



September 9, 2026

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

Dear Ms. Emond,

AstraZeneca appreciates the opportunity to comment on ICER's August 12, 2026 Draft Evidence Report on aldosterone synthase inhibitors (ASI) for the treatment of hypertension.¹ We have identified two assumptions that materially affect the report's conclusions:

1. ICER's assumption that 20% of eligible patients will initiate ASI treatment in the first year substantially overstates the likely real-world uptake and the resulting budget impact; and
2. ICER's comparator selection does not adequately account for important differences in mechanism of action, tolerability, intended clinical use, and the patient populations in which these therapies have been evaluated.

ICER should correct both issues before publishing its Final Evidence Report. At a minimum, any conclusions based on the current uptake and comparator assumptions must be explicitly qualified. The final assessment must also incorporate the complete publicly available evidence for baxdrostat, including the recently presented 52-week efficacy and safety data. These corrections are particularly important because ICER is assessing a substantial population with significant unmet need: patients whose blood pressure remains uncontrolled despite treatment with two or more antihypertensive therapies.

Patients Uncontrolled on Two Therapies Represent a Material Unmet Need

A recent US observational study found that, compared with patients controlled on exactly two antihypertensive classes, patients whose blood pressure remained uncontrolled on exactly two classes had higher risks of stroke, myocardial infarction, heart failure, chronic kidney disease progression, end-stage kidney disease, and all-cause mortality.² The consequences extend beyond clinical events: uncontrolled hypertension also imposes substantial costs on the healthcare system and a significant quality of life burden on patients.²⁻⁴

While medication nonadherence⁵ and treatment related side effects⁶⁻⁸ can contribute to poor blood pressure control, persistent elevation may also reflect dysregulation of the aldosterone

pathway, which is not directly addressed by most available antihypertensives.⁹⁻¹² Recent evidence also found dysregulated aldosterone was similarly prevalent among patients with uncontrolled hypertension receiving exactly two antihypertensive classes and patients with resistant hypertension receiving three or more classes.¹³ These findings demonstrate that aldosterone dysregulation is not confined to resistant hypertension and that patients uncontrolled on two therapies are a clinically relevant population for ICER's assessment.

ICER's Uptake Assumption is Not Credible and Materially Overstates Budget Impact

ICER's budget impact analysis assumes that 20% of the eligible patient population will initiate ASI treatment in each of the five years modeled.¹ This assumption is not consistent with observed uptake patterns for newly launched cardiovascular (CV) therapies and is likely to materially overstate budget impact. The assumption does not adequately account for payer coverage decisions and utilization management, treatment sequencing, clinician education and adoption, patient preferences, and the time required for a new therapy to be incorporated into guidelines and routine clinical practice.¹⁴ These factors significantly constrain uptake, particularly during the first year following launch.

Real-world CV launch experience demonstrates the scale of this overstatement. Entresto achieved approximately 2% uptake among eligible patients during its first year following launch.¹⁵ ICER's 20% assumption is therefore approximately ten times the observed first-year uptake of a relevant CV launch analogue. The number of patients who are epidemiologically eligible for treatment cannot reasonably be considered equivalent to the number likely to receive treatment soon after launch. Many eligible patients will not be immediately identified, offered treatment, receive payer coverage, or begin therapy.

Action: ICER should replace the 20% first-year uptake assumption in its base case analysis with a more realistic estimate of approximately 2%, followed by an evidence-based adoption curve in subsequent years.

This correction is material. ICER's own analysis shows that uptake of approximately 2% would keep the modeled budget impact below its threshold, even when using the list price without discounts or rebates.¹ ICER's finding that baxdrostat may exceed the budget impact threshold is therefore driven by an unsupported uptake assumption, not a credible estimate of expected near-term use.

ICER's Choice of Comparators Does Not Reflect Clinical Practice or the Distinctive Evidence Base for ASIs

ICER compares ASIs with spironolactone, eplerenone, amiloride, and amlodipine as though these medicines represent broadly equivalent treatment options across the modeled populations. They do not. Their mechanisms, tolerability, clinical use, and supporting evidence differ materially.

Mineralocorticoid receptor antagonists (MRAs) are relevant treatment options in resistant hypertension, but ICER has not justified treating them as equivalent comparators across Populations 1 and 2. Spironolactone and eplerenone block the mineralocorticoid receptor resulting in compensatory increase of circulating aldosterone, while baxdrostat inhibits aldosterone synthase and reduces aldosterone production.¹⁶ MRA use is also constrained by hyperkalemia, monitoring requirements, tolerability, and treatment discontinuation.^{8; 17-19} Among patients who were on two or more antihypertensive classes, spironolactone and eplerenone were only dispensed to 5.4% and 0.3% of patients respectively, according to a real-world evidence (RWE) study conducted by CVS Healthspire which analyzed a large national pharmacy database.²⁰ ICER's analysis must account for these differences rather than assume clinical interchangeability.

Amiloride is generally reserved for narrower clinical circumstances, including patients with hypokalemia or intolerance to MRAs.⁴ Amiloride was dispensed in 0.1% of patients on two or more antihypertensive classes according to a RWE study conducted by CVS Healthspire.²⁰ It is therefore not a representative comparator for the broader populations modeled by ICER.

ICER's amlodipine comparison relies on indirect and methodologically mismatched evidence. ICER acknowledges in the Draft Evidence Report that it did not find placebo-controlled trials that examined the use of amlodipine as a third-line agent. Instead, ICER estimated the effect of amlodipine based on trials of single-pill fixed combination therapies including amlodipine (triple therapy) compared with non-amlodipine dual combination therapy clinical trials.²¹⁻²⁴ Estimating the effect of amlodipine based on differences between single-pill triple-combination and dual-combination therapy trials introduces additional uncertainty and is methodologically distinct from the evidence base available for ASIs. ASIs have been evaluated primarily as add-on therapy in patients receiving stable background of two or more antihypertensive regimens, whereas amlodipine studies often included washout or run-in periods and assessed initiation of new combination therapy rather than treatment intensification in patients already receiving two or more antihypertensive therapies.²¹⁻²⁴ As a result, the amlodipine evidence base may not provide an appropriate basis for comparison with ASIs.

More broadly, indirect comparisons based solely on blood pressure reduction do not fully capture the biological and clinical distinctions between these interventions. For example, evidence suggests that excess aldosterone is associated with increased CV and kidney disease progression independent of blood pressure.^{25; 26} Because ASIs directly inhibit aldosterone production, they may offer clinical benefits beyond blood pressure lowering.

Action: ICER should revise its comparator framework to reflect real-world clinical use and the comparability of the underlying evidence. Comparisons that are not clinically or methodologically aligned should be removed from the base case or presented as sensitivity analyses. If ICER retains them, the Final Evidence Report must explicitly characterize the resulting clinical, cost-effectiveness, and budget-impact conclusions as highly uncertain.

ICER Must Incorporate the Complete 52-Week Evidence Base

ICER's draft assessment reflects the 12-week evidence available at the time of its analysis.²⁷ Publicly available 52-week results now provide material longer-term evidence for baxdrostat. At week 52, baxdrostat (2 mg) demonstrated a placebo adjusted reduction in mean seated systolic blood pressure of 12.6 mmHg (95% CI, -16.7 to -8.5; $p < 0.0001$), with safety findings consistent with the 12 week results.²⁸

Action: ICER must incorporate these data into its final clinical and economic assessments. A Final Evidence Report based only on the 12-week evidence, despite the availability of 52-week data, would be materially incomplete and potentially misleading, particularly regarding the durability of baxdrostat's effect and its longer-term safety profile.

Conclusion:

ICER must therefore:

1. Replace its unsupported 20% first year uptake assumption with an approximately 2% base case, followed by an evidence-based adoption curve;
2. Revise its comparator framework or explicitly qualify any conclusions derived from clinically and methodologically mismatched evidence; and
3. Incorporate the publicly available 52-week efficacy and safety data for baxdrostat.

These are not peripheral methodological refinements. Each materially affects the report's conclusions. If left uncorrected, the Final Evidence Report will overstate baxdrostat's budget impact, convey a degree of comparative certainty that the evidence does not support, and present a materially incomplete and potentially misleading assessment of baxdrostat.

Patients, clinicians, payers, and policymakers should be able to rely on ICER's Final Evidence Report as rigorous, balanced, and current. In its present form, the Draft Evidence Report does not meet that standard.

Sincerely,

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Biopharmaceuticals Business Unit,
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RE: ICER Draft Report – Aldosterone Synthase Inhibitors for the Treatment of Hypertension

Dear ICER Review Team,

Mineralys Therapeutics, Inc. (Mineralys) appreciates the opportunity to respond to the draft evidence report for ICER's evaluation on aldosterone synthase inhibitors (ASIs) for the treatment of hypertension (HTN). Mineralys is the manufacturer of lorundrostat, an oral ASI and investigational product currently under review by the United States (US) Food and Drug Administration (FDA) for the treatment of uncontrolled HTN (uHTN) and resistant HTN (rHTN).

We appreciate ICER's continued engagement throughout this review and the opportunity to provide feedback on the draft report. We respectfully offer the following comments and recommendations to help ensure the report appropriately reflects current clinical guidelines, real-world treatment patterns, and the available clinical evidence.

1. Unmet Need in Uncontrolled and Resistant HTN

Despite the widespread use of antihypertensives (AHTs), HTN remains prevalent and inadequately controlled.¹⁻³ HTN affects an estimated 48% or 120 million adults in the US.³ Among those treated with two or more AHTs, approximately 50% have uHTN, defined as blood pressure (BP) $\geq 130/80$ mm Hg in individuals taking AHTs.^{1,4} Further, an estimated 10 million US adults meet the criteria for apparent rHTN, defined as BP above goal despite treatment with 3 AHTs with complementary mechanisms of action or BP at goal but requiring ≥ 4 AHTs.¹

HTN, particularly uHTN, is associated with substantial morbidity and mortality. Inadequate BP control increases the risk for cardio-renal-metabolic complications, including heart failure and chronic kidney disease.⁵ In the US, HTN has been the primary or contributing cause of over 600,000 deaths annually.⁶ Compared to individuals with controlled HTN or normotensive adults, those with treated but uncontrolled HTN and apparent rHTN have higher risks of cardiovascular disease (CVD) outcomes and CVD mortality, and in some cohorts, higher risk of all-cause mortality.⁷⁻⁹ Together, the high prevalence of uHTN and its associated clinical consequences underscore the need for additional treatment approaches that can help more patients achieve and maintain BP control.

Dysregulated aldosterone is a key biological driver of uHTN, including rHTN, and is estimated to affect approximately 30% of people with HTN.¹⁰⁻¹² Until recently, treatment approaches for uHTN generally involved adding or intensifying AHTs, which may not directly address the underlying dysregulation of aldosterone.¹³ Although other therapies can block the downstream effects of aldosterone, treatment may be accompanied by compensatory increases in aldosterone levels.¹⁴⁻¹⁶ By targeting aldosterone synthesis, ASI therapy has the potential to improve BP control among patients with dysregulated aldosterone and, through improved BP control, reduce the long-term risk of cardiovascular and other cardio-renal-metabolic complications. ASIs represent an important and efficacious new therapeutic option in a previously under-innovated HTN space.

2. Lorundrostat Clinical Trials

Clinical studies evaluating lorundrostat have reported BP efficacy and safety findings while also validating aldosterone as an integral therapeutic target in uHTN and rHTN.¹⁷ This includes two

pivotal, registrational trials – the Phase 3 Launch-HTN trial and Phase 2 Advance-HTN trial – which support robust, durable, and clinically meaningful reductions in systolic BP by lorundrostat.¹⁷⁻¹⁹ Lorundrostat was generally well tolerated in both trials with a favorable safety profile.^{18,19} Summaries of both trials are provided below.

In the Phase 2 Advance-HTN trial, participants discontinued their AHTs and a standardized, optimized background regimen, with confirmed adherence, was initiated for 3 weeks.¹⁸ Those failing to achieve systolic BP (SBP) of ≤ 130 mm Hg with 24-hour ambulatory BP monitoring were deemed to have confirmed uncontrolled and resistant HTN and were randomized. At Week 12, the change in 24-hour average SBP was -15.4 mm Hg with lorundrostat 50 mg, compared with -7.4 mm Hg with placebo (placebo-adjusted difference of -7.9 mm Hg; $p=0.001$).¹⁸ BP reduction was observed throughout the 24-hour period.^{18,20-22} This finding is clinically meaningful given the established association between 24-hour average SBP and long-term outcomes; when 24-hour average systolic BP rises by 9.5 mm Hg, the risk of all-cause mortality increases by 30%.²²

In the Phase 3 Launch-HTN trial, participants remained on their existing background treatment (including a thiazide or thiazide-like diuretic) for a run-in and those failing to achieve goal were randomized.¹⁹ BP reduction was measured through in-office automated office systolic BP monitoring at trough, 24 hours following administration of the previous dose.¹⁹ By Week 6, lorundrostat demonstrated a least-squares mean reduction in in-office SBP of -16.9 mm Hg compared with -7.9 mm Hg for placebo (placebo-adjusted difference -9.1 mm Hg; $p<0.001$).¹⁹ Importantly, BP reduction accrued through Week 12 (-19.0 mm Hg vs. -7.3 mm Hg; placebo-adjusted difference -11.6 mm Hg; $p<0.001$). BP reduction was observed beginning at Week 2, with continued improvement and maintenance of effect through Week 12.¹⁹

While ICER did include Launch-HTN in its Clinical Trial Diversity Rating Tool, it did not evaluate Advance-HTN. Launch-HTN enrolled 47% women and 29% Black or African American participants.¹⁹ In Advance-HTN, women were also well represented, with 40% enrolled, and 53% of the participants enrolled were Black/African American.¹⁸

Robust clinical data from the two pivotal registrational Launch-HTN and Advance-HTN trials support the efficacy and safety profile of lorundrostat across diverse patient populations.

3. Network Meta-Analysis (NMA)

ICER's NMA combined studies with meaningful clinical and methodological heterogeneity, limiting the validity of the results and contributing to substantial uncertainty in the comparative estimates. As stated by ICER, "95% credible intervals were wide and included potentially clinically significant differences in both directions" for several comparisons. We recommend that ICER revise the NMA approach as follows:

First, ICER should not include data from Advance-HTN or Target-HTN in the NMA due to important differences in trial design, endpoint assessment, and patient characteristics that limit comparability with other trials. Although ICER states they included trials aligned to BaxHTN and Launch-HTN, there are known differences with other included studies that may violate the similarity assumptions required for valid cross-trial comparisons. Target-HTN was a proof-of-concept, dose-ranging trial that enrolled participants who continued on their usual background AHT regimen.²³ Advance-HTN enrolled patients with confirmed rather than apparent uncontrolled/resistant hypertension; assigned patients to initiate a standardized

background AHT regimen consisting of olmesartan, indapamide, hydrochlorothiazide and/or amlodipine upon enrollment; and assessed different BP endpoints (ambulatory versus office). Additionally, Black or African American participants, who respond differently to renin-angiotensin-aldosterone system (RAAS) treatment, were represented 53% and 29% in Advance-HTN and Launch-HTN, respectively.^{18,19} Collectively, these differences may impact the size of the treatment effects, meaning placebo-adjusted BP reductions are not directly comparable across trials and may bias indirect comparisons.²⁴ If the cross-trial differences are not appropriately addressed, the NMA should be treated cautiously as the results may reflect the underlying cross-trial differences in design, populations, or endpoint measurement rather than true differences between treatments.

Second, ICER's NMA should consistently use data from the same timepoint for all interventions. ICER's NMA currently includes BP measurements at different follow-up timepoints ranging from 6 to 26 weeks. AHT effects may accrue over time as patients reach steady-state response, background therapies stabilize, adherence patterns emerge, and placebo responses change. For lorundrostat, ICER currently uses 6-week Launch-HTN data in their NMA. BP reduction continued to accrue through Week 12, with lorundrostat demonstrating a least-squares mean reduction in automated office systolic BP of -19.0 mm Hg compared with -7.3 mm Hg for placebo, corresponding to a placebo-adjusted difference of -11.6 mm Hg.¹⁹ Limiting the NMA to consistent timepoints would allow for fair comparisons of interventions in the review, while comparing a treatment assessed early in follow-up with another assessed later may inaccurately characterize BP lowering.

Third, ICER should only pool BP endpoints that are consistent in measurement methods. The NMA incorporated BP endpoints measured using different methods, including ambulatory and automated in-office BP. These measures are not interchangeable;²⁵ ambulatory BP captures BP over a 24-hour period, including nighttime and early-morning values, whereas automated in-office BP reflects a standardized clinic-based measurement at a single point in time. Differences in measurement approach can influence the magnitude of observed BP reductions, placebo response, and variability across studies, therefore increasing uncertainty in the NMA estimates of BP lowering.

Fourth, ICER's NMA should only include studies with comparable and consistently defined background therapies. Background AHT treatment may vary by study period, geography, protocol, and clinician practice, creating differences in baseline risk and standard of care that can compromise comparability across studies. In the lorundrostat trials, patients randomized to placebo continued background AHTs; over one-third of patients in Advance-HTN and approximately half of patients in Launch-HTN were already receiving a calcium channel blocker.^{18,19} Accordingly, the placebo arms do not represent an absence of calcium channel blocker therapy and may not be directly comparable with control arms in studies evaluating initiation of amlodipine or using materially different background regimens. ICER should therefore carefully assess background treatment within each included study and restrict the NMA to trials with sufficiently comparable background therapy. Without appropriately addressing differences in background therapies, the results from the NMA may reflect differences in underlying standard of care rather than differences in treatment effects.

Finally, ICER should not include open-label studies in the NMA. The inclusion of open-label amloride studies introduces additional risk of bias compared with randomized, double-blind controlled trials and may further increase uncertainty in the comparative estimates. Because

treatment assignment and outcome assessment are not blinded in open-label designs, they are prone to measurement, detection, or reporting biases that can impact results. Including open-label studies in the NMA increases uncertainty in the comparative estimates and introduces additional biases from the lack of blinding.

Mineralys recommends that ICER appropriately accounts for heterogeneity across trials by 1) removing Advance-HTN and Target-HTN from the analysis; 2) consistently using 12-week endpoints for the included trials; 3) including BP endpoints that are consistent in measurement methods; 4) including studies with comparable background therapies; and 5) excluding open-label studies. Given the above limitations in the ICER analysis and the resulting wide credible intervals reflecting uncertainty in the comparative effectiveness estimates, ICER's NMA findings should be interpreted with caution.

4. Comparator Selection: Amiloride and Eplerenone

The inclusion of amiloride and eplerenone as comparators in the evaluation should be reconsidered given their limited role in the management of rHTN. Current ACC/AHA guidelines do not recommend amiloride as part of the standard treatment pathway for rHTN.²⁵ In US clinical practice, amiloride is not broadly adopted and its use is inconsistent.²⁶ Eplerenone may similarly have limited relevance as a comparator because of its relatively low use in current US practice compared with more commonly used therapies such as spironolactone.²⁵ As a result, comparisons against amiloride and eplerenone may be of limited relevance to clinicians and payers seeking to understand how ASIs perform relative to therapies commonly used in practice.

Mineralys strongly recommends that ICER remove amiloride and eplerenone as comparators in this review. More broadly, we encourage ICER to ensure their comparator selection reflects current clinical practice.

5. Limitations of ICER's Economic Model

ICER's economic model does not fully capture the clinical and economic benefits of ASIs for patients with HTN. Mineralys makes the following recommendations to help ensure that the model appropriately reflects the available clinical evidence.

First, the proposed economic model should be more comprehensive in capturing the clinical complications experienced by patients with uHTN and rHTN, including angina, atrial fibrillation, chronic kidney disease stages, and cognitive impairment. These are clinically meaningful complications in patients with HTN and can contribute substantially to long-term morbidity, healthcare resource use, mortality risk, and decrements in quality of life, and therefore they are relevant for the economic model. Excluding these events may therefore understate the full clinical and economic impact of BP-lowering agents.

Second, ICER's economic model should incorporate AEs associated with AHTs, including both their costs and quality-of-life impacts. At minimum, ICER should include clinically relevant AEs that are expected to differ across comparators, particularly hormonal effects such as gynecomastia, breast tenderness, erectile dysfunction, and menstrual irregularities, as well as events requiring additional monitoring or management, including electrolyte abnormalities like hyponatremia and hyperkalemia. Unlike other treatment options, ASIs provide targeted inhibition of aldosterone synthesis. ASIs do not directly interact with sex hormone receptors and therefore may avoid anti-androgenic adverse effects associated with steroidal MRAs.²⁷ Although

MRAs are recommended for rHTN, their use in routine clinical practice remains limited and may be constrained by off-target androgenic AEs, tolerability concerns, and poor treatment adherence.^{25,27-30} The safety findings of lorundrostat observed in clinical studies to date has not included reports of off-target androgenic adverse events.^{18,19,23,27} Excluding AEs from the economic model may understate meaningful differences across treatments, particularly in a population that often requires multi-drug therapy and may be vulnerable to tolerability issues that influence discontinuation, switching, monitoring, and downstream healthcare resource use.

Third, ICER should incorporate estimates of treatment discontinuation that are specific to the treatment and population being modelled. In the base-case analysis, discontinuation of lorundrostat in the first three months is estimated to be 10% based on data from Launch-HTN, whereas the discontinuation rate of eplerenone and amiloride was 7.7%, based on a real-world study that examined Swedish patients receiving calcium channel blockers. Alternative estimates, including a US-based analysis that looked specifically at MRA use in the real world, found discontinuation rates of 73% of users, with the median time to discontinuation of 90 days.³¹ Given differences in patient behaviors across geographies and available evidence for the products being considered, as well as the sensitivity of results to the value of this input, we encourage ICER to ensure the best available data is being utilized to prevent biasing results.

Finally, 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 caregiver quality of life, caregiver costs and dynamic pricing. As 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.

Mineralys recommends that ICER first update their NMA to address the methodological limitations noted above. Because the NMA results are a main driver of the cost-effectiveness results, ICER's cost-effectiveness findings should be carefully interpreted in light of the NMA's acknowledged limitations. In addition, we recommend that ICER update their cost-effectiveness model to include all relevant clinical and economic benefits of ASIs for HTN, including clinical complications, AEs, appropriate input values, and broader elements of value. Excluding these elements introduces bias and decreases confidence in ICER's cost-effectiveness results.

Sincerely,

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Mineralys Therapeutics

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September 9, 2026

Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Dear Ms. Emond:

On behalf of the American Association of Kidney Patients (AAKP), the nation's largest independent kidney patient organization, we are writing this letter to highlight the urgent and unmet need to treat hypertension and high blood pressure as central drivers for kidney damage and kidney disease. In that context, we are commenting on ICER's Draft Evidence Report, "*Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value*," dated August 12, 2026. Under a separate submission, we also joined the formal comments submitted by our long-time allies with the National Forum's Value & Access Collaborative (V&AC). Those comments reflect not only our concerns as the largest kidney patient consumer organization, but also the shared concerns of a larger coalition of patient, medical expert, public health, public policy and payer organizations who believe the report is lacking and in need of substantive revision. For your awareness, AAKP has also been a long-standing member and ally of the Partnership to Improve Patient Care, under the leadership of former Congressman, and long-time patient advocate, The Honorable Tony Coelho.

Our central concerns with the ICER Draft Evidence Report are related to the underlying structural bias and myopic nature of the ICER economic analysis and the overwhelming lack of substantive inclusion of insight data. We find the draft report lacking in the real world evidence available from the people most impacted by hypertension and the communities that are disproportionately bearing the burdens – America's minority communities. We are concerned that if this draft report is finalized without substantive revision and balance, it will, in fact, exacerbate health disparities.

AAKP has worked for years to make certain that White House and the Congress balance regulatory and payment policies with the lived experiences of patients. AAKP, along with the larger kidney community, have been highly successful in securing White House initiatives, Executive Orders and legislation in the arena of kidney care and new innovations based on substantive inclusion of patient voices. In fact, the two largest policy efforts that have impacted American kidney care have their direct origins in patient experience and meaningful patient engagement. The historic 1973 passage of the modern End State Disease Program administered by the Centers for Medicare and Medicaid Services and the historic 2019 *Executive Order on Advancing American Kidney Health* were each developed with patients at the decision table as well as engaged partners across all parameters of implementation. These were not simply "check off the box" efforts to engage patients. To the contrary, elected, appointed and career

federal officials turned to patients to craft policies that had direct financial implications totaling billions of dollars in taxpayer funds – and to this day, federal agencies and Congress continue to do so. Based on this history, it is puzzling – and disheartening – to witness ICER reliance on economic models that are out of touch and disrespectful to the kidney patient community and our sensibilities as informed consumers in the marketplace. Further, with the known evidence related to the long-term impact of hypertension on American kidney health, especially among minority Americans, we find it alarming that ICER would insert itself into the decision-making between patients and the doctors they choose and trust for managing their hypertension and kidney health. Restricting new innovations entering the market and denying medical experts tools they could choose from to treat the most problematic conditions and negatively impacted patients makes little sense in this era of medical innovation – and era we have termed the Decade of the Kidney™ based on the promising and hopeful advances in science and innovation.

Further, we believe that this draft report was prepared using a model that relied upon a narrow silo of information uninformed by expert patient views, but also the evolving science and national discussion centered around Cardio Kidney Metabolic (CKM) health. The growing national consensus for preventive care is to consider the whole needs of the person and to closely examine the benefit to both patients and taxpayers of delaying and stopping disease progression and multiple organ damage and failure. AAKP is national and global leader for patient advocates in this emerging field of medicine. Based on our interactions with research and medical experts over the past five years in this arena, we have only heard about the unmet needs in regard to more solutions – not once have we heard from an expert concerned about cost alone as it related to solutions. We believe that is because the true and total comparative cost of not addressing these issues intelligently - including greater long-term disease burdens, disability, unemployment and more negatively impacted families – makes the case and demand for new therapeutics rather obvious.

We look forward to the upcoming meeting on this issue and the public dialogue related to ICER's Draft Evidence Report, "*Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value.*"

Sincerely,



Edward V. Hickey, III
AAKP President
Chair, AAKP Veterans Health Initiative
Chronic Kidney Disease Patient



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Dear Ms. Emond:

Thank you for the opportunity to comment on ICER's Draft Evidence Report, "*Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value*," dated August 12, 2026.

The Mended Hearts, Inc., the nation's oldest and largest peer-to-peer support organization for cardiovascular patients, families, and caregivers, appreciates ICER's continued commitment to incorporating patient voice throughout the review process, and we offer the following comments from the perspective of the patients we serve: those living daily with uncontrolled and treatment-resistant hypertension.

1. The report accurately reflects the barriers our community lives with every day.

We want to first affirm what the draft already captures well: clinical inertia, pill burden, and intolerance of existing fourth-line options are not abstract concerns for our members, but rather the reason so many patients remain above goal for months or years. Members of our community have shared that side effects from spironolactone, particularly gynecomastia and the fear of hyperkalemia, lead them to decline escalation of therapy altogether rather than accept those tradeoffs. When a patient stops advocating for their own care because the next available option feels worse than the disease, that is a meaningful harm, even if it is difficult to quantify in a clinical trial.

2. Tolerability is itself a patient-important outcome, not a secondary consideration.

We ask ICER to weigh the tolerability profile of ASIs, particularly the absence of reported gynecomastia and the comparatively lower risk of hyperkalemia, as a genuine benefit to patients, not merely a footnote pending long-term cardiovascular data. For patients who have already declined or discontinued a mineralocorticoid receptor antagonist (MRA) because of these side effects, a better-tolerated option that achieves comparable blood pressure control may be the difference between staying on therapy and abandoning treatment entirely. We

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would encourage the final report to give this consideration appropriate weight, especially for the population in this review who have not yet tried, or could not tolerate, a third first-line agent.

3. Insurance barriers and the burden of the appeals process.

Even when a treatment is available and appropriate for a patient, access is often decided long before a prescription reaches the pharmacy counter. Some of our members regularly describe being required to fail on one or more older, cheaper medications before an insurer will approve a newer option — even when a clinician has already determined, based on that patient's history or side effect profile, that the older drug is unlikely to work or unlikely to be tolerated. For patients with uncontrolled hypertension, every month spent working through step therapy requirements is a month spent with blood pressure above goal, and elevated risk of stroke, heart attack, or kidney damage does not pause while paperwork is pending.

When a prior authorization is denied, the appeals process itself becomes its own health burden. Patients tell us they often do not know how to file an appeal, do not have a clinician's office with the staff time to assist, or give up after a denial simply because the process is confusing or exhausting to navigate while also managing a chronic illness. Older adults, patients with lower health literacy, and those without a consistent primary care relationship are especially likely to abandon treatment altogether rather than pursue an appeal — meaning the patients most likely to face access barriers are often the same patients already facing the greatest disparities in blood pressure control.

We recognize that ICER does not set insurance policy or utilization management criteria. However, we ask that the final report acknowledge these real-world access barriers directly, and that ICER encourage payers to design utilization management policies for ASIs that do not impose step therapy requirements on patients who have already demonstrated intolerance to MRAs, and that streamline rather than burden the appeals process for patients with resistant or uncontrolled hypertension.

4. The equity findings deserve emphasis, not just documentation.

We appreciate ICER's inclusion of the Health Improvement Distribution Index findings showing that Black Americans, who experience disproportionately higher rates of hypertension and resistant hypertension, could see greater benefit from effective treatment. Our members from underserved communities report greater difficulty reaching blood pressure goals, whether due to access barriers, food insecurity, or simply not being offered the full range of treatment options. We encourage ICER to carry this finding through prominently into the final report's conclusions and any subsequent stakeholder deliberations, not just the supplementary tables.



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5. Caregiver impact is real and should not be minimized.

The draft rightly notes the improved blood pressure control may reduce caregiver burden by preventing disability from stroke, kidney disease, or cognitive decline. We hear frequently from spouses and family caregivers about the toll of caring for a loved one after a hypertension-related cardiovascular event. We support continued attention to this caregiver dimension as ICER's assessments evolve.

We thank ICER for the rigor and transparency of this review, and for the meaningful role patient input has already played in shaping it. The Mended Hearts, Inc. remains committed to ensuring that the patients living with uncontrolled and resistant hypertension are represented not as a population in a model, but as people navigating real, daily tradeoffs in their care.

Respectfully,

Mandy Sandkuhler
Director, Partnerships and Communications
The Mended Hearts, Inc.

Primary Aldosteronism Foundation
Comments on ICER's Draft Evidence Report: Aldosterone Synthase Inhibitors for the Treatment of Hypertension

The Primary Aldosteronism Foundation (PAF) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's Draft Evidence Report, Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value, evaluating FDA-approved baxdrostat (Baxfendy) and investigational lorundrostat, which is not currently FDA-approved, for uncontrolled and resistant hypertension.[1]

PAF is a nonprofit patient advocacy organization dedicated to improving awareness, diagnosis, treatment, research, and outcomes for people affected by primary aldosteronism (PA). Our central concern is not that ICER has chosen the wrong hypertension populations to evaluate. Rather, it is that a broad population-average assessment can obscure clinically important heterogeneity within those populations - particularly patients whose hypertension is driven by inappropriate aldosterone production.

Primary aldosteronism is the most common endocrine cause of secondary hypertension and is especially prevalent in resistant hypertension.[2,3] Yet PA remains profoundly underrecognized. Because aldosterone synthase inhibitors (ASIs) directly suppress aldosterone production, an assessment of their effectiveness and value should explicitly consider the patients in whom aldosterone excess is itself the disease mechanism. PAF respectfully asks ICER to make that distinction more visible in the revised Evidence Report.

1. Primary Aldosteronism Is Common, Underdiagnosed, and Highly Relevant to ICER's Modeled Population

The 2025 AHA/ACC hypertension guideline estimates that PA occurs in approximately 5% to 10% of people with hypertension and approximately 20% of those with resistant hypertension; the 2025 Endocrine Society guideline describes PA as the most common endocrine cause of secondary hypertension.[2,3] Contemporary research also supports a continuum of renin-independent aldosterone production across hypertension severity rather than a rare, discrete disorder confined to classic hypokalemic cases.[5,8]

Recognition in clinical practice has not kept pace with prevalence. In a U.S. cohort of 4,660 people with resistant hypertension, only 2.1% underwent recommended PA screening within two years.[4] In a nationwide direct-to-patient study of 694 hypertensive adults who met indications for PA testing, 25.4% had a positive result suggesting PA; 57% were already receiving care from an endocrinologist, cardiologist, or nephrologist but had not previously been tested.[6] Underdiagnosis is only part of the problem: many patients are also underserved by current care pathways, with gaps in access to appropriate screening, specialist evaluation, subtype assessment, and disease-specific treatment.

ICER estimates 10,042,828 eligible patients in Population 1 and 2,516,732 in Population 2, for a combined eligible prevalent population of 12,559,560.[1, pp. 31-32] Given the prevalence and screening gap above, a meaningful portion of this modeled population may have unrecognized PA or other forms of aldosterone-mediated hypertension. However, the proportion with PA within these modeled populations remains uncertain, and general hypertension trial results do not by themselves establish PA-specific comparative efficacy. That uncertainty is precisely why PA should be acknowledged explicitly: identifying the underlying disease can change treatment pathways, relevant comparators, and interpretation of value.

2. PA Is Not Simply Hypertension That Is More Difficult to Control

PA carries cardiovascular and renal risk beyond that explained by blood-pressure elevation alone. The 2025 AHA/ACC guideline states that, compared with primary hypertension, PA is associated with approximately 2.0-fold higher risk of heart failure, 2.8-fold higher risk of stroke, 1.7-fold higher risk of coronary artery disease, 4.0-fold higher risk of atrial fibrillation, and increased kidney damage, even after accounting for hypertension severity.[2] A meta-analysis of 31 studies involving 3,838 patients with PA and 9,284 with essential hypertension likewise found significantly greater risks of stroke, coronary artery disease, atrial fibrillation, and heart failure in PA.[7]

ICER's economic model appropriately uses systolic blood-pressure reduction to estimate downstream cardiovascular and kidney events because long-term outcome data for ASIs are not yet available.[1] PAF agrees that benefits not demonstrated in clinical evidence should not simply be assumed. However, in a population that includes patients with aldosterone-mediated disease, a model driven principally by blood-pressure reduction cannot capture a potential treatment effect on aldosterone-mediated risk beyond blood pressure if such an effect ultimately proves to exist.

PAF is not asserting that baxdrostat or lorundrostat has been demonstrated to reduce cardiovascular or renal events independently of blood-pressure lowering. That remains an important unanswered question. PAF asks ICER to distinguish uncertainty about PA-specific baseline risk from uncertainty about comparative treatment effects. Because MRAs also target aldosterone-mediated disease, neither PA's excess risk nor an ASI's mechanism alone establishes additional benefit over appropriate MRA therapy.

3. Heterogeneity Within the ICER Population May Produce Meaningfully Different Treatment Value

ICER itself notes that its economic models represent average findings across broad groups and should not be presumed to represent the clinical or cost outcomes of any specific patient.[1, p. iii] That limitation is especially important here. The populations labeled uncontrolled or resistant hypertension are not biologically or clinically uniform. They include patients with different causes of hypertension, different degrees of aldosterone dysregulation, different prior treatment histories, different tolerability of established therapies, and different opportunities for disease-specific intervention.

For a patient whose hypertension is driven by autonomous aldosterone production, an aldosterone-directed therapy may ultimately have a different clinical value proposition than it does when evaluated simply as another blood-pressure-lowering option across a broad resistant-hypertension population. The same is true for patients who cannot tolerate or achieve adequate control with mineralocorticoid receptor antagonists (MRAs), compared with patients who do well on inexpensive established therapy.

This is not an argument that ASIs have already been proven more effective or more cost-effective in PA. It is an argument that population-average estimates can conceal clinically meaningful differences in disease biology, treatment alternatives, and potential benefit. Where evidence permits, PAF encourages subgroup or scenario analyses using explicit assumptions about baseline risk, comparative efficacy, tolerability, and available alternatives. Where evidence is insufficient, ICER should identify the missing evidence and discuss the limits of applying population-average estimates to PA.

4. ICER's Standardized 20% Uptake Convention Should Be Distinguished From Expected Real-World Adoption

For its five-year budget-impact analysis, ICER assumes that 20% of each eligible population initiates an ASI in each year - approximately 2,008,565 patients per year in Population 1 and 503,346 per year in Population 2.[1, pp. 31-33] This approach is consistent with ICER's standardized Reference Case methodology for estimating potential budget impact over a five-year horizon; it should not be interpreted as a forecast that 20% of eligible patients will actually initiate therapy in the first year or in any particular year.[9]

ICER's Reference Case assumes that an equal proportion of prevalent patients (20%) is treated each year over five years, reaching cumulative 100% uptake at five years.[9] The Reference Case explicitly states that this approach is not intended to represent the most likely real-world budget impact; rather, it provides calculations that allow decision-makers to apply their own assumptions.[9] Potential budget impact is based on the incremental health care cost of using the new therapy relative to relevant existing therapy, including cost offsets, rather than gross drug spending alone.[9] At baxdrostat's reported annual net price of \$10,950, ICER estimates that approximately 2% of the eligible population could be treated before reaching its \$821 million annual potential budget-impact threshold.[1, pp. 33-34] That result should be understood within this standardized five-year framework, not as a first-year treatment forecast.

The same implementation gap is visible within resistant hypertension itself. In a national analysis, only 9.0% of U.S. adults with apparent treatment-resistant hypertension were taking an MRA despite guideline recommendations.[10] PAF has also received repeated anecdotal reports from patients with difficult-to-control or resistant hypertension describing physician reluctance to prescribe a newly approved ASI and insurance coverage restrictions. These observations are unsystematic and should not be used as a quantitative uptake estimate, but they reinforce the practical gap between eligibility and treatment initiation.

PAF therefore asks ICER to make the five-year convention and its purpose prominent in the Evidence Report and, where feasible, illustrate alternative initiation and persistence patterns reflecting physician familiarity, multidrug treatment complexity, prior authorization, out-of-pocket cost, patient preference, monitoring requirements, and treatment persistence. Slower adoption may reduce near-term spending but can also reflect unmet need; it does not establish cost-effectiveness or eliminate affordability concerns.

5. Established MRAs Remain Essential, but Underuse and Tolerability Create Heterogeneous Unmet Need

PAF strongly recognizes spironolactone and eplerenone as important, effective, and comparatively inexpensive therapies for PA and resistant hypertension. Spironolactone is an appropriate comparator for new aldosterone-directed therapies. The question is not whether MRAs work; it is whether average MRA effectiveness and low acquisition cost fully represent the treatment experience of every patient.

In a retrospective two-center study of 155 patients receiving long-term medical therapy for PA, 52.3% experienced at least one treatment-related adverse effect; 22.6% required a dose reduction, 10.3% switched medications, and 11.0% stopped medical therapy. Side effects were more common with spironolactone and with higher doses.[11] In addition, the low national use of MRAs in apparent resistant hypertension suggests that guideline availability does not automatically translate into real-world utilization.[10]

For patients who tolerate and respond well to an inexpensive MRA, the incremental value of an ASI may be modest. For others, assessment should distinguish spironolactone-related hormonal adverse effects from hyperkalemia or kidney-function limitations, which ASIs may also present. Alternative established therapies remain relevant comparators; the relative value of an ASI depends on demonstrated comparative benefit, tolerability, treatment burden, and cost. ICER should preserve this heterogeneity rather than allow a population-average comparison to imply uniform patient value.

6. Patient-Reported Outcomes Are an Important Evidence Gap

ICER appropriately notes that direct data on the effects of baxdrostat or lorundrostat on health-related quality of life are not yet available.[1] PAF has heard from some patients taking baxdrostat who describe improvements in general well-being or nonspecific symptoms beyond the numerical change in blood pressure. These reports are anecdotal and unsystematic; they do not establish a treatment effect independent of blood-pressure lowering.

They do, however, identify an evidence gap. Recurring patient observations can generate research questions that conventional endpoints do not answer. PAF encourages future ASI studies to incorporate validated patient-reported outcomes addressing symptoms, functioning, medication burden, tolerability, treatment experience, and health-related quality of life.

7. ASIs Should Advance - Not Obscure - Diagnosis and Disease-Specific Care

The 2025 Endocrine Society guideline suggests screening all individuals with hypertension for PA, subject to health-system resources and feasibility, and recommends PA-specific therapy once the diagnosis is established.[3] This distinction matters because PA is not homogeneous. Patients with lateralizing disease may be candidates for adrenalectomy, which can provide targeted and potentially curative treatment; patients with bilateral disease generally require long-term targeted medical therapy. An ASI response does not establish PA or determine laterality. Appropriate diagnostic evaluation should remain available, with subtype evaluation pursued when surgical treatment is feasible and desired; patients not pursuing surgery may appropriately receive PA-specific medical therapy without completing that pathway.[3]

There is already early evidence that an ASI can act directly on PA biology. In a small, open-label phase 2a study of 15 patients with PA, baxdrostat treatment was associated with reductions in blood pressure and aldosterone production and correction of hypokalemia in those affected.[12] These findings support further PA-specific investigation but do not establish superiority to established treatment or long-term cardiovascular or renal benefit.

The arrival of ASIs therefore creates both an opportunity and a risk. These therapies may help move hypertension care toward a more mechanism-based approach, but they could also mask an underlying diagnosis if a patient with unrecognized PA experiences improved blood pressure and is never evaluated for potentially curable disease. PAF strongly believes that the introduction of ASIs should be accompanied by greater attention to PA recognition, screening, diagnosis, and appropriate subtype evaluation - not less.

This principle has been central to PAF since its founding. Patients with PA should not disappear into a broad category labeled 'hypertension' simply because a medication can lower their blood pressure. Patients deserve access to effective and tolerable therapeutic options. They also deserve to know why they have hypertension.

Recommendations

The Primary Aldosteronism Foundation respectfully asks ICER to:

1. Explicitly recognize PA as the most common endocrine cause of secondary hypertension and as a common, severely underdiagnosed contributor to apparent treatment-resistant hypertension.
2. Make the heterogeneity of the modeled populations explicit, including differences in underlying aldosterone biology, treatment history, MRA tolerability, and disease-specific treatment pathways; where evidence permits, consider subgroup or scenario analyses using explicit assumptions about baseline risk, comparative efficacy, tolerability, and available alternatives.
3. Acknowledge that a model driven principally by systolic blood-pressure reduction may not capture the full long-term value of suppressing pathological aldosterone if benefits beyond blood-pressure lowering are eventually demonstrated, while clearly stating that such outcome benefits have not yet been established for ASIs.
4. Clearly distinguish the approximately 12.56-million-person eligible prevalent population from ICER's standardized assumption of 20% treatment initiation in each year of the five-year budget-impact horizon; explain that the convention is not a real-world market forecast and, where feasible, illustrate alternative initiation and persistence patterns.
5. Recognize the essential role and low cost of MRAs while distinguishing spironolactone-related hormonal adverse effects from hyperkalemia or kidney-function limitations and incorporating real-world underuse, treatment persistence, and resulting heterogeneity in unmet need.
6. Recognize patient-reported outcomes as an important evidence gap and emphasize that ASI availability should complement - not replace - appropriate PA recognition, diagnosis, subtype evaluation, and disease-specific care.

Conclusion

PAF welcomes scientific innovation in the treatment of aldosterone-mediated hypertension and recognizes the limitations of the evidence currently available for ASIs. Our request is not that ICER assume unproven benefits or assign favorable value to a new class simply because its mechanism is novel. It is that ICER avoid allowing a broad, population-average hypertension framework to obscure patients whose biology, disease burden, therapeutic alternatives, and potential value are materially different.

An assessment of therapies designed specifically to suppress aldosterone production is incomplete without meaningful consideration of primary aldosteronism - a common, consequential, treatable, and profoundly underdiagnosed disease defined by inappropriate aldosterone production. PAF respectfully asks ICER to ensure that PA and the patients who live with it are explicitly represented in the revised Evidence Report.

Disclosure

PAF receives grant support from Mineralys Therapeutics and has previously received grant support from AstraZeneca for patient education activities. PAF independently developed these comments and retained full editorial control. Working drafts were shared with Mineralys Therapeutics and AstraZeneca solely for factual and technical review.

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September 9, 2026

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Submitted Electronically: publiccomments@icer-review.org

Dear Ms. Edmond:

Thank you for the opportunity to comment on ICER's Draft Evidence Report, "*Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value*," dated August 12, 2026.

We appreciate ICER's willingness to review comments and recommendations from the National Forum's Value & Access Collaborative (V&AC). The undersigned V&AC members, representing patient, provider, payer, and public health organizations, jointly offer the following feedback for ICER's consideration in the development of the revised review report.

Hypertension remains one of the most significant drivers of cardiovascular morbidity and mortality in the United States. The ongoing hypertension epidemic is costing lives, independence, and money. Clearly, the current treatment arsenal is insufficient, as evidenced by the fact that <50% of people with hypertension have it under control (Centers for Disease Control & Prevention, 2026). Resistant hypertension, in particular, disproportionately affects communities already facing structural barriers to health and well-being, and contributes to persistent gaps in blood pressure control. Given the burden of disease and the limitations of existing therapies, the evaluation of new aldosterone synthase inhibitors (ASIs) such as baxdrostat and lorundrostat is both timely and important.

We respectfully offer the following recommendations.

Inputs to the Economic Model

A. Patient Perspectives Should Be Included in the Economic Dataset

We appreciate ICER's inclusion of patient perspectives in the narrative report. However, patient-reported experience, including pill burden, side effects, adherence challenges, and barriers to access, directly affects real-world outcomes and should be incorporated into the economic model dataset. Without this, payers relying on the model may overlook critical patient-important outcomes.

Recent evidence underscores the central role of adherence and tolerability in hypertension management (Burnier & Egan, *Circulation Research*, 2020). These factors materially influence blood pressure control and long-term cardiovascular risk and should be reflected in ICER's modeling.

Key Model Assumptions

A. Uptake Assumptions

ICER assumes that 20% of eligible patients will receive baxdrostat in its first year. This assumption is inconsistent with real-world adoption patterns for new cardiovascular therapies.

Studies show that early uptake of novel cardiometabolic therapies typically remains in the low single digits (typically 5–6% in year one) due to multiple factors, such as payer controls, step therapy, prior authorization, and slow clinician adoption (Reiter-Brennan et al., *Cardiovascular endocrinology & metabolism*, 2020; Anderson TS, et. al, *Healthc (Amst)*., 2018).

Overestimating uptake inflates budget impact and may lead to inappropriate conclusions about affordability. We recommend revising uptake assumptions to more accurately align with contemporary adoption trends.

B. Tolerability and Discontinuation

Older mineralocorticoid receptor antagonists (MRAs) such as spironolactone are effective but frequently discontinued due to endocrine side effects, including gynecomastia, reduced kidney function, hyperkalemia risk, and the impact of side effects on patients' quality of life (Richard et al., *Pragmatic and Observational Research*, 2025). These tolerability barriers limit real-world effectiveness and contribute to persistent uncontrolled hypertension.

ASIs may reduce these barriers due to their non-steroidal mechanism. ICER's model should incorporate discontinuation rates and tolerability-related adherence patterns, which are well-documented in contemporary literature.

C. Fairness in Access Considerations

ICER notes disparities in blood pressure control but does not incorporate them into the model. Resistant hypertension disproportionately affects Black adults and individuals with lower socioeconomic status (Akinyelure OP, et al. *Journal of the American Heart Association*, 2024; Abrahamowicz, AA, et al. *Current Cardiology Reports*, 2023). Access to specialized care and newer therapies is uneven across geographic and demographic groups.

We recommend that ICER incorporate disparities-relevant parameters including differential access, geographic variation, and disparities in tolerability and adherence into the revised model.

Clinical Inputs and Outcomes

A. Short-Term Trials and Surrogate Outcomes

ICER correctly notes that long-term outcomes data for ASIs are not yet available. However, short-term blood pressure reduction remains a useful surrogate for long-term cardiovascular risk reduction (Weintraub, WS, et al. *European Heart Journal*, 2015; BPLTTC, *Lancet*, 2021). Early hypertension trials rarely include long-term outcomes; this is standard for emerging therapies.

We recommend that ICER contextualize the absence of long-term outcomes within typical hypertension drug development and avoid prematurely assigning “comparable or inferior” ratings based solely on short-term data.

Additionally, results from a longer study comparing baxdrostat to standard of care (SOC) plus placebo were recently presented during the European Society of Cardiology (ESC) Congress. The study showed that not baxdrostat achieved significantly lower SBP than SOC plus placebo. The positive difference in SBP reduction is not only durable over a full year, it is actually greater at 52 weeks (Williams B, et al, ESC Congress, 2026).

B. Patient-Important Outcomes

Patient-important outcomes, including pill burden, tolerability, and adherence, are central to real-world hypertension management. These factors influence symptom burden, long-term cardiovascular risk, and health outcomes.

We recommend that ICER incorporate validated patient-reported outcome measures and contemporary adherence research into the model.

Cost-Effectiveness and Access

A. Early Cost-Effectiveness Estimates Should Be Interpreted with Caution

Cost-effectiveness for new therapies is inherently uncertain. Historical precedent demonstrates that early acquisition cost does not predict long-term affordability. PCSK9 inhibitors and GLP-1 receptor agonists both saw substantial improvements in access following price adjustments and payer policy changes (MacDougall DE, et al. *Circulation*, 2024; Centers for Medicare & Medicaid Services, 2024).

We recommend that ICER emphasize the uncertainty inherent in early cost-effectiveness modeling and avoid conclusions that may inadvertently create access barriers.

B. Budget Impact Analysis

We urge ICER to exercise caution in presenting budget impact estimates. Budget impact analyses based on unrealistic pricing assumptions or uptake rate estimates that exceed historic

patterns have previously been used to justify access restrictions for therapies that are otherwise cost-effective.

We recommend that ICER clearly distinguish cost-effectiveness findings from budget impact projections and avoid linking budget impact to recommended price ranges.

5. Access Considerations

Access to high-quality hypertension care is uneven across the United States. Many patients lack access to healthcare, contributing to persistent uncontrolled hypertension and disparities in outcomes (Hardy ST, et al, *Hypertension*, 2024).

ASIs may offer an important alternative for patients who cannot tolerate MRAs, who face adherence barriers, or who lack access to specialized care. ICER's model should reflect the real-world variability in access and the potential for new therapies to reduce inequities.

Conclusion

We appreciate ICER's thorough review and its commitment to transparency and stakeholder engagement. We respectfully urge ICER to incorporate patient perspectives, contemporary real-world evidence, fair access considerations, and realistic uptake assumptions into the revised evidence report.

We look forward to continued engagement throughout the review process.

Sincerely,

Members of the Value & Access Collaborative, representing the following organizations:

National Forum for Heart Disease & Stroke Prevention (convener)

Alliance for Aging Research

Alliance for Patient Access

American Association of Heart Failure Nurses

American Association of Kidney Patients

American Pharmacists Association Foundation

Association of Black Cardiologists

BallengeRx Consulting

HealthyWomen

Partnership to Advance Cardiovascular Health

Partnership to Improve Patient Care

Preventive Cardiovascular Nurses Association

WomenHeart

World Hypertension League

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NPLB Response to the Public Comments on Draft Evidence Report on Hypertension

Thank you for the opportunity to provide comments on ICER's draft evidence report evaluating Aldosterone Synthase Inhibitors (ASIs) for the treatment of hypertension [1]. 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.

1. Background: key issues identified in the draft evidence report

ICER's draft evidence report concludes that the ASIs under review, lorundrostat and baxdrostat, are not cost-effective at plausible list prices. Our review of the report, its modeling analysis plan, and its cited evidence identified structural issues in two specific areas that, taken together, artificially bias the value estimates downward and make the published results far more uncertain and irrelevant than presented.

Efficacy foundations

The comparative-effectiveness inputs rest on a fragile network meta-analysis: a single head-to-head trial in the network, three incompatible blood-pressure measurement methods pooled together, and a credible interval for lorundrostat wider than its own trial's confidence interval.

Discontinuation assumptions are asymmetric: ASIs carry trial-derived first-cycle discontinuation penalties that comparators do not, producing results such as eplerenone dominating lorundrostat, despite a smaller blood-pressure reduction. This result was reversed in ICER's own "no discontinuation" scenario.

The comparison is also misaligned with clinical reality: patients who would receive an ASI in practice are likely to have already exhausted these treatment options.

Omitted value elements and dynamic pricing

The "modified societal perspective" accounts for a narrow subset of value elements important to patients and society: productivity costs attach only to acute-event states (a layer that moves the ratio ~1%).

The model holds each drug's launch price constant over a lifetime horizon and evaluates a single patient cohort, ignoring price changes over time due to genericization and in-class competition. It also fails to consider the benefits to every future patient cohort.

These considerations motivated us to conduct two exploratory analyses to illustrate the impacts of these modeling choices on the value estimates. Because the limitations above apply to both ASIs, we conducted both analyses on lorundrostat, the drug with the less favorable published results in the assessment. The first analysis tests how sensitive ICER's published cost-effectiveness ratios are to dynamic pricing and future cohorts; the second provides an independent estimate of lorundrostat's potential societal value using the NPLB Generalized Cost-Effectiveness Analysis (GCEA) calculator [2].

2. Exploratory Analysis 1: relaxing the constant-price, single-cohort assumptions

Using ICER's published outputs [1], we replicated each incremental cost-effectiveness ratio between non-dominated pairs involving lorundrostat in the base case and the "no discontinuation" scenario analysis. We approximated the possible lifetime drug cost trajectory, and then replaced the index cohort's lifetime drug cost with a population-weighted average across the patients the drug will actually treat: 10.3 million prevalent u/rHTN patients at launch [3, 4] plus ~500,000 newly incident patients per year [5]. We examined the impacts of considering the benefits to 30 and 70 future cohorts, separately. Prices follow the GCEA Best Practice path — a 95% reduction [2] at year-13 loss of exclusivity [6], reflecting genericization only (a shallower, IQVIA-observed erosion path [7] yields the same conclusion; see Appendix I).

Table 1 — Base case

Comparator	ICER as published	Current cohort only (10.3M)	+ 30 future cohorts (25.3M)	+ 70 future cohorts (45.3M)
Spironolactone	\$1,419,000	\$1,416,500 (−0.2%)	\$997,500 (−30%)	\$749,100 (−47%)
Amiloride	\$1,492,000	\$1,489,300 (−0.2%)	\$1,039,100 (−30%)	\$772,200 (−48%)

Table 2 — No-discontinuation scenario analysis

Comparator	ICER as published	Current cohort only (10.3M)	+ 30 future cohorts (25.3M)	+ 70 future cohorts (45.3M)
Eplerenone	\$16,956,000	\$11,331,500 (−33%)	\$7,025,000 (−59%)	\$5,115,400 (−70%)
Amiloride	\$1,436,000	\$974,500 (−32%)	\$621,200 (−57%)	\$464,600 (−68%)

Adjusting these two assumptions alone moved the published ratios by 30–48% in the base case and up to 70% under ICER's own no-discontinuation scenario. A single-cohort model captured essentially none of genericization's value (−0.2%) in the base case. Due to the discontinuation assumption in the base case, the current prevalent patients stopped treatment long before generic entry. The value of long-term price erosion was captured almost entirely in patients who have not yet started treatment, which the current model did not reflect. *The published ratios should therefore be read as highly sensitive to structural choices that were neither varied nor disclosed as drivers.*

3. Exploratory Analysis 2: a more comprehensive GCEA estimate of societal value

We also built a societal value estimate using the NPLB GCEA calculator, grounded in the LAUNCH-HTN Phase 3 trial [8]. Each value element is derived from a controlled-state and an uncontrolled-state anchor, blended by each arm's trial-observed control rate (44.1% lorundrostat vs. 24.1% placebo, on top of background therapy). Appendix II documents the full derivations of the inputs. The analysis quantifies a subset of value elements including life expectancy, quality of life, healthcare cost offsets, productivity, caregiver burden, and non-medical costs, using conservative assumptions. We also consider the values of 70 future annual patient cohorts with 0.5% population growth.

We explored two scenarios. Compared with the base case, the optimistic scenario also accounts for the quality-of-life improvement patients experience from the higher certainty of keeping blood pressure under control, including reduced worry about stroke and heart attack and freedom from the cycle of medication escalation. This was modeled as a 0.02 utility uplift on a daily basis and benchmarked against analogous published values for needle-free administration in food allergy [9], worry about hypoglycemia [10], and the treatment burden of warfarin [11].

The findings suggest that the societal value-based price for lorundrostat ranges from **\$18,767 per year (base case) to \$26,913 per year (optimistic case)**.

4. Takeaways and recommendations

ICER's published cost-effectiveness ratios are highly uncertain: relaxing just two structural assumptions, constant pricing and a single treated cohort, moves the ratios by 30–70%, using only ICER's own published model outputs.

A conservative GCEA analysis considering only a subset of its value elements shows that lorundrostat is worth \$19,000–\$27,000 per year before it goes generic. This value is higher than the assumed price of \$10,950 (WAC) per year, representing a bargain for patients and society. In reality, competition will likely drive down the net price of drugs in this class following launch. This means society will likely spend only a modest fraction of the value this class of drugs generates for patients.

Appendix I — Technical Documentation for Exploratory Analysis I

A. Replication of ICER's published results

ICER reports costs and QALYs rounded for display, so unrounded incremental QALYs are recovered from each published ratio [1]:

$$\Delta QALY = \Delta \text{Cost}(\text{published totals}) \div \text{ICER}(\text{published})$$

Anchors:

vs. spironolactone (base): $\Delta \text{Cost} = \$150,700 - \$122,800 = \$27,900$; $\Delta QALY = 27,900 \div 1,419,000 = 0.019662$

vs. amiloride (base): $\Delta \text{Cost} = \$150,700 - \$123,400 = \$27,300$; $\Delta QALY = 27,300 \div 1,492,000 = 0.018298$

vs. amiloride (Scenario 3): $\Delta \text{Cost} = \$250,000 - \$122,000 = \$128,000$; $\Delta QALY = 128,000 \div 1,436,000 = 0.089136$

vs. eplerenone (Scenario 3): $\Delta \text{Cost} = \$250,000 - \$126,000 = \$124,000$; $\Delta QALY = 124,000 \div 16,956,000 = 0.007313$

vs. eplerenone (base case): dominated – reverses under equal persistence

vs. spironolactone (Scenario 3): $\Delta QALY < 0$ – dominated

Validation — reproducing ICER's threshold prices at \$150,000/QALY:

spironolactone: \$1,364 vs. published \$1,400 | eplerenone: \$758 vs. \$760 | amiloride: \$1,489 vs. \$1,500

B. Distribution of drug spending over time

Effective discounted treatment-years bundle discontinuation and ICER's 3% within-cohort discounting:

$$T_{\text{eff}} (\text{base case}) = \text{lifetime drug cost} \div \text{annual price} = \$28,500 \div \$10,950 = 2.6027 \text{ yrs}$$

$$T_{\text{eff}} (\text{no discontinuation}) = \$133,000 \div \$10,950 = 12.146 \text{ yrs}$$

Base case — geometric weights:

$$w(t) = d^t, \text{ with } \sum d^t = 1 \div (1 - d) = T_{\text{eff}} \rightarrow d = 1 - 1/2.6027 = 0.6158$$

No discontinuation — survival-based weights:

$$w(t) = e^{(-h \cdot t)} \div 1.03^t, \text{ with } h = 0.055825 \text{ calibrated so that } \sum w(t) = 12.146$$

Robustness checks using alternative distribution: Weibull ($k = 0.5, 0.7$) and an ICER-mimicking hybrid (10% first-quarter drop plus constant hazard) move the 30-cohort saving by less than five points, all toward larger savings — the geometric shape is the conservative choice.

C. Price paths

$$\text{GCEA Best Practice: } m(y) = 1 \text{ for } y < 13; \quad m(y) = 0.05 \text{ for } y \geq 13$$

$$\text{IQVIA Historical Data Analysis: } m(y) = 1 \text{ for } y < 13; \quad m(y) = \{0.34, 0.26, 0.23, 0.22, 0.20, 0.20, 0.20, 0.19, 0.19, 0.19\} \text{ for post-LOE years 1-10; } 0.19 \text{ thereafter}$$

GCEA Best Practice models the price drop due to genericization only — the 95% reduction is the NPLB GCEA Calculator default [2]. IQVIA Historical Data Analysis (Aitken/IMS 2016 [7]; implementation in Cohen et al. 2025, Appendix B1.1.3 [12]) reflects both generic entry and competition during the branded period.

D. Cohort-level drug cost

A cohort starting in calendar year c spends treatment-year t in calendar year $c + t$:

$$\text{Cost}(c) = \$10,950 \times \sum_t w(t) \times m(c + t)$$

Under the GCEA Best Practice path this reduces to brand-years at full price plus generic-years at 5% of price:

$$\begin{aligned} \text{brand-years}(c) &= (1 - d^{(13-c)}) \div (1 - d) \quad \text{for } c < 13; \quad 0 \quad \text{for } c \geq 13 \\ \text{generic-years}(c) &= T_{\text{eff}} - \text{brand-years}(c) \end{aligned}$$

Illustrative values (base case):

cohort 0:	2.598 brand-yrs	→	\$28,450	(99.8% of spending precedes LOE)
cohort 10:	1.995 brand-yrs	→	\$22,178	
cohort 12:	1.000 brand-yrs	→	\$11,828	
cohort 13+:	0 brand-yrs	→	\$1,425	

E. Population weighting

Cohort 0 is the prevalent pool; each subsequent cohort is the annual incident flow:

$$\begin{aligned} N(0) &= 10.3\text{M}; \quad N(c) = 0.5\text{M} \text{ for } c \geq 1; \quad \text{weight}(c) = N(c) \times 1.02^{(-c)} \\ \text{Average drug cost} &= \sum N(c) \cdot \text{Cost}(c) \cdot 1.02^{(-c)} \div \sum N(c) \cdot 1.02^{(-c)} \end{aligned}$$

Prevalent pool: Carey et al. 2019 [3] (pooled NHANES, ACC/AHA $\geq 130/80$ definition; 9.2M under $\geq 140/90$), verified via the open-access Bakris 2024 text [4]. Incident flow — no published national figure exists; constructed two ways:

$$\begin{aligned} \text{(i) flow-based:} \quad &0.7 \text{ per } 100 \text{ patient-years (Daugherty 2012 [5])} \times \approx 61\text{M treated adults} \approx 430\text{K/yr} \\ \text{(ii) steady-state:} \quad &10.3\text{M prevalent} \div \approx 18\text{-yr mean duration} \approx 570\text{K/yr} \end{aligned}$$

Working figure: 500K/yr. The prevalent bolus carries 47.9% of total discounted weight at 30 cohorts and 35.5% at 70.

F. Recomputing the ratio — treatment of incremental benefits

The population-weighted ICER is defined over both incremental costs and incremental benefits, each aggregated across cohorts with the same weights (cohort size $\times$ 2% societal discount):

$$\text{ICER} = \sum N(c) \cdot d(c) \cdot \Delta \text{Cost}(c) \div \sum N(c) \cdot d(c) \cdot \Delta \text{QALY}(c), \quad \text{where } d(c) = 1.02^{(-c)}$$

Incremental benefits are therefore included, and discounted across cohorts identically to costs. Every cohort receives the same per-patient incremental QALYs, so $\Delta \text{QALY}(c)$ is a constant, ΔQALY , for all c :

$$\begin{aligned} \Delta \text{QALY}(c) &= \Delta \text{QALY} \quad \text{for all } c \quad \rightarrow \quad \text{denominator} = \Delta \text{QALY} \times \sum N(c) \cdot d(c) \\ \text{ICER} &= [\sum N(c) \cdot d(c) \cdot \Delta \text{Cost}(c) \div \sum N(c) \cdot d(c)] \div \Delta \text{QALY} = (\text{population-weighted avg } \Delta \text{Cost}) \div \Delta \text{QALY} \end{aligned}$$

A constant treated symmetrically in numerator and denominator factors out of the ratio. Each cohort's incremental cost differs from the published figure only through its drug cost:

$$\Delta\text{Cost}(c) = \Delta\text{Cost}(\text{published}) - [\text{DrugCost}(\text{index cohort}) - \text{DrugCost}(c)]$$

$$\text{ICER}(\text{new}) = [\Delta\text{Cost}(\text{published}) - (\text{DrugCost}(\text{index}) - \text{DrugCost}(\text{population-weighted avg}))] \div \Delta\text{QALY}$$

Comparators are already generic, so their costs do not change.

G. Full results grid

Population-weighted average lifetime drug cost (within-scope saving vs. index cohort in parentheses):

Scope	Base case — GCEA Best Practice	Base case — IQVIA Historical	No disc. — GCEA Best Practice	No disc. — IQVIA Historical
Index cohort	\$28,500	\$28,500	\$133,000	\$133,000
Current cohort only	\$28,450 (0.2%)	\$28,462 (0.1%)	\$91,868 (30.9%)	\$98,979 (25.6%)
+ 30 future cohorts	\$20,213 (29.1%)	\$21,602 (24.2%)	\$60,374 (54.6%)	\$72,164 (45.7%)
+ 70 future cohorts	\$15,330 (46.2%)	\$17,394 (39.0%)	\$46,409 (65.1%)	\$59,975 (54.9%)

Resulting cost-effectiveness ratios, all non-dominated pairs:

Comparator / scenario	Price change assumption	Published	Current only	+ 30 cohorts	+ 70 cohorts
Spironolactone — base	GCEA Best Practice	\$1,419,000	\$1,416,500	\$997,500	\$749,100
Spironolactone — base	IQVIA Historical	\$1,419,000	\$1,417,100	\$1,068,200	\$854,200
Amiloride — base	GCEA Best Practice	\$1,492,000	\$1,489,300	\$1,039,100	\$772,200
Amiloride — base	IQVIA Historical	\$1,492,000	\$1,489,900	\$1,115,000	\$885,000
Eplerenone — no disc.	GCEA Best Practice	\$16,956,000	\$11,331,500	\$7,025,000	\$5,115,400
Eplerenone — no disc.	IQVIA Historical	\$16,956,000	\$12,303,900	\$8,637,200	\$6,970,400
Amiloride — no disc.	GCEA Best Practice	\$1,436,000	\$974,500	\$621,200	\$464,600
Amiloride — no disc.	IQVIA Historical	\$1,436,000	\$1,054,300	\$753,500	\$616,700

Base-case eplerenone and no-discontinuation spironolactone pairs are dominated and not shown (see §A).

H. Additional Key Assumptions

- Zero population growth, despite rising u/rHTN prevalence.
- No gross-to-net discount on lorundrostat (ICER's WAC placeholder retained).
- Limitations: incident flow is a constructed estimate (430–570K range), not a directly published national figure.

GCEA Societal Value Analysis — Detailed Technical Documentation

Intervention: Lorundrostat

Indication: Uncontrolled & Treatment-Resistant Hypertension (u/rHTN)

This document is the detailed technical documentation for the Generalized Cost-Effectiveness Analysis (GCEA) of lorundrostat in uncontrolled and treatment-resistant hypertension, in three parts:

- 1. Analytic Approach — a brief overview of the methodology
- 2. Input Overview — summary table of key inputs by treatment arm
- 3. Detailed Input Derivation — full derivation, citations, and methodological notes for every input

1. Analytic Approach

The analysis compares the lifetime cost and benefits for both the Status Quo (placebo added to patients' ongoing background antihypertensive therapy) and lorundrostat arms, using the NPLB GCEA calculator [2]. The NPLB GCEA calculator is a user-friendly tool that allows users to conduct rapid back-of-the-envelope calculations to assess the potential size of the societal benefits as well as key value drivers for treatments of interest [13].

The analysis is grounded in the LAUNCH-HTN Phase 3 trial [8]. For each arm, inputs for each value element are based on the proportion of patients achieving systolic blood pressure below 130 mmHg at week 6 by automated office measurement. This binary endpoint maps directly onto the controlled-versus-uncontrolled framework in which the burden literature is written.

Trial findings: Lorundrostat: 44.1% controlled; placebo: 24.1% (multiple imputation; observed 44.0% and 24.1%). The predecessor Phase 2b trial (ADVANCE-HTN) [14] used a stricter threshold on a different measurement method (<125 mmHg by ambulatory monitoring at week 4; 41% vs. 18%), so the two trials' control rates are not directly comparable.

For each arm, the arm-specific input for each value element is calculated as a weighted average:

$$\text{Arm value} = (\% \text{ controlled} \times \text{controlled-state anchor}) + (\% \text{ uncontrolled} \times \text{uncontrolled-state anchor})$$

With lorundrostat at 44.1% controlled and placebo at 24.1%, the same two anchors produce both arms' values for every module; the arms differ only through the weights. The burden literature is far better developed for controlled versus uncontrolled hypertension than for millimetre-level gradations.

The calculator applies each blended value as a constant across the model horizon, a structural simplification of the NPLB calculator design. The blend assumes that the benefits are available from day one at full magnitude. In reality, part of the cross-sectional gap between controlled and uncontrolled patients reflects accumulated disease history that a newly controlled patient does not immediately shed, so the true incremental benefit phases in over several years.

Inputs for controlled and uncontrolled state anchors are derived from a mix of sources including clinical trial publications and peer-reviewed publications (e.g., claims analyses and survey studies). The detailed derivations of these inputs are described below.

2. Input Overview

Input	Lorundrostat — Base case	Lorundrostat — Optimistic	Status Quo
Patient Count (US)	10.3 million (u/rHTN; counted per the aTRH ≥130/80 definition), prevalence rates unchanged, population grows at 0.5% annually		
Average Age at Model Entry	~62 yrs		
Model Time Horizon	30 yrs		
Willingness-to-Pay (\$/QALY)	\$150,000		
Discount Rates	3% (traditional CEA), 2% (GCEA)		
Life Expectancy (yrs)	19.31	19.31	18.49
QoL Utility	0.706	0.726	0.694
Healthcare Utilization Cost (\$/yr)	+\$6,366	+\$6,366	+\$8,644
Productivity (hrs lost/yr)	27.9	27.9	31.2
Caregiver Hours (hrs/yr)	53.6	53.6	67.0
Direct Non-medical costs (\$/yr)	+\$156	+\$156	+\$176

3. Detailed Input Derivation

For each of the inputs, we categorize them by one of the three tier labels:

[O] Observed — directly read from a named source;

[A] Anchored — grounded in analogous published data via an explicit bridging calculation;

[P] Premise — a modeling assumption with no direct empirical anchor.

Basic Set-Up

Patient Count (US): 10.3 million

Source: Carey et al., AHA scientific statement on apparent treatment-resistant hypertension, using pooled US NHANES data [3], as quoted in the open-access Bakris cost study used below [4]. Population: US adults meeting the aTRH definition under the ACC/AHA $\geq 130/80$ mmHg threshold (9.2 million under the older $\geq 140/90$ threshold) — a direct match to the modeled population. Consistent in magnitude with ICER's independently constructed eligible population (12.5 million). Terminology: the modeled population is referred to as u/rHTN throughout, matching the trial; the prevalence count is anchored to the stricter aTRH epidemiological definition, which makes it conservative. The aTRH label is retained below only where it describes what a specific source measured.

Tier: Observed [3, 4]

Average Age at Model Entry: ~62 years

Source: LAUNCH-HTN [8]. Population: the trial population itself — pooled mean age across arms of 61.4–61.8 years, rounded to 62 for life-table lookups; 53% male / 47% female, used for all sex-weighted calculations.

Tier: Observed [8]

Model Time Horizon: 30 years

A fixed modeling convention. From age 62, a 30-year horizon extends beyond age 92, capturing the full remaining lifetime of essentially the entire cohort; discounting and mortality attrition make results insensitive to horizon beyond roughly 30 years.

Tier: Anchored

Willingness-to-Pay: \$150,000 per QALY

The standard US benchmark for health-gain valuation, applied to quality-adjusted life-year gains in the calculator.

Tier: Premise

Discount Rates: 2% per year, within lifetime and across cohorts

Health outcomes and costs are discounted at 2% per year — applied both within each patient's lifetime and across future cohorts — per GCEA best practice [13]. Traditional CEA convention uses 3%; the GCEA framework applies 2% throughout, and this analysis follows the GCEA convention.

Tier: Anchored [13]

Life Expectancy

Life Expectancy — Controlled State: 21.60 years

Source: Social Security Administration period life table, 2023 table from the 2026 Trustees Report [15]. Population: the US general population — a patient with controlled blood pressure is assumed to match general-population remaining life expectancy (20.29 years for a 62-year-old man; 23.08 for a woman). This revision adopts the 2023 table, which superseded the 2022 table used previously (19.61/22.50).

$$(0.53 \times 20.29) + (0.47 \times 23.08) = 21.60 \text{ yrs}$$

Tier: Observed [15]

Life Expectancy — Uncontrolled State: 17.50 years

Source: the UCC-SMART prospective cohort (Groenland et al.) [16], which found a 4.1-year shorter median life expectancy in patients with apparent treatment-resistant hypertension versus hypertensive patients without treatment resistance. Population: a European single-centre cohort of patients with established vascular disease, evaluated at age 50. No US-based life-expectancy deficit specific to this patient population exists; this source is used to approximate the potential burden. Because the source cohort is sicker than the LAUNCH-HTN population, the 4.1-year deficit could overstate the gap.

$$21.60 - 4.1 = 17.50 \text{ yrs}$$

Tier: Anchored [16]

Life Expectancy by Arm: Status Quo 18.49 yrs; Lorundrostat 19.31 yrs

$$\text{Lorundrostat: } (0.441 \times 21.60) + (0.559 \times 17.50) = 19.31$$

$$\text{Status Quo: } (0.241 \times 21.60) + (0.759 \times 17.50) = 18.49$$

Incremental life-years gained: +0.82.

Tier: Anchored

Quality of Life

QoL Utility — Controlled State: 0.74; Uncontrolled State: 0.68 (SF-6D)

Source: Carris et al. [17], comparing SF-6D utilities between adults with apparent treatment-resistant hypertension (on four or more antihypertensive classes) and adults with non-resistant hypertension. Population: nationally representative US Medical Expenditure Panel Survey data, 2000–2011 (2,501 aTRH among 57,150 hypertensive adults; aTRH cohort mean age 68). Utilities: 0.68 (aTRH) versus 0.74 (non-resistant), $P < 0.0001$. Both anchors come from this single study.

Tier: Observed [17]

QoL Utility by Arm: Status Quo 0.694; Lorundrostat 0.706

$$\text{Lorundrostat: } (0.441 \times 0.74) + (0.559 \times 0.68) = 0.706$$

$$\text{Status Quo: } (0.241 \times 0.74) + (0.759 \times 0.68) = 0.694$$

Annual quality-adjusted life-year gain: +0.0120 per year. As a cross-check, the US EQ-5D-5L population norm for hypertension is 0.794 [18]; pairing it with plausible uncontrolled-state values from the EQ-5D literature yields differentials of 0.06–0.064 — independently convergent with the single-source SF-6D gap used here.

Tier: Anchored

Interpreting the adjusted utility difference

The multivariable-adjusted utility difference in the source is 0.02 (95% CI 0.01–0.03) — demographics and comorbidities absorb roughly two-thirds of the raw 0.06 gap. Several of the adjusted-away comorbidities are, however, partly

consequences of prolonged uncontrolled blood pressure — mediators rather than confounders — so full adjustment over-corrects. The two figures are therefore best read together as describing the timing of the benefit: the adjusted 0.02 approximates the early-years gain for a newly controlled patient who retains accumulated comorbidities, while the unadjusted 0.06 approximates the steady-state gain as avoided comorbidity accumulation compounds — consistent with the phase-in described in Section 1. The adjusted figure also serves as the conservative sensitivity (annual QALY gain 0.0040 instead of 0.0120).

Additional Daily Quality of Life from Achieving Blood-Pressure Control: 0.02 uplift for lorundrostat (Optimistic case input)

Reflects the additional quality of life a patient experiences on a daily basis from getting blood pressure under control — reduced worry about stroke and heart attack, freedom from the cycle of medication escalation, and the lived difference of being at goal — beyond what the measured SF-6D differential captures. While utility estimates for uncontrolled HTN among the u/rHTN population do not exist in the existing literature, we assumed a 0.02 uplift in utility associated with the lorundrostat arm. This was based on utility estimates from: (1) daily quality-of-life gain due to needle-free administration for food allergy patients (range: 0.0088 to 0.0168) [9]; (2) quality-of-life loss due to worry of hypoglycemia not under control (range: 0.01 to 0.03) [10]; and (3) treatment burden associated with warfarin (0.013) [11].

Tier: Premise [9, 10, 11]

Healthcare Costs

Cost Differential, Uncontrolled vs. Controlled: \$11,389 per year (2026 USD)

Source: Bakris et al. [4], the only claims-based, within-population controlled-versus-uncontrolled cost comparison for this disease (full text openly accessible). Population: US commercial claims (IQVIA PharMetrics Plus), adults with apparent treatment-resistant hypertension and stage 3–4 chronic kidney disease. The adjusted difference in total medical and pharmacy costs between apparent-uncontrolled ($\geq 130/80$) and controlled patients was \$10,055 per patient per year (95% CI \$6,741–\$13,646; 2021 USD). Inflation to 2026 uses the BLS medical-care CPI [19], chaining the July twelve-month changes for 2022 through 2026 (+4.8%, –0.5%, +3.2%, +3.5%, +1.7%).

$$\text{\$10,055 (2021 USD)} \times 1.133 = \text{\$11,389}$$

Tier: Anchored [4, 19]

What the differential contains: downstream event costs

Because the differential is measured over total follow-up spending in a claims population, it already embeds the downstream consequences of uncontrolled blood pressure that occurred during follow-up — hospitalizations for stroke, myocardial infarction, and heart failure, emergency care, and the outpatient intensification that follows such events. Decomposition in the source confirms this: the gap is predominantly outpatient (\$6,514) and inpatient (\$3,202) spending rather than pharmacy (\$325).

⚠ Gap / caveat: The source population is not a full match to the trial population, and its two mismatches cut in opposite directions, so the net bias is ambiguous: enrichment for chronic kidney disease (stages 3–4) plausibly inflates the differential (anti-conservative); but the controlled group was older and sicker at baseline — more heart failure, atrial fibrillation, and peripheral vascular disease, with baseline costs \$40,094 versus \$37,235 — and the study's 130/80 threshold is looser than a trial-grade definition, both of which compress the differential (conservative).

Healthcare Costs by Arm: premium over the controlled state — Status Quo +\$8,644/yr; Lorundrostat +\$6,366/yr

Because both arms blend the same two anchors, the incremental result depends only on the differential — absolute cost levels cancel and are not separately anchored. A previously used absolute-level source (a 2014 conference abstract) could not be verified against any accessible source and has been retired; for context, CDC analyses place hypertension-attributable spending at \$3,211 per patient per year in the general hypertensive population [20], and total spending in the CKD-enriched Bakris population at \$37,000–\$40,000 per year.

$$\text{Lorundrostat: } 0.559 \times \text{\$11,389} = \text{+\$6,366}$$

Status Quo: $0.759 \times \$11,389 = +\$8,644$

Tier: Anchored [4]

Dynamics

Loss of Exclusivity: year 13; price reduction at LOE: 95% (GCEA Best Practice)

As a small molecule, lorundrostat is assumed to lose exclusivity after 13 years — consistent with observed market exclusivity periods for new molecular entities of 13.0–14.1 years [6] — with a 95% price reduction, the NPLB calculator default (GCEA Best Practice). Erosion of this depth is observed in markets attracting six or more generic entrants [21], the expected case for a once-daily oral in a ten-million-patient market. An alternative, shallower erosion path based on IQVIA historical net-price data (66% deepening to 81%) is implemented in Appendix I.

Tier: Anchored [6]

Population structure: prevalent pool plus annual incident cohorts

Future cohorts are modeled as the population actually arrives: the 10.3 million prevalent patients at launch (see Basic Set-Up), plus approximately 500,000 newly incident patients per year constructed from the only US incidence study (0.7 cases per 100 patient-years among treated hypertension [5], applied to the ≈ 61 million treated pool $\approx 430,000/\text{yr}$) and cross-checked by a steady-state calculation ($10.3\text{M} \div \approx 18\text{-year mean duration} \approx 570,000/\text{yr}$). Population growth is set to 0.5%. Cohorts initiating after LOE are treated at generic prices; the full mechanics, price paths, and cohort-scope results are documented in Appendix I and Appendix III.

Tier: Anchored [3, 5]

Productivity

Annual Work Hours Lost — Controlled State: 18.7 hrs/yr; Uncontrolled State: 35.1 hrs/yr

Source: Unmuessig et al. [22], the only US study comparing lost work time by blood-pressure control status. Population: insured, currently employed members of a single Washington-state health system, with control defined at 140/90 — structurally healthier than the trial population, so the measured gap likely understates the true difference (conservative). Employees with uncontrolled hypertension lost nearly twice as much work time to absenteeism as those with controlled blood pressure — 1.35 versus 0.72 hours per two-week period ($P=.001$). Presenteeism showed no significant per-person difference in the same study, so the base case counts absenteeism only. Hours are annualized over 26 two-week periods and carried in natural units; monetization is performed within the calculator.

Controlled: $0.72 \times 26 = 18.7 \text{ hrs/yr}$

Uncontrolled: $1.35 \times 26 = 35.1 \text{ hrs/yr}$

Lorundrostat: $(0.441 \times 18.7) + (0.559 \times 35.1) = 27.9 \text{ hrs/yr}$

Status Quo: $(0.241 \times 18.7) + (0.759 \times 35.1) = 31.2 \text{ hrs/yr}$

Tier: Observed [22]

Why this likely undercounts productivity impacts

The base-case figure should be read as a floor. It counts absenteeism only, while presenteeism typically carries two to four times absenteeism's cost in the chronic-disease literature and is hardest to detect in exactly the setting the source studied. It excludes the extensive margin entirely — reduced employment probability, early retirement, and disability exit — which is plausibly the largest channel for a condition whose sequelae are disabling. The source population is structurally healthier than the trial population, compressing the measured gap. And unpaid household production is not counted. One adjustment runs the other way: the hours are per employed person, applied here to a cohort of which only

roughly half works at age 62 and less thereafter. On balance the true societal productivity impact is likely understated, but it remains a minor value element under any plausible correction and is presented accordingly.

Tier: Anchored

Caregiver Burden

Caregiver Hours — Controlled State: 16.1 hrs/yr

Source: Dunbar et al., the AHA's projected costs of informal caregiving for cardiovascular disease [23]. Population: US Health and Retirement Study respondents aged 54 and older — a good age match to the modeled cohort. Informal caregiving attributable to hypertension averages 0.31 hours per week per patient; the general hypertension population is predominantly treated and controlled, so this serves as the controlled-state anchor. One caregiver per patient is assumed.

$$0.31 \times 52 = 16.1 \text{ hrs/yr}$$

Tier: Observed [23]

Caregiver Hours — Uncontrolled State: 83.2 hrs/yr

Source: Joo et al. [24] (full text openly accessible via CDC Stacks). Population: US Health and Retirement Study respondents aged 50 and older with heart failure, who received about 1.6 more hours per week of informal caregiving than otherwise similar older adults. No caregiving data exist for uncontrolled hypertension specifically; the heart-failure figure — the predominant end-stage complication of resistant hypertension, measured in the same survey framework and age group as the controlled-state anchor — is used to approximate the potential burden. This replaces a previously used figure (1.95 hours per week) that could not be verified against any accessible source.

$$1.6 \times 52 = 83.2 \text{ hrs/yr}$$

Tier: Anchored [23, 24]

Δ Gap / caveat: *The strongest assumption in the analysis: most uncontrolled patients have not developed heart failure, so the anchor likely overstates average burden (anti-conservative). A lower-bound sensitivity — twice the general-hypertension figure (32.2 hrs/yr) — bounds it. The source also reports caregiving hours of 3.9 per week for non-Hispanic Black versus 1.4 for White respondents, an equity gradient relevant to a future distributional analysis.*

Caregiver Hours by Arm: Status Quo 67.0 hrs/yr; Lorundrostat 53.6 hrs/yr

$$\text{Lorundrostat: } (0.441 \times 16.1) + (0.559 \times 83.2) = 53.6 \text{ hrs/yr}$$

$$\text{Status Quo: } (0.241 \times 16.1) + (0.759 \times 83.2) = 67.0 \text{ hrs/yr}$$

Hours are carried in natural units; monetization is performed within the calculator. One caregiver per patient is assumed.

Tier: Anchored

Direct Non-Medical Costs

Transportation: \$100/yr controlled; \$200/yr uncontrolled

Physician visits and laboratory monitoring are already captured in the claims-based cost differential and are excluded here to avoid double-counting; only transportation is retained, as a working assumption. Published visit-frequency data suggest similar visit counts for controlled and uncontrolled treated hypertension, implying a true offset near zero — a \$0 sensitivity is appropriate.

$$\text{Lorundrostat: } (0.441 \times \$100) + (0.559 \times \$200) = \$156/\text{yr}$$

$$\text{Status Quo: } (0.241 \times \$100) + (0.759 \times \$200) = \$176/\text{yr}$$

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Appendix III — Excel File Used for Exploratory Analysis I (provided separately)