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Ultomiris demonstrated statistically significant and clinically meaningful reduction of proteinuria in adults with immunoglobulin A nephropathy in I CAN Phase III trial

Ultomiris delivered rapid reduction in proteinuria as early as week 10

Results show potential for terminal C5 complement inhibition with Ultomiris as a disease-modifying treatment option for IgAN

Positive high-level results from a prespecified interim analysis of the I CAN Phase III trial showed that *Ultomiris* (ravulizumab) met its primary endpoint, demonstrating a statistically significant and clinically meaningful reduction of proteinuria, based on 24-hour urine protein creatinine ratio (UPCR), at week 34 in adults with immunoglobulin A nephropathy (IgAN) who are at risk of disease progression. The primary endpoint of change from baseline in estimated glomerular filtration rate (eGFR) will be measured at week 106.

IgAN is a rare, inflammatory disease of the kidneys that can lead to chronic kidney disease (CKD) and progress to end-stage kidney disease (ESKD). It begins when the body develops abnormal IgA proteins resulting in immune complexes that are deposited in the kidneys causing damage. The deposition of these complexes activates the complement system, leading to terminal complement-driven inflammation. This results in damage and loss of essential parts of the kidney, including cells in the glomeruli, the part of the kidneys that filters and cleans the blood. Over time, this damage impacts the ability of the kidneys to function properly.[1]

More than 560,000 people are diagnosed with IgAN in the US, EU5 and Japan, of which more than 60 percent are eligible for IgAN treatment.[2-5]

Jonathan Barratt, MD, Mayer Professor of Renal Medicine, University of Leicester, United Kingdom, and I CAN trial investigator, said: "Many people living with IgAN continue to progress to kidney failure, ultimately requiring dialysis or a transplant - outcomes that can place profound burden on patients' daily lives - despite advances in care. The interim I CAN results demonstrate that blocking terminal complement activation, a central driver of kidney inflammation in IgAN, with *Ultomiris* may play a promising role in reducing proteinuria. We look forward to understanding the full clinical impact of *Ultomiris* in treating this disease following study completion at two years."

Marc Dunoyer, Chief Executive Officer, Alexion, AstraZeneca Rare Disease, said: "These positive data demonstrate that C5 complement inhibition with *Ultomiris* results in a rapid and clinically meaningful reduction in proteinuria as early as week 10 and underscores its potential as a disease-modifying approach in IgAN. We look forward to filing these data with regulatory authorities in key regions, while in parallel, advancing this Phase III trial towards completion."

The safety profile observed in this trial was consistent with the known profile of *Ultomiris*, with no new safety concerns identified.

The company will seek accelerated approval in key markets and will present these results at a forthcoming medical meeting.

Notes

Immunoglobulin A Nephropathy (IgAN)
Immunoglobulin A nephropathy (IgAN) is a rare, inflammatory disease of the kidneys that can lead to chronic kidney disease (CKD) and progress to end-stage kidney disease (ESKD). It begins when the body develops abnormal IgA proteins resulting in immune complexes that are deposited in the kidneys causing damage. The deposition of these complexes activates the complement system, leading to terminal complement-driven inflammation. This results in damage and loss of essential parts of the kidney, including cells in the glomeruli, the part of the kidneys that filters and cleans the blood. Over time, this damage impacts the ability of the kidneys to function properly, resulting in chronic kidney disease that can progress to end-stage kidney disease.[1]

The signs and symptoms of IgAN can include blood in the urine (haematuria), foamy urine (proteinuria), swelling in hands and feet (oedema) and high blood pressure (hypertension).[6] Most people with IgAN do not experience symptoms in the early stages of the disease, and therefore, it often goes undetected until it has progressed. At diagnosis, irreversible kidney damage may have already occurred.[5,7] Approximately half of people with IgAN who have elevated protein levels in urine or reduced kidney function are at-risk of progression to ESKD, or kidney failure, within 10 years of diagnosis.[8]

I CAN (ALXN1210-IgAN-320)
I CAN (ALXN1210-IgAN-320) is a global, Phase III, randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of *Ultomiris* in adults with immunoglobulin A nephropathy (IgAN) who are at risk of disease progression. Participants were on stable concomitant IgAN treatment(s) consistent with standard of care for at least three months prior to screening.[9]

Participants were randomised 1:1 to receive either *Ultomiris* or placebo, administered intravenously for a total of 106 weeks. Patients in the treatment arm received a loading dose of *Ultomiris* on Day 1, followed by regular weight-based maintenance dosing of *Ultomiris* beginning on Day 15 and then every eight weeks through the 106-week blinded treatment period. Patients who completed the randomised control period had the option to enter an open-label access period.[9]

The primary endpoints are change from baseline in proteinuria based on 24-hour urine protein creatinine ratio (UCPR)

at week 34 and change from baseline in estimated glomerular filtration rate (eGFR) at week 106, assessed at the interim analysis and final analysis, respectively. Key secondary endpoints for the final analysis include reduction in 24-hour UPCR ≥ 50% from baseline at week 34, change from baseline in proteinuria based on 24-hour UPCR at week 10, time to sustained ≥ 30% eGFR decline up to week 106 and time to first occurrence of composite kidney event up to week 106. The trial was designed to enrol approximately 510 participants from 28 countries across North America, South America, Europe, Asia and Australia.[9]

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 Diseases, 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

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

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Matthew Bowden
Company Secretary
AstraZeneca PLC

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