Data from the MIRROR Randomized Controlled Trial of KRYSTEXXA® (pegloticase) Injection with Methotrexate Published in Arthritis & Rheumatology

September 14, 2022

-- Month 6 data showed a greater than 30 percentage-point increase in efficacy, and a significant reduction in infusion reactions from 31% to 4% --

-- Publication of data follows U.S. Food and Drug Administration (FDA) approval of expanded labeling of KRYSTEXXA co-administered with methotrexate on July 7, 2022 --

DUBLIN--(BUSINESS WIRE)--Sep. 14, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the publication of data from the MIRROR randomized controlled clinical trial of KRYSTEXXA (pegloticase) injection with methotrexate, a commonly used immunomodulator, in *Arthritis & Rheumatology* [https://doi.org/10.1002/art.42335].

"The publication of this data coupled with the recently expanded labeling provides clinicians the opportunity to evolve how we care for patients with uncontrolled gout," said Suneet Grewal, M.D., co-author and rheumatologist at East Bay Rheumatology Medical Group, Inc. "Our patients often live with the impact of uncontrolled gout for 10 to 15 years before seeing a specialist. They have significant comorbidities like hypertension and chronic kidney disease, as well as inflammation and damage from urate crystals formed because of chronically elevated uric acid levels. These insights should encourage more clinicians to focus on care that rapidly reduces the urate burden and will change the course of disease for more patients."

The co-administration of KRYSTEXXA with an immunomodulator like methotrexate has increasingly been employed for patients with uncontrolled gout (chronic gout refractory to oral therapies) to help reduce the development of anti-drug antibodies, which can affect treatment efficacy.[1,2] Following a series of case studies and an open-label study, the MIRROR randomized controlled trial (*Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving KRYSTEXX*A trial, NCT03994731) was conducted[3-5] and evaluated differences in treatment response for KRYSTEXXA with methotrexate compared to KRYSTEXXA with placebo.

The primary endpoint was the proportion of serum uric acid (sUA) responders defined as sUA <6 mg/dL for 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 <6 mg/dL for at least 80% of the time, and the proportion of participants with complete resolution of at least one tophus with no new tophus and no single tophus showing progression (using digital photography) at Week 52 in subjects with tophi at baseline.[6]

The Month 6 MIRROR randomized controlled trial results included:

- **Greater than 30 percentage-point increase in patient response rate during Month 6 (p<0.0001):** 71% (71 of 100) of patients randomized to receive KRYSTEXXA with methotrexate vs 39% (20 of 52) of patients randomized to receive KRYSTEXXA with placebo achieved the primary efficacy endpoint. [6]
- **Marked reduction in infusion reactions:** during the treatment period, 4% (4 of 96) of patients who received KRYSTEXXA with methotrexate experienced infusion reactions vs 31% (15 of 49) of patients who received KRYSTEXXA with placebo. No new safety signals were observed. [6]
- **Over a 20 percentage-point increase in the complete resolution of at least one tophus at Week 24 (p=0.043):** among patients with validated tophi at baseline, 35% (18 of 52) of patients who were randomized to receive KRYSTEXXA with methotrexate had complete resolution of at least one tophus at Week 24 vs 14% (4 of 29) of patients who were randomized to receive KRYSTEXXA with placebo. [6]

Concentrations of methotrexate polyglutamates were maintained during the treatment course for patients randomized to receive KRYSTEXXA with methotrexate, confirming compliance with methotrexate therapy. In addition, methotrexate polyglutamate concentrations were in the same range as those reported for oral methotrexate use in patients with rheumatoid arthritis.[6]

A total of 152 participants were randomized 2:1 to a four-week run-in and treatment period with oral methotrexate (15 mg/week) or placebo, followed by bi-weekly infusions of KRYSTEXXA (8 mg) with either methotrexate or placebo for 52 weeks. The mean patient age was 55 years. At screening, patients had on average a 14-year history of gout (time since first diagnosis), 76% (115 of 152) of patients had an investigator-identified tophi, and all had experienced at least 1 gout flare in the prior year (10.8±14.2 flares/patient). In addition, comorbidity prevalence was high, with hypertension (63%), gastrointestinal disorders (38%) and stage 3 chronic kidney disease (32%, eGFR <60 ml/min/1.73m^2) noted most frequently. Baseline characteristics were balanced across treatment groups.[6]

"Since acquiring KRYSTEXXA, Horizon has made significant investments to deliver on the improved efficacy and reduced infusion reactions we see in the publication of MIRROR data," said Brian LaMoreaux, M.D., M.S., senior medical director, Horizon. "Our unmatched focus on those living with uncontrolled gout continues to drive clinical development to improve the patient experience with KRYSTEXXA as well as our early-stage gout programs."

More information on KRYSTEXXA with methotrexate is available in the Prescribing Information and at KRYSTEXXAhcp.com. Patients with questions can speak to a Gout Nurse Advocate at 833-469-4688.

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 Horizon's future development plans. 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 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

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