.4)
Week 8	39 (95.1)	2	34	35	7	0	78 (92.9)	117 (93.6)
Week 12	38 (92.7)	2	34	35	7	0	78 (92.9)	116 (92.8)
Week 16	36 (87.8)	3	36	29	9	0	77 (91.7)	113 (90.4)
Week 20	36 (87.8)	2	36	30	8	1	77 (91.7)	113 (90.4)
Week 24	36 (87.8)	3	33	30	7	2	75 (89.3)	111 (88.8)
Week 30	34 (82.9)	3	31	29	8	4	75 (89.3)	109 (87.2)

Source: Table 14.1.6.3, CSR for Trial MGL-3196-05
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; N, number of subjects in treatment arm; n, number of subjects in subset

Dosing by study visit in the extension study is shown in Table 211. Most subjects enrolled in the extension study received resmetirom at a dose of 80 mg throughout the treatment period. A few number of subjects also received doses of 60 and 100 mg.

Table 211. Resmetirom Doses Received by Study Visit, Trial MGL-3196-05 Extension Study

	MGL-3196					
Visit	40 mg n	60 mg n	80 mg n	100 mg n	120 mg n	Total (N= 31) n (%)
Ext Baseline Day 1	0	9	20	2	0	31 (100.0)
Ext Week 4	1	11	14	4	1	31 (100.0)
Ext Week 8	0	10	13	6	1	30 (96.8)
Ext Week 12	0	7	16	5	2	30 (96.8)
Ext Week 16	0	6	17	5	2	30 (96.8)
Ext Week 20	0	4	19	4	2	29 (93.5)
Ext Week 24	0	2	20	5	2	29 (93.5)
Ext Week 28	0	0	22	5	2	29 (93.5)
Ext Week 32	0	0	21	6	2	29 (93.5)

Source: Table 14.1.6.3e, CSR for MGL-3196-05
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; N, number of subjects in treatment arm; n, number of subjects in subset

PK Results

For both resmetirom and MGL-3623, predose plasma concentrations at Weeks 2 and 4, and postdose concentrations at Week 2, were generally higher in subjects who dose adjusted to 60 mg at Week 4. This is expected given that dose adjustments were based on PK measurements at Week 2. From Week 8 through the remainder of the study, median resmetirom trough concentrations were generally comparable, ranging from 1.27 to 1.83 ng/mL in subjects who remained on 80 mg, and 2.08 to 3.17 ng/mL in subjects who had doses adjusted to 60 mg at Week 4 (refer to Tables 14.2.850.1 and 14.2.850.2, IR Response, CSR for MGL-3196-05, November 30, 2023).

At Week 2, all subjects randomized to resmetirom received a dose of 80 mg. Week 2 C_{max} occurred at approximately 2 hours postdose for resmetirom and 4 hours postdose for MGL-3623, with mean (CV%) values of 551 (94%) ng/mL and 176 (51%) ng/mL, respectively. $AUC_{0\text{-}inf}$ was estimated based on samples collected up to 8 hours postdose at Week 2. The mean (CV%) $AUC_{0\text{-}inf}$ for resmetirom and MGL-3623 was 4404 (83%) ng*h/mL and 1811 (47%) ng*h/mL, respectively.

In the extension study, one postdose PK sample was collected at Week 2, 4 hours postdose, at the approximate T_{max}. Mean (CV%) plasma concentration of resmetirom and MGL-3623 4 hours postdose at Week 2 was 523 (57%) ng/mL and 188 (42%) ng/mL, respectively. These values are consistent with observations in the main study. Throughout the extension study, from Week 2 onward, median resmetirom trough concentrations ranged from 1.74 to 5.12 ng/mL.

PD Results

Main Study

The percent change in liver fat fraction by MRI-PDFF at Week 12 is shown in Table 212. Relative and absolute reduction in liver fat fraction at Weeks 12 and 36 is shown in Figure 40. At Week 12, subjects receiving resmetirom had greater relative reduction in liver fat fraction as compared to subjects receiving placebo (least squares mean [LSM] difference [95% CI=22.5 [-32.9, -12.2]%). When compared across exposure groups using a resmetirom AUC threshold of 2700 ng*h/mL, subjects in what the Applicant refers to as the *high exposure group* (i.e., resmetirom AUC ≥2700 ng*h/mL) had greater relative reduction in liver fat fraction relative to subjects in the *low exposure group*. Note that the rationale for using a cutoff of 2700 ng*h/mL to define low and high resmetirom exposure groups is unclear. A similar trend was observed based on SHBG group, in which subjects in the high SHBG group (i.e., SHBG change from baseline ≥75%) had greater relative reduction in liver fat fraction relative to subjects in the low SHBG group.

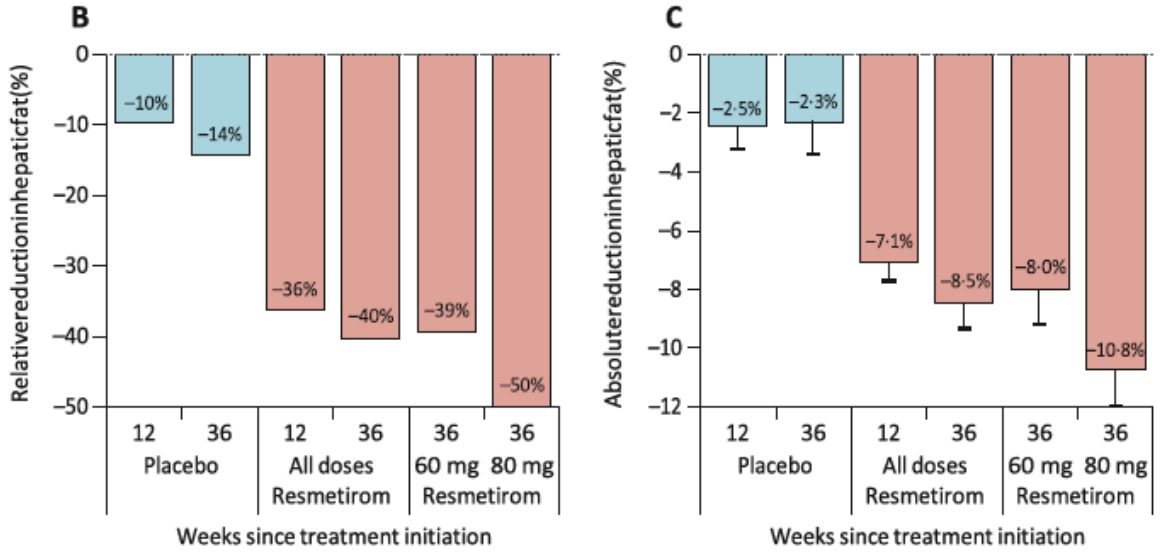
Relative and absolute reductions in liver fat fraction at Week 36 were comparable-to-greater relative to that at Week 12. At Week 36, relative and absolute reductions in liver fat fraction were greater among subjects who received 80 mg relative to subjects who had doses adjusted to 60 mg.

Table 212. Percent Change From Baseline to Week 12 in Liver Fat Fraction by MRI-PDFF

	n	Placebo, % (SE)	n	MGL-3196, % (SE)	LS mean difference from baseline (95% CI)	p value
Week 12 relative to baseline	38	-10.4% (4.3)	78	-32.9% (3.0)	-22.5% (-32.9, -12.2)	<0.0001
High exposure group			44	-39.7% (3.9)	-29.3% (-40.6, -18.0)	<0.0001
Low exposure group			34	-24.1% (4.4)	-13.8% (-25.8, -1.7)	0.025
High SHBG Group			48	-38.7% (3.7)	-28.3% (-39.4, -17.2)	<0.0001
Low SHBG Group			30	-23.7% (4.7)	-13.3% (-25.8, -0.8)	0.037
Fibrosis Stage 0-1	19	-14.0% (6.6)	45	-34.3% (4.3)	-20.3% (-36.1, -4.5)	0.0127
Fibrosis Stage 2-3	19	-7.1% (5.3)	33	-30.9% (4.0)	-23.7% (-37.0, -10.5)	0.0007
<5% weight loss	31	-3.8% (4.5)	70	-31.5% (3.0)	-27.8% (-38.4, -17.1)	<0.0001
≥5% weight loss	7	-36.4 (10.5)	8	-47.9 (9.7)	-11.5% (-44.0, 20.9)	0.4542

Source: Table 15, CSR for MGL-3196-05.
Note: The high exposure group consisted of individuals with 2700 ng·hr/mL or more estimated AUC, and the low exposure group consisted of individuals with an estimated AUC of less than 2700 ng·hr/mL. The high SHBG group consisted of individuals with 75% or greater change from baseline at Week 12. Exposure and SHBG groups were prespecified on the basis of blinded data and compared with all placebo patients (Week 12 n=38, Week 26 n+34).
Abbreviations: Auc, area under the plasma concentration-time curve; CI, confidence interval; LS, least squares; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; SE, standard error; SHBG, sex hormone binding globulin

Figure 40. Relative and Absolute Change From Baseline to Week 12 or Week 36 in Liver Fat Fraction by MRI-PDFF



Source: Figure 3, CSR for MGL-3196-05
B) Relative median fat reduction at Week 12 and Week 36 in placebo (n=38) and MGL-3196 (n=78).
C) Absolute mean fat reduction at Week 12 and Week 36 in placebo (n=34) and MGL-3196 (n=74). At Week 36, for MGL-3196 60 mg, n=36, and for 80 mg, n=33
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; MRI-PDFF, magnetic resonance imaging-proton density fat fraction

Week 36 assessments by dose group in MRI-PDFF, liver biopsy response, and fasting lipids are shown in Table 213. Data indicate that a greater proportion of subjects who received resmetirom were considered NASH resolution responders without an increase in fibrosis. This includes a larger proportion of subjects who received 80 mg relative to subjects who dose adjusted to 60 mg at Week 4.

Table 213. Week 36 Assessments in MRI-PDFF, Liver Biopsy Response, Fasting Lipids, and SHBG by Dose Group

Assessment	Placebo		Resmetirom 60 mg		Resmetirom 80 mg	
MRI-PDFF Week 36, n	32		36		33	
Baseline (median)		18.1		21.0		20.2
Relative CFB (median)		-14.5		-39.4		-50.2
Absolute CFB, mean (SE)		-2.5 (1.1)		-8.0 (1.2)		-10.8 (1.2)
Responders ≥20%, (%)		32.4		55.5		63.6
Responders ≥ 30%, (%)		28.1		72.2		84.8
Liver Biopsy (% biopsies)	34		36		33	
2-point NAS reduction		32.4		55.5		63.6
NASH resolution		6.5		19.4		39.4
NASH resolution (w/o fibrosis increase)		6.5		19.4		33.3
Lipids						
BL LDL-C, mean (SD)	35	116.5 (26.8)	36	106.6 (30.5)	34	110.1 (29.5)
LDL-C, %CFB (SE)	35	5.9 (3.6)	36	-8.9 (2.3)	34	-15.3 (3.3)
LDL-C (BL ≥100 mg/dL), %CFB (SE)	24	6.7 (4.9)	21	-15.2 (2.8)	20	-21.5 (3.9)
BL ApoB, mean (SD)	35	103.4 (26.8)	36	97.8 (22.0)	34	104.5 (23.1)
ApoB, %CFB (SE)	35	4.9 (3.5)	36	-14.5 (1.9)	34	-21.2 (2.3)
ApoB (BL LDL-C ≥100 mg/dL, %CFB (SE)	24	7.4 (4.8)	21	-18.9 (2.3)	20	-24.9 (2.7)
BL triglycerides, mean (SD)	34	148.1 (65.7)	36	149.6 (52.0)	34	203.3 (98.2)
Triglycerides, %CFB (SE)	34	18.5 (6.6)	36	-8.2 (5.2)	34	-27.3 (3.4)
Triglycerides (BL>150 mg/dL) (SE)	14	5.0 (11.1)	16	-16.5 (6.4)	21	-29.5 (5.1)
SHBG		NA	36	99.8	33	105.5

Source: Table 32, Summary of Clinical Efficacy
Note: For the per protocol analysis of Week 36 completers, the 60 mg dose group was defined as a dose decrease from 80 mg to 60 mg at Week 4 (based on Week 2 drug exposure). The 80 mg group included four patients whose dose was increased to 100 mg at Week 4. Patients with major protocol deviations (i.e., compliance, taking excluded medications; n=4) were not included in the analysis; one Week 36 completer did not have an adequate liver biopsy and was included only in MRI-PDFF and lipid analyses. Patients with MRI-PDFF <10% at baseline were excluded from MRI-PDFF analysis only, for both the placebo and treatment group.
Abbreviations: ApoB, apolipoprotein B; BL, baseline; CFB, change from baseline; LDL-C, very low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; n, number of subjects in subset; NA, not applicable; NAS, nonalcoholic fatty liver disease (NAFLD) activity score; NASH, nonalcoholic steatohepatitis; SD, standard deviation; SE, standard error; SHBG, sex hormone binding globulin

Extension Study

The percent change from baseline in liver fat fraction by MRI-PDFF to Week 12 and Week 36 in the extension study by dose group is shown in Table 214. Absolute and relative reductions from

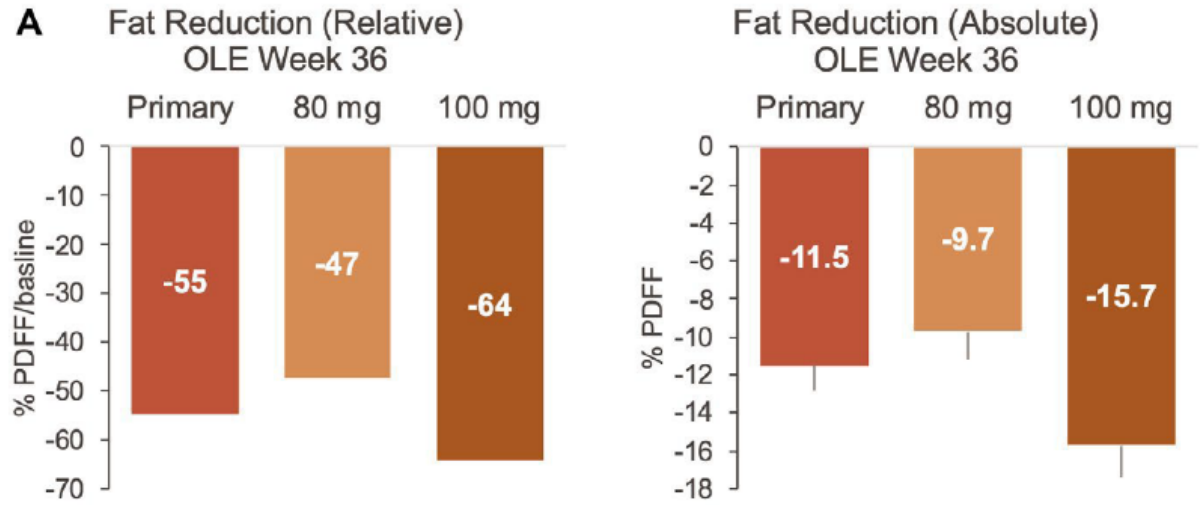
Baseline to Week 36 in liver fat fraction by MRI-PDFF are shown in Figure 41. Note that among subjects who were randomized to receive resmetirom in the main study, Baseline refers to main Study Baseline. The percent change from Baseline to extension study Week 12 and 36 in liver fat fraction was similar between subjects who received placebo in the main study and transitioned to resmetirom in the extension study and subjects who continued on resmetirom from the main study into the extension study. When compared by dose, greater reductions were observed in subjects who received 100 mg, relative to subjects who received 80 mg. However, any conclusions on dose-response are limited as the extension study was conducted in an open-label manner and the sample size was limited (i.e., N=7 for resmetirom 100 mg).

Table 214. Percent Change From Baseline to Week 12 and Week 36 in Liver Fat Fraction by MRI-PDFF (MGL-3196-05 Extension Study)

	n	Pbo/Res Mean (SE)	P-Value	n	Res/Res Mean (SE)	P-Value	n	All Mean (SE)	P-value
Week 12 %CFB	13	-39.9 (4.2)	<0.0001	15	-33.5 (5.6)	<0.0001	28	-36.4 (3.6)	<0.0001
Week 36 %CFB	11	-52.0 (7.1)	<0.0001	15	-45.8 (5.1)	<0.0001	26	-48.4 (4.2)	<0.0001
Primary	11	-52.0 (7.1)	<0.0001	10	-52.6 (5.2)	<0.0001	21	-52.3 (4.4)	<0.0001
80 mg							19	-44.6 (4.9)	<0.0001
100 mg							7	-58.8 (6.8)	<0.0001
Week 12 CFB	13	-7.4 (1.4)	0.0002	15	-7.8 (1.8)	0.0006	28	−7.6 (1.1)	<0.0001
Week 36 CFB	11	-10.1 (2.0)	0.0005	15	-10.3 (1.7)	<0.0001	26	−10.2 (1.3)	<0.0001
Primary	11	-10.1 (2.0)	0.0005	10	-12.2 (2.2)	0.0003	21	−11.1 (1.5)	<0.0001
80 mg							19	−8.7 (1.5)	<0.0001
100 mg							7	−14.3 (1.9)	0.0003

Source: Table 32, CSR for MGL-3196-05
Note: Baseline is defined as the value at the main study screening visit for Res/Res patients and main study Week 36 for former Pbo/Res patients. Week 12 and 36 are OLE Week 12 and 36, respectively. Patients with >9.5% weight loss or gain from baseline to OLE Weeks 12 and 36 and patients who are not compliant were excluded from the respective analysis. The means, standard errors, and p-values come from a paired *t* test.
Abbreviations: CFB, change from baseline; MRI-PDFF, proton density fat fraction-magnetic resonance imaging; OLE, open-label extension; Pbo, placebo; Res, MGL-3196/resmetirom; SE, standard error

Figure 41. Relative and Absolute Change From Baseline to Week 36 in Liver Fat Fraction by MRI-PDFF (MGL-3196-05 Extension Study)



Source: Figure 11, CSR for MGL-3196-05
Note: Data shown in the primary population includes subjects transitioned from placebo to resmetirom in the extension study, or patients continuing on resmetirom with a dose increase during the extension study. Dose shown is the final dose received.
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; MRI-PDFF, magnetic resonance imaging-proton density fat fractio; OLE, pen-label extension

14.2.14. Phase 3 Study in NASH Patients, Trial MGL-3196-11

Note that a Week 52 Interim Study Report was provided for accelerated approval based on histology, and MGL-3196-11 is ongoing to confirm the clinical benefit. Refer to Section 6.2 for details.

Title

A phase 3, multinational, double-blind, randomized, placebo-controlled study of MGL-3196 (resmetirom) in patients with NASH and fibrosis to resolve NASH and reduce progression to cirrhosis and/or hepatic decompensation.

Study Design

In this study, subjects with biopsy-proven NASH (NAFLD Activity Score [NAS] of at least 1 in steatosis, ballooning degeneration, and lobular inflammation) with fibrosis stage 1B, 2, or 3 were randomized 1:1:1 to receive 80 mg or 100 mg resmetirom, or placebo QD for up to 52 weeks. Randomization was stratified by type 2 diabetes status and fibrosis stage (F1 or F2 versus F3). Liver biopsies were performed for all subjects at screening, and 52 weeks. The co-primary endpoints were assessed at Week 52.

Dosage Regimen

All subjects randomized to resmetirom treatment received a dose of 80 or 100 mg. Dose adjustments at Weeks 12 and 24 based on free T4 were prespecified in the protocol, as a decrease

in free T4 is a safety concern. Note that no dose reductions were made later than Week 24, and the dose was not reduced to <60 mg.

- If subjects presented with a ≥30% decrease from baseline in free T4 to <0.7 ng/dL at Weeks 4 and 8, doses were reduced by 20 mg at Week 12.
  - Subjects on 100 mg received 80 mg
  - Subjects on 80 mg received 60 mg
- If subjects continued to present with ≥30% decrease from baseline in free T4 to <0.7 ng/dL at Weeks 16 and 20, doses were reduced by another 20 mg at Week 24.
  - Only applicable to subjects who initially received 100 mg → doses would be reduced to 60 mg

Doses of resmetirom ranging from 60 to 100 mg were administered using a tablet formulation (formulation 8). Note that formulation 8 is nearly the same as the TBM formulation (formulation 8A) except for a tablet color change.

Trial MGL-3196-11 also included an open-label treatment arm for subjects with histologic conversion to cirrhosis at Week 52.

A total of 12 subjects had doses adjusted per protocol at Week 12 based on free T4. This included 10 subjects randomized to 100 mg and 2 subjects randomized to 80 mg.

Inclusion/Exclusion Criteria

Screening MRI-PDFF ≥8% was required. This study enrolled subjects with eGFR ≥45 mL/min/1.73 m^2. Subjects presenting with cirrhosis on liver biopsy (stage 4 fibrosis), or hepatic decompensation or impairment were excluded. Subjects with hyperthyroidism, untreated clinical hypothyroidism, or who had a thyroidectomy were also excluded. Use of glucagon-like peptide 1 agonist therapy or high-dose vitamin E (>400 IU/day) was prohibited unless subjects were on a stable dose for 24 weeks prior to biopsy.

Use of the following medications were prohibited: obeticholic acid, ursodeoxycholic acid, or NASH therapeutics; OATP transporter inhibitors (e.g., gemfibrozil, cyclosporine A, or protease inhibitors); OAT3 inhibitors (e.g., probenecid); BCRP inhibitors (e.g., sulfasalazine or eltrombopag); substrates of UGT1A4 and 1A9; drugs historically associated with NAFLD; drugs with known liver toxicity; chronic use of oral corticosteroids.

Substrates of CYP2C8 were either restricted (e.g., pioglitazone permitted at 15 mg/day) or prohibited (e.g., repaglinide). Strong inhibitors of CYP2C8, such as gemfibrozil and trimethoprim, were prohibited. CYP2C8 inducers were prohibited.

Statins were permitted if subjects were on a stable dose for at least 30 days prior to randomization. Statin doses were limited as follows:

- Atorvastatin, pravastatin, and lovastatin: up to 40 mg/day
- Simvastatin and rosuvastatin: up to 20 mg/day
- Pitavastatin: up to 2 mg/day

PK/PD Sample Collection

In the first 1,100 subjects, blood PK samples were collected predose on Day 1 and at Weeks 4, 8, 16, 24, 36, 44, and 52. An additional postdose PK sample was collected at Week 8, 2 to 6 hours postdose. For subsequent subjects, PK samples were collected predose on Day 1 and Weeks 4, 12, 24, 38 and 52. An additional postdose PK sample was collected at Week 8, 2 to 6 hours postdose.

In all subjects, MRI-PDFF was conducted at screening, and at Weeks 16 and 52. FibroScan was conducted at Screening and at Week 52.

In this review, the calibration of MRI-PDFF was not reviewed.

In the first 1,100 subjects, samples to assess thyroid axis hormones, SHBG, and fasting lipid parameters were collected on Day 1 and Weeks 4, 8 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. In subsequent subjects, samples to assess thyroid axis hormones and SHBG were collected on Day 1 and at Weeks 4, 8, 12, 24, 38, and 52. Fasting lipid parameters were assessed on Day 1 and at Weeks 4, 12, 24, 38, and 52.

PK Results

Plasma concentrations of resmetirom and MGL-3623 by timepoint and dose group were summarized from subjects in the Applicant's primary analysis population (fibrosis stage F1B, F2, and F3) that did not have a dose modification within the 52-week analysis period. All subjects received resmetirom at a dosage of 80 or 100 mg QD. Across the 52-week treatment period, median trough concentrations of resmetirom and MGL-3623 in subjects who received 100 mg were 1.2- to 2.2-fold and 1.1- to 1.6-fold greater, respectively, than that in subjects who received 80 mg (refer to Tables 14.2.850.11 and 14.2.850.12, IR Response, CSR for MGL-3196-11, November 30, 2023).

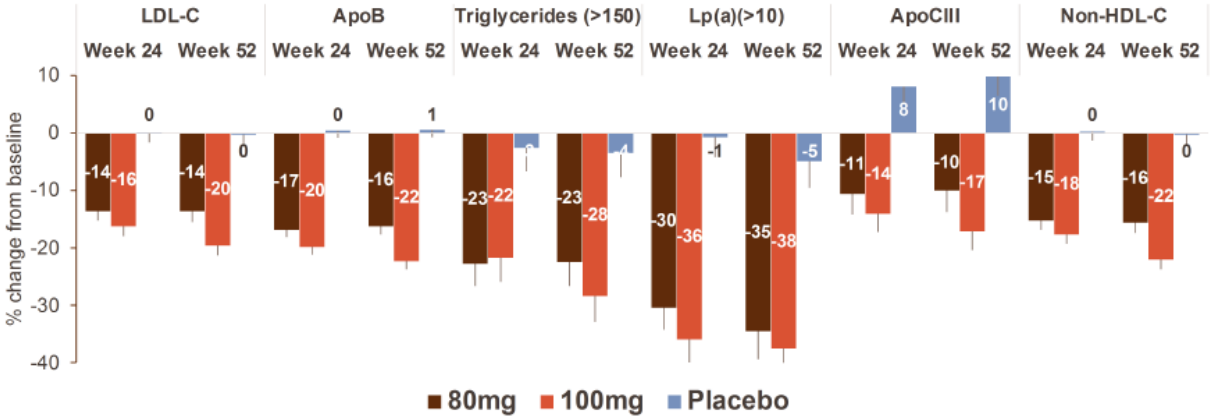
One postdose sample was collected at Week 8, 2-6 hours postdose, corresponding with the approximate T_{max}. For resmetirom, postdose concentrations at Week 8 were approximately 1.5-fold greater for subjects in the 100 mg group relative to subjects in the 80 mg group (mean [CV%]=1168 [102%] ng/mL and 804 [103%] ng/mL for the 100 mg and 80 mg groups, respectively). For MGL-3623, postdose concentrations at Week 8 were approximately 1.2-fold greater for subjects in the 100 mg group relative to subjects in the 80 mg group (mean [CV%]=222 [82%] ng/mL and 187 [77%] ng/mL for the 100 mg and 80 mg groups, respectively).

These data were incorporated in PopPK analyses of resmetirom in patients with NASH. For additional details, refer to Section 14.5.

PD Results

Percent change from baseline in lipid parameters, including LDL-C, by dose group are shown in Figure 42. Results indicate that subjects randomized to resmetirom at either dose had greater reductions in lipid parameters relative to subjects randomized to placebo. When comparing the 80 and 100 mg resmetirom groups, reductions in lipid parameters were comparable, although there appeared to be numerically greater improvements for subjects randomized to 100 mg. No appreciable increase in response was observed from Week 24 to Week 52.

Figure 42. Percent Change From Baseline in Lipid Parameters at Weeks 24 and 52



Source: Figure 9, page 96, CSR for MGL-3196-11
Note: Data shown from the modified intent-to-treat population including NASH subjects with fibrosis stages F1B, F2, and F3.
Abbreviations:
Abbreviations: ApoB, apolipoprotein B; ApoCIII, apolipoprotein C-III; CSR, clinical study report; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a), non-HDL-C, non-high-density lipoprotein cholesterol

Change in hepatic fat fraction by MRI-PDFF from baseline to Week 52 is shown in Table 215. Subjects randomized to the resmetirom groups had greater reductions from baseline in hepatic fat fraction by MRI-PDFF relative to subjects who received placebo, with LSM percent change from baseline (standard error) of -35.4 (2.8)%, -46.6 (2.8)%, and -8.7 (2.7)% for 80 mg, 100 mg, and placebo, respectively. Subjects who received 100 mg had greater absolute and percent reductions in hepatic fat fraction relative to subjects who received 80 mg. Relative to placebo, a greater proportion of subjects in the resmetirom groups also had at least 30 or 50% relative reduction in MRI-PDFF at Week 52. Among subjects receiving 100 mg resmetirom, a numerically greater proportion achieved these endpoints relative to subjects receiving 80 mg.

Table 215. Absolute and Percent Change From Baseline to Week 52 in Hepatic Fat Fraction by MRI-PDFF

	Resmetirom 80 mg (n = 322)	Resmetirom 100 mg (n = 323)	Placebo (n = 321)
n	233	222	230
Baseline Mean (SD)	18.2 (6.8)	17.2 (6.7)	17.9 (6.6)
Mean Change from Baseline (SE)	-7.1 (0.46)	-8.5 (0.47)	-2.0 (0.36)
LS Mean of Percent Change from Baseline (SE)	-35.4 (2.8)	-46.6 (2.8)	-8.7 (2.7)
LS Mean of Percent Change from Baseline Compared to Placebo (95% CI)	-26.7% (-32.9, -20.6)	-37.9% (-44.2, -31.7)	
p-value	<0.0001	<0.0001	

Source: Table 32, page 108, CSR for MGL-3196-11
Note: Data shown from the modified intent-to-treat population, including NASH subjects with fibrosis stages F1B, F2, and F3.
Note: The LS Means, CIs, and p-values were obtained using an ANCOVA model with baseline value, baseline type 2 diabetes status, fibrosis stage at baseline as covariates.
Note: Patients that were F3 at eligibility and reevaluated as F4 at baseline by either pathologist were included in this analysis.
Abbreviations: ANCOVA, analysis of covariance: CI, confidence interval; LS, least squares; mITT, modified intent-to-treat; SD, standard deviation; SE, standard error

FibroScan measurements, including vibration-controlled transient elastography liver stiffness measurements, and assessments of hepatic steatosis by controlled attenuation parameter (CAP) are shown in Table 216. Among subjects with F2 and F3 fibrosis, a greater proportion of subjects randomized to 80 or 100 mg resmetirom achieved 25 or 30% improvements in vibration-controlled transient elastography liver stiffness measurements relative to subjects who were randomized to placebo. Odds ratios for 25 or 30% improvement were numerically greater for subjects receiving 100 mg relative to subjects receiving 80 mg. Improvements in steatosis by CAP were greater for subjects receiving resmetirom relative to those receiving placebo. CAP response was comparable between the 80 and 100 mg dose groups.

Table 216. FibroScan VCTE and CAP Results at Week 52 by Fibrosis Stage

	LS Mean %CFB or CFB (SE) Resmetirom 80 mg (N = 322)	LS Mean %CFB or CFB (SE) Resmetirom 100 mg (N = 323)	LS Mean %CFB or CFB (SE) Placebo (N = 321)	LS Mean Difference or OR Resmetirom 80 mg from PBO (95% CI)	p-Value	LS Mean Difference or OR Resmetirom 100 mg from PBO (95% CI)	p-Value
FibroScan VCTE/LSM, kPa							
F1B – Week 52 n	12	10	17				
Improving ≥25% – n (%)	6 (50.0%)	7 (70.0%)	4 (23.5%)	3.7 (0.70, 19.1)	0.1258	10.0 (1.3, 75.3)	0.0187
Improving ≥30% – n (%)	5 (41.7%)	6 (60.0%)	4 (23.5%)	2.7 (0.50, 14.0)	0.2528	4.5 (0.78, 25.5)	0.0983
Worsening≥25% – n (%)	1 (8.3%)	0	5 (29.4%)	0.17 (0.02, 2.0)	0.1435	0	0.0373
Worsening ≥30% – n (%)	1 (8.3%)	0	5 (29.4%)	0.17 (0.02, 2.0)	0.1435	0	0.0373
F2 – Week 52n	84	76	89				
Improving ≥25% – n (%)	37 (44.0%)	38 (50.0%)	31 (34.8%)	1.5 (0.80, 2.7)	0.2154	1.9 (1.0, 3.6)	0.0430
Improving ≥30% – n (%)	28 (33.3%)	31 (40.8%)	23 (25.8%)	1.4 (0.75, 2.8)	0.2754	2.0 (1.0, 3.8)	0.0454
Worsening≥25% – n (%)	10 (11.9%)	8 (10.5%)	13 (14.6%)	0.80 (0.33, 1.9)	0.6170	0.68 (0.26, 1.8)	0.4251
Worsening ≥30% – n (%)	7 (8.3%)	5 (6.6%)	12 (13.5%)	0.57 (0.21, 1.5)	0.2653	0.47 (0.16, 1.4)	0.1718
F3 – Week 52 n	163	167	162				
Improving ≥25% – n (%)	67 (41.1%)	80 (47.9%)	43 (26.5%)	2.0 (1.2, 3.1)	0.0050	2.5 (1.6, 4.0)	<0.0001
Improving ≥30% – n (%)	56 (34.4%)	65 (38.9%)	29 (17.9%)	2.5 (1.5, 4.2)	0.0006	2.9 (1.7, 4.7)	<0.0001
Worsening≥25% – n (%)	24 (14.7%)	18 (10.8%)	30 (18.5%)	0.77 (0.43, 1.4)	0.3765	0.53 (0.28, 1.0)	0.0476
Worsening ≥30% – n (%)	21 (12.9%)	17 (10.2%)	21 (13.0%)	1.01 (0.53, 1.9)	0.9816	0.76 (0.39, 1.5)	0.4325
FibroScan CAP, dB/M							
Week 52 – n	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)	<0.0001	-26.9 (-36.2, -17.5)	<0.0001

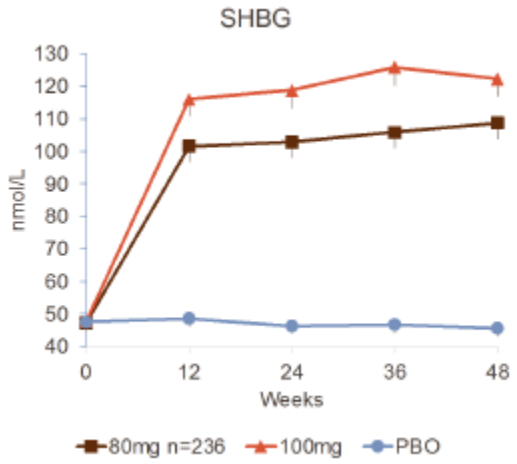
Source: Table 39, page 125, CSR for MGL-3196-11
Note: The LS Means, CIs, and p-values were obtained using an ANCOVA model with baseline value, baseline type 2 diabetes status, fibrosis stage at baseline as covariates.
Note: The odds ratio, 95% CIs, and p-values were obtained using a stratified CMH approach, with baseline type 2 diabetes status as the stratification factor.
Note: Patients that were F3 at eligibility and reevaluated as F4 at baseline by either pathologist were included in this analysis.
Abbreviations: ANCOVA, analysis of covariance: CAP, controlled attenuation parameter; CFB, change from baseline; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; LS, least squares; mITT, modified intent-to-treat; PBO, placebo; SD, standard deviation; SE, standard error; VCTE, vibration controlled transient elastography

Thyroid Hormones

For detailed analysis on changes in thyroid hormone parameters, including SHBG, TSH, and free and TT3 and T4 in Trial MGL-3196-11, refer to the consult review from the Division of General Endocrinology in DARRTS dated December 20, 2023.

SHBG levels over time are shown in Figure 43. Subjects receiving resmetirom at either dose had larger increases in SHBG relative to subjects with placebo. Numerically larger increases in SHBG were observed among subjects who received resmetirom at 100 mg relative to 80 mg. SHBG levels plateaued at Week 12, with levels remaining consistent for the remainder of the treatment period.

Figure 43. SHBG Levels Over Time by Dose Group



Source: Figure 13, page 111, CSR for MGL-3196-11
Note: Data shown from the modified intent-to-treat population, including NASH subjects with fibrosis stages F1B, F2, and F3.
Abbreviations: CSR, clinical study report; F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; MGL-3196, resmetirom; NASH, nonalcoholic steatohepatitis; PBO, placebo; SHBG, sex hormone binding globulin

Reductions in free T4 were observed from Baseline to Week 52 among subjects receiving 80 or 100 mg resmetirom relative to subjects receiving placebo. Numerically greater reductions were observed among subjects who received 100 mg relative to those who received 80 mg. Changes in free T4 were not different between subjects not on thyroxine treatment and subjects treated with thyroxine.

14.2.15. Phase 3 Study in Patients With NAFLD, Trial MGL-3196-14

Title

52-week, phase 3 study to evaluate safety and biomarkers of resmetirom (MGL-3196) in patients with NAFLD (MAESTRO-NAFLD-1).

Objectives

Primary

- To evaluate the safety and tolerability of QD oral administration of 80 or 100 mg resmetirom versus matching placebo.

Key Secondary

- To determine the effect of QD oral administration of 80 or 100 mg resmetirom versus placebo on the percent change from baseline at Week 24 in LDL-C.
- To determine the effect of QD oral administration of 80 or 100 mg resmetirom versus placebo on the percent change from baseline at Week 24 in apoB.

- To determine the effect of QD oral administration of 80 or 100 mg resmetirom versus placebo on the percent change from baseline at Week 16 in hepatic fat fraction by MRI-PDFF.
- To determine the effect of QD oral administration of 80 or 100 mg resmetirom versus placebo on the percent change from baseline at Week 24 in triglycerides in subjects with baseline triglycerides >150 mg/dL.
- To determine the effect of QD oral administration of 80 or 100 mg resmetirom versus placebo on the percent change after 52 weeks on FibroScan CAP score.
- To determine the effect of QD oral administration of 80 or 100 mg resmetirom versus placebo after 52 weeks on FibroScan vibration-controlled transient elastography (kPa) in patients with baseline liver stiffness measure kPa ≥7.2.

Other Secondary Objectives

- To look at changes in inflammation and fibrosis biomarkers (cytokeratin-18, adiponectin, pro-C3, and enhanced liver fibrosis test).

Exploratory

- To assess the effects of resmetirom on thyroid hormones (free T4, free T3, TSH) and SHBG

Study Design

This study was designed as a multicenter, randomized, double-blind, placebo-controlled study with an open-label arm in subjects with NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH." A parallel open-label arm enrolled subjects with compensated NASH cirrhosis (Child-Pugh A). Subjects were randomized 1:1:1:1 to one of the following study arms:

- Double-blind resmetirom 80 mg
- Double-blind resmetirom 100 mg
- Double-blind placebo
- Open-label resmetirom 100 mg (open-label non-cirrhotic (OLNC) arm)

Initially, subjects taking higher dose thyroxine (>75 µg/day) or with eGFR ≥30 and <45 mL/min/1.73 m^2 were enrolled directly into the OLNC arm. Note that biopsy screen failure subjects from Trial MGL-3196-11 who met biopsy criteria for MGL-3196-14 were eligible for enrollment into the OLNC arm. After a protocol amendment, subjects on higher dose thyroxine were eligible for randomization into any of the four arms. After enrollment of 171 subjects into the OLNC arm, randomization was stopped, and subsequent subjects were randomized 1:1:1 into one of the three remaining arms.

Randomization was stratified by type 2 diabetes status and history of documented atherosclerotic cardiovascular disease. All subjects received their assigned treatment for 52 weeks.

All noncirrhotic subjects randomized to resmetirom treatment received a dose of 80 or 100 mg. Dose adjustments at Weeks 12 and 24 based on free T4 were prespecified in the protocol, as described below. Note that for subjects in the double-blind arms, dose reductions were not made

later than Week 24, and the dose was not reduced to <60 mg. Subjects in the open-label arm may have had doses reduced earlier than Week 12 or later than Week 24 at the discretion of the Investigator.

- If subjects presented with ≥30% decrease from baseline in free T4 to <0.7 ng/dL at Weeks 4 and 8, doses were reduced by 20 mg at Week 12
  - Subjects on 100 mg received 80 mg
  - Subjects on 80 mg received 60 mg
- If subjects continued to present with ≥30% decrease from baseline in free T4 to <0.7 ng/dL at Weeks 16 and 20, doses were reduced by another 20 mg at Week 24
  - Only applicable to subjects who initially received 100 mg → doses would be reduced to 60 mg

Doses of resmetirom ranging from 60 to 100 mg were administered using a tablet formulation (formulation 8). Note that formulation 8 is nearly the same as the TBM formulation (formulation 8A) except for a tablet color change.

Subjects with compensated NASH cirrhosis were eligible for enrollment in an open-label arm in which all subjects received 80 mg resmetirom. Data in subjects with NASH cirrhosis and subjects with moderate renal impairment were not provided in this CSR.

Inclusion/Exclusion Criteria

The study enrolled participants aged ≥18 years with NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as "presumptive NASH." Eligible subjects may have had a FibroScan kPa ≥5.5 to <8.5; CAP ≥280 dB/m, or magnetic resonance elastography ≥2 to <4 kPa with MRI-PDFF ≥8% liver fat. The eligible population was also allowed to include some subjects with biopsy-proven NASH/NAFLD with steatosis. A cohort of subjects with compensated NASH cirrhosis (Child-Pugh A) were also enrolled. This study enrolled subjects with eGFR ≥45 mL/min/1.73 m^2 in double-blind treatment arms, or subjects with eGFR between 30 and 45 in an open-label treatment arm.

Subjects were required to be on stable, standard care dyslipidemia therapy for at least 30 days prior to randomization, including:

- Atorvastatin, pravastatin, and lovastatin: up to 40 mg/day
- Simvastatin and rosuvastatin: up to 20 mg/day
- Pitavastatin: up to 2 mg/day
- Bile acid sequestrants (if taken at least 4 hours after or 4 hours before study drug)

Subjects presenting with cirrhosis on liver biopsy (stage 4 fibrosis) were excluded from randomized arms. Subjects with decompensated cirrhosis were excluded from the study. Subjects with hyperthyroidism or untreated clinical hypothyroidism were also excluded. Use of glucagon-like peptide 1 agonist therapy or high-dose vitamin E (>400 IU/day) was prohibited unless subjects were on a stable dose for 24 weeks prior to biopsy.

Use of the following medications were prohibited: obeticholic acid, ursodeoxycholic acid, or NASH therapeutics; OATP transporter inhibitors (e.g., gemfibrozil, cyclosporine A, or protease

inhibitors); OAT3 inhibitors (e.g., probenecid); BCRP inhibitors (e.g., sulfasalazine or eltrombopag); substrates of UGT1A4 and 1A9; drugs historically associated with NAFLD; drugs with known liver toxicity; chronic use of oral corticosteroids; and warfarin.

Substrates of CYP2C8 were either restricted (e.g., pioglitazone permitted at 15 mg/day) or prohibited (e.g., repaglinide). Strong inhibitors of CYP2C8, such as gemfibrozil and trimethoprim, were prohibited. CYP2C8 inducers were prohibited.

Subject Disposition

A total of 972 subjects were randomized to the three double-blind arms, including 327 subjects who were randomized to receive 80 mg resmetirom, 325 subjects who received 100 mg resmetirom, and 320 subjects who received placebo. Among subjects randomized to double-blind arms, 79% (770/972) of subjects completed the Week 52 visit. A total of 171 subjects were randomized to the OLNC arm. In the open-label arm, 88.9% (152/171) of subjects completed the 52-week treatment period.

A total of 14 subjects had doses adjusted per protocol at Week 12 based on free T4. This included 12 subjects randomized to 100 mg in the double-blind or open-label arms, and 2 subjects randomized to 80 mg.

PK/PD Sample Collection

Blood PK samples were collected predose on Day 1 and at Weeks 2, 4, 8, 16, 24, 36, 44, and 52. An additional postdose PK sample was collected at Week 8, 2 to 6 hours postdose.

MRI-PDFF and magnetic resonance elastography was conducted at screening, and at Weeks 16 and 52. FibroScan was conducted on Day 1 and at Week 52.

In this review, the calibration of MRI-PDFF was not reviewed.

Samples to assess thyroid axis hormones, SHBG, and fasting lipid parameters were collected on Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

PK Results

All subjects received resmetirom at a dosage of 80 or 100 mg QD. Across the 52-week treatment period, median trough concentrations of resmetirom in subjects who received 100 mg were 1.4- to 2.3-fold greater than that in subjects who received 80 mg. Median trough concentrations of MGL-3623 in subjects who received 100 mg were 1.3- to 2.0-fold greater than that in subjects who received 80 mg (refer to Tables 14.2.850.11 and 14.2.850.12, CSR for MGL-3196-14, IR Response November 30, 2023).

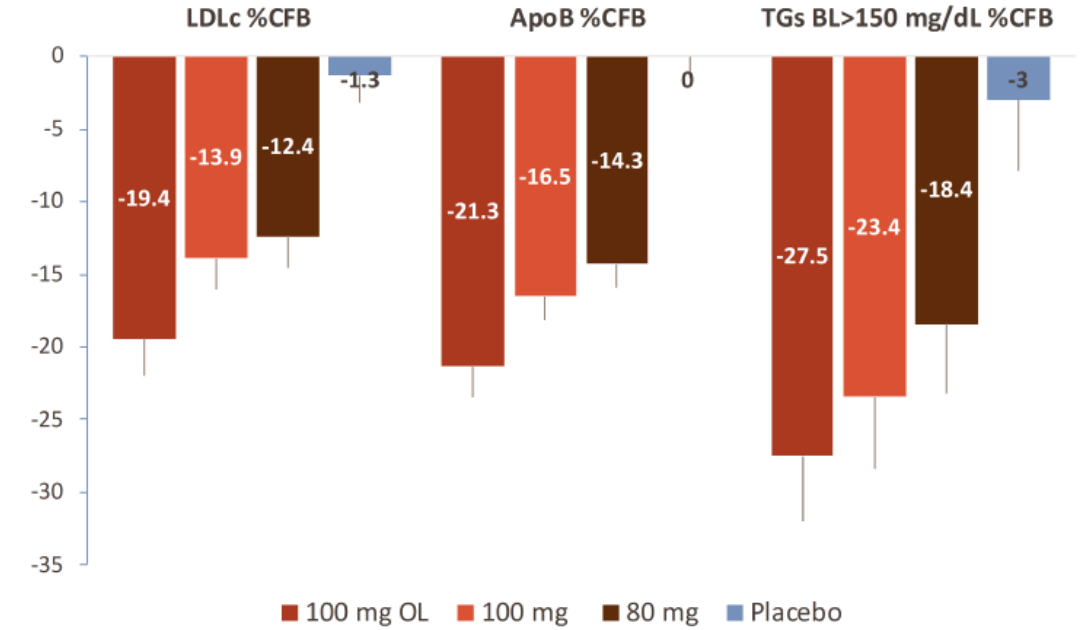
One postdose sample was collected at Week 8, 2 to 6 hours postdose, corresponding with the approximate T_{max}. For resmetirom, postdose concentrations at Week 8 were approximately 1.3-fold greater for subjects in the 100 mg group relative to subjects in the 80 mg group (mean [CV%]=1044 [114%] ng/mL and 784 [111%] ng/mL for the 100 mg and 80 mg groups, respectively). For MGL-3623, postdose concentrations at Week 8 were approximately 1.1-fold greater for subjects in the 100 mg group relative to subjects in the 80 mg group (mean [CV%]=227 [82%] ng/mL and 206 [76%] ng/mL for the 100 mg and 80 mg groups, respectively).

These data were incorporated in PopPK analyses of resmetirom in patients with NASH. For additional details, refer to Section 14.5.

PD Results

Percent change from baseline to Week 24 in lipid parameters, including LDL-C, apoB, and triglycerides (in subjects with baseline triglycerides >150 mg/dL), by dose group, are shown in Figure 44. Results indicate that subjects receiving resmetirom at either dose had greater reductions in lipid parameters relative to subjects who received placebo. When comparing the 80 and 100 mg resmetirom groups, reductions in lipid parameters were comparable, although there appeared to be numerically greater improvements for subjects in the 100 mg dose groups (i.e., double-blind and open-label).

Figure 44. Percent Change From Baseline to Week 24 in Lipid Parameters



Source: Figure 5, page 95, CSR for MGL-3196-14.
Note: Error bars represent standard errors.
Abbreviations: ApoB, apolipoprotein B; BL, baseline; CFB, change from baseline; LDL-C (or LDLc), low-density lipoprotein cholesterol; OL, open-label; TG, triglyceride
Change in hepatic fat fraction by MRI-PDFF from baseline to Weeks 16 and 52 is shown in Table 217. Change in steatosis by FibroScan CAP from baseline to Week 52 is shown in Table 218. Results for MRI-PDFF and CAP are visually depicted in Figure 45.

Subjects in the resmetirom groups had greater reductions from Baseline in hepatic fat fraction by MRI-PDFF relative to subjects who received placebo. There was no appreciable difference observed in MRI-PDFF between Weeks 16 and 52. Subjects who received 100 mg had numerically greater percent reductions in hepatic fat fraction relative to subjects who received 80 mg.

Improvements in steatosis by CAP were greater for subjects receiving resmetirom relative to those receiving placebo. CAP response was greater for subjects receiving 100 mg relative to those receiving 80 mg.

Table 217. Absolute and Percent Change in Hepatic Fat Fraction by MRI-PDFF From Baseline to Weeks 16 and 52

Parameter Analysis Visit Statistic	OLNC (N=158)	Resmetirom 100 mg DB (N=268)	Resmetirom 80 mg DB (N=255)	Placebo DB (N=268)
Week 16				
Baseline Mean (SD)	17.9 (7.1)	18.0 (7.3)	17.4 (6.6)	17.7 (6.8)
Analysis Visit Mean (SE)	10.2 (0.5)	10.3 (0.4)	10.5 (0.4)	16.9 (0.5)
LS Mean of %CFB (SE)	-45.3 (3.1)	-45.1 (2.6)	-41.4 (2.6)	-6.5 (2.6)
95% CI	(-51.3, -39.2)	(-50.3, -39.9)	(-46.6, -36.2)	(-11.7, -1.3)
LS Mean of %CFB Compared to Placebo (SE)	-38.8 (3.2)	-38.6 (2.7)	-34.9 (2.8)	-
97.5% CI	(-45.9, -31.7)	(-44.7, -32.5)	(-41.1, -28.7)	-
P-value	<0.0001	<0.0001	<0.0001	-
Week 52				
Baseline Mean (SD)	17.9 (7.1)	18.0 (7.3)	17.4 (6.6)	17.7 (6.8)
Analysis Visit Mean (SE)	9.3 (0.5)	10.2 (0.4)	10.6 (0.4)	15.7 (0.4)
LS Mean of %CFB (SE)	-49.2 (3.5)	-44.0 (3.0)	-38.9 (3.0)	-10.1 (3.0)
95% CI	(-56.1, -42.4)	(-49.9, -38.2)	(-44.7, -33.0)	(-15.9, -4.3)
LS Mean of %CFB Compared to Placebo (SE)	-39.1 (3.6)	-33.9 (3.1)	-28.8 (3.1)	-
97.5% CI	(-47.1, -31.1)	(-40.8, -27.0)	(-35.8, -21.7)	-
P-value	<0.0001	<0.0001	<0.0001	-

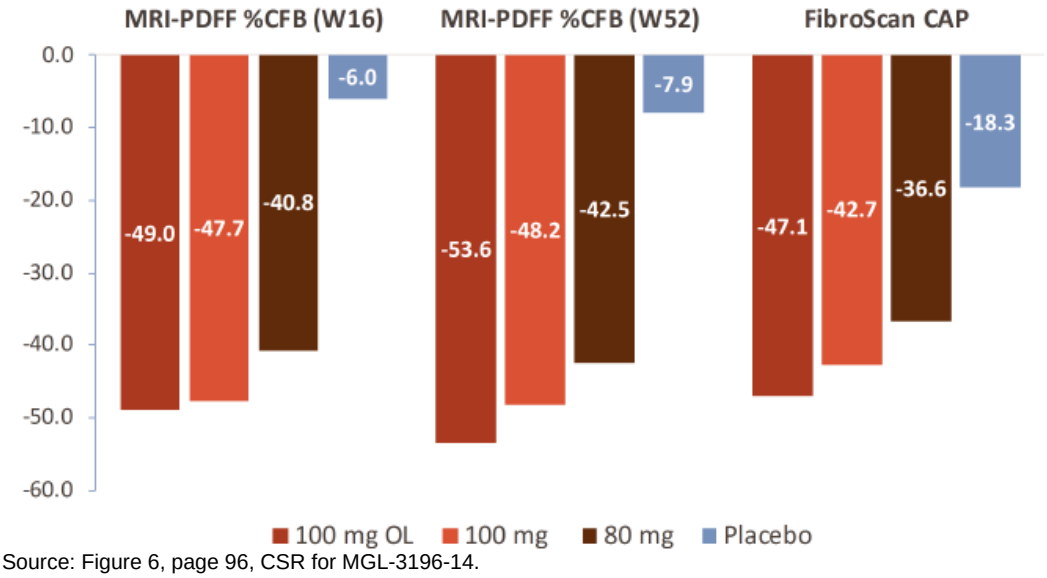
Source: Table 15, page 73, CSR for MGL-3196-14
Note: Data imputed for missing results at Week 52 using LOCF from Week 16.
Note: OLNC group includes open-label noncirrhotic patients randomized on or before July 1, 2020.
Note: Analysis excludes patients from sites 2020 and 2025.
Abbreviations: CFB, change from baseline; CI, confidence interval; DB, double-blind; LDL, low-density lipoprotein; LOCF, last observation carried forward; OLNC, open-label noncirrhotic; SD, standard deviation; SE, standard error

Table 218. FibroScan CAP Results at Week 52

Parameter Analysis Visit Statistic	OLNC (N=147)	Resmetirom 100 mg DB (N=270)	Resmetirom 80 mg DB (N=260)	Placebo DB (N=260)
Week 52				
Baseline Mean (SD)	339.6 (36.7)	340.7 (34.3)	339.3 (32.9)	344.7 (34.8)
Analysis Visit Mean (SE)	296.9 (4.4)	300.6 (3.3)	305.9 (3.2)	326.8 (2.7)
LS Mean of CFB (SE)	-46.0 (4.8)	-42.8 (4.0)	-36.7 (3.9)	-18.4 (3.9)
95% CI	(-55.3, -36.6)	(-50.5, -35.0)	(-44.3, -29.1)	(-26.0, -10.7)
LS Mean of CFB Compared to Placebo (SE)	-27.6 (5.0)	-24.4 (4.2)	-18.3 (4.2)	-
97.5% CI	(-38.7, -16.5)	(-33.8, -15.1)	(-27.8, -8.9)	-
P-value	<0.0001	<0.0001	<0.0001	-

Source: Table 17, page 77, CSR for MGL-3196-14
Note: OLNC group includes open-label noncirrhotic patients randomized on or before July 1, 2020.
Note: Analysis excludes patients from sites 2020 and 2025.
Abbreviations: CAP, controlled attenuation parameter; CFB, change from baseline; CI, confidence interval; DB, double-blind; LS, least squares; OLNC, open-label noncirrhotic; SD, standard deviation; SE, standard error

Figure 45. Median Percent Change From Baseline in Hepatic Fat Fraction by MRI-PDFF (Weeks 16 and 52) or FibroScarn CAP (Week 52)



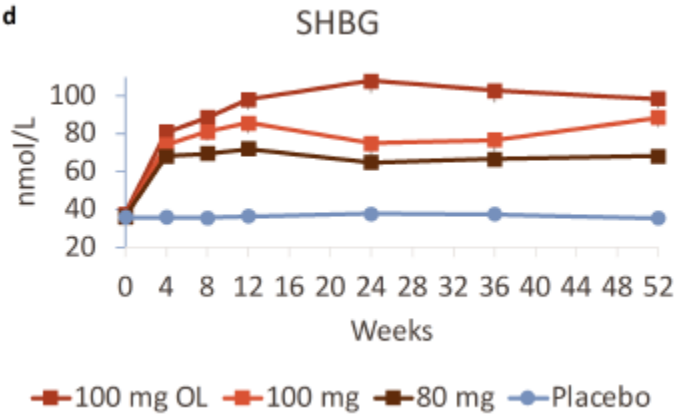
Source: Figure 6, page 96, CSR for MGL-3196-14.
Abbreviations: CAP, controlled attenuation parameter; CFB, change from baseline; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; OL, open-label; W, week

Thyroid Hormones

For detailed analysis on changes in thyroid hormone parameters, including SHBG, TSH, and free and TT3 and T4 in Trial MGL-3196-14, refer to the consult review from the Division of General Endocrinology by in DARRTS dated December 20, 2023.

SHBG levels over time are shown in Figure 46. Subjects receiving resmetirom at either dose had larger increases in SHBG relative to subjects with placebo. Numerically larger increases in SHBG were observed among subjects who received resmetirom at 100 mg relative to 80 mg. SHBG levels plateaued at Week 12, with levels remaining consistent from Weeks 12 to 52.

Figure 46. SHBG Levels Over Time by Dose Group



Source: Figure 4, page 90, CSR for MGL-3196-14
Note: 100 mg OL = subjects in the OLNC arm who receive 100 mg; 100 mg = subjects randomized to 100 mg in the double-blind arm; 80 mg = subjects randomized to 80 mg in the double-blind arm.
Abbreviations: CSR, clinical study report; MGL-3196, resmetirom; OL, open-label; OLNC, open-label noncirrhotic; SHBG, sex hormone binding globulin

Reductions in free T4 were observed from baseline to Week 52 among subjects receiving 80 or 100 mg resmetirom, relative to subjects receiving placebo. Numerically greater reductions were observed among subjects who received 100 mg relative to those who received 80 mg. Changes in free T4 were not different between subjects not on thyroxine treatment and subjects treated with thyroxine.

14.3. Bioanalytical Method Validation and Performance

Quantitation of Resmetirom and MGL-3623 in Plasma

Four bioanalytical methods have been developed and validated to quantitate resmetirom in human plasma. Three of these methods are also validated to quantitate metabolite MGL-3623:

- Method MN10081 ((b) (4))
  - Method to quantitate resmetirom
  - Used in Trials VIA-3196-01 and VIA-3196-02
- Method MN12062 ((b) (4))
  - Method to quantitate resmetirom and MGL-3623
  - Used in Trials VIA-3196-02, MGL-3196-03, MGL-3196-04, MGL-3196-07, MGL-3196-08, MGL-3196-09, MGL-3196-10, MGL-3196-12, MGL-3196-15, MGL-3196-16, and MGL-3196-17.
    - Note that use of method MN12062 in VIA-3196-02 was to quantitate resmetirom in cohort 6 (80 mg cohort) only and to quantitate MGL-3623 in all cohorts.
    - Note that this method in MGL-3196-10 was used to quantitate resmetirom and MGL-3623 in all subjects with noncirrhotic or cirrhotic NASH and some non-NASH subjects.
- Method BTM-2703-R0/BTM-2703-R1 ((b) (4)).
  - Method to quantitate resmetirom and MGL-3623.
  - Used in Trial MGL-3196-10.
    - Note that this method in MGL-3196-10 was used to quantitate resmetirom and MGL-3623 in non-NASH subjects only.
- Method MBL-16309 ((b) (4)).
  - Method to quantitate resmetirom and MGL-3623.
  - Used in Trials MGL-3196-05, MGL-3196-11, MGL-3196-14, and MGL-3196-20
    - Note that Trial MGL-3196-11 is still ongoing and, thus, no interim bioanalytical report was provided.
    - This is acceptable as in-study bioanalysis of samples from MGL-3196-05, MGL-3196-14, and MGL-3196-20 was acceptable.

Method MN10081

Validation for method MN10081 is described in report MC11B-0090: "Validation of a Method for the Determination of VIA-3196 [resmetirom] in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection". In this method, resmetirom and resmetirom-d_6 (internal standard) are extracted using a solvent extraction procedure from human plasma containing dipotassium (K_2) ethylene diamine tetraacetic acid (K_2EDTA) as the anticoagulant. Extracts are reconstituted and then analyzed via reverse-phase high-performance liquid chromatography (HPLC). The mobile phase (0.2% acetic acid in water or 25:75 methanol-acetonitrile mixture) was nebulized using heated nitrogen in a Z-spray source/interface set to electrospray positive mode. Ionized compounds are detected using tandem mass spectrometry (MS/MS).

Table 219. Bioanalytical Method Validation for Plasma, MN10081

Method Parameters	Method Details
Bioanalytical method review summary	Method validation adequate to support results in Trials VIA-3196-01 and VIA-3196-02
Method description	Sample extraction from K_2EDTA human plasma via solvent extraction; separation and detection using high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS)
Materials used for calibration curve, QCs, **and** concentration	VIA-3196 (resmetirom), Lot# DUG-AJ-124(4), (b) (4)
Validated assay range	Resmetirom: 0.0500 to 100 ng/mL in human plasma
Source **and** lot of internal standard reagents	VIA-3196-d_6 (resmetirom-d_6), Lot# 36084-195-A, (b) (4)
Regression model **and** weighting	Linear regression of ln-transformed peak height ratios (resmetirom to internal standard) vs. ln-transformed standard concentrations

Source: Summary of Biopharmaceutic Studies; Validation Report MC11B-0090; bioanalysis reports MC11B-0117 and MC12B-0035
Abbreviations: (b) (4).; HPLC-MC/MS, high-performance liquid chromatography tandem mass spectrometry; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; QC, quality control; VIA-3196, resmetirom

Table 220. Validation Parameters for MN10081

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy & precision from accepted validation runs	No. of standard calibrators from LLOQ to ULOQ	11	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ Resmetirom	-5.6 to 6.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ Resmetirom	≤7.6%	Yes
QCs performance during accuracy & precision from accepted validation runs	Cumulative accuracy (%bias) in 4 QCs Resmetirom	-8.7 to -1.4%	Yes
	Interbatch %CV Resmetirom	≤12.3%	Yes
Selectivity and matrix effect	Six lots of blank human plasma were evaluated. In all cases, no interference was observed in the retention times of resmetirom and resmetirom-d_6		Yes
	Six individual control matrix samples spiked with resmetirom at the LLOQ were evaluated in triplicate. In five lots, the percent bias was within 15% for at least 2/3 replicates. The overall lot acceptance was 83.3%		

Validation Parameters	Method Validation Summary	Acceptability
Extraction recovery	The mean percent recovery for resmetirom and resmetirom-d_6 was 64.8% and 71.4%, respectively.	Yes
Hemolysis effect	Not assessed. Acceptable as this method was only used to quantitate resmetirom in healthy subjects.	Yes
Lipemic effect	Not assessed. Acceptable as this method was only used to quantitate resmetirom in healthy subjects.	Yes
Dilution linearity	Accuracy and precision demonstrated for resmetirom at 500 ng/mL at dilution factors of 1:10 and 1:100 (%bias 2.2 and -2.0%; %CV ≤1.8%)	Yes
Benchtop/process stability	Room temperature stability of resmetirom in human plasma established for up to 24 hours (%bias -11.3 to -2.8% and %CV ≤5.5%). Processed sample (extracts) stability established for up to 6 hours at room temperature (percent difference of 0.98%) and up to 85 days at -20 °C (percent difference of 2.3%). Re-injection stability of processed extracts was established for up to 48 hours under refrigeration (5 °C).	Yes
Freeze-thaw stability	Established for up to four freeze-thaw cycles at -70 °C (%bias -9.3 to -1.6% and %CV ≤12.1%).	Yes
Long-term storage	Established stability for resmetirom in human plasma at -20 °C for up to 34 days (%bias -2.0 to 3.1% and %CV ≤6.7%) and -70 °C for up to 217 days (%bias -0.6 to 2.0% and %CV ≤1.6%).	Yes
Carryover	Across six replicates of blank samples injected immediately following standards at the ULOQ, two demonstrated carryover < 20% of analyte response at the LLOQ. The remaining four replicates showed carryover >20%. The mean carryover was 18.8%, but this mean is driven by two replicates with 0% carryover. No corrective measures were implemented (e.g., injection of blank samples after samples with expected high concentration).	No

Source: Summary of Biopharmaceutic Studies; Validation reports MC11B-0090 and MC11B-0257
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Observations of carryover >20% of analyte response at the LLOQ are expected to primarily impact those samples with low concentration following quantitation of samples with high concentration. Method MN10081 performed acceptably in Trials VIA-3196-01 and VIA-3196-02. It therefore does not appear that carryover had a large impact on the quantitation of samples in these studies.

Method MN12062

Validation for method MN12062 is described in report MC12B-0176, "Validation of a Method for the Determination of VIA-3196 [resmetirom] and VIA-3196-M1 [MGL-3623] in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection." In this method, resmetirom, MGL-3623, resmetirom-d_6 (internal standard), and MGL-3623-$^{13}C_3{}^{15}N_2$ (internal standard) are extracted using a solvent extraction procedure from human plasma containing K_2EDTA as the anticoagulant. Extracts are reconstituted and then analyzed via reverse-phase HPLC (different column used from Method MN10081). The mobile phase (0.05% acetic acid in water or 25:75 methanol-acetonitrile mixture) was nebulized using heated

nitrogen in a Z-spray source/interface set to electrospray negative mode. Ionized compounds are detected using MS/MS.

Table 221. Bioanalytical Method Validation for Plasma, MN12062

Method Parameters	Method Details
Bioanalytical method review summary	Method validation adequate to support results in Trials VIA-3196-02, MGL-3196-03, MGL-3196-04, MGL-3196-07, MGL-3196-08, MGL-3196-09, MGL-3196-10, MGL-3196-12, MGL-3196-15, MGL-3196-16, and MGL-3196-17
Method description	Sample extraction from K_2EDTA human plasma via solvent extraction; separation and detection using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)
Materials used for calibration curve, QCs, and concentration	• Resmetirom, Lot# DUG-AJ-124(4), (b) (4) • Resmetirom, Lot# 12AK0171B, (b) (4) • MGL-3623, Lot# MOR-S-19(2), (b) (4)
Validated assay range	• Resmetirom: 1.00 to 1000 ng/mL in human plasma • MGL-3623: 1.00 to 1000 ng/mL in human plasma
Source and lot of internal standard reagents	• Resmetirom-d_6, Lot# 36084-195-A, (b) (4) • MGL-3623-$^{13}C_3{}^{15}N_2$, Lot# CLE-I-109-19, (b) (4)
Regression model **and** weighting	Linear regression of ln-transformed peak height ratios (resmetirom or MGL-3623 to internal standard) vs. ln-transformed standard concentrations

Source: Summary of Biopharmaceutic Studies; validation report MC12B-0176; bioanalysis reports MC12B-0035, MC15B-0187, MC16B-0104, MC17B-0188, MC18B-0011, MC18B-0280, MC19B-0175, MC21B-0037, MC20B-0286, MC21B-0254
Abbreviations: (b) (4).; MGL-3196, resmetirom; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; QC, quality control

Table 222. Validation Parameters for MN12062

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy and precision from accepted validation runs	No of standard calibrators from LLOQ to ULOQ	10	Yes
	Cumulative accuracy (% bias) from LLOQ to ULOQ		Yes
	Resmetirom	-2.0 to 1.6%	
	MGL-3623	-4.5 to 4.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ		Yes
	Resmetirom	≤7.5%	
	MGL-3623	≤6.4%	
QCs performance during accuracy & precision from accepted validation runs	Cumulative accuracy (% bias) in 4 QCs		Yes
	Resmetirom	-1.3 to -0.3%	
	MGL-3623	-4.7 to 0.5%	
	Interbatch %CV		Yes
	Resmetirom	≤ 9.1%	
	MGL-3623	≤ 14.4%	
Selectivity & matrix effect	Six lots of blank human plasma were evaluated. In all cases, no interference was observed at the retention times of resmetirom and MGL-3623.		Yes
	Six individual control matrix samples were spiked with resmetirom or MGL-3623 at low and high QCs. For both species, no matrix effect was observed in all lots at the low QC. At the high QC, no matrix effect was observed in 5/6 lots. In the remaining lot, neither		

Validation Parameters	Method Validation Summary	Acceptability
	resmetirom nor MGL-3623 and their respective internal standards were detected.	
Extraction recovery	The mean percent recovery for resmetirom and MGL-3623 were 92.8% and 93.5%, respectively. The mean percent recovery for resmetirom-d_6 MGL-3623-$^{13}C_3{}^{15}N_2$ were 92.3% and 92.2%, respectively.	Yes
Interference & specificity	No interference with quantitation of resmetirom and MGL-3623 was observed when QC samples were spiked with simvastatin, simvastatin acid, rosuvastatin or N-desmethyl rosuvastatin at concentrations of 30, 40, 20, and 5 ng/mL, respectively. No interference with quantitation of resmetirom and MGL-3623 was observed when QC samples were spiked with furesomide, clopidogrel, clopidogrel thiol, and clopidogrel carboxylic acid at concentrations of 1500, 5, 20, and 2500 ng/mL, respectively.	Yes
Hemolysis effect	In three lots of blank hemolyzed plasma, no interference was observed at the retention times of resmetirom and MGL-3623. In hemolyzed matrix samples spiked with resmetirom or MGL-3623 at the LLOQ, the percent bias was within 20% for at least 2/3 replicates in all lots.	Yes
Lipemic effect	Three replicates of low and high QC samples were prepared in lipemic plasma. Lipemia had no impact on the quantitation of resmetirom or MGL-3623 (%bias=1.7 to 7.5%; %CV ≤2.6%)	Yes
Dilution linearity	Accuracy and precision demonstrated for resmetirom and MGL-3623 at 5000 ng/mL at dilution factors of 1:10 and 1:100 (resmetirom: %bias -0.4 and -0.2%; %CV ≤10.4%) (MGL-3623: %bias -0.4 and -0.6%; %CV ≤11.4%)	Yes
Benchtop/process stability	Room temperature stability of resmetirom and MGL-3623 in human plasma established for up to 25 hours (%bias -1.3 to 3.0% and %CV ≤10.8%). Processed sample (extracts) stability for MGL-3623 established for up to 6 hours at room temperature (percent difference of 2.9%) and up to 59 days at -20 °C (percent difference of 2.2%). Re-injection stability of processed extracts was established for up to 5 days under refrigeration (5 °C).	Yes
Freeze-thaw stability	Established for up to eight freeze-thaw cycles at -70 °C (%bias -5.7 to 2.0% and %CV ≤10.3%).	Yes
Long-term storage	Established stability for resmetirom and MGL-3623 in human plasma at -20 °C for up to 56 days (%bias -8.0 to 3.7% and %CV ≤8.6%). Stability for resmetirom was established at -70 °C for up to 299 days (%bias -3.3 to 0.5% and %CV ≤4.3%). Stability for MGL-3623 was established at -70 °C for up to 274 days (%bias 8.8 to 9.3% and %CV ≤1.4%).	Yes
Carryover	Across six replicates of blank samples injected immediately following standards at the ULOQ, carryover <20% of analyte response at the LLOQ was demonstrated for 6/6 lots for resmetirom and 6/6 lots for MGL-3623.	Yes

Source: Summary of Biopharmaceutic Studies; Validation reports MC12B-0176, MC15B-0180, and MC12B-0269
Abbreviations: CV, coefficient of variation; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Note that the in-study bioanalysis report for MGL-3196-08 indicates that the overall between-run %CV for low quality control (QC) samples for resmetirom and MGL-3623 using method MN12062 was 20.1% and 20.6%, respectively, and therefore falls above 15%. All included runs met QC acceptance criteria (i.e., at least 2/3 of total QCs and at least 50% at each concentration level within 15% of nominal values). All other QCs and calibration standards for resmetirom and MGL-3623 had %CV values that fell within 15%.

The high %CV is likely due to the Inclusion of outlier values in the calculation. A single high value each among low QC calculations for resmetirom and MGL-3623 yielded %CV values outside of acceptance criteria. When these values are excluded, overall (between-run) %CV = 5.7% and 5.1% for resmetirom and MGL-3623 low QCs, respectively, and therefore fall within 15%. In addition, ISR conducted on approximately 10% of study samples passed acceptance criteria.

Method BTM-2703-R0 and BTM-2703-R1

Validation for method BTM-2703-R0 is described in report 642-R9111, "Determination of MGL-3196 and MGL-3623 in Human K_2EDTA Plasma by LC-MS/MS." The method was changed to BTM-2703-R1 to accommodate a change in internal standard from resmetirom-d_6 to resmetirom-d_7. Partial validation was described in report 642-R9111A2.

In this method, resmetirom, MGL-3623, resmetirom-d_6 or resmetirom-d_7 (internal standard), and MGL-3623-$^{13}C_3{}^{15}N_2$ (internal standard) are extracted using acetonitrile-induced protein precipitation from human plasma containing K_2EDTA as the anticoagulant. Samples are analyzed via reverse-phase HPLC. Ionized compounds are detected using MS/MS. Electrospray ionization in negative ion mode was used.

Table 223. Bioanalytical Method Validation for Plasma, BTM-2703-R0 and BTM-2703-R1

Method Parameters	Method Details
Bioanalytical method review summary	Method validation adequate to support results in Trial MGL-3196-10
Method description	Sample extraction from K_2EDTA human plasma via protein precipitation; separation and detection using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)
Materials used for calibration curve, QCs, and concentration	• Resmetirom, Lot# 12AK0171B, (b) (4) • MGL-3623, Lot# IN-SSB-B-107, (b) (4) • MGL-3623, Lot# 18AK0227L, (b) (4)
Validated assay range	• Resmetirom: 1.00 to 1000 ng/mL in human plasma • MGL-3623: 1.00 to 1000 ng/mL in human plasma
Source and lot of internal standard reagents	• Resmetirom-d_6, Lot# 36084-195-A, (b) (4) • Resmetirom-d_7, Lot# IN-APR-R-58-2, (b) (4) • MGL-3623-$^{13}C_3{}^{15}N_2$, Lot# CJC-B-136-2, (b) (4)
Regression model and weighting	Linear regression with $1/x^2$ weighting

Source: Summary of Biopharmaceutic Studies; Validation reports 642-R9111 and 642-R9111A2; bioanalysis report 642-R11426
Abbreviations: (b) (4).; HPLC-MS/MS, high-performance liquid chromatography tandem mass spectrometry; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; MGL-3196, resmetirom; QC, quality control

Table 224. Validation Parameters for BTM-2703-R0 and BTM-2703-R1

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy and precision from accepted validation runs	No of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ		Yes
	Resmetirom	-5.0 to 2.8%	
	MGL-3623	-1.4 to 1.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ		Yes
	Resmetirom	≤8.3%	
	MGL-3623	≤10.0%	
QCs performance during accuracy and precision from accepted validation runs	Cumulative accuracy (%bias) in 4 QCs		Yes
	Resmetirom	-5.1 to 6.9%	
	MGL-3623	1.8 to 5.0%	
	Interbatch %CV		Yes
	Resmetirom LLOQ	15.8%	
	Resmetirom QCs	≤7.7%	
	MGL-3623	≤11.5%	
Selectivity **and** matrix effect	Six lots of blank human plasma were evaluated. For resmetirom, 5/6 lots showed no interference in >20% of response at the LLOQ. For MGL-3623, 6/6 lots showed no interference in >20% of response at the LLOQ. No interference >in 5% of response for the internal standards at the LLOQ was observed. Six individual control matrix samples were spiked with resmetirom or MGL-3623 at low and high QCs. For both species, no matrix effect was observed in all lots at the low and high QCs.		Yes
Extraction recovery	The overall percent recovery for resmetirom and MGL-3623 were 98.5% and 97.7%, respectively.		Yes
Interference & specificity	No interference of the analytes on the internal standards were observed when resmetirom or MGL-3623 were spiked at the ULOQ. The mean peak area was < % of that in accepted standards and QC samples. No interconversion between resmetirom and MGL-3623 was observed in samples spiked at the high QC.		Yes
Hemolysis effect	Six replicates of resmetirom and MGL-3623 spiked at low and high QCs were evaluated in blank 2% hemolyzed plasma. For both species, the percent bias ranged from 0.7 to 7.6% and the %CV was ≤5.0%, indicating no effect of hemolysis.		Yes
Lipemic effect	Not assessed. Acceptable as this method was only used to quantitate resmetirom and MGL-3623 in non-NASH subjects in Trial MGL-3196-10.		Yes
Dilution linearity	Accuracy and precision demonstrated for resmetirom and MGL-3623 at 7800 ng/mL at a dilution factor of 1:10 (%bias 2.4%; %CV ≤7.3%)		Yes
Benchtop/process stability	Room temperature stability of resmetirom and MGL-3623 in human plasma established for up to 6 hours (%bias -2.7 to 8.7% and %CV ≤8.4%). Processed sample (extracts) stability established for up to 214 hours at 4 °C (%bias 2.8 to 8.3%; %CV ≤5.7%) Re-injection stability of processed extracts was established for up to 67 hours under refrigeration (4 °C) (%bias -2.7 to 8.8%; %CV ≤9.5%)		Yes

Validation Parameters	Method Validation Summary	Acceptability
Freeze-thaw stability	Established for up to five freeze-thaw cycles at -20 and -70 °C (%bias -1.7 to 9.0% and %CV ≤14.3%).	Yes
Long-term storage	Established stability for resmetirom and MGL-3623 in human plasma at -20 and -70 °C for up to 391 days (%bias -10.3 to 6.7% and %CV ≤10.2%).	Yes
Carryover	Across four replicates each in three runs of blank samples injected immediately following standards at the ULOQ, carryover <20% of analyte response and <5% of IS response at the LLOQ was demonstrated for all lots for resmetirom and MGL-3623.	Yes

Source: Summary of Biopharmaceutic Studies; Validation reports 642-R9111 and 642-R9111A2
Abbreviations: CV, coefficient of variation; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; LLOQ, lower limit of quantification; NASH, nonalcoholic steatohepatitis; QC, quality control; ULOQ, upper limit of quantification

Note that the in-study bioanalysis report for MGL-3196-10 indicates that the overall between-run %CV for low QC samples for resmetirom using method BTM-2703-R0 was 16.0%, and therefore fell above 15%. All included runs met QC acceptance criteria (i.e., at least 2/3 of total QCs and at least 50% at each concentration level within 15% of nominal values). All other QCs and calibration standards for resmetirom and MGL-3623 had %CV values that fell within 15%. The overall between-run %CV for resmetirom low QCs fell within 15% when using method BTM-2703-R1.

When runs from BTM-2703-R0 and BTM-2703-R1 are combined, the overall between-run accuracy and precision for the resmetirom low QC samples are acceptable (%Bias = -1.4%; %CV = 14.5%). Thus, quantitation of resmetirom in plasma in Trial MGL-3196-10 is considered acceptable.

Method MBL-16309

Validation for method MBL-16309 is described in report RPT16309, "Validation of an LC-MS/MS Method for the Determination of MGL-3196 and its Metabolite MGL-3196-M1 [MGL-3623] in Human K_2EDTA Plasma." In this method, resmetirom, MGL-3623, resmetirom-d_6 (internal standard), and MGL-3623-$^{13}C_3{}^{15}N_2$ (internal standard) are extracted using a liquid-liquid extraction procedure from human plasma containing K_2EDTA as the anticoagulant. Extracts are reconstituted and then analyzed via reverse-phase HPLC with MS/MS. Compounds are monitored by an MS/MS system equipped with an electrospray ionization source in positive ion mode.

Table 225. Bioanalytical Method Validation for Plasma, MBL-16309

Method Parameters	Method Details
Bioanalytical method review summary	Method validation adequate to support results in Trials MGL-3196-05, MGL-3196-14, and MGL-3196-20
Method description	Sample extraction from K_2EDTA human plasma via liquid-liquid extraction; separation and detection using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)
Materials used for calibration curve, QCs, and concentration	• Resmetirom, Lot# 12AK0171B, (b) (4) • MGL-3623, Lot# IN-SSB-B-107, (b) (4)
Validated assay range	• Resmetirom: 1 to 1000 ng/mL in human plasma

Method Parameters	Method Details
	• MGL-3623: 1 to 1000 ng/mL in human plasma
Source and lot of internal standard reagents	• Resmetirom-d_6, Lot# 36084-195-A, (b) (4) • MGL-3623-$^{13}C_3{}^{15}N_2$, Lot# CLE-I-109-19, (b) (4)
Regression model and weighting	Linear regression with $1/x^2$ weighting

Source: Validation report RPT-16309; bioanalysis reports RPT16310-SA-1.0, RPT20218-SA1-1.0, and RPT22281-SA1-1.0 (IND 122865)
Abbreviations: (b) (4).; HPLC-MS/MS, high-performance liquid chromatography tandem mass spectrometry; IND, investigational new drug; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; MGL-3196, resmetirom; QC, quality control

Table 226. Validation Parameters for MBL-16309

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy & precision from accepted validation runs	No of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ		Yes
	Resmetirom	-3.0 to 1.0%	
	MGL-3623	-1.0 to 3.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ		Yes
	Resmetirom	≤7.4%	
	MGL-3623	≤13.2%	
QCs performance during accuracy **and** precision from accepted validation runs	Cumulative accuracy (%bias) in 4 QCs		Yes
	Resmetirom	-2.0 to 1.0%	
	MGL-3623	-4.8 to -0.3%	
	Interbatch %CV		Yes
	Resmetirom	≤12.8%	
	MGL-3623	≤14.4%	
Selectivity & matrix effect	Six lots of blank human plasma were evaluated. In all cases, no interference was observed at the retention times of resmetirom, MGL-3623, and the respective internal standards. Six individual control matrix samples were spiked with resmetirom or MGL-3623 at low and high QCs to evaluate internal standard-normalized matrix effects. For both species, no matrix effects were observed (resmetirom: mean IS-normalized matrix effect of 0.96 to 0.99; %CV ≤9.7%) (MGL-3623: mean IS-normalized matrix effect of 0.94 to 0.98; %CV ≤6.7%)		Yes
Extraction recovery	The percent recovery for resmetirom and MGL-3623 ranged from 82.0 to 85.6% and 81.0 to 84.9%, respectively. The mean percent recovery for resmetirom-d_6 and MGL-3623-$^{13}C_3{}^{15}N_2$ was 87.2% and 87.7%, respectively.		Yes
Ruggedness	Ruggedness was determined at 4 QCs to assess whether changes in HPLC column, LC-MS/MS system, and/or injection volume impact measurement of resmetirom or MGL-3623. Results indicate that changes in these factors do not impact measurements.		Yes
Hemolysis effect	Not assessed. Hemolysis did not impact quantitation of resmetirom or MGL-3623 in validation results for methods MN12062 and BTM-2703-R0		Yes
Lipemic effect	Not assessed. Lipemia did not impact quantitation of resmetirom or MGL-3623 in validation results for method MN12062		Yes
Dilution linearity	Accuracy and precision demonstrated for resmetirom and MGL-3623 at 5000 ng/mL at a dilution factor of 1:10 (resmetirom: %bias -3.4 and % CV=3.0%) (MGL-3623: %bias -5.6 and % CV=2.1%)		Yes

Validation Parameters	Method Validation Summary	Acceptability
Benchtop/process stability	Room temperature stability of resmetirom and MGL-3623 in human plasma established for up to 18 hours (%bias -2.7 to 6.3% and %CV ≤7.2%). Autosampler stability for resmetirom and MGL-3623 were established at 4 °C for 165 hours (%bias -5.3 to 6.0% and %CV ≤ 9.7%). Extract stability was established at 4 °C for 143 hours (%bias -5.7 to -0.3% and %CV ≤6.5%). Re-injection stability of processed extracts was established for up to 5 days under refrigeration (5 °C).	Yes
Freeze-thaw stability	Established for up to three freeze-thaw cycles at -20 °C (%bias 1.7 to 6.8% and %CV ≤8.6%) and -70 °C (%bias 0.7 to 5.3% and %CV ≤8.4%).	Yes
Long-term storage	Established stability for resmetirom and MGL-3623 in human plasma at -20 °C for up to 2289 days (%bias -3.5 to 10.3% and %CV ≤5.8%).	Yes
Carryover	Blank samples injected immediately following standards at the ULOQ did not show any significant carryover for resmetirom for MGL-3623.	Yes

Source: Validation report RPT-16309
Abbreviations: CV, coefficient of variation; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Quantitation of Resmetirom and MGL-3623 in Urine

Two bioanalytical methods have been developed and validated to quantitate resmetirom and MGL-3623 in human urine.

- Method MN12063 ((b) (4))
  - Used in Trials VIA-3196-02, MGL-3196-07, MGL-3196-10, and MGL-3196-12
    - Note that this method in MGL-3196-10 was used to quantitate resmetirom and MGL-3623 in all subjects with noncirrhotic or cirrhotic NASH and some non-NASH subjects.
- Method BTM-2704-R0/BTM-2704-R1 ((b) (4))
  - Used in Trial MGL-3196-10
    - Note that this method in MGL-3196-10 was used to quantitate resmetirom and MGL-3623 in non-NASH subjects only.

Method MN12063

Validation for method MN12063 is described in report MC12B-0177, "Validation of a Method for the Determination of MGL-3196 [resmetirom] and MGL-3623 in Stabilized Human Urine using High-Performance Liquid Chromatography with MS/MS Detection." In this method, resmetirom, MGL-3623, resmetirom-d_6 (internal standard), and MGL-3623-$^{13}C_3{}^{15}N_2$ (internal standard) are extracted using a solvent extraction procedure from human urine stabilized by the addition of 20% v/v of 70% isopropyl alcohol solution. Extracts are reconstituted and then analyzed via reverse-phase HPLC. The mobile phase (0.05% acetic acid in water or 25:75 methanol-acetonitrile mixture) was nebulized using heated nitrogen in a Z-spray source/interface set to electrospray negative mode. Ionized compounds are detected using MS/MS.

Table 227. Bioanalytical Method Validation for Urine, MN12063

Method Parameters	Method Details
Bioanalytical method review summary	Method validation adequate to support results in Trials VIA-3196-02, MGL-3196-07, MGL-3196-10, and MGL-3196-12
Method description	Sample extraction from K_2EDTA human plasma via solvent extraction; separation and detection using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)
Materials used for calibration curve, QCs, and concentration	• Resmetirom, Lot# DUG-AJ-124(4), (b) (4) • Resmetirom, Lot# 12AK0171B, (b) (4) • MGL-3623, Lot# MOR-S-19(2), (b) (4) • MGL-3623, Lot# 18AK0227L, (b) (4)
Validated assay range	• Resmetirom: 1.00 to 1000 ng/mL in human plasma • MGL-3623: 10.00 to 10,000 ng/mL in human plasma
Source and lot of internal standard reagents	• Resmetirom-d_6, Lot# 36084-195-A, (b) (4) • MGL-3623-$^{13}C_3{}^{15}N_2$, Lot# CLE-I-109-19, (b) (4)
Regression model & weighting	Linear regression of log-transformed peak height ratios (resmetirom or MGL-3623 to internal standard) vs. log-transformed standard concentrations

Source: Summary of Biopharmaceutic Studies; Validation report MC12B-0177; bioanalysis report MC12B-0207, MC17B-0242, MC19B-0176, MC19B-0168

Abbreviations: (b) (4).; HPLC-MS/MS, high-performance liquid chromatography tandem mass spectrometry; IND, investigational new drug; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; MGL-3196, resmetirom; QC, quality control; VIA-3196, resmetirom

Table 228. Validation Parameters for MN12063

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy and precision from accepted validation runs	No of standard calibrators from LLOQ to ULOQ	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ		Yes
	Resmetirom	-2.4 to 2.0%	
	MGL-3623	-5.0 to 4.8%	
	Cumulative precision (%CV) from LLOQ to ULOQ		Yes
	Resmetirom	≤6.4%	
	MGL-3623	≤9.3%	
QCs performance during accuracy and precision from accepted validation runs	Cumulative accuracy (%bias) in 4 QCs		Yes
	Resmetirom	-2.6 to -2.1%	
	MGL-3623	-5.3 to 3.2%	
	Interbatch %CV		Yes
	Resmetirom	≤12.1%	
	MGL-3623	≤12.9%	
Selectivity & matrix effect	Six lots of blank human plasma were evaluated. In all cases, no interference was observed at the retention times of resmetirom and MGL-3623. Six individual control matrix samples were spiked with resmetirom or MGL-3623 at the LLOQ. For both species, no matrix effect was observed in all lots.		Yes
Extraction recovery	The mean percent recovery for resmetirom and MGL-3623 was 90.4% and 92.0%, respectively. The mean percent recovery for resmetirom-d_6 MGL-3623-$^{13}C_3{}^{15}N_2$ was 95.2% and 92.2%, respectively.		Yes
Dilution linearity	Accuracy and precision demonstrated for resmetirom and MGL-3623 at 4000 ng/mL and 40,000 ng/mL, respectively, at dilution factors of		Yes

Validation Parameters	Method Validation Summary	Acceptability
	1:10 and 1:100 (resmetirom: %bias -8.8 and -5.8%; %CV ≤13.1%) (MGL-3623: %bias -6.5%; % CV ≤12.5%)	
Bench-top/process stability	Room temperature stability of resmetirom and MGL-3623 in stabilized and unstabilized human urine established for up to 24 hours (%bias -14.0 to 4.4% and %CV ≤17.8%). Re-injection stability of processed extracts was established for up to 7 days under refrigeration (5 °C).	Yes
Freeze-thaw stability	Established for up to four freeze-thaw cycles at -70 °C (%bias -11.5 to 0.5% and %CV ≤19.0%).	Yes
Long-term storage	Established stability in human urine at -70 °C for up to 315 days.	Yes
Carryover	Across twelve replicates of blank samples injected immediately following standards at the ULOQ, carryover <20% of analyte response at the LLOQ was demonstrated for 10/12 lots for both resmetirom and MGL-3623	Yes

Source: Summary of Biopharmaceutic Studies; Validation report MC12B-0177
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Note that the in-study bioanalysis report for VIA-3196-02 reports a %CV ranging from 18.0 to 31.0% for all MGL-3623 QCs. This is due to the inclusion of outliers in the calculation. When outliers are excluded from analysis, overall (between-run) %CV=5.3% and 10.7% for medium and high QCs, respectively, and therefore meets acceptance criteria. The overall %CV for low QCs=16.0% after exclusion of outliers and therefore still falls above 15%.

Despite this, all included runs met QC acceptance criteria (i.e., at least 2/3 of total QCs and at least 50% at each concentration level within 15% of nominal values). In addition, all calibration standards for resmetirom and MGL-3623 fell within 15%. Quantitation of MGL-3623 in urine in Trial VIA-3196-02 may be acceptable, but the results should be interpreted with caution considering these observations.

Method BTM-2704-R0 and BTM-2704-R1

Validation for method BTM-2704-R0 is described in report 642-R9112: "Determination of MGL-3196 and MGL-3623 in Human Urine by LC-MS/MS". The method was changed to BTM-2704-R1 to accommodate a change in internal standard from resmetirom-d_6 to resmetirom-d_7. Partial validation was described in report 642-R9112A2.

In this method, resmetirom, MGL-3623, resmetirom-d_6 or resmetirom-d_7 (internal standard), and MGL-3623-$^{13}C_3{}^{15}N_2$ (internal standard) are extracted using acetonitrile-induced protein precipitation from human urine using 70% isopropyl alcohol as a stabilizer. Samples are analyzed via reverse-phase HPLC. Ionized compounds are detected using MS/MS. Electrospray ionization in negative ion mode was used.

Table 229. Bioanalytical Method Validation for Urine, BTM-2704-R0 and BTM-2704-R1

Method Parameters	Method Details
Bioanalytical method review summary	Method validation adequate to support results in Trial MGL-3196-10
Method description	Sample extraction from K_2EDTA human plasma via protein precipitation; separation and detection using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)

Method Parameters	Method Details
Materials used for calibration curve, QCs, and concentration	• Resmetirom, Lot# 12AK0171B, (b) (4) • MGL-3623, Lot# IN-SSB-B-107, (b) (4) • MGL-3623, Lot# 18AK0227L, (b) (4)
Validated assay range	• Resmetirom: 1.00 to 1000 ng/mL in human plasma • MGL-3623: 10.0 to 10,000 ng/mL in human plasma
Source and lot of internal standard reagents	• Resmetirom-d_6, Lot# 36084-195-A, (b) (4) • Resmetirom-d_7, Lot# IN-APR-R-58-2, (b) (4) • MGL-3623-$^{13}C_3{}^{15}N_2$, Lot# CJC-B-136-2, (b) (4)
Regression model and weighting	Linear regression with $1/x^2$ weighting

Source: Summary of Biopharmaceutic Studies; Validation reports 642-R9112 and 642-R9112A1; bioanalysis report 642-R11426
Abbreviations: (b) (4).; HPLC-MS/MS, high-performance liquid chromatography tandem mass spectrometry; K_2EDTA, dipotassium (K_2) ethylene diamine tetraacetic acid; MGL-3196, resmetirom; QC, quality control

Table 230. Validation Parameters for BTM-2704-R0 and BTM-2704-R1

Validation Parameters	Method Validation Summary		Acceptability
Calibration curve performance during accuracy and precision from accepted validation runs	No of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ		Yes
	Resmetirom	-0.8 to 2.0%	
	MGL-3623	-3.9 to 2.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ		Yes
	Resmetirom	≤8.8%	
	MGL-3623	≤4.7%	
QCs performance during accuracy and precision from accepted validation runs	Cumulative accuracy (%bias) in 4 QCs		Yes
	Resmetirom	-4.6 to 0.8%	
	MGL-3623	-2.0 to 2.0%	
	Interbatch %CV		Yes
	Resmetirom	≤12.5%	
	MGL-3623	≤5.7%	
Selectivity and matrix effect	Six lots of blank human plasma were evaluated. For resmetirom and MGL-3623, 6/6 lots showed no interference in >20% of response at the LLOQ. No interference in >5% of response for the internal standards at the LLOQ was observed. No matrix effects were observed at the low and high QCs for resmetirom and MGL-3623.		Yes
Extraction recovery	The overall percent recovery for resmetirom and MGL-3623 was 100.8% and 99.4%, respectively.		Yes
Interference & specificity	No interference of the analytes on the internal standards were observed when resmetirom or MGL-3623 were spiked at the ULOQ. The mean peak area was < 5% of that in accepted standards and QC samples.		Yes
Dilution linearity	Accuracy and precision demonstrated for resmetirom and MGL-3623 at 2000 ng/mL and 20,000 ng/mL at a dilution factor of 1:10		Yes
Benchtop/process stability	Room temperature stability of resmetirom and MGL-3623 in human urine established for up to 5.5 hours.		Yes

Validation Parameters	Method Validation Summary	Acceptability
	Processed sample (extracts) stability established for up to 171.5 hours at room temperature. Re-injection stability of processed extracts was established for up to 187.5 hours at room temperature	
Freeze-thaw stability	Established for up to five freeze-thaw cycles at -20 and -70 °C.	Yes
Long-term storage	Established stability for resmetirom and MGL-3623 in human urine at -20 and -70 °C for up to 365 days (%bias -3.3 to 1.5% and %CV ≤7.6%).	Yes
Carryover	No carryover was observed in double blank samples evaluated for injection carryover	Yes

Source: Summary of Biopharmaceutic Studies; Validation reports 642-R9112 and 642-R9112A1
Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Note that the in-study bioanalysis report for MGL-3196-10 indicates that the overall between-run %CV for low QC samples for resmetirom using method BTM-2704-R0 was 16.8% and therefore fell above 15%. All included runs met QC acceptance criteria (i.e., at least 2/3 of total QCs and at least 50% at each concentration level within 15% of nominal values). All other QCs and calibration standards for resmetirom and MGL-3623 had %CV values that fell within 15%. The overall between-run %CV for resmetirom low QCs fell within 15% when using method BTM-2704-R1. Thus, quantitation of resmetirom in urine in Trial MGL-3196-10 is considered acceptable.

PK of Other Species in DDI Studies

PK of the following species were also measured in DDI studies across the clinical development program:

- Simvastatin and relevant metabolites (Trial MGL-3196-15)
- Pravastatin and relevant metabolites (Trial MGL-3196-15)
- Rosuvastatin and relevant metabolites (Trial MGL-3196-03)
- Atorvastatin and relevant metabolites (Trial MGL-3196-04)
- Pioglitazone and relevant metabolites (Trial MGL-3196-09)
- I- and (*S*)-warfarin (Trial MGL-3196-16)

The method validation reports are as follows:

- Simvastatin: RPT16919-AD1-1.0 ((b) (4))
- Pravastatin: RPT20908-MV1-2.0 ((b) (4))
- Rosuvastatin: MC09B-0224 ((b) (4))
- Atorvastatin: MC16B-0089 ((b) (4))
- Pioglitazone: MC18B-0188 ((b) (4)
- Warfarin: RPT18911-MV1-1.0 ((b) (4))

Simvastatin, Pravastatin, and Warfarin

Method validation and in-study analysis findings for simvastatin, pravastatin, and warfarin are acceptable.

Rosuvastatin

For rosuvastatin and N-desmethyl rosuvastatin, in-study analysis indicates that the between-run %CV for high QC samples was 20.2%, which falls above 15%.

- In both cases, this finding is due to the inclusion of one outlier value in one analytical run that was included in statistics calculation. Exclusion of this value from the calculation would yield %CV values below 15%
- Inter-run precision and accuracy is acceptable for all other QCs and calibration standards.
- ISR conducted on approximately 10% of samples passed with a rate of 100% for rosuvastatin and 97% for N-desmethyl rosuvastatin.

Conclusion

Overall, quantitation of rosuvastatin and N-desmethyl rosuvastatin in MGL-3196-03 is considered acceptable.

Atorvastatin

For atorvastatin and all metabolites, during method validation the intraday %CV values for the low QC in a single analytical run (AR09) were above 15% (range 17.7 to 22.3%). In addition, the intraday %CV for the LLOQ in one analytical run (AR08) for p-hydroxyatorvastatin-only was above 20% (value of 20.5%).

- For data in AR09 at the low QC (all species), in each case this was due to one of the six replicates falling outside 15% relative error from the theoretical value. For data in AR08 at the LLOQ (p-hydroxyatorvastatin), this was due to one of the six replicates falling outside 20% relative error from the theoretical value.
- For all other analytical runs during validation, intraday precision and accuracy were acceptable.
- Interday precision and accuracy during method validation for all species were acceptable.
- During in-study bioanalysis in MGL-3196-04, precision and accuracy were acceptable.
- ISR conducted on approximately 9.7% of samples passed with a rate ≥94.9% for all species.

Conclusion

Overall, quantitation of atorvastatin and metabolites in MGL-3196-04 is considered acceptable.

Pioglitazone

During in-study analysis of hydroxy-pioglitazone, it was determined that the primary stock standard was diluted to double the concentration intended (see investigation record LIR-19004). This stock standard was used to prepare working standards and QC samples. Thus, all calibration

standards and QCs were reprocessed at double the concentration. This only impacted hydroxy-pioglitazone samples and not any pioglitazone samples.

- Per the Applicant's investigation record (LIR-19004), the Applicant reprocessed analytical run AR01 using the adjusted hydroxy-pioglitazone concentrations and compared it to a repeat run using newly prepared standards and QCs (IR01). Per the Applicant, "the evaluation of %difference between the recalculated AR01 and the IR01 run [was] 95.6%, indicating that reprocessing all of the runs with the corrected standard concentrations will achieve accurate results."
- Concentrations of calibration standards and QCs were therefore reported at double the concentration evaluated during method validation (i.e., up to 1000 ng/mL versus 500 ng/mL).
- All study samples quantitated to concentrations below the upper-calibration range of 500 ng/mL established during method validation.
- Accuracy and precision of calibration standards and QCs at these higher concentrations were acceptable.
- ISR conducted on approximately 11% of samples passed with a rate of 100% for pioglitazone and hydroxy-pioglitazone.

Conclusion

Overall, quantitation of pioglitazone and hydroxy-pioglitazone in MGL-3196-09 is considered acceptable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

This section is not applicable to the resmetirom drug product.

14.5. Pharmacometrics Assessment

14.5.1. Population PK Analysis

14.5.1.1. Review Summary

In general, the Applicant's PopPK analysis is considered acceptable for the purpose of characterizing the PK profile of resmetirom (MGL-3196) in patients with NASH with liver fibrosis. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the model was used to support the current submission as outlined in Table 231.

Table 231. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model	FDA's Comments
(b) (4)	(b) (4) See details in Section 14.5.1.4. (b) (4) (b) (4) Overall, the reviewer deems it is not necessary to dose based on age. Based on the assessment of different body weight cutoffs (Section 14.5.1.4), 100 kg as a more reasonable body weight cutoff than 80 kg and will give better efficacy outcome. The final dosing recommendation will be "80 mg for patients < 100 kg and 100 mg for patients >= 100 kg". Refer to Section 23 for labeling.

The PK of REZDIFFRA were not affected by age, gender, or race.

The results from the population PK model suggest a faster clearance of REZDIFFRA in patients with higher body weight. No parameter was identified other than body weight in the exposure-response model of REZDIFFRA that impacted efficacy parameters.

Renal Impairment

The PK of REZDIFFRA and its metabolite, MGL-3623, were studied in patients with mild to moderate renal impairment. Renal excretion was determined to be a minor route of elimination. Based on the results from a population PK analysis of patients, the effect of mild or moderate renal impairment on apparent clearance (CL/F) of REZDIFFRA was minimal and not clinically relevant. REZDIFFRA has not been studied in patients with severe renal impairment.

Hepatic Impairment

The disposition of REZDIFFRA and its metabolite was compared in non-NASH subjects with hepatic impairment (mild [N=10], moderate [N=10], and severe [N=3] as indicated by the Child-Pugh method) and subjects with normal hepatic function (n=8) following repeated 80 mg dosing of REZDIFFRA for 6 days.

Compared to subjects with normal hepatic function, the resmetirom C_{max} and AUC, following repeated 80 mg dosing for 6 days, were increased by 9% and 22%, respectively, in subjects with mild hepatic impairment, and by 35% and 115%, respectively, in patients with moderate hepatic impairment. No dose adjustment of REZDIFFRA is necessary for patients with mild (Child-Pugh Class A); a dose of 60 mg is recommended for moderate (Child– Pugh Class B) hepatic impairment.

Compared to subjects with normal hepatic function, the REZDIFFRA C_{max} and AUC, following repeated 80 mg dosing for 6 days, were increased by 44% and 387%, respectively, in subjects

Utility of the Final Model		FDA's Comments
	with severe hepatic impairment. Use of REZDIFFRA in patients with severe hepatic impairment is contraindicated. The PK of resmetirom and its metabolite was compared in NASH patients, with NASH cirrhosis categorized with mild hepatic impairment (Child-Pugh Class A) and non-cirrhotic NASH following repeated 100 mg dosing of REZDIFFRA for 6 days. The PK disposition of REZDIFFRA was not altered in NASH cirrhosis patients with mild hepatic impairment (Child-Pugh Class A) compared with non-cirrhotic NASH patients. No dosing adjustment is required in NASH cirrhotic patients with mild hepatic impairment.	
	Clopidogrel: Administration of repeated doses of REZDIFFRA 100 mg/day in healthy subjects in the presence of steady-state clopidogrel, a CYP 2C8 and OATP inhibitor, increased the AUC of REZDIFFRA 1.7-fold and the C_{max} 1.3-fold. HMG-CoA reductase inhibitors (statins): REZDIFFRA mildly increased plasma concentrations of some statins.	Co-admnistration of clopidogrel and statins were identified as significant covariates in PopPK analysis. NASH subjects who received a concomitant administration of statins with resmetirom presented a CL/F approximately 2% lower ($exp^{-0.0207}$) than that observed in NASH subjects with fibrosis stage F0, F1 or F2. NASH subjects who received concomitant administration of clopidogrel with resmetirom presented a CL/F approximately 50% lower ($exp^{-0.682}$) than that observed in NASH subjects with fibrosis stage F0 or F1-F2.

Source: Generated by the FDA review team
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450; FDA, U.S. Food and Drug Administration; F0, fibrosis stage 0; F1-F2, fibrosis stage 1-2; N, number of subjects in treatment arm; NASH, nonalcoholic steatohepatitis; OATP, organic anion transporting polypeptide; PopPK, population PK; PK, pharmacokinetic; QD, once daily

14.5.1.2. Introduction

The primary objectives of the Applicant's analysis were to:

- Perform PopPK analyses of resmetirom and its main metabolite, MGL-3623, and identify sources of variability in patients with NASH.
- Exposure parameters derived with the above population model will be used for exposure-response (E-R) analysis to ultimately support dosing of resmetirom in patients with NASH.

14.5.1.3. Model Development

Data

The final PopPK analyses were based on PK data from 13 studies. The study design, study population, and timing of blood samples varied among the 13 clinical studies. Brief descriptions of the studies included are presented in Table 232.

The final nonlinear mixed effects modeling data file for analysis contained 19207 PK observations from 2034 subjects. Table 233 provides summary statistics of the baseline demographic covariates in the analysis dataset. nonlinear mixed effects modeling 7.5.0 was used for nonlinear mixed-effect PopPK modeling. R (version 4.2.2) was used for dataset preparation, exploration, and visualization.

Table 232. Summary of Studies With PK Sampling Included in Population PK Analysis

Subject Population	Study Protocol ID	Study Description	Study Treatments	Planned Subjects	Relevant Plasma PK Sampling for Resmetirom
Healthy	VIA-3196-01	A Randomized, Double-blind, Placebo-Controlled, Ascending Single-Dose Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of VIA-3196 in Healthy Subjects	Single oral dose of 0.25, 1, 2.5, 5, 10, 20, 50, 100 or 200 mg VIA-3196 or matching placebo on Day 1, fasting. The 10-mg cohort only will receive a second oral dose approximately 7 days later, following a high-fat meal.	8 subjects per cohort, 6 to receive VIA-3196 (total, 54 subjects) and 2 to receive placebo (total, 18 subjects).	**Day 1:** Predose, 0.25, 0.5, .75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose **Day 3:** in the morning
Healthy	VIA-3196-02	A Randomized, Double-blind, Placebo-Controlled, Ascending Multiple-Dose Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of VIA-3196 in Healthy Subjects	The subjects received 14 daily doses of 5, 20, 50, 80, 100, or 200 mg VIA-3196 or matching placebo on Protocol Days 1 to 14.	The total sample size planned for this study was 48 subjects across 6 cohorts (8 subjects per cohort; 6 received VIA-3196 and 2 received placebo). At the end of the study, 46 subjects completed and were analyzed with 34 subjects receiving VIA-3196 and 12 subjects receiving placebo. Two subjects received VIA-3196 but did not complete the study: one subject withdrew due to an adverse event and the other subject withdrew due to personal reasons.	**Day 1:** Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, & 12 hours postdose **Day 2:** Predose **Day 3:** Predose **Day 6:** Predose **Day 9:** Predose **Day 12:** Predose **Day 14:** Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, & 12 hours postdose **Day 15:** 24 Hours after last dose on Day 14
Healthy	MGL-3196-03	A Single Center, Open-label, Drug Interaction Study of MGL-3196 with Rosuvastatin and Simvastatin in Healthy Subjects	**Day 1:** Simvastatin 20 mg tablet **Day 3:** Day 1 Treatment B Rosuvastatin 10 mg tablet **Day 6 to 11:** MGL-3196 200 mg (4 x 50 mg) capsules **Day 12:** Simvastatin 20 mg tablet & MGL-3196 200 mg (4 x 50 mg) capsules **Days 13:** MGL-3196 200 mg (4 x 50 mg) Capsules **Day 14:** Rosuvastatin 10 mg tablet & MGL-3196 200 mg (4 x 50 mg) capsules **Days 14, 15, and 16:** MGL-3196 200 mg (4 x 50 mg) capsules	A total of 25 subjects entered and completed the study according to protocol.	**Day 6:** predose, 0.5 1, 2, 3, 4, 6, 8, 12, & 24 hours postdose **Day 10:** Predose **Day 12:** Predose **Day 13:** Predose **Day 14:** Predose, 0.5 1, 2, 3, 4, 6, 8, 12, & 24 hours postdose
Healthy	MGL-3196-04	A Single Center, Open-label, Drug Interaction Study of MGL-3196 with Atorvastatin in Healthy Subjects	**Day 1:** Atorvastatin 20 mg tablet **Day 4 to 12:** MGL-3196 100 mg (2 x 50 mg) capsules **Day 10:** Atorvastatin 20 mg tablet	A total of 14 subjects entered and completed the study according to protocol.	**Day 4:** predose, 0.5 1, 2, 3, 4, 6, 8, 12, & 24 hours postdose **Day 6:** Predose **Day 7:** Predose **Day 9:** predose, 0.5 1, 2, 3, 4, 6, 8, 12, & 24 hours postdose **Day 12:** Predose **Day 13:** Predose
Healthy	MGL-3196-09	A Single Center, Open-Label, Drug Interaction Study of MGL-3196 with	**Day 1 and Day 10:** 15 mg pioglitazone tablet	16 Subjects	**Day 4:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, & 24 **Day 6:** Predose **Day 7:** Predose
		Pioglitazone and to Assess Food Effect in Healthy Subjects	**Day 4 to Day 16:** 100 mg MGL-3196 Tablet Formulation (1 x 40 mg tablet and 1 x 60 mg tablet)		**Day 9:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, & 24 **Day 10:** 0.5, 1, 2, 3, 4, 6, 8, 12, & 24 **Day 12:** Predose **Day 13:** Predose **Day 14:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, & 24 **Day 16:** Predose **Day 17:** Predose
Cirrhosis and Healthy Controls	MGL-3196-10	A Phase I, Open Label, Non-randomized Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Multiple Oral Doses of MGL-3196 in Subjects with Varying Degrees of Hepatic Impairment and Healthy Matched Control Subjects with Normal Hepatic Function	**Day 1 to Day 6:** MGL-3196 (80 mg; 2 x 40 mg tablets);	100 Subjects total (6 cohorts)	**Day 1:** Predose, 0.5, 1, 2, 3, 4, 6, 8 & 12 hours post-dose **Day 2:** Predose **Day 3:** Predose **Day 6:** Predose, 0.5, 1, 2, 3, 4, 6, 8 & 12 hours **Day 7:** Predose **Day 8:** Predose
Healthy	MGL-3196-12	A Single Center, Open-Label, Drug Interaction Study of MGL-3196 with Clopidogrel in Healthy Subjects	**Day 1:** MGL-3196 (100 mg; 1x 100 mg tablet) **Day 3:** 300 mg clopidogrel **Day 4 to Day 11:** 75 mg clopidogrel **Day 6 to Day 14:** MGL-3196 (100 mg; 1x 100 mg tablet)	20 healthy subjects	**Day 1:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 & 24 hours **Day 6:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 & 24 hours **Day 8:** Predose **Day 9:** Predose **Day 10:** Predose **Day 11:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 & 24 hours **Day 12:** Predose **Day 13:** Predose **Day 14:** Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 & 24 hours

Subject Population	Study Protocol ID	Study Description	Study Treatments	Planned Subjects	Relevant Plasma PK Sampling for Resmetirom
Healthy	MGL-3196-15	A Single-Center, Open-label, Drug Interaction Study of Resmetirom with Pravastatin and Simvastatin in Healthy Subjects	Resmetirom 100 mg was be administered at approximately the same time in the morning for 10 days from Day 5 through Day 14. On Day 9, pravastatin was also administered in the evening and pravastatin and simvastatin were co-administered with resmetirom in the morning of Day 11 and Day 13, respectively.	25 healthy subjects	**Day 5:** Predose and 0.5, 1, 2, 3, 4, 6, 8, 12 and h post dose **Day 6:** Predose **Day 7:** Predose **Day 8:** Predose **Day 9:** Predose **Day 10:** Predose **Day 11:** Predose and 0.5, 1, 2, 3, 4, 6, 8, 12 and h post dose **Day 12:** Predose **Day 13:** Predose and 0.5, 1, 2, 3, 4, 6, 8, 12 and h post dose **Day 14:** Predose
Healthy	MGL-3196-16	A Single-Center, Open-label, Drug Interaction Study to Assess the Effect	Resmetirom 100 mg will be orally administered at approximately the same time daily, from Day 14	25 healthy subjects	**Day 14:** Predose, and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 postdose **Day 16:** Predose
		of Resmetirom on Warfarin in Healthy Subjects	through Day 21.		**Day 18:** Predose **Day 20:** Predose **Day 21:** Predose, and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 postdose
Healthy	MGL-3196-17	A Randomized, Positive and Placebo-Controlled Cross-over Trial to Evaluate the Effects of Resmetirom (MGL-3196) Administration on Cardiac Repolarization in Healthy Subjects	Resmetirom 200 mg daily administration for 6 days	36 healthy adult subjects	**Day 1 and Day 6:** predose, and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 h postdose.
NASH	MGL-3196-05	A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo Controlled Study of MGL-3196 in Patients With Non Alcoholic Steatohepatitis	Placebo 80 mg MGL-3916	117 (1:2 Placebo to Resmetirom)	**Day 1:** Predose **Weeks 2:** Predose **Week 4:** Predose and at 2, 4, 6, & 8 hours post dose **Week 8:** Predose **Week 16:** Predose **Week 24:** Predose **Week 36:** Predose
NASH	MGL-3196-11	A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation	Placebo 80 mg MGL-3196 100 mg MGL-3196	**Interim Analysis:** 900 patients (300 per treatment arm) with at least 450 patients with fibrosis stage F3. **Exploratory Group for Interim Analysis:** Fibrosis Stage 1 Patients (F1B plus high-risk F1A/F1C)	**Day 1:** Predose **Week 4:** Predose **Week 8:** 2 to 6 hours after dosing (sparse) **Week 16:** Predose **Week 24:** Predose **Week 36:** Predose **Week 44:** Predose **Week 52:** Predose
NAFLD	MGL-3196-14	A 52-Week, Phase 3 Study to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients with Non-alcoholic Fatty Liver Disease (NAFLD) (MAESTRO NAFLD-1)	Placebo 80 mg MGL-3196 100 mg MGL-3196	800 total patients: Up to 200 Open Label 600 in double blind treatment groups (200 per dosing arm)	**Day 1:** Predose **Week 2 (Non-cirrhotic Patients):** Predose **Week 2 (Cirrhotic Patients):** 4 to 6 hours (sparse) **Week 4:** Predose **Week 8:** 4 to 6 hours after dosing (sparse) **Week 16:** Predose **Week 24:** Predose **Week 36:** Predose **Week 44:** Predose **Week 52:** Predose

Source: Table cited from Appendix 1 "Overview of Study Design and Populations" in Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382_PK
Abbreviations: F1, fibrosis stage; MGL-3196, resmetirom; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic; VIA-3196, resmetirom

Table 233. Summary of Baseline Demographic Covariates for Analysis

Baseline Characteristics	Non-NASH Patients (N=299)	NASH Patients				
		F0 (N=33)	F1-F2 (N=1078)	F3 (N=426)	Overall F0, F1-F2, F3 (N=1537)	F4 (N=198)
Age (years)						
Mean (CV%)	40.6 (30.4%)	54.2 (27.3%)	55.8 (20.8%)	57.1 (18.6%)	56.1 (20.4%)	61.4 (14.3%)
Median	40.0	57.0	57.0	58.0	57.0	61.0
[Min, Max]	[18.0, 75.0]	[22.0, 76.0]	[18.0, 83.0]	[19.0, 81.0]	[18.0, 83.0]	[25.0, 80.0]
Body Weight (kg)						
Mean (CV%)	79.9 (16.6%)	109 (24.6%)	100 (20.7%)	100 (22.9%)	101 (21.5%)	98.0 (23.6%)
Median	79.4	106	98.0	97.6	98.0	94.8
[Min, Max]	[51.8, 131]	[56.7, 163]	[52.7, 205]	[56.6, 185]	[52.7, 205]	[52.0, 195]
BMI (kg/m^2)						
Mean (CV%)	27.1 (12.4%)	39.1 (20.9%)	35.6 (17.5%)	35.7 (19.2%)	35.7 (18.1%)	35.4 (19.8%)
Median	27.0	36.8	35.0	34.5	34.9	35.0
[Min, Max]	[19.4, 38.6]	[28.3, 60.7]	[22.1, 70.9]	[21.8, 67.8]	[21.8, 70.9]	[20.7, 58.9]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)	2 (1.0%)
ALP (U/L)						
Mean (CV%)	71.7 (32.7%)	76.9 (31.0%)	71.8 (33.1%)	76.2 (35.3%)	73.1 (33.8%)	85.2 (46.8%)
Median	69.0	75.0	68.0	72.0	70.0	74.0
[Min, Max]	[20.0, 185]	[36.0, 159]	[27.0, 222]	[27.0, 268]	[27.0, 268]	[36.0, 286]
AST (U/L)						
Mean (CV%)	20.7 (49.4%)	39.5 (66.0%)	41.4 (68.0%)	55.3 (55.6%)	45.2 (65.3%)	40.5 (65.7%)
Median	19.0	34.0	33.0	49.0	37.0	33.5
[Min, Max]	[6.00, 100]	[4.00, 136]	[6.00, 265]	[11.0, 214]	[4.00, 265]	[8.00, 200]
Total Bilirubin (µmol/L)						
Mean (CV%)	22.4 (47.9%)	28.3 (43.3%)	28.6 (59.9%)	41.5 (51.3%)	32.2 (59.6%)	39.4 (61.3%)
Median	20.0	28.0	23.0	37.0	27.0	34.5
[Min, Max]	[9.00, 118]	[7.00, 64.0]	[7.00, 202]	[11.0, 156]	[7.00, 202]	[11.0, 213]
eGFR ($mL/min/1.73m^2$)						
Mean (CV%)	94.0 (20.4%)	85.5 (20.0%)	91.1 (25.0%)	93.1 (24.7%)	91.6 (24.8%)	92.2 (28.2%)
Median [Min, Max]	91.6 [59.7, 180]	83.0 [62.7, 120]	88.7 [32.6, 182]	91.4 [39.0, 172]	89.3 [32.6, 182]	90.3 [30.3, 192]
eGFR (mL/min)						
Mean (CV%)	104 (20.6%)	106 (26.3%)	110 (27.4%)	112 (28.8%)	110 (27.8%)	109 (34.0%)
Median [Min, Max]	102 [64.8, 192]	101 [65.9, 170]	107 [34.7, 238]	108 [44.8, 260]	107 [34.7, 260]	103 [36.9, 261]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)	2 (1.0%)

Baseline Characteristics	Non-NASH Patients (N=299)	NASH Patients				
		F0 (N=33)	F1-F2 (N=1078)	F3 (N=426)	Overall F0, F1-F2, F3 (N=1537)	F4 (N=198)
Hepatic Function						
Normal	264 (88.3%)	33 (100%)	1078 (100%)	426 (100%)	1537 (100%)	0 (0%)
Mild Hepatic Impairment	10 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	198 (100%)*
Moderate Hepatic Impairment	10 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Severe Hepatic Impairment	15 (5.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal Function						
Normal	213 (71.2%)	23 (69.7%)	780 (72.4%)	305 (71.6%)	1108 (72.1%)	136 (68.7%)
Mild Renal Impairment	86 (28.8%)	10 (30.3%)	268 (24.9%)	112 (26.3%)	390 (25.4%)	51 (25.8%)
Moderate Renal Impairment	0 (0%)	0 (0%)	30 (2.8%)	8 (1.9%)	38 (2.5%)	9 (4.5%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)	2 (1.0%)
Sex						
Female	91 (30.4%)	20 (60.6%)	619 (57.4%)	233 (54.7%)	872 (56.7%)	130 (65.7%)
Male	208 (69.6%)	13 (39.4%)	459 (42.6%)	193 (45.3%)	665 (43.3%)	68 (34.3%)
Race						
White	227 (75.9%)	26 (78.8%)	966 (89.6%)	379 (89.0%)	1371 (89.2%)	183 (92.4%)
Black or African American	54 (18.1%)	5 (15.2%)	51 (4.7%)	6 (1.4%)	62 (4.0%)	5 (2.5%)
Asian	11 (3.7%)	1 (3.0%)	22 (2.0%)	15 (3.5%)	38 (2.5%)	7 (3.5%)
Other	7 (2.3%)	1 (3.0%)	39 (3.6%)	26 (6.1%)	66 (4.3%)	3 (1.5%)
Dose Level (First Dose)						
0.25 mg	6 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1 mg	6 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2.5 mg	6 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5 mg	12 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
10 mg	6 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
20 mg	12 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
40 mg	7 (2.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
50 mg	12 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
60 mg	9 (3.0%)	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)	3 (1.5%)
80 mg	38 (12.7%)	15 (45.5%)	494 (45.8%)	224 (52.6%)	733 (47.7%)	171 (86.4%)
100 mg	113 (37.8%)	18 (54.5%)	583 (54.1%)	202 (47.4%)	803 (52.2%)	24 (12.1%)
200 mg	72 (24.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clopidogrel Intake						
No	279 (93.3%)	31 (93.9%)	1066 (98.9%)	418 (98.1%)	1515 (98.6%)	196 (99.0%)
Yes	20 (6.7%)	2 (6.1%)	12 (1.1%)	8 (1.9%)	22 (1.4%)	2 (1.0%)
Statin Intake						
No	236 (78.9%)	21 (63.6%)	621 (57.6%)	214 (50.2%)	856 (55.7%)	109 (55.1%)
Yes	63 (21.1%)	12 (36.4%)	457 (42.4%)	212 (49.8%)	681 (44.3%)	89 (44.9%)
Bile Acid Sequestrants Intake						
No	299 (100%)	32 (97.0%)	998 (92.6%)	403 (94.6%)	1433 (93.2%)	168 (84.8%)
Yes	0 (0%)	0 (0%)	10 (0.9%)	3 (0.7%)	13 (0.8%)	3 (1.5%)
Missing	0 (0%)	1 (3.0%)	70 (6.5%)	20 (4.7%)	91 (5.9%)	27 (13.6%)

Source: Tables 1 and 2 from "Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-PK
Note: Statins included rosuvastatin, simvastatin, atorvastatin or pravastatin.
Note: bile acid sequestrants included cholestyramine, colesevelam, and colestipol.
*NASH subjects with fibrosis stage F4 in Trials MGL-3196-11 and MGL-3196-14 presented with either mild or moderate hepatic impairment (based on Child-Pugh score)
Note: Mild hepatic impairment=Child-Pugh A; moderate hepatic impairment=Child-Pugh B; severe hepatic impairment=Child-Pugh C; normal renal function (eGFR=60 to 89 mL/min); moderate renal impairment (eGFR=30 to 59 mL/min).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; BSA, body surface area; CV, coefficient of variation; eGFR, estimated glomerular filtration rate derived with the MDRD-4 equation; CV, coefficient of variation, F0, 1, 2, 3, fibrosis stages 0, 1, 2, 3; max, maximum, min, minimum, MGL-3196, resmetirom;N, number of subjects in treatment arm; n, number of subjects in subset; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic

Base Model

The final base model was a two-compartment PK model with lag time. The absorption of resmetirom was described by a mixed order absorption model, which consisted of a zero-order

input into a deport compartment followed by a first-order absorption into the central compartment (Figure 47). The base model was developed using phase 1 and 2 clinical studies with rich sampling data.

The potential time-and dose-dependency of resmetirom was evaluated as part of the base PK model development. For multiple dosing, the effect of time on the apparent clearance (CL/F) was evaluated using a saturable model as described in Equation 1.

Equation 1. Saturable Model

$$Parameter_i = Parameter_{Typical} \times \left[1 - Emax \times \left(\frac{Number\ of\ Dose^{Gamma}}{ET_{50}{}^{Gamma} + Number\ of\ Dose^{Gamma}}\right)\right]$$

Source: "Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-PK. Page 21/331
Note: Where E_{max}=the maximum effect of time on CL/F, number of Dose=number of dose administered after the first dose, ET_{50}=the number of doses associated with 50% of the maximum effect, gamma=sigmoidal factor.

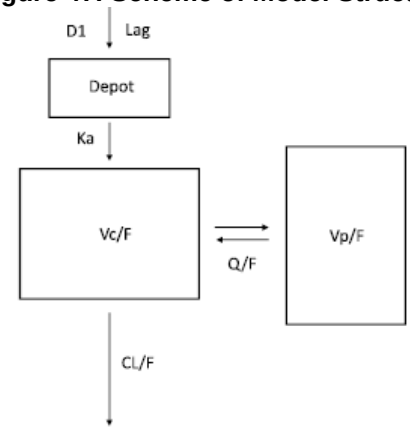
The effect of dose on CL/F was evaluated using a power model as presented in Equation 2.

Equation 2. Power Model

$$Parameter_i = Parameter_{Typical} \times \left(\frac{Dose_i}{80\ mg}\right)^{THETA}$$

Source: "Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-PK. Page 21/331
Note: Where THETA is the exponent for the dose proportionality assessment (i.e., a positive parameter with a 95% CI excluding 0 would suggest that the CL/F increases with dose, while a negative THETA with a 95% CI excluding 0 would suggest that the CL/F decreases with dose). The power model was centered on the most current dose administered across studies (i.e., 80 mg).

Figure 47. Scheme of Model Structure



Source: Figure 5 from "Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-PK.
Abbreviations: ka, first-order rate constant of absorption; D1, duration of zero-order absorption; Tlag, lag time of absorption; CL/F, apparent clearance; Q/F, apparent intercompartmental clearance; Vc/F, apparent central volume of distribution; Vp/F, apparent peripheral volume of distribution

Covariate Analysis

The impact of covariates was explored by plotting the relationship between random effect of PK parameters (ETA) and covariates of interests. These plots included smoothing function (locally estimated scatterplot smoothing), Pearson coefficients of correlation, and the corresponding

Pearson correlation p-value for each relationship. Box plots were used to describe the relationship for categorical covariates. The intrinsic factors include BW, sex, and BMI in NASH subjects after taking into account BW, age, race, subject populations (NASH stage: F0, F1to F2, F3; non-NASH: normal, mild, moderate and severe HI), renal function (eGFR), and renal impairment (normal, mild, moderate, and severe not on dialysis). The extrinsic factors include DDI on CL/F of resmetirom, statin (rosuvastatin, simvastatin, atorvastatin, or pravastatin), clopidogrel, and bile acid sequestrants at baseline.

The effect of a subset of intrinsic (i.e., fibrosis stage in NASH subjects and effect of HI in non-NASH subjects) and extrinsic (concomitant medications of statins, clopidogrel, and bile acid sequestrants) covariates was evaluated using a univariate approach. Statistically significant covariates using the above univariate approach were included in the model using a full model approach whereby all covariates were tested simultaneously. A covariate with a 95% CI including the null hypothesis (i.e., 0) was excluded from the final model.

Based on the results, the model was simplified by removing the effect of concomitant administration of bile acid sequestrants. The concomitant administration impacts of statin and clopidogrel were retained in the final model. Although statin was retained in the PopPK model, its impact to CL/F in NASH subjects were minor (geometric mean 0.150 versus 0.161 L/h/kg for with and without statin). The estimate in PopPK model is also small. (-0.0207). Other covariates such as HI in non-NASH subjects (mild, moderate and severe) and fibrosis stage F0, F3, and F4 were retained in the model to potentially tease out effects relative to NASH subjects with fibrosis stage F1 to F2. BW was identified as the most important covariate describing the variability in CL/F and Vc/F of resmetirom. Weight-adjusted CL/F and Vc/F were derived to evaluate potential residual effects of other intrinsic factors; no residual effects of age, sex, BMI, or race were observed after taking into account difference in BW.

14.5.1.4. Final Model

The final PopPK analysis was performed by using all 13 clinical study data as shown in Table 232. Absorption parameters and peripheral compartments were fixed based on values obtained from the rich sample analysis (phase 1 and 2 studies) during base PopPK model development, and population estimates were used to model the concentration-time profiles of resmetirom in phase 3 studies with sparse samples. The absorption of resmetirom was described with a duration of absorption (D1) of 3.99 h, a Ka of 0.840 h^{-1}, and an absorption lag time of 0.240 h. Only CL/F and Vc/F parameters as well as covariate effects were estimated based on the whole pooled dataset including phase 3 studies (Trials MGL-3196-11 and MGL-3196-14).

The parameter estimates for the final PopPK models are listed in Table 234.

Table 234. Population Parameter Estimates of Final PopPK Model for Resmetirom

Parameters	Estimates	%RSE	95%CI	Shrinkage (%)
Ka (1/h)	0.840 (fixed)	--	--	--
D1 (h)	3.99 (fixed)	--	--	--
Tlag (h)	0.240 (fixed)	--	--	--
F_{ToT} (fraction)	1.00 (fixed)	--	--	--
CL/F (L/h)	30.6	2.35	29.2, 32.0	--
Q/F (L/h)	4.62 (fixed)	--	--	--

Parameters	Estimates	%RSE	95%CI	Shrinkage (%)
Vc/F (L)	42.1	4.41	38.5, 45.7	--
Vp/F (L)	20.0 (fixed)	--	--	--
Time effect – Imax on CL/F (fraction)	0.485 (fixed)	--	--	--
Time effect -$Dose_{50}$ on CL/F	1.76 (fixed)	--	--	--
Time effect -Hill on CL/F	1.42 (fixed)	--	--	--
Dose effect on CL/F	-0.0710	43.7	-0.132, -0.0102	--
Weight on CL/Q	1.39	4.95	1.25, 1.52	--
Weight on Vc/Vp	1.38	5.71	1.22, 1.53	--
Study 005 on CL	0.351	36.8	0.0983, 0.605	--
Fibrosis stage 3 on CL/F	-0.0213	161	-0.0884, 0.0458	--
Fibrosis stage 4 on CL/F	-0.295	14.6	-0.380, -0.211	--
Non-NASH with normal hepatic function or Mild HI on CL/F	0.452	12.9	0.337, 0.566	--
Non-NASH moderate HI on CL/F	-0.174	130	-0.617, 0.269	--
Non-NASH severe HI on CL/F	-1.00	15.5	-1.31, -0.698	--
Statin on CL/F	-0.0207	103	-0.0625, 0.0210	--
Clopidogrel on CL/F	-0.683	5.29	-0.754, -0.612	--
IIV (%BSV)				
On Ka	7.72 (fixed)	--	--	93.4%
On D1	31.2 (fixed)	--	--	63.1%
On CL/F	55.3	1.92	53.3, 57.4	17.0%
On Vc/F	121	3.98	112, 131	36.7%
Residual Error				
Log additive error	1.01	0.290	1.00, 1.01	NA
Log Additive Error for Trials VIA-3196-01 and VIA 3196-02	0.721 fixed	NA	NA	NA

Source: Table 3, “Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH),” Report No. MADR-PMX mgL3196-2382-PK

Note: Population PK parameters are for a typical NASH patient with a body weight of 98 kg, fibrosis 0, 1, or 2 who received an 80 mg dose who did not receive statin or clopidogrel.

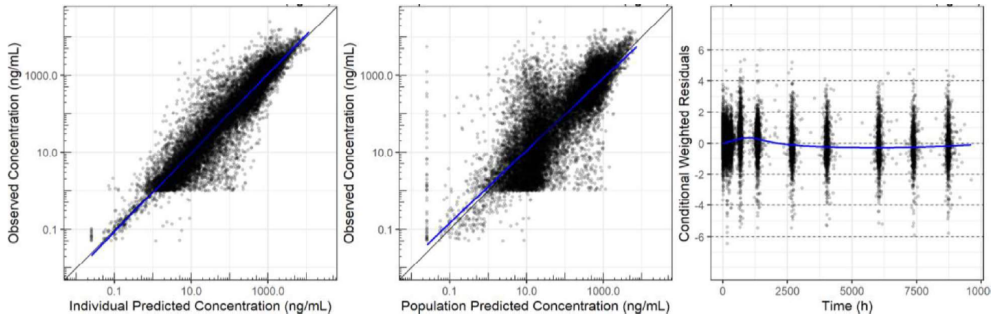
Note: BSV (RSE) and shrinkage could not be estimated for absorption (Ka, D1, Tlag, FTOT) and peripheral parameters (Q/F and Vp/F) due to sparse data available in phase 3 studies.

Abbreviations: Ka, first-order rate constant of absorption; D1, duration of zero-order absorption; Tlag, lag time of absorption; FTOT, total relative bioavailability; Imax, maximum effect of multiple doses on CL; Dose50, number of dose associated with 50% of maximum effect on CL; CL/F, apparent clearance; Q/F, apparent intercompartmental clearance; Vc/F, apparent central volume; Vp/F, apparent peripheral volume; NA, not applicable

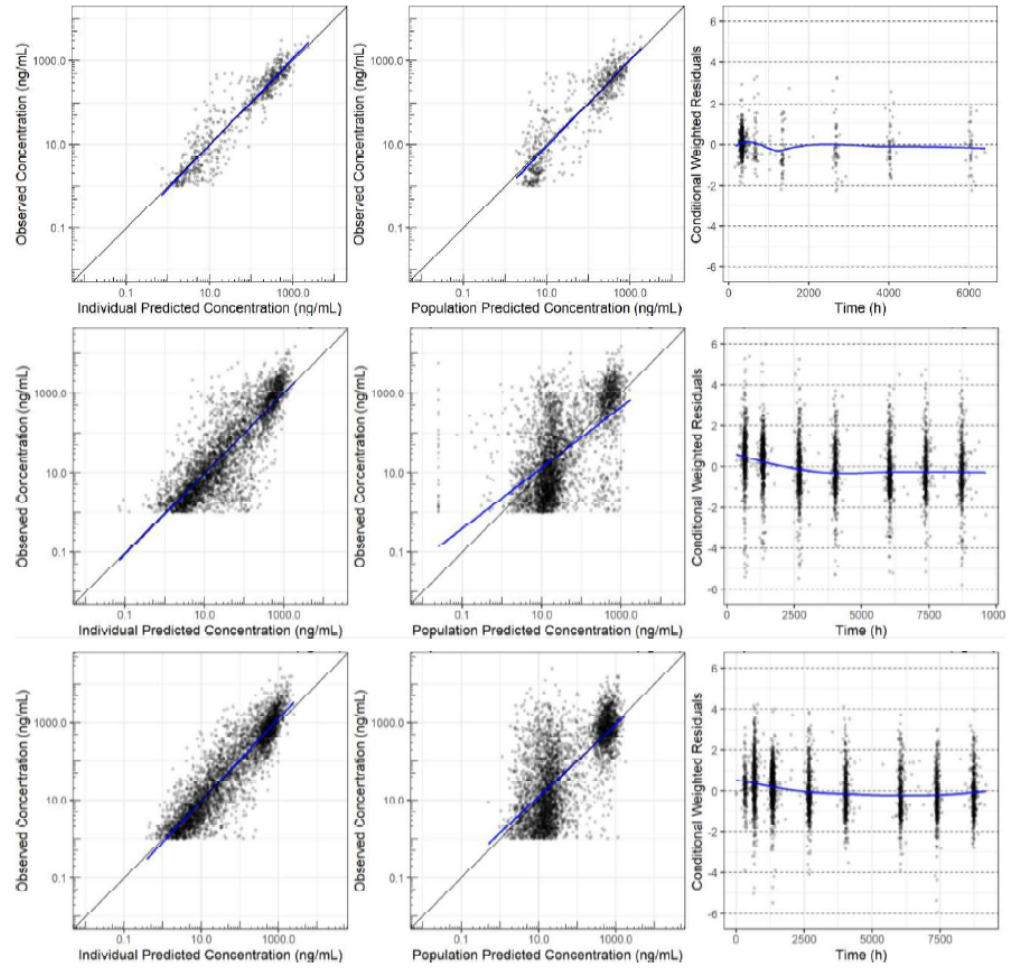
The goodness-of-fit plots for the final PopPK model are shown in Figure 48. The prediction-corrected visual predictive check (pcVPC) plot for the final PopPK model is shown in Figure 49. The reviewer deems that the final model overall provides a good description of the resmetirom phase 2 and 3 study PK data.

Figure 48. Goodness-of Fit Plots for the Final PopPK Model

All Studies



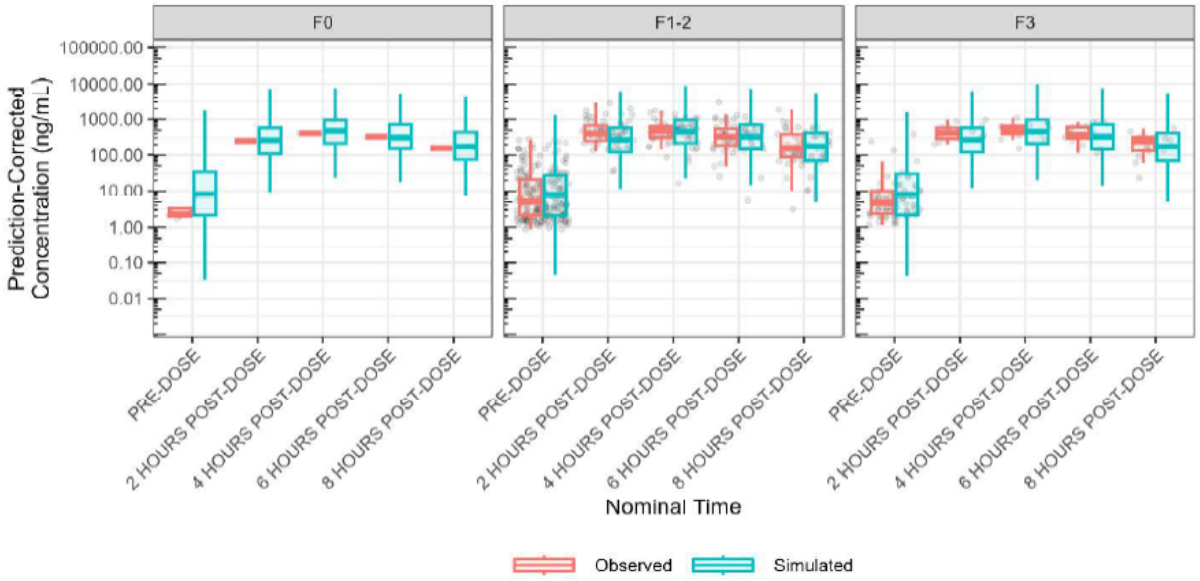
MGL-3196-05 (Top Panels), MGL-3196-11 (Middle Panels), and MGL-3196-14 (Bottom Panels)



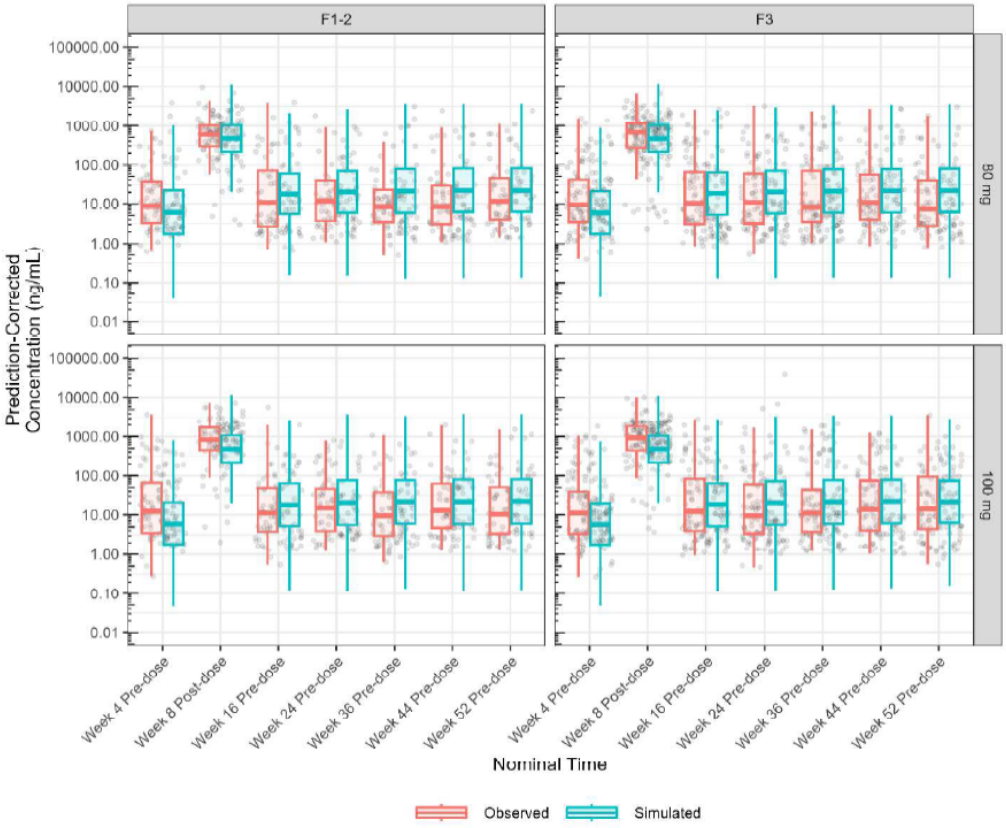
Source: Figure 6 and 7 from Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-PK.
Abbreviations: MGL-3196, resmetirom; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic; PopPK, population PK

Figure 49. pcVPCs for the Final PK Model

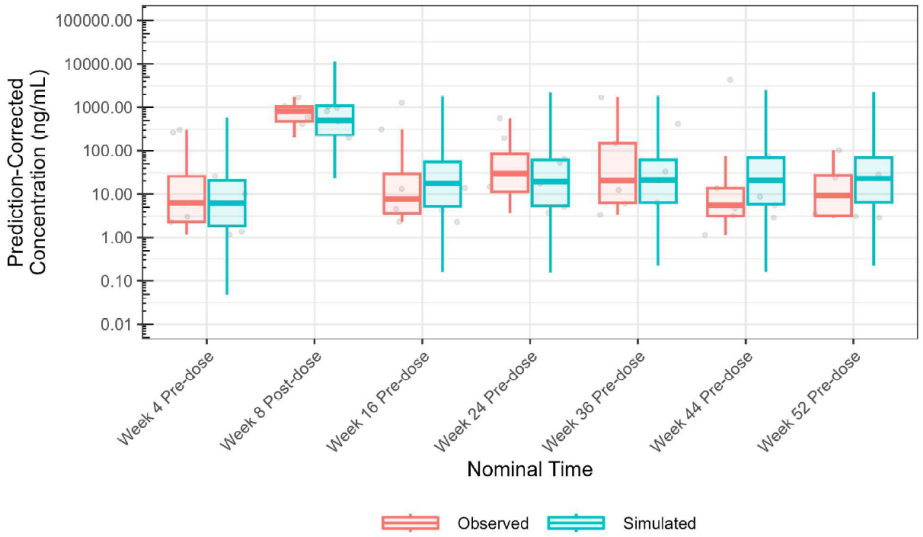
Trial MGL-3196-05 (Phase 2)



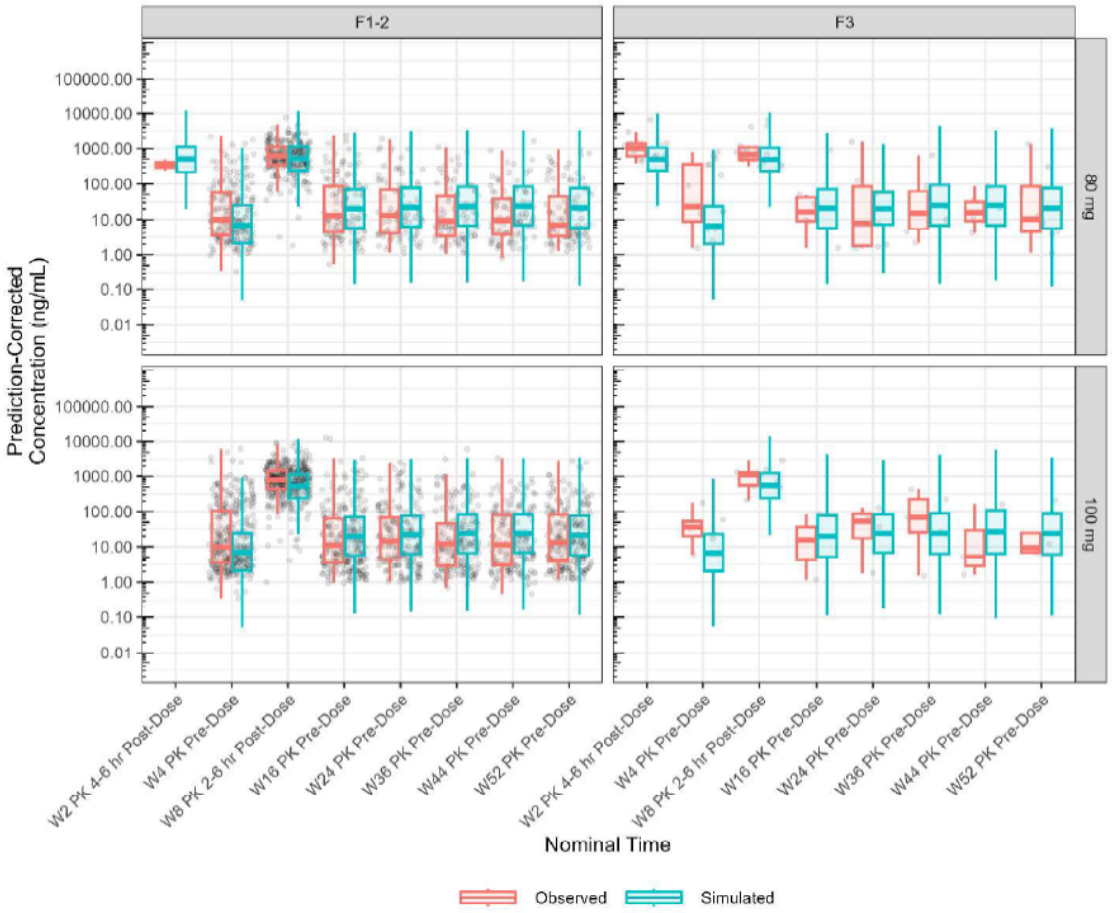
Trial MGL-3196-11 in Patients With NASH With Fibrosis (Phase 3)



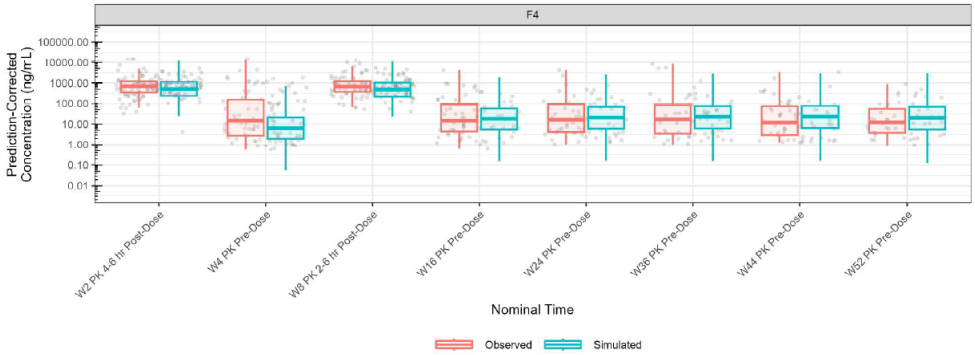
Fibrosis Stage F4



Trial MGL-3196-14 in NAFLD Patients at increased risk of NASH based on noninvasive testing (Phase 3)



Fibrosis Stage F4



Source: Figure 8 from "Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-PK
Abbreviations: F1, 2, 3, 4, fibrosis stage 1, 2, 3, 4; MGL-3196, resmetirom; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; pcVPC, prediction-corrected visual predictive check (VPC); PK, pharmacokinetic; W, week

The Applicant also developed a final PopPK model for resmetirom active metabolite MGL-3623. MGL-3623 is approximately 28-fold less active for THR-β than resmetirom. The final PopPK model of MGL-3623 is shown in Table 235.

Table 235. Population Parameter Estimates of Final PopPK Model for Metabolite MGL-3623

Parameter	Estimate	RSE%	95% CI	Shrinkage
Typical Values - Absorption				
Kf (1/h)	1.20 Fixed	NA	NA	NA
D1/Fm (h)	3.32 Fixed	NA	NA	NA
Tlag (h)	0.379 Fixed	NA	NA	NA
Fror (Fraction)	1.00 Fixed	NA	NA	NA
Typical Values - Disposition				
CL/Fm (L/h)	62.5	1.74	60.4 , 64.7	NA
Q /Fm (L/h)	6.35 Fixed	NA	NA	NA
Vc/Fm (L)	298	2.48	284 , 313	NA
Vp/Fm (L)	52.2 Fixed	NA	NA	NA
Typical Values – Time and Dose Effects				
Time Effect - I_{max} on CL/F (fraction)	0.165 Fixed	NA	NA	NA
Time Effect - $Dose_{50}$ on CL/F (unitless)	2.29 Fixed	NA	NA	NA
Time Effect - Hill on CL/F (unitless)	0.544 Fixed	NA	NA	NA
Dose Effect on CL/F	-0.0959	53.0	-0.196 , 0.00379	NA
Covariate Effects				
Weight on CL/Q	0.960	5.71	0.852 , 1.07	NA
Weight on Vc/Vp	1.11	6.76	0.960 , 1.25	NA
Study 005 on CL/Fm	0.154	50.9	0.000393 , 0.307	
Fibrosis Stage 3 on CL/Fm	-0.0848	28.1	-0.132 , -0.0382	NA
Fibrosis Stage 4 on CL/Fm	-0.132	25.2	-0.197 , -0.0665	NA
Non-NASH with normal hepatic function or Mild HI on CL/Fm	0.245	18.3	0.157 , 0.333	NA
Non-NASH moderate HI on CL/Fm	-0.179	93.5	-0.506 , 0.149	
Non-NASH severe HI on CL/Fm	-0.781	15.8	-1.02 , -0.539	NA
Statin on CL/Fm	-0.00649	262	-0.0398 , 0.0268	NA
Clopidogrel on CL/Fm	-0.169	21.9	-0.242 , -0.0964	NA
Between Subject Variability				
On Kf	55.2 Fixed	NA	NA	69.8%
On D1	22.6 Fixed	NA	NA	74.4%
On CL/Fm	35.8	2.51	34.0 , 37.6	26.5%
On Vc/Fm	48.3	2.45	46.0 , 50.7	27.7%
Residual Error				
Log Additive Error	0.891	0.191	0.888 , 0.895	NA
Log Additive Error for Study VIA-3196-01 and VIA-3196-02	0.552 Fixed	NA	NA	NA

Source: Table 27 from "Population Pharmacokinetics Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-PK

Note: Population PK parameters for the metabolite are for a typical NASH patient with a body weight of 98 kg, a fibrosis stage F0, F1, or F2 who received an 80 mg dose who did not receive statin or clopidogrel.

Note: BSV (RSE) and shrinkage could not be estimated for absorption (Kf, D1/Fm, Tlag, FmTOT) and peripheral parameters (Q/Fm and Vp/Fm) due to sparse data available in phase 3 studies.

Abbreviations: Kf, first-order rate constant of metabolite formation; D1/Fm, duration of zero-order metabolite formation D1; Tlag, lag time of metabolite formation; FmTOT, fraction metabolized; Imax, maximum effect of multiple doses on CL/Fm; Dose50, number of dose associated with 50% of maximum effect on CL/Fm; CL/Fm, apparent metabolite formation clearance; Q/Fm, apparent metabolite intercompartmental clearance; Vc/Fm, apparent central volume of metabolite; Vp/F, apparent peripheral volume of metabolite

(b) (4)

An IR was sent to Applicant on November 3, 2023, to ask for study of different BW cutoffs for PK of resmetirom. In the Applicant's IR response dated 11/15/2023,[5] the Applicant provided descriptive statistics of exposure parameters of resmetirom for the 80 mg and 100 mg dose by 10 kg BW increments up to 110 kg and ≥ 110 kg as shown in Table 236.

[5] DARRTS, NDA 217785, 0036, 11/15/2023, Clinical Pharmacology/Response to Information Request

Table 236. Descriptive Statistics of Exposure Parameters of Resmetirom for the 80 and 100 mg Dose by 10 kg Body Weight Increments up to 110 kg and >110 kg

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	8180	5750	5030	4400	3550	9610	7550	7600	6250	3900
[Q05;Q95]	[3950;18200]	[3400;13400]	[2530;10900]	[2860;7440]	[1840;6230]	[2440;25600]	[5000;23300]	[4050;20500]	[3590;14900]	[2330;9890]
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	1140	870	795	644	504	1370	1200	1060	966	647
[Q05;Q95]	[664;1890]	[428;1270]	[358;1140]	[381;951]	[255;821]	[288;2010]	[689;1780]	[437;1420]	[499;1370]	[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	341	240	210	183	148	400	315	316	261	163
[Q05;Q95]	[165;759]	[142;560]	[105;455]	[119;310]	[76.5;259]	[102;1070]	[208;970]	[169;856]	[150;622]	[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	25.5	18.4	12.0	14.1	9.77	29.7	22.2	51.0	22.1	12.8
[Q05;Q95]	[4.23;336]	[3.36;277]	[3.13;270]	[2.93;104]	[1.91;107]	[4.32;686]	[5.57;502]	[4.23;604]	[4.06;291]	[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
$t_{1/2\alpha}$ (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	1.15	1.24	1.02	1.12	1.11	1.44	1.08	1.37	1.34	1.30
[Q05;Q95]	[0.610;2.24]	[0.599;2.41]	[0.607;2.48]	[0.567;2.56]	[0.575;2.51]	[0.570;2.49]	[0.601;2.55]	[0.655;2.72]	[0.517;2.35]	[0.655;2.73]
Geometric Mean	1.13	1.21	1.10	1.12	1.16	1.26	1.16	1.39	1.14	1.24
$t_{1/2\beta}$ (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	4.53	4.41	4.29	4.50	4.45	4.41	4.43	5.29	4.65	4.50
[Q05;Q95]	[3.68;11.1]	[3.68;13.4]	[3.69;14.2]	[3.73;15.8]	[3.63;10.0]	[3.52;15.8]	[3.78;15.1]	[3.75;27.3]	[3.77;11.6]	[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

Source: Table 1 from Response to FDA request for information. dated 11/3/2023
Abbreviations: $AUC_{tau,ss}$, area under the curve over the dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{ave,ss}$. Average concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; $T_{1/2\alpha}$, distribution half-life; $T_{1/2\beta}$, elimination half-life; CV, coefficient of variation; Q05, 5th quantile; Q95, 95th quantile

The Applicant also provided evaluation of baseline weight on key efficacy outcomes with resmetirom 80 mg and 100 mg, as shown in Table 237. Similar to the overall shallow dose-response and E-R relationship between 80 mg and 100 mg, there were no remarkable differences in response rates between 80 mg and 100 mg in each body-weight band and across weight bands. Nevertheless, the response rates in subjects ≥110 kg tended to be lower with 80 mg than with 100 mg. The response rate of consensus fibrosis improvement or NASH resolution was 17.2% and 17.2% in the 80 mg group, respectively, and 25% and 27.8% in the 100 mg group, respectively.

Table 237. Evaluation of Baseline Weight on Key Efficacy Outcomes With Resmetirom 80 mg and 100 mg

Assessment	Resmetirom 80 mg					Resmetirom 100 mg				
	<80 kg	80 - <90 kg	90 - <100 kg	100 - <110 kg	≥110 kg	<80 kg	80 - <90 kg	90 - <100 kg	100 - <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)

Source: Table 2 from Response to FDA request for information, dated 11/3/2023
Note: For NASH resolution and fibrosis responder status, subjects with composite clinical endpoints, missing responses, and week 52 biopsies out-of-window are considered nonresponders
Abbreviations: MITT, modified intent-to-treat; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; SHBG, sex hormone binding globulin

14.5.2. E-R Analysis

14.5.2.1. Review Summary

The Applicant conducted E-R analysis to evaluate the relationships between the exposure of resmetirom and PD, imaging biomarkers, as well as efficacy and safety/tolerability endpoints to support dosing of resmetirom in NASH patients. The two phase 3 studies # MGL-3196-11 (N=1050) and MGL-3196-14 (N=1340) are included in the analysis. The evaluated endpoints are listed below.

PD Biomarkers

- SHBG at Week 52
- FT4 at Week 52
- Low-density lipoprotein cholesterol (LDL-C) at Week 52
- Apolipoprotein B (ApoB) at Week 52

Imaging Biomarkers

- Hepatic fat fraction variable based on MRI-PDFF at Week 52
- ≥30% reduction in MRI-PDFF at Week 52
- ≥50% reduction in MRI-PDFF at Week 52

Efficacy Endpoints

- NASH resolution or fibrosis response at Week 52

Safety/Tolerability Endpoints

- Diarrhea (yes/no, first instance, grade>1)
- Nausea (yes/no, first instance, grade>1)
- Any gastrointestinal (GI) events (yes/no, first instance, grade>1)

Overall, the Applicant's E-R analysis is considered acceptable for the purpose of characterizing the E-R relationships of resmetirom and its PD, imaging biomarker, efficacy and safety endpoints.

Table 238. Specific Comments on Applicant's E-R Analysis

Utility of the Final Model		FDA's Comments
(b) (4)	Administration of REZDIFFRA increases sex hormone binding globulin (SHBG) and decreases the prohormone free thyroxine (FT4), LDL-C, apolipoprotein B, triglycerides, and total cholesterol and decreases liver fat content as measured by magnetic resonance imaging protein density fat fraction (MRI-PDFF) or controlled attenuation parameter (CAP).	(b) (4)

Source: Generated by the FDA review team
Abbreviations: CAP, controlled attenuation parameter; E-R, exposure-response; FT4, free thyroxine; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; SHBG, sex hormone binding globulin

14.5.2.2. E-R Analysis for PD Biomarkers

14.5.2.2.1. SHBG at Week 52

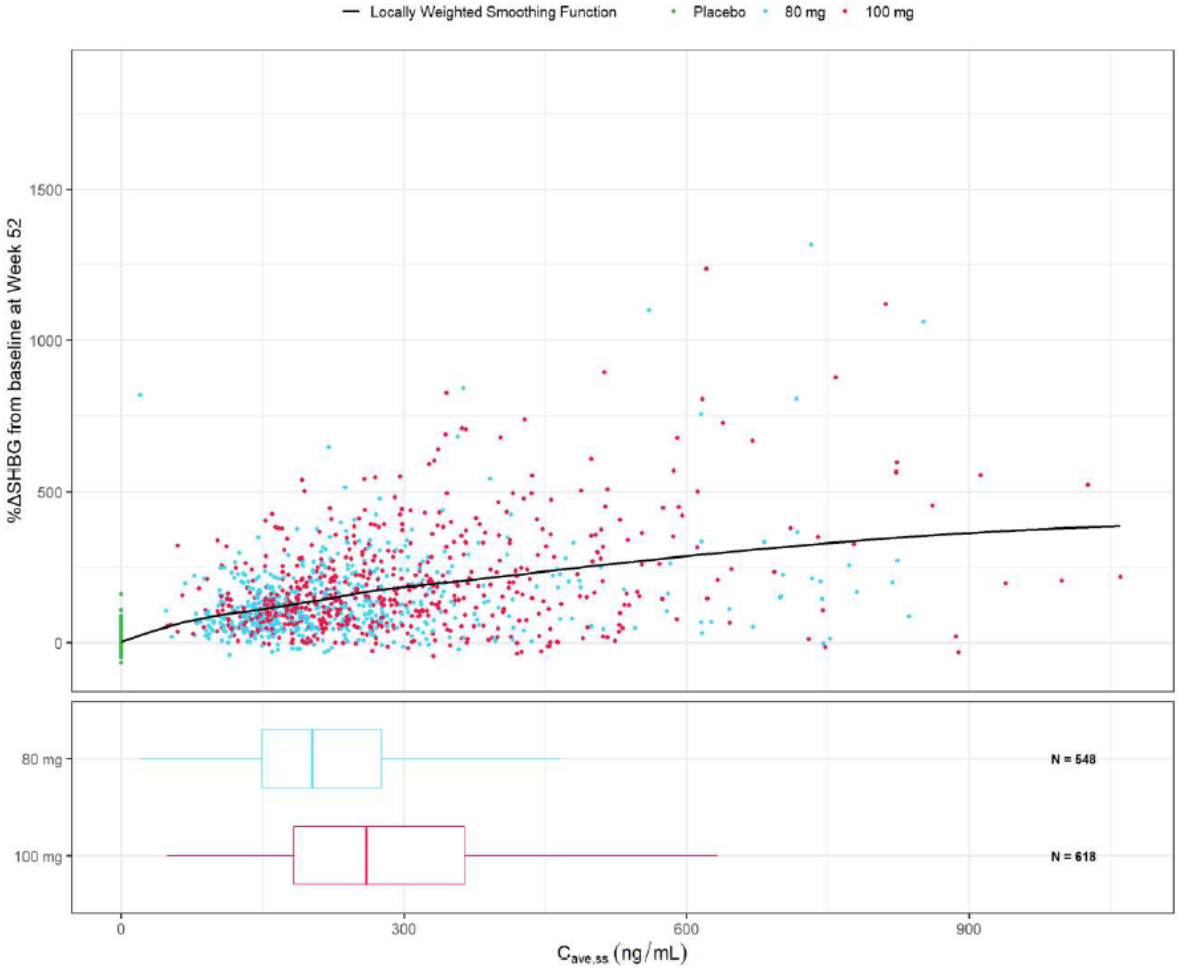
The Applicant developed a logistic regression model to assess the potential relationship between resmetirom exposure and ΔSHBG (%) at Week 52. The E-R relationship between resmetirom $C_{ave,ss}$ and the percent change from baseline SHBG (% SHBG) at Week 52 is shown in Figure 50. SHBG binds sex hormones such as testosterone, and estrogen. Thyroid hormones increase SHBG production. Higher exposure to resmetirom, a THR agonist is associated with a higher level of SHBG. A maximum effect (E_{max}) model was used to fit the E-R of ΔSHBG (%) at Week 52 (see Equation 3) and the final model estimates are presented in Table 239.

Equation 3. E_{max} Model for Exposure-Response of SHBG

$$\mathrm{SHBG}_{Week52} = E_0 \times \left[1 + E_{max} \times \left(\frac{{C_{ave,ss}}^{\gamma}}{EC_{50}^{\gamma} + {C_{ave,ss}}^{\gamma}}\right)\right]$$

Source: Section 7.3 "Exposure Response Analysis" from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: Where E_{max}=the maximum effect of resmetirom on ΔSHBG% week 52.
Abbreviations: $C_{ave,ss}$, average concentration at steady state; E_0, baseline response; EC_{50}, half maximal effective concentration; E_{max}, maximal effect; NASH, nonalcoholic steatohepatitis SHBG, sex hormone binding globulin

Figure 50. Exposure-Response Relationship for %ΔSHBG at Week 52



Source: Figure 2 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: Top 1%: 12 concentration points between 1064.09 and 1748.41 are not presented.
Abbreviations: $C_{ave,ss}$, average concentration at steady state; NASH, nonalcoholic steatohepatitis; SHBG, sex hormone binding globulin

Table 239. Exposure-Response E_{max} Model Parameters for %ΔSHBG at Week 52

Parameter	Estimate	RSE%	95% CI
Typical Values			
E_{max} (fraction)	2.22	16.9	1.49 – 2.96
EC_{50} (ng/mL)	277	27.3	129 – 426
Hill Coefficient (unitless)	1.00 Fixed	n/a	n/a
Between Subject Variability			
On E_{max}	70.8	5.85	62.9 – 79.2
Residual Error			
Proportional Error (%)	25.2	4.43	23.0 – 27.4
Covariate Effects			
Fibrosis Stage F0 (unitless)	-0.0431	555	-0.512 – 0.425
Fibrosis Stage F3 (unitless)	0.00153	3347	-0.0987 – 0.102
Fibrosis Stage F4 (unitless)	-0.177	55.4	-0.369 – 0.0153
Sex (female) on E_{max}	0.320	15.2	0.225 – 0.416
Race (Asian) on E_{max}	0.490	39.4	0.112 – 0.868

Source: Table 2 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER

Note: The reference subjects is a white male NASH patient, <65 years with fibrosis stage F1 to F2 with a former or current history of alcohol intake.

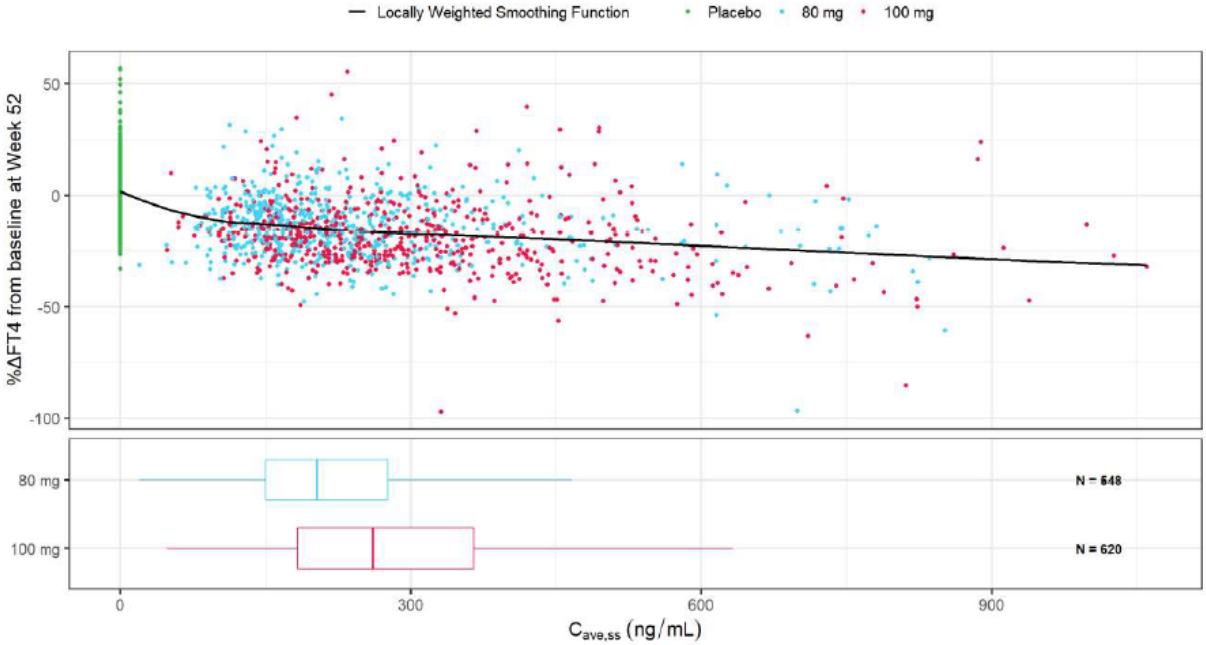
Abbreviations: E_{max}, maximum effect; EC_{50}, effective $C_{ave,ss}$ associated with 50% of the maximum effect, RSE, relative standard error; CI, confidence interval

Based on the analysis, the E-R relationship for ΔSHBG (%) at Week 52 was characterized by a 2.2-fold E_{max} increase and an EC_{50} of 277 ng/mL. Median exposure associated with 100 mg dose of resmetirom (267 ng.h/mL) were close to EC_{50}. The effect of fibrosis stage F0, F3 and F4 on ΔSHBG are highly variable and not statistically significant. Female patients presented a 37.7% higher (i.e., $exp^{0.320}$) E_{max} relative to male patients. Asian patients presented a 63.2% higher (i.e., $exp^{0.490}$) E_{max} relative to white patients. No effect of BW on E_{max} was identified as part of the covariate analysis.

14.5.2.2.2. Free Thyroxine at Week 52

The Applicant developed a logistic regression model to assess the potential relationship between resmetirom exposure and ΔFT4 (%) at Week 52. The E-R relationship of resmetirom $C_{ave,ss}$ for ΔFT4(%) at Week 52 is shown in Figure 51. The final E_{max} model estimates are presented in Table 240. Higher exposure of resmetirom was associated with a reduction in % FT4.

Figure 51. Exposure-Response Relationship for %ΔFT4 at Week 52



Source: Figure 4 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER.
Abbreviations: $C_{ave,ss}$, average concentration at steady state; FT4, free thyroxine; NASH, nonalcoholic steatohepatitis

Table 240. Exposure-Response E_{max} Model Parameters for %ΔFT4 at Week 52

Parameter	Estimate	RSE%	95% CI
Typical Values			
E_{max} (fraction)	-0.323	13.3	-0.407 – -0.238
EC_{50} (ng/mL)	234	27.7	107 – 361
Hill Coefficient (unitless)	1.00 Fixed	NA	NA
Between Subject Variability			
On E_{max}	33.4	9.37	27.3 – 39.6
Residual Error			
Proportional Error (%)	15.0	3.54	14.0 – 16.0
Covariate Effects			
Fibrosis Stage F0 (unitless)	-0.00995	1764	-0.354 – 0.334
Fibrosis Stage F3 (unitless)	0.0503	111	-0.0593 – 0.160
Fibrosis Stage F4 (unitless)	-0.136	71.9	-0.328 – 0.0558

Source: Table from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MAD3R-PMX mgL3196-2382-ER
Note: The reference subjects is a white male NASH patient <65 years, with fibrosis stage F1 to F2 with a former or current history of alcohol intake.
Abbreviations: E_{max}, maximum effect; EC_{50}, effective $C_{ave,ss}$ associated with 50% of the maximum effect, RSE, relative standard error; CI, confidence interval

Based on the analysis, the E-R relationship for ΔFT4 (%) at Week 52 was characterized by a maximum reduction of 32.3% and an EC_{50} of 234 ng/mL. The 100 mg dose resulted in an exposure close to maximum reduction of FT4 ~30%. The effect of fibrosis stage F0, F3, and F4 on ΔFT4 are highly variable and not statistically significant.

The Applicant also conducted analysis for the probability of ≥30% decrease from baseline in FT4 to <0.7 ng/dL at Weeks 4 and 8. Per study protocol, these qualified patients who have a ≥ 30% decrease from baseline in FT4 to <0.7 ng/dL at Weeks 4 and 8 can decrease their dose by 20 mg from original 100 mg or 80 mg at week 12. The probability of ≥30% decrease from

baseline in FT4 to <0.7 ng/dL at Weeks 4 and 8 as a function of resmetirom $C_{ave,ss}$ was evaluated using a logistic regression model. Parameter estimates derived with the logistic regression are listed in Table 241. A statistically significant E-R relationship was observed, whereby higher $C_{ave,ss}$ values were associated with a higher probability of FT4 decrease to <0.7 ng/dL at Weeks 4 and 8. Based on this result, the Applicant specified a dose reduction by 20 mg in the study protocol based on resmetirom average plasma concentration at steady-state concentrations. The Applicant conducted a receiver operating characteristic analysis to identify a cutoff of $C_{ave,ss}$ of resmetirom associated with maximizing the probability of a ≥30% decrease from baseline in FT4 to <0.7 ng/dL at Weeks 4 and 8, which is 350 ng/mL.

Table 241. Exposure-Response Parameters for the Probability of Baseline in FT4 to <0.7 ng/dL at Weeks 4 and 8

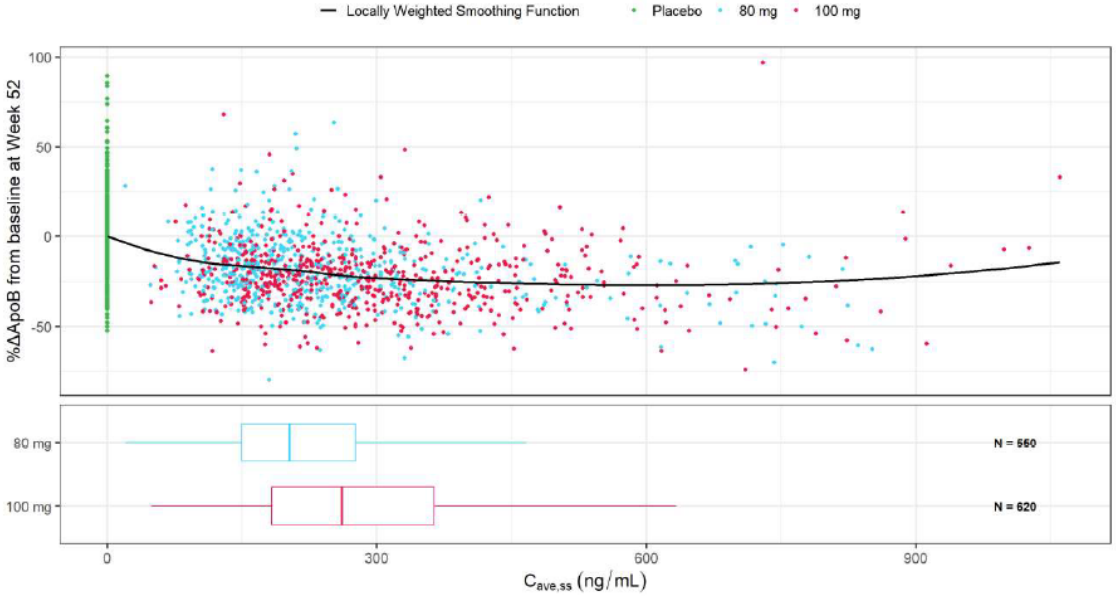
Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-5.93	0.361	(-6.71, -5.28)	<0.001
Slope (for 1 ng/mL increment of $C_{ave,ss}$)	0.00335	0.000468	(0.00246, 0.00431)	<0.001

Source: Table 5 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: CI, confidence interval; $C_{ave,ss}$, average concentration under steady state conditions; SE, standard error

14.5.2.2.3. Apolipoprotein B (ApoB) at Week 52

The Applicant developed a logistic regression model to assess the potential relationship between resmetirom exposure and ΔApoB (%) at Week 52. The E-R relationship of resmetirom $C_{ave,ss}$ for the raw and percent change from baseline ApoB (%ΔApoB) at Week 52 is shown in Figure 52. The final E_{max} model estimates are presented in Table 242.

Figure 52. Exposure-Response Relationship for %ΔApoB at Week 52



Source: Figure 9 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Abbreviations: ApoB, apolipoprotein B; $C_{ave,ss}$, average concentration at steady state; NASH, nonalcoholic steatohepatitis

Table 242. Exposure-Response E_{max} Model Parameters for %ΔApoB at Week 52

Parameter	Estimate	RSE%	95% CI
Typical Values			
E_{max} (fraction)	-0.245	14.1	-0.313 – -0.177
EC_{50} (ng/mL)	101	24.9	51.5 – 150
Hill Coefficient (unitless)	1.18	33.8	0.398 – 1.96
Between Subject Variability			
On E_{max}	20.5	12.3	15.6 – 25.4
Residual Error			
Proportional Error (%)	20.9	2.48	19.9 – 22.0
Covariate Effects			
Fibrosis Stage F0 (unitless)	-0.787	102	-2.37 – 0.790
Fibrosis Stage F3 (unitless)	0.220	22.8	0.122 – 0.319
Fibrosis Stage F4 (unitless)	0.0517	288	-0.240 – 0.344
Sex (female) on E_{max}	0.174	32.1	0.0643 – 0.283

Source: Table 6 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: The reference subjects is a white male NASH patient <65 years with fibrosis stage F1-F2 with a former or current history of alcohol intake.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; E_{max}, maximum effect; EC_{50}, effective $C_{ave,ss}$ associated with 50% of the maximum effect, RSE, relative standard error

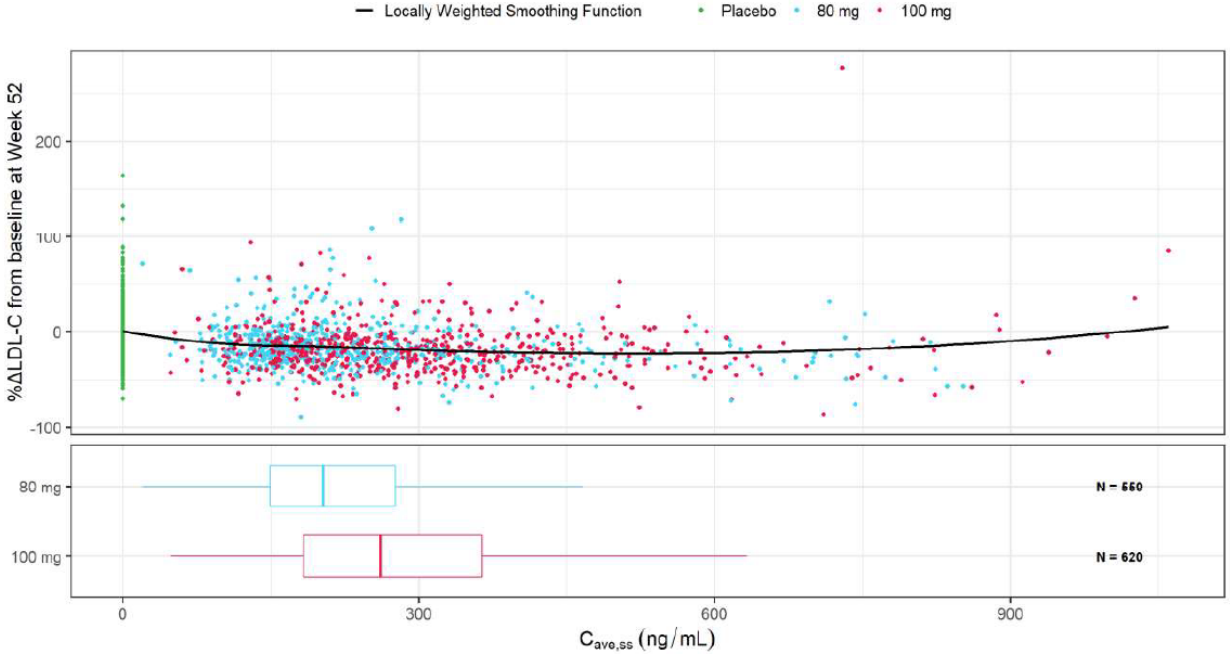
The effect of fibrosis stage F3 was statistically significant with 24.6% higher E_{max} relative to patients with F1-F2 (i.e., $exp^{0.22}$). The effect of fibrosis stage F0 and F4 were not statistically significant which could be due to low subject numbers (N=32 and 103 for F0 and F4, respectively) and high variability.

14.5.2.2.4. LDL-C at Week 52

The Applicant developed a logistic regression model to assess the potential relationship between resmetirom exposure and LDL-C at Week 52. The E-R relationship of resmetirom $C_{ave,ss}$ for the

percent change from baseline LDL-C (%ΔLDL-C) at Week 52 is shown in Figure 53. The final E_{max} model estimates are presented in Table 243.

Figure 53. Exposure-Response Relationship for %ΔLDL-C at Week 52



Source: Figure 11 from "Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-ER.
Abbreviations: $C_{ave,ss}$, average concentration at steady state; LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis

Table 243. Exposure-Response E_{max} Model Parameters for %ΔLDL-C at Week 52

Parameter	Estimate	RSE%	95% CI
Typical Values			
E_{max} (fraction)	-0.172	11.1	-0.210, -0.135
EC_{50} (ng/mL)	61.6	25.9	30.4, 92.8
Hill Coefficient (unitless)	1.59	42.3	0.272, 2.91
Between Subject Variability			
On E_{max}	6.84	52.6	0.194 – 13.9
Residual Error			
Proportional Error (%)	26.8	4.37	24.5 – 29.1
Covariate Effects			
Fibrosis Stage F0 (unitless)	-0.403	105	-1.23 – 0.427
Fibrosis Stage F3 (unitless)	0.286	18.5	0.182 – 0.390
Fibrosis Stage F4 (unitless)	0.389	33.6	0.133 – 0.645
Statin Intake on E_{max}	1.08	8.98	0.887 – 1.27
Elderly (age >65) on E_{max}	0.273	19.9	0.167 – 0.379

Source: Table 7 from "Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-ER.
Note: The reference subjects is a white male NASH patient <65 years with fibrosis stage F1-F2 with a former or current history of alcohol intake.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; E_{max}, maximum effect; EC_{50}, effective $C_{ave,ss}$ associated with 50% of the maximum effect, RSE, relative standard error

The data show that the 80 and 100 mg dose levels result in a similar reduction of LDL-C at week 52 (near maximal reduction). The effect of fibrosis stage F3 and F4 were statistically significant, with 33.0%, and 47.6% higher E_{max} relative to subjects with F1 to F2 (i.e., $exp^{0.286}$ and $exp^{0.389}$),

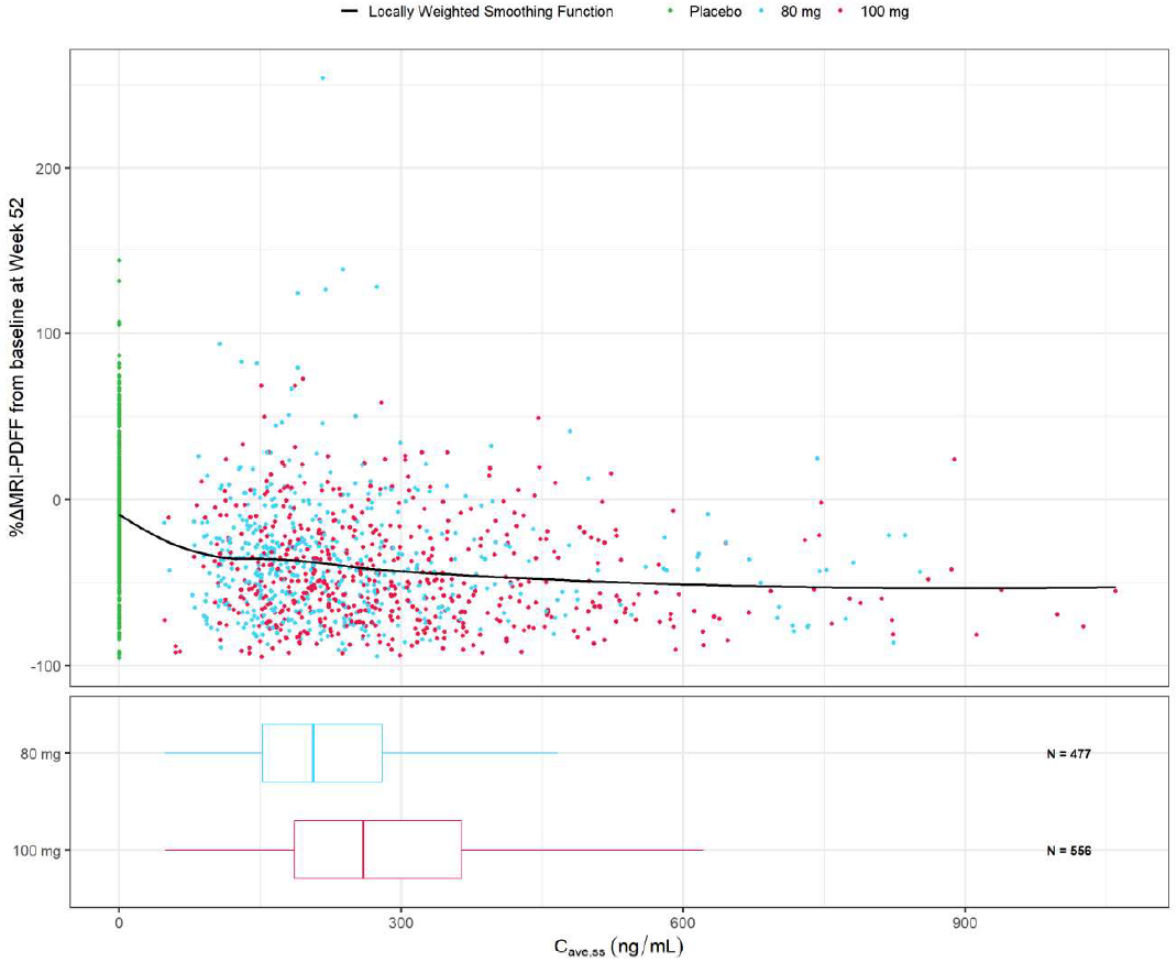
respectively. The effect of fibrosis stage F0 was not statistically significant, which could be due to low subject numbers (N=32) and high variability. A typical patient on a statin with an LDL of 2.18 mmol/L baseline is expected to have an E_{max} value 20% lower relative to a typical patient with a baseline LDL of 2.69 mmol/L, which is representative of the overall population. Elderly (age >65) subjects presented a 31.4% higher E_{max} relative to non-elderly subjects.

14.5.2.3. E-R Analysis of Imaging Biomarkers

14.5.2.3.1. MRI-PDFF at Week 52

MRI-PDFF at Week 52 is a noninvasive measure of liver fat content and is expressed as a percentage of the liver. The E-R relationship of resmetirom $C_{ave,ss}$ for percentage change from baseline MRI-PDFF (%ΔMRI-PDFF) at Week 52 is shown in Figure 54. The final E_{max} model estimates are presented in Table 244. Higher exposure of resmetirom has a trend to associate with a reduction in MRI-PDFF. However, the data variability is high.

Figure 54. Exposure-Response Relationship for %ΔMRI-PDFF at Week 52



Source: Figure 13 from "Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-ER.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; MRI-PDFF, magnetic resonance imaging-proton density fat fraction

Table 244. Exposure-Response E_{max} Model Parameters of % MRI-PDFF at Week 52

Parameter	Estimate	RSE%	95% CI
Typical Values			
E_{max} (fraction)	-0.589	8.62	-0.688 , -0.489
EC_{50} (ng/mL)	81.3	36.6	23.0 – 140
Hill Coefficient (unitless)	1.00 Fixed	n/a	n/a
Between Subject Variability			
On E_{max}	20.2	6.60	17.6 – 22.9
Residual Error			
Proportional Error (%)	48.0	2.57	45.5 – 50.4
Covariate Effects			
Fibrosis Stage F0 (unitless)	-0.257	215	-1.34 – 0.827
Fibrosis Stage F3 (unitless)	-0.0539	121	-0.182 – 0.0738
Fibrosis Stage F4 (unitless)	-0.474	46.5	-0.906 – -0.0419

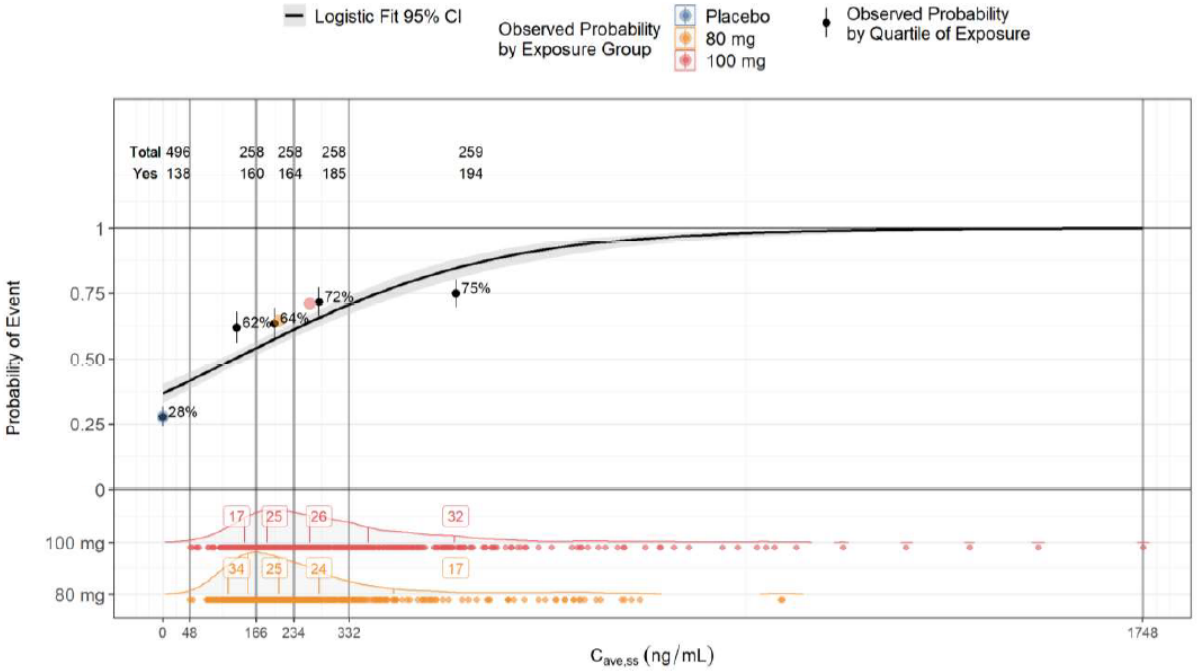
Source: Table 8 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER

Note: The reference subjects is a white male NASH patient <65 years with fibrosis stage F1-F2 with a former or current history of alcohol intake.

Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; E_{max}, maximum effect; EC_{50}, effective $C_{ave,ss}$ associated with 50% of the maximum effect, MRI-PDFF, magnetic resonance imaging-proton density fat fraction; RSE, relative standard error

The Applicant also conducted analysis for the probability of ≥30% reduction in MRI-PDFF at Week 52 as a function of resmetirom $C_{ave,ss}$ at Week 52 (Figure 55). The parameter estimates derived with the logistic regression are listed in Table 245. A statistically significant E-R relationship was observed, where higher $C_{ave,ss}$ values were associated with a higher probability of ≥30% reduction in MRI-PDFF at Week 52.

Figure 55. Exposure-Response for Resmetirom $C_{ave,ss}$ on Probability of ≥30% Reduction in MRI-PDFF at Week 52



Source: Figure 14 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: The lower panel represents the distribution of $C_{ave,ss}$ for the 80 and 100 mg doses at Week 52. The number presented in the four boxes for the 80 and 100 mg doses represents the percentage of subjects in the 1st, 2nd, 3rd, and 4th quartiles (for a total of 100%). Orange and red circles represent individual values for the 80 and 100 mg doses at Week 52, respectively.
Note: The middle panel includes the model-predicted probability of response (solid black line) with 95% CI (grey shaded area). The observed response for each quartile is presented with a black circle.
Note: The upper panel presents the total number of patients in each quartile and the total response ("Yes") in each quartile. The number of responders ("Yes") relative to the total number of patients is also presented in the middle panel. For example, a total 194 responders out of 259 patients in the 4th quartile corresponds to an observed 75% response.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat fraction

Table 245. Exposure-Response Parameters for the Probability of ≥ 30% Reduction in MRI-PDFF at Week 52

Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-0.547	0.0796	(-0.705, -0.393)	<0.001
Slope (for 1 ng/mL increment of $C_{ave,ss}$)	0.00429	0.000366	(0.00359, 0.00502	<0.001

Source: Table 9 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions, CI, confidence interval; $C_{ave,ss}$, average concentration under steady state conditions; SE, standard error

Similar analysis was conducted for the probability of ≥50% reduction in MRI-PDFF at Week 52. A statistically significant E-R relationship was observed, where higher $C_{ave,ss}$ values were associated with a higher probability of ≥50% reduction in MRI-PDFF at Week 52 (Table 246).

Table 246. Exposure-Response Parameters for the Probability of ≥50% Reduction in MRI-PDFF at Week 52

Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-1.41	0.0885	(-1.58, -1.24)	<0.001
Slope (for 1 ng/mL increment of $C_{ave,ss}$)	0.00393	0.000336	(0.00329, 0.00460)	<0.001

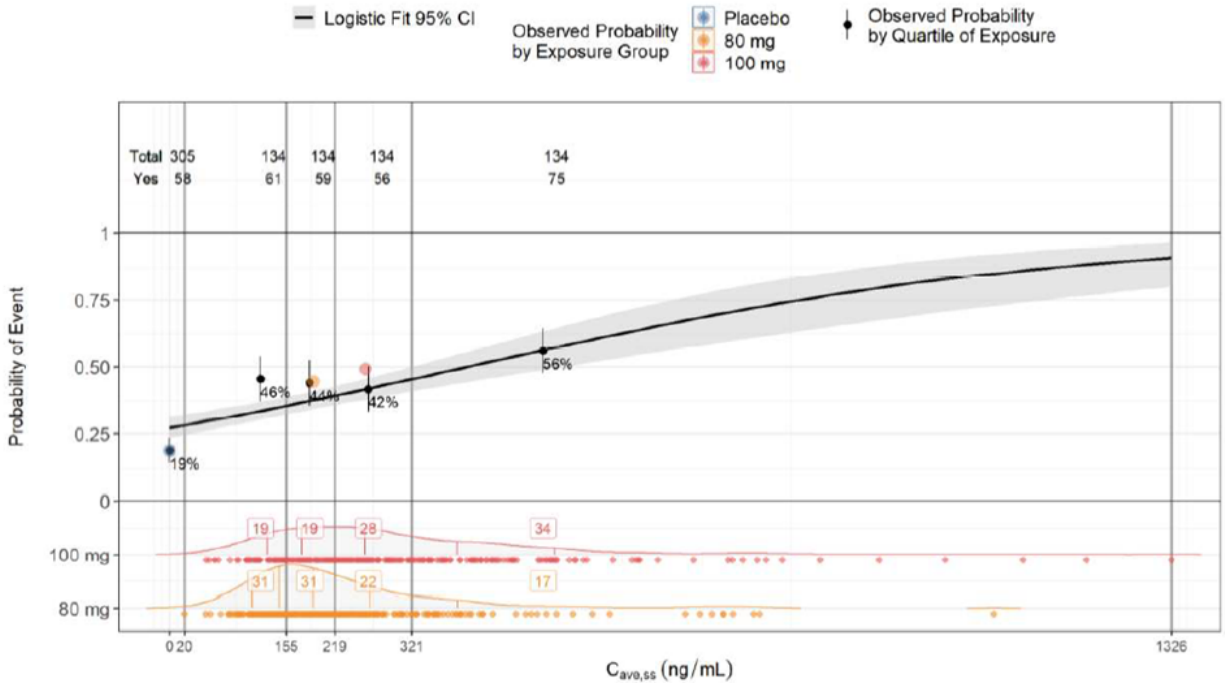
Source: Table 12 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; SE, standard error

14.5.2.4. E-R Analysis of Efficacy Endpoints

14.5.2.4.1. NASH Resolution or Fibrosis Response at Week 52

The probability of NASH resolution or fibrosis response as a function of resmetirom $C_{ave,ss}$ at Week 52 in Trial MGL-3196-11 is shown in Figure 56. Higher $C_{ave,ss}$ values of resmetirom were associated with a higher probability of response at Week 52. Parameter estimates derived with the logistic regression for the probability of response at Week 52 are listed in Table 247.

Figure 56. Exposure-Response for the Probability of NASH Resolution or Fibrosis Response* at Week 52 as Function of Resmetirom $C_{ave,ss}$



Source: Figure 16 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: The lower panel represents the distribution of $C_{ave,ss}$ for the 80 and 100 mg doses at Week 52. The number presented in the four boxes for the 80 and 100 mg doses represents the percentage of subjects in the 1st, 2nd, 3rd, and 4th quartiles (for a total of 100%). Orange and red circles represent individual values for the 80 and 100 mg doses at Week 52, respectively.
Note: The middle panel includes the model-predicted probability of response (solid black line) with 95% CI (grey shaded area). The observed response for each quartile is presented with a black circle.
Note: The upper panel presents the total number of patients in each quartile and the total response ("Yes") in each quartile. The number of responders ("Yes") relative to the total number of patients is also presented in the middle panel. For example, a total 75 responders out of 134 patients in the 4th quartile corresponds to an observed 56% response.
*Of note, analyses were based on a combined response rate of NASH resolution and fibrosis response, while NASH resolution with no worsening of fibrosis or improvement in fibrosis with no worsening of NASH are coprimary efficacy endpoints. As such the overall response rate is higher than the response rate for individual primary endpoints.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; NASH, nonalcoholic steatohepatitis

Table 247. Exposure-Response Parameters for the Probability of Response (NASH Resolution or Fibrosis Response)

Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-0.981	0.104	(-1.19, -0.781)	<0.001
Slope (for 1 ng/mL increment of $C_{ave,ss}$)	0.00249	0.000413	(0.00170, 0.00332)	<0.001

Source: Table 15 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; NASH, nonalcoholic steatohepatitis; SE, standard error

The predicted and observed responses are shown in Table 248. The observed probabilities are very similar for C_{ave} Q1, Q2, and Q3, but increase at Q4. Compared to the 80 mg QD dose, the 100 mg QD dose has a higher percentage (34% versus 17%) of subjects in the C_{ave} Q4 and a lower percentage (19% versus 31%) of subjects in the C_{ave} Q1.

Table 248. 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)

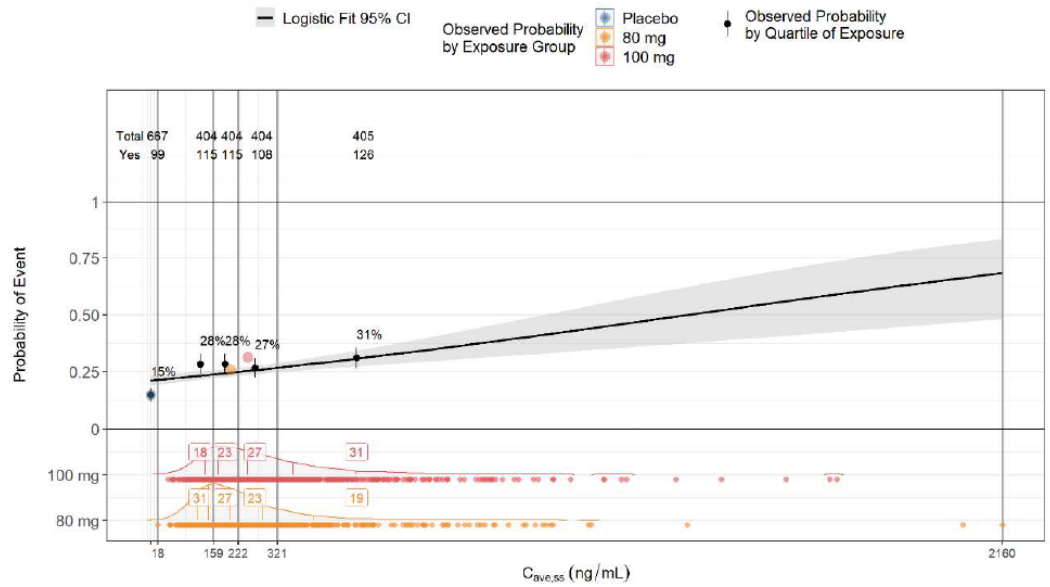
Source: Table 16 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; N, number of subjects; NASH, nonalcoholic steatohepatitis; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile

14.5.2.5. E-R Analysis of Safety Endpoints

14.5.2.5.1. Probability of Diarrhea (Grade ≥1)

The median time to the first instance of diarrhea was 17 days. An E-R analysis was performed to assess the relationship between the $C_{ave,ss}$ of resmetirom on Day 17 and the probability of diarrhea based on data collected in Trials MGL- 3196-11 and MGL-3196-14 (Figure 57). Parameters derived with the logistic regression model for the probability of diarrhea are listed in Table 249.

Figure 57. Exposure-Response for the Impact of Resmetirom $C_{ave,ss}$ on Probability of Diarrhea (Grade ≥1)



Source: Figure 21 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: The lower panel represents the distribution of $C_{ave,ss}$ for the 80 and 100 mg doses. The number presented in the four boxes for the 80 and 100 mg doses represents the percentage of subjects in the 1st, 2nd, 3rd, and 4th quartiles (for a total of 100%). Orange and red circles represent individual values for the 80 and 100 mg doses at Week 52, respectively.
Note: The middle panel include the model-predicted probability of response (solid black line) with 95% CI (grey shaded area). The observed response for each quartile is presented with a black circle.
Note: The upper panel presents the total number of patients in each quartile and the total response ("Yes") in each quartile. The number of responders ("Yes") relative to the total number of patients is also presented in the middle panel. For example, a total 126 responders out of 405 patients in the 4th quartile corresponds to an observed 31% response.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval

Table 249. Exposure-Response Parameters for the Probability of Diarrhea (Grade ≥1)

Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-1.31	0.0675	(-1.45, -1.18)	<0.001
Slope (for 1 ng/mL increment of $C_{ave,ss}$)	0.000963	0.000219	(0.000533, 0.00140)	0.00218

Source: Table 27 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: CI, confidence interval; $C_{ave,ss}$, average concentration under steady state conditions; SE, standard error

A statistically significant E-R relationship was observed for the probability of diarrhea with $C_{ave,ss}$. The predicted probabilities of diarrhea according to the $C_{ave,ss}$ are listed in Table 250. All diarrhea events were transient and resolved rapidly.

Table 250. Model-Predicted and Observed Probabilities of Diarrhea (Grade ≥1) 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	667	0.00	21.2	(19.1 - 23.5)	14.8	(12.1 - 17.5)
Q1: [18.4 - 159)	404	125	23.3	(21.5 - 25.2)	28.5	(24.1 - 32.9)
Q2: [158.6 - 222)	404	189	24.4	(22.6 - 26.2)	28.5	(24.1 - 32.9)
Q3: [222 - 321)	404	264	25.8	(23.9 - 27.7)	26.7	(22.4 - 31.1)
Q4: [321 - 2161]	405	549	30.8	(27.4 - 34.4)	31.1	(26.6 - 35.6)

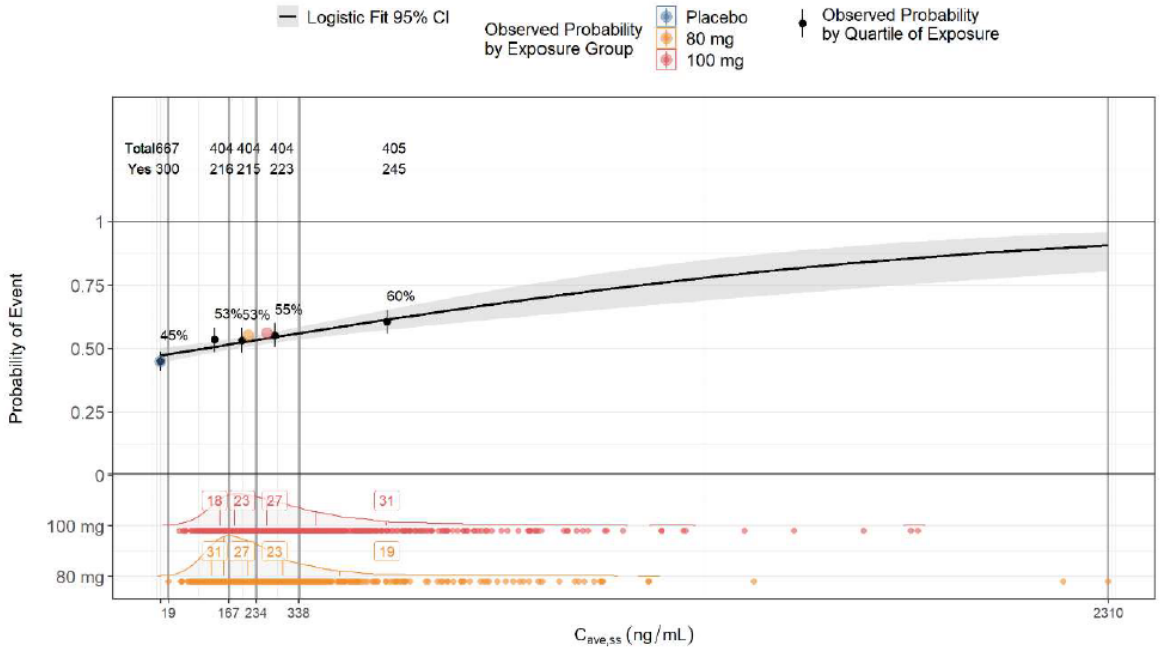
Source: Table 28 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER

Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile

14.5.2.5.2. Probability of Any GI Events

The median time to the first instance of any GI event (grade ≥1) was 20 days. An E-R analysis was performed to assess the relationship between the $C_{ave,ss}$ of resmetirom on Day 20 and the probability of any GI events (Grade ≥1) based on data collected in Trial MGL-3196-11 and MGL-3196-14 (Figure 58). Parameters derived with the logistic regression model for the probability of GI events are listed in Table 251.

Figure 58. Exposure-Response for the Impact of Resmetirom $C_{ave,ss}$ on Probability of Any GI Events (Grade ≥1)



Source: Figure 22 from "Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH)," Report No. MADR-PMX mgL3196-2382-ER.

Note: The lower panel represents the distribution of $C_{ave,ss}$ for the 80 and 100 mg doses. The number presented in the four boxes for the 80 and 100 mg doses represents the percentage of subjects in the 1st, 2nd, 3rd, and 4th quartiles (for a total of 100%). Orange and red circles represent individual values for the 80 and 100 mg doses at Week 52, respectively.

Note: The middle panel include the model-predicted probability of response (solid black line) with 95% CI (grey shaded area). The observed response for each quartile is presented with a black circle.

Note: The upper panel presents the total number of patients in each quartile and the total response ("Yes") in each quartile. The number of responders ("Yes") relative to the total number of patients is also presented in the middle panel. For example, a total 245 responders out of 405 patients were observed in the 4th quartile, which represents an observed percentage of 60%.

Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; GI, gastrointestinal

A statistically significant E-R relationship was observed for the probability of any GI events with $C_{ave,ss}$ (Table 251). The predicted probabilities of any GI events according to the $C_{ave,ss}$ are listed in Table 252. All GI events were transient and resolved rapidly.

Table 251. Exporsure- Response Parameters for the Probability of Any GI Events (Grade ≥1)

Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-0.110	0.0589	(-0.226, 0.00511)	0.0619
Slope (for 1 ng/mL increment of $C_{ave,ss}$ on Day 20)	0.00103	0.000207	(0.000635, 0.00145)	<0.001

Source: Table 30 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: CI, confidence interval; $C_{ave,ss}$, average concentration under steady state conditions; GI, gastrointestinal; SE, standard error

Table 252. Model-Predicted and Observed Probabilities of Any GI Events (Grade ≥1) According to Resmetirom $C_{ave,ss}$

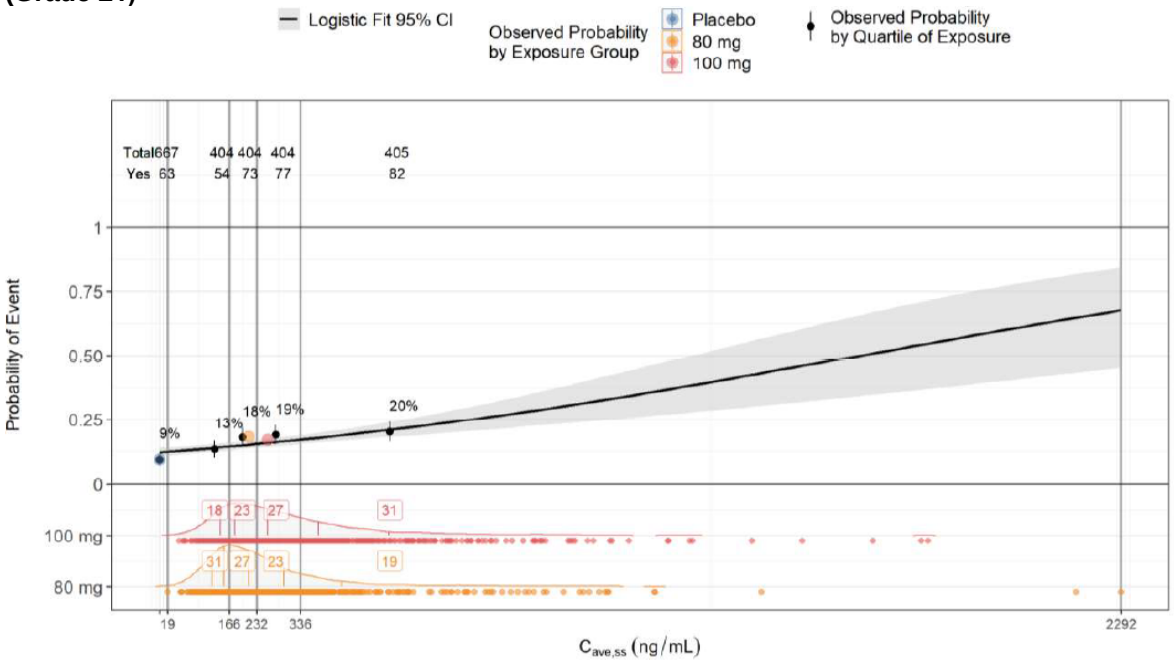
$C_{ave,ss}$ (ng/mL)	N	Mean $C_{ave,ss}$ (ng/mL)	Estimated Probability (%)	Estimated 95% CI (%)	Observed Probability (%)	Observed 95% CI (%)
Placebo	667	0.00	47.3	(44.4 - 50.1)	45.0	(41.2 - 48.8)
Q1: [19.3 - 167)	404	132	50.7	(48.5 - 52.8)	53.5	(48.6 - 58.3)
Q2: [167 - 234)	404	199	52.4	(50.3 - 54.5)	53.2	(48.4 - 58.1)
Q3: [234 - 338)	404	279	54.5	(52.3 - 56.7)	55.2	(50.4 - 60.1)
Q4: [338 - 2310]	405	553	61.4	(57.4 - 65.2)	60.5	(55.7 - 65.3)

Source: Table 31 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; GI, gastrointestinal; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile

14.5.2.5.3. Probability of Nausea (Grade ≥1)

The median time to the first instance of nausea (grade ≥1) was 9 days. An E-R analysis was performed to assess the relationship between the $C_{ave,ss}$ of resmetirom on Day 9 and the probability of nausea (Grade ≥1) based on data collected in Trials MGL-3196-11 and MGL-3196-14 (Figure 59).

Figure 59. Exposure-Response for the Impact of Resmetirom $C_{ave,ss}$ on Probability of Nausea (Grade ≥1)



Source: Figure 23 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: The lower panel represents the distribution of $C_{ave,ss}$ for the 80 and 100 mg doses. The number presented in the four boxes for the 80 and 100 mg doses represents the percentage of subjects in the 1st, 2nd, 3rd, and 4th quartiles (for a total of 100%). Orange and red circles represent individual values for the 80 and 100 mg doses at Week 52, respectively.
Note: The middle panel include the model-predicted probability of response (solid black line) with 95% CI (grey shaded area). The observed response for each quartile is presented with a black circle.
Note: The upper panel presents the total number of patients in each quartile and the total response ("Yes") in each quartile. The number of responders ("Yes") relative to the total number of patients is also presented in the middle panel. For example, a total 82 responders out of 405 patients were observed in the 4th quartile, which represents an observed percentage of 20%.
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval

A statistically significant E-R relationship was observed for the probability of nausea with $C_{ave,ss}$ (Table 253). The predicted probabilities of nausea according to the $C_{ave,ss}$ are listed in Table 254. All nausea were transient and resolved rapidly.

Table 253. Exposure-Response Parameters for the Probability of Nausea (Grade ≥1)

Parameters	Estimate	SE	95% CI	P-value
Intercept (Placebo)	-1.98	0.0808	(-2.14, -1.82)	<0.001
Slope (for 1 ng/mL increment of $C_{ave,ss}$)	0.00119	0.000230	(0.000732, 0.00164)	<0.001

Source: Table 33 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Note: the intercept is representative of the placebo effect (i.e., a $C_{ave,ss}$ of 0 ng/mL).
Abbreviations: $C_{ave,ss}$, average concentration under steady state conditions; CI, confidence interval; SE, standard error

Table 254. Model-Predicted and Observed Probabilities of Nausea (Grade ≥1) 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	667	0.00	12.2	(10.6 - 13.9)	9.45	(7.23 - 11.7)
Q1: [19.2 - 166)	404	131	13.9	(12.5 - 15.5)	13.4	(10.1 - 16.7)
Q2: [166 - 232)	404	198	14.9	(13.5 - 16.4)	18.1	(14.3 - 21.8)
Q3: [232 - 335)	404	277	16.1	(14.6 - 17.8)	19.1	(15.2 - 22.9)
Q4: [335 - 2292]	405	549	21.0	(18.1 - 24.1)	20.3	(16.3 - 24.2)

Source: Table 34 from Exposure-Response Analysis of Resmetirom in Patients with Nonalcoholic Steatohepatitis (NASH), Report No. MADR-PMX mgL3196-2382-ER
Abbreviations: Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

14.6. Pharmacogenetics

14.6.1. Background

Submission Description

Resmetirom (also referred to as MGL-3196) is an oral THR-β agonist. The Applicant is seeking approval for the treatment of NASH with liver fibrosis.

Specific Issues/Questions

The Applicant evaluated effects of (1) variants in PK-related genes on resmetirom and metabolite MGL-3623 PK and (2) variants associated with risk for NASH on resmetirom efficacy. The Applicant concluded that BW was the most important factor, while adenosine triphosphate binding cassette subfamily G member 2 (ABCG2) genotype was not, in explaining resmetirom PK variability. The Applicant also stated that efficacy in PNPLA3 rs738409 subgroup analyses was similar to primary efficacy results in the Phase 2 study. This review focused on results from Phase 2 and 3 studies to (1) verify the effect of ABCG2 genotype (rs2231142, rs2231137) on resmetirom PK with additional evaluation of treatment-emergent adverse events (TEAEs) by ABCG2 rs2231142 genotype, and (2) summarize efficacy by genotype for variants associated with risk for NASH (PNPLA3 rs738409, TM6SF2 rs58542926, TMC4 rs641738).

14.6.2. Assessment

Materials Reviewed

Data Sources

Reports and datasets relevant to genomic analyses of the review are listed in Table 255.

Table 255. Reports and Datasets Relevant to Genomic Analyses of Resmetirom

Report	Dataset(s)
Clinical study report: MGL-3196-05 MGL-3196-05:14 Tables, figures and graphs referred to but not included in the text	• Data copied from p. 2026 of additional tables (reviewer-generated dataset) (Seq 0003) • Adpp.xpt (Seq 0003) • Adsl.xpt (Seq 0003) • Adae.xpt (Seq 0015)
MGL-3196-11 Week 52 interim clinical study report	• Adsl.xpt (Seq 0009) • Adae.xpt (Seq 0003)
Clinical Information Amendment – Response to FDA Request for Information dated 2023-09-08 (received 2023-09-21)	None
Clinical Information Amendment – Response to FDA Request for Information dated 2023-09-08 – Follow Up (received 2023-11-03)	• Expgenph2.xpt (Seq 0031) • Expgenph3.xpt (Seq 0031)

Source: Generated by an FDA reviewer
Abbreviations: MGL-3196, resmetirom

Phase 1 trials, MGL-3196-12, -15, -16, -17, Phase 2 trial, MGL-3196-05, and Phase 3 trials, MGL-3196-11 and MGL-3196-14, included genomic analyses of PK-related genes involved in resmetirom metabolism or transport (ABCG2 [encodes BCRP], CYP2C8, solute carrier organic anion transporter family member 1B1 [encodes OATP1B1]). Phase 2 trial, MGL-3196-05, and Phase 3 trial, MGL-3196-11, included genomic analyses of variants associated with risk for NASH (PNPLA3 rs738409, TM6SF2 rs58542926, TMC4 rs641738).

Analysis Methods

PK and TEAEs by ABCG2 Genotype

For Phase 2 study, Study 05, dose adjustment by ABCG2 rs2231142 (c.421C>A) genotype for all participants with available genotyping data (n=79 total) was summarized by the reviewer. Of note, rs2231142 G/G corresponds to c.421C/C and G/T+T/T corresponds to c.421C/A+A/A.

Dose adjustments were allowed at Week 4 based on Week 2 combined resmetirom and MGL-3623 AUC_{inf} estimates (ng*hr/mL)±% change in SHBG. For example, if AUC_{inf} ≤5500, the dose was continued at 80 mg; if AUC_{inf} >5500, the dose was reduced to 60 mg; if AUC_{inf} ≥11000 and SHBG ≤+150%, the dose was reduced to 60 mg; and if AUC_{inf} ≥11000 and SHBG >+150%, the dose was reduced to 40 mg.

For Phase 2 study, Study 05, resmetirom and MGL-3623 AUC_{0-8h} and estimated resmetirom AUC_{0-24h} (ng*hr/mL) at week 2 were compared by ABCG2 rs2231142 genotype (G/G versus G/T+T/T) (n=79 total) with a two-sample t-test by the Applicant and verified by the reviewer. Given the small sample size of participants homozygous for the ABCG2 rs2231142 T allele (T/T), grouping participants homozygous (T/T) with heterozygous (G/T) for analyses was considered appropriate by the reviewer. Results presented by the Applicant for the Phase 2 study, Study 05, signaled that participants who carried a T allele at ABCG2 rs2231142 may have higher exposure to both resmetirom and MGL-3623. Therefore, an IR was submitted requesting that the Applicant perform multivariable analyses to evaluate genotype with other significant covariates on resmetirom and MGL-3623 PK, including for pooled Phase 1 data in healthy participants, and to ask whether genotyping data were available from Phase 3 studies.

The Applicant performed multivariable linear regression analyses with resmetirom or MGL-3623 log-transformed dose-corrected $AUC_{0\text{-}24,SS}$ as the dependent variable and BW and genotype as independent variables for pooled Phase 1 studies 12, 15, 16, and 17. The Applicant performed multivariable linear regression analyses with resmetirom or MGL-3623 log-transformed dose-corrected $AUC_{0\text{-}24,week\ 52}$ as the dependent variable and BW, genotype, and a BW*genotype interaction term as independent variables for participants with available genotyping data in Phase 2 study, Study 05 (n=79 total), and in pooled Phase 3 studies, Studies 11 and 14 (n=1120 total). Exposures were derived from a PopPK model.

The reviewer computed minor allele frequencies by race (Asian, Black or African American, white, and Other) for ABCG2 rs2231142 and rs2231137 in Phase 2 and 3 studies. MGL-3623 is 28-fold less active than resmetirom. Thus, the following analyses in the review focus on resmetirom. The reviewer verified results from multivariable analyses in Phase 2 and 3 studies and evaluated the ratio of LSM estimates for ABCG2 genotype from the model deemed most appropriate. The reviewer evaluated TEAEs by ABCG2 rs2231142 genotype for participants in the 12-week treatment period safety population who received resmetirom and had genotype data available in Study 05 (n=73 total). The reviewer evaluated TEAEs by ABCG2 rs2231142 genotype for participants in the safety population with baseline F1b, F2, or F3 fibrosis who received resmetirom and had genotype data available in Study 11 (n=477 total). The reviewer also performed the above analyses for the subset of patients with F2 and F3 fibrosis at baseline in studies 05 and 11, including minor allele frequencies by race, multivariable models (n=34 total for Study 05, n=452 total for Study 11), and TEAEs by ABCG2 rs2231142 genotype (n=31 total for Study 05, n=417 total for Study 11).

Efficacy by Variants Associated With Risk for NASH

In Phase 2 study, Study 05, the Applicant performed subgroup analyses for week 12 primary efficacy endpoint and analyses of NASH biopsy responders at week 36 in the modified intent-to-treat population with post-baseline liver biopsy for multiple endpoints (1-point reduction in NAS, 2-point reduction in NAS, 2-point reduction in NAS and either a ≥1point reduction in lobular inflammation or hepatocellular ballooning, and 2-point reduction in NAS and no worsening of fibrosis) by PNPLA3 rs738409 genotype.

In Phase 3 study, Study 11, the Applicant performed subgroup analyses for NASH resolution based on consensus response in the paired biopsies population by PNPLA3 rs738409, TM6SF2 rs58542926, and TMC4 rs641738 genotypes. The paired biopsies population included patients in the week 52 modified intent-to-treat population who took at least one dose of study medication, had a baseline liver biopsy, and finished the week 52 visit with an acceptable liver biopsy. In addition, the Applicant performed subgroup analyses for fibrosis improvement at week 52 based on consensus by PNPLA3 rs738409 genotype.

Biomarker Description

Type and Measurement Method

Genomic testing details are provided in Table 256.

Table 256. Genomic Testing Information for Phase 1, 2, and 3 Studies

Study	Lab	Genotyping Platform	Genes and Alleles/Variants Tested
MGL-3196-12	(b) (4)	TaqMan	• ABCG2 rs2231142 • CYP2C8*2 (rs11572103), CYP2C8*3 (rs11572080), CYP2C8*4 (rs1058930)
		Sanger sequencing	ABCG2 rs2231137
MGL-3196-15		TaqMan	• ABCG2 rs2231142 • CYP2C8*2 (rs11572103), CYP2C8*3 (rs11572080), CYP2C8*4 (rs1058930) SLCO1B1*5 (rs4149056), SLCO1B1*1B (rs2306283)†
		Sanger sequencing	ABCG2 rs2231137
MGL-3196-16		TaqMan	• ABCG2 rs2231142 • CYP2C8*2 (rs11572103), CYP2C8*3 (rs11572080), CYP2C8*4 (rs1058930) • SLCO1B1*5 (rs4149056), SLCO1B1*1B (rs2306283)†
		Sanger sequencing	ABCG2 rs2231137
MGL-3196-17		TaqMan	• ABCG2 rs2231142, ABCG2 rs2231137 • CYP2C8*2 (rs11572103), CYP2C8*3 (rs11572080, rs10509681), CYP2C8*4 (rs1058930) • SLCO1B1*5 (rs4149056), SLCO1B1*1B (rs2306283, rs4149056)‡
MGL-3196-05		TaqMan	PNPLA3 rs738409
		TaqMan	ABCG2 rs2231142
MGL-3196-11		TaqMan	• ABCG2 rs2231142, ABCG2 rs2231137 • PNPLA3 rs738409 • TM6SF2 rs58542926 • TMC4 rs641738
MGL-3196-14		TaqMan	• ABCG2 rs2231142, ABCG2 rs2231137 • PNPLA3 rs738409 • TM6SF2 rs58542926 • TMC4 rs641738

Source: Reviewer generated table based on response to information request received on 2023-09-21.
† Formerly SLCO1B1*1B, but now defines SLCO1B1*37 when present alone (Ramsey et al. 2023).
‡ Defines SLCO1B1*15 (Ramsey et al. 2023).
Abbreviations: MGL-3196, resmetirom

ABCG2 encodes BCRP, an efflux transporter with wide expression including on the apical membrane of hepatocytes where it eliminates its substrates from the blood. ABCG2 rs2231137 (p.Gln141Lys) has been reported to have no effect on BCRP expression, localization, or

function. ABCG2 rs2231142 (p.Val12Met) has been reported to decrease BCRP expression owing to increased protein degradation (reviewed in (Fohner et al. 2017)).

PNPLA3 rs738409 (p.Ile148Met) has been the genetic factor most robustly associated with the risk for developing NASH as well as increased risk of progression to hepatocellular carcinoma (HCC). TM6SF2 rs58542926 (p.Glu167Lys) has been associated with the risk for developing NASH and progression to HCC, but has also been reported to have lower risk of cardiovascular events. TMC4/MBOAT7 rs641738 (p.Glu17Gly) has been associated with risk for developing NASH, inflammation, fibrosis, and progression to HCC (reviewed in (Eslam et al. 2018; Perakakis et al. 2020)).

14.6.3. Evidence Analysis

Question 1: Does PGx Variation in ABCG2 Impact Resmetirom PK?

Clinical PK

Results from the Applicant's multivariable analyses for pooled phase 1 studies found that after accounting for BW, genotype of variants in various PK-related genes (ABCG2 rs2231142 and rs2231137, solute carrier organic anion transporter family member 1B1 rs4149056 and rs2306283, CYP2*C8* rs11572103, rs11572080, and rs1058930) did not significantly impact resmetirom exposure.

ABCG2 rs2231142 and rs2231137 genotype totals for all participants with genotype available in Phase 2 and Phase 3 studies (studies 05, 11, and 14) and for participants with genotype available who had fibrosis stage F2 or F3 at baseline (studies 05 and 11) are provided in Table 257. The minor allele frequencies for Asians were lower than the reference value according to dbSNP for rs2231142 in Study 05 and rs2231137 in phase 3 studies. This is likely due to limited sample sizes (n=2 in Study 05; n=2 in study 05 F2+F3; n=27 in Studies 11 and 14; n=11 in Study 11 F2+F3). Otherwise, minor allele frequencies were generally consistent with reference values.

Table 257. ABCG2 rs2231142 and rs2231137 Genotype Totals for All Subjects With Genotyping Data and for the Subset of Subjects With F2 or F3 Baseline Fibrosis in Phase 2 and 3 Studies

PK-Related Genes	Genotype	Study 05	Study 05 (F2+F3)	Studies 11 & 14	Study 11 (F2+F3)
ABCG2 rs2231142, n	G/G	56	23	855	353
	G/T	22	11	239	90
	T/T	1	0	26	9
ABCG2 rs2231137, n	C/C	N/A	N/A	938	379
	C/T	N/A	N/A	162	66
	T/T	N/A	N/A	20	7

Source: Reviewer's analysis (Expgenph2.xpt [Seq 0031], Expgenph3.xpt [Seq 0031], Adsl.xpt [Study 05, Seq 0003], Adsl.xpt [Study 11, Seq 0009])
Abbreviations: F[#], fibrosis stage; N/A, not applicable; n, number of subjects

Results for exposure of resmetirom and MGL-3623 by ABCG2 rs2231142 genotype in the Phase 2 study, Study 05, are provided in Table 258. Compared to rs2231142 G/G, G/T+T/T genotypes had significantly higher mean AUC for resmetirom and MGL-3623. These results suggest that rs2231142 T allele carriers have higher exposure (~1.8-fold) to resmetirom. In Phase 2 studies, Study 05, 18 of 23, participants who carried a T allele at ABCG2 rs2231142 qualified for a dose

reduction at week 4. The average combined AUC_{inf} was 5024 ng*hr/mL for rs2231142 G/G and 8766 ng*hr/mL for rs2231142 G/T+T/T.

Table 258. Resmetirom and MGL-3623 AUC Stratified by ABCG2 rs2231142 Genotype in Phase 2, Study 05

ABCG2 Genotype	Mean Resmetirom AUC_{8h} at Week 2 (Predose up to 8 hr Postdose) (ng*hr/mL)	Mean MGL-3623 AUC_{8h} at Week 2 (Predose up to 8 hr Postdose) (ng*hr/mL)	Mean Estimated Resmetirom AUC_{24h} (ng*hr/mL)
All resmetirom treated patients			
G/G (n=56)	3457	1542	3975
G/T+T/T (n=23)	6305	2459	7323
p-value†	0.0009‡	<0.0001	0.005‡
All resmetirom treated patients with outliers removed			
G/G (n=55)	3519	1568	4044
G/T+T/T (n=22)	5316	2402	6173
p-value†	0.002	<0.0001	0.02

Source: Reviewer's analysis (reviewer-generated dataset from p. 2026 of MGL-3196-05- 14 Tables, Figures and Graphs Referred to but Not Included in the Text [Seq 0003])
†Two-sample t-test p-value
‡Reviewer's p-value results differed from Applicant's p-value results, but overall interpretation remains unchanged as both values were statistically significant
Abbreviations: AUC, area under the concentration-time curve; n, number of subjects

Results from multivariable analyses for the Phase 2 and Phase 3 studies are provided in Table 259 and Table 260, respectively. The Applicant performed an additional multivariable model with a BW*genotype interaction term (model 3) and concluded that BW was the most important factor in explaining resmetirom PK, but not rs2231142 genotype based on this model. However, there is not a clear rationale to include the interaction term in the model. Therefore, the reviewer deemed the model with BW and genotype as independent variables (model 2) as the most appropriate. Results from model 2 for both Phase 2 and Phase 3 studies suggest that compared to ABCG2 rs2231142 G/G, G/T+T/T genotypes have a significantly higher AUC after accounting for BW. ABCG2 rs2231142 genotype was not statistically significant in the Phase 3 study, Study 11, F2+F3 subset. ABCG2 rs2231137 genotype did not have a significant effect on resmetirom exposure in Phase 3 studies.

Table 259. Multiple Regression Analyses for the Effect of ABCG2 rs2231142 Genotype on Log-Transformed Dose-Corrected $AUC_{0-24,ss}$ at Week 2 of Resmetirom in Phase 2, Study 05

Independent Variables	Model 1 Log(AUC) ~Body Weight		Model 2† Log(AUC)~Body Weight+Genotype		Model 3 Log(AUC)~Body Weight+Genotype+Body Weight*Genotype	
	Estimates (SE)	p-value	Estimates (SE)	p-value	Estimates (SE)	p-value
Phase 2 study 05 (n=79)						
(Intercept)	5.0 (0.3)	<0.001	4.9 (0.3)	<0.001	4.7 (0.3)	<0.001
Body weight	-0.01 (0.003)	<0.001	-0.01 (0.003)	<0.001	-0.01 (0.003)	<0.001
Rs2231142 (G/T+T/T)			0.5 (0.1)	<0.001	0.9 (0.6)	0.1
Body weight*rs2231142					-0.005 (0.006)	0.4
Phase 2 study 05 F2+F3 (n=34)						
(Intercept)	5.0 (0.5)	<0.001	5.0 (0.5)	<0.001		
Body weight	-0.01 (0.005)	0.01	-0.01 (0.005)	0.003		
Rs2231142 (G/T+T/T)			0.6 (0.2)	0.02		

Source: Reviewer's analysis (Expgenph2.xpt [Seq 0031], Adsl.xpt [Seq 0003])

† Model 2 was deemed most appropriate by the reviewer. The Applicant based conclusions on model 3.

Abbreviations: AUC, area under the concentration-time curve (AUC was dose-corrected in the models); $AUC_{0-24,ss}$, area under the concentration-time curve from time 0 to 24 hours at steady-state; n, number of subjects; SE, standard error

Table 260. Multiple Regression Analyses for the Effect of ABCG2 rs2231142 and rs2231137 Genotype on Log-Transformed, Dose-Corrected $AUC_{0\text{-}24,ss}$ at Week 52 of Resmetirom in Phase 3 Studies

	Model 1 Log(AUC)~Body Weight		Model 2† Log(AUC)~Body Weight+Genotype		Model 3 Log(AUC)~Body Weight+Genotype+Body Weight*Genotype	
Independent Variables	**Estimates (SE)**	**p-value**	**Estimates (SE)**	**p-value**	**Estimates (SE)**	**p-value**
Phase 3 studies 11 + 14 (n=1120)						
(Intercept)	5.4 (0.06)	<0.001	5.4 (0.06)	<0.001	5.4 (0.07)	<0.001
Body weight	-0.01 (0.0006)	<0.001	-0.01 (0.0006)	<0.001	-0.01 (0.0007)	<0.001
Rs2231142 (G/T+T/T)			0.09 (0.03)	0.004	0.2 (0.2)	0.1
Body weight*rs2231142					-0.001 (0.002)	0.3
Phase 3 study 11 F2+F3 (n=452)						
(Intercept)	5.5 (0.1)	<0.001	5.5 (0.1)	<0.001		
Body weight	-0.01 (0.001)	<0.001	-0.01 (0.001)	<0.001		
Rs2231142 (G/T+T/T)			0.06 (0.05)	0.2		
Phase 3 studies 11 + 14 (n=1120)						
(Intercept)	5.4 (0.06)	<0.001	5.4 (0.06)	<0.001	5.4 (0.07)	<0.001
Body weight	-0.01 (0.0006)	<0.001	-0.01 (0.0006)	<0.001	-0.01 (0.0007)	<0.001
Rs2231137 (C/T+T/T)			0.05 (0.04)	0.2	0.01 (0.2)	0.9
Body weight*rs2231137					0.0004 (0.002)	0.8
Phase 3 study 11 F2+F3 (n=452)						
(Intercept)	5.5 (0.1)	<0.001	5.4 (0.1)	<0.001		
Body weight	-0.01 (0.001)	<0.001	-0.01 (0.001)	<0.001		
Rs2231137 (C/T+T/T)			0.05 (0.06)	0.4		

Source: Reviewer's analysis (Expgenph3.xpt [Seq 0031], Adsl.xpt [Seq 0009])

† Model 2 was deemed most appropriate by the reviewer. The Applicant based conclusions on model 3.

Abbreviations: AUC, area under the concentration-time curve (AUC was dose-corrected in the models); $AUC_{0\text{-}24,ss}$, area under the concentration-time curve from time 0 to 24 h at steady-state; n, number of subjects; SE, standard error

Reviewer-calculated LSM estimates for model 2 are provided in Table 261. In Phase 2 study, Study 05, the ratio of LSM estimates for rs2231142 (G/T+T/T)/(G/G) was 1.14 (3.98/3.49) for all participants and 1.17 (4.03/3.43) for the F2+F3 subset. For model 2 in Phase 3 studies, the ratio of LSM estimates for rs2231142 (G/T+T/T)/(G/G) was 1.02 (4.22/4.13) for all participants and 1.01 (4.16/4.10) for the F2+F3 subset. Overall, these results support that ABCG2 rs2231142 and rs2231137 genotypes do not alter resmetirom PK to a clinically significant extent.

Table 261. LSM Estimates for ABCG2 rs2231142 Genotype for Phase 2 Study 05 and Phase 3 Study 11

	Rs2231142 Genotype	All Subjects		F2 and F3	
Study	Rs2231142 Genotype	LSM (SE)	95% CI	LSM (SE)	95% CI
Phase 2 Study 05	G/G	3.49 (0.069)	3.36-3.63	3.43 (0.136)	3.16-3.71
	G/T+T/T	3.98 (0.108)	3.76-4.19	4.03 (0.197)	3.63-4.44
Phase 3 Study 11	G/G	4.13 (0.015)	4.10-4.16	4.10 (0.024)	4.05-4.14
	G/T+T/T	4.22 (0.027)	4.17-4.28	4.16 (0.046)	4.07-4.25

Source: Reviewer's analysis (Expgenph2.xpt [Seq 0031], Expgenph3.xpt [Seq 0031], Adsl.xpt [Study 05, Seq 0003]), Adsl.xpt [Study 11, Seq 0009])
Abbreviations: CI, confidence interval; F[#], fibrosis stage; LSM, least squares mean; SE, standard error

Clinical Safety

TEAEs by ABCG2 rs2231142 genotype in Phase 2 study, Study 05, are provided in Table 262. Overall, there were no obvious trends in TEAEs by genotype.

Table 262. TEAEs in the 12-Week Treatment Period Safety Population by ABCG2 rs2231142 Genotype for Phase 2, Study 05

	Safety Population and Received Resmetirom†			Safety Population With F2 or F3 Baseline Fibrosis and Received Resmetirom‡		
	ABCG2 rs2231142, n (%)			ABCG2 rs2231142, n (%)		
TEAE Severity	G/G n=50	G/T n=22	T/T n=1	G/G n=20	G/T n=11	T/T n=0
TEAE maximum severity						
Mild	24 (48)	14 (64)	1 (100)	12 (60)	7 (64)	0 (0)
Moderate	15 (30)	2 (9)	0 (0)	4 (20)	1 (9)	0 (0)
Severe	1 (2)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Drug-related TEAE maximum severity						
Mild	21 (42)	8 (36)	0 (0)	11 (55)	3 (27)	0 (0)
Moderate	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TE-SAE	1 (2)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
TEAE leading to study drug discontinuation	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Reviewer's analysis (Expgenph2.xpt [Seq 0031], Adsl.xpt [Seq 0003], Adae.xpt [Seq 0015])
† Genotype available for 73 of 84 participants (87%)
‡ Genotype available for 31 of 36 participants (86%)
Abbreviations: F[#], fibrosis stage; n, number of subjects; TEAE, treatment-emergent adverse event; TE-SAE, treatment-emergent serious adverse event

TEAEs by ABCG2 rs2231142 genotype in Phase 3 study, Study 11, are provided in Table 263. A higher rate of any TEAEs ≥Grade 3 was observed in ABCG2 rs2231142 T/T genotype, but

this may be due to small sample size. Overall, there were no obvious trends in TEAEs by genotype.

Table 263. TEAEs in the Safety Population by ABCG2 rs2231142 Genotype for Phase 3, Study 11

	Safety Population With F1b, F2, or F3 Baseline Fibrosis and Received Resmetirom[†]			Safety Population With F2 or F3 Baseline Fibrosis and Received Resmetirom[‡]		
	ABCG2 rs2231142, n (%)			ABCG2 rs2231142, n (%)		
TEAE	G/G n=371	G/T n=99	T/T n=7	G/G n=328	G/T n=82	T/T n=7
Any TEAE	343 (92)	89 (90)	7 (100)	327 (100)	82 (100)	7 (100)
Any TEAEs ≥Grade 3	46 (12)	13 (13)	2 (29)	45 (14)	12 (15)	2 (29)
Any treatment-related TEAEs ≥Grade 3	5 (1)	0 (0)	0 (0)	5 (2)	0 (0)	0 (0)
Any treatment-related Serious TEAE	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Any TEAE leading to study-drug discontinuation	11 (3)	1 (1)	0 (0)	11 (3)	1 (1)	0 (0)

Source: Reviewer's analysis (Expgenph3.xpt [Seq 0031], Adsl.xpt [Seq 0009]), Adae.xpt [Seq 0003])
[†]Genotype available for 477 of 645 participants (74%)
[‡]Genotype available for 417 of 614 participants (68%)
Abbreviations: F[#], fibrosis stage; n, number of subjects; TEAE, treatment-emergent adverse event

Question 2: Does PNPLA3, TM6SF2, or TMC4 Genotype Impact Drug Efficacy?

Clinical Efficacy

PNPLA3 rs738409, TM6SF2 rs58542926, and TMC4 rs641738 genotype totals by study are provided in Table 264.

Table 264. PNPLA3 rs738409, TM6SF2 rs58542926, and TMC4 rs641738 Genotype Totals in Phase 2 and 3 Studies

Genotype Study	Genotype Total, n		
PNPLA3 rs738409	C/C	C/G	G/G
Phase 2 Study 05[†]	31	58	36
Phase 3 Study 11[‡]	231	344	165
TM6SF2 rs58542926	C/C	C/T	T/T
Phase 3 Study 11[‡]	595	135	10
TMC4 rs641738	T/T	T/C	C/C
Phase 3 Study 11[‡]	214	364	162

Source: Applicant's analysis; summary of Table 11 from Study 05 clinical study report and Appendix 2 from response to information request received on 2023-11-03
[†] Safety population
[‡] Paired biopsies population
Abbreviations: n, number of subjects

Subgroup analyses for week 12 primary efficacy endpoint by PNPLA3 rs738409 genotype for Phase 2 study, Study 05, are provided in Table 265. Responses to resmetirom were similar across genotypes. In analyses of NASH biopsy responders at week 36 in the modified intent-to-treat population for participants with post-baseline liver biopsy, participants with PNPLA3 rs738409 C/C appeared to have numerically higher response rates on placebo as compared to C/G or G/G for endpoints assessed. Overall, no obvious trends were observed between PNPLA3 genotype and response.

Table 265. Week 12 Primary Efficacy Endpoint by PNPLA3 Genotype in Phase 2, Study 05

	Resmetirom			Placebo		
PNPLA3 rs738409 Genotype	**C/C n=24**	**C/G n=39**	**G/G n=15**	**C/C n=5**	**C/G n=16**	**G/G n=17**
MRI-PDFF % change from baseline to Week 12 (LS mean)†	-31	-35	-30	-19	-7	-12

Source: Applicant's analysis; summary of Table 14.2.1.2.8 from Study 05 clinical study report
† MRI-PDFF evaluable population
Abbreviations: LS, least squares; MRI-PDFF, proton density fat fraction magnetic resonance imaging; n, number of subjects

Subgroup analyses for NASH resolution based on consensus response in the paired biopsies population by PNPLA3 rs738409, TM6SF2 rs58542926, and TMC4 rs641738 genotypes for Phase 3 study, Study 11, are provided in Table 266. Compared to TM6SF2 rs58542926 C/C or C/T, T/T appeared to have numerically higher response rates at resmetirom 80 mg and 100 mg, but small sample sizes likely contribute to these results. Responses were similar in subgroup analyses for fibrosis improvement at week 52 based on consensus in the paired biopsies population by PNPLA3 rs738409 genotype. Overall, responses were generally similar across genotypes within treatment arms and no obvious trends were observed.

Table 266. NASH Resolution Based on Consensus Response in Paired Biopsies Population by PNPLA3, TM6SF2, or TMC4 Genotype in Phase 3 Study 11

		PNPLA3 rs738409			TM6SF2 rs58542926			TMC4 rs641738		
Dose	**Response, n (%)†**	**C/C**	**C/G**	**G/G**	**C/C**	**C/T**	**T/T**	**T/T**	**T/C**	**C/C**
80 mg	Yes	29 (39)	33 (27)	12 (24)	60 (30)	11 (29)	3 (43)	19 (26)	40 (32)	15 (29)
	No	45 (61)	91 (73)	38 (76)	143 (70)	27 (71)	4 (57)	53 (74)	84 (68)	37 (71)
100 mg	Yes	27 (38)	37 (36)	20 (36)	69 (37)	13 (31)	2 (67)	25 (38)	42 (39)	17 (30)
	No	45 (62)	66 (64)	35 (64)	116 (63)	29 (69)	1 (33)	40 (62)	67 (61)	39 (70)
Placebo	Yes	11 (13)	6 (5)	7 (12)	21 (10)	3 (5)	0 (0)	8 (10)	12 (9)	4 (7)
	No	74 (87)	111 (95)	53 (88)	186 (90)	52 (95)	0 (0)	69 (90)	119 (91)	50 (93)

Source: Applicant's analysis; summary of Appendix 2 from response to information request received on 2023-11-03
† Percentages are based on total number of responses by genotype in each treatment arm.
Abbreviations: NASH, nonalcoholic steatohepatitis

14.6.4. Recommendations

Summary

Compared to ABCG2 rs2231142 G/G, T allele carriers (G/T+T/T) had significantly higher resmetirom (~1.8 fold) and MGL-3623 (~1.6 fold) $AUC_{0\text{-}8hr}$ in analyses from Phase 2 study, Study 05. ABCG2 genotype was further evaluated in multivariable analyses which included BW in Phase 2 and 3 studies. The reviewer found that compared to ABCG2 rs2231142 G/G, T allele carriers (G/T+T/T) had significantly increased AUC after accounting for BW in analyses from Phase 2 and 3 data, but the ratio of LSM estimates supports the conclusion that ABCG2 genotype does not alter PK to a clinically significant extent (estimated 1 to 17%). The reviewer also found no obvious trends in TEAEs by ABCG2 rs2231142 genotype in Phase 2 Study 05 and Phase 3 Study 11.

Labeling

Resmetirom is a BCRP substrate, ABCG2 genotype was studied throughout drug development with similar results across studies in patients with NASH, and there are no clinical DDI studies

with BCRP inhibitors. Therefore, we recommend including ABCG2 genotype in the list of specific populations with no clinically significant PK changes in Section 12.3 of the label.

Postmarketing Studies

There are no pharmacogenetic postmarketing studies recommended at this time.

15. Study/Trial Design

Table 267 displays the protocol summary for Trial MGL-3196-11, and Figure 61 displays the trial schematic for Trial MGL-3196-11. Table 268 displays protocol summary for Trial MGL-3196-14, and Figure 63 displays the trial schematic for Trial MGL-3196-14.

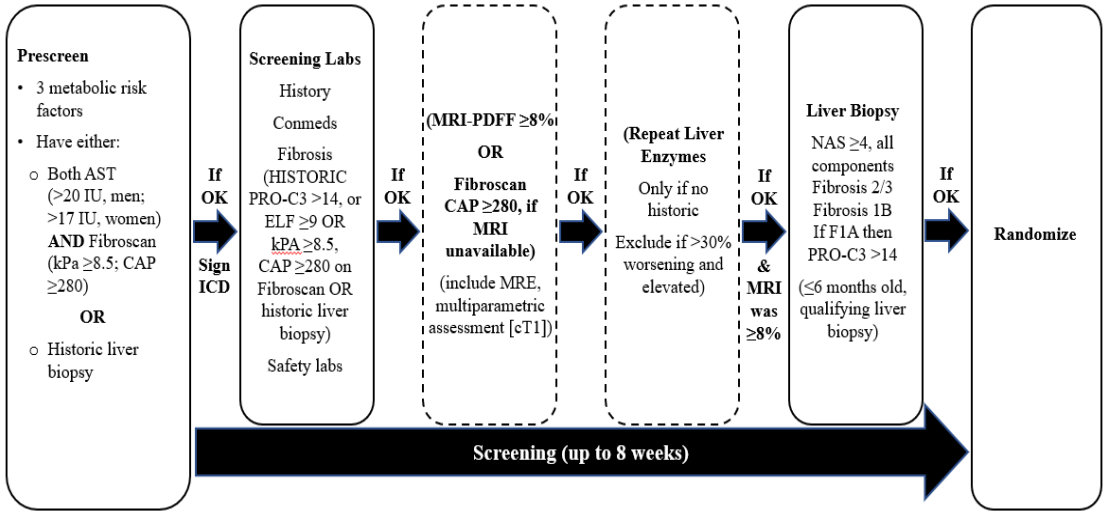
Table 267. Protocol Summary, Trial MGL-3196-11

Protocol Number	MGL-3196-11
Title	A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in Patients With Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation
Phase	3
Principal/ Coordinating Investigator:	Stephen Harrison, MD
Study Objectives	All study objectives will be assessed in F1B, F2, and F3 patients. Patients in the combined F0, F1A/C group will be assessed for the endpoints in an exploratory manner at both the Week 52 and Month 54 Analyses. **Week 52 Analysis Dual Primary Objectives** For Week 52 Analysis, the dual primary objectives were to demonstrate resmetirom efficacy on : • Resolution of NASH associated with an at least 2-point reduction in NAS and without worsening of fibrosis. • Histological improvement demonstrated by at least a 1-point improvement in fibrosis with no worsening of NAS (total of 3 NAS components: ballooning, lobular inflammation, and steatosis). **Week 52 Key Secondary Objectives** For the Week 52 Analysis, the key secondary objective was to determine the effect of resmetirom on the percent change from baseline at 24 weeks in directly measured low-density lipoprotein cholesterol (LDL-C). **Month 54 Analysis Primary Objective** For the Month 54 analysis, the primary objective is the time to experiencing an adjudicated composite clinical outcome event. The composite clinical outcome is composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or gastroesophageal variceal hemorrhage], histological progression to cirrhosis, and a confirmed increase of model for end-stage liver disease (MELD) score from <12 to ≥15).

	Week 52 Secondary Objectives For Week 52 Analysis, the secondary objectives were to determine the effect of resmetirom on: • Histological improvement from baseline at 52 weeks (improvement in NAS, overall and in each component with either no worsening or 1-point improvement in fibrosis, resolution of fibrosis, 2-stage fibrosis responders, both NASH resolution responder and fibrosis responder, and no worsening of fibrosis) • Safety and tolerability • MRI-PDFF, MRE, VCTE and CAP parameters • Liver parameters, including ALT, AST, and GGT • Cardiovascular and lipid parameters • NASH inflammation and fibrosis biomarkers • Quality of life (QOL), as assessed by the NAFLD/NASH Chronic Liver Disease Questionnaire (CLDQ), the Short Form Liver Disease Quality of Life, and the Work Productivity and Activity Index (WPAI)-NASH • Percent change in liver volume and spleen volume **Month 54 Secondary Objectives** For the Month 54 analysis, in addition to describing the distribution of the individual events within the Composite Clinical Outcome, the secondary objectives are effect of resmetirom on: • Histological improvement from baseline at 54 months (resolution of NASH, fibrosis responder, improvement in NAS overall and in each component with either no worsening or 1-point improvement in fibrosis, no worsening of fibrosis, resolution of fibrosis, 2-stage Fibrosis Responders, both NASH resolution responder and fibrosis responder) • Safety and tolerability • MRI-PDFF. MRE, VCTE, CAP parameters • Liver parameters, including ALT, AST, and GGT. • Cardiovascular and lipid parameters • NASH inflammation and fibrosis biomarkers • QOL, as assessed by the NAFLD/NASH CLDQ, SF-LDQOL, and the WPAI-NASH. • Percent change in liver volume and spleen volume • Time to experiencing an adjudicated modified composite clinical outcome event of type 1. The type 1 modified composite clinical outcome is composed of liver transplant and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or gastroesophageal variceal hemorrhage], and confirmed increase of MELD from <12 to ≥15). Multiple Week 52 and Month 54 exploratory objectives were specified.

Number of Patients	Planned: 2000 Analyzed: 1050 (full population); 888 (F2/F3 population)
Target Population	Male and female patients ≥18 years of age with biopsy-proven NASH.
Study Design	Subjects will be randomized in a 1:1:1 manner, stratified by type-2 diabetes status (presence/absence) and fibrosis stage (1, 2, or 3) based on eligibility biopsy read of fibrosis stage score. All patients will be monitored for the Composite Clinical Outcome endpoint and suspected liver-related events will be reviewed by a blinded EAC. The Final Primary Analysis for the Composite Clinical Outcome endpoint will occur after all patients have completed their scheduled biopsy at 54 months (or discontinued early). There will be an interim analysis performed by an unblinded team, of the final primary endpoint when 110 Composite Clinical Outcome events have occurred. This will be overseen by the unblinded Data Monitoring Committee (DMC). The DMC will serve to assess the progress of the trial, including the safety data and the critical efficacy endpoints in accordance with the DMC Charter, and to recommend whether to continue, modify, or stop the trial. Only the external, independent DMC members, statistician(s), and unblinded team supporting the DMC will have access to unblinded data/comparative results.
Test Product	Two doses of resmetirom, 80 mg and 100 mg, given orally once daily were evaluated compared to placebo. Dose adjustments were made during the trial based on decreases from baseline in free thyroxine (FT4) to <0.7 ng/dL. No dose reductions were made later than Week 24 and the patient's dose was not reduced to <60 mg. Blindness will be maintained during dose reduction.
Reference Product	Placebo matching resmetirom dose strengths
Statistical Methods	See Section 6.2 for discussion on analysis population, primary and secondary efficacy endpoints, and statistical methods for trial MGL-3196-11. The safety endpoints for this study included: adverse events (AEs), clinical laboratory assessments, vital signs, 12-lead electrocardiograms (ECGs), concomitant medications, clinical assessments, and MELD scores. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used for assessing the severity of AEs and laboratory tests. The AEs were be coded using a version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA).
Eligibility	Subject prescreening criteria is in Figure 60 below.

Figure 60. Prescreening and Screening Sequence



Source: Applicant provided protocol for Trial MGL-3196-11, version 6.0
Repeat liver enzymes are to be collected where indicated in an attempt to establish a stable baseline of ALT and AST with no 30% worsening of elevated levels.
Dotted box or parentheses, test not mandatory; prescreening FibroScan values may be used for liver biopsy eligibility
Abbreviations: ALT, alanine aminotransferase; AST; aspartate aminotransferase; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; MGL-3196, resmetirom; NAS, nonalcoholic fatty liver disease (NAFLD) activity score

Three metabolic risk factors were to be selected using a slightly modified version of the International Diabetes Foundation (IDF) criteria : Large waist or Body mass index (BMI) ≥30 kg/m^2 (except for Asian patients who met criteria for obesity with BMI ≥27.5 kg/m^2); Dyslipidemia; Hypertension; Type 2 Diabetes or documented insulin resistance.

Historic liver biopsy should be less than 2 years old.

Key Inclusion and Exclusion Criteria for trial MGL-3196-11 are discussed in Section 6.2.1.2.

Safety Monitoring

An unblinded independent DMC will evaluate safety data. The DMC will also review information from the blinded EAC's which includes cardiovascular assessments, potential MACE, potential DILI, and liver endpoint adjudication results.

Summary of Assessments

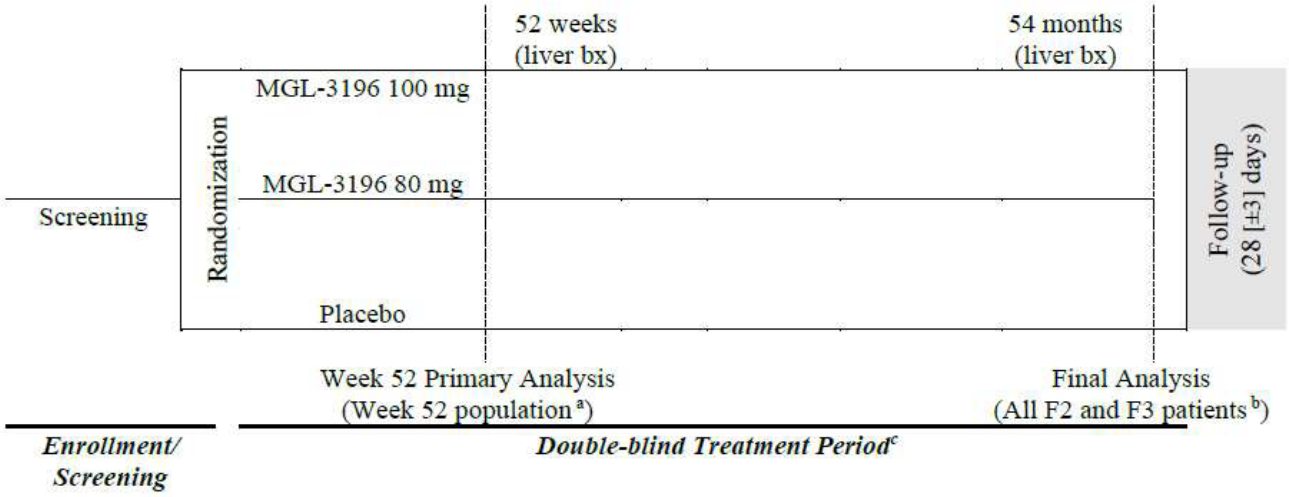
- Year 1, for first 1100 subjects study visits will be every 4 weeks. Post baseline the following safety monitoring will be done:
  - Health-related QoL assessment at weeks 24 and 52

	- Physical examinations, vital signs, nutritional and lifestyle counseling, and MELD score at every visit - ECG (12-lead) at week 4, 8, 20, 28, 36, and 52 - MRI-PDFF, MRE, cT1, Fibroscan, liver biopsy, DEXA at 52 week 52 - Laboratory: ▪ Hematology, chemistry, coagulation, SHBG, thyroid axis hormones, fasting lipid, serum/urine pregnancy test, and UA will be done at every visit. ▪ Endocrinology at week 52 ▪ Cardiac enzymes, ALP isoenzymes, additional fasting lipids, PAI-1, PRO-C3, other biomarkers, and PK sample at Week 12, 24, 36, and 52 ▪ Alcohol test at Weeks 4, 12, 20, 28, 36, 44, 52 - AEs, concomitant medications and alcohol consumption will be assessed continuously. • For subsequent subjects, study visits will be every 4 weeks till week 16, and then at week 24, 38 and 52. Post baseline, safety monitoring for Year 1 for these subjects will be done as follows: - Health-related QoL assessment at weeks 24 and 52 - Physical examinations, vital signs, nutritional and lifestyle counseling, and MELD score at every visit, except week 16 for MELD score - ECG (12-lead) at week 4, 8, 24 and 52 - MRI-PDFF, MRE, cT1, Fibroscan, liver biopsy, DEXA at week 52. MRI-PDFF, MRE, cT1 will also be assessed at week 16. - Laboratory: ▪ Hematology, chemistry, coagulation, SHBG, thyroid axis hormones, serum/urine pregnancy test, PK sample, and UA at every visit, except week 16 ▪ Fasting lipid, will be done at weeks 4, 12, 24, 38, and 52 ▪ Endocrinology at week 52 ▪ Cardiac enzymes, ALP isoenzymes, additional fasting lipids, PRO-C3, other biomarkers, at Weeks 24, and 52 ▪ PAI-1 at weeks 12,24,38, and 52 ▪ Alcohol test at Weeks 4, 12, 24, 38, and 52 - AEs, concomitant medications and alcohol consumption will be assessed continuously. • For Years 2 to 4.5, study visits will begin at Month 15, and will be every 3 months, till Month 54. Post baseline, safety monitoring will be done as follows: - Health-related QoL assessment every 6 months starting at month 18 till Month 54 or early termination - Physical examinations, vital signs, nutritional and lifestyle counseling, and MELD score at every visit - ECG (12-lead) every 6 months starting at month 18 till Month 54 or early termination

	- MRI-PDFF, MRE, cT1 at month 36 and 54 - Optional Fibroscan at month 24, 36, 48, and 54 - Liver biopsy and DEXA at month 54 - Laboratory: ▪ Hematology, chemistry, coagulation, SHBG, thyroid axis hormones, fasting lipid, serum/urine pregnancy test, PK sample, and UA at every visit ▪ Endocrinology at month 54 ▪ Cardiac enzymes, ALP isoenzymes at month 24, 36, and 54 ▪ PAI-1 at month 54 ▪ PRO-C3 and other biomarkers every 6 months beginning at month 18 till Month 54 or early termination ▪ Alcohol test at month 24, 36, 48 and 54 AEs, concomitant medications and alcohol consumption will be assessed continuously.

Source: Applicant provided protocol for Trial MGL-3196-11, version 6.0
Abbreviations: DEXA, dual x-ray absorptiometry; F0, F1, F2, F3, fibrosis stages 0, 1, 2, 3; FSH, follicle stimulating hormone; LB, liver biopsy; LH, luteinizing hormone; MACE, major adverse cardiac events; MGL-3196, resmetirom; mITT, modified intent-to-treat; PRO-C3, N-terminal type III collagen propeptide; SAF, steatosis, activity, and fibrosis; SAP, statistical analysis plan; W, week

Figure 61. Schematic, Trial MGL-3196-11



Source: Applicant provided protocol for Trial MGL-3196-11, version 6.0
Note: Liver bx=biopsy will be required 52 weeks and 54 months after randomization.
[a] The Week 52 Primary Analysis to assess the NASH Resolution Response and Fibrosis Response conducted on the mITT-LB-W52 population.
[b] The final primary analysis of the composite clinical outcome endpoint will occur when all subjects have completed the study (or discontinued early).
Abbreviations: F2, fibrosis stage 2; F3, fibrosis stage 3; LB, liver biopsy; MGL-3196, resmetirom; mITT, modified intent-to-treat; NASH, nonalcoholic steatohepatitis

Table 268. Protocol Summary, Trial MGL-3196-14

Protocol Number	MGL-3196-14
Title	A 52-Week, Phase 3 Study to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients with Nonalcoholic Fatty Liver Disease (NAFLD) (MAESTRO-NAFLD-1)
Phase	3
Principal/ Coordinating Investigator:	Stephen Harrison, MD
Study Objectives	**Primary Objective** To evaluate the safety and tolerability of once-daily, oral administration of 80 or 100 mg resmetirom versus matching placebo as measured by the incidence of adverse events (AEs) over 52 weeks.

	Key Secondary Objectives To determine the effect of resmetirom on: • Percent change from baseline to Week 24 in LDL-C, ApoB, TGs in subjects with baseline TGs > 150 mg/dL. • Percent change from baseline to Week 16 in hepatic fat fraction by MRI-PDFF. • FibroScan controlled attenuation parameter (CAP) score. • FibroScan vibration controlled transient elastography (VCTE) (kPa) in subjects with baseline LSM kPa ≥7.2 **Secondary Objectives** To determine the effect of resmetirom on: • Percent change from baseline to Week 24 in LDL-C and Apo B in patients with baseline LDL-C ≥ 100 mg/dL. • Percent change from baseline to Week 24 in Lipoprotein(a) [Lp(a)] in patients with baseline Lp(a) > 10 nmol/L. • Percent change from baseline to Week 48 in LDL-C, LDL-C in patients with baseline LDL-C ≥ 100 mg/dL, ApoB, ApoB in patients with baseline LDL-C ≥ 100 mg/dL, TGs in patients with baseline TGs > 150 mg/dL, <=150 and all TGs, Lp(a) in patients with baseline Lp(a) > 10 nmol/L • Change from baseline to Week 24 and Week 48 in Triglyceride rich lipoprotein-cholesterol (TRL-C), non-HDL-C, Apolipoprotein C-III, Lipoprotein particles (LDL, VLDL, HDL), Triglycerides • The proportion of very high-risk patients reaching LDL-C < 70 mg/dL or total treatment population reaching LDL-C < 100 mg/dL after 24 and 48 weeks of therapy. • Absolute and percent change after 16 weeks in percent hepatic fat fraction and on proportion of patients with ≥ 30% or ≥50% relative reduction in hepatic fat fraction by MRI-PDFF. • Absolute and percent change after 52 weeks in percent hepatic fat fraction, and on proportion of patients with ≥ 30% or ≥50% relative reduction in hepatic fat fraction by MRI-PDFF. • Liver parameters after 52 weeks • Inflammation and fibrosis biomarkers after 52 weeks, including: CK-18, adiponectin, PRO-C3, ELF test and 3 direct components of ELF, Reverse T3 (RT3) • Physical health-related and systemic aspects of QOL after 52 weeks, and Systemic Symptoms domains of CLDQ-NASH and the Activity domain of the WPAI-NASH QOL instruments. Multiple Exploratory objectives were specified.
Number of Patients	Planned: 1400, 969 NAFLD subjects included in pooled safety population analysis.

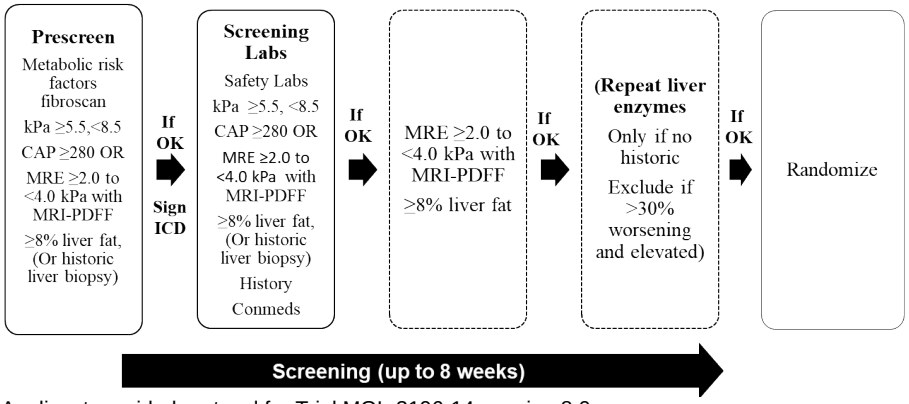
Target Population	Male and female patients ≥ 18 years of age with NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as “presumptive NASH” (not NAFL), and a cohort of patients with compensated NASH cirrhosis (Child Pugh-A).
Study Design	See Figure 63. This is a multicenter, double-blind, randomized, placebo-controlled study with an open-label arm in NAFLD who were at increased risk of NASH based on noninvasive testing, which the Applicant defined as “presumptive NASH” (not NAFL) patients, and an open-label arm with patients with compensated NASH cirrhosis (Child Pugh-A). After the first approximately 30 patients are enrolled in the open-label arm, patients who qualify for the study will be randomized in a 1:1:1:1 manner to receive double-blind resmetirom 100 mg, resmetirom 80 mg, matching placebo, or open-label resmetirom given orally once daily in the morning for 52 weeks. Implementation of an alternative dosing schedule due to tolerability issues or patient convenience may be permitted. Following enrollment of approximately 175 patients (excluding patients with moderate renal impairment [eGFR ≥ 30 and < 45 calculated using MDRD-6] and patients with compensated NASH cirrhosis), in total in the open-label arm randomization will switch to 1:1:1 (double-blind resmetirom 100 mg, resmetirom 80 mg, or matching placebo). Doses may be decreased in patients in open-label and blinded arms. The randomization will be stratified by baseline T2D status (presence/absence) and the population with documented ASCVD. After all patients have completed the 52-week study, the objectives, including Week 24 key secondary objectives, will be assessed. At Week 16, hepatic fat fraction will be assessed on serial MRI-PDFF (key secondary endpoint). Safety will be assessed throughout the study.
Test Product	Resmetirom 80 or 100 mg resmetirom tablets for oral administration given once daily. The tablet is manufactured in 40, 60, 80, and 100 mg dose strengths. Dose Adjustments are specified based on ≥ 30% decrease from baseline in FT4 to < 0.7 ng/dL, and tolerability concerns. To maintain the blind, the process to reduce the dose will be initiated by an unblinded team member. In the compensated NASH cirrhosis cohort, recommended to reduce dose to 60 mg based on post dose exposure > 1500 ng/ml and SHBG > 200% increased from baseline. Based on investigator discretion and/or discussion with Sponsor, the dose in cirrhotics may also be reduced to 40 mg every day or 80 mg every other day after the baseline visit.
Reference Product	Placebo matching resmetirom dose strengths

Statistical Methods	**Study Endpoints** ***Primary Endpoint*** The primary endpoint is the incidence of treatment-emergent adverse events (timeframe: for up to 52 weeks treatment and 30 days follow-up). ***Key Secondary Endpoints*** Key secondary endpoints that will be tested in a (fixed sequence) hierarchical manner by following the same order as they are listed: percent change from baseline to Week 24 in LDL-C; percent change from baseline to Week 24 in ApoB; percent change from baseline to Week 16 in the hepatic fat fraction variable based on MRI-PDFF; percent change from baseline to Week 24 in TGs in patients with baseline TGs > 150 mg/dL; change from baseline in FibroScan controlled attenuation parameter (CAP) scores; change from baseline to Week 52 in FibroScan VCTE (kPa) in patients with baseline kPa ≥7.2 and a Week 52 or end of treatment FibroScan (VCTE). ***Safety Analysis*** The primary endpoint is analysis of safety. The primary objective, safety, will be analyzed descriptively. ***Analyses of the Key Secondary Endpoints*** The key secondary endpoints analyses will be performed based on the mITT Population, defined as patients with baseline and at least one postbaseline assessment based on the study estimand for each key secondary endpoint. Other analyses include the per protocol population. ***Sample Size Determination*** This study is anticipated to include approximately 1,400 patients. Power determination for the first key secondary endpoint, percent change in LDL-C.

Eligibility

Subject prescreening criteria is displayed in Figure 62.

Figure 62. Prescreening and Screening Sequence



Source: Applicant provided protocol for Trial MGL-3196-14, version 8.0
Note: Dotted box or parentheses, test not mandatory; if eligible, prescreening FibroScan, no need to repeat at screening; Patients screened for MGL-3196-11 who failed eligibility because of liver biopsy do not need to repeat screening. Labs, if within 10 weeks of randomization. Patients with an eligible MRI-PDFF, if within 8 weeks (+3 days) of randomization, do not need a repeat MRI-PDFF for eligibility
Abbreviations: CAP, controlled-attenuation parameter; MGL-3196, resmetirom; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction

Key Inclusion Criteria

- Must be willing to participate in the study and provide written informed consent.
- Male and female adults ≥ 18 years of age.
- Contraception requirements for female participants of reproductive potential or male participants sexually active with a partner of childbearing potential.
- Suspected or confirmed diagnosis of NASH/NAFLD suggested by the historical data. Meet one of the following criteria.
  - Fibroscan with kPa ≥ 5.5 and < 8.5; CAP ≥ 280 $dB.m^{-1}$ OR MRE ≥ 2.0 and < 4.0; MRI-PDFF ≥ 8% liver fat consistent with steatosis and fibrosis stage ≥ 1 and < 4.
  - Recent liver biopsy (< 2 years) documenting NASH/NAFLD with steatosis showing one of the following:
    - NAS ≥ 4, steatosis ≥ 1, with fibrosis stage 0 (F0) OR with F1A/1C and PRO-C3 < 14
    - NAS < 4 steatosis ≥ 1, with fibrosis stage ≤ 3
    - NAS ≥ 4, steatosis ≥ 1, fibrosis stage ≤ 3, without ballooning

	▪ NAS = 3, steatosis 1, ballooning 1, inflammation 1 with F2 or F3 ▪ NAS = 3, ballooning 0 with F2 or F3 - For the compensated NASH cirrhosis arm, eligible patients must have compensated NASH cirrhosis diagnosed by liver biopsy showing NASH with F4 stage fibrosis (either historic or recent biopsy) or a historic biopsy with NASH F2-F3 fibrosis with subsequent progression to NASH cirrhosis as diagnosed by an expert hepatologist/gastroenterologist. The investigator should be able to document a sensible rationale/evidence that the underlying condition is NASH cirrhosis and not cirrhosis due to a different etiology. Cirrhosis must be well-compensated with no history of decompensation. - Compensated NASH cirrhosis at screening and baseline includes - Child-Pugh A (score 5–6) (may have either mild HE OR mild diuretic responsive ascites OR albumin < 3.5 and ≥ 3.2 ▪ MELD < 12 at screening/baseline ▪ Albumin ≥ 3.2. ▪ Bilirubin < 2 (unless documented Gilbert's Syndrome). • Patients must meet NAFLD/NASH criteria before obtaining an MRI-PDFF • Must be on stable, standard care dyslipidemia therapy for ≥ 30 days prior to randomization. Statin doses will be restricted. Patients on atorvastatin 40 mg may be switched to 10 or 20 mg rosuvastatin as atorvastatin is considered unsafe in cirrhosis. • Estimated GFR ≥ 45 (double-blind treatment arms) or ≥ 30 and < 45 (open-label treatment arm) by the Modification of Diet in Renal Disease 6-variable formula (MDRD-6). **Key Exclusion Criteria** • History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening • Regular use of drugs historically associated with NAFLD, and known hepatotoxins for more than 4 weeks within the last 8 weeks prior to the initial screening • Thyroid diseases, including active hyperthyroidism or untreated hypothyroidism • 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 ≥ 5% total body weight within 12 weeks prior to randomization • HbA1c > 9.0% • Glucagon-like peptide 1 [GLP-1] agonist therapy or high dose vitamin E (> 400 IU/day) unless stable for ≥ 24 weeks prior to randomization • Presence of cirrhosis on liver biopsy defined as stage 4 fibrosis is excluded from randomized arms. Patients with compensated NASH cirrhosis are eligible for the compensated NASH cirrhosis open-label active treatment arm. Patients

	with decompensated cirrhosis defined by hepatic encephalopathy ≥ 2, ascites due to cirrhosis requiring chronic diuretic treatment, or history of variceal bleeding are excluded • Diagnosis of HCC • MELD score ≥ 12, due to liver disease • Hepatic decompensation or impairment • Chronic liver diseases including primary biliary cholangitis, primary sclerosing cholangitis, Hepatitis B or C, and others • Active autoimmune disease • Serum ALT > 250 U/L. • Use of Pioglitazone > 15 mg per day • Platelet count < 140,000/mm^3. Patients with platelets < 140,000 and ≥ 100,000 /mm^3 are eligible if fibrosis-4 index (Fib-4) < 3.5. Compensated NASH cirrhotic patients qualifying for the open-label active treatment arm may have platelet counts ≥ 70,000/mm^3, irrespective of Fib-4. • History of biliary diversion Uncontrolled hypertension, arrhythmia, elevated QTcF interval, heart failure (New York Heart Association Class II or IV heart failure or known left ventricular ejection fraction <30%), or heart disease
Safety Monitoring	An unblinded independent DMC will evaluate safety data. The DMC will safety data including serious adverse events (SAEs) and pharmacodynamic results. The DMC will also review information from the blinded EAC, which includes cardiovascular assessments and potential MACE. A hepatic adjudication committee will review potential DILI episodes as defined in the protocol. **Summary of Assessments** • Study visits will be at Weeks 2, 4, and then every 4 weeks till Week 52. Post baseline the following safety monitoring will be done: • Health-related QoL assessment at weeks 24 and 52 • Child-Pugh Score at Weeks 2, 4, 12, 24,36, 48 and 52 • Physical examinations, vital signs, nutritional and lifestyle counseling at every visit • MELD, NAFLD fibrosis score, APRI, FIB-4 at Weeks 2,12,24, 36, 48, and 52 • ECG (12-lead) at week 2, 4, 8, 20, 28, 36, and 52 • MRI-PDFF, MRE, cT1 at Weeks 16 and 52 • Fibroscan and DEXA at Week 52 • Laboratory:

	- Hematology, chemistry, coagulation, SHBG, thyroid axis hormones, fasting lipid, serum/urine pregnancy test, and UA will be done at every visit. - Endocrinology at week 52 - Cardiac enzymes, ALP isoenzymes, additional fasting lipids, PAI-1, PRO-C3, other biomarkers, RT 3, at Week 12, 24, 36, and 52. Additional fasting lipids and PAI-1 will also be done Week 48. - Alcohol test (CDT) at Weeks 4, 12, 20, 28, 36, 44, 52 • AEs, concomitant medications and alcohol consumption will be assessed continuously.

Source: Applicant provided protocol for Trial MGL-3196-14, version 8.0
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DEXA, dual x-ray absorptiometry; FSH, follicle stimulating hormone; LH, luteinizing hormone; MDRD-6, modification of diet in renal disease 6-variable formula; MGL-3196, resmetirom; non-HDL-C, non-high-density lipoprotein cholesterol

Figure 63. Schematic, Trial MGL-3196-14

<table>
<tr><th>Enrollment/ Screening</th><th>Open-Label</th><th colspan="2">1:1:1:1 Randomization</th><th>1:1:1 Randomization (Blinded Treatment)</th><th>Follow-Up</th></tr>
<tr><td rowspan="6"></td><td rowspan="6">Resmetirom 100 mg (initial approximately 30 patients)</td><td rowspan="3">Blinded treatment</td><td>Resmetirom 100 mg</td><td>resmetirom 100 mg</td><td rowspan="6"></td></tr>
<tr><td>Resmetirom 80 mg</td><td>resmetirom 80 mg</td></tr>
<tr><td>Placebo</td><td>Placebo</td></tr>
<tr><td rowspan="4">Open-Label</td><td>Resmetirom 100 mg (until a total of approximately 175 open-label patients)</td><td></td></tr>
<tr><td colspan="2">Compensated NASH cirrhosis[1]</td></tr>
<tr><td colspan="2">Moderate renal impairment[2]</td></tr>
<tr><td colspan="2">MGL-3196-11 screen fails[3]</td></tr>
<tr><td>Up to 8 Weeks</td><td colspan="4">52-Week treatment period</td><td>28 days±3 Post Treatment</td></tr>
</table>

Source: Applicant provided protocol for Trial MGL-3196-14, version 8.0
[1.] Subjects with compensated NASH cirrhosis will enroll into open-label 80 mg treatment arm.
[2.] Subjects with eGFR ≥30 and <45 (calculated using MDRD-6) enroll directly into the open-label 100 mg treatment arm.
[3.] Subjects who screen fail from Trial MGL-3196-11 because of a liver biopsy result of either F2 or F3 with NAS 3, steatosis 1, ballooning 1, inflammation 1, or NAS 3 and ballooning 0 are eligible for the open-label 100 mg treatment arm.
Abbreviations: NASH, nonalcoholic steatohepatitis

16. Efficacy

16.1. Histopathology Read Process

Primary reads followed the steps below according to the Applicant:

1. About 20 groups of 5 random screen failure liver biopsies, 50 screening liver biopsies, and 50 Week-52 liver biopsies from the same participants were prepared. The 50 screening liver biopsies were mixed in a box labeled “Screening”, and the 50 Week-52 liver biopsies were boxed separately and labeled “52-weeks.”
2. Two pathologists read the 20 groups of liver biopsies independently to rate scores for steatosis, ballooning and lobular inflammation, and fibrosis stage.

16.2. Additional Histology Analyses

16.2.1. Number of Participants in Each Response Category for SAP Endpoint Definitions

Table 269 presents the number of participants in each response category (i.e., responder, two pathologists disagree, and nonresponder) when the primary analysis of the Week 52 primary endpoints uses the endpoint definitions as specified in SAP using Agency's analysis population. Table 270 presents the same sets of results when the endpoint definitions are as specified in SAP except that the improvement or worsening of fibrosis stage follows Agency's consideration (i.e., a change from any stage 1 [i.e., 1A, 1B, or 1C] to stage 2 of fibrosis is a worsening of fibrosis, and a change from stage 2 to any stage 1 is an improvement in fibrosis). About 5% of participants fall in a different response category when the endpoint definition changes from the guidance endpoint. The conclusions of these analyses were consistent with that of the primary analyses and support the beneficial treatment effect of resmetirom 80 mg and resmetirom 100 mg compared to placebo.

Table 269. Week 52 Interim Analysis Primary Endpoints Based on SAP Endpoint Definitions, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Endpoint Statistic Pathologist Read	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296
Resolution of NASH and no worsening of liver fibrosis (SAP endpoint)			
Model-based response rate (%)[1]	9	24	28
Responder; two pathologists agree, n (%)	15 (5)	56 (19)	52 (18)
Two pathologists disagree, n (%)	24 (8)	33 (11)	64 (22)
Nonresponder; two pathologists agree, n (%)	255 (87)	209 (70)	180 (61)
Difference in response rate vs. placebo[1] (95% CI)[2]		15 (10, 21)	19 (14, 25)
p-value[3]		<0.0001	<0.0001
Improvement of fibrosis and no worsening of NASH (SAP endpoint)			
Model-based response rate (%)[1]	14	24	24
Responder; two pathologists agree, n (%)	25 (9)	47 (16)	45 (15)
Two pathologists disagree, n (%)	30 (10)	46 (15)	54 (18)
Nonresponder; two pathologists agree, n (%)	239 (81)	205 (69)	197 (67)
Difference in response rate vs. placebo[1] (95% CI)[2]		10 (4, 16)	11 (5, 16)
p-value[3]		0.0004	0.0001

Source: Statistical reviewer analysis of adsl.xpt and admi.xpt datasets.
Note: The response value for a subject is 1 if the two pathologists agree that the subject is a responder, 0.5 if the two pathologists disagree, and 0 if the two pathologists agree that the subject is a nonresponder. Participants without a liver biopsy or with a liver biopsy outside of the target analysis window were considered nonresponders. Participants with a missing histopathology reading by a pathologist were considered rated as nonresponder by the pathologist.
[1] Calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The response rate in the placebo group can be calculated from the comparison with the resmetirom 80 mg or 100 mg group, and the results are similar. The presented results for the placebo group are based on the comparison with the resmetirom 100 mg group.
[2] 95% Wald CIs based on Mantel-Haenszel mean score statistics.
[3] Calculated using CMH test stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3).
Abbreviations: CI, confidence interval; NASH, nonalcoholic hepatitis

Table 270. Week 52 Interim Analysis Primary Endpoints Based on SAP Endpoint Definitions With Agency Consideration for Improvement or Worsening of Fibrosis, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Endpoint Statistic Pathologist Read	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296
Resolution of NASH and no worsening of liver fibrosis (SAP endpoint with Agency consideration for improvement or worsening of fibrosis)			
Model-based response rate (%)[1]	9	24	28
Responder; two pathologists agree, n (%)	15 (5)	55 (18)	51 (17)
Two pathologists disagree, n (%)	23 (8)	34 (11)	65 (22)
Nonresponder; two pathologists agree, n (%)	256 (87)	209 (70)	180 (61)
Difference in response rate vs. placebo[1] (95% CI)[2]		15 (10, 21)	19 (14, 25)
p-value[3]		<0.0001	<0.0001
Improvement of fibrosis and no worsening of NASH (SAP endpoint with Agency consideration for improvement or worsening of fibrosis)			
Model-based response rate (%)[1]	16	25	27
Responder; two pathologists agree, n (%)	31 (11)	51 (17)	55 (19)
Two pathologists disagree, n (%)	31 (11)	46 (15)	51 (17)
Nonresponder; two pathologists agree, n (%)	232 (79)	201 (67)	190 (64)
Difference in response rate vs. placebo[1] (95% CI)[2]		9 (3, 15)	12 (6, 17)
p-value[3]		0.002	0.0001

Source: Statistical reviewer analysis of adsl.xpt and admi.xpt datasets
Note: The response value for a subject is 1 if the two pathologists agree that the subject is a responder, 0.5 if the two pathologists disagree, and 0 if the two pathologists agree that the subject is a nonresponder. Participants without a liver biopsy or with a liver biopsy outside of the target analysis window were considered nonresponders. Participants with a missing histopathology reading by a pathologist were considered rated as nonresponder by the pathologist.
[1] Calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The response rate in the placebo group can be calculated from the comparison with the resmetirom 80 mg or 100 mg group, and the results are similar. The presented results for the placebo group are based on the comparison with the resmetirom 100 mg group.
[2] 95% Wald CIs based on Mantel-Haenszel mean score statistics.
[3] Calculated using CMH test stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3).
Abbreviations: CI, confidence interval; NASH, nonalcoholic hepatitis

16.2.2. Multiple Imputation Sensitivity Analysis for Week 52 Primary Endpoints

In the primary analysis of the Week 52 primary endpoints, missing data were considered nonresponders. The SAPs and Addenda specified sensitivity analyses using multiple imputation (MI), which made the missing-at-random (MAR) assumption. While these sensitivity analyses assume MAR for the purposes of investigating the impact of missing data, it is not clear that a MAR assumption is reasonable for missing data due to study discontinuation; participants who discontinue the study within 52 weeks, and therefore discontinue study treatment, likely do not incur the same benefit on long-term clinical outcomes as those participants who remain on long-term treatment. The ultimate goal of treatment is to have a beneficial effect on clinical outcomes, not only on histological surrogate endpoints.

The SAPs Version 1.0 and 3.0 prespecified the following MI steps:

- Missing values for the primary endpoints would be imputed using a logistic regression model adjusting for treatment group, baseline type 2 diabetes (presence or absence), baseline fibrosis stage (stage 2 or 3), and pathologist. Seed was specified as 83860444.
- The results from the Cochran-Mantel-Haenszel test used in the primary analysis would be normalized and pooled across the 50 imputed datasets using Rubin's rule (Rubin 1987).

The first SAP Addendum (December 15, 2022, submitted after unblinding) specified the following:

- Spearman correlation coefficient between the two pathologists from the available data would be used to generate a correlated pair of binary data for the missing values in the primary endpoints.
- The Cochran-Mantel-Haenszel test statistics would be transformed using the Wilson & Hilferty transformation (Wilson and Hilferty 1931), as described in (Ratitch et al. 2013), before pooling, using Rubin's rule (Rubin 1987).

The second SAP Addendum specified the same steps as the first SAP Addendum and specified that results would be pooled across 100 imputed datasets, instead of the 50 imputed datasets specified in Versions 1.0 and 3.0. However, it was not clear for each participant with missing values how the probability of being a responder read by each pathologist would be generated (i.e., whether the probability of being a responder would be generated based on the logistic regression model specified in SAPs Version 1.0 and 3.0).

In the interim CSR, the Applicant submitted results based on the second SAP Addendum; for each participant with missing values, the probability of being a responder read by each pathologist was estimated as the proportion of responders among all participants with observed data from that pathologist.

The Agency additionally evaluated the MI using the following steps:

- Step 1, as specified in the SAPs Version 1.0 and 3.0.
- The results from the Cochran-Mantel-Haenszel test used in the primary analysis would be transformed using the Wilson & Hilferty transformation (Wilson and Hilferty 1931), as described in(Ratitch et al. 2013), and pooled across the 100 imputed datasets using Rubin's rule (Rubin 1987).

Table 271 presents the results for the sensitivity analyses of the primary endpoints based on MI, as specified by the Applicant in the SAP Addenda and additional MI performed by the Agency. The conclusions of sensitivity analyses were consistent with that of the primary analyses and support the beneficial treatment effect of resmetirom 80 mg and resmetirom 100 mg compared to placebo.

Table 271. Sensitivity Analysis Results Based on Multiple Imputation, Week 52 Interim Analysis Primary Endpoint, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads and FDA Draft Guidance for Industry), Trial MGL-3196-11

Analysis	Placebo N=294 (%)[1]	80 mg N=298 (%)[1]	100 mg N=296 (%)[1]	Risk Difference 80 mg-Placebo[1] (95% CI)[2]	p-value 80 mg[3]	Risk Difference 100 mg-Placebo[1] (95% CI)[2]	p-value 100 mg[3]
Resolution of NASH and no worsening of liver fibrosis							
Agency primary analysis[4]	11	26	30	15 (10, 21)	<0.0001	19 (13, 25)	<0.0001
MI as specified in SAP Addenda[5]	13	33	41	20 (14, 27)	<0.0001	27 (21, 34)	<0.0001
Additional MI performed by Agency[6]	13	33	40	21 (14, 27)	<0.0001	27 (21, 34)	<0.0001
Improvement of fibrosis and no worsening of NASH							
Agency primary analysis[4]	14	23	26	9 (4, 15)	0.0009	12 (7, 18)	<0.0001
MI as specified in SAP Addenda[5]	16	29	35	13 (7, 20)	0.0001	19 (12, 26)	<0.0001
Additional MI performed by Agency[6]	16	30	35	13 (7, 20)	<0.0001	19 (12, 25)	<0.0001

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt dated September 7, 2023 and admi.xpt datasets

1. Calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3).
2. 95% Wald CIs based on Mantel-Haenszel mean score statistics.
3. Calculated using CMH test stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). For multiple imputation, results from the CMH test were transformed using the Wilson & Hilferty transformation and pooled across 100 imputed datasets using Rubin's rule.
4. Agency primary analysis uses eligibility read to define the analysis population with F2 or F3 fibrosis and the baseline fibrosis stage for the stratification factor, and uses primary reads to define the primary endpoints according to the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018).
5. Missing values were imputed using correlated pairs of binary data where the probability of being a responder for each pathologist was estimated as the proportion of responders among all participants with available data determined by the pathologist, and the correlation was estimated by the Spearman correlation coefficient between the two pathologists from the available data.
6. Missing values were imputed using a logistic regression model adjusting for treatment group, baseline type 2 diabetes (presence or absence), baseline fibrosis stage (stage 2 or 3), and pathologist.

Abbreviations: CI, confidence interval; MI, multiple imputation; NASH, nonalcoholic hepatitis; SAP, statistical analysis plan

16.2.3. Generalized Estimating Equation for Week 52 Primary Endpoints

The SAPs specified that a generalized estimating equation model would be fit assuming the responder status rated by the two pathologists were repeated measurements for the same participant. The model would adjust for treatment groups, baseline type 2 diabetes status (presence or absence), baseline fibrosis stage (stage 2 or 3), pathologists, and treatment-by-pathologist interaction, and would use a logit link function and a compound symmetric covariance structure.

Table 272 presents results from the generalized estimating equation model submitted by the Applicant in the interim CSR for Trial MGL-3196-11; the analysis population is as specified by the Applicant and included all F1B, F2, and F3 participants (as defined by the Applicant's algorithm) who were randomized on or before July 31, 2021, excluding participants who were missing a Week 52 biopsy due to the COVID-19 pandemic; there were 318 participants in the placebo group, 316 in the resmetirom 80 mg group, and 321 in the resmetirom 100 mg group in this population. Despite the difference in the analysis population and the endpoint definitions, the conclusions from the generalized estimating equation model were consistent with that of the primary analyses and support the beneficial treatment effect of resmetirom 80 mg and resmetirom 100 mg compared to placebo.

Table 272. Results Based on GEE, Week 52 Interim Analysis Primary Endpoint, All Participants With Stage 1B, 2, or 3 Fibrosis (as Defined by Applicant) Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads and SAP), Trial MGL-3196-11

Endpoint	Risk Difference 80 mg-Placebo (95% CI)	p-value 80 mg	Risk Difference 100 mg-Placebo (95% CI)	p-value 100 mg
Resolution of NASH and no worsening of liver fibrosis	18 (12, 23)	<0.0001	21(15, 27)	<0.0001
Improvement of fibrosis and no worsening of NASH	10 (4, 15)	0.0003	11 (6, 16)	<0.0001

Source: Interim clinical study report MGL-3196-11 Table 18 (page 85).
Abbreviations: CI, confidence interval; GEE, generalized estimating equation; NASH, nonalcoholic hepatitis; SAP, statistical analysis plan

16.2.4. Composite Strategy to Handle Intercurrent Events of Treatment Discontinuation

Table 273 presents efficacy results that use composite strategy to handle intercurrent events of treatment discontinuation for the endpoint of resolution of NASH and no worsening of liver fibrosis. There is one participant affected for this endpoint and the results support the beneficial treatment effect of resmetirom 80 mg and resmetirom 100 mg compared to placebo. There is no participant affected for the endpoint of improvement of fibrosis and no worsening of NASH.

Table 273. Week 52 Interim Analysis Primary Endpoint Results Using Composite Strategy to Handle Treatment Discontinuation, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads and FDA Draft Guidance for Industry), Trial MGL-3196-11

Resolution of NASH and No Worsening of Liver Fibrosis	Placebo N=294	Resmetirom 80 mg N=298	Resmetirom 100 mg N=296
Model-based response rate (%)[1]	11	26	30
Responder; two pathologists agree, n (%)	18 (6)	60 (20)	54 (18)
Two pathologists disagree, n (%)	29 (10)	37 (12)	68 (23)
Nonresponder; two pathologists agree, n (%)	247 (84)	201 (67)	174 (59)
Difference in response rate vs. placebo[1] (95% CI)[2]		15 (10, 21)	19 (13, 24)
p-value[3]		<0.0001	<0.0001

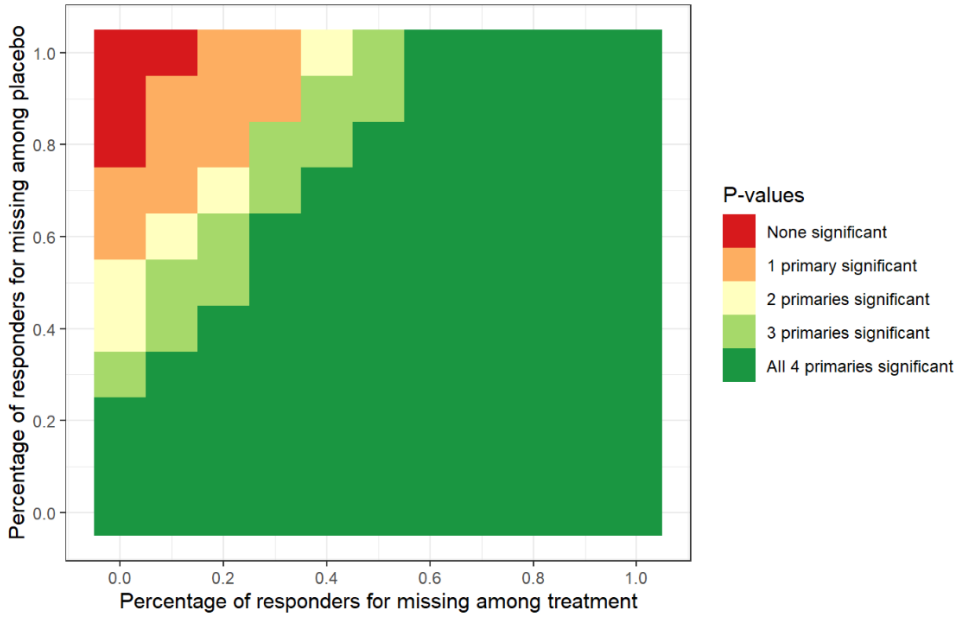
Source: Statistical reviewer analysis of adsl.xpt and admi.xpt datasets.
Note: The response value for a subject is 1 if the two pathologists agree that the subject is a responder, 0.5 if the two pathologists disagree, and 0 if the two pathologists agree that the subject is a nonresponder. Participants without a liver biopsy or with a liver biopsy outside of the target analysis window were considered nonresponders. Participants with a missing histopathology reading by a pathologist were considered rated as nonresponder by the pathologist.
Note: FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment* (December 2018).
[1] Calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The response rate in the placebo group can be calculated from the comparison with the resmetirom 80 mg or 100 mg group and the results are similar. The presented results for the placebo group are based on the comparison with the resmetirom 100 mg group.
[2] 95% Wald CIs based on Mantel-Haenszel mean score statistics. 95% CIs cannot be used to determine statistical significance.
[3] Calculated using CMH test stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3).
Abbreviations: CI, confidence interval; NASH, nonalcoholic hepatitis

16.2.5. Additional Tipping Point Analysis Results

Figure 64 presents a consolidation of the tipping point analyses results presented in Figure 5 in Section 6.2.1.4 for each of the four separate hypotheses (i.e., two dose groups of resmetirom and the two histologic surrogate endpoints) assuming the same percentage of responders for missing data in each treatment arm for each of the hypotheses and combining those into a single summary of the number of statistically significant results.

Some of the four hypotheses start to become nonsignificant in scenarios where there were 30% or more responders assumed for the missing values in the placebo group compared to the resmetirom groups and 50% or less responders were assumed for the missing values in the resmetirom groups. Given the available data, it is unlikely that there are 30% or more responders in the placebo group compared to the resmetirom groups among missing values. Additionally, the tipping points to nonsignificant results for all four hypotheses only occurred when the following pairs of percentages of responder were used to impute the missing values in the placebo and resmetirom groups, (80%, 0%), (90%, 0%), (100%, 0%), (100%, 10%), where the first percentage in each pair represent the percentage of responder used to impute the missing values in the placebo group, and the second percentage in each pair represent the percentage of responder used to impute the missing values in the resmetirom 80 mg or 100 mg group. Therefore, the tipping point assumptions were considered implausible.

Figure 64. Week 52 Interim Analysis Primary Endpoint Tipping Point Analysis Results Assuming Same Percentage of Responders for Missing Values Across Hypotheses, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads and FDA Draft Guidance for Industry), Trial MGL-3196-11



Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt datasets
Note: p-values from the CMH test were transformed using the Wilson & Hilferty transformation and pooled across 100 imputed datasets using Rubin's rule.
Note: FDA draft guidance for industry, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (December 2018).
Abbreviations: Cochran-Mantel-Haenszel (test); FDA, U.S. Food and Drug Administration

16.2.6. Subgroup Analyses by Different Weight Cutoffs

Table 274 and Table 275 present subgroup results by different weight cutoffs supporting Figure 2 in Section 6.1 comparing resmetirom 80 mg and 100 mg to placebo for primary analyses of the Week 52 primary endpoints as performed in Section 6.3.2. There were no clear differential results by weight subgroups comparing resmetirom 80 mg or 100 mg to placebo.

Table 274. Subgroup Analyses by Different Weight Cutoffs for Resolution of NASH and No Worsening of Liver Fibrosis by Eligibility Read in All Participants With Stage 2 or Stage 3 Fibrosis Randomized on or Before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Subgroup Type	N	Placebo N=294 (%)	80 mg N=298 (%)	100 mg N=296 (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Overall	888	11	26	30	15 (10, 21)	19 (13, 25)
Weight cutoff 80 kg						
<80 kg	161	11	30	30	18 (5, 32)	19 (6, 32)
≥80 kg	727	11	26	30	15 (8, 21)	19 (13, 25)
Weight cutoff 90 kg						
<90 kg	306	15	30	32	16 (5, 26)	18 (8, 28)
≥90 kg	582	9	24	29	15 (9, 22)	20 (13, 27)
Weight cutoff 100 kg						
<100 kg	465	13	30	30	17 (9, 25)	17 (9, 25)
≥100 kg	423	9	23	30	14 (6, 21)	21 (13, 29)
Weight cutoff 110 kg						
<110 kg	613	11	30	32	19 (12, 26)	21 (14, 28)
≥110 kg	275	11	19	27	7 (-2, 17)	15 (5, 26)
Weight cutoff 120 kg						
<120 kg	724	12	29	31	17 (10, 23)	19 (13, 25)
≥120 kg	164	5	17	26	12 (1, 23)	20 (8, 33)
Weight cutoff 130 kg						
<130 kg	794	11	28	32	17 (11, 23)	20 (14, 26)
≥130 kg	94	7	10	20	3 (-11, 17)	13 (-3, 28)
Weight categories						
<80 kg	161	11	30	30	18 (5, 32)	19 (6, 32)
≥80 to <90 kg	145	17	30	35	12 (-4, 27)	18 (2, 33)
≥90 to <100 kg	159	9	30	26	20 (6, 34)	17 (4, 29)
≥100 to <110 kg	148	5	31	36	26 (12, 40)	31 (17, 45)
≥110 to <120 kg	111	19	23	30	4 (-13, 20)	10 (-7, 27)
≥120 to <130 kg	70	3	24	35	22 (5, 39)	31 (10, 53)
≥130 kg	94	7	10	20	3 (-11, 17)	13 (-3, 28)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Percentages of responders and differences in response rates were calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The 95% CIs are Wald CIs based on Mantel-Haenszel mean score statistics.
Abbreviations: CI, confidence interval; NASH, nonalcoholic hepatitis

Table 275. Subgroup Analyses by Different Weight Cutoffs for Improvement of Fibrosis and No Worsening of NASH in All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or before July 31, 2021 (Endpoints Defined by Primary Reads), Trial MGL-3196-11

Subgroup Type	N	Placebo N=294 (%)	80 mg N=298 (%)	100 mg N=296 (%)	Risk Difference 80 mg-Placebo (95% CI)	Risk Difference 100 mg-Placebo (95% CI)
Overall	888	14	23	26	9 (4, 15)	12 (7, 18)
Weight cutoff 80 kg						
<80 kg	161	10	26	29	16 (2, 29)	18 (5, 32)
≥80 kg	727	15	23	26	8 (2, 14)	11 (5, 17)
Weight cutoff 90 kg						
<90 kg	306	15	28	29	14 (4, 24)	15 (4, 25)
≥90 kg	582	14	21	25	7 (0, 13)	11 (4, 18)
Weight cutoff 100 kg						
<100 kg	465	16	27	27	11 (3, 19)	11 (2, 19)
≥100 kg	423	12	19	26	7 (0, 15)	14 (6, 21)
Weight cutoff 110 kg						
<110 kg	613	13	26	27	13 (6, 19)	14 (7, 21)
≥110 kg	275	16	18	25	2 (-8, 12)	9 (-1, 19)
Weight cutoff 120 kg						
<120 kg	724	14	25	27	11 (4, 17)	13 (7, 19)
≥120 kg	164	13	18	24	4 (-8, 17)	11 (-2, 23)
Weight cutoff 130 kg						
<130 kg	794	14	24	26	10 (4, 16)	12 (6, 18)
≥130 kg	94	14	22	28	10 (-8, 28)	15 (-2, 31)
Weight categories						
<80 kg	161	10	26	29	16 (2, 29)	18 (5, 32)
≥80 to <90 kg	145	20	30	30	13 (-2, 28)	10 (-5, 26)
≥90 to <100 kg	159	19	23	22	3 (-11, 16)	3 (-11, 17)
≥100 to <110 kg	148	6	22	28	16 (5, 28)	22 (10, 34)
≥110 to <120 kg	111	19	18	26	-1 (-18, 15)	7 (-9, 24)
≥120 to <130 kg	70	12	15	13	2 (-15, 18)	1 (-20, 21)
≥130 kg	94	14	22	28	10 (-8, 28)	15 (-2, 31)

Source: Reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Note: Percentages of responders and differences in response rates were calculated using the Mantel-Haenszel method stratified by baseline type 2 diabetes status (presence or absence) and fibrosis stage (F2 or F3). The 95% CIs are Wald CIs based on Mantel-Haenszel mean score statistics.
Abbreviations: CI, confidence interval; NASH, nonalcoholic hepatitis

16.2.7. Intra- and Inter-Reader Reliability on Histology

The SAPs specified that the intra-reader reliability would be estimated for both pathologists by comparing the eligibility read and the primary read of the screening liver biopsy. However, because only one pathologist read the screening liver biopsy at screening for the eligibility read, the Applicant only evaluated the intra-reader reliability for pathologist A. Weighted kappa coefficients using Cicchetti-Allison weights, where disagreements further from the diagonal of perfect agreement have smaller weights, would be provided for fibrosis stage, ballooning, lobular inflammation, steatosis, and NAS score.

The SAPs also specified that the inter-reader reliability would be estimated by comparing the primary read by the two pathologists for both the screening and Week 52 liver biopsies. Weighted kappa coefficients using Cicchetti-Allison weights would be provided for histological features and NAS score for both the screening and Week 52 liver biopsies, and the responder status for both Week 52 primary endpoints.

Table 276 and Table 277 present the results for intra- and inter-reader reliability, and Table 278 presents contingency table for Week 52 interim analysis primary endpoints by two pathologists. The results show that the weighted kappa coefficients are all around 0.4 for the histologic feature lobular inflammation, indicating a low agreement for lobular inflammation both within pathologist A and across the two pathologists. Additionally, it is not clear why the weighted kappa coefficients for histologic features across the two pathologists are consistently higher for Week 52 liver biopsy than the screening liver biopsy.

Table 276. Intra- and Inter-Reader Reliability for Histological Features and NAS Score, Trial MGL-3196-11

Reliability Type	Fibrosis Stage	Ballooning	Lobular Inflammation	Steatosis	NAS
Pathologist A intra-reader reliability	0.65	0.60	0.44	0.74	0.54
Inter-reader reliability					
Screening liver biopsy	0.56	0.35	0.33	0.50	0.41
Week 52 liver biopsy	0.65	0.52	0.36	0.62	0.62

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Note: Weighted kappa coefficients using Cicchetti-Allison weights were calculated.
Abbreviations: NAS, NAFLD activity score

Table 277. Inter-Reader Reliability for Responder Status for Week 52 Interim Analysis Primary Endpoints, Trial MGL-3196-11

Resolution of NASH and No Worsening of Liver Fibrosis	Improvement of Fibrosis and No Worsening of NASH
0.54	0.53

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Weighted kappa coefficients using Cicchetti-Allison weights were calculated.
Abbreviations: NASH, nonalcoholic hepatitis

Table 278. Contingency Tables for Week 52 Interim Analysis Primary Endpoints by Two Pathologists on Primary Reads, Trial MGL-3196-11

Resolution of NASH and No Worsening of Liver Fibrosis (SAP Endpoint)			
		Pathologist B	
		Responder	Nonresponder
Pathologist A	Responder	133	94
	Nonresponder	37	440

Improvement of Fibrosis and No Worsening of NASH (SAP Endpoint)			
		Pathologist B	
		Responder	Nonresponder
Pathologist A	Responder	122	76
	Nonresponder	54	452

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, dated September 7, 2023, and admi.xpt
Based on observed data. Missing data were considered nonresponders in the primary analysis of the Week 52 interim analysis primary endpoints by Agency.
Abbreviations: NASH, nonalcoholic hepatitis; SAP, statistical analysis plan

16.3. Additional LDL-C Analysis Details and Results

16.3.1. Analysis Details for Key Secondary Endpoint

The analysis population specified by the Applicant differed from that specified for the primary endpoints and included participants who were missing a Week 52 biopsy due to the COVID-19 pandemic; the analysis population was defined as all F1B, F2, and F3 participants who were randomized on or before July 31, 2021. The Agency used the same analysis population as that used for the primary endpoints to analyze the key secondary endpoint, defined as all F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021.

The SAP prespecified a mixed-effect model for repeated measures (MMRM) to compare resmetirom 80 mg to placebo and resmetirom 100 mg to placebo. The percentage change in LDL-C from baseline to all fasting visits (Weeks 4 to 52 by four-week increments except Week 8) would be modeled. Week 8 was excluded because it represented a nonfasting visit. The MMRM model adjusted for baseline LDL-C, treatment group, visit (categorical in weeks), baseline type 2 diabetes (presence or absence), baseline fibrosis stage (stage 2 or 3), baseline LDL-C-by-visit interaction, and treatment-by-visit interaction. An unstructured covariance matrix was used in the analysis. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

For the primary analysis of the key secondary endpoint, the SAP additionally specified imputation methods for missing LDL-C measurements caused by COVID-19 pandemic based on strategies including last observation carried forward and MI.

The second SAP Addendum after unblinding specified that in addition to the analyses specified in the SAP, an analysis of covariance (ANCOVA) model would be used to perform analyses on the multiply imputed datasets. Details for the ANCOVA model were not provided in the second SAP Addendum. The interim CSR submitted results from an ANCOVA model based on multiply

imputed datasets where missing LDL-C measurements caused by COVID-19 pandemic were imputed using the method specified in the SAP, as described in Section 16.3.2.

The datasets for LDL-C submitted by the Applicant did not clearly define which LDL-C measurements were missing due to the COVID-19 pandemic. Therefore, the Agency was not able to evaluate the prespecified analysis or the analysis submitted in the interim CSR. To compare to the results submitted by the Applicant from their analyses, the Agency evaluated the key secondary endpoint using MMRM without first imputing the missing LDL-C measurements caused by the COVID-19 pandemic. The MMRM assumes MAR for the missing measurements.

16.3.2. Imputation for Missing LDL-C Measurement Caused by COVID-19 Pandemic

In the primary analysis of the key secondary endpoint, the SAPs specified that missing LDL-C measurements caused by the COVID-19 pandemic would be imputed using the following steps:

- For Weeks 16 to 52, if the LDL-C measurement at the prior visit was not missing, missing values were imputed by the measurement at the prior visit; otherwise, missing values were imputed by the following visit.
- For Week 12, if the LDL-C measurement at Week 16 was not missing, missing values were imputed by the measurement at Week 16; otherwise, missing values were imputed by Week 4.
- For visits where the missing LDL-C measurements caused by COVID-19 pandemic were still missing following the single imputation above, the missing values would be imputed assuming MAR, adjusting for visit (categorical in weeks), treatment group, baseline type 2 diabetes (presence or absence), and baseline fibrosis stage (stage 2 or 3).

As the analysis method for the key secondary endpoint—MMRM—assumes MAR for missing values, the Agency evaluated the key secondary endpoint using MMRM without first imputing the missing LDL-C measurements caused by the COVID-19 pandemic.

16.3.3. Missing Data for Key Secondary Endpoint

Table 279 presents the number and the percentage of participants who had missing data for the key secondary endpoint LDL-C at each study week (visit) where the data were used for the key secondary endpoint analysis. The percentage of participants who had missing data for the key secondary endpoint increases over study week, and the percentage of participants who had missing data is higher when the dose of resmetirom is higher.

Table 279. Missing Key Secondary Endpoint LDL-C by Study Week, Week 52 Interim Analysis, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Study Week	Placebo N=294 n (%)	Resmetirom 80 mg N=298 n (%)	Resmetirom 100 mg N=296 n (%)
Baseline	1 (0.3)	6 (2.0)	4 (1.4)
Week 4	8 (2.7)	13 (4.4)	9 (3.0)
Week 12	13 (4.4)	25 (8.4)	34 (11.5)
Week 16	17 (5.8)	23 (7.7)	36 (12.2)
Week 20	25 (8.5)	27 (9.1)	50 (16.9)
Week 24	25 (8.5)	29 (9.7)	35 (11.8)
Week 28	24 (8.2)	38 (12.8)	51 (17.2)
Week 32	25 (8.5)	39 (13.1)	49 (16.6)
Week 36	28 (9.5)	38 (12.8)	45 (15.2)
Week 40	30 (10.2)	45 (15.1)	55 (18.6)
Week 44	38 (12.9)	44 (14.8)	55 (18.6)
Week 48	35 (11.9)	46 (15.4)	59 (19.9)
Week 52	33 (11.2)	40 (13.4)	57 (19.3)

Source: Statistical reviewer analysis using Applicantsubmitted dataset adsl.xpt, dated September 7, 2023, admi.xpt and adlbc.xpt.
Abbreviations: LDL-C, low-density lipoprotein-cholesterol

16.3.4. Results for Key Secondary Endpoint

Table 280 presents the Applicant's-submitted results for the key secondary endpoint based on MMRM and ANCOVA analyses of multiply imputed data and Agency-performed analysis based on MMRM analyses using observed data without prior imputation. The results show that regardless of the analysis method, the comparisons of both resmetirom 80 mg and 100 mg groups to placebo group meet statistical significance on the key secondary endpoint.

Table 280. Key Secondary Endpoint Results, Week 52 Interim Analysis, Trial MGL-3196-11

LDL-C (mmol/L)	Placebo	Resmetirom 80 mg	Resmetirom 100 mg	LS Mean Difference 80 mg-Placebo	p-value 80 mg[4]	LS Mean Difference 100 mg-Placebo	p-value 100 mg[4]
	N=294	N=298	N=296				
Baseline, mean (SD)[1]	2.8 (1.1)	2.8 (1.0)	2.6 (1.0)				
Week 24, mean (SD)[1]	2.7 (1.0)	2.3 (0.8)	2.2 (0.8)				
Percent Change From Baseline to Week 24, LS Mean (95% CI)							
MMRM on multiply imputed data[2, 3]	N=321	N=322	N=323				
	1.0 (-1.9, 4.0)	-12.8 (-16, -9.8)	-14.3 (-17, -11)	-13.5 (-17, -10)	<0.0001*	-15.3 (-19, -12)	<0.0001*
ANCOVA on multiply imputed data[2]	N=321	N=321	N=323				
	0.11 (-3.2, 3.4)	-13.6 (-17, -10)	-16.3 (-20, -13)	-13.7 (-17, -10)	<0.0001*	-16.4 (-20, -13)	<0.0001*
Agency analysis based on MMRM[1, 3]	N=294	N=298	N=296				
	1.9 (-0.9, 4.7)	-11.7 (-15, -8.9)	-14.0 (-17, -11)	-13.5 (-17, -10)	<0.0001*	-15.9 (-20, -12)	<0.0001*

Source: Interim Clinical Study Report MGL-3196-11 Table 22 (page 96), Applicant response to IR, dated January 22, 2024, and statistical reviewer analysis using Applicant-submitted dataset adsl.xpt, dated September 7, 2023, admi.xpt and adlbc.xp.

[1] Based on observed data in the analysis population used by Agency, which was defined as all F2 and F3 participants as determined by eligibility read who were randomized on or before July 31, 2021.

[2] Applicant submitted results based on the analysis population specified by the Applicant, which was defined as all F1B, F2, and F3 participants (as defined by the Applicant's algorithm based on primary reads) who were randomized on or before July 31, 2021. Participants who were missing a Week 52 biopsy due to the COVID-19 pandemic were included in the analysis for key secondary endpoint. The sample sizes for the resmetirom 80 mg group differ by one subject in the two analyses submitted by the Applicant.

[3] LS means and LS mean differences were estimated from a mixed-effect model for repeated measures (MMRM) for percentage change in LDL-C from baseline, adjusting for baseline LDL-C, treatment group, visit (categorical in weeks), baseline type 2 diabetes (presence or absence), baseline fibrosis stage (stage 2 or 3), baseline LDL-C-by-visit interaction, and treatment-by-visit interaction, using within-arm means at mean values of the covariates.

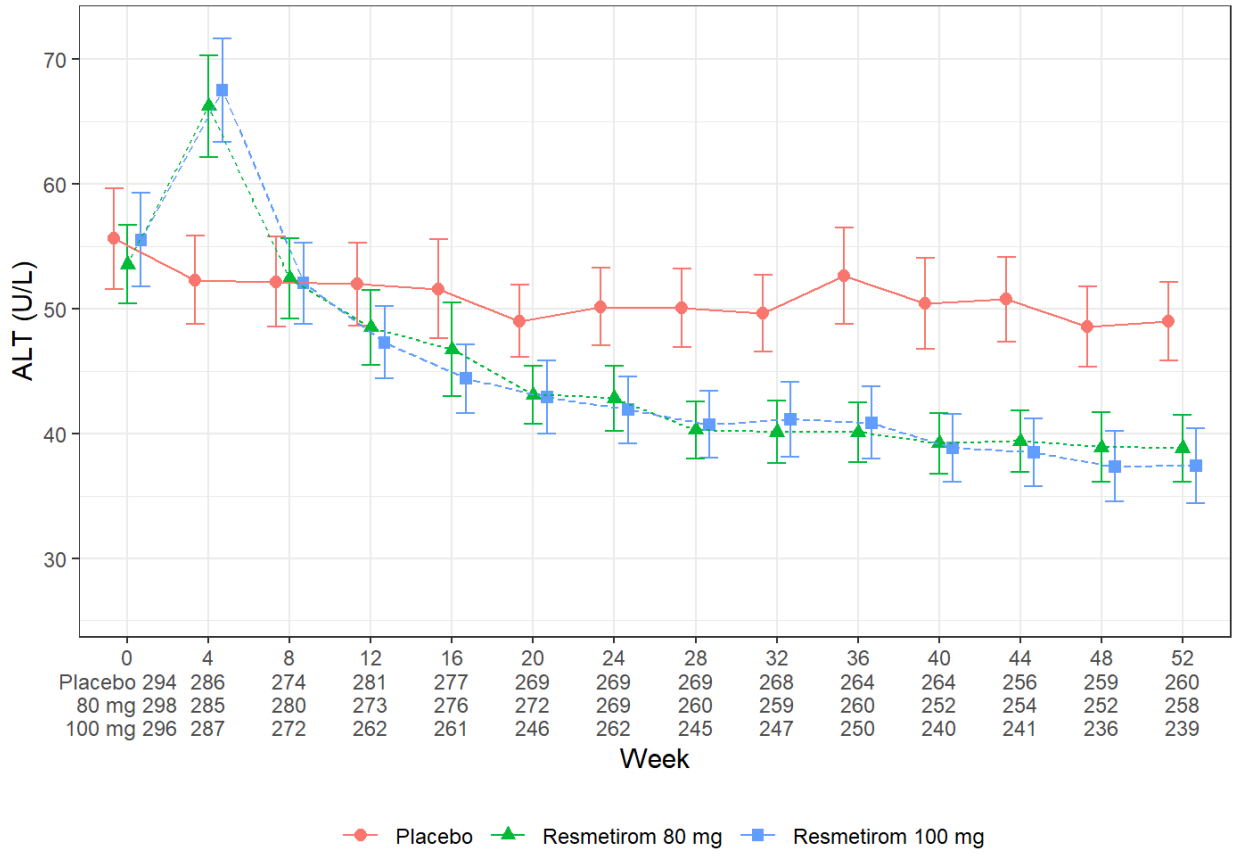
* Denotes statistical significance.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LDL-C, low-density lipoprotein-cholesterol; LS, least squares; MMRM, mixed-effect model for repeated measures; SD, standard deviation; SE, standard error

16.4. Additional Liver Enzyme Analysis Results

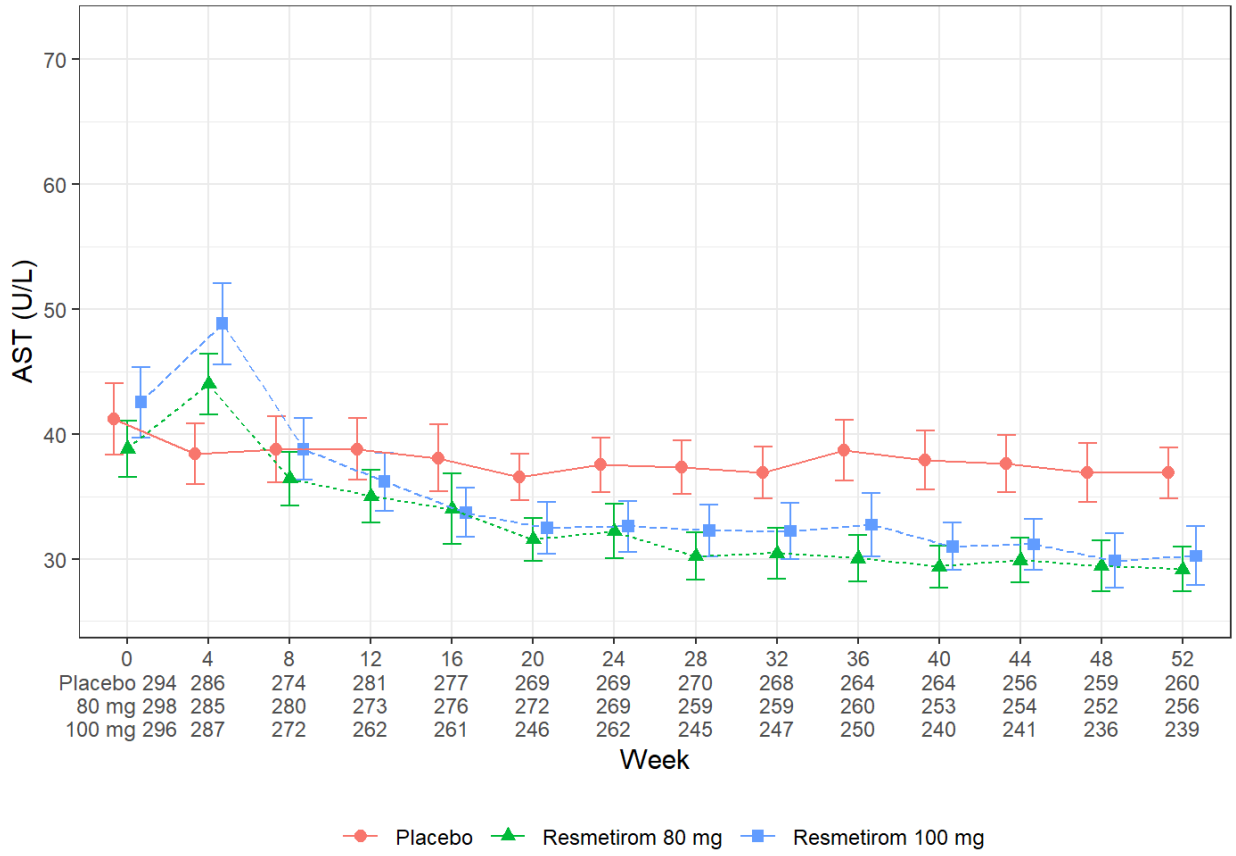
Figure 65, Figure 66, Table 281, and Table 282 present the summary of ALT and AST by treatment groups from baseline to Week 52 using observed data in the Agency's analysis population. ALT and AST in the resmetirom groups increased at Week 4 while a similar increase was not seen in the placebo group. There was a trend of lower ALT and AST in resmetirom groups as compared to the placebo group starting after Week 12 through Week 52. Given the limitations of analyses using only observed data, the impact of dropouts on the observed pattern was explored and the pattern was robust.

Figure 65. Average ALT by Treatment Groups From Baseline to Week 52, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11



Source: Statistical reviewer analysis using Applicant-submitted dataset adsl.xpt, dated September 7, 2023, admi.xpt and adlbc.xpt.
Note: The number of observations at each study week were marked under x-axis. 95% Wald confidence intervals based on observed data were presented.
Abbreviations: ALT, alanine aminotransferase; MGL-3196, resmetirom

Figure 66. Average AST by Treatment Groups From Baseline to Week 52, All Participants With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11



Source: Statistical reviewer analysis using Applicant-submitted dataset adsl.xpt, dated September 7, 2023, admi.xpt and adlbc.xpt
Note: The number of observations at each study week were marked under x-axis. 95% Wald confidence intervals based on observed data were presented.
Abbreviations: AST, aspartate aminotransferase; MGL-3196, resmetirom

Table 281. Average ALT (U/L) by Treatment Groups From Baseline to Week 52, All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Study Week	Placebo N=294 (95% CI)	Resmetirom 80 mg N=298 (95% CI)	Resmetirom 100 mg N=296 (95% CI)
0	56 (52, 60)	54 (50, 57)	56 (52, 59)
4	52 (49, 56)	66 (62, 70)	67 (63, 72)
8	52 (49, 56)	52 (49, 56)	52 (49, 55)
12	52 (49, 55)	48 (45, 51)	47 (44, 50)
16	52 (48, 56)	47 (43, 50)	44 (42, 47)
20	49 (46, 52)	43 (41, 45)	43 (40, 46)
24	50 (47, 53)	43 (40, 45)	42 (39, 45)
28	50 (47, 53)	40 (38, 43)	41 (38, 43)
32	50 (47, 53)	40 (38, 43)	41 (38, 44)
36	53 (49, 57)	40 (38, 43)	41 (38, 44)
40	50 (47, 54)	39 (37, 42)	39 (36, 42)

Study Week	Placebo N=294 (95% CI)	Resmetirom 80 mg N=298 (95% CI)	Resmetirom 100 mg N=296 (95% CI)
44	51 (47, 54)	39 (37, 42)	38 (36, 41)
48	49 (45, 52)	39 (36, 42)	37 (35, 40)
52	49 (46, 52)	39 (36, 42)	37 (34, 40)

Source: Statistical reviewer analysis using Applicant-submitted dataset adsl.xpt, dated September 7, 2023, admi.xpt and adlbc.xpt
Note: Missing data were ignored in the analyses. 95% Wald confidence intervals based on observed data were presented.
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; MGL-3196, resmetirom; N, number of subjects in treatment arm

Table 282. Average AST (U/L) by Treatment Groups From Baseline to Week 52, All Subjects With Stage 2 or Stage 3 Fibrosis by Eligibility Read Randomized on or Before July 31, 2021, Trial MGL-3196-11

Study Week	Placebo N=294 (95% CI)	Resmetirom 80 mg N=298 (95% CI)	Resmetirom 100 mg N=296 (95% CI)
0	41 (38, 44)	39 (37, 41)	43 (40, 45)
4	38 (36, 41)	44 (42, 46)	49 (46, 52)
8	39 (36, 41)	36 (34, 39)	39 (36, 41)
12	39 (36, 41)	35 (33, 37)	36 (34, 38)
16	38 (35, 41)	34 (31, 37)	34 (32, 36)
20	37 (35, 38)	32 (30, 33)	32 (30, 35)
24	38 (35, 40)	32 (30, 34)	33 (31, 35)
28	37 (35, 39)	30 (28, 32)	32 (30, 34)
32	37 (35, 39)	30 (28, 33)	32 (30, 34)
36	39 (36, 41)	30 (28, 32)	33 (30, 35)
40	38 (36, 40)	29 (28, 31)	31 (29, 33)
44	38 (35, 40)	30 (28, 32)	31 (29, 33)
48	37 (35, 39)	29 (27, 31)	30 (28, 32)
52	37 (35, 39)	29 (27, 31)	30 (28, 33)

Source: Statistical reviewer analysis using Applicant-submitted dataset adsl.xpt, dated September 7, 2023, admi.xpt and adlbc.xpt
Note: Missing data were ignored in the analyses. 95% Wald confidence intervals based on observed data were presented.
Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; MGL-3196, resmetirom; N, number of subjects in treatment arm

17. Clinical Safety

Information which provides additional supportive context regarding safety information are presented in this section.

17.1. Additional Tables and Figures, Trial MGL-3196-11 (F2/F3 Population)

17.1.1. Serious Adverse Events, Trial MGL-3196-11 (F2/F3 Population)

Table 283 displays serious adverse events (SAEs) by system organ class (SOC) and narrow FDA medical query (FMQ), occurring at an exposure-adjusted incidence rate (EAIR) greater than 0.2 per 100 person-years (PY) in either dose arm in the F2 /F3 population in Trial MGL-3196-11, irrespective of relatedness or severity. SOCs with incidence rates less than placebo are not presented. Each FMQ is aligned to a single SOC based on clinical judgment. But, some FMQs may contain preferred terms (PTs) from more than one SOC. Not all PTs are captured by FMQs. Refer to Section 7.6.1.3 for the definition of SAEs.

Table 283. Subjects With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow) (Occurring at EAIR ≥0.2 Per 100 PY in Either Drug Dose Arm), Safety Population, Trial MGL-3196-11 (F2/F3 Population)

System Organ Class FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Infections and infestations (SOC)					
Bacterial Infection	2/433.8 (0.5)	6/429.5 (1.4)	4/401.8 (1.0)	0.9 (-0.4, 2.6)	0.5 (-0.8, 2.1)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)					
Malignancy	3/433.1 (0.7)	1/434.1 (0.2)	6/403.9 (1.5)	-0.5 (-1.8, 0.7)	0.8 (-0.7, 2.6)
Renal and urinary disorders					
Renal & urinary tract infection	0/434.6 (0)	3/432.5 (0.7)	2/404.4 (0.5)	0.7 (-0.2, 2.0)	0.5 (-0.4, 1.8)
Acute kidney injury	0/434.6 (0)	1/434.3 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Musculoskeletal and connective tissue disorders					
Arthritis	2/433.4 (0.5)	3/434.2 (0.7)	0/406.6 (0)	0.2 (-1.1, 1.6)	-0.5 (-1.7, 0.5)
Fracture	0/434.6 (0)	1/432.9 (0.2)	2/405 (0.5)	0.2 (-0.7, 1.3)	0.5 (-0.4, 1.8)
Arthralgia	0/434.6 (0)	1/434.1 (0.2)	1/405.6 (0.2)	0.2 (-0.7, 1.3)	0.2 (-0.6, 1.4)
Back pain	0/434.6 (0)	1/434.1 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Myalgia	0/434.6 (0)	1/434 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Tendinopathy	0/434.6 (0)	1/434 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Gastrointestinal disorders					
Pancreatitis	0/434.6 (0)	2/434.8 (0.5)	1/406.5 (0.2)	0.5 (-0.4, 1.7)	0.2 (-0.6, 1.4)
Hepatobiliary disorders					
Hepatic injury	0/434.6 (0)	0/434.8 (0)	2/406.7 (0.5)	0.0 (-0.9, 0.9)	0.5 (-0.4, 1.8)
Cholecystitis	0/434.6 (0)	1/434.2 (0.2)	1/404.9 (0.2)	0.2 (-0.7, 1.3)	0.2 (-0.6, 1.4)
Skin and subcutaneous tissue disorders					
Rash	0/434.6 (0)	2/432.8 (0.5)	1/406.2 (0.2)	0.5 (-0.4, 1.7)	0.2 (-0.6, 1.4)
Urticaria	0/434.6 (0)	1/433.9 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Endocrine disorders					
Hyperglycemia	0/434.6 (0)	0/434.8 (0)	1/405.5 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Hypoglycemia	0/434.6 (0)	1/433.7 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Ear and labyrinth disorders					
Vertigo	0/434.6 (0)	0/434.8 (0)	1/406.2 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Blood and lymphatic system disorders					
Anemia	0/434.6 (0)	1/434.5 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)

System Organ Class FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
General disorders and administration site conditions					
Volume depletion	0/434.6 (0)	0/434.8 (0)	1/405.3 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Dizziness	0/434.6 (0)	0/434.8 (0)	1/406.2 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Fatigue	0/434.6 (0)	0/434.8 (0)	1/406.2 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Nervous system disorders					
Somnolence	0/434.6 (0)	0/434.8 (0)	1/406.2 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Stroke and TIA	0/434.6 (0)	1/434.8 (0.2)	1/406.5 (0.2)	0.2 (-0.7, 1.3)	0.2 (-0.6, 1.4)
Paresthesia	0/434.6 (0)	1/434.3 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Syncope	0/434.6 (0)	1/434.1 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Psychiatric disorders					
Self-harm	0/434.6 (0)	0/434.8 (0)	1/406.2 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Mania	0/434.6 (0)	1/434.7 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Respiratory, thoracic, and mediastinal disorders					
Pneumonitis	0/434.6 (0)	0/434.8 (0)	1/406.2 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)
Respiratory failure	0/434.6 (0)	1/434.1 (0.2)	0/406.6 (0)	0.2 (-0.7, 1.3)	0.0 (-0.9, 0.9)
Vascular disorders (SOC)					
Hypotension	0/434.6 (0)	0/434.8 (0)	1/405.3 (0.2)	0.0 (-0.9, 0.9)	0.2 (-0.6, 1.4)

Source: adae.xpt; Software: R Generated by clinical data scientist.
Note: FMQs are standardized groupings of similar adverse event terms intended to assist with the identification of potential safety issues during the review of clinical trial safety data. Each FMQ is aligned to a single SOC based on clinical judgment. Some FMQs may contain PTs from more than one SOC. Not all PTs are included in FMQs.
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; incl, including; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term; py, person-years (at risk); PY, person-years (total exposure); SOC, system organ class; TIA, transient ischemic attack

17.1.2. Treatment-Emergent Adverse Events, Trial MGL-3196-11 (F2/F3 Population)

Table 284 displays TEAEs by preferred term (PT) for the F2 and F3 population. The data presented is truncated at EAIR greater than 3 per 100 PY in either dose arms. Events displayed are regardless of relatedness or severity. See Section 7.4 for definition of TEAE. Also see Section 7.6.1.5 for discussion on TEAEs in the F2/F3 population.

Table 284. Subjects With Adverse Events (Occurring at EAIR ≥3 Per 100 PY in Either Dose Arm), Safety Population, Trial MGL-3196-11 (F2/F3 Population)

Preferred Term	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Diarrhea	52/377.6 (13.8)	78/346 (22.5)	98/299.4 (32.7)	8.8 (2.6, 15.3) *	19.0 (11.7, 26.9) *
Nausea	36/400.4 (9.0)	65/359.2 (18.1)	51/351.6 (14.5)	9.1 (3.9, 14.7) *	5.5 (0.6, 10.7) *
COVID-19	60/397.5 (15.1)	62/399.3 (15.5)	48/374.7 (12.8)	0.4 (-5.1, 6.0)	-2.3 (-7.7, 3.1)
Arthralgia	36/395.7 (9.1)	45/389.4 (11.6)	33/377.8 (8.7)	2.5 (-2.1, 7.1)	-0.4 (-4.7, 4.0)
Pruritus	18/412.4 (4.4)	24/402 (6.0)	36/369.3 (9.7)	1.6 (-1.6, 4.9)	5.4 (1.7, 9.5) *
Abdominal pain	18/414.5 (4.3)	27/409.9 (6.6)	32/373.1 (8.6)	2.2 (-1.0, 5.7)	4.2 (0.7, 8.1) *
Vomiting	15/423.5 (3.5)	27/409.5 (6.6)	30/378.9 (7.9)	3.1 (0.0, 6.4) *	4.4 (1.1, 8.1) *
Fatigue	27/401.5 (6.7)	31/405.2 (7.7)	25/383.8 (6.5)	0.9 (-2.9, 4.8)	-0.2 (-3.9, 3.5)
Headache	28/402.5 (7.0)	31/400.5 (7.7)	21/381.6 (5.5)	0.8 (-3.1, 4.7)	-1.5 (-5.1, 2.1)
Constipation	18/416.3 (4.3)	20/415.3 (4.8)	28/372.3 (7.5)	0.5 (-2.5, 3.6)	3.2 (-0.2, 6.9)
Urinary tract infection	25/412.1 (6.1)	30/405.8 (7.4)	28/386.1 (7.3)	1.3 (-2.3, 5.1)	1.2 (-2.5, 5.0)
Type 2 diabetes mellitus	21/417.7 (5.0)	23/415.3 (5.5)	21/384.8 (5.5)	0.5 (-2.7, 3.8)	0.4 (-2.8, 3.8)
Upper respiratory tract infection	15/417.8 (3.6)	22/420.2 (5.2)	7/403 (1.7)	1.6 (-1.3, 4.7)	-1.9 (-4.4, 0.4)
Muscle spasms	18/415.5 (4.3)	13/415.9 (3.1)	19/387.4 (4.9)	-1.2 (-4.1, 1.5)	0.6 (-2.5, 3.8)
Nasopharyngitis	12/421.1 (2.8)	13/424.3 (3.1)	19/385.2 (4.9)	0.2 (-2.3, 2.7)	2.1 (-0.7, 5.1)
Rash	11/422.5 (2.6)	11/422.9 (2.6)	19/388.2 (4.9)	-0.0 (-2.4, 2.4)	2.3 (-0.4, 5.3)
Dizziness	6/430.1 (1.4)	17/418 (4.1)	17/392.3 (4.3)	2.7 (0.5, 5.3) *	2.9 (0.7, 5.7) *
Cough	12/420.3 (2.9)	13/424.4 (3.1)	17/394.5 (4.3)	0.2 (-2.3, 2.7)	1.5 (-1.2, 4.3)
Gastroesophageal reflux disease	8/428.6 (1.9)	17/418.5 (4.1)	7/402.6 (1.7)	2.2 (-0.1, 4.8)	-0.1 (-2.2, 1.9)
Decreased appetite	4/429.7 (0.9)	5/430.9 (1.2)	14/390.3 (3.6)	0.2 (-1.4, 1.9)	2.7 (0.7, 5.2) *
Myalgia	9/425.5 (2.1)	6/430.2 (1.4)	13/392.8 (3.3)	-0.7 (-2.8, 1.2)	1.2 (-1.1, 3.8)

Source: adae.xpt; Software: R Generated by clinical data scientist
Note: Median analysis duration is 73.7 weeks (resmetirom 80 mg), 65.6 weeks (resmetirom 100 mg), and 67.7 weeks (placebo).
Note: Coded as MedDRA preferred terms (version 25.0)
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; py, person-years (at risk); PY, person-years (total exposure)

Table 285 displays TEAEs by SOC and FMQ (narrow) for the F2/ F3 population. The data presented is truncated at EAIR greater than 3 per 100 PY in either dose arms. FMQs displayed are regardless of relatedness or severity.

Table 285. Subjects With Adverse Events (Occurring at EAIR ≥3 Per 100 PY in Either Dose Arm), by System Organ Class, FDA Medical Query (Narrow), Safety Population, Trial MGL-3196-11 (F2/F3 Population)

System Organ Class FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Gastrointestinal disorders					
Diarrhea	52/377.6 (13.8)	79/345.1 (22.9)	98/299.4 (32.7)	9.1 (2.9, 15.7) *	19.0 (11.7, 26.9) *
Nausea	36/400.4 (9.0)	66/357.5 (18.5)	51/351.6 (14.5)	9.5 (4.3, 15.1) *	5.5 (0.6, 10.7) *
Abdominal pain	53/383.5 (13.8)	47/387.8 (12.1)	58/353.2 (16.4)	-1.7 (-6.9, 3.4)	2.6 (-3.0, 8.4)
Vomiting	16/423.5 (3.8)	28/407.8 (6.9)	30/378.9 (7.9)	3.1 (-0.0, 6.5)	4.1 (0.8, 7.9) *
Constipation	18/416.3 (4.3)	20/415.3 (4.8)	28/372.3 (7.5)	0.5 (-2.5, 3.6)	3.2 (-0.2, 6.9)
Infections and infestations					
Bacterial infection	56/381.8 (14.7)	60/368.5 (16.3)	56/362.1 (15.5)	1.6 (-4.1, 7.4)	0.8 (-4.8, 6.5)
Nasopharyngitis	35/397.8 (8.8)	44/399.7 (11.0)	31/380 (8.2)	2.2 (-2.2, 6.7)	-0.6 (-4.8, 3.6)
Fungal infection	16/418.3 (3.8)	4/431.2 (0.9)	16/389.2 (4.1)	-2.9 (-5.4, -0.9) *	0.3 (-2.6, 3.2)
Musculoskeletal and connective tissue disorders					
Arthralgia	36/395.7 (9.1)	45/389.4 (11.6)	33/377.8 (8.7)	2.5 (-2.1, 7.1)	-0.4 (-4.7, 4.0)
Arthritis	17/421.7 (4.0)	22/422.6 (5.2)	21/386.9 (5.4)	1.2 (-1.8, 4.3)	1.4 (-1.7, 4.7)
Myalgia	11/424.2 (2.6)	7/428.1 (1.6)	15/391.6 (3.8)	-1.0 (-3.2, 1.1)	1.2 (-1.3, 4.0)
Tendinopathy	9/430.2 (2.1)	14/422.4 (3.3)	13/397.4 (3.3)	1.2 (-1.1, 3.7)	1.2 (-1.1, 3.7)
Endocrine disorders					
Hyperglycemia	45/399 (11.3)	45/392.2 (11.5)	37/364.9 (10.1)	0.2 (-4.6, 5.0)	-1.1 (-5.9, 3.6)
Skin and subcutaneous tissue disorders					
Pruritus	20/409.8 (4.9)	25/401.9 (6.2)	40/365.2 (11.0)	1.3 (-2.0, 4.8)	6.1 (2.2, 10.4) *
Rash	21/410.5 (5.1)	18/415.8 (4.3)	37/371.1 (10.0)	-0.8 (-3.9, 2.3)	4.9 (1.1, 9.1) *
Renal and urinary disorders					
Renal & urinary tract infection	28/410.3 (6.8)	37/398.7 (9.3)	36/377.4 (9.5)	2.5 (-1.5, 6.6)	2.7 (-1.3, 7.0)
General disorders and administration site conditions					
Fatigue	35/394.2 (8.9)	36/401.4 (9.0)	33/375.9 (8.8)	0.1 (-4.2, 4.3)	-0.1 (-4.4, 4.2)
Dizziness	11/425.7 (2.6)	26/411.7 (6.3)	30/382.9 (7.8)	3.7 (0.9, 6.9) *	5.3 (2.2, 8.8) *
Decreased appetite	4/429.7 (0.9)	5/430.9 (1.2)	14/390.3 (3.6)	0.2 (-1.4, 1.9)	2.7 (0.7, 5.2) *
Peripheral edema	15/421 (3.6)	10/426.8 (2.3)	16/392.9 (4.1)	-1.2 (-3.8, 1.2)	0.5 (-2.3, 3.4)

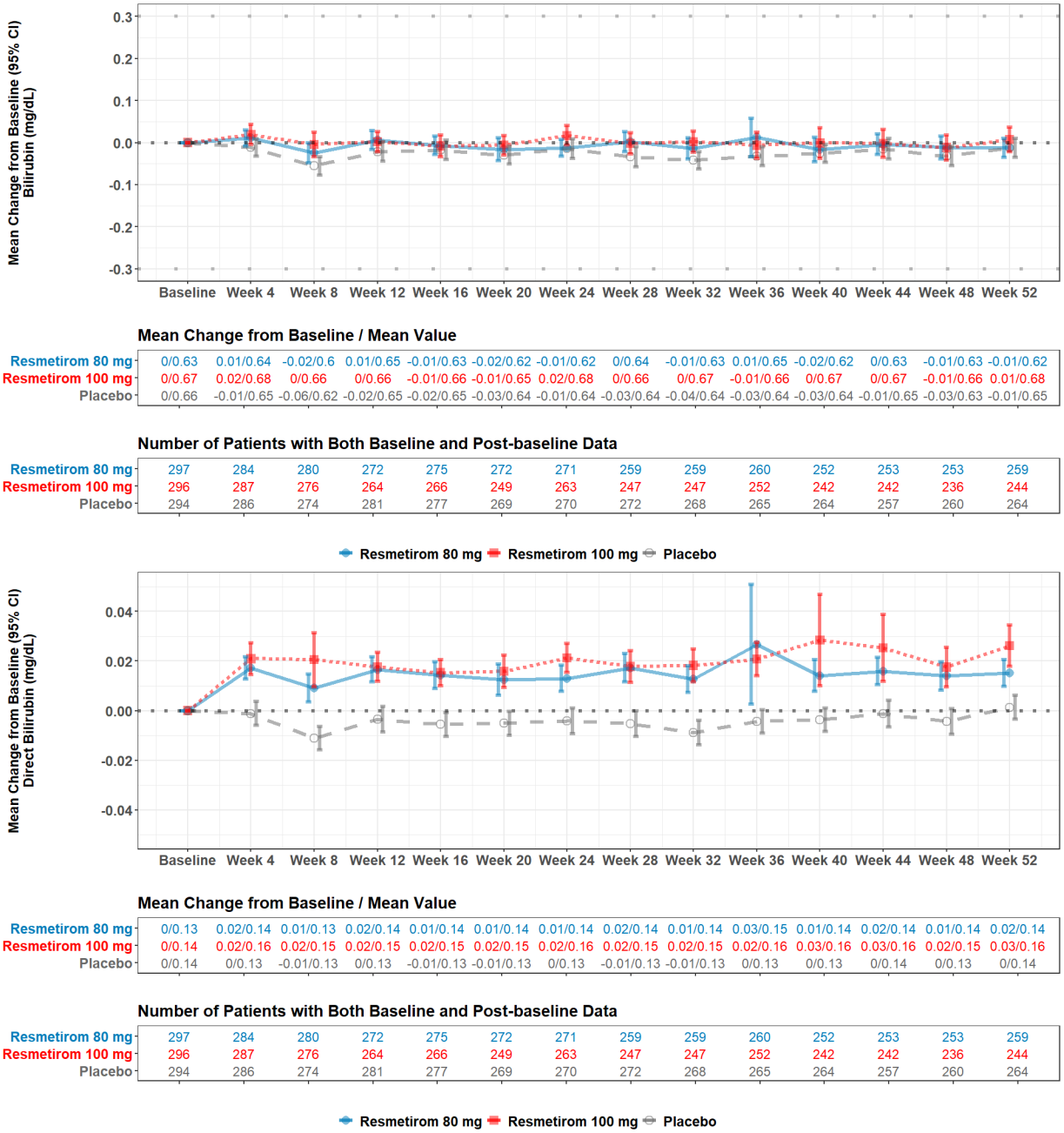
System Organ Class FMQ (Narrow)	Placebo PY=434.6 N=294 n/py (EAIR)	Resmetirom 80 mg PY=434.8 N=298 n/py (EAIR)	Resmetirom 100 mg PY=406.6 N=296 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Nervous system disorders					
Headache	32/396.6 (8.1)	34/396.5 (8.6)	24/379 (6.3)	0.5 (-3.6, 4.7)	-1.7 (-5.7, 2.1)
Respiratory, thoracic and mediastinal disorders					
Cough	14/419.2 (3.3)	15/423.2 (3.5)	18/393.8 (4.6)	0.2 (-2.5, 2.9)	1.2 (-1.6, 4.2)
Psychiatric disorders					
Depression	7/429.3 (1.6)	11/422.4 (2.6)	12/395 (3.0)	1.0 (-1.1, 3.2)	1.4 (-0.7, 3.9)

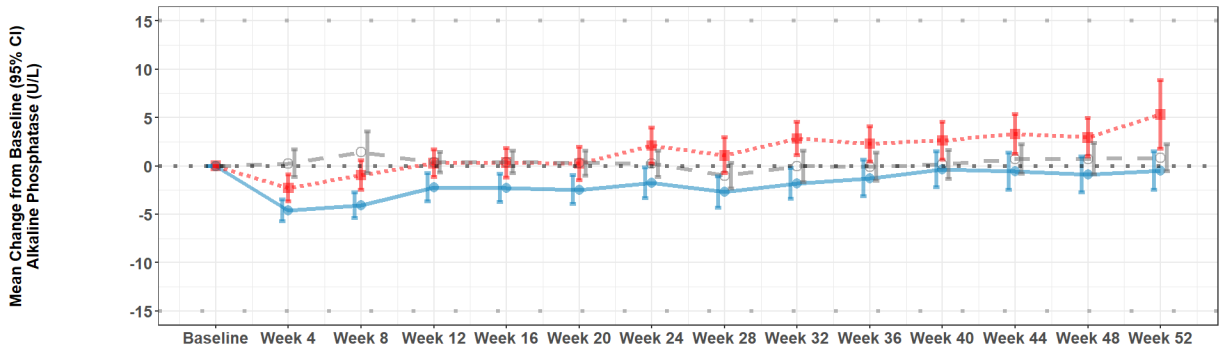
Source: adae.xpt; Software: R Generated by clinical data scientist.
* Indicates rows where the 95% confidence interval excludes zero.
Note: FMQs are standardized groupings of similar adverse event terms intended to assist with the identification of potential safety issues during the review of clinical trial safety data. Each FMQ is aligned to a single SOC based on clinical judgment. Some FMQs may contain PTs from more than one SOC. Not all PTs are included in FMQs.
Note: Median analysis duration is 73.7 weeks (Resmetirom 80 mg), 65.6 weeks (Resmetirom 100 mg), and 67.7 weeks (Placebo).
Note: Risk or EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; N, number of subjects in treatment arm; n, number of subjects with at least one event; PT, preferred term; py, person-years (at risk); PY, person-years (total exposure); SOC, system organ class; TIA, transient ischemic attack

17.1.3. Liver Biochemistry, Trial MGL-3196-11 (F2/F3 Population)

Figure 67 displays the mean changes in total bilirubin, direct bilirubin, ALP. and gamma glutamyl transferase in the F2/F3 population. Detailed discussion on these is in Section 7.6.1.6.

Figure 67. Mean Change in TB, DB, ALP, and GGT Values From Baseline Over Time, Safety Population, Trial MGL-3196-11 (F2/F3 Population)



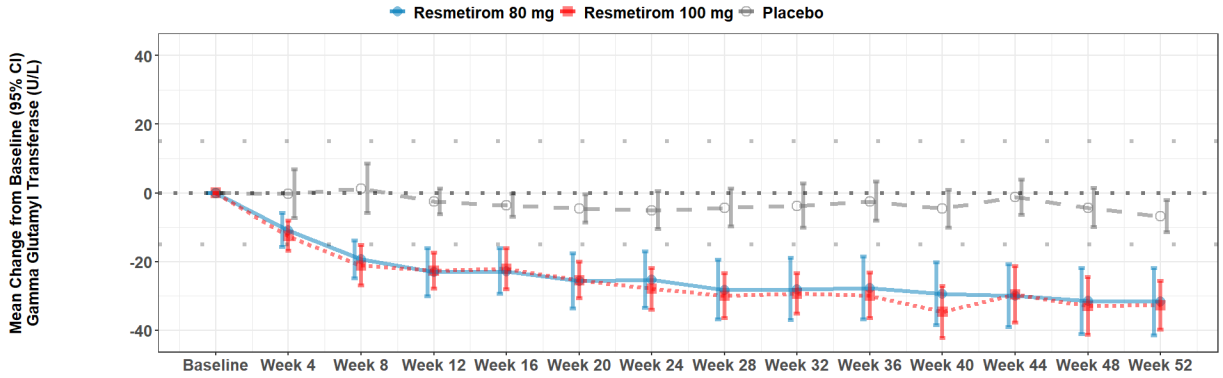


Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/75	-4.6/70	-4.1/70	-2.2/71	-2.3/71	-2.5/72	-1.8/72	-2.7/71	-1.8/71	-1.3/72	-0.34/73	-0.54/73	-0.89/73	-0.47/73
Resmetirom 100 mg	0/75	-2.3/72	-0.96/74	0.27/75	0.33/76	0.22/75	2.1/77	1.1/76	2.8/78	2.3/77	2.6/78	3.3/78	2.9/78	5.3/80
Placebo	0/71	0.25/72	1.4/72	0.36/71	0.38/71	0.29/71	0.21/71	-1/70	-0.05/71	-0.1/71	0.15/71	0.7/72	0.72/72	0.84/72

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	297	284	280	272	275	272	270	259	259	260	252	253	253	259
Resmetirom 100 mg	296	287	276	264	266	249	263	247	247	252	242	242	236	244
Placebo	294	286	274	281	277	269	270	272	268	265	264	257	260	264



Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/86	-11/75	-19/66	-23/64	-23/62	-26/59	-25/60	-28/57	-28/56	-28/56	-29/55	-30/57	-32/53	-32/53
Resmetirom 100 mg	0/88	-13/76	-21/66	-23/60	-22/62	-25/56	-28/59	-30/56	-29/55	-30/58	-35/55	-30/56	-33/53	-33/54
Placebo	0/75	-0.24/75	1.3/75	-2.5/72	-3.7/72	-4.6/70	-5.1/70	-4.3/71	-3.8/71	-2.5/72	-4.6/70	-1.3/73	-4.3/69	-6.8/68

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	297	284	280	272	275	272	271	259	259	260	252	253	253	259
Resmetirom 100 mg	296	287	276	264	266	249	263	247	247	252	242	242	236	244
Placebo	294	286	274	281	277	269	270	272	268	265	264	257	260	264

Resmetirom 80 mg Resmetirom 100 mg Placebo

Source: adlbc2.xpt; Software: R, Generated by clinical data scientist.
Note: Figures do not include timepoints with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
Note: Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; TB, total bilirubin; DB, direct bilirubin; ALP, alkaline phosphatase; GGT: gamma glutamyl transferase

17.2. Additional Tables and Figures, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

17.2.1. Deaths, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Table 286 lists the individual subject deaths in the pooled safety population with review findings from case narratives. Only one death occurred in Trial MGL-3196-14. These deaths were not related to the study drug. See Section 7.6.2.2 for more details.

Table 286. Listing of All Individual Subject Deaths, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Trial Dose Arm	Subject ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death Preferred Term	Relatedness	FDA's Findings
MGL-3196-11 80 mg	(b) (6)	25y	M	154	157	Road traffic accident	Unrelated	Subject with history significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus. Relevant medications history is significant for diphenhydramine, cannabis, venlafaxine. On Study Day 157, subject was involved in a fatal vehicle accident (was "t-boned," per family member). The death certificate listed the manner of death as an accident and cause of death as hinge fracture of skull and blunt impact head injuries. An autopsy report was not available.
MGL-3196-11 80 mg	(b) (6)	60y	M	157	170	Cardiac arrest COVID-19	Unrelated	Subject with history significant for cerebral infarction, type 2 diabetes, diabetic neuropathy, diabetic retinopathy, obesity, peripheral arterial occlusive disease, and thrombosis. Relevant medication history is significant for clopidogrel, enoxaparin, insulin. On Study Day 157, subject was hospitalized due to Covid-19 infection associated with respiratory failure. He was started on non-invasive ventilation (NIV) and intravenous insulin due to high blood glucose levels. He had elevated inflammatory markers and was started on antibiotics. After 11

Trial Dose Arm	Subject ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death Preferred Term	Relatedness	FDA's Findings
								days of NIV, the subject was safely switched to oxygen by mask and switched to nasal cannula after a few days. He was also started on oral feeds. Unfortunately, on Day 170, he suffered cardiorespiratory arrest and could not be resuscitated, and died the same day. Autopsy confirmed that cardiac arrest was the cause of death with signs of respiratory failure due to SARS-CoV-2.
MGL-3196-11 100 mg	(b) (6)	69y	M	793	933	Cholestasis Hodgkin's Disease	Unrelated	Case discussed in detail in Section 7.7.1.
MGL-3196-11 100 mg	(b) (6)	64y	M	197	213	Intracardiac thrombus Prosthetic cardiac valve thrombosis	Unrelated	See Table 37, Section 7.6.1.2 See Table 37, Section 7.6.1.2
MGL-3196-14 100 mg	(b) (6)	67y	F	364		Myocardial infarction	Unrelated	Subject with history significant for angina pectoris, aortic valve sclerosis, coronary artery arteriosclerosis, carotid artery stenosis (s/p endarterectomy), coronary artery bypass, hypertension, obesity, and hypothyroidism. Relevant medications include atorvastatin, ezetimibe, glyceryl nitrate, hydrochlorothiazide, isosorbide mononitrate, metoprolol, levothyroxine. On Study Day 141, subject had symptoms of dark urine and clay-colored stools. She underwent MRI of the abdomen which showed a mass at the lower pole of the left kidney, which showed post-contrast enhancement suspicious of renal cell carcinoma (RCC). She met with urology and was scheduled for a left retroperitoneoscopic nephrectomy. She underwent the procedure on Study Day 250 with no complications.

Trial Dose Arm	Subject ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death Preferred Term	Relatedness	FDA's Findings
								On Study Day 153, subject underwent CT of abdomen, which showed partly calcified stone on the gallbladder neck. This was followed by a HIDA scan which was abnormal. She met with a surgeon who recommended cholecystectomy, which she had on Day 207 with no complications. On Study Day 348 she had an episode of generalized pruritus and study drug was interrupted. On Study Day 365, subject was helping someone in distress and overexerted herself and had a myocardial infarction (MI). She was pronounced dead at the scene and was not taken to hospital. An autopsy was not performed.
MGL-3196-11 Placebo	(b) (6)	52y	M	264	263	Death	Unrelated	See Table 37, Section 7.6.1.2.

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist and clinical reviewer from clinical study reports for Trials MGL-3196-11 and MGL-3196-14.
Note: Median analysis duration is 52.1 weeks (Resmetirom 80 mg), 52.1 weeks (Resmetirom 100 mg), and 52.3 weeks (Placebo).
Note: This pooled analysis includes patients from the Resmetirom 80 mg, Resmetirom 100 mg, and Placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: AE, adverse event; F, female; ID, identifier; y,years; M, male; NA, not applicable; MRI, magnetic resonance imaging; CT, computed tomography

17.2.2. Serious Adverse Events Trial, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Table 287 displays SAEs by SOC and FDA Medical Query (narrow), occurring at an EAIR greater than 0.2 per 100 PY in either dose arm in the pooled population, irrespective of relatedness or severity. If the FMQ is noted to be in higher incidence in placebo, it is not displayed. Please see Section 7.6.2.3 for detailed discussion.

Table 287. Subjects With Serious Adverse Events (Occurring at EAIR ≥0.2 Per 100 PY in Either Drug Dose Arm) by System Organ Class and FDA Medical Query (Narrow), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Infections and infestations					
Bacterial infection	6/790.8 (0.8)	10/769.8 (1.3)	8/759.1 (1.1)	0.5 (-0.5, 1.7)	0.3 (-0.7, 1.4)
Pneumonia	2/792.4 (0.3)	5/774.4 (0.6)	0/767.1 (0)	0.4 (-0.3, 1.3)	-0.3 (-0.9, 0.2)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)					
Malignancy	9/789 (1.1)	2/776.4 (0.3)	10/762.2 (1.3)	-0.9 (-1.9, -0.1) *	0.2 (-1.0, 1.4)
Renal and urinary disorders					
Renal & urinary tract infection	0/792.8 (0)	5/773.6 (0.6)	2/764.9 (0.3)	0.6 (0.2, 1.5) *	0.3 (-0.2, 1.0)
Cardiac disorders					
Myocardial infarction	2/790.7 (0.3)	2/776.4 (0.3)	4/766.1 (0.5)	0.0 (-0.7, 0.7)	0.3 (-0.5, 1.1)
Acute coronary syndrome	3/790.6 (0.4)	2/776.4 (0.3)	4/766.1 (0.5)	-0.1 (-0.9, 0.6)	0.1 (-0.7, 1.0)
Myocardial ischemia	3/790 (0.4)	3/775.6 (0.4)	4/766.1 (0.5)	0.0 (-0.8, 0.8)	0.1 (-0.7, 1.0)
Heart failure	2/792.4 (0.3)	1/776.5 (0.1)	2/765.9 (0.3)	-0.1 (-0.8, 0.5)	0.0 (-0.7, 0.7)
Musculoskeletal and connective tissue disorders					
Arthritis	3/791.2 (0.4)	4/775.4 (0.5)	1/766.5 (0.1)	0.1 (-0.7, 1.0)	-0.2 (-1.0, 0.4)
Fracture	0/792.8 (0)	2/775.1 (0.3)	2/765.5 (0.3)	0.3 (-0.2, 0.9)	0.3 (-0.2, 1.0)
Gastrointestinal disorders					
Pancreatitis	0/792.8 (0)	2/777.2 (0.3)	2/765.8 (0.3)	0.3 (-0.2, 0.9)	0.3 (-0.2, 1.0)
Hepatobiliary disorders					
Hepatic injury	0/792.8 (0)	1/777.2 (0.1)	2/767.2 (0.3)	0.1 (-0.4, 0.7)	0.3 (-0.2, 1.0)
Respiratory, thoracic, and mediastinal disorders					
Respiratory failure	0/792.8 (0)	2/775.9 (0.3)	0/767.1 (0)	0.3 (-0.2, 0.9)	0.0 (-0.5, 0.5)
Skin and subcutaneous tissue disorders					
Rash	0/792.8 (0)	2/775.2 (0.3)	1/766.7 (0.1)	0.3 (-0.2, 0.9)	0.1 (-0.4, 0.7)

System Organ Class FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Vascular disorders					
Hypotension	0/792.8 (0)	0/777.2 (0)	2/765.7 (0.3)	0.0 (-0.5, 0.5)	0.3 (-0.2, 1.0)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: FMQs are standardized groupings of similar adverse event terms intended to assist with the identification of potential safety issues during the review of clinical trial safety data. Each FMQ is aligned to a single SOC based on clinical judgment. Some FMQs may contain PTs from more than one SOC. Not all PTs are included in FMQs.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with at least one event; PT, preferred term; py, person-years (at risk); PY, person-years (total exposure)

17.2.3. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Table 288 displays the AEs observed in the pooled population by SOC where AEs with EAIRs greater than equal to 0.2 per 100 PY in either dose arm in the pooled population. See Section 7.6.2.4 for detailed discussion.

Table 288. Subjects With Adverse Events (Occurring at EAIR ≥0.2 Per 100 PY in Either Dose Arm) Leading to Treatment Discontinuation by System Organ Class, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any AE leading to discontinuation	31/791.5 (3.9)	52/770.3 (6.8)	56/761.7 (7.4)	2.8 (0.6, 5.2) *	3.4 (1.1, 5.9) *
Gastrointestinal disorders	9/792.6 (1.1)	28/772.7 (3.6)	29/763 (3.8)	2.5 (1.0, 4.2) *	2.7 (1.2, 4.4) *
Skin and subcutaneous tissue disorders	3/792.6 (0.4)	1/777.2 (0.1)	11/766.2 (1.4)	-0.2 (-1.0, 0.4)	1.1 (0.1, 2.2) *
Nervous system disorders	3/792.7 (0.4)	7/775.3 (0.9)	1/767.1 (0.1)	0.5 (-0.3, 1.5)	-0.2 (-1.0, 0.4)
Hepatobiliary disorders	3/792.6 (0.4)	6/777.1 (0.8)	6/766.9 (0.8)	0.4 (-0.4, 1.3)	0.4 (-0.4, 1.4)
Musculoskeletal and connective tissue disorders	3/792.6 (0.4)	4/777.1 (0.5)	0/767.1 (0)	0.1 (-0.7, 1.0)	-0.4 (-1.1, 0.1)

System Organ Class	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	2/792.6 (0.3)	2/777.3 (0.3)	3/767.1 (0.4)	0.0 (-0.7, 0.7)	0.1 (-0.6, 0.9)
Cardiac disorders	1/792.8 (0.1)	2/777.2 (0.3)	2/767.2 (0.3)	0.1 (-0.5, 0.8)	0.1 (-0.5, 0.8)
Metabolism and nutrition disorders	0/792.8 (0)	0/777.2 (0)	2/767.1 (0.3)	0.0 (-0.5, 0.5)	0.3 (-0.2, 1.0)
Respiratory, thoracic, and mediastinal disorders	0/792.8 (0)	0/777.2 (0)	2/767.1 (0.3)	0.0 (-0.5, 0.5)	0.3 (-0.2, 1.0)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Table 289 is an expanded table with FDA Medical Queries (FMQs) occurring at EAIR ≥0.1 per 100 PY in either drug dose arm leading to treatment discontinuation in the pooled population. This corresponds to AEs leading to treatment discontinuation reported by at least one subject in the trial arms, irrespective of relatedness or severity. See Section 7.6.2.4 for detailed discussion.

Table 289. Subjects With Adverse Events (Occurring at EAIR ≥0.1 Per 100 PY in Either Drug Dose Arm) Leading to Treatment Discontinuation by FDA Medical Query (Narrow), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14^

FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Diarrhea	1/792.8 (0.1)	15/775.5 (1.9)	20/764.5 (2.6)	1.8 (0.9, 3.1) *	2.5 (1.5, 3.9) *
Nausea	4/792.8 (0.5)	7/775.9 (0.9)	9/766.6 (1.2)	0.4 (-0.5, 1.4)	0.7 (-0.3, 1.8)
Headache	1/792.8 (0.1)	7/775.3 (0.9)	0/767.1 (0)	0.8 (0.1, 1.8) *	-0.1 (-0.7, 0.4)
Hepatic injury	4/792.6 (0.5)	7/776.9 (0.9)	5/766.8 (0.7)	0.4 (-0.5, 1.4)	0.1 (-0.7, 1.1)
Abdominal pain	2/792.6 (0.3)	6/775.6 (0.8)	6/766.9 (0.8)	0.5 (-0.2, 1.5)	0.5 (-0.2, 1.5)
Pruritus	1/792.7 (0.1)	1/777.2 (0.1)	6/766.9 (0.8)	0.0 (-0.6, 0.6)	0.7 (-0.0, 1.6)
Vomiting	2/792.8 (0.3)	3/777.1 (0.4)	6/766.8 (0.8)	0.1 (-0.6, 0.9)	0.5 (-0.2, 1.5)
Rash	1/792.7 (0.1)	0/777.2 (0)	5/767.1 (0.7)	-0.1 (-0.7, 0.4)	0.5 (-0.1, 1.4)
Dyspepsia	2/792.6 (0.3)	3/776.7 (0.4)	3/767 (0.4)	0.1 (-0.6, 0.9)	0.1 (-0.6, 0.9)

FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Urticaria	0/792.8 (0)	0/777.2 (0)	3/767.1 (0.4)	0.0 (-0.5, 0.5)	0.4 (-0.1, 1.1)
Constipation	1/792.7 (0.1)	0/777.2 (0)	2/767 (0.3)	-0.1 (-0.7, 0.4)	0.1 (-0.5, 0.8)
Fatigue	1/792.7 (0.1)	2/777.1 (0.3)	1/767.1 (0.1)	0.1 (-0.5, 0.8)	0.0 (-0.6, 0.6)
Thrombosis	0/792.8 (0)	0/777.2 (0)	2/767.2 (0.3)	0.0 (-0.5, 0.5)	0.3 (-0.2, 1.0)
Pancreatitis	0/792.8 (0)	1/777.2 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Dizziness	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Palpitations	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Arrhythmia	0/792.8 (0)	1/777.1 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Decreased appetite	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Fall	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Viral infection	0/792.8 (0)	1/777.2 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Fracture	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Arthralgia	0/792.8 (0)	1/777.1 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Back pain	0/792.8 (0)	1/777.2 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Myalgia	0/792.8 (0)	1/777.1 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)
Irritability	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Dyspnea	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Thrombosis venous	0/792.8 (0)	0/777.2 (0)	1/767.1 (0.1)	0.0 (-0.5, 0.5)	0.1 (-0.4, 0.7)
Hemorrhage	0/792.8 (0)	1/777.2 (0.1)	0/767.1 (0)	0.1 (-0.4, 0.7)	0.0 (-0.5, 0.5)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: FMQs are standardized groupings of similar adverse event terms intended to assist with the identification of potential safety issues during the review of clinical trial safety data. Each FMQ is aligned to a single SOC based on clinical judgment. Some FMQs may contain PTs from more than one SOC. Not all PTs are included in FMQs.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
^ Subjects with at least one AE leading to discontinuation are presented
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

17.2.4. Treatment-Emergent Adverse Events, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

See Section 7.4 for definitions of TEAEs for both, Trials MGL-3196-11 and MGL-3196-14. See Section 7.6.2.5 for detailed discussion on TEAEs in the pooled population.

Table 290 displays the TEAEs reported in the pooled population by SOC, occurring at an EAIR greater than equal to 1 per 100 PY in either dose arm. As seen in the F2/F3 population, AEs belonging to the GI disorders SOC were most common.

Table 290. Subjects With Adverse Events by System Organ Class (Occurring at EAIR ≥1 Per 100 PY in Either Dose Arm), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Any AE	584/200.7 (291.0)	613/190 (322.6)	596/164.7 (362.0)	31.6 (-3.1, 66.5)	70.9 (33.8, 108.8) *
Gastrointestinal disorders	308/514.9 (59.8)	366/427.9 (85.5)	385/396 (97.2)	25.7 (14.8, 36.9) *	37.4 (25.8, 49.4) *
Musculoskeletal and connective tissue disorders	229/590.6 (38.8)	230/583.9 (39.4)	233/561.1 (41.5)	0.6 (-6.6, 7.8)	2.8 (-4.6, 10.1)
Nervous system disorders	149/661.7 (22.5)	158/654 (24.2)	147/653.2 (22.5)	1.6 (-3.6, 6.9)	-0.0 (-5.2, 5.2)
Metabolism and nutrition disorders	143/691.3 (20.7)	123/691.6 (17.8)	152/642.1 (23.7)	-2.9 (-7.6, 1.7)	3.0 (-2.1, 8.1)
Skin and subcutaneous tissue disorders	134/669.4 (20.0)	125/668.3 (18.7)	138/641.5 (21.5)	-1.3 (-6.1, 3.4)	1.5 (-3.5, 6.5)
Respiratory, thoracic, and mediastinal disorders	82/733.8 (11.2)	84/717.2 (11.7)	93/708 (13.1)	0.5 (-3.0, 4.1)	2.0 (-1.7, 5.6)
Renal and urinary disorders	49/755.3 (6.5)	43/751.3 (5.7)	56/728.2 (7.7)	-0.8 (-3.3, 1.8)	1.2 (-1.5, 4.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	39/763.6 (5.1)	21/761.3 (2.8)	46/743.8 (6.2)	-2.3 (-4.5, -0.4) *	1.1 (-1.3, 3.6)
Cardiac disorders	35/770.8 (4.5)	44/748.8 (5.9)	44/740.7 (5.9)	1.3 (-1.0, 3.7)	1.4 (-0.9, 3.8)
Blood and lymphatic system disorders	33/770.7 (4.3)	32/756.4 (4.2)	39/744 (5.2)	-0.1 (-2.2, 2.1)	1.0 (-1.3, 3.3)
Hepatobiliary disorders	36/778.9 (4.6)	35/759.7 (4.6)	36/754.2 (4.8)	-0.0 (-2.2, 2.2)	0.2 (-2.1, 2.4)
Immune system disorders	31/769.4 (4.0)	28/752.8 (3.7)	35/743.7 (4.7)	-0.3 (-2.4, 1.7)	0.7 (-1.5, 2.9)
Reproductive system and breast disorders	28/770.8 (3.6)	38/751.2 (5.1)	34/740.3 (4.6)	1.4 (-0.7, 3.6)	1.0 (-1.1, 3.1)
Ear and labyrinth disorders	20/774.9 (2.6)	25/757.8 (3.3)	30/743.6 (4.0)	0.7 (-1.0, 2.5)	1.5 (-0.4, 3.4)
Endocrine disorders	9/785.1 (1.1)	13/768.5 (1.7)	22/749.9 (2.9)	0.5 (-0.7, 1.9)	1.8 (0.4, 3.4) *

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Table 291 displays TEAEs by PT for the pooled population. The data presented is truncated at EAIR greater than equal to 3 per 100 PY in either dose arm. Events displayed are regardless of relatedness or severity.

Table 291. Subjects With Common Adverse Events (Occurring at EAIR ≥3 Per 100 PY in Either Dose Arm), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

Preferred Term	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Diarrhea	102/701.9 (14.5)	172/622.4 (27.6)	215/561.1 (38.3)	13.1 (8.2, 18.3) *	23.8 (18.1, 29.9) *
Nausea	67/739 (9.1)	114/666.4 (17.1)	122/653.9 (18.7)	8.0 (4.3, 12.0) *	9.6 (5.7, 13.7) *
COVID-19	97/736.4 (13.2)	102/723.8 (14.1)	85/711.6 (11.9)	0.9 (-2.9, 4.8)	-1.2 (-4.9, 2.5)
Arthralgia	67/732 (9.2)	78/711.7 (11.0)	64/712.9 (9.0)	1.8 (-1.5, 5.2)	-0.2 (-3.3, 3.0)
Abdominal pain	33/762.3 (4.3)	47/737 (6.4)	61/709.1 (8.6)	2.0 (-0.3, 4.5)	4.3 (1.7, 7.0) *
Vomiting	31/771.4 (4.0)	38/743.2 (5.1)	58/725 (8.0)	1.1 (-1.1, 3.3)	4.0 (1.5, 6.6) *
Pruritus	31/763.2 (4.1)	44/732.9 (6.0)	57/715.1 (8.0)	1.9 (-0.3, 4.3)	3.9 (1.4, 6.6) *
Fatigue	43/747.2 (5.8)	57/730.7 (7.8)	43/730.8 (5.9)	2.0 (-0.6, 4.8)	0.1 (-2.4, 2.7)
Headache	54/742.9 (7.3)	56/730.9 (7.7)	52/724 (7.2)	0.4 (-2.4, 3.2)	-0.1 (-2.9, 2.7)
Back pain	56/740.6 (7.6)	56/739.8 (7.6)	48/725.3 (6.6)	0.0 (-2.8, 2.9)	-0.9 (-3.7, 1.8)
Urinary tract infection	52/755.4 (6.9)	56/735.5 (7.6)	50/734.9 (6.8)	0.7 (-2.0, 3.5)	-0.1 (-2.8, 2.6)
Type 2 diabetes mellitus	44/760.2 (5.8)	43/747.4 (5.8)	48/725 (6.6)	-0.0 (-2.5, 2.4)	0.8 (-1.7, 3.4)
Constipation	34/767.3 (4.4)	41/739.2 (5.5)	44/723.2 (6.1)	1.1 (-1.2, 3.5)	1.7 (-0.7, 4.1)
Dizziness	22/775.6 (2.8)	41/744.6 (5.5)	37/742.8 (5.0)	2.7 (0.6, 4.9) *	2.1 (0.2, 4.3) *
Cough	22/774.2 (2.8)	21/762.4 (2.8)	31/745.5 (4.2)	-0.1 (-1.8, 1.7)	1.3 (-0.6, 3.3)
Rash	22/773.7 (2.8)	27/754.4 (3.6)	28/740.9 (3.8)	0.7 (-1.1, 2.6)	0.9 (-0.9, 2.9)
Nasopharyngitis	17/771.9 (2.2)	21/760.4 (2.8)	23/742.6 (3.1)	0.6 (-1.1, 2.2)	0.9 (-0.8, 2.7)
Abdominal distension	26/769.6 (3.4)	24/751.1 (3.2)	29/742 (3.9)	-0.2 (-2.1, 1.7)	0.5 (-1.4, 2.5)
Osteoarthritis	12/788.9 (1.5)	24/762 (3.1)	13/759.4 (1.7)	1.6 (0.1, 3.3) *	0.2 (-1.1, 1.6)
Sinusitis	24/776.1 (3.1)	31/756.6 (4.1)	24/754.3 (3.2)	1.0 (-0.9, 3.0)	0.1 (-1.7, 1.9)
Gastroesophageal reflux disease	17/780.3 (2.2)	28/755.5 (3.7)	17/756.8 (2.2)	1.5 (-0.2, 3.4)	0.1 (-1.5, 1.6)

Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: Coded as MedDRA preferred terms (version 25.1)
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

Table 292 displays TEAEs by SOC and FMQ (narrow) for the pooled population. The data presented is truncated at EAIR greater than or equal to 3 per 100 PY in either dose arms. Events displayed are regardless of relatedness or severity.

Table 292. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow) (Occurring at EAIR ≥3 Per 100 PY in Either Dose Arm), Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Gastrointestinal disorders					
Diarrhea	102/701.9 (14.5)	173/621.5 (27.8)	215/561.1 (38.3)	13.3 (8.4, 18.5) *	23.8 (18.1, 29.9) *
Nausea	67/739 (9.1)	115/664.7 (17.3)	122/653.9 (18.7)	8.2 (4.5, 12.2) *	9.6 (5.7, 13.7) *
Abdominal pain	95/714.6 (13.3)	89/703.5 (12.7)	110/675.8 (16.3)	-0.6 (-4.4, 3.1)	3.0 (-1.1, 7.1)
Vomiting	32/771.4 (4.1)	39/741.6 (5.3)	59/724.1 (8.1)	1.1 (-1.1, 3.4)	4.0 (1.5, 6.7) *
Constipation	34/767.3 (4.4)	41/739.2 (5.5)	44/723.2 (6.1)	1.1 (-1.2, 3.5)	1.7 (-0.7, 4.1)
Infections and infestations					
Bacterial infection	108/708.4 (15.2)	109/689.9 (15.8)	112/688.6 (16.3)	0.6 (-3.6, 4.7)	1.0 (-3.2, 5.2)
Nasopharyngitis	61/736 (8.3)	69/728.9 (9.5)	52/731.1 (7.1)	1.2 (-1.9, 4.3)	-1.2 (-4.1, 1.7)
Fungal infection	22/773 (2.8)	13/769.2 (1.7)	24/745.4 (3.2)	-1.2 (-2.8, 0.4)	0.4 (-1.4, 2.2)
Musculoskeletal and connective tissue disorders					
Arthralgia	67/732 (9.2)	78/711.7 (11.0)	64/712.9 (9.0)	1.8 (-1.5, 5.2)	-0.2 (-3.3, 3.0)
Back pain	71/731 (9.7)	72/728.5 (9.9)	65/715.5 (9.1)	0.2 (-3.1, 3.4)	-0.6 (-3.8, 2.6)
Arthritis	27/777.1 (3.5)	42/751.7 (5.6)	38/734 (5.2)	2.1 (-0.0, 4.4)	1.7 (-0.4, 3.9)
Tendinopathy	18/782.1 (2.3)	23/758.7 (3.0)	23/752.2 (3.1)	0.7 (-0.9, 2.5)	0.8 (-0.9, 2.5)
Fracture	24/779.4 (3.1)	27/758 (3.6)	20/751.7 (2.7)	0.5 (-1.4, 2.4)	-0.4 (-2.2, 1.3)
General disorders and administration site conditions					
Fatigue	53/739.4 (7.2)	66/725.8 (9.1)	53/721.4 (7.3)	1.9 (-1.0, 4.9)	0.2 (-2.6, 3.0)
Dizziness	34/766.1 (4.4)	56/734.5 (7.6)	60/726.6 (8.3)	3.2 (0.7, 5.8) *	3.8 (1.3, 6.5) *
Peripheral edema	28/771.3 (3.6)	22/762.3 (2.9)	26/749 (3.5)	-0.7 (-2.6, 1.1)	-0.2 (-2.1, 1.8)
Pyrexia	23/771.7 (3.0)	18/763.3 (2.4)	17/755.6 (2.2)	-0.6 (-2.4, 1.1)	-0.7 (-2.5, 0.9)
Renal and urinary disorders					
Renal & urinary tract infection	56/753 (7.4)	66/727 (9.1)	61/724.6 (8.4)	1.6 (-1.3, 4.7)	1.0 (-1.9, 3.9)
Nervous system disorders					
Headache	59/737 (8.0)	65/723.7 (9.0)	56/721.2 (7.8)	1.0 (-2.0, 4.0)	-0.2 (-3.2, 2.7)
Skin and subcutaneous tissue disorders					
Pruritus	34/760.4 (4.5)	46/731.8 (6.3)	64/709 (9.0)	1.8 (-0.5, 4.3)	4.6 (1.9, 7.4) *
Rash	40/757.7 (5.3)	48/741.5 (6.5)	59/717.2 (8.2)	1.2 (-1.3, 3.7)	2.9 (0.3, 5.7) *
Respiratory, thoracic, and mediastinal disorders					
Cough	27/771.1 (3.5)	26/759.5 (3.4)	32/744.8 (4.3)	-0.1 (-2.0, 1.9)	0.8 (-1.2, 2.9)

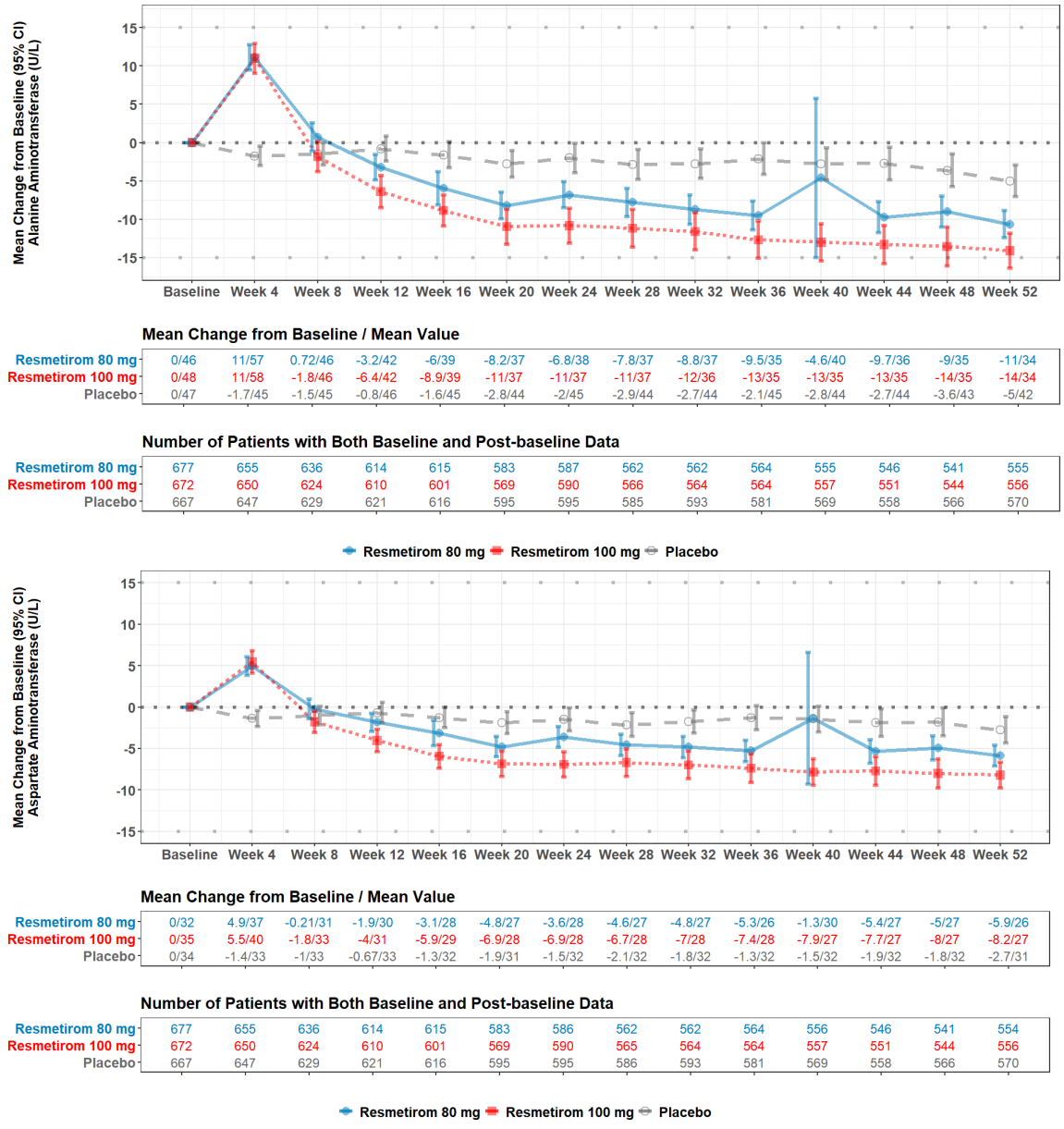
System Organ Class FMQ (Narrow)	Placebo PY=792.8 N=667 n/py (EAIR)	Resmetirom 80 mg PY=777.2 N=679 n/py (EAIR)	Resmetirom 100 mg PY=767.1 N=673 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Blood and lymphatic system disorders					
Anemia	21/777.6 (2.7)	25/761.4 (3.3)	29/750.7 (3.9)	0.6 (-1.2, 2.4)	1.2 (-0.7, 3.1)

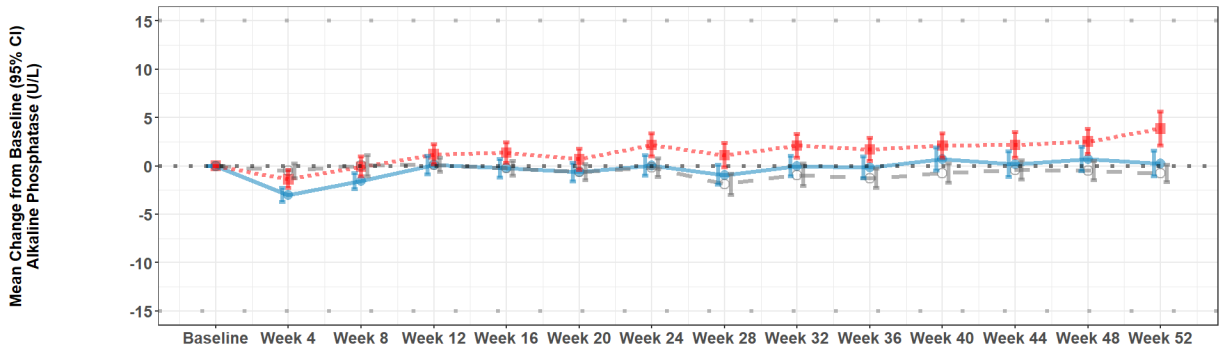
Source: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R Generated by clinical data scientist.
Note: FMQs are standardized groupings of similar adverse event terms intended to assist with the identification of potential safety issues during the review of clinical trial safety data. Each FMQ is aligned to a single SOC based on clinical judgment. Some FMQs may contain PTs from more than one SOC. Not all PTs are included in FMQs.
Note: Median analysis duration is 52.1 weeks (resmetirom 80 mg), 52.1 weeks (resmetirom 100 mg), and 52.3 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between total treatment and placebo.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
* Indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA Medical Query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

17.2.5. Liver Biochemistry, Pooled Analyses, Trials MGL-3196-11 and MGL-3196-14

Figure 68 displays the mean changes in liver biochemistries in the pooled population. For discussion see Section 7.6.2.6.

Figure 68. Mean Change From Baseline Over Time for Liver Analytes, Safety Population, Pooled Trials MGL-3196-11 and MGL-3196-14



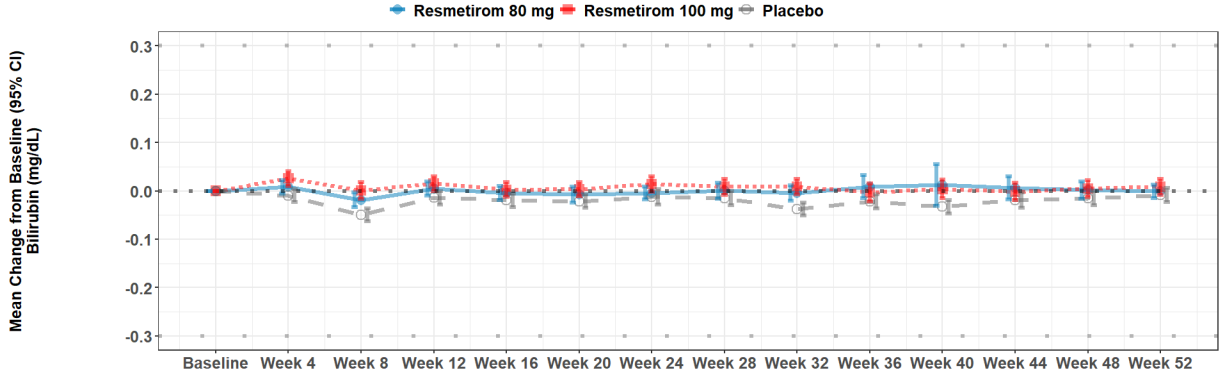


Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/73	-3/70	-1.6/71	0.07/72	-0.26/72	-0.66/71	0.01/73	-0.94/71	-0.03/72	-0.18/72	0.7/73	0.19/73	0.71/73	0.22/73
Resmetirom 100 mg	0/73	-1.4/71	-0.08/73	1.2/74	1.3/74	0.67/74	2.2/75	1.1/74	2.1/75	1.7/75	2.1/75	2.1/75	2.5/76	3.9/77
Placebo	0/71	-0.51/71	0/71	0.13/71	-0.25/71	-0.64/70	-0.19/70	-1.9/69	-0.93/70	-1.3/70	-0.75/70	-0.44/71	-0.51/71	-0.78/71

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	677	655	636	614	615	583	586	562	562	564	556	546	541	555
Resmetirom 100 mg	672	650	624	610	601	569	590	566	564	564	557	551	544	556
Placebo	667	647	629	621	616	595	595	586	593	581	569	558	566	570

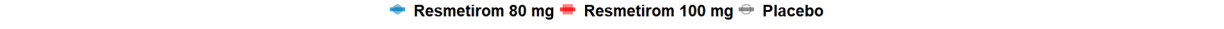


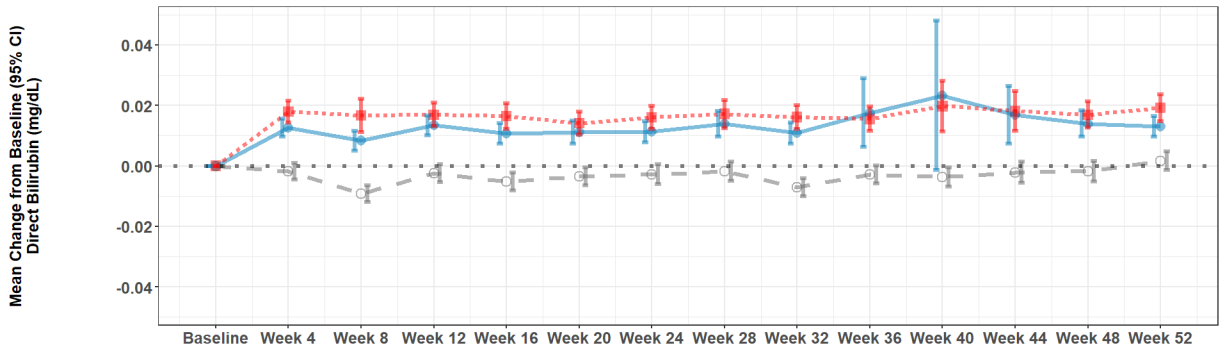
Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/0.61	0.01/0.62	-0.02/0.59	0.01/0.62	0/0.61	-0.01/0.6	0/0.61	0/0.61	0/0.61	0.01/0.62	0.01/0.63	0.01/0.62	0/0.62	0/0.61
Resmetirom 100 mg	0/0.62	0.03/0.65	0/0.62	0.01/0.64	0/0.63	0/0.63	0.01/0.63	0.01/0.63	0.01/0.63	0/0.62	0/0.63	0/0.63	0/0.63	0.01/0.64
Placebo	0/0.63	-0.01/0.62	-0.05/0.59	-0.01/0.62	-0.02/0.62	-0.02/0.61	-0.01/0.62	-0.02/0.63	-0.04/0.61	-0.02/0.62	-0.03/0.61	-0.02/0.62	-0.02/0.62	-0.01/0.63

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	677	655	636	614	615	583	587	562	562	564	556	546	541	555
Resmetirom 100 mg	672	650	624	610	601	569	590	566	564	564	557	551	544	556
Placebo	667	647	629	621	616	595	595	586	593	581	569	558	566	570





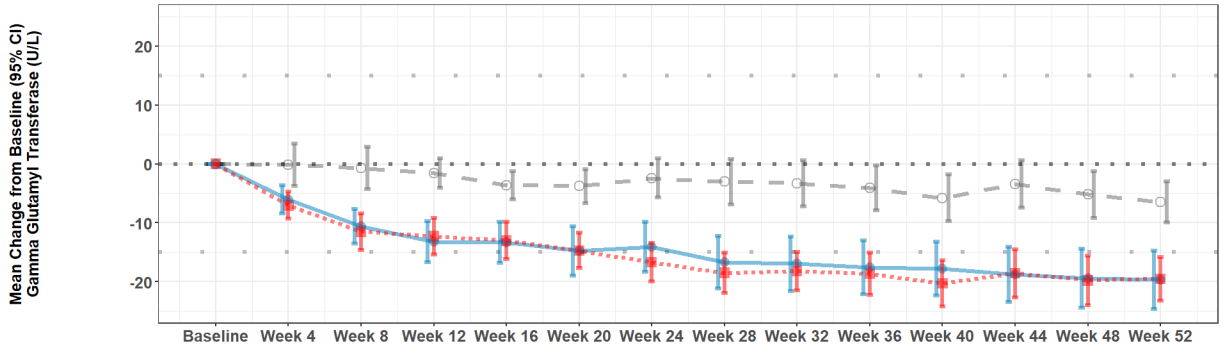
Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/0.12	0.01/0.13	0.01/0.13	0.01/0.13	0.01/0.13	0.01/0.13	0.01/0.13	0.01/0.13	0.01/0.13	0.02/0.14	0.02/0.14	0.02/0.14	0.01/0.13	0.01/0.13
Resmetirom 100 mg	0/0.12	0.02/0.14	0.02/0.14	0.02/0.14	0.02/0.14	0.01/0.14	0.02/0.14	0.02/0.14	0.02/0.14	0.02/0.14	0.02/0.14	0.02/0.14	0.02/0.14	0.02/0.14
Placebo	0/0.12	0/0.12	-0.01/0.12	0/0.12	-0.01/0.12	0/0.12	0/0.12	0/0.12	-0.01/0.12	0/0.12	0/0.12	0/0.12	0/0.12	0/0.13

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	677	655	636	614	615	583	587	562	562	564	556	546	541	555
Resmetirom 100 mg	672	650	624	610	601	569	590	566	564	564	557	551	544	556
Placebo	667	647	629	621	616	595	595	586	593	581	569	558	566	570

Resmetirom 80 mg Resmetirom 100 mg Placebo



Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	0/65	-6/59	-11/54	-13/53	-13/52	-15/50	-14/51	-17/48	-17/48	-18/46	-18/47	-19/47	-19/45	-20/45
Resmetirom 100 mg	0/63	-7.1/57	-12/51	-12/49	-13/49	-15/46	-17/46	-19/44	-18/44	-19/45	-20/44	-19/44	-20/43	-20/44
Placebo	0/63	-0.19/62	-0.75/61	-1.6/61	-3.7/59	-3.8/58	-2.4/60	-3/59	-3.3/59	-4.1/58	-5.8/56	-3.4/59	-5.2/56	-6.5/56

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Resmetirom 80 mg	677	655	636	614	615	583	587	562	562	564	556	546	541	555
Resmetirom 100 mg	672	650	624	610	601	569	590	566	564	564	557	551	544	556
Placebo	667	647	629	621	616	595	595	586	593	581	569	558	566	570

Resmetirom 80 mg Resmetirom 100 mg Placebo

Source: ISS adlbc2.xpt; Software: R Generated by clinical data scientist.
Note: Figures do not include timepoints with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Note: Only central laboratory data are included in the analysis.
Note: This pooled analysis includes subjects from the resmetirom 80 mg, resmetirom 100 mg, and placebo arms from Trials MGL-3196-11 and MGL-3196-14.
Abbreviations: CI, confidence interval; Intl., international; ISS, integrated summary of safety

17.3. Additional Analyses Related to Key Safety Issues

17.3.1. Additional Tables Related to Section on Treatment-Related Changes in Thyroid Hormones

Table 293 displays mean change from baseline to Week 52 in Trial MGL-3196-11 for thyroid hormones. The table is excerpted from a consult review completed by FDA endocrinologists. See Section 7.7.2 for discussion.

Table 293. Thyroid Hormones: Summary of Mean Change From Baseline to Week 52 (Conventional Units), Safety Population – F1B, F2, F3

Thyroid Hormone Parameter	LS Mean %CFB or CFB (SE) Resmetirom 80 mg (N=322)	LS Mean %CFB or CFB (SE) Resmetirom 100 mg (N=323)	LS Mean %CFB or CFB (SE) Placebo (N=321)	LS Mean Difference Resmetirom 80 mg From PBO (95% CI)	p-value	LS Mean Difference Resmetirom 100 mg From PBO (95% CI)	p-value
Not on Thyroxine at Baseline							
FT4, ng/dL							
n	248	229	245				
Baseline mean (SD)	1.1 (0.18)	1.1 (0.18)	1.1 (0.16)				
Week 52 CFB (SE)	-0.16 (0.011)	-0.21 (0.011)	0.02 (0.010)	-0.18 (-0.20, -0.16)	<0.0001	-0.23 (-0.25, -0.20)	<0.0001
Week 52 %CFB (SE)	-13.83 (0.97)	-17.56 (1.0)	2.48 (0.95)	-16.31 (-18.4, -14.2)	<0.0001	-20.04 (-22.2, -17.9)	<0.0001
TSH, mIU/L							
n	248	229	245				
Baseline mean (SD)	2.0 (1.0)	2.0 (1.1)	1.9 (0.98)				
Week 52 CFB (SE)	-0.23 (0.056)	-0.20 (0.058)	-0.08 (0.055)	-0.15 (-0.27, -0.03)	0.0143	-0.12 (-0.24, 0)	0.0554
FT3, ng/L							
n	248	229	245				
Baseline mean (SD)	3.0 (0.40)	3.0 (0.42)	3.1 (0.39)				
Week 52 CFB (SE)	-0.01 (0.032)	-0.08 (0.033)	-0.02 (0.031)	0.01 (-0.06, 0.08)	0.7964	-0.06 (-0.13, 0.01)	0.0926
TT3, (ug/L)							
n	248	229	245				
Baseline mean (SD)	1.2 (0.25)	1.2 (0.24)	1.2 (0.22)				
Week 52 CFB (SE)	-0.02 (0.015)	-0.05 (0.015)	-0.01 (0.015)	-0.01 (-0.04, 0.02)	0.5981	-0.04 (-0.08, -0.01)	0.0116

Thyroid Hormone Parameter	LS Mean %CFB or CFB (SE) Resmetirom 80 mg (N=322)	LS Mean %CFB or CFB (SE) Resmetirom 100 mg (N=323)	LS Mean %CFB or CFB (SE) Placebo (N=321)	LS Mean Difference Resmetirom 80 mg From PBO (95% CI)	p-value	LS Mean Difference Resmetirom 100 mg From PBO (95% CI)	p-value
rT3, ng/dL							
n	247	232	244				
Baseline mean (SD)	18.3 (5.3)	18.7 (5.7)	18.3 (5.6)				
Week 52 CFB (SE)	-4.5 (0.33)	-4.9 (0.34)	0.19 (0.33)	-4.7 (-5.4, -3.9)	<0.0001	-5.1 (-5.9, -4.4)	<0.0001
On Thyroxine at Baseline							
FT4, ng/dL							
n	31	36	41				
Baseline mean (SD)	1.3 (0.23)	1.2 (0.31)	1.2 (0.21)				
Week 52 CFB (SE)	-0.18 (0.041)	-0.26 (0.037)	0.02 (0.036)	-0.21 (-0.29, -0.12)	<0.0001	-0.29 (-0.37, -0.21)	<0.0001
Week 52 %CFB (SE)	-14.04 (3.571)	-20.61 (3.252)	3.83 (3.148)	-17.87 (-25.23, -10.51)	<0.0001	-24.44 (-31.57, -17.31)	<0.0001
TSH, mIU/L							
n	31	36	41				
Baseline mean (SD)	2.0 (1.89)	2.6 (1.46)	2.2 (1.79)				
Week 52 CFB (SE)	-0.63 (0.272)	-0.13 (0.252)	-0.22 (0.241)	-0.41 (-0.97, 0.15)	0.1494	0.09 (-0.46, 0.63)	0.7507
FT3, ng/L							
n	31	36	41				
Baseline mean (SD)	2.7 (0.38)	2.8 (0.72)	2.8 (0.41)				
Week 52 CFB (SE)	0.04 (0.089)	-0.03 (0.081)	-0.02 (0.079)	0.05 (-0.13, 0.23)	0.5806	-0.01 (-0.19, 0.17)	0.9161
TT3, ug/L							
n	31	36	41				
Baseline mean (SD)	1.0 (0.15)	1.1 (0.26)	1.1 (0.21)				
Week 52 CFB (SE)	0.02 (0.037)	-0.02 (0.034)	0.02 (0.033)	0.01 (-0.07, 0.08)	0.8623	-0.04 (-0.12, 0.03)	0.2838
rT3, ng/dL							
n	31	37	38				
Baseline mean (SD)	20.7 (6.12)	22.2 (8.12)	19.1 (5.62)				
Week 52 CFB (SE)	-5.11 (0.935)	-6.34 (0.848)	-0.01 (0.842)	-5.09 (-7.05, -3.13)	<0.0001	-6.33 (-8.24, -4.41)	<0.0001

Source: Applicant provided Tables 14.3.4.1.5.3.2.1, 14.3.4.1.5.3.4.1, CSR, MGL-3196-11.
Abbreviations: CFB, change from baseline; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; LS, least squares; rT3, reverse triiodothyronine; SE, standard error; TBG, thyroxine binding globulin; TSH, thyrotropin

Table 294 displays the changes from baseline to Week 52 in mean FT4, TSH, and T3 levels in Trial MGL-3196-14. These are similar to those in Trial MGL-3196-11. Table excerpted from the Division of General Endocrinology consult review.

Table 294. Summary of Thyroid Hormones at Baseline and Change From Baseline or Percent Change From Baseline at Week 52; Trial MGL-3196-14, Safety Population

	OLNC (n=169)		Resmetirom 100mg DB (n=314)			Resmetirom 80mg DB (n=320)			Placebo DB (n=309)
Thyroid Hormone Parameter	LSM CFB or %CFB (SE)	95% CI	LSM CFB or %CFB (SE)	LSM Difference (97.5% CI)	p-value	LSM CFB or %CFB (SE)	LSM Difference (97.5% CI)	p-value	LSM CFB or %CFB (SE)
Not on Thyroxine at Baseline									
FT4, ng/dL									
n		81			234			217	231
Baseline mean (SD)		1.1 (0.2)			1.1 (0.2)			1.1 (0.2)	1.1 (0.2)
Week 52 %CFB	-18.9 (2.2)	-23.3 to -14.5	-14.3 (1.6)	-15.4 (-19.0 to -11.7)	<0.0001	-9.9 (1.6)	-11.0 (-14.7 to -7.3)	<0.0001	1.1 (1.6)
Week 52 CFB	-0.2 (0.0)	-0.3 to -0.2	-0.2 (0.0)	-0.2 (-0.2 to -0.1)	<0.0001	-0.1 (0.0)	-0.1 (-0.2 to -0.1)	<0.0001	0.0 (0.0)
TSH, mIU/L									
n		81			234			217	230
Baseline mean (SD)		2.2 (1.3)			2.2 (1.3)			2.0 (1.1)	2.2 (1.0)
Week 52 CFB	-0.2 (0.1)	-0.4 to -0.0	-0.3 (0.1)	-0.1 (-0.2 to 0.1)	0.33	-0.3 (0.1)	0.0 (-0.1 to 0.2)	0.96	-0.3 (0.1)
FT3, ng/L									
n		81			234			217	231
Baseline mean (SD)		3.0 (0.4)			3.0 (0.4)			2.9 (0.4)	3.0 (0.4)
Week 52 CFB	-0.1 (0.1)	-0.2 to 0.0	-0.1 (0.0)	0.0 (-0.1 to 0.1)	0.84	-0.1 (0.0)	0.1 (-0.0 to 0.2)	0.19	-0.1 (0.0)
rT3, ng/dL									
n		82			236			217	231
Baseline mean (SD)		16.5 (5.1)			16.1 (4.2)			17.5 (4.9)	16.5 (4.4)
Week 52 CFB	-3.5 (0.5)	-4.4 to -2.6	-2.9 (0.3)	-3.8 (-4.5 to -3.0)	<0.0001	-2.5 (0.3)	-3.3 (-4.1 to -2.6)	<0.0001	0.9 (0.3)
On Thyroxine at Baseline									
FT4, ng/dL									
n		70			29			33	26
Baseline mean (SD)		1.3 (0.2)			1.1 (0.2)			1.3 (0.3)	1.2 (0.2)
Week 52 %CFB	-14.8 (3.0)	-20.8 to -8.8	-19.2 (3.8)	-23.0 (-33.5 to -12.5)	<0.01	-6.4 (3.9)	-10.2 (-20.3 to 0.0)	0.0251	3.8 (3.9)
Week 52 CFB	-0.2 (0.0)	-0.3 to -0.2	-0.2 (0.0)	-0.2 (-0.3 to -0.1)	<0.0001	-0.2 (0.0)	-0.2 (-0.3 to -0.1)	<0.0001	0.0 (0.0)
TSH, mIU/L									
n		70			29			33	26
Baseline mean (SD)		2.4 (2.3)			3.0 (4.4)			1.6 (1.2)	2.2 (1.6)
Week 52 CFB	0.4 (1.2)	-1.9 to 2.7	-0.6 (1.5)	0.0 (-4.0 to 4.1)	0.99	-0.9 (1.5)	-0.3 (-4.2 to 3.7)	0.89	-0.6 (1.5)
FT3, ng/L									
n		70			29			33	26
Baseline mean (SD)		2.7 (0.6)			2.6 (0.4)			2.9 (0.7)	2.7 (0.4)
Week 52 CFB	-0.1 (0.1)	-0.3 to 0.0	-0.0 (0.1)	-0.0 (-0.3 to 0.3)	0.98	0.0 (0.1)	0.0 (-0.2 to 0.3)	0.80	-0.0 (0.1)

Thyroid Hormone Parameter	OLNC (n=169)		Resmetirom 100mg DB (n=314)			Resmetirom 80mg DB (n=320)			Placebo DB (n=309)
	LSM CFB or %CFB (SE)	95% CI	LSM CFB or %CFB (SE)	LSM Difference (97.5% CI)	p-value	LSM CFB or %CFB (SE)	LSM Difference (97.5% CI)	p-value	LSM CFB or %CFB (SE)
rT3, ng/dL									
n		70			29			33	26
Baseline mean (SD)		20.1 (5.3)			18.1 (6.8)			19.6 (5.6)	18.6 (5.5)
Week 52 CFB	-3.9 (0.8)	-5.5 to -2.2	-4.9 (1.0)	-5.5 (-8.3 to -2.7)	<0.0001	-3.8 (1.0)	-4.4 (-7.1 to -1.7)	0.0004	0.6 (1.0)

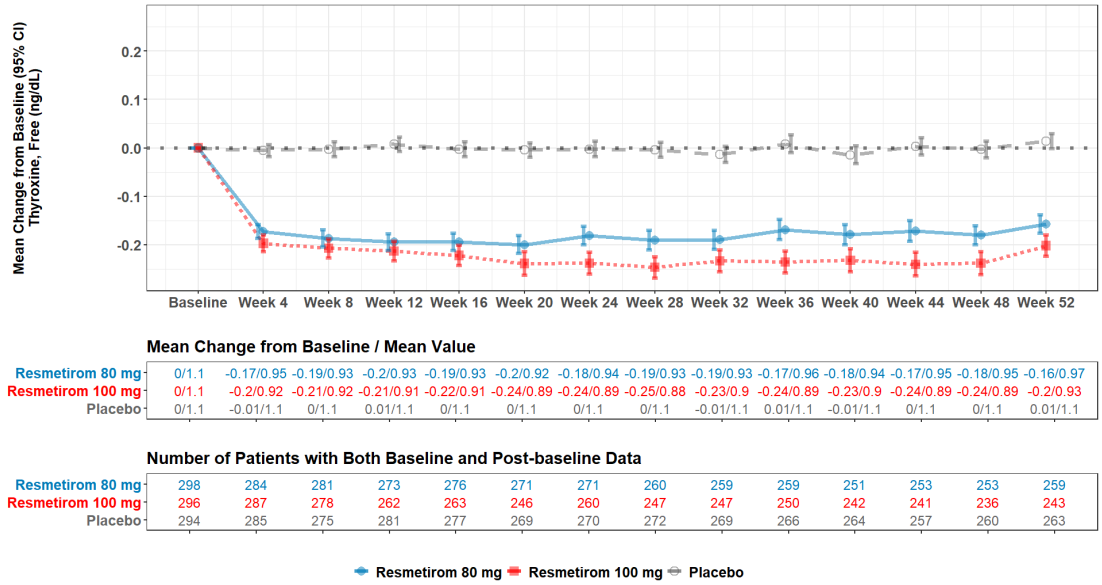
Source: Applicant provided Table 41, in clinical study report, MGL-3196-14

Note: Free T4 reported as both CFB and percent CFB at Week 52. All other thyroid hormones reported as CFB at Week 52.

Abbreviations: CFB, change from baseline; CI, confidence interval; DB, double-blind; FT3, free triiodothyronine; FT4 = free thyroxine; LSM, least squares mean; OLNC, open-label non-cirrhotic; rT3, reverse triiodothyronine; SE, standard error; T3, triiodothyronine; T4, thyroxine; TBG, thyroxine binding globulin; TSH, thyroid stimulating hormone

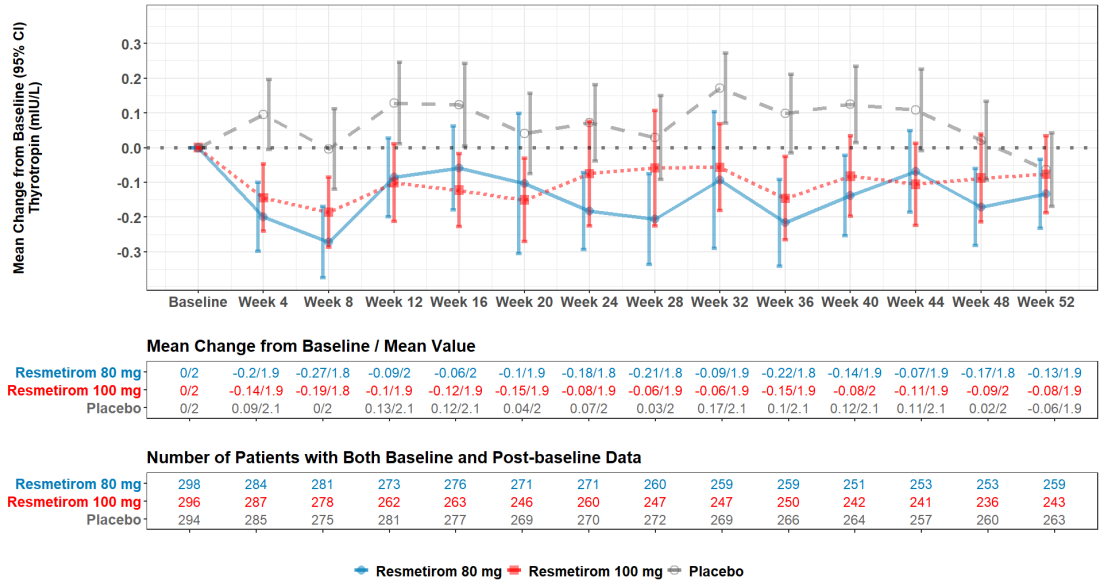
Figure 69 and Figure 70display mean changes in FT4 and TSH from baseline over time in the F2/F3 population. See Section 7.7.2 for discussion.

Figure 69. Mean Change in Free Thyroxine From Baseline Over Time, Safety Population, Trial MGL-3196-11 (F2/F3 Population)



Source: adlbc2.xpt; Software: R Generated by clinical data scientist
Note: Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Note: Only central laboratory data are included in the analysis.
Note: Normal range: Free thyroxine, 0.7-1.6 ng/dL; free triiodothyronine, 2-4.4 ng/dL; thyrotropin (TSH), 0.4-4 mIU/L
Abbreviations: CI, confidence interval

Figure 70. Mean Change in Thyrotropin From Baseline Over Time, Safety Population, Trial MGL-3196-11 (F2/F3 Population)



Source: adlbc2.xpt; Software: R Generated by clinical data scientist
Note: Figures do not include timepoints with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Note: Only central laboratory data are included in the analysis.
Note: Normal range: Free thyroxine, 0.7-1.6 ng/dL; free triiodothyronine, 2-4.4 ng/dL; thyrotropin (TSH), 0.4-4 mIU/L.
Abbreviations: CI, confidence interval

17.3.2. Additional Tables Related to Treatment-Related Changes in Sex Hormones

Table 295 lists the changes from baseline to week 52 in sex hormones, by sex in Trial MGL-3196-11. See Section 7.7.7 for detailed discussion.

Table 295. Changes From Baseline to Week 52 in Sex Hormones, by Sex, Trial MGL-3196-11, Safety Population – F1B, F2, F3

Sex Hormone Parameter	LS Mean %CFB or CFB (SE) Resmetirom 80 mg (N = 322)	LS Mean %CFB or CFB (SE) Resmetirom 100 mg (N = 323)	LS Mean %CFB or CFB (SE) Placebo (N = 321)	LS Mean Difference Resmetirom 80 mg From PBO (95% CI)	p-value	LS Mean Difference Resmetirom 100 mg From PBO (95% CI)	p-value
Females							
Estradiol, ng/L (female)							
n	160	147	155				
Baseline mean (SD)	28.6 (37.0)	32.1 (56.3)	32.8 (65.9)				
Week 52 CFB (SE)	17.7 (8.0)	30.6 (8.3)	1.8 (8.0)	15.9 (-1.3, 33.1)	0.0699	28.8 (11.3, 46.3)	0.0013
FSH, mIU/mL (female)							
n	160	148	155				
Baseline mean (SD)	39.2 (25.7)	39.3 (22.6)	39.8 (23.2)				
Week 52 CFB (SE)	-0.54 (0.89)	0.63 (0.92)	-1.3 (0.89)	0.79 (-1.1, 2.7)	0.4173	2.0 (0.02, 3.9)	0.0478
LH, mIU/mL (female)							
n	160	148	155				
Baseline mean (SD)	23.5 (14.1)	24.2 (13.2)	23.3 (12.0)				
Week 52 CFB (SE)	-0.93 (0.69)	0.80 (0.72)	-0.60 (0.70)	-0.33 (-1.8, 1.2)	0.6638	1.40 (-0.11, 2.9)	0.0688
Free testosterone, nmol/L (female)							
n	121	110	106				
Baseline mean (SD)	0 (0.01)	0 (0.01)	0 (0.01)				
Week 52 CFB (SE)	0 (0.001)	0 (0.001)	0 (0.001)	0	0.5438	0	0.6502
Testosterone, ug/L (female)							
n	160	147	156				
Baseline mean (SD)	0.2 (0.17)	0.2 (0.16)	0.1 (0.24)				
Week 52 CFB (SE)	0.15 (0.019)	0.19 (0.020)	0.00 (0.019)	0.15 (0.10, 0.19)	<0.0001	0.19 (0.14, 0.23)	<0.0001

Sex Hormone Parameter	LS Mean %CFB or CFB (SE) Resmetirom 80 mg (N = 322)	LS Mean %CFB or CFB (SE) Resmetirom 100 mg (N = 323)	LS Mean %CFB or CFB (SE) Placebo (N = 321)	LS Mean Difference Resmetirom 80 mg From PBO (95% CI)	p-value	LS Mean Difference Resmetirom 100 mg From PBO (95% CI)	p-value
SHBG, nmol/L (female)							
n	159	145	155				
Baseline mean (SD)	58.2 (71.7)	48.9 (44.5)	55.7 (54.6)				
Week 52 %CFB (SE)	193.0 (15.3)	251.8 (16.0)	15.6 (15.5)	177.4 (144.3, 210.5)	<0.0001	236.2 (202.3, 270.0)	<0.0001
Week 52 CFB (SE)	74.1 (6.0)	94.0 (6.3)	0.82 (6.1)	73.3 (60.3, 86.2)	<0.0001	93.2 (79.9, 106.5)	<0.0001
Males							
Estradiol, ng/L (male)							
n	118	118	128				
Baseline mean (SD)	28.0 (11.6)	27.6 (10.9)	29.3 (12.1)				
Week 52 CFB (SE)	8.9 (1.3)	11.0 (1.3)	-0.15 (1.2)	9.0 (6.3, 11.8)	<0.0001	11.2 (8.4, 13.9)	<0.0001
Free testosterone, nmol/L (male)							
n	116	108	127				
Baseline mean (SD)	0.2 (0.09)	0.2 (0.11)	0.2 (0.07)				
Week 52 CFB (SE)	0.04 (0.009)	0.03 (0.009)	0.02 (0.008)	0.02 (0, 0.04)	0.0686	0.01 (-0.01, 0.03)	0.3513
Testosterone, ug/L (male)							
n	118	118	128				
Baseline mean (SD)	3.5 (1.6)	3.7 (2.0)	3.3 (1.5)				
Week 52 CFB (SE)	2.6 (0.3)	3.5 (0.3)	0.44 (0.2)	2.2 (1.6, 2.8)	<0.0001	3.0 (2.5, 3.6)	<0.0001
FSH, mIU/mL (male)							
n	118	119	128				
Baseline mean (SD)	8.1 (7.7)	7.8 (9.7)	7.2 (6.5)				
Week 52 CFB (SE)	1.1 (0.2)	1.7 (0.2)	0.01 (0.2)	1.10 (0.6, 1.6)	<0.0001	1.7 (1.1, 2.2)	<0.0001
LH, mIU/mL (male)							
n	118	119	128				
Baseline mean (SD)	6.3 (4.1)	6.0 (4.6)	6.1 (4.0)				
Week 52 CFB (SE)	1.7 (0.3)	1.9 (0.3)	-0.10 (0.3)	1.8 (1.1, 2.4)	<0.0001	2.0 (1.4, 2.7)	<0.0001

Sex Hormone Parameter	LS Mean %CFB or CFB (SE) Resmetirom 80 mg (N = 322)	LS Mean %CFB or CFB (SE) Resmetirom 100 mg (N = 323)	LS Mean %CFB or CFB (SE) Placebo (N = 321)	LS Mean Difference Resmetirom 80 mg From PBO (95% CI)	p-value	LS Mean Difference Resmetirom 100 mg From PBO (95% CI)	p-value
SHBG, nmol/L (male)							
n	116	117	128				
Baseline mean (SD)	36.0 (17.2)	41.4 (27.1)	37.0 (20.8)				
Week 52 %CFB (SE)	108.0 (11.2)	174.0 (10.9)	0.74 (10.1)	107.3 (83.4, 131.2)	<0.0001	173.3 (149.4, 197.2)	<0.0001
Week 52 CFB (SE)	41.9 (4.2)	60.8 (4.1)	1.53 (3.8)	40.4 (31.4, 49.4)	<0.0001	59.3 (50.3, 68.3)	<0.0001

Source: Table 69, CSR, MGL-3196-11.
Abbreviations: 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

17.3.3. Additional Tables Related to Malignancy

Table 296 and Table 297 display the full list of neoplasms noted in Trials MGL-3196-11 and MGL-3196-14, respectively. For full discussion on malignancy refer to Section 7.7.10.

Table 296. AESI Assessment, Malignancies, Safety Population, Trial MGL-3196-11

Malignancies	Placebo PY=516.7 N=349 n/py (EAIR)	Resmetirom 80 mg PY=510.9 N=352 n/py (EAIR)	Resmetirom 100 mg PY=487.8 N=349 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
AE grouping related to AESI	21/495.8 (4.2)	15/497.7 (3.0)	24/471.9 (5.1)	-1.2 (-3.8, 1.2)	0.9 (-1.9, 3.7)
Lipoma	1/515.9 (0.2)	1/509.9 (0.2)	2/487.3 (0.4)	0.0 (-0.9, 0.9)	0.2 (-0.7, 1.3)
Squamous cell carcinoma	0/516.7 (0)	0/510.9 (0)	1/486.3 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Urothelial papilloma	0/516.7 (0)	0/510.9 (0)	1/486.4 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Invasive lobular breast carcinoma	0/516.7 (0)	0/510.9 (0)	1/486.6 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Benign neoplasm of thyroid gland	0/516.7 (0)	0/510.9 (0)	1/486.6 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Testicular germ cell tumor	0/516.7 (0)	0/510.9 (0)	1/486.7 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Eyelid seborrheic keratosis	0/516.7 (0)	0/510.9 (0)	1/487 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Angiomyolipoma	0/516.7 (0)	0/510.9 (0)	1/487.2 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Colon cancer	0/516.7 (0)	0/510.9 (0)	1/487.3 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Hemangioma of bone	0/516.7 (0)	0/510.9 (0)	1/487.3 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Adenocarcinoma of colon	0/516.7 (0)	0/510.9 (0)	1/487.4 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)

Malignancies	Placebo PY=516.7 N=349 n/py (EAIR)	Resmetirom 80 mg PY=510.9 N=352 n/py (EAIR)	Resmetirom 100 mg PY=487.8 N=349 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Acrochordon	0/516.7 (0)	0/510.9 (0)	1/487.4 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Oral papilloma	0/516.7 (0)	0/510.9 (0)	1/487.5 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Skin cancer	0/516.7 (0)	0/510.9 (0)	1/487.8 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Benign gastric neoplasm	0/516.7 (0)	0/510.9 (0)	1/487.8 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Breast cancer	0/516.7 (0)	0/510.9 (0)	1/487.8 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Non-Hodgkin's lymphoma	0/516.7 (0)	0/510.9 (0)	1/487.8 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Hepatic neoplasm	0/516.7 (0)	0/510.9 (0)	1/487.8 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Hepatocellular carcinoma	0/516.7 (0)	0/510.9 (0)	1/487.8 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Hodgkin's disease	0/516.7 (0)	0/510.9 (0)	1/487.9 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Papillary thyroid cancer	0/516.7 (0)	0/510.9 (0)	1/487.9 (0.2)	0.0 (-0.7, 0.8)	0.2 (-0.5, 1.2)
Skin papilloma	2/512.1 (0.4)	0/510.9 (0)	2/486.1 (0.4)	-0.4 (-1.4, 0.4)	0.0 (-1.1, 1.1)
Melanocytic naevus	1/516.3 (0.2)	3/508 (0.6)	1/487.2 (0.2)	0.4 (-0.6, 1.6)	0.0 (-0.9, 1.0)
Malignant melanoma	1/515.2 (0.2)	0/510.9 (0)	1/486.9 (0.2)	-0.2 (-1.1, 0.6)	0.0 (-0.9, 1.0)
Elastofibroma	0/516.7 (0)	1/510 (0.2)	0/487.8 (0)	0.2 (-0.5, 1.1)	0.0 (-0.7, 0.8)
Fibroma	0/516.7 (0)	1/508.9 (0.2)	0/487.8 (0)	0.2 (-0.5, 1.1)	0.0 (-0.7, 0.8)
Neuroma	0/516.7 (0)	1/510.7 (0.2)	0/487.8 (0)	0.2 (-0.5, 1.1)	0.0 (-0.7, 0.8)
Philadelphia positive acute lymphocytic leukemia	0/516.7 (0)	1/511 (0.2)	0/487.8 (0)	0.2 (-0.5, 1.1)	0.0 (-0.7, 0.8)
Plasma cell myeloma	0/516.7 (0)	1/510.8 (0.2)	0/487.8 (0)	0.2 (-0.5, 1.1)	0.0 (-0.7, 0.8)
Bladder neoplasm	1/516.5 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Bladder transitional cell carcinoma	1/516.5 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Transitional cell carcinoma	1/516.4 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Neoplasm prostate	1/516.3 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
B-cell small lymphocytic lymphoma	1/516.3 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Neoplasm	1/516.3 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Neuroendocrine carcinoma	1/515.7 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Invasive ductal breast carcinoma	1/515.7 (0.2)	1/510.1 (0.2)	0/487.8 (0)	0.0 (-0.9, 0.9)	-0.2 (-1.1, 0.6)
Sweat gland tumor	1/515.7 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Benign neoplasm of adrenal gland	1/515.5 (0.2)	0/510.9 (0)	0/487.8 (0)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Squamous cell carcinoma of skin	1/515.4 (0.2)	1/508.5 (0.2)	0/487.8 (0)	0.0 (-0.9, 0.9)	-0.2 (-1.1, 0.6)
Fibrous histiocytoma	1/514.6 (0.2)	1/510.2 (0.2)	0/487.8 (0)	0.0 (-0.9, 0.9)	-0.2 (-1.1, 0.6)
Basal cell carcinoma	5/511.8 (1.0)	2/510.2 (0.4)	3/485.5 (0.6)	-0.6 (-1.9, 0.6)	-0.4 (-1.7, 0.9)

Malignancies	Placebo PY=516.7 N=349 n/py (EAIR)	Resmetirom 80 mg PY=510.9 N=352 n/py (EAIR)	Resmetirom 100 mg PY=487.8 N=349 n/py (EAIR)	Resmetirom 80 mg vs. Placebo EAIR Difference (95% CI)	Resmetirom 100 mg vs. Placebo EAIR Difference (95% CI)
Seborrheic keratosis	3/510.7 (0.6)	1/509.5 (0.2)	1/486.3 (0.2)	-0.4 (-1.6, 0.6)	-0.4 (-1.5, 0.6)
Pituitary tumor benign	2/516.1 (0.4)	0/510.9 (0)	0/487.8 (0)	-0.4 (-1.4, 0.4)	-0.4 (-1.4, 0.4)
Neoplasm skin	3/515 (0.6)	0/510.9 (0)	0/487.8 (0)	-0.6 (-1.7, 0.2)	-0.6 (-1.7, 0.2)

Source: adae.xpt; Software: R
Note: Median analysis duration is 71.8 weeks (resmetirom 80 mg), 66.1 weeks (resmetirom 100 mg), and 69.6 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; PY, person-years (total exposure); py, person-years (at risk);

Table 297. AESI Assessment, Malignancies, Safety Population, Trial MGL-3196-14

Malignancies	Placebo N=318 n (%)	Resmetirom 80 mg N=327 n (%)	Resmetirom 100 mg N=324 n (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
AE grouping related to AESI	18 (5.7)	6 (1.8)	21 (6.5)	-3.8 (-7.1, -1.0) *	0.8 (-3.0, 4.7)
Acrochordon	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Angiofibroma	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
B-cell small lymphocytic lymphoma stage I	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
B-cell type acute leukemia	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Basal cell carcinoma	4 (1.3)	1 (0.3)	2 (0.6)	-1.0 (-2.9, 0.6)	-0.6 (-2.6, 1.1)
Benign breast neoplasm	0	1 (0.3)	0	0.3 (-0.9, 1.7)	0.0 (-1.2, 1.2)
Benign neoplasm of thyroid gland	0	1 (0.3)	0	0.3 (-0.9, 1.7)	0.0 (-1.2, 1.2)
Cholangiocarcinoma	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Clear cell renal cell carcinoma	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Colorectal adenoma	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Dysplastic naevus	1 (0.3)	1 (0.3)	0	-0.0 (-1.5, 1.4)	-0.3 (-1.8, 0.9)
Endometrial cancer	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Eye naevus	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Hemangioma of skin	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Hepatocellular carcinoma	0	1 (0.3)	0	0.3 (-0.9, 1.7)	0.0 (-1.2, 1.2)
Invasive ductal breast carcinoma	1 (0.3)	0	1 (0.3)	-0.3 (-1.8, 0.9)	-0.0 (-1.5, 1.4)
Lipoma	0	0	2 (0.6)	0.0 (-1.2, 1.2)	0.6 (-0.6, 2.2)
Lung adenocarcinoma	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)

Malignancies	Placebo N=318 n (%)	Resmetirom 80 mg N=327 n (%)	Resmetirom 100 mg N=324 n (%)	Resmetirom 80 mg vs. Placebo Risk Difference % (95% CI)	Resmetirom 100 mg vs. Placebo Risk Difference % (95% CI)
Melanocytic naevus	1 (0.3)	0	1 (0.3)	-0.3 (-1.8, 0.9)	-0.0 (-1.5, 1.4)
Meningioma benign	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Metastases to lymph nodes	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Neoplasm	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Neoplasm skin	0	0	2 (0.6)	0.0 (-1.2, 1.2)	0.6 (-0.6, 2.2)
Papillary thyroid cancer	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Prostate cancer	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Prostate cancer stage IV	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Seborrheic keratosis	2 (0.6)	0	3 (0.9)	-0.6 (-2.3, 0.5)	0.3 (-1.4, 2.1)
Soft tissue sarcoma	0	0	1 (0.3)	0.0 (-1.2, 1.2)	0.3 (-0.9, 1.7)
Squamous cell carcinoma	3 (0.9)	0	3 (0.9)	-0.9 (-2.7, 0.2)	-0.0 (-1.9, 1.9)
Squamous cell carcinoma of skin	1 (0.3)	0	0	-0.3 (-1.8, 0.9)	-0.3 (-1.8, 0.9)
Uterine leiomyoma	2 (0.6)	1 (0.3)	1 (0.3)	-0.3 (-2.0, 1.1)	-0.3 (-2.0, 1.2)

Source: adae.xpt; Software: R
Note: Median analysis duration is 71.8 weeks (resmetirom 80 mg), 66.1 weeks (resmetirom 100 mg), and 69.6 weeks (placebo).
Note: EAIR difference (with 95% confidence interval) is shown between treatment and placebo.
Note: Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable;

18. Clinical Virology

This section is not applicable to the resmetirom drug product.

19. Clinical Microbiology

This section is not applicable to the resmetirom drug product.

20. Mechanism of Action/Drug Resistance

Refer to Section 5.2 for a discussion of mechanism of action.

21. Other Drug Development Considerations

Data Integrity-Related Consults (Office of Scientific Investigations)

Two clinical site inspections and an inspection of the Applicant were completed by the Office of Scientific Investigations. Based on the results of these inspections, the studies (MGL-3196-11, MGL-3196-14, and MGL-3196-18) appear to have been conducted adequately and the clinical data generated by the sites and submitted by the Applicant appear acceptable in support of the NDA.

The clinical sites were chosen using a risk-based approach, based primarily on numbers of subjects enrolled.

Inspection of Site # 172: October 30, 2023 to November 3, 2023

Twenty-five subjects were reviewed for each of the three studies.

For Study 3196-11, a total of 143 potential participants were screened and 81 were screen failures. The other 62 subjects were randomized. Of these, 24 subjects withdrew consent (early termination). The study was ongoing at the time of inspection.

For Study 3196-14, a total of 123 potential participants were screened. Of these, 43 were screen failures. The other 80 subjects were randomized. Of these, 8 subjects withdrew consent (early termination) and 72 subjects completed the trial.

For Study 3196-18, the subjects rolled over from the other studies. There was a total of 68 subjects who were randomized. Of these, 45 subjects completed the study and 14 subjects withdrew consent (early termination).

The inspection reviewed the processes and records related to the authority and administration of the clinical trials, the protocols, the Institutional Review Board documentation, subject records, financial disclosures, investigational product controls and accountability, the monitoring of the studies, informed consents, signed investigator agreements, AE reporting, and concomitant medication.

The inspection identified a delayed SAE report of a seizure in Study 3196-18, which was ultimately reported. Otherwise, no underreporting of AEs was identified.

Inspection of Site #116: November 13, 2023 to November 17, 2023

A total of 168 subjects were screened for Study 3196-11, and, of these, 57 subjects were enrolled; of these 15 subjects withdrew consent. The study was ongoing at the time of inspection but closed to enrollment.

A total of 61 subjects were screened for Study 3196-14, and, of these, 44 subjects were enrolled; 6 subjects discontinued the study; and 36 subjects completed this study.

For Study 3196-18, the site screened and enrolled 34 subjects, of which 23 subjects completed this study. The first subject received study drug on December 22, 2021, and the study was still ongoing at the time of inspection.

The inspector reviewed the case history records of 25 subjects in each study. This included the informed consent forms, case report forms (CRFs), medical records, laboratory reports, radiology and ultrasound reports, and ECG tracings and reports. Source documents were compared against the electronic CRFs and data listings provided with the submission. Other documents reviewed included drug accountability records; site correspondence with the Applicant, monitors, and Institutional Review Board; and regulatory records, including FDA 1572s and financial disclosure records.

Data discrepancies were identified between source documents and eCRFs regarding relatedness to study drug for six AEs in four subjects in Study 3196-14. At the end of the inspection, the inspector discussed data discrepancies in AE relatedness between source records and eCRFs (where eCRF data matched data listings) in four subjects in Study 3196-14. These AEs were considered by the clinical investigator to be mild or moderate in severity and were not SAEs. No under-reporting of AEs was identified.

Inspection of Madrigal Pharmaceuticals, Inc.: November 20, 2023 to November 30, 2023

The inspectors covered the three main clinical protocols submitted for this NDA (Study 3196-11, Study 3196-14, and Study 3196-18). Fourteen (14) clinical sites were selected for review during the inspection consisting of Study 3196-11 (4 domestic and 2 foreign sites), Study 3196-14 (5 domestic sites) and Study 3196-18 (3 domestic sites). Applicant compliance was assessed by reviewing ClinicalTrials.gov component requirements, site training, safety monitoring, control of investigational product, financial disclosure, qualifications and training documentation for CRAs who served as clinical site monitors, independent data monitoring committee records, contract research organization contracts, protocol deviations, and safety data.

Overall, the Applicant’s oversight and monitoring for the three studies appeared adequate.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The Office of Scientific Investigations was consulted and performed clinical inspections of two clinical investigators, Drs. Sam Moussa and Guy Neff, as well as Madrigal Pharmaceuticals, Inc., for Trials MGL-3196-11, MGL-3196-14, and MGL-3196-18.

Based on the inspection results, the studies appear to have been conducted adequately and the clinical data generated by these sites and submitted by the Applicant appear acceptable in support of this NDA.

The inspector reviewed the case history records of 25 subjects in each study for each investigator. This included the informed consent forms, CRFs, medical records, laboratory reports, radiology and ultrasound reports, and ECG tracings and reports. Source documents were compared against the electronic CRFs and data listings provided with the submission. Other documents reviewed included drug accountability records; site correspondence with the Applicant, monitors, and Institutional Review Board; and regulatory records, including FDA 1572s and financial disclosure records.

For the inspection of Madrigal Pharmaceuticals, Inc., the inspectors covered the three clinical protocols submitted or this NDA (Study 3196-11, Study 3196-14, and Study 3196-18). Fourteen (14) clinical sites were selected for review during the inspection consisting of Study 3196-11 (4 domestic and 2 foreign sites), Study 3196-14 (5 domestic sites), and Study 3196-18 (3 domestic sites).

Applicant compliance was assessed by reviewing ClinicalTrials.gov component requirements, site training, safety monitoring, control of investigational product, financial disclosure, qualifications and training documentation for CRAs who served as clinical site monitors, Independent Data Monitoring Committee records, contract research organization contracts, protocol deviations, and safety data.

(b) (4) was responsible for monitoring site activities per written agreements. Monitoring reports for the selected sites were reviewed during the inspection. No major deviations from the clinical monitoring plan were observed. Madrigal PV and (b) (4) were responsible for seriousness, causality, and expectedness determinations of AEs. Madrigal was responsible for submitting expedited safety events to FDA. The procedures of safety reporting were reviewed.

Overall, the Applicant's oversight and monitoring for the three studies appeared adequate.

23. Labeling: Key Changes

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted in an amendment on March 13, 2024 (Table 298). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys

clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 298. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
1 INDICATIONS AND USAGE	(b) (4) The revised indication is: "REZDIFFRA is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis)." Limitations of Use (LOU) was added for patients with decompensated cirrhosis and patients (b) (4) Because there is lack of evidence regarding known hazards of REZDIFFRA in subjects with decompensated cirrhosis to contraindicate the use, this risk is placed under the LOU. The Limitations of Use is "Avoid use of REZDIFFRA in patients with decompensated cirrhosis *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*. (b) (4) Because NASH is used in our regulatory documents for fast track, breakthrough therapy designation, and priority review associated with the NDA, we will maintain NASH as the terminology in the labeling. Additionally, until there is a more universal acceptance of the new terminology, we will hold off on incorporating NASH in labeling or other formal Agency documents outside of communications with sponsors. The phrase "in conjunction with diet and exercise" was added to the indication 1) to align with indication statements of other drugs for metabolic dysfunction-associated conditions, such as type 2 diabetes mellitus and 2) to align with the nutrition and exercise counseling that was incorporated into the REZDIFFRA phase 3 study protocol.
2 DOSAGE AND ADMINISTRATION	(b) (4) It was determined that the dosage (b) (4) should be based on body weight. The final dosing recommendation is 80 mg for patients <100 kg and 100 mg for patients ≥100 kg. Refer to Sections 6.1 of the Integrated Assessment Review for additional information.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	Subsection 2.2. Dosage Modifications for Drug Interactions was added for adults who concomitantly take CYP2C8 inhibitors. Concomitant use of REZDIFFRA with strong CYP2C8 inhibitors is not recommended and dosage should be reduced for moderate CYP2C8 inhibitors (<100 kg, reduce REZDIFFRA to 60 mg once daily and ≥100 kg, reduce to 80 mg once daily). Refer to Section 8.2.3.1 of the Integrated Assessment Review for additional information.
4 CONTRAINDICATIONS	(b) (4)
5 WARNINGS AND PRECAUTIONS	(b) (4) the following subsections were added to include clinically significant adverse reactions (ARs) that are serious. • 5.1 Drug-Induced Hepatotoxicity; added due to one probable DILI case that occurred in a safety trial, consistent with drug induced autoimmune (DI-ALH) phenotype. Refer to Section 7.7.1 of the Integrated Assessment Review for additional information. • 5.2 Gallbladder-Related Adverse Reactions; added as Subsection 5.2 and revised to include obstructive pancreatitis (gallstone) because it is a severe and serious complication of cholelithiasis, which should be conveyed to the prescriber to ensure the safety of patients. "Gallstone" was added in parenthesis to clarify the cause of pancreatitis. • 5.3 Drug Interactions with Certain Statins; added due to the importance of potential reactions, and likelihood of coadministration of statins with REZDIFFRA.
6 ADVERSE REACTIONS	• Added an initial list of serious and otherwise important adverse reactions described in other labeling sections at the beginning of Section 6, per the FDA guidance for industry, *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006). • Revised to focus primarily on adverse reactions that occurred in the pivotal trial (Study 11), for which resmetirom will be approved. – Included information about common ARs (gastrointestinal-related), hypersensitivity, gallbladder-related ARs, and less common ARs.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	• (b) (4) • Revised adverse reactions to be presented in exposure-adjusted incidence rates (EAIRs) per 100 PY because it accurately represents the long-term safety data beyond 52-weeks. • The EAIRs for gallbladder-related adverse reactions were presented with less specificity because the Applicant raised concerns about potential unblinding of ongoing study. • Revised thyroid function tests to include trial data on the decrease in prohormone free T4 (FT4). • Information regarding the entirety of the safety population (n=2019) and the similarities in adverse reactions seen across both Study 11 and Study 14 were added.
7 DRUG INTERACTIONS	Revised to include the following drug interactions and relevant clinical impact and interventions: • Effects of other drugs on REZDIFFRA – Strong or moderate CYP2C8 inhibitors and organic anion-transporting polypeptides (OATP) 1B1 and 1B3 inhibitors • Effects of REZDIFFRA on other drugs – Statins and CYP2C8 substrates. Refer to Section 14.1.7 of the Integrated Assessment Review for additional information.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy and 8.2 Lactation: • Revised to describe the relevant nonclinical data, in line with the Pregnancy and Lactation Labeling Rule. (b) (4) there are no available clinical data regarding REZDIFFRA use in pregnancy to inform safety or dosing. Refer to DPMH/Maternal Health Review uploaded to DARRTS on December 20, 2023, for additional information. Subsection 8.5 Geriatric Use: • Revised to include the indicated population from Trial 1 (pivotal trial) and conclusionary statements about differences in REZDIFFRA response in geriatric patients compared with adults <65 years of age in accordance with 21 CFR 201.57(c)(9)(v). Subsection 8.7 Hepatic Impairment: • Revised to recommend avoiding use in patients with decompensated cirrhosis and moderate to severe hepatic impairment (Child-Pugh Class B or C). A statement was added that safety and effectiveness of REZDIFFRA have not been established in patients with NASH cirrhosis.
9 DRUG ABUSE AND DEPENDENCE	N/A

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
10 OVERDOSAGE	(b) (4) [redacted]
12 CLINICAL PHARMACOLOGY	Subsection 12.1 Mechanism of Action: • Revised the Established Pharmacologic Class (EPC) as recommended by the nonclinical team ("REZDIFFRA is a thyroid hormone receptor-beta [THR-β agonist]"). • Revised to include the timing of observed PD effects. • (b) (4) [redacted] Subsection 12.2 Pharmacodynamics: • (b) (4) [redacted] • Revised when liver fat content, prohormone FT4 and sex hormone binding globulin (SHBG) changes were observed. Subsection 12.3 Pharmacokinetics: • Revised for clarity and consistency with the FDA guidance for industry, *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016). • Summarized the PK data in NASH patients in a table for easier presentation. Removed PK data in healthy subjects to avoid confusion and in light of the impact of body weight on exposure. • Included ABCG2 genotype in the list of specific populations and indicated there are no clinically significant PK changes. • Added a section on body weight under Specific Populations to describe the effect of body weight on resmetirom exposure. • (b) (4) [redacted]
13 NONCLINICAL TOXICOLOGY	Subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility was revised to the following: • Carcinogenesis: resmetirom showed drug-induced tumors in rats and mice. • Mutagenesis: resmetirom was negative in all genotoxicity assays; results from genotoxicity testing of the metabolite MGL-3623 were added • Impairment of Fertility: resmetirom showed no effect in rats. Refer to Section 13.1 of the Integrated Assessment Review for additional information.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
14 CLINICAL STUDIES	• The following revisions were made: • [redacted] revised to describe the indicated population (noncirrhotic NASH patients with F2-F3 fibrosis) in the pivotal trial. • Demographic and baseline characteristics were placed in a table format. • The endpoint was aligned with the endpoints specified in the FDA draft guidance for industry, *Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment* (December 2018) [redacted] a table, which presents the results for each pathologist separately for each endpoint. Refer to Section 16.2 of the Integrated Assessment Review for additional information. • [redacted] • The efficacy analysis was presented as table with individual pathologist (Pathologist A and Pathologist B) response rates for each endpoint, as this presentation was considered more clinically interpretable [redacted]
17 PATIENT COUNSELING INFORMATION	Revisions were made to add the regulatory required statement in 21 CFR 201.57(c), "Advise the patient to read the FDA-approved patient labeling (Patient Information)." Revisions were also made to align with the additional information added to Section 5 Warnings and Precautions (i.e., drug-induced hepatotoxicity, gallbladder-related adverse reactions, drug interaction with statins).
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Section 11 Description was revised to include the active ingredient and the Established Pharmacologic Class was updated to align with HL and Subsection 12.1. Section 16 How Supplied/Storage and Handling was revised to [redacted] update the storage statement for clarity. Refer to the Integrated Quality Assessment.

Source: Integrated Assessment Review and Integrated Quality Assessment
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s):LDL-C, low-density lipoprotein cholesterol; PI, Prescribing Information; PK, pharmacokinetic

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- USPI
- Patient package insert
- Carton and container labeling

24. Postmarketing Requirements and Commitments

24.1. Postmarketing Requirements

Accelerated Approval Requirements PMR

Because resmetirom is being approved under the accelerated approval regulations, 21 CFR 314.500 (subpart H), Madrigal must conduct an adequate and well-controlled trial to verify and describe clinical benefit.

PMR 4577-1

Complete Trial MGL-3196-11, a randomized, double-blind, placebo-controlled 54-month trial in patients with NASH and liver fibrosis to demonstrate clinical benefit on the composite endpoint of progression to cirrhosis, hepatic decompensation events, liver transplant, and mortality.

- Study/Trial Completion: 08/2028
- Final Report Submission: 03/2029

Required PMRs Under the Pediatric Research Equity Act (21 U.S.C. 355c)

Postmarketing requirements under the Pediatric Research Equity Act 21 U.S.C. 355c are listed below.

PREA PMR 4577-2

Conduct a study of the safety, PK, and efficacy of REZDIFFRA in postpubertal pediatric patients ages 12 to 17 years with NASH with stage F2 and F3 fibrosis.

- Draft Protocol Submission: 04/2025
- Final Protocol Submission: 10/2025
- Study/Trial Completion: 01/2028
- Final Report Submission: 08/2028

PREA PMR 4577-3

Conduct a study of the safety, PK, and efficacy of REZDIFFRA in prepubertal pediatric patients ages 6 through 12 years with NASH with stage F2 and F3 fibrosis.

- Draft Protocol Submission: 04/2027
- Final Protocol Submission: 10/2027
- Study/Trial Completion: 07/2030
- Final Report Submission: 02/2031

Required PMRs Under FDCA Section 505(o)

Safety-related postmarketing requirements under the Food, Drug, and Cosmetic Act Section 505(o) are listed below.

PMR 4577-4

Descriptive pregnancy safety study: Conduct a worldwide descriptive study that collects prospective and retrospective data from women exposed to resmetirom during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes should be assessed through the first year of life. The minimum number of patients should be specified in the protocol.

- Draft Protocol Submission: 09/2024
- Final Protocol Submission: 03/2025
- Interim Report: 06/2027
- Study/Trial Completion: 03/2030
- Final Report Submission: 09/2030

PMR 4577-5

Clinical Lactation Study (milk only): Perform a lactation study (milk only) in lactating women who have received resmetirom to measure the concentration of resmetirom in breast milk using a validated assay and to assess any reported adverse effects on the breastfed infant.

- Draft Protocol Submission: 09/2024
- Final Protocol Submission: 03/2025
- Study/Trial Completion: 03/2027
- Final Report Submission: 09/2027

PMR 4577-6

Conduct a clinical study to evaluate the effects of severe renal impairment on the PK of resmetirom and its major metabolite(s). Design and conduct the trial in accordance with the FDA

draft guidance for industry, *Pharmacokinetics in Patients With Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* (September 2020).

- Draft Protocol Submission: N/A
- Final Protocol Submission: 11/2023
- Study/Trial Completion: 01/2025
- Final Report Submission: 06/2025

24.2. Postmarketing Commitments

PMCs Under FDCA Section 506B

Postmarketing commitments issued under the Food, Drug, and Cosmetic Act Section 506B are listed below.

PMC 4577-7

Conduct a clinical DDI study to evaluate the effects of resmetirom on the PK of a sensitive substrate of BCRP. Design and conduct the trial in accordance with the FDA guidance for industry, *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020a).

- Draft Protocol Submission: 07/2024
- Final Protocol Submission: 09/2024
- Study/Trial Completion: 03/2025
- Final Report Submission: 07/2025

PMC 4577-8

Conduct a clinical DDI study to evaluate the effects of an inhibitor of OATP1B1 and OATP1B3 on the PK of resmetirom. Design and conduct the trial in accordance with the FDA guidance for industry, *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020a).

- Draft Protocol Submission: 04/2024
- Final Protocol Submission: 06/2024
- Study/Trial Completion: 12/2024
- Final Report Submission: 04/2025

Non-505B CMC PMC

The chemistry, manufacturing, and controls postmarketing commitment is listed below.

CMC PMC 4577-9

Complete the environmental fate and ecotoxicity studies for resmetirom and submit a final environmental analysis report.

- Draft Protocol Submission: N/A
- Final Protocol Submission: N/A
- Study/Trial Completion: N/A
- Final Report Submission: 03/2025

25. Financial Disclosure

Table 299. Covered Clinical Studies: Trials MGL-3196-11, MGL-3196-14, and MGL-3196-18

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 266		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Source: Generated by the FDA review team.
Abbreviation: FDA, Food and Drug Administration

26. References

26.1. Literature

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26.2. Guidance for Industry

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26.3. Website

(b) (4)

(b) (4)

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26.4. Report

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27. Review Team

Table 300. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Taiye Adedeji, PharmD, Ayanna Augustus Bryant, PhD (CPMS)
Nonclinical reviewer	Fang Cai, PhD, Fresnida Ramos, PhD
Nonclinical team leader	David Joseph, PhD
OCP reviewer(s)	Amer Al-Khouja,PhD, Shen “Steven” Li, PhD, Yun Wang, PhD, (Pharmacometrics), Karryn Crisamore, PhD (Genomics)
OCP team leader(s)	Insook Kim, PhD, Jiang Liu, PhD, (Pharmacometrics), Sarah Dorff, PhD (Genomics)
Clinical reviewer	Ashish Dhawan, MD, MSPH
Clinical team leader	Gerri Baer, MD
Biometrics reviewer	Jiabei Yang, PhD
Biometrics team leader	Rebecca Hager, PhD
Cross-disciplinary team leader	Gerri Baer, MD
Division director (pharm/tox)	Andrew Goodwin, PhD
Division director (OCP)	Chandrahas Sahajwalla, PhD.
Supervisory Mathematical Statistician (OB)	Karen Higgins, ScD
Designated Division Signatory (clinical)	George Makar, MD, MSCE
Division director (clinical)	Joseph Toerner, MD
Office director (or designated signatory authority)	Nikolay Nikolov, MD

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 301. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Hamid Shafiei, PhD
OPDP	Meeta Patel, PharmD, Adewale Adeleye, PharmD
OSI	Min Lu, MD Glenn Mannheim, MD
OSE/DEPI	Joel Weissfeld, MD, MPH Benjamin Booth, PhD, Xi Wang, PhD
OSE/DMEPA	Susan Hakeem, PharmD, Valerie Vaughan, PharmD
OSE/DRISK	Leah Hart, PharmD, Timothy Bernheimer, PharmD
ADL	Katherine Won, PharmD
DILI	Paul Hayashi, MD
DDS	Judith Racoosin, MD
DPMH	Tamara Johnson, MD, MS; Kristie Baisden, DO
DGE	Shannon Sullivan, MD, PhD; Geanina Roman-Popoveniuc, MD
CDRH	Dolly Singh, PhD; Irene Tebbs, PhD

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology

27.1. Reviewer Signatures

Table 27-302 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Gerri Baer OII DHN	Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 23-26, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Gerri Baer

Digitally signed by Gerri Baer

Date: 3/14/2024 10:47 AM EDT
GUID: 2024314144720

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Karen Higgins OB DBIII	Sections: 6.2, 6.3, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Karen Higgins

Digitally signed by Karen Higgins

Date: 3/14/2024 10:49 AM EDT
GUID: 2024314144926

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Rebecca Hager OB DBIII	Sections: 6.2, 6.3, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Rebecca Hager

Digitally signed by Rebecca Hager

Date: 3/14/2024 10:49 AM EDT
GUID: 2024314144931

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Hamid Shafiei OPQAII DPQAVII	Sections: Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Hamid Shafiei

Digitally signed by Hamid Shafiei

Date: 3/14/2024 10:50 AM EDT
GUID: 2024314145027

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Hamid Shafiei OPQAII DPQAVII	Sections: Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Hamid Shafiei

Digitally signed by Hamid Shafiei

Date: 3/14/2024 10:51 AM EDT
GUID: 2024314145111

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Fresnida Ramos OII DPTII	Sections: 5.1, 5.2, 13.1, 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Fresnida Ramos

Digitally signed by Fresnida Ramos

Date: 3/14/2024 10:51 AM EDT
GUID: 2024314145136

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Ayanna Augustus Bryant ORO DROII	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Ayanna Augustus Bryant**

Digitally signed by Ayanna Augustus

Date: 3/14/2024 10:54 AM EDT
GUID: 2024314145429

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	David Joseph OII DPTII	Sections: 5.1, 5.2, 7.1, 7.7.6, 8.3, 8.4, 13.1, 13.2, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **David Joseph**

Digitally signed by David Joseph

Date: 3/14/2024 10:54 AM EDT
GUID: 2024314145452

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Jiabei Yang OB DBIII	Sections: 6.2, 6.3, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jiabei Yang

Digitally signed by Jiabei Yang

Date: 3/14/2024 10:56 AM EDT
GUID: 2024314145634

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Associate Director for Labeling	Katherine Won OII DHN	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Katherine Won

Digitally signed by Katherine Won

Date: 3/14/2024 10:57 AM EDT
GUID: 202431414573

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Associate Director for Labeling	Katherine Won OII DHN	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Katherine Won

Digitally signed by Katherine Won

Date: 3/14/2024 10:57 AM EDT
GUID: 2024314145738

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Insook Kim OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Insook Kim

Digitally signed by Insook Kim

Date: 3/14/2024 11:01 AM EDT
GUID: 202431415155

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Non-Clinical Reviewer Discipline Secondary Reviewer	David Joseph OII DPTII	Sections: 5.1, 5.2, 7.1, 7.7.6, 8.3, 8.4, 13.1, 13.2, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: David Joseph

Digitally signed by David Joseph

Date: 3/14/2024 11:02 AM EDT
GUID: 20243141525

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Genomics Reviewer Discipline Tertiary Reviewer	Michael Pacanowski OCP DTPM	Sections: 8.1, 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Michael Pacanowski

Digitally signed by Michael Pacanow

Date: 3/14/2024 11:02 AM EDT
GUID: 20243141524

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Ashish Dhawan OII DHN	Sections: 1-4, 6, 7, 15, 17-19, 23-26	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Ashish Dhawan

Digitally signed by Ashish Dhawan

Date: 3/14/2024 11:06 AM EDT
GUID: 202431415613

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Jiang Liu OCP DPM	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jiang Liu

Digitally signed by Jiang Liu

Date: 3/14/2024 11:07 AM EDT
GUID: 20243141576

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Chandrahas Sahajwalla OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Chandrahas Sahajwalla

Digitally signed by Chandrahas Saha

Date: 3/14/2024 11:07 AM EDT
GUID: 202431415742

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Genomics Reviewer Discipline Primary Reviewer	Karryn Crisamore OCP DTPM	Sections: 8.1, 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Karryn Crisamore

Digitally signed by Karryn Crisamore

Date: 3/14/2024 11:08 AM EDT
GUID: 202431415816

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Genomics Reviewer Discipline Secondary Reviewer	Sarah Dorff OCP DTPM	Sections: 8.1, 14.6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Sarah Dorff

Digitally signed by Sarah Dorff

Date: 3/14/2024 11:08 AM EDT
GUID: 202431415820

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Amer Al-Khouja OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Amer Al-Khouja

Digitally signed by Amer Al-Khouja

Date: 3/14/2024 11:08 AM EDT
GUID: 202431415822

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Primary Reviewer	Yun Wang OCP DPM	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Yun Wang

Digitally signed by Yun Wang

Date: 3/14/2024 11:14 AM EDT
GUID: 2024314151414

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Division Signatory	George Makar OII DHN	Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 23-26, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: George Makar

Digitally signed by George Makar

Date: 3/14/2024 11:14 AM EDT
GUID: 2024314151441

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Reviewer	Insook Kim OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Insook Kim

Digitally signed by Insook Kim
Sign on behalf of Shen Li
Date: 3/14/2024 11:29 AM EDT
GUID: 2024314152952

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Clearer	Suresh Doddapaneni OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Suresh Doddapaneni

Digitally signed by Suresh Doddapar

Date: 3/14/2024 11:38 AM EDT
GUID: 2024314153821

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Non-Clinical Reviewer Discipline Primary Reviewer	Fang Cai OII DPTII	Sections: 7.1, 8.3, 8.4, 13.1, 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Fang Cai

Digitally signed by Fang Cai

Date: 3/14/2024 11:43 AM EDT
GUID: 2024314154334

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Taiye Adedeji ORO DROII	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	

Signature: Taiye Adedeji

Digitally signed by Taiye Adedeji

Date: 3/14/2024 11:43 AM EDT
GUID: 2024314154337

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Carmen Booker OII DPTII	Sections: 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Carmen Booker

Digitally signed by Carmen Booker

Date: 3/14/2024 11:59 AM EDT
GUID: 2024314155942

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Non-Clinical Reviewer Discipline Tertiary Reviewer	Carmen Booker OII DPTII	Sections: 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Carmen Booker

Digitally signed by Carmen Booker

Date: 3/14/2024 12:00 PM EDT
GUID: 202431416016

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GERRI R BAER
03/14/2024 11:57:15 AM

GEORGE A MAKAR
03/14/2024 12:06:19 PM

NIKOLAY P NIKOLOV
03/14/2024 12:13:38 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA217785
Drug Name:	Resmetirom (MGL-3196)
Indication(s):	Treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis
Applicant:	Madrigal Pharmaceuticals, Inc. 200 Barr Harbor Dr., Stuie 400, West Conshohocken, PA 19428, USA Laboratory for 2-years rats, 2-year mice studies: (b) (4) (b) (4) Laboratory for 6-month mice study: (b) (4) (b) (4)
Consult Received Date(s):	Received 7/19/2023
Documents Reviewed:	Studies 0475mm72-001 (mice), 0474rm72-001 (rats), and 2835-002 (6-month transgenic mouse) and the electronic tumor data (SEND or Tumor.xpt) were submitted on 6/9/2023 (via NDA 217785/ S0001).
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, MS
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	CDER/OND/OII/ Division of Hepatology and Nutrition (DHN)
Nonclinical Team:	Fresnida Ramos, Ph.D.; David B Joseph, Ph.D.
Project Manager:	Taiye Adedeji
Keywords:	Carcinogenicity, Dose response

Table of Contents

1 Summary

This review evaluates statistically the data of the 2-year oral carcinogenicity study of Resmetirom (referred to as MGL-3196 hereafter) in Sprague-Dawley rats, the 2-year oral carcinogenicity study of MGL-3196 in CD-1 mice, and the data of a GLP 26-week study of MGL-3623 by oral gavage in CByB6F1- Tg(HRAS)2Jic mice . The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality).

For the 2-year rat study:
Rats (65/sex/group) were dosed by oral gavage with MGL-3196 daily for up to 104 weeks. The respective MGL-3196 doses in the saline control (SC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 1, 6, and 30 mg/kg/day for male and female rats.

The reviewer's survival data analysis results showed a statistically significant dose response relationship in mortality in both male and female rats when compared with vehicle control. The death rates for the high dosed group (30 mg/kg/day) were statistically significantly higher than the death rates of vehicle control groups for both male and female rats. The survival analysis didn't show any statistically significantly difference between the vehicle control group and saline control group.

The reviewer's tumor data analysis results showed that MGL-3196 cause a statistically significant positive dose response in the incidences of a rare tumor fibroadenoma, benign in mammary gland in male rats only when compared with vehicle control group ($p=0.0021 <0.025$). For this tumor type, the incidences rate of the high dosed group was statistically significantly greater than that of the vehicle control group ($p=0.0244 <0.05$).

MGL-3196 also cause a statistically significant a positive dose response in the incidences of a rare tumor adenocarcinoma, malignant in small intestine, jejunum in male rats when compared with the vehicle control group ($p=0.0225<0.025$). For this tumor type, the incidences rate of the high dosed group was not statistically significantly greater than that of the vehicle control group. Note of the positive dose response was not statistically significant in the incidence rats of combined adenocarcinoma in duodenum, ileum, and jejunum ($p=0.0635$). See Table 1 for tumor incidences and p-values of the tumor types mentioned above.

The tumor analysis didn't show any statistically significant difference in tumor incidence rates between the vehicle control group and saline control group.

Table 1: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Controls in Rats

Sex	Organ name	Tumor name	0 mg/kg/day V Control P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline C (SC) P - VC vs. SC
Male	gland, mammary	Fibroadenoma, benign	0/63 (39)	0/60 (38)	2/62 (38)	4/61 (27)	0/62 (36)
			0.0021 *	NC	0.2403	0.0244 **	NC
	Small intestine, jejunum	Adenocarcinoma, malignant	0/54 (35)	0/44 (31)	1/50 (30)	2/42 (18)	0/43 (27)
			0.0225 *	NC	0.4615	0.1110	NC
	C_Small intestine	Adenocarcinoma,	1/47 (32)	0/41 (29)	2/44 (27)	2/38 (17)	0/35 (21)

Sex	Organ name	Tumor name	0 mg/kg/day V Control P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline C (SC) P - VC vs. SC
	Duodenum+ileum Jejunum	malignant	0.0635	1.0000	0.4355	0.2731	1.0000

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

For the 2-year mouse study:
Mice (65/sex/group) were dosed by oral gavage with MGL-3196 daily for up to 104 weeks. The respective MGL-3196 doses in the saline control (SC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 3, 30, and 100 mg/kg/day for male and female mice.

The reviewer's survival data analyses showed a statistically significant dose response relationship in mortality in male mice only when compared with vehicle control group ($p<0.05$). The mortality rates in high dosed groups were statistical significantly higher than vehicle control group for male mice ($p<0.05$). The survival analysis didn't show any statistically significantly difference between the vehicle control group and saline control group.

The reviewer's tumor data analysis results showed that MGL-3196 cause a statistically significant positive dose response in the incidence of common tumor of carcinoma, hepatocellular, the combined tumor of adenoma hepatocellular and carcinoma hepatocellular, and the rare tumor of hepatoblastoma in liver for male mice ($p=0.000<0.005$, $p=0.000<0.005$, $p=0.0079<0.025$, respectively) when compared with vehicle control group. For these tumor types, the incidences rates of all treated groups were not statistically significantly higher than the incidence rate of the vehicle control group. For these tumor types, the incidences were numerically smaller in saline control group compared to vehicle control group.

For female mice, MGL-3196 also cause a statistically significant positive dose response in the incidence of the rare tumor of leiomyoma benign and the combination of leiomyoma benign tumor with leiomyosarcoma malignant tumor in uterus or combined with cervix ($p=0.0248<0.025$ and $p=0.0086<0.025$, $p=0.0213$, respectively) when compared with vehicle control group. Only for the combined tumor type in uterus or in combined uterus and cervix, the incidence rates of high dose group were statistically significantly higher than those of the vehicle control group ($p=0.0354<0.05$ and $p=0.035<0.05$ respectively).

The tumor analysis didn't show any statistically significant difference in tumor incidence rates between the vehicle control group and saline control group.

Table 2: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Male	Liver	Carcinoma, Hepatocellular,	9/65 (49)	0/65 (49)	2/65 (41)	17/65 (42)	6/65 (50)
		Malignant	0.0000 *	1.0000	0.9912	0.0179	0.8779

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
		C_B+M/Hepatocellular	16/65 (49)	1/65 (50)	6/65 (41)	24/65 (45)	11/65 (52)
			0.0000 *	1.0000	0.9882	0.0344	0.9372
		Hepatoblastoma, Malignant	0/65 (47)	0/65 (49)	0/65 (41)	3/65 (35)	0/65 (50)
			0.0079 *	NC	NC	0.0739	NC
Female	Uterus	Leiomyoma, Benign	0/65 (38)	2/65 (45)	0/65 (40)	4/65 (41)	0/65 (41)
			0.0248 *	0.2909	NC	0.0674	NC
		C_leiomyoma/Leiomyosarcoma	0/65 (38)	2/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
			0.0086 *	0.2909	NC	0.0354 **	NC
	Uterus/ Cervix	C_leiomyoma/Leiomyosarcoma	0/65 (38)	3/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
			0.0213 *	0.1544	NC	0.0354 **	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively

For the 6-month transgenic mouse study:

Mice (25/sex/group) were dosed by oral gavage with MGL-3623 daily for up to 26 weeks. The respective MGL-3623 doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 15, 300, and 1500 mg/kg/day for both male and female mice. The positive control group received intraperitoneal injection of 75 mg/kg of NM N-Methyl-N-nitrosourea at Day 1.

Excluding the positive control group, the survival analyses didn't show any statistically significant dose response relationship in mortality in males and females when compared with vehicle control group. The mortality rates for the positive control group were statistically significantly higher than that for the vehicle control group for both male and female mice. The survival analysis didn't show any statistically significantly difference between the vehicle control group and water control group.

Excluding the positive control group, the tumor analysis showed that there were no statistically significant positive dose response relationships among the MGL-3623 treated groups and the vehicle control group for male and female mice. However, the incidence rates of the following tumor types were statistically significantly higher for positive control group compared to vehicle control group: the papilloma benign tumor in skin and stomach and the lymphoma malignant tumor in whole body for both male and female mice.

2 Background

The sponsor, Madrigal Pharmaceuticals, Inc., was submitting, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, a New Drug Application (NDA) for MGL-3196 (resmetirom), a liver-directed, oral, once-daily, thyroid hormone receptor (THR)-□ -selective agonist under development with the Division of Hepatology and Nutrition (formerly the Division of Gastroenterology and Inborn Errors Products) for the treatment of non-alcoholic steatohepatitis (NASH).

The carcinogenic potential of MGL-3196 (resmetirom) was evaluated in 2-year carcinogenicity studies in CD-1 mice and Sprague Dawley rats. MGL-3623 is a major metabolite of resmetirom that has been shown to be present in human plasma at >10% of the parent drug. Thus, a comprehensive toxicology package was conducted with MGL-3623 to evaluate its potential toxicity including repeat-dose toxicity studies in mice for up to 90 days, in vitro and in vivo genotoxicity studies, a 6-month carcinogenicity study in transgenic rasH2 mice, and an EFD study in rats.

The sponsor submitted two 2-year carcinogenicity study reports: Study 0475mm72-001: "A 104-Week Oral Oncogenicity Study of MGL-3196 by Oral Gavage in Mice" and Study 0474rm72-001: "A 104-Week Oral Oncogenicity Study of MGL-3196 by Oral Gavage in Rats", and study 2835-002: "A GLP 26 Week Study of MGL-3623 by Oral Gavage in CByB6F1-Tg(HRAS)2Jic Mice". The study reports and the electronic SEND and/or Tumor.xpt datasets were submitted on 6/9/2023 (via NDA 217785/S0001).

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidences rate as dose increases. Results of this review have been discussed with the nonclinical team.

3 Rat Study- 0474rm72-001

Study Report: **0474rm72-001.pdf (statistical report on page 11141)**
SAS data: **SEND**

The objective of this study was to evaluate the carcinogenicity of MGL-3196 when administered orally, via gavage, once daily to Sprague Dawley rats for two years. The study design was as follows:

Group	Dose Level (mg/kg/day)	Concentration (mg/ml)	Dose Volume (ml/kg)	Number of Animals	
				Male	Female
1. Saline Control	0	0	10	65	65
2. Vehicle Control	0	0	10	65	65
3. MGL-3196 Low-dose	1	0.1	10	65	65
4. MGL-3196 Mid-dose	6	0.6	10	65	65
5. MGL-3196 High dose	30	3.0	10	65	65

File Name: NDA217785Carcin.doc

The following parameters and endpoints were evaluated in this study: mortality/survival, clinical signs and masses, body weight, body weight gains, food consumption, toxicokinetic parameters, and macroscopic and microscopic examinations.

3.1 Sponsor's Analyses

The sponsor's analyses were reported by The Principal Investigator, Statistical Analyses of Survival and Tumorogenicity (address: (b) (4) .

3.1.1 Survival Analysis

A log-rank dose response trend test of survival rates was performed utilizing ordinal coefficients. In addition, a generalized Wilcoxon test for survival was used to make pairwise comparisons of each treated group with the control group. The trend test and pairwise comparisons were conducted individually for each control group. In addition, a comparison was made of the two control groups. All tests were 2-sided at the 0.05 significance level.

Survival times in which the status of the animal's death was classified as an accidental death or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's concluded results: Males and females dosed with 30 mg/kg MGL-3196 were terminated early on week 86 and week 92, respectively, due to decreased survival rate, however only survival in the males was statistically significantly lower than control animals.

3.1.2 Tumor Data Analysis

The FDA draft Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001) was used as a guidance for the statistical analysis of tumor incidence data.

Grouping of tissues (e.g., "femur bone marrow" and "sternum bone marrow" combined under "bone marrow") was performed for analysis purposes. All leukemias or other systemic tumors were grouped under the organ name "systemic". All metastases and invasive tumors were considered secondary and not included in the analysis unless the primary tumor cannot be identified.

The incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed. The following fixed intervals were used for the incidental tumor analyses: weeks 0-50, 51-80, and 81-end of study (up to terminal sacrifices), and terminal sacrifice. All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the terminal sacrifice interval for the incidental

finding analyses. For example, among male's terminal sacrifices began on Study Day 604 (Week 87). All male natural deaths and sacrifices that occurred after the first male sacrifice on Study Day 604 were included in the terminal sacrifice interval. All tumors in the scheduled terminal sacrifice were considered incidental for the purpose of statistical analysis. Tumors for which the day of detection was earlier than the day of necropsy were classified as mortality-independent.

The following analyses were conducted separately for each sex. The incidence of each tumor type was analyzed with a trend test using ordinal coefficients. In addition, pairwise comparisons of each active treatment group with the control group were conducted. Both the trend test and pairwise comparisons were conducted individually for each control. Additionally, the vehicle control was compared to the saline control. All tests were 1-sided.

An exact permutation test was conducted for analyses with low tumor incidence.

In addition to the Peto analysis, tumors were statistically analyzed using the poly-3 statistical analysis as first described by Bailer and Portier (1988) and modified by Bieler and Williams (1993). For each tumor "X", tumor bearing animals were assigned a weighted at-risk score = 1. Likewise, non-tumor bearing animals that lived the full study period were assigned a weighted at-risk score = 1. Non-tumor bearing animals that died prior to the end of the full study period were assigned a weighted at-risk score, based on the time of death, according to the following formula: (day of death/full study period). The weighted number of animals at-risk (Nw) in each group was calculated for each tumor individually and defined as the sum of these weighted at-risk scores across a treatment group.

Conceptually, Nw estimates the weighted number of animals at risk based on the cumulative time on study of all animals in a group. If all non-tumor bearing animals in a group survived until the scheduled terminal sacrifice, then Nw = N (the weighted number of animals at risk = the original number of animals in the group). If at least one nontumor bearing animal died prior to the scheduled terminal sacrifice then Nw < N. Thus, Nw is a reflection of group mortality in that early deaths of non-tumor bearing animals yield a smaller Nw relative to N.

Trend tests and pairwise comparisons were conducted as described for the Peto analysis. Conditional exact p-values were calculated using SAS® proc multtest with dose level coefficients, the weighted number of animals at risk (rounded to the nearest integer), and assuming the row and column totals are fixed. Statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.005 and 0.025 significance levels for common and rare tumors, respectively. Pairwise comparisons with the control group were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. At the direction of the study director, the Principal Investigator – Histopathology Evaluation classified tumors as rare or common using a 1% benchmark.

Sponsor's concluded results: Neoplastic findings due to MGL-3196 administration were restricted to an increased incidence of mammary gland fibroadenomas in the high dose (30 mg/kg/day) males and females.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 6/9/2023 (via NDA 217785/S0001). The vehicle control group was compared to the treated groups (pairwise and trend) and vehicle control group was compared to saline control (pairwise only) for the survival analyses and the tumor analyses.

3.2.1 Data Quality

The sponsor only submitted the electronic SEND datasets on 6/9/2023 (via NDA 217785/S0001). The data quality was acceptable.

3.2.2 Survival Analysis

The survival distributions of rates in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 4A and 4B in the appendix for male and female rats, respectively.

Reviewer's findings: Male and female rats dosed with 30 mg/kg MGL-3196 were terminated early on week 86 and week 92, respectively. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 49 (75%), 43 (66%), 43 (66%), 50 (77%), or 49 (75%) in male rats and 49 (75%), 47 (72%), 48 (74%), 47 (72%), or 49 (75%) in female rats in the SC, VC, LD, MD, or HD groups, respectively. The survival analyses showed a statistically significant dose response relationship in mortality in male and female rats when compared with vehicle control. The death rates for the high dosed group (30 mg/kg/day) were statistically significantly higher than the death rates of vehicle control groups for male and female rats.

The survival analysis didn't show any statistically significantly difference between the vehicle control group and saline control group.

3.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor

before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidences pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group.

This reviewer performed separate tumor data analyses to test the positive dose responses in tumor incidence rates using the vehicle control and to test the pairwise comparisons between the vehicle control and each treated group and saline control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 7A, and 7B in the appendix for the comparison of vehicle control group with treated group and saline control group for male rats and female rats, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control groups.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Rats

Sex	Organ name	Tumor name	0 mg/kg/day V Control P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline C (SC) P - VC vs. SC
Male	Gland, mammary	Fibroadenoma, benign	0/63 (39) 0.0021 *	0/60 (38) NC	2/62 (38) 0.2403	4/61 (27) 0.0244 **	0/62 (36) NC
	Small intestine, jejunum	Adenocarcinoma, malignant	0/54 (35) 0.0225 *	0/44 (31) NC	1/50 (30) 0.4615	2/42 (18) 0.1110	0/43 (27) NC
	C_Small intestine Duodenum+ileum Jejunum	Adenocarcinoma, malignant	1/47 (32) 0.0635	0/41 (29) 1.0000	2/44 (27) 0.4355	2/38 (17) 0.2731	0/35 (21) 1.0000
	Gland, thyroid	C_follicular cell_B+M,	1/65 (41) 0.0381	1/65 (42) 0.7590	0/65 (38) NC	3/65 (26) 0.1688	5/65 (39) 0.0890
	Gland, prostate	C_ Carcinoma, urothelial+ Carcinoma	0/65 (41) 0.0323	0/65 (42) NC	0/65 (38) NC	2/65 (26) 0.1541	0/65 (38) NC

File Name: NDA217785Carcin.doc

Sex	Organ name	Tumor name	0 mg/kg/day V Control P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline C (SC) P - VC vs. SC
Female	Gland, mammary	Fibroadenoma, benign	37/64 (54)	38/65 (55)	38/65 (54)	47/65 (55)	34/63 (51)
			0.0083	0.5564	0.5000	0.0298	0.6596
		C_Adenoma+	41/64 (54)	40/65 (55)	38/65 (54)	48/65 (55)	38/63 (51)
		Fibroadenoma	0.0294	0.6672	0.7586	0.1077	0.6528

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, a positive dose response was statistically significant in the incidences of a rare tumor fibroadenoma, benign in mammary gland in male rats only when compared with vehicle control group (p=0.0021 <0.025). For this tumor type, the incidences rate of the high dosed group was statistically significantly greater than that of the vehicle control group (p=0.0244 <0.05). For this tumor type, the incidences rates were much higher for female rats in all groups, didn't reach the statistical threshold as a common tumor (p=0.0083>0.005 for dose response, p=0.0298 >0.1 for pairwise comparison).

A positive dose response was statistically significant in the incidences of a rare tumor adenocarcinoma, malignant in small intestine, jejunum in male rats when compared with the vehicle control group (p=0.0225<0.025). For this tumor type, the incidences rate of the high dosed group was not statistically significantly greater than that of the vehicle control group. Note of the positive dose response was not statistically significant in the incidence rats of combined adenocarcinoma in duodenum, ileum, and jejunum (p=0.0635>0.005).

The tumor analysis didn't show any statistically significant difference in tumor incidence rates between the vehicle control group and saline control group.

4 Mouse Study- 0475mm72-001

Study Report: 0475mm72-001.pdf (statistical report on page 10454)
SAS data: SEND database

The objective of this study was to evaluate the carcinogenicity of MGL-3196 when administered orally, via gavage, once daily to Crl:CD1® (ICR) mice for two years. The study design was as follows:

Group	Dose Level (mg/kg/day)	Concentration (mg/ml)	Dose Volume (ml/kg)	Number of Animals	
				Male	Female
1. Saline Control	0	0	10	65	66
2. Vehicle Control	0	0	10	66	66
3. MGL-3196 Low-dose	3	0.3	10	65	65
4. MGL-3196 Mid-dose	30	3.0	10	65	65
5. MGL-3196 High dose	100	10	10	65	65

The following parameters and endpoints were evaluated in this study: mortality/survival, clinical signs, body weights, body weight gains, food consumption, toxicokinetic parameters, and macroscopic and microscopic examinations.

4.1 Sponsor's Analyses

The sponsor's analyses were reported by The Principal Investigator, Statistical Analyses of Survival and Tumorogenicity (address: (b) (4) .

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: Among males there was a statistically significant decreasing trend, relative to dose, in animal survival when compared with both the saline and vehicle control groups. The survival rate in the 100 mg/kg/day group was significantly less than both the saline and vehicle control groups. The survival rate in the 30 mg/kg/day group was significantly less than the saline group. Among females, survival in the 3 mg/kg/day group was significantly greater when compared with the vehicle control group.

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study.

Sponsor's findings: MGL-3196 induced carcinogenicity was limited to the livers of male mice, and only at the highest dose tested. It consisted of hepatoblastomas, hepatocellular adenomas, and carcinomas in Group 5 (100 mg/kg/day) males. No evidence of MGL-3196-induced carcinogenicity occurred in males dosed at ⩽30 mg/kg/day or in females dosed at ⩽100 mg/kg/day.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 6/9/2023 (via NDA 217785/S0001). The vehicle control group was compared to the treated groups (pairwise and trend) and vehicle control group was compared to saline control (pairwise only) for the survival analyses and the tumor analyses.

4.2.1 Data Quality

The sponsor submitted both SEND datasets and Tumor.xpt on 6/9/2023 (via NDA 217785/S0001. The data quality was acceptable. The statistical analyses for the 2-year mice study were based on the Tumor.xpt datasets.

4.2.2 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings: The termination started at Week 100 for male mice and 97 for female mice. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 41 (63%), 45 (68%), 34 (52%), 49 (75%), or 49 (75%) in male mice and 43 (65%), 52 (79%), 37 (57%), 42 (657%), or 45 (69%) in female mice in the SC, VC, LD, MD, or HD groups, respectively. The survival analyses show a statistically significant dose response relationship in mortality in males only when compared with vehicle control group ($p<0.05$). The mortality rates in high dose treated groups were statistical significantly higher than vehicle control group for male mice ($p<0.05$).

The survival analysis didn't show any statistically significantly difference between the vehicle control group and saline control group.

4.2.3 Tumor Data Analysis

This reviewer performed separate tumor data analyses to test the positive dose responses in tumor incidence rates using the vehicle control and to test the pairwise comparisons between the vehicle control and each treated group and saline control group using the same method that was used for the rat study. The tumor rates and the p-values of the tested tumor types are listed in Tables 8A, and 8B in the appendix for the comparison of vehicle control group with treated group and saline control group for male mice and female mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control groups.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Male	Liver	Carcinoma, Hepatocellular,	9/65 (49)	0/65 (49)	2/65 (41)	17/65 (42)	6/65 (50)
		Malignant	0.0000 *	1.0000	0.9912	0.0179	0.8779
		C_B+M/Hepatocellular	16/65 (49)	1/65 (50)	6/65 (41)	24/65 (45)	11/65 (52)
			0.0000 *	1.0000	0.9882	0.0344	0.9372
		Hepatoblastoma, Malignant	0/65 (47)	0/65 (49)	0/65 (41)	3/65 (35)	0/65 (50)

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
			0.0079 *	NC	NC	0.0739	NC
	Lungs	Adenocarcinoma,	4/65 (49)	5/65 (50)	12/65 (45)	7/65 (38)	6/65 (51)
		Bronchioloalveolar, Malignant	0.0853	0.5130	0.0167	0.1354	0.3963
		C_B+M/Bronchioloalveolar	10/65 (50)	11/65 (51)	20/65 (46)	10/65 (39)	14/65 (53)
			0.2676	0.5205	0.0117	0.3516	0.2964
	Stomach	C_Adenoma+Adenocarcinoma	0/65 (47)	0/65 (49)	0/65 (41)	2/65 (35)	0/65 (50)
			0.0405	NC	NC	0.1792	NC
	Whole	Hemangiosarcoma	1/65 (48)	2/65 (50)	0/65 (41)	4/65 (37)	1/65 (50)
	Body		0.0319	0.5155	1.0000	0.1099	0.7627
Female	Uterus	Leiomyoma, Benign	0/65 (38)	2/65 (45)	0/65 (40)	4/65 (41)	0/65 (41)
			0.0248 *	0.2909	NC	0.0674	NC
		C_leiomyoma/Leiomyosarcoma	0/65 (38)	2/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
			0.0086 *	0.2909	NC	0.0354 **	NC
	Uterus/	C_leiomyoma/Leiomyosarcoma	0/65 (38)	3/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
	Cervix		0.0213 *	0.1544	NC	0.0354 **	NC
	Lungs	Adenocarcinoma,	4/65 (39)	1/65 (44)	6/65 (42)	4/65 (42)	1/65 (41)
		Bronchioloalveolar, Malignant	0.2918	0.9802	0.4176	0.6852	0.9761
		C_B+M/Bronchioloalveolar	9/65 (40)	6/65 (45)	15/65 (45)	11/65 (44)	4/65 (42)
			0.2100	0.9181	0.1935	0.4960	0.9732

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively

Based on the criteria of adjustment for multiple testing discussed above, the positive dose response was statistically significant in the incidence of common tumor of carcinoma, hepatocellular, the combined tumor of adenoma hepatocellular and carcinoma hepatocellular, and the rare tumor of hepatoblastoma in liver for male mice ($p=0.000<0.005$, $p=0.000<0.005$, $p=0.0079<0.025$, respectively) when compared with vehicle control group. For these tumor types, the incidences rates of all treated groups were not statistically significantly higher than the incidence rate of the vehicle control group. For these tumor types, the incidences were numerically smaller in saline control group compared to vehicle control group.

For female mice, there was a statistically significant positive dose response in the incidence of the rare tumor of leiomyoma benign and the combination of leiomyoma benign tumor with leiomyosarcoma malignant tumor in uterus or combined these tumor types in uterus and cervix ($p=0.0248<0.025$, $p=0.0086<0.025$, and $p=0.0213$, respectively) when compared with vehicle control group. Only for the combined tumor type in uterus or in combined uterus and cervix, the incidence rates of high dose group were statistically significantly higher than those of the vehicle control group ($p=0.0354<0.05$ and $p=0.035<0.05$ respectively).

The tumor incidence rates were similar between the vehicle control group and saline control group except the incidence rates of the adenocarcinoma, bronchioloalveolar, malignant tumor and the combination of malignant bronchioloalveolar with benign bronchioloalveolar were numerically higher in vehicle control group than that in the saline control group in female mice.

5 Transgenic Mouse Study- 2835-002

Study Report: 2835-002.pdf (statistical report on page 933)
SAS data: SEND database

The objective of this study was to evaluate the carcinogenicity of MGL-3623 when given once daily by oral gavage for 26 weeks in CByB6F1-Tg(HRAS)2Jic (hemizygous) [RasH2] mice. The study design was as follows:

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	Main Study	
					No. of Males	No. of Females
1	Vehicle Control	0	10	0	25	25
2	MGL-3623	15	10	1.5	25	25
3	MGL-3623	300	10	30	25	25
4	MGL-3623	1500	10	150	25	25
5	Positive Control (NMU)	75	10	7.5	15	15
98	Water Control	0	10	0	12	12

The following parameters and endpoints were evaluated in this study: mortality/survival, clinical signs, body weights, body weight gains, food consumption, toxicokinetic parameters, and macroscopic and microscopic examinations.

5.1 Sponsor's Analyses

The sponsor's analyses were reported by (b) (4)

5.1.1 Survival Analysis

Intercurrent mortality data was analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test. If this overall test was significant ($p<0.05$) and there were more than 2 groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: There was no MGL-3623-related mortality in this study.

5.1.2 Tumor Data Analysis

Tumor incidence data was analyzed using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test was calculated, and Fisher's exact test was used to compare each treatment group with the control group (Agresti, 2002; Zar, 1999). Trend test was applied for all control and treatment groups able to be arranged in a strictly increasing

dose level. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al. (Peto et al, 1980).

The Poly-3 method was used to assess prevalence of tumors (Bailer and Portier, 1988; Bieler and Williams, 1993). The survival-adjusted rates based on the risk weights are displayed. The tests of significance included both an overall trend and pair-wise comparisons of each treatment group with the control. All p-values are reported using upper-tailed tests. Evaluation criteria (p-values of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%) (Haseman, 1983). The evaluation criteria from the FDA (FDA CDER, 2001) are given in the following table.

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors were tested at 0.005 and 0.025 significance levels, respectively, using upper-tailed tests.	Common and rare tumors were tested at 0.01 and 0.05 significance levels, respectively, using upper-tailed tests.

Sponsor's findings: There was no MGL-3623-related neoplastic lesions were evident in either sex up to or including 1500 mg/kg/day.

5.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 6/9/2023 (via NDA 217785/S0001). The vehicle control group was compared to the treated groups (pairwise and trend) and vehicle control group was compared to water control group (pairwise only) or positive control group (pairwise only) for the survival analyses and the tumor analyses.

5.2.1 Data Quality

The sponsor only submitted the electronic SEND datasets on 6/9/2023 (via NDA 217785/S0001). The data quality was acceptable.

5.2.2 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 3A and 3B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 3A and 3B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 6A and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: The termination started at Week 26. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 1 (8%), 0, 0, 2 (8%), 0, or 5 (33%) in male mice and 1 (8%), 1 (4%), 0, 1 (4%), 2 (8%) or 6 (40%) in female mice in the WC, VC, LD, MD, HD, or PC groups, respectively. Excluding the positive control

group, the survival analyses didn't show any statistically significant dose response relationship in mortality in males and females when compared with vehicle control group. The mortality rates for the positive control group were statistically significantly higher than that for the vehicle control group for both male and female mice.

The survival analysis didn't show any statistically significantly difference between the vehicle control group and water control group.

5.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The adjusted levels of significance for testing a positive dose response in the 6-month mice study are 0.05 and 0.05 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 6-month mice study are 0.05 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 9A, 9B, 9C, and 9D in the appendix for male and female transgenic mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 for pairwise comparisons of positive control group and vehicle control group.

Tumor Rates and P-Values for Pairwise Comparisons of Vehicle Control with Positive Control in Transgenic Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle (VC)	75 mg Positive (PC) P - VC vs. PC
Male	Skin	Papilloma, benign	0/25 (25)	7/15 (13)
				0.0001 **
	Stomach	Papilloma, benign	0/25 (25)	14/15 (14)
				0.0000 **
	Whole Body	Lymphoma, malignant	0/25 (25)	3/15 (14)
				0.0398 **
Female	Skin	Papilloma, benign	0/25 (25)	8/15 (13)
				0.0000 **
	Stomach	Papilloma, benign	0/25 (25)	12/15 (14)
				0.0000 **
	Whole Body	Lymphoma, malignant	0/25 (25)	5/15 (14)
				0.0035 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships among the MGL-3623 treated groups and vehicle control group for male and female Transgenic mice when data of the

positive control group were excluded. However, the incidence rates of tumor types listed in above table were statistically significantly higher for positive control group compared to vehicle control group.

The tumor analysis didn't show any statistically significant difference in tumor incidence rates between the vehicle control group and water control group.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6
cc:
Dr. Fresnida Ramos
Dr. David B. Joseph
Dr. Yi Tsong
Dr. Karl Lin

6 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Saline Control		Vehicle Control		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 50	1	1.54	2	3.08	3	4.62	3	4.62	5	7.69
51 - 80	16	26.15	13	23.08	11	21.54	15	27.69	34	60.00
81 - 104	30	72.31	27	64.62	28	64.62	31	75.38	10	75.38
Accidental Death	2	3.08	1	1.54	1	1.54	1	1.54		
Terminal sacrifice	16	24.62	22	33.85	22	33.85	15	23.08	16	24.62
Total	65		65		65		65		65	

Table 1B: Intercurrent Mortality Rate in Female Rats

	Saline Control		Vehicle Control		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 50	3	4.62	5	7.69	4	6.15	4	6.15	2	3.08
51 - 80	19	33.85	16	32.31	20	36.92	24	43.08	31	50.77
81 - 104	27	75.38	25	70.77	22	70.77	18	70.77	16	75.38
Accidental Death			1	1.54	2	3.08	1	1.54		
Terminal sacrifice	16	24.62	18	27.69	17	26.15	18	27.69	16	24.62
Total	65		65		65		65		65	

Table 2A: Intercurrent Mortality Rate in Male Mice

	Saline Control		Vehicle Control		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 50	2	3.08	2	3.08	2	3.08	7	10.77	4	6.15
51 - 80	6	12.31	9	16.92	11	20.00	14	32.31	21	38.46
81 - 104	31	60.00	31	64.62	20	50.77	26	72.31	23	73.85
Accidental Death	2	3.08	2	3.08	1	1.54	2	3.08	1	1.54
Terminal sacrifice	24	36.92	21	32.31	31	47.69	16	24.62	16	24.62
Total	65	.	65	.	65	.	65	.	65	.

Table 2B: Intercurrent Mortality Rate in Female Mice

	Saline Control		Vehicle Control		Low Dose		Mid Dose		High Dose	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 50	3	4.62	3	4.62	.	.	4	6.15	3	4.62
51 - 80	13	24.62	18	32.31	15	23.08	18	33.85	18	32.31
81 - 104	24	61.54	25	70.77	20	53.85	20	64.62	22	66.15
Accidental Death	2	3.08	5	7.69	2	3.08	.	.	2	3.08
Terminal sacrifice	23	35.38	14	21.54	28	43.08	23	35.38	20	30.77
Total	65	.	65	.	65	.	65	.	65	.

Table 3A: Intercurrent Mortality Rate in Male Transgenic Mice

Week	Water C		Vehicle C		Low Dose		Mid Dose		High Dose		Positive C	
Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13							1	4.00			1	6.67
14 - 26	1	8.33					1	8.00			4	33.33
Terminal sacrifice	11	91.67	25	100.0	25	100.0	23	92.00	25	100.0	10	66.67
Total	12		25		25		25		25		15	.

Table 3B: Intercurrent Mortality Rate in Female Transgenic Mice

Week	Water C		Vehicle C		Low Dose		Mid Dose		High Dose		Positive C	
Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13									1	4.00	1	6.67
14 - 26	1	8.33	1	4.00			1	4.00	1	4.00	5	40.00
Terminal sacrifice	11	91.67	24	96.00	25	100.0	24	96.00	24	96.00	9	60.00
Total	12		25		25		25		25		15	.

Table 4A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. SC
Dose-Response (Likelihood Ratio)	<.0001	0.6599	0.2321	<.0001	0.6599
Homogeneity (Log-Rank)	<.0001	0.6559	0.2238	<.0001	0.6559

Table 4B: Intercurrent Mortality Comparison in Female Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. SC
Dose-Response (Likelihood Ratio)	0.0324	0.6376	0.8424	0.0345	0.6376
Homogeneity (Log-Rank)	0.1379	0.6337	0.8400	0.0316	0.6337

Table 5A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. SC
Dose-Response (Likelihood Ratio)	0.0002	0.2201	0.1779	0.0023	0.5574
Homogeneity (Log-Rank)	0.0004	0.2160	0.1709	0.0019	0.5512

Table 5B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. SC
Dose-Response (Likelihood Ratio)	0.7214	0.0323	0.4665	0.4589	0.2694
Homogeneity (Log-Rank)	0.1991	0.0292	0.4607	0.4510	0.2628

Table 6A: Intercurrent Mortality Comparison in Male Transgenic Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. WC	VC vs. PC
Dose-Response (Likelihood Ratio)	0.7088	NC	0.0935	NC	0.1334	0.0010
Homogeneity (Log-Rank)	0.1058	NC	0.1531	NC	0.1489	0.0019

Table 6B: Intercurrent Mortality Comparison in Female Transgenic Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. WC	VC vs. PC
Dose-Response (Likelihood Ratio)	0.6896	0.2390	0.9885	0.9885	0.5872	0.0045
Homogeneity (Log-Rank)	0.7978	0.3173	0.9885	0.9885	0.5731	0.0035

Table 7A: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Male Rats

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Adipose tissue	Adenocarcinoma, malignant	0/65 (41)	0/65 (42)	1/65 (38)	0/65 (26)	0/65 (38)
		0.4354	NC	0.4810	NC	NC

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Artery, aorta	Lymphoma, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	1/65 (39) 0.7405
Bone marrow	Lymphoma, malignant	4/65 (43) 0.9984	1/65 (43) 0.9724	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
	Sarcoma, histiocytic, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Brain	Glioma, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	1/65 (39) 0.7405
	Granular cell tumor, malignant	0/65 (41) 0.4354	0/65 (42) NC	1/65 (38) 0.4810	0/65 (26) NC	0/65 (38) NC
	Lymphoma, malignant	2/65 (42) 0.9788	1/65 (43) 0.8838	0/65 (38) 1.0000	0/65 (26) 1.0000	1/65 (39) 0.8654
	Schwannoma, malignant	1/65 (42) 0.6795	0/65 (42) 1.0000	1/65 (38) 0.7275	0/65 (26) 1.0000	0/65 (38) 1.0000
Ear	Adenoma, zymbal's gland, benign	2/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
	Carcinoma, zymbal's gland, malignant	0/65 (41) 0.7211	1/65 (42) 0.5060	0/65 (38) NC	0/65 (26) NC	0/65 (38) NC
Epididymis	Lymphoma, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
	Mesothelioma, malignant	0/65 (41) 0.7625	2/65 (43) 0.2590	0/65 (38) NC	0/65 (26) NC	1/65 (39) 0.4875
Esophagus	Lymphoma, malignant	0/65 (41) NC	0/65 (42) NC	0/65 (38) NC	0/65 (26) NC	2/65 (40) 0.2407
Eye	Lymphoma, malignant	1/64 (41) 1.0000	0/65 (42) 1.0000	0/63 (37) 1.0000	0/62 (25) 1.0000	1/62 (38) 0.7339
	Schwannoma, malignant	1/64 (41) 1.0000	0/65 (42) 1.0000	0/63 (37) 1.0000	0/62 (25) 1.0000	0/62 (37) 1.0000
Foot	Lymphoma, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Gland, adrenal	Adenocarcinoma, malignant	0/65 (41) 0.4354	0/65 (42) NC	1/65 (38) 0.4810	0/65 (26) NC	0/65 (38) NC
	Adenoma, adrenocortical, benign	0/65 (41) 0.3890	0/65 (42) NC	2/65 (38) 0.2282	0/65 (26) NC	0/65 (38) NC
	Lymphoma, malignant	2/65 (42) 0.8795	1/65 (42) 0.8795	1/65 (39) 0.8654	0/65 (26) 1.0000	2/65 (40) 0.6735
	Pheochromocytoma, benign	6/65 (42) 0.5925	8/65 (44) 0.4228	8/65 (40) 0.3469	4/65 (28) 0.6412	6/65 (40) 0.5863
	Pheochromocytoma, malignant	3/65 (42) 0.1637	2/65 (43) 0.8273	0/65 (38) 1.0000	3/65 (28) 0.4556	4/65 (40) 0.4723
	Sarcoma, histiocytic, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Gland, harderian	Lymphoma, malignant	0/65 (41) 0.7230	1/65 (43) 0.5119	0/65 (38) NC	0/65 (26) NC	1/65 (39) 0.4875
Gland, lacrimal	Lymphoma, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	1/65 (39)

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
		1.0000	1.0000	1.0000	1.0000	0.7405
Gland, mammary	Fibroadenoma, benign	0/63 (39)	0/60 (38)	2/62 (38)	4/61 (27)	0/62 (36)
		0.0021 *	NC	0.2403	0.0244 **	NC
	Lipoma, benign	0/63 (39)	1/60 (39)	0/62 (37)	0/61 (25)	0/62 (36)
		0.7214	0.5000	NC	NC	NC
	Lymphoma, malignant	1/63 (40)	0/60 (38)	0/62 (37)	0/61 (25)	1/62 (37)
		1.0000	1.0000	1.0000	1.0000	0.7334
Gland, parathyroid	Adenoma, benign	0/58 (35)	1/59 (38)	0/58 (33)	0/62 (24)	0/58 (34)
		0.7308	0.5205	NC	NC	NC
Gland, pituitary	Adenoma, pars distalis, benign	19/65 (45)	14/65 (45)	15/65 (44)	8/65 (31)	11/65 (42)
		0.8730	0.9055	0.8431	0.9580	0.9645
	Adenoma, pars intermedia, benign	0/65 (41)	0/65 (42)	0/65 (38)	1/65 (26)	0/65 (38)
		0.1769	NC	NC	0.3881	NC
	Carcinoma, pars distalis,	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Lymphoma, malignant	1/65 (41)	2/65 (43)	0/65 (38)	0/65 (26)	1/65 (39)
		0.9133	0.5181	1.0000	1.0000	0.7405
	Meningioma, benign	0/65 (41)	0/65 (42)	0/65 (38)	1/65 (26)	0/65 (38)
		0.1769	NC	NC	0.3881	NC
	Schwannoma, malignant	1/65 (42)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
Gland, prostate	Carcinoma, malignant	0/65 (41)	0/65 (42)	0/65 (38)	1/65 (26)	0/65 (38)
		0.1769	NC	NC	0.3881	NC
	Carcinoma, urothelial, malignant	0/65 (41)	0/65 (42)	0/65 (38)	1/65 (27)	0/65 (38)
		0.1824	NC	NC	0.3971	NC
	C_ Carcinoma, urothelial+ Carcinoma	0/65 (41)	0/65 (42)	0/65 (38)	2/65 (26)	0/65 (38)
		0.0323	NC	NC	0.1541	NC
	Lymphoma, malignant	2/65 (42)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Sarcoma, histiocytic, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
Gland, salivary	Fibrosarcoma, malignant	0/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.7211	0.5060	NC	NC	NC
	Lymphoma, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	1/65 (39)
		1.0000	1.0000	1.0000	1.0000	0.7405
	Schwannoma, benign	0/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	1/65 (39)
		NC	NC	NC	NC	0.4875
Gland, seminalvesicle	Lymphoma, malignant	1/65 (41)	0/64 (41)	0/65 (38)	0/65 (26)	2/65 (40)
		1.0000	1.0000	1.0000	1.0000	0.4906
	Sarcoma, histiocytic, malignant	1/65 (41)	0/64 (41)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
Gland, thyroid	Adenoma, c-Cell, benign	11/65 (44)	20/65 (46)	14/65 (43)	9/65 (31)	20/65 (44)
		0.6832	0.0519	0.2941	0.4480	0.0367
	Adenoma, follicular cell, benign	1/65 (41)	0/65 (42)	0/65 (38)	2/65 (27)	4/65 (39)
		0.0858	1.0000	1.0000	0.3455	0.1642
	Carcinoma, c-Cell, malignant	3/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Carcinoma, follicular cell, malignant	0/65 (41)	1/65 (42)	0/65 (38)	1/65 (26)	1/65 (39)
		0.2241	0.5060	NC	0.3881	0.4875

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
	C_follicular cell_B+M,	1/65 (41)	1/65 (42)	0/65 (38)	3/65 (26)	5/65 (39)
		0.0381	0.7590	NC	0.1688	0.0890
	Lymphoma, malignant	0/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	2/65 (40)
		NC	NC	NC	NC	0.2407
Heart	Carcinoma, malignant	0/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.7211	0.5060	NC	NC	NC
	Lymphoma, malignant	2/65 (42)	1/65 (42)	0/65 (38)	0/65 (26)	3/65 (40)
		0.9783	0.8795	1.0000	1.0000	0.4766
	Schwannoma, endocardial, malignant	1/65 (41)	1/65 (42)	1/65 (38)	1/65 (26)	1/65 (39)
		0.3737	0.7590	0.7339	0.6291	0.7405
Kidney	Adenoma, benign	0/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.7211	0.5060	NC	NC	NC
	Lipoma, benign	0/65 (41)	0/65 (42)	0/65 (38)	1/65 (26)	0/65 (38)
		0.1769	NC	NC	0.3881	NC
	Liposarcoma, malignant	0/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	1/65 (39)
		NC	NC	NC	NC	0.4875
	Lymphoma, malignant	3/65 (42)	1/65 (43)	1/65 (39)	0/65 (26)	1/65 (39)
		0.9372	0.9447	0.9327	1.0000	0.9327
Large intestine, colon	Lymphoma, malignant	1/61 (39)	0/58 (38)	0/58 (35)	0/56 (22)	0/54 (33)
		1.0000	1.0000	1.0000	1.0000	1.0000
Large intestine, rectum	Lymphoma, malignant	1/61 (39)	0/60 (40)	0/61 (36)	0/57 (23)	1/54 (34)
		1.0000	1.0000	1.0000	1.0000	0.7180
Larynx	Lymphoma, malignant	1/65 (41)	0/65 (42)	0/64 (37)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
Liver	Adenocarcinoma, malignant	0/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	1/65 (39)
		NC	NC	NC	NC	0.4875
	Adenoma, hepatocellular, benign	1/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.9236	0.7590	1.0000	1.0000	1.0000
	Carcinoma, hepatocellular, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Lymphoma, malignant	4/65 (43)	2/65 (43)	2/65 (39)	0/65 (26)	2/65 (40)
		0.9464	0.8990	0.8754	1.0000	0.8818
	Sarcoma, histiocytic, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
Lung	Carcinoma, bronchioloalveolar, malignant	0/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.7211	0.5060	NC	NC	NC
	Lymphoma, malignant	4/65 (43)	2/65 (43)	2/65 (39)	0/65 (26)	3/65 (40)
		0.9464	0.8990	0.8754	1.0000	0.7527
	Sarcoma, histiocytic, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000
Lymph node, inguinal	Lymphoma, malignant	0/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.7211	0.5060	NC	NC	NC
Lymph node, lumbar	Pheochromocytoma, malignant	0/65 (41)	1/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		0.7211	0.5060	NC	NC	NC
	Sarcoma, histiocytic, malignant	1/65 (41)	0/65 (42)	0/65 (38)	0/65 (26)	0/65 (38)
		1.0000	1.0000	1.0000	1.0000	1.0000

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Lymph node, mandibular	Lymphoma, malignant	4/65 (43) 0.9984	1/65 (43) 0.9724	0/65 (38) 1.0000	0/65 (26) 1.0000	2/65 (40) 0.8818
Lymph node, mesenteric	Hemangioma, benign	1/64 (40) 0.0880	0/65 (42) 1.0000	0/64 (37) 1.0000	2/65 (27) 0.3541	0/65 (38) 1.0000
	Lymphoma, malignant	4/64 (42) 0.9767	2/65 (43) 0.9044	1/64 (38) 0.9646	0/65 (26) 1.0000	2/65 (40) 0.8878
	Sarcoma, histiocytic, malignant	1/64 (40) 1.0000	0/65 (42) 1.0000	0/64 (37) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Mass	Hemangioma, benign	1/65 (41) 0.0858	0/65 (42) 1.0000	0/65 (38) 1.0000	2/65 (27) 0.3455	0/65 (38) 1.0000
	Lymphoma, malignant	4/65 (43) 0.9464	2/65 (43) 0.8990	2/65 (39) 0.8754	0/65 (26) 1.0000	3/65 (40) 0.7527
	Mesothelioma, malignant	0/65 (41) 0.7625	2/65 (43) 0.2590	0/65 (38) NC	0/65 (26) NC	1/65 (39) 0.4875
	Sarcoma, histiocytic, malignant	1/65 (41) 0.9236	1/65 (42) 0.7590	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Muscle, skeletal	Lymphoma, malignant	0/65 (41) NC	0/65 (42) NC	0/65 (38) NC	0/65 (26) NC	1/65 (39) 0.4875
	Sarcoma, histiocytic, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Nerve, sciatic	Lymphoma, malignant	0/64 (40) NC	0/65 (42) NC	0/64 (38) NC	0/65 (26) NC	1/65 (39) 0.4937
Pancreas	Adenocarcinoma, malignant	0/65 (41) 0.4354	0/65 (42) NC	1/65 (38) 0.4810	0/65 (26) NC	1/64 (38) 0.4810
	Adenoma, acinar cell, benign	0/65 (41) 0.1769	0/65 (42) NC	0/65 (38) NC	1/65 (26) 0.3881	0/64 (38) NC
	Adenoma, islet cell, benign	2/65 (41) 0.9274	5/65 (44) 0.2468	6/65 (40) 0.1240	0/65 (26) 1.0000	4/64 (40) 0.3259
	Carcinoma, islet cell, malignant	0/65 (41) 0.7211	1/65 (42) 0.5060	0/65 (38) NC	0/65 (26) NC	0/64 (38) NC
	Lymphoma, malignant	2/65 (42) 0.9046	2/65 (43) 0.7009	1/65 (39) 0.8654	0/65 (26) 1.0000	1/64 (39) 0.8654
Site, uncertain primary	Adenocarcinoma, mucinous, malignant	0/65 (41) 0.4354	0/65 (42) NC	1/65 (38) 0.4810	0/65 (26) NC	0/65 (38) NC
	Carcinoma, malignant	0/65 (41) 0.2308	1/65 (42) 0.5060	0/65 (38) NC	1/65 (27) 0.3971	0/65 (38) NC
Skin	Adenoma, sebaceous, benign	0/65 (41) NC	0/65 (42) NC	0/65 (38) NC	0/65 (26) NC	1/65 (39) 0.4875
	Basal cell tumor, benign	0/65 (41) 0.3896	0/65 (42) NC	2/65 (39) 0.2345	0/65 (26) NC	0/65 (38) NC
	Carcinoma, basal cell, malignant	0/65 (41) 0.4392	0/65 (42) NC	1/65 (39) 0.4875	0/65 (26) NC	0/65 (38) NC
	Carcinoma, squamous cell, malignant	0/65 (41) 0.7211	1/65 (42) 0.5060	0/65 (38) NC	0/65 (26) NC	0/65 (38) NC
	Fibroma, benign	1/65 (41) 0.3413	1/65 (42) 0.7590	2/65 (39) 0.4810	1/65 (26) 0.6291	0/65 (38) 1.0000
	Fibrosarcoma, malignant	0/65 (41) 0.5402	1/65 (42) 0.5060	1/65 (39) 0.4875	0/65 (26) NC	0/65 (38) NC

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
	Fibrosarcoma, pleomorphic, malignant	0/65 (41) NC	0/65 (42) NC	0/65 (38) NC	0/65 (26) NC	1/65 (39) 0.4875
	Keratoacanthoma, benign	1/65 (41) 0.3842	1/65 (42) 0.7590	1/65 (38) 0.7339	1/65 (27) 0.6400	1/65 (39) 0.7405
	Lipoma, benign	1/65 (41) 0.6872	0/65 (42) 1.0000	1/65 (39) 0.7405	0/65 (26) 1.0000	1/65 (39) 0.7405
	Lymphoma, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	2/65 (40) 0.4906
	Sarcoma, histiocytic, malignant	0/65 (41) 0.7211	1/65 (42) 0.5060	0/65 (38) NC	0/65 (26) NC	0/65 (38) NC
Small intestine, duodenum	Adenocarcinoma, malignant	1/56 (37) 1.0000	0/46 (31) 1.0000	0/54 (32) 1.0000	0/46 (19) 1.0000	0/41 (25) 1.0000
Small intestine, ileum	Adenocarcinoma, malignant	0/49 (32) 0.3578	0/44 (31) NC	2/48 (29) 0.2219	0/41 (17) NC	0/36 (22) NC
Small intestine, jejunum	Adenocarcinoma, malignant	0/54 (35) 0.0225 *	0/44 (31) NC	1/50 (30) 0.4615	2/42 (18) 0.1110	0/43 (27) NC
	Lymphoma, malignant	2/49 (33) 0.9740	1/44 (31) 0.8690	0/48 (28) 1.0000	0/41 (17) 1.0000	1/36 (23) 0.8032
C_Small intestine Duodenum+ileum Jejunum	Adenocarcinoma, malignant	1/47 (32) 0.0635	0/41 (29) 1.0000	2/44 (27) 0.4355	2/38 (17) 0.2731	0/35 (21) 1.0000
	Lymphoma, malignant	1/54 (36) 1.0000	0/44 (31) 1.0000	0/50 (29) 1.0000	0/42 (17) 1.0000	0/43 (27) 1.0000
Spinal column	Lymphoma, malignant	0/65 (41) 0.7230	1/65 (43) 0.5119	0/65 (38) NC	0/65 (26) NC	0/65 (38) NC
Spleen	Adenocarcinoma, malignant	0/65 (41) 0.4354	0/65 (42) NC	1/65 (38) 0.4810	0/65 (26) NC	0/65 (38) NC
	Lymphoma, malignant	4/65 (43) 0.9464	2/65 (43) 0.8990	2/65 (39) 0.8754	0/65 (26) 1.0000	3/65 (40) 0.7527
	Sarcoma, histiocytic, malignant	1/65 (41) 1.0000	0/65 (42) 1.0000	0/65 (38) 1.0000	0/65 (26) 1.0000	0/65 (38) 1.0000
Stomach	Adenocarcinoma, malignant	0/65 (41) 0.4354	0/65 (42) NC	1/65 (38) 0.4810	0/65 (26) NC	1/65 (39) 0.4875
	Lymphoma, malignant	2/65 (42) 0.9783	1/65 (42) 0.8795	0/65 (38) 1.0000	0/65 (26) 1.0000	2/65 (40) 0.6735
Testis	Leydig cell tumor, benign	1/65 (41) 0.3610	0/65 (42) 1.0000	5/65 (39) 0.0894	1/65 (26) 0.6291	1/65 (39) 0.7405
	Mesothelioma, malignant	0/65 (41) 0.7211	1/65 (42) 0.5060	0/65 (38) NC	0/65 (26) NC	0/65 (38) NC
Thymus	Lymphoma, malignant	3/60 (40) 1.0000	0/62 (40) 1.0000	0/59 (36) 1.0000	0/60 (24) 1.0000	2/55 (33) 0.7554
	Thymoma, benign	1/60 (39) 1.0000	0/62 (40) 1.0000	0/59 (36) 1.0000	0/60 (24) 1.0000	0/55 (32) 1.0000
Trachea	Lymphoma, malignant	0/61 (38) NC	0/63 (41) NC	0/62 (37) NC	0/61 (24) NC	1/60 (37) 0.4933

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Urinary bladder	Lymphoma, malignant	0/61 (39) NC	0/54 (36) NC	0/60 (36) NC	0/56 (22) NC	1/53 (34) 0.4658
	Sarcoma, histiocytic, malignant	1/61 (39) 1.0000	0/54 (36) 1.0000	0/60 (36) 1.0000	0/56 (22) 1.0000	0/53 (33) 1.0000
Whole body	Hemangioma	1/65 (41) 0.0858	0/65 (42) 1.0000	0/65 (38) 1.0000	2/65 (27) 0.3455	0/65 (38) 1.0000
	Lymphoma, malignant	4/65 (43) 0.9315	2/65 (43) 0.8990	2/65 (39) 0.8754	0/65 (26) 1.0000	3/65 (40) 0.7527

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 7B: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Female Rats

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Adipose tissue	Lipoma, benign	0/65 (39) 0.2153	0/65 (36) NC	0/65 (38) NC	1/65 (31) 0.4429	0/65 (39) NC
Body cavity, abdominal	Sarcoma, histiocytic, malignant	0/64 (38) 0.7343	1/65 (37) 0.4933	0/64 (38) NC	0/65 (30) NC	0/63 (38) NC
Body cavity, cranial	Schwannoma, malignant	0/65 (39) 0.7292	1/65 (37) 0.4868	0/65 (38) NC	0/65 (30) NC	0/65 (39) NC
Bone marrow	Lymphoma, malignant	1/65 (39) 0.9280	1/65 (37) 0.7400	0/65 (38) 1.0000	0/65 (30) 1.0000	0/65 (39) 1.0000
Brain	Carcinoma, pars distalis, malignant	2/65 (39) 0.3152	1/65 (37) 0.8700	2/64 (38) 0.6826	2/65 (31) 0.6013	3/65 (41) 0.5240
	Glioma, malignant	0/65 (39) 0.4718	0/65 (36) NC	1/64 (37) 0.4868	0/65 (30) NC	2/65 (41) 0.2595
Cervix	Leiomyosarcoma, malignant	0/65 (39) NC	0/65 (36) NC	0/65 (38) NC	0/65 (30) NC	1/65 (40) 0.5063
	Schwannoma, malignant	0/65 (39) 0.4792	0/65 (36) NC	1/65 (39) 0.5000	0/65 (30) NC	0/65 (39) NC
Ear	Adenoma, zymbal's gland, benign	0/65 (39) 0.4792	0/65 (36) NC	1/65 (39) 0.5000	0/65 (30) NC	0/65 (39) NC
	Fibrosarcoma, malignant	1/65 (40) 1.0000	0/65 (36) 1.0000	0/65 (38) 1.0000	0/65 (30) 1.0000	1/65 (40) 0.7532
Eye	Schwannoma, malignant	0/65 (39) 0.7273	1/64 (36) 0.4800	0/64 (38) NC	0/65 (30) NC	0/65 (39) NC
Gland, adrenal	Adenoma, adrenocortical, benign	1/65 (39)	3/65 (37)	2/65 (38)	2/65 (31)	6/65 (41)

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
		0.3589	0.2877	0.4901	0.4134	0.0623
	Liposarcoma, malignant	0/65 (39)	0/65 (36)	0/65 (38)	1/65 (31)	0/65 (39)
		0.2153	NC	NC	0.4429	NC
	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9280	0.7400	1.0000	1.0000	1.0000
	Pheochromocytoma, benign	4/65 (41)	0/65 (36)	1/65 (38)	2/65 (31)	1/65 (40)
		0.4220	1.0000	0.9667	0.8225	0.9708
	Pheochromocytoma, malignant	0/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	1/65 (40)
		NC	NC	NC	NC	0.5063
Gland, harderian	Schwannoma, malignant	0/65 (39)	1/65 (37)	0/64 (37)	0/64 (30)	0/65 (39)
		0.7273	0.4868	NC	NC	NC
Gland, mammary	Adenocarcinoma, malignant	7/64 (41)	5/65 (38)	12/65 (42)	5/65 (34)	4/63 (40)
		0.6206	0.7867	0.1623	0.7216	0.8956
	Adenoma, benign	4/64 (39)	3/65 (37)	2/65 (38)	6/65 (33)	7/63 (41)
		0.0755	0.7623	0.8940	0.2649	0.2891
	Fibroadenoma, benign	37/64 (54)	38/65 (55)	38/65 (54)	47/65 (55)	34/63 (51)
		0.0083	0.5564	0.5000	0.0298	0.6596
	C_Adenoma+Fibroadenoma	41/64 (54)	40/65 (55)	38/65 (54)	48/65 (55)	38/63 (51)
		0.0294	0.6672	0.7586	0.1077	0.6528
Gland, parathyroid	Adenoma, benign	0/62 (38)	1/61 (35)	1/61 (36)	0/62 (29)	0/64 (39)
		0.5773	0.4795	0.4865	NC	NC
	Carcinoma, c-Cell, malignant	1/62 (38)	0/61 (35)	0/61 (36)	0/62 (29)	0/64 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
Gland, pituitary	Adenoma, pars distalis, benign	36/65 (50)	28/65 (46)	26/64 (45)	33/65 (46)	40/65 (53)
		0.2340	0.9151	0.9526	0.6012	0.4298
	Carcinoma, pars distalis, malignant	2/65 (39)	1/65 (37)	3/64 (38)	2/65 (31)	3/65 (41)
		0.3196	0.8700	0.4875	0.6013	0.5240
	Lymphoma, malignant	0/65 (39)	1/65 (37)	0/64 (37)	0/65 (30)	0/65 (39)
		0.7273	0.4868	NC	NC	NC
Gland, thyroid	Adenoma, c-Cell, benign	19/65 (44)	9/65 (40)	18/65 (44)	13/65 (36)	17/65 (43)
		0.4487	0.9881	0.6669	0.8081	0.7131
	Adenoma, follicular cell, benign	0/65 (39)	0/65 (36)	1/65 (38)	0/65 (30)	1/65 (40)
		0.4755	NC	0.4935	NC	0.5063
	Carcinoma, c-Cell, malignant	1/65 (39)	1/65 (37)	1/65 (38)	0/65 (30)	0/65 (39)
		0.7980	0.7400	0.7468	1.0000	1.0000
Heart	Lymphoma, malignant	1/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	0/65 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
Kidney	Lipoma, benign	0/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	1/65 (39)
		NC	NC	NC	NC	0.5000
	Lymphoma, malignant	1/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	0/65 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Nephroblastoma, malignant	0/65 (39)	0/65 (36)	2/65 (40)	0/65 (30)	0/65 (39)
		0.4468	NC	0.2532	NC	NC
Large intestine, cecum	Leiomyoma, benign	0/65 (39)	1/62 (35)	0/64 (38)	0/64 (30)	0/63 (39)
		0.7254	0.4730	NC	NC	NC
Larynx	Lymphoma, malignant	0/64 (38)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
		0.7343	0.4933	NC	NC	NC
Liver	Adenoma, hepatocellular, benign	4/65 (39)	0/65 (36)	0/65 (38)	1/65 (31)	0/65 (39)
		0.7092	1.0000	1.0000	0.9524	1.0000
	Cholangioma, benign	1/65 (39)	2/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9250	0.4800	1.0000	1.0000	1.0000
	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9280	0.7400	1.0000	1.0000	1.0000
Lung	Carcinoma, malignant	0/65 (39)	1/65 (37)	1/65 (38)	1/65 (31)	0/65 (39)
		0.2469	0.4868	0.4935	0.4429	NC
	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9280	0.7400	1.0000	1.0000	1.0000
Lymph node, mandibular	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/63 (37)	0/65 (30)	0/65 (39)
		0.9270	0.7400	1.0000	1.0000	1.0000
Lymph node, mesenteric	Hemangioma, benign	0/65 (39)	1/64 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.7292	0.4868	NC	NC	NC
	Lymphoma, malignant	1/65 (39)	1/64 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9280	0.7400	1.0000	1.0000	1.0000
Mass	Hemangioma, benign	1/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9280	0.7400	1.0000	1.0000	1.0000
	Hemangiosarcoma, malignant	0/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	1/65 (40)
		NC	NC	NC	NC	0.5063
	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/65 (38)	1/65 (31)	0/65 (39)
		0.4706	0.7400	1.0000	0.6932	1.0000
	Sarcoma, histiocytic, malignant	0/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.7292	0.4868	NC	NC	NC
Mesentery	Lipoma, benign	0/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	1/65 (40)
		0.7292	0.4868	NC	NC	0.5063
Ovary	Granulosa cell tumor, benign	0/65 (39)	1/64 (36)	1/65 (38)	1/65 (31)	1/65 (39)
		0.2488	0.4800	0.4935	0.4429	0.5000
	Hemangioma, benign	1/65 (39)	0/64 (36)	0/65 (38)	0/65 (30)	0/65 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
Pancreas	Adenoma, acinar cell, benign	0/65 (39)	0/65 (36)	0/65 (38)	1/65 (31)	0/65 (39)
		0.2153	NC	NC	0.4429	NC
	Adenoma, islet cell, benign	0/65 (39)	0/65 (36)	1/65 (38)	0/65 (30)	0/65 (39)
		0.4755	NC	0.4935	NC	NC
	Leiomyosarcoma, malignant	0/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	1/65 (40)
		NC	NC	NC	NC	0.5063
Site, uncertain primary	Carcinoma, malignant	0/64 (38)	0/65 (36)	0/65 (38)	1/65 (31)	0/65 (39)
		0.2168	NC	NC	0.4493	NC
Skin	Fibroma, benign	0/65 (39)	1/65 (36)	0/64 (38)	0/64 (30)	1/65 (40)
		0.7273	0.4800	NC	NC	0.5063
	Fibrosarcoma, malignant	1/65 (40)	0/65 (36)	0/64 (38)	0/64 (30)	0/65 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Hemangiosarcoma, malignant	0/65 (39)	0/65 (36)	0/64 (38)	0/64 (30)	1/65 (40)
		NC	NC	NC	NC	0.5063
	Keratoacanthoma, benign	0/65 (39)	0/65 (36)	0/64 (38)	1/64 (31)	0/65 (39)

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	1 mg/kg/day Low (L) P - VC vs. L	6 mg/kg/day Mid (M) P - VC vs. M	30 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
		0.2153	NC	NC	0.4429	NC
	Lipoma, benign	0/65 (39)	0/65 (36)	0/64 (38)	0/64 (30)	1/65 (40)
		NC	NC	NC	NC	0.5063
Small intestine, ileum	Lymphoma, malignant	1/61 (37)	0/60 (34)	0/59 (34)	0/58 (27)	0/61 (37)
		1.0000	1.0000	1.0000	1.0000	1.0000
Small intestine, jejunum	Leiomyoma, benign	0/62 (37)	0/62 (35)	0/61 (36)	1/61 (29)	0/63 (39)
		0.2117	NC	NC	0.4394	NC
Spleen	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.9280	0.7400	1.0000	1.0000	1.0000
Thymus	Lymphoma, malignant	0/64 (38)	1/65 (37)	0/62 (36)	1/65 (31)	0/62 (38)
		0.2725	0.4933	NC	0.4493	NC
	Thymoma, benign	0/64 (38)	1/65 (36)	0/62 (36)	1/65 (31)	0/62 (38)
		0.2733	0.4865	NC	0.4493	NC
	Thymoma, malignant	0/64 (38)	1/65 (36)	0/62 (36)	1/65 (31)	0/62 (38)
		0.2733	0.4865	NC	0.4493	NC
	C_Thymoma_B+M	0/64 (38)	2/65 (36)	0/62 (36)	2/65 (31)	0/62 (38)
		0.1472	0.2400	NC	0.1982	NC
Uterus	Adenocarcinoma, endometrial, malignant	0/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	1/65 (39)
		NC	NC	NC	NC	0.5000
	Adenoma, endometrial, benign	0/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.7292	0.4868	NC	NC	NC
	Carcinoma, embryonal, malignant	0/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	1/65 (40)
		NC	NC	NC	NC	0.5063
	Carcinoma, squamous cell, malignant	0/65 (39)	0/65 (36)	1/65 (39)	0/65 (30)	0/65 (39)
		0.4792	NC	0.5000	NC	NC
	Polyp, endometrial stromal, benign	4/65 (41)	8/65 (39)	8/65 (41)	7/65 (34)	4/65 (41)
		0.2381	0.1508	0.1746	0.1607	0.6439
	Sarcoma, histiocytic, malignant	0/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.7292	0.4868	NC	NC	NC
	Stromal sarcoma, endometrial, malignant	1/65 (39)	0/65 (36)	0/65 (38)	0/65 (30)	0/65 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
	C_Stromal sarcoma+Polyp, endometrial stromal	5/65 (39)	8/65 (36)	8/65 (38)	7/65 (30)	4/65 (39)
		0.2889	0.2408	0.2734	0.2507	0.7590
Vagina	Granular cell tumor, benign	1/65 (39)	0/65 (36)	0/64 (37)	0/65 (30)	0/65 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
Whole body	Hemangioma	1/65 (39)	1/65 (37)	0/65 (38)	0/65 (30)	0/65 (39)
		0.7879	0.7400	1.0000	1.0000	1.0000
	Lymphoma, malignant	1/65 (39)	1/65 (37)	0/65 (38)	1/65 (31)	0/65 (39)
		0.4706	0.7400	1.0000	0.6932	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 8A: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Male Mice

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Adrenal Gland	Adenoma, Adrenocortical, Benign	1/62 (45) 0.9165	2/65 (50) 0.5399	0/63 (39) 1.0000	0/63 (33) 1.0000	1/64 (49) 0.7735
	Adenoma, Subcapsular Cell, Benign	3/62 (45) 0.2447	2/65 (49) 0.8447	1/63 (39) 0.9228	3/63 (34) 0.5205	3/64 (49) 0.7013
	Carcinoma, Adrenocortical, Malignant	1/62 (44) 1.0000	0/65 (49) 1.0000	0/63 (39) 1.0000	0/63 (33) 1.0000	0/64 (49) 1.0000
	Carcinoma, Subcapsular Cell, Malignant	1/62 (45) 1.0000	0/65 (49) 1.0000	0/63 (39) 1.0000	0/63 (33) 1.0000	0/64 (49) 1.0000
	Pheochromocytoma, Malignant	0/62 (44) 0.4364	0/65 (49) NC	1/63 (39) 0.4699	0/63 (33) NC	0/64 (49) NC
Brain	Glioma, Malignant	0/65 (47) 0.4451	0/65 (49) NC	1/65 (42) 0.4719	0/65 (35) NC	0/65 (50) NC
Gallbladder	Adenoma, Benign	0/54 (41) NC	0/53 (41) NC	0/52 (32) NC	0/46 (24) NC	1/55 (43) 0.5119
Harderian Gland	Adenoma, Benign	9/65 (49) 0.9806	4/65 (50) 0.9674	2/65 (41) 0.9912	1/65 (35) 0.9970	6/64 (50) 0.8779
	Carcinoma, Malignant	0/65 (47) 0.7699	2/65 (49) 0.2579	0/65 (41) NC	0/65 (35) NC	0/64 (50) NC
Kidney	Adenoma, Renal Cell, Benign	0/65 (47) 0.3212	2/65 (49) 0.2579	1/65 (41) 0.4659	1/65 (35) 0.4268	0/65 (50) NC
	Carcinoma, Renal Cell, Malignant	0/65 (47) NC	0/65 (49) NC	0/65 (41) NC	0/65 (35) NC	1/65 (50) 0.5155
Lacrimal Gland	Adenoma, Benign	1/64 (46) 1.0000	0/63 (48) 1.0000	0/64 (40) 1.0000	0/64 (34) 1.0000	0/64 (50) 1.0000
Larynx	Papilloma, Benign	0/63 (46) NC	0/63 (48) NC	0/64 (40) NC	0/65 (35) NC	1/64 (49) 0.5158
Liver	Adenoma, Hepatocellular, Benign	8/65 (47) 0.0088	1/65 (50) 0.9990	4/65 (41) 0.9049	10/65 (39) 0.2379	5/65 (51) 0.9119
	C_ Hepatocellular_ B+M	16/65 (49) 0.0000 *	1/65 (50) 1.0000	6/65 (41) 0.9882	24/65 (45) 0.0344	11/65 (52) 0.9372
	Carcinoma, Hepatocellular, Malignant	9/65 (49) 0.0000 *	0/65 (49) 1.0000	2/65 (41) 0.9912	17/65 (42) 0.0179	6/65 (50) 0.8779
	Cholangioma, Benign	0/65 (47) 0.2035	0/65 (49) NC	0/65 (41) NC	1/65 (35) 0.4268	0/65 (50) NC
	Hepatoblastoma, Malignant	0/65 (47) 0.0079 *	0/65 (49) NC	0/65 (41) NC	3/65 (35) 0.0739	0/65 (50) NC
Lungs	Adenocarcinoma, Bronchioloalveolar, Malignant	4/65 (49) 0.0853	5/65 (50) 0.5130	12/65 (45) 0.0167	7/65 (38) 0.1354	6/65 (51) 0.3963
	Adenoma, Bronchioloalveolar, Benign	6/65 (48) 0.7091	6/65 (50) 0.6492	8/65 (42) 0.2861	3/65 (36) 0.8325	8/65 (51) 0.4352
	C_B+M/Bronchioloalveolar	10/65 (50) 0.2676	11/65 (51) 0.5205	20/65 (46) 0.0117	10/65 (39) 0.3516	14/65 (53) 0.2964
Mammary Gland	Adenocarcinoma, Malignant	0/64 (46) 0.2047	0/65 (49) NC	0/65 (41) NC	1/65 (35) 0.4321	0/64 (49) NC

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Pancreas	Adenoma, Islet Cell, Benign	0/65 (47) NC	0/65 (49) NC	0/65 (41) NC	0/65 (35) NC	1/65 (50) 0.5155
	Carcinoma, Acinar Cell, Malignant	1/65 (47) 1.0000	0/65 (49) 1.0000	0/65 (41) 1.0000	0/65 (35) 1.0000	0/65 (50) 1.0000
Pituitary Gland	Adenoma, Benign	0/63 (46) 0.2511	1/61 (47) 0.5054	0/58 (35) NC	1/63 (33) 0.4177	1/58 (46) 0.5000
	Carcinoma, Pars Distalis, Malignant	0/63 (46) 0.7143	1/61 (47) 0.5054	0/58 (35) NC	0/63 (33) NC	0/58 (46) NC
Skeletal Muscle	Rhabdomyoma, Benign	0/65 (47) 0.4386	0/65 (49) NC	1/64 (40) 0.4598	0/65 (35) NC	0/65 (50) NC
Skin	Papilloma, Benign	0/65 (47) 0.4419	0/65 (49) NC	1/65 (41) 0.4659	0/65 (35) NC	1/65 (50) 0.5155
Stomach	Adenocarcinoma, Malignant	0/65 (47) 0.2035	0/65 (49) NC	0/65 (41) NC	1/65 (35) 0.4268	0/65 (50) NC
	Adenoma, Benign	0/65 (47) 0.2035	0/65 (49) NC	0/65 (41) NC	1/65 (35) 0.4268	0/65 (50) NC
	C_Adenoma+Adenocarcinoma	0/65 (47) 0.0405	0/65 (49) NC	0/65 (41) NC	2/65 (35) 0.1792	0/65 (50) NC
	Papilloma, Benign	0/65 (47) 0.0721	1/65 (49) 0.5104	0/65 (41) NC	2/65 (35) 0.1792	0/65 (50) NC
Tail	Schwannoma, Benign	0/65 (47) NC	0/65 (49) NC	0/65 (41) NC	0/65 (35) NC	1/65 (50) 0.5155
Testes	Leydig Cell Tumor, Benign	5/63 (46) 0.8270	6/64 (48) 0.5305	6/65 (42) 0.4349	2/65 (35) 0.8903	5/64 (49) 0.6699
	Seminoma, Malignant	0/63 (46) NC	0/64 (48) NC	0/65 (41) NC	0/65 (35) NC	1/64 (49) 0.5158
Thyroid Gland	Adenoma, Follicular Cell, Benign	1/62 (45) 1.0000	0/64 (48) 1.0000	0/64 (40) 1.0000	0/62 (32) 1.0000	1/63 (49) 0.7735
	Carcinoma, Follicular Cell, Malignant	0/62 (45) 0.1988	0/64 (48) NC	0/64 (40) NC	1/62 (33) 0.4231	0/63 (49) NC
Trachea	Papilloma, Benign	0/65 (47) 0.4419	0/65 (49) NC	1/65 (41) 0.4659	0/65 (35) NC	0/65 (50) NC
Whole body	Hemangioma	1/65 (47) 0.6605	1/65 (49) 0.7629	2/65 (41) 0.4483	0/65 (35) 1.0000	0/65 (50) 1.0000
	Hemangiosarcoma	1/65 (48) 0.0319	2/65 (50) 0.5155	0/65 (41) 1.0000	4/65 (37) 0.1099	1/65 (50) 0.7627
	C_Hemangiosarcoma + Hemangioma	2/65 (48) 0.1174	3/65 (51) 0.5290	2/65 (41) 0.6299	4/65 (37) 0.2235	1/65 (50) 0.8863

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 8B: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Female Mice

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
Adrenal Gland	Adenoma, Subcapsular Cell, Benign	0/65 (38)	0/65 (44)	1/64 (39)	2/65 (41)	0/65 (41)
		0.0613	NC	0.5065	0.2661	NC
	Carcinoma, Adrenocortical, Malignant	0/65 (38)	1/65 (45)	0/64 (39)	0/65 (40)	1/65 (41)
		0.7654	0.5422	NC	NC	0.5190
	Lipoma, Benign	0/65 (38)	1/65 (44)	0/64 (39)	0/65 (40)	0/65 (41)
		0.7640	0.5366	NC	NC	NC
	Pheochromocytoma, Benign	1/65 (38)	0/65 (44)	0/64 (39)	1/65 (40)	1/65 (41)
		0.4363	1.0000	1.0000	0.7659	0.7718
Brain	Meningioma, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (40)	0/65 (41)
		0.2469	NC	NC	0.5128	NC
Cervix	Carcinoma, Squamous Cell, Malignant	1/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	0/65 (41)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Fibroma, Benign	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		NC	NC	NC	NC	0.5190
	Leiomyosarcoma, Malignant	0/65 (38)	1/65 (44)	0/65 (40)	0/65 (40)	0/65 (41)
		0.7654	0.5366	NC	NC	NC
	Schwannoma, Malignant	1/65 (38)	0/65 (44)	0/65 (40)	1/65 (40)	0/65 (41)
		0.4340	1.0000	1.0000	0.7659	1.0000
	Stromal Sarcoma, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (40)	0/65 (41)
		0.2469	NC	NC	0.5128	NC
Duodenum	Adenocarcinoma, Malignant	0/59 (34)	1/60 (43)	0/60 (38)	0/58 (38)	0/59 (38)
		0.7778	0.5584	NC	NC	NC
	Adenoma, Benign	0/59 (34)	0/60 (42)	0/60 (38)	1/58 (38)	0/59 (38)
		0.2500	NC	NC	0.5278	NC
Harderian Gland	Adenoma, Benign	3/65 (39)	3/65 (44)	2/65 (40)	2/65 (41)	5/65 (42)
		0.6900	0.7181	0.8285	0.8358	0.3989
Liver	Adenoma, Hepatocellular, Benign	0/65 (38)	1/65 (44)	0/65 (40)	0/65 (40)	0/65 (41)
		0.7654	0.5366	NC	NC	NC
	C_ Hepatocellular_ B+M	0/65 (38)	1/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		0.4938	0.5366	NC	NC	0.5190
	Carcinoma, Hepatocellular, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		NC	NC	NC	NC	0.5190
Lungs	Adenocarcinoma, Bronchioloalveolar, Malignant	4/65 (39)	1/65 (44)	6/65 (42)	4/65 (42)	1/65 (41)
		0.2918	0.9802	0.4176	0.6852	0.9761
	Adenoma, Bronchioloalveolar, Benign	5/65 (39)	5/65 (45)	10/65 (43)	7/65 (43)	3/65 (41)
		0.2892	0.7191	0.1753	0.4502	0.8838
	C_B+M/Bronchioloalveolar	9/65 (40)	6/65 (45)	15/65 (45)	11/65 (44)	4/65 (42)
		0.2100	0.9181	0.1935	0.4960	0.9732
Mammary Gland	Adenocarcinoma, Malignant	0/63 (37)	3/63 (44)	2/64 (40)	0/62 (38)	0/64 (40)
		0.8133	0.1552	0.2666	NC	NC
Ovary	Cystadenocarcinoma, Malignant	0/65 (38)	1/65 (44)	0/65 (40)	0/65 (40)	0/65 (41)
		0.7654	0.5366	NC	NC	NC
	Cystadenoma, Benign	0/65 (38)	0/65 (44)	1/65 (40)	0/65 (40)	2/65 (42)

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
		0.4938	NC	0.5128	NC	0.2725
	Granulosa Cell Tumor, Benign	0/65 (38)	3/65 (45)	0/65 (40)	2/65 (41)	2/65 (41)
		0.3027	0.1544	NC	0.2661	0.2661
	Granulosa Cell Tumor, Malignant	1/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		1.0000	1.0000	1.0000	1.0000	0.7718
	Luteoma, Benign	0/65 (38)	0/65 (44)	1/65 (40)	0/65 (40)	0/65 (41)
		0.4938	NC	0.5128	NC	NC
	Tumor, Sertoli Cell, Benign	0/65 (38)	0/65 (44)	2/65 (40)	2/65 (41)	0/65 (41)
		0.0720	NC	0.2597	0.2661	NC
	C_Sertoli Cell + Granulosa Cell	0/65 (38)	3/65 (45)	2/65 (40)	4/65 (42)	2/65 (41)
	Benign	0.0775	0.1544	0.2597	0.0708	0.2661
	C_Sertoli Cell + Granulosa Cell	1/65 (38)	3/65 (45)	2/65 (40)	4/65 (42)	3/65 (41)
	Benign + Malignant	0.1434	0.3745	0.5195	0.2123	0.3370
Pituitary Gland	Adenoma, Benign	2/64 (38)	5/63 (44)	0/63 (39)	1/63 (39)	3/65 (41)
		0.9104	0.2815	1.0000	0.8847	0.5365
Site, Primary Uncertain	Sarcoma, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		NC	NC	NC	NC	0.5190
Skin	Basosquamous Tumor, Benign	0/65 (38)	0/65 (44)	1/65 (40)	0/65 (40)	0/65 (41)
		0.4938	NC	0.5128	NC	NC
	Chondroma, Benign	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	0/65 (41)
		0.2515	NC	NC	0.5190	NC
	Fibrosarcoma, Malignant	3/65 (39)	0/65 (44)	1/65 (40)	0/65 (40)	0/65 (41)
		0.9352	1.0000	0.9453	1.0000	1.0000
	Papilloma, Benign	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (40)	0/65 (41)
		0.2469	NC	NC	0.5128	NC
	Pilomatrixoma, Benign	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	0/65 (41)
		0.2515	NC	NC	0.5190	NC
Sternum	Chondrosarcoma, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	0/65 (41)
		0.2515	NC	NC	0.5190	NC
Systemic	Hemangioma, Benign	2/65 (39)	8/65 (46)	1/65 (41)	3/65 (42)	1/65 (41)
		0.7732	0.0768	0.8888	0.5356	0.8888
	Hemangiosarcoma, Malignant	1/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	1/65 (41)
		0.4410	1.0000	1.0000	0.7718	0.7718
	Lymphoma, Malignant	11/65 (42)	6/65 (46)	4/65 (42)	9/65 (44)	12/65 (45)
		0.4145	0.9670	0.9898	0.8117	0.5768
	Mast Cell Tumor, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		NC	NC	NC	NC	0.5190
	Sarcoma, Histiocytic, Malignant	1/65 (38)	1/65 (44)	0/65 (40)	1/65 (41)	2/65 (42)
		0.5426	0.7883	1.0000	0.7718	0.5380
Thyroid Gland	Adenoma, C-Cell, Benign	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	2/65 (41)
		NC	NC	NC	NC	0.2661
	Carcinoma, Follicular Cell,	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	0/65 (41)
	Malignant	0.2515	NC	NC	0.5190	NC
Urinary Bladder	Carcinoma, Urothelial, Malignant	0/65 (38)	0/65 (44)	1/65 (40)	0/65 (40)	0/65 (41)
		0.4938	NC	0.5128	NC	NC
Uterus	Adenocarcinoma, Endometrial,	2/65 (39)	4/65 (45)	0/65 (40)	0/65 (40)	0/65 (41)
	Malignant	0.9902	0.4089	1.0000	1.0000	1.0000

Organ name	Tumor name	0 mg/kg/day Vehicle C P - Trend	3 mg/kg/day Low (L) P - VC vs. L	30 mg/kg/day Mid (M) P - VC vs. M	100 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline (SC) P - VC vs. SC
	C_leiomyoma/Leiomyosarcoma	0/65 (38)	2/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
		0.0086 *	0.2909	NC	0.0354 **	NC
	Granular Cell Tumor, Benign	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		NC	NC	NC	NC	0.5190
	Leiomyoma, Benign	0/65 (38)	2/65 (45)	0/65 (40)	4/65 (41)	0/65 (41)
		0.0248 *	0.2909	NC	0.0674	NC
	Leiomyosarcoma, Malignant	0/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	0/65 (41)
		0.2515	NC	NC	0.5190	NC
	Lymphangioma, Benign	0/65 (38)	0/65 (44)	0/65 (40)	0/65 (40)	1/65 (41)
		NC	NC	NC	NC	0.5190
	Polyp, Endometrial Stromal, Benign	6/65 (39)	6/65 (45)	6/65 (42)	8/65 (43)	3/65 (42)
		0.2628	0.7197	0.6744	0.4643	0.9385
	Sarcoma, Endometrial Stromal, Malignant	2/65 (39)	1/65 (45)	1/65 (40)	2/65 (41)	1/65 (41)
		0.3917	0.9041	0.8844	0.7111	0.8888
Uterus/ Cervix	C_leiomyoma/Leiomyosarcoma	0/65 (38)	3/65 (45)	0/65 (40)	5/65 (42)	0/65 (41)
		0.0213 *	0.1544	NC	0.0354 **	NC
	C_ Polyp, Endometrial Stromal_ Sarcoma + Polyp	8/65 (38)	7/65 (45)	7/65 (40)	11/65 (42)	4/65 (41)
		0.1522	0.8073	0.7502	0.3886	0.9562
Whole body	Hemangioma	2/65 (39)	8/65 (46)	1/65 (41)	3/65 (42)	1/65 (41)
		0.7722	0.0768	0.8888	0.5356	0.8888
	Hemangioma/Hemangiosarcoma	3/65 (39)	8/65 (46)	1/65 (41)	4/65 (42)	2/65 (42)
		0.6828	0.1581	0.9480	0.5421	0.8427
	Hemangiosarcoma	1/65 (38)	0/65 (44)	0/65 (40)	1/65 (41)	1/65 (41)
		0.4410	1.0000	1.0000	0.7718	0.7718
	Lymphoma, malignant	11/65 (42)	6/65 (46)	4/65 (42)	9/65 (44)	12/65 (45)
		0.4145	0.9670	0.9898	0.8117	0.5768

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 9A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Transgenic Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	15 mg/kg/day Low (L) P - VC vs. L	300 mg/kg/day Mid (M) P -V C vs. M	1500 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
Brain	Hemangiosarcoma, malignant	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/12 (12)
		NC	NC	NC	NC	0.3243
Epididymis	Hemangiosarcoma, malignant	0/25 (25)	0/25 (25)	0/25 (24)	1/25 (25)	0/12 (12)
		0.2525	NC	NC	0.5000	NC
Foot	Papilloma, benign	0/25 (25)	1/25 (25)	0/25 (24)	0/25 (25)	0/12 (12)
		0.7475	0.5000	NC	NC	NC
Gland, harderian	Adenoma, benign	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/12 (12)
		NC	NC	NC	NC	0.3243
Gland, prostate	Lymphoma, malignant	0/25 (25)	1/24 (24)	0/25 (24)	0/25 (25)	0/12 (12)
		0.7449	0.4898	NC	NC	NC

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Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	15 mg/kg/day Low (L) P - VC vs. L	300 mg/kg/day Mid (M) P -V C vs. M	1500 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
Lung	Adenoma, bronchioloalveolar, benign	5/25 (25) 0.7263	2/25 (25) 0.9509	0/25 (24) 1.0000	2/25 (25) 0.9509	0/12 (12) 1.0000
Multicentric neoplasm	Hemangioma, benign	0/25 (25) 0.4949	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC	0/12 (12) NC
Spleen	Hemangiosarcoma, malignant	1/25 (25) 0.1671	0/25 (25) 1.0000	2/24 (24) 0.4844	2/25 (25) 0.5000	1/12 (12) 0.5495
Stomach	Papilloma, benign	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000	0/12 (12) NC
Thymus	Lymphoma, malignant	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	0/12 (12) NC
	Mesothelioma, malignant	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/12 (12) 0.3243
Whole Body	Hemangioma	0/25 (25) 0.2525	0/25 (25) NC	1/25 (24) 0.4898	0/25 (25) NC	0/12 (12) NC
	Hemangiosarcoma	1/25 (25) 0.0663	0/25 (25) NC	2/25 (25) 0.5000	3/25 (25) 0.3046	2/12 (12) 0.2407
	C_Hemangiosarcoma + Hemangioma	1/25 (25) 0.0818	0/25 (25) NC	3/25 (25) 0.3046	3/25 (25) 0.3046	2/12 (12) 0.2407
	Lymphoma, malignant	0/25 (25) 0.4949	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	0/12 (12) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 for both common tumor and rare tumor. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both common tumor and a rare tumor.

Table 9B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Transgenic Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	15 mg/kg/day Low (L) P - VC vs. L	300 mg/kg/day Mid (M) P -V C vs. M	1500 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
Gland, thyroid	Adenoma, follicular cell, benign	0/25 (25) 0.7500	1/25 (25) 0.5000	0/25 (25) NC	0/25 (25) NC	0/12 (11) NC
Lung	Adenoma, bronchioloalveolar, benign	0/25 (25) 0.2500	0/25 (25) NC	0/25 (25) NC	1/25 (25) 0.5000	0/12 (11) NC
	Carcinoma, bronchioloalveolar, malignant	0/25 (25) 0.6263	1/25 (25) 0.5000	1/25 (25) 0.5000	0/25 (25) NC	0/12 (11) NC
	C_bronchioloalveolar_M+B	0/25 (25) 0.2964	1/25 (25) 0.5000	1/25 (25) 0.5000	1/25 (25) 0.5000	0/12 (11) NC
Ovary	Fibroma, benign	0/24 (24) 0.7576	1/25 (25) 0.5102	0/25 (25) NC	0/25 (25) NC	0/12 (11) NC
Skin	Hemangiosarcoma, malignant	0/25 (25) 0.1869	0/25 (25) NC	1/25 (25) 0.5000	1/25 (25) 0.5000	0/12 (11) NC

Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	15 mg/kg/day Low (L) P - VC vs. L	300 mg/kg/day Mid (M) P -V C vs. M	1500 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Water (WC) P - VC vs. WC
Skin/ Subcutis	Hemangiosarcoma, malignant	1/25 (25) 0.7525	0/25 (25) 1.0000	1/25 (25) 0.7551	0/25 (25) 1.0000	0/12 (11) 1.0000
	Lymphangiosarcoma, malignant	0/25 (25) 0.2500	0/25 (25) NC	0/25 (25) NC	1/25 (25) 0.5000	0/12 (11) NC
Spleen	Hemangiosarcoma, malignant	6/25 (25) 0.8807	0/25 (25) 1.0000	0/25 (25) 1.0000	1/25 (25) 0.9952	1/12 (12) 0.9533
Thymus	Thymoma, malignant	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/12 (11) 1.0000
Whole Body	Hemangiosarcoma	7/25 (25) 0.7868	0/25 (25) 1.0000	2/25 (25) 0.9884	2/25 (25) 0.9884	1/12 (12) 0.9720

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 for both common tumor and rare tumor. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both common tumor and a rare tumor.

Table 9C: Tumor Rates and P-Values Pairwise Comparisons of Vehicle Control with Positive Control in Male Transgenic Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (VC)	75 mg Positive (PC) P - VC vs. PC
Liver	Lymphoma, malignant	0/25 (25)	1/15 (14) 0.3590
Lung	Adenoma, bronchioloalveolar, benign	5/25 (25)	0/15 (13) 1.0000
	Lymphoma, malignant	0/25 (25)	1/15 (13) 0.3421
Lymph node, mandibular	Lymphoma, malignant	0/25 (25)	1/15 (14) 0.3590
Lymph node, mesenteric	Lymphoma, malignant	0/25 (25)	1/15 (14) 0.3590
Skin	Papilloma, benign	0/25 (25)	7/15 (13) 0.0001 **
Spleen	Hemangiosarcoma, malignant	1/25 (25)	0/15 (13) 1.0000
	Lymphoma, malignant	0/25 (25)	3/15 (14) 0.0398 **
Stomach	Carcinoma, squamous cell, malignant	0/25 (25)	2/15 (13) 0.1110
	Hemangiosarcoma, malignant	0/25 (25)	1/15 (13) 0.3421
	Papilloma, benign	0/25 (25)	14/15 (14) 0.0000 **
Thymus	Lymphoma, malignant	0/25 (25)	3/14 (13) 0.0339 **
Tongue	Papilloma, benign	0/25 (25)	1/15 (13) 0.3421
Whole Body	Hemangiosarcoma	1/25 (25)	1/15 (13) 0.5733
	Lymphoma, malignant	0/25 (25)	3/15 (14)

Organ name	Tumor name	0 mg/kg/day Vehicle (VC)	75 mg Positive (PC) P - VC vs. PC
			0.0398 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for a common tumor and a rare tumor, respectively.

Table 9D: Tumor Rates and P-Values Pairwise Comparisons of Vehicle Control with Positive Control in Female Transgenic Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (VC)	75 mg Positive (PC) P - VC vs. PC
Gland, harderian	Adenocarcinoma, malignant	0/25 (25)	1/15 (12)
			0.3243
Skin	Adenocarcinoma, malignant	0/25 (25)	1/15 (12)
			0.3243
	Papilloma, benign	0/25 (25)	8/15 (13)
			0.0000 **
Skin/Subcutis	Hemangiosarcoma, malignant	1/25 (25)	0/15 (12)
			1.0000
Spleen	Hemangiosarcoma, malignant	6/25 (25)	0/15 (12)
			1.0000
Stomach	Carcinoma, squamous cell, malignant	0/25 (25)	2/15 (12)
			0.0991
	Papilloma, benign	0/25 (25)	12/15 (14)
			0.0000 **
Thymus	Lymphoma, malignant	0/25 (25)	5/15 (14)
			0.0035 **
Tongue	Papilloma, benign	0/25 (25)	1/15 (12)
			0.3243
Whole Body	Hemangiosarcoma	7/25 (25)	0/15 (12)
			1.0000
	Lymphoma, malignant	0/25 (25)	5/15 (14)
			0.0035 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for a common tumor and a rare tumor, respectively.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

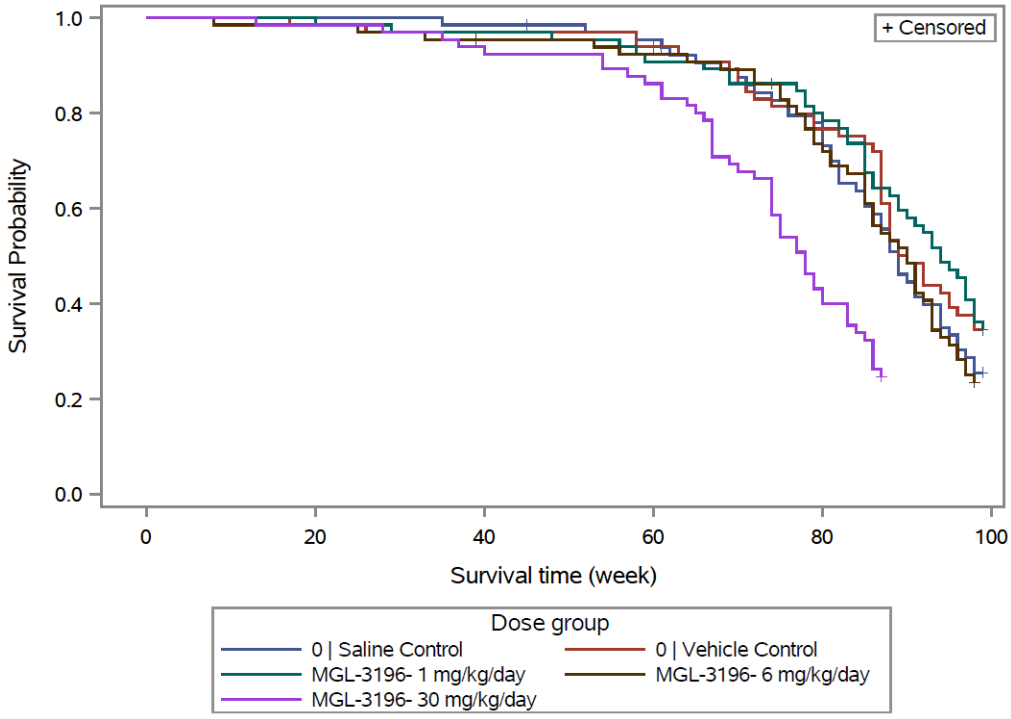


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

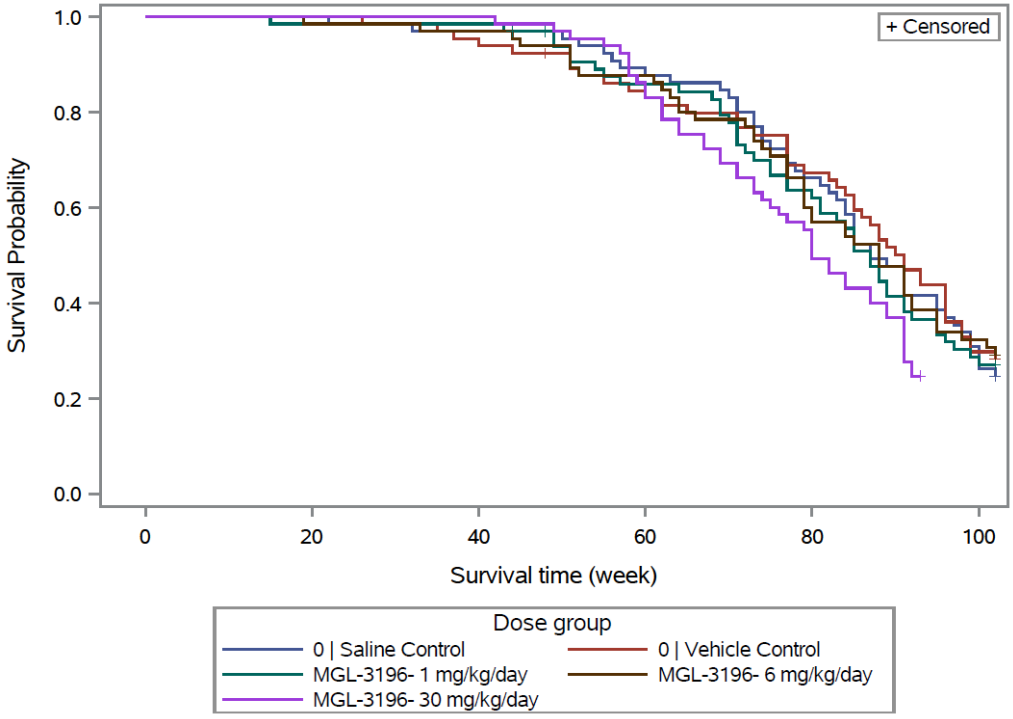


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

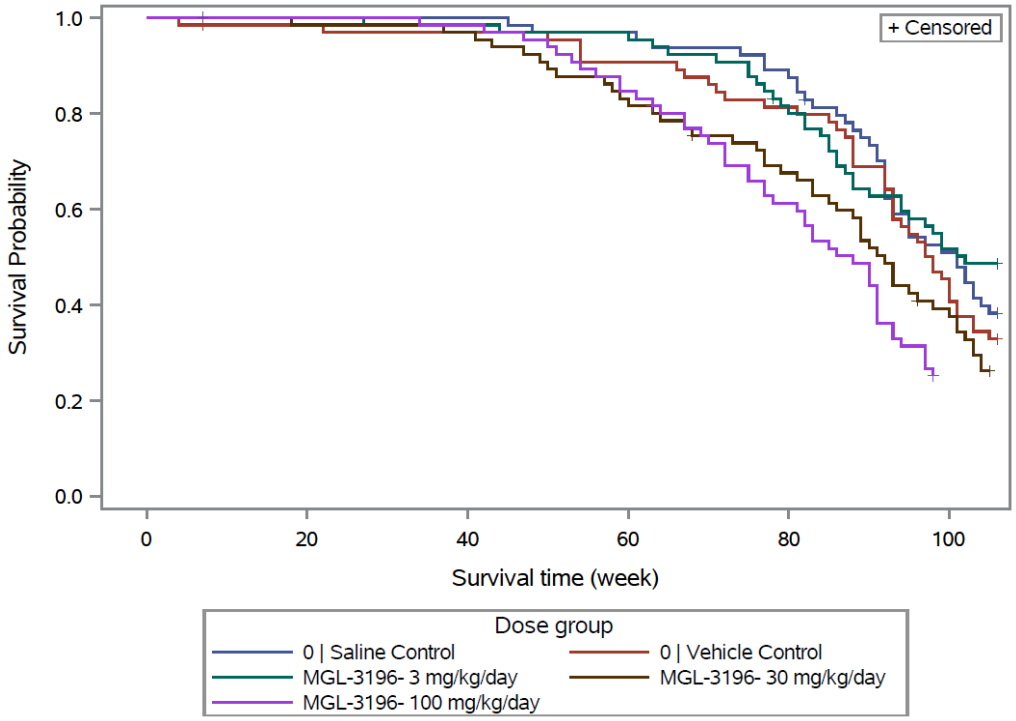


Figure 2B: Kaplan-Meier Survival Functions for Female Mice

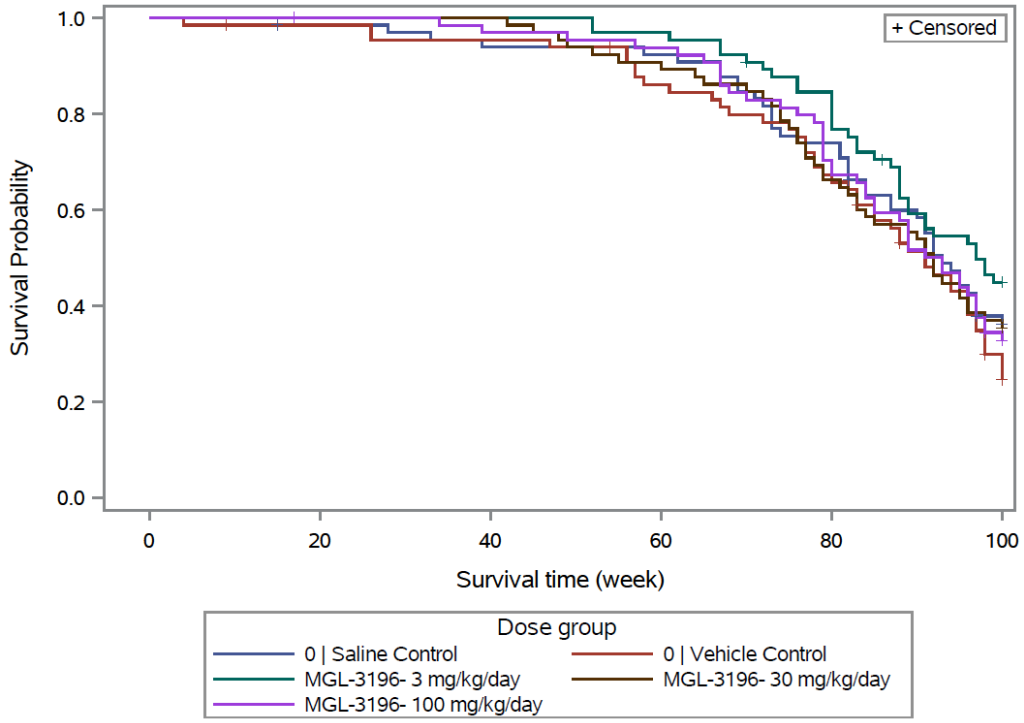


Figure 3A: Kaplan-Meier Survival Functions for Male Transgenic Mice

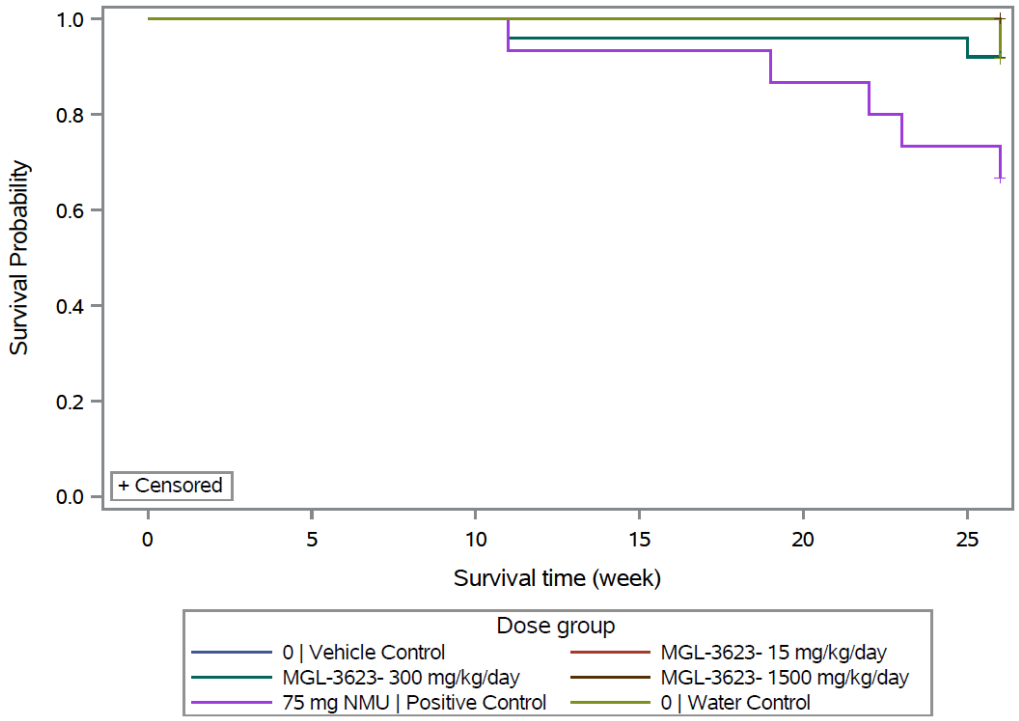
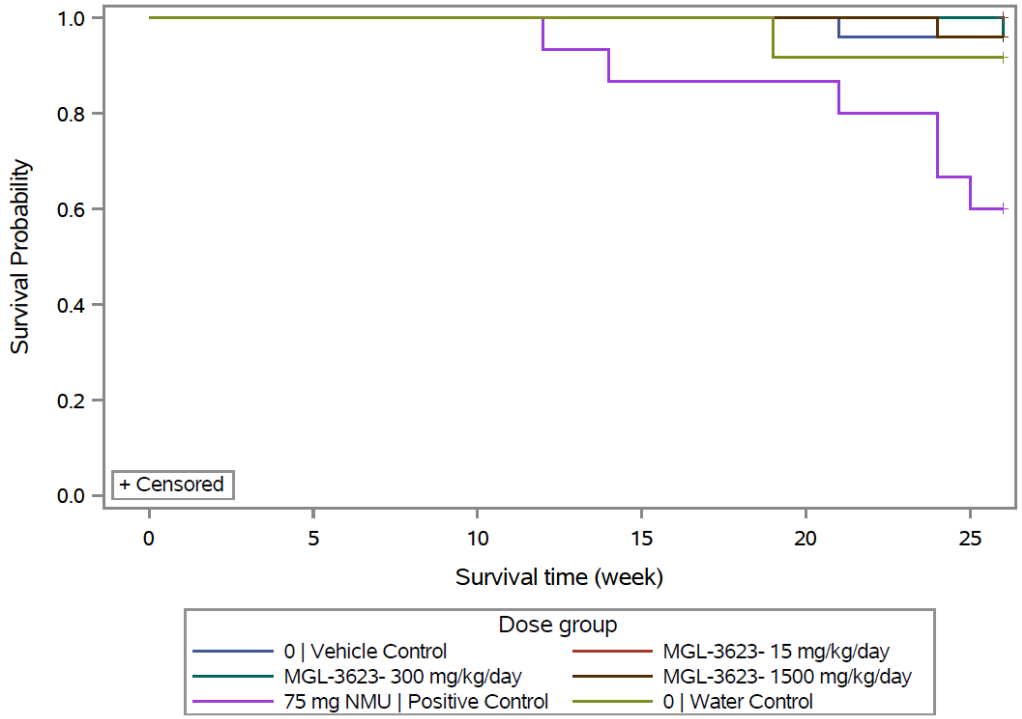


Figure 3B: Kaplan-Meier Survival Functions for Female Transgenic Mice



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