

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214662Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date: August 13, 2021

To: Lisa Skarupa
Regulatory Project Manager
**Division of Medical Imaging and Radiation Medicine
(DMIRM)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): LIVMARLI (maralixibat)

Dosage Form and Route: oral solution

Application Type/Number: NDA 214662

Applicant: Mirium Pharmaceuticals, Inc.

1 INTRODUCTION

On January 29, 2021, Mirium Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) for LIVMARLI (maralixibat) oral solution. LIVMARLI (maralixibat) oral solution is a New Molecular Entity (NME) with a proposed indication for the treatment of cholestatic pruritus in patients with Alagille Syndrome (ALGS) 1 year of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Medical Imaging and Radiation Medicine (DMIRM) on February 18, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for LIVMARLI (maralixibat) oral solution.

2 MATERIAL REVIEWED

- Draft LIVMARLI (maralixibat) PPI and IFU received on January 29, 2021, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on August 3, 2021.
- Draft LIVMARLI (maralixibat) Prescribing Information (PI) received on January 29, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 3, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

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

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

Memorandum

Date: August 13, 2021

To: Lisa Skarupa, Regulatory Project Manager (DG)
Joette Meyer, Associate Director for Labeling (DG)

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

Subject: OPDP Labeling Comments for Livmarli (maralixibat) oral solution

NDA: 214662

In response to DG's consult request dated February 17, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Livmarli.

Labeling: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DG on August 3, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor and received by email on August 13, 2021, and we do not have any comments.

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

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: July 15, 2021
Requesting Office or Division: Division of Hepatology and Nutrition (DHN)
Application Type and Number: NDA 214662
Product Name and Strength: Livmarli (maralixibat) oral solution, 9.5 mg/mL
Applicant/Sponsor Name: Mirum Pharmaceuticals Inc
OSE RCM #: 2020-1857-1 and 2021-253-1
DMEPA 1 Safety Evaluator: Sarah K. Vee, PharmD
DMEPA 1 Team Leader: Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 8, 2021 for Livmarli. Division of Hepatology and Nutrition (DHN) requested that we review the revised container label and carton labeling for Livmarli (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

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

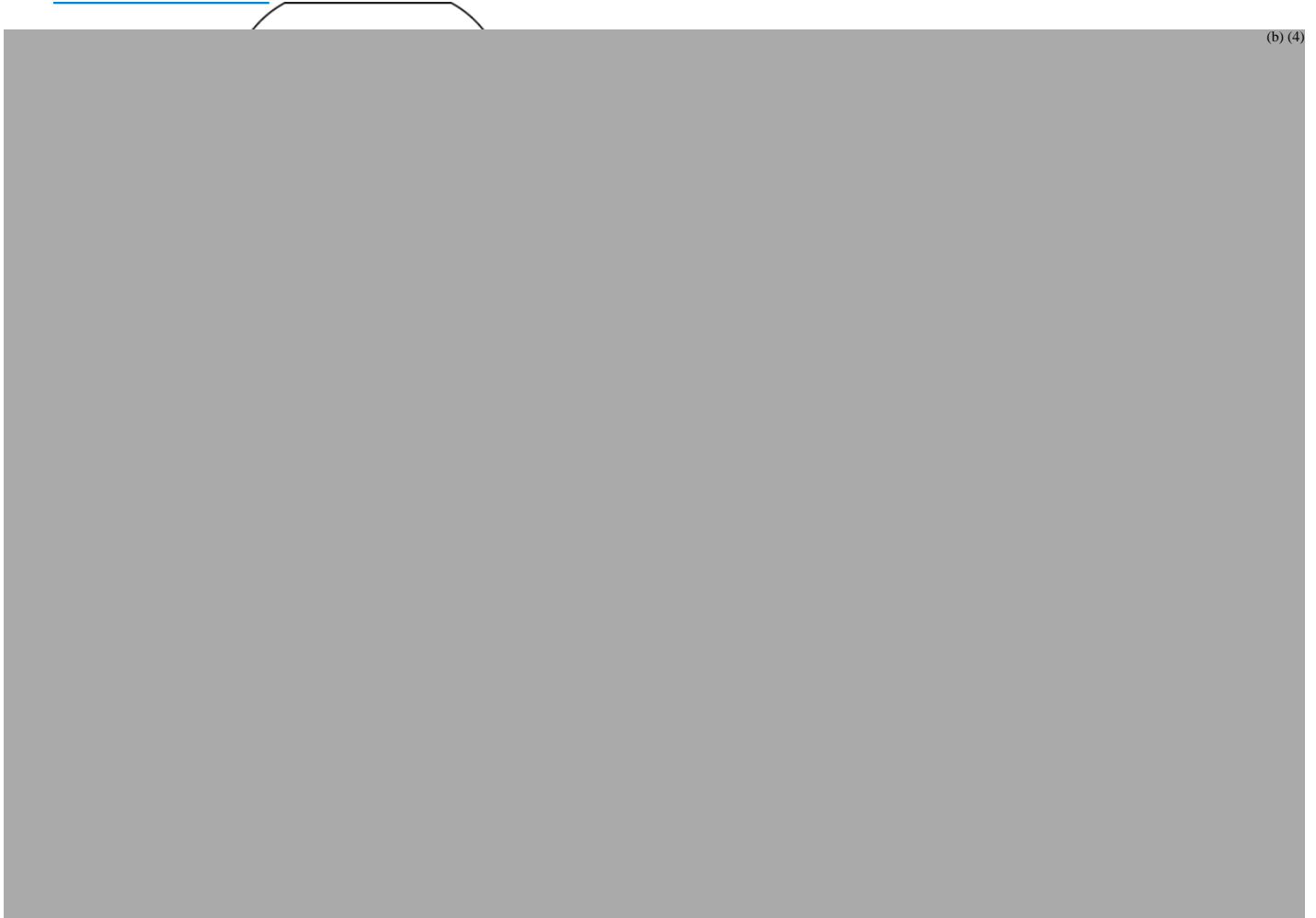
^a Vee S. Label and Labeling Review for Livmarli (NDA 214662). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); YYYY MON DD. RCM No.: 2020-1857 and 2021-253.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 8, 2021

Container labels



Carton labeling



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Clinical Inspection Summary Report

Date	June 30, 2021
From	Zana Marks, M.D., M.P.H. Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Charmaine Stewart, M.D., Medical Officer George Makar, M.D., Clinical Team Leader Lisa Skarupa, RPM Division of Hepatology and Nutrition (DHN) Office of New Drugs (OND)
NDA #	214662
Applicant	Mirum Pharmaceuticals, Inc.
Drug	Maralixibat
NME (Yes/No)	Yes
Therapeutic Classification	Apical sodium-dependent bile acid transporter inhibitor
Proposed Indication	For the treatment of cholestatic pruritis in patients with Alagille syndrome (ALGS) 1 year of age and older.
Consultation Date	March 25, 2021
Review Priority	Priority
Summary Goal Date	July 29, 2021
Action Goal Date	September 29, 2021
PDUFA Date	September 29, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from the study LUM001-304 were submitted to the Agency in support of this New Drug Application (NDA 214662) for the use of maralixibat for the treatment of cholestatic pruritis in patients with Alagille syndrome (ALGS) 1 year of age and older. Three clinical investigators who participated in Study LUM001-304 including Dr. Loreto Hierro [Site 040], Dr. Dorota Gliwicz-Miedzinska [Site 080], Dr. Etienne Sokal [Site 090] and the sponsor Mirum Pharmaceutical Inc. were inspected.

Dr. Alastair Baker [Site 001] Great Britain was initially selected for clinical site inspection as well. However, logistics related to COVID 19 pandemic concerns resulted in a cancellation for this site inspection.

The inspections found no significant regulatory violations at neither the three investigator sites nor the sponsor Mirum Pharmaceutical Inc. The Applicant's submitted clinical data

listings were verifiable against source records, with no discrepancies identified. The clinical data generated by the inspected investigators appear reliable. Based on the results of these inspections, Study LUM001-304 appears to have been conducted adequately, and the clinical data generated from the inspected entities appear to be reliable in support of this NDA.

II. BACKGROUND

This application is mission critical as maralixibat (maralixibat chloride), a new molecular entity, is a small molecule that acts as a potent, selective inhibitor of the ileal bile acid transporter (IBAT) also known as the apical sodium-dependent bile acid transporter (ASBT).

Maralixibat was granted the following designations:

- Orphan drug designation (2013)
- Rare pediatric disease designation (2019)
- Breakthrough therapy designation (2019)

It is being developed to treat cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older. ALGS is accompanied by cholestatic liver disease and usually associated with severe unremitting pruritus diagnosed during infancy and childhood. Debilitating pruritus and sometimes progressive liver disease may lead to surgical intervention and even liver transplantation in this pediatric population. The NDA 214662 was submitted to the agency on January 29, 2021.

Study LUM001-304 titled ICONIC Study: Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical, Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome is a randomized, placebo-controlled, drug withdrawal study with a long-term open label (OL) extension in children with Alagille syndrome (ALGS) designed to evaluate the efficacy and safety of maralixibat.

In general, patients were eligible to participate in this study if they were male/female between the ages of 12 months and 18 years inclusive with a diagnosis of ALGS. They must have demonstrated evidence of cholestasis by one or more of the following:

- a. Total serum bile acid > 3xULN for age.
- b. Conjugated bilirubin > 1 mg/dL.
- c. Fat soluble vitamin deficiency otherwise unexplainable.
- d. GGT > 3xULN for age.
- e. Intractable pruritus explainable only by liver disease

It also required average daily score >2 on the Itch Reported Outcome (ItchROTM) questionnaire (0=none; 4=very severe pruritus) for 2 consecutive weeks in the screening period, prior to dosing.

The duration of the study included an 18-week open label run-in period (OL phase), a 4-week randomized double-blind, placebo-controlled drug-withdrawal period (randomized withdrawal phase; RWD), a 26-week stable dosing period at doses up to 400 µg/kg/day (after randomized withdrawal phase; AWD) and an optional long-term treatment period (long-term extension phase; LTE). Study duration for participants was expected to be approximately 52 weeks. Participants who completed at least 48 weeks of treatment and were eligible to receive further treatment could continue in the 52-week optional long-term follow-up treatment period.

Study participants received maralixibat, up to 400 µg/kg/day, during the initial OL treatment period of the study. After completing the 6-week dose escalation period and the 12-week stable-dosing period, participants were randomized 1:1 in a 4-week double-blind maralixibat withdrawal period to placebo or remained on maralixibat. Participants then entered a 26-week long-term stable-dosing period and all participants received maralixibat up to 400 µg/kg/day. Participants were considered for an initial 52-week optional long-term treatment period, if eligible, and received up to 400 µg/kg/day or the highest tolerated dose below the 400 µg/kg/day dose.

The protocol specified primary efficacy endpoint of Study LUM001-304 was the mean change from Week 18 to Week 22 of fasting serum bile acid (sBA) levels in participants who previously responded to maralixibat treatment, as defined by a reduction in sBA $\geq$ 50% from baseline to Week 12 or Week 18 in the mITT population.

For this inspection, the clinical review division also requests the verification of the secondary efficacy endpoint: The comparison of the ItchRO (ObsRO) during a 4 week randomized withdrawal after the open-label treatment demonstrating worsening of itch symptoms with placebo and the maintenance of benefit on itch with maralixibat.

A total of 31 subjects were enrolled into the study at 10 study sites in Europe and Australia.

III. RESULTS (by Site)

1. Loreto Hierro, M.D. [Site 040]

Hospital Universitario La Paz
Unidad Central de Investigacion Clinica y Ensayos Clinicos
Edificio Maternidad
Paseo de la Castellana, 261
Madrid 28046
Spain

Dr. Hierro was inspected on April 12-16, 2021 as a data audit for Study LUM001-304. This was the first FDA clinical inspection of the investigator.

Dr. Hierro consented and screened 3 subjects into Study LUM001-304. All 3 subjects were eligible and were randomized and treated with either the investigational product

or placebo, including 2 subjects assigned to A4250 120ug/kg/day and 1 subject assigned to placebo. Of the three subjects enrolled at the site, two completed the treatment phase of the study and one subject [REDACTED] (b) (6) was withdrawn due to the need for liver transplantation.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, protocol deviations, laboratory tests, and electronic case report forms (CRFs). Blinding procedures were reviewed. Regulatory documentation was also examined, including the Ethics Committee (EC) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, site training records, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

The records were sufficient to document the existence of each subject, as well as their historical and current medical conditions. Site data recorded in the study records was compared to endpoint data and adverse events in the data line listings and no discrepancies were observed. Subjects [REDACTED] (b) (6) and [REDACTED] (b) (6) experienced serious adverse events according to the study records on site. The events were reported to the sponsor in a timely manner. All other adverse events in the study documentation were also reported in a timely manner.

The blinded serum bile acid (sBA) results were not present at the site and a request was made to retrieve them from the sponsor or CRO. The sponsor provided a spreadsheet with the sBA results for each subject. The data matched the data in the line listings but was not the source data from the lab. An additional request was made of the sponsor to supply the original laboratory results from the [REDACTED] (b) (4) laboratory. This document was received and no discrepancies were observed.

Minor protocol deviations were observed. They consisted mainly of out of window visits usually due to the participants' inability to travel and missing lab draws during the beginning of the study. These deviations were reported to the sponsor as required. The protocol deviations were discussed with Dr. Hierro at the close-out meeting. No Form FDA 483, Inspectional Observations was issued.

2. **Etienne Sokal, M.D. [Site 090]**
Cliniques Universitaires- Saint-Luc
Gastropediatrie
Avenue Hippocrate, 10
Brussels, 1200
Belgium

Dr. Sokal was inspected on May 31- June 4, 2021 as a data audit for Study LUM001-304. This was the first FDA clinical inspection of the investigator.

Dr. Sokal consented and screened 5 subjects into Study LUM001-304. Three subjects completed the first 48 weeks. Subject (b) (6) withdrew from participation in the study to receive a liver graft. Subjects (b) (6) developed adverse events (AEs) that resulted in their discontinuing participation in the study. Prior to the discontinuations all 5 subjects were eligible and were randomized and treated with either the investigational product or placebo, including 3 subjects assigned to A4250 120 ug/kg/day and 2 subjects assigned to placebo.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, protocol deviations, laboratory tests, and electronic case report forms (CRFs). Blinding procedures were reviewed. Regulatory documentation was also examined, including the Ethics Committee (EC) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, site training records, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

In general records were found to be complete, orderly, and demonstrated general compliance with the protocol. There appeared to be no under reporting of adverse events or protocol deviations.

Eligibility and primary endpoint data were verifiable. Serum bile acid results, random eDiary data for the ItchRo scores were verified. The Pediatric Quality of Life questionnaire (PedsQL) for all primary visits were verified.

The primary efficacy assessment in this study was pruritus severity as measured by the itch reported outcome measures (ItchRO Observer and Patient) administered as a twice daily electronic diary (ePro by ERT). Subjects 9 years of age or older were to independently complete the patient instrument: ItchRO (Pt). Subjects between 5 and 8 years of age, or where the investigator has expressed concern about the subject's ability to reliably complete the data (e.g., due to developmental delay) were to complete the patient instrument with the assistance of the caregiver, if needed. There was no patient report for subjects under the age of 5 years, only the ItchRO Observer. The site was provided a USB with all the ePro data at the end of the study. A spot check of the audit trails for diary completion times appeared consistent for each subject and there were no suspicious patterns.

However, during the Inspection at Dr. Sokal's site the inspector noticed a discrepancy between the data collected in the eCRFs and the BIMO listings provided in the NDA 214662. Specifically, the data for the "Pediatric Quality of Life Inventory (Subject Report) Emotional Functioning" was present in the eCRF for Patient LUM001-304-(b) (6) treated at Dr. Sokal's site but was absent from BIMO Listing h.18 for Site 090 submitted in the NDA. Mirum launched an investigation to determine the source of this discrepancy. Reportedly, a typographical error in the SAS program used to prepare that particular listing was determined to be the source of the error. This typo resulted in

the data for the “CHILD REPORT” (those aged 8-12 years old) being omitted from the BIMO listing h.18 Pediatric Quality of Life Inventory (Subject Report) Emotional Functioning.

The underlying datasets were not impacted.

Further investigation revealed that this issue originated in the SAS program used to generate the Study LUM001-304 Interim CSR Listing 16.6.10.2.2 titled “Pediatric Quality of Life Inventory (Subject Report) Emotional Functioning”. As noted above, this issue impacted all Pediatric Quality of Life Inventory data from those aged 8-12 years old. There was a total of 4 patients impacted, including Patient LUM001-304- (b) (6) at Dr. Sokal’s site. The other 3 patients were from sites not pertinent to this review.

Overall, the data appeared reliable and verifiable.

Discussion items at the conclusion of the inspection included some good documentation practice (GDP) deficiencies such as investigators not dating their signatures when reviewing paper records, making recommendations or medication changes.

Records to document the dosage and start date of Vitamin D supplementation for Subject (b) (6) were insufficient. Dr Sokal stated, the Vitamin D may have been prescribed by the primary care physician at a dose that was not deemed to be therapeutic for this subject.

The IP was not shipped consistently with temperature monitoring devices and documentation did not consistently demonstrate other methods to ensure the IP was shipped under label conditions were engaged.

No Form FDA 483, Inspection Observations was issued.

3. Dorota Gliwicz-Miedzinska, M.D. [Site 080]

Instytut “Pomnik-Centrum Zdrowia Dziecka”
Klinika Gastroenterologii, Hepatologii
Zaburzen Odzywiania
Aleja Dzieci Polskich 20
04-730 Warszawa
Poland

Dr Gliwicz-Miedzinska was inspected on June 14-18/2021 as a data audit for Study LUM001-304. The final EIR report is pending.

Dr Gliwicz-Miedzinska consented and screened 3 subjects into Study LUM001-304 [Subjects (b) (6)]. Two subjects, (b) (6) were enrolled in the study. Subject

(b) (6) had insufficient ItchRo scores and did not meet inclusion criteria #12. Only one subject completed the study (b) (6). Subject (b) (6) terminated early after 48 weeks due to the development of enlarged lymph nodes found on imaging. The subjects eligible to participate were randomized and treated with the placebo.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, protocol deviations, laboratory tests, and electronic case report forms (CRFs). Blinding procedures were reviewed. Regulatory documentation was also examined, including the Ethics Committee (EC) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, site training records, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

In general, records were found to be complete and orderly. There appeared to be no under reporting of adverse events or protocol deviations. Eligibility and primary endpoint data were verifiable. The ItchRO observations for morning and evening, the Clinician Scratch Scale, the Xanthoma scale, and the Weight/height scales were verifiable with source records with no discrepancies noted.

Serum bile acid results were assessed by the sponsor and then shared with the principle investigator. There appeared to be no discrepancies and were verifiable. The PedsQL questionnaires for all primary visits were verified. Secondary assessments included spot checking for fat soluble vitamins. The adverse events that were assessed and documented included clotting issues, fractures, and diarrhea. There were two serious adverse events filed with the sponsor within 24 hours.

Reviewer's Comment: The inspector reported minimal gaps in daily documentation of the AM/PM eDiary readings for the ItchRo Observations up to Week 48. Gaps of ItchRo after 48 weeks were apparent but the PI explained that the Subject (b) (6) was to return after 3 months during the extension period and answer the ItchRo for two consecutive weeks. It is reported that Subject (b) (6) was compliant in this task and required minimal oversight.

Overall, the data appeared to be reliable and verifiable. No Form FDA 483, Inspectional Observations, was issued.

**4. Mirum Pharmaceuticals, Inc.
950 Tower Lane, Suite 1050
Foster City, CA 94404**

Mirum Pharmaceuticals, Inc. (Mirum) was inspected May 5-7, 2021 and May 10-12, 2021. This was the first FDA inspection of this Sponsor. This surveillance inspection covered the responsibilities of Mirum as the sponsor for the study drug maralixibat as

used in Study LUM001-304 titled “Long-term, open-label study with a double-blind, placebo-controlled, randomized drug withdrawal period of LUM001, an apical, sodium-dependent bile acid transporter inhibitor (ASBTi) in patients with Alagille Syndrome”.

The inspector reviewed records that included but were not limited to presentations, organizational charts, contracts, transfer of obligations, standard operating procedures (SOPs), monitoring plans, monitoring reports, qualifications of monitors, laboratory data, eDiary data, test article procedures and documentation, and pharmacovigilance procedures and documentation.

Mirum had written procedures in place for selection and oversight of vendors. (b) (4) was contracted to conduct study management activities. Study management activities included study site monitoring, drug accountability, safety reporting, regulatory submissions, data management, Interactive Web Response System (IWRS), central lab and specialty lab testing, eDiary, patient travel and reimbursement, and patient recruitment and retention.

A joint meeting with (b) (4) and Mirum Protocol Deviation Review followed the internal meeting convened every three months by (b) (4) to review the Protocol Deviation Log, extracted from (b) (4) PD tracking system. Inspection review of the study’s Major Protocol Deviation List and the Study List of Protocol Deviations found no issues.

Training and site initiation visits (SIV) were conducted. SIV documentation showed the study sites reviewed received training, confirmed qualifications, and informed the study site in regard to all aspects of the study, including the protocol and study procedures.

A review of the monitoring reports for the study sites reviewed during this inspection found no issues with monitoring. On site monitoring was being conducted within appropriate timeframes. The EDC was reviewed and showed queries made by monitors within the data audits. Monitoring reports indicated the monitors were conducting source data verification and source document review.

As a result of the COVID-19 pandemic, Mirum and (b) (4) approved a plan in April 2020 to allow remote monitoring procedures and visits. These were included in the Clinical Monitoring Plan and the firm’s COVID-19 Continuity Plan.

The firm performed quality assurance (QA) audits for the participating clinical sites. They also conducted QA audits for the vendors used in the study.

The firm contracted pharmacovigilance duties to (b) (4) Clinical investigators are to report SAEs within 24 hours of awareness to (b) (4) who performs triage/medical assessment and enters the SAE in Argus, its drug safety database. (b) (4) is responsible for assessment of expectedness and Mirum is responsible for the review and approval of causality and expectedness assessment. If

follow-up information is needed, (b) (4) sends the query to the investigator. Mirum completes the final review. If the SAE is identified as a SUSAR, a 7 or 15-day IND safety report is submitted to FDA by (b) (4) is responsible for reporting SUSARS to IRBs/ECs.

There were CAPAs related to late submission of six SUSARs for maralixibat. (b) (4) held the safety data for Mirum prior to July 2020. At that time the data was transferred to a safety database company acquired by Mirum (b) (4). Mirum Medical Safety Operations noted inconsistencies in the legacy safety data and a comprehensive safety review was initiated and completed in April 2021. There were five cases, with one of the cases having two SAE's occurring between 2013 and 2015, Expectedness was either not assessed or determined as expected when they should have been assessed as unexpected per the reference safety information (RSI). An additional case in 2014 was serious and there is no evidence the prior sponsor (Shire) submitted the case as an expedited safety report to regulatory authorities. These six unreported cases occurred prior to Mirum assuming sponsorship. According to the CAPA, the newly identified expedited safety reports were distributed for submission to the appropriate regulatory authorities, IECs/IRBs, and investigators on 5/10/21.

Subjects are given an eDiary device with ePRO software installed on the eDiary. The assessment of pruritis in this study is the ItchRO assessment from the eDiary. The caregiver and/or subject were instructed to enter itch severity in the morning and in the evening each day in the eDiary for the duration of the study. The data was sent directly to (b) (4), the responsible entity for data management of the study. (b) (4) collected the data, performed validation and evaluation, and packaged the data to Mirum and the Data Monitoring Committee.

The clinical investigators were required to electronically sign the completed eCRFs for each subject before the data were archived or submitted to FDA. Inspection confirmed that Mirum and (b) (4) received PDF archives of the EDC data from (b) (4), the EDC for the study, at the end of the study. Inspection verified that (b) (4) sent certified copies of the site source data through an enclosed USB storage device to the investigator sites on 10/26/2020.

Inspection verified that the test article was properly labeled in each language based on the master English label. All shipping excursions and temperature excursions of the IP were found to be acceptable and in accordance with the study's Pharmacy Manual. IP accountability records for the inspected sites [040, 080, and 090] were consistent with the firm's SOP (b) (4)

At the close-out meeting, there were no discussion items to address. No Form FDA 483, Inspection Observations, was issued.

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Zana Marks , M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

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Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Documentation
Review Division /Division Director
Review Division/Medical Officer
Review Division /Medical Team Leader
Review Division /Project Manager
OSI/Office Director
OSI/DCCE/ Division Director
OSI/DCCE/GCPAB Chief
OSI/DCCE/GCPAB Team Leader
OSI/ GCP Program Analysts
OSI/Database Project Manager

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INTRODUCTION AND BACKGROUND

On November 12, 2020, the applicant (Mirum Pharmaceuticals) submitted a new original NDA 214662 for maralixibat oral solution for approval. The Division of Hepatology and Nutrition (DHN) consulted the Division of Pediatric and Maternal Health (DPMH) on January 4, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- On November 12, 2020, the applicant submitted an NDA for maralixibat oral solution with the proposed indication for the treatment of cholestatic pruitis in patients with Alagille Syndrome age 1 year and older via the 505(b)(1) pathway.
- On September 4, 2013, maralixibat was granted Orphan Drug Designation.
- On October 23, 2019, maralixibat was granted Breakthrough Therapy Designation.
- On December 2, 2019, maralixibat was granted Rare Pediatric Disease Designation.
- On August 10, 2020, Mirum Pharmaceutical requested a priority review voucher for NDA 214662.
- On August 11, 2020, the proprietary name Livmarli was deemed conditionally acceptable by the FDA.
- On October 12, 2020, Mirum Pharmaceutical requested priority review designation for NDA 214662.

Drug Characteristics¹

Drug Class ²	Ileal bile acid transporter (IBAT) inhibitor
Mechanism of action ²	Maralixibat acts by inhibiting IBAT in the terminal ileum, thereby interrupting the enterohepatic circulation of bile acids and reducing systemic bile acid levels.
Dose and Administration	Starting dose is 190 µg/kg orally daily, 30 min before first meal of day; increase to 380 µg/kg daily after one week.
Metabolism	No maralixibat metabolites have been detected in plasma, and maralixibat also undergoes minimal metabolism in the gastrointestinal tract. Following a single oral dose of ¹⁴ C-maralixibat, fecal excretion was found to be the major route of elimination with <1% excreted in the urine.
Molecular weight	710.41 Dalton (salt); 674.96 Dalton (free base)
Half life	NA
Protein Binding ³	>90%, highly bound in vitro (see table below)
Bioavailability ⁴	<1%
Proposed Serious Adverse Reactions ⁵	Increased liver test, fat-soluble vitamin deficiency, gastrointestinal adverse reactions vs diarrhea and abdominal pain

¹ Based on Applicant's Proposed Labeling with DHN Review Team Input.

² Based on discussion with DHN Pharmacology Toxicology Team.

³ Based on discussion with DHN Pharmacology Toxicology Team. Protein binding was evaluated in vitro only, and it depends on species.

⁴ Based on discussion with DHN Pharmacology Toxicology Team.

⁵ Based on discussion with DHN Clinical Team.

Reviewer comment:

In our discussion with the DHN Clinical Pharmacology team, it was confirmed that the oral absorption of maralixibat appears to be low (~1%), but not minimal.

REVIEW

PREGNANCY

Alagille Syndrome and Pregnancy⁶

Alagille Syndrome is a rare (1/30,000 to 1/70,000)^{7,8} genetic syndrome that is inherited in an autosomal dominant fashion with mutations in the JAG1 gene in more than 90 percent of patients; a small percentage have mutations in the NOTCH2 gene. Alagille Syndrome is characterized by the paucity of interlobular bile ducts and characterized by conjugated hyperbilirubinemia, elevated serum aminotransferases and gamma-glutamyl transpeptidase (GGTP). Clinical presentations are variable and associated features include

- Hepatic manifestations such as chronic cholestasis, jaundice, cirrhosis, pruritus, xanthomas
- Cardiac murmur or anomalies
- Butterfly vertebrae
- Eye findings, most commonly posterior embryotoxon
- Dysmorphic facies, consisting of broad nasal bridge, triangular facies, and deep-set eyes
- Renal involvement

Short stature, failure to thrive, and developmental delay are common in Alagille syndrome. Approximately 75% of patients with Alagille syndrome live to at least 20-years of age. Factors contributing to mortality are complex congenital heart disease (15%), intracranial bleeding (25%) and hepatic disease, potentially leading to hepatic transplantation.⁹

Current management depends on treatment of disease in each affected organ system. The key considerations include:

- Management of cholestatic liver disease conservatively by treating malabsorption.
- Management of pruritus with ursodiol, rifampin, or bile acid sequestrants.
- Management of malnutrition and associated growth failure and pubertal delay. High energy supplements with medium chain triglycerides for failure to thrive and fat-soluble vitamin (A, D, E, K) supplementation are often needed.⁹
- Management of cardiac or renal disease as needed.
- Low threshold for brain imaging in the setting of head trauma due to higher risk of vascular anomalies.

⁶ Erlichman J, et al. Causes of cholestasis in neonates and young infants. UpToDate.

https://www.uptodate.com/contents/causes-of-cholestasis-in-neonates-and-young-infants?search=alagille%20syndrome&source=search_result&selectedTitle=1~25&usage_type=default&display_rank=1 Accessed 1/8/2021.

⁷ Danks DM, Campbell PE, Jack I, Rogers J, Smith AL (1977) Studies of the etiology of neonatal hepatitis and biliary atresia. Arch Dis Child 52:360–367

⁸ Morton A, Sailesh Kumar. Alagille syndrome and pregnancy. Obstetric Medicine 2019; 0(0): 1-3. DOI: 10.1177/1753495X19849738

⁹ Antsaklis A, et al. Alagille syndrome. Journal of Obstetrics and Gynaecology 2011; 31(5): 450-451.

Pregnant people with Alagille syndrome are very rare. Eleven successful pregnancies (out of twenty-nine total cases) throughout the published literature were summarized in a 2019 case report.⁸ Of these, fetal growth restriction was present in seven pregnancies (64%), pre-eclampsia in two pregnancies (18%), and one case of postpartum maternal pulmonary edema. Neonatal death following cardiac surgery occurred in one case. Several published data noted a mild parental phenotype with more intense manifestations in the offspring.¹⁰ Elmslie et al. reported relatively high miscarriage rates after 10 weeks' gestation in 6 of 22 female subjects (27%) with ALGS.¹¹ Maternal cholestasis may be associated with increased risk of fetal compromise, spontaneous preterm birth and stillbirth.^{8,12} Maternal management considerations for pregnancy include consideration for the severity of cardiac disease, pulmonary hypertension, cirrhosis, portal hypertension, and renal disease. Fat-soluble vitamin levels should be monitored and replaced if deficient. Those with cirrhosis are at an increased rate of maternal and fetal morbidity and mortality.¹³

Nonclinical Experience

No effects on embryo-fetal development were observed in pregnant rats treated orally with up to 1000 mg/kg/day (approximately 3367 to 12547 times the maximum recommended dose based on AUC (area under the plasma concentration-time curve]) or in pregnant rabbits treated orally with up to 250 mg/kg/day (approximately 1277 to 4758 times the maximum recommended dose based on AUC) during the period of organogenesis. No effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 750 mg/kg/day during organogenesis through lactation. Maternal systemic exposure to maralixibat at the maximum dose tested was approximately 2525 to 9409 times the maximum recommended dose based on AUC.

The reader is referred to the Nonclinical comments within the integrated review.

Review of Clinical Trials

There were no pregnant patients enrolled in any of the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a literature review in Embase, Pubmed, Micromedex,¹⁴ and ReproTox.¹⁵

¹⁰ Antsaklis A, et al. Alagille syndrome. *Journal of Obstetrics and Gynaecology* 2011; 31(5): 450-451.

¹¹ Elmslie FV, Vivian AJ, Gardiner H, et al. Alagille syndrome: family studies. *J Med Genet* 1995; 32: 264-268. 1995/04/01.

¹² Goh SK, Gull SE, Alexander GJ. Pregnancy in primary biliary cirrhosis complicated by portal hypertension: report of a case and review of the literature. *BJOG*. 2001; 108:760-2.

¹³ Reau N, et al. Pregnancy in women with pre-existing chronic liver disease. UpToDate https://www.uptodate.com/contents/pregnancy-in-women-with-pre-existing-chronic-liver-disease?search=primary%20biliar%20cirrhosis%20and%20pregnancy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3439089617 Accessed 1/8/2021.

¹⁴ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 1/8/2021

¹⁵ Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 1/8/2021.

Embase and Pubmed were searched for “maralixibat” and “pregnancy,” “maralixibat” or “maralixibat” and “fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage.”

- There is no published literature on maralixibat use in pregnancy.

Micromedex¹⁴ and ReproTox¹⁵ contain no information on maralixibat.

Reviewer comment:

In animal reproductive studies, no adverse effects were observed on fetal growth or development in rats. There are no data on the use of maralixibat in pregnancy.

Based on its mechanism of action, inhibition of ileal bile acid transporters may inhibit absorption of bile salts, dietary fats, and lipid soluble vitamins. Alagille Syndrome is often associated with malnutrition, and fat-soluble vitamin supplementation is often needed. Because maralixibat may inhibit absorption of fat-soluble vitamins and because Alagille Syndrome itself causes fat-soluble vitamin depletion, the combination of the drug and disease may result in excess vitamin depletion in this population. Fat soluble vitamin supplementation is part of standard care in Alagille Syndrome. Because pregnancy is a sensitive period where normal fetal development is dependent on maternal intake of fat-soluble vitamins, monitoring for fat-soluble vitamin deficiency and supplementation of fat-soluble vitamin is especially important for pregnant patients with Alagille Syndrome who take maralixibat. The reader is referred to the DPMH’s Discussion and Conclusion at the end of this review.

LACTATION

Nonclinical Experience

In a pre- and postnatal development study, maralixibat was orally administered to rats at doses up to 750 mg/kg/day during organogenesis through lactation. The concentrations of maralixibat in rat pup plasma were 3.5 to 6.8 times higher than the maternal plasma concentration. No effects on postnatal development were observed.

The reader is referred to the Nonclinical comments within the integrated review.

Reviewer comment:

Although there were no animal lactation studies, pre- and post-natal developmental studies were conducted with maralixibat. Maralixibat was detected in rat pup plasma. In discussion with the DHN Pharmacology Toxicology Team, the team noted that the presence of maralixibat in rat pup plasma was likely due to transfer from rat milk and not from prenatal exposure. However, the lactating rats were given maralixibat at human exposure multiples that were 257 to 956 times the maximum recommended human dose (MRHD) of 28.5 mg per day, which would explain the higher concentrations of maralixibat in rat pup plasma. The clinical significance of this finding is uncertain.

Review of Clinical Trials

Lactating patients were excluded from clinical trials.

Review of Literature

DPMH's Review of Literature

A search was performed using the sources noted below, and the following findings were retrieved:

A search in PubMed and Embase was performed using the search terms “maralixibat” AND “lactation” and “maralixibat” AND “breastfeeding.”

- No articles were found on the use of maralixibat during lactation.

LactMed,¹⁶ Briggs,¹⁷ and Hale¹⁸ contain no information on maralixibat.

Reviewer comment:

It is not known if maralixibat is present in human breastmilk. There are no data on the effect of maralixibat on the breastfed child or the effect on milk production. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Carcinogenesis

A carcinogenicity study in RasH2 transgenic mice showed no carcinogenic effects. Mice in this study were administered doses of maralixibat approximately 65-fold (males) and 200-fold (females) higher than the recommended human dose, for 6 months.

Mutagenesis

Maralixibat was negative in the bacterial reverse mutation (Ames) assay, the in vitro chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and the in vivo rat micronucleus test.

Impairment of Fertility

No effects on fertility were observed in female rats treated orally with up to 2000 mg/kg/day or in male rats treated orally with up to 750 mg/kg/day.

The reader is referred to the Nonclinical comments within the integrated review.

Review of Clinical Trials

There are no specific reports of fertility issues noted in any of the clinical trials.

¹⁶ <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 1/8/2021.

¹⁷ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 1/8/2021.

¹⁸ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 1/8/2021.

Review of Literature

DPMH's Review of Literature

DPMH conducted a published literature review by using the sources noted below, and the following findings were retrieved:

DPMH conducted a published literature review on PubMed and Embase using term “maralixibat” and “fertility,” “maralixibat” AND “reproduction,” “maralixibat” AND “contraception.” No relevant articles were retrieved.

ReproTox¹⁹ contains no information on maralixibat.

Reviewer comment:

There are no data on the effect of maralixibat on fertility in humans. In animal reproduction studies, maralixibat does not appear to effect fertility at a dose in the clinical range. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Maralixibat has low absorption following oral administration, and maternal use at the proposed clinical dose is not expected to result in measurable fetal exposure to maralixibat. There are no data on the use of maralixibat in humans during pregnancy. In animal reproduction studies, maralixibat administered in pregnancy did not result in embryotoxicity or structural malformation.

Based on its mechanism of action, maralixibat may inhibit the absorption of dietary fats and lipid soluble vitamins as well as bile salts. Alagille Syndrome is often associated with malnutrition, and fat-soluble vitamin supplementation is a part of the standard of care for managing Alagille Syndrome. Fat soluble vitamins are necessary for normal development in a growing fetus, and maralixibat use may add further insult to an already depleted fat-soluble vitamin storage in a pregnant patient with Alagille Syndrome. Fat-soluble vitamin depletion in pregnancy may be detrimental to a growing fetus; therefore, based on discussion with the DHN Clinical Team, DPMH agrees with adding language about monitoring for fat soluble vitamin deficiency in pregnant patients and supplementing fat-soluble vitamins if needed under 8.1, Clinical Considerations.

Alagille syndrome is a rare disease with an incidence rate of 1/30,000 to 1/70,000. Only 11 successful pregnancies have been reported in published literature to date⁷. Additionally, the systemic absorption following oral administration of maralixibat is low, and maternal use is not expected to result in fetal exposure to LIVMARLI. Therefore, DPMH does not recommend any postmarketing pregnancy study at this time.

Lactation

Maralixibat has low absorption following oral administration, and breastfeeding is not expected to result in measurable exposure of the infant to maralixibat at the clinical dose. There are no

¹⁹ ReproTox. Accessed 1/8/2021.

data on the presence of maralixibat in human milk, the effects of the drug on the breastfed infant, or on milk production.

Although there were no animal lactation studies, pre- and post-natal developmental studies were conducted with maralixibat. There were no adverse effects noted on postnatal development; however, maralixibat was detected in rat pup plasma. In discussion with the DHN Pharmacology Toxicology Team, the team noted that the presence of maralixibat in rat pup plasma was likely due to transfer from rat milk and not from prenatal exposure. The lactating rats were given doses of maralixibat at human exposure multiples that were 257 to 956 times the MRHD of 28.5 mg per day, which would explain the higher concentrations of maralixibat in rat pup plasma. The clinical significance of this finding is uncertain.

Because there is low absorption of the drug after oral administration, breastfeeding is not expected to result in significant exposure of the infant to LIVMARLI. Therefore, DPMH does not recommend lactation study at this time.

Females and Males of Reproductive Potential

There are no reports of maralixibat adversely effecting human fertility. Based on animal studies, maralixibat has no effect on male fertility and no effects on mating in either sex. There are no data to suggest maralixibat interacts with systemic hormonal contraceptive. DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS

DPMH proposes edits to subsections 8.1 and 8.2 of labeling for the new NDA and in compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling



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/s/

WENJIE SUN
06/28/2021 09:32:50 AM

MIRIAM C DINATALE
06/28/2021 09:38:16 AM

LYNNE P YAO
06/28/2021 10:14:39 AM

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

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

Date of This Review:	June 9, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 214662
Product Name, Dosage Form, and Strength:	Livmarli (maralixibat) oral solution, 9.5 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mirum Pharmaceuticals Inc
FDA Received Date:	August 31, 2020, November 11, 2020, and January 29, 2021
OSE RCM #:	2020-1857 and 2021-253
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Livmarli (maralixibat oral solution), the Division of Hepatology and Nutrition (DHN) requested that we review the proposed Livmarli prescribing information (PI), instructions for use (IFU), updated use related risk analysis (URRA), and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Updated URRA	F
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, IFU, container labels, and carton labeling for maralixibat to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI, IFU and the proposed carton and container labels. We provide our recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant.

In addition, we had completed a review of their URRA on July 14, 2020 under IND 119917 and found that no additional data was warranted to support the marketing application; however, we recommended they update their URRA to address some additional issues identified (Appendix B). The Applicant submitted an updated URRA on November 11, 2020. Our review of the updated URRA finds it acceptable, and our determination that no additional data is warranted to support the marketing application is unchanged.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR DIVISION OF HEPATOLOGY AND NUTRITION (DHN)

A. Prescribing Information

1. Dosage and Administration Section

- a. The dosage and administration section include the error prone symbols, “μ” which might be misinterpreted. We recommend replacing the symbol “μ” with the intended meaning (mc) to prevent misinterpretation and confusion.
- b. The use of trailing zeros is identified in the Dosing and Administration section in Full Prescribing Information. The use of trailing zeros may cause a ten-fold misinterpretation. Remove the trailing zeroes to avoid confusion.
- c. For Table 1, we recommend deleting the dispenser size column to reduce clutter. The correct volume syringe should be provided by the pharmacy.
- d. For Table 1, we recommend revising the weight range to reflect the entire weight range (e.g., 5 to 6.9 instead of 5 to 6).
- e. Section 2.3 Administration: Due to our understanding of post-marketing reports, (b) (4) may have the opposite of intended meaning

(b) (4)
We recommend deleting the statement (b) (4)

2. Instructions for Use

- a. We recommend deleting Table 1 to reduce clutter. The correct volume syringe should be provided by the pharmacy and the information presented may cause confusion. Patient and/or the caregiver will be provided with instructions on the correct dose and dispenser size by the healthcare provider.

3. Add the following statements to Section 17: “Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy.” We recommend this due to evidence that suggests the use of an oral syringe may decrease the risk of wrong dose error, particularly when measuring smaller doses.

4.2 RECOMMENDATIONS FOR MIRUM PHARMACEUTICALS INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The strength statement lacks prominence and readability. As currently presented, the dosage form statement competes in prominence with the strength statement. Consider moving the dosage form statement below the

strength statement, increase the strength statements font size and differentiate between the color fonts for each statement.

2. To ensure consistency with the Prescribing Information, revise the statement, [REDACTED] (b) (4) to read
"Recommended Dosage: See prescribing information."
3. Include the statements "Date of first opening __/__/__." [REDACTED] (b) (4) in bold font under storage information on the container label and carton labeling. Additionally, the "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling.

B. Container Label

1. As currently presented, the format and location for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
2. Location of the lot number is not indicated. Please indicate where this important information will be located.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Livmarli received on November 11, 2020 from Mirum Pharmaceuticals Inc.

Table 2. Relevant Product Information for Livmarli	
Initial Approval Date	N/A
Active Ingredient	maralixibat
Indication	indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older.
Route of Administration	oral
Dosage Form	oral solution
Strength	9.5 mg/mL
Dose and Frequency	190 microgram/kg once daily, increase to 380 microgram/kg once daily after 1 week
How Supplied	30 mL bottle
Storage	Store unopened bottle at 20°C to 25°C (68°F to 77°F); [see USP Controlled Room Temperature].
	(b) (4)
	Always store with cap on the bottle.
	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 14, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “maralixibat”. Our search identified four previous reviews^a, and we considered our previous recommendations to see if they are applicable for this current review.

^a Barlow M. Comparative Analyses & Proactive Risk Assessment Review for Maralixibat (IND 119917). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 14. RCM No.: 2020-480.

APPENDIX F. USE RELATED RISK ANALYSIS

November 11, 2020

[\\CDSESUB1\evsprod\nda214662\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\alagille-syndrome\5354-other-stud-rep\livmarli\5354-livmarli-urra.pdf](#)

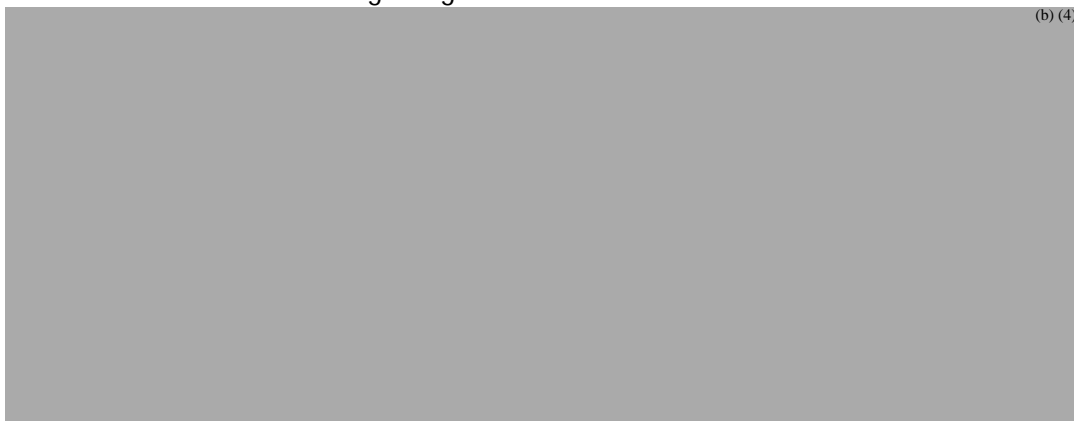
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Livmarli labels and labeling submitted by Mirum Pharmaceuticals Inc.

- Container label received on November 11, 2020.
- Carton labeling received on November 11, 2020
- Instructions for Use received on November 11, 2020, available from [\\CDSESUB1\evsprod\nda214662\0002\m1\us\114-labeling\draft\labeling\livmarli-ifu.docx](#)
- Prescribing Information (Image not shown) received on November 11, 2020, available from [\\CDSESUB1\evsprod\nda214662\0002\m1\us\114-labeling\draft\labeling\livmarli-draft-label-text.docx](#)

G.2 Label and Labeling Images



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



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/s/

SARAH K VEE
06/09/2021 10:37:39 AM

IDALIA E RYCHLIK
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Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

Version Date: April 30, 2021

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)

Through: Shetarra Walker, MD, MSCR, Clinical Team
Leader, DPMH
John J. Alexander, MD, MPH, Deputy Director
DPMH

NDA Number: 214,662

Applicant: Mirum Pharmaceuticals, Inc.

Drug: Livmarli (maralixibat chloride)

Indication: Treatment of cholestatic pruritus in patients with
Alagille Syndrome (ALGS) 1 year and older

**Dosage Form and
Route of Administration:** Solution for oral (PO) administration

Proposed Pediatric Regimen: 190 µg/kg orally per day (QD), 30 min before first
meal of day; increase to 380 µg/kg QD after one
week

Division Consult Request: The Division of Hepatology and Nutrition (DHN)
requests DPMH assistance in labeling of this new
molecular entity (NME) for treatment of ALGS.

Background

The applicant is developing Livmarli (maralixibat chloride) for the treatment of ALGS.

The following disease summary is taken from Online Mendelian Inheritance in Man (OMIM; <https://omim.org/>) and UpToDate websites on April 16, 2021.

Alagille syndrome is an autosomal dominant condition, caused by one of two mutations (“AS-1” per OMIM #: 118450; “AS-2” per OMIM # 610,205), and is characterized by pruritus (40% of patients) attributed to chronic cholestasis (95 to 100% of patients). Together, the two forms have an incidence of approximately 1/70,000 live births. Patients are usually diagnosed within 3 months of birth with unconjugated hyperbilirubinemia, pruritus, characteristic facies, pulmonic stenosis, and ring-like corneal opacities (posterior embryotoxon). The cholestasis is associated with paucity of bile ducts on histopathology. The severity of pruritus varies from patient to patient and within the same patient over time. Many patients progress to cirrhosis/end stage liver disease (ESLD), requiring orthotopic liver transplants. Patients may also develop interstitial nephritis or membranoproliferative glomerulonephritis. Some patients also have vertebral butterfly anomalies and may develop xanthomas. Mortality from disease is 17 to 28% due to visceral organ failure (liver, cardiac, renal). Patients with mild phenotypes and without extrahepatic complications commonly reach adulthood.

There are no approved treatments for the ALGS; however, many patients receive off-label treatment with ursodeoxycholic acid (UDCA), bile acid sequestrants (e.g., cholestyramine) and other drugs (e.g., naltrexone) for perceived pruritus reduction.

Maralixibat is an inhibitor of the apical sodium-dependent bile acid transporter (ASBT). Maralixibat is minimally absorbed and is proposed to act by inhibiting ASBT in the terminal ileum. This action interrupts the enterohepatic circulation of bile acids and reduces systemic bile acid levels which are pruritogenic.

Efficacy was assessed in a single placebo-controlled clinical trial of 31 patients (1 to 15 years old at enrollment, median age 5 years). All patients were first treated with maralixibat once daily for 18-weeks, followed by a 4-week randomized, double-blind, placebo-controlled period. After the control period, all patients received open-label treatment for up to 2 years to allow for collection of additional safety data. (b) (4)

(b) (4) patients could switch to ½ dose administered twice daily (BID) for the open-label extension period (b) (4) DHN has stated that all but one patient elected to switch to BID dosing.

Labeling Review

There are no proposed boxed warnings, Contraindications (section 4), (b) (4)

DPMH’s labeling recommendations focus on sections 1 (Indications and Usage), 2 (Dosage and Administration), and 8.4 (Pediatric Use). Review of the remaining sections [e.g., 6 (Adverse Reactions) and 14 (Clinical Studies)] is deferred to DHN and other disciplines (e.g., Clinical Pharmacology and Statistics).

For this review, text which DPMH recommends deleting is noted by ~~strike-out~~, and any text which DPMH recommends adding is noted in **bold red**. The comments below were provided to DHN on April 30, 2021. The reader is directed to final approved labeling which may include revised language not addressed in this review.

1. Indications and Usage

LIVMARLI is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older.

Reviewer comment: The proposed indication conforms to the conditions of the clinical study and is acceptable pending establishment of efficacy by DHN and Statistics.

2. Dosage and Administration

2.1 Dosing

The recommended ^{(b) (4)} once daily (QD), taken ^{(b) (4)} 30 minutes before the first meal of the day. ^{(b) (4)}. Refer to the dosing by weight guidelines presented in [Table 1](#).

Table 1: Individual Dose ^{(b) (4)} by Patient Weight

Patient Weight (kg)	Days 1-7 (190 µg/kg ^{(b) (4)})		Beginning Day 8 (380 µg/kg ^{(b) (4)})	
	Volume QD (mL)	Dosing dispenser size (mL)	Volume QD (mL)	Dosing dispenser size (mL)
5-6	0.10	0.5	0.20	0.5
7-9	0.15		0.30	
10-12	0.20		0.45	
13-15	0.30		0.60	1.0
16-19	0.35	0.70		
20-24	0.45	0.90		
25-29	0.50	1.00		
30-34	0.60	1.0	1.25	3.0
35-39	0.70		1.50	
40-49	0.90		1.75	
50-59	1.00		2.25	
60-69	1.25	3.0	2.50	
70 or higher	1.50		3.00	

PO=orally; QD=once daily.

Reviewer comment: The regimen above only allows for QD dosing. (b) (4)

(b) (4)
Under this circumstance, the description in section 14 could cause confusion with the dosing instructions in section 2. One option to address this issue is to delete (b) (4) from section 14. The other option is to (b) (4)

2.2 Missed Dose

If a dose is missed, it should be taken as soon as possible (b) (4) within 12 hours of the time it is usually taken, and the original dosing schedule resumed. If a dose is missed by more than 12 hours, the dose can be omitted and the original dosing schedule resumed.

2.3 Administration

A calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dosing dispenser) will be provided by the pharmacy to measure and deliver the prescribed dose accurately (b) (4)

(b) (4)
(b) (4)

Reviewer comment: The above edits for section 2.2 and 2.3 are recommended for clarity.

8.4 Pediatric Use

The safety and effectiveness of LIVMARLI for the treatment of cholestatic pruritus in pediatric patients with Alagille syndrome have been established in one (b) (4) study of patients 1 to 15 years of age (N=31). Additional safety information was obtained from four (b) (4) studies in patients up to 21 years of age (N=55) [see Adverse Reactions (6) and Clinical Studies (14)].

(b) (4)

The safety and effectiveness of LIVMARLI have not been established in patients less than 1 year of age (b) (4)

Reviewer comment: The above edit is recommended to clarify the basis of approval.

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/s/

ETHAN D HAUSMAN
04/30/2021 09:24:05 AM

SHETARRA E WALKER
04/30/2021 09:25:38 AM

JOHN J ALEXANDER
04/30/2021 11:06:35 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 19, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Navi Bhandari, RPM / Lisa Skarupa, RPM
DHN

Subject: QT Consult to NDA 214662 (SDN 002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/17/2021 regarding the sponsor's request to waive a TQT study. We reviewed the following materials:

- Sponsor's hERG study report (SN 0012; [link](#));
- Sponsor's hERG study raw data (SN 0002; [link](#));
- Study MRX-102 clinical study report (SN 0002; [link](#));
- Request to waive a TQT study (including Highlight of Clinical Pharmacology and Cardiac Safety in Appendix 1) (SN 0002; [link](#));
- Propose label (SN 0002; [link](#)); and
- Previous IRT reviews under IND 119917 dated 11/13/2019, 03/26/2020, 04/20/2020, 05/07/2020 in DARRTS.

1 Responses for the Division

We agree with the sponsor's request to waive a thorough QT study. The product demonstrates a relatively low systemic exposure at approximately 3-times the maximum recommended therapeutic dose ($C_{max} = \sim 4$ nM at 100 mg dose in the fasting condition). The sponsor's in vitro hERG study provided a large safety margin at this dose level. The PK and ECG data do not suggest large mean increases in the QTc interval in the food effect study that studied doses up to 3-times the maximum recommended therapeutic dosing regimen.

We agree with the sponsor's proposed label which omitted 12.2 Electrophysiology. This is consistent with IRT's current practice for other locally acting drug products that have minimal systemic exposure.

2 BACKGROUND

2.1 Product Information

Maralixibat (MW: 675 g/mol) is a potent inhibitor of the apical sodium-dependent bile acid transporter (ASBT, also known as the ileal bile acid transporter [IBAT]), a transmembrane protein localized on the luminal surface of ileal enterocytes. Mirum (the sponsor) is developing maralixibat chloride oral solution (9.5 mg/mL) for the treatment of pruritus associated with Alagille syndrome (ALGS). The proposed clinical doses is 190 ug/kg orally QD, and increase to 380 ug/kg QD after one week. It is recommended that the drug is administered 30 min before first meal of day to maximize its pharmacodynamic effect through post-prandial bile flow.

No metabolites have been identified in plasma, whole blood, or urine in a human ADME study. Following oral administration, Maralixibat is minimally absorbed in humans. In humans, PK parameters can only be assessed at suprathreshold doses due to the lack of measurable plasma concentration after oral dosing at therapeutic dose levels. The plasma half-life appears to be in the range of 2 to 7 hours, and plasma drug levels do not significantly increase with multiple dosing. Plasma exposures increase with increasing doses in an approximately proportional to less than proportional manner from 50 mg to 500 mg. However, dose proportionality assessment is challenging due to the lack of measurable plasma drug concentrations.

Maralixibat has a very low risk of being a victim of drug-drug interactions, as it is minimally metabolized, and is not a substrate for CYP450 enzymes or drug transporters including P-gp and BCRP. It is also unlikely that other disease states, such as renal or hepatic impairment, will materially impact systemic exposure.

2.2 Sponsor's position related to the question

Fasting condition was considered the highest exposure scenario. Previously the IRT agreed with the sponsor's proposal to incorporate QT assessment in the planned food effect study MRX-102 and to conduct a concentration-QTc analysis only if substantial systemic exposure is observed in the fasted state. The sponsor was also recommended to conduct by-timepoint analysis to support QTc assessment for the highest proposed clinical dose (400 ug/kg). Refer to IRT reviews under IND 119917 dated 03/26/2020, 04/20/2020, and 05/07/2020 in DARRTS.

In the current submission, the sponsor is requesting a waiver of the thorough QT study based on the following reasons: (1) the minimal absorption of maralixibat following oral administration and a very low risk of high plasma exposures through intrinsic or extrinsic factors, (2) no significant inhibition of hERG by Maralixibat (1% or less versus controls at the highest feasible dose tested of 1 μ M), (3) the very large (>2,000-fold) safety margins established by the nonclinical safety pharmacology studies, (4) the existing clinical safety data which have not identified any impact of maralixibat on ECG parameters, and (5) results from the clinical food effect Study MRX-102 showing very low drug plasma levels at all doses tested including a suprathreshold dose of 100 mg.

2.3 Nonclinical Cardiac Safety

In the current submission, the sponsor provided raw data from Study mrx-nc-003. FDA's independent analysis of the submitted electrophysiology data shows that maralixibat inhibited hERG current by -2.8% at 1 μ M. IC₅₀ is far greater than 1 μ M and the hERG safety margin of maralixibat is expected to be greater than 5920x (*refer to Appendix for a detailed review of sponsor's submission*). In conclusion, results from the sponsor's experiments suggest that maralixibat has a low risk for QT prolongation by direct inhibition of hERG channel at the therapeutic exposure level.

In addition, the sponsor provided the following description of in vivo study results:

no effects on cardiac conduction were observed in the maralixibat nonclinical safety pharmacology study in dog following single oral administration up to 20 mg/kg (Study EX4898), achieving maximum plasma concentrations of 5.72 ng/mL, or following IV administration of up to 0.28 mg/kg (Study EX4887), achieving a maximum plasma concentration of 6270 ng/mL. This plasma drug concentration tested in the dog cardiovascular safety study established more than a 2600-fold margin to the mean total C_{max} concentration of 2.4 ng/mL in humans at the highest dose tested of 500 mg, and more than 14,000-fold to the mean total C_{max} concentration of 0.44 ng/mL after a 30 mg dose.

2.4 Clinical Cardiac Safety

Maralixibat was first evaluated as a potential lipid-lowering agent in a development program that included over 1400 adult patients (in 12 clinical studies where patients received daily doses up to 100 mg over 28 days and at daily doses up to 40 mg over 10 weeks). Information supporting the safety of maralixibat in pediatric patients with ALGS includes data from a total of 86 pediatric patients in 5 clinical studies. Supportive safety data are also obtained from 1 Study in 33 pediatric patients with PFIC.

Pooled results from all 5 studies in pediatric patients (1 year of age and older) with ALGS received doses of < 400 (ie, 70, 140, and 280) μ g/kg/day, 400 μ g/kg/day, and > 400 (ie, 560 and 800) μ g/kg/day). Among the total of 86 patients, 67 patients have been exposed to maralixibat for at least 12 months. A total of 5 patients experienced a TEAE in the cardiac disorders SOC. One patient in the high (> 400 μ g/kg/day) dose group experienced an SAE of cardiac disorder with a severity of Grade 3/4. One patient in the low (<400 μ g/kg/day) dose group experienced an SAE of pericardial effusion with a severity of Grade 2. Neither SAE were related as determined by the Investigator. Other events were Grade 1 in severity.

There have been no cardiac disorder TEAEs in the study of pediatric patients with PFIC.

ECG examinations were performed in multiple completed clinical studies, including pediatric patients (N=39), adult patients (N=982), and healthy subjects (N=304) who were exposed to various doses (up to 500 mg single dose) and durations (up to 13 weeks) of treatment with maralixibat. All completed clinical studies demonstrated that there were no clinically meaningful changes in QT intervals or in other ECG parameters. Thus, there have been no safety concerns for QT prolongation risk following Maralixibat administration in the clinical program.

2.5 Summary results of QTc assessments

In the most recent MRX-102 food effect study, the sponsor collected serial PK data and Holter ECG data in healthy volunteers who received 30 mg (fasting/fed), 45 mg (fasting/fed), or 100 mg

(fasting) doses of Maralixibat (n=12 at each dose level). Study results suggested low plasma concentrations following oral administration of Maralixibat in the fasting condition. A summary of key PK parameters from this study is shown below:

Plasma PK Parameters ^a	30 mg Fasted (N=12)	30 mg Fed (N=8)	45 mg Fasted (N=12)	45 mg Fed (N=9)	100 mg Fasted (N=12)
AUC _∞ (h*ng/mL)	5.74 (30.1); 4	NC	5.73 (35.6); 4	NC	13.0 (73.2); 10
AUC _{last} (h*ng/mL)	2.24 (214.1); 12	0.514 (164.8); 8	3.07 (162.5); 12	1.40 (98.0); 9	10.2 (82.9); 12
C _{max} (ng/mL)	1.27 (99.0); 12	0.437 (44.5); 8	1.50 (55.2); 12	0.564 (45.7); 9	3.05 (52.3); 12
T _{max} ^b (h)	0.75 (0.50 – 2.00); 12	2.50 (0.50 – 6.00); 8	0.50 (0.50 - 2.58); 12	3.00 (0.50 – 4.00); 9	0.75 (0.50 – 3.00); 12
t _{1/2} (h)	1.61 (76.3); 4	NC	1.44 (66); 4	NC	1.97 (56.4); 10
T _{last} ^b (h)	4.00 (1.50 - 6.03); 12	4.00 (0.50 – 6.00); 8	5.00 (1.00 – 8.00); 12	4.00 (3.00 – 24.00); 9	8.00 (3.00 – 12.00); 12

Abbreviation: NC = Not Calculated; ^a Geometric Mean (CV% GeoMean); n; ^b Median (Min - Max); n

Reviewer’s comment:

- *The maximum exposure is approximately 1.8 nM and 4.3 nM at the 30 mg or 100 mg dose in the fasting condition. The reviewer agreed with the sponsor that a formal concentration-QTc analysis can be waived.*
- *The average body weight in the 100 mg dose group is 78 kg. Body weight based dosing is 1.2 mg/kg. This provided approximately 3-fold coverage for the maximum recommended therapeutic dose.*

There were no meaningful changes in ECG parameters in the study. For the cardiodynamic evaluation, when noted, bi-phasic T-waves, U-waves, and categorical QT or QTcF outliers were infrequent. Mean changes from baseline for HR and QTcF were not clinically significant, and did not show a dose-dependent pattern.

Reviewer’s comment: *The reviewer’s exploratory analysis on available PK/ECG data also suggested a lack of positive exposure-response relationship between drug concentration and change-from-baseline QTc. The reviewer’s analysis confirmed that no subjects experienced QTcF>480 msec or change-from-baseline QTcF>60 msec during drug treatment.*

2.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

3 APPENDIX I: REVIEW OF SUPPORTING NONCLINICAL DATA

The in vitro hERG data were reviewed to assess its QT prolongation potential.

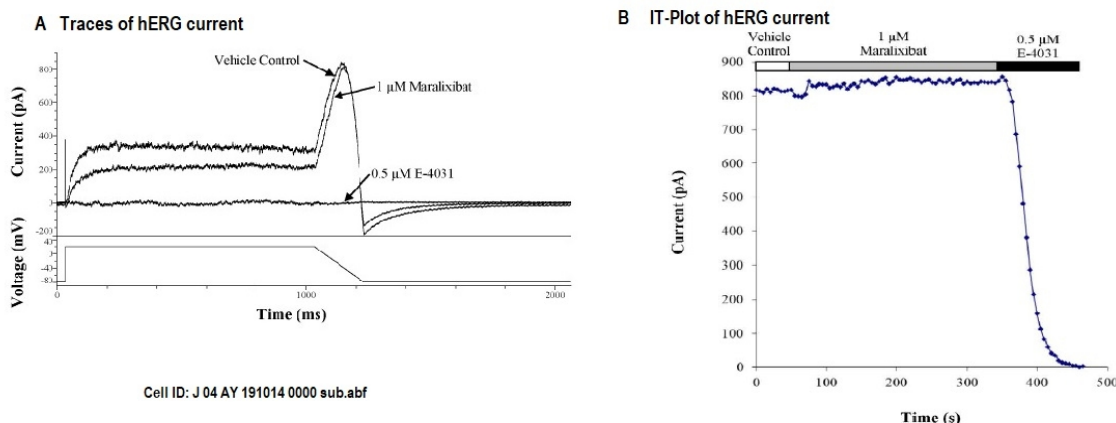
3.1 Sponsor's submission

The sponsor evaluated the effects of maralixibat on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report ([mrx-nc-003](#)) describes the potential effects of maralixibat on the hERG current in HEK293 cells.

The hERG current was assessed at near-physiological temperature (33-35°C), and was evoked by depolarizing the cell from -80 mV to +20 mV for 1 s, followed by a repolarizing ramp down to -80 mV (-0.5 V/s). The voltage waveform was repeated every 5 seconds and the peak current was measured during ramp down voltage step. In the presence of test or positive control article, peak current was monitored until a new steady state emerged. One test article concentration was tested per cell, followed by E-4031 (500 nM) application to eliminate hERG current completely. The residual current was subtracted offline from the recorded current to isolate the hERG component for drug inhibition assessment. Solution samples were collected from the outflow of the perfusion apparatus for concentration verification analysis. There were negligible deviations (<10 % max difference) from the nominal concentrations at 3 and 10 µM. Drug concentrations at 0.3 and 1 µM were not verified in this study because a suitable method could not be validated for the analysis of test article formulations at 0.3 and 1 µM.

Maralixibat inhibited hERG currents (Mean ± SEM, n=3) by $-0.7 \pm 1.9\%$ at 0.3 µM and $-1.2 \pm 0.9\%$ at 1 µM versus $-0.2 \pm 0.9\%$ (n = 3) in vehicle control. Example traces and IT-plot of maralixibat on hERG current are shown in **Figure 1**.

Figure 1. Example traces and IT-plot of maralixibat on hERG current



Source: Figure 1 and Figure 2 in study report mrx-nc-003

Inhibitions of hERG currents at 0.3 and 1 µM were not statistically significant ($p < 0.05$) when compared to vehicle control values. No usable data could be obtained at the 3 and 10 µM concentrations due to disruption of the giga-ohm seal required for successful patch clamp recordings. The IC₅₀ of maralixibat on hERG was expected to be greater than 1 µM. The positive control (60 nM terfenadine) inhibited hERG potassium current by $85.4 \pm 0.8\%$ (n=6, Mean ± SEM).

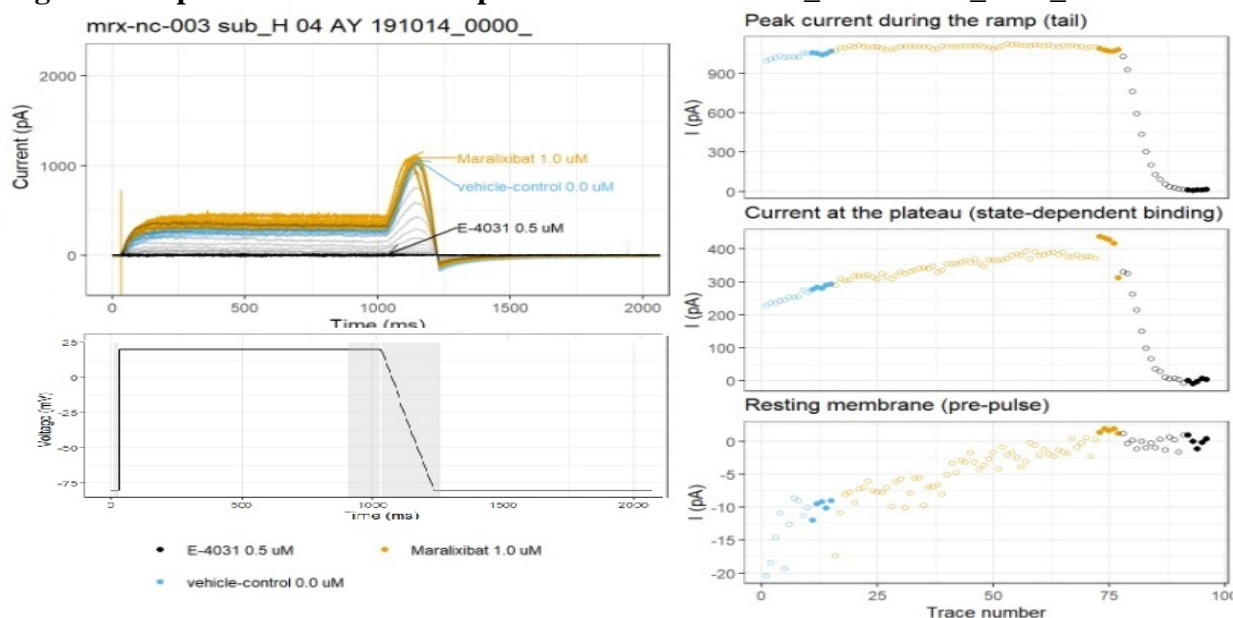
3.2 Reviewer's assessment and data reanalysis

Original electrophysiology data ([data set](#)) for hERG study were provided by the sponsor. An IRT reviewer reanalyzed these files to assess data quality and verify study report conclusions. For data quality assessment, holding current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

The voltage protocols used and stimulation frequencies are quite similar to that recommended by the FDA ([link](#)), and the reviewer does not anticipate protocol differences to impact hERG current pharmacology.

Representative analysis from one cell of hERG study (mrx-nc-003) is shown in **Figure 2**. The top left panel shows all recorded traces from this cell; the bottom left panel, voltage waveform used to evoke hERG current (shaded gray region highlights where peak hERG tail current was measured). Traces recorded in control solution are shown in blue, following 1.0 μM maralixibat application in orange; and following application of E-4031, a selective hERG blocker, in black. Time course plots (peak ramp current, step current and resting membrane current) of hERG current are shown on the right panel.

Figure 2: Representative hERG experiment from cell H 04_AY 191014_0000_sub



The time course plot of peak current at plateau (middle right) in **Figure 2** showed that current amplitudes in control (blue) were not stable prior to drug application. The hERG currents at plateau showed a trend of run-up. The holding currents (bottom right panel) were not stable throughout the recording in this cell. After analyzing the I-T plots of all cells, the results showed that the run-up pattern of hERG currents at plateau could be seen in most of cells. In addition, we noticed that the vehicle-control and 1 μM Maralixibat labels in Figure 1 of the sponsor's report are incorrect (swapped). The hERG current at plateau was larger in 1 μM Maralixibat than in vehicle-control due to hERG run-up. However, the hERG current during the ramp (for hERG measurement) were stable in all cells.

HERG current amplitudes (measured from the ramp current) from the last 5 traces acquired in control (blue solid circles) and in drug solutions were then averaged to calculate % inhibition by that concentration. E-4031 subtraction was performed to eliminate those non-hERG currents. Results of maralixibat and positive control on hERG current are summarized in **Table 1**.

Table 1. Effects of maralixibat on hERG current

Test article	N	Mean (%)	SD (%)	SEM(%)
Vehicle Control	3	2.1	9.5	5.5
Maralixibat 0.3 μ M	3	5.8	9.0	5.2
Maralixibat 1.0 μ M	3	2.8	0.7	0.4
Terfenadine 60 nM	6	-86.3	2.3	1.0

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall interpretation and conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that maralixibat acutely inhibited hERG current by -5.8% and -2.8% at 0.3 μ M and 1 μ M, respectively. Thus, IC₅₀ is far greater than 1 μ M and cannot be determined from this study. The hERG safety margin of maralixibat is provided in the following table:

Table 2. Safety Margin of maralixibat on hERG Current

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC ₅₀ (μ M)	Mol Weight (g/mol)	Safety Margin (Ratio)
Maralixibat	3.05	96%	0.12	>1	710.41	> 5920x

3.3 Summary

The sponsor swapped the labels of vehicle-control and 1 μ M Maralixibat in Figure 1 of the report. The hERG current at plateau (+ 20 step) was larger in 1 μ M Maralixibat than in vehicle-control due to the hERG run-up. However, the hERG current during the ramp were stable in all cells. The run-ups of current at plateau had minimal effects on hERG current measurement since ramp current were measured for drug pharmacology analysis in this study.

Although the hERG study showed deviations from the best practice for an in vitro assay according to the new ICH S7B Q&A 2.1 ([link](#)), the assay results suggest it has a low risk for QTc prolongation by direct inhibition of hERG (hERG safety margin: > 5920x). The limitations of the hERG assay will not substantially impact this large hERG safety margin.

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/s/

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