April 17, 2026

Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800, Boston, MA 02108
publiccomments@icer.org

RE: Comments on Draft Scoping Document for ICER's Review of Aldosterone Synthase Inhibitors for the Treatment of Hypertension

We appreciate the opportunity to comment on the draft scoping document, released on March 30, 2026, for review of aldosterone synthase inhibitors (ASIs) for the treatment of hypertension (HTN). AstraZeneca has reviewed the document and offers the following comments.

BENEFITS BEYOND HEALTH AND SPECIAL ETHICAL PRIORITIES

HTN is a condition of relevance for the healthcare system with significant unmet need.

HTN affects approximately 45-50% of adults in the United States (US),[1; 2] underscoring the need for novel and effective treatments. Consistent 24-hour blood pressure (BP) control is an important clinical outcome in patients with uncontrolled HTN (uHTN) on two or more antihypertensive therapies (AHTs).[3-5] Multiple studies have demonstrated that 24-hour BP is a more powerful predictor of cardiovascular (CV) events than a clinic-based measurement.[6; 7] When 24-hour average systolic blood pressure (SBP) rises by 9.5 mmHg, the risk of all-cause mortality increases by 30%.[6]

There is substantial unmet need despite currently available treatments.

Despite being on two or more AHTs, an estimated 50% of adults in the US with HTN do not reach the American Heart Association (AHA)/American College of Cardiology (ACC) guideline-recommended BP target of <130/80 mmHg resulting in negative clinical, economic, and humanistic consequences.[8; 9] Besides medication adherence[10] and treatment-related side effects,[11-13] failure to reach BP goals results from the inability of current AHTs to directly target aldosterone production.[14-17]

Baxdrostat offers an innovation for effective treatment by means of its mechanism of action.

Aldosterone, a key hormone within the renin-angiotensin-aldosterone system, plays a central role in long-term BP regulation.[14; 16; 17] Beyond its classical mineralocorticoid receptor (MR)-mediated effects on BP and electrolytes, aldosterone exerts harmful pathophysiological effects through both MR-dependent and MR-independent pathways.[18] These direct pathogenic effects of aldosterone further exacerbate HTN. Current AHTs do not directly target aldosterone production, resulting in an increase in aldosterone that has important efficacy and safety implications.[19; 20] Both persistent aldosterone production and circulating aldosterone exposure leads to inflammation, fibrosis, and structural changes in the heart, vasculature, and kidneys.[14; 16; 17] There

is a need for effective therapies with novel mechanisms of action (MoA) to reduce the burden of costly and resource-intensive clinical events associated with uncontrolled BP and its underlying causes. Baxdrostat, an aldosterone synthase inhibitor (ASI), has a novel mechanism of action, inhibiting aldosterone synthase to lower aldosterone levels and reduce sodium retention,[17; 21] thereby offering more effective treatment options for patients with uHTN or resistant HTN (rHTN).

POPULATION

Both uHTN and rHTN should be considered populations of interest given the unaddressed underlying pathophysiology for HTN. However, for modeling purposes, we recommend defining uHTN as uncontrolled patients treated with two AHTs while actively seeking care (e.g., who had recent therapy change in the past 12 months), rather than limiting the definition to patients who cannot tolerate a third AHT. The BaxHTN Phase 3 trial was conducted in patients with either uHTN, defined by mean seated-SBP ≥140 mmHg and <170 mmHg despite treatment with 2 (uHTN) or ≥3 (rHTN) AHTs of different classes.[22] The trial achieved its primary and secondary endpoints,[22] supporting the use of baxdrostat in both populations. Despite widespread use of available AHTs, approximately 50% of patients remain above BP goals,[8; 9] and limiting the uHTN population to only those who cannot tolerate a third AHT could delay access to novel and effective treatments.

We recognize the importance of including kidney function as an outcome of BP control for all patients with HTN. We caution against doing a subgroup analysis by chronic kidney disease (CKD) using the baxdrostat Phase 3 trials (i.e., BaxHTN and Bax24)[22; 23] given the limited number of patients with estimated glomerular filtration rate <60 mL/min/1.73 m².

COMPARATORS

We recommend specifying comparators by uHTN and rHTN separately. We disagree with including spironolactone and eplerenone (MR antagonists [MRAs]) as comparators in both uHTN and rHTN populations, as MRAs are not an appropriate real-world comparator for many patients. MRAs have not been studied in patients on two AHTs and guidelines do not recommend MRA use for uHTN. They are not standard of care, have low uptake and high discontinuation rates,[8; 24; 25] and present safety and tolerability concerns outlined below. In addition, it is important to underscore the differences in MoAs between ASIs and MRAs. While baxdrostat inhibits aldosterone synthase to decrease aldosterone production directly, MRAs block the MR where aldosterone acts, which can lead to compensatory increases in circulating aldosterone levels.[21]

Additionally, MRAs are associated with side effects that limit their general use.[13; 26] Spironolactone carries risks related to its anti-androgenic activity, including breast tenderness, gynecomastia, menstrual irregularities, and sexual dysfunction.[13] There are also well-known challenges with medication adherence among patients with HTN, which may be due to poor tolerability, polypharmacy/pill burden, and the chronic nature of HTN, all of which can

negatively impact clinical outcomes, healthcare resource use and costs, as well as patient quality of life.[27-31] Baxdrostat offers a strong efficacy and better safety/tolerability profile that may support improved adherence.

We also disagree with including amiloride as a comparator for uHTN and rHTN populations. For example, its use is limited to patients with hypokalemia or MRA-intolerance.[9]

Summary of Recommendations:

- For uHTN (2 AHTs): Baxdrostat should be compared with lorundrostat and usual care/ watchful waiting (delayed intensification defined as taking no action to add a 3rd AHT).
- For rHTN (≥3 AHTs): Baxdrostat should be compared with lorundrostat and usual care/ watchful waiting (delayed intensification/taking no action to add another AHT).

OUTCOMES

We agree with the outcomes listed in the draft scope. HTN is a multisystem disease and a major modifiable risk factor for CV events, kidney outcomes (including CKD, end-stage kidney disease, and the need for dialysis and transplant), eye disease, as well as cognitive decline.[9; 32]

However, we recommend adding the following outcomes, given their established links to HTN:

- Eye disease (e.g., diabetic retinopathy, hypertensive retinopathy)[33]
- Additional kidney outcomes: CKD incidence, CKD progression, urine albumin creatine ratio[34]
- Additional cognitive function outcomes: mild cognitive impairment[35]
- Peripheral arterial disease[36]
- Both ambulatory and seated BP outcomes should be used: office seated BP, office diastolic BP, 24-hour ambulatory BP monitoring (ABPM), nighttime ABPM, daytime ABPM, and BP variability

We also emphasize the importance of including tolerability and adverse effects as outcomes, as current AHTs have well-recognized side-effect limitations that affect overall tolerability, including the abovementioned risks with MRAs.[11-13; 26] Adverse-event disutilities and costs associated with managing these adverse events should be incorporated into the modeling.

SETTINGS

We are aligned with the focus on outpatient settings in the US.

Thank you for the opportunity to provide comments. Please do not hesitate to contact me should you have any questions or require further clarification.

Sincerely,
Meredith Bishop, PharmD, MBA
Medical Head of Baxdrostat, US Medical Affairs, AstraZeneca

AstraZeneca

REFERENCES

[1]Muntner P, Miles MA, Jaeger BC, Hannon Iii L, Hardy ST et al. (2022) Blood Pressure Control Among US Adults, 2009 to 2012 Through 2017 to 2020. *Hypertension* 79 (9): 1971-1980.

[2]Million Hearts (Web Page) Estimated Hypertension Prevalence, Treatment, and Control Among US Adults: Tables. Updated Available online at: https://millionhearts.hhs.gov/files/Estimated-Hypertension-Prevalence-tables-508.pdf. Accessed: April 8, 2026.

[3]Narita K, Hoshide S, Kario K (2022) Nighttime Home Blood Pressure Is Associated With the Cardiovascular Disease Events Risk in Treatment-Resistant Hypertension. *Hypertension* 79 (2): e18-e20.

[4]Kario K, Hoshide S, Mizuno H, Kabutoya T, Nishizawa M et al. (2020) Nighttime Blood Pressure Phenotype and Cardiovascular Prognosis: Practitioner-Based Nationwide JAMP Study. *Circulation* 142 (19): 1810-1820.

[5]Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M et al. (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 39 (33): 3021-3104.

[6]Staplin N, de la Sierra A, Ruilope LM, Emberson JR, Vinyoles E et al. (2023) Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *Lancet* 401 (10393): 2041-2050.

[7]Niiranen TJ, Maki J, Puukka P, Karanko H, Jula AM (2014) Office, home, and ambulatory blood pressures as predictors of cardiovascular risk. *Hypertension* 64 (2): 281-286.

[8]Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P (2019) Prevalence of Apparent Treatment-Resistant Hypertension in the United States. *Hypertension* 73 (2): 424-431.

[9]Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D et al. (2025) 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Hypertension* 82 (10): e212-e316.

[10]Parati G, Lombardi C, Pengo M, Bilo G, Ochoa JE (2021) Current challenges for hypertension management: From better hypertension diagnosis to improved patients' adherence and blood pressure control. *Int J Cardiol* 331 262-269.

[11]Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L et al. (2011) Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation* 123 (15): 1611-1621.

[12]Flack JM, Buhnerkempe MG, Moore KT (2024) Resistant Hypertension: Disease Burden and Emerging Treatment Options. *Curr Hypertens Rep* 26 (5): 183-199.

[13]Shah SS, Zhang J, Gwini SM, Young MJ, Fuller PJ et al. (2024) Efficacy and safety of mineralocorticoid receptor antagonists for the treatment of low-renin hypertension: a systematic review and meta-analysis. *J Hum Hypertens* 38 (5): 383-392.

[14]Parati G, Ogedegbe G, Agiro A, Luan S, Davis H et al. (2026) The Burden, Outcomes, and Management of Patients with Aldosterone Dysregulation: A Targeted Literature Review. *Adv Ther*

[15]Lassen MCH, Ostrominski JW, Claggett BL, Wijkman MO, Lee J et al. (2026) Spectrum of Primary Aldosteronism and Risk of Cardiovascular Outcomes: The Atherosclerosis Risk in Communities Study. *JAMA Cardiol* 11 (4): 341-351.
[16]Brown JM (2024) Adverse Effects of Aldosterone: Beyond Blood Pressure. *J Am Heart Assoc* 13 (7): e030142.
[17]Verma S, Pandey A, Pandey AK, Butler J, Lee JS et al. (2024) Aldosterone and aldosterone synthase inhibitors in cardiorenal disease. *Am J Physiol Heart Circ Physiol* 326 (3): H670-H688.
[18]Buffolo F, Tetti M, Mulatero P, Monticone S (2022) Aldosterone as a Mediator of Cardiovascular Damage. *Hypertension* 79 (9): 1899-1911.
[19]Sawathiparnich P, Kumar S, Vaughan DE, Brown NJ (2002) Spironolactone abolishes the relationship between aldosterone and plasminogen activator inhibitor-1 in humans. *J Clin Endocrinol Metab* 87 (2): 448-452.
[20]Brown NJ (2013) Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat Rev Nephrol* 9 (8): 459-469.
[21]Mazzieri A, Battistoni S, Reboldi G (2026) Aldosterone synthase inhibitors in hypertension and chronic kidney disease: double the benefit? *Curr Opin Nephrol Hypertens* 35 (3): 337-346.
[22]Flack JM, Azizi M, Brown JM, Dwyer JP, Fronczek J et al. (2025) Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension. *N Engl J Med* 393 (14): 1363-1374.
[23]Azizi M, Brown JM, Dwyer JP, Flack JM, Jones ESW et al. (2026) Effect of baxdrostat on ambulatory blood pressure in patients with resistant hypertension (Bax24): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 407 (10532): 988-999.
[24]Derington CG, Bress AP, Herrick JS, Jacobs JA, Zheutlin AR et al. (2023) Antihypertensive Medication Regimens Used by US Adults With Hypertension and the Potential for Fixed-Dose Combination Products: The National Health and Nutrition Examination Surveys 2015 to 2020. *J Am Heart Assoc* 12 (11): e028573.
[25]Fernandez CS, Bhalla V, Weil J, Coto E, Erhard C et al. (2025) High Rates Of Mineralocorticoid Receptor Antagonist Discontinuation In Patients With Hypertension: Insights From The EnligHTN Study. *Journal of Hypertension* 43 (Suppl 1): e58-e59.
[26]Pitt B, Williams GH (2024) Aldosterone Synthase Inhibitors and Mineralocorticoid Receptor Antagonists: Competitors or Collaborators? *Circulation* 149 (6): 414-416.
[27]Burnier M, Egan BM (2019) Adherence in Hypertension. *Circ Res* 124 (7): 1124-1140.
[28]Kim E, Lee HH, Kim EJ, Cho SMJ, Kim HC et al. (2025) Factors associated with medication adherence among young adults with hypertension. *Clin Hypertens* 31 e18.
[29]Kengne AP, Briere JB, Zhu L, Li J, Bhatia MK et al. (2024) Impact of poor medication adherence on clinical outcomes and health resource utilization in patients with hypertension and/or dyslipidemia: systematic review. *Expert Rev Pharmacoecon Outcomes Res* 24 (1): 143-154.
[30]Lee JS, Segura Escano R, Therrien NL, Kumar A, Bhatt A et al. (2024) Antihypertensive Medication Adherence and Medical Costs, Health Care Use, and Labor Productivity Among People With Hypertension. *J Am Heart Assoc* 13 (21): e037357.

[31]Peng X, Wan L, Yu B, Zhang J (2025) The link between adherence to antihypertensive medications and mortality rates in patients with hypertension: a systematic review and meta-analysis of cohort studies. *BMC Cardiovasc Disord* 25 (1): 145.
[32]Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR et al. (2023) Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. *Circulation* 148 (20): 1606-1635.
[33]Dziedziak J, Zaleska-Zmijewska A, Szaflik JP, Cudnoch-Jedrzejewska A (2022) Impact of Arterial Hypertension on the Eye: A Review of the Pathogenesis, Diagnostic Methods, and Treatment of Hypertensive Retinopathy. *Med Sci Monit* 28 e935135.
[34]Burnier M, Damianaki A (2023) Hypertension as Cardiovascular Risk Factor in Chronic Kidney Disease. *Circ Res* 132 (8): 1050-1063.
[35]Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA (2007) Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 64 (12): 1734-1740.
[36]Abraham AT, Mojaddedi S, Loseke IH, Bray C (2024) Hypertension in Patients With Peripheral Artery Disease: An Updated Literature Review. *Cureus* 16 (6): e62246.

MINERALYS

April 17, 2026

RE: ICER Draft Scoping Document – Aldosterone Synthase Inhibitors for the Treatment of Hypertension

Dear ICER Review Team,

Mineralys Therapeutics, Inc. (Mineralys) appreciates the opportunity to provide input for this important review on aldosterone synthase inhibitors (ASIs) for the treatment of hypertension (HTN). Despite the widespread use of antihypertensives (AHTs), HTN remains prevalent and inadequately controlled.[1-3] Dysregulated aldosterone has been found to be prevalent in approximately 30% of patients with uncontrolled, including resistant HTN, and is associated with cardio-renal-metabolic syndrome (CRMS) risk.[4-7] By targeting aldosterone synthesis, ASIs lower blood pressure (BP) and reduce aldosterone levels, with the potential to mitigate risk of CRMS events.[8]

Mineralys is the manufacturer of lorundrostat, an oral ASI, which is an investigational product currently under review by the United States (US) FDA. Aldosterone-directed treatments do not exist in the current treatment armamentarium. Mineralocorticoid receptor antagonists (MRAs) such as spironolactone represent only 4% of overall use, which may be due to off-target androgenic adverse events (AEs), as ICER notes, and low adherence.[9-11] No off-target AEs were observed for lorundrostat in the studies conducted to date.[12-14]

In the Advance-HTN trial, participants discontinued their AHTs, and a standardized, optimized background regimen, with confirmed adherence, was initiated for 3 weeks.[12] Those failing to achieve systolic BP of ≤125 mm Hg with 24-hour ambulatory BP monitoring (ABPM) were deemed to have confirmed uncontrolled and resistant HTN and were randomized. At Week 12, the change in 24-hour average systolic BP was −15.4 mm Hg with lorundrostat 50 mg, compared with −7.4 mm Hg with placebo (placebo-adjusted differences of −7.9 mm Hg; P = 0.001).[12] BP reduction was observed throughout the 24-hour period, including early morning, when patients with hypertension are at a higher risk of cardiovascular events.[12, 15-17] When 24-hour average systolic BP rises by 9.5 mm Hg, the risk of all-cause mortality increases by 30%.[17]

In the Phase 3 Launch-HTN trial, participants remained on their existing background treatment for a run-in and those failing to achieve goal were randomized.[14] Lorundrostat demonstrated BP reduction, through in-office automated office systolic BP monitoring (AOSBP), which was measured 24 hours following administration of the previous dose.[14] By Week 6, lorundrostat achieved a least-squares mean reduction in-office systolic BP of −16.9 mm Hg compared with −7.9 mm Hg for placebo (placebo-adjusted difference −9.1 mm Hg; P < 0.001).[14] Importantly, BP reduction accrued through Week 12 (−19.0 mm Hg vs. −7.3 mm Hg; placebo-adjusted difference −11.6 mm Hg; P < 0.001). Results indicate early treatment response, continued improvement, and durability through Week 12.[14]

In addition, the BP lowering effects with lorundrostat were observed across a range of clinically relevant subgroups, including African American patients and women, suggesting applicability across diverse, difficult-to-treat populations with uncontrolled and resistant hypertension.[8,10]

Mineralys offers the following comments and recommendations on ICER's draft scope.

1. Alignment of Population Definitions with 2025 American College of Cardiology and American Heart Association (ACC/AHA) Hypertension Guidelines[18]

The populations of interest in the draft scoping document are defined as *adults with uncontrolled HTN (uHTN) despite use of 2 AHTs and who do not tolerate a third guideline-recommended AHT* and *adults with uncontrolled resistant HTN, not on spironolactone or eplerenone*. These

definitions are not fully aligned with ACC/AHA guidelines[18] and therefore may limit the clinical relevance of the review.

Firstly, ACC/AHA guidelines do not define HTN populations based on intolerance to a third agent.[18] By anchoring the population definition on intolerance, ICER risks introducing a non-standard subgroup. Secondly, ACC/AHA guidelines define resistant HTN as BP above goal despite use of 3 AHT medications with complementary mechanisms of action (including a diuretic) at maximally tolerated doses, or controlled BP requiring ≥4 agents.[18] Importantly, this definition is independent of prior MRA use. By restricting the population to patients not on spironolactone or eplerenone, ICER will inadvertently mix treatment history with disease definition, exclude clinically relevant patients with prior MRA use/unable to tolerate MRAs, and create misalignment with both guideline-based care and clinical trial populations.

Mineralys strongly recommends that ICER: 1) define the uHTN population as patients receiving ≥2 agents with BP above goal, with intolerance evaluated as a subgroup rather than a defining criterion; and 2) align the resistant HTN population to guideline definitions.

2. Outcomes of Importance

Mineralys recognizes the emphasis on patient-important clinical outcomes in the draft scoping document. At the same time, in the absence of long-term cardiovascular (CV) outcomes data for newer therapies such as ASIs, BP reduction remains the most appropriate and clinically meaningful basis for comparison with established agents such as spironolactone. A 10 mm Hg reduction in systolic BP is associated with reduced risk of major CV events and mortality.[19] A large network meta-analysis of 42 randomized trials (144,220 patients) demonstrated a strong, linear relationship between achieved systolic BP and risk of CV events and mortality, with progressively lower risk observed at lower achieved BP levels.[20] A 20 mm Hg reduction in systolic BP was associated with ~40% reduction in CV risk.[20] Therefore, Mineralys encourages ICER to treat BP reduction as the most important comparative endpoint given the relationship between achieved systolic BP and CV risk.

Mineralys strongly recommends that ICER emphasize the importance of BP reduction in comparing efficacy of different agents and its correlation with CV health.

3. Comparator Selection: Amiloride and Clinical Relevance

Mineralys believes that the inclusion of amiloride as a comparator warrants reconsideration. Importantly, amiloride is not part of standard guideline-recommended care for resistant HTN.[18] In US clinical practice, amiloride is not broadly adopted and its use is inconsistent.[21] Inclusion of amiloride risks introducing comparisons that are not reflective of routine care pathways.[18, 22] Furthermore, the evidence base is limited relative to MRAs.[18] Combination use with spironolactone or eplerenone does not represent a standardized, guideline-based treatment pathway in US resistant HTN management, and it introduces overlapping potassium-sparing pharmacology with associated hyperkalemia risk.[23, 24]

Mineralys strongly recommends that ICER remove amiloride as a comparator in this review. More broadly, we encourage ICER to ensure their comparator selection reflects clinical viability and durability.

4. Clinical Framing: Where ASIs Are Most Likely to Be Used

ICER acknowledges the persistent lack of control and limitations of MRA therapy. However, Mineralys would like to emphasize the clinical real-world need for ASIs. The key clinical

inflection point for new therapies is not simply the number of AHTs a patient receives, but the point where further treatment intensification becomes inhibited.[12] Patients may continue to have uncontrolled BP despite renin-angiotensin-aldosterone system (RAAS) blockade, calcium channel blockers, and diuretics, as acknowledged by clinical guidelines and observed in real-world practice;[18, 25] additional medications may offer only limited benefit. In real-world practice, this can lead to lack of BP control despite multiple therapies or limitations in existing options due to tolerability, persistence, or treatment complexity.[25, 26] As patients progress through lines of therapy, the prevalence of elevated aldosterone levels increases significantly.[4] Therefore, therapies targeting aldosterone synthase inhibition, as an alternative biological pathway, may be clinically relevant for patients with uncontrolled and resistant HTN who are using existing therapies with complimentary mechanisms of action.[10, 11]

Mineralys believes that the scope of the ICER review should reflect the uncontrolled and resistant HTN population, where unmet need is greatest and where ASIs are most likely to be used.

5. Treatment Comparisons

The draft scoping document states that direct and indirect evidence may be used in a network meta-analysis of selected outcomes. When conducting treatment comparisons, consider the following differences that exist across trials:

- Differences at baseline (e.g., baseline systolic BP, treatment resistance, comorbidities).[27]
- Variability in patients and background therapy optimization.[24] Note: Advance-HTN participants had confirmed, not apparent HTN. This affects placebo response, meaning placebo-adjusted BP reductions are not directly comparable across trials and may bias indirect comparisons if not appropriately addressed.[24] Black or African American participants, who responded differently to RAAS treatment, were represented 53% and 28% in Advance-HTN and Launch-HTN, respectively.[12, 14]

When conducting treatment comparisons, we encourage ICER to take careful consideration of cross trial differences such as baseline characteristics, background therapy optimization, and study design.

6. Additional Considerations

Mineralys encourages ICER to ensure the review reflects all data critical for understanding real-world applicability, including: 1) both uncontrolled and resistant populations; 2) US demographics (e.g., women, African American/Black, and Hispanic patients); 3) consistent efficacy and safety across trials and subgroups;[12, 14, 28] and 4) emerging data in key populations (e.g., CKD).[29] We appreciate ICER's inclusion of the modified societal perspective and encourage a holistic consideration of the full societal burden on patients and caregivers, including value elements such as productivity loss and dynamic pricing. ASIs are subject to price declines due to market dynamics and eventual genericization, models should incorporate dynamic pricing, rather than constant lifetime pricing, to avoid overstating long-term costs.

Sincerely,

Tiffany Burt
Senior Vice President, Mineralys Therapeutics, Inc.

References

1. Carey RM, Sakhuja S, Calhoun DA, et al. Prevalence of Apparent Treatment-Resistant Hypertension in the United States. Hypertension. 2019;73(2):424–31.

2. Egan BM, Zhao Y, Axon RN, et al. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011;124(9):1046–58. Epub 20110808.

3. Million Hearts. Estimated Hypertension Prevalence, Treatment, and Control Among U.S. Adults. [updated May 12, 2023]; Available from: https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html.

4. Brown JM, Siddiqui M, Calhoun DA, et al. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study. Ann Intern Med. 2020;173(1):10–20. Epub 20200526.

5. Hundemer GL, Curhan GC, Yozamp N, et al. Renal Outcomes in Medically and Surgically Treated Primary Aldosteronism. Hypertension. 2018;72(3):658–66.

6. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018;6(1):41–50. Epub 20171109.

7. Verma S, Pandey A, Pandey AK, et al. Aldosterone and aldosterone synthase inhibitors in cardiorenal disease. Am J Physiol Heart Circ Physiol. 2024;326(3):H670–H88. Epub 20231222.

8. Fioretti F, Testani JM, Tio MC, et al. Aldosterone and Aldosterone Modulation in Cardio-Kidney Diseases. J Am Coll Cardiol. 2025;86(5):354–73.

9. Mineralys. Data on File. IQVIA. July 2025.

10. Azizi M, Riancho J, Amar L. Aldosterone Synthase Inhibitors: A Revival for Treatment of Renal and Cardiovascular Diseases. J Clin Endocrinol Metab. 2025;110(3):e557–e65.

11. Patel SK, Teoh H, Saunthar A, et al. The Emerging Role of Aldosterone Synthase Inhibitors in Overcoming Renin-Angiotensin-Aldosterone System Therapy Limitations: A Narrative Review. Card Fail Rev. 2025;11:e20. Epub 20250818.

12. Laffin LJ, Kopjar B, Melgaard C, et al. Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension. N Engl J Med. 2025;392(18):1813–23. Epub 20250423.

13. Laffin LJ, Rodman D, Luther JM, et al. Aldosterone Synthase Inhibition With Lorundrostat for Uncontrolled Hypertension: The Target-HTN Randomized Clinical Trial. JAMA. 2023;330(12):1140–50.

14. Saxena M, Laffin L, Borghi C, et al. Lorundrostat in Participants With Uncontrolled Hypertension and Treatment-Resistant Hypertension: The Launch-HTN Randomized Clinical Trial. JAMA. 2025;334(5):409–18.

15. Kario K, Ishikawa J, Pickering TG, et al. Morning hypertension: the strongest independent risk factor for stroke in elderly hypertensive patients. Hypertens Res. 2006;29(8):581–7.

16. Renna NF, Ramirez JM, Murua M, et al. Morning blood pressure surge as a predictor of cardiovascular events in patients with hypertension. Blood Press Monit. 2023;28(3):149–57. Epub 20230413.

17. Staplin N, de la Sierra A, Ruilope LM, et al. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. Lancet. 2023;401(10393):2041–50. Epub 20230505.

18. Jones DW, Ferdinand KC, Taler SJ, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2025;86(18):1567–678. Epub 20250814.

19. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–67. Epub 20151224.

20. Bundy JD, Li C, Stuchlik P, et al. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. JAMA Cardiol. 2017;2(7):775–81.

21. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018;72(5):e53–e90.

22. Lee CJ, Ihm SH, Shin DH, et al. Spironolactone vs Amiloride for Resistant Hypertension: A Randomized Clinical Trial. JAMA. 2025;333(23):2073–82.

23. Palmer BF, Clegg DJ. Hyperkalemia across the Continuum of Kidney Function. Clin J Am Soc Nephrol. 2018;13(1):155–7. Epub 20171107.

24. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059–68. Epub 20150920.

25. Mohl JT, Moreno CA, Sadik K, et al. Evaluation of Blood Pressure Control, Medication Adherence, and Therapeutic Inertia in US Patients With Hypertension Prescribed Multiple Antihypertensives. J Am Heart Assoc. 2025;14(12):e034787. Epub 20250616.

26. Champaneria MK, Patel RS, Oroszi TL. When blood pressure refuses to budge: exploring the complexity of resistant hypertension. Front Cardiovasc Med. 2023;10:1211199. Epub 20230621.

27. Dias S, Welton N, Sutton A, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011 (last updated September 2016). Report No.

28. Feldman JM, Frishman WH, Aronow WS. Emerging Therapies for Treatment-Resistant Hypertension: A Review of Lorundrostat and Related Selective Aldosterone Synthase Inhibitors. Cardiol Rev. 2026;34(2):113–6. Epub 20240215.

29. Weir MR, Bhaduri S, Lee K, et al., editors. Lorundrostat, a Novel Aldosterone Synthase Inhibitor (ASI), in Participants with Uncontrolled Hypertension, CKD, and Albuminuria: Results from Explore-CKD: FR-OR091. ASN Kidney Week 2025; 2025 November 6–9, 2025; Houston, Texas, USA: J Am Soc Nephrol. 2025;36(10S).

Thank you for the opportunity to provide comments on ICER's draft scope evaluating Aldosterone Aynthase Inhibitors (ASIs) for the treatment of hypertension. No Patient Left Behind (NPLB) is a nonprofit coalition of biotechnology innovators, investors, healthcare professionals, economists, and patient advocates working to ensure that patients have access to the medicines they need today and in the future. Please find our recommendations on ICER's draft scope below.

Any proposed health economic model should holistically consider a range of societal value elements that are important to patients living with uncontrolled and resistant hypertension (u/rHTN) and their family members. Below are four relevant and quantifiable elements of value supported by published, peer-reviewed evidence that can be estimated using established methodology.[1]

1. **Patient Productivity.** Uncontrolled and resistant hypertension predominantly affects adults of working age. CDC surveillance data indicate a median age of diagnosis in the mid-50s, and most patients managing u/rHTN in clinical practice are still in the workforce.[2,3] This is not a disease of retirement; it is a disease that burdens patients during their most economically productive decades. US employer data directly quantify the cost: workers with uncontrolled hypertension lose nearly twice as many hours per two-week period compared to those with controlled blood pressure (1.35 vs. 0.72 hours).[4] Across the millions of adults with u/rHTN, this recoverable productivity is substantial, measurable, and entirely ignored by a health care system perspective.[5,6] ICER can operationalize this by computing a weighted average of productivity costs for controlled and uncontrolled patients, with weights derived from the BP control rates observed in the trial arms. ***Recommendation: Include patient productivity in the societal perspective***.

2. **Family and Caregiver Spillover.** Even generally controlled hypertension generates measurable caregiver burden: AHA/HRS survey data from 16,731 adults document 0.31 hours of caregiver time per week for patients with hypertension, even before any serious complications occur.[7] That is the floor. For patients with uncontrolled or resistant hypertension, where the trajectory toward heart failure, stroke, chronic kidney disease, and dementia is meaningfully more likely, that burden escalates substantially: 1.6 hours/week for heart failure and 6.1 hours/week for stroke in the same dataset. The burden accumulates not because hypertension is uniquely catastrophic in isolation, but because uncontrolled blood pressure is the upstream driver of catastrophic conditions. Effective BP control reduces patient risk and reduces the caregiving demands of the downstream outcomes imposed on families. ICER's scoping document acknowledges caregiver quality of life as a benefit beyond health; the evidence supports quantifying it, not describing it. A practical approach is to calculate a weighted average of caregiver hours for controlled and uncontrolled health states, using BP control rates from the trial arms as weights, then translate those hours to costs using standard wage rates. ***Recommendation: Quantify caregiver costs in the economic model, starting from the general HTN baseline and scaling to downstream comorbidities.***

3. **Dynamic Net Health System Costs (Genericization).** Aldosterone synthase inhibitors (ASIs) are small molecules that go generic. Post-loss-of-exclusivity (LOE) price declines are

well-documented and substantial: 51% in the first year following generic entry, with cumulative declines reaching up to 95% thereafter.[8] Price dynamics also begin before generic entry. Both baxdrostat and lorundrostat are under FDA review for treatment of hypertension. Branded competition within the ASI class is likely to exert downward price pressure during the exclusivity period itself, well before any generic enters the market. An economic model that assumes a constant drug price over a lifetime horizon overstates cost in both the branded and post-exclusivity periods, systematically misrepresenting the long-run cost of treatment for every future patient cohort. This is a near-universal blind spot: 95% of published cost-effectiveness analyses omit genericization entirely,[9] and ICER's own assessments are included in that figure. Whittington and colleagues have made the affirmative methodological case for incorporating dynamic pricing[10] and their subsequent empirical work demonstrates that post-LOE prices can be reliably estimated from cost-of-goods-sold data, removing the standard uncertainty rationale for omitting them.[11] ***Recommendation: Adopt a stacked cohort model reflecting drug price dynamics over the full treatment lifecycle with price drop of 95% after 14 years of product launch.***

4. **Outcome Certainty and Risk Reduction.** Patients with u/rHTN face near-term actuarial risk of stroke, heart attack, heart failure, kidney failure, and dementia.[12,13,14,15] Empirical evidence confirms these patients are risk-averse — they value the certainty of better outcomes derived from a more effective treatment for u/rHTN beyond the expected QALY gain.[16,17,18] This value is real, patient-centered, and quantifiable via the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) methodology. ***Recommendation: Include a GRACE-based sensitivity analysis.***

The four value elements above are those for which the evidence base is most developed and the patient-population relevance most direct. But they are not exhaustive. Additional value elements — including scientific knowledge spillover generated by a first-in-class mechanism, real option value for adjacent indications such as primary aldosteronism and heart failure with preserved ejection fraction, and adherence-adjusted effectiveness from a therapy that addresses a key tolerability barrier of the current standard of care — may also be applicable and warrant qualitative consideration at minimum. The methodological tools to estimate the four elements above are established and available;[19] their exclusion is a choice, not a technical constraint.

The consequences of that choice are empirically demonstrable: an NPLB analysis of 20 ICER assessments found that adjusting for just two societal value elements — disease severity and risk aversion (via GRACE) and dynamic pricing — increased the share of medicines producing value for money from 8 of 20 to 17 of 20, with the majority of societal value flowing to patients and society rather than innovators in 13 of those cases.[20] A separate stepwise GCEA for a chronic disease treatment similarly found that incorporating a broader set of societal value elements reduced the incremental cost-effectiveness ratio by 93% compared with the conventional health system perspective model.[21] These are subsets of the value elements NPLB urges ICER to consider here; the full picture is likely to show an even larger divergence.

Incorporating additional value elements beyond the immediate assessment matters. Systematically underestimating the true societal value of innovative medicines has real consequences: access barriers for patients who need treatment, distorted price signals that reduce

incentives to invest in future innovation for undertreated populations, and a framework that structurally disadvantages therapies targeting exactly the working-age, racially diverse, and chronically undertreated communities that bear the greatest burden of uncontrolled hypertension. Getting the value framework right is not a nice to have. It is a prerequisite for improving and expanding care for patients.

References

[1] Shafrin J, Kim J, Cohen JT, et al. Valuing the societal impact of medicines and other health technologies: a user guide to current best practices. Forum Health Econ Policy. 2024;27(1):29–116. doi:10.1515/fhep-2024-0014.

[2] Fryar CD, Kit B, Carroll MD, Afful J. Hypertension prevalence, awareness, treatment, and control among adults age 18 and older: United States, August 2021–August 2023. NCHS Data Brief, no. 511. National Center for Health Statistics. 2024. doi:10.15620/cdc/164016.

[3] Saxena M, Bhatt DL, Laffin LJ, et al. Lorundrostat for uncontrolled hypertension: the LAUNCH-HTN randomized clinical trial. JAMA. 2025;334(5):409–418.

[4] Unmuessig V, Navar AM, Mulder H, et al. Workplace productivity loss associated with hypertension. J Clin Hypertens. 2016;18(11):1097–1103.

[5] Sullivan PW, Ghushchyan V, Wyatt HR, Wu EQ, Hill JO. Productivity costs associated with cardiometabolic risk factor clusters in the United States. Value Health. 2007;10(6):443–450.

[6] MacLeod KE, Ye Z, Donald B, et al. A literature review of productivity loss associated with hypertension in the United States. Popul Health Manag. 2022;25(3):297–308.

[7] Dunbar SB, Khavjou OA, Bakas T, et al. Projected costs of informal caregiving for cardiovascular disease: 2015 to 2035. Circulation. 2018;137(19):e558–e577.

[8] Aitken M. Medicines use and spending in the U.S.: a review of 2015 and outlook to 2020. IMS Institute for Healthcare Informatics. 2016.

[9] Neumann PJ, Podolsky MI, Basu A, Ollendorf DA, Cohen JT. Do cost-effectiveness analyses account for drug genericization? A literature review and assessment of implications. Value Health. 2022;25(1):59–68.

[10] Whittington MD, Neumann PJ, Cohen JT, Campbell JD. The case for including dynamic drug pricing in cost-effectiveness analyses under the IRA. Health Affairs Forefront. October 18, 2023. doi:10.1377/forefront.20231016.197078.

[11] Whittington MD, Mattingly TJ. Estimating a drug's price after loss of exclusivity as a function of its cost of goods sold. Appl Health Econ Health Policy. 2025;23(1):75–83.

[12] Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–967.

[13] Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure. Lancet. 2021;397(10285):1625–1636.

[14] Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2(7):775–781.

[15] Sim JJ, Shi J, Kovesdy CP, Kalantar-Zadeh K, Jacobsen SJ. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. Kidney Int. 2015;88(3):622–632.
[16] Mulligan K, Baid D, Doctor JN, Phelps CE, Lakdawalla DN. Risk preferences over health: empirical estimates and implications for medical decision-making. J Health Econ. 2024;94:102857.
[17] Lakdawalla DN, Malani A, Reif J. The insurance value of medical innovation. J Public Econ. 2017;145:94–102.
[18] Lakdawalla DN, Phelps CE. Health technology assessment with diminishing returns to health: the generalized risk-adjusted cost-effectiveness (GRACE) approach. Value Health. 2021;24(2):244–249.
[19] Flack JM, Ferdinand KC, Bhatt DL, et al. Baxdrostat for treatment-resistant hypertension. N Engl J Med. 2025. doi:10.1056/NEJMoa2507109.
[20] Arndorfer S, Incerti D, Masia N, Lakdawalla DN, Phelps CE. Getting the math right when measuring the value of new medicines. EntityRisk White Paper. 2023.
[21] Chou JW, Graf M, Díaz Espinosa O, et al. Generalized cost-effectiveness analysis to assess treatment value in hepatitis C. Am J Manag Care. 2023;29(12):696–703. doi:10.37765/AJMC.2023.89468.