Horizon Therapeutics plc Initiates MIRROR Randomized Controlled Trial Evaluating KRYSTEXXA® (pegloticase injection) in Combination with Methotrexate to Increase Response Rates and Duration of Therapy

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- Approach informed by regulatory guidance and real-world clinical experience -

DUBLIN--(BUSINESS WIRE)--Jun. 20, 2019-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the initiation of a clinical trial evaluating KRYSTEXXA® (pegloticase injection) in combination with methotrexate as a strategy to increase the durability of response for patients living with chronic gout refractory to conventional therapies – also known as uncontrolled gout.

Treatment with biologic medicines can, in some patients, trigger the body's immune system to develop anti-drug antibodies. These anti-drug antibodies can reduce the effectiveness of the biologic therapy. Immunomodulators, such as methotrexate, are often co-prescribed with biologics to help reduce this reaction. The ***M****ethotrexate to* ***I****ncrease* ***R****esponse* ***R****ates in Patients With Uncontrolled G****O****ut* ***R****eceiving KRYSTEXXA (MIRRORrandomized controlled trial (RCT)),* will evaluate the use of methotrexate as an immunomodulator to meaningfully reduce immune response to KRYSTEXXA in adult patients living with uncontrolled gout. The trial will assess whether the combination of KRYSTEXXA with methotrexate can enhance the demonstrated response rate of KRYSTEXXA, will confirm the safety and tolerability and provide information on the pharmacokinetics (PK) of the combined use. The primary endpoint will be the ability of KRYSTEXXA with methotrexate versus KRYSTEXXA alone to maintain a serum uric acid <6 mg/dL through Month 6. The MIRROR RCT follows the MIRROR open-label (OL) evaluation that was initiated last fall and is now fully enrolled (NCT03635957).

The trial initiation is informed by the positive results of an independent case series led by John K. Botson, M.D., R.Ph. C.C.D. and Jeff R. Peterson, M.D., presented at the 2018 American College of Rheumatology (ACR) meeting with updates presented at the 2019 European Congress of Rheumatology (EULAR), which demonstrated that the use of methotrexate with KRYSTEXXA was well tolerated and led to an improved overall response. In the series, all of the ten sequential patients sustained lower sUA levels over the course of the observation period (target <6 mg/dL) when receiving KRYSTEXXA combined with pre-treatment and co-administration of methotrexate, 15 mg orally once-weekly.[1-2]

"To address the systemic burden of uncontrolled gout on patients, we need to reduce serum uric acid levels rapidly and effectively," said John K. Botson M.D., R.Ph., C.C.D., president, Alaska Rheumatology Alliance and rheumatologist, Orthopedic Physicians Alaska. "In our case series, we found that the use of methotrexate, which is a well understood and broadly utilized immunomodulator, may attenuate the immune response to KRYSTEXXA. We believe this combination may allow more patients on KRYSTEXXA to continue their treatment."

In the trial, 135 adult patients will be randomized to receive methotrexate or placebo for four weeks and then receive treatment with KRYSTEXXA and methotrexate or KRYSTEXXA and placebo for 52 weeks, with the primary endpoint measured at Month 6, followed by a six-month follow-up period. The co-prescription of KRYSTEXXA and methotrexate is investigational and its safety and efficacy have not been established.

"We believe in continued evaluation of our therapies to achieve the best possible outcome for every patient," said Paul Peloso, M.D., M.Sc., vice president and therapeutic area head, rheumatology, Horizon. "We've accelerated our plans for this trial based on the response seen in recent real-world case studies and the ongoing open-label evaluation, an approach aligned with our strategy to address the burden of disease from the lens of what's most important to patients."

About Uncontrolled Gout

Gout is a chronic, progressive inflammatory form of arthritis that is caused by excess uric acid in the body and needs to be managed aggressively.[3] Over time uric acid can build up and form deposits, called tophi, inside the body and joints, which can have harmful effects including causing damage to the underlying bone.[4] Patients with uncontrolled gout continue to have abnormally high levels of uric acid and continued symptoms of gout despite the use of conventional therapies. KRYSTEXXA is the only biologic approved by the U.S. Food and Drug Administration (FDA) for the treatment of uncontrolled gout in adult patients.

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 researching, developing and commercializing medicines that address critical needs for people impacted by rare and rheumatic 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, follow us @HorizonNews on Twitter, like us on Facebook or explore career opportunities on LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the potential benefits of combining methotrexate treatment with KRYSTEXXA and expectations regarding the MIRROR clinical trial. 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 MIRROR trial will be consistent with results of prior trials or Horizon's expectations, and the risks associated with clinical development of drug candidates. 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. Pretreatment and co-administration with methotrexate improved durability of pegloticase response: a prospective, observational, proof-of-concept, case series. Poster presented at the 2018 Annual Scientific Meeting of the American College of Rheumatology (ACR), Chicago, IL, USA; October 19–24, 2018.
2. Pretreatment and co-administration with methotrexate improved durability of pegloticase response: a prospective, observational, proof-of-concept, case series. Poster presented at the 2019 Annual European Congress of Rheumatology (EULAR),Barcelona, Spain; June 12-15, 2019.
3. Keuhn, B. Chronic Disease Approaches Needed to Curb Gout's Growing Burden. Journal of the American Medical Association. 2018;319(13):1308-1309.
4. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and

Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136-3141.

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