Portola Investor Room

Portola Pharmaceuticals Presents New Analysis from the ANNEXA-4 Study of its Factor Xa Inhibitor Reversal Agent Andexxa® in Patients with Acute Gastrointestinal Bleeding

- Effective Hemostasis Achieved in 82% of Evaluable Patients with Acute Gastrointestinal Bleeding -

- Data to be Presented at ACG 2019 Annual Scientific Meeting as Part of Ongoing ANNEXA-4 Sub-Analysis Clinical Data Plan -

SOUTH SAN FRANCISCO, Calif., Oct. 28, 2019 /PRNewswire/ -- Portola Pharmaceuticals, Inc.® (Nasdaq: PTLA) today announced the presentation of a new exploratory analysis of data from ANNEXA-4, the Company's Phase 3b/4 trial of its Factor Xa inhibitor antidote Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo], in a key subgroup of patients with acute gastrointestinal (GI) bleeding while taking a Factor Xa inhibitor.

The data will be featured at the American College of Gastroenterology (ACG) 2019 Annual Scientific Meeting in San Antonio, Texas, during a plenary session on Tuesday, October 29, 2019, from 3:25 p.m. CDT to 3:35 p.m. CDT (Location: Stars at Night Ballroom – B4; Plenary Session 3B, Abstract 53).

GI bleeding is a common type of anticoagulant-related bleeding that occurs in the upper or lower GI tract. Among the 352 patients in the ANNEXA-4 study, 90 (26%) were treated for acute GI bleeding and 62 (18%) were evaluable for hemostatic efficacy. Among this subset, 82% (n=51/62) achieved excellent or good hemostasis (stoppage of bleeding) over the 12-hour period following treatment with Andexxa, as determined by an independent adjudication committee. This is consistent with the 82% (n=204/249) reported in the full ANNEXA-4 study across patients with all types of bleeds (e.g., GI, intracranial hemorrhages and other sites of bleeding). Both the exploratory analysis and full study results showed that Andexxa rapidly and potently reversed anti-factor Xa activity.

Patients with GI bleeding were considered efficacy evaluable if they were determined to have major bleeding, as defined by hemodynamic compromise or bleeding associated with a hemoglobin (Hb) drop $\geq$ 2 g/dL or a baseline Hb $\leq$ 8 g/dL, and a baseline anti-factor Xa activity $\geq$ 75 ng/mL ($\geq$ 0.25 IU/mL for enoxaparin patients).

Among the 90 safety evaluable patients with acute GI bleeding, and within 30 days of enrollment, thrombotic events occurred in six patients (7%) and death occurred in 10 patients (11%), consistent with the full ANNEXA-4 study results and the high background thrombotic risk of the enrolled patient population. No thrombotic events were observed among the 40 (44%) patients who re-started oral anticoagulation therapy. By comparison, among the 352 safety evaluable patients in ANNEXA-4 and within 30 days of enrollment, thrombotic events occurred in 34 patients (9.7%) and death occurred in 49 patients (13.9%). All of the thrombotic events occurred in patients who delayed or did not re-start anticoagulation therapy with a Factor Xa inhibitor during the follow-up period.

"Major bleeding associated with use of Factor Xa inhibitors is a serious and life-threatening complication," said Deborah Siegal, M.D., ACG presenter and assistant professor in the Department of Medicine of the Faculty of Health Sciences at McMaster University in Hamilton, Ontario. "This ANNEXA-4 sub-analysis of patients with bleeding in the GI tract – the most common site of anticoagulant-related bleeding – continues to demonstrate the consistency of the hemostatic efficacy and safety of Andexxa."

The use of Factor Xa inhibitors is growing rapidly because of their efficacy and safety profile compared to enoxaparin and warfarin in preventing and treating thromboembolic conditions such as stroke, pulmonary embolism and venous thromboembolism (VTE). This growth has come with a related increase in the incidence of hospital admissions and deaths related to bleeding, the major complication of anticoagulation. In 2017, there were approximately 150,000 hospital admissions attributable to Factor Xa inhibitor-related bleeding and approximately 2,100 bleeding-related deaths per month in the U.S.

"We are pleased that these data continue to highlight the durability of the hemostatic efficacy of Andexxa across patient populations, including those who experience Factor Xa inhibitor-related bleeding in more common sites such as the GI tract," said Scott Garland, Portola's president and chief executive officer. "The presentation of this analysis is part of our long-term strategy to build awareness of the clinical data supporting Andexxa, and become the standard of care for the hundreds of thousands of patients taking Factor Xa inhibitors who may require access to this potentially life-saving medicine."

Andexxa is a recombinant protein specifically designed to bind to Factor Xa inhibitors and rapidly reverse their anticoagulant effect. Andexxa was approved by the FDA in May 2018 as the first and only antidote indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexxa received both U.S. Orphan Drug and FDA Breakthrough Therapy designations and was approved under the FDA's Accelerated Approval pathway based on the change from baseline in anti-factor Xa activity in healthy volunteers. It is marketed in Europe as Ondexxya® (andexanet alfa).

ANNEXA-4 Study Design

ANNEXA-4 is a global, prospective, single-arm, open-label clinical trial designed to evaluate andexanet alfa in patients who present with an acute major bleed while receiving apixaban, rivaroxaban, edoxaban or enoxaparin. This multi-center cohort study was not randomized, and all participants received andexanet alfa given as a bolus dose over 20-30 minutes followed by a two-hour (120 minute) infusion. Patients received a low or high dose infusion depending on which Factor Xa inhibitor they received and the time since they received the last dose. Patients were evaluated for 30 days following andexanet alfa administration. The co-primary efficacy endpoints are the maximum percent reduction in anti-factor Xa activity and assessment of hemostasis over 12 hours following the infusion. Hemostatic efficacy was assessed by an independent endpoint adjudication committee using predetermined criteria as either excellent, good or poor/none. Among the safety endpoints were mortality and thrombotic events at 30 days, and the development of antibodies to Andexxa or to native Factor X and Factor Xa.

IMPORTANT SAFETY INFORMATION FOR ANDEXXA [coagulation factor Xa (recombinant), inactivated-zhzo]

BOXED WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST AND SUDDEN DEATHS

See full prescribing information for complete boxed warning

Treatment with Andexxa has been associated with serious and life-threatening adverse events, including:

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

Indication
Andexxa [coagulation factor Xa (recombinant), inactivated-zhzo] is a recombinant modified human Factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Limitation of Use
Andexxa has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

SELECT IMPORTANT SAFETY INFORMATION

Thromboembolic and Ischemic Risk
The thromboembolic and ischemic risks were assessed in 185 patients who received the Generation 1 product and in 124 patients who received the Generation 2 product. The median time to first event was six days, and patients were observed for these events for 30 days following Andexxa infusion. Of the 86 patients who received Generation 1 product and were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic event, ischemic event, cardiac event or death.

Monitor patients treated with Andexxa for signs and symptoms of arterial and venous thromboembolic

events, ischemic events, and cardiac arrest. To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with Andexxa.

The safety of Andexxa has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within two weeks prior to the life-threatening bleeding event requiring treatment with Andexxa. Safety of Andexxa also has not been evaluated in patients who received prothrombin complex concentrates, recombinant Factor VIIa, or whole blood products within seven days prior to the bleeding event.

Re-elevation or Incomplete Reversal of Anti-FXa Activity

The time course of anti-FXa activity following Andexxa administration was consistent among the healthy volunteer studies and the ANNEXA-4 study in bleeding patients. Compared to baseline, there was a rapid and substantial decrease in anti-FXa activity corresponding to the Andexxa bolus. This decrease was sustained through the end of the Andexxa continuous infusion. The anti-FXa activity returned to the placebo levels approximately two hours after completion of a bolus or continuous infusion. Subsequently, the anti-FXa activity decreased at a rate similar to the clearance of the FXa inhibitors.

Thirty-eight patients who received the Generation 1 product were anticoagulated with apixaban and had baseline levels of anti-FXa activity > 150 ng/mL. Nineteen of these 38 (50%) patients experienced a > 93% decrease from baseline anti-FXa activity after administration of Andexxa. Eleven patients who were anticoagulated with rivaroxaban had baseline anti-FXa activity levels > 300 ng/mL. Five of the 11 patients experienced a > 90% decrease from baseline anti-FXa activity after administration of Andexxa. Anti-FXa activity levels for patients who received the Generation 2 product were not available.

Adverse Reactions

The most common adverse reactions (≥ 5%) in patients receiving Andexxa were urinary tract infections and pneumonia.

The most common adverse reactions (≥ 3%) in healthy volunteers treated with Andexxa were infusion-related reactions.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 Generation 1 Andexxa-treated healthy subjects were tested for antibodies to Andexxa as well as antibodies cross-reacting with Factor X (FX) and FXa. Low titers of anti-Andexxa antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (days 44 to 48). To date, the pattern of antibody response in patients in the ANNEXA-4 study has been similar to that observed in healthy volunteers with 6% (6/98) of the patients having antibodies against Andexxa. None of these anti-Andexxa antibodies were neutralizing. No antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/98) to date. There is insufficient data to assess for the presence of anti-Andexxa antibodies for subjects received the Generation 2 product.

About Portola Pharmaceuticals, Inc.

Portola Pharmaceuticals is a global, commercial-stage biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutics that could significantly advance the fields of thrombosis and other hematologic conditions. The Company's first two commercialized products are Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo], marketed in Europe as Ondexxya® (andexanet alfa), and Bevyxxa® (betrixaban). The company also is advancing cerdulatinib, a SYK/JAK inhibitor being developed for the treatment of hematologic cancers. Founded in 2003 in South San Francisco, California, Portola has operations in the United States and Europe.

Forward-Looking Statements

Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding Portola's long-term strategy to build awareness of the clinical data supporting Andexxa, and become the standard of care for the patients taking Factor Xa inhibitors who may require a reversal agent and the potential benefit of Andexxa. Risks that contribute to the uncertain nature of the forward-looking statements include: the risk that physicians, patients and payers may not see the benefits of utilizing Andexxa for the indications for which it is approved; our ability to continue to manufacture our products and to expand approved manufacturing facilities; the possibility of unfavorable results from additional clinical trials involving Andexxa; our ability to grow our commercial operations in the EU and generate product revenue within projected timelines and budget; the risk that we may not obtain additional regulatory approvals necessary to expand or maintain approved indications for Andexxa; our expectation that we will incur losses for the foreseeable future and will need additional funds to finance our operations; the accuracy of our estimates regarding expenses and capital requirements; our ability to successfully build a hospital-based sales force and commercial infrastructure; our ability to obtain and maintain intellectual property protection for our product candidates; our ability to retain key scientific or management personnel and general market conditions. These and other risks and uncertainties are described more fully in our most recent filings with the Securities and Exchange Commission, including our most recent quarterly report on Form 10-Q. All forward-looking statements contained in this press release speak only as of the date on which they were made. We undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

SOURCE Portola Pharmaceuticals, Inc.®

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ANNEXA-4-Study-of-its-Factor-Xa-Inhibitor-Reversal-Agent-Andexxa-R-in-Patients-with-Acute-Gastrointestinal-Bleeding