Sustained Patient Response to KRYSTEXXA® (pegloticase) Injection with Methotrexate Compared to KRYSTEXXA Alone Shown through Month 12 in MIRROR Randomized Controlled Trial

November 8, 2022

-- Month 12 results from MIRROR randomized controlled trial to be featured on Nov. 13, 11:45 a.m. EST during plenary session at the American College of Rheumatology Convergence 2022 --

-- Imaging analyses visualize impact of KRYSTEXXA with methotrexate on reducing uric acid deposits in the joints, with a 95% mean reduction over 52 weeks, as well as reductions in vascular inflammation --

DUBLIN--(BUSINESS WIRE)--Nov. 8, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that Month 12 data from the MIRROR randomized controlled trial of KRYSTEXXA® (pegloticase) injection with methotrexate will be featured in Plenary I as part of the American College of Rheumatology Convergence 2022. Additional presentations include new imaging analyses describing the effects of urate-lowering therapy on joint health and vascular inflammation for people with chronic gout refractory to conventional therapies, also known as uncontrolled gout.

"These Month 12 data further validate the effectiveness of the co-treatment approach using KRYSTEXXA with methotrexate, reinforcing the data shown at six months of treatment and demonstrating the durability of the reduced immunogenicity and safety findings," said John K. Botson M.D., R.Ph., C.C.D., presenting author and president, Alaska Rheumatology Alliance and rheumatologist, Orthopedic Physicians Alaska. "Interestingly, the one-year data show higher resolution of tophi, indicating there may be continued therapeutic benefit for patients beyond six months of treatment."

Month 12 MIRROR randomized controlled trial results reinforce durable efficacy of co-treatment

This analysis extends the MIRROR randomized controlled trial body of data through Month 12 (Weeks 48-52) of treatment, showing a sustained patient response rate and similar safety profile to the Month 6 findings. Of patients randomized to receive KRYSTEXXA with methotrexate, 60% (60 of 100) achieved serum uric acid (sUA) level less than 6 mg/dL for at least 80% of of the time during Month 12 treatment versus 30.8% (16 of 52) for those randomized to receive KRYSTEXXA with placebo. Of patients with validated tophi at baseline, 53.8% (28 of 52) in the KRYSTEXXA with methotrexate group had complete resolution of at least one tophus, no new tophus and no single tophus showing progression at Week 52 compared with 31.0% (9 of 29) in the KRYSTEXXA with placebo group. Pharmacokinetic and immunogenicity findings through treatment Month 12 were consistent with Month 6 findings, indicating higher KRYSTEXXA exposure and lower KRYSTEXXA immunogenicity in those who received methotrexate co-therapy.

12-month Findings of the Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled GOut Receiving Pegloticase (MIRROR RCT)

Imaging studies demonstrate effect of aggressive urate-lowering therapy on urate deposits in the joints and vasculature

An imaging analysis from the MIRROR randomized controlled trial used dual-energy computed tomography (DECT) to visualize and quantify monosodium urate (MSU) crystal deposits, which are caused by elevated uric acid levels, in the hands, elbows, feet and knees of participating uncontrolled gout patients at specified timepoints throughout the 52-week treatment period. In total, eight participants were included in the imaging analysis (six received KRYSTEXXA with methotrexate and two received KRYSTEXXA with placebo). MSU volume had markedly decreased in both treatment groups at Week 52 (decrease of 93.8% across nine imaging regions in the KRYSTEXXA with methotrexate group, decrease of 95.7% across four regions in the KRYSTEXXA with placebo group). These volume reductions were comparable in different regions of the same patients and occurred similarly with sustained urate-lowering in both treatment groups.

Reduction in Monosodium Urate Crystal Deposit Volume During the MIRROR RCT Trial in Patients Treated with Pegloticase Plus Methotrexate Co-therapy: A Serial Dual-Energy Computed Tomography (DECT) Analysis

The Mount Sinai Hospital initiated a trial using DECT imaging and fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) to quantify the presence of MSU deposits in the vasculature of uncontrolled gout patients and correlate this to vascular inflammation to further understand (or identify) a possible link between uncontrolled gout and cardiovascular risk.

In this analysis, ten patients with uncontrolled gout were treated with co-therapy of an immunomodulator (azathioprine or methotrexate) and KRYSTEXXA every two weeks for up to six months. DECT and FDG-PET/CT scans were completed at baseline and after up to six months of treatment to detect vascular MSU deposition and arterial inflammation. The analysis found a statistically significant decrease in arterial inflammation after treatment [standard uptake value mean (p=0.0003) and SUV max (p=0.0090)] across all arteries studied and a trend toward a decrease in MSU volume.

Assessing Urate Deposition and Inflammation in the Vasculature of Gout Patients Using Dual Energy Computed Tomography and Positron Emission Tomography Pre and Post Pegloticase - a Pilot Study. Investigator-initiated trial

"Imaging is a powerful tool to better understand joint damage associated with gout and how aggressive urate-lowering therapy can substantially improve the gout burden," said Ada Kumar, M.D., medical director, Horizon. "With imagery also depicting a reduction in arterial inflammation, further evaluation may illustrate how rapidly reducing urate burden impacts not only the joints but also inflammation of the vasculature."

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 of reducing urate burden on the joints and vascular inflammation. 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

1. KRYSTEXXA (pegloticase) [prescribing information] Horizon.
2. Strand V, Balsa A, Al-Saleh J, et al. *BioDrugs*. 2017;31:299-316.
3. Botson J, Tesser JHR, Bennett R, et al. Pegloticase in Combination With Methotrexate in Patients With Uncontrolled Gout: A Multicenter, Open-label Study (MIRROR). *J Rheumatol.* 2021;48(5):767-774. doi: 10.3899/jrheum.200460.
4. 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.
5. 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.
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

View source version on businesswire.com: https://www.businesswire.com/news/home/20221108005040/en/

Investors:

Tina Ventura
Senior Vice President, Chief Investor Relations Officer
Investor-relations@horizontherapeutics.com

Erin Linnihan
Executive Director, Investor Relations
Investor-relations@horizontherapeutics.com

U.S. Media:

Amanda Phraner
Senior Director, Product Communications
media@horizontherapeutics.com

Ireland Media Contact:

Gordon MRM
Ray Gordon
ray@gordonmrm.ie

Source: Horizon Therapeutics plc