March 25, 2009

Regeneron Announces Initiation of Phase 3 Gout Program with ARCALYST(R) (rilonacept)

TARRYTOWN, N.Y.--(BUSINESS WIRE)--Mar. 25, 2009-- Regeneron Pharmaceuticals, Inc. (Nasdaq: **REGN**) today announced that patient enrollment has been initiated in the Phase 3 program evaluating the efficacy and safety of ARCALYST® (rilonacept), also known as IL-1 (interleukin-1) Trap, in the prevention of gout flares associated with the initiation of urate-lowering drug therapy and in the treatment of acute gout attacks. ARCALYST is approved 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.

This Phase 3 program with ARCALYST in gout was designed following discussions with the United States Food and Drug Administration. It will consist of four clinical studies. The North American-based **PRE-SURGE**

1 (**PRE**ventative **S**tudy against **UR**ate-lowering drug-induced **G**out **E**xacerbations) study and the global **PRE-SURGE 2** study are each evaluating the number of gout flares per patient over the first 16 weeks of initiation of allopurinol therapy. Allupurinol is used to reduce serum uric acid levels in patients with gout. 240 patients will be randomized on a 1:1:1 basis to receive one of the following treatment regimens:

- ARCALYST 160 milligrams (mg) as an initial loading dose, followed by weekly 80 mg subcutaneous injections
- ARCALYST 320 mg as an initial loading dose, followed by weekly 160 mg subcutaneous injections
- Weekly placebo injections

The global **SURGE** (**S**tudy **U**tilizing **R**ilonacept in **G**out **E**xacerbations) study in patients experiencing an acute gout attack is evaluating pain during the initial 72 hours of treatment. 225 patients will be randomized on a 1:1:1 basis to receive one of the following treatment regimens:

- ARCALYST 320 mg administered by subcutaneous injection on day 1 plus oral placebo taken for 12 days
- ARCALYST 320 mg administered by subcutaneous injection on day 1 plus oral indomethacin (an anti-inflammatory drug currently indicated for the treatment of gout) taken for 12 days
- Placebo administered by subcutaneous injection on day 1 plus oral indomethacin taken for 12 days

The last of the four studies, the global **RE-SURGE** (**RE**view of **S**afety **U**sing **R**ilonacept in preventing **G**out **E**xacerbations) study, is evaluating the safety of ARCALYST versus placebo over 16 weeks in patients who are at risk for gout flares because they are taking urate-lowering drug treatment. 300 patients will receive placebo and 900 patients will receive ARCALYST dosed at 320 mg as an initial loading dose, followed by weekly 160 mg subcutaneous injections. Patients can be taking any of four urate-lowering drugs, allopurinol, febuxostat, probenecid, or sulfinpyrizone, with no requirements in the study design as to the total number of patients taking each.

“Nearly one and a half million Americans are treated for gout each year, but significant unmet medical needs persist,” said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. “Although chronic urate-lowering therapy is generally effective in achieving long-term gout symptom control, many patients discontinue treatment because they cannot tolerate painful gout flares that occur during the first few months of therapy. In the acute gout setting, treatment with available anti-inflammatory drugs is limited by inadequate pain relief or safety concerns in many patients. This comprehensive Phase 3 program reflects our enthusiasm for the potential role of ARCALYST® (rilonacept) therapy in these two gout patient populations. Initial data from this program are expected next year.”

The Phase 3 program in gout is supported by data from two previous studies of ARCALYST. In a Phase 2 study of gout patients initiating therapy with allopurinol to lower their uric acid levels, treatment with ARCALYST produced a statistically significant reduction versus placebo in the incidence of gout flares. In this 83-patient, double-blind, placebo-controlled study, the mean number of flares per patient over the first 12 weeks of urate-lowering therapy was 0.79 with placebo and 0.15 with ARCALYST (p=0.0011), an 81 percent reduction. In the first 12 weeks of treatment, 45.2 percent of patients treated with placebo experienced a gout flare and, of those, 47.4 percent had more than one flare. Among patients treated with ARCALYST, only 14.6 percent experienced a gout flare (p=0.0037 versus placebo) and none had more than one flare. No drug-related serious adverse events were reported in patients receiving ARCALYST treatment. Injection-site reaction was the most commonly reported adverse event with ARCALYST treatment.

In a Phase 1, single-blind study of 10 patients with chronic active gout, patients received placebo for two weeks and were then treated with ARCALYST. Treatment with ARCALYST resulted in a statistically significant reduction in patient pain scores, the

key symptom measure in persistent gout. Mean patient pain scores were substantially reduced during blinded active treatment (-41 percent, p=0.025, during the first two weeks of active treatment, and -56 percent, p <0.004, after six weeks of active treatment), as compared to changes during the blinded two-week placebo run-in period (-13 percent, which was not statistically significant). After six weeks of ARCALYST treatment, 70 percent of patients achieved at least a 50 percent improvement in their pain scores; whereas none of the patients achieved a 50 percent improvement in their pain scores during the placebo run-in period. In this study, in which safety was the primary endpoint measure, treatment with ARCALYST was generally well tolerated with injection-site reaction being the only reported drug-related adverse event.

About Gout

Gout is characterized by the deposition of uric acid crystals, a bodily waste product normally excreted by the kidneys, in the joints of the toes, ankles, knees, wrists, fingers, and elbows. These uric acid crystals can stimulate the release of inflammatory mediators, including interleukin-1 (IL-1), which result in acute flares of joint pain and inflammation. In patients with occasional gout attacks, treatment often involves the use of non-steroidal anti-inflammatory drugs, such as indomethacin, which offer inadequate pain relief or safety concerns for some patients. There are 1.4 million patients treated for acute gout attacks each year in the U.S.

In patients with frequent gout attacks who have elevated blood levels of uric acid, chronic treatment with uric acid-lowering medicines, such as allopurinol, is prescribed to eliminate the uric acid crystals and prevent reformation. During the first months of urate-lowering drug therapy, while uric acid blood levels are being reduced, the break up of the uric acid crystals can result in release of IL-1, causing acute flares of joint pain and inflammation. Anti-inflammatory therapy with colchicine is sometimes used to help prevent these flares. However, the side effects associated with use of colchicine, which include diarrhea, abdominal cramps, nausea, and vomiting, can limit patients' adherence to both colchicine and urate-lowering drug treatment. Approximately 750,000 gout patients initiate urate-lowering drug therapy in the U.S. each year.

Rationale for the Clinical Exploration of Use of ARCALYST®

(rilonacept) in the Treatment of Gout

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, including gout. In gout, uric acid crystals stimulate the production of IL-1, which causes an inflammatory response in the joints and surrounding tissues.

ARCALYST is an agent that inhibits IL-1. It 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 an inflammatory response in body tissue. Once attached to ARCALYST, IL-1 cannot bind to the cell-surface receptors and is eventually eliminated from the body.

Important Information About ARCALYST® (rilonacept)

ARCALYST is indicated 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.

IL-1 blockade may interfere with immune response to infection. Serious, life-threatening infections have been reported in patients taking ARCALYST. ARCALYST should be discontinued if a patient develops a serious infection**. Taking ARCALYST with tumor necrosis factor inhibitors is not recommended because this may increase the risk of serious infections.**

Patients should not receive a live vaccine while taking ARCALYST. Vaccinations administered while taking ARCALYST may not be effective. It is recommended that patients receive all recommended vaccinations prior to initiation of ARCALYST. Treatment with immunosuppressants, including ARCALYST, may result in an increase in risk of malignancies. Patients should be monitored for changes in their lipid profiles and provided medical treatment, if warranted. Hypersensitivity reactions associated with ARCALYST administration have been rare.

In the initial development program for ARCALYST six serious adverse reactions were reported by four patients: *Mycobacterium intracellulare* infection, gastrointestinal bleeding and colitis, sinusitis and bronchitis, and *Streptococcus pneumoniae* meningitis. The most common adverse reactions reported with ARCALYST® (rilonacept) in patients previously not treated with ARCALYST in the six-week, double-blind, placebo-controlled study phase of the pivotal CAPS program were injection-site reactions (48 percent versus 13 percent with placebo) and upper respiratory tract infections (26 percent versus 4 percent with placebo).

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, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, inflammatory diseases, and pain, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

Forward Looking Statement

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. 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 (SEC), including its Form 10-K for the year ended December 31, 2008. 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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