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Regeneron Announces FDA Acceptance of ARCALYST® (rilonacept) Supplemental Biologics License Application for Review

TARRYTOWN, N.Y., Nov. 22, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the Company's supplemental Biologics License Application (sBLA) for ARCALYST Injection for Subcutaneous Use for the prevention of gout flares in patients initiating uric acid-lowering therapy. Under the Prescription Drug User Fee Act (PDUFA), the goal for a standard review of an sBLA is ten months from submission, for a target action date of July 30, 2012.

"Based on the positive data from our Phase 3 efficacy studies and the more than 1300 patients in our safety study, we believe that ARCALYST has the potential to become an important new therapy for patients with gout who are initiating uric acid-lowering therapies," stated George D Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "Gout is a serious and sometimes debilitating disease, characterized by elevated levels of uric acid in the blood, which requires treatment with uric acid-lowering therapy to avoid gout flares and its long-term complications. Unfortunately, its management is often impeded by painful gout flares that occur early during treatment with standard-of-care uric acid-lowering therapies. The availability of a treatment that can help avoid gout flares during the initial months of uric acid-lowering therapy has the potential to help patients with this disease."

The sBLA submission for ARCALYST is based on positive efficacy data from PRE-SURGE 1, a North American Phase 3 trial, and PRE-SURGE 2, a similarly designed global Phase 3 trial. Both trials met the primary endpoint of reduction in the mean number of gout flares per patient during the 16-week treatment period in patients initiating uric acid-lowering therapy.

ARCALYST was generally well tolerated with the incidence of serious adverse events generally well-balanced across the placebo and ARCALYST groups. Injection site reactions, usually considered mild, were reported more commonly with ARCALYST than with placebo. A third study, RE-SURGE, evaluated the safety of ARCALYST in patients who were at risk for gout flares because they were initiating or taking uric acid-lowering drug treatment. This study showed that ARCALYST was generally well tolerated and the safety profile was consistent with that reported in the PRE-SURGE 1 and PRE-SURGE 2 studies.

About the Phase 3 ARCALYST Program in Gout

In the PRE-SURGE 1 and PRE-SURGE 2 studies, 488 patients were randomized to receive one of the following treatment regimens: ARCALYST 160 milligrams (mg) as an initial subcutaneous loading dose followed by weekly 80mg subcutaneous injections for 16 weeks, or ARCALYST 320mg as an initial subcutaneous loading dose followed by weekly 160mg subcutaneous injections for a total of 16 weeks, or subcutaneous weekly placebo injections for 16 weeks.

The North American PRE-SURGE 1 (**PRE**ventative **S**tudy against **UR**ate lowering drug-induced **G**out **E**xacerbations) study was a double-blind, placebo-controlled study which evaluated the number of gout flares per patient over the first 16 weeks following initiation of allopurinol therapy. Patients who received ARCALYST (rilonacept) at a weekly, self-administered, subcutaneous dose of 160mg had an 80% decrease in mean number of gout flares ($p<0.0001$) and patients receiving the 80mg dose had a 73% decrease compared to the placebo group ($p<0.0001$).

Overall in PRE-SURGE 1, the cumulative rate of infections was 17.3% in patients treated with ARCALYST 160mg, 18.8% in patients treated with ARCALYST 80mg, and 22.8% in placebo patients. No deaths were reported in this study.

The global PRE-SURGE 2 (**PRE**ventative **S**tudy against **UR**ate-lowering drug-induced **G**out **E**xacerbations) study was a double-blind, placebo-controlled study which evaluated the number of gout flares per patient over the first 16 weeks following initiation of allopurinol therapy. Patients who received ARCALYST at a weekly, self-administered, subcutaneous dose of 160mg had a 72% decrease in mean number of gout flares ($p<0.0001$) and patients who received the 80mg dose had a 72% decrease compared to the placebo group ($p<0.0001$).

Overall in PRE-SURGE 2, the cumulative rate of infections was 27.4% in patients treated with ARCALYST 160mg, 28.0% in patients treated with ARCALYST 80mg, and 25.6% in placebo patients. No deaths were reported in this study.

In both trials, a gout flare was defined as patient-reported acute articular pain typical of a gout attack that was deemed (by the patient and/or the investigator) to require treatment with an anti-inflammatory therapeutic and involved at least three of four signs/symptoms (joint swelling, redness, tenderness, and pain) and one or more of the following: rapid onset of pain, decreased range of motion, joint warmth, or other symptoms similar to a prior gout flare.

The global RE-SURGE (**RE**view of **S**afety **U**sing **R**ilonacept in preventing **G**out **E**xacerbations) study was a double-blind, placebo-controlled study primarily focused on evaluation of safety. A total of 1315 patients who were at risk for gout flares because they were initiating or taking uric acid-lowering drug treatment were randomly assigned in a 1:3 ratio to receive either weekly placebo injections for 16 weeks or weekly subcutaneous injections of ARCALYST dosed at 320mg as an initial loading dose and 160mg thereafter for a total of 16 weeks. In this trial, a gout flare was defined as patient-reported acute articular pain typical of a gout attack that was deemed (by the patient and/or the investigator) to require treatment with an anti-inflammatory therapeutic.

Overall, in RE-SURGE, the cumulative rate of infections was 20.1% in patients treated with ARCALYST and 19.1% in placebo patients. Serious infections were reported in 0.5% of patients treated with ARCALYST® and 0.9% of placebo patients. Deaths were reported for 0.3% of patients treated with ARCALYST and 0.9% of placebo patients. The mean number of gout flares during the 16week treatment period was significantly lower in the ARCALYST 160mg treatment group when compared to placebo (0.51 and 1.73, respectively, a 71% reduction, $p < 0.0001$). The proportion of patients with at least one gout flare was significantly lower in the ARCALYST 160mg group when compared to placebo at week 16 (25.7% [245/952] vs. 51.1% [165/323, $p < 0.0001$].

About Gout

Gout is a condition that occurs when the bodily waste product, uric acid, is deposited in the joints and/or soft tissues. In the joints, these uric acid crystals cause inflammation, which leads to pain, swelling, redness, warmth, and stiffness in the joints. Treatment guidelines recommend that patients with elevated uric acid levels who experience multiple gout attacks each year should receive chronic uric acid-lowering therapy, such as allopurinol. Untreated chronic gout can lead to joint and kidney damage. Uric acid-lowering therapy can prevent the occurrence of gout attacks with long-term use and reduce the risk of organ damage. Approximately 750,000 gout patients initiate allopurinol therapy each year. During the first months of allopurinol therapy while uric acid blood levels are being reduced, the break up of the uric acid crystals can result in stimulation of inflammatory mediators, including interleukin-1 (IL-1), resulting in acute flares of joint pain and inflammation. These acute flares can result in patient non-adherence to long-term uric acid-lowering therapy and resultant poor disease control.

Rationale for the Clinical Exploration of Use of ARCALYST® (rilonacept) in the Prevention of Gout Flares in Patients Initiating Uric Acid-lowering Therapy

Interleukin-1 (IL-1) is a protein secreted by infection-fighting cells in the blood and tissues. In many cases, IL-1 acts as a messenger to help regulate immune and inflammatory responses by attaching to cell-surface receptors in cells that participate in the body's immune system. In excess, it can be harmful and has been shown to be a key driver of inflammation in a variety of diseases. In patients with gout who are initiating uric acid-lowering therapy, redistributed uric acid crystals stimulate the production of IL-1, which triggers an inflammatory response in the joints and surrounding tissues, resulting in acute gout flares.

Rilonacept, known in the scientific literature as IL-1 Trap, is an agent that inhibits IL-1. It was designed using Regeneron's proprietary Trap technology. Specifically, rilonacept is designed to attach to and neutralize IL-1 in the blood stream before the IL-1 can attach to cell-surface receptors and generate signals that can trigger disease activity in body tissue. Once attached to rilonacept, IL-1 cannot bind to the cell-surface receptors and is eventually eliminated from the body.

Important information about ARCALYST

ARCALYST, is currently indicated in the U.S. for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. Rilonacept is also approved, but not marketed, in the E.U. for the same patient population. ARCALYST is not approved, but is currently under review by the U.S. FDA, for the prevention of gout flares in patients initiating uric acid-lowering therapy.

IL-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept. Rilonacept should be discontinued if a patient develops a serious infection. Taking rilonacept with tumor necrosis factor inhibitors is not recommended because this may increase the risk of serious infections. Treatment with rilonacept should not be initiated in patients with active or chronic infections. Patients should not receive a live vaccine while taking rilonacept. It is recommended that patients receive all recommended vaccinations prior to initiation of treatment with rilonacept. Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted. Hypersensitivity reactions associated with rilonacept administration have been rare. Please see the full Prescribing Information for ARCALYST® (rilonacept), available online at www.regeneron.com/ARCALYST-fpi.pdf.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron markets two products, ARCALYST® (rilonacept) Injection For Subcutaneous Use and EYLEA™ (afibercept) Injection. Regeneron also has completed several

Phase 3 studies and is conducting an additional Phase 3 clinical trial for the product candidate ZALTRAP® (afibercept) Concentrate for Intravenous Infusion. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on the Regeneron web site at www.regeneron.com.

Forward Looking Statements

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron, and actual events or results may differ materially from these forward-looking statements.

These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible actions by FDA relating to ARCALYST® for the prevention of gout flares in patients initiating uric acid-lowering therapy, the possible therapeutic applications of Regeneron's product candidates and research and clinical programs now underway or planned, the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's other late-stage product candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its products and drug candidates, competing drugs that may be superior to Regeneron's products and drug candidates, uncertainty of market acceptance of Regeneron's products and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi and Bayer HealthCare, to be canceled or terminated, and risks associated with third party intellectual property and pending or future litigation relating thereto. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2010 and Form 10-Q for the quarter ended September 30, 2011. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

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