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ARCALYST® (rilonacept) Meets Primary and All Secondary Endpoints in Second Phase 3 Trial for Prevention of Gout Flares in Patients Initiating Uric Acid-Lowering Therapy

- **Additional large Phase 3 safety study confirms safety and efficacy results**
- **Regeneron plans to submit supplemental Biologics License Application (sBLA) in mid-2011**

TARRYTOWN, N.Y., Feb. 28, 2011 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced that in a second Phase 3 study (PRE-SURGE 2) in gout patients initiating allopurinol therapy, ARCALYST (rilonacept) met the primary and all secondary study endpoints. The primary endpoint was the number of gout flares per patient over the 16-week treatment period. Patients who received ARCALYST at a weekly, self-administered, subcutaneous dose of either 160 milligrams (mg) or 80 mg had a 72% decrease in mean number of gout flares compared to the placebo group ($p < 0.0001$). These results were consistent with those previously reported in the first, identical Phase 3 efficacy study (PRE-SURGE 1).

ARCALYST (also known as IL-1 Trap) also met all secondary endpoints of the study. Compared to placebo, treatment with ARCALYST reduced the proportion of patients who experienced at least one gout flare during the study period by 63% for ARCALYST 160mg ($p < 0.0001$) and by 54% for ARCALYST 80 mg ($p = 0.0001$). Compared to placebo, treatment with ARCALYST reduced the proportion of patients who experienced two or more flares by 82% for ARCALYST 160 mg ($p < 0.0001$) and by 74% for ARCALYST 80 mg ($p = 0.0002$).

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.

"Gout, a serious and sometimes debilitating disease, is rapidly growing in prevalence throughout the world. Unfortunately, its management is often hampered by the occurrence of painful gout flares early during treatment with standard-of-care uric acid-lowering therapy," stated George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "We are pleased that this study confirmed the efficacy findings from the PRE-SURGE 1 trial demonstrating that treatment with ARCALYST reduced the incidence of such flares. With these positive Phase 3 trials in patients with gout initiating uric acid-lowering therapy, we plan to submit a supplemental Biologics License Application for U.S. regulatory approval in mid-2011."

Regeneron also announced the results from a third Phase 3 study (RE-SURGE), which evaluated the safety of ARCALYST versus placebo over 16 weeks in 1,315 patients who were at risk for gout flares while initiating or taking uric acid-lowering drug treatment. In this study, ARCALYST® (rilonacept) was generally well tolerated, and the safety profile was consistent with that reported in the PRE-SURGE 1 and PRE-SURGE 2 studies. Specifically, other than injection site reactions, the incidence of treatment-emergent adverse events was generally well-balanced among the 985 patients who received ARCALYST at a weekly, self-administered, subcutaneous dose of 160 mg and the 330 patients who received placebo.

In the RE-SURGE Phase 3 safety study, injection site reactions, usually considered mild, were reported more commonly with ARCALYST (15.2%) than with placebo (3.3%). Overall, 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.

In this safety study, efficacy was evaluated as a secondary endpoint, and all secondary endpoints were achieved. Compared to placebo, patients who received ARCALYST had a 71% decrease in mean number of patient-reported gout flares ($p < 0.0001$). Compared to placebo, treatment with ARCALYST reduced the proportion of patients who reported at least one gout flare during the study period by 50% ($p < 0.0001$) and reduced the proportion of patients who reported two or more flares by 66% ($p < 0.0001$).

Detailed data from both the PRE-SURGE 2 and RE-SURGE studies will be presented at future scientific conferences. The safety and efficacy of ARCALYST in the gout setting have not been evaluated by the U.S. Food and Drug Administration. ARCALYST is not approved for use in gout.

About the PRE-SURGE 2 Study

The Global **PRE-SURGE 2** (**PRE**ventative Study against **UR**ate-lowering drug-induced **G**out **EX**acerbations) 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. The trial was conducted in South Africa, Germany, and parts of Asia. In the 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 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. A total of 248 patients were randomized on a 1:1:1 basis to receive one of the following treatment regimens:

- ARCALYST 160 mg as an initial subcutaneous loading dose, followed by weekly 80 mg subcutaneous injections for a total of 16 weeks
- ARCALYST 320 mg as an initial subcutaneous loading dose, followed by weekly 160 mg subcutaneous injections for a total of 16 weeks
- Subcutaneous weekly placebo injections for 16 weeks

Primary and key secondary endpoint results were as follows:

	Placebo	ARCALYST® (rilonacept) 80 mg	ARCALYST® (rilonacept) 160 mg
n	82	82	84*
Primary endpoint			
Mean # of flares per patient (% reduction compared to placebo)	1.23	0.35 (72% reduction) (p<0.0001)	0.34 (72% reduction) (p<0.0001)
Key secondary endpoints			
Proportion of patients with greater than or equal to 1 flare (% reduction compared to placebo)	56.1%	25.6% (54% reduction) (p=0.0001)	20.5% (63% reduction) (p<0.0001)
Proportion of patients with greater than or equal to 2 flares (% reduction compared to placebo)	32.9%	8.5% (74% reduction) (p=0.0002)	6.0% (82% reduction) (p<0.0001)

* One patient did not report flare data and was excluded from efficacy analyses

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

Specific adverse events that occurred at a frequency of at least 5% in any study group were: injection site reaction (17.9% with ARCALYST 160 mg, 12.2% with ARCALYST 80 mg, and 1.2% with placebo), upper respiratory tract infection (15.5% with ARCALYST 160 mg, 12.2% with ARCALYST 80 mg, and 12.2% with placebo), influenza viral infection (6.0% with ARCALYST 160 mg, 6.1% with ARCALYST 80 mg, and 7.3% with placebo), taking more than the recommended dose (4.8% with ARCALYST 160 mg, 7.3% with ARCALYST 80 mg, and 2.4% with placebo), and headache (1.2% with ARCALYST 160 mg, 6.1% with ARCALYST 80 mg, and 3.7% with placebo).

About the PRE-SURGE 1 Study

Regeneron previously announced the results of the identical North American-based **PRE-SURGE 1 (PREventative Study against URate-lowering drug-induced Gout Exacerbations)** study, 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 160 mg had an 80% decrease in mean number of gout flares and patients receiving the 80 mg dose had a 73% decrease compared to the placebo group (p<0.0001).

ARCALYST also met all secondary endpoints of the study. Compared to placebo, treatment with ARCALYST reduced the proportion of patients who experienced at least one gout flare during the study period by 65% for ARCALYST 160 mg (p<0.0001) and by 60% for ARCALYST 80 mg (p=0.0002). Compared to placebo, treatment with ARCALYST reduced the proportion of patients who experienced two or more flares by 88% for ARCALYST 160 mg (p<0.0001) and by 84% for ARCALYST 80 mg (p<0.0001).

Primary and key secondary endpoint results were as follows:

	Placebo	ARCALYST® (rilonacept) 80 mg	ARCALYST® (rilonacept) 160 mg
n	79	80	81 [^]
Primary endpoint			
Mean # of flares per patient (% reduction compared to placebo)	1.06	0.29 (73% reduction) (p<0.0001)	0.21 (80% reduction) (p<0.0001)
Key secondary endpoints			
Proportion of patients with greater than or equal to(1 flare (% reduction compared to placebo)	46.8%	18.8% (60% reduction) (p=0.0002)	16.3% (65% reduction) (p<0.0001)
Proportion of patients with greater than or equal to(2 flares (% reduction compared to placebo)	31.6%	5.0% (84% reduction) (p<0.0001)	3.7% (88% reduction) (p<0.0001)

[^] One patient did not report flare data and was excluded from efficacy analyses

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

Specific adverse events that occurred at a frequency of at least 5% in any study group were: injection site reaction (19.8% with ARCALYST 160 mg, 8.8% with ARCALYST 80 mg, and 1.3% with placebo), upper respiratory tract infection (9.9% with ARCALYST 160 mg, 8.8% with ARCALYST 80 mg, and 7.6% with placebo), lower respiratory tract infection (0% with ARCALYST 160 mg, 5.0% with ARCALYST 80 mg, and 2.5% with placebo), musculoskeletal pain/discomfort (6.2% with ARCALYST 160 mg, 7.5% with ARCALYST 80 mg, and 8.9% with placebo), and headache, (3.7% with ARCALYST 160 mg, 6.3% with ARCALYST 80 mg, and 1.3% with placebo).

About the RE-SURGE Study

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. The trial was conducted in the United States, South Africa, Germany, and parts of Asia. A total of 1,315 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 (n=330) for 16 weeks or weekly subcutaneous injections of ARCALYST dosed at 320 mg as an initial loading dose and 160 mg thereafter (n=985) 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, 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® (rilonacept) and 0.9% of placebo patients. Deaths were reported for 0.3% of patients treated with ARCALYST and 0.9% of placebo patients.

Specific adverse events that occurred at a frequency of at least 5% in any study group were: injection site reaction (15.2% with ARCALYST and 3.3 % with placebo), musculoskeletal pain/ discomfort (11.2% with ARCALYST and 9.7% with placebo), headaches (9.5% with ARCALYST and 8.8% with placebo), joint-related signs and symptoms (7.3% with ARCALYST and 7.3% with placebo), and taking more than the recommended dose (5.6% with ARCALYST and 6.4% with placebo).

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, heat, 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. Allopurinol reduces the production of uric acid in the body to prevent the occurrence of gout attacks with long-term use. 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. Anti-inflammatory therapy with colchicine is sometimes used to help prevent these flares.

However, the side effects associated with colchicine, which include diarrhea, abdominal cramps, nausea, and vomiting, can limit patients' adherence to both colchicine and allopurinol treatment.

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.

Rilonacept, also known as IL-1 Trap, is an agent that inhibits IL-1. It was designed using the same proprietary Trap technology used to develop Regeneron's other product candidates, VEGF Trap and VEGF Trap-Eye. 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

Rilonacept, marketed as 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. The safety and efficacy of ARCALYST® (rilonacept) in the gout setting have not been evaluated by the U.S. Food and Drug Administration. ARCALYST is not approved for use in gout.

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, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. 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 Regeneron's web site at www.regeneron.com.

Regeneron Forward Looking Statement

This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing 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 license or collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. 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, 2010. 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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