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Baxfendy approved in the US as the first and only aldosterone synthase inhibitor treatment for adults with hypertension

Approval based on BaxHTN Phase III results showing statistically significant and clinically meaningful reduction in systolic blood pressure in patients with uncontrolled or resistant hypertension

Baxfendy 2mg lowered systolic blood pressure by 15.7 mmHg (9.8 mmHg placebo-adjusted) from baseline in BaxHTN trial

AstraZeneca's *Baxfendy* (baxdrostat) has been approved in the US as a first-in-class aldosterone synthase inhibitor (ASI) for the treatment of hypertension in combination with other antihypertensive medications, to lower blood pressure in adults who are not adequately controlled.

There are 1.4 billion people worldwide living with hypertension.[1] In the US, approximately 50% of patients living with hypertension who are already taking multiple antihypertensive medications still struggle with persistently elevated blood pressure,[2] which is a leading risk factor for cardiovascular disease and premature death.[3,4] Hypertension is the most prevalent and significant modifiable cardiovascular risk factor worldwide, accounting for more deaths and disability than any other modifiable risk.[5-7]

Baxfendy is a first-in-class, highly selective and potent ASI designed to lower blood pressure in a new way by specifically inhibiting the production of aldosterone,[8] a hormone that raises blood pressure to unhealthy levels and increases the risk of heart and kidney problems.[9-11]

The approval by the US Food and Drug Administration (FDA) was based on positive results from the BaxHTN Phase III trial,[12] with *Baxfendy* demonstrating statistically significant and clinically meaningful seated systolic blood pressure reduction at both 2mg and 1mg doses in patients with uncontrolled and resistant hypertension on two or more medications. *Baxfendy* was generally well-tolerated with no unanticipated safety findings.

Dr. Bryan Williams, Chair of Medicine at University College London, and BaxHTN primary investigator, said: "We have been waiting for an innovative medication like *Baxfendy* for hypertension for many years. Its novel way of lowering blood pressure has the potential to transform clinical practice by targeting a root cause of persistently uncontrolled hypertension. In addition, the nearly double-digit placebo-adjusted systolic blood pressure reduction achieved with *Baxfendy* is exciting and clinically meaningful for clinicians and patients. Epidemiological data indicate that a 10 mmHg decrease in systolic blood pressure is associated with a roughly 20% lower risk of serious cardiovascular events."

John M. Clymer, Executive Director, National Forum for Heart Disease & Stroke Prevention, said: "Hypertension remains a staggeringly widespread silent killer and a leading risk factor for stroke, heart attack, kidney damage and dementia. Tens of millions of people struggle to control their blood pressure despite lifestyle changes and currently available treatments. Innovative, new treatments could help millions protect their heart, kidney and brain health."

Ruud Dobber, Executive Vice President, BioPharmaceuticals Business Unit, AstraZeneca, said: "The approval of *Baxfendy* offers a much-needed, first-in-class innovation for people living with persistently uncontrolled hypertension who have not responded to or tolerated existing medicines. In the US, about 23 million patients are uncontrolled despite being on two or more medicines for hypertension, which is a disease that has seen little therapeutic progress for the past two decades."

In the BaxHTN Phase III trial,[13] published in the *New England Journal of Medicine*,[12] *Baxfendy* (baxdrostat) demonstrated statistically significant and clinically meaningful efficacy for the treatment of patients with hypertension on top of standard of care. At week 12, the absolute reduction from baseline in mean seated SBP was 15.7 mmHg (95% confidence interval [CI], -17.6 to -13.7) and placebo-adjusted reduction was 9.8 mmHg (95% CI, -12.6 to -7.0; p<0.001) for the 2mg dose. For the 1mg dose, the absolute reduction from baseline was 14.5 mmHg (95% CI, -16.5 to

-12.5) and placebo-adjusted reduction was 8.7 mmHg (95% CI, -11.5 to -5.8; p<0.001). The reduction in mean seated SBP with placebo was 5.8 mmHg (95% CI, -7.9 to -3.8). Results were consistent across both uncontrolled and treatment-resistant subgroups.

Notes

Uncontrolled hypertension

Hypertension is a medical condition characterised by consistently high blood pressure levels, affecting an estimated 1.4 billion people worldwide.[1,14,15] Over time, this can damage blood vessels and vital organs, increasing the risk of serious health problems such as heart attack, stroke, heart failure and kidney disease.[14,15]

Treated but uncontrolled patients with hypertension are at a significantly greater risk of all-cause mortality, heart-disease specific mortality, stroke-related mortality, CVD-specific mortality and dementia than patients whose hypertension is controlled. A large meta-analysis found that lowering systolic blood pressure by 10 mmHg can reduce the risk of major adverse cardiovascular events by around 20%,[16] underscoring the urgent need for new treatments that target a key hypertension pathway at its source.

An observational study of nearly 60,000 patients studied over a median of 9.7 years showed that a 9.5 mmHg increase in SBP was associated with a 30% increase in risk of all-cause mortality and 41% increase in risk of cardiovascular death.[17] Studies have shown that increased night-time blood pressure is associated with higher cardiovascular risk,[18,19] and patients with hypertension have a higher risk of cardiovascular events like heart attack, stroke and death around the time of their morning blood pressure surge.[20,21]

Aldosterone, a hormone that raises blood pressure to unhealthy levels by promoting sodium and water retention[9,10] is a key contributor to persistently uncontrolled hypertension. Elevated aldosterone levels, along with factors such as obesity, high salt intake and various genetic or secondary conditions,[22] are strongly associated with poor blood pressure control and the progression of heart failure and kidney disease. When left untreated, hypertension significantly increases the risk of cardiovascular and kidney-related complications.[5,14,23]

BaxHTN trial

The BaxHTN Phase III trial[13] had three components to it that supported the following endpoints. The primary endpoint was assessed during a 12-week double-blind, placebo-controlled period. A total of 796 patients were characterised in a 1:1:1 ratio to receive *Baxfendy* 2mg, 1mg or placebo once daily on top of standard of care [2 antihypertensive agents at baseline, one of which is a diuretic for uncontrolled hypertension and ≥ 3 antihypertensive agents at baseline, one of which is a diuretic for resistant hypertension].The primary efficacy endpoint was the difference in mean change from baseline in seated SBP at week 12 between participants treated with baxdrostat (2mg or 1mg separately) and participants treated with placebo. Persistence of efficacy was assessed during a randomised withdrawal period from week 24 to week 32. Approximately 300 patients treated with *Baxfendy* 2mg were re-randomised in a 2:1 ratio to either continue receiving baxdrostat 2mg or placebo for the 8 weeks. SBP at the end of the 8 weeks was compared with placebo and the *Baxfendy* 2mg dose. Long-term safety was assessed at the end of the 52 weeks compared to a standard of care arm.

Additional confirmatory secondary endpoints include the effect of *Baxfendy* versus placebo on seated SBP at week 12 in the resistant hypertension subpopulation, the effect of *Baxfendy* versus placebo on seated diastolic blood pressure at week 12, and proportion of participants achieving seated SBP less than 130 mmHg at week 12.

Baxfendy and the clinical development programme

Baxfendy is a first-in-class, highly selective and potent, oral, small molecule that inhibits aldosterone synthase,[8] an enzyme encoded by the CYP11B2 gene, which is responsible for the synthesis of aldosterone in the adrenal gland.[10] In clinical trials, *Baxfendy* was observed to significantly lower aldosterone levels without affecting cortisol levels across a wide range of doses.[24,25]

As part of a broad development programme, *Baxfendy* is currently being investigated in clinical trials in other conditions where high aldosterone plays a role in elevating cardiorenal risk, including as a monotherapy for primary aldosteronism,[26] and in combination with dapagliflozin for chronic kidney

disease and hypertension,[27,28] and the prevention of heart failure in patients with hypertension.[29] Additional clinical data for *Baxfendy* in hypertension includes positive data from the Bax24 Phase III trial,[30] which showed a statistically significant and highly clinically meaningful placebo-adjusted reduction of 24-hour ambulatory systolic blood pressure in patients with resistant hypertension, with full results published in *The Lancet*.[31]

AstraZeneca acquired *Baxfendy* through its purchase of CinCor Pharma, Inc. in February 2023.[32]

AstraZeneca in CVRM
Cardiovascular, Renal and Metabolism (CVRM), part of BioPharmaceuticals, forms one of AstraZeneca's main disease areas and is a key growth driver for the Company. By following the science to understand more clearly the underlying links between the heart, kidneys, liver and pancreas, AstraZeneca is investing in a portfolio of medicines for organ protection by slowing or stopping disease progression, and ultimately paving the way towards regenerative therapies. The Company's ambition is to improve and save the lives of millions of people, by better understanding the interconnections between CVRM diseases and targeting the mechanisms that drive them, so we can detect, diagnose and treat people earlier and more effectively.

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.

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