Ultragenyx Receives European Commission Decision for Evkeeza® (evinacumab) Expanded Indication in Children Aged 5 Years and Older with Homozygous Familial Hypercholesterolemia (HoFH)

December 18, 2023 1:00 PM EST

For the first time, paediatric patients aged 5-11 years with HoFH in the EU have access to a first-in-class medicine to treat an ultrarare, inherited form of high cholesterol

NOVATO, Calif., Dec. 18, 2023 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced that the European Commission (EC) has extended the approval of Evkeeza® (evinacumab) as an adjunct to diet and other lipid-lowering therapies to treat children aged 5 to 11 years with homozygous familial hypercholesterolemia (HoFH). Evkeeza is the first angiopoietin-like 3 (ANGPTL3) inhibitor treatment indicated for children as young as 5 years old to control dangerously high levels of low-density lipoprotein cholesterol (LDL-C) caused by HoFH. Evkeeza initially received EC decision as an adjunct to diet and other lipid-lowering therapies in adolescents and adults aged 12 years and older with HoFH in June 2021.

“This approval heralds a new era for treatment of children 5 to 11 years of age with HoFH,” stated Albert Wiegman, M.D., Ph.D. and Professor, Department of Paediatrics at Amsterdam University Medical Center. “The addition of Evkeeza to aggressive baseline lipid-lowering therapy nearly halves LDL-C levels in a disorder with an extremely high risk of premature cardiovascular disease in young patients, where achieving LDL-C goals otherwise isn’t possible."

This EC decision follows the positive recommendation from the Committee for Medicinal Products for Human Use received in November 2023 and is based on the results of a Phase 3 open-label study in patients ages 5-11 years with HoFH.[1] Despite treatment with other lipid-lowering therapies, children entered the Phase 3 trial with an average LDL-C level of 264 mg/dL, more than twice the target (<110 mg/dL) for paediatric patients with HoFH. With the addition of Evkeeza, children (n=14) were able to reduce their LDL-C by 48% at week 24 on average. Significant reductions were also observed in other key secondary endpoints including levels of apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C) and total cholesterol. The safety profile of Evkeeza was consistent with the safety profile observed in adults and paediatric patients aged 12 years and older, with the additional adverse reaction of fatigue (reported in 3 patients).

“It is with immense joy that the international community of parents and caregivers of children with HoFH welcomes this approval, because this is a potentially life-changing therapy for the children and their parents affected by this rare and severe disorder,” stated Magdalena Daccord, chief executive officer of FH Europe. “As we advocate for childhood screening and detection to help improve early HoFH diagnosis, it is key to be able to offer to young patients appropriate and innovative treatment solutions along with lifestyle management. That said, it will be a true success once this therapy option is available to all those who need it as soon as they need it to support their treatment goals.”

Evkeeza is delivered via 60-minute intravenous infusion once monthly (every 4 weeks). The treatment is now reimbursed and commercially available to prescribe for appropriate patients with HoFH in the U.S., Canada, Italy and Germany. It is also available via early access schemes in Austria and France.

"It is critical to reduce LDL levels as early as possible for all people living with HoFH especially given that children as young as 5 years of age are at risk for severe cardiac events that can be life threatening,”[2] said Eric Crombez, M.D., chief medical officer at Ultragenyx. “With its novel mechanism, Evkeeza combined with other lipid-lowering therapies has demonstrated the ability to significantly reduce LDL cholesterol levels beyond historical standard of care, which could have a transformational impact for these younger patients.”

[1] *Wiegman A. Evinacumab for Pediatric Patients With Homozygous Familial Hypercholesterolemia. Circulation. 2023. https://doi.org/10.1161/CIRCULATIONAHA.123.065529.*

[2] *Widhalm K et al. Sudden death in a 4-year-old boy: a near-complete occlusion of the coronary artery caused by an aggressive low-density lipoprotein receptor mutation (W556R) in homozygous familial hypercholesterolemia. J Pediatr 2011;158:167*

About the Pivotal Paediatric Trial

The three-part, single-arm, open-label trial evaluated Evkeeza added to other lipid-lowering therapies in paediatric patients with HoFH aged 5 to 11 years. Part A (n=6) was a Phase 1b trial designed to assess the pharmacokinetics (PK), safety and tolerability of Evkeeza. Part B (n=14) evaluated the efficacy of Evkeeza during a 24-week treatment period and enrolled patients with an average age of 9 years. Among them, 86% were on statins, 93% were on ezetimibe, 50% were on LDL apheresis and 14% were on lomitapide. Patients received Evkeeza 15 mg/kg every four weeks delivered intravenously in addition to their baseline lipid-lowering treatment regimen. The primary endpoint was change in LDL-C at week 24. Secondary endpoints included the effect of Evkeeza on other lipid parameters (i.e., apolipoprotein B, non-high-density lipoprotein cholesterol, lipoprotein[a] and total cholesterol), efficacy by mutation status, safety and tolerability, immunogenicity and PK. Patients who completed Part A or B were allowed to, and all did, continue treatment in Part C (n=20), a completed Phase 3 extension trial. This trial was not designed to evaluate the effect of Evkeeza on cardiovascular events.

Evkeeza was well tolerated in this patient population. The most common adverse events (AEs) occurring in >15% of patients were COVID-19 (n=15), pyrexia (n=5), headache (n=4), throat pain (oropharyngeal pain, n=4) as well as upper abdominal pain, diarrhea, vomiting, fatigue, nasopharyngitis, rhinitis and cough (all n=3). Most reported AEs were mild or moderate, and none led to study discontinuation.

About Homozygous Familial Hypercholesterolemia (HoFH)

HoFH is a devastating form of inherited hypercholesterolemia, affecting 1 in 300,000 people globally and approximately 1,600 people in the European

Union. HoFH occurs when two copies of the familial hypercholesterolemia (FH)-causing genes are inherited, one from each parent, resulting in dangerously high levels (>400 mg/dL) of LDL-C, or bad cholesterol. Patients with HoFH are at risk for premature atherosclerotic disease and cardiac events at an early age.

About Evkeeza® (evinacumab)

Evinacumab, the active substance in Evkeeza, attaches to a protein in the body called ANGPTL3 and blocks its effects. ANGPTL3 is involved in controlling cholesterol levels and blocking its effect reduces the level of cholesterol in the blood. Evkeeza is delivered via an infusion every month (4 weeks).

Evkeeza is approved by the European Commission (EC) as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of paediatric patients aged 5 years and older with homozygous familial hypercholesterolemia (HoFH). The effects of Evkeeza on cardiovascular morbidity and mortality have not been determined. Regeneron Pharmaceuticals, Inc. discovered and developed Evkeeza, and commercializes the product in HoFH in the U.S. under the generic name evinacumab-dgnb, with dgnb as the suffix designated in accordance with Nonproprietary Naming of Biological Products Guidance for Industry issued by the FDA. Ultragenyx is responsible for commercialization efforts for Evkeeza in countries outside of the U.S.

IMPORTANT SAFETY INFORMATION FOR EVKEEZA (evinacumab)

The most common side effects may include symptoms of the common cold, such as runny nose (nasopharyngitis) and for children aged 5 to 11 years feeling tired (fatigue). Evkeeza can cause serious allergic reactions. Tell your doctor or nurse immediately if you get any symptoms of a severe allergic reaction: swelling – mainly of the lips, tongue or throat, which makes it difficult to swallow or breathe, breathing problems or wheezing, feeling dizzy or fainting, rash, hives, itching. The drip will be stopped immediately and you may need to take other medicines to control the reaction.

Who should not use EVKEEZA?

You should not be given Evkeeza if you are allergic to evinacumab or any of the other ingredients of this medicine. Evkeeza is not recommended for children below the age of 5 because there is not yet enough information on its use in this group of patients.

Tell your doctor if you are taking, have recently taken or might take any other medicines.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Evkeeza may harm your unborn baby. Tell your doctor immediately if you become pregnant while you are being treated with Evkeeza. If you are able to become pregnant, you should use effective contraception to avoid becoming pregnant. Use effective contraception while you are being treated with Evkeeza and use effective contraception for at least 5 months after the last dose of Evkeeza. Talk to your doctor about the best contraception method for you during this time.

If you are breast-feeding or plan to breast-feed, ask your doctor for advice before you are given this medicine. It is not known if Evkeeza passes into the breast milk.

If you get any side effects, talk to your doctor or nurse. By reporting side effects you can help provide more information on the safety of this medicine.

Please see full product information, including Summary of Product Characteristics and Package Leaflet: Information for the patient.

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, anticipated cost or expense reductions, the timing, progress and plans for its clinical programs and clinical studies, future regulatory interactions, and the components and timing of regulatory submissions 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 the Company's clinical development programs, commercial success of its products and product candidates, continued 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, 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 Ultragenyx's collaboration agreement with Regeneron to commercialize Evkeeza outside of the United States, to be terminated; uncertainty and potential delays related to clinical drug development; uncertainties and unpredictability of obtaining regulatory approval for the Company's product candidates and the scope of such potential regulatory approval; smaller than anticipated market opportunities for the Company's products and product candidates; fluctuations in buying or distribution patterns by distributors and specialty pharmacies; competition to the Company's products and product candidates; potential undesirable or serious side effects from the Company's products or product candidates; the Company's ability to effectively manage the expansion of its commercial organization; market acceptance of the Company's current or future products; uncertainties related to insurance coverage and reimbursement status of newly approved products; manufacturing risks and supply chain disruptions; 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 product 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 3, 2023, 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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