CLINICAL STUDY REPORT

Study Title:	A Multicentre Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome
Short Title:	**IMAGINE:** Maralixibat (LUM001), an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Pediatric Subjects with Alagille Syndrome
Study Drug:	Maralixibat (or maralixibat chloride; formerly LUM001)
Indication:	Treatment of cholestatic liver disease in patients with Alagille syndrome (ALGS)
Study Sponsor:	Mirum Pharmaceuticals, Inc. 950 Tower Lane, Suite 1050 Foster City, CA 94404
Chief Medical Officer:	Ed Tucker, MD, MBA Mirum Pharmaceuticals, Inc. 950 Tower Lane, Suite 1050 Foster City, CA 94404
Study Number:	LUM001-303
Study Phase:	2
Study Initiation Date:	17 October 2013 (first participant first visit)
Study Completion Date:	17 June 2020 (last participant last visit)
Regulatory Agency Identifier Number:	EudraCT No: 2013-003832-54

Report Date:	**Document Version**	**Date**
	Final Report	01 December 2020
	Interim Report	20 July 2020

This study was performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents.

All unpublished information contained in this document is the confidential property of sponsor and may not be disclosed to parties not associated with the clinical investigation or used for any purpose without prior written consent of Mirum Pharmaceuticals, Inc.

OVERVIEW

Name of Sponsor/Company:	Mirum Pharmaceuticals, Inc.
Name of Study Drug:	Maralixibat chloride (formerly LUM001)
Study Title:	A Multicentre Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium- Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects with Alagille Syndrome
Study Number:	LUM001-303
Study Phase:	2
PIP Number:	EMEA-001475-PIP02-13
Number of Study Centers and Country:	Multicenter study in 3 clinical sites in the United Kingdom that participated in Study LUM001-302
Publications:	None
Study Period:	17 October 2013 to 17 June 2020 This final synoptic CSR represents the final data after all enrolled participants had completed their final (or ET) study visit (17 June 2020). An interim CSR, v1.0, presented results up to the data cutoff date of 01 December 2019.
Methodology:	The interim CSR presents the methodology for Study LUM001-303. Protocol Amendment 5.1 (dated 08 February 2019) was in effect since the cutoff date of the interim CSR (01 December 2019).
Number of Participants (Planned and Analyzed):	Study LUM001-303 included 19 participants; there were no screen failures. All 19 participants were included in the safety analysis set.
Diagnosis and Main Criteria for Inclusion and Exclusion:	The interim CSR for Study LUM001-303 presents inclusion and exclusion criteria.
Study Drugs, Dose, and Mode of Administration:	The interim CSR for Study LUM001-303 presents study drug, dose, and mode of administration.
Duration of Study:	For an individual participant, the study participation period consisted of a 4-week dose-escalation period, an 8-week dose-optimization period, a 60-week stable dosing period, a 52-week follow-up treatment period, and a long-term follow-up treatment period. A safety follow-up phone call was made by the study site 30 days after the last dose of maralixibat. The furthest analysis time point reached by any participants was Week 336.
Study Objectives and Endpoints	The interim CSR for Study LUM001-303 presents study objectives and endpoints.

SUMMARY OF RESULTS AND CONCLUSIONS

DISPOSITION OF PARTICIPANTS

The Interim CSR for Study LUM001-303 presented demography and baseline characteristics.

In brief: a total of 19 participants were enrolled and treated in the core study (Day 1 to Week 72), with 5 of these participants assigned placebo in LUM001-302 (PBO-MRX group) and 14 of these participants assigned to any dose level of maralixibat in LUM001-302 (MRX-MRX group).

Thirteen participants discontinued study before completing study treatment (as discussed in the interim CSR). The 6 participants who were still enrolled at the time of the interim CSR data cutoff have completed study treatment; for disposition information, see also Table 14.1.1 and Listing 16.2.

EXPOSURE AND COMPLIANCE

Overall, the mean treatment duration (SD) was 883.1 (674.84) days.

The mean (SD) treatment duration increased from 811.1 (569.31) days to 883.1 (674.84) days between the data cutoff date of the interim CSR and the final database lock for this final CSR.

In the overall study population, the median duration of maralixibat exposure was unchanged from the interim report (516 days; see Table 14.3.1 and Listing 16.4.1).

In the overall population, mean (SD) maralixibat compliance for Day 1 to EOT was 99.27% (1.061). Maralixibat mean (SD) compliance was 99.58% (0.372) for the long-term follow-up period (see Table 14.1.2 and Listing 16.4.2).

All 6 participants who were still on study at the time of the interim CSR data cutoff were receiving BID dosing: 1 participant received a maximum dose of 280 µg/kg/day, and 5 participants received the maximum dose of 560 µg/kg/day. Since the data cutoff of the interim report, there were no dose modifications. All dose modifications were reported in the interim CSR. For a per participant listing of dose modifications, see Listing 16.4.3.

See Appendix 9.2 for the sample case report form. See Appendix 9.6 for the updated study interventions batch numbers.

PROTOCOL DEVIATIONS

The interim CSR for Study LUM001-303 presented protocol deviations; there were no protocol deviations since the interim report (see Listing 16.3).

EFFICACY RESULTS

Note that primary and secondary objectives were defined as “up to and including Week 72” while the endpoints evaluate the change from baseline to Week 48. The interim report included the results for the Week 48 endpoint as well as the long-term results including Week 72 and subsequent visits. For participants who were assigned maralixibat in Study LUM001-302, results at each post-baseline analysis visit included up to 13 more weeks of treatment than participants who were assigned placebo in Study LUM001-302. The maralixibat baseline values were used and defined as the values on the day maralixibat treatment started in either Study

LUM001-303 (for the PBO-MRX group) or Study LUM001-302 (for the MRX-MRX group), where appropriate. Missing data due to treatment interruptions experienced for operational reasons between protocol amendments should be taken into account when interpreting results between Week 72 and Week 124.

Serum Bile Acids

The statistically significant reduction (improvement; mean change from baseline) in sBA concentrations in the overall population at Week 48 is discussed in the interim CSR.

Consistent with the interim CSR, over the study duration, in the overall population, the reduction (improvement) in mean change from maralixibat baseline in sBA was statistically significant ($p \leq 0.05$) at the majority of timepoints through Week 324 (see Table 14.2.2).

Treatment interruptions and progressively smaller sample size should be considered when interpreting statistical testing during those periods. A by-participant listing of sBA results is provided in Listing 16.1.1.

ItchRO(Obs)

The statistically significant reduction (improvement) from baseline in ItchRO(Obs) weekly average morning severity score in the overall population at Week 48 is discussed in the interim CSR.

Consistent with the interim CSR, over the study duration, in the overall population, the reduction (improvement) in mean change from maralixibat baseline in ItchRO(Obs) weekly average morning score was statistically significant ($p \leq 0.05$) at the majority of timepoints through Week 278 (See Table 14.2.1).

Treatment interruptions and progressively smaller sample size should be considered when interpreting statistical testing during those periods. A by-participant listing of ItchRO scores is provided in Listing 16.1.1.

Biochemical Markers of Cholestasis and Liver Disease Biochemical Markers

Refer to the interim CSR for discussion of biochemical markers of cholestasis and liver disease. For final data, including ATX, C4, and FGF-19, see Listings 16.1.1 and 16.5.1.

Clinician Xanthoma Severity Score

Refer to the interim CSR for discussion of Clinician Xanthoma Severity Score. For final data, see Listing 16.1.1.

Other Efficacy Endpoints

Refer to the interim CSR for discussion of height, weight, BMI z-score, lipids, Clinician Scratch Score, care-giver impression of change–xanthoma severity, and Pediatric Quality of Life evaluation. For final data, see Listings 16.5.2, 16.5.3, 16.1.1, and 16.1.2.

PHARMACOKINETIC RESULTS

A formal PK analysis could not be conducted due to the very low systemic exposure. The vast majority of maralixibat drug levels results were below the LLOQ (0.25 ng/mL). The highest drug level measured was 2.58 ng/mL (see Listing 16.10). See Appendix 9.13 for bioanalysis report.

SAFETY RESULTS

The mean (SD) treatment duration for the overall study population was 883.1 (674.84) days.

The safety profile for maralixibat remains consistent with the interim CSR (see Tables 14.3.1, 14.3.2.1, 14.3.2.2, and 14.3.2.3, and Listings 16.6.1 and 16.6.3).

Since the interim CSR, there were no new participants with AESIs, SAEs, or AEs that led to treatment discontinuation (see Listings 16.6.2.1, 16.6.2.2, 16.6.2.3, and 16.6.2.4). One participant who had previously reported SAEs had newly reported SAEs of lower respiratory tract infection and right ventricular failure. These events were considered not related to study treatment (see Listing 16.6.3).

See Appendix 10 for narrative updates with additional data since the interim CSR for AESIs, SAEs, and AEs that led to study discontinuation, as applicable.

For information through the end of the study that has not been discussed in the final synoptic clinical study report, see Appendix 8.2 for the following listings: safety laboratory listings (Listings 16.7.1, 16.7.2, 16.7.3, 16.7.4, 16.7.5, and 16.7.6), clinical laboratory tests (Listing 16.7.7), pregnancy test results (Listing 16.7.8), vital signs (Listing 16.8.1), physical examination (Listing 16.8.2), telephone contact (Listing 16.8.3), concomitant medications (Listings 16.9.1 and 16.9.2), and palatability (Listing 16.11). See Appendix 9.10 for Interlaboratory Standardization Methods and Laboratory Quality Assurance Procedures updated since the interim CSR.

CONCLUSIONS

The conclusions on the efficacy and safety profile of this study have not changed since the interim study report.

- Treatment with maralixibat resulted in clinically and statistically significant improvement in sBA and pruritus.
- The safety profile of maralixibat was consistent with that reported in the interim CSR: maralixibat is considered to be safe and well tolerated. Most subjects had TEAEs that were generally mild or moderate in severity. There were no life-threatening events or deaths in Study LUM001-303.
- Since the interim CSR, there were no new participants with AESIs, SAEs, or AEs that led to treatment discontinuation.

APPENDICES