



Higher Response Rates in RECIPE Randomized Controlled Trial of KRYSTEXXA® (pegloticase injection) Concomitantly Used with the Immunomodulator Mycophenolate Mofetil

November 2, 2020

-- Primary study endpoint demonstrates 86 percent response rate for patients receiving co-therapy of KRYSTEXXA and mycophenolate mofetil --

-- RECIPE RCT results will be detailed during an oral presentation on Nov. 7 at 5:20 p.m. ET as part of the American College of Rheumatology Convergence 2020 --

-- Mycophenolate mofetil is one of several immunomodulators that, when used concomitantly with KRYSTEXXA, have shown an increase in response rates for people living with uncontrolled gout --

-- Horizon to host an online discussion with Puja Khanna, M.D., M.P.H., co-primary investigator for RECIPE, on Nov. 10 at 7 p.m. ET --

DUBLIN--(BUSINESS WIRE)--Nov. 2, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced data from the first randomized controlled clinical trial (RCT) of KRYSTEXXA (pegloticase injection) concomitantly used with an immunomodulator showed improved response rates as compared to KRYSTEXXA monotherapy. *Reducing Immunogenicity of Pegloticase (RECIPE)* demonstrated that 86.4 percent of patients (19 of 22) receiving co-therapy of KRYSTEXXA with the immunomodulator mycophenolate mofetil achieved serum uric acid (sUA) \leq 6 mg/dL through Month 3, the primary study endpoint, compared to 40.0 percent of patients (4 of 10) receiving KRYSTEXXA monotherapy. The data are being presented as part of the [American College of Rheumatology \(ACR\) Convergence 2020](#), Nov. 5 – 9, 2020.

While KRYSTEXXA has been traditionally used as a biologic monotherapy with a clinically demonstrated impact on chronic gout refractory to conventional therapies (uncontrolled gout), recent literature suggests that adding an immunomodulator has the potential to increase the durability of response to KRYSTEXXA.¹ The safety and efficacy of KRYSTEXXA co-prescribed with an immunomodulator has not been established by any health authorities.

“Given the significant physical disability and risks associated with gout, reducing the burden of urate is critical to improving overall patient outcomes and quality of life,” said Kenneth Saag, M.D., M.Sc., co-principal investigator for the RECIPE trial, Jane Knight Lowe Professor of Medicine and Director of the Division of Clinical Immunology and Rheumatology at the University of Alabama at Birmingham. “Working with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Horizon, the University of Michigan and leading clinical centers across the United States we were able to conduct the RECIPE randomized controlled trial and demonstrate that the co-treatment approach appears to deliver clinically meaningful results for people living with uncontrolled gout.”

Data from the double-blind, placebo-controlled RECIPE trial illustrate the effect of a co-treatment regimen of KRYSTEXXA with mycophenolate mofetil. In the study, 35 adult patients with uncontrolled gout were randomized (3:1) to receive either mycophenolate mofetil or placebo for two weeks prior to starting KRYSTEXXA (12 infusions of 8 mg every 2 weeks). Thirty-two patients participated in the trial, with three patients discontinuing prior to the first KRYSTEXXA infusion. During the trial, patients continued to receive either mycophenolate mofetil (1g) twice daily or placebo with KRYSTEXXA for 12 weeks. After Month 3, all patients received only KRYSTEXXA 8 mg IV every two weeks for 12 weeks, providing a full course of KRYSTEXXA therapy (through Month 6). The study evaluated the proportion of patients who reached and maintained response to therapy (defined as sUA levels less than 6 mg/dL over 12 weeks), as well as the safety of the regimen.

In total, 86.4 percent (19 of 22) of patients receiving co-therapy of KRYSTEXXA and mycophenolate mofetil achieved serum uric acid \leq 6 mg/dL at Month 3 versus 40.0 percent (4 of 10) of patients in the KRYSTEXXA and placebo arm, with a sustained response at Month 6 in 68.2 percent (15 of 22) of patients versus 30.0 percent (3 of 10) of patients, respectively. In the mycophenolate mofetil/KRYSTEXXA arm, no (0 of 22 patients) infusion reactions were reported compared to 30.0 percent (3 of 10) of patients reporting infusion reactions in the placebo/KRYSTEXXA arm. Additional adverse events reported for the mycophenolate mofetil/KRYSTEXXA arm versus the placebo/KRYSTEXXA arm include musculoskeletal (36.0 percent vs 10.0 percent), respiratory (18.0 percent vs 0 percent) and infections (9.0 percent vs 0 percent). These are consistent with the established safety of the therapies.² (*Reducing Immunogenicity of Pegloticase [RECIPE] with Concomitant Use of Mycophenolate Mofetil in Patients with Refractory Gout —A Phase 2 Double Blind Randomized Controlled Trial*[Abstract 0952](#))

“The significant improvement in maintaining the urate levels at Month 3 and sustained improvement through Month 6 of the RECIPE trial provide preliminary data to support the use of immunomodulation to help patients achieve a sustained response to urate lowering therapy,” said Puja Khanna, M.D., M.P.H., associate professor and rheumatologist at the University of Michigan, and co-primary investigator for the RECIPE trial. “Our data adds to the growing body of evidence on the concomitant use of KRYSTEXXA with an immunomodulator to ultimately help more patients receive a full course of therapy and improve outcomes. This approach will help shift the treatment paradigm in uncontrolled gout.”

Horizon will [host an online discussion on Nov. 10 at 7 p.m. ET](#) about KRYSTEXXA and immunomodulation, featuring Puja Khanna, M.D., M.P.H., co-primary investigator for RECIPE, and moderated by Brian LaMoreaux, M.D., M.S., Horizon medical director.

Additional Data Presentations at ACR

- Topline 12-month data from the prospective, open-label MIRROR trial showed 78.6 percent (11 of 14 patients) reached the

primary endpoint, responding to treatment at Month 6, and that eight of these patients continued KRYSTEXXA therapy with methotrexate and were responders at Month 12. In the trial, 14 patients received oral methotrexate (15 mg/week) and folic acid (1 mg/day) four weeks prior to the first KRYSTEXXA infusion and continued during the therapy period (8 mg every 2 weeks). The primary outcome was the proportion of responders during Month 6 (sUA <6 mg/dL for at least 80.0 percent of the time). The proportion of patients experiencing flares markedly and progressively decreased over time (flares in 13 of 14 patients in the first 12 weeks and in 2 of 8 patients in weeks 37-52). The co-therapy was well tolerated overall. No new serious adverse events occurred beyond Month 6; one serious adverse event of sepsis secondary to cholecystitis occurred in the first six months as previously reported. (*A Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving Pegloticase (MIRROR): 12-Month Results of an Open-Label Study* [Abstract 0677](#))

- Real-world trends of the concomitant use of KRYSTEXXA with either methotrexate or azathioprine indicate sustained growth of this treatment approach. From 2015 to 2018, the co-therapy rates of KRYSTEXXA and an immunomodulator were consistently low (1.2 percent–3.9 percent). In 2019, the frequency of use jumped to 15.0 percent and early 2020 data (Jan. to June) shows continued growth of this trend with 16.8 percent of uncontrolled gout patients treated concomitantly with KRYSTEXXA and an immunomodulator. (*Trends in Immunomodulation/pegloticase Co-therapy from 2015-2019: A Claims Database Study*, [Abstract 0665](#))

“Throughout recently presented case studies, community practice reports and now, controlled trials, we have seen a consistent pattern that the concomitant use of KRYSTEXXA with immunomodulators commonly used by clinicians can help optimize patient outcomes,” said Paul Peloso, M.D., M.Sc., vice president and therapeutic area head, rheumatology, Horizon. “In line with our efforts to deliver insights that can advance the quality of care, the data we’re presenting can help inform clinical decision making about the right approach to reach treatment goals for people with uncontrolled gout.”

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 mycophenolate mofetil) treatment with KRYSTEXXA and expectations regarding additional clinical trials and adoption of 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 additional clinical trials 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, Peterson J. Pretreatment and Coadministration With Methotrexate Improved Durability of Pegloticase Response. *JCR: Journal of Clinical Rheumatology*. 2020; Publish Ahead of Print. doi:10.1097/rhu.0000000000001639.
2. Official HCP Site for CellCept® (mycophenolate mofetil). Cellcept.com. <https://www.cellcept.com/hcp.html>. Published 2020. Accessed October 20, 2020.

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