Data Support the Use of KRYSTEXXA® (pegloticase) Injection with Methotrexate to Treat Uncontrolled Gout in People With Mild-to-Moderate Chronic Kidney Disease

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-- MIRROR randomized controlled trial data to be presented during Kidney Week 2022 show consistent kidney function, eGFR levels, for people receiving KRYSTEXXA with methotrexate throughout the treatment period --

DUBLIN--(BUSINESS WIRE)--Nov. 5, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced new data that indicate KRYSTEXXA (pegloticase) injection with weekly oral methotrexate effectively treats uncontrolled gout without compromising kidney function. These findings are presented as part of the American Society of Nephrology (ASN) Kidney Week, Nov. 3-6, 2022.

“Given that one in four adults with moderate-to-severe chronic kidney disease is impacted by gout, addressing the underlying cause of disease without compromising kidney function is paramount,” said Abdul Abdellatif, M.D. F.A.S.N., adjunct assistant professor, Baylor College of Medicine Nephrology Division, and Kidney Hypertension Transplant Clinic of CLS Health. “These data are encouraging and suggest that KRYSTEXXA with methotrexate effectively addressed the systemic burden of uncontrolled gout and did not lead to renal function decline in patients with mild-to-moderate chronic kidney disease.”

As part of the *Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving KRYSTEXXA trial [MIRROR randomized controlled trial (RCT)*], baseline estimated glomerular filtration rate (eGFR) measurements, an indication of kidney function, were recorded in both the KRYSTEXXA with methotrexate and KRYSTEXXA with placebo arms prior to beginning treatment with methotrexate. Changes were recorded at defined timepoints based on the treatment group and baseline eGFR status. Patients were divided into eGFR at or over 60 mL/min/1.73 m^2 and eGFR under 60 mL/min/1.73 m^2, with less than 60 mL/min/1.73 m^2 potentially indicating kidney disease. Patients with an eGFR less than 40 mL/min/1.73 m^2 were excluded from the clinical trial.

In both the KRYSTEXXA with methotrexate and KRYSTEXXA with placebo treatment groups, eGFR levels were stable during the four-week methotrexate/placebo run-in period. By Week 24 of KRYSTEXXA treatment, eGFR improved from baseline by 5.3 mL/min/1.73 m^2 in the methotrexate group and by 4.3 mL/min/1.73 m^2 in the placebo group. Greater than 30% of patients in each treatment group had a baseline eGFR between 40-60 mL/min/1.73 m^2. The renal function improvements seen in both treatment arms were shared by these patients with baseline mild-to-moderate chronic kidney disease.

eGFR Changes in Uncontrolled Gout Patients Randomized to Receive Methotrexate or Placebo as Co-therapy to Pegloticase: MIRROR RCT Findings

“The findings of this analysis offer further confidence that even those with compromised kidney function may benefit from KRYSTEXXA with methotrexate used to treat uncontrolled gout,” said Brad Marder, M.D., medical director, Horizon. “With the recently expanded labeling to include the use of KRYSTEXXA with methotrexate and the broad community support for this treatment strategy, these data help further inform physicians’ decision making to improve their gout patients’ outcomes.”

About MIRROR Randomized Controlled Trial

The co-administration of KRYSTEXXA with an immunomodulator like methotrexate has increasingly been employed in patients with uncontrolled gout to help reduce the development of antidrug antibodies, which can affect treatment efficacy with biologics.[1,2] Following a series of community case studies and an open-label evaluation, the MIRROR randomized controlled trial (*Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving KRYSTEXX*A trial, NCT03994731) was conducted.[3-5] The trial evaluated differences in treatment response for KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA with placebo. The primary endpoint was defined as the proportion of serum uric acid (sUA) responders defined as sUA less than 6 mg/dL at least 80% of the time during Month 6 (Weeks 20-24). The study’s secondary endpoints included the proportion of sUA responders during Month 12 (Weeks 48-52), defined as sUA less than 6 mg/dL at least 80% of the time, and the proportion of participants with complete resolution of at least one tophus, no new tophus and no single tophus showing progression (using digital photography) at Week 52 in subjects with tophi at baseline. A total of 152 participants were randomized 2:1 to run-in and treatment periods with oral methotrexate (15 mg/week) or placebo, followed by a 52-week treatment period of KRYSTEXXA (8-mg bi-weekly infusions) with either methotrexate or placebo. The trial demonstrated a 32-percentage point improvement ($p<0.0001$) in treatment response rate, with 71% of patients (71 of 100) who were randomized to receive KRYSTEXXA with methotrexate achieving a sustained urate-lowering response during Month 6, compared to 39% (20 of 52) of those randomized to receive KRYSTEXXA with placebo.[1,6]

About KRYSTEXXA

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult 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.

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- **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. Delayed 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 and closely monitored for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Serum uric acid levels should be monitored prior to each infusion and treatment discontinued if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency should be screened prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. 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 formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Caution should be exercised in patients who have congestive heart failure and patients should be closely monitored following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial: gout flares, arthralgia, COVID-19, nausea and fatigue; **KRYSTEXXA alone:** gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reactions, pain in extremity, hypertension and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials: gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Full Prescribing Information, **including Boxed Warning**.

About Horizon

Horizon is a global biotechnology company 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, 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 KRYSTEXXA co-administered with methotrexate for uncontrolled gout and the impact of the additional data on treatment decisions. 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 related to the adoption of co-administration of KRYSTEXXA with methotrexate for uncontrolled gout. For a further description of these and other risks facing Horizon, please see the risk factors described in Horizon's filings with the U.S. 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

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6. Botson J, et al. A Randomized Placebo-Controlled Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving Pegloticase (MIRROR RCT): Primary Efficacy and Safety Findings. *Arthritis Rheumatol.* Accepted Author Manuscript. doi: 10.1002/art.42335

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