CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217785Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 122865
Request Receipt Date	February 17, 2023
Product	MGL-3196 (Resmetirom)
Indication	Nonalcoholic steatohepatitis (NASH) with fibrosis
Drug Class/Mechanism of Action	Thyroid hormone receptor (THR) agonist
Sponsor	Madrigal Pharmaceuticals, Inc.
ODE/Division	OII/DHN
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	April 18, 2023

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR).* ***Link this review to the incoming BTDR.*** *Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The Sponsor is developing MGL-3196 (resmetirom), an oral, once-daily thyroid hormone receptor (THR)-β agonist for the treatment of non-alcoholic steatohepatitis (NASH) with fibrosis.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Disease

Nonalcoholic fatty liver disease (NAFLD) can be categorized histologically into nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH). NAFL is defined as an accumulation of ≥ 5% fat in the liver (hepatic steatosis) when no other causes of secondary liver fat accumulation are present. NASH is characterized by the presence of steatosis, inflammatory changes, and ballooning degeneration of hepatocytes. NAFLD affects approximately 25% of the population globally, whereas NASH prevalence is estimated to be between 1.5% and 6.5%. Presence of fibrosis is the strongest predictor of mortality (1). NAFL has been considered as a benign condition, with the presence of bland steatosis without features of NASH. However, NASH can be a progressive disease that might advance to cirrhosis with complications (e.g., variceal bleeding, hepatic encephalopathy, ascites), hepatocellular carcinoma, liver transplantation, or death. The incidence of liver transplantation secondary to NASH is increasing. NASH is also associated with increased risk of major adverse cardiac events.

No FDA approved pharmacological treatments for NASH are available. Lifestyle management with diet and exercise is currently considered the standard treatment. Thus, NASH is a serious condition with unmet medical need.

Investigational Agent

Resmetirom is an orally active, liver-directed, partial agonist of thyroid hormone receptor β (THR-β). The Sponsor states resmetirom has 28-fold selectivity for THR-β versus THR-α compared to triiodothyronine (T3), thereby it will provide liver-mediated metabolic benefits of thyroid hormone without unwanted systemic actions of thyroid hormone in heart and bone. In addition, in contrast to thyroid hormone, which may be rapidly metabolized in the liver because of deiodinase activity, resmetirom is insensitive to deiodinase action. Data suggest that a condition of liver-specific hypothyroidism exists in livers of patients with NAFLD/NASH, particularly those with more advanced disease. Beneficial effects of resmetirom on cholesterol, triglycerides (TGs), and liver TGs, with a reduction in inflammatory and fibrosis gene transcripts characteristic of NASH were observed in preclinical animal models.

The Sponsor is developing resmetirom for the treatment of NASH with fibrosis. The Sponsor is conducting four phase 3 clinical trials (see below). Trial MGL-3196-11 collected liver histology to support endpoints for a potential subpart H accelerated approval pathway (Part 1, complete), followed by the study of long-term clinical outcomes in non-cirrhotic NASH patients with liver fibrosis (Part 2, ongoing). The Sponsor submitted the key efficacy results from the 52 Week analysis of MGL-3196-11 (MAESTRO-NASH) to support the BTDR.

- MGL-3196-11 (MAESTRO-NASH): A phase 3, multinational, double-blind, randomized, placebo-controlled study of MGL-3196 (resmetirom) in patients with non-alcoholic steatohepatitis (NASH) and fibrosis to resolve NASH and reduce progression to cirrhosis and/or hepatic decompensation.

- MGL-3196-14 (MAESTRO-NAFLD-1): A 52-week, phase 3 study to evaluate safety and biomarkers of resmetirom (MGL-3196) in patients with NAFLD.

- MGL-3196-18 (MAESTRO-NAFLD-OLE): A 52-week, phase 3, open-label extension study, with a double-blind lead-in, to evaluate safety and biomarkers of resmetirom (MGL-3196) in patients with NAFLD (an extension study of the completed patients from MGL-3196-14 including non-cirrhotic and cirrhotic NASH patients).

- MGL-3196-19 (MAESTRO-NASH-OUTCOMEs): An event driven clinical outcome study in patients with well-compensated CP-A NASH cirrhosis to evaluate resmetirom versus placebo as measured by time to experiencing a first adjudicated Composite Clinical Outcome event, defined as any of the following: all-cause mortality, liver transplant, and significant hepatic events including hepatic decompensation events (ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage) and confirmed increase of Model for End-stage Liver Disease (MELD) score from < 12 to ≥ 15

Regulatory History

- IND opening phase 2 clinical trial was determined to be safe to proceed on August 24, 2016
- Type B End of Phase 2 (EOP2) meeting on September 27, 2018
- Fast track designation was granted on October 18, 2019
- Type C meeting to discuss a future clinical trial for subjects with NASH with compensated cirrhosis (Trial MGL-3196-19) on February 16, 2022
- Type C meeting to discuss multiple issues relevant to the phase 3 development program on August 22, 2022
- Request for Preliminary BTDR Advice on February 8, 2023 – the Division informed the Sponsor that the summary data from the phase 3 trial MGL-3196-11 might be adequate for BTDR.
- Type B Pre-NDA meeting on February 27, 2023

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor submitted the preliminary results from the ongoing phase 3 trial MGL-3196-11 (MAESTRO-NASH) to support the BTDR application. The Sponsor assessed the following endpoints at Week 52 of the clinical trial.

- Primary endpoints: NASH resolution (ballooning 0, inflammation 0 to 1) with ≥ 2-point reduction in NAS (NAFLD Activity Score) and no worsening of fibrosis OR reduction in fibrosis stage by ≥ 1 point with no worsening of NAS on Week 52 biopsy. The proposed primary endpoints are surrogate endpoints, considered reasonably likely to predict clinical benefit to support accelerated approval.
- Secondary endpoints: percent change in low-density lipoprotein (LDL)-cholesterol at Week 24 compared with the baseline value

The primary endpoints chosen by the Sponsor are accepted by the Division as surrogate endpoints that are reasonably likely to predict clinical benefit as outlined in the draft guidance for industry *Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment.*[3]

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

[3] https://www.fda.gov/media/119044/download

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

  Acceptable clinical endpoints are an improvement in a composite endpoint of all-cause mortality, liver transplant, decompensation events (hepatic encephalopathy, ascites, variceal bleeding, etc.), change in MELD score from less than or equal to 12 to more than 15, progression to cirrhosis on histopathology in patients without cirrhosis at baseline.

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

  At present, there is no validated surrogate endpoint for NASH that can support traditional approval.

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

  Because of the slow progression of NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, the Division recommends sponsors consider the following liver histological improvements as endpoints reasonably likely to predict clinical benefit to support accelerated approval:

  Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and NAS of 0-1 for inflammation, 0 for ballooning, and any value for steatosis;

  OR

  Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis);

  OR

  Both resolution of steatohepatitis and improvement in fibrosis (as defined above).

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

For substantial evidence of clinical effectiveness reasonably likely to predict clinical benefit, histology is the only biomarker currently accepted by the Division.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

  At present, there is no FDA-approved therapy for NASH.

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

  Several drugs have been used off-label for the treatment of NASH. According to the clinical guidelines by the American Association for the Study of Liver Diseases (AASLD), off-label pioglitazone use has been recommended in patients with biopsy proven NASH with or without type 2 diabetes mellitus (T2DM). Furthermore, vitamin E use has also been recommended for treatment of biopsy-proven NASH in nondiabetics (2).

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[4].

The following drugs have been granted BTD for NASH (**Table 1**):

1. Obeticholic acid (Sponsor- Intercept), under IND (b) (4) was granted BTD on January 28, 2015, as the phase 2 trial achieved its primary endpoint (b) (4)

2. (b) (4)

3. Lanifibranor (Sponsor - Inventiva, S.A), under IND (b) (4) , was granted BTD on October 8, 2020, as the phase 2 trial achieved the primary endpoint (b) (4) histologic endpoints.

4. Efruxifermin (Sponsor - Akero Therapeutics), under IND (b) (4) was granted BTD on December 6, 2022, as the phase 2 trial demonstrated a significant improvement in liver fibrosis (b) (4)

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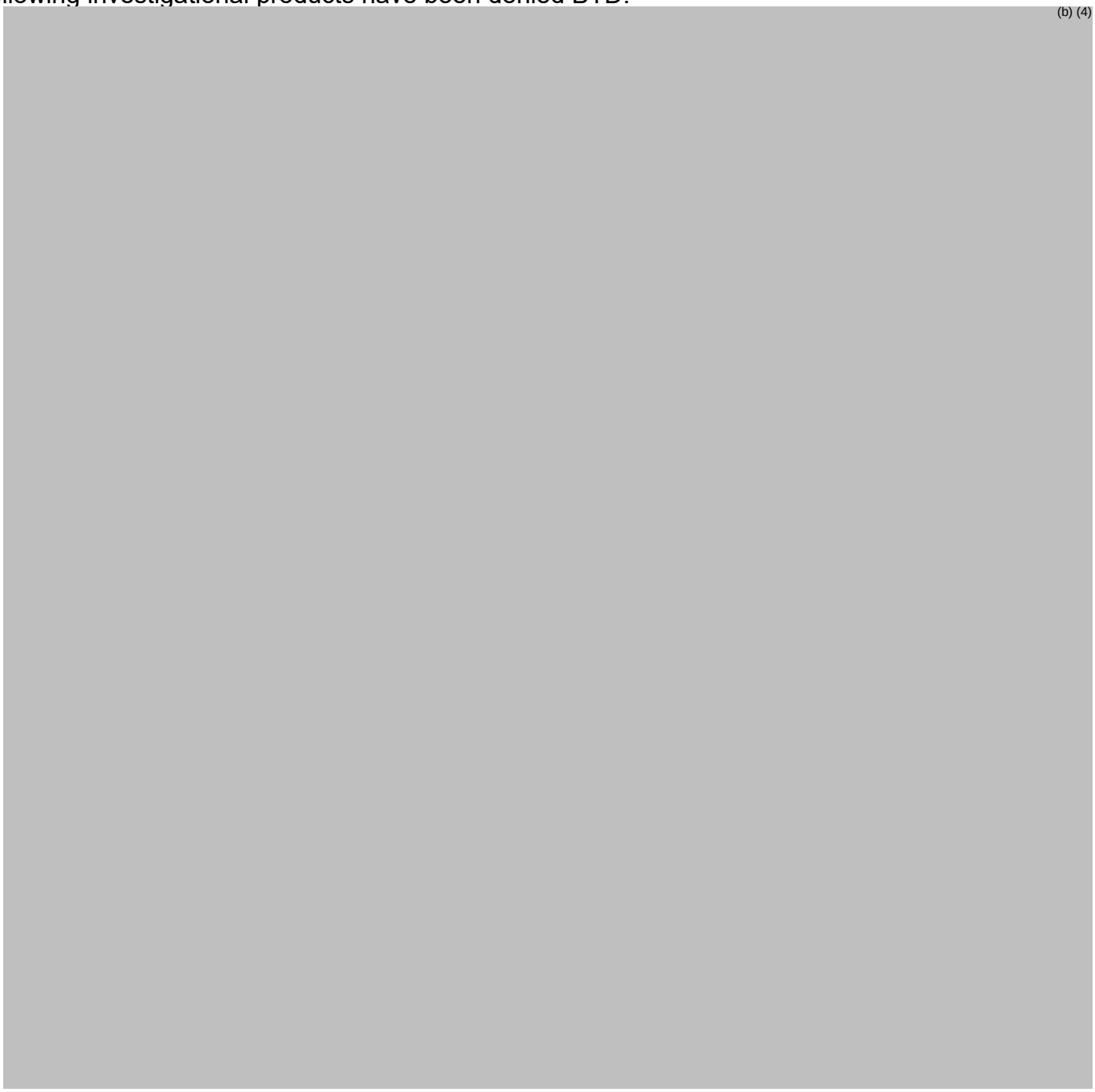
[4] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

The following investigational products have been denied BTD:

(b) (4)



11. Information related to the preliminary clinical evidence:

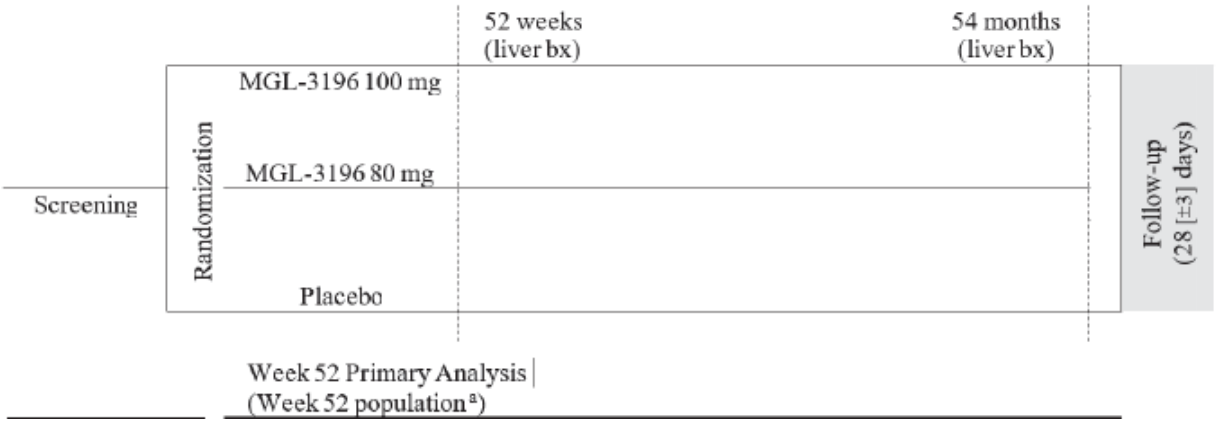
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[5], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The Sponsor submitted the preliminary efficacy data obtained from the ongoing phase 3 trial MAESTRO-NASH (Study MGL-3196-11) at Week 52 to support the current BTDR (**Figure 1**).

[5] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

The phase 3 trial comprises two stages: Week 52 Analysis and Month 54 Analysis. The key objective of Week 52 Analysis is to assess histologic endpoints (i.e., surrogate endpoints) to support subpart H, whereas the key objective of Month 54 Analysis is to assess clinical outcomes to support traditional marketing approval.

Figure 1. Schematic of Study MGL-3196-11



Source: Study MGL-3196-11 Protocol Version 5.0

The baseline characteristics of the subjects included in the 52 Week Analysis were balanced across treatment arms as shown in **Table 2**.

Table 2. Baseline Characteristics for MAESTRO-NASH (Study MGL-3196-11)

	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)	Overall (N=966)
Age mean (SD)	56 (12)	57 (11)	57 (11)	57 (11)
Female n, (%)	182 (57)	182 (56)	178 (56)	542 (56)
White n, (%)	291 (90)	291 (90)	281 (88)	863 (89)
Hispanic or Latino n, (%)	71 (22)	81 (25)	52 (16)	204 (21)
BMI mean (SD)	36 (6)	36 (7)	35 (7)	36 (7)
Type 2 Diabetes n, (%)	224 (70)	213 (66)	210 (65)	647 (67)
Hypertension n, (%)	243 (76)	254 (79)	257 (80)	754 (78)
Dyslipidemia n, (%)	230 (71)	236 (73)	223 (70)	689 (71)
Hypothyroid n, (%)	38 (12)	46 (14)	45 (14)	129 (13)
FibroScan VCTE kPa mean (SD)	13 (7)	14 (7)	13(6)	13 (7)
FibroScan CAP mean (SD)	346 (37)	349 (39)	347 (37)	348 (38)
MRI-PDFF mean (SD)	18 (7)	17 (7)	18 (7)	18 (7)
Baseline Liver Biopsy				
NAS ≥ 5 n, (%)	266 (83)	288 (89)	253 (79)	807 (84)
1B n, (%)	16 (5)	15 (5)	18 (6)	49 (5)
2 n, (%)	107 (33)	100 (31)	112 (35)	319 (33)
3 n, (%)	199 (62)	208 (64)	191 (60)	598 (62)

BMI = body-mass index; CAP = controlled attenuation parameter; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; NAS = NAFLD activity score; SD = standard deviation; VCTE = vibration-controlled transient elastography.

Table 3 summarizes the trial design and the key efficacy results. The trial demonstrated a significant improvement in primary endpoints (i.e., histological efficacy endpoints accepted by

the Division as surrogate endpoints reasonably likely to predict clinical benefit) in both doses of resmetirom arms (i.e., 80 mg and 100 mg) compared with the placebo arm.

All baseline and Week 52 biopsies were read independently by two central pathologists using glass slides, and the results were combined using Cochran-Mantel-Haenszel (CMH) model to generate a single treatment effect, as shown in **Table 3**. The Sponsor also analyzed the histologic endpoints based on the consensus reads of digitized images by the two central pathologists in cases where the two pathologists disagreed on the primary endpoints (the result is shown in Table 3 on page 11 of the BTDR application). Both analyses revealed consistent results that are clinically meaningful and statistically significant to demonstrate significant improvement for both primary endpoints.

Additionally, both resmetirom arms reached a key secondary endpoint (i.e., change in LDL cholesterol). The key secondary endpoint on LDL is proposed as a safety endpoint, given that cardiovascular disease and stroke are important comorbidities in patients with NASH.

Table 3. Summary of Ongoing Clinical Trial Supporting the BTDR - MAESTRO-NASH (Study MGL 3196-11) : Proportion of subjects who achieved primary and secondary endpoints

Study ID **Phase** **Duration**	**Study Design** **Key Enrollment Criteria**	**Week 52 Key Endpoints**	**Sample Size and Results**		
			Resmetirom 80 mg (n=316)	**Resmetirom 100 mg (n=321)**	**Placebo (n=318)**
MGL-3196-11 Phase 3 54 Months	**Study Design** • Double blind, randomized placebo controlled, multicenter trial (1:1:1 assignment to placebo, resmetirom 80mg or 100mg orally once a day) • Dose: two doses of daily oral Resmetirom 80mg or 100mg and placebo • Sample size: total enrollment for the trial is about 2000. For the current primary Week 52 analysis, data from approximately 966 subjects are available. **Key Enrollment criteria** • Subjects ≥18 years of age with 3 out of 5 metabolic risk factors (i.e., BMI ≥ 30 kg/m^2, elevated triglycerides, reduced HDL cholesterol, hypertension, Type 2 diabetes mellitus) • ≥ 8% liver fat on MRI-PDFF • Biopsy proven NASH within ≤ 6 months of randomization with	**Dual Primary Endpoints:** • NASH resolution (ballooning 0, inflammation 0 or 1) with ≥ 2-point reduction in NAS (NAFLD activity score) and no worsening of fibrosis • At least 1-stage improvement in fibrosis by liver biopsy with no worsening of NAS **Key Secondary Endpoint:** • Percent change in directly measured low-density lipoprotein cholesterol (LDL-C) between baseline and Week 24	26%* 24%* -12%*	30%* 26%* -16%*	10% 14% 1%

	fibrosis stage 1 to 3 and NAS of ≥ 4 (at least 1 point in Steatosis, Ballooning degeneration, Lobular inflammation) • Patients with active hyperthyroidism were excluded. Patients with untreated clinical hypothyroidism were excluded.				

Source: Generated by the clinical reviewer using BTDR application and MGL3196-11 Study Protocol Version 5.0 submitted by the Sponsor
* p<0.001 compared to the placebo arm

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

  The data the Sponsor provided to support the current BTDR are considered preliminary clinical evidence of substantial efficacy – subjects who were treated with 80mg and 100mg of resmetirom for 52 weeks demonstrated a substantial improvement in the primary histologic endpoints that are accepted as surrogate endpoints reasonably likely to predict a clinical benefit (**Table 3**). The improvement in the histologic endpoints in both active treatment arms was statistically significant compared with the placebo arm.

  The reviewer has not identified deficiencies in the trial that could decrease the persuasiveness of the preliminary evidence of effectiveness. When the complete efficacy and safety data from the ongoing phase 3 trial are submitted as part of the NDA, we may identify potential deficiencies that negatively affect the benefit-risk assessment of the study drug. However, at present, the preliminary efficacy results the Sponsor submitted appear robust and persuasive.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

  The most advantageous aspect of this clinical program when evaluating the preliminary clinical evidence was the sample size and the duration of the trial. As **Table 1** highlights, the Sponsor's clinical trial had a substantially larger sample size compared with the other programs that were granted BTD. The study duration was also longer than some other programs. Because of these factors, the presented preliminary efficacy data seem at least as persuasive as other clinical programs listed in **Table 1**.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

  Resmetirom has been well-tolerated in the Sponsor's development program. The most common adverse events were diarrhea and nausea of mild intensity. No difference was

observed in the rate of serious adverse events, TEAEs leading to study drug discontinuation, or MACE, between the resmetirom and the placebo arms.

A detailed review of the safety profile in the phase 3 clinical program is expected to commence as soon as the NDA application is filed. However, at present, the Division has not identified a concerning safety signal that negatively affects Division's recommendation to grant BTD.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

The Sponsor demonstrated that a daily administration of resmetirom 80mg or 100mg over 52 weeks significantly improved dual primary endpoints: "NASH resolution with ≥ 2-point reduction in NAS and no worsening of fibrosis" and "At least 1-stage improvement in fibrosis by liver biopsy with no worsening of NAS" in a phase 3 clinical trial that enrolled 966 subjects with biopsy-proven NASH. Nominally, a higher proportion of subjects who received 100 mg of resmetirom achieved the dual endpoints than 80 mg of resmetirom (**Table 3**). The Division accepts these endpoints in NASH clinical trials as surrogate endpoints that are reasonably likely to predict a clinical benefit.

The preliminary efficacy results the Sponsor submitted to support the current BTDR are promising in that the clinical trial was substantially larger than those of other NASH programs that have been granted BTD. A pre-NDA meeting was held on February 27, 2023. The Sponsor plans to submit study MGL3196-11 as one adequate and well controlled study, with confirmatory evidence to support a subpart H NDA application. Although the Division's risk-benefit assessment in the NDA review process might change the overall impression of resmetirom as a therapeutic option for NASH, the preliminary evidence of efficacy data is substantial and persuasive, and the safety profile also seems acceptable. The Division recommends granting BTD.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division and the Sponsor had a pre-NDA meeting on February 27, 2023. The Sponsor plans to pursue accelerated approval pathway based on the histologic surrogate endpoints assessed in their phase 3 trial MGL-3196-11 (MAESTRO-NASH). The same trial will collect clinical outcomes for up to 54 months. The Sponsor is also studying subjects with NASH and compensated cirrhosis in a phase 3 trial MGL-3196-19 (MAESTRO-NASH-OUTCOMEs). The Division expects to embark on the NDA review as soon as the application is filed.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Angulo, P., et al. (2015). Liver Fibrosis, but No Other Histologic Features, Is Associated with Long-term Outcomes of Patients with Nonalcoholic Fatty Liver Disease. Gastroenterology, 149(2), 389-397 e310.
2. Chalasani, N., et al. (2018). The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology, 67(1), 328-357.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

TORU MATSUBAYASHI
04/10/2023 12:26:13 PM

GERRI R BAER
04/11/2023 10:19:20 AM

FRANK A ANANIA
04/11/2023 10:34:49 AM

IND 122865

MEETING MINUTES

Madrigal Pharmaceuticals, Inc.
Chief Medical Officer, President, Research & Development
200 Barr Harbor Drive
Suite 200
West Conshohocken, PA 19428

Attention: Scott Wesselkamper
Senior Manager, Regulatory Affairs

Dear Dr. Wesselkamper:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for resmetirom (MGL-3196).

We also refer to the teleconference between representatives of your firm and the FDA on February 27, 2023. The purpose of the meeting was to discuss the development of resmetirom for the treatment of NASH in preparation for an NDA submission during the first half of 2023. Madrigal is requesting FDA's scientific and regulatory input to guide the content of this NDA submission for resmetirom.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me at Taiye.Adedeji@fda.hhs.gov or at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Taiye Adedeji, PharmD
Senior Regulatory Health Project Manager
Hepatology and Nutrition
Division of Regulatory Operations for Immunology
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 27, 2023
Meeting Location: 1:00 PM to 2:00 PM US Eastern Time

Application Number: IND 122865
Product Name: Resmetirom; MGL-3196
Indication: Treatment of Non-Alcoholic Steatohepatitis (NASH)

Sponsor Name: Madigral Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: George Makar, MD, MSCE, (Acting) Deputy Director, DHN
Meeting Recorder: Taiye Adedeji, PharmD, Senior Regulatory Project Manager

FDA ATTENDEES

- Frank Anania, MD, FACP, AGAF, FAASLD, (Acting) Director, DHN
- George Maker, MD, MSCE, (Acting) Deputy Director, DHN
- Judy Racoosin, MD, MPH, Deputy Director for Safety (DDS), DHN
- Gerri Baer, MD, FAAP, Lead Physician, DHN
- Toru Matsubayashi, MD, MPH, DrPH, Medical Officer, DHN
- David Joseph, PhD, Supervisory Pharmacologist, Division of Pharmacology/Toxicology for Immunology and Inflammation (DPT-II)
- Fang Cai, PhD, Nonclinical Reviewer, DPT-II
- Insook Kim, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP)/Office of Clinical Pharmacology (OCP)
- Shen (Steven) Li, PhD, Clinical Pharmacology Reviewer, DIIP/OCP
- Rebecca Hager, PhD, Biostatistics Team Leader, Division of Biometrics III (DBIII)
- Xueying Wang, PhD, Biostatistics Reviewer, DBIII
- Jiabei Yang, PhD, Biostatistics Reviewer, DBIII
- Stephen Chang, PharmD, MPH, Associate Director for Labeling (ADL), DHN
- Y. Veronica Pei, MD, MEd, MPH, Associate Director of Biomedical Informatics for DHN (BIRBD/ODES/OND)
- Chad Reissig, PhD, Supervisory Pharmacologist, CSS
- Ayanna Augustus Bryant, PhD, RAC, Chief, Project Management Staff, Division of Regulatory Operations for Immunology and Inflammation (DRO-II)
- Taiye Adedeji, PharmD, Senior Regulatory Project Manager, DRO-II

SPONSOR ATTENDEES

- Rebecca Taub, MD, President of R&D and Chief Medical Officer
- [redacted] (b) (4) Consultant to Madrigal
- Dominic Labriola, PhD SVP, Chief Data and Analytics Officer
- Sudeep Kundu, PhD VP, Biostatistics
- [redacted] (b) (4) Consultant to Madrigal, [redacted] (b) (4)
- Rubina Mondal, MS Sr. Dir, Global Regulatory Affairs
- Stephen Dodge, PhD SVP, Global Medical Affairs
- Tom Hare, MS SVP, Clinical Management
- Ed Chiang, MS SVP, Clinical and Technical Operations
- Kristina Cochrane, MS Ex. Dir. Pharmacovigilance
- Eric Solon, PhD Ex. Dir. Non-clinical
- Mark Ferguson, PhD Sr. Dir. Project Management
- Robert Waltermire, PhD SVP, Chief Pharmaceutical Development Officer

1.0 BACKGROUND

Resmetirom (MGL-3196) is a selective thyroid hormone receptor-β agonist currently under development for the treatment of nonalcoholic steatohepatitis (NASH) in patients with fibrosis stages F2-F3 to resolve NASH, [redacted] (b) (4)

Fast Track designation was granted for non-alcoholic steatohepatitis (NASH) on October 18, 2019.

The Sponsor is currently conducting the following phase 3 trials to potentially support a subpart H accelerated approval pathway and long-term clinical outcome in non-cirrhotic NASH patients with liver fibrosis:

- MGL-3196-11 (MAESTRO-NASH): A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients with Non-Alcoholic Steatohepatitis (NASH) and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation.

- MGL-3196-14 (MAESTRO-NAFLD-1): A 52-week, Phase 3 Study to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients with Non-alcoholic Fatty Liver Disease (NAFLD).

- MGL-3196-18 (MAESTRO-NAFLD-OLE): A 52-week, Phase 3, Open-label Extension Study, with a Double-blind Lead-in, to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients with NAFLD (an extension

study of the completed patients from MGL-3196-14 including non-cirrhotic and cirrhotic NASH patients).

On November 30, 2022, the Sponsor submitted a request for a type B Pre-NDA meeting to discuss the development of resmetirom for the treatment of NASH in preparation for an NDA submission during the first half of 2023. Madrigal is requesting FDA's scientific and regulatory input to guide the content of this NDA submission for resmetirom.

The questions from the meeting package, submitted and received on January 27, 2023, are shown in *italic font*, the Division's responses are shown in **bold font** and the meeting discussion are shown in ***bold italics font***.

FDA sent Preliminary Comments to Madigral Pharmaceuticals, Inc. on February 22, 2023.

2.0 DISCUSSION

Question 1: Does the Agency agree that the format and overall content reflected in the proposed NDA Table of Contents is complete and adequate for FDA review?

FDA Response to Question 1:

MGL-3196-18 is not listed in section 5.3.5.1 of the proposed NDA Table of Contents, and MGL-3196-14 is not listed in Table 6, page 24 of the Meeting package which lists the studies to be included in the summary of clinical safety (SCS) and four-month safety update report (SUR). Clarify if one or both studies will be submitted in the NDA.

If the study reports for MGL-3196-14 or -18 will be submitted to support the safety database, ensure they are submitted at the time of the NDA submission. The data submitted to support safety should be substantively complete at time of NDA submission.

We agree that the format and overall content as reflected in the proposed table of contents appears consistent with eCTD Comprehensive Table of Contents Headings and Hierarchy.[1] However, the final determination will be made at the time of the NDA review.

We have the following general comments on the submission of information and datasets for clinical studies:

[1] https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40

- **Include in the NDA submission all components supporting the study reports, such as protocols and amendments (with dates), Statistical Analysis Plans (SAPs) and amendments (with dates), generated treatment assignment lists, the actual treatment allocations (along with the date of randomization), annotated case report forms (CRFs), etc.**

- **Include the treatment assignments, baseline assessments, and key demographic variables in the appropriate datasets to facilitate conducting the analyses. Include all variables needed for conducting all primary, secondary, supplemental, and sensitivity analyses included in the study report. All analyses included in the study report should be replicable using the variables submitted in the datasets.**

- **The analysis dataset documentation (Define.xml) should include adequate detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code representing categorical variables.**

Meeting Discussion
No discussion occurred.

Question 2: Does the Agency agree that the proposed documents from the nonclinical program are sufficient to support an NDA submission for the NASH indication?

FDA Response to Question 2:

We agree that the nonclinical studies listed in your meeting package appear sufficient to support an NDA submission for the indication of NASH. However, the final determination will be made during the review of your NDA.

Meeting Discussion
No discussion occurred.

Question 3: Does the Agency agree on the overall content and datasets for the clinical pharmacology and biopharmaceutics sections?

FDA Response to Question 3:

It is premature to comment on your clinical pharmacology data package intended for an NDA filing; however, your proposed overall content and datasets appear reasonable.

We have the following comments for clinical pharmacology data package.

- **Provide adequate justification, including but not limited to, the available PK and/or safety data in patients with varying degree of renal impairment in your NDA submission to support use of the product in patients with renal impairment. You stated that the degree of renal impairment will be included in the population PK covariate analysis while no dedicated renal impairment study has been conducted. You also stated that the safety data from a small cohort of subjects with moderate renal impairment from MGL-3196-14 will be discussed separately and not combined with any other patient populations. While it is unclear if patients with severe renal impairment have been enrolled in the phase 3 trials to support assessment of effects of severe renal impairment on PK via population PK analyses, we recommend you also address the dosing for patients with severe renal impairment.**

- **Submit electronic datasets for the PK and PD concentration data, PK parameters, and complete bioanalytical reports, including assay method validation reports and in-study bioanalytical assay reports for all studies with PK components in your NDA submission.**

- **Submit data to allow the evaluation of the validity of the bioanalytical assay for any PD markers that are important for safety or efficacy assessment.**

- **If the to-be-marketed formulation is different from the formulation used in pivotal clinical trial(s), a relative bioavailability study may need to be conducted to bridge two formulations.**

- **We remind you that a food-effect study should be conducted with the to-be-marketed formulation, if the TBM formulation is different from the formulation used in pivotal clinical trial(s).**

Meeting Discussion:

The Sponsor clarified that patients with severe renal impairment were not enrolled in the clinical trials. FDA recommended conducting a reduced design renal impairment study with subjects with severe renal impairment and compare the PK with that in subjects with normal renal function. The Sponsor acknowledged the recommendation and agreed to conduct this study.

Question 4: Does the Agency agree on the adequacy of the pharmacometrics (population pharmacokinetics and exposure-response) analyses as described in the pharmacometrics analysis plan to support an NDA submission?

FDA Response to Question 4:

It is premature to comment on the adequacy of the pharmacometrics components intended for an NDA filing; however, your overall approach appears to be reasonable.

We recommend that you submit the population PK and exposure-response models, data, and program codes based on the guidelines provided on the FDA webpage, Model/Data Format.[2]

Meeting Discussion
No discussion occurred.

Question 5: Does the Agency agree that the clinical efficacy and safety data from the pivotal Phase 3 study MAESTRO-NASH, along with supportive studies, are sufficient to support an NDA for resmetirom for the treatment of patients with NASH and liver fibrosis?

FDA Response to Question 5:

It is premature to agree.

See previous communications (Final Written Responses dated August 22, 2022, and December 8, 2022) regarding disagreements and concerns regarding the primary analysis population and method of biopsy interpretations.

The NDA should contain details regarding:

a. **The consensus reading process. The Type D meeting package submitted on October 20, 2022, stated that the consensus process was "still under development". Clarify whether baseline histology was also assessed via consensus method.**

b. **The reasons for treatment and study discontinuation, including the details regarding "Withdrawal by patient (other than AE)" as presented in Table 14.1.1.3 in Appendix 4 of the meeting package. Additionally, include details on the reason for discontinuation or inability/delay of biopsy due to the COVID-19 pandemic.**

For each analysis provided in the study report, provide the following:

[2] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

c. **Biopsy read method (individual pathologist or consensus read) used to determine inclusion in the analysis, i.e., the analysis population.**

d. **Biopsy read method (individual pathologist or consensus read) used to determine baseline histology used in the analysis.**

e. **Biopsy read method (individual pathologist or consensus read) used to determine Week 52 histology outcomes used in the analysis.**

Ensure that the datasets submitted to replicate the efficacy analyses include for each histology outcome (baseline and post-baseline) results from each read method (individual pathologist or consensus read) and flags denoting the biopsy read method (i.e., Pathologist A, Pathologist B, Consensus method). Additionally, see Response to Question 8.

The Agency will conduct the primary evaluation based on the principles that we have pre-specified in previous communications to you. Submit the results of analyses using the following analysis population and biopsy read method in your NDA submission:

f. **Analysis population including all F2/F3 subjects who were randomized on or before July 31, 2021 (the sponsor-specified cutoff data for the Week 52 analyses).**

    i. **This includes subjects with missing data due to a "COVID-related reason". The study report should provide details on the COVID-related reason which led to the missing biopsy evaluation.**

g. **Consensus reading – this is particularly important as the rate of disagreement concerning responder status between pathologists on both primary endpoints increases from the placebo arm to the low dose arm to the high dose arm (Table 14.2.1.1.3.6 and Table 14.2.1.2.3.6 on pages 44 and 55 of Appendix 4 of meeting package).**

We request the following analyses in the NDA submission:

h. **Pathologist A results – analysis includes subjects with F2/F3 (and meeting NAFLD Activity Score (NAS) inclusion criteria) at baseline as determined by pathologist A with final efficacy assessment also determined by pathologist A**

i. **Pathologist B results – analysis includes subjects with F2/F3 (and meeting NAS inclusion criteria) at baseline as determined by pathologist B with final efficacy assessment also determined by pathologist B**

j. Consensus results – analysis includes subjects with F2/F3 (and meeting NAS inclusion criteria) at baseline as determined by consensus read process with final efficacy assessment also determined by consensus read

Additional analyses may be requested through information requests during NDA review.

Meeting Discussion

The Sponsor summarized data suggesting similarities between F1b and F2. The Sponsor provided their rationale for a lack of discrimination between F1b and F2. FDA responded that this will be a review issue.

The Sponsor discussed the consensus read process and stated that results are consistent across different analyses. The Sponsor inquired whether FDA had any additional recommendations for analyses to address concerns raised in the preliminary comments. FDA stated that the Sponsor should provide the details of the consensus read process in the NDA submission and reiterated that the intentions of the preliminary comments were to ensure complete submission of the data needed to conduct the NDA review and to ensure general consistency across results. FDA did not have any additional recommended analyses, and stated that the request for the consensus analyses was intended to address concern about clinical interpretability issues when there is disagreement between the two pathologists.

Question 6: Does the Agency agree with the proposal for the safety information that will be provided in the 4-month safety update report?

FDA Response to Question 6:

We agree with your proposal to have a data cut within six months of the NDA submission date for the SCS as you have proposed on page 24 of your meeting package, and that the SUR will provide the additional information after that data cut point from ongoing studies (MGL3196-11, -18, and -19).

Refer to our comment in question 1 regarding a request for clarity regarding if the study report for MGL3196-14 or MGL3196-18 will be provided at the time of NDA submission.

Also refer to our comment in response to question 8 regarding adverse events of special interest (AESIs) as these should be included in MGL3196-11 and any other study that is being submitted to support the safety database (MGL3196-14 or -18).

Meeting Discussion
No discussion occurred.

Question 7: Does the Agency agree with the proposed criteria and structure for submission of patient safety narratives and electronic case report forms (eCRFs)?

FDA Response to Question 7:

Yes, we agree.

Meeting Discussion
No discussion occurred.

Question 8: Does the Agency agree with the CSE (ISE)/SCS (ISS) documentation and pooling strategy for the NDA?

FDA Response to Question 8:

It is premature to agree without the SAP for the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) available for review. We acknowledge they will be submitted at the time of NDA submission.

In addition, refer to our Final Written Response, dated November 8, 2022, in response to the questions posed in your September 22, 2022, meeting package for additional comments regarding pooling strategies for efficacy and safety data.

As noted in prior comments, the Agency's primary efficacy analysis will be based on subjects with baseline F2/F3 fibrosis in MGL3196-011.

Include flags in the ADaM Subject-level Analysis (ADSL) datasets that identify subjects with the following baseline histologic criteria.

a. **F2/F3 (and meeting NAS inclusion criteria) at baseline as determined by pathologist A**

b. **F2/F3 (and meeting NAS inclusion criteria) at baseline as determined by pathologist B**

c. **F2/F3 (and meeting NAS inclusion criteria) at baseline as determined by consensus read (if consensus reading included rereading of baseline pathology)**

Ensure that AESIs will be included in the SCS for MGL3196-011 for the 1050 subjects that will be supporting the NDA application. Table 6 on page 24 of your

meeting package references the contents of the SCS and SUR. Table 6 does not include AESIs for MGL3196-011, however section 13.4.4.6 states that AESIs will be included in the ISS/SCS.

Meeting Discussion
No discussion occurred.

Question 9: Does the Agency agree with the indication in the proposed label?

FDA Response to Question 9:

It is premature to discuss the proposed label. However, the primary indication in the product label will reflect the population for which a clinically relevant need for treatment exists, and for which favorable benefit:risk was established.

Meeting Discussion
No discussion occurred.

Question 10: Are there other questions that the Agency would like to discuss?

FDA Response to Question 10:

Refer to additional comments below.

Additional Comments:

1. **Provide the maximum daily amount of elemental iron, based on your proposed maximum daily dose, in your NDA submission.**

   We note that (b) (4) is the coating used for your MGL-3196 tablet formulation. Yellow and red iron oxide are two components (b) (4) Based on 21 CFR 73.1200[3], the maximum daily intake of the color additive synthetic iron oxide from drugs ingested by man shall not exceed 5 mg, calculated as elemental iron per day.

   The reported amount (mg elemental iron per day) should be supported by full details of your calculations. For example, if you propose a maximum daily dose of 100 mg MGL-3196, this would require daily ingestion of one

[3] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=73.1200
[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

40-mg tablet and one 60-mg tablet. The drug product composition indicates that the resulting daily intake of [redacted] would be [redacted] mg for this dose regimen. Therefore, your calculations would need to show the amount of total iron oxide (yellow and red) contained in [redacted] mg [redacted] and the elemental iron equivalent.

Meeting Discussion
No discussion occurred.

2. **Additional Thyroid Safety Analyses:**

   a) **In addition to your proposal to include the number of subjects who required resmetirom dose adjustments (either up or down titration) based on changes in fT4 and impact of protocol specified dose adjustments on TSH, fT4, and fT3, include an adequate justification for the dose adjustment algorithms that were used in the phase 3 trials, in which resmetirom doses were adjusted based on serum fT4 with or without serum SHBG level.**

   b) **Include the proportion of subjects who experienced a shift in TSH, fT4, and fT3 from normal at baseline to low or high at various points in the trials. These analyses should be presented in a tabular format and should include data for the entire study population and for subgroups of subjects with and without hypothyroidism at baseline.**

   c) **Include the proportion of subjects requiring initiation or change in any thyroid hormone replacement therapy (not just levothyroxine), as some subjects may have been on other forms of thyroid hormone replacement (e.g., combination of levothyroxine and liothyronine or desiccated thyroid extract).**

Meeting Discussion:
The Sponsor requested clarification about the plan to review the thyroid safety analyses. FDA informed the Sponsor that the Division of General Endocrinology (DGE) would be involved in the thyroid safety review. FDA emphasized the importance of the safety evaluation for a first-in-class drug intended for long-term use that has effects on thyroid hormone axis.

The Sponsor inquired about the acceptability of their plans to present results on worsening of fibrosis, as requested by an external party, in a way that does not unblind results on worsening of fibrosis for F3 subjects, as this would be providing information on clinical outcomes continuing to be evaluated in the ongoing study (refer to appended Sponsor responses). FDA stated that in terms of blinding,

the Sponsor's planned assessments presented on the attached slides 7 and 8 were acceptable, as there was not unblinding of information about progression to cirrhosis.

POST-MEETING COMMENTS

Application Orientation Meeting
We acknowledge your intent to submit a request for an application orientation meeting at the time of NDA submission. Please note that application orientation meetings are granted at the discretion of the review team and such meetings will not be based on PDUFA timelines. We will review your request at the time it is submitted and will provide a response thereafter.

Consensus Readings of Baseline Histology
As stated in your responses to the preliminary comments and confirmed during the meeting, for approximately 25% of subjects, there is neither a consensus read nor agreement between the two pathologists on their baseline histology assessment.

Conduct a blinded consensus reading of the baseline histology for these subjects for inclusion in the NDA submission. Include a flag in the efficacy dataset(s) indicating which consensus reads were conducted prior to unblinding the trial and those conducted after unblinding the trial.

CONTROLLED SUBSTANCE STAFF

1. ***Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry Assessment of Abuse Potential of Drugs, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.*** [4]

2. ***Based on information provided in your meeting briefing package, it appears resmetirom has a low or no potential for abuse. To support your NDA submission, we recommend providing the following:***

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

a. ***Provide your receptor binding assessments of resmetirom, which should include an evaluation of receptor sites associated with abuse, including (but not limited to) N-methyl-D-aspartate (NMDA), ion-channel complexes (e.g., calcium, potassium, chloride), and various transporters (e.g., dopamine, serotonin, GABA).***

b. ***Provide and discuss results of your tissue distribution studies, which may be useful to determine whether resmetirom is CNS active and able to enter the brain.***

c. ***Provide an assessment of the abuse-related adverse event profile of your drug in all phases of clinical studies, consistent with recommendations in section V.B of the above-mentioned guidance.***

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

At the time of NDA submission, the Sponsor intends to request an application orientation meeting, rolling submission and priority review.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slides and Sponsor's comments in response to the Preliminary Comments dated February 22, 2023.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 20, 2022, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[5]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[6] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[7]

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[5] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[7] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[8]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[9] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

[8] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[10]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[11] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[12]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD

[10] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[11] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[12] https://www.fda.gov/media/109533/download

Guidance will be subject to rejection. For more information, please visit FDA.gov.[13]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[14]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[15]

[13] http://www.fda.gov/ectd
[14] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[15] https://www.fda.gov/media/85061/download

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

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/s/

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03/24/2023 11:31:24 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122865

MEETING MINUTES

Madrigal Pharmaceuticals, Inc.
Attention: Rebecca Taub, M.D.
Chief Medical Officer, Executive Vice President, Research & Development
200 Barr Harbor Drive
Suite 400
West Conshohocken, PA 19428

Dear Dr. Taub:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MGL-3196.

We also refer to the meeting between representatives of your firm and the FDA on November 7, 2018. The purpose of the meeting was to discuss your clinical study development plan, proposed phase 3/4 clinical protocol, and statistical analysis plan intended to support the New Drug Application (NDA) submission of MGL-3196 for the treatment of non-alcoholic steatohepatitis (NASH).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H.,
C.P.H.M., G.W.C.P.M.
CAPT/United States Public Health Service
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: November 7, 2018; 10:00 AM – 11:00 AM (EST)
Meeting Location: FDA White Oak Building 22, Room 1311

Application Number: IND 122865
Product Name: MGL-3196
Indication: **treatment of nonalcoholic steatohepatitis**
Sponsor/Applicant Name: Madrigal Pharmaceuticals, Inc.

Meeting Chair: Dr. Erica Lyons
Meeting Recorder: CAPT Anissa Davis-Williams

FDA ATTENDEES

Dragos Roman, M.D., Acting Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Lisa M. Soule, M.D., Associate Director, DGIEP
Bindi Nikhar, M.D., Acting Deputy Director, DGIEP
Erica Lyons, M.D., Acting Clinical Team Leader, DGIEP
Suna Seo, M.D., M.Sc., Medical Reviewer, DGIEP
Insook Kim, Ph.D., Team Leader, Division of Clinical Pharmacology III (DCPIII)
Dilara Jappar, Ph.D., Clinical Pharmacologist, DCPIII
Shen Li, Ph.D., Clinical Pharmacologist, DCPIII
David Joseph, Ph.D., Lead Pharmacologist, DGIEP
Lei Nie, Ph.D., Acting Deputy Division Director, Division of Biometrics III (DBIII)
Min Min, Ph.D., Statistical Reviewer, DBIII
Amanda Cartee, M.D., FDA Fellow, DGIEP

SPONSOR ATTENDEES

Rebecca Taub, M.D.	Chief Medical Officer, Executive VP, Research & Development
Edward Chiang, M.S.	VP, Clinical Operations
Thomas Hare, M.S.	Senior VP, Clinical Management
Eric Solon, Ph.D.	Senior Director, Pharmacology and ADME
John Franc, M.B.A.	VP, External Scientific Affairs & Global Project Lead

(b) (4)	(b) (4) Consultant to Madrigal
	Consultant in Toxicology and Pathology
	Consultant in Preclinical Development (Remote)
	Consultant in Clinical Pharmacology
	Consultant in Biostatistics
	(b) (4)
	Consultant in Regulatory Affairs
	Consultant in Regulatory Affairs
	Consultant in API Chemical Process R&D (remote)
	Consultant in Drug Product Formulation and Process (remote)
	Consultant in CMC Regulatory Affairs (Remote)
	Consultant in Analytical Chemistry (Remote)

1.0 BACKGROUND

MGL-3196 is being developed for the treatment of (b) (4) NASH. The drug is a liver-directed, orally-active agonist for the thyroid hormone receptor (THR) which, based on a functional rather than simple receptor binding assay, the Sponsor claims is approximately 28-fold selective for the beta receptor versus alpha receptor as compared to the active thyroid hormone, triiodothyronine (T3).

According to Madrigal, a total of 315 subjects who participated in clinical studies have been treated with MGL-3196 as of 20 March 2018; 153 healthy volunteers have been treated in phase 1 studies and 162 subjects have been treated in the ongoing phase 2 studies, MGL-3196-05 and MGL-3196-06.

Madrigal submitted a meeting request to discuss the clinical study development plan, proposed phase 3/4 clinical protocol and statistical analysis plan that would support the New Drug Application (NDA) submission of MGL-3196 for the treatment of NASH.

The meeting was granted and held face-to-face.

FDA sent Preliminary Comments to Madrigal on November 2, 2018.

2. DISCUSSION

Questions from Madrigal are in plain text. Comments from the FDA are in **bold text.** Meeting Discussion in in ***bold italics.***

Overall Meeting Discussion:
Madrigal summarized the findings contained within their responses to the Agency's meeting preliminary comments. The Agency acknowledged Madrigal's submission and clarified that their responses had not been discussed internally, and therefore, agreement would not be reached at this time. An exploratory discussion, as below, followed regarding Madrigal's plans for a future proposal to be reviewed by the Agency.

Madrigal emphasized that 60 mg was not anticipated to be an effective therapeutic dose of MGL-3196 and inquired about the prior dosing limitation recommended by the Agency. This limitation, based on AUC of combined exposure to parent drug and the major human metabolite MGL-3623 (MGL-3196-M1), was previously recommended based on animal toxicology data. Madrigal recently submitted additional toxicity data on the metabolite MGL-3623, and the new data addressed the Agency's concern about the poorly characterized toxicity potential of the metabolite and its association with biliary hyperplasia in a 9-month toxicity study in dogs. Therefore, the Agency agreed with Madrigal's position that the expected range of AUC values (<11,000 ng•hr/mL of parent drug alone in a large majority of subjects) at the proposed doses (80 and 100 mg/day) is acceptable from a nonclinical safety perspective. The Agency suggested that, based on currently available nonclinical toxicology data, higher doses could also be explored.

The Agency reiterated the importance of performing adequate dose-ranging prior to proceeding to phase 3 development and the risk of a failed trial should an inappropriate dose(s) be selected. Madrigal proposed several additional options for future program development, including a proposal to evaluate placebo, 80 mg, and 100 mg in a seamless design registration trial. FDA emphasized the importance of utilizing a histologic endpoint for dose-ranging regardless of the overall development program selected. The Agency advised Madrigal that it would be reasonable to submit their draft proposal as a WRO meeting request for review, and to anticipate additional discussion prior to reaching agreement.

See below for additional post-meeting comments by each response item.

2.1. Clinical

Question 1: Does the Division agree with the design of the proposed Phase 3/4 pivotal study in NASH patients including the dosing strategy, study population, sample size and statistical assumptions, inclusion/exclusion criteria as well as the proposed primary and key secondary endpoints? (draft protocol included in Appendix 1; Investigator's Brochure v5 SN0026)

FDA Response to Question 1:
No, we do not agree with the design of the proposed phase 3/4 pivotal study in patients with NASH. See comments below:

Dose Selection:

1. **We do not agree with your rationale for dose selection, proposed dose, or the dose adjustment plan in your phase 3/4 trial. The completed phase 2 study (MGL-3196-05) provided some preliminary evidence of efficacy as a proof-of-concept study; however, it did not identify an optimal dose to be evaluated in the phase 3/4 study. Therefore, we recommend you conduct a robust dose-ranging phase 2b study to identify the optimal dose prior to initiating your phase 3/4 trial. We recommend you perform a phase 2b trial with histologic endpoints that includes several dose groups (e.g., 60 mg, 80 mg and 100 mg) and placebo, and then take the most effective dose(s) to be studied in phase 3/4.**

   Alternatively, you may consider a seamless phase 2b/3/4 study. For a seamless trial design, your statistical analysis plan (SAP) will need to describe the planned analysis for the entire seamless phase 2b/3/4 trial before starting the phase 2b trial.

Madrigal Email Response dated November 6, 2018:
See attachment

Post Meeting Comment:
Currently the proposed doses of 80 mg and 100 mg provide a narrow dose range. FDA recommends that Madrigal explore a wider dose range to identify an optimal dose, provided that the safety of higher dose(s) can be justified.

Study Population:

2. **We do not agree with your proposal to include F1 patients. To support a marketing application using an accelerated approval pathway, the Division currently recommends conducting phase 3 trials that enroll NASH patients with histologically-proven NASH with fibrosis stage >F1 and <F4. Should F1 patients be included in your trial, we recommend that these patients also have high risk factors for progression, as you have proposed. The F1 patients should be excluded from the primary efficacy analysis and limited to exploratory purposes only.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
Madrigal expressed agreement with the Agency's recommendation to exclude any patients with F1 fibrosis from the efficacy analysis population and acknowledged that the F1 population they intend to enroll into the proposed phase 3/4 trial would be for exploratory analysis purposes only.

Endpoints:

3. **Your proposed primary endpoint of "resolution of NASH associated with an at least 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" is acceptable, as are your definitions of "resolution of NASH" as the total absence of ballooning (score = 0), absent or mild inflammation (score 0 to 1), with allowance for the presence of steatosis (score 0 to 3) and "no worsening of fibrosis" as any progression ≥ 1 stage. However, we recommend that the histologic endpoint of interest be evaluated in a phase 2b dose-ranging study prior to initiation of phase 3 study as stated above.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
See Overall Meeting Discussion above. There was no further discussion of endpoints.

4. **The hepatic decompensation events in the composite clinical outcomes endpoint should be pre-specified with clear definitions. We recommend defining ascites as "ascites requiring chronic diuretic treatment" and hepatic encephalopathy (HE) as "HE grade 2 or above requiring at least a 24-hour hospitalization." Variceal hemorrhage should be defined as "variceal bleeding requiring hospitalization and transfusion of blood."**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

5. **We remind you that an acceptable secondary endpoint intended to support labeling claims should measure different manifestations of the disease and should not provide redundant information with the primary endpoint or any other secondary endpoint. In order for any of your pre-specified secondary endpoints to be considered to support labeling claims, specify appropriate multiplicity adjustments to control overall type I error rate.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

6. **We recommend you also evaluate the normalization of LDL-c, Apoprotein B (Apo-B), and Triglycerides, in addition to the percent change from baseline, as secondary efficacy endpoints.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Enrollment Criteria:

7. **Please note that FDA does not recognize "metabolic syndrome" as a distinct indication, but rather as a cluster of individual indications. We agree with the risk factors in the proposed Modified Criteria for Diagnosis of the Metabolic Syndrome (Synopsis Table 1, Protocol MGL-3196-XX pg. 10), but recommend that you replace the term "metabolic syndrome" with "metabolic risk factors."**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

8. **The relationship between Inclusion Criteria #4 and #5 is unclear. Clarify whether subjects could qualify for enrollment by meeting either Criterion #4 or #5, or whether Criterion #4 is intended as an initial screen to identify potential enrollees who must then meet Criterion #5.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion at this time.

9. **All qualifying historical biopsies should be obtained within 6 months before randomization (Inclusion Criterion #5. Protocol MGL-3196-XX pg. 39).**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

10. **For laboratory-based eligibility criteria, specify the reference ranges to inform the "ULNs" (upper limits of normal) in your protocol.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

11. Patients with Type 2 diabetes (T2DM) should be reasonably well-controlled, as defined by a HbA1C of 6-8%. The proposed HbA1C threshold of ≥ 9% would allow inclusion of patients with significantly poor glycemic control, and is not acceptable.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
Madrigal requested comment to their response proposal to revise the hemoglobin A1C (HbA1c) exclusion criterion to ≥9%. The Agency stated that rationale for the recommendation to exclude subjects with HbA1c >8% was to ensure that efforts had been made to provide appropriate standard of care management for patients with type 2 diabetes prior to and during the trial, and that consideration for a higher threshold could be given provided documentation of efforts to achieve a reasonably well-controlled state for patients with HbA1c >8% was provided.

12. Patients should be on a stable dose of concomitant medications for ≥ 3 months, (other than Vitamin E, as below), especially diabetic medications (Exclusion item #7) and statin therapy (Exclusion item #15).

Madrigal Email Response dated November 6, 2018:
See attachment

Post Meeting Comment:
Enrollment of subjects on stable doses of statin therapy for 6 weeks at study enrollment is acceptable.

13. Patients on Vitamin E therapy should be on a stable dose for ≥ 6 months. See Response to Question 8 below.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

14. Patients with Gilbert's Syndrome with elevated total bilirubin may be included provided they have a normal reticulocyte count, hemoglobin, and direct bilirubin (<0.3 mg/dL) (Exclusion criterion 11.d).

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

15. Patients should be excluded for platelet count <150,000/mm^3.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
The Agency agreed to Madrigal's proposal to allow platelet count of <140,000/ mm3 as an exclusion criterion.

16. Patients with hepatocellular carcinoma should be explicitly excluded.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

17. Given the concerns regarding fetal exposure, two highly-effective birth control methods, including at least one barrier method of contraception, should be included as an enrollment criterion for women of childbearing potential. Reliance on abstinence from heterosexual intercourse is acceptable only if that is the subject's habitual practice.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Prohibited Concomitant Therapy:

18. In addition to the list of drugs that you have proposed to prohibit during the study, you should also prohibit the concomitant use of following therapies until the result of relevant *in vivo* drug interaction (DDI) studies become available:

- **a. Substrates of OAT3 (furosemide), as MGL-3196 is a moderate inhibitor of OAT3**
- **b. OATP inhibitors (e.g., cyclosporine A), as MGL-3196 is a substrate of transporters OATP1B1 and OATP1B3**
- **c. Substrates of UGT and BESP, as MGL-3196 is an inhibitor of UGT and MGL-3623 is an inhibitor of BSEP**

d. Strong inhibitors of P-gp and BCRP, as MGL-3196 is a substrate for P-gp and BCRP and MGL-3623 is a substrate of BCRP

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion at this time.

Dose Administration:

19. Please clarify your dosing instructions in the proposed phase 3 study regarding food. Please see WRO Response to Question 4, dated 9/27/2018.

Madrigal Email Response dated November 6, 2018:
See attachment

Post Meeting Comments:
Your food effect study should be conducted with the to-be-marketed formulation at the highest clinical dose to be marketed. Instructions regarding administration of drug in relation to food in phase 3 trial should be informed by the result of the food effect study.

Bioanalytical Assay for Biomarker/PD:

20. We recommend that you measure any biomarkers that are important for safety or efficacy assessments by adequately validated assay methods throughout the development program. The same assay method should be used across the study sites throughout the study duration in a consistent manner, or a central laboratory(ies) should analyze the samples. If multiple bioanalytical assay methods/ local laboratories will be used, we recommend that cross-comparison among methods be performed to allow comparison of your biomarker values obtained by different assay methods. Refer to *Guidance for Industry Bioanalytical Method Validation* for detail https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Study Procedures:

21. Histology slides should be read by a central reader, not local pathologists. Please clarify the role of local pathologists and ensure that the protocol clearly states the biopsy reading by a central reader (see Section 19.2 Appendix 2 in Protocol MGL-3196-XX).

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Data Analysis:

22. In your phase 3 trial, the primary histological endpoint is to be tested at the interim analysis when 900 subjects have completed their Week 52 visit, and the clinical efficacy endpoint is to be tested after all subjects have completed 54 months of treatment. You need to maintain the study blind between the interim and the final analyses. In order to preserve the integrity of the entire phase 3/4 trial, interim analyses must be conducted by an independent party with an appropriate firewall implemented. This should be described in your SAP.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

23. We encourage you to conduct the noninvasive biomarker sub-study as an exploratory analysis. Please note that the pre-specified exploratory analysis of noninvasive tests will be considered purely data-gathering exploration, and will not supersede, replace, or influence histological endpoints for the efficacy assessment of MGL-3196.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

24. Regarding your proposed significance level (0.01 for phase 3 and 0.04 for phase 4), please refer to the response to Question 7. We have the following additional comments:

- **You propose that the key secondary endpoints at Week 52 will be tested in the hierarchical order at the α=0.01 level of significance. Please clarify your decision rule regarding the first key secondary efficacy endpoint, which**

includes three parameters (LDL-C, Apo-B and Triglycerides) in the endpoint.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

- **For dealing with dropouts, you propose to impute the dropouts as non-responders in the primary analysis of the primary histology efficacy endpoint. To assess the impact of the dropouts, the SAP should specify the approaches to handle missing data in the primary histology endpoint. For example, you should consider other approaches to handle data missing at random (MAR) such as the MI (i.e., multiple imputations). Furthermore, because the missing data can be informative [i.e., missing not at random (MNAR)], you should also consider approaches such as pattern mixture models, selection models, and tipping point analyses.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion at this time.

- **In the key secondary efficacy analysis, you propose to use last observation carried forward (LOCF) as the missing data imputation method; however, we do not recommend the use of LOCF. If you choose to apply LOCF in dealing with missing data, you should provide suitable justification. For efficacy endpoints whose analyses utilize an ANCOVA model, a no-change-from-baseline imputation approach should serve as the primary missing data handling approach.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion at this time.

- **In the event the normality assumptions are clearly violated, you should pre-specify an alternative nonparametric approach to your primary analysis. In addition, for both your parametric and non-parametric approaches, provide details of how to you plan to calculate the confidence intervals (CIs).**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion at this time.

- **In addition to analyzing the intent-to-treat population for your primary analysis and the per protocol population for your sensitivity analysis, you should also conduct analyses based on a modified intent-to-treat population defined as patients who take a least one dose of study medication.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

- **Please submit detailed SAPs for the phase 3/4 study(ies) to the Agency for review prior to conducting the phase 3 component. The SAPs should include, but is not limited to, the primary and key secondary endpoints, primary analysis methods as well as the multiple comparison procedure to control the overall type I error rate, missing data imputation method, rationale for sample size decision. Major changes to the statistical analysis plan (e.g., primary and key secondary endpoints, primary analysis methods, multiplicity adjustment method, and missing data handling) after the start of a trial may compromise the interpretability of the results and/or present significant review concerns.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Question 2: Does the Division agree that the planned safety evaluations, particularly related to monitoring and assessment of hepatic and cardiovascular events, performed at each study visit and the frequency of visits as described in the 'Schedule of Assessments' section of the protocol are appropriate for the Phase 3/4 study?

FDA Response to Question 2:
In addition to follow-up at 4 weeks from study completion or discontinuation, we recommend patients be followed at ≥ 3 months after an early termination.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:

No further discussion needed.

Specify both individual patient discontinuation rules and trial stopping criteria within the protocol.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

To protect subject safety, you need to provide a detailed clinical management protocol to evaluate and respond to cases of new elevations (or new elevations from baseline) in transaminases or tests of liver function. You need to have a plan to evaluate subjects for other causes of liver injury and for the potential of drug-induced liver injury (DILI) and include protocol responses to persistent or new deterioration of hepatic function.

For new elevations in transaminases greater than 2x ULN in patients with normal baseline values or 2x baseline in subjects with abnormal baseline values, repeat measurement should be performed within 48 hours. If elevations persist, patients should be evaluated for other causes of transaminase elevations and with tests of hepatic function. If no other cause is found, then the patients need to be "Monitored Closely" and the drug should be discontinued per the recommendations for subjects with normal baseline liver function in the *Guidance for Industry - Drug Induced Liver Injury: Premarketing Clinical Evaluation* (available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf)

For patients with abnormal baseline indices, see recommendation (c) below.

The guidance provides recommendations for monitoring and decision-making for drug discontinuation in trials that enroll subjects who have normal liver transaminases and bilirubin at baseline. Drug should be discontinued, and the subject followed until resolution of symptoms or signs in the following situations:

- **ALT or AST >8x ULN**
- **ALT or AST >5x ULN for more than 2 weeks**
- **ALT or AST >3x ULN and (TB >2x ULN or INR >1.5)**
- **ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)**

Given that the population you plan to study will have baseline elevations in liver biochemistries, the criteria outlined in the DILI Guidance may not be applicable. Therefore, the Division recommends that you incorporate the following in your protocol to address management of subjects with elevations in baseline liver biochemistries:

a) Baseline values should be established (by at least two samples obtained at least 4 weeks and no more than 8-12 weeks apart) to account for disease-related changes in liver enzymes and bilirubin while on study that may otherwise be inappropriately attributed to study drug. The differences in repeat measurements of baseline serum AST, ALT, ALP and total bilirubin (TBL) should be small (<20%) to be eligible for study entry. You should not enroll subjects with evidence of worsening liver function based on the 2 initial laboratory values used to establish the baseline.

b) If subjects with abnormal baseline liver indices develop elevations of AST or ALT >2x baseline or total bilirubin >1.5x baseline values during the study, repeat testing should be performed within 48 -72 hours. If there are persistent elevations (ALT or AST >2x baseline or TBL >1.5x baseline values) upon repeat testing, then close observation (testing and physical examination 2-3 times per week) should be implemented and discontinuation of drug should be considered (see c below).

c) A decision to discontinue or temporarily interrupt the study drug should be considered based on factors that include how much higher than baseline ALT and AST were relative to the upper limit of normal (ULN) and how much the on-study ALT and AST levels have increased relative to baseline, in addition to whether there is concomitant elevation of bilirubin or INR. You need to discontinue or temporarily interrupt the study drug:

- **If baseline measurements (BLM) were <2x ULN, discontinue if ALT or AST increases to >5x BLM**
- **If BLM ≥2x ULN but <5x ULN, discontinue if ALT or AST increases to >3x BLM**
- **If BLM ≥ 5x ULN, discontinue if ALT or AST increases to >2x BLM**
- **Discontinue if ALT or AST increase > 2x BLM <u>AND</u> the increase is accompanied by a concomitant increase in TBL to >2x BLM <u>OR</u> the INR concomitantly increases by >0.2**
- **In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).**

d) If a patient lives in a remote area, laboratory testing can be performed locally, and the results should be promptly communicated to the investigator site.

e) Close Observation for Suspected DILI includes:

- **Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.**
- **Obtaining a more detailed history of symptoms and prior or concurrent diseases.**

- **Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.**
- **Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.**
- **Obtaining a history of exposure to environmental chemical agents.**
- **Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).**
- **Considering gastroenterology or hepatology consultations.**

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
Madrigal expressed concern about the recommendation that there be <20% variability between screening labs to establish a patient's baseline [see a) above]. The Agency recommended that Madrigal propose an alternative threshold or screening procedure to establish baseline in the upcoming proposal for consideration.

See Overall Meeting Discussion above.

Post Meeting Comments:
Madrigal's response to the Agency's recommended DILI monitoring appears reasonable.

Question 3: Does the Division agree that the proposed plan/involvement for the Data Safety Monitoring Board (Phase 3/4) and Endpoint Adjudication Committee for long-term outcome events (Phase 4) ensure adequate oversight and monitoring of the study? (The draft DMC charter is included in Appendix 2, and draft EAC charter in Appendix 3).

FDA Response to Question 3:
Your data safety monitoring board should include hepatologists. We strongly recommend inclusion of a DILI expert in both your Data Safety Monitoring Board as well as the Composite Clinical Outcome Endpoint Adjudication Committee.

See response to Question 1 (Item 22) regarding maintenance of study blinding.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Question 4: Does the Division agree that complete resolution of NASH on overall histopathologic interpretation at 12 months (with a NAS of ballooning of 0 and an inflammation score of 0-1) with at least a 2-pt improvement in NAS AND no worsening of fibrosis (NASH/CRN Brunt-Kleiner scale), as determined by liver biopsy, is appropriate as a surrogate endpoint for the NASH indication?

FDA Response to Question 4:
While not a validated surrogate endpoint, we agree that your proposed histologic endpoint is an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit evaluable under an accelerated approval pathway to be followed by a confirmatory clinical benefit assessment trial, 21 CFR 314 Subpart H. See Responses to Question 1 and 5.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Question 5: Does the Division agree that if the surrogate endpoint proposed as the primary endpoint in Question #4 above was met then the proposed Phase 3 study would support an accelerated approval path?

FDA Response to Question 5:
It is premature to discuss the suitability of the proposed trial to support an accelerated approval pathway. Please see comments above regarding dose-ranging, trial design, statistical analysis, and eligibility criteria.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

Question 6: Does the Division agree that the proposed safety database which will include all completed, ongoing and planned clinical studies is adequate to support an NDA for MGL-3196 for the treatment of NASH?

FDA Response to Question 6:
No, we do not agree. Given that your drug is a new chemical entity, and because it is intended to be used chronically, you need, at a minimum, to address the exposure requirements specified in the ICH Guidance E1A: *The Extent of Population Exposure to Assess Clinical Safety For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*, regardless of whether marketing approval is sought under the

accelerated or regular approval pathways. The ICH Guidance has recommended that 1500 subjects be exposed to the investigational product (with 300 to 600 exposed for 6 months, and 100 exposed for 1 year).

For those products characterized as chronic use products in the ICH guidance E1A, FDA recommends that the 1500 subjects include only those who have been exposed to the product in multiple dose studies, because many adverse events (AEs) of concern (e.g., hepatotoxicity, hematologic events) do not appear with single doses or very short-term exposure. Also, the 300 to 600 subjects exposed for 6 months and 100 subjects exposed for 1 year should have been exposed to relevant doses (i.e., doses generally in the therapeutic range). Furthermore, given the intended chronic use of your product and the fact that it is a new chemical entity, we will expect to see substantively more than the minimum of 100 patients exposed for a year in the NDA submission (see the FDA Guidance for Industry *Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post-approval Clinical Investigations* at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291158.pdf.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
The Agency reminded Madrigal that the ICH Guidance E1A requirements for the safety database should be met at the time of their NDA submission regardless of whether marketing approval is sought under the accelerated or regular approval pathway. Madrigal clarified that the projected number of patients provided in their response (Table 3, page 25) included those patients who would be enrolled in the phase 4 trial at the time of the NDA submission. The Agency inquired as to Madrigal's plan to include those subjects, as it would require breaking of the study blind for those patients enrolled in the ongoing phase 4 trial. Both the Agency and Madrigal acknowledged the complexity of this proposal.

2.2. Biostatistical Questions

Question 7: Does the Division agree that the proposed size of the safety and efficacy population, and the proposed statistical analysis plan to distribute the alpha spend of 0.05 over the Phase 3/4 study (0.01 and 0.04, respectively) are acceptable in support of an NDA?

FDA Response to Question 7:
No, we do not agree. Generally, two adequate and well-controlled trials are needed to provide substantial evidence of efficacy. The adequacy of a single trial to support approval will be determined by its ability to support the efficacy claim based on the strength of the results. If only one clinical trial is used to support the approval, refer to the Guidance for Industry - *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf.

The guidance provides examples of characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim, including internally consistency across study subsets, persuasive evidence of the treatment effect in multiple endpoints, statistically very persuasive finding with a very low p-value.

In addition, since you proposed to test four key secondary efficacy endpoints in phase 3 study in a hierarchical order at a certain alpha level, we remind you that if any key secondary efficacy endpoint fails to achieve the significance, the alpha level for the phase 3 study cannot be recycled for testing phase 4 primary efficacy endpoints.

Madrigal Email Response dated November 6, 2018:
See attachment

Post Meeting Comment:
FDA is open to continued discussion via a teleconference to discuss the statistical considerations for the seamless design.

Question 8: Does the Division agree with the stratification factors for the proposed Phase 3/4 study?

FDA Response to Question 8:
We agree with stratification by baseline T2DM status (presence/absence) and fibrosis stage (i.e., 2 or 3). Additionally, we recommend that you perform subgroup analyses based on use of Vitamin E use (yes/no) if patients on Vitamin E are included. Regarding the F1 population, please refer to the response to Question 1 (Item 2).

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

2.3. Additional Comments Regarding Previous WRO Response (Question #6)

Previous Question 6: Based on the completed and planned analyses of the concentration-QTc at therapeutic exposures of MGL-3196 from the Holter-monitored, single and multiple ascending dose Phase 1 studies (VIA-3196-01 and VIA-3196-02, respectively) demonstrating no concern for QTc prolongation, the QTc data from the completed Phase 1 and Phase 2 studies where serial 12-lead ECGs were obtained also showing no QTc concerns and the clinical adverse event profile of MGl-3196, does the Division agree that the need for a thorough QTc study could be obviated?

FDA Response to Previous Question 6:
No, we do not agree. You have not identified the highest clinically relevant exposure (e.g., exposure due to drug-drug interaction or organ impairment) for the therapeutic dose, nor have you demonstrated that the doses included in the SAD and MAD studies (VIA-3196-01,VIA-3196-02) would characterize the QTc at sufficiently high multiples (e.g., at least 2-fold) of such highest clinically relevant exposure, in order to waive the need for a separate positive control (ICH E14 Q&A (R3)) to use these studies as a thorough QT (TQT) substitute. We recommend that you submit justification for the dosing or conduct a TQT study to satisfy ICH E14 if the doses included in the SAD/MAD studies do not provide the expected exposure margin. The TQT study can be designed using concentration-QTc analysis as the primary analysis.

Madrigal Email Response dated November 6, 2018:
See attachment

Post Meeting Comment:
Your proposals to perform a concentration-QTc analysis, decrease the intensity of ECGs to standard trial practice, and obtain peak ECGs in all subjects appears reasonable.

2.4 Additional Comments Regarding Chemistry, Manufacturing, and Controls

As clinical development proceeds, we encourage you to request a CMC-focused meeting to discuss drug substance regulatory starting materials and specifications.

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
No further discussion needed.

2.5 Additional Comments Regarding Dose Limitation in Clinical Trials

We refer to the following statement in your meeting package:

"In conclusion, the totality of the data support that MGL-3623 (MGL-3196-M1) does not contribute to the biliary hyperplasia observed in dogs and, therefore, Madrigal considers it appropriate to base any future plasma exposure limit on MGL-3196 exposure only."

We agree with your assessment. Therefore, the mean exposure limit for MGL-3196 in clinical trials should be established at 5445 ng•hr/mL (1/10th of the mean AUC from male and female dogs at the NOAEL in the 9-month toxicology study).

Madrigal Email Response dated November 6, 2018:
See attachment

Meeting Discussion:
See Overall Meeting Discussion above.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

5.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

6.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

8.0 NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

9.0 UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

10.0 ATTACHMENTS AND HANDOUTS

Madrigal Email Response dated November 6, 2018.

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/

ANISSA A DAVIS
11/15/2018