



Target Enrollment Reached in MIRROR Randomized Controlled Trial Evaluating KRYSTEXXA® (pegloticase injection) Co-Prescribed with Methotrexate as an Immunomodulator to Enhance Response Rates for People Living with Uncontrolled Gout

July 22, 2020

-- Randomized controlled trial will add to results from prior open-label trial and in-practice case series --

DUBLIN--(BUSINESS WIRE)--Jul. 22, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that the Company has reached target patient enrollment for its *Methotrexate to Increase Response Rates in Patients With Uncontrolled GOut Receiving KRYSTEXXA* [(MIRROR) randomized controlled trial (RCT)]. MIRROR RCT is the largest randomized trial to evaluate the efficacy and safety of the concomitant use of KRYSTEXXA® (pegloticase injection) with methotrexate as an immunomodulator to help more people with chronic gout refractory to conventional therapies – also known as uncontrolled gout – achieve a complete and durable response.

"Reducing the burden of urate is critical to improving overall outcomes and quality of life for our patients living with uncontrolled gout," said Jeff R. Peterson, M.D., president, Washington Rheumatology Alliance and a director at Northwest Rheumatism Society and Western Washington Medical Group Arthritis Clinic's clinical research department. "The MIRROR randomized controlled trial was designed based on data and in-practice experiences to date, which suggest that an immunomodulation strategy can attenuate the immune reaction that occurs with many biologics and increase the durability of response of KRYSTEXXA. I anticipate a treatment paradigm shift as more data becomes available for physicians to evaluate the use of immunomodulation with KRYSTEXXA for their patients with uncontrolled gout."

MIRROR RCT has reached its target enrollment of 135 patients; those currently in the screening process, if eligible once the screening is complete, will randomize. Based on recent screening activity, the final number of patients who randomize will likely slightly exceed the initial target. Patients are randomized to receive methotrexate or placebo for four weeks and then treatment with KRYSTEXXA and methotrexate or KRYSTEXXA and placebo for 52 weeks. The primary endpoint is the proportion of serum uric acid (sUA) responders defined as sUA < 6 mg/dL at least 80% of the time during Month 6. Safety will be assessed through Month 12. Preliminary results are expected in the first half of 2021.¹

KRYSTEXXA has traditionally been used as a monotherapy in patients with uncontrolled gout, however an accumulating body of evidence suggests that co-prescribing an immunomodulator such as methotrexate has the potential to increase the durability of response to KRYSTEXXA.²⁻⁶ The MIRROR RCT follows the MIRROR open-label trial ([NCT03635957](#)), which showed a 79 percent (11 of 14 patients) response rate (sUA < 6 mg/dL) at Month 6 when KRYSTEXXA was co-administered with methotrexate, an immunomodulator commonly prescribed by rheumatologists.² In addition, two independent, in-practice case series showed 80³ and 100 percent⁴ of patients (8 of 10 patients, 10 of 10 patients; respectively) received a full course of treatment with the concomitant use of KRYSTEXXA and methotrexate. No new safety concerns were identified in these studies, but the findings are limited by the small sample sizes. Details can be found [here](#) and [here](#). Additional data on the co-prescription of KRYSTEXXA with other commonly used immunomodulators, leflunomide and azathioprine, further support the immunomodulation approach and indicate potential flexibility in the choice of immunomodulator.^{5,6}

"The steady enrollment in this trial, especially through the challenges associated with the COVID-19 pandemic, illustrates physicians' enthusiasm for this therapeutic strategy to maximize the treatment for uncontrolled gout by mitigating the effects of anti-drug antibodies," said Paul M. Peloso, M.D., M.Sc., vice president and therapeutic area head, rheumatology, Horizon. "Aligned with the rheumatology community's experience of using immunomodulation with KRYSTEXXA, we believe the data from this trial will add to the growing body of evidence on emerging approaches to treat this challenging disease and better equip physicians to reduce the impact of uncontrolled gout on their patients' lives."

More information about the MIRROR RCT is available at [clinicaltrials.gov](#) ([NCT03994731](#)).

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 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 combining methotrexate treatment with KRYSTEXXA, expectations regarding the MIRROR RCT, including expected enrollment size and timelines, and expectations regarding physicians adopting a combination approach in treating patients with uncontrolled gout. 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 RTC will be consistent with results of prior trials or other data or Horizon's expectations, the risks associated with clinical development of drug candidates and risks related to competition or other factors that may change physician treatment strategies. 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. Botson J, Peloso PM, Obermeyer K, LaMoreaux B, Weinblatt ME, Peterson J. *Pegloticase response improvement by co-treatment with methotrexate: results from the MIRROR open-label clinical trial in patients with uncontrolled gout*. Poster presented at the European League Against Rheumatism (EULAR) European E-Congress of Rheumatology 2020 (EULAR E-Congress 2020), virtual; June 3-6, 2020.
3. Botson J, Peterson J. *Pretreatment and co-administration with methotrexate improved durability of pegloticase response: A prospective, observational, proof-of-concept, case series*. Poster presented at the European League Against Rheumatism (EULAR) Annual European of Rheumatology 2019, Barcelona, Spain; June 12-15, 2019.
4. Albert J, Hosey T, LaMoreaux B. *Pegloticase response rate in uncontrolled gout patients co-treated with methotrexate: experience in a community rheumatology practice*. Poster presented at the European League Against Rheumatism

(EULAR) European E-Congress of Rheumatology 2020 (EULAR E-Congress 2020), virtual; June 3-6, 2020.

5. Masri K, Winterling K. *Leflunomide co-therapy with pegloticase in uncontrolled gout*. Poster presented at the European League Against Rheumatism (EULAR) European E-Congress of Rheumatology 2020 (EULAR E-Congress 2020), virtual; June 3-6, 2020.
6. Rainey H, Bariff HSB, Yeo A., Lipsky P. *Companion Immunosuppression with Azathioprine Increases the frequency of Persistent Responsiveness to pegloticase in patients with chronic refractory gout*. Poster presented at the European League Against Rheumatism (EULAR) European E-Congress of Rheumatology 2020 (EULAR E-Congress 2020), virtual; June 3-6, 2020.

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Source: Horizon Therapeutics plc