Pooled analyses of the roxadustat global Phase III

This announcement contains inside information

10 May 2019 07:00 BST

Pooled analyses of the roxadustat global Phase III programme confirmed cardiovascular safety

Cardiovascular safety endpoints evaluated across CKD patients not on dialysis, on incident dialysis and on stable dialysis

Better outcome vs. epoetin alfa in incident-dialysis patients and comparable to placebo in patients not on dialysis

AstraZeneca today announced top-line results from the pooled cardiovascular (CV) safety analyses of the global Phase III programme for roxadustat, a first-in-class hypoxia-inducible-factor prolyl hydroxylase inhibitor (HIF-PHI). The global pivotal Phase III trials evaluated roxadustat for treatment of anaemia in patients with chronic kidney disease (CKD) across the non-dialysis-dependent (NDD), incident (newly-initiated) dialysis (ID), and stable dialysis patient groups.

These pooled CV safety assessments of roxadustat are part of the overall benefit/risk assessment that will inform discussions with regulatory authorities. One of the key CV safety endpoints is major adverse CV events (defined as MACE), evaluating a composite of all-cause mortality, stroke and myocardial infarction in pooled analyses comparing roxadustat vs. placebo in NDD and vs. epoetin alfa in dialysis-dependent (DD) patients. Another key CV safety endpoint evaluated MACE plus heart failure requiring hospitalisation and unstable angina requiring hospitalisation (defined as MACE+).

Pooled MACE/MACE+ in NDD patients

In the pooled analysis of over 4,300 patients, and based on the totality of the adjudicated evidence, the MACE/MACE+ analyses between roxadustat and placebo showed no clinically-meaningful difference.

Pooled MACE/MACE+ in ID patients

In the pool of 1,500 ID patients, a pre-specified sub-population of DD patients, MACE/MACE+ results indicate that ID patients on roxadustat do better than those who are on epoetin alfa. ID patients are a better population to compare roxadustat vs. epoetin alfa than the stable dialysis population, where patients are stable not only on dialysis but also on erythropoietin.

Pooled MACE/MACE+ in DD patients

In the pooled analysis of around 4,000 patients, and based on the totality of the adjudicated evidence, the MACE/MACE+ analyses between roxadustat and epoetin alfa showed no clinically-meaningful difference.

Mene Pangalos, Executive Vice President, R&D BioPharmaceuticals, said: "We are pleased to report these data from the largest clinical programme in the world evaluating this new class of medicines. These results add to the growing body of positive evidence to support roxadustat for the treatment of anaemia in chronic kidney disease patients, following our announcement that the primary efficacy endpoints were met for the OLYMPUS and ROCKIES trials in December 2018. There is a significant unmet medical need among patients living with chronic kidney disease, and we look forward to working with FibroGen to prepare for regulatory submissions of roxadustat."

Further analyses of overall safety are ongoing and will inform the benefit/risk profile.

AstraZeneca and FibroGen Inc. (FibroGen) will begin discussions with the US Food and Drug Administration (FDA) to prepare for regulatory submission, which is anticipated in the second half of 2019. Roxadustat is currently approved in China for the treatment of patients with anaemia in DD CKD.

About roxadustat

Roxadustat is a HIF-PHI that promotes erythropoiesis by increasing endogenous production of erythropoietin and improving iron regulation and overcoming the negative impact of inflammation on haemoglobin synthesis and red blood-cell production by downregulating hepcidin. Use of roxadustat has been shown to induce coordinated erythropoiesis, increasing red blood-cell count while maintaining plasma erythropoietin levels within or near normal physiologic range, in multiple subpopulations of CKD patients, including in the presence of inflammation and without a need for supplemental intravenous iron.

About the global Phase III clinical programme

FibroGen, the originator, and AstraZeneca are collaborating on the development and commercialisation of roxadustat for the treatment of anaemia in patients with CKD in the US, China, and other global markets. FibroGen and Astellas Pharma Inc. (Astellas) are collaborating on the development and commercialisation of roxadustat for the treatment of anaemia in patients with CKD in territories including Japan, Europe, the Commonwealth of Independent States, the Middle East, and South Africa.

The global Phase III programme consists of more than 9,000 patients and was conducted by AstraZeneca, FibroGen and Astellas.

The OLYMPUS, ALPS and ANDES trials evaluated roxadustat vs. placebo in NDD patients; HIMALAYAS evaluated roxadustat vs. epoetin alfa in ID patients; and ROCKIES, SIERRAS and PYRENEES evaluated roxadustat vs. epoetin alfa in DD patients.

The AstraZeneca-sponsored trial OLYMPUS demonstrated a statistically-significant and clinically-meaningful improvement in haemoglobin vs. placebo in NDD patients. The AstraZeneca-sponsored trial ROCKIES demonstrated a statistically-significant improvement in haemoglobin vs.

epoetin alfa in DD patients.

In the CV pooled safety analyses, safety was characterised based on a number of key CV analyses from the Phase III programme, including MACE outcomes and MACE+ outcomes (MACE plus hospitalisation for unstable angina and hospitalisation for heart failure outcomes). Overall, the analyses will evaluate the totality of evidence for roxadustat and assess the overall benefit-risk profile, to overcome potential bias of a single-arm trial analysis.

About anaemia in CKD

Anaemia can be a serious medical condition in which patients have insufficient red blood cells and low levels of haemoglobin, a protein in red blood cells that carries oxygen to cells throughout the body.1,2 Anaemia in CKD is associated with increased risk of hospitalisation, CV complications and death,3 also frequently causing significant fatigue, cognitive dysfunction and decreased quality of life.4 Severe anaemia is common in patients with CKD, cancer, myelodysplastic syndrome, inflammatory diseases and other serious illnesses.

Anaemia is particularly prevalent in patients with CKD, which affects more than 200 million patients worldwide and is generally a progressive disease characterised by gradual loss of kidney function that may eventually lead to kidney failure.

In the US, according to the United States Renal Data System, a majority of dialysis-eligible CKD patients are currently on dialysis. Of the approximately 507,000 patients receiving dialysis in the US as of 2016, approximately 80% were being treated with erythropoiesis-stimulating agents (ESA) for anaemia.5 Patients seldom receive ESA treatment until they initiate dialysis therapy.

About AstraZeneca in CV, Renal & Metabolism (CVRM)

CV, renal and metabolism together form one of AstraZeneca's main therapy areas and a key growth driver for the Company. By following the science to understand more clearly the underlying links between the heart, kidneys and pancreas, AstraZeneca is investing in a portfolio of medicines to protect organs and improve outcomes by slowing disease progression, reducing risks and tackling co-morbidities. Our ambition is to modify or halt the natural course of CVRM diseases and potentially regenerate organs and restore function, by continuing to deliver transformative science that improves treatment practices and CV health for millions of patients worldwide.

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular, Renal & Metabolism and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visitastrazeneca.com and follow us on Twitter @AstraZeneca.

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