



MIRROR Open-Label Trial Data Published in Journal of Rheumatology Show 79 Percent of Patients Achieved a Complete Response Using KRYSTEXXA® (pegloticase injection) with Methotrexate

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-- Data adds to growing body of evidence on immunomodulation with KRYSTEXXA and emerging approaches to reduce the impact of uncontrolled gout on patients' lives --

DUBLIN--(BUSINESS WIRE)--Sep. 16, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the publication of the complete dataset on the primary endpoint from its **Methotrexate to Increase Response Rates in Patients With Uncontrolled Gout Receiving KRYSTEXXA** (MIRROR) open-label trial in the *Journal of Rheumatology* [<https://doi.org/10.3899/jrheum.200460>].

Horizon's MIRROR clinical program includes the completed multi-center, open-label trial as well as an ongoing randomized controlled trial (RCT). The trial series seeks to validate clinical practice experience showing that adding commonly-used immunomodulatory therapies, such as methotrexate, to the KRYSTEXXA (pegloticase injection) treatment regimen for chronic gout refractory to conventional therapies – also known as uncontrolled gout – may help to reduce patients' immune reaction to biologic therapy and thus potentially increase the durability of response.

In the open-label trial, 79 percent of patients who received both KRYSTEXXA and methotrexate (11 of 14 enrolled patients) maintained therapeutic response during Month 6 (defined as sUA <6 mg/dL).¹ The safety and efficacy of KRYSTEXXA co-prescribed with methotrexate has not been established by any health authorities.

"Treatment with biologic medicines such as KRYSTEXXA can, in some people, trigger the body's immune system to develop anti-drug antibodies," said John R. P. Tesser, M.D., FACP, FACR, practicing rheumatologist and principal investigator at Arizona Arthritis & Rheumatology Associates in Phoenix. "When we look at rheumatoid arthritis, collective experience shows that many biologics have an improved response rate when they are co-prescribed with methotrexate. This is due both to methotrexate's direct effect on the disease and its ability to reduce anti-drug antibodies that may neutralize or clear the biologic. The co-prescription of KRYSTEXXA with methotrexate employs insights on how this immunomodulator may reduce the development of anti-drug antibodies and ultimately shift treatment approaches for uncontrolled gout."

In addition, the journal *Rheumatology and Therapy* recently published an independent, in-practice case series which showed that 80 percent (8 of 10 patients) received a full course of treatment with the concomitant use of KRYSTEXXA and methotrexate.² A [prospective observational case series](#) presented at EULAR 2019 showed 100 percent of patients (10 of 10 patients) received a full course of treatment with the concomitant use of KRYSTEXXA and methotrexate.³ No new safety concerns were identified in these studies, but the findings are limited by the study sizes.

"When used concomitantly, the trends we have seen in rheumatology practices are increasingly validated through this body of peer-reviewed data, giving more credence to an immunomodulation strategy and the paradigm shift we're seeing in treatment approaches," said Paul M. Peloso, M.D., M.Sc., vice president and therapeutic area head, rheumatology, Horizon. "Our goal through the ongoing MIRROR clinical program is to provide robust, controlled evidence to support clinicians as they seek to reduce the burden of urate and improve outcomes for patients living with uncontrolled gout."

As Horizon continues to evaluate its therapeutic approaches to help every patient achieve the best possible outcomes, the company recently announced that the MIRROR RCT has reached target enrollment. 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. Preliminary results are expected in the first half of 2021.⁴ More information about the MIRROR RCT is available at [clinicaltrials.gov \(NCT03994731\)](https://clinicaltrials.gov/ct2/show/study/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 immunomodulator (including methotrexate) treatment with KRYSTEXXA, expectations regarding the MIRROR RCT, including expected timelines for data, 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 RCT 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

1. 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*. 2020;jrheum.200460.
2. 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.
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. National Institute of Health. Study of KRYSTEXXA[®] (pegloticase) plus methotrexate in patients with uncontrolled gout (MIRROR RCT). <https://www.clinicaltrials.gov/ct2/show/NCT03994731>. Accessed Sept. 1, 2020.

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