Aldosterone Synthase Inhibitors for the Treatment of Hypertension: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

October 1, 2026

Table of Contents

Manufacturers 2

AstraZeneca 2

Mineralys 7

Patient Groups 18

American Association of Kidney Patients (AAKP) 18

Mended Hearts 20

Primary Aldosteronism Foundation (PAF) 24

Other Advocacy Organizations 35

National Forum for Disease & Stroke Prevention Value Access Collaborative (V&AC) 35

No Patient Left Behind (NPLB) 39

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#	Comment	ICER Response
Manufacturers		
AstraZeneca		
1.	**<u>Patients Uncontrolled on Two Therapies Represent a Material Unmet Need</u>** 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 nonadherence[5] and treatment related side effects[6-8] 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.	*We appreciate the additional background information provided and have updated the background section of our Evidence Report with relevant information and references.*
2.	**<u>ICER's Uptake Assumption is Not Credible and Materially Overstates Budget Impact</u>** 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	*Our assumption of 100% uptake over 5 years, or 20% uptake each year is an approach that we take for all ICER reviews. This assumption is not meant to represent real-world, forecasted uptake but to provide a framework for analysis that decision-makers can use to make their own*

	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	*assumptions for expected uptake in their population of patients. The goal of ICER's analysis is to signal if the potential budget impact of a new treatment may be difficult for the health system to manage over the short term under assumptions of optimal clinical utilization, based on the proportion of patients that could be treated at different price points without crossing the ICER annual budget impact threshold.*

	a credible estimate of expected near-term use.	
3.	**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	*When considering comparators to include in the review, ICER heard from clinical experts that mineralocorticoid receptor antagonists (MRAs) and amiloride were considered reasonable options for those with uncontrolled resistant hypertension, and clinical practice guidelines state that MRAs are the preferred 4th line agent in this group. Therefore, in clinical practice, when faced with a patient with resistant hypertension who requires an additional agent, clinicians and patients would be choosing between MRAs, amiloride, and the new ASI agents. Similarly, for patients with uncontrolled hypertension who require a 3rd agent and have not tried a 3rd first-line agent, both clinical experts and clinical practice guidelines support amlodipine as a third first-line agent and thus clinicians and patients would be choosing between amlodipine and ASIs. Our review attempts to provide relevant information to assist clinicians and patients who would be choosing a 3rd or 4th agent.* *We acknowledge that real-world use of MRAs and amiloride may in part be affected by issues around safety and tolerability, however we heard repeatedly that the greater issues are around clinical inertia. These same issues occur with initiating second and third antihypertensive drugs even though these are generally very well tolerated.* *We have acknowledged the limitations of data for amlodipine in the report. Despite the limitations, amlodipine has been shown to be an effective, tolerable antihypertensive with demonstrated cardiovascular benefits and is commonly used as a third agent. Thus, we continue to feel that the comparison of ASIs to*

	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.	*amlodipine in the uncontrolled hypertension population on two agents is an appropriate and useful one.* *Finally, we agree that indirect comparisons have limitations. We strongly encourage head-to-head randomized controlled trials of ASIs against active comparators and each other to generate definitive comparative data.*

	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.	
4.	**<u>ICER Must Incorporate the Complete 52-Week Evidence Base</u>** 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. **<u>Conclusion:</u>** 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	*Thank you for sharing the newly presented 52-week analysis of baxdrostat. We have incorporated the data as appropriate into the clinical evidence sections discussing the treatment durability and harms of the drug.*

	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.	
Mineralys Therapeutics		
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) ≥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	*We appreciate the additional background information provided and have updated the background section of our Evidence Report with relevant information and references.*

	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	*To best reflect the diverse populations in lorundrostat and baxdrostat studies, we expanded ICER's Clinical Trial Diversity Rating Tool beyond pivotal Phase 3 trials to include Advance-HTN, Target-HTN, and other key studies. Updated ratings are available in Table 3.1 and Supplement D1 of the evidence report.*

	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	*As part of our assessment of NMA feasibility, we reviewed the study design and baseline characteristics of the Target-HTN, Advance-HTN, and Launch-HTN trials (Supplement Tables D2.2 and D3.1) and determined them to be comparable across the network of studies, particularly on the variables of age, sex, and baseline systolic blood pressure. We used data from the same treatment regimen, lorundrostat 50 mg once daily, from each of the trials to help further ensure comparability between trials.* *The Population 1 NMA only included data from the Launch-HTN trial. A review of the data inputs used in the Population 3 NMA (Supplement Table D2.10) confirms that the treatment effect sizes between the Launch, Advance, and Target studies are similar in magnitude (- 8.8, -7.9, -9.6, respectively). Removing the Advance and Target trials inputs from this NMA would not alter our conclusions.* *The differences in proportion of Black/African-American participants between trials does not present a high risk of bias in our NMA. In our subgroup analysis review of the lorundrostat Launch-*

	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.	*HTN and baxdrostat BaxHTN trials (Supplement Table D6.1), we saw that the two aldosterone synthase inhibitors work similarly across Black and White patients. Additionally, the earlier lorundrostat trial, Advance-HTN (phase 2b, 53% Black), reported that lorundrostat's efficacy was similar in the study's Black and non-Black participants.* *Because indirect comparisons cannot replace direct evidence, we strongly encourage head-to-head randomized controlled trials of lorundrostat against active comparators to generate definitive comparative data.* *Retaining all relevant lorundrostat trials in our analysis offers the most complete look at the current evidence. We will continue highlighting these trial-level differences and wide credible intervals so readers can interpret the estimates with the right context.*
4.	**Network Meta-Analysis (NMA):** **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]	*We agree on the importance of using trial data at similar timepoints and created a visual showing that to be the case in our NMAs (Figure 3.1).* *Our use of 6-week data for the Launch-HTN trial was due to data availability constraints. The 12-week placebo-adjusted difference in systolic BP (SBP) quoted in the comment (-11.6 mmHg) was an exploratory outcome and was not stratified by our two populations of interest. We would welcome data from Mineralys comparing lorundrostat 50 mg versus placebo on the SBP treatment difference (95% CI) at 12 weeks, stratified by baseline antihypertensive regimen intensity, specifically, lorundrostat 50 mg added on top of a 2-drug baseline regimen and*

	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.	*lorundrostat 50 mg added on top of a 3-or-more-drug baseline regimen.*
5.	**Network Meta-Analysis (NMA):** **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.	*Our use of a mix of 24-hour ambulatory, in-office, and at-home measurement is due to data availability constraints.* *In our discussion of limitations of our NMA, we noted that "the 24-hour ambulatory blood pressure monitoring approach is regarded as the gold standard given its comprehensive capture of blood pressure control beyond the office setting, including overnight readings." We commend Mineralys for the use of the 24-hour measurement in the earlier Phase 2 Advance-HTN trial and encourage its use in any future trials.*
6.	**Network Meta-Analysis (NMA):** **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	*We recognize that background antihypertensive treatments are varied across studies and may have an impact on treatment effects, which is why we conducted separate NMAs breaking out the populations of patients whose blood pressure was above goal despite the use of three or more antihypertensive medications at maximally tolerated dose (Population 1) and two antihypertensive medications and who have not been treated with a third first-line agent recommended by clinical guidelines (Population 3).* *Across the lorundrostat and baxdrostat studies included in our NMA, patients were most commonly on the following background medications at baseline, in descending order of frequency: thiazide or*

	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.	*thiazide-like diuretics, ACE inhibitors or ARBs, calcium channel blockers, and beta blockers.* *In our subgroup analysis review of the lorundrostat Launch-HTN and baxdrostat BaxHTN trials (Supplement Table D6.1), we found no difference in magnitude of treatment effect between patients on 2 and 3 or more antihypertensive treatments.*
7.	**Network Meta-Analysis (NMA):** **Finally, ICER should not include open-label studies in the NMA.** The inclusion of open-label amiloride 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.	*Our inclusion of the open-label SPARE study was based on our desire to include a head-to-head trial of two relevant treatments, spironolactone and amiloride.* *We noted its open-label study design as a limitation and rated the study as High Risk of Bias using the Cochrane Risk of Bias 2 tool.* *We explored the exclusion of SPARE and two other trials from the Population 1 NMA as a sensitivity analysis (Supplement Table D2.8).*
8.	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.	*See responses above.*
9.	**Comparator Selection: Amiloride and Eplerenone:**	*We acknowledge that real-world use of eplerenone and amiloride may be limited; however, the fact remains that these are*

	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.	*guideline-recommended, effective drugs for treating hypertension and thus we have included them as relevant comparators. When the 2025 AHA/ACC guidelines discuss MRAs, they include both spironolactone and eplerenone as options. While MRAs may be preferred 4th line therapy for those with resistant hypertension, guidelines do state that amiloride is a reasonable alternative if MRA is unable to be used (see 2025 AHA/ACC guidelines section 5.6, Resistant Hypertension and Renal Denervation).*
10.	**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	*We thank Mineralys for noting this concern. We believe our model is sufficiently comprehensive as it currently stands and previous models assessing interventions for hypertension have also made the simplifications and assumptions our model has made. We do not know of a hypertension model that can capture all of the complications Mineralys proposes. Most importantly, we do not have robust evidence to include estimates of the impact of treatment on these complications as they were not included as secondary end points in the clinical trials.*

	economic model. Excluding these events may therefore understate the full clinical and economic impact of BP-lowering agents.	
11.	**Limitations of ICER's Economic Model: 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.	*As mentioned in the draft report, we chose not to incorporate AEs directly given the low incidence of treatment-related serious adverse events and the consequent lack of meaningful impact on model findings and conclusions, which is our standard modeling practice, and following precedence of prior models in hypertension that have omitted. We did incorporate the hormonal effects that are experienced with spironolactone through a higher discontinuation probability each cycle, as mentioned in the Adverse Events section of the report supplement.*
12.	**Third, ICER should incorporate estimates of treatment discontinuation that are specific to the treatment and population being modelled.**	*We thank Mineralys for providing an alternative study with data on discontinuation to consider. While we agree that patient behaviors may differ across geographies, we applied the same*

	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.	*discontinuation function across all treatment groups. We selected our source study because it aligned well with the disease status of our patient population and provided sufficient data to construct a discontinuation function. That study also assessed persistence across multiple drug classes in patients with hypertension. In contrast, the study provided by Mineralys assessed only MRA use in patients with heart failure and chronic kidney disease. Finally, we tested several scenarios around our discontinuation assumption, and none changed our conclusion.*
13.	**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.	*Consistent with best practices in HTA, ICER does not as a rule consider "dynamic pricing" in economic evaluation unless there is known timing for patent expiry and certainty around expected changes in price (both during the period of patent protection and following generic entry). This is rarely if ever accomplished in practice because there is a high degree of variability in patent extension practices, delays in generic development and marketing, and other such factors.* *We understand that there has been recent interest in some circles in incorporating dynamic pricing into economic models; these approaches have assumed, however, that reductions in cost from generic or biosimilar entry should accrue to the price of the originator product rather than serve as a benefit to society. Other approaches have attempted to discern the shares of value that should accrue to the originator developer and society. We continue to observe this debate closely and will consider updating our methods once a consensus has been reached.*

		Regarding the full societal burden, we are limited to the evidence available for us, not only for documentation of societal impacts but also evidence of treatment impact on them.
14.	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.	*Please refer to previous comments regarding the NMA and not including all requested elements in the economic model.*

#	Comment	ICER Response
Patient Groups		
American Association of Kidney Patients (AAKP)		
1.	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	*Thank you for this comment. We agree health disparities are an important topic to address in the care of patients with hypertension. However, we disagree with the characterization of our patient engagement process. For each review, we seek out input from the major disease-specific patient advocacy organizations and patients who are living with the condition that is the subject of our review. Our process also includes multiple opportunities for feedback from the broader patient and advocacy communities, including explicit review of early drafts of our report. In addition, we invite patients with the condition under review to participate in our public meetings through both oral comments and formal participation throughout the meeting as part of a policy roundtable. ICER has also recruited patients and patient advocates to serve on the voting panels of its core public programs. These voting panels are composed of patients, clinicians, and health policy researchers with broad expertise in evaluating evidence on clinical effectiveness and comparative value. We have purposefully recruited the panel membership for a diversity in experience and background to ensure the objectivity of the deliberations at the meeting.*

	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.	
2.	Further, with the known evidence related to the long-term impact of hypertension on American kidney health, especially among minority Americans, their hypertension and kidney health we find it alarming that ICER would insert itself into the decision-making between patients and the doctors they choose and trust for managing.	*ICER's reports are intended to be used on a population level. Therapeutic decisions should be made on an individual level taking into account best evidence and individual patient values and preferences. We are not attempting to dictate clinical decisions for specific individuals; clinical decisions should always be between patients and physicians and reflect patient preferences and risk tolerance.*
3.	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.	*ICER never recommends restricting access to any medical interventions. We critically evaluate the current evidence for efficacy and recommend a fair price for medications based on how well they work. We urge manufacturers and health insurers to work together to ensure that everyone in society can benefit from innovation that helps patients obtain treatments at a fair price.* *When we overpay for one drug because manufacturers set the price too high or pay for drugs whose efficacy is not clear or whose benefit over existing treatments is uncertain, there are real costs to everyone in society. Everyone experiences higher insurance premiums. And some of us may not be able to afford insurance, which leads to more people becoming underinsured or*

		uninsured. When individuals don't have insurance, they usually end up with worse health outcomes, and they may end up paying more for a drug that they need. *For more context/information on this question, see this ICER.org blog*
4.	Further, we believe that this draft report was prepared using a model that relied upon a narrow silo of information uniformed 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.	*The ICER process included significant patient engagement, see response #1 above detailing the patient engagement process. We acknowledge the need for effective medications in this disease space. Our economic analysis evaluates the expected clinical and economic impact of two new treatments using the best available evidence to inform discussions around fair pricing. It does not seek to inform the merits of developing new treatments generally.*
Mended Hearts		
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	*We thank Mended Hearts for its engagement with ICER, and we appreciate your comment that we were able to reflect potential barriers to care accurately throughout our report.*

	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 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.**	*We agree that tolerability is an important aspect of any medication. We have acknowledged in the report that ASIs may be more tolerable than MRAs.*
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	*We appreciate this comment and have tried to characterize these barriers in the Stakeholder Input section of the report. We also note that manufacturers can improve access to new products by picking value-based prices, and that ICER's Cornerstones of Fair Access white paper details Fair*

	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	*Design criteria for cost sharing and prior authorization protocols that should guide payer coverage policies to ensure transparent and efficient processes that do not delay patient access to effective medications.*

	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.	*Thank you for this perspective. In addition to the discussion of health equity in our report, health equity issues will be highlighted and addressed at the upcoming public meeting, during the voting panel session and the policy roundtable.*
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	*Thank you for this comment highlighting the important role of caregivers in the care of people with hypertension. We agree with this sentiment. Caregiver impact is an important part of our "Benefits Beyond Health and Special Ethical Priorities" section of our report and will also be discussed at ICER's upcoming public meeting, during the comparative effectiveness panel's voting session and during the policy roundtable.*

	model, but as people navigating real, daily tradeoffs in their care.	
Primary Aldosteronism Foundation (PAF)		
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.	*Thank you for this comment. We agree that there is heterogeneity in the hypertension population, and that the treatment resistant hypertension population is likely enriched with patients with primary aldosteronism (PA). We have added more information to the background section of the report about PA. We also examined the available subgroups in the Phase III baxdrostat and lorundrostat trials; those trials do not separate out people with PA, so we are unable to comment on the efficacy of ASIs in this important subgroup. Ongoing trials may provide evidence of efficacy of ASIs in the PA population.*
2.	**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	*Thank you for this comment. We agree that the treatment resistant hypertension population is likely to have people with undiagnosed PA. Two of our comparators for this review are the mineralocorticoid receptor antagonists, spironolactone and eplerenone, which are first-line treatment for PA. Thus, our analysis is likely to be relevant to the PA population.*

	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.	

3.	**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	*Thank you for this comment and as above, we agree that PA is an important subgroup in treatment resistant hypertension. We look forward to data on the impact of ASIs on cardiovascular and renal outcomes in the PA subgroup from ongoing and future clinical trials.*

	MRAs also target aldosterone-mediated disease, neither PA's excess risk nor an ASI's mechanism alone establishes additional benefit over appropriate MRA therapy.	
4.	**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	*We thank the Primary Aldosteronism Foundation for this comment. We agree that the population modelled is clinically heterogeneous. However, there is not yet robust evidence of differential treatment effect across the subgroups the Foundation identifies, and the ASI trials do not currently report data that would allow us to model these subgroups. We encourage the manufacturers to include analyses stratified by these subgroups in future trials. Consistent with ICER's Value Assessment Framework, separate evidence ratings and value-based prices for subgroup are provided only when there is robust, high-quality evidence of substantial differences in comparative clinical effectiveness, which the current evidence does not meet for these subgroups.*

	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.	
5.	**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	*Our assumption of 100% uptake over 5 years, or 20% uptake each year is an approach that we take for all ICER reviews. This assumption is not meant to represent real-world, forecasted uptake but to provide a framework for analysis that decision-makers can use to make their own assumptions for expected uptake in their population of patients. The goal of ICER's analysis is to signal if the potential budget impact of a new treatment may be difficult for the health system to manage over the short term under assumptions of optimal clinical utilization, based on the proportion of patients that could be treated at different price points without crossing the ICER annual budget impact threshold.*

	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.	

6.	**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.	*We agree that tolerability of MRAs is an aspect of their relatively low utilization, and have discussed this in the Background, Adverse Events, and Summary and Comment sections of the report. Because data from clinical trials do not differentiate between participants who were not able to tolerate MRAs from others, we are not able to make any assessments of relative benefit in participants who are not able to tolerate MRAs.*

7.	**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.	*Thank you for this comment. We agree that patient-reported outcomes are important and also encourage clinical trial sponsors to collect validated patient-reported outcomes as part of their trial protocols.*
8.	**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	*Thank you for highlighting the challenges facing clinicians and patients in the diagnosis and treatment of PA. We agree that these are important issues that should be addressed by the clinical and scientific community; however, they are outside of the scope of this ICER review.*

	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.	
9.	The Primary Aldosteronism Foundation respectfully asks ICER to: 1. Explicitly recognize PA as the most common endocrine cause of	*We thank the Primary Aldosteronism Foundation for their thorough review of our Draft Report and appreciate the comments*

	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	*and suggestions. Please see above for responses to the comments.*

	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.	

#	Comment	ICER Response
Other Advocacy Organizations		
National Forum for Disease & Stroke Prevention Value Access Collaborative (V&AC)		
1.	**<u>Inputs to the Economic Model</u>** **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.	*We appreciate this comment and agree that adherence and tolerability in hypertension management are important. We do include treatment discontinuation, which incorporates treatment tolerability, based on real-world data. Adherence to treatment is inherent in our estimates but is aligned with adherence in the source studies. We do not have sufficient evidence on the independent impact of adherence on outcomes to incorporate explicitly. We also acknowledge that pill burden is a potentially important consideration, but there is sufficient evidence for the treatments assessed in the model to estimate an independent effect of pill burden on outcomes.*
2.	**<u>Key Model Assumptions</u>** **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 &*	*Our assumption of 100% uptake over 5 years, or 20% uptake each year is an approach that we take for all ICER reviews. This assumption is not meant to represent real-world, forecasted uptake but to provide a framework for analysis that decision-makers can use to make their own assumptions for expected uptake in their population of patients. The goal of ICER's analysis is to signal if the potential budget impact of a new treatment may be difficult for the health system to manage over the short term under assumptions of optimal clinical utilization, based on the proportion of patients that could be treated at different price points without crossing the ICER annual budget impact threshold.*

	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.	
3.	**<u>Key Model Assumptions</u>** **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	*We appreciate this comment regarding MRA discontinuation. As noted in our Treatment Discontinuation section, our model applies a higher discontinuation factor to spironolactone, resulting in a greater probability of discontinuation in each model cycle.*
4.	**<u>Key Model Assumptions</u>** **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	*We agree that disparities in blood pressure control and in access to specialized care are significant concerns. However, for this assessment, our subgroup analysis was limited to clinical heterogeneity, for which robust evidence of differential treatment effect is required. Factors such as differential access and geographic variation are outside the scope of the current analysis. We will, however, raise these considerations for discussion at the policy roundtable. We also note that, consistent with ICER's health equity guidance, we do not calculate different value-based prices for different groups of patients based on race,*

	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.	*ethnicity, or socioeconomic status, and a single value-based price is recommended for all patients.*
5.	**<u>Clinical Inputs and Outcomes</u>** **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).	*Thank you for this comment. We agree that blood pressure reduction is generally associated with cardiovascular risk reduction. However, the degree of cardiovascular risk reduction is not consistent across drugs and drug classes. For example, doxazosin was associated with higher risk of cardiovascular events compared with chlorthalidone in the ALLHAT trial (JAMA. 2000;283(15):1967–1975), and a Cochrane review found that treatment with beta-blockers were inferior to calcium channel blockers for cardiovascular disease outcomes and no better than placebo for coronary heart disease outcomes (Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database of Systematic Reviews 2017, Issue 1). Thus, it is difficult to predict with certainty a drug's effects on cardiovascular outcomes. The 52-week data from the baxdrostat trial do not include data on cardiovascular outcomes.* *Our ratings reflect our understanding of the current data for ASIs – that they are effective blood pressure lowering agents to a similar degree to other antihypertensives, but that their impact of cardiovascular outcomes has not yet been established. Because ASIs do not yet have data showing cardiovascular benefit and a drug such as amlodipine has long-term data showing established cardiovascular benefit, we feel that a "comparable or inferior" rating (C-) is appropriate for the current level of data. We acknowledge in the Executive Summary and the report that this rating would change in the future if data showing additional benefits from ASIs is published.*

6.	**<u>Clinical Inputs and Outcomes</u>** **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.	*Thank you for this suggestion. We agree that patient-important outcomes are important to include in our assessment. We did not find any data on pill burden, tolerability, or adherence for the ASIs, as these were either not collected in clinical trials or reported in the data presented.*
7.	**<u>Cost-Effectiveness and Access</u>** **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.	*We understand that uncertainty in the evidence at the time of product launch can lead to uncertainty in cost-effectiveness findings. However, price negotiations occur at launch in the US and therefore we must make do with the evidence available. ICER's work produces a fair price range that can serve as a useful input to these negotiations, and has been very influential in prior reviews of cardiovascular medications, including with both PCSK9 inhibitors – explicitly in the case of one manufacturer – and with GLP-1s as a result of competition and market forces for patients not covered by insurance. If the price for baxdrostat were brought down to a value-based price or the launch price for lorundrostat is in the ICER HBPB range, we will, of course, acknowledge that these therapies are cost-effective and encourage payers to cover them as such.*
8.	**<u>Cost-Effectiveness and Access</u>** **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.	*Our assumption of 100% uptake over 5 years, or 20% uptake each year is an approach that we take for all ICER reviews. This assumption is not meant to represent real-world, forecasted uptake but to provide a framework for analysis that decision-makers can use to make their own assumptions for expected uptake in their population of patients. The goal of ICER's analysis is to signal if the potential budget impact of a new treatment may be difficult for the health system to manage over the short term under assumptions of optimal clinical*

	We recommend that ICER clearly distinguish cost-effectiveness findings from budget impact projections and avoid linking budget impact to recommended price ranges.	*utilization, based on the proportion of patients that could be treated at different price points without crossing the ICER annual budget impact threshold.*
9.	**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, el 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	*We agree that there are barriers to high-quality hypertension care in the US, particularly for populations who have traditionally not been equitably served by the healthcare system. However, having overpriced drugs does not lead to better access in such communities. We have indicated the degree to which a community may benefit from an effective therapy through our calculation of the Health Improvement Distribution Index (HIDI). Some of these issues are addressed in our report in the Stakeholder Input and Benefits Beyond Health and Special Ethical Priorities sections and will also be highlighted during the upcoming public meeting.*
No Patient Left Behind (NPLB)		
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	*Thank you for this comment. We acknowledge the limitations of the network meta-analysis; however, because there is an absence of direct comparison data between the interventions and comparators of interest, the NMA is necessary. We conducted several sensitivity analyses to assess the robustness of our NMA to our findings and conclusions.* *We strongly encourage head-to-head trials between agents; if these data were available, indirect comparisons would not be necessary.*

	wider than its own trial's confidence interval.	
2.	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.	*We appreciate this comment. All five treatments share the same long-term persistence function, with the only difference being that baxdrostat and lorundrostat carry their own trial-observed three-month discontinuation in the first cycle. Using each agent's best available evidence is appropriate, and assuming the newer agents persist like established generics from day one is not supported. Applying the same trial-based approach to the comparators using their most recent hypertension trials (PATHWAY-2 and ESAX-HTN), would incorporate lower first-cycle discontinuation than the model currently does, making the cost-effectiveness of the ASIs even less favorable. Regardless, the base-case conclusion is driven by acquisition cost relative to a small blood-pressure benefit, not by the first-cycle discontinuation input, and it holds in our same discontinuation and no discontinuation scenario analyses.* *The comparators also reflect the guideline-recommended add-on options for resistant hypertension, and the model captures sequencing, as patients who discontinue return to their baseline regimen. Even where an ASI is used only after these options are exhausted, the relevant question remains its incremental value versus the next-best alternative, and the incremental cost-effectiveness ratios, driven primarily by drug acquisition cost relative to generics, would not be expected to change.*
3.	***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,	*Consistent with best practices in HTA, ICER does not as a rule consider "dynamic pricing" in economic evaluation unless there is known timing for patent expiry and certainty around expected changes in price (both during the period of patent protection and following generic entry). This is rarely if ever accomplished in practice because there is a high degree of variability in patent extension practices, delays in generic development and marketing, and other such factors.*

	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].	*We understand that there has been recent interest in some circles in incorporating dynamic pricing into economic models; these approaches have assumed, however, that reductions in cost from generic or biosimilar entry should accrue to the price of the originator product rather than serve as a benefit to society. Other approaches have attempted to discern the shares of value that should accrue to the originator developer and society. We continue to observe this debate closely and will consider updating our methods once a consensus has been reached.*
4.	**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	*We appreciate this analysis. Generalized cost-effectiveness analysis is not part of our reference case or of standard US value-assessment methods. Aggregating value across multiple future incident cohorts, and building assumed genericization into the analysis, are likewise not standard cost-effectiveness practice. Our reference case evaluates a single treated cohort at the current price, which is the decision-relevant price during the period of market exclusivity.*

	exclusivity [6], reflecting genericization only (a shallower, IQVIA-observed erosion path [7] yields the same conclusion; see Appendix I). (Comment below in reference to Table 1—Base Case Table 2—No discontinuation scenario analysis) 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.*	
5.	**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	*We appreciate the exploratory GCEA analysis but do not consider it appropriate for the base case or for threshold analyses to determine the health benefit price benchmark (HBPB). Incorporating the value elements that the comment notes is not standard practice in US value assessments and ICER's framework evaluates many of these considerations alongside the cost-effectiveness estimate, rather than adding them to the HBPB. We welcome NPLB to publish their model, inputs, and derivations in a peer-reviewed journal where the assumptions can be fully evaluated.*

	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)**.	
6.	**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	*We appreciate the comment. As previously mentioned, GCEA is not part of our reference case or of standard US value-assessment methods. We welcome NPLB to publish their model, inputs, and derivations in a peer-reviewed journal where the assumptions can be fully evaluated.*

	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.	