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## **CymaBay Therapeutics Announces Top Line Efficacy and Safety Data From Its Phase 2 Study of Mbx-8025 in Patients With Primary Biliary Cholangitis (PBC)**

- **Study stopped early after review of safety and efficacy data demonstrated clear proof-of-concept and opportunity for further dose reduction to optimize clinical safety and efficacy**
- **Large statistically significant decreases seen for ALP in patients receiving MBX-8025; reversible dose related liver enzyme elevations observed**

NEWARK, Calif., May 31, 2016 (GLOBE NEWSWIRE) -- CymaBay Therapeutics, Inc. (NASDAQ:CBAY), a clinical-stage biopharmaceutical company developing therapies to treat metabolic diseases with high unmet medical need, today announced that it has discontinued its current Phase 2 study of MBX-8025 in patients with Primary Biliary Cholangitis (PBC) after determining that the study met its objective of establishing proof-of-concept for MBX-8025 by showing marked improvements in biochemical markers of cholestasis. The study also identified a treatment emergent signal of transaminase elevations. Subsequent studies will investigate lower doses to optimize risk benefit. MBX-8025 is an orally administered potent and selective peroxisome proliferator-activated receptor delta (PPAR $\delta$ ) agonist.

"We are very pleased that this study demonstrated that MBX-8025 has a potent anti-cholestatic activity that could have meaningful therapeutic benefit to patients with PBC," said Harold Van Wart, Ph.D., President and Chief Executive Officer of CymaBay Therapeutics. "Having achieved clinical proof-of-concept, we can now focus on dose optimization to maximize the benefit to risk ratio in subsequent studies."

"I am impressed by the magnitude of the ALP lowering in this patient population and by the fact that it was not accompanied by pruritus," said Keith Lindor, M.D., Dean of the College of Health Solutions, Arizona State University. "I hope that CymaBay continues to explore this agent for cholestasis using lower doses."

### **Study details**

The study was a placebo controlled, double blind, dose ranging study of 12 weeks duration in patients who had an inadequate response to ursodiol, as characterized by a persistent elevation in ALP. The study planned to enroll approximately 75 patients who were randomized to receive placebo, 50 or 200 mg doses of MBX-8025. The goal of the study was to assess whether the improvements in biochemical markers of cholestasis observed previously for MBX-8025 in other patient populations would be observed in patients with PBC.

The primary endpoint was the percent change in alkaline phosphatase (ALP). A secondary endpoint was the responder rate for patients achieving the composite criteria of serum ALP values less than 1.67xULN with a decrease of at least 15% and normal levels of total bilirubin (TBIL). ALP values were blinded to everyone involved in the study. Additional secondary endpoints were changes in gamma glutamyl transferase (GGT), TBIL and 5'-nucleotidase, other recognized biochemical markers of cholestasis. As these markers were part of the safety surveillance, they were only blinded with respect to the dosing group. It became apparent early in the study that many patients were showing pronounced decreases in these secondary efficacy endpoints, even greater decreases than those observed in earlier clinical studies, suggesting that MBX-8025 was exhibiting a potent anti-cholestatic effect.

During the study, three cases of asymptomatic increases in transaminases were observed (two in the 200 mg and one in the 50 mg cohorts). All three were reversible on cessation of treatment and were not accompanied by elevation of TBIL. No transaminase signal was observed in prior Phase 2 studies in which over 120 patients were treated with MBX-8025 at doses between 50 and 200 mg. Since the study had already shown a clear efficacy signal, the company made the decision to discontinue the study, with the knowledge that additional studies at lower doses would be needed.

After the study was unblinded, changes in the primary endpoint ALP were analyzed using data available for the 26 subjects enrolled in the study and completing at least two weeks of treatment. According to the original statistical

plan, changes in ALP were calculated using the last observation carried forward (LOCF). While additional data may become available as patients complete ongoing study termination visits, this is not expected to affect the results appreciably.

The mean decreases from baseline in ALP for the 50 and 200 mg dose groups were 57% and 62%, respectively, vs. 0.37% for placebo ( $p < 0.0001$  for both). The responder rates for the placebo, 50 and 200 mg groups were 10%, 67% and 100%, respectively. The p-values comparing the responder rates for the 50 and 200 mg groups vs. placebo were 0.020 and 0.0004 (Fisher's Exact Test), respectively. Thus, MBX-8025 exhibits a rapid and potent anti-cholestatic effect in patients with PBC. The lack of a dose response suggests that lower doses could be effective as well.

#### Summary of Treatment Effects on Alkaline Phosphatase

Treatment Group	N	Baseline (U/L)	Change (%)	Responder Rate <sup>‡</sup> (%)
Placebo	10	239	-0.37	10
MBX-8025 (50 mg)	9	313	-57 <sup>***</sup>	67 <sup>*</sup>
MBX-8025 (200 mg)	7	280	-62 <sup>***</sup>	100 <sup>**</sup>

\* $p < .05$  \*\* $p < .001$  \*\*\* $p < .0001$  vs. placebo

<sup>‡</sup> Percent of patients responding according to composite criteria of (1) final ALP < 1.67xULN (2) change in ALP > 15% and (3) total bilirubin < ULN

Patients receiving study drug also demonstrated improvements in metabolic parameters, including reductions of LDL-C of 16 and 26% for the 50 and 200 mg dose groups, respectively, vs. 0.8% for placebo after two weeks of dosing. It is also noteworthy that, despite the potent anti-cholestatic effect, no adverse events of pruritus were reported on treatment.

A recently completed preclinical study with MBX-8025 show that the main route of elimination of the drug is through bile and that the drug is concentrated in bile. Since patients with PBC have impaired bile flow, we believe that the exposure of the drug to the liver in patients with PBC could have been higher than in prior clinical studies in subjects with normal liver function, explaining both the more potent anti-cholestatic effect and the transaminase signal.

#### Conference Call

CymaBay will host a conference call today, May 31, 2016, at 8:00 a.m. ET / 5:00 a.m. PT to discuss the top line results of this Phase 2 study. The call can be accessed by dialing 1-855-327-6837 (domestic) and 1-631-891-4304 (international) five minutes prior to the start of the call. A slide presentation to be used in connection with the call entitled "MBX-8025 Phase 2 Study in Primary Biliary Cholangitis (PBC)" has been posted on CymaBay's website and can be accessed at <http://ir.cymabay.com/presentations>. A live audio webcast of the call can be accessed under the Investors section of CymaBay's website at <http://ir.cymabay.com/events> and will be available for 14 days following the call.

#### About MBX-8025

MBX-8025 is a potent and selective agonist of PPAR $\delta$ , a nuclear receptor important for lipid transport, storage and metabolism in liver and muscle. MBX-8025 has shown favorable effects on lipid and metabolic parameters in a Phase 2 study in patients with mixed dyslipidemia. Treatment effects observed include lowering of LDL-C with selective depletion of pro-atherogenic dense LDL-C particles, decreases in triglycerides and increases in HDL-C, as well as decreases in hsCRP, a biomarker of cardiovascular inflammation. CymaBay has completed a pilot Phase 2 clinical study showing that MBX-8025 lowers LDL-C in patients with homozygous familial hypercholesterolemia (HoFH). The U.S. Food and Drug Administration (FDA) has granted the Company orphan drug designation for MBX-8025 as a treatment for HoFH and Fredrickson types I and V hyperlipoproteinemia. MBX-8025 also suppresses the synthesis of bile acids as well as upregulates hepatic transporters that export bile acids from the liver. Thus, it has an anti-cholestatic activity that may be beneficial to patients with primary biliary cholangitis (PBC). A Phase 2 study demonstrating that MBX-8025 improves markers of cholestasis in patients with PBC has recently been completed.

#### About CymaBay

CymaBay Therapeutics, Inc. (CBAY) is a clinical-stage biopharmaceutical company developing therapies to treat metabolic diseases with high unmet medical need, including serious rare and orphan disorders. MBX-8025 is a potent, selective, orally active PPAR $\delta$  agonist. A Phase 2 study of MBX-8025 in patients with mixed dyslipidemia

established that it has an anti-atherogenic lipid profile. CymaBay has completed a pilot Phase 2 study of MBX-8025 in patients with homozygous familial hypercholesterolemia and a Phase 2 study in patients with primary biliary cholangitis, establishing proof-of-concept in both indications. Arhalofenate, CymaBay's other product candidate, is a potential Urate-Lowering Anti-Flare Therapy that has completed five Phase 2 studies in gout patients. Arhalofenate has been found to reduce painful flares in joints while at the same time promoting excretion of uric acid by the kidney. This dual action addresses both the signs and symptoms of gout while managing the underlying pathophysiology of hyperuricemia.

### **Cautionary Statements**

The statements in this press release, including those statements regarding the structure and conduct of clinical trials, future performance of CymaBay's product candidates, the potential of MBX-8025 to treat homozygous familial hypercholesterolemia or primary biliary cholangitis, the potential of MBX-8025 to be therapeutically effective at doses lower than previously studied, the therapeutic and commercial potential of CymaBay's product candidates, and any of the targeted indications for the potential future development or commercialization of CymaBay's product candidates are forward looking statements that are subject to risks and uncertainties. Actual results and the timing of events regarding the further development of CymaBay's product candidates could differ materially from those anticipated in such forward-looking statements as a result of risks and uncertainties, which include, without limitation, risks related to: the success, cost and timing of any of CymaBay's product development activities, including clinical trials of MBX-8025 and arhalofenate; effects observed in trials to date which may not be repeated in the future; any delays or inability to obtain or maintain regulatory approval of CymaBay's product candidates in the United States or worldwide; and the ability of CymaBay to obtain sufficient financing to complete development, regulatory approval and commercialization of its product candidates in the United States and worldwide. Additional risks relating to CymaBay are contained in CymaBay's filings with the Securities and Exchange Commission, including without limitation its most recent Annual Report on Form 10-K and Form 10-Q and other documents subsequently filed with or furnished to the Securities and Exchange Commission. CymaBay disclaims any obligation to update these forward-looking statements except as required by law.

For additional information about CymaBay visit [www.cymabay.com](http://www.cymabay.com).

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