CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217785Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	217785
Applicant Name	Madrigal Pharmaceuticals, Inc.
Drug Product Name	Trade Name (resmetirom)
Dosage Form	Tablet
Proposed Strength(s)	60 mg, 80 mg,100 mg
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	100 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis
Drug Product Description	Madrigal Pharmaceuticals, Inc. has submitted this 505(b)(1) application for Trade Name (resmetirom) tablets 60 mg, 80 mg, and 100 mg indicated for the treatment of adults with nonalcoholic steatohepatitis with liver fibrosis. Tablets should be taken orally once daily with a maximum daily dose of 100 mg. The active ingredients, resmetirom is a thyroid hormone receptor beta (THR-b) selective agonist. It has not been previously approved or marketed as a drug in the United States and therefore, it is classified as a New Molecular Entity (NME). 60 mg tablets are white oval-shaped film-coated tablets debossed with “P60” on one side and plain on the other side. 80 mg tablets are yellow oval-shaped film-coated tablets debossed with “P80” on one side and plain on the other side. 100 mg tablets are beige

	to pinkish oval-shaped film-coated tablets debossed with “P100” on one side and plain on the other side. Each tablet contains resmetirom as the active ingredient and the following colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. Opadry film coating consists of polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, red iron oxide (100 mg tablets), yellow iron oxide (80 mg and 100 mg tablets). Components used in compositions of the drug product are all compendial materials and/or composed from compendial materials. Trade Name (resmetirom) tablets are packaged as 30-count or 90-count tablets in a high-density polyethylene bottle with a child-resistant closure and an induction seal. This drug product should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15 °C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C – 25°C (68°F – 77°F); excursion permitted 15°C – 30°C (59°F – 86°F) [see USP controlled room temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Fredrich Burnette, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Zhengfang Ge, PhD	Hamid Shafiei, PhD
	Manufacturing	Mesfin Abdi, PhD	Jean Tang, PhD
	Biopharmaceutics	Kalpana Paudel, PhD	Tapash Ghosh, PhD
	Microbiology	Mesfin Abdi, PhD	Jean Tang, PhD
	Other (specify)	Xiaoqin Wu, PhD	James Laurenson, PhD

	Environmental Assessment		
	RBPM	Megan Nguyen	
	ATL	Hamid Shafiei, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application is recommended for approval with the following expiration dating periods when packaged in the proposed container closure and stored at proposed storage condition of 20°C – 25°C (68°F – 77°F):

- 36 months for the drug products 60 mg, 80 mg, and 100 mg packaged in 30 count bottles.
- 2onths for the drug products 80 mg and 100 mg packaged in 90-count bottles.
- 18 months for the drug products 80 mg and 100 mg packaged in 7-count bottles (physician samples).

The CMC-recommended PI labeling as well as container and carton labels revisions have been communicated to the applicant on January 26, 2024 and were accepted by the applicant. Therefore, no additional labeling memorandum is needed for the approval of this application from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, resmetirom, and drug product, Trade Name (resmetirom) tablets 60 mg, 80 mg, and 100 mg.

- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

- The CMC revisions on labels/labeling have been communicated to the applicant and the recommended CMC revisions have been accepted by the applicant.

- The applicant's current environmental assessment report has been reviewed and accepted by the OPQ environmental assessment team which also includes a recommendation of an agreed post-marketing

commitment (PMC) from the applicant to provide additional environment assessment data post-approval.

Therefore, this application is recommended for approval from the OPQ perspective with following expiration dating periods:

- 36 months for the drug products 60 mg, 80 mg, and 100 mg packaged in 30 count bottles.
- 24 months for the drug products 80 mg and 100 mg packaged in 90-count bottles.
- 18 months for the drug products 80 mg and 100 mg packaged in 7-count bottles (physician samples).

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Review & EI Statement - Adequate
QPA for EA(s): Choose Yes or No.

5. **Life-Cycle Considerations**
   Established Conditions per ICH Q12: No
   Comments:

   Comparability Protocols (PACMP): No
   Comments:

   Additional Lifecycle Comments:
   None

Application Technical Lead Name and Date:

Hamid Shafiei, PhD
Senior Pharmaceutical Quality Assessor
Branch IV/DNDP II/ONDP/OPQ

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CHAPTER III: ENVIRONMENTAL

For more details about the items in this template, please see
Chapter III (Environmental) of the NDA IQA Guide (OPQ-ALL-WI-0006)

R REGIONAL INFORMATION

During the IND phase (IND 122865), the applicant submitted a claim of categorical exclusion (CE) from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. While the EIC of resmetirom is (b) (4) ppb, and thus lower than the 1 ppb CE level, FDA considered the initially provided data to be inadequate to exclude extraordinary circumstances, per 21 CFR 25.21, primarily because thyroid disrupting chemicals including resmetirom's analogue thyroxine (T4) have been reported to cause toxic effects in fish at environmentally relevant concentrations below the 1 ppb CE level [1,2]. To allow FDA to determine whether extraordinary circumstances can be excluded, the applicant submitted under the NDA 217785 a plan for refining the EIC and conducting environmental fate and ecotoxicity studies. The EIC refinement will consider human metabolism, excretion, and depletion in the sewage treatment plant. The ongoing fish assay is a fish early life stage toxicity test (OECD 210), which will be used to determine whether additional fish short-term reproduction assay (OECD 229) and fish sexual development test (OECD 234) are needed, which in turn would be used to determine whether the extended one-generation reproduction test (OECD 240) is needed. The applicant stated that the OECD 210 was used as the initial fish assay as thyroid hormone pathways are important for early development in fish.

Assessment: Adequate

FDA agrees with the proposed plan for EIC refinement and environmental fate and ecotoxicity studies. According to the provided preliminary data, approximately 1% of administered resmetirom is excreted from humans as unchanged parent compound, and 70% of the proposed metabolites are expected to have very low or non-existent thyroid hormone receptor (THR) activity. Also, resmetirom may be less toxic than triiodothyronine (T3) and T4 to fish as clinical and nonclinical data have demonstrated that resmetirom is significantly less potent than T3 and T4 at THR-β and has no activity on THR-α. Based on this preliminary information, FDA expects that approval of this drug application likely would not result in a significant environmental impact at the expected level of exposure, and thus the claim of CE is tentatively accepted. Results of EIC refinement as well as environmental fate and ecotoxicity studies will be used to further support the conclusion of no significant impacts and thus exclusion of extraordinary circumstances. Since

the latter studies (beyond OECD 210) are expected to be completed by Q3 2024, an updated report is expected to be submitted in Q4 2024 and thus will not be available by the review due date. Therefore, a postmarketing commitment (PMC) might be needed, depending on whether any additional preliminary data submitted prior to the decision date confirms the claim of no extraordinary circumstances.

Reference:

1. Sharma and Patiño, 2013. Regulation of gonadal sex ratios and pubertal development by the thyroid endocrine system in zebrafish (*Danio rerio*). General and Comparative Endocrinology 184, 111–119.
2. Sharma et al., 2016. Effects of thyroid endocrine manipulation on sex-related gene expression and population sex ratios in Zebrafish. General and Comparative Endocrinology 235, 38–47.

Primary Environmental Assessor Name and Date: Xiaoqin Wu, 12/16/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): James P. Laurenson, 12/18/2023

Title:	New Drug Application (NDA) Integrated Quality Assessment Template
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Effective Date:	Revision: 09
Total Pages:	19

Template Revision: 03

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

(b) (4)

	(choose "Adequate", "Inadequate", or "N/A")	(If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Resmetirom is the established name
Route(s) of administration	Adequate	For oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	60 mg, 80 mg, 100 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	Adequate	Not scored
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

(b) (4)

	“Inadequate”, or “N/A”)	e issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Take orally with or without food
For parenteral products: include statement: *“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”*	N/A	

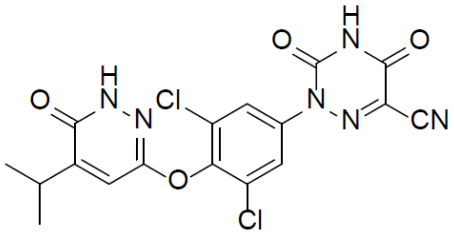
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

(b) (4)

	(choose “Adequate”, “Inadequate”, or “N/A”)	s If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	- Tablets
Strength(s) in metric system	Adequate	- 60 mg, 80 mg, 100 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	- Oval shaped film coated, white, yellow, or beige tablets debossed P60, P80, or P100 for 60 mg, 80 mg, 100 mg respectively
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	- No score
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	- Established name not included. Revise to include established name as "PROPRIETARY NAME (resmetirom) tablets" in the sharePoint
Dosage form(s) and route(s) of administration	Adequate	- tablets
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	- the inactive ingredients are arranged into alphabetical order in sharePoint
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	- a selective, liver-directed, THR-beta agonist

Chemical name, structural formula, molecular weight	Adequate	- chemical name: 2-[3,5-Dichloro-4-((6-oxo-5-(propan-2-yl)-1,6-dihydropyridazin-3-yl)oxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile - molecular formular: $C_{17}H_{12}Cl_2N_6O_4$ - molecular weight: 435.22 - molecular structure: 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	- Resmetirom [redacted] (b) (4) low aqueous solubility below pH 6 and [redacted] (b) (4) solubility above pH 7 (0.44 mg/mL at pH 7.04).

2. Section 11 (DESCRIPTION) Continued

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	- replace '[redacted] (b) (4) solubility above pH 7…" with "higher solubility above pH 7…" in sharePoint
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is	N/A	

fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).		

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	tablets
Strength(s) in metric system	Adequate	60 mg, 80 mg, 100 mg
Available units (e.g., bottles of 100 tablets)	Adequate	60mg: 30 counts 80 mg: 30 and 90 counts 100 mg: 30 and 90 counts (b) (4) [redacted]
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	provided
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	- Store at 20-25°C (68 to 77°F). Excursions permitted to 15−30°C (59° to 86°F) [see USP Controlled - Room Temperature].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	- packaged in white high-density polyethylene bottles closed with a child-resistant closure containing an induction seal

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients

[e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Manufactured by: UPM Pharmaceuticals (Bristol, TN)

Manufactured for: Madrigal Pharmaceuticals, Conshohocken, PA

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	PATIENT INFORMATION <PROPRIETARY NAME [PHONETIC SPELLING]> (resmetirom) Tablets, for oral use
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	- Store PROPRIETARY NAME at room temperature between 68 to 77 degrees F (20-25 degrees C)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	- Active ingredient: resmetirom
Alphabetical listing of inactive ingredients (if applicable)	Adequate	- Is rearranged in alphabetic order sharePoint
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	- provided

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Container label of 60 mg tablets in 30 counts displayed below)

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

Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Inadequate	- "for oral use" should be added to the c/c labels
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Adequate}*

- **Add "for oral used" on the c/c labels as "Tradename ((resmetriom) tablets, for oral use"**

3. ITEMS FOR ADDITIONAL ASSESSMENT

Minor editorial changes listed in the above tables of each section of the PI review were updated in the final labeling in the SharePoint which will be conveyed to the applicant. "For oral use" should be added to the c/c labels has been communicated to the applicant

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Overall Assessment and Recommendation:

The NDA is now recommended for Approval from the labeling perspective with the above recommendation. Dr. H. Shafiei, the ATL, will add the final labels to the combined CMC assessment once the labels are finalized.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Julia Pinto, Ph. D.
CHIEF, BRANCH III/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 1/08/2024 09:28:13AM
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Julia Pinto

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Date: 1/08/2024 10:51:30AM
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BIOPHARMACEUTICS

Product Background:

NDA: 217785

Drug Product Name / Strength: Resmetirom Tablets/ 60 mg, 80 mg, 100 mg

Indication: Treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis

Route of Administration: Oral

Applicant Name: Madrigal Pharmaceuticals, Inc.

Review Recommendation: **ADEQUATE**

Review Summary:
The Applicant intends to seek approval of MGL-3196 (Resmetirom) 60 mg, 80 mg, or 100 mg immediate-release tablets for the treatment of NASH *via* the 505 (b)(1) pathway. Resmetirom is a thyroid hormone receptor beta (THR-β) selective agonist, indicated for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Biopharmaceutics review is focused on the evaluation and acceptability of bridging of formulations, biowaiver request, dissolution method, and acceptance criterion.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE
The following dissolution method was found to be acceptable for the proposed drug product for Quality Control (QC) purposes during the IND stage:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sample time points
Apparatus 2	75	1% SDS in water / 37 ± 0.5°C	900	10, 20, 30, 45, 60 minutes

The details can be found in the link below:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806c65b3

The Applicant's proposed acceptance criterion *Q*= (b)(4) *% in 30 minutes* is deemed acceptable based on the dissolution data submitted.

Formulation development and bridging: ADEQUATE from Biopharm perspective
Resmetirom was initially available in capsule form to support the earlier Phase 1 and Phase 2 clinical studies. Formulations 5 and 6 had strengths of 40 mg and 60 mg, respectively.

A tablet formulation, Formulation 7, was developed to address (b) (4) issues encountered with the capsule formulations. The Applicant conducted an in vivo relative BA study (MGL-3196-08) to compare capsule Formulation 5 (40 mg) and Formulation 6 (60 mg) to tablet Formulation 7 (100 mg). The assessment of these clinical studies is under the purview of Office of Clinical Pharmacology (OCP). The dissolution profiles for capsule Formulation 6 and tablet Formulation 7 in Quality Control (QC) medium are similar.

Tablet Formulation 7 was modified to Formulation 8 for Phase 3 (pivotal) MGL-3196-11 studies. These formulations have the same (b) (4) composition and differ only in a minor adjustment to the (b) (4) composition to improve (b) (4). Tablet Formulation 8 has higher level of (b) (4) compared to tablet Formulation 7. However, the total excipient change is (b) (4). The dissolution profiles for Formulation 7 and 8 in QC medium is similar. Phase 3 studies are complete using Formulation 8 i.e, safety and efficacy data is available on Formulation 8. Therefore, no further in vitro or in vivo bridging data is needed.

In response to the FDA feedback received, the Applicant implemented a change in the non-functional tablet coating color for further differentiation of tablet strengths intended for commercialization for 60 and 80 mg tablets. The tablet coating colors for the 60 mg (white) and 80 mg (yellow) commercial drug product are (b) (4) (b) (4) are known as Formulation 8A. No change in tablet coating color is being made for the commercial 100 mg tablets, which will remain the original beige color (Formulation 8). The dissolution profiles for tablet Formulation 8 and 8A for 60 mg and 80 mg strengths are similar.

Biowaiver Request: ADEQUATE from Biopharm perspective

The biowaiver request was submitted by the Applicant for the lower strengths. However, all three strengths 60, 80, and 100 mg were used in the Pivotal Phase 3 study MGL-3196-11. The Phase 3 study is deemed acceptable by the OCP. In addition, the PK is dose proportional over the proposed dose range. The in vitro drug release profile of all strengths was found to be similar in QC dissolution medium. Therefore, the biowaiver request is not applicable.

List of Submissions being reviewed:
Sequence 0003 Original

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

From Biopharmaceutics perspective, NDA 217785 for Resmetirom tablets (60 mg, 80 mg, and 100 mg) is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment:

Solubility:

The solubility of resmetirom at 37 ºC was evaluated as a function of pH in aqueous buffer over the range of approximately pH 1-8, and in unbuffered distilled water. The results (Table 1) show that resmetirom is poorly soluble at low pH, with the solubility increasing at neutral and basic pH.

Table 1 Solubility of Resmetirom as a Function of pH at 37°C

pH	Resmetirom Solubility (mg/mL)
1.09	None detected
1.92	0.0001
2.93	None detected
3.98	None detected
5.01	0.0003
6.02	0.04
Distilled water, pH 6.5 (unbuffered)	0.16
7.04	0.44
7.95	3.8

Permeability:
The Applicant mentions that permeability is estimated to be medium to low and therefore may be classified as a BCS 4 molecule. However, no data is provided and no request for BCS designation has been made.

Dissolution: See below.

1. Composition of proposed drug product:

The quantitative composition of Resmetirom Tablets is listed in the table below.

Table 2: Resmetirom Tablets Commercial Formulation 8 (100 mg) and 8A (60 mg and 80 mg)

Component	Quantity (mg/tablet)			Quantity (% w/w)	Function	Reference to Standard
	60	80	100			
Resmetirom (b) (4)	60	80	100	(b) (4)	Active	In-house
Microcrystalline Cellulose					(b) (4)	USP/NF
Mannitol						USP/NF
Croscarmellose Sodium						USP/NF
Colloidal Silicon Dioxide						USP/NF
Magnesium Stearate						USP/NF
Total Tablet Core				(b) (4)		
Tablet Coating						
Opadry II White Powder[1]	(b) (4)	-	-	(b) (4)	Coating	Supplier
Opadry II Yellow Powder[2]	-	(b) (4)	-		Coating	Supplier
Opadry II Beige Powder[3]	-	-	(b) (4		Coating	Supplier
Total Tablet Weight	**309**	**412**	**515**	**100**		

1. Opadry II White is composed of polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.
2. Opadry II Yellow is composed of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide
3. Opadry II Beige is composed of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide and red iron oxide.
4. (b) (4)

2. In vitro dissolution method and acceptance criterion:

The following dissolution method was found to be acceptable for the proposed drug product for QC purposes during the IND stage:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sample time points
Apparatus 2	75	1% SDS in water / 37 ± 0.5°C	900	10, 20, 30, 45, 60 minutes

The details can be found in the link below:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806c65b3

The Applicant's proposed acceptance criterion *Q*= (b) (4) *% in 30 minutes* is deemed acceptable based on the dissolution data submitted.

Formulation development and bridging

Resmetirom capsule Formulation 5 and 6 and tablet Formulation 7

Resmetirom was initially available in capsule form in 0.25 mg, 2.5 mg, 10 mg, and 50 mg strengths to support the earlier clinical studies. Later studies used two strengths: 40 mg and 60 mg. Resmetirom capsule formulations were used in Phase 2 studies (MGL-3196-05 and MGL-3196-06) and Phase 1 studies up to and including MGL-3196-08.

A tablet formulation, Formulation 7, was developed to address (b) (4) issues encountered with the capsule formulations. Formulation 7 was designed (b) (4) as 40 mg or 60 mg resmetirom tablets (b) (4) (b) (4) (b) (4)

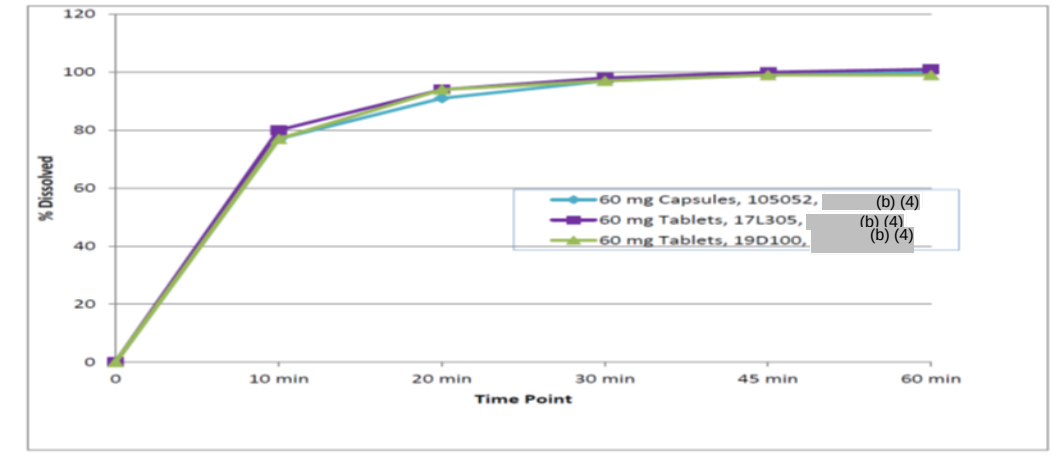
The Applicant conducted an in vivo relative BA study (MGL-3196-08) to compare capsule Formulations 5 (40 mg) and 6 (60 mg) (batches 1709158 and 1709161, respectively) with tablet Formulation 7 (100 mg). In this study, relative bioavailability of a 100 mg dose of resmetirom tablets (achieved using a 40 mg tablet plus a 60 mg tablet) to a 100 mg dose of resmetirom capsules (achieved using a 40 mg capsule plus 60 mg capsule) was demonstrated in clinical study MGL-3196-08. The assessment of these clinical studies is under the purview of OCP. The batches used in the study are shown in the table below.

Table 3: Drug Product Batches used in MGL-3196-08 (Relative Bioavailability Study)

Clinical Study	Drug Product Strength (mg)	Drug Product Formulation	Drug Product Batch Number
MGL-3196-08	40	5 (Capsule)	1612130
MGL-3196-08	60	6 (Capsule)	1612131
MGL-3196-08	40	7 (Tablet)	17L304
MGL-3196-08	60	7 (Tablet)	17L305

The Applicant provided dissolution data for capsule Formulation 6 and tablet Formulation 7, and the profiles are similar as shown in the figure below.

Figure 1 **Comparative Dissolution Profiles of 60 mg Doses of Capsule Formulation 6 (batch 105052), Tablet Formulation 7 (batch 17L305), and Tablet Formulation 8 (batch 19D100)**



Tablet Formulation 7 and Pivotal Clinical Phase 3 tablet Formulation 8

Tablet Formulation 7 was modified to Formulation 8 at 40, 60, 80 and 100 mg dose strengths for Phase 3 (pivotal) MGL-3196-11 studies. These formulations have the same (b) (4) composition and differ only in a minor adjustment to the (b) (4) composition to improve (b) (4). The % w/w composition of resmetirom tablets Formulation 7 and Formulation 8 is provided in the below table. Tablet Formulation 8 has higher level of (b) (4) compared to tablet Formulation 7. However, the total excipient change is (b) (4).

Table 4: Composition of Resmetirom Tablets 60 mg, 80 mg and 100 mg (Formulations 7 and 8)

Component	Quantity (%w/w)		Function
	Formulation 7 (40 mg and 60 mg tablets)	Formulation 8 (40 mg[1], 60 mg, 80 mg, and 100 mg tablets)	
(b) (4)			
Resmetirom			
Microcrystalline Cellulose			
Mannitol			
Croscarmellose Sodium			
Colloidal Silicon Dioxide			
Magnesium Stearate			
(b) (4)			
Total Tablet Core	**100**	**100**	
Tablet Coating			
(b) (4)			

1. 40 mg tablets were used in clinical trials but are not proposed for commercialization in NDA 217785.
2. (b) (4)

The Applicant provided comparative dissolution data for 60 mg formulation 7 and 8 in QC medium as shown in Figure 1 above. The dissolution profiles are similar for all formulations. Phase 3 studies are complete using Formulation 8 i.e, safety and efficacy data is available on Formulation 8. Therefore, any further in vitro or in vivo bridging data is not needed.

Pivotal Clinical Phase 3 tablet Formulation 8 and commercial Formulations 8A for 40 and 60 mg:
In response to the FDA feedback received November 4, 2022 for a Type C CMC meeting, and as agreed via a Type D CMC meeting for which FDA response was received March 23, 2023, the Applicant implemented a change in the non-functional tablet coating color for further differentiation of tablet strengths intended for commercialization. (b) (4) The tablet coating colors for the 60 mg (white) and 80 mg (yellow) commercial drug product (b) (4) are known as Formulation 8A. No change in tablet coating color is being made for the commercial 100 mg tablets, which will remain the original beige color (Formulation 8).

The Applicant provided dissolution data for tablet Formulation 8 and 8A for 60 mg and 80 mg strengths, and the profiles are similar as shown in the figures below.

Figure 2: Comparative Dissolution Profiles of Resmetirom Tablets, 80 mg for Formulation 8 (Opadry II Beige coating) and Formulation 8A (Opadry II Yellow coating)

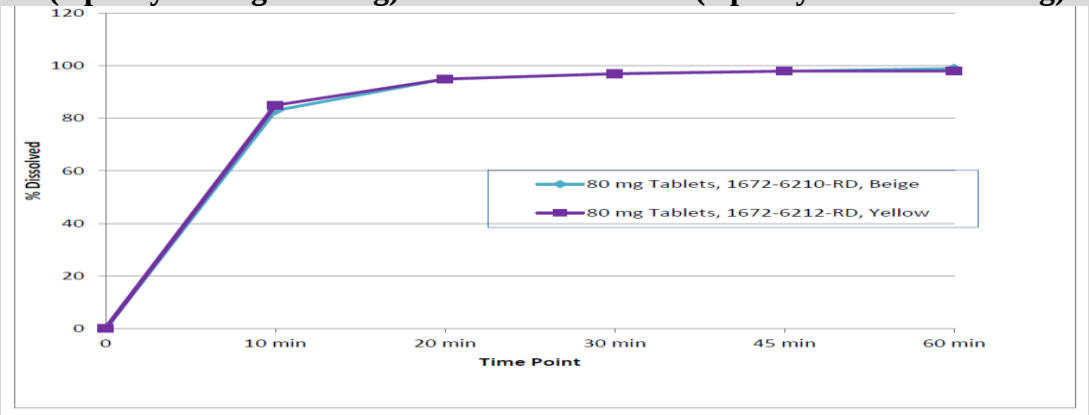
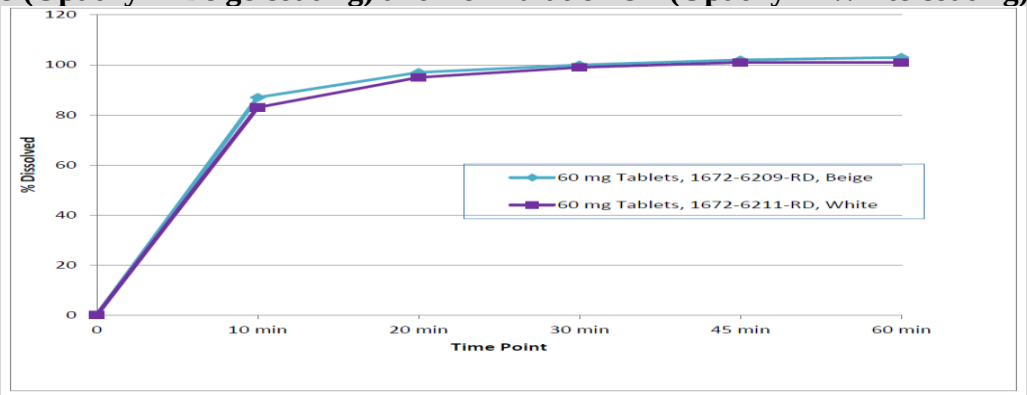


Figure 3: Comparative Dissolution Profiles of Resmetirom Tablets, 60 mg for Formulation 8 (Opadry II Beige coating) and Formulation 8A (Opadry II White coating)



Biowaiver Request: Adequate

The biowaiver request was submitted by the Applicant for the lower strengths. However, all three strengths 60, 80, and 100 mg were used in the Pivotal Phase 3 study MGL-3196-11 (see table below for the batches used). The Phase 3 study is deemed acceptable by the OCP which was communicated in an email on 1/2/2024. In addition, the PK is dose proportional over the proposed dose range. Therefore, the biowaiver request is not applicable. The in vitro drug release profile of all strengths was found to be similar in QC dissolution medium as shown below. Resmetirom tablets are immediate-release tablets (b) (4) . Drug product tablet strengths are proportionally similar in their active and inactive ingredients.

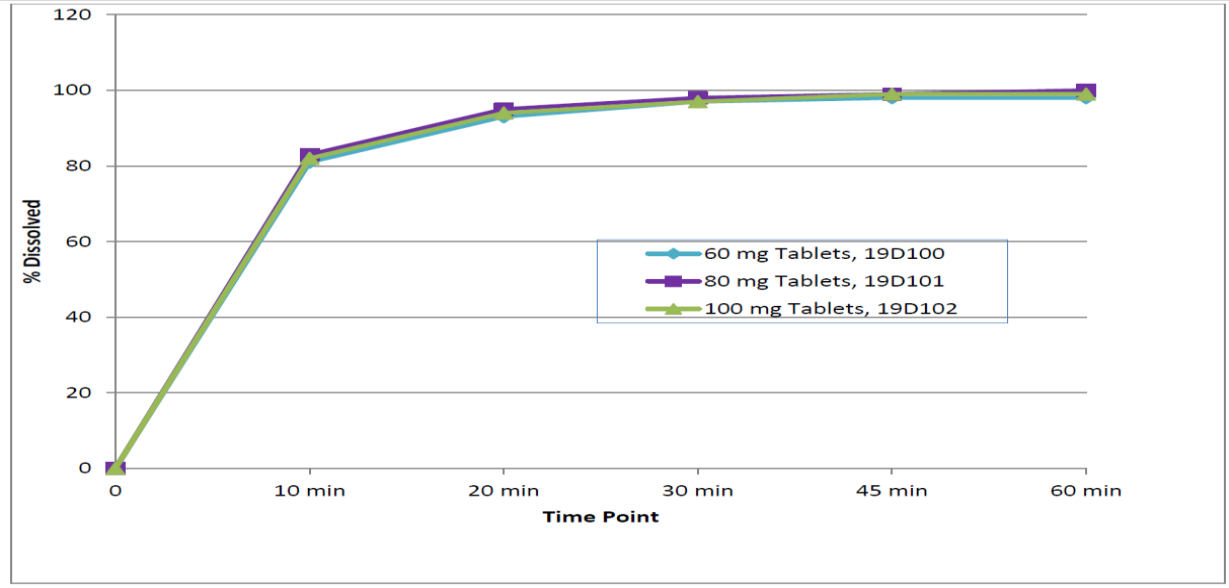
Table 1 Drug Product Batches used in MGL-3196-11 (Pivotal Clinical Study)

Clinical Study	Drug Product Strength (mg)	Drug Product Formulation (Tablets)	Drug Product Batch Number
MGL-3196-11	60	8	18J196
MGL-3196-11	60	8	19D100
MGL-3196-11	60	8	19G215
MGL-3196-11	60	8	19J275
MGL-3196-11	60	8	21H387
MGL-3196-11	80	8	18J197
MGL-3196-11	80	8	19B045
MGL-3196-11	80	8	19D101
MGL-3196-11	80	8	19G216
MGL-3196-11	80	8	19J276
MGL-3196-11	80	8	19M393
MGL-3196-11	80	8	20F214
MGL-3196-11	80	8	21G345
MGL-3196-11	80	8	22E119
MGL-3196-11	100	8	18J198
MGL-3196-11	100	8	19A018
MGL-3196-11	100	8	19A019
MGL-3196-11	100	8	19B046
MGL-3196-11	100	8	19D102
MGL-3196-11	100	8	19J277
MGL-3196-11	100	8	19M394
MGL-3196-11	100	8	20C099
MGL-3196-11	100	8	20F215
MGL-3196-11	100	8	20F216
MGL-3196-11	100	8	21J448
MGL-3196-11	100	8	22E120

Resmetirom tablets (all strengths) have all been tested using the same approved *in vitro* dissolution method. The dissolution profiles for three representative batches of resmetirom tablets used in MGL-3196-11, one of each strength, are presented in the below figure. The dissolution

profiles of resmetirom tablets 60 mg, 80 mg, and 100 mg are similar showing consistent *in vitro* behavior.

Figure 4: Comparative Dissolution Profiles of Representative Resmetirom Tablets 60 mg (batch 19D100), 80 mg (batch 19D101), and 100 mg (batch 19D102) used in MGL-3196-11, n=12 each



Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.
***Secondary Reviewer Name*:** Tapash Ghosh, Ph.D.

Kalpana Paudel

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Tapash Ghosh

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