# First Patient Enrolls in FORWARD Trial to Evaluate Monthly Dosing of KRYSTEXXA® (pegloticase injection) and Methotrexate to Treat Uncontrolled Gout

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*-- New Clinical Trial Complements Ongoing Efforts to Evolve the Patient Experience with KRYSTEXXA --*

DUBLIN--(BUSINESS WIRE)--Mar. 25, 2021-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the first patient has enrolled in a clinical trial that will evaluate a monthly dosing regimen of 16 mg of KRYSTEXXA (pegloticase injection) concomitantly used with methotrexate to treat people with chronic gout refractory to conventional therapy, also known as uncontrolled gout. The current recommended dosing of KRYSTEXXA for adult patients is 8 mg given as intravenous infusions every two weeks, with each dose infused over at least two hours.

"Uncontrolled gout is a serious and painful condition that can cause people difficulty in their normal activities and impact the way they lead their daily lives," said Suneet Grewal, M.D., investigator and rheumatologist at East Bay Rheumatology Medical Group. "When we successfully treat patients with KRYSTEXXA we can reduce the uric acid levels and resolve tophi. Exploring ways to impact the patient experience, including doubling the dose of KRYSTEXXA and infusing it every four weeks with concomitant methotrexate, may allow us to reduce the treatment burden for patients and help maximize benefit."

The *Four-Weekly Administration for Urate Reduction* (FORWARD) is an adaptive, staggered-start trial designed to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of KRYSTEXXA administered monthly (Q4W). An initial patient cohort will receive 15 mg oral methotrexate every week for four weeks and then continue receiving the oral methotrexate weekly with 16 mg of KRYSTEXXA infused every four weeks over at least two hours. Whether another dose will be tested in a second cohort will be determined from preliminary analysis of the initial 16 mg cohort. The primary outcome for this 48-week trial is the proportion of responders during Month 6 of treatment [serum uric acid (sUA) <6 mg/dl at least 80 percent of the time], as well as time to and duration of normalization of sUA. In total, the trial aims to enroll up to 30 adults with uncontrolled gout. The safety and efficacy of this dosing regimen have not been evaluated or approved by any health authority.

“Our ongoing commitment to patients fuels our research to impact both the experience and outcomes for people living with uncontrolled gout,” said Paul M. Peloso, M.D., M.Sc., vice president and therapeutic area head, rheumatology, Horizon. “The FORWARD trial complements our clinical trial assessing shorter-infusion duration options, which enrolled its first patient last fall and continues our efforts to evolve the patient experience with KRYSTEXXA.”

Additional details on the study sites and protocol can be found at www.clinicaltrials.gov (NCT04762498).

**About KRYSTEXXA**

**INDICATIONS AND USAGE**

KRYSTEXXA® (pegloticase injection) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

**Important Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.**

**IMPORTANT SAFETY INFORMATION**

**WARNING: ANAPHYLAXIS AND INFUSION REACTIONS**

**Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Serum uric acid levels should be monitored prior to infusions, and healthcare providers should consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after

discharge from the healthcare setting.

**CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA**

Patients should be screened for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA should not be administered to these patients.

**GOUT FLARES**

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

**CONGESTIVE HEART FAILURE**

KRYSTEXXA has not been studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Caution should be exercised when using KRYSTEXXA in patients who have congestive heart failure, and patients should be monitored closely following infusion.

**ADVERSE REACTIONS**

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

**Please see Full Prescribing Information and Medication Guide for more information.**

**About Horizon**

Horizon is focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our pipeline is purposeful: we apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives. For more information on how we go to incredible lengths to impact lives, please visit www.horizontherapeutics.com and follow us on Twitter, LinkedIn, Instagram and Facebook.

**Forward-Looking Statements**

This press release contains forward-looking statements, including, but not limited to, statements related to the scope and design of the FORWARD clinical trial, the potential of KRYSTEXXA, including potential improvements in patient experience, and business and other statements that are not historical facts. These forward-looking statements are based on Horizon's current expectations and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks regarding whether results of the FORWARD trial will be consistent with results of other trials; whether Horizon experiences delays in completing the FORWARD trial, whether the results of any clinical trials will be sufficient to support labeling changes or result in changes in prescribing behavior; impacts of the COVID-19 pandemic and actions taken to slow its spread; risks relating to Horizon's ability to successfully implement its business strategies; risks inherent in developing novel medicine candidates and existing medicines for new indications; risks associated with regulatory approvals; competition, including potential generic competition; the ability to protect intellectual property and defend patents; regulatory obligations and oversight, including any changes in the legal and regulatory environment in which Horizon operates and those risks detailed from time-to-time under the caption "Risk Factors" and elsewhere in Horizon's filings and reports with the SEC. Horizon undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information.

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