Ultragenyx Announces Phase 3 Orbit and Cosmic Results for Setrusumab (UX143) in Osteogenesis Imperfecta

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Neither study achieved its primary endpoint of reduction in annualized clinical fracture rate compared to placebo (Orbit) or bisphosphonates (Cosmic)

Both studies achieved the secondary endpoint of improvements in bone mineral density with strong statistical significance

The Company will implement significant expense reductions

NOVATO, Calif., Dec. 29, 2025 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced results from the Phase 3 Orbit and Cosmic studies for setrusumab (UX143) in Osteogenesis Imperfecta (OI). Neither study achieved statistical significance against the primary endpoints of reduction in annualized clinical fracture rate compared to placebo or bisphosphonates, respectively. Both studies achieved the secondary endpoints of improvements in bone mineral density (BMD) against comparators. There was no change in the safety profile observed.

“We are surprised and disappointed by these results given the promising data from our Phase 2 study and the lack of approved treatment options available to patients with OI who live with significant pain, disability, and disease burden,” said Emil Kakkis, M.D., Ph.D., chief executive officer and president of Ultragenyx. “We continue to explore the data to gain deeper understanding of the findings.”

Orbit and Cosmic Results
In the Orbit study, participants experienced statistically significant and substantial improvements in BMD compared to placebo, at levels consistent with the treatment effect observed in the Phase 2 portion of the study. These BMD changes were not accompanied by a corresponding reduction in annualized fracture rates and there was a low fracture rate in the placebo group.

In the pediatric Cosmic study, patients had a substantially higher baseline fracture rate compared to the patients enrolled in Orbit. In this younger patient population, meaningful improvements in BMD were associated with a reduction in annualized fracture rate for setrusumab treated patients compared to bisphosphonate treated patients, though the reduction did not meet statistical significance.

Ultragenyx is conducting additional analyses on the data across both studies, including on other bone health and clinical endpoints beyond fractures, to assess next steps for the program given the totality of these data.

The Company will implement expense reductions
Ultragenyx is evaluating its planned operations and will promptly define and implement significant expense reductions.

Dr. Kakkis continued: “While we are disappointed by these results, we continue to build our commercial revenue from four approved products and prepare for a transformational year ahead with potentially two near-term gene therapy launches and a pivotal Phase 3 readout in Angelman syndrome.”

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 studies: 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. The pivotal Phase 3 portion of the study enrolled 159 patients at 45 sites across 11 countries, with participants randomized 2:1 to receive setrusumab or placebo, and a primary efficacy endpoint of annualized clinical fracture rate.

The global Phase 3 Cosmic study evaluated the effect of setrusumab on reduction in annualized fracture rate in patients aged 2 to <7 years compared to bisphosphonates. The Cosmic study enrolled 69 patients at 21 sites across 7 countries with patients randomized 1:1 to receive setrusumab or intravenous bisphosphonates (IV-BP) therapy.

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.

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 Ultragenyx
Ultragenyx is a biopharmaceutical company committed to bringing novel products to patients for the treatment of serious rare and ultra-rare 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.

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, including the company's plans to define and implement expense reductions, business plans and objectives for UX143, expectations regarding the tolerability and safety of UX143, and future clinical and regulatory developments for UX143, including next steps for the UX143 program, 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 risk that fast track or breakthrough designations by the FDA may not lead to faster development or regulatory review or approval process and does not increase the likelihood that UX143 will receive marketing approval, 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 Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 5, 2025, 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-/).

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