Ultragenyx Announces Completion of Enrollment in Phase 3 Orbit and Cosmic Studies Evaluating Setrusumab (UX143) for the Treatment of Osteogenesis Imperfecta (OI)

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NOVATO, Calif., April 30, 2024 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced that all patients have been enrolled across the Phase 3 *Orbit* and *Cosmic* studies evaluating setrusumab (UX143) in pediatric and young adult patients with osteogenesis imperfecta (OI). The pivotal Phase 3 portion of the *Orbit* study has randomized 158 patients ages 5 to 25 years, and the *Cosmic* study has completed enrollment of 66 patients ages 2 to <7 years.

“We would like to thank the OI community for its support, trust and participation as we complete this important step in the advancement of the setrusumab program,” said Eric Crombez, M.D., chief medical officer at Ultragenyx. “The interim Phase 2 *Orbit* study results show a rapid and clinically meaningful decrease in fracture rate, giving us confidence in our ability to bring this potential new treatment to patients living with OI. Our goal is to provide patients and their families a novel treatment that can significantly reduce the burden of fractures and improve their quality of life by building new and stronger bone.”

“From a clinical perspective the important thing is that we are potentially closer to the goal of having a treatment for children - including very young children - with osteogenesis imperfecta,” stated Nick Bishop, Professor of Paediatric Bone Disease at University of Sheffield Medical School. “The interim Phase 2 results are very encouraging, and the speed with which we have been able to complete recruitment into both the *Orbit* and *Cosmic* studies clearly reflects the positive views of the study clinicians as a whole regarding this investigational therapy.”

Data presented at the American Society for Bone and Mineral Research 2023 Annual Meeting (ASBMR) from the Phase 2 portion of the *Orbit* study showed that treatment with setrusumab reduced the median annualized fracture rate by 67% and this reduction was associated with continuing large and meaningful improvements in bone mineral density (BMD). Setrusumab was generally well tolerated with no drug-related serious adverse events (SAEs) reported and no reports of drug-related hypersensitivity. Additional longer-term Phase 2 safety and efficacy data from the *Orbit* study are expected in the second half of 2024.

About the Setrusumab Phase 3 Program
Ultragenyx is developing setrusumab in pediatric and young adult patients across OI sub-types I, III and IV with two late-stage trials: the pivotal Phase 2/3 *Orbit* study and Phase 3 *Cosmic* study.

The global, seamless Phase 2/3 *Orbit* study is evaluating the effect of setrusumab on clinical fracture rate in patients aged 5 to 25 years. In the Phase 2 portion, 24 patients were randomized 1:1 to receive setrusumab at one of two doses to determine the optimal dosing strategy for Phase 3. The pivotal Phase 3 portion of the study has enrolled an additional 158 patients at 45 sites across 11 countries, with subjects randomized 2:1 to receive setrusumab or placebo, and a primary efficacy endpoint of annualized clinical fracture rate. All patients will transition to an extension period and receive open-label setrusumab after the Phase 3 primary analysis is complete.

The global Phase 3 *Cosmic* study is an open-label, randomized, active-controlled study in patients aged 2 to <7 years. Patients are randomized 1:1 to receive setrusumab or intravenous bisphosphonates (IV-BP) therapy to evaluate reduction in total fracture rate. The *Cosmic* study has enrolled 66 patients at 21 sites across 7 countries.

There are up to two planned interim analyses for the *Orbit* study, and the first is anticipated by year-end or early 2025 based on the timing of enrollment. The first analysis will have a stringent threshold of $p \leq 0.001$. If the threshold is not met, a second interim analysis will occur a few months after, followed by a final analysis at 18 months. Interim analyses will not be reported to the company by the data monitoring committee unless they are positive. In the event of a positive interim analysis, the patients will complete a final visit prior to transitioning to the open-label extension study and reporting of topline results.

About Osteogenesis Imperfecta (OI)
Osteogenesis Imperfecta (OI) includes a group of genetic disorders impacting bone metabolism. Approximately 85% to 90% of OI cases are caused by genetic variants in the *COL1A1* or *COL1A2* genes, leading to either reduced or abnormal collagen and changes in bone metabolism. The collagen mutations in OI can result in increased bone brittleness, which contributes to a high rate of fractures. Patients with OI also exhibit inadequate production of new bone and excess bone resorption, resulting in decreased bone mineral density, bone fragility and weakness. OI can also lead to bone deformities, abnormal spine curvature, pain, decreased mobility, and short stature. No treatments are globally approved for OI, which affects approximately 60,000 people in commercially accessible geographies.

About Setrusumab (UX143)
Setrusumab is a fully human monoclonal antibody that inhibits sclerostin, a negative regulator of bone formation. Blocking sclerostin is expected to increase new bone formation, bone mineral density and bone strength in OI. In mouse models of OI, the use of anti-sclerostin antibodies was shown to increase bone formation, improve bone mass to normal levels, and increase bone strength against fracture force testing to normal levels.

In 2019 Mereo BioPharma completed the Phase 2b dose-finding study (*ASTEROID*) for setrusumab in 112 adults with OI. The *ASTEROID* study demonstrated treatment with setrusumab resulted in a clear, dose-dependent and statistically significant effect on bone formation and bone density at multiple anatomical sites among adult participants with OI.

Ultragenyx and Mereo BioPharma are collaborating on the development of setrusumab globally based on the collaboration and license agreement between the parties. The companies have developed a comprehensive late-stage program to continue development of setrusumab in pediatric and young adult patients across OI sub-types I, III and IV.

About Ultragenyx Pharmaceutical Inc.
Ultragenyx is a biopharmaceutical company committed to bringing novel products to patients for the treatment of serious rare and ultrarare genetic diseases. The company has built a diverse portfolio of approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, for which there are typically no approved therapies treating the underlying disease.

The company is led by a management team experienced in the development and commercialization of rare disease therapeutics. Ultragenyx's strategy is predicated upon time- and cost-efficient drug development, with the goal of delivering safe and effective therapies to patients with the utmost urgency.

For more information on Ultragenyx, please visit the company's website at: www.ultragenyx.com.

Ultragenyx Forward-Looking Statements and Use of Digital Media
Except for the historical information contained herein, the matters set forth in this press release, including statements related to Ultragenyx's expectations and projections regarding its future operating results and financial performance, business plans and objectives for UX143, expectations regarding the tolerability and safety of UX143, and future clinical and regulatory developments for UX143 are forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements involve substantial risks and uncertainties that could cause our clinical development programs, collaboration with third parties, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainty of clinical drug development and unpredictability and lengthy process for obtaining regulatory approvals, the ability of the company and Mereo BioPharma to successfully develop UX143, the company's ability to achieve its projected development goals in its expected timeframes, risks related to adverse side effects, risks related to reliance on third party partners to conduct certain activities on the company's behalf, the potential for any license or collaboration agreement, including the company's collaboration agreement with Mereo to be terminated, smaller than anticipated market opportunities for the company's products and product candidates, manufacturing risks, competition from other therapies or products, and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the company's future operating results and financial performance, the timing of clinical trial activities and reporting results from same, and the availability or commercial potential of Ultragenyx's products and drug candidates. Ultragenyx undertakes no obligation to update or revise any forward-looking statements.

For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of Ultragenyx in general, see Ultragenyx's Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 21, 2024, and its subsequent periodic reports filed with the SEC.

In addition to its SEC filings, press releases and public conference calls, Ultragenyx uses its investor relations website and social media outlets to publish important information about the company, including information that may be deemed material to investors, and to comply with its disclosure obligations under Regulation FD. Financial and other information about Ultragenyx is routinely posted and is accessible on Ultragenyx's Investor Relations website (https://ir.ultragenyx.com/) and LinkedIn website (https://www.linkedin.com/company/ultragenyx-pharmaceutical-inc-/).

Contacts

Investors
Joshua Higa
+1-415-475-6370
ir@ultragenyx.com

Media
Carolyn Wang
+1-415-225-5050
media@ultragenyx.com