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31 March 2026

Efzimfotase alfa demonstrated positive results from global Phase III clinical programme in hypophosphatasia

MULBERRY randomised, placebo-controlled trial showed efzimfotase alfa demonstrated statistically significant and clinically meaningful improvement in bone health in treatment-na•ve paediatric patients

CHESTNUT randomised, open-label, active-controlled trial demonstrated safety and tolerability of efzimfotase alfa in paediatric patients previously treated with Strensiq with maintenance of therapeutic benefit

HICKORY randomised, placebo-controlled trial showed numerical improvement but did not achieve statistical significance in the primary endpoint in treatment-na•ve adolescents and adults; results indicate clinically meaningful benefit in a combination of prespecified subgroups of adolescents and adults with paediatric-onset HPP

The efzimfotase alfa (ALXN1850) Phase III clinical programme, designed to study a broad hypophosphatasia (HPP) patient population, demonstrated positive results. The global clinical programme, which included two randomised, placebo-controlled trials and one randomised, open-label, active-controlled paediatric switch trial, enrolled 196 patients spanning children, adolescents and adults with either paediatric-onset or adult-onset HPP across 22 countries.

Addressing unmet needs for people living with HPP
Efzimfotase alfa is an investigational enzyme replacement therapy designed to offer lower injection volume, less frequent dosing over *Strensiq* (asfotase alfa) and close critical gaps in care within the broader HPP patient population.

Paediatric clinical trials
The MULBERRY Phase III trial in children (2 to <12 years of age) with HPP who have not been previously treated with *Strensiq,* showed that efzimfotase alfa met its primary endpoint. Results demonstrated a statistically significant and clinically meaningful improvement in bone health from baseline compared to placebo, as measured by Radiographic Global Impression of Change (RGI-C) Score at week 25. In addition, statistically significant improvement was observed in the key secondary endpoint of change from baseline in Rickets Severity Score (RSS) at week 25. Additional secondary endpoints measuring physical function (Six-Minute Walk Test) and motor proficiency (Paediatric Outcomes Data Collection Instrument or PODCI) further supported the overall clinical benefit of efzimfotase alfa in the paediatric population.

Positive high-level results from the CHESTNUT Phase III trial showed that efzimfotase alfa was well-tolerated and demonstrated a favourable safety profile in paediatric patients (2 to <12 years of age) switching from *Strensiq* and maintained the treatment benefit of *Strensiq* on bone health at week 25, as measured by secondary endpoints RGI-C and RSS.

Adolescent and adult clinical trial
In the HICKORY Phase III trial, efzimfotase alfa showed numerical improvement but did not achieve statistical significance in the primary endpoint of Six-Minute Walk Test (6MWT) in adolescents and adults (12 years of age and older) with HPP who have not been previously treated with *Strensiq*, compared to placebo at week 25. This was largely due to better-than-expected results observed in the adult-onset HPP placebo group. However, treatment with efzimfotase alfa demonstrated nominally significant improvements in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) in the overall study population.

In a combination of prespecified subgroups of adolescents and adults with paediatric-onset HPP, efzimfotase alfa showed nominally statistically significant and clinically meaningful benefits in mobility,

as measured by 6MWT, as well as key secondary endpoints measuring physical function and pain reduction, compared to placebo.

Initial findings from the ongoing, long-term, open-label extension of the HICKORY trial show continued improvement in the primary and key secondary endpoints at week 48. Participants who switched from placebo to efzimfotase alfa after the randomised period also showed clinically meaningful improvements across multiple efficacy outcomes after 24 weeks of treatment.

Efzimfotase alfa was well-tolerated and had an acceptable safety profile across the MULBERRY, CHESTNUT and HICKORY clinical trials.

Eric Rush, MD, Clinical Geneticist, ChildrenÕs Mercy Hospital Kansas, Professor of Paediatrics, University of Missouri-Kansas City School of Medicine and lead principal investigator in the MULBERRY trial, said: ÒThe results from the global MULBERRY clinical trial demonstrate efzimfotase alfaÕs potential to address the underlying pathophysiology of HPP and to prevent and reverse the substantial skeletal and functional impacts of this lifelong rare disease. I am encouraged by these results and the potential for this innovative, investigational therapy to redefine care in HPP with a convenient self-administered option taken every two weeks.Ó

Kathryn Dahir, MD, Director of the Programme for Metabolic Bone Disorders at Vanderbilt Health and Associate Director for Clinical Research Translation, Professor in the Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism and lead investigator in the HICKORY trial, said: ÒFindings from the broad HICKORY registrational trial, the first to include patients with adult-onset disease, highlight the heterogeneity of the disease and the value of assessing a range of clinically meaningful endpoints across diverse patient populations. The results indicate a clinically relevant impact on mobility, physical function, pain and fatigue, demonstrating the potential for efzimfotase alfa to improve outcomes for patients living with this disease.Ó

Marc Dunoyer, Chief Executive Officer, Alexion, AstraZeneca Rare Disease, said: ÒThe efzimfotase alfa clinical programme, comprised of three global Phase III trials, was the first to include patients with both paediatric- and adult-onset HPP with heterogeneous manifestations beyond bone. We are encouraged by the improvements observed across this patient population who exhibit a wide range of severity and clinical characteristics. Collectively, these results support the potential for efzimfotase alfa to transform the treatment paradigm for people living with this rare disease.Ó

These data will be presented at a forthcoming medical meeting and shared with global regulatory authorities.

Notes

Hypophosphatasia
Hypophosphatasia (HPP) is a rare, chronic, inherited metabolic disease caused by deficient activity of the enzyme alkaline phosphatase (ALP), which is important for building healthy bones and supporting proper muscle function.[1] HPP is characterised by defective mineralisation (the process that hardens and strengthens bones and teeth), impaired calcium and phosphate regulation and functional impairments, such as muscle weakness, neurologic symptoms, generalised fatigue and pain that can be debilitating.[1,2] HPP can be progressive and clinical manifestations may evolve over time. While diagnosis rates vary by geography, there are an estimated 11,500 people diagnosed with HPP across the US, Germany, France, UK, Italy, Spain, Japan and China.[3-6] A recent study from the US estimated diagnosed prevalence at 2.8 per 100,000 people.[7] HPP affects people of all ages, with approximately 80% of people living with HPP being adults.[1,2,7]

MULBERRY
MULBERRY is a global Phase III randomised, double-blind, placebo-controlled, multicentre trial evaluating the efficacy and safety of efzimfotase alfa (ALXN1850) in paediatric patients (2 to <12 years of age) with hypophosphatasia (HPP) who have not been previously treated with *Strensiq* (asfotase alfa). The trial enrolled 29 patients from 14 countries across North America, South America, Europe and Asia.[8]

Patients were required to have an HPP diagnosis and the presence of HPP-related rickets on skeletal X-rays and low serum alkaline phosphatase (ALP) activity. Eligible patients also needed to demonstrate either a variant in *ALPL*, the gene encoding ALP, or elevated levels of plasma pyridoxal 5'-phosphate (PLP), a biomarker of HPP.[8]

Patients were randomised 2:1 to receive efzimfotase alfa at one of three doses based on predefined weight ranges or placebo, once every two weeks via subcutaneous injection for 24 weeks. The primary endpoint Radiographic Global Impression of Change (RGI-C) Score was assessed at the end of the randomised evaluation period (Day 169), along with multiple secondary endpoints measuring skeletal health and physical function, including change from baseline in the Rickets Severity Score (RSS), Six-Minute Walk Test (6MWT), Bruininks-Oseretsky Test of Motor Proficiency Score (BOT-2) and Peabody Developmental Motor Scales Score (PDMS-3).[8]

Patients who completed the randomised evaluation period were eligible to continue into an open-label extension period evaluating the safety and efficacy of efzimfotase alfa, which is ongoing.[8]

CHESTNUT
CHESTNUT is a global Phase III randomised, open-label, active-controlled, multicentre trial evaluating the safety and tolerability of efzimfotase alfa in paediatric patients (2 to <12 years of age) with hypophosphatasia (HPP) who have been treated with 6 mg/kg per week of *Strensiq* (asfotase alfa) for at least 6 months prior to study initiation. The trial enrolled 43 patients from seven countries globally.[9]

Patients were required to have an HPP diagnosis and have been treated with *Strensiq* for at least 6 months before the start of the trial with open growth plates confirmed by X-ray.[9]

Patients were randomised 1:1 to receive efzimfotase alfa at one of three doses based on predefined weight ranges once every two weeks or 6 mg/kg/week of *Strensiq* via 3x or 6x subcutaneous injections per week for 24 weeks. The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs) at the end of the randomised evaluation period. Key secondary endpoints include change from baseline in the Rickets Severity Score (RSS) and Radiographic Global Impression of Change (RGI-C).[9]

Patients who completed the randomised evaluation period were eligible to continue into an open-label extension period evaluating the safety and efficacy of efzimfotase alfa, which is ongoing.[9]

HICKORY
HICKORY is a global Phase III randomised, double-blind, placebo-controlled, multicentre trial evaluating the efficacy and safety of efzimfotase alfa (ALXN1850) in adolescents (12 to <18 years of age) and adults with hypophosphatasia (HPP) who have not been previously treated with *Strensiq* (asfotase alfa). The trial enrolled 124 patients from 17 countries across North America, South America, Europe, Asia and Australia.[10]

Patients were required to have a HPP diagnosis and either a variant in *ALPL*, the gene encoding alkaline phosphatase (ALP), or elevated levels of plasma pyridoxal 5'-phosphate (PLP), a biomarker of HPP. Eligible patients needed to demonstrate low ALP levels and two separate Six-Minute Walk Tests (6MWTs) at or below 85% of the predicted distance adjusted for age, sex, weight and height, without a probable cause other than HPP.[10]

Patients were randomised 2:1 to receive efzimfotase alfa at one of three doses based on predefined weight ranges or placebo, once every two weeks via subcutaneous injection for 24 weeks. The primary endpoint of change from baseline in 6MWT was assessed at the end of the randomised evaluation period (Day 169), along with multiple key secondary endpoints measuring physical function, pain, fatigue, quality of life and safety, including change from baseline in 30-second Sit to Stand (STS) Test Score, Lower Extremity Functional Scale (LEFS) Score, Brief Pain Inventory Short Form (BPI-SF) Score and Functional Assessment of Chronic Illness Therapy Ð Fatigue (FACIT-Fatigue) Score.[10]

Patients who completed the randomised evaluation period were eligible to continue into an open-label extension period evaluating the safety and efficacy of efzimfotase alfa, which is ongoing.[10]

Efzimfotase alfa (ALXN1850)

Efzimfotase alfa (ALXN1850) is an investigational enzyme replacement therapy (ERT) designed to demonstrate efficacy and safety in a broad range of patients with hypophosphatasia (HPP) aged ³2 years, including patients without overt bone manifestations. Efzimfotase alfa is being developed as a subcutaneous treatment administered every two weeks to replace the deficient alkaline phosphatase (ALP) enzyme activity that is the underlying cause of HPP.

Alexion
Alexion, AstraZeneca Rare Disease, is focused on serving patients and families affected by rare diseases and devastating conditions through the discovery, development and delivery of life-changing medicines. A pioneering leader in rare disease for more than three decades, Alexion was the first to translate the complex biology of the complement system into transformative medicines, and today it continues to build a diversified pipeline across disease areas with significant unmet need, using an array of innovative modalities. As part of AstraZeneca, Alexion is continually expanding its global geographic footprint to serve more rare disease patients around the world. It is headquartered in Boston, US.

AstraZeneca
AstraZeneca (LSE/STO/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZenecaÕs innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on social media @AstraZeneca.

Contacts
For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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This announcement contains information that AstraZeneca PLC is obliged to make public pursuant to the EU Market Abuse Regulation (596/2014) and the assimilated EU Market Abuse Regulation (596/2014) as it forms part of the law of the United Kingdom by operation of the European Union (Withdrawal) Act 2018. This announcement was submitted for publication, through the agency of the contact person(s) set out above, at 7:00 BST on 31 March 2026.