Horizon Therapeutics plc Initiates ADVANCE Trial Evaluating KRYSTEXXA® (pegloticase injection) with Methotrexate for People Who Previously Developed Anti-Drug Antibodies on KRYSTEXXA Monotherapy

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-- Trial evaluates opportunity to improve outcomes based on emerging data that immunomodulation may offer clinical benefit --

DUBLIN--(BUSINESS WIRE)--May 27, 2021-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the first patient has enrolled in the ADVANCE trial evaluating the concomitant use of KRYSTEXXA (pegloticase injection) with methotrexate for people with uncontrolled gout who were not able to achieve a complete response when previously treated with KRYSTEXXA monotherapy.

For people with chronic gout refractory to conventional therapies (uncontrolled gout), KRYSTEXXA offers a unique mechanism of action that converts urate into allantoin which can more easily and efficiently be excreted by the kidneys.[1] Similar to other biologic medicines, patients on KRYSTEXXA monotherapy can develop anti-drug antibodies that prevent them from completing a full course of therapy. Increasingly, immunomodulating therapies, such as methotrexate, have been employed to help reduce the development of anti-drug antibodies.[2] With this understanding, the ADVANCE trial will evaluate if repeating the course of KRYSTEXXA therapy with an immunomodulator as co-therapy may help more patients, who previously lost response with KRYSTEXXA monotherapy, to achieve a complete response.

"We are acutely aware of the impact systemic urate deposition has on patients, notably the permanent damage to joints, bone erosion and the increased risk of kidney disease," said Orrin Troum, M.D., clinical professor of medicine and voluntary faculty member in the Division of Rheumatology at the Keck School of Medicine, University of Southern California and rheumatologist with Providence Saint John's Health Center in Santa Monica, California. "To help maximize treatment options, the ADVANCE trial incorporates insights from current rheumatology practice."

ADVANCE is an open-label trial designed to evaluate the efficacy and safety of KRYSTEXXA used with methotrexate for people with uncontrolled gout who previously lost response when treated with KRYSTEXXA monotherapy. The trial will enroll 30 patients. The primary endpoint is the response rate, defined as a serum uric acid level of <6 mg/dL for at least 80 percent of the time during Month 6. Participants will receive 8 mg infusions of KRYSTEXXA every two weeks, along with a weekly course of 15 or 25 mg (depending on their renal function) of methotrexate administered subcutaneously, after a methotrexate run-in period, which provides a preferred pharmacokinetics profile for this trial.[3] The safety and efficacy of KRYSTEXXA co-prescribed with methotrexate has not been evaluated or approved by any health authority.

"As the impact of systemic urate deposition becomes better understood, having options to treat and re-treat patients is increasingly important for patients with uncontrolled gout and systemic urate deposition," said Theresa Podrebarac M.D., MSc., senior vice president, clinical development, Horizon. "We believe a substantial portion of patients who were not complete responders to treatment with KRYSTEXXA monotherapy could be good candidates for this approach and that insights from this trial could help shape clinical care for those with uncontrolled gout."

Additional details on the study sites and protocol can be found at www.clinicaltrials.gov (NCT04772313).

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 patients 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 statements regarding the potential benefits of combining methotrexate treatment with KRYSTEXXA, expectations regarding the ADVANCE clinical trial, including expected enrollment size and design, and expectations regarding physicians adopting a combination approach in treating patients with uncontrolled gout. These forward-looking statements are based on management's expectations and assumptions as of the date of this press release and actual results may differ materially from those in these forward-looking statements as a result of various factors. These factors include, but are not limited to, risks regarding whether results of the ADVANCE clinical trial will be consistent with results of prior trials or other data or Horizon's expectations, the risks associated with clinical development of drug candidates and risks related to competition or other factors that may change physician treatment strategies. For a further description of these and other risks facing Horizon, please see the risk factors described in Horizon's filings with the United States Securities and Exchange Commission, including those factors discussed under the caption "Risk Factors" in those filings. Forward-looking statements speak only as of the date of this press release and Horizon undertakes no obligation to update or revise these statements, except as may be required by law.

References

1. KRYSTEXXA (pegloticase) [prescribing information]
2. Strand V, et al. *BioDrugs.* 2017;31:299-316.
3. National Institute of Health. Pegloticase and Methotrexate Co-administered in Patients with Uncontrolled Gout Who Have Previously Failed Pegloticase Monotherapy. https://clinicaltrials.gov/ct2/show/NCT04772313. Accessed May 18, 2021.

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