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Update on Phase III trial of *Ultomiris* in adults and adolescents with thrombotic microangiopathy after haematopoietic stem cell transplant

High-level results from the ALXN1210-TMA-313 Phase III clinical trial showed that *Ultomiris* (ravulizumab) did not achieve statistical significance for the primary endpoint of event-free survival through 26 weeks compared to placebo in adults and adolescents (aged 12 years or older) with thrombotic microangiopathy after haematopoietic stem cell transplant (HSCT-TMA). The primary endpoint was defined as the time from randomisation until TMA-related clinical worsening or death, whichever occurred first.

In paediatric patients with HSCT-TMA, the ALXN1210-TMA-314 open-label Phase III trial of *Ultomiris* demonstrated clinically meaningful overall survival of 87.2% at 26 weeks and 73.4% at 52 weeks, as previously disclosed.[1,2] Alexion, AstraZeneca Rare Disease is advancing regulatory filings for *Ultomiris* in paediatric patients with HSCT-TMA, based on these results and data from ALX-TMA-502, an external control study, which further supports clinically meaningful benefit on overall survival.[1-3]

Ultomiris showed a trend toward treatment benefit in adults and adolescents with HSCT-TMA at 26 weeks compared to placebo. Discussions with health authorities are ongoing regarding the interpretation of these data, including in the context of real-world evidence.[3]

Following HSCT, a procedure used with increasing frequency to treat some types of cancers and other diseases, the devastating and potentially life-threatening complication of TMA may occur.[4,5] TMA can result in blood clots and damage to the walls of the smallest blood vessels in the circulatory system, which may lead to organ failure and death.[6] HSCT-TMA is estimated to affect fewer than 6,000 people in the US.[7]

Christopher Dvorak, MD, Professor and Chief of the Division of Pediatric Allergy, Immunology and Bone Marrow Transplantation at UCSF Benioff Children's Hospitals, said: "Children who develop HSCT-TMA have an extremely poor prognosis without targeted treatment. While the scientific understanding of this condition continues to evolve, survival remains a critical measure of clinical benefit. The overall survival results observed in this Phase III paediatric trial are clinically meaningful for this young patient population with significant unmet need and may lead to a targeted treatment option for children facing this serious, post-transplant complication."

Vincent Ho, MD, Director of Clinical Operations, Adult Hematopoietic Stem Cell Transplantation and Institute Physician at Dana-Farber Cancer Institute, Professor of Medicine at Harvard Medical School, said: "HSCT-TMA is a serious complication after stem cell transplant with high rates of associated morbidity and mortality and for which effective therapy remains an area of great unmet need. Conducting a global, randomised trial in this complex, life-threatening, post-transplant condition is exceedingly difficult. While the Phase III trial in adults and adolescents did not meet the primary endpoint, the results add new, important insights to advance the field. Continued evaluation of these data together with results collected from recent, real-world experience will further advance clinical understanding and treatment of this complex transplant complication."

Marc Dunoyer, Chief Executive Officer, Alexion, said: "As the largest, global registrational programme conducted across a broad population of patients with HSCT-TMA and the only placebo-controlled trial in this adult population, these trials have demonstrated the potential of *Ultomiris* to improve survival in paediatric patients with this complex condition. We are moving forward with regulatory filings, with the goal of bringing a new treatment option to paediatric patients with HSCT-TMA and their families as quickly as possible. At the same time, we will continue engagement with global health authorities on potential next steps for the adult indication, as we advance additional analyses in the context of real-world data."

The safety profile observed across the ALXN1210-TMA-313 and ALXN1210-TMA-314 trials was consistent with the known safety profile of *Ultomiris* and with that seen in patients undergoing HSCT.

Alexion plans to present these data at a forthcoming medical meeting.

Ultomiris has been granted Orphan Drug Designation in the US and Japan for the treatment of HSCT-TMA, as well as Breakthrough Therapy designation by the US FDA for the treatment of paediatric patients with HSCT-TMA.

Notes

HSCT-TMA

Haematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) is a rare, severe and potentially life-threatening type of TMA that occurs following HSCT, a procedure used with increasing frequency to treat some types of cancers and other diseases.[4,5] It is thought that factors associated with HSCT (i.e., conditioning regimens and other complications) induce overactivation and/or dysregulation of the complement system, driving HSCT-TMA. Symptoms of HSCT-TMA can overlap with those of other conditions, which can lead to a misdiagnosis and/or a significant delay in receiving an accurate diagnosis.[4] HSCT-TMA can be fatal, with one-year survival rates in paediatric patients estimated between 17% and 44% and one-year overall survival rates ranging from approximately 17% to 58% in adults, based upon scientific literature.[8-10]

TMAs are a group of severe and potentially life-threatening rare disorders that cause blood clots and damage to the walls of the smallest blood vessels in the circulatory system. These blood clots can cause injury to organs that may lead to organ failure and death.[6] Signs, symptoms and complications of TMA include organ damage (most commonly in the kidneys), low platelet count, red blood cell abnormalities [i.e. anaemia, fragmented red cells (schistocytes)], blood clots and high blood pressure.[11-14]

ALXN1210-TMA-313

ALXN1210-TMA-313 is a global, Phase III, randomised, double-blind, placebo-controlled, multicentre trial evaluating the safety and efficacy of *Ultomiris* in adult and adolescent (aged 12 years or older) participants who have thrombotic microangiopathy (TMA) after haematopoietic stem cell transplant (HSCT). Participants were required to have received HSCT within the past 12 months at the time of screening, as well as a diagnosis of TMA that persisted for at least 72 hours after the initial management of any triggering condition or agent.[15]

The dosing regimen was confirmed in an open-label, single-arm period (Stage 1) based on data analysis after 14 participants had completed 21 days of treatment. Patients enrolled thereafter in the study were randomised 1:1 to receive either *Ultomiris* or placebo administered intravenously for a total of 26 weeks, in addition to best supportive care (Stage 2). Patients in the Stage 2 treatment arm received a loading dose of *Ultomiris* on Days 1, 5 and 10, followed by regular weight-based maintenance dosing of *Ultomiris* beginning on Day 15, every eight weeks through the treatment period. Upon completion of the treatment period, participants were followed for an additional 26 weeks.[15]

The primary endpoint is event-free survival during the 26-week treatment period, defined as the time from randomisation until clinical worsening or death. Key secondary endpoints include overall survival, non-relapse mortality and TMA response criteria. The trial enrolled 146 patients from 18 countries across North America, South America, Europe, Asia and Australia.[15]

ALXN1210-TMA-314

ALXN1210-TMA-314 is a global, Phase III, open-label, single-arm, multicentre study evaluating the safety and efficacy of *Ultomiris* in paediatric patients (aged 28 days to less than 18 years of age) with thrombotic microangiopathy (TMA) after haematopoietic stem cell transplantation (HSCT). Participants were required to have received HSCT within the past 12 months at the time of screening, as well as a diagnosis of TMA that persisted for at least 72 hours after the initial management of any triggering condition or agent.[16]

The dosing regimen was confirmed based on data analysis after at least 10 participants had completed 21 days of treatment. All patients received a loading dose of *Ultomiris* on Days 1, 5 and 10, followed by regular weight-based maintenance dosing of *Ultomiris* beginning on Day 15 and administered every four weeks for patients weighing less than 20 kg or every eight weeks for patients weighing at least 20

kg through the 26-week treatment period, in addition to best supportive care. The administration of supplemental doses of *Ultomiris* between maintenance doses was guided by prespecified protocol requirements.[16]

The primary endpoint is complete TMA response (defined as a composite measure of haematologic and renal parameters) at 26 weeks. Secondary endpoints include overall survival, non-relapse mortality and TMA response criteria. Upon completion of the treatment period, patients were followed for an additional 26 weeks. The trial enrolled 41 patients from seven countries across North America, Europe and Asia.[16]

ALX-TMA-502

ALX-TMA-502 is a global, observational, secondary real-world, retrospective study to assess overall survival in adult and paediatric participants (≥ 28 days of age at the time of diagnosis) diagnosed with HSCT-TMA within 52 weeks after stem cell transplantation. The study included two cohorts (complement inhibitor treatment-naïve participants and participants treated with eculizumab) for adult and paediatric participants, respectively. The HSCT-TMA diagnosis was required to have occurred at least 52 weeks before the eligibility assessment date.[3]

The study was conducted to provide historical control data and real-world contextualisation in the treatment of HSCT-TMA. The primary endpoint is overall survival through 52 weeks after diagnosis, defined as the number of days from the date of TMA diagnosis to the date of death. Secondary endpoints include overall survival at 100 days and 26 weeks after diagnosis; and non-relapse mortality through 100 days, 26 weeks, and 52 weeks after diagnosis. In this study, data were collected from 307 patients in 10 countries across North America, South America, Europe, and Asia.[3]

Ultomiris

Ultomiris (ravulizumab), the longest-acting C5 complement inhibitor, provides immediate, complete and sustained complement inhibition. The medication works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system. When activated in an uncontrolled manner, the complement cascade over-responds, leading the body to attack its own healthy cells. Following a loading dose, *Ultomiris* is administered intravenously every eight weeks in adults, or every four or eight weeks in paediatric patients (based on body weight).

Ultomiris is approved in the US, EU, Japan and other countries for the treatment of certain adults with paroxysmal nocturnal haemoglobinuria (PNH) and is also approved for certain children with PNH in the US, EU and other countries.

Ultomiris is also approved in the US, EU, Japan and other countries for the treatment of certain adults and children with atypical haemolytic uraemic syndrome (aHUS).

Additionally, *Ultomiris* is approved in the US, EU, Japan, China and other countries for the treatment of certain adults with generalised myasthenia gravis (gMG).

Further, *Ultomiris* is approved in the US, EU, Japan, China and other countries for the treatment of certain adults with neuromyelitis optica spectrum disorder (NMOSD).

Ultomiris is being assessed as a treatment for additional indications as part of a broad development programme.

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 Disease, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's 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

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