



## MIRROR Open-Label Study Topline Data of Methotrexate with KRYSTEXXA (pegloticase injection) Indicates Significant Improvement in Response Rate

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-- Seventy-Nine Percent of Patients Achieved a Complete Response --

-- New Data Continues to Support Immunomodulation Strategy to Improve Patient Outcomes --

DUBLIN--(BUSINESS WIRE)--Jan. 13, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) announced today topline results from its MIRROR open-label study in which methotrexate with KRYSTEXXA® (pegloticase injection) provided an increased durability of response for people living with chronic gout refractory to conventional therapies – also known as uncontrolled gout.

Data from the *Methotrexate to Increase Response Rates in Patients With Uncontrolled GOut Receiving KRYSTEXXA (MIRROR\_OL)* shows that 79 percent, or 11 of 14 patients, achieved a complete response, defined as the proportion of serum uric acid (sUA) responders (sUA < 6 mg/dL) at Month 6. Detailed results from the study will be presented at a future medical meeting. The co-prescription of KRYSTEXXA and methotrexate is investigational and its safety and efficacy have not been established.

KRYSTEXXA has demonstrated rapid reduction in sUA levels for people with uncontrolled gout; however, treatment with biologic medicines can, in some, trigger the body's immune system to develop anti-drug antibodies. These anti-drug antibodies can reduce the effectiveness of the biologic therapy. Immunomodulators such as methotrexate, which is commonly used by rheumatologists, can help reduce this reaction.

The MIRROR open-label pilot study follows other studies that showed an improved response rate when KRYSTEXXA is co-administered with methotrexate. This includes an independent case series presented at the Annual European Congress of Rheumatology meeting in June 2019 in which the administration of KRYSTEXXA with methotrexate resulted in a 100 percent response (10 of 10 patients) as defined by greater than 80 percent of sUA levels being maintained at goal (<6.0 mg/dL) during the treatment period.<sup>1</sup> Further, a separate case series presented at the American College of Rheumatology meeting in November 2019 resulted in an 80 percent response (8 of 10 patients) as defined by receiving ≥12 infusions without loss of sUA response.<sup>2</sup>

"There is a growing body of data supporting the potential of KRYSTEXXA plus methotrexate rather than KRYSTEXXA therapy alone," said Paul Peloso, M.D., M.Sc., vice president and therapeutic area head, rheumatology, Horizon. "We continuously evaluate our therapies to ensure every patient can achieve the best possible outcomes. With a 79 percent response rate in combination with methotrexate, which is significantly higher than the 42 percent response rate in the KRYSTEXXA Phase 3 clinical program that evaluated KRYSTEXXA alone, more people living with uncontrolled gout may be able to benefit from a full course of therapy."

Horizon is currently conducting a separate, placebo-controlled MIRROR trial ([NCT03994731](#)) evaluating the use of KRYSTEXXA and methotrexate. The trial, with 135 randomized patients, is designed to enable the potential for submission of results to the U.S. Food and Drug Administration (FDA) for update to the label.

In addition, Horizon is planning to evaluate the impact of administering KRYSTEXXA over a shorter infusion duration. The initial proof-of-concept work will begin mid-2020. Currently, KRYSTEXXA is infused over a two-hour or longer timeframe. A shorter infusion duration could meaningfully improve the experience and convenience for patients, physicians and sites of care.

### 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](http://www.horizontherapeutics.com), follow us [@HorizonNews](#) on Twitter, like us on [Facebook](#) or explore career opportunities on [LinkedIn](#).

#### **Forward Looking Statements**

This press release contains forward-looking statements, including statements regarding the potential benefits of combining methotrexate treatment with KRYSTEXXA, timing and plans for future development efforts and potential regulatory submissions. 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 placebo-controlled MIRROR trial will be consistent with results of prior trials or Horizon's expectations, and the risks associated with clinical development of drug candidates. 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. Pretreatment and co-administration with methotrexate improved durability of pegloticase response: a prospective, observational, proof-of-concept, case series. [Poster presented at the 2019 Annual European Congress of Rheumatology \(EULAR\)](#), Madrid, Spain; June 12-15, 2019
2. Subcutaneous or oral methotrexate exposure and response to pegloticase in uncontrolled gout patients in a community rheumatology practice. [Poster presented at the 2019 Annual Scientific Meeting of the American College of Rheumatology \(ACR/ARP\)](#), Atlanta, GA, USA; November 8 – 13, 2019.

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