Analysis of Safety in Maralixibat-Treated Participants With Progressive Familial Intrahepatic Cholestasis: Data From MARCH-PFIC

Poster # WED-282

Alexander Miethke,[1] Adib Moukarzel,[2] Gilda Porta,[3] Joshue Covarrubias Esquer,[4] Piotr Czubkowski,[5] Felipe Ordoñez,[6] Manila Candusso,[7] Amal A. Aqul,[8] Robert H. Squires,[9] Etienne Sokal,[10] Daniel D'Agostino,[11] Ulrich Baumann,[12] Lorenzo D'Antiga,[13] Nagraj Kasi,[14] Nolwenn Laborde,[15] Cigdem Arikan,[16] Chuan-Hao Lin,[17] Susan Gilmour,[18] Naveen Mittal,[19] Fang Kuan Chiou,[20] Simon P. Horslen,[9] Wolf-Dietrich Huber,[21] Susan David-Feliciano,[22] Elaine Chien,[22] Douglas B. Mogul,[22] Will Garner,[22] Tiago Nunes,[22] Anamaria Lascau,[22] Pamela Vig,[22] Vera Hupertz,[23] Regino Gonzalez-Peralta,[24] Udeme Ekong,[25] Jane Hartley,[26] Noemie Laverdure,[27] Nadia Ovchinsky,[28] Richard J. Thompson[29]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [2]Hotel Dieu De France Saint Joseph University Hospital, Beirut, Lebanon; [3]Hospital Sírio-Libanês, Sao Paulo, Brazil; [4]Nois De Mexico SA De CV, Jalisco, Mexico; [5]The Children's Memorial Health Institute, Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, Warsaw, Poland; [6]Cardioinfantil Foundation - Lacardio, Bogota, Colombia; [7]Ospedale Pediatrico Bambino Gesu Irccs, Lazio, Italy; [8]University of Texas Southwestern Medical Center, Dallas, TX, USA; [9]UPMC Children's Hospital of Pittsburgh, Pediatrics, Pittsburgh, PA, USA; [10]Ucluovian, Cliniques Universitaires St Luc, Pediatric Hepatology, Brussels, Belgium; [11]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [12]Hannover Medical School, Pediatric Gastroenterology and Hepatology, Hannover, Germany; [13]Hospital Papa Giovanni XXIII, Paediatric Hepatology, Gastroenterology and Transplantation, Bergamo, Italy; [14]Medical University of South Carolina, Charleston, SC, USA; [15]Hôpital des Enfants – CHU Toulouse, Toulouse, France; [16]Koc University School of Medicine, Istanbul, Turkey; [17]Children's Hospital Los Angeles, Los Angeles, CA, USA; [18]University of Alberta, Pediatrics, Alberta, Canada; [19]University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; [20]KK Women's and Children's Hospital, Singapore; [21]Medical University of Vienna, Vienna, Austria; [22]Mirum Pharmaceuticals, Inc., Foster City, CA, USA; [23]Cleveland Clinic Children's, Cleveland, OH, USA; [24]AdventHealth for Children and AdventHealth Transplant Institute, Pediatric Gastroenterology, Hepatology, and Liver Transplant, Orlando, FL, USA; [25]Medstar Georgetown University Hospital, Medstar Georgetown Transplant Institute, Washington DC, USA; [26]Birmingham Women and Children's Hospital, Birmingham, UK; [27]Hôpital Femme Mère Enfant, Hospices Civils De Lyon, Pediatric Hepato Gastroenterology and Nutrition Unit, Lyon, France; [28]New York University Grossman School of Medicine, New York, NY, USA; [29]King's College London, Institute of Liver Studies, London, UK

Background

- PFIC is a group of genetic disorders that result in disrupted bile composition and chronic cholestasis.[1]
  - Key clinical manifestations include debilitating pruritus, impaired growth, reduced quality of life, and progressive liver disease.[1]
- Current treatments include off-label antipruritic treatments, surgical biliary diversion, liver transplantation, and IBAT inhibitors.[1,2]
- Maralixibat (MRX) is a novel, minimally absorbed, orally administered inhibitor of the IBAT that interrupts the enterohepatic circulation of bile acids.[3]
  - MRX is approved for the treatment of cholestatic pruritus in patients with ALGS ≥2 months of age in the EU and ≥3 months of age in the US.[3,4]
- A 26-week, randomized, phase 3 clinical trial (MARCH-PFIC) was conducted to evaluate the efficacy and safety of MRX for the treatment of participants with PFIC.[5,6]
  - MARCH-PFIC is the largest and most genetically inclusive clinical trial of PFIC to date and included participants with variants in *BSEP*, *FIC1*, *MDR3*, *TJP2*, *MYO5B*, *ABCB11*, and *ATP8B1*.
  - The trial achieved its primary end point of reduction in cholestatic pruritus, secondary end point of reduction in sBA, and exploratory end points of improved bilirubin and growth.

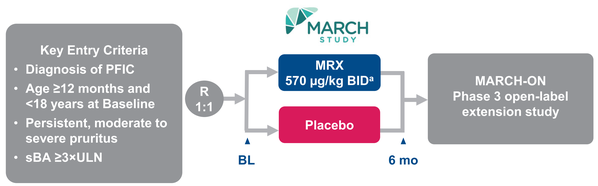
Objective

- To report detailed analyses of safety data from the MARCH-PFIC clinical trial.

Methods

- TEAEs and laboratory data from the MARCH-PFIC clinical trial were analyzed.
- TEAE severity grade 1 was defined as mild and grade 2 was defined as moderate.

Figure 1. MARCH-PFIC Phase 3 Study Design[5]



[a]MRX 570 µg/kg is equivalent to 600 µg/kg MRX chloride.

Results

Table 1. Key Demographics and Baseline Characteristics (N=93)

Variable	MRX (n=47)	Placebo (n=46)
Age, mean, y	4.8	4.7
Sex, male, %	43	48
Pruritus, ItchRO(Obs), mean	2.8	2.9
Total sBA, µmol/L, mean	263	243
UDCA usage, %	83	85
Rifampicin usage, %	55	50
ALT, U/L, mean	108	121
Total bilirubin, µmol/L, mean	70.1	65.0
Direct bilirubin, µmol/L, mean	51.3	47.9
Height *z* score, mean	-2.0	-1.9
Weight *z* score, mean	-1.6	-1.2

- Patients were well matched between MRX and placebo groups.

Table 2. Summary of TEAEs in Full-Study Cohort (N=93)

TEAE, n (%)	MRX (n=47)	Placebo (n=46)
Any TEAE	47 (100)	43 (93.5)
Severe TEAE[a]	3 (6.4)	3 (6.5)
Serious TEAE[b]	5 (10.6)	3 (6.5)
TEAE leading to discontinuation	1 (2.1)	0
TEAE leading to death	0	0
Most common TEAE, diarrhoea	27 (57.4)	9 (19.6)

[a]The severe TEAEs were pruritus, constipation, and UTI in the MRX group, and pruritus (2 cases) and increased AFP in the placebo group.
[b]The serious TEAEs were cholestasis, idiopathic pneumonia syndrome, increased blood bilirubin, UTI (3 times in the same participant), constipation (which was the severe event above, in the same participant as the UTIs), and UTI (which was the severe event above) in the MRX group, and accidental exposure to product, coagulopathy, vitamin K deficiency, seizure, and viral gastroenteritis in the placebo group. None were deemed treatment related (except 1 event of mild bilirubin increased in MRX); all resolved without any dose modifications.

- One participant had a TEAE of mild diarrhoea that led to discontinuation; no severe diarrhoea events were reported.
- Serious TEAEs were reported in 10.6% of participants receiving MRX and 6.5% of participants receiving placebo.
  - One SAE was deemed treatment related (mild bilirubin increase in the MRX group).
- No deaths were reported.

Table 3. TEAEs of Clinical Interest Occurring in ≥5% of Participants in Either Arm, by FMQ and Preferred Term

TEAE, n (%)	MRX (n=47)	Placebo (n=46)
Gastrointestinal		
Diarrhoea	27 (57.4)	9 (19.6)
Abdominal pain	12 (25.5)	6 (13)
Constipation	4 (8.5)	2 (4.3)
Gastroenteritis	3 (6.4)	2 (4.3)
Haematochezia	3 (6.4)	1 (2.2)
Vomiting	3 (6.4)	5 (10.9)
Liver function tests		
Transaminase AEs	8 (17)	3 (6.5)
Increased ALT	6 (12.8)	3 (6.5)
Hyperbilirubinemia	7 (14.9)	9 (19.6)
FSV deficiency	13 (27.7)	16 (34.8)
Fractures	3 (6.4)	0

Liver function tests

- No clinically meaningful changes were observed in either group from Baseline in transaminase levels.
- Among the 8 participants receiving MRX who had transaminase elevations, 6 had resolution of the elevation without drug interruption; 2 had ongoing stable elevation even after drug interruption (n=1) or dose reduction (n=1), and both ultimately resumed prior maximum dose.
- No participants discontinued MRX due to transaminase elevation.

FSV deficiency

- There is no evidence to suggest that MRX treatment contributes to FSV deficiency.
  - No clinically meaningful changes from Baseline in serum levels of vitamin A, D, or E were observed in the study population under regular FSV supplementation due to chronic cholestasis.
  - Participants treated with placebo experienced more FSV deficiency events than those treated with MRX.
  - INR decreased (improved) at every timepoint assessed with a mean change from Baseline of -0.3 for MRX vs -0.03 for placebo at Week 26.

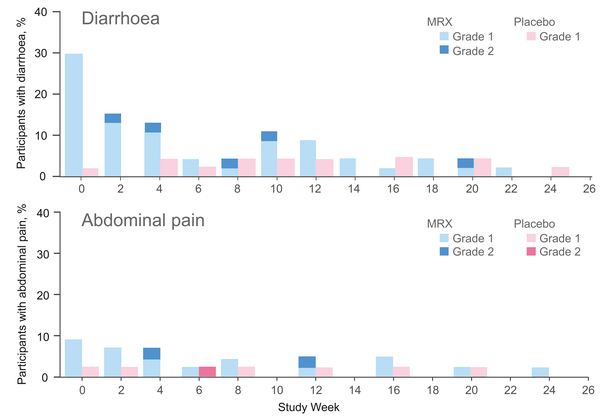
Fractures

- None were considered treatment related, as all had clear alternative causes for fracture, including pre-existing vitamin D deficiency, that were stable or improved on MRX.

Gastrointestinal events

- Diarrhoea and abdominal pain were mild and transient, with a median duration of 5.5 days for diarrhoea.
- In nearly all instances, abdominal pain was concurrent with diarrhoea.

Figure 2. Incidence of Gastrointestinal Events



MRX	47	46	46	46	45	45	45	44	44	43	43	43	38
Placebo	46	46	46	46	45	45	45	42	42	42	42	42	40

Conclusions

- MARCH-PFIC is the largest phase 3 trial to date in children with PFIC.
- MRX was overall well tolerated, with no new safety signals observed.
  - The most frequent AEs were gastrointestinal and were generally mild and self-limiting with only 5.5 days duration.
  - FSV deficiency and increased bilirubin occurred less frequently in the MRX group compared with the placebo group.
  - Overall, no changes in liver enzymes were observed over the duration of the study, and individual elevations were mild and transient; there were no discontinuations.
- All SAEs resolved without any dose reductions.
- Overall, dosing with MRX was shown to be well tolerated, with an acceptable safety profile for chronic dosing.

Abbreviations

AE, adverse event; AFP, alpha-fetoprotein; ALGS, Alagille syndrome; ALT, alanine aminotransferase; BID, twice daily; BL, baseline; FMQ, FDA MedDRA Query; FSV, fat-soluble vitamin; IBAT, ileal bile acid transporter; INR, international normalized ratio; ItchRO(Obs), itch-reported outcome (observer); MRX, maralixibat; PFIC, progressive familial intrahepatic cholestasis; R, randomized; sBA, serum bile acid; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; UTI, urinary tract infection.

Disclosures

A Miethke is a consultant and has a sponsored research agreement for Mirum Pharmaceuticals, Inc. F Ordoñez is a speaker for Alexion Pharmaceuticals and Valentech Pharma. A Aql is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Sarepta Therapeutics. E Sokal is the founder and chairman of Cellaïon, an investigator for Mirum Pharmaceuticals, Inc., Albireo, and Intercept, and an advisor for Albireo. U Baumann is a consultant for Mirum Pharmaceuticals, Inc., Albireo, and Vivet Pharmaceuticals. L D'Antiga is a consultant and advisor for Mirum Pharmaceuticals, Inc., Albireo, Selecta, Vivet Pharmaceuticals, Tome, Spark, Genespire, and Alexion. N Kasi is a consultant for Mirum Pharmaceuticals, Inc. N Mittal is an investigator for Mirum Pharmaceuticals, Inc. SP Horslen is a hepatic safety adjudication committee (HSAC) member at Albireo and has received a research grant from Mirum Pharmaceuticals, Inc. R Gonzalez-Peralta has received a research grant from Mirum Pharmaceuticals, Inc., and is an advisor, teacher, and educator for Mirum Pharmaceuticals, Inc., and Albireo. U Ekong is a steering committee member for Mirum Pharmaceuticals, Inc. S David-Feliciano, E Chien, DB Mogul, W Garner, T Nunes, A Lascau, and P Vig are employees of and shareholders in Mirum Pharmaceuticals, Inc. N Ovchinsky is a consultant for Albireo and received research support to her institution from Mirum Pharmaceuticals, Inc., Albireo, and Travere. RJ Thompson is a consultant for Mirum Pharmaceuticals, Inc., Albireo, Generation Bio, Rectify Therapeutics, and Alnylam and a shareholder in Generation Bio and Rectify Therapeutics. A Moukarzel, G Porta, J Covarrubias Esquer, P Czubkowski, M Candusso, RH Squires, D D'Agostino, N Laborde, C Arikan, CH Lin, S Gilmour, FK Chiou, WD Huber, V Hupertz, J Hartley, and N Laverdure have nothing to disclose.

Acknowledgments

The authors would like to thank the clinical trial participants, as well as their families, and investigators for their participation in the MARCH-PFIC clinical study. Maralixibat is owned by Mirum Pharmaceuticals, Inc. This analysis was funded by Mirum Pharmaceuticals, Inc. Medical writing support for the development of this poster was provided by PRECISIONscientia in Yardley, PA, USA, which was funded by Mirum Pharmaceuticals, Inc.

References

1. Kamath BM, et al. *Liver Int.* 2020;40(8):1812-1822. **2.** BYLVAY. Prescribing information. Albireo Pharmaceuticals Inc.; 2021. **3.** LIVMARLI. Prescribing information. Mirum Pharmaceuticals Inc.; 2023. **4.** LIVMARLI. Summary of product characteristics. Mirum Pharmaceuticals, Inc.; 2022. **5.** ClinicalTrials.gov identifier: NCT03905330. Updated October 27, 2022. Accessed April 18, 2023. https://clinicaltrials.gov/ct2/show/NCT03905330. **6.** Thompson RJ, et al. Presented at: American Association for the Study of Liver Diseases; November 4-8, 2022; Washington, DC.

Presented at European Association for the Study of the Liver (EASL) Congress; 21-24 June 2023; Vienna, Austria