CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217785Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	March 12, 2024
Reviewer(s):	Joel L. Wessfeld, MD MPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD MS Division of Epidemiology I
Division Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo -- Pregnancy
Drug Name(s):	resmetirom
Application Type/Number:	NDA 217785
Applicant/sponsor:	Madigral Pharmaceuticals, Inc.
OSE RCM #:	2023-5594

EXPEDITED ARIA SUFFICIENCY TEMPLATE FOR PREGNANCY SAFETY CONCERNS

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 217785 seeks Subpart H (accelerated) approval for resmetirom as a treatment for non-alcoholic steatohepatitis (NASH), a type of fatty liver disease characterized on liver biopsy by hepatocyte ballooning, lobular inflammation, and (in severe cases) fibrosis. In some patients, liver fibrosis progresses to cirrhosis, liver failure, and death. Non-alcoholic fatty liver disease typically occurs "in the fifth and sixth decades of life."[a]

Resmetirom is a small-molecular-weight (435.22 daltons; 4.5-hour half-life) orally administered agonist of thyroid hormone receptor beta (THR-β), a nuclear hormone receptor expressed by hepatocytes. Activation of hepatic THR-β promotes synthesis of several proteins important to hepatocyte mitochondrial function and lipid metabolism.[b]

1.2. Describe the Safety Concern

The safety concern stems from: (1) complete absence of human data about the safety of resmetirom when used during pregnancy and (2) magnitude of exposure anticipated for women in reproductive age groups.[c]

The Division of Pediatrics and Maternal Health (DPMH) explained the safety concern by noting that "there are no data available to inform the safety of resmetirom use during pregnancy."[d]

Animal reproduction studies indicate potential for adverse effects on embryo-fetal development. Specifically, pre-clinical studies of resmetirom in:

- Pregnant rabbits showed adverse effects on fetal viability and weight at maternal exposures equal to 3.5 times maximum recommended human dose (MRHD).
- Pregnant rats showed no effects on embryo-fetal development at maternal exposures equal to 21 times the MRHD.
- Pregnant rabbits showed no effects on embryo-fetal development at maternal exposures equal to 2.8 times MRHD.
- Rats showed no maternal or developmental toxicity at maternal exposures (during organogenesis through lactation) equal to 7.2 times MRHD.

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[a] Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. Semin Liver Dis. 2001;21(1):17-26.

[b] Karim G, Bansal MB. Resmetirom: An Orally Administered, Small-molecule, Liver-directed, beta-selective THR Agonist for the Treatment of Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis. touchREV Endocrinol. 2023;19(1):60-70.

[c] Baisden K, T Johnson, and LP Yao. Division of Pediatrics and Maternal Health PLLR Labeling Memorandum. Filed under NDA 217785 on December 20, 2023 (DARRTS Reference ID: 5297282).

[d] Ibid., p 6.

Hepatologists in the Division of Hepatology and Nutrition (DHN) anticipate low levels of pregnancy exposure to resmetirom.[e] DHN explained that NASH is not uncommon in the overall U.S. population. However, NASH with moderate to advanced fibrosis (the indicated population for resmetirom treatment) represents a minority of the entire NASH patient population.[f] Additionally, DHN used study data from NDA 217785 to estimate the relative size of the moderate-to-advanced NASH population with childbearing potential at 4 percent. Finally, DHN described NASH natural history as "relatively indolent" such that clinicians might be reasonably expected to defer resmetirom treatment until after pregnancy. For these reasons, DHN and DPMH endorsed a descriptive pregnancy safety study (DPSS) as a preferred approach.[g]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

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[e] Baer G, Email communication on January 16, 2024, filed in RM Client as [RE_NDA 217785_Request for Completion of Insufficiency Memo.pdf] on January 16, 2024 as Object ID: 090026fc8067afe6.

[f] Estimated by DEPI at 33% from information in Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018 Oct;69(4):896-904.

[g] Instead of a traditional (internally controlled) pregnancy registry.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: A descriptive pregnancy safety study (DPSS), defined as a protocol-driven uncontrolled (single-arm) observational cohort study that collects detailed data for descriptive analysis.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☒ Exposures
☒ Outcomes
☒ Covariates
☐ Analytical Tools

Exposures/Outcomes/Covariates: Descriptive pregnancy safety studies use targeted questionnaires to collect detailed and specific information about important confounders (e.g., body mass index and illicit drug use) and the timing of drug exposures in relation to well-defined pregnancy outcomes. Data elements considered appropriate for collection by targeted questionnaire include study drug and concomitant drug exposures during pregnancy and results from newborn physical examinations. Data collection occurs at pre-determined intervals (e.g., at study enrollment, mid-point of pregnancy, estimated delivery date, 3-6 months postpartum, and 12 months postpartum). Well-documented case narratives that include detailed clinical information acquired directly from primary sources (e.g., medical records and providers) facilitate causal assessment of relationships between drug exposures during pregnancy and adverse outcomes from pregnancy. ARIA precludes use of targeted questionnaires for data collection.

2.5. Please include the proposed PMR language in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to resmetirom during pregnancy 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.

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/

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Clinical Review Memorandum

Division of Hepatology and Nutrition
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDA (IND)	217785 (122865)
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Resmetirom
Indication	Non-cirrhotic NASH
Applicant	Madrigal Pharmaceuticals
Requesting Division	Division of Hepatology and Nutrition (DHN)
Primary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Other Reviewers	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Feb 26, 2024

I. Executive Summary

We do not think the DILI risk should prevent approval if efficacy is established and supports a favorable benefit versus risk. Three of the four cases of liver injury requested for review are concerning for DILI possibly or probably attributable to resmetirom. The approximate number of patients expose to resmetirom was 3000. We considered one case as probable resmetirom liver injury meeting Hy's Law criteria, but the liver injury has a drug induced autoimmune like hepatitis (DI-ALH) phenotype. It is unclear whether this phenotype carries the mortality risk suggested by Hy's Law. We concluded another two cases as at least possible DILI due to resmetirom. One also had autoimmune hepatitis features. The fourth case was unlikely DILI. If approved, labeling should emphasize the appropriate indication of NASH with F2 or F3 fibrosis (b) (4). Our detailed assessment and recommendations are in Sections IV and V below.

II. Background

Resmetirom is a small, new molecular entity, taken orally. It is a thyroid hormone receptor beta agonist for the treatment of noncirrhotic, non-alcoholic steatohepatitis (NASH) (b) (4). Another liver-selective thyroid hormone receptor agonist (eprotirome) demonstrated potential for liver injury in a phase 3 trial treating familial hypercholesterolemia.[1] Development of eprotirome was stopped. Structural formulas for resmetirom and eprotirome are shown in the **Appendix, Figure A**.

The resmetirom NDA was submitted under the accelerated approval pathway. IND number was 122865. Two doses were tested in the pivotal trial (MGL-3196-11): 100 mg and 80 mg. The Applicant also conducted two additional trials to support safety (MGL-3196-14 and MGL-3196-18) in their phase 3 program.

1. MGL-3196-11 (Study 11): pivotal trial, population included F1b/F2/F3 subjects with biopsy-proven NASH. Both doses demonstrated modest efficacy on the primary endpoints: NASH resolution and fibrosis improvement.
2. MGL-3196-14 (Study 14): The study population included adults with presumed NASH (mostly based on non-invasive tests). These also included screen failures from study 11. Trial is not included for efficacy assessment.
3. MGL-3196-18 (study 18): This study was primarily a roll-over study of subjects who completed study 14.

DHN requested the DILI Team assess four subjects with liver injury for attribution to resmetirom; two were jaundiced. Subjects (b) (6) and (b) (6) were enrolled in Study 14. Subjects (b) (6) and (b) (6) were in Study 11. The DILI Team estimates that 3000 subjects were exposed to resmetirom across these three studies.

III. Significant Review Findings

Non-clinical data:

We did not include a full write-up for the non-clinical and toxicologic data regarding DILI risk, but our abbreviated review suggests a mixed picture for DILI risk. Resmetirom is hepatically metabolized and excreted via feces. Lipophilicity by log-P was 3.6 consistent with potential DILI Risk.[2] In animal studies there was scattered inflammation, necrosis, and cholestasis on liver histology. However, we found no data suggesting reactive metabolite formation, covalent binding to

[1] Sjouke B, et al. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Diab Endo*. 2014; 2:455-63.
[2] Chen M, et al. High Lipophilicity and High Daily Dose of Oral Medications Are Associated With Significant Risk for Drug-Induced Liver Injury. *Hepatology*. 2013; 58:388-96.

other molecules, time dependent inhibition, or significant transport inhibition. There were no data from mitochondrial toxicity studies. (**Appendix, Table 1**).

Case reviews: Our subject level review was limited to the four cases identified by DHN. We assessed one as probable, two as possible and one as unlikely DILI due to resmetirom.

1. Subject (b) (6) (Study MGL-3196-14): We assessed this case as probable DILI due to resmetirom and meeting Hy's law criteria. However, the DILI phenotype best fits drug induced autoimmune-like hepatitis (DI-ALH). See **Appendix** for the case summary. 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 autoimmune hepatitis is supported by the subject's sex, age, pre-treatment histology, pre-treatment "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).[3],[4] While the biopsy on the second bout only hinted at DI-ALH, the sample was suboptimal. The main competing diagnosis is autoimmune hepatitis (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 elevations, when resmetirom was held (**Appendix, Figure B**). However, the severe and more rapid injury with resmetirom rechallenge is difficult to dismiss as coincidence, and quick 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 is mentioned by the applicant, but the very high ALT, lack of AP elevation, lack of symptoms (fever, abdominal tenderness, or pain), and lack of duct dilation do not support this liver injury explanation. While the patient meets Hy's Law criteria, it's unclear whether DI-ALH carries a 10% mortality risk, particularly because a therapy (corticosteroids) may be available.

2. Subject (b) (6) (Study MGL-3196-14): We assessed this case is at least possible if not probable DILI due to resmetirom. This case might also fit with DI-ALH. See **Appendix** for the case summary. While 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 autoimmune hepatitis features rather than de novo autoimmune hepatitis (AIH). Indeed, she may not have needed the immunosuppression as her liver enzymes had already

[3] Andrade RJ, et al. Nomenclature, diagnosis, and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report. *J of Hep*. 2023; article in press. https://doi.org/10.1016/j.jhep.2023.04.033.
[4] Bjornsson E, et al. Drug-Induced Autoimmune Hepatitis: Clinical Characteristics and Prognosis. *Hepatology*. 2010; 51:2040-8.

improved substantially (**Appendix, Figure C**). A liver biopsy would have been helpful but was not done probably because the liver tests were coming down. The local provider chose azathioprine initially but then switched to mycophenolate (MMF) without explanation. Such a switch may indicate lower confidence that this is de novo AIH. Standard of care for AIH is long-term azathioprine. MMF has the advantage of easy tapering due to its shorter half-life. In DI-ALH, immunosuppressive medications, when applied, are typically tapered off. A successful taper would tip the likelihood toward DI-ALH (probable) over AIH.

3. Subject (b) (6) (MGL-2196-11): We assessed this case as possible DILI due to resmetirom. See **Appendix** for the case summary. The latency of 110 days and dechallenge are consistent with DILI. Dechallenge is consistent with multiple myeloma (MM) in the liver or a paraneoplastic event because the MM was not treated and the MM was "stage 1, indolent." Resmetirom drug level was high at 6020 ng/ml at liver injury onset compared to 253 ng/ml three weeks earlier. The increased drug level does not necessarily mean the drug caused the injury; rather, the high level may be a result of the injury. Nevertheless, it raises concerns that any liver injury may increase risk of subsequent hepatotoxicity if there is a DILI dose relationship. HAV IgM was inconclusive due to low titer, and we wonder if this low titer is due to MM which can interfere with serologic tests (false negative).[5] On the other hand, false positive results in patients with MM or other hyper-paraprotein disorders have been reported for syphilis and galactomannan.[6,7] 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.

4. Subject (b) (6) (MGL-3196-11): We assessed this case as unlikely DILI due to resmetirom. See **Appendix** for the case summary. The latency is too long at over 765 days, 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. Also, there was no dechallenge washout. Though rare, severe cholestasis with or without documented vanishing bile duct syndrome (VBDS) is described with Hodgkin's

[5] King RI, et al. How paraproteins can affect laboratory assays: spurious results and biological effects. *Pathology*. 2010; 41:397-401.
[6] Russell-Jones R, et al. Essential mixed cryoglobulinaemia with false-positive serological tests for syphilis. *Br J Vener Dis*. 1983; **59**(1): 33-36
[7] Ko JH, et al. Multiple myeloma as a major cause of false-positive galactomannan tests in adult patients with cancer. *J Infect.* 2016; 72:233-239.

lymphoma.[8],[9],[10],[11] Liver biopsy may be indicative of a bile duct injury and impending VBDS with "intervening stroma" or fibrosis of the bile ducts. Also, the biopsy had only "rare portal areas identified," so the sample may have been small or inadequate. Hodgkin's with a paraneoplastic cholestatic injury would be a unifying diagnosis as opposed to suggesting a rare, long latency DILI that coincidentally occurred with the Hodgkin's presentation.

IV. Conclusions

Non-clinical data were mixed for DILI risk (**Appendix, Table 1**). Resmetirom is hepatically metabolized, but data did not support reactive metabolite formation or covalent binding. Lipophilicity by log P measurement was elevated suggesting potential DILI risk, and some liver necrosis and inflammation occurred in animal studies. Therefore, DILI occurrence in the clinical trials is possible based on non-clinical data.

Three of the four cases are concerning for potential DILI due to resmetirom. One case (Case (b) (6)) fits Hy's Law criteria but also had a drug induced autoimmune like hepatitis (DI-ALH) phenotype. The simplified AIH score is 6-7 (probable AIH),[12] and DI-ALH cases often have high AIH scores. We favor 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 in addition to NASH. We speculate that resmetirom caused a DI-ALH in a patient predisposed to such an injury. Such predisposition is a common hypothesis for DI-ALH pathophysiology. The Sponsor responded to an information request regarding this case. The response did not change our assessment. Our review of the Sponsor's response is in the **Addendum**.

We assessed a second case (Subject (b) (6)) as possible DILI due to resmetirom, and it too had autoimmune features. The injury was mild. The narrative suggests that AIH was diagnosed, but no biopsy was done. While this subject got immunosuppression, it is not clear that such treatment was needed. The enzymes had fallen 60-70% before immunosuppression, and it is unknown if the subject was able to taper off therapy. Successful taper would be unusual for de novo AIH but typical of DI-ALH. We assessed the third case (Subject (b) (6) as possible DILI due to resmetirom. This case was confounded by an

[8] Lieberman DA. Intrahepatic Cholestasis Due to Hodgkin's Disease. *J Clin Gastro*.1986; 8:304-7.
[9] Yalcin S, et al. Extrahepatic Hodgkin's Disease with Intrahepatic Cholestasis: Report of Two Cases. *Oncology*. 1999; 57:83-5.
[10] Deacon AJ, et al. Relapsed nodular lymphocyte-predominant Hodgkin lymphoma presenting as severe paraneoplastic hepatitis: a case report. *J Med Case Reports.* 2023; 17(269):1-7. https://doi.org/10.1186/s13256-023-04014-9
[11] Hubscher SG, et al. Vanishing Bile Duct Syndrome: A Possible Mechanism for Intrahepatic Cholestasis in Hodgkin's Lymphoma. *Hepatology*. 1993; 17:70-77
[12] Hennes EM, et al. Simplified Criteria for the Diagnosis of Autoimmune Hepatitis. *Hepatology*. 2008; 48:169-76.

inconclusive anti-HAV IgM test and concurrent indolent multiple myeloma. The fourth case was unlikely DILI.

The two cases with AIH features raise questions about (a) safety of resmetirom use in subjects with an autoimmune liver disorder and (b) possible need for a higher diagnostic certainty of F2 or F3 fibrosis NASH without underlying autoimmune liver disease. While one Hy's Law case out of 3000 subjects exposed typically raises a concern for post-market risk of significant DILI, the phenotype of DI-ALH makes applicability of Hy's Law less clear. Some jaundiced hepatocellular DILIs may have lower rate of mortality than that suggested by Hy's Law.[13] Nitrofurantoin liver injury can be fatal, while minocycline may be less severe. Both are frequently cited examples of DI-ALH. Also, if DI-ALH is recognized early and immunosuppression applied, the mortality risk could be mitigated. Liver enzymes are generally checked while on resmetirom as part of NASH care, and considering autoimmune liver disease is typically part of evaluation for diagnosing NASH. Thus, we can support approval if efficacy is established and supports a favorable benefit versus risk. However, there should be labeling for this DILI risk, and post-market research plans for DILI detection may be appropriate.

V. Recommendations

1. We would not hold up approval based on the three liver injury cases if efficacy is established and supports a favorable benefit versus risk.
2. Should resmetirom be approved, we will work with our parent division (DHN) and its primary reviewers to determine appropriate labeling for proper use and indication as well as liver injury risk. We can also provide advice on possible post-market research and surveillance needs.

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[13] Barritt AS, et al. Assessment of Hy's Law in the Drug-Induced Liver Injury Network (DILIN). *Hepatology*. 2022; 76:s1439.

Abbreviations:

AIH: autoimmune hepatitis
ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
ANA: anti-nuclear antibody
ASMA: anti-smooth muscle antibody
AST: aspartate aminotransferase
CPK: creatinine phosphokinase
CT: computerized tomography
DB: direct bilirubin
DI-ALH: drug induced autoimmune like hepatitis
DILI: drug-induced liver injury
GB: gallbladder
GGT: gamma-glutamyl transferase
ID: identification
INR: international normalized ratio
IP: investigational product
LDH: lactate dehydrogenase
MRI: magnetic resonance imaging
NASH: non-alcoholic steatohepatitis
MASH: metabolic dysfunction associated steatohepatitis
PBC: primary biliary cholangitis
TB: total bilirubin
ULN: upper limit of normal
US: ultrasound

Addendum: Evaluation of sponsor response to information request.

DHN sent an information request (IR) for more data on case (b) (6). The Sponsor responded on Dec 7, 2023,[14] and we review each response below. DHN's requests are in *blue italics* below.

a. Latest clinical update for subject (b) (6) which should include liver enzymes (ALT, AST, ALP, GGT), bilirubin (direct and total), and other pertinent investigations.

The sponsor confirms that this subject had normal liver analytes as of (b) (6) (Study Day 391): ALT 33 U/L, AST 23 U/L, AP 64 U/L, TB 0.46 mg/dL. This response is adequate.

b. *ANA titer prior to treatment with resmetirom.*

Pre-treatment ANA titer was "not available" and stored serum was "out-of-stability window" for titer determination. This response is adequate.

c. *ANA titer after resolution of (b) (6) liver injury.*

The sponsor will work with contract research organization to obtain a post liver injury ANA titer. We await these data. A decline to negative or very low titer may suggest DI-ALH. This response is adequate.

d. *IgG level after resolution of (b) (6) liver injury.*

The sponsor will work with contract research organization to obtain a post liver injury IgG titer. We await these data. The sponsor suggests the "IgG values were never significantly changed from baseline or elevated at any time." We disagree. The IgG level increased with each liver injury rising to an abnormal 1770 mg/dL (ULN 1600 mg/dL) which is 1.11 x ULN garnering two points on the simplified autoimmune hepatitis (AIH) score.[15] This response is adequate.

e. *HLA analysis for autoimmune hepatitis (AIH) HLA associated haplotypes.*

The sponsor "will work with an HLA-licensed contract research organization to analyze common alleles associated with AIH in this patient and provide FDA with these data when available." This response is adequate.

f. *Comparative, unblinded central reading of all three liver biopsies if not done already. If more than one liver histopathologist was involved in the NDA's*

[14] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - Cover Letter 12/07/2023 - Response to Clinical Information Request

[15] Hennes EM, et al. Simplified Criteria for the Diagnosis of Autoimmune Hepatitis. *Hepatology*. 2008; 48:169-76.

primary outcome determination, then these pathologists should come to consensus on histologic readings for this case. Provide these consensus readings for this case.

Study MDL-3196-14 did not have a central pathologist. The screening biopsy that disqualified the subject from Study MGL-3196-11 was read by a second pathologist (Path B) who concurred with the initial read (Path A). Biopsy #3 done during MDL-3196-14 on (b) (6), will be digitalized, but it is unclear if it will be over-read by another liver histopathologist. Biopsy #4 was of "inadequate, despite multiple attempts to get suitable tissue and will not be reviewed." It is not clear to the DILI Team why slides from any biopsy that produced a pathologist's report, albeit limited by tissue size, cannot be digitalized for over-read. Re-cuts of tissue should not be necessary if preserved slides are obtained. We believe the making and storing of stained slides are standard of practice. Therefore, this response is inadequate or needs clarification.

The sponsor also provided an Introduction and 73 pages of "Supplemental Information" including an updated narrative, tables of laboratory results, imaging reports and histology summary statements.[16] Data from the transplant center and subsequent follow-up were included, but no original pathology reports were sent. We updated our review of the case in the **Appendix** based on this additional data, but still consider Subject (b) (6) as having probable DI-ALH.

Overall, the sponsor makes two arguments to exonerate resmetirom. We disagree with both arguments and disagree with the Investigator's overall opinion that the "Hepatitis acute x 2" were "NOT RELATED" to resmetirom.[17]

1. In the Introduction, the Sponsor suggests DI-ALH in 2019, well before study entry, "cannot be entirely ruled out as a cause autoimmune-related DILI" given the subjects history of "self-medication, including herbal medications and dietary supplements."[18] We believe this information supports probable DI-ALH due to resmetirom because there was no specific medication or HDS identified and taken by the patient, pre-study and during the study. However, the patient did have a positive rechallenge with resmetirom. The history of possible prior DI-ALH may suggest a susceptibility to this type of injury from xenobiotics, thus supporting or neutral for DI-ALH due to resmetirom but does not exonerate it.

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[16] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#5)
[17] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#13)
[18] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#3)

2. The sponsor argues that the second liver injury was "consistent with acute cholecystitis triggering increased hepatic and biliary inflammation in a patient with underlying autoimmune biliary process."[19] The sponsor provides a reference for this hypothesis. We reviewed their argument and the reference. We firmly disagree for the following reasons:

(a) The reference provided describes a patient with cholecystitis *and common bile duct stones,* but no autoimmune features.[20] Subject (b) (6) did *not* have common duct stones based on one CT, two MRIs and one ultrasound (US). Subject (b) (6) had autoimmune features on biopsy and serologies. Therefore, this reference has no relevance to Subject (b) (6). Elevation in aminotransferases in the 1000-2000 U/L range are described *with common bile duct stones*,[21],[22],[23] but *not* with cholecystitis alone. Indeed, one retrospective study of 183 cholecystitis cases suggest aminotransferase elevations are modest with cholecystitis alone (mean 119 U/L, maximum of 616 U/L).[24] Subject (b) (6) had an ALT of over 3000 U/L. Moreover, TB elevations are modest with cholecystitis alone (mean 1.5 mg/dL, maximum of 9.3 mg/dL). Subject (b) (6) had peak TB was 15.3 mg/dL. Therefore, Subject (b) (6)'s liver analytes are extreme outliers for cholecystitis alone, and we know of no data to support induction of autoimmune hepatitis flare with cholecystitis, were it present.

(b) We do not think this subject had cholecystitis. The subject had no fever, leukocytosis, abdominal pain, or tenderness making acute or chronic cholecystitis with such severe liver enzyme and TB elevations highly unlikely.

(c) Ultrasound (US) is better for the diagnosis of cholecystitis compared to CT,[25] and subject (b) (6)'s US did not diagnosis cholecystitis. US's performance is enhanced by the technician and radiologist consideration of abdominal tenderness from the US transducer (i.e., Murphy's Sign). Compared to CT, US has better positive (75% vs. 50%) and negative predictive values (97% vs.

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[19] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#13)

[20] Fatima H, et al. Acute Severe Transaminitis as a Unique Presentation of Chronic Cholecystitis. *Cureus*. 2021; e16102. DOI: 10.7759/cureus.16102: 1-7.

[21] Nathwani RA, Kumar SR, Reynolds TB, Kaplowitz N. Marked elevation in serum transaminases: an atypical presentation of choledocholithiasis. Am J Gastroenterol. 2005; 100:295-298.

[22] Fortson WC, et al. Marked elevation of serum transaminase activity associated with extrahepatic biliary tract disease. *J Clin Gastroenterol*. 1985; 7:502-505.

[23] Tetangco EP, et al. Markedly Elevated Liver Enzymes in Choledocholithiasis in the absence of Hepatocellular Disease: Case Series and Literature Review. *J of Inv Med High Impact Case Reports.* 2016; 1-3. DOI: 10.1177/2324709616651092.

[24] Chang CW, et al. Acute transient hepatocellular injury in cholelithiasis and cholecystitis without evidence of choledocholithiasis. *World J Gastroenterol*. 2009; 15:3788-3792.

[25] Shakespear JS, at al. CT Findings of Acute Cholecystitis and Its Complications. *AJR*; 194:1523-9

89%).[26] Thus, the subject's negative ultrasound would have a negative predictive value of 97% versus the CT's positive predictive value of just 50%, particularly in the absence of clinical findings discussed in item (b) above. Imaging findings of gallbladder wall thickening by CT or US can be nonspecific and associated with hepatitis of varying etiologies including DILI.

(d) If Subject (b) (6) had severe liver injury due to cholecystitis, then she should have had a cholecystectomy. She was transferred to a liver transplant center and was evaluated for four days as an inpatient. Such centers typically have more liver expertise compared to non-transplant hospitals. The center did not recommend cholecystectomy, and in fact, thought DILI was most likely.

Overall, the clinical presentation, course, objective data, and external opinion at a transplant center do not support a diagnosis of cholecystitis.

[26] Harvey RT, Miller WT Jr. Acute biliary disease: initial CT and follow-up US versus initial US and follow-up CT. *Radiology* 1999; 213:831–836.

Appendix: Structural formulas, three Case Summaries and non-clinical data

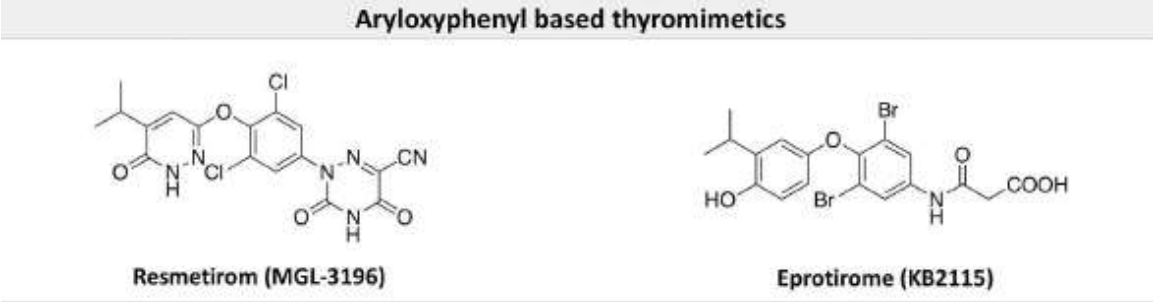

Figure A: Chemical structures of eprotirome and resmetirom.[27]

1. Case [redacted] (Study MGL-3196-14):

Summary: This is a 60-year-old female, white, with MASH who developed elevated aminotransferases approximately 57 days after starting resmetirom (unblinded). Initial dose was 80 mg/day. At baseline, the subject's BMI was 44.8 kg/m2. Relevant medical history, besides MASH, included hyperlipidemia, hypertension, and coronary atherosclerosis. Alcohol history was one to two beers a month.

On [redacted] (Day -482), a liver biopsy #1 did not show significant steatosis but did show "portal hepatitis" without interface activity, and "form frustre" of autoimmune hepatitis or DILI were considered. (The reason for the biopsy being done was not given.) ANA and AMA were "elevated," but concurrent medications relevant to DILI risk were nil. On [redacted] (Day -48), a second liver biopsy #2 was notable for 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." With that biopsy, the subject went on through study screening with baseline ALT, AST, and TB were 35 U/L, 23 U/L, and 0.4 mg/dL, respectively, and [redacted] (Day 1). ALP was not provided but graphic suggests a level around 100 U/L to 150 U/L (**Figure A**).

The subject started resmetirom at 80 mg/day on [redacted] (Day 1). No clinical events were reported until [redacted] (Day 57), when ALT, AST, and TB were 236 U/L, 123 U/L, and 0.6 mg/dL, respectively (ALP was not provided but graphic suggests a level around 100 U/L to 150 U/L). No symptoms were mentioned. There was no mention of study drug change. By [redacted] (Day 61), ALT, AST, AP, and TB were 355 U/L, 176 U/L, not provided (~100 U/L), and 0.6 mg/dL, respectively. Still no symptoms were mentioned. But the study drug was held on [redacted] (Day 64). Thereafter, liver enzymes fell but then increased again to peak on [redacted] (Day 103), ALT, AST, AP, and

[27] Saponaro F, et al. Selective Thyroid Hormone Receptor-Beta (TR-β) Agonists: New Perspectives for the Treatment of Metabolic and Neurodegenerative Disorders. Front Med. 2020; 7:1-14 https://doi.org/10.3389/fmed.2020.00331

TB were 400 U/L, 212 U/L, not provided (~100 U/L), and 0.6 mg/dL, respectively (**Figure A**). At the time of this first injury, ANA was positive at >1:2560 without previous baseline value. AMA was also positive (135 U; ULN=20) but retrospective testing of baseline serum was AMA positive at 120 U. IgG was 1310 mg/dL compared to 1250 at baseline (ULN = 1600). At the time of injury, ASMA was indeterminate; anti-SLA and anti-LKM were both negative. No viral serologies or imaging results provided. However, liver biopsy #3 was done on (b) (6), (Day 124, 60 days off drug). It showed no NASH, but mild portal inflammation with rare plasma cells. The findings were "no evocative of active autoimmune disease." There was "no interface hepatitis." Nevertheless, the biopsy did "not favor DILI but most probably an autoimmune disease."[28]

By (b) (6) (Day 197), her ALT and AST were back to baseline, but resmetirom restart was delayed until (b) (6) (Day 253) due to COVID-19 pandemic delays. She started CoQ-10 for "cardiac health" on (b) (6) (Day 265) but no other new agents mentioned. She did well until (b) (6) (Day 274) when she developed non-serious dyspepsia and diarrhea. She stopped the CoQ-10. No liver analytes were checked until (b) (6) (Day 281; Day 28 for rechallenge), when her ALT, AST, AP, and TB were 3226 U/L, 2429 U/L, 140 U/L (ULN = 149) and 10.9 mg/dL (DB 8 mg/dL). WBC was 6.7 x10^3/ul and remained normal throughout this liver injury.[29] The highest AP by multiples of ULN was 1.1 (127 U/L; ULN 116) by central lab.[22] By then she had fatigue and loss of appetite, but no fever, abdominal pain, or tenderness ("completely benign abdominal examination"). Resmetirom was stopped that day (Rechallenge Day 28). For this second liver injury evaluation testing was robust, and included negative acute serologies for HAV, HBV, HEV, CMV, SARS-CoV2 and EBV. HCV antibody and HCV RNA were negative. Autoimmune markers were positive for ANA (>1:1250) and AMA again. IgG level was now elevated at 1770 mg/dL (ULN = 1600). CT with IV contrast ((b) (6), Day 281) showed gallstones with GB wall thickening, pericholecystic fluid without duct dilation with "high suspicion of acute cholecystitis." There was no mention of GB hyperenhancement. MRI ((b) (6) Day 283) showed "no intra or extrahepatic biliary duct dilatation. No filling defects. There is 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."[30] Transjugular liver biopsy (**liver biopsy #4**, (b) (6), Day 285, rechallenge Day 32) was a small, showing mixed mild to moderate portal inflammation with occasionally plasma cells and stage 0 fibrosis. Narrative read the following: "Obviously it is

[28] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#15)
[29] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#66)
[30] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#33)

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?)."[31] There was no mention of concerns for duct obstruction on histology. US ((b) (6), Day 292) showed the gallbladder to be "thickened due to nondistended state." There was no mention of bile duct dilation or cholecystitis. No cholangiogram was done.

An (b) (6) (Day 292, Day 39 of rechallenge), the subject was transferred to a liver transplant center where hepatology felt the "elevated liver enzymes – likely severe DILI as supported by outside liver biopsy."

No transplant was needed. ALT and AST fell by 50% in about five days, but TB remained elevated in the 15-16 mg/dL range until it began to fall several days later. No immunosuppression was given and the subject was discharge to home. Eventually liver analytes returned to normal by (b) (6) (Day 340; Day 87 after re-challenge).

[31] NDA217785 (217785 - 0042 - (42) - 2023-12-07 - ORIG-1 /Clinical/Response To Information Request) - 1.11.3 Clinical Information Amendment - Response to FDA Request for Information dated 12/05/2023 (#21)

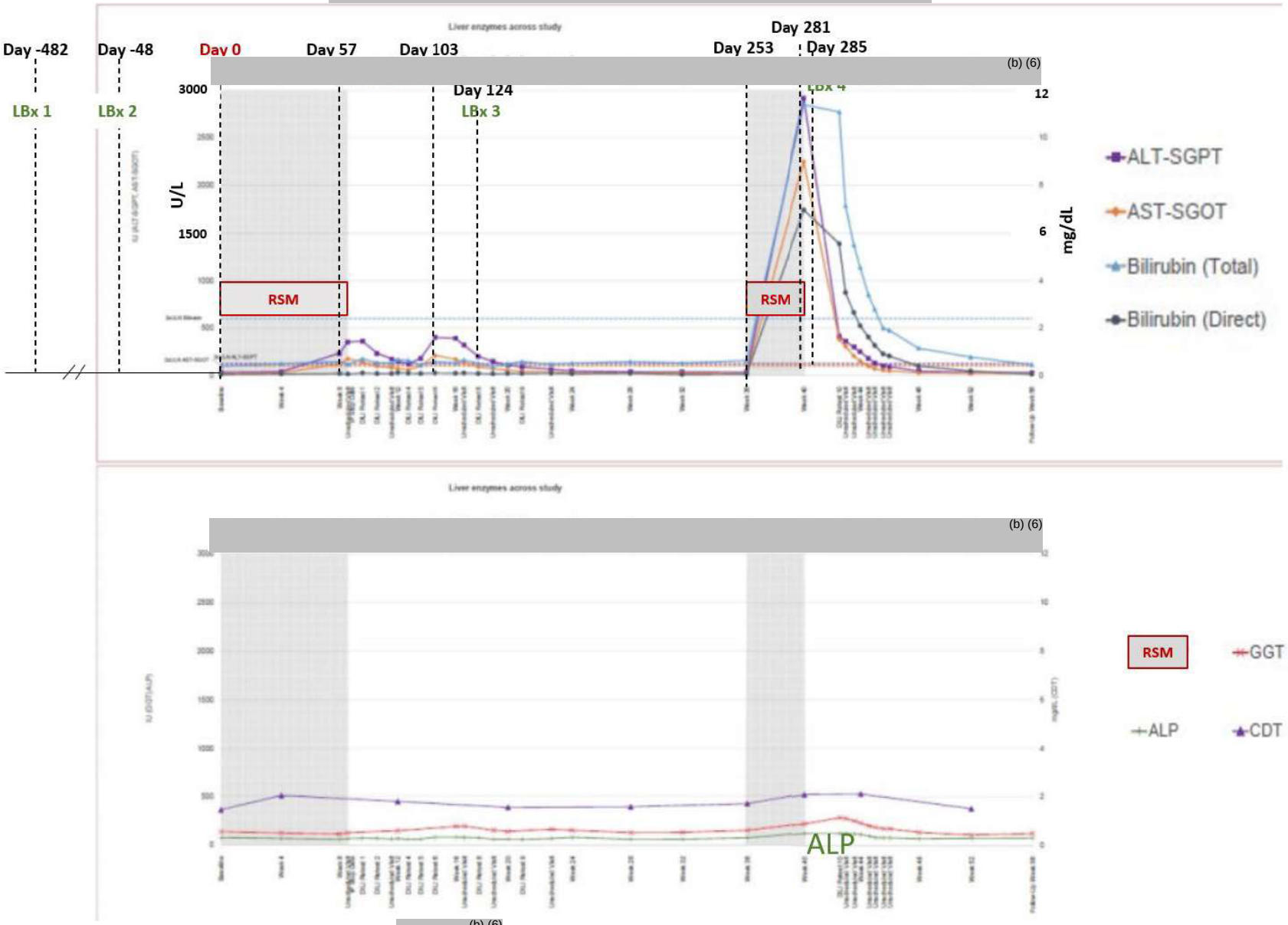

Figure B: Liver analytes over time for Case (b) (6)[32] RSM = resmetirom

[32] Adapted from NDA217785 (217785 - 0003 - (3) - 2023-07-14 - ORIG-1 /Multiple Categories/Subcategories) - MGL-3196-14 - 14 Tables, Figures, and Graphs (#3479)

2. Case [redacted] (Study MGL-3196-14): This is a 78-year-old female, white, with NASH related cirrhosis who developed elevated aminotransferases approximately 140 days after starting study drug (unblind, resmetirom). At baseline, the subject's BMI was not provided. Relevant medical history, besides the target disease, included Childs A (CP 5) and MELD 8 status for her cirrhosis. Alcohol history was not provided. Concurrent medications relevant to DILI risk were nil. The subject's ALT, AST, AP, and TB were 48 U/L, 51 U/L, 85 U/L, and 0.73 mg/dL, respectively. Her IgG level was mildly elevated at 1730 mg/dL (ULN 1600); other immunoglobulin levels were normal; AMA, ASMA, anti-LSA were negative. No ANA data were provided.

The subject started resmetirom at 80 mg/d on [redacted] (Day 1). On [redacted] (Day 83), the dose was decreased to 60 mg/d. No reason for the dose decrease was provided. The study protocol does not have dose reduction built in.

On [redacted] (Day 141), ALT, AST, AP, and TB were 148 U/L, 193 U/L, 143 U/L and 1.39 mg/dL, respectively. No symptoms were mentioned. The study drug was stopped on [redacted] (Day 142). Thereafter, liver enzymes and TB remained elevated in the injury onset range for four months, but then fell (**Figure B**). 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 was result was not provided.

On [redacted] (Day 230), a diagnosis of autoimmune hepatitis (AIH) was made. However, there was no mention of a liver biopsy. Still no symptoms were mentioned, and no treatment was immediately rendered. Immunosuppression started on [redacted] (Day 250), azathioprine 50 mg/d for two weeks followed by mycophenolate mofetil 500 mg BID which is “ongoing.” By the time of immunosuppression start, liver enzymes had already fallen by approximately 60-70% of peak levels (**Figure B**). Thereafter, liver enzymes and TB fell back to baseline by [redacted] (Day 281). No other evaluation test information was provided. Liver imaging was not mentioned. It is unclear if the subject is still on immunosuppressive medications.

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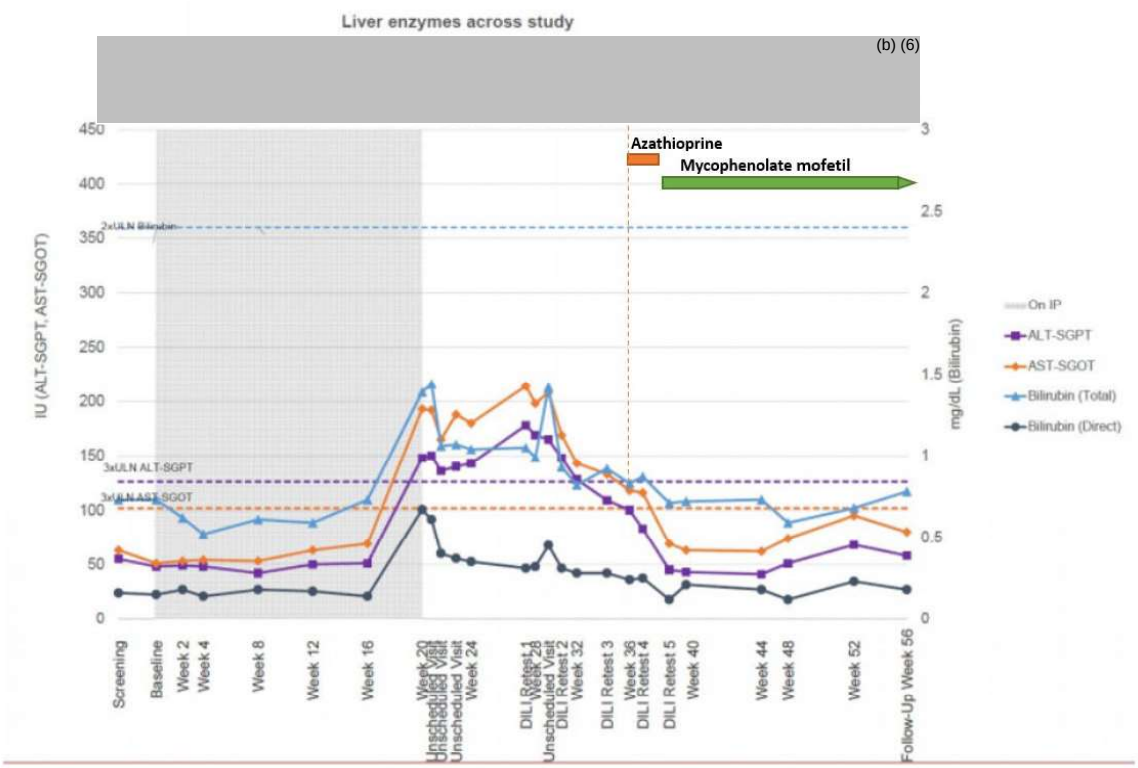

Figure C: Liver analytes over time for Case (b) (6).[33] Resmetirom dosing in gray.

3. Case (b) (6) (Study MGL-3196-11):

Summary: This is a 46-year-old female, white, with MASH (Stage 1 fibrosis) who developed elevated aminotransferases approximately 110 days after starting resmetirom (unblinded). Initial dose was 80 mg/day. At baseline, the subject's BMI was 27 kg/m^2. Relevant medical history, besides the target disease, included diabetes and being overweight. Alcohol history was not provided. Concurrent medications relevant to DILI risk were nil. The subject's ALT, AST, AP, and TB were 39 U/L, 26 U/L, 62 U/L, and 0.42 mg/dL, respectively.

The subject started resmetirom at 80 mg/d on (b) (6) (Day 1). She did well with stable liver analytes through (b) (6) (Day 56). On that day resmetirom "PK" was 253 ng/ml. Also, at that time, she was diagnosed with grade 2, stage 1 "indolent multiple myeloma" (MM). No further liver analytes were provided until (b) (6) (Day 110), when ALT, AST, AP, and TB were 578 U/L, 448 U/L, 64 U/L and 1.1 mg/dL, respectively. The subject had no symptoms. There was no mention of resmetirom dose change, but on that day, resmetirom PK was 6020 ng/ml. By (b) (6) (Day 112), ALT, AST, AP, and TB were 813 U/L, 777 U/L, 80 U/L and 1.0 mg/dL, respectively. The subject still had no symptoms. Resmetirom was stopped. Evaluation testing ensued (see below). Thereafter, liver analytes improved with >50% decline from peak for ALT, AST, occurring

[33] NDA217785 (217785 - 0003 - (3) - 2023-07-14 - ORIG-1 /Multiple Categories/Subcategories) - MGL-3196-14 - 14 Tables, Figures, and Graphs - Addendum (#1068)

within four to twelve days (**Figure D**). Return to baseline occurred within 28 days after peak values.

Evaluation testing included negative acute serologies for HBV and CMV. Anti-HCV antibody was also negative. HAV IgM was inconclusive at 21.7 (<18 negative; >22 positive). EBV results were equivocal with an "atypical serology profile that may correspond to past EBV infection with loss of anti-EBNA IgG or recent infection without detection of anti-VCA IgM."[34] HCV RNA testing was not done. Autoimmune markers were negative for ASMA, but no ANA result was provided. IgG level was normal. Liver imaging was not mentioned.

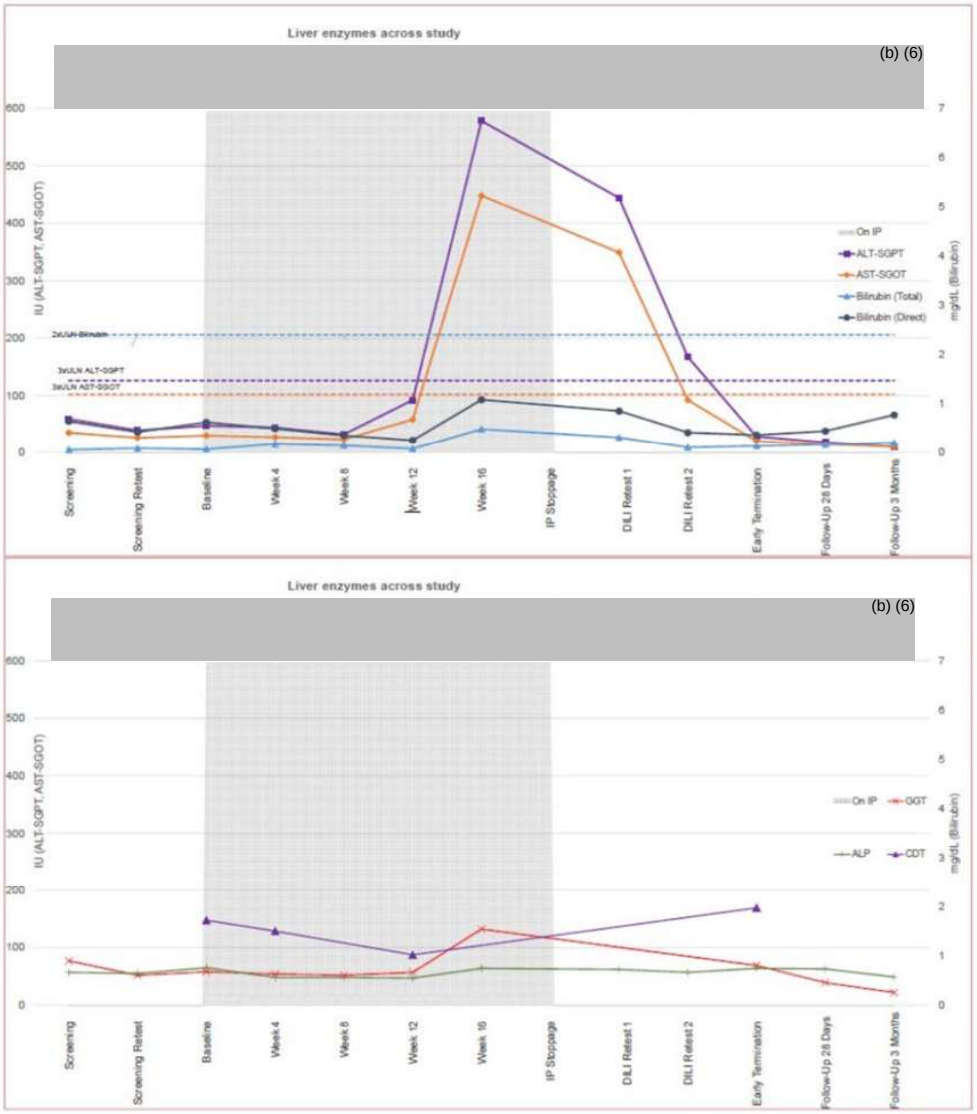

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Figure D: Liver analytes over time for Case (b) (6).[35] Resmetirom dosing in gray.

[34] NDA217785 (217785 - 0003 - (3) - 2023-07-14 - ORIG-1 /Multiple Categories/Subcategories) - MGL-3196-11 - 14. Tables, Figures and Graphs (#2388)

[35] NDA217785 (217785 - 0003 - (3) - 2023-07-14 - ORIG-1 /Multiple Categories/Subcategories) - MGL-3196-11 - 14. Tables, Figures and Graphs (#2389)

4. Case [redacted] (Study MGL-3196-11):

Summary: This is a 69-year-old male, white, with who developed elevated liver enzymes and bilirubin approximately 765 days after starting resmetirom. Initial dose was 100 mg/day. At baseline, the subject's BMI was not provided. Relevant medical history, besides the target disease, included diabetes, hypertension, hyperlipidemia, aortic atherosclerosis, and splenomegaly. Alcohol history was not provided. Concurrent medications relevant to DILI risk included atorvastatin (no dates given). No mention of herbals or dietary supplements. The subject's baseline ALT, AST, AP, and TB were not provided.

The subject started study drug (resmetirom) at 100 mg on [redacted] (Day 1). No further events or labs related to the liver were provided until [redacted], (Day 730), ALT, AST, AP, and TB were 22 U/L, 18 U/L, 61 U/L, and 0.6 mg/dL, respectively.

On [redacted], (Day 762), the subject fell, but did not seek medical care immediately. On [redacted], (Day 765), ALT, AST, AP, and TB were up mildly at 66 U/L, 115 U/L, 119 U/L and 0.7 mg/dL, respectively. Still no liver related symptoms were mentioned. There was no mention of study drug change. He presented later to his PCP on [redacted] (Day 792) with jaundice; ALT, AST, AP, and TB were 204 U/L, 291 U/L, 1255 U/L and 16.4 mg/dL, respectively. INR was 1.5. In retrospect he had had one month of fatigue and weight loss, but no mention of fever. Study drug was stopped that day. He was admitted and went on to be diagnosed with Hodgkin's lymphoma with diffuse retroperitoneal, cervical and mediastinal lymphadenopathy (biopsied), but no ductal dilation or obstruction by ERCP. Liver biopsy 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…. Trichrome stains showed septal and bridging fibrosis (cirrhosis), … 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. Unclear what if any chemotherapy was rendered. He was later hospitalized with a GI bleed and hypotension. He died on [redacted].

Evaluation testing included a positive AMA. Otherwise, no viral tests were provided. Autoimmune markers were not done or provided other than the AMA. IgG level was not checked. Liver imaging by CT, PET and US showed no obvious etiology for liver injury.

The applicant did not provide a table or line graph of laboratory results.

Table A: Summary of toxicology data[36]

Item	Finding
In Vitro Studies	
Major CYPs or UGTs	CYP2C8
Reactive metabolites (i.e., glutathione trapping)	Low potential for reactive metabolite formation
Mitochondria studies/inhibition	Not assessed
Time dependent inhibition	No time-dependent inhibition on the common CYPs
LogP (lipophilicity) values >3 associated with increased DILI risk	3.6
Covalent binding	Low potential for covalent binding
Transporter (BSEP or MRP2 inhibition)	Weak BSEP inhibition, No for MRP2
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	ALT increase seen in mouse studies. ALP increase seen dog studies
Liver histopathology findings (animal species)	Single cell necrosis in mice. Multi-focal areas of mixed inflammation and necrosis in rats; cholestasis and bile duct hyperplasia in dogs.

[36] Table made by DILI Team

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/s/

PAUL H HAYASHI
03/11/2024 10:44:01 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 9, 2024
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 217785
Product Name, Dosage Form, and Strength:	Rezdiffra (resmetirom) tablets, 60 mg, 80 mg, 100 mg
Applicant/Sponsor Name:	Madrigal Pharmaceuticals, Inc.
TTT ID #:	2023-5596-2
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 1, 2024 for Rezdiffra. The Division of Hepatology and Nutrition (DHN) requested that we review the revised container labels and carton labeling for Rezdiffra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to an information request (IR) from DHN sent via email communication on January 26, 2024 and the Proprietary Name Conditionally Acceptable letter issued on February 1, 2024.

2 CONCLUSION

The Applicant implemented all of the recommendations and we have no additional recommendations at this time.

6 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

SUSAN HAKEEM
02/09/2024 09:02:13 AM

VALERIE S VAUGHAN
02/09/2024 09:05:28 AM

Clinical Inspection Summary

Date	1/31/2024
From	Glenn Mannheim, M.D., Physician Min Lu, M.D., M.P.H., Lead Physician Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Taiye Adedeji, Sr Regulatory Health Project Officer Ashish Dhawan, M.D., Clinical Reviewer, DHN Gerri Baer, M.D., Lead Physician, DHN George Makar, M.D., Associate Director, DHN Nikolay Nikolov, M.D., Office Director, CDER Judy Racoosin, M.D., Deputy Director Safety, DHN
NDA #	217785
Applicant	Madrigal Pharmaceuticals, Inc.
Drug	Resmetirom (MGL-3196)
NME	Yes
Proposed Indication	Treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis
Review Priority	Priority
Consultation Request Date	8/29/2023
Summary Goal Date	2/14/2024
Action Goal Date	3/14/2024
PDUFA Date	3/14/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators (Drs. Moussa and Neff) and the sponsor (Madrigal Pharmaceuticals, Inc., Conshohocken, PA) were inspected for Studies 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 sponsor appear acceptable in support of this NDA.

II. BACKGROUND

This NDA is for the use of MGL-3196 (Resmetirom), a liver-directed, oral, once-daily, thyroid hormone receptor (THR) selective agonist for the proposed treatment of non-alcoholic steatohepatitis (NASH), a severe form of nonalcoholic fatty liver disease (NAFLD).

MGL-3196 (Resmetirom) for the treatment of non-alcoholic steatohepatitis (NASH) was assessed in three Phase 3 efficacy studies (MGL-3196-11, MGL-3196-14 and MGL-3196-18).

MGL-3196-11

This was a multinational, randomized, double-blind, placebo-controlled study in adult patients with NASH and fibrosis. Study patients were randomized in a 1:1:1 ratio to receive resmetirom 80 mg, resmetirom 100 mg, or matching placebo orally once daily for up to 54 months. The interim primary efficacy analysis was planned and performed at Week 52 to support the NDA submission.

Dual primary objectives at Week 52 analysis were to determine the effect of once-daily oral 80 or 100 mg resmetirom versus matching placebo: 1) on NASH, as measured by the resolution of NASH associated with at least a 2-point reduction in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) and without worsening of fibrosis by liver biopsy after 52 weeks of treatment (Week 52 Primary Endpoint) in the Week 52 Liver Biopsy; and, 2) on histological improvement from baseline demonstrated by at least a 1-point improvement in fibrosis (NASH Clinical Research Network [CRN] system) by liver biopsy with no worsening of NAS (total of 3 NAS components: ballooning, lobular inflammation, and steatosis) at Week 52. For F1B patients, a 1-point improvement in fibrosis would be a change to F0. For F2 patients, a 1-point improvement in fibrosis would be a change to F1A or F1C (a change of F2 to F1B is not considered a 1-point improvement). A "Fibrosis Responder "was defined as at least a 1-point reduction in fibrosis stage with no worsening of NAS as compared with the baseline liver biopsy.

The key secondary objective at Week 52 is to determine the effect of once-daily oral 80 or 100 mg resmetirom versus matching placebo on the percent change from Baseline at 24 weeks in directly measured low-density lipoprotein cholesterol (LDL-C).

The study enrolled 1050 subjects (352, 80 mg resmetirom; 349, 100 mg resmetirom maralixibat and 349 placebo). Study subjects were from 14 countries.

The study was initiated on June 20, 2019, and the date of data cut-off for the submitted interim study report was July 31, 2022. The study is ongoing.

MGL-3196-14

This was a 52 week, double-blind, placebo-controlled study with an open-label arm in patients with NAFLD (presumptive NASH, not non-alcoholic fatty liver) and a parallel-enrolling open-label arm with patients with compensated NASH cirrhosis (Child Pugh-A). Participants were randomized 1:1:1:1 to receive either daily 100 mg, 80 mg, placebo, or open-label 100 mg resmetirom.

The primary objective was to evaluate the safety and tolerability of once-daily, oral resmetirom (80 or 100 mg) versus matching placebo. The key secondary objectives were to determine the

effect of once-daily, oral (80 or 100 mg) resmetirom versus matching placebo on the percent change from baseline to Week 24 in: 1) low-density lipoprotein cholesterol (LDL-C); 2) apolipoprotein B (ApoB); and, 3) triglycerides in those with baseline levels > 150 mg/dL; and, to Week 16 in hepatic fat fraction by MRI-PDFF; and, after 52 weeks CAP scores.

The study enrolled 1143 subjects, of which 972 were randomized to the three double-blind arms (100 mg resmetirom [n=325],80 mg resmetirom [n=327], or placebo [n=320]) and 171 patients were randomized to the 100 mg OLNC arm. One subject in the double-blind 100 mg resmetirom group and 2 subjects in the placebo group were randomized but did not receive study drug as study sites were closed due to COVID-19.

Study subjects were from 79 US sites. The study was initiated on December 16, 2019, which the last subject completed on December 13, 2021.

MGL-3196-18

This was a 52-week, open-label extension study, with a double-blind lead-in, in patients with NAFLD. This was a roll-over study for patients who completed Study MGL-3196-14. It also included screen failures from MGL-3196-11, MGL-3196-19 [(CP-A/B (score <8) NASH cirrhosis)] or de novo patients who did not previously screen for a Phase 3 resmetirom clinical trials.

The primary objective was to evaluate the safety and tolerability of once-daily, oral resmetirom for 52 weeks.

The study analyzed 615 subjects. Study subjects were from 71 US sites. The study was initiated on July 09, 2021, with the study ongoing with open enrollment. The data cutoff for the interim report was September 30, 2022.

III. RESULTS (By Site):

1. **Sam E. Moussa, M.D./Site # 116**
   2585 North Wyatt Drive
   Tucson, AZ 85712
   Inspection Dates: 11/13-11/17/2023

   This is the second FDA inspection of this clinical investigator. A previous inspection concluded on 11/21/2019 with no regulatory violations noted. Twenty-five subjects were reviewed for each of the three studies.

A total of 168 subjects were screened for Study 3196-11; and, of these, 57 subjects were enrolled, of which, 15 subjects withdrew consent. The first subject was randomized and received study drug on 07/10/2019, and the last subject was randomized on 03-06-2023. The study was still ongoing and closed to enrollment at the time of inspection. There were 10 serious AE's (SAE's), and 2 deaths. All were determined by the investigator as being unrelated to the study drug.

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. The first subject was randomized and received study drug on 01/15/2020. The study closed at this stie on 06/15/2023. There were 4 SAE's. No deaths occurred.

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 12/22/2021 and the study was still ongoing at the time of inspection. There were 2 SAE's. No deaths occurred.

The inspector reviewed the case history records of 25 subjects in each study. This included the informed consent forms (ICFs), case report forms (CRFs), medical records, laboratory reports, radiology and ultrasound reports, and electrocardiogram (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 sponsor, monitors, and institutional review board (IRB); and regulatory records, including FDA 1572s and financial disclosure records.

For Study 3196-11, liver biopsy for the primary efficacy endpoint was done at the site with provided materials and training. The site sent unstained liver biopsy slides to (b) (4) to be stained. Blinded glass slides from biopsies for Week 52 were sent in batches to two central pathologists for reading. The biopsy scores were not available at site to verify at the time of the inspection. The study was ongoing.

Data discrepancies were identified between source documents and eCRFs regarding relatedness to study drug for six adverse events (AEs) in four subjects in Study 3196-14. Data discrepancies consisted of: AE of diarrhea related on AE log but not related in eCRF (Subject (b) (6)); AE of worsening nausea, not related on AE log, but related in eCRF (Subject (b) (6)); AEs of pseudomonas infection, community acquired pneumonia, and sepsis, listed as possibly being related on AE log, but not related in the eCRF (Subject (b) (6)); and, AE of worsening headache not related on AE log but related in eCRF (Subject (b) (6)). The eCRF data matched the FDA data listings for these AE relatedness data discrepancies.

At the end of the inspection, the inspector discussed data discrepancies in AE relatedness between source records & 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.

Reviewer Comments: Although attribution of the above AEs should have been correctly reported, this may not have significant impact on the safety profile of the study drug.

2. Guy W. Neff, M.D./Site # 172
6230 University Parkway, Suite 203
Sarasota, FL 34240
Inspection Dates: 10/30-11/03/2023

This was the first FDA inspection for Dr. Neff. 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 IRB documentation, subject records, financial disclosures, investigational product (IP) controls and accountability, the monitoring of the studies, informed consents, signed investigator agreements, adverse event reporting, and concomitant medication.

For Study 3196-11, liver biopsy for the primary efficacy endpoint was done at the site with provided materials and training. Blinded glass slides from biopsies for Week 52 were sent in batches to two central pathologists for reading. The site does not have access to the scores.

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.

Reviewer Comments: Although the SAE should have been reported timely, this delayed reporting was isolated and should not have any impact on the safety profile of the study drug because it was eventually reported.

3. Madrigal Pharmaceuticals Inc
400 Tower Drive
200 Barr Harbor Drive, Suite 200
Conshohocken, PA 19428
Inspection Dates: 11/20-11/30/2023

There is no prior inspection history for Madrigal Pharmaceutical 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).

Sponsor 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, CRO 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 adverse events. Madrigal was responsible for submitting expedited safety events to FDA. The procedures of safety reporting were reviewed.

For Study 3196-11, the sponsor provided the biopsy workflow sheet during the inspection. The liver biopsy was done at the site with provided materials and training. Blinded glass slides from biopsies for baseline and Week 52 were sent in batches to two central pathologists for reading. Neither central reader would have information on subject or MGL IDs. Reports with their results was uploaded to the (b) (4) portal in separate folders based on who read the slides. The reports in the portal would be retrieved by (b) (4)'s Data Management team for data entry; a separate database was created for reads. The transcribed data was submitted to (b) (4) (unblinded) for statistical analysis. The procedures were reviewed during the inspection. The sponsor did not have access to the scores at the time of inspection to verify the primary efficacy endpoint for sites. The study was ongoing.

Overall, the sponsor's oversight and monitoring for the three studies appeared adequate.

{See appended electronic signature page}

Glenn Mannheim, MD
Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CONCURRENCE:

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Branch Chief
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cc:

Central Document Room/NDA 217,785
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Division of Hepatology & Nutrition/Associate Director/George Makar
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OSI/DCCE/GCPAB/Physician/Glenn Mannheim
OSI/GCPAB Program Analyst/Yolanda Patague
OSI/GCPAB Program Analyst/Loreto-Corazon Lim

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 23, 2024

To: Taiya Adedeji, Project Manager, DHN

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for PROPRIETARY NAME (resmetirom) tablets, for oral use

NDA: 217785

In response to DHN's consult request dated August 30, 2023, OPDP has reviewed the proposed product labeling (PI) and Patient Prescribing Information (PPI) for resmetirom.

Labeling: OPDP has some comments on the proposed labeling based on the draft labeling received by electronic mail from DHN on January 11, 2024.

OPDP has no additional comments on the PPI, that was entered into DARRTS by DMPP on January 23, 2024.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 23, 2024
To:	Taiye Adedeji, PharmD Senior Regulatory Health Project Manager **Division of Hepatology and Nutrition (DHN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (resmetirom)
Dosage Form and Route:	tablets for oral use
Application Type/Number:	NDA 217785
Applicant:	Madrigal Pharmaceuticals, Inc.

1 INTRODUCTION

On July 14, 2023, Madrigal Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA)/ New Molecular Entity 217785 for TRADENAME (resmetirom) tablets for oral use. Per the Applicant, this NDA proposes an indication for the treatment of adults with non-alcoholic steatohepatitis (NASH) with liver fibrosis.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Hepatology and Nutrition (DHN) on August 30, 2023, for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (resmetirom) tablets for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (resmetirom) PPI received on July 14, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on January 12, 2024.
- Draft TRADENAME (resmetirom) Prescribing Information (PI) received on July 14, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on January 11, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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01/23/2024 09:44:33 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health PLLR Labeling Memorandum

Date: December 18, 2023 **Date consulted:** September 8, 2023

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
DPMH

Lynne P. Yao, MD, OND, Division Director
DPMH

To: Taiye Adedeji, Regulatory Project Manager (RPM)
Division of Hepatology and Nutrition (DHN)

Drug: Resmetirom tablets

NDA: 217785

Applicant: Madrigal Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling (PLLR) and Pregnancy and Lactation Related Postmarketing Requirements (PMRs)

Proposed Indication: A thyroid hormone receptor beta (THR-Beta) selective agonist for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Consult Question: "DHN requests DPMH review of proposed PLLR labeling"

INTRODUCTION

On July 14, 2023, the applicant, Madrigal Pharmaceuticals, Inc., submitted a new drug application (NDA 217785) a new molecular entity (NME) resmetirom tablets. On September 8, 2023, the Division of Hepatology and Nutrition (DHN) consulted the Division of Pediatrics and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The proposed indication for resmetirom is a thyroid hormone receptor beta (THR-Beta) selective agonist for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis. Currently, there are no approved therapies for NASH.
- Resmetirom has been granted fast track and breakthrough therapy. This NDA was also granted a rolling review on May 22, 2023. Drug development of resmetirom has been conduced under IND 122865.

Drug Characteristics[1]

- *Mechanism of action*: (b) (4)
- *Dosage and administration:* 100 mg orally once daily
- *Molecular weight*: 435.22 Daltons
- *Protein-binding:* 99%
- *Half-life:* 4.5 hours
- (b) (4)
- *Warnings and Precautions*: cholecystitis and cholelithiasis
- *Adverse reactions*: diarrhea, nausea, pruritis, vomiting, abdominal pain, constipation, and dizziness.

Condition: Nonalcoholic Fatty Liver Disease (NAFLD) and Pregnancy

- NAFLD is a spectrum of disease characterized by hepatic steatosis in the absence of excess alcohol consumption. NAFLD ranges from a more benign condition of nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), which is at the more severe. In NAFL, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is associated with lobular inflammation and apoptosis that can lead to fibrosis and cirrhosis.[2]

[1] Resmetirom (NDA 217785) proposed package insert.
[2] Chopra S. et al, "Management of nonalcoholic fatty liver disease in adults." www.uptodate.com. Accessed 11/15/2023.

- Although the exact prevalence is unknown, it is estimated in the U.S. that approximately 25% of the population has NAFLD, 3-10% have NASH, and 400,000 have NASH-related cirrhosis.[3,4]
- A recent study used weighted discharge data from the US national inpatient sample to evaluate temporal trends of NAFLD in pregnancies after 20 weeks gestation and compared outcomes to pregnancies with other chronic liver disease (CLDs) or no CLD. Among 18,574,225 pregnancies, 5,640 had NAFLD and 115,210 had other, non-NAFLD CLD. Pregnancies with NAFLD nearly tripled from 10.5/100,000 pregnancies in 2007 to 28.9/100,000 in 2015. Compared to the other groups, patients with NAFLD during pregnancy more frequently experienced gestational diabetes (7-8% vs 23%), hypertensive complications (4% vs 16%), postpartum hemorrhage (3-5% vs 6%), and preterm birth (5-7% vs 9%), all p values ≤ 0.01.[5]
- A 2020 review article on fatty liver in pregnancy notes the negative outcomes associated with NAFLD are not exclusively associated with GDM. Adverse outcomes also include pre-eclampsia (adjusted RR, 6.68; 95% CI, 3.61–12.38), infants large for gestational age (adjusted OR, 4.03; 95% CI, 2.84–5.70) [26] and preterm delivery.[6]

DATA REVIEW

PREGNANCY

Nonclinical Experience[7]

In animal reproduction studies, adverse effects on embryo-fetal development occurred in pregnant rabbits treated with resmetirom at 3.5 times the maximum recommended dose during organogenesis. These effects were associated with maternal toxicity, whereas no embryo-fetal effects were observed at lower dose levels with better tolerance in pregnant rabbits. No embryo-fetal developmental effects occurred in pregnant rats treated with resmetirom or the metabolite MGL-3623. A pre- and postnatal development study in rats with maternal dosing of resmetirom during organogenesis through lactation showed a decrease in birthweight and increased incidence of stillbirths and mortality (postnatal days 1-4) at 37 times the maximum recommended dose. These effects were associated with marked suppression of maternal T4, T3, and TSH levels. Refer to the Nonclinical Review by David Joseph, PhD.

Reviewer's Comment

The Nonclinical Review Team noted no effects on postnatal development were observed at doses up to 30 mg/kg/day (7.2 times the maximum recommended dose based on AUC). Overall, the Nonclinical Review Team concluded that the animal reproductive toxicity data do not raise any major concerns for use of resmetirom during pregnancy.[6]

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[3] Estes C. et al, "Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology, 67:123-33.

[4] Dufour J.F. et al, "Current therapies and new developments in NASH," Gut 2022, 71:2123-34.

[5] Sarkar M, et al. Non-alcoholic fatty liver disease in pregnancy is associated with adverse maternal and perinatal outcomes. Journal of Hepatology 2020 vol. 73 516-522.

[6] Azzaroli F, et al, "Fatty Liver in Pregnancy: A narrative review of two distinct conditions." Expert Review of Gastroenterology & Hepatology 2020, 14:2, 127-135.

[7] DPMH email communication with Nonclinical Reviewer David Joseph, PhD, dated 11/13/2023.

Clinical Experience

Clinical Trials

Pregnant women were excluded from clinical trials with resmetirom. The applicant stated no pregnancy exposures occurred during clinical development.

The efficacy of resmetirom was evaluated based on an interim analysis at Week 52 in Trial 1 (NCT03900429), a 54-month, randomized, double-blind, placebo-controlled trial in patients with a baseline or recent liver biopsy showing NASH with fibrosis stage 2 or 3 and a NAFLD Activity Score (NAS) of atleast 4. A total of 888 patients were randomized 1:1:1 to receive placebo (n=294), resmetirom 80mg (n=298), or resmetirom 100 mg (n=296), in addition to standard of care, including standard modest lifestyle modification. Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension. Overall, the mean (SD) age at baseline was 57 (11) years, 56 (~9% of subjects were between 18-40 years, ~67% were 40-65 years, and ~24% were >65y).[8]

Reviewer's Comment
Overall, the indicated population for resmetirom is mostly comprised of ages beyond peak reproductive years. Although enrollment of females of reproductive potential was lower in the clinical trial compared to older females, it is still possible that use in pregnancy may occur. Thus, it is important to collect safety data in pregnant women exposed to resmetirom.

Published Literature

- The applicant did not perform a review of published literature.
- DPMH performed a literature search in PubMed, Embase, Micromedex[9], TERIS[10], Reprotox[11], and Briggs[12] to find any relevant articles regarding resmetirom use during pregnancy. Search terms included: "resmetirom" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No relevant articles were identified.

Reviewer's Comment
Overall, there is no available clinical data regarding resmetirom use in pregnancy to inform safety or dosing. The Clinical Review Team noted at the mid-cycle meeting that effects of uncertain clinical significance such as decreases in free T4 (FT4) and increases in sex hormone binding globulin (SHBG) were observed in clinical trials with resmetirom. DHN consulted the Division of General Endocrinology (DGE) to assist with the clinical review of resmetirom safety. DPMH discussed with the DGE Review Team (Dr. Geanina Roman-Popoveniuc and Dr. Shannon Sullivan) whether or not prescribers

[8] Source: Clinical Team Slides Internal Midcycle Meeting for Resmetirom NDA 217785.
[9]Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 10/17/2023.
[10]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 10/17/2023.
[11]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/17/2023.
[12] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide , 9th Ed. 2011.

should be informed in 8.1 Pregnancy labeling regarding potential effects of resmetirom on maternal thyroid levels or additional need for monitoring during pregnancy.[13]

The DGE Review Team noted the effect of resmetirom on thyroid function tests does not appear to be clinically significant, as small numerical changes in thyroid hormone levels were noted during the studies. The DGE Review Team does not recommend additional labeling for thyroid monitoring in pregnant women taking resmetirom for the following reasons: 1) the changes in thyroid function tests (TFTs) in euthyroid individuals taking resmetirom were minimal and generally did not result in thyroid function out of the normal ranges. Therefore, euthyroid pregnant women do not need to be monitored more frequently than non-pregnant adults taking resmetirom 2) clinical practice guidelines for management of hypothyroidism during pregnancy already recommend increased frequency of thyroid monitoring in pregnant women due to the need to adjust levothyroxine (LT4) doses during this period (in order to maintain TFTs in the pregnancy-adjusted reference range). If a hypothyroid woman on LT4 is also taking resmetirom during pregnancy, additional monitoring beyond what is already recommended in guidelines is not necessary.

Moreover, the DGE Review Team discussed their recommendations with the DHN Review Team. Considering the small, transient fluctuations in thyroid function seen in a minority of patients of no clinical significance, (b) (4) *information about changes in TFTs observed in clinical trials will be included in Section 6 of labeling* (b) (4) *Overall, the DGE Review Team concluded pregnant women taking resmetirom would not be expected to have TFTs changes any different than those observed in non-pregnant adults during clinical trials (i.e., small, transient, and not clinically significant). Thus, DGE determined that additional thyroid monitoring during pregnancy is not warranted and asserted that a statement in Section 8 is not needed.*[14]

LACTATION

Nonclinical Experience

Animal lactation studies have not been conducted with resmetirom. Refer to the Nonclinical Review by David Joseph, PhD.

Clinical Experience

Clinical Trials

Lactating women were excluded from clinical trials with resmetirom. No lactation cases have been reported.

Published Literature

- The applicant did not perform a review of published literature.

[13] DPMH email communication with DGE Review Team (Dr. Geanina Roman-Popoveniuc and Dr. Shannon Sullivan) dated 11/15/2023.

[14] DPMH email communication with Dr. Shannon Sullivan DGE Team Leader dated 12/15/23.

- DPMH performed a literature search in *Medications and Mother's Milk*[15], Micromedex[9], Reprotox[11], PubMed, and Embase to find any relevant articles related to resmetirom use during lactation. Search terms included: "resmetirom" AND "lactation" OR "breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[1]

In the rat fertility and early embryonic development study, there were no effects of resmetirom on male or female fertility, reproductive organs, or reproductive function at oral doses up to 30 mg/kg/day. Refer to the Nonclinical Review by David Joseph, PhD.

Published Literature

- The applicant did not perform a review of published literature.
- DPMH performed a literature search in PubMed, Embase, and Reprotox[11] to find any relevant articles regarding resmetirom use and effects on fertility. Search terms included: "resmetirom" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION/CONCLUSIONS

Pregnancy

Pregnant women were excluded from resmetirom clinical trials and no pregnancy exposures were reported during the clinical development program. Overall, there are no available data on the use of resmetirom in pregnancy to evaluate for a drug-associated risk of major birth defect, miscarriage, or other adverse maternal or fetal outcomes. Therefore, DPMH recommends PLLR labeling in section 8.1 Risk Summary describe the lack of available clinical data regarding resmetirom use in pregnancy and summarize the nonclinical data from animal reproduction studies. In addition, DPMH recommends including a Clinical Consideration heading regarding the risk of underlying NAFLD in pregnancy, including NASH with liver fibrosis.

Regarding pregnancy-related postmarketing requirements (PMRs), DPMH recommends issuing a PMR for a descriptive pregnancy safety study (DPSS). Currently, there are no data available to inform the safety of resmetirom use during pregnancy. While use of resmetirom in females of reproductive potential is expected to be less common than older females based on the proposed indication (NASH with liver fibrosis), exposure is still anticipated in this population including pregnant women.

Lactation

Lactating women were excluded from resmetirom clinical trials and no lactation exposure cases were reported. Overall, there are no available data regarding the presence of resmetirom in human or animal milk, the effects on the breastfed infants, or the effects on milk production. Therefore, DPMH recommends PLLR labeling in subsection 8.2 Risk Summary to describe the lack of available clinical and nonclinical data regarding resmetirom use in lactation. DPMH also recommends including the following benefit/risk statement: "the developmental and health benefits of breastfeeding should be considered

[15] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

along with the mother's clinical need for resmetirom and any potential adverse effects on the breastfed infant from resmetirom or from the underlying maternal condition."

Regarding lactation-related PMRs, DPMH issuing a PMR for a milk-only lactation study. Currently, there are no data available to inform the safety of resmetirom use during lactation. While use in females of reproductive potential is expected to be less common than older females based on the proposed indication (NASH with liver fibrosis), exposure is still anticipated in this population including lactating women. Safety data in infants exposed during lactation should be collected during the lactation study and for pregnancy cases reported in the DPSS PMR with continued resmetirom use during lactation.

Fertility

DPMH recommends omitting subsection 8.3 of resmetirom labeling. DPMH did not identify any data to suggest resmetirom use would have an adverse effect on fertility. Pregnancy testing and contraception headings will not be included.

LABELING RECOMMENDATIONS

DPMH proposed labeling recommendations for subsections 8.1 and 8.2 of resmetirom labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations below with DHN on November 20, 2023. DPMH refers to the final NDA action for final labeling.

(b) (4)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSULTATION

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 12/15/2023

FROM: Geanina Roman-Popoveniuc, MD, Medical Officer, Division of General Endocrinology (DGE)

THROUGH: Shannon Sullivan, MD, PhD – Clinical Team Leader, DGE
Naomi Lowy, MD – Deputy Director, DGE

TO: Taiye Adedeji – RPM, Division of Hepatology and Nutrition (DHN)
Ashish Dhawan, MD - Medical Officer, DHN
Gerri Baer, MD – Clinical Team leader, DHN
George Makar, MD – Deputy Director, DHN

SUBJECT: Review of the safety data associated with resmetirom for treatment of NASH (NDA 217785) with respect to thyroid function, HPA axis function, and bone metabolism.

I. Background and basis for consult

On August 15, 2023, the Division of General Endocrinology (DGE) received a consultation request from the Division of Hepatology and Nutrition (DHN) to review the safety data pertaining to thyroid function, HPA axis function, SHBG, and bone metabolism for resmetirom in the treatment of non-alcoholic steatohepatitis (NASH) (NDA 217785). The Sponsor is seeking approval of resmetirom for the treatment of noncirrhotic NASH with liver fibrosis to improve NASH severity and fibrosis. The proposed doses are resmetirom 80 mg and 100 mg tablets, administered orally once daily.

Non-alcoholic fatty liver disease (NAFLD) is a condition in which there is excessive fat accumulation in the liver.[1] NASH is the active, progressive form of NAFLD, characterized by hepatic steatosis with inflammation and hepatocyte injury with or without fibrosis. NAFLD and NASH are both associated with several comorbid conditions, including metabolic syndrome, obesity, type 2 diabetes, hypertension, dyslipidemia, hypothyroidism, and increased cardiovascular (CV) risk, including CV death. Chronic NASH leads to increased morbidity and mortality from progression of liver disease, including progression to cirrhosis, liver failure, and hepatocellular carcinoma. Currently, there are no approved therapies for NASH.

[1] LaBreque d et al. Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis World Gastroenterology Organization Global Guidelines http://www.worldgastroenterology.org/NAFLD-NASH.html, 2012

Data suggest that progressive hepatic hypothyroidism occurs in chronic liver disease and 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 thyroid hormone receptor–beta (THR-ß) target gene in the liver.[2] Population studies have also shown associations between NAFLD and overt hypothyroidism, subclinical hypothyroidism and thyroid hormone in the low normal range.[3, 4] The deficiency in THR-β activity in livers affected by NASH cannot be corrected by treatment with thyroid hormone because thyroid hormone is rapidly metabolized in NASH livers due to the action of deiodinases. Additionally, treatment with exogenous thyroid hormone, which acts primarily in the periphery at thyroid hormone receptor–alpha (THR-α) to exert its effects, has undesirable systemic actions in euthyroid individuals, particularly effects on the heart and bone.

The Sponsor is developing resmetirom, an orally active, partial agonist of THR-β, for the treatment of NASH. THR-β stimulation improves mitochondrial function and lipid metabolism in the liver. According to the Sponsor, resmetirom, when compared to the active thyroid hormone triiodothyronine (T3), has 28-fold selectivity for THR-β, the predominant thyroid hormone receptor subtype in the liver, versus THR-α, the predominant receptor subtype in heart and bone. Thus, the Sponsor believes resmetirom may provide liver-mediated metabolic benefits of thyroid hormone, while avoiding the unwanted systemic actions of thyroid hormone in heart and bone mediated through THR-α. Additionally, unlike thyroid hormone, which may be rapidly metabolized in the liver due to the deiodinase activity, resmetirom is insensitive to deiodinase action.

The clinical development program for resmetirom for treatment of NASH includes twelve Phase 1 studies, two Phase 2 studies, and four Phase 3 studies (**Figure 1**, **Appendix**).

DGE previously provided consult responses to DHN regarding safety monitoring for potential endocrine-related effects of resmetirom in the treatment of subjects with NASH in Trials MGL-3169-11, MGL-3169-14, and MGL-3196-19 (refer to consults dated September 2, 2016; December 23, 2020; and January 31, 2022, in DARRTS). Briefly, DGE recommended that, in order to minimize the risk of hypothyroidism or hyperthyroidism in subjects treated with resmetirom, subjects with abnormal TSH, free/total T4 or free/total T3 levels at any point during the trials should undergo resmetirom dose reduction, and subjects with persistently abnormal thyroid function tests should be discontinued from treatment. Additionally, DGE recommended that the trials include enough subjects with normal thyroid function who are not taking thyroid hormone replacement therapy at baseline to allow adequate assessment of the effects of resmetirom on endogenous thyroid function, because inclusion of subjects receiving thyroid replacement therapy or subjects with abnormal TSH at baseline in the trial could limit interpretation of any direct effects of resmetirom on thyroid function. Lastly, DGE recommended that subjects on anti-thyroid medications for treatment of underlying hyperthyroidism to be excluded from the trials.

DGE provided another consult response regarding the safety data pertaining to the effect of resmetirom on thyroid function that the Sponsor proposed to include in an NDA (refer to

[2] Nomura S, et al. 'Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis', J Clin Invest, 1975; 56: 643-52
[3] Ludwig U, et al. Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: A cross-sectional study of a random population sample aged 18 to 65 years. BMC Endocr Disord. 2015;15:41
[4] Bano A, et al. Thyroid function and the risk of nonalcoholic fatty liver disease: The Rotterdam study. J Clin Endocrinol Metab. 2016;101: 3204–11

consult dated March 3, 2023, in DARRTS). While the Sponsor's proposal regarding thyroid function monitoring appeared overall acceptable, DGE recommended also including data regarding the number of subjects who required resmetirom dose adjustments (either up or down titration) based on changes in FT4; the impact of protocol-specified dose adjustments on TSH, FT4, and FT3; and an adequate justification for the dose adjustment algorithms used in the phase 3 trials (in which resmetirom dose was adjusted based on serum FT4, with or without serum SHBG level). Lastly, DGE recommended the Sponsor include the proportion of subjects requiring initiation or change in any thyroid hormone replacement therapy during the trial.

With this consult request, DHN asked DGE to review the thyroid, HPA axis function, and bone metabolism safety data submitted to NDA 217785, which is currently under review for the use of resmetirom in the treatment of NASH.

II. Review of safety data

Trial MGL-3196-11

Study design

Trial MGL-3196-11 is a double-blind, randomized, placebo-controlled trial in subjects with NASH and fibrosis of 54-months duration, assessing the efficacy of resmetirom on NASH resolution, reduction in liver fibrosis, and reduction in progression to cirrhosis and/or hepatic decompensation. Subjects were treated with resmetirom 80 mg or 100 mg/day or matching placebo (randomization ratio 1:1:1). The randomization was stratified by baseline type 2 diabetes status (presence/absence) and fibrosis stage (F1, F2, or F3). At Week 12, doses were decreased by 20 mg to 60 mg and 80 mg, respectively, in subjects with ≥30% decrease from baseline in free thyroxine (fT4) to <0.7 ng/dL at Weeks 4 and 8. For subjects who underwent a reduction in dose to 80 mg/day, if the fT4 at Weeks 16 and 20 continued to be ≥30% decreased from baseline and <0.7 ng/dL, the dose was further decreased to 60 mg at Week 24. Dose reductions beyond Week 24 and to less than 60 mg were not permitted. This is an ongoing study. With this NDA submission, the Sponsor presented clinical efficacy and safety data after 52 weeks of treatment.

Relevant exclusion criteria pertaining to endocrine function included presence of thyroid diseases (i.e., active hyperthyroidism; untreated clinical hypothyroidism, defined by thyroid stimulating hormone (TSH) >7 IU/L with symptoms of hypothyroidism or >10 IU/L without symptoms). Patients with subclinical hypothyroidism, patients on stable levothyroxine (LT4) therapy up to 75 mcg per day, and patients with history of thyroidectomy and on replacement dose of LT4 > 75 mcg per day were allowed to participate. Regular use of drugs historically associated with NAFLD (which included but were not limited to amiodarone, systemic oral glucocorticoids, tamoxifen, estrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids except testosterone replacement, were not allowed.

Relevant endocrine-related safety assessments included: 1) thyroid hormone assessments [free thyroxine (FT4), total T4, free triiodothyronine (FT3), total T3, thyroid stimulating hormone (TSH), reverse T3 (rT3)] every 4 weeks; 2) sex hormone assessments [follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total and free testosterone]

at baseline and week 52; and 3) bone assessment with DXA scan and bone turnover markers at baseline and week 52.

Patients disposition

Overall, 1050 patients were randomized to the three double-blind treatment arms (80 mg resmetirom [n=352], 100 mg resmetirom [n=349], or placebo [n=349]). Discontinuation rates were slightly higher in the resmetirom treatment arms compared to placebo (15% resmetirom 80 mg vs 20% resmetirom 100 mg vs 12% placebo), and the rate of discontinuation due to AEs were also slightly higher in the resmetirom arms compared to placebo (5% resmetirom 80 mg vs 9% resmetirom 100 mg vs 4% placebo). The mean age of the subjects was 57 years, and the proportion of female subjects enrolled was slightly higher than males (56% vs 44%). The mean age and sex distribution was similar amongst treatment arms.

Concomitant relevant medications for this consult during the study were (resmetirom 80 mg vs resmetirom 100 mg vs placebo): testosterone products: 10 (3.1%) vs 9 (2.8%) vs7 (2.2%); estrogen products: 10 (3.1%) vs 18 (5.6%) vs 14 (4.4%); biotin: 5 (1.6%) vs 9 (2.8%) vs 9 (2.8%); progesterone/estrogen fixed comb: 8 (2.5%) vs 8 (2.5%) vs 3 (0.9%); thyroid hormones: 42 (13%) vs 56 (17.3%) vs 46 (14.3%). Of those patients on thyroid hormone therapy, the majority were treated with levothyroxine only therapy, with ≤1% treated with combination T4/T3, or T3 alone therapy.

Trial MGL-3196-14 is a double-blind, placebo-controlled trial of 52 weeks duration, evaluating the safety and efficacy of resmetirom on liver biomarkers in subjects with nonalcoholic fatty liver disease (NAFLD), a precursor to NASH, without steatosis. Subjects were randomized to resmetirom 80 mg or 100 mg/day or matching placebo, or into a resmetirom 100 mg/day open-label non-cirrhotic (OLNC) treatment arm (1:1:1:1). The OLNC treatment arm allowed inclusion of subjects on thyroxine >75 μg/day (which the randomized, double-blind treatment arms were not allowed to include) in order to assess the safety and efficacy of resmetirom and higher doses of thyroxine (>75 μg/day) dosed concomitantly in the target NAFLD population so that potential pharmacodynamic interactions, effects on thyroid hormones, and long-term safety with respect to thyroid function could be assessed. Safety was carefully monitored in the open-label arm, including assessment of symptoms, signs, and laboratory evaluations related to excess thyroxine. Following enrollment of 171 patients in the OLNC treatment arm, patients on thyroxine >75 μg were also enrolled into the double-blind arm and switched to 1:1:1 randomization (resmetirom 100 mg, resmetirom 80 mg, or matching placebo) (Amendment 3). Dose adjustments based on serum FT4 level were conducted in a similar fashion as Trial MGL-3196-11.

This study enrolled male and female patients ≥18 years of age with a suspected or confirmed diagnosis of NASH/NAFLD. The relevant exclusion criteria pertaining to endocrine function were similar to trial MGL-3196-11. Of note, subjects on thyroxine treatment at baseline were allowed to have small adjustments of thyroxine dose (12.5 to 25 mcg every 4 weeks) as per usual care during the study. Also, investigators were asked to review TSH levels, particularly in open-label and double-blind patients on thyroxine, at screening, baseline, and throughout the study to determine whether to make dose adjustments in thyroxine (or recommend thyroxine dose adjustments to the patient's PCP). According to the protocol, small dose adjustments in thyroxine (12.5 to 25 mcg every 4 weeks) to maintain TSH target were expected and considered consistent with "stable" thyroxine therapy in subjects on thyroxine at baseline. The sponsor also considered small adjustments in the thyroxine dose due to more

efficient conversion of T4 to T3 in the liver (and reduced reverse T3) that occurs with resmetirom treatment to be expected.

The endocrine safety assessments were similar to trial MGL-3196-11.

Patients Disposition

Overall, 972 patients were randomized to the three double-blind arms (100 mg resmetirom [n=325], 80 mg resmetirom [n=327], or placebo [n=320]) and 171 patients were randomized to the 100 mg OLNC arm. Discontinuation rates were similar across double-blind arms (21% resmetirom 80 mg vs 25% resmetirom 100 mg vs 21% placebo). Most patients discontinued from the double-blind arms of the study due to patient withdrawal (other than AE) or were lost to follow-up.

The number of subjects on thyroxine replacement therapy in the double-blind treatment arms was relatively similar (10.5% resmetirom 80 mg vs 12% resmetirom 100 mg vs 11% placebo), of whom the majority were on thyroxine ≤75 mcg/day (7.4% resmetirom 80 mg vs 7.6 % resmetirom 100 mg vs 8.8% placebo). Of the 176 subjects in the OLNC 100 mg resmetirom arm, 76 (44.4%) subjects were on thyroxine therapy, and 65 (38%) subjects were on thyroxine > 75 mcg daily [the remaining 11 (6.4%) subjects were on thyroxine ≤75 mcg/day].

There was a greater percentage of patients on thyroxine replacement therapy in the open-label arm (44.4%) compared with the double-blind arms (10.5% to 12%).

Concomitant relevant medications for this consult during the study included the following (resmetirom 80 mg vs resmetirom 100 mg vs placebo): testosterone products [19 (5.8%) vs 9 (2.8%) vs 9 (2.8%)]; estrogen products [10 (3.1%) vs 8 (2.5%) vs 11 (3.5%)]; biotin [12 (3.7%) vs 10 (3.1%) vs 18 (5.7%)]; progesterone/estrogen fixed combination [5 (1.5%) vs 5 (1.5%) vs 1 (0.3%)]; thyroid hormones [39 (12%) vs 38 (12%) vs 38 (12%)], with the majority taking levothyroxine only therapy, and < 1% taking T4/T3 combination therapy or T3 alone therapy).

Trial MGL-3196-18 is an open-label extension trial with a double-blind lead-in period in 1080 subjects who either completed Trial MGL-3196-14 or were screen failures in Trial MGL-3196-11. Subjects were randomized to single-blind 80 mg or 100 mg resmetirom daily, and up-titrated to 100 mg at Week 12 of the open-label extension period. However, similarly to the other phase 3 trials, the dose was down titrated at Week 12 to 60 mg and 80 mg, respectively, for subjects with a ≥30% decrease in FT4 to <0.7 ng/dL at Weeks 4 and 8 of the extension period.

Trial MGL-3196-11 represents the study conducted by the Sponsor for registrational purposes for the indication treatment of patients with non-cirrhotic NASH with mild (F1), moderate (F2) and advanced (F3) fibrosis. Based on efficacy data, DHN is considering granting a narrower indication: treatment of patients with non-cirrhotic NASH with moderate (F2) and advanced (F3) fibrosis. According to the DHN review team, efficacy data from trials MGL-3196-14 and MGL-3196-18 will not be included in labeling or inform the final indication because the primary objective of these trials was to evaluate safety and tolerability of the drug, and not efficacy. However, safety data from trials MGL-3196-14 and MGL-3196-18 is being included in the overall safety review. Given the similarity in design of trials MGL-3196-11 and MGL-3196-14 and the fact that the non-cirrhotic NASH/NALFD patient

population in these studies represent a spectrum of NASH at different stages of disease progression but with similarly high overall metabolic and safety risk, a pooled safety analysis was also performed by DHN in order to provide a comprehensive assessment of the safety of resmetirom.

DGE evaluated the safety data pertaining to endocrine-related assessments in all three phase 3 trials, with a focus on trial MGL-3196-11, which was conducted for registrational purposes. DGE has summarized data from trials MGL-3196-14 and MGL-3196-18 as appropriate to answer the consult question.

Safety Results on Endocrine-Related Assessments

Thyroid Hormone Assessment Results

Study MGL-3196-11
The changes in thyroid hormone levels were assessed according to baseline use of exogenous thyroxine products because exogenous thyroxine and underlying hypothyroidism may confound the interpretation of results.

FT4
A 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 treatment at baseline, analysis of FT4 levels showed an absolute (percent) change from baseline to week 52 of -0.16 (-14%) ng/dL in the resmetirom 80 mg group and -0.21 (-18%) ng/dL in the resmetirom 100 mg group, respectively, compared to no change in placebo group. However, in the resmetirom-treated subjects, the absolute numerical changes in the mean FT4 values from baseline to week 52 remained within normal ranges (0.7 to 1.6 ng/dL). (
Table 1) Similar changes in FT4 levels were noted 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 4-8), with FT4 remaining relatively stable throughout the remainder of the study.

TSH
In subjects not on thyroxine at baseline, a small reduction in mean TSH values that remained within normal limits were seen in both resmetirom treatment arms compared to placebo at Week 52: -0.23 mIU/L in the resmetirom 80 mg group and -0.20 mIU/L in resmetirom 100 mg group and are unlikely to be clinically meaningful. Similar small reductions in mean TSH levels were seen in subjects on thyroxine at baseline (-0.63 mIU/L in the resmetirom 80 mg group and -0.13 mIU/L in the resmetirom 100 mg group). (
Table 1)

FT3 and TT3
No meaningful changes in the active thyroid hormones, FT3 and TT3 were observed (
Table 1). However, interpretation of FT3 and TT3 results should be made with caution, since FT3 has a very short half-life, and TT3 may be affected by increases in SHBG levels seen with resmetirom. A resmetirom-induced lowering effect on reverse T3 (RT3), which is elevated in patients with NASH, and a resulting improved T3/RT3 ratio were also noted. (RT3 is an inactive thyroid hormone that has no clinical significance in thyroid function

homeostasis. Therefore, the effects of resmetirom on RT3 were not further addressed in this review.)

Table 1. Thyroid Hormones: Summary of Mean Change from Baseline to Week 52 (Conventional Units) (Safety Population – F1B, F2, F3)

	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
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: Tables 14.3.4.1.5.3.2.1, 14.3.4.1.5.3.4.1, CSR, MGL-3196-11

Similar changes from baseline to Week 52 in mean FT4, TSH, and T3 levels as described above in Study MGL-3196-11 were observed in Study MGL-3196-14 (**Table 5**, **Appendix**).

Shift in thyroid hormones

FT4

The shifts in the thyroid axis hormones from baseline through week 52 to any abnormal occurrence post-baseline by thyroxine status at baseline were also evaluated (**Table 6, Appendix)**. In subjects not on thyroxine at baseline, a higher proportion of subjects in the resmetirom 80 mg and 100 mg treatment groups compared with placebo (15% vs 29% vs 3%, respectively) had a shift from baseline FT4 levels ≥0.7 ng/dL to at least one measurement below 0.7 ng/dL (i.e., the lower normal limit) post-baseline. Similar results were observed for subjects treated with thyroxine at baseline (16% vs 33% vs 0%, respectively) (**Table 6**, **Appendix**).

TSH

Among subjects not on thyroxine at baseline, a shift in TSH from a baseline of ≥0.3 mIU/L to <0.3 mIU/L (the lower normal limit) post-baseline was seen in small numbers of subjects in the resmetirom 80 mg and 100 mg groups compared to placebo (4% vs 2% vs 1% ,

respectively) (**Table 6**, **Appendix**). Among subjects who were on thyroxine at baseline, a higher proportion of subjects in the resmetirom 80 mg and 100 mg treatment groups compared with placebo had at least one occurrence of TSH < 0.3 mIU/L post-baseline (28% vs 30% vs 5%). It is noted that the percent of subjects with TSH decline to < 0.3 mIU/L post-baseline was higher among subjects who were on thyroxine at baseline (i.e., had underlying thyroid disease) compared to subjects not on thyroxine at baseline.

A shift in TSH level from a baseline TSH ≤ 4.5 to TSH >4.5 at any time during the study occurred less frequently in subjects not on thyroxine at baseline (6% vs 8% vs 11%), compared to subjects who were on thyroxine therapy at baseline (18% vs 28% vs 19%), although the frequency amongst treatment arms in all subjects was similar between resmetirom-treated and placebo-treated subjects, making these data difficult to interpret.

The decreases in FT4 levels occurred in a larger number of subjects than for TSH. The Sponsor hypothesizes that the effect on FT4 levels is primarily a result of resmetirom-induced increases in deiodinase-1 (DO1) activity, which increases hepatic conversion of FT4 to T3. A suppressive effect on TSH suggests an effect of resmetirom at the pituitary level, where THR-β is the predominant thyroid hormone receptor subtype. Despite the small changes observed in thyroid hormone levels, the overall maintenance of normal TSH (which is the most reliable and sensitive marker of the thyroid function) and T3 levels during the study reflect the ability of the hypothalamic-pituitary-thyroid (HPT) axis to maintain normal thyroid function with resmetirom treatment.

A shift in the FT4 and TSH levels from normal to abnormal occurred overall in a higher percent of subjects who were on thyroxine therapy at baseline (**Table 6**, **Appendix**), suggesting that subjects with impaired thyroid function at baseline may be more susceptible to resmetirom-induced effects on the thyroid hormone axis.

To further understand the clinical significance of the thyroid abnormalities in subjects who experienced shifts in thyroid hormone from normal to outside normal ranges, DGE asked the Sponsor to provide details with regards to thyroid hormone evolution during the study for subjects with at least two consecutive abnormal thyroid hormone values for each of the following abnormalities: FT4 < 0.7 ng/dL, TSH < 0.3 mIU/L, and TSH > 4.5 mIU/L.

Subjects not on thyroxine at baseline (i.e., euthyroid subjects)
In subjects not on thyroxine at baseline, the proportion of subjects with declines in FT4 to < 0.7 ng/dL, TSH < 0.3 mIU/L, or TSH > 4.5 mIU/L on at least two consecutive occasions was lower that the proportion having any single abnormal value. (**Table 2**).

Table 2. Thyroid Hormone Abnormalities in Subjects not on Thyroxine at Baseline, Study MGL-3196-11 (Non-Cirrhotic NASH Safety Population - F1B, F2, F3)

Abnormality	**Resmetirom 80 mg (N=283)**	**Resmetirom 100 mg (N=277)**	**Placebo (N=276)**
Patients with abnormality at any post-baseline assessment, but not at Baseline[1], n (%)			
Free T4 < 0.7 ng/dL	46 (16.3)	82 (29.6)	7 (2.5)
TSH < 0.3 mIU/L	10 (3.5)	9 (3.2)	3 (1.1)

TSH > 4.5 mIU/L	22 (7.8)	23 (8.3)	31 (11.2)
Patients with abnormality at two or more consecutive post-baseline assessments, but not at Baseline[1], n (%)			
Free T4 < 0.7 ng/dL	29 (10.2)	52 (18.8)	2 (0.7)
TSH < 0.3 mIU/L	2 (0.7)	3 (1.1)	0
TSH > 4.5 mIU/L	4 (1.4)	8 (2.9)	5 (1.8)

[1] Patients with missing baseline data are counted as not having an abnormality at Baseline.
Source: Table 3, Sponsor Response to IR dated November 17, 2023

The thyroid function tests evolution during the study of each subject with decline in FT4 < 0.7 ng/dL on at least two consecutive occasions was reviewed by the clinical reviewer. Only 10 (3.5%) of all subjects in the resmetirom 80 mg arm and 19 (6.8%) in the resmetirom 100 mg arm had persistently low FT4 during the trial. Despite persistently low FT4 levels, TSH values remained within normal reference ranges in the majority of cases, with the exception of 2 subjects (one in resmetirom 80 mg, and one in resmetirom 100 mg arms) in whom TSH levels transiently declined to < 0.3 mIU/mL (for 8 weeks in both subjects), and then normalized spontaneously. In the subjects with transient declines in FT4, TSH remained within normal limits throughout the study. The nadir of FT4 generally occurred after week 4 (around weeks 8-12). Many of the subjects who developed low FT4 had low normal FT4 levels at baseline (0.7-0.8 ng/dL), therefore, the absolute decrease from baseline in FT4 was quite small and unlikely to be clinically significant. Four subjects ([redacted] (b) (6) [redacted]) with decline in FT4 < 0.7 ng/dL on at least two consecutive occasions were reported to have an AE of hypothyroidism (due to low FT4 level) and were started on levothyroxine therapy (**Table 8**, **Appendix**). None of these subjects reported symptoms associated with hypothyroidism. In 3 of these 4 subjects, FT4 improved (in two subjects to normal and in one subject FT4 still remained low, but T3 normalized) and TSH remained normal after initiation of thyroxine therapy initiation. In the 4th subject, resmetirom was stopped due to the AE of hypothyroidism (based on low FT4, T3 and TSH), and was started on levothyroxine 25 ug daily, with subsequent normalization of TFTs (refer to **Table 8**, **Appendix**, for details).

In summary, the declines in FT4 to below the normal range on at least two consecutive occasions occurred in a minority of subjects (10-19%) and were transient in most subjects. The fact that TSH remained normal in these subjects suggests that hypothalamic-pituitary-thyroid function (HPT) remained intact. The small number of subjects with persistently low FT4 also maintained normal TSH (and T3) during study, again suggestive of preserved HPT axis function. Although a few subjects were started on low dose levothyroxine therapy based on the low FT4 levels, the clinical utility of initiation of thyroid hormone replacement therapy in this clinical scenario of transiently low FT4 with normal TSH is not established.

Of the 5 subjects with decline in TSH < 0.3 mIU/L on at least two consecutive occasions, only one subject ([redacted] (b) (6) [redacted], resmetirom 80 mg arm) had persistently low TSH during the study. This subject maintained normal FT4 until month 21, followed by a further decrease in TSH and elevation in FT4 and total T3 levels above the normal range at month 24, suggestive of subclinical hypothyroidism, followed by overt hyperthyroidism. This subject had elevated thyroid peroxidase antibodies at baseline, suggesting underlying autoimmune thyroid disease. Additional subjects with transiently low TSH also had abnormalities in FT4 and/or TT3 levels that were transient in nature. One subject ([redacted] (b) (6) [redacted]) had low TSH and

low FT4 following resmetirom initiation (week 4 to week 12), followed by normalization of TSH but with persistently low FT4 (week 16 to week 52). This subject was started on thyroxine therapy because of the persistently low FT4 after week 52, which resulted in normalization of FT4 (from 0.5 to 1.4 ng/dL), but suppression of TSH (from 1.4 to 0.005 mIU/L), indicating iatrogenic hyperthyroidism.

In summary, the thyroid hormone changes in subjects with declines in TSH < 0.3 mIU/L suggest that any TSH-lowering effect of resmetirom is transient and is likely not clinically meaningful.

Of the 12 subjects with increase in TSH > 4.5 mIU/L on at least two consecutive occasions, the increases were small in magnitude (mostly in 4.5-5.5 mIU/L range, not exceeding 8.0 mIU/L) and transient, and the FT4 levels remained within normal ranges in all subjects. In two of the 12 subjects, low dose levothyroxine was started as a result of TSH increase, with subsequent normalization of TSH. Overall, the changes in TSH were small and transient, similar to what was seen with the other thyroid hormone abnormalities. Given that the incidence of TSH >4.5 mIU/L was similar between resmetirom and placebo treatment arms, an effect of resmetirom on TSH increase is not clear.

Resmetirom was discontinued due to an AE of hypothyroidism in only a single subject during the study (refer to **Table 8**, **Appendix**, for details).

Subjects on thyroxine at baseline
The number of subjects who were on thyroxine at baseline and developed thyroid hormone abnormalities during Study MGL-3196-11 is shown in
Table 3.

Table 3. Thyroid Abnormalities in Subjects on Thyroxine at Baseline, Study MGL-3196-11 (Non-Cirrhotic NASH Safety Population - F1B, F2, F3)

Abnormality	**Resmetirom 80 mg (N=39)**	**Resmetirom 100 mg (N=46)**	**Placebo (N=45)**
Patients with abnormality at any post-baseline assessment, but not at Baseline[1], n (%)			
Free T4 < 0.7 ng/dL	6 (15.4)	15 (32.6)	0
TSH < 0.3 mIU/L	9 (23.1)	15 (32.6)	4 (8.9)
TSH > 4.5 mIU/L	7 (17.9)	14 (30.4)	9 (20.0)
Patients with abnormality at two or more consecutive post-baseline assessments, but not at Baseline[1], n (%)			
Free T4 < 0.7 ng/dL	2 (5.1)	11 (23.9)	0
TSH < 0.3 mIU/L	4 (10.3)	8 (17.4)	1 (2.2)
TSH > 4.5 mIU/L	2 (5.1)	5 (10.9)	3 (6.7)

[1] Patients with missing baseline data are counted as not having an abnormality at Baseline.
Source: Table 6, Sponsor Response to IR dated November 17, 2023

Of the 13 subjects with decline in FT4 < 0.7 ng/dL on at least two consecutive occasions, 5 subjects (6% of all subjects treated with resmetirom) had persistently low FT4. Similar to

subjects not on thyroxine who experienced decline in FT4 < 0.7 ng/dL during the study, TSH remained stable, within normal limits. Only one subject with TSH increase had thyroxine dose increased because of low FT4, with resulting normalization of thyroid function tests. (**Table 7**, **Appendix**)

Of the 12 subjects with TSH decreased to < 0.3 mIU/L on at least two consecutive occasions, the decreases in TSH were typically not associated with abnormalities in other thyroid hormones (FT4, TT3), and were transient. Five of the 12 subjects had thyroxine dose decreased as a result of the decrease in TSH, which resulted in initial 'improvements' in the TSH level, but in some cases lead to fluctuations in thyroid hormones requiring multiple additional dose adjustments, suggesting the initial dose adjustment may not have been necessary, or that the degree of initial dose adjustment was too aggressive (**Table 7**, **Appendix**).

Of the 7 subjects with increase in TSH > 4.5 mIU/L on at least two consecutive occasions, the increases were small in magnitude (mostly in 4.5-8 mIU/L range), were transient, and were not associated with abnormalities in FT4. Only two subjects had a TSH increase >20 mIU/L, each on a single occasion. No subject had levothyroxine dose increased as a result of increase in TSH.

Resmetirom was not discontinued or interrupted in any of these subjects with thyroid function abnormalities.

In summary, subjects on thyroxine at baseline had an overall higher incidence of TSH abnormalities (both decrease and 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 HPT axis.

AEs of hypothyroidism, hyperthyroidism and "TSH decrease"
While the incidence of AEs related to thyroid function abnormalities (e.g., hypothyroidism, hyperthyroidism) was overall low during studies MGL-3196-11 and MGL-3196-14, more subjects in the resmetirom arms were noted to have thyroid-related AEs compared to placebo [AE 'hypothyroidism' (20 subjects in the resmetirom arm and 3 subjects in placebo arm); AE 'TSH decreased' (7 subjects in the resmetirom arm, 0 placebo); AE 'hyperthyroidism' (2 subjects in the resmetirom arm, 0 placebo)]. DGE requested that the Applicant provide further details regarding the criteria used for reporting thyroid-related AEs and initiating treatment during the studies.

AEs of hypothyroidism
The AE of hypothyroidism was reported in 14 (2.5%) subjects in the resmetirom arm and one (0.4%) subject in the placebo arm in Study MGL-3196-11. Of the 14 subjects, 2 subjects were on thyroxine at baseline. After reviewing the laboratory data, this reviewer concluded that only nine subjects had AEs of 'hypothyroidism' based on TFTs and were started on low dose levothyroxine with subsequent decline in TSH to below normal or normalization of TSH (**Table 8**, **Appendix**). In one subject, resmetirom was discontinued due to the AE of 'hypothyroidism', with subsequent normalization of FT4, T3 and TSH levels (refer to narrative **Table 8**, **Appendix**, for details).

In study MGL-3196-14, the majority (5/6) of subjects who had an AE of hypothyroidism during the study were on thyroxine therapy at baseline.

In subjects on thyroxine at baseline, some had transient TSH elevation after starting resmetirom, without changes in FT4 or TT3, and did not require thyroxine dose adjustment.

In summary, a small (< 3%) proportion of subjects had AE of hypothyroidism during the study based on abnormal TFTs, which improved with low dose thyroxine replacement therapy.

AE "TSH decreased"
In study MGL-3196-11, six subjects in resmetirom arm had AEs of 'TSH decreased,' four of whom were on thyroxine at baseline (**Table 9**, **Appendix**). Overall, the AE of 'TSH decreased' was mild, transient, and not clinically significant. In a few cases, either the dose of thyroxine therapy and/or the resmetirom dose was adjusted due to the decrease in TSH, with variable results on thyroid function tests.

In summary, the AE of TSH reduced occurred in a small number of subjects treated with resmetirom, with most of them having hypothyroidism and being treated with levothyroxine at baseline. The clinical meaningfulness of mild decreases in TSH while on resmetirom treatment cannot be determined with the small sample size and the observed findings.

AE of 'hyperthyroidism'
AEs of hyperthyroidism was reported in only two subjects (one subject in Study MGL-3196-11 and one subject in Study MGL-3196-14) (**Table 10**, **Appendix**). Both subjects were treated with thyroid hormone replacement at baseline. The AE was reported based on mild TSH decline with normal FT4 and T3 in both subjects, which improved with thyroxine dose reduction.

AEs of signs/symptoms potentially related to hyperthyroidism or hypothyroidism
To further examine the possible clinical significance of shifts in thyroid hormones, particularly the reduction in FT4, AEs potentially suggestive of hyperthyroidism and hypothyroidism were evaluated in the pooled safety data of non-cirrhotic NASH/NALFD subjects from studies MGL-3196-11 and MGL-3196-14 (**Table 11, Appendix**).

There was no difference between resmetirom arms and placebo in occurrence of any AEs potentially related to hyperthyroidism (e.g., fatigue, tachycardia, irritability, anxiety, insomnia), or hypothyroidism (e.g., fatigue, constipation, myalgia).

Resmetirom dose reduction based on FT4 levels
In Study 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] had resmetirom dose reduced 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 (**Table 4**). Slight changes in mean FT3, T3 and TSH levels were also noted, but were within normal reference ranges both before, and after dose adjustment.

Table 4. Thyroid Axis Hormones: Summary of Observed Values and Change from Prior to Dose Adjustment, Study MGL-3196-11 (Safety Population - F1B, F2, F3)

Parameter	**MGL-3196 80 mg**	**MGL-3196 100 mg**	**Placebo**
Visit	(N=322)	(N=323)	(N=321)

Statistics	Obs.	CFDAB	Obs.	CFDAB	Obs.	CFDAB
Free T4 (ng/dL)						
Dose Adjustment Baseline [1]						
n	2	2	10	10	0	0
Mean (SD)	**0.525 (0.02)**		**0.577 (0.12)**			
First Visit After Dose Adjustment [2]						
n	2	2	10	10	0	0
Mean (SD)	**0.705 (0.03)**	**0.180 (0.04)**	**0.678 (0.14)**	**0.101 (0.04)**		
T3 (ug/L)						
Dose Adjustment Baseline [1]						
n	2	2	10	10	0	0
Mean (SD)	**0.95 (0.07)**		**0.90 (0.16)**			
First Visit After Dose Adjustment [2]						
n	2	2	10	10	0	0
Mean (SD)	**1.20 (0.00)**	**0.25 (0.05)**	**1.10 (0.14)**	**0.20 (0.04)**		
FT3 (ng/L)						
Dose Adjustment Baseline [1]						
n	2	2	10	10	0	0
Mean (SD)	**2.50 (0.14)**		**2.36 (0.25)**			
First Visit After Dose Adjustment [2]						
n	2	2	10	10	0	0
Mean (SD)	**3.10 (0.00)**	**0.60 (0.10)**	**2.60 (0.34)**	**0.24 (0.09)**		
TSH (mIU/L)						
Dose Adjustment Baseline [1]						
n	2	2	10	10	0	0
Mean (SD)	**2.705 (1.65)**		**1.555 (0.89)**			
First Visit After Dose Adjustment [2]						
n	2	2	10	10	0	0
Mean (SD)	**2.565 (1.83)**	**-0.140 (0.13)**	**1.714 (0.95)**	**0.159 (0.22)**		

Abbreviation: Obs. = observed; CFDAB = change from dose adjustment baseline.
[1] The dose adjustment baseline is defined as the last non-missing measurement obtained before the first dose adjustment for the patient that was made due to meeting the criteria for free thyroxine.
[2] The First Visit After Dose Adjustment is defined as the first non-missing measurement obtained at a scheduled visit after dose adjustment.
[3] For observed values, mean and SD are presented. For CFDAB, mean and SE are presented
Source: Table 14.3.4.1.5.4.2, CSR, MGL-3196-11

A similar low proportion of subjects required resmetirom dose adjustment during Study MGL-3196-14: 12 (2.4%) subjects had their doses reduced from 100 mg resmetirom to 80 mg and 2 (0.6%) subjects had dose reduced 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)

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

Sex Hormones

Resmetirom increases the synthesis of sex hormone binding globulin (SHBG), a liver protein responsible for the transport of the inactive sex hormones (e.g., total testosterone, estradiol). The increase from baseline to week 52 in SHBG in response to resmetirom therapy ranged from 100% to 250% and correlated with response to treatment based on degree of

improvement in liver fibrosis. As such, the Sponsor considers SHBG to be a biomarker of response to therapy.

The change from baseline to Week 52 in HP-gonadal (HPG) axis hormones, including sex hormones binding to SHBG, was assessed during Study MGL-3196-11. As expected, increases in all sex hormones were noted in subjects treated with resmetirom, in both sexes (**Table 12**, **Appendix**). Statistically significant changes were notable for estradiol, total testosterone, FSH and LH 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 finding 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, DGE reviewed the AEs reporting in the System Organ Class (SOC) Reproductive system and breast disorders in the pooled safety analyses of trials MGL-3196-11 and MGL-3196-14. (**Error! Reference source not found.and Table 14, Appendix)**

In males, there was a very low incidence of AEs of erectile dysfunction (1.2% resmetirom 80 mg vs 0.6% resmetirom 100 mg vs 1.1% placebo) and gynecomastia (0.3% placebo, and no subjects in resmetirom arms), with no difference between resmetirom arms and placebo. (**Table 13, Appendix**)

Likewise, in females, a very low incidence (< 1.5%) of AEs of the reproductive system was seen (**Table 14, Appendix**).

In conclusion, given small number of events, their transient nature and low severity, as well as the presence of confounding factors in all cases, a causal relationship between the study drug 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 not of clinical significance.

Bone metabolism

Resmetirom is a THR-β partial agonist with high selectivity for hepatic THR-β. However, potential off target adverse effects of resmetirom via THR-α agonism may affect bone metabolism.

In Study 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 ≥30 ng/L vs <30 ng/L at baseline; subjects taking thyroxine vs not taking thyroxine; subjects with weight loss ≥5% vs < 5% at week 52).

Evaluation of the T-score changes in the female subjects with estradiol < 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 (change from baseline to week 52 in femoral neck T-score were: -0.056 in resmetirom 80 mg arm vs -0.067 in resmetirom 100 mg arm vs -0.072 in placebo arm; change from baseline to week 52 in lumbar spine T score were: -0.043 in resmetirom 80 mg arm vs -0.101 in resmetirom 100

mg arm vs 0.009 in placebo arm). Similarly, there was no notable differences observed between resmetirom and placebo arms when evaluating the Z-score changes in the female subjects with estradiol > 30 ng/L (i.e., pre-menopausal), in whom Z-score values are most reliable. No clinically significant differences in T-scores and Z-scores between resmetirom and placebo arm were noted in any of the other subgroups.

The Sponsor also evaluated the bone mineral density (BMD) data using shift tables of BMD T-score risk category for fracture (i.e., Normal risk = T-Score ≥-1.0; Low Density = T-Score ≥-2.5 and <-1.0; Possible Osteoporosis = T-Score <-2.5) in the different subgroups based on sex and baseline estradiol level, baseline thyroxine intake, and weight loss at week 52. The Sponsor defined the subgroup with the highest potential risk for fractures as the females with estradiol <30 (post-menopausal), who were not taking thyroxine at baseline, and who had weight loss <5% at Week 52 (**Table 15, Appendix**). In this subgroup, there were very few (1-2) subjects that progressed from a lower to a higher risk category of fracture based on T-score, and the incidence was similar between resmetirom arms and placebo. Similar findings of very few shifts from lower to higher risk category with no difference between resmetirom treatment arms and placebo were noted in all the other subgroups (e.g., female subjects not taking thyroxine at baseline, estradiol ≥ 30 ng/L at baseline, and weight loss <5% at Week 52; female subjects not taking thyroxine at baseline and weight loss <5% at Week 52; female subjects taking thyroxine at baseline and weight loss <5% at Week 52).

Evaluation of bone turnover markers in the subgroup of subjects with the highest potential risk for fractures (i.e., post-menopausal females, who were not taking thyroxine at baseline, and who had weight loss <5% at Week 52) revealed small increases in both P1NP (a bone formation marker) and CTX-1 (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 remain unknown.

The incidence of AEs of fracture, osteopenia and osteoporosis was similar between resmetirom and placebo treatment arms in Study 11, in pooled data from studies 11 and 14, and in Study 18, which allowed an assessment of long-term exposure on bone (approx. 2 years), indicating no increase in fracture risk due to resmetirom therapy.

There were 5 SAEs of fractures in 4 subjects in Study 11: 2 subjects in resmetirom 80 mg arm (ankle fracture, pelvic fracture, spinal fracture) and 2 subjects in resmetirom 100 mg arm (humerus fracture, cervical vertebral fracture). The SAE of cervical vertebral fracture led to study drug discontinuation. DGE reviewed the case narratives of the 4 subjects with SAEs of fractures and 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 recovered/resolved.

Evaluation of the AEs of fractures and osteoporosis in Study 18, which was a 52-week extension study of Study 14 evaluating the safety of resmetirom in subjects with NAFLD, showed no increase incidence of these events with long-term exposure (i.e., approx. 2 years) to resmetirom. The incidence of AEs of fractures and osteoporosis in placebo to resmetirom arm compared to resmetirom to resmetirom arm were as follows: AE fracture: 2.3% (placebo to resmetirom arm) vs 2.1% (resmetirom to resmetirom arm) and AE osteoporosis: 1.2% (placebo to resmetirom arm) vs 0 (resmetirom to resmetirom arm), respectively.

In summary, after 1 year of treatment with resmetirom, there was no evidence of drug-induced adverse effect on bone metabolism based on clinical adverse events and BMD assessments by DXA. However, the long-term effect of the drug on bone metabolism remains unknown.

III. Materials reviewed for consult

a. DHN Consult request form
b. Endocrine consultations for IND 122865, dated September 2, 2016; December 23, 2020; and January 31, 2022 and March 7, 2023
c. NDA 217785 submission, to include: clinical trials protocol and clinical study reports for Trials MGL-3196-11, MGL-3196-14, MGL-3196-18, Clinical Overview, Summary of Clinical Safety
d. Literature regarding: resmetirom action; thyroid hormones action at cellular level, including role of thyroid hormone receptors and thyroid hormone transport proteins; sex hormones and SHBG

IV. DGE Consult Response

DHN asked DGE to review the safety data pertaining to thyroid function, HPA axis function, and bone metabolism for resmetirom for the treatment of non-alcoholic steatohepatitis (NASH) submitted to NDA 217785 and to provide recommendations regarding labeling.

There are two thyroid hormone receptors (THR) subtypes: THR-α, which is the predominant receptor subtype in heart and bone, and THR-β, which is the predominant receptor subtype in liver and kidneys. All THR agonists can bind to both subtypes, although the affinity of different THR agonists towards each of the receptor subtypes is variable. Resmetirom, a liver-directed, highly selective, partial agonist for THR-β, is being developed for treatment of NASH. THR-β stimulation is believed to improve mitochondrial function and decreases fat synthesis in the liver.

Preclinical studies identified thyroid, bone and gonadal adverse effects as potential safety signals of resmetirom. However, in the phase 2 trial of resmetirom in subjects with NASH (trial MGL-30196-05), changes in thyroid function, reproductive function, and bone metabolism were minimal (if any), transient and are not considered clinically significant. Similar to the phase 2 trials, longer term data from phase 3 showed small fluctuations in thyroid hormones in some patients; these fluctuations were generally transient in nature and do not appear to be clinically meaningful (i.e., did not cause clinical symptoms or result in TFTs outside of the normal range). Phase 3 data did not identify any safety risks of resmetirom to bone or reproductive function.

Summary of endocrine-related safety findings in the phase 3 trials

<u>Thyroid function tests</u>
Small fluctuations in FT4 were seen in resmetirom-treated subjects during the trial, which rarely lead 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 TFTs were transient in nature and did not lead to thyroid-related symptoms in any subject. Changes of similar magnitude were seen in subjects who were euthyroid at baseline compared to those who were hypothyroid and taking thyroid hormone replacement therapy. Overall, the normal function of the hypothalamic-pituitary-thyroid (HPT) axis was maintained during resmetirom treatment despite small, transient, clinically insignificant fluctuations in thyroid hormone levels seen in some patients during the trial.

Regarding thyroid safety, the Sponsor included the following statement in Section 6, Adverse Reactions, under Laboratory tests:

> *"(b) (4) A decrease in prohormone FT4 of mean (b) (4) was seen in patients treated with PROPRIETARY NAME, (b) (4) changes in active hormone T3 or in TSH. There were no clinical findings associated with FT4 decreases."*

DGE agrees with sponsor's proposed language, and suggests the following additional language:

> **Mild, transient fluctuations in thyroid hormone levels may occur during treatment with resmetirom. Consider monitoring thyroid function in patients taking resmetirom as clinically appropriate.**

This statement may be considered for Section 2 (Dosing and Administration) and/or Section 6 (Adverse Reactions) of the product label.

After discussion with DHN at an internal meeting on December 14, 2023, the following language was agreed upon to be included in Section 6 only, without any additional language in Section 2 of labeling:

> **A decrease in prohormone FT4 of mean (b) (4) was seen in patients treated with PROPRIETARY NAME, (b) (4) changes in active hormone T3 or in TSH. There were no clinical findings associated with FT4 decreases** [*sponsor's proposed language*]**. Consider monitoring thyroid function in patients taking PROPRIETARY NAME, as clinically indicated** [DGE's recommended additional language]**.**

Sex hormones

The changes observed in the inactive forms of sex hormones in resmetirom-treated subjects are expected findings related to drug-induced increase in SHBG and are of no clinical significance.

DGE does not recommend any labeling for a potential risk to reproductive function.

Bone metabolism

No clinically significant changes in bone mineral density or increase in fracture risk were seen in resmetirom-treated subjects compared to placebo after 52 weeks of treatment.

DGE does not recommend any labeling for a potential risk to bone.

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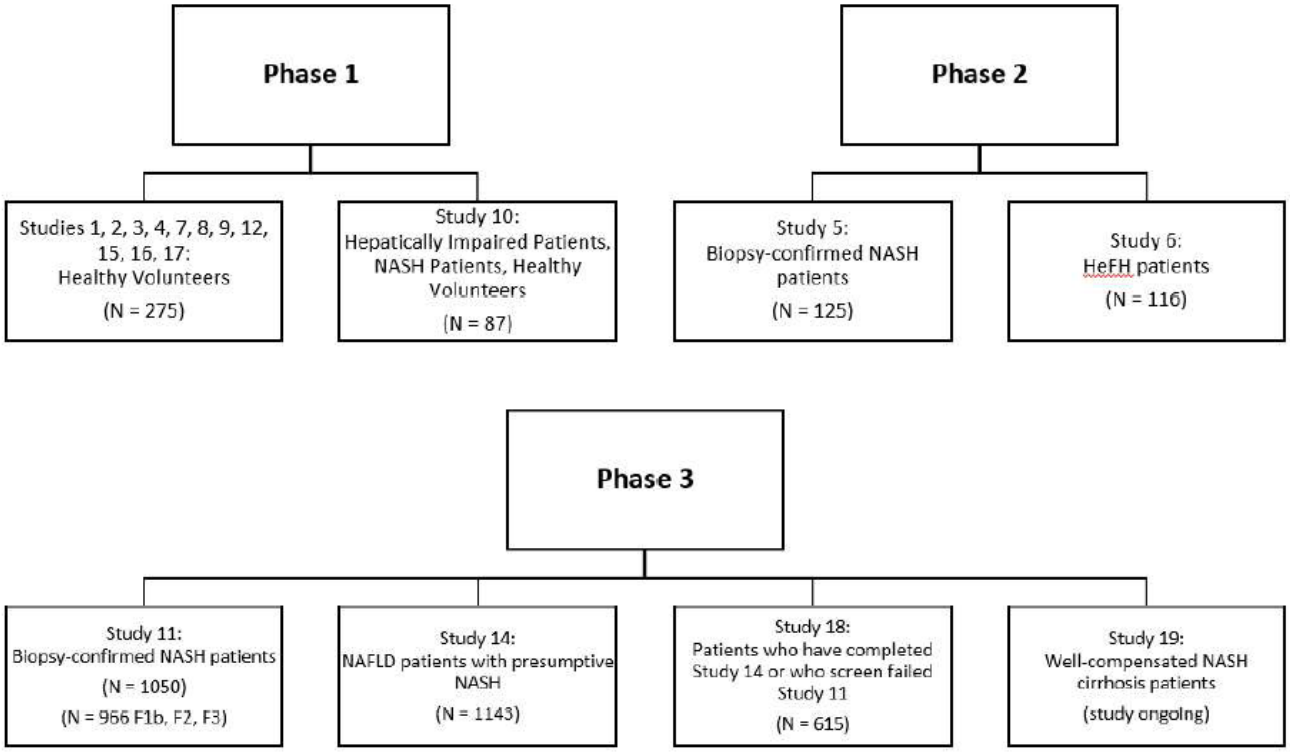
Appendices

Figure 1. Resmetirom Clinical Development Program



Source: Figure 3, Clinical Overview

Table 5. Summary of Thyroid Hormones at Baseline and Change from Baseline or Percent Change from Baseline at Week 52; Study MGL-3196-14, Analysis Population: Safety

	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)
Not on Thyroxine at Baseline									
FT4, ng/dL (not on thyroxine)									
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 (not on thyroxine)									
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 (not on thyroxine)									
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 (not on thyroxine)									
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 (thyroxine-treated)									
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 (thyroxine-treated)									
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 (thyroxine-treated)									
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)
rT3, ng/dL (thyroxine-treated)									
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)

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

Note: Free T4 reported as both CFB and percent CFB at Week 52. All other thyroid hormones reported as CFB at Week 52.

Source: Table 41, CSR, MGL-3196-14

Table 6. Thyroid Axis Hormones: Shifts from Baseline to Any Occurrence Post-baseline through Week 52 by Thyroxine Status at Baseline (Safety Population – F1B, F2, F3), Study MGL-3196-11

Test (unit) Category	Resmetirom 80mg (N=322)	Resmetirom 100mg (N=323)	Placebo (N=321)
Not on Thyroxine at Baseline	283	277	276
Thyrotropin (mIU/L)			
Patients with baseline ≥0.3	279	272	273
Patients with baseline ≥0.3 with any result <0.3 during study	**10 (3.6)**	**6 (2.2)**	**2 (0.7)**
p-value, active vs placebo*	0.0216	0.1533	
Patients with baseline ≤4.5	277	265	267
Patients with baseline ≤4.5 with any result >4.5 during study	**17 (6.1)**	**22 (8.3)**	**30 (11.2)**
p-value, active vs placebo*	0.0344	0.2554	
Thyroxine, Free (ng/dL)			
Patients with baseline ≥0.7	279	273	274
Patients with baseline ≥0.7 with any result <0.7 during study	**43 (15.4)**	**79 (28.9)**	**7 (2.6)**
p-value, active vs placebo*	<0.0001	<0.0001	
Patients with baseline ≤1.6	277	273	274
Patients with baseline ≤1.6 with any result >1.6 during study	3 (1.1)	0	8 (2.9)
p-value, active vs placebo*	0.1237	0.0044	
Triiodothyronine, Free (ng/L)			
Patients with baseline ≥1.7	279	273	275
Patients with baseline ≥1.7 with any result <1.7 during study	1 (0.4)	4 (1.5)	2 (0.7)
p-value, active vs placebo*	0.5550	0.4075	
Patients with baseline ≤5	279	274	275
Patients with baseline ≤5 with any result >5 during study	3 (1.1)	1 (0.4)	3 (1.1)
p-value, active vs placebo*	0.9858	0.3182	
On Thyroxine at Baseline	**39**	**46**	**45**
Thyrotropin (mIU/L)			
Patients with baseline ≥0.3	35	43	43
Patients with baseline ≥0.3 with any result <0.3 during study	**9 (25.7)**	**13 (30.2)**	**2 (4.7)**
p-value, active vs placebo*	0.0074	0.0015	
Patients with baseline ≤4.5	33	43	41
Patients with baseline ≤4.5 with any result >4.5 during study	**6 (18.2)**	**12 (27.9)**	**8 (19.5)**
p-value, active vs placebo*	0.8865	0.3726	

Thyroxine, Free (ng/dL)			
Patients with baseline ≥0.7	38	46	45
Patients with baseline ≥0.7 with any result <0.7 during study	**6 (15.8)**	**15 (32.6)**	**0**
p-value, active vs placebo*	0.0052	<0.0001	
Patients with baseline ≤1.6	34	42	42
Patients with baseline ≤1.6 with any result >1.6 during study	2 (5.9)	1 (2.4)	3 (7.1)
p-value, active vs placebo*	0.8284	0.3113	
Triiodothyronine, Free (ng/L)			
Patients with baseline ≥1.7	38	45	45
Patients with baseline ≥1.7 with any result <1.7 during study	**4 (10.5)**	**2 (4.4)**	**0**
p-value, active vs placebo*	0.0257	0.1561	
Patients with baseline ≤5	37	45	45
Patients with baseline ≤5 with any result >5 during study	1 (2.7)	3 (6.7)	0
p-value, active vs placebo*	0.2728	0.0797	

* P-values are obtained using a student's t-test to compare the proportions between each active treatment group and placebo, assuming equal variances.
Source: Table 68, CSR, MGL-3196-11

Table 7. Thyroxine Treatment Changes at Any Time in Subjects on Thyroxine at Baseline Who had Two or More Consecutive Thyroid Hormone Abnormalities, Study MGL-3196-11 (Safety Population - F1B, F2, F3)

Patient ID/ Age/Sex/ Resmetirom dose	Study date	TSH (mIU/L)	FT4 (ng/dL)	T3 (ug/L)	Thyroxine dose	AE
FT4< 0.7 ng/dL						
(b) (6) / 70/M/80 mg	Baseline	10 ↑	0.9	1	25 ug daily	
	Week 4	5.4 ↑	0.4 ↓	0.8		
	Week 8	6.4 ↑	0.4 ↓	0.8	↑ to 25 ug 2×/wk + 50 ug 5×/wk,	
	Week 16	3.8	0.7	1.2		
	Week 24	4.8	0.8	1.1		
	Week 36	2.7	0.7	1		
	Week 52	3.8	0.9	1.1		
Comments: subject had 2 more LT4 dose adjustments at unknown dates, as follows: ↑ to 50 ug daily (? date), ↓ to 25 ug 2×/wk (? date)						
TSH < 0.3 mIU/L						
(b) (6) / 60/F/80 mg	Baseline	1.2	1.6	0.9	75 ug daily	
	Week 4	0.1 ↓	1.5	1.0		
	Week 8	0.3 ↓	1.2	0.8		
	Week 16	0.3 ↓	1.2	0.9		
	Week 24	0.1 ↓	1.4	0.7		
	Week 36	0.2 ↓	1.2	0.8		AE TSH decreased
	Week 52	0.2 ↓	1.1	0.8	↓ to 50 ug every other day	
	Month 15	11 ↑	0.8	0.5 ↓		
	Month 18	3.9	1.1	0.7		

	Month 24	0.5	1.2	0.9		
Comments: - *The decrease in LT4 dose from 75 ug daily to 50 ug every other day was too aggressive, which resulted in the subsequent increase in TSH above normal levels (i.e., 11 mIU/L)* - *subject had one more LT4 dose adjustment at unknown date, as follows: ↑ to 75 ug every other day (? date).*						
(b) (6) / 65/F/100 mg	Baseline	1.4	1.1	0.8	75 ug daily	
	Week 4	0.2 ↓	1.0	0.9		
	Week 8	0.06 ↓	1.1	0.8		
	Week 16	0.005 ↓	0.9	0.8	↓ 50 ug every other day	
	Week 24	0.02 ↓	0.9	0.8		
	Week 36	0.1	0.7	0.7 ↓		
	Week 40	1.2	0.4 ↓	0.5 ↓		
	Week 48	3.2	0.4 ↓	0.4 ↓		
	Week 52	6.1	0.2 ↓	0.3 ↓		
Comments: - *The decrease in LT4 dose from 75 ug daily to 50 ug every other day was too aggressive, which resulted in the subsequent decrease below normal reference ranges of both FT4 and T3 levels, and an increase in TSH above normal levels (i.e., 6 mIU/L).* - *subject had 4 more LT4 dose adjustments at unknown date, as follows: ↑ to 75 ug every other day; ↑ to 50 ug 4×/wk + 75 ug 3×/wk (? date); ↓ to 50 ug daily (? date); ↓ to 25 ug daily(? date).*						
(b) (6) / 62/F/100 mg	Baseline	0.9	0.9	0.8	75 ug daily	
	Week 4	0.005 ↓	0.6	0.9		
	Week 8	0.002 ↓	0.6	0.8		AE TSH decreased
	Week 16	0.6	0.8	0.7	↓ to 50 ug daily	
	Week 20	0.02 ↓	0.7	0.9		
	Week 28	0.4	0.5 ↓	0.7 ↓		
	Week 36	0.7	0.4 ↓	0.7 ↓		
	Week 48	0.3 ↓	0.6 ↓	0.6 ↓		
	Week 52	0.4	0.6 ↓	0.7 ↓		
Comments: the decrease in LT4 dose at week 16 resulted in subsequent normalization of TSH, but FT4 and T3 levels decreased below normal range. Note: consider in such cases adjusting the resmetirom dose from 100 mg to 80 mg.						
(b) (6) / 77/F/100 mg	Baseline	0.48	1.5	1.2	50 ug daily	
	Week 4	0.1 ↓	1.8 ↑	1.2		
	Week 8	0.1 ↓	1.6	1.2		
	Week 12	0.1	1.2	1.2		AE TSH decreased
	Week 16	0.06 ↓	1.3	1.3		
	Week 20	2.0	0.8	0.9		
	Week 24	5.3 ↑	0.7	1.0		
	Week 28	4.4	0.8	1.0	↑ 75 ug daily	
	Week 36	4.3	0.7	1.0		
	Week 40	0.8	1.0	1.1		
	Week 52	2.7	1.0	1.0		
(b) (6) / 57/F/100 mg	Baseline	0.9	1.3	1.0	125 ug daily	
	Week 4	0.7	1.2	0.9		
	Week 8	0.3 ↓	1.3	1.1	↓ to 100 ug daily	
	Week 12	0.3 ↓	1.1	1.1		
	Week 16	1.1	1.0	1.0		
	Week 24	1.1	1.0	0.9		
	Week 28	4.9 ↑	0.8	0.4 ↓		
	Week 32	21 ↑	0.8	0.6 ↓		AE hypothyroidism
	Week 36	0.1 ↓	1.5	1.5		
	Week 40	0.2 ↓	1.3	1.2		
	Week 48	0.1 ↓	1.0	1.1		

	Week 52	2.2	1.1	1.0		
Comments: - *subject had 5 more LT4 dose adjustments at unknown date, as follows: ↑ to 125 ug daily (? date); ↓ to 112.5 ug daily (? date); ↑ to 125 ug daily (? date); ↓ to 112 ug daily (? date); ↓ to 88 ug daily (? date).*						
(b) (6) / 76/F/100 mg	Baseline	1.2	1.1	0.9	75 ug daily	
	Week 4	0.3	1.1	0.7		
	Week 8	0.2	1.0	0.6		
	Week 12	0.6	0.9	0.8		
	Week 16	0.3	1.0	0.7 ↓		
	Week 24	0.3	1.0	0.8		
	Week 28	0.5	0.9	0.7 ↓		
	Week 36	0.4	1.0	0.8		
	Week 48	0.2	1.0	0.8		
	Week 52	0.1	1.0	0.9		
	Month 15	0.3	1.0	0.9	↓ to 50 ug daily	
	Month 18	2.7	0.8	0.7 ↓		
	Month 21	0.8	0.8	0.7 ↓		
Comments: the decrease in LT4 to 50 ug daily, while normalized TSH, resulted in borderline low T3						
(b) (6) / 72/F/100 mg	*Baseline*	*0.7*	1.2	1.4	50 ug daily	
	Week 4	0.4 ↓	0.9	1.2		
	Week 8	0.3 ↓	1.0	1.4		
	Week 12	0.9	0.9	1.2		
	Week 16	1.4	1.0	1.3		
	Week 24	0.9	0.7	1.2		
	Week 28					
	Week 36	0.8	0.8	1.4		
	Week 44	1.4	0.8	1.4	↑ to 100 ug daily	
	Week 52	0.3 ↓	1.0	1.2		
	Month 18	0.1 ↓	1.1	1.3		
Comment: unclear why subject had LT4 dose increased to 100 ug daily at week 44, as TFTs were within normal ranges; subsequent TSH decreased as a result of LT4 dose increase.						
TSH >4.5 mIU/L						
(b) (6) 69/F/100 mg	Baseline	2.0	1.3	0.9	75 ug daily	
	Week 4	1.2	0.6	0.9		
	Week 8	1.2	0.8	0.8		
	Week 16	0.5	1.1	0.8		
	Week 24	0.9	1.0	0.8		
	Week 32	0.3	0.8	0.7		
	Week 36	1.1	0.7	1.0		
	Week 44	6.7	0.3	0.7		
	Week 48	6.7	0.5	1.2	↓ to 40 ug daily	
	Week 52	1.8	0.8	0.8		
Comment: Unclear why subject had dose of LT4 decrease from 75 ug daily to 40 ug daily, when LT4 dose should have been increased based on TSH levels; interestingly, TSH level normalized at subsequent visit; note: 40 ug daily is not a commercially available dose of LT4.						

Normal reference range: TSH: 0.4-4.0 mIU/L; FT4:0.7 -1.6 ng/dL; T3: 0.8-2.0 ug/L.

Source: Clinical reviewer, with data excerpted from Table 7 and Appendix Section 3.1.2., Response to Information Request dated Nov 17, 2023.

Table 8. Subjects who Reported AE of Hypothyroidism and Who were Not on Thyroxine at Baseline, Study MGL-3196-11

Patient ID/Age/Sex/Resmetirom dose	Study date	TSH (mIU/L)	FT4 (ng/dL)	T3 (ug/L)	Treatment provided for AE	AE
(b) (6) / 66/M/80 mg	Baseline	3.1	0.8	0.7	LT4/T3 19/4.5 ug daily started on study day 8	hypothyroidism
	Week 4	2.6	0.7	1.1		
	Week 8	2.4	0.8	0.7		
	Week 16	4.4	0.8	1.1		
	Week 24	4.5	0.7	1.3		
	Week 28	5.7	0.7	1.5		
	Week 36	2.9	0.7	1.2		
Comment: AE of hypothyroidism occurred on study day 8, without any elevation in TSH; reason for AE and LT4/T3 initiation was unclear.						
(b) (6) 66/F/80 mg	Baseline	3.1	1.08	0.9		
	Week 24	4.5	0.9	1.0		hypothyroidism
	Week 28	5.7	1.1	1.1	LT4 50 ug daily	
	Week 32	2.0	1.5	0.9		
	Week 36	2.9	1.2	1.0		
(b) (6) / 50/M/80 mg	Baseline	3.2	1.2	1.3		
	Week 24	5.8	1.2	1.2	LT4 50 ug daily	hypothyroidism
	Week 28	4.3	1.1	1.2		
	Week 32	3.3	1.8	1.1		
	Week 40	2.1	1.1	1.1		
	Week 52	4.7	1.2	1.4		
0907-0003/69/F/80 mg	Baseline	2.21	0.9	1.2		
	Week 20	2.5	0.77	1.4		
	Week 24	2.25	0.74	1.3	LT5 50 ug daily	hypothyroidism
	Week 28	0.6	1.04	1.2		
	Week 32	0.75	0.92	1.1		
	Week 40	0.61	0.89	1.0		
	Week 52	0.65	0.88	1.0		
Comment: unclear why subject was started on LT4 therapy at week 24, as TFTs were wnl. As a result, TSH decreased to 0.6, but remained wnl.						
(b) (6) /59/F/100 mg	Baseline	3.6	1.1	1.0		
	Week 24	3.02	0.8	0.9		
	Week 32	2.5	0.9	1.1		
	Week 52	3.0	0.8	1.0		
	Month 18	3.0	0.9	0.9		
	Month 21	4.5	0.8	1.1	LT4 25 ug daily	hypothyroidism
	Month 24	3.0	0.9	1.0		
(b) (6) /48/F/100 mg	Baseline	5.6	1.2	1.3		
	Week 12	3.2	0.9	1.0		
	Week 16	4.7	0.9	1.0	LT4 25 ug daily	hypothyroidism
	Week 20	3.0	0.8	0.9		
	Week 24	1.9	1.0	0.8		
	Week 36	1.3	1.1	1.0		
	Week 52	0.8	0.9	0.8		
Comments: subject had evidence of mild subclinical hypothyroidism at baseline, based on TSH of 5.6, which improved to normal ranges during the study.						
(b) (6) /50/M/100 mg	Baseline	3.5	0.9	1.0		
	Week 12	4.2	0.6	1.0		
	Week 24	3.1	0.6	1.0		
	Week 28	4.7	0.6	1.1	LT4 75 ug daily	hypothyroidism
	Week 32	1.9	0.8	0.9		
	Week 52	1.2	1.2	1.2		

(b) (6) /48/F/100 mg	Baseline	3.8	0.9	1.4		
	Week 12	2.1	0.6	0.9		
	Week 24	1.9	0.5	1.0		
	Week 32	1.9	0.4	0.6	LT4 50 ug daily	hypothyroidism
	Week 40	0.5	0.6	1.2		
	Week 52	2.1	0.5	1.0		
Comments: subject had LT4 started based on low FT4 and T3 levels , while TSH was wnl; FT4 did not improve as a result of LT4 therapy.						
(b) (6) / 66/M/100 mg	Baseline	2.1	0.9	0.9		
	Week 8	2.0	0.7	0.8		
	Week 12	0.5	1.0	1.1		
	Week 16	0.1	0.9	1.0		
	Week 20	4.5	0.5	0.6		
	Week 24	15.2	0.5	0.8	LT4 25 ug daily ; resmetirom interrupted	hypothyroidism
	Week 28	16.2	0.7	1.0		
	Week 36	7.2	0.9	1.1		
	Week 44	3.8	1.1	1.0		
	Week 52	3.6	0.9	1.0		
(b) (6) 69/M/100 mg	Baseline	6.7	0.8	1.1		hypothyroidism
	Week 8	8.6	0.9	0.8		
	Week 16	7.6	0.8	1.1		
	Week 24	5.7	0.7	1.0		
	Week 32	8.2	0.8	0.9		
	Week 52	5.1	0.7	1.0		
Comment: subject with mildly elevated TSH at baseline, which remained stable throughout the study; was not started on LT4.						
(b) (6) /54/M/100 mg	Baseline	3.0	0.9	0.9		
	Week 8	3.7	0.7	0.9		
	Week 24	2.9	0.7	1.0		
	Week 28	1.4	0.7	0.9	LT4 50 ug daily	hypothyroidism
	Week 48	0.09	1.0	1.0		
	Week 52	0.18	1.1	1.2		
	Month 15	1.1	0.8	0.7		
Comment: subject started on LT4 while TSH was normal, possibly due to borderline low FT4; TSH decreased below lower normal range as a result of LT4 initiation.						
(b) (6) /66/F/100 mg	Baseline	1.7	1.1	1.1		
	Week 12	1.0	0.4	0.7		
	Week 24	1.3	0.4	0.6		
	Week 28	0.5	0.3	0.7		
	Week 32	0.38	0.3	0.5	LT4 25 ug daily; resmetirom stopped	hypothyroidism
	Week 36	3.7	0.6	0.7		
	Week 44	1.9	1.1	1.2		
	Week 52	1.6	1.1	1.0		
Comment: Subject discontinued from study drug due to an AE of hypothyroidism. The subject was a 66-year-old woman, weight 72 kg, with type 2 diabetes and hyperlipidemia who was randomized to resmetirom 100 mg daily. The subject was noted to have a low FT4 and T3 with normal TSH starting at week 12, with subsequent decrease in TSH to 0.38 mIU/L at week 32 with persistently low FT4 and T3, suggesting mild central hypothyroidism. At week 36, resmetirom was stopped and the patient was started on levothyroxine 25 mcg daily. Thyroid function tests normalized at subsequent visits. According to the Sponsor, the observed drug-related effect on thyroid function was likely due to the very high exposure to resmetirom. The patient had advanced fibrosis consistent with early cirrhosis, and patient's low body weight <80 kg and age >65 years may also have contributed to increased exposure to the drug. According to						

the proposed label, the recommended resmetirom dose in such a patient is 80 mg daily, based on body weight (b) (4) *correction.*

Normal reference range: TSH: 0.4-4.0 mIU/L; FT4:0.7 -1.6 ng/dL; T3: 0.8-2.0 ug/L.

Source: Clinical reviewer, with data excerpted from Table 10 and Listing 3.3, Response to IR dated Nov 17, 2023.

Table 9. Subjects with AE of TSH Decreased, Study MGL-3196-11

Patient ID/Age/Sex/Resmetirom dose	Study date	TSH (mIU/L)	FT4 (ng/dL)	T3 (ug/L)	Treatment provided for AE	AE
(b) (6) / 60/F/80 mg	Baseline	1.25	1.6	0.9	LT4 75 ug daily	
	Week 4	0.1	1.5	1.0		
	Week 12	0.32	1.2	0.9		
	Week 24	0.1	1.4	0.7		
	Week 32	0.6	1.2	0.8		
	Week 36	0.25	1.2	0.8	No change in LT4 dose	TSH decreased
	Week 44	0.2	1.3	0.8		
	Week 52	0.2	1.1	0.8		
	Month 18	3.4	1.1	0.7		
	Month 24	0.5	1.3	0.9		
(b) (6) / 55/F/80 mg	Baseline	0.4	1.5	1.4		
	Week 4	0.2	1.2	1.4		
	Week 12	0.1	1.2	0.9		TSH decreased
	Week 24	0.6	1.0	1.2		
	Week 32	0.1	1.3	1.1		
	Week 36	0.1	1.4	1.2		
	Week 44	0.2	1.1	1.1		
	Week 52	0.4	1.1	1.2		
	Month 18	0.005	1.3	1.5		
	Month 24	0.005	2.5	3.6		
Comment: TSH progressively decreased with overt hyperthyroidism at month 24; patient had increased TPO antibodies at baseline, suggestive of underlying autoimmune thyroid disease; study drug continued.						
(b) (6) / 62/F/100 mg	Baseline	0.03	1.8	0.8	LT4 125 ug daily	
	Week 4	0.005	1.5	0.9		TSH decreased
	Week 8	0.005	1.4	0.8	LT4 decreased to 112 ug daily	
	Week 12	0.005	1.5	0.8		
	Week 24	0.005	1.2	0.8		
	Week 32	0.04	0.9	0.8		
	Week 36	0.21	0.8	0.5		
Comment: subject with suppressed TSH at 0.03 at baseline, due to over-replacement therapy with LT4. TSH likely further decreased due to resmetirom therapy; Study drug continued.						
(b) (6) / 77/F/100 mg	Baseline	0.5	1.5	1.2	LT4 50 ug daily	
	Week 4	0.1	1.8	1.2		
	Week 12	0.1	1.2	1.2	No change in LT4	TSH decreased
	Week 20	2.0	0.8	0.9		
	Week 24	5.3	0.7	1.0		
	Week 32	4.2	0.7	1.0	LT4 increased to 75 ug daily	
	Week 36	4.3	0.7	1.0		

	Week 44	2.8	0.9	1.0		
	Week 52	2.7	1.0	1.0		
	Month 18	6.1	1.0	1.1		
(b) (6) / 62/F/100 mg	Baseline	1.0	0.9	0.8	LT4 75 ug daily	
	Week 4	0.005	0.6	0.9	Study drug interrupted	TSH decreased
	Week 12	0.005	0.7	0.9		
	Week 16	0.6	0.8	0.7	LT4 decreased to 50 ug daily	
	Week 20	0.02	0.7	0.9		
	Week 28	0.4	0.5	0.7		
	Week 36	0.7	0.4	0.7		
	Week 52	0.4	0.7	0.7		
	Month 18	0.3	0.5	0.5		
Comment: study drug interrupted due to AE of TSH decreased; unclear if study drug resumed; LT4 dose also decreased from 75 ug to 50 ug daily; TSH subsequently improved to low normal ranges, while FT4 and T3 remained borderline possibly due to both, study drug and LT4 dose reduction.						
(b) (6) 69/F	Baseline	1.1	1.3	1.0		
	Week 4	0.06	0.8	1.0		TSH decreased
	Week 12	0.25	0.5	0.9		
	Week 16	0.7	0.5	0.8		
	Week 20	0.8	0.5	0.7		
	Week 28	1.3	0.5	0.8		
	Week 36	2.2	0.5	0.7		
	Week 52	1.4	0.5	0.7	LT4 75 ug daily started approx. 45 days prior to month 15	
	Month 15	0.005	1.3	1.4		
	Month 18	0.005	1.4	1.0		
Comment: subject with transient TSH decreased post resmetirom initiation, while FT4 stably low at 0.5; LT4 started after end of week 52, which resulted in TSH suppression with normalization in FT4 (i.e., subclinical iatrogenic hyperthyroidism).						

Normal reference range: TSH: 0.4-4.0 mIU/L; FT4:0.7 -1.6 ng/dL; T3: 0.8-2.0 ug/L.

Source: Clinical reviewer, with data excerpted from Table 11 and Listing 3.3, Response to IR dated Nov 17, 2023.

Table 10. Subjects with AE Hyperthyroidism, Studies MGL-3196-11 and MGL-3196-14

Patient ID/Age/Sex/Resmetirom dose	**Study date**	**TSH (mIU/L)**	**FT4 (ng/dL)**	**T3 (ug/L)**	**Treatment provided for AE**	**AE**
Study MGL-3196-11						
(b) (6) /58/F /100 mg	Baseline	0.65	0.9	1.9	On Thyroid 90 ug daily at baseline	
	Week 4	0.14	0.9	1.9	Thyroid dose decreased to 60 ug daily	Hyperthyroidism
	Week 8	1.08	0.7	1.6		
	Week 16	1.3	0.6	1.1		
	Week 24	1.1	0.6	1.0		
	Week 36	0.7	0.6	1.3		
	Week 52	1.0	0.7	1.7		
Study MGL-3196-14						

(b) (6) 68/M/80 mg	Baseline	1.5	1.2	0.8	On LT4 150 ug daily at baseline	
	Week 8	2.0	1.2	0.7		
	Week 16	2.0	1.3	0.7		
	Week 24	0.8	1.3	0.7		
	Week 36	0.4	1.1	0.7		
	Week 40	0.3	1.3	0.8		Hyperthyroidism
	Week 48	0.2	1.1	0.8	LT4 dose reduced	
	Week 52	0.3	1.1	0.8		

Normal reference range: TSH: 0.4-4.0 mIU/L; FT4:0.7 -1.6 ng/dL; T3: 0.8-2.0 ug/L.

Source: Clinical reviewer, with data excerpted from Table 12 and Listings 3.3 and 3.4, Response to IR dated Nov 17, 2023

Table 11. Patients 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	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)
AEs possibly related to hyperthyroidism					
Fatigue	66/725.8 (9.1)	53/721.4 (7.3)	53/739.4 (7.2)	1.9 (-1.0, 4.9)	0.2 (-2.6, 3.0)
Tachycardia	7/773.8 (0.9)	8/763.1 (1.0)	5/789.3 (0.6)	0.3 (-0.7, 1.3)	0.4 (-0.6, 1.5)
Tremor	7/772.2 (0.9)	5/765 (0.7)	1/791.8 (0.1)	0.8 (0.1, 1.8) *	0.5 (-0.1, 1.4)
Irritability	1/776.3 (0.1)	3/765.8 (0.4)	4/788.4 (0.5)	-0.4 (-1.2, 0.3)	-0.1 (-1.0, 0.7)
Anxiety	21/763.1 (2.8)	20/752.7 (2.7)	22/776.9 (2.8)	-0.1 (-1.8, 1.7)	-0.2 (-1.9, 1.6)
Insomnia	16/764.7 (2.1)	18/756.8 (2.4)	21/771.7 (2.7)	-0.6 (-2.3, 1.0)	-0.3 (-2.0, 1.3)
AEs possibly related to hypothyroidism					
Fatigue	66/725.8 (9.1)	53/721.4 (7.3)	53/739.4 (7.2)	1.9 (-1.0, 4.9)	0.2 (-2.6, 3.0)
Constipation	41/739.2 (5.5)	44/723.2 (6.1)	34/767.3 (4.4)	1.1 (-1.2, 3.5)	1.7 (-0.7, 4.1)
Arthralgia	78/711.7 (11.0)	64/712.9 (9.0)	67/732 (9.2)	1.8 (-1.5, 5.2)	-0.2 (-3.3, 3.0)
Myalgia	16/763.5 (2.1)	19/750.1 (2.5)	19/777.1 (2.4)	-0.3 (-1.9, 1.2)	0.1 (-1.6, 1.8)

Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); FMQ, FDA medical query; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk).

Source: Clinical Data Scientist: MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R; Asterisk (*) indicates that 95% confidence interval excludes zero.

Table 12. Changes from Baseline to Week 52 in Sex Hormones, by Sex, Trial MGL-3196-11 (Safety Population – F1B, F2, F3)

	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
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
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

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

Source: Table 69, CSR, MGL-3196-11

Table 13. Patients With Adverse Events by Male-Specific FDA Medical Query (Narrow) and Preferred Term, Male Safety Population, Trial Pooled Trials MGL-3196-11 and MGL-3196-14

System Organ Class FMQ (Narrow) Preferred Term	Resmetirom 80 mg PY=335.5 N=299 n/py (EAIR)	Resmetirom 100 mg PY=347.4 N=299 n/py (EAIR)	Placebo PY=364.6 N=307 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)					
Gynecomastia (FMQ)	0/335.5 (0)	0/347.4 (0)	1/364.4 (0.3)	-0.3 (-1.6, 0.9)	-0.3 (-1.6, 0.8)
Gynecomastia	0/335.5 (0)	0/347.4 (0)	1/364.4 (0.3)	-0.3 (-1.6, 0.9)	-0.3 (-1.6, 0.8)
Erectile dysfunction (FMQ)	4/332.6 (1.2)	2/346.5 (0.6)	4/361.6 (1.1)	0.1 (-1.8, 2.1)	-0.5 (-2.3, 1.1)
Erectile dysfunction	4/332.6 (1.2)	2/346.5 (0.6)	4/361.6 (1.1)	0.1 (-1.8, 2.1)	-0.5 (-2.3, 1.1)

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 patients in treatment arm; n, number of patients with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class.

Source: Clinical Data Scientist, MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R

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

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

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 patients in treatment arm; n, number of patients with adverse event; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class.

Source: Clinical Data Scientist, MGL-3196-11 adae.xpt, MGL-3196-14 adae.xpt; Software: R

Table 15. Shift Table of Bone Mineral Density T Score Risk Category Results – Observed Data (Intent-to-Treat Population, Subgroup: Female Subjects Not Taking Thyroxine at Baseline, Estradiol <30 ng/L at Baseline, and Weight Loss <5% at Week 52, Trial MGL-3196-11

	Resmetirom 80 mg			Resmetirom 100 mg			Placebo		
	Normal N (%)	Low Density N (%)	Possible Osteoporosis N (%)	Normal N (%)	Low Density N (%)	Possible Osteoporosis N (%)	Normal N (%)	Low Density N (%)	Possible Osteoporosis N (%)
Femoral Neck									
Normal	40 (51.3)	2 (2.6)	0	32 (52.5)	3 (4.9)	0	41 (50.0)	2 (2.4)	0
Low Density	6 (7.7)	25 (32.1)	0	2 (3.3)	21 (34.4)	0	4 (4.9)	31 (37.8)	0
Possible Osteoporosis	0	1 (1.3)	1 (1.3)	0	1 (1.6)	0	0	0	0
Missing	3 (3.8)	0	0	1 (1.6)	0	0	2 (2.4)	1 (1.2)	0
Femoral Total									
Normal	67 (85.9)	1 (1.3)	0	47 (77.0)	0	0	64 (78.0)	1 (1.2)	0
Low Density	1 (1.3)	6 (7.7)	0	2 (3.3)	10 (16.4)	0	2 (2.4)	11 (13.4)	0
Possible Osteoporosis	0	0	0	0	0	0	0	0	0
Missing	3 (3.8)	0	0	1 (1.6)	0	0	3 (3.7)	0	0
Spine Adjusted Total									
Normal	54 (69.2)	2 (2.6)	0	45 (73.8)	2 (3.3)	0	52 (63.4)	2 (2.4)	0
Low Density	2 (2.6)	14 (17.9)	0	1 (1.6)	8 (13.1)	0	4 (4.9)	18 (22.0)	0
Possible Osteoporosis	0	1 (1.3)	1 (1.3)	0	1 (1.6)	3 (4.9)	0	0	2 (2.4)
Missing	1 (1.3)	1 (1.3)	0	1 (1.6)	0	0	2 (2.4)	1 (1.2)	0
Spine Total									
Normal	55 (70.5)	1 (1.3)	0	45 (73.8)	2 (3.3)	0	52 (63.4)	2 (2.4)	0
Low Density	3 (3.8)	14 (17.9)	0	1 (1.6)	8 (13.1)	0	4 (4.9)	17 (20.7)	0
Possible Osteoporosis	0	0	1 (1.3)	0	1 (1.6)	3 (4.9)	0	1 (1.2)	2 (2.4)
Missing	1 (1.3)	1 (1.3)	0	1 (1.6)	0	0	2 (2.4)	1 (1.2)	0

Note: Category Criteria: Normal = T Score ≥-1.0; Low Density = T Score ≥-2.5 and <-1.0; Possible Osteoporosis = T Score <-2.5; Column headers are baseline status and row headers are status at the post-baseline visit.

Source: Table 71, Interim CSR

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12/20/2023 07:31:17 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 7, 2023
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 217785
Product Name, Dosage Form, and Strength:	Resmetirom tablets, 60 mg, 80 mg, 100 mg
Applicant/Sponsor Name:	Madrigal Pharmaceuticals, Inc.
TTT ID #:	2023-5596-1
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 31, 2023 for Resmetirom. The Division of Hepatology and Nutrition (DHN) requested that we review the revised prescribing information, container labels and carton labeling for Resmetirom (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant will need to replace the placeholder "Tradename" with the intended proprietary name when one has been found conditionally acceptable. Beyond this, the Applicant implemented all of our previous container label and carton labeling recommendations and we have no additional recommendations at this time.

9 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Hakeem, S. Label and Labeling Review for Resmetirom (NDA 217785). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 OCT 16. TTT ID No.: 2023-5596.

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11/07/2023 02:40:12 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 16, 2023
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 217785
Product Name, Dosage Form, and Strength:	Resmetirom tablets, 60 mg, 80 mg, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Madrigal Pharmaceuticals, Inc.
FDA Received Date:	July 14, 2023
TTT ID #:	2023-5596
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Resmetirom tablets, the Division of Hepatology and Nutrition (DHN) requested that we review the proposed Resmetirom prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 217785 is a 505(b)(1) application submitted on July 14, 2023.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C—NA
FDA Adverse Event Reporting System (FAERS)*	D—NA
Other	E—NA
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Madrigal Pharmaceuticals, Inc.

4 RECOMMEDATIONS FOR DIVISION OF HEPATOLOGY AND NUTRITION (DHN)

Table 2. Identified Issues and Recommendations for Division of Hepatology and Nutrition (DHN)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented in the *Dosage and Administration* section, body weight is presented in two units of measure, kilograms and pounds.	Only metric units (e.g., kilograms) should be used.	Remove reference to weight in pounds.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Body weight is presented in two units of measure, kilograms and pounds.	Only metric units (e.g., kilograms) should be used.	Remove reference to weight in pounds.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the storage statement contains the dash symbol, "-". Additionally, the first temperature in the range is missing the degree symbol and the units of measurement (e.g., °C and °F).	The storage statement should be clearly stated to mitigate the risk of storage errors.	To provide clarity, replace the dash symbol with its intended meaning, "to". Additionally, insert the missing degree symbol (°) and the units of measurement (C) and (F) after the first temperature of each temperature range. Revise the sentence to read "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."
2.	Under the subheading *60 mg Tablets*, the colon is missing between the national drug code (NDC) and numeric portion of the strength.	The NDC or strength could be misread.	Add a colon to separate the NDC from strength, for example, revise to read: NDC 82576-060-30: 60 mg tablets (30 count)

Table 2. Identified Issues and Recommendations for Division of Hepatology and Nutrition (DHN)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	(b) (4)		
Patient Information			
1.	In the *How should I store PROPRIETARY NAME* section, the temperature range is presented without the degree symbol (°) and units of measurement, (F) and (C), following each temperature in the range.	The storage statement should be clearly stated to mitigate the risk of storage errors.	To provide clarity, revise the storage statement to read "Store PROPRIETARY NAME at room temperature between 68°F to 77°F (20°C to 25°C)."

5 RECOMMENDATIONS FOR MADRIGAL PHARMACEUTICALS, INC.

Table 3. Identified Issues and Recommendations for Madrigal Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The proposed proprietary name, "(b) (4)", is included on the proposed container labels and carton labeling.	The proposed proprietary name, (b) (4), was found unacceptable by the Agency as communicated in the Proprietary Name Request Unacceptable letter communicated on October 2, 2023.	Replace all references to "(b) (4)", with the placeholder "TRADENAME" in the intended font size and location. Once a proprietary name is found conditionally acceptable, you can then replace the placeholder, "TRADENAME" with the conditionally acceptable proprietary name and submit the revised labeling for our review.

Table 3. Identified Issues and Recommendations for Madrigal Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the storage statement contains the dash symbol, "-". Additionally, the first temperature in the range is missing the degree symbol and the units of measurement (e.g., °C and °F).	The storage statement should be clearly stated to mitigate the risk of storage errors.	To provide clarity, replace the dash symbol with its intended meaning, "to". Additionally, insert the missing degree symbol (°) and the units of measurement, (C) and (F), after the first temperature of each temperature range. Revise the sentence to read "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].".

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Resmetirom that Madrigal Pharmaceuticals, Inc. submitted on July 14, 2023.

Table 4. Relevant Product Information for Resmetirom	
Initial Approval Date	N/A
Active Ingredient	Resmetirom
Indication	Treatment of non-alcoholic steatohepatitis (NASH) in patients with liver fibrosis
Route of Administration	Oral
Dosage Form	Tablet
Strength	60 mg, 80 mg, 100 mg
Dose and Frequency	80 mg to 100 mg once daily
How Supplied	<u>60 mg Tablets</u> PROPRIETARY NAME tablets are white oval-shaped film-coated tablets (b) (4) debossed "P60" on one side and plain on the other side. • NDC 82576-060-30 60 mg tablets (30 count) <u>80 mg Tablets</u> PROPRIETARY NAME tablets are yellow oval-shaped film-coated tablets (b) (4) debossed P80 on one side and plain on the other side. (b) (4) • NDC 82576-080-30: 80 mg tablets (30 count) • NDC 82576-080-90: 80 mg tablets (90 count) <u>100 mg Tablets</u> PROPRIETARY NAME tablets are beige to pink (b) (4) oval-shaped film-coated tablets (b) (4) debossed P100 on one side and plain on the other side. (b) (4) • NDC 82576-100-30: 100 mg tablets (30 count) • NDC 82576-100-90: 100 mg tablets (90 count)
Storage	Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Excursions to 15°C to 30°C (59°F to 86°F) are permitted.

Table 4. Relevant Product Information for Resmetirom	
Container Closure	Resmetirom tablets are packaged in white, high-density polyethylene (HDPE) bottles with child resistant, induction-sealed caps.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 25, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, “Resmetirom” and “NDA 217785”. Our search identified one previous review.[a]

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[a] Vaughan, V. Medication Error Review – Response to OPQ Consult for Resmetirom IND 122865. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 02. TTT ID No. 2022-2658.

APPENDIX C. —NA

APPENDIX D. —NA

APPENDIX E. —NA

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error experiences with similar products, we reviewed the following Resmetirom labels and labeling submitted by Madrigal Pharmaceuticals, Inc.

- Container label(s) received on July 14, 2023.
- Carton labeling received on July 14, 2023.
- Prescribing Information and Patient Information (Image not shown) received on July 14, 2023
    - Proposed Prescribing Information available from the following link: \\CDSESUB1\EVSPROD\nda217785\0003\m1\us\114-labeling\draft\labeling\resmetirom-pi-draft-label-text.pdf
    - Proposed Patient Information available from the following link: \\CDSESUB1\EVSPROD\nda217785\0003\m1\us\114-labeling\draft\labeling\resmetirom-patient-info.pdf.

F.2 Label and Labeling Images

Container labels

9 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

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