GSK announces positive Phase III efficacy and safety data for daprodustat in patients with anaemia due to chronic kidney disease

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- Late-breaking data from the daprodustat ASCEND-ND and ASCEND-D trials at the American Society of Nephrology's Kidney Week 2021 confirms the potential for a new oral treatment for patients with anaemia due to chronic kidney disease in both non-dialysis and dialysis settings

- Data from five Phase III studies demonstrated that daprodustat improved or maintained haemoglobin within target levels, without increased cardiovascular risk when compared to standard of care

- Pivotal trials in non-dialysis and dialysis populations published simultaneously in the New England Journal of Medicine

GlaxoSmithKline plc (LSE/NYSE: GSK) today announced positive results from the Phase III ASCEND (Anaemia Studies in Chronic Kidney Disease: Erythropoiesis via a novel prolyl hydroxylase inhibitor Daprodustat) programme for daprodustat, an investigational oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), during a presentation at the American Society of Nephrology's Kidney Week 2021. The positive primary efficacy and safety results confirm the potential for daprodustat to be a new oral treatment for patients with anaemia due to chronic kidney disease (CKD) in both non-dialysis and dialysis settings. Daprodustat was developed based upon the unique Nobel Prize-winning science that demonstrated how cells sense and adapt to oxygen availability.

The ASCEND programme is comprised of five Phase III studies assessing the efficacy and safety of daprodustat for the treatment of anaemia due to CKD across the CKD disease course. The programme enrolled over 8,000 patients who were treated for up to 4.26 years. Daprodustat was well tolerated in both non-dialysis and dialysis populations as assessed in the primary analysis. Data on daprodustat, including results from the two pivotal Phase III studies focused on non-dialysis (ASCEND-ND) and dialysis (ASCEND-D) patients, were shared at the American Society of Nephrology's meeting in a combined late-breaking oral presentation. Results for ASCEND-ND and ASCEND-D were also published simultaneously in the New England Journal of Medicine.

The ASCEND-ND and ASCEND-D studies each independently met their primary efficacy and safety endpoints. Efficacy results from both Phase III studies demonstrated that daprodustat improved or maintained patients within their target haemoglobin (Hb) range. In addition, results from the prespecified primary safety analysis of the intention-to-treat (ITT) population showed similar rates of major adverse cardiovascular events (MACE), defined as all-cause mortality, non-fatal myocardial infarction or non-fatal stroke independently within each trial. In the ASCEND-ND trial, results showed a hazard ratio reflecting time to first occurrence of MACE of 1.03; 95% CI, (0.89 to 1.19), achieving non-inferiority with the pre-defined margin of 1.25. In the ASCEND-D trial, results showed a hazard ratio reflecting time to first occurrence of MACE of 0.93; 95% CI, (0.81-1.07), achieving non-inferiority with the pre-defined margin of 1.25. The outcomes in each study and across treatment arms confirmed no increased cardiovascular risk for daprodustat compared to an erythropoietin stimulating agent (ESA), the current standard of care.

The most commonly reported adverse events in patients receiving daprodustat included hypertension, diarrhoea, dialysis hypotension, peripheral oedema and urinary tract infection.

Daprodustat is the first oral HIF-PHI to clearly show positive efficacy, along with no increased cardiovascular risk as assessed in the primary analysis of MACE in the ITT population compared to an ESA, across both non-dialysis patients and dialysis patients.

Dr. Hal Barron, Chief Scientific Officer and President, R&D, GSK, said,

> Over 700 million people suffer from chronic kidney disease worldwide, and an estimated 1-in-7 of these patients suffers from anaemia. Grounded in research based on Nobel Prize-winning science, we believe these data show daprodustat has the potential to transform the treatment landscape for these patients, many of whom have limited treatment options today.

In addition to the primary analysis of the ITT population, several additional supplementary analyses were performed for both ASCEND-ND and ASCEND-D trials. Further details can be found in the New England Journal of Medicine publication.

Data from three additional trials within the ASCEND programme provided further support for the use of daprodustat. The ASCEND-TD trial showed positive efficacy results for three-times weekly dosing, in addition to the once-daily dosing regimen evaluated in ASCEND-ND and ASCEND-D studies, providing data to support additional dosing options for daprodustat. Additional results demonstrated treatment with daprodustat led to significant improvement compared to placebo in non-dialysis dependent patients' Hb levels and quality of life by measure of SF-36 vitality score (as determined by level of fatigue) in the ASCEND-NHQ trial, as well as the ability to maintain Hb levels in the high-risk incident dialysis population in the ASCEND-ID trial.

Dr. Ajay Singh, nephrologist/principal investigator, Chair of Executive Steering Committee and Steering Committee for the ASCEND Programme and Senior Associate Dean for Postgraduate Medical Education, Harvard Medical School, said,

> As a nephrologist who regularly treats patients with anaemia due to chronic kidney disease, I think these are ground-breaking results and show that daprodustat has potential to be transformative for these patients. The ASCEND programme was designed to represent anaemia management in practice today, and these results provide strong clinical evidence to help nephrologists as they make the right treatment decisions for their patients.

Sir Peter J. Ratcliffe, Professor of Medicine, University of Oxford, Francis Crick Institute and Nobel laureate, said,

> Derived from decades of research investigating how the cells sense and adapt to oxygen availability, it's extraordinary to see

how this work has been translated into positive clinical evidence within the ASCEND programme. The data shared today demonstrate the importance of following the science and how better understanding the body's natural responses enables us to create medicines that can have a meaningful impact on patients' lives.

Daprodustat is currently approved in Japan as Duvroq for patients with renal anaemia. It is not approved anywhere else in the world. The results from the Phase III ASCEND programme will be used to support regulatory filings with health authorities worldwide.

Results from the ASCEND-ND and ASCEND-D trials

- ASCEND-ND (Anaemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Non-Dialysis) enrolled 3,872 non-dialysis dependent patients with anaemia associated with CKD who were either switched from standard of care (ESA) or not currently receiving ESA therapy to receive daprodustat or ESA control (darbepoetin alfa). Iron management protocols were instituted across both arms in the study. The study met its primary safety and efficacy endpoints. Results showed daprodustat improved and/or maintained Hb within target level (10-11.5 g/dL) for these patients, and the primary safety analysis of the ITT population showed that daprodustat achieved non-inferiority compared to ESA control.

- ASCEND-D (Anaemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Dialysis) enrolled 2,964 dialysis patients with anaemia associated with CKD who were switched to receive daprodustat or ESA control from a standard of care ESA therapy. A uniform iron management protocol was instituted across both arms of the study. The study met its primary safety and efficacy endpoints. Results showed daprodustat improved or maintained Hb within target levels (10-11.5 g/dL) for these patients, and the primary safety analysis of the ITT population showed that daprodustat achieved non-inferiority compared to ESA control.

Chronic kidney disease (CKD), characterised by progressive loss of kidney function, is an increasing global public health burden. Risk factors for CKD include hypertension, diabetes, obesity and primary renal disorders. However, it is often poorly diagnosed and undertreated in patients with early-stage CKD, such as those not on

dialysis.

Daprodustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), belongs to a novel class of oral medicines indicated for the treatment of anaemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis. Inhibition of oxygen-sensing prolyl hydroxylase enzymes stabilises hypoxia-inducible factors, which can lead to transcription of erythropoietin and other genes involved in the correction of anaemia, similar to the physiological effects that occur in the body at high altitude. Daprodustat has been developed to provide a convenient oral treatment option for patients with anaemia associated with CKD.

GSK is a science-led global healthcare company. For further information please visit www.gsk.com/about-us.

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