Data Presented from the MIRROR Randomized Controlled Trial Demonstrate KRYSTEXXA® (pegloticase injection) Plus Methotrexate Resulted in Significant Improvement in Efficacy and Safety (Infusion Reactions) Compared to KRYSTEXXA Monotherapy

June 1, 2022

-- Data through Month 6 showed a greater than 32% increase in patient response rate and infusion reactions were reduced from 31% to 4% --

-- Oral presentation on MIRROR randomized controlled trial to be held at The EULAR 2022 European Congress of Rheumatology on June 2, 2022 at 11:35 a.m. CEST --

-- In March, the FDA granted priority review for the supplemental Biologic License Application of KRYSTEXXA plus methotrexate with an expected Prescription Drug User Fee Action date of July 7, 2022 --

DUBLIN--(BUSINESS WIRE)--Jun. 1, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the presentation of new KRYSTEXXA® (pegloticase injection) datasets on the primary endpoint results from the MIRROR randomized clinical trial and analyses of the pharmacokinetics of KRYSTEXXA plus methotrexate. Additional presentations by Horizon during The EULAR 2022 European Congress of Rheumatology, June 1 – 4 in Copenhagen, include the exploratory findings from the PROTECT trial of KRYSTEXXA with immunomodulation in kidney transplant patients and the impact of chronic gout refractory to conventional therapies (uncontrolled gout).

“Substantial evidence shows KRYSTEXXA plus methotrexate can change the course of care for patients,” said Theresa Podrebarac, M.D., MSc., senior vice president, clinical development, Horizon. “Results from the MIRROR randomized controlled trial reflects Horizon’s significant investment in the research and development of KRYSTEXXA to improve patient outcomes and show a clear increase in patient response rate and reduction in infusion reactions. This multi-year effort and collaboration with the medical community brings new hope to address the burden of disease for people living with uncontrolled gout.”

Month 6 results from MIRROR randomized controlled trial

The MIRROR randomized controlled trial outcomes provided a clear view of improvements in patient response and reductions in infusion reactions for KRYSTEXXA plus low-dose (15 mg/week) methotrexate compared to KRYSTEXXA plus placebo. Results from evaluation during Month 6 included:

- **Patient response rate increased by greater than 32% (p<0.0001):** response rate in the group randomized to receive KRYSTEXXA plus methotrexate was 71.0% (71 of 100) of patients as compared to 38.5% (20 of 52) of patients randomized to receive KRYSTEXXA plus placebo. As the primary endpoint, response rate was defined as serum uric acid (sUA) less than 6 mg/dL for more than 80% of the time during Weeks 20-24.
- **Infusion reactions were significantly reduced:** 4.2% (4 of 96) of patients who were randomized to receive KRYSTEXXA plus methotrexate experienced an infusion reaction vs. 30.6% (15 of 49) of patients who were randomized to receive KRYSTEXXA plus placebo.
- **Complete resolution of at least one tophus improved by 20.8% (p=0.043):** 34.6% (18 of 52) of patients who were randomized to receive KRYSTEXXA plus methotrexate had complete resolution of at least one tophus at Week 24 vs. 13.8% (4 of 29) of patients who were randomized to receive KRYSTEXXA plus placebo.

No new safety concerns were identified.

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving Pegloticase (MIRROR RCT): 6-month efficacy and safety findings (OP0171, June 2, 11:35-11:45 am CEST, Auditorium 15)

“When we look at the results from the MIRROR randomized controlled trial in addition to the previous open label results and multiple in-practice case series, the evidence reinforces the use of KRYSTEXXA plus methotrexate in treating patients with uncontrolled gout,” said study author and co-primary investigator John K. Botson, M.D., R.Ph., C.C.D., president, Alaska Rheumatology Alliance and rheumatologist, Orthopedic Physicians Alaska. “Given what we know about the impact of uncontrolled gout on joints, organs and its correlation to metabolic syndrome and chronic kidney disease, the urgency to address the underlying burden remains paramount. Results from this trial provide further insights for clinicians to consider in their approach for treating patients with uncontrolled gout.”

Pharmacokinetics of KRYSTEXXA and methotrexate polyglutamates

Systemic exposures of KRYSTEXXA and its immunogenicity in uncontrolled gout patients were evaluated during the MIRROR randomized controlled trial to determine methotrexate exposure in uncontrolled gout patients through Month 6 of treatment with KRYSTEXXA plus oral methotrexate (15 mg/week). Preinfusion blood samples were collected to measure methotrexate polyglutamates (MTX-PGs, including MTX-PG_{1-5}) in red blood cells. Pre and postinfusion serum samples were also obtained to measure trough (Cmin) and peak (Cmax) concentrations of KRYSTEXXA, respectively, at multiple visits.

Overall, higher Cmax and Cmin of KRYSTEXXA were observed in patients randomized to receive KRYSTEXXA plus methotrexate than in those randomized to receive KRYSTEXXA plus placebo. Median (Q1, Q3) Cmax was 3.01 (1.94, 3.94) µg/mL for patients randomized to receive KRYSTEXXA plus methotrexate and 2.66 (1.45, 3.20) µg/mL for those randomized to receive KRYSTEXXA plus placebo. Improved KRYSTEXXA

response was associated with higher concentrations of the medicine.

KRYSTEXXA plus methotrexate reduced the incidence of new anti-PEG antibody formation. The proportion of subjects with an increase from baseline in anti-PEG Ab titers or who were negative at baseline and developed an anti-PEG Ab response at least one post-dose time point during KRYSTEXXA treatment through Month 6 was 23.2% (22 of 95) for patients randomized to receive KRYSTEXXA plus methotrexate compared to 50.0% (24 of 48) for patients randomized to receive KRYSTEXXA plus placebo.

Concentrations of MTX-PGs were maintained during the treatment course for patients randomized to receive KRYSTEXXA plus methotrexate, suggesting compliance with methotrexate administration. In addition, MTX-PG concentrations were in the same range as those reported for low-dose oral methotrexate use in patients with rheumatoid arthritis, suggesting no impact of KRYSTEXXA on methotrexate pharmacokinetics.

Pharmacokinetics of Pegloticase and Methotrexate Polyglutamate(s) in Patients with Uncontrolled Gout Receiving Pegloticase and Co-treatment with Methotrexate (Poster View 8, POS1163)

About MIRROR Randomized Controlled Trial

The combination of KRYSTEXXA with an immunomodulator like methotrexate has increasingly been employed for 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[3,4] 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. The trial evaluated differences in treatment response for KRYSTEXXA plus methotrexate compared to KRYSTEXXA plus placebo. The primary endpoint was defined as the proportion of serum uric acid (sUA) responders defined as sUA <6 mg/dL at least 80% of the time during Month 6 (weeks 20 - 24). A total of 152 participants were randomized 2:1 to run-in and treatment periods with a low dose of 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 trial demonstrated a 32.5-percentage point improvement ($p<0.0001$) in treatment response rate, with 71.0% of patients (71 of 100) who were randomized to receive KRYSTEXXA plus methotrexate achieving a sustained urate-lowering response during Month 6, compared to 38.5% (20 of 52) of those randomized to receive KRYSTEXXA plus placebo.

About KRYSTEXXA

INDICATION 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 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 plus methotrexate for uncontrolled gout and Horizon's research and development plans and strategy. 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 or on what terms the FDA may approve Horizon's supplemental Biologic License Application related to the use of KRYSTEXXA with methotrexate, whether additional data from clinical trials or other analyses will be required or consistent with prior data or Horizon's expectations and risks related to the adoption of co-treatment of KRYSTEXXA plus 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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2. Strand V, Balsa A, Al-Saleh J, et al. *BioDrugs*. 2017;31:299-316.
3. Albert J, Hosey T, LaMoreaux B. Increased Efficacy and Tolerability of Pegloticase in Patients With Uncontrolled Gout Co-Treated With Methotrexate: A Retrospective Study. *Rheumatol Ther*. 2020;7(3):639-648. doi: 10.1007/s40744-020-00222-7.
4. Botson JK, Peterson J. Pretreatment and Coadministration With Methotrexate Improved Durability of Pegloticase Response: An Observational, Proof-of-Concept Case Series. *J Clin Rheumatol*. 2022 Jan 1;28(1):e129-e134. doi: 10.1097/RHU.0000000000001639.

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