Mirum Pharmaceuticals Presents New Data Demonstrating Durable Improvements in Clinical Outcome Measures in Patients with PFIC2 and Alagille Syndrome Treated with Maralixibat

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Late breaker presentation of long-term analysis of Phase 2 INDIGO study shows sustained response and clinically-relevant growth accelerations in PFIC2 responders

Data from Phase 2b ICONIC study show profound and durable improvements in itch severity and serum bile acids in children with Alagille syndrome

FOSTER CITY, Calif., April 15, 2019 /PRNewswire/ -- Mirum Pharmaceuticals today announced the presentation of Phase 2 clinical data at The International Liver Congress™ 2019, demonstrating the potential of maralixibat, the company's lead product candidate, to durably improve clinical outcomes for children with progressive familial intrahepatic cholestasis type 2 (PFIC2) and Alagille syndrome.

In a late breaker presentation, the company unveiled a long-term analysis from the INDIGO study, an ongoing Phase 2 clinical trial, showing sustained response and clinically-relevant improvements in height and weight in PFIC2 patients who were maralixibat responders, with benefits on both pruritus (itch) and biomarkers of cholestasis in those patients, compared to partial or non-responders.

In the Phase 2 ICONIC study in children with Alagille syndrome, maralixibat treatment led to profound and durable improvement in pruritis, xanthomas (lipid accumulation in the skin) and bile acids over 48 weeks. All of these findings were statistically significant.

Both of these rare cholestatic diseases are caused by genetic mutations and involve accumulation of excess bile acid in the liver and systemically. Untreated, these conditions can lead to liver failure and inflict life-altering symptoms including stunted growth and severe, debilitating itching. Under current standard of care, patients often require a liver transplant and are at higher risk of many serious health issues. Maralixibat works by binding to an important carrier protein known as the apical sodium dependent bile acid transporter (ASBT), thereby reducing the uptake and the circulating levels of bile acids. Mirum is planning to advance maralixibat into phase 3 clinical trials this year in children with PFIC and ALGS.

"The disease-modifying potential observed in these studies provide optimism for the children and their families who face these life-threatening diseases and the day-to-day struggle of managing the impact their condition has on their lives," said Richard Thompson, M.D., professor of molecular hepatology, King's College London. "We eagerly anticipate the initiation of the Phase 3 studies of maralixibat as it brings us one step closer to an effective treatment that could potentially restore health and quality of life for patients."

Phase 2 INDIGO Study in PFIC

The INDIGO study is a Phase 2 open-label study of maralixibat in patients with PFIC. A total of 33 patients were enrolled in the study and the dose of maralixibat was escalated up to 280 mg/kg/day over 13 weeks and maintained for up to 72 weeks. The primary efficacy analysis was serum bile acid (sBA) change from baseline to week 13. Secondary endpoints included a caregiver Itch Reported Outcome (ItchRO (Obs)) score (0 = none; 4 = severe itch), alanine transaminase (ALT) and total bilirubin (TB) levels. While the primary efficacy analysis of sBA change from baseline to week 13 did not reach statistical significance for the overall group, a pre-specified 48-week analysis of the INDIGO study demonstrated a profound treatment response in a subset of PFIC2 patients. This formed the basis for Breakthrough Therapy designation for PFIC2 granted by the U.S. Food and Drug Administration (FDA). A 72-week post-hoc analysis showed that PFIC2 treatment responders experienced a durable and clinically relevant acceleration in growth parameters, as compared to partial or non-responders.

A total of 25 of the 33 patients in the study had PFIC2, and the median age was 4.0 years. Mean reduction for all patients in sBA at weeks 13 and 48 was 29 and 59 mmol/L respectively. In the 72-week analysis, six patients were considered multi-parameter responders, having experienced sBA normalization or reduction from baseline greater than or equal to 70 percent and an ItchRO (Obs) of 0 or improvement of greater than or equal to one point and 11 subjects were responders on pruritus (partial responders) with a 1.0 or greater reduction in ItchRO (Obs).

After 48 and 72 weeks of treatment, height and weight z-score mean change from baseline was compared. The z-score is the degree (i.e. the number of standard deviations) by which a child's height or weight differs from that of healthy children of the same age. Overall, treatment responders exhibited a clinically meaningful acceleration in both growth parameters (height and weight) over the treatment period, while partial and non-responders fell further behind their healthy peers ($p < 0.05$). The data are summarized in the table below. Furthermore, subsequent to the 72-week treatment period, a seventh patient fulfilled responder criteria on sBA and pruritus when the dose was increased, which led to a similar growth spurt.

	Responders (n=6)	**Partial or Non-Responders** (n=19)
Height z-Score (Mean Change from Baseline at Week 48)	0.55	-0.29
Height z-Score (Mean Change from Baseline at Week 72)	0.61	-0.59
Weight z-Score (Mean Change from Baseline at Week 48)	0.42	-0.29
Weight z-Score (Mean Change from Baseline at Week 72)	0.32	-0.37

Maralixibat was generally well tolerated. Treatment-emergent adverse events (TEAEs) were reported in all patients, and in 22 of the patients, the

TEAEs were considered potentially related to maralixibat. Serious TEAEs were reported in 15 patients, of which 5 of the patients experienced events considered potentially related to maralixibat. There was one TEAE that lead to discontinuation that was deemed not related to maralixibat. The most frequent TEAEs were fever, diarrhea, cough and abdominal pain.

The data was presented by Dr. Miethke under the title "Growth analysis in children with progressive familial intrahepatic cholestasis treated with the apical sodium-dependent bile acid transporter inhibitor maralixibat," during the Late Breaker session on Saturday, April 13, 2019.

Phase 2 ICONIC Study in Alagille Syndrome

The ICONIC study was a Phase 2b placebo-controlled drug withdrawal study. The primary endpoint was change in sBA during the randomized drug withdrawal period in subjects who had reduced sBA at week 12 or week 18, and secondary endpoints included improvements in ItchRO (Obs) score, Clinician Xanthoma Severity Scale, Pediatric Quality of Life Inventory (PedsQL) and safety parameters.

A total of 31 children (mean age 5.4 years) were enrolled in the study. All patients in the study were treated for 18 weeks with maralixibat (up to 400 mg/kg/day) before they were randomized to receive either placebo (n=16) or the same dose of maralixibat (n=13) for 4 weeks. After the randomized withdrawal period, all patients were treated with maralixibat for the remainder of the 48 weeks. Of the 31 patients enrolled in the study, 29 completed the withdrawal period and 28 completed 48 weeks of treatment.

Overall, treatment with maralixibat significantly reduced sBA levels compared to placebo during the withdrawal period. Maralixibat treatment also led to clinically relevant and statistically significant improvements in itch severity, and xanthoma severity over the course of the study. The data are summarized in the table below.

Endpoint	**p-value**
Primary Endpoint:	
Change in sBA during the randomized drug withdrawal period in responders (defined as reduction of sBA ≥ 50% from baseline to week 12 or week 18)	<0.05
Other Prespecified Endpoints:	
ItchRO (Obs) during randomized drug withdrawal period	<0.0001
sBA during randomized drug withdrawal period	<0.05
ItchRO (Obs)from baseline to one year (overall population)	<0.0001
sBA change from baseline to one year (overall population)	<0.01
Improvement in clinician xanthoma score at one year	<0.01

Maralixibat was generally well tolerated. TEAEs were reported in 30 patients, most of which were mild or moderate in severity. Four patients had serious TEAEs (all considered unrelated to maralixibat), with two TEAEs leading to discontinuation (both considered unrelated to maralixibat). The most frequent TEAEs were diarrhea and abdominal pain.

The data was presented under the title "Phase 2 open-label study with a placebo-controlled drug withdrawal period of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with Alagille syndrome: a 48-week efficacy analysis," by Emmanuel Gonzales, Professor of Paediatrics, Hôpital Bicêtre in the clinical developments in rare liver disease session on Saturday, April 13, 2019.

Volixibat Phase 2 Clinical Trial in NASH

Also presented at the conference were data from a Phase 2 study conducted by Shire of volixibat, Mirum's second product candidate, also a minimally absorbed, oral inhibitor of ASBT, in patients with non-alcoholic steatohepatitis (NASH). Development of volixibat in NASH was discontinued after Shire completed this study. Mirum is exploring volixibat for adult cholestasis indications where the drug may have the potential for clinical benefits.

A total of 197 participants were enrolled in the double-blind, placebo-controlled dose finding study. The study showed no difference in MRI proton density fat fraction, serum ALT or histology in patients with NASH receiving volixibat compared to placebo. Changes were observed in secondary endpoints related to bile acid synthesis, LDL and C4, both of which are indicative of ASBT inhibition by volixibat. There were no deaths or SAEs in the study, and the most common adverse event was diarrhea (volixibat 73.5 percent; placebo 20.4 percent).

The abstract entitled "Safety, tolerability and efficacy of volixibat, an apical sodium-dependent bile acid transporter inhibitor, in adults with non-alcoholic steatohepatitis: 24-week interim analysis results from a phase 2 study," was presented by Philip Newsome, director, Centre for Liver Research & Professor of Experimental Hepatology, University of Birmingham and Consultant Hepatologist at the Liver Unit, Queen Elizabeth Hospital, Birmingham.

About Maralixibat
Maralixibat is a novel, minimally-absorbed, orally administered investigational drug being evaluated in several rare cholestatic liver diseases for pediatric populations. Maralixibat inhibits the apical sodium dependent bile acid transporter (ASBT), thereby preventing bile acids from accumulating in the body. More than 1,500 patients have received maralixibat with more than 100 patients having received maralixibat as an investigational treatment for Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC). In a 48-week analysis, ALGS patients taking maralixibat had reductions in bile acids and pruritus compared to placebo. In a Phase 2 PFIC study, a subset of PFIC2 patients responded to maralixibat, which led to maralixibat's Breakthrough Therapy designation from the U.S. Food and Drug Administration in PFIC2. Maralixibat was generally well tolerated throughout the study. The most frequent adverse events were diarrhea, abdominal pain and vomiting.

About Volixibat
Volixibat is an orally-administered, minimally absorbed, highly potent and selective inhibitor of ASBT, thereby preventing bile acids from accumulating in the liver. Mirum is exploring adult cholestasis indications where volixibat may have potential.

About Mirum Pharmaceuticals
Mirum Pharmaceuticals, Inc. is a clinical-stage therapeutics company developing a novel approach for treating cholestatic liver diseases, with an immediate focus on rare pediatric conditions. The company's lead product candidate, maralixibat, is a Phase 3-ready investigational oral drug with an established safety profile and efficacy data in several indications, including Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis

(PFIC). Backed by investors including NEA, Deerfield Management, Frazier Healthcare Partners, Novo Holdings A/S, Pappas Capital, RiverVest Venture Partners and Rock Springs Capital, Mirum is dedicated to bringing innovation to patients as quickly and efficiently as possible. For more information, visit MirumPharma.com.

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