September 6, 2011

Phase 2a Study of Selective Oral JAK3 Inhibitor VX-509 Showed Significant Improvements in Signs and Symptoms of Rheumatoid Arthritis

-12-week data support initiation of Phase 2b study to evaluate longer treatment duration for VX-509-

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that treatment with the investigational selective oral JAK3 inhibitor VX-509 in a Phase 2a trial resulted in substantial and statistically significant improvements in multiple measurements of rheumatoid arthritis (RA) activity. The 12-week study met its two primary endpoints, defined as a statistically significant improvement in the proportion of people who achieved at least a 20 percent improvement in the signs and symptoms of RA, also known as ACR_{20}, and a statistically significant improvement from baseline in Disease Activity Score 28 (DAS28).

The study evaluated four doses of VX-509, and data from the treatment arms of the two highest doses (100 mg and 150 mg) showed statistically significant ACR_{20}, ACR_{50}, ACR_{70} and DAS28 responses as compared to placebo. The 150 mg treatment arm showed ACR_{20}, ACR_{50}, ACR_{70} and DAS28 responses of 66 percent, 49 percent, 22 percent and -3.06, respectively, while the placebo arm showed responses of 29 percent, 7 percent, 2 percent and -1.25. Overall, the most frequently reported class of adverse event in the VX-509 and placebo arms was infections. The most common individual adverse events observed, which occurred in approximately five percent or less of people in the study, were nausea, headache and increased alanine transaminase (ALT), regardless of treatment arm. Five percent of people discontinued treatment due to adverse events in the placebo group, compared to 8 percent of all people who received VX-509.

"These early results are encouraging and provide strong support that the selective targeting of JAK3 by VX-509 may represent a new approach to the treatment of RA and other autoimmune and inflammatory diseases," said Peter Mueller, Ph.D., Executive Vice President, Global Research and Development, and Chief Scientific Officer for Vertex. "In people who received VX-509, the signs and symptoms of RA continued to improve throughout the 12-week study. We look forward to initiating a longer-duration trial to explore the potential for additional improvements in RA activity and to further establish the safety profile of VX-509."

Data from this study will be submitted for presentation at an upcoming medical meeting. Based on the results announced today, VX-509 will next be evaluated as part of a six-month Phase 2b study in RA. This study is expected to evaluate once-daily (QD) and twice-daily (BID) doses of VX-509 in combination with methotrexate, a commonly prescribed disease-modifying antirheumatic drug (DMARD) for RA that is frequently used in combination with other RA medicines.

About the Study

This double-blind, randomized, placebo-controlled Phase 2a study of VX-509 enrolled 204 people with active moderate to severe RA. The study enrolled people who had an inadequate response to at least one currently available non-biologic (non-injectable) DMARD. The study evaluated four dose levels of VX-509, which was given twice daily (BID) for 12 weeks. Patients did not receive methotrexate during this study, but could have received it prior to the study. Approximately 40 clinical trial sites participated in the trial in the United States and Europe.

Efficacy Data

The study met its two primary endpoints, which were the proportion of people who achieved an ACR_{20} response at week 12 and the change from baseline in DAS28 at week 12. Additional secondary endpoints were used to evaluate the clinical activity of VX-509, including ACR_{50} and ACR_{70} responses at week 12. The ACR responses and DAS scores observed in the two highest dose groups for VX-509 indicated continuous and statistically significant improvements in the signs and symptoms of RA, with these effects being observed in some patients as early as the first week of the study. ACR responses and DAS scores are provided below and are based on an intent-to-treat analysis where patients who discontinued treatment prior to week 12 were counted as non-responders (failures) in the efficacy analyses, regardless of their response to treatment:

American College of Rheumatology Responses at Week 12:

VX-509 (n=163)	ACR_{20}	ACR_{50}	ACR_{70}
25 mg (n=41)	39% (*p=0.485)*	17% (*p=0.312)*	7% (*p=0.616)*
50 mg (n=41)	61% (*p=0.007)*	32% (*p=0.011)*	12% (*p=0.201)*
100 mg (n=40)	65% (*p=0.002)*	38% (*p=0.001)*	18% (*p=0.029)*
150 mg (n=41)	66% (*p=0.002)*	49% (*p<0.001)*	22% (*p=0.014)*
Placebo (n=41)	29%	7%	2%

An additional analysis of ACR responses was conducted for people in the study who completed 12 weeks of treatment with VX-509. ACR_{20} response rates of 46 percent, 76 percent, 81 percent and 82 percent were observed for people who received 25 mg, 50 mg, 100 mg and 150 mg of VX-509, respectively, compared to 41 percent in the placebo arm.

Disease Activity Scores at Week 12:

VX-509	DAS28 Improvement from Baseline
25 mg	-1.75 (*p=0.155)*
50 mg	-2.60 (*p<0.001)*
100 mg	-2.70 (*p<0.001)*
150 mg	-3.06 (*p<0.001)*
Placebo	-1.25

DAS28 Remission:

The study also evaluated the proportion of patients in each treatment arm who experienced clinical remission, defined as a patient with a DAS28 score of less than 2.6 at week 12. In this study, 35 percent and 37 percent of people achieved DAS28 remission in the 100 mg and 150 mg treatment groups, respectively, compared to 7 percent of people in the placebo arm.

Safety Data

At least 80 percent of all people in each of the VX-509 treatment groups completed the 12-week treatment course, and 68 percent of people who received placebo completed treatment. Eight percent of people who received VX-509 discontinued treatment due to adverse events, compared to 5 percent of people who received placebo. Overall, the most frequently reported class of adverse event in the VX-509 and placebo arms was infections, which occurred in 17 percent of people who received placebo and in 17 percent of people who received VX-509. The most common individual adverse events observed in both the placebo and VX-509 treatment arms were nausea (5 percent), headache (4 percent) and increased alanine transaminase (ALT) (4 percent). Dose-related low-level increases in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were observed in people who received VX-509. Discontinuations due to adverse events occurred more frequently in the 100 mg and 150 mg VX-509 dose groups. Serious adverse events occurred in 2 percent of people in the placebo treatment group, compared to 5 percent in the VX-509 treatment groups. The most common serious adverse events in the VX-509 treatment arms were infections. There were no serious adverse events related to measurements in ALT.

In the 100 mg dose group of the study, one patient died of a hemorrhagic stroke, reported as unrelated to VX-509. Also in this dose group, one patient died of pneumonia. This patient received VX-509 and other medicines also associated with a potential increase in susceptibility to infections. As a result, a contribution of VX-509 to the severity of the pneumonia in this patient cannot be ruled out.

There were no declines observed in measures of hemoglobin or neutrophils among people who received VX-509 compared to those who received placebo. Two percent of all people who received VX-509 discontinued treatment due to lack of efficacy, compared to 14 percent in the placebo group.

About VX-509

VX-509 is an investigational oral medicine being developed by Vertex that is designed to selectively inhibit Janus kinase 3, or JAK3. JAK3 is one of four JAK family kinases, which include JAK1, JAK2, JAK3 and Tyk2. In autoimmune diseases, JAK3 is an

essential component of the signaling cascade that contributes to the abnormal immune response that results in chronic inflammation and, in the case of RA, irreversible damage to cartilage and bones. Specific inhibition of JAK3 represents a new approach to the treatment of a range of autoimmune diseases. Based on *in vitro* data, VX-509 has demonstrated a high degree of potency and selectivity for inhibition of JAK3. VX-509 has been shown to be greater than 1000-fold more selective for JAK3 compared to non-JAK kinases and approximately 25- to 150-fold more selective for JAK3 compared to other JAK isotypes in cell-based assays. This high level of selectivity was confirmed in clinical studies where potent dose-related inhibition of a JAK3 dependent biomarker was observed while little to no effect was shown against a JAK2/JAK1 dependent biomarker. VX-509 was discovered by Vertex scientists.

About Rheumatoid Arthritis

RA is a chronic inflammatory disease that affects 1 percent to 2 percent of the world's population, including 1.5 million adults in the United States.[1,9] The disease causes destruction of joint cartilage and erosion of adjacent bone, resulting in deformity, loss of function, substantial disability and, for many, the need for joint replacement. Many people with RA suffer progressive disability over time,[2,3] pain,[4] work loss,[5] substantial health care costs,[6] and premature death.[7] Approximately 80 percent of people with RA become disabled within 20 years of diagnosis.[8]

The treatment of RA focuses on reducing symptoms and inhibiting progression of the disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may reduce the symptoms of pain, swelling and stiffness, but they do not alter the natural course of the disease. Disease-modifying antirheumatic drugs (DMARDs) have shown effects in slowing the progression of joint damage and time to disability and thus altering the natural history of RA. While recently approved medicines are effective in a portion of patients, a significant number of people with RA do not respond adequately or become refractory to these medicines, creating a significant need for new approaches to RA treatment.

About Endpoints in RA: ACR and DAS Responses

The most common endpoints in RA clinical studies are ACR and DAS responses. ACR responses are defined as the proportion of patients in a trial who achieve at least a pre-specified percent improvement in the signs and symptoms of RA, as measured by tender and swollen joint counts and other criteria. For example, an ACR_{20} response reflects the proportion of people who had at least a 20 percent improvement in both tender and swollen joints in addition to improvements in other criteria such as C-reactive protein (CRP), Health Assessment Questionnaire (HAQ) disability scores and others. DAS responses, including DAS28, are derived from an assessment of multiple measurements of RA, including tender and swollen joints, C-reactive protein (CRP) and a patient's assessment of general health.

About Vertex

Vertex creates new possibilities in medicine. Our team discovers, develops and commercializes innovative therapies so people with serious diseases can lead better lives.

Vertex scientists and our collaborators are working on new medicines to cure or significantly advance the treatment of hepatitis C, cystic fibrosis, epilepsy and other life-threatening diseases.

Founded more than 20 years ago in Cambridge, MA, we now have ongoing worldwide research programs and sites in the U.S., U.K. and Canada.

Special Note Regarding Forward-Looking Statements:

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including statements regarding (i) the results from the completed Phase 2a trial supporting initiation of a Phase 2b trial to evaluate longer treatment durations for VX-509 in people with RA; (ii) the possibility that selective targeting of JAK3 by VX-509 may represent a new approach to treatment of RA and other autoimmune and inflammatory diseases; (iii) the potential that a longer-duration trial would show any or additional improvements in RA activity and further establish the safety profile of VX-509; and (iv) the potential clinical trial design for the expected Phase 2b trial. While Vertex believes the forward-looking statements contained in this press release are accurate, these statements are subject to risks and uncertainties that could cause actual outcomes to vary materially from the outcomes referenced in the forward-looking statements. These risks and uncertainties include, among other things, the risks that efforts to develop VX-509 may not proceed due to technical, scientific, commercial, financial or other reasons, that clinical trials may not proceed as planned, that longer-duration clinical trials of VX-509 may not show any or any additional improvements in RA activity, that a safety profile for VX-509 could be established in further nonclinical studies or clinical trials that could put further development of VX-509 in jeopardy or adversely effect its therapeutic value, and other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission and available through the Vertex's website at **www.vrtx.com**. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

References:

1. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality. Am J Epidemiol. 1980;111:87-98.

2. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum. 1984;27:864-72.

3. Sherrer YS, Bloch DA, Mitchell DM, Young DY, Fries JF. The development of disability in rheumatoid arthritis. Arthritis Rheum. 1986;29:494-500.

4. Callahan LF, Brooks RH, Summey JA, Pincus T. Quantitative pain assessment for routine care of rheumatoid arthritis patients, using a pain scale based on activities of daily living and a visual analog pain scale. Arthritis Rheum. 1987;30:630-6.

5. Yelin E, Meenan R, Nevitt M, Epstein W. Work disability in rheumatoid arthritis: effects of disease, social, and work factors. Ann Intern Med. 1980;93:551-6.

6. Verstappen SM, Bijlsma JW, Verkleij H, Buskens E, Blaauw AA, ter Borg EJ,et al; Utrecht Rheumatoid Arthritis Cohort Study Group. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum. 2004;51:488-97.

7. Pincus T, Brooks RH, Callahan LF. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. Ann Intern Med. 1994;120:26-34.

8. Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum. 2001;44:2746-9.

9 Arthritis Rheum. 2010 Jun;62(6):1576-82. [Data source: Patient Cohort, Minnesota]

(VRTX-GEN)

Vertex Pharmaceuticals Incorporated
Investors
Michael Partridge, 617-444-6108
or
Lora Pike, 617-444-6755
or
Matthew Osborne, 617-444-6057
or
Media
Zachry Barber, 617-444-6992
mediainfo@vrtx.com
or
Dawn Kalmar
mediainfo@vrtx.com

Source: Vertex Pharmaceuticals Incorporated