Cymabay Therapeutics Announces Positive Results From Its Phase 2 Clinical Study of Arhalofenate in Combination With Febuxostat

Results Indicate That Arhalofenate Increases the Fractional Excretion of Uric Acid With Low Intraday Variations and Increases the Serum Uric Acid Responder Rate in Combination With Febuxostat

NEWARK, CA -- (Marketwired) -- 01/12/15 -- CymaBay Therapeutics Inc. (NASDAQ: CBAY) today announced positive preliminary results from its clinical study of arhalofenate administered in combination with febuxostat (Uloric™, Takeda Pharmaceutical Company Limited). Arhalofenate is a once-daily, oral candidate for the treatment of gout with a unique dual mechanism of action which lowers serum uric acid (sUA) while also reducing the occurrence of gout flares.

Current treatment guidelines for gout recommend the use of urate lowering drugs to reverse hyperuricemia in order to remove deposits of proinflammatory urate crystals. The minimal goal of this treatment is to reduce sUA levels to below 6 mg/dL; reducing sUA values to below 5 or 4 mg/dL is particularly desirable for patients with advanced disease in order to dissolve urate deposits (known as tophi) within a practical timeframe. Many patients treated with currently marketed xanthine oxidase inhibitors (allopurinol or febuxostat) alone do not reach these goals.

Arhalofenate blocks the reabsorption of uric acid in the proximal tubules of the kidney by inhibiting a renal uric acid transporter called URAT1. This leads to the excretion of uric acid into the urine (a uricosuric effect) that could provide additional sUA lowering when used in combination with xanthine oxidase inhibitors. In an earlier study, CymaBay showed that the combination of arhalofenate (400 and 600 mg) and febuxostat (80 mg) markedly lowered sUA in gout patients.

In the present Phase 2 clinical study, the sUA lowering of additional combinations of arhalofenate (600 and 800 mg) and febuxostat (40 and 80 mg) were evaluated. In addition, data have been collected to understand the time course of the uricosuric effect. Arhalofenate has a long serum half-life (~50 hours) and serum levels reach steady state
Arhalofenate has a long serum half-life (~50 hours) and serum levels reach steady state gradually. The time course of changes in sUA, urinary uric acid (uUA) and the fractional excretion of uric acid (FEUA) as monotherapy have been examined over the first 2 weeks. Analysis of arhalofenate and febuxostat drug levels to assess for a potential drug-drug interaction is underway and will be reported in a subsequent communication.

**Clinical Study of Co-administration of Arhalofenate and Febuxostat**

This study was an open label Phase 2 study carried out at a single center on two separate cohorts (n = 16 each) of gout patients with baseline sUA levels of 9.4 and 9.2 mg/dL, respectively (clinicaltrials.gov NCT02252835). The patients were either treatment naïve or willing to discontinue uric acid lowering therapy. All dosing was once daily oral and the patients received colchicine for flare prophylaxis. One cohort received arhalofenate 600 mg for 2 weeks followed by sequential one week periods of co-administration of febuxostat 80 mg followed by 40 mg. During the final two weeks, febuxostat 40 mg was administered as monotherapy. The second cohort had a similar design in which patients received arhalofenate 800 mg for 2 weeks, followed sequentially by one week of co-administration of 40 mg followed by 80 mg of febuxostat. Dosing with febuxostat at 80 mg was then continued for two additional weeks. sUA was assessed at multiple time points including at the end of each treatment period for both cohorts. uUA was measured for 8 patients in the cohort receiving arhalofenate 800 mg monotherapy on selected days over three time intervals (9 am to 3 pm, 3 pm to 9 pm and 9 pm to 9 am), allowing FEUA values to be assessed.

The sUA levels for patients receiving arhalofenate 800 mg decreased gradually over 14 days with approximately half of the decrease by day 7. Intraday variations in mean sUA were small (< 10%) on all days. In contrast, uUA increased over the 14 day treatment period. Correspondingly, FEUA values increased over baseline for each day assessed during the 14 day treatment period and did not vary appreciably during the day. FEUA values ranged from ~4.6 (morning) to ~3.5% (night) at baseline and from ~5.8% (morning) to ~4.7% (night) on day 14, respectively. The increases from baseline to day 14 were significant (p < .001). These data are consistent with the view that serum levels of arhalofenate slowly (> 2 weeks) equilibrate to steady state producing gradual decreases in sUA, increases in uUA and increases in FEUA. The small intraday variations in arhalofenate levels likewise produce small intraday variation in sUA, uUA and FEUA. This slow, natural equilibration eliminates the need for dose titration of arhalofenate.

The responder rates (percentage of patients reaching goal) for the sUA targets of < 6, < 5 and < 4 mg/dL for both doses of febuxostat and all four combinations of febuxostat and arhalofenate are shown in the table below. The addition of arhalofenate to either dose of febuxostat increases the responder rates for all sUA targets. The combination of febuxostat (80 mg) and arhalofenate (800 mg) is particularly effective with 79% of patients achieving the target of < 4 mg/dL (p < .05).

<p>| Responder Rate (% patients with sUA &lt; Target) |</p>
<table>
<thead>
<tr>
<th>Febuxostat (mg)</th>
<th>Arhalofenate (mg)</th>
<th>Target (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 6</td>
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<tr>
<td>40</td>
<td>0</td>
<td>47</td>
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<tr>
<td>40^a</td>
<td>600</td>
<td>79</td>
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<tr>
<td>40^a</td>
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<td>100**</td>
</tr>
<tr>
<td>80</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>80^b</td>
<td>600</td>
<td>94</td>
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<tr>
<td>80^b</td>
<td>800</td>
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*p < .05 ** p < .01 *** p < .001
(a) Comparison vs. 40 mg and (b) 80 mg febuxostat monotherapy

The combination of arhalofenate and febuxostat was well tolerated. There were no serious adverse events and only one severe adverse event of uncontrolled hypertension not deemed to be related to the study drugs. There was one case of elevated liver transaminases that emerged after the initiation of febuxostat in the second cohort. No patient in the study experienced a > 1.5X elevation in creatinine or had a value greater than the upper limit of normal.

"These results indicate that arhalofenate has very attractive characteristics for a uricosuric drug and that it has the potential to be used in combination with febuxostat to provide clinically meaningful lowering of serum uric acid for patients with gout," said Pol Boudes, MD, Chief Medical Officer of CymaBay. "This combination of oral agents has the potential to lower serum uric acid levels into the range needed to promote dissolution of debilitating uric acid crystals, thereby providing a potential treatment alternative for gout patients."

**About Arhalofenate**

Arhalofenate is a potential novel treatment for gout that has a dual mechanism of action. In clinical studies completed to date, arhalofenate has consistently demonstrated the ability to both reduce serum uric acid and reduce gout flares. Arhalofenate lowers serum uric acid by blocking the reabsorption of uric acid in the proximal tubules of the kidney by inhibiting a renal uric acid transporter called URAT1. This leads to the excretion of uric acid into the urine (a uricosuric effect). In addition, arhalofenate has an inherent anti-inflammatory activity that is well suited to treating gout. Data from preclinical models show that it blocks the urate crystal-induced production of IL-1β, explaining its ability to reduce gout flares. This dual mechanism of action differentiates arhalofenate from all currently available treatments for gout. Arhalofenate has established a favorable safety profile in clinical trials involving nearly 1,000 patients exposed to date.

**About Hyperuricemia and Gout**

Gout is a chronic, progressive rheumatic disease, caused by an inflammatory response to uric acid crystals deposited in joints and soft tissues as a result of excess uric acid in the
blood (hyperuricemia). Chronic recurrence of gout flares in joints leads to tissue destruction with loss of function and debilitation. According to the NHANES (2007-2008) study, the incidence of hyperuricemia in the US is over 45 million and over 8 million have progressed to a diagnosis of gout.

About CymaBay

CymaBay Therapeutics, Inc. (NASDAQ: CBAY) is a clinical-stage biopharmaceutical company developing therapies to treat metabolic diseases with high unmet medical need, including serious rare and orphan disorders. Arhalofenate, the company’s lead product candidate, has shown two therapeutic actions in a single drug in Phase 2a gout studies. In gout patients, arhalofenate is intended to prevent painful flares in joints while at the same time promoting excretion of serum uric acid (sUA) by the kidney, thereby addressing both the signs and symptoms of gout and the hyperuricemia that is the root cause of the disease. In addition to the study described above, CymaBay has a second ongoing 12-week Phase 2b clinical trial in patients with gout which is powered to detect statistically significant reductions in gout flares. CymaBay's second product candidate, MBX-8025 is a potent, selective, orally active PPAR-δ agonist. A Phase 2 study of MBX-8025 in patients with mixed dyslipidemia established that it has an anti-atherogenic lipid profile. We are in the process of initiating a pilot study in patients with homozygous familial hypercholesterolemia.

Cautionary Statements

The statements in this press release regarding the potential of arhalofenate in combination with febuxostat to treat gout are forward looking statements that are subject to risks and uncertainties. Risks that could cause actual results to differ from these statements include: the study was a small study of two cohorts with only 16 patients in each cohort and therefore the statistical significance of positive results is not as great as would be obtained in a trial with significantly more patients, and therefore different results may be obtained in a larger clinical trial; CymaBay may experience a number of unforeseen events during further and larger clinical trials for arhalofenate that could delay or prevent the commencement and/or completion of clinical trials, which may prevent the commercialization of arhalofenate; arhalofenate has not been approved by the FDA, and obtaining regulatory approval is difficult and may never be obtained. Additional risks relating to CymaBay are contained in CymaBay's Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on November 14, 2014. CymaBay disclaims any obligation to update these forward-looking statements except as required by law.

For additional information about CymaBay visit www.cymabay.com.

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