INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

KarXT for Schizophrenia
Response to Public Comments on Draft Evidence Report

January 25, 2024

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Response to Comments from Individuals Living with Schizophrenia

ICER would like to thank all individuals living with schizophrenia who took the time to share their experiences, real-world perspectives, and to express the need for new and better treatments. There were key themes around the impact of the disease on daily life, the challenges experienced with current medications available, and hopes for new therapies, which we have summarized below.

Additional details from these perspectives have been included in Section 2, Patient and Caregiver Perspectives, of the Evidence Report. These comments have also been incorporated into the public comment folio posted to ICER's website on January 25, 2024, along with this summary. Both the folio and this summary will also be shared with the voting council members participating in the upcoming public meeting on February 9th, 2024 to help inform their deliberation on the evidence.

Impact of Disease on Daily Life

Individuals living with schizophrenia shared that they strive to be productive members of society, but the disease makes it challenging as it has drastically changed their day-to-day lives. For many individuals, both schizophrenia itself and the side effects of some of the medications have made it difficult to hold a job or pursue higher education. Many individuals shared that they had to give up on their career goals or dream jobs because of symptoms of their disease or side effects of medication. Even after finding a medication that worked for them, some individuals shared that day-to-day tasks, like going to the grocery store, can still be challenging. Maintaining personal relationships was also mentioned as a challenge, leading to feelings of isolation and loneliness. Many of the symptoms highlighted as most challenging include, but are not limited to, delusions, auditory hallucinations, anxiety, paranoia, and intrusive thoughts.

Challenges with Current Medications

Even with medication, individuals highlighted that their challenging symptoms are not all well managed. Many individuals mentioned that the need to try many different drugs (more than 20 for one individual) over many years (a decade for another individual) before finding one that worked well enough. Individuals highlighted many burdensome side effects of even the drugs that worked best for them, including restlessness, sedation, weight gain, lethargy, and suppressed emotions. These side effects often interfered with the quality of their day-to-day life and limited their ability to participate in activities they enjoy.

Hope for New Therapies

All individuals mentioned how a therapy with fewer side effects would be very valuable to improving their quality of life, particularly if a therapy has fewer metabolic complications and/or did not cause emotional suppression. There was also hope that future medications would address the "killers" associated with schizophrenia, such as weight gain/diabetes, isolation/loneliness, and suicide. In terms of symptom relief, individuals expressed a need for a medication that would work for all symptoms associated with schizophrenia in order to minimize the number of medications needed, especially for symptoms such as negative thoughts. Overall, individuals shared that they are looking for a reliable medication that works day-to-day that could also be taken over longer intervals (monthly or bi-monthly). The goal should be complete recovery, but individuals emphasized that even a medication that better reduces symptoms with minimal side effects would be valuable.

#	Comment	Response/Integration
Manufacturers		
Karuna Therapeutics		
1.	**<u>Recommendation 1: Include contemporary cost and disutility of tardive dyskinesia as base case.</u>** ICER has included a scenario analysis where KarXT exhibits no risk of TD while the other modeled comparators have a 0.5% risk in each model cycle. Karuna believes this scenario is warranted in the base case analysis due to the unique target product profile and mechanism of action for KarXT and the absence of TD observed in the acute trials. TD is believed to result from the chronic blockade of dopamine D2 and possibly D3 receptors, a common mechanism of action shared by all antipsychotics. While the second-generation antipsychotics (SGAs) are associated with a lower risk of developing TD than first-generation treatments, 21% of patients treated with SGAs are nonetheless reported to experience TD.1 People with schizophrenia who develop TD have significantly worse health-related quality of life and social withdrawal compared to those without TD. TD can also persist for years or even decades; with only 33% or less of patients experiencing remission, and the associated patient impact and financial burden therefore persisting through the patient's lifetime.2 These impacts also extend to caregivers and payers. The cost of an initial event of TD has a significant financial burden of $12,732 based on the latest data from the Agency for Healthcare Research and Quality (AHRQ)3 and patients with TD have significantly worse health related quality of life compared to those without.4 In addition, the pharmaceutical interventions for TD such as deutetrabenazine extended release (AUSTEDO® XR) and valbenazine (INGREZZA®) are costly. The cost of deutetrabenazine ranges from $2,360 to $7,081 for a 30 day supply while valbenazine ranges from $7,302 to $8,022 for a 30 day supply.5 The monthly acquisition costs for TD drugs underscore the related financial burden faced by payers and patients for what is often a long-term, irreversible condition resulting from currently utilized treatments for schizophrenia. ICER has previously documented the cost burden associated with TD treatments in its 2016 assessment of valbenazine and deutetrabenazine. Incremental cost-effectiveness ratios were calculated at $752,000 and $1.1 million per quality-adjusted life year (QALY), respectively, over a lifetime horizon. TD was not observed in the acute setting for patients receiving KarXT, and due to KarXT's unique muscarinic, non-dopaminergic mechanism of action, it is recommended that ICER assume in the base case analysis that TD will not be	There is no evidence for KarXT's effect on tardive dyskinesia, but we do have trial evidence for KarXT and extrapyramidal symptoms. In the trial data we do have, KarXT was still associated with extrapyramidal symptoms (3.2% in the KarXT arm and 1% in the placebo arm). Because extrapyramidal symptoms still occurred with KarXT treatment, there was no evidence to suggest that there would be a benefit of KarXT on tardive dyskinesia. We encourage the manufacturer to further develop this evidence and we have reported a highly optimistic scenario should the evidence suggest KarXT is not associated with any tardive dyskinesia. We do not use the costs from the newer tardive dyskinesia treatments in this economic model because they have not become standard of care among the patient population with tardive dyskinesia.

	associated with KarXT treatment during neither the acute nor the maintenance treatment phases.	
2.	**Recommendation 2: Introduce risk and impact of agranulocytosis associated with clozapine.** Due to the variation between response of prior first- and second-treatments in the model and most patient time being spent in the third treatment health state where they may receive clozapine, the risk of neutropenia, risk of death associated with neutropenia, cost of routine blood testing, disutility of neutropenia, and associated monitoring and treatment costs for severe neutropenia associated with clozapine should be included in the model base case analysis to ensure a comprehensive and relevant base case assessment. Clozapine's FDA-approved label includes a Boxed Warning for severe neutropenia due to agranulocytosis, which can lead to serious and fatal infections. According to Li et al., the overall prevalence of agranulocytosis and associated death are 0.4% (95% CI 0.3–0.6%) and 0.05% (95% CI 0.03–0.09%) for patients treated with clozapine, respectively.[6] All patients receiving clozapine must undergo routine blood testing while on treatment and for 4 weeks after treatment discontinuation. While all patients in the model eventually reach third-line treatment with clozapine in a market basket during the modeled lifetime time horizon, the time spent on this treatment varies based on the performance of the preceding first-line and second-line treatment regimens included in the model. The clinical importance of this is highlighted by the two models, Davies and Park, cited by ICER for the maintenance phase structure of the model, which included increased mortality associated with clozapine use. The inclusion by both Davies and Park[7,8] in their published models and the FDA Boxed Warning for severe neutropenia due to agranulocytosis associated clozapine treatment support the relevance and importance to include these costs and outcomes in the ICER base case analysis.	We are not modeling clozapine specifically, but rather a basket of treatments and the basket has costs and outcomes that are characteristic of the treatments within the basket. Not modeling the risk and impact of agranulocytosis is a simplification of the model, but not one that will drive the findings, and is aligned with our approach of modeling a basket of treatments rather than one specific treatment. In studies that have modeled clozapine specifically, agranulocytosis was not a major driver of cost-effectiveness. For example, in the model built by Park et al., a different death rate due to agranulocytosis impacted the incremental cost-effectiveness ratio by less than 0.2%.
3.	**Recommendation 3: Make third treatment basket clozapine only, as a scenario analysis.** The third treatment sequence in the model consists of a treatment basket of 36% risperidone, 34% olanzapine, and 30% clozapine. ICER cites Kane et al.,[9] for the 30% clozapine uptake, and states that 30% of patients diagnosed with schizophrenia are treatment-resistant and therefore clozapine is a suitable treatment if they discontinued two prior antipsychotics. Based on Kane et al.,[9] the model assumes that of those who discontinue two prior treatments, only 30% of these patients would be considered treatment-resistant. However, this application is inconsistent with the data presented by Kane et al., which states 30% of patients are treatment-resistant and to establish this classification, patients must demonstrate inadequate response to two different antipsychotics.[9] Since	Our model is not a treatment sequencing model, but rather a model to isolate the effects of KarXT. We had extensive conversations with clinical experts about clozapine. We heard from clinical experts that clozapine utilization is low and it is certainly not the case in the real-world that patients transition to clozapine for the remainder of their treatment after they only fail two antipsychotics. We received feedback from the clinical experts we engaged that the 30% that we are assuming is likely too high and is a generous assumption to make for the intervention.

	ICER's model is a treatment sequencing model, upon second-line treatment discontinuation, all patients would be classified as treatment-resistant and eligible for treatment with clozapine. This would also be consistent with the Davies and Park models[7,8] cited by ICER. In summary, Karuna recommends reassessing how the Kane et al.,9 reference is being applied to the third-line treatment assumption. The current method employed implicitly assumes that 70% of patients remain on second-line treatment when transitioning to this health state, until 18.2% go off treatment at 20 years or death. This method also allows for patients to initiate therapy they did not adequately respond to. Therefore, Karuna recommends that third-line treatment in the model should include only clozapine as a scenario analysis along with recommendation 2; this would be more aligned to treatment guidelines, consistent with prior economic evaluations, in line with ICER's acute response methods, and may be a better representative as the last treatment in a lifetime treatment sequencing model for schizophrenia.	The treatment sequence we model, and the assumptions we make around discontinuation and treatment stopping, balances the variability in treatment sequence and outcomes with the typically lifelong treatment needed for schizophrenia.
Otsuka America Pharmaceutical, Inc		
1.	First, we generally agree with the assumptions made by ICER to compensate for the lack of long-term safety and efficacy data to date. Given that the current efficacy and safety data is for a five week acute treatment only, assumptions based on published data for other second-generation antipsychotic drugs for longer term efficacy and safety seem appropriate.[i]	Thank you for your comment.
2.	Finally, the Draft Evidence Report notes that participants in ICER's patients and caregivers focus groups expressed "great hope that KarXT's novel mechanism of action" would better treat cognitive symptoms than current medications. The Draft Evidence Report also acknowledges cautious comments on these claims. We agree with the need to be cautious about these claims given the lack of data. We suggest that ICER include any evidence supporting this hope in the Draft Evidence Report and address how it plans to incorporate cognitive data and findings in the event it later becomes available for KarXT.	Thank you for your suggestion. We did not find any substantive evidence in support of this potential benefit at this time. If substantial new evidence becomes available, ICER may decide to update its assessment using the new evidence. In addition, ICERs models are available online so that manufacturers and payers can update them at any time with new information in addition to inputs tailored to their specific populations and costs.
3.	On page 15 of the document ("Patient and Caregiver Perspective"), we suggest revising the language "Side effects of currently available therapies can be severe including significant weight gain and movement disorders. Because of this, people with schizophrenia often discontinue their medication, which leads to suicide, incarceration, or involuntary hospitalization" to instead read "Side effects of currently available therapies can be severe including significant weight gain and movement disorders. Because of this, people with schizophrenia often	Thank you for catching this. We have made the recommended change.

	discontinue their medication, which **may lead to** suicide, incarceration, or involuntary hospitalization."	

#	Comment	Response/Integration
Clinical Experts		
Dr. Rimal Bera, MD		
1.	The cost of treating a patient with schizophrenia, as noted in your Background and Scoping document, is estimated to be $343 billion in the United States.[1] However, this report fails to review the totality of the economic impact of schizophrenia by leaving out indirect costs of the disease such as housing costs, ancillary costs spent by caregivers, costs related to reduced quality of life, and other non-medical costs associated with this chronic disease. The economic impact could be far greater than quantified here in 2021. A study from The Schizophrenia and Psychosis Action Alliance about the Economic Impact of Schizophrenia in 2020 was $282 billion, demonstrating an approximate 22% increase in cost from 2020 to 2021.[2] The impact of schizophrenia is only expected to grow as prices increase, with the majority of the costs being associated with indirect health care expenses.[3] Without an accurate financial consideration, the impact of a potential new treatment option may be inadequate.	Our objective is not to assess the comprehensive societal burden of schizophrenia as a condition, but rather to isolate the costs and effects of KarXT (a potential treatment for schizophrenia). For KarXT's cost-effectiveness to be affected by these indirect costs, KarXT would need to impact these indirect costs. While many of the costs associated with schizophrenia are outside of the healthcare system, there is no evidence to suggest that KarXT will differentially impact these costs outside of the health system versus other medications. Additionally, all costs used in the economic model were inflated to 2022 US dollars following the practices for inflation in ICER's reference case. Further the $343 billion estimate in the background statement was not directly used in the economic model but was rather stated as context in the background section of the report.
2.	While the economic burden on society is notable, the impact on individual patients is equally valuable. In my experience working with patients with schizophrenia, loss of quality of life, inability to find and adhere to treatment options, and access barriers to treatment are some of the most difficult issues patients face. The ability to access treatments in a timely manner without access barriers is critical to helping patients with schizophrenia live healthy and productive lives. Health insurers often use cost-effectiveness evaluations to negatively determine formulary placement or place barriers to treatments. An unfavorable or inconclusive review will only	ICER reports can improve access when manufacturers choose a fair price. ICER believes that fair pricing should lead to fair access.

	enhance the barriers already in place that prevent patients with schizophrenia from seeking and receiving treatment.	
3.	It is also important to recognize the disproportionate impact of schizophrenia on minoritized communities. As mentioned in the Scoping Document, Black Americans are more likely to be diagnosed with schizophrenia and are more likely to go untreated.[4] However, the societal impacts continue to be left out of the economic evaluation. Additionally, one in three people experiencing homelessness have a serious mental illness like schizophrenia and one in seven people in prison have a serious mental illness.[5] The final cost analysis fails to include any consideration of the impact on the criminal justice system. Instead, since trials are still in process, any meaningful impact that treatment for patients would have on the criminal justice system is dismissed.	For KarXT's cost-effectiveness to be affected by these indirect costs, KarXT would need to impact these indirect costs. While many of the costs associated with schizophrenia are outside of the healthcare system, there is no evidence to suggest that KarXT will impact these costs outside of the health system compared with other therapies. Additionally, it is not true that the final cost analysis failed to consider the impact on the criminal justice system. In the modified societal perspective scenario analysis, criminal justice impacts were modeled and the impact of KarXT on the criminal justice system was extrapolated based on the number of relapses.
4.	A diagnosis of schizophrenia can be extremely hard on patients and can come after many years of misdiagnoses, stigma, and access barriers to treatment. As noted, some treatments for schizophrenia can develop unwanted side effects. The possibility of new treatment options should not be stifled by access barriers. Patients deserve the right to work with their providers to find the best treatment option for them without unneeded hindrances. Such a conversation can only occur after FDA approval which is not likely until 2024. Xanomeline tartrate/trospium chloride is an innovative treatment that has a different mechanism of action and throughout early trials has been shown to reduce side effects commonly associated with antipsychotics. This treatment is unique from other antipsychotics because rather than targeting D2 dopamine and serotonin receptors, it targets muscarinic receptors. Muscarinic receptors indirectly affect dopamine transmitters involved in mediating SMI symptoms. This treatment is the first potential medicine that can stimulate muscarinic receptors to help mediate schizophrenia while simultaneously combating undesirable side effects that can be found with psychotherapeutic drugs (weight gain, agitation, tardive dyskinesia, diabetes, sedation). No medication comes without the possibility of side effects, however, the ability to lessen or eliminate side effects such as those commonly associated with antipsychotic drugs would be extremely important for patients with schizophrenia. Often, it	When looking at individual patients, individual treatments will typically be more or less valuable than their average value based on the individual response. However, manufacturers do not vary their price based on patient response and so ICER's goal is to suggest an average fair price across a population. We agree that having different therapies is inherently a benefit for patients and is a potential other benefit. As such, we have explicitly added it to that section in the report. However, since every therapy is in some sense a "different therapy", it would not make sense to pay a higher price for this benefit.

	is difficult for patients with SMI to adhere to treatments because of the side effects.[6] Adherence to treatment releases pressure from the health care system, as patients are less likely to need emergency care and are more likely to hold employment and stay healthier longer.[7] Each patient responds to treatments differently, hence why there is a need to consider each patient's personal experience with treatments rather than a collective. What works for one patient might not work for another, but the possibility of options without onerous restrictions- that place barriers not only on patients but providers- is of utmost importance.	
5.	ICER's continued reliance on the quality-adjusted life year is of great concern. As mentioned throughout these comments, schizophrenia is a wide-ranging chronic disease that has unique impacts on each individual patient. Attempting to utilize a metric that fails to capture individual impacts on a person living with this disease can potentially be harmful. There has been significant criticism of the QALY and similar metrics. In 1992 the United States Department of Health and Human Services found that the state of Oregon's cost-effectiveness ratios derived from the use of the QALY was discriminatory and violated the Americans with Disabilities Act. There are also efforts at the federal level to eliminate the use of the QALY and QALY like metrics from federal programs. As the health care system continues to progress towards one prioritizing personalized medicine, I'd encourage ICER to prioritize methods that also place an emphasis on how emerging and innovating treatments can prove value for the individual patient.	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value
6.	There is no way to capture what progress means for all patients, but rather the individual experience is far more important. Any formula that attempts to evaluate perfect health will fall short for patients with schizophrenia and ultimately ignores what treatment can mean for an individual. No improvement is too small and should be celebrated rather than dismissed because it does not fit into the equation. While ICER notes that the QALY and the evLYG are commonly used metrics in cost-effectiveness analyses, it's important to recognize that these metrics do not evaluate clinical analysis. It also fails to incorporate factors such as disease severity, equity of access, or unmet need and I urge you to recognize its limitations.	As noted, ICER does not base its comparative effectiveness assessments on any particular formula or on the cost-effectiveness of a therapy. The other points made are addressed as potential other benefits and contextual considerations.
7.	As indicated in the Draft Evidence Report, around 3.9 million people are living with schizophrenia, with numbers growing every year. Cost effectiveness evaluations that provide inaccurate estimates can erect unnecessary barriers that make	While, conceivably, inaccurate cost-effectiveness analyses could affect access,

	it more difficult for patients to access treatment options that are important to their quality of life and management of their disease. Worse, given the demographic realities, these barriers will disproportionately harm minorities and could widen health care disparities. I urge you to consider input from clinicians, patients and caregivers who directly work with disease daily to understand what the value of treatment options would mean for this community.	a far bigger issue for access is the price set by the manufacturer. ICER feels that an important consideration for all stakeholders should be pricing of KarXT should it be confirmed to not promote metabolic syndrome. If that is the case, it could be reasonable to use KarXT as an early line treatment, and pricing choices could prevent this from happening.
Dr. Ciaran Michael Considine, PhD, ABPP		
1.	As a neuropsychologist, I work to garner a relationship and build trust with my patients experiencing serious mental illnesses. Often due to societal stigma, barriers to care and workforce shortages, patients with serious mental illness can be hesitant about receiving a diagnosis. As acknowledged in the Draft Evidence report, anosognosia is also a prevalent barrier to care for patients. My research and presentation of managing anosognosia in clinical practice at the Clinical Neurological Society of America Time demonstrates that I understand firsthand how important it is to build a relationship to create a diagnosis and find a treatment plan that works for their individual needs. Patients with serious mental illnesses often step through medication after medication to find which works best for them. Antipsychotic treatments often are accompanied by a host of side effects. Additional options allow the patient and provider to identify which treatment best satisfies the needs of the individual patient. As noted in the Draft Evidence Report, serious mental illnesses such as schizophrenia can be challenging and isolating, but that does not mean patients cannot find meaningful outcomes with treatments.[8]	Thank you. We are glad that our brief summary of a complex area has reasonably captured your perspective.
2.	KarXT has clinically demonstrated the possibility of treating the symptoms associated with schizophrenia without producing unwanted side effects. Through my extensive background working with patients with movement disorders such as TD at Vanderbilt University, I understand the impact of what a treatment option that eliminates such side effects would mean for a patient's success, adherence, and quality of life. If an option such as KarXT were to become available, it would allow clinicians and patients another tool to try to manage schizophrenia. As it stands, an unfavorable or inconclusive analysis of KarXT could limit the ability of prescribers to use this tool if FDA	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.

	approval occurs. As you proudly state on your website more than 75% of private insurers PBMs, and multiple employer coalitions use ICER's assessments to inform formulary decisions, coverage criteria and price negotiations. A hasty review that lacks adequate data can undermine the relationship clinicians spend so long cultivating by placing a barrier between what patients deserve and what they will face at the pharmacy. KarXT is a novel treatment for schizophrenia that has demonstrated efficacy and safety in its preliminary clinical trials. This treatment will now face the FDA for further review and long-term impact. Without this additional data, no true assessment can be made of the effectiveness of this treatment compared to others. The analysis relies heavily on assumptions because the timing of the review is premature. This review must make significant presumptions on the long-term efficacy, side effects, and adherence because of the lack of data that can only come during the FDA review. Simply put, additional data on the long-term impact of this treatment, specifically regarding the incidence of tardive dyskinesia, would allow for a more comprehensive assessment. I urge the committee to wait until further data is presented to make a comparison between KarXT and any antipsychotic.	Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.
3.	The continued usage of the QALY and evLYG remains a concern in an analysis of the cost-effectiveness of any treatment. These measurements are discriminatory in nature and diminish the improvements that patients experience. The goal of the cost-effectiveness analysis is to help inform policy decisions that affect patients' lives, yet things that are often deemed "valuable" from patients are inadequately represented through metrics like the QALY. The overreaching decisions based on an unattainable perfect health score impact patients' access to treatments regardless of what the treatment could mean for the patient. To say that dismissing cost-effectiveness is rejecting patients' lived experience is contradictory to the stated purpose of the QALY and evLYG which works to evaluate an entire patient population, not their individual experiences.[9] Furthermore, the use of the QALY is considered an inappropriate metric by many state and federal entities. The United States Department of Health and Human Services found that certain states use of the QALY was discriminatory and violated the Americans with Disabilities Act. Currently, there is federal legislation to stop the use of the QALY and similar metrics from federal programs, as well as a number of states that are working to enact similar legislation. This	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value. Throughout our assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. In other words, if a treatment adds a year of life to a patient population – whether treating individuals with Alzheimer's disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability –

	demonstrates the changing tide moving away from the metrics used in this review.	that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension. The evLY is not discriminatory and neither the evLY nor the QALY diminishes the improvements that patients experience.
4.	I recognize and understand the need to ensure that resources are spent wisely and effectively. However, this particular review fails to capture data that may have a significant impact on the final determination. The potential for additional treatment options provide value to millions of individuals living with schizophrenia. Cost-effectiveness evaluations that lack significant data ultimately may serve as a barrier for patients. Additionally, I oppose the use of the QALY to evaluate the cost-effectiveness of this treatment. Lack of data aside, the individual experience is often left out of this equation. I urge you to consider the limitations of the QALY and find other ways to explore the importance of treatment options for patients.	We agree that having different therapies is inherently a benefit for patients and is a potential other benefit. As such, we have explicitly added it to that section in the report. However, since every therapy is in some sense a "different therapy", it would not make sense to pay a higher price for this benefit. We would be interested in what methods of cost-effectiveness evaluations you favor.
Dr. Peter J. Weiden, MD		
1.	**<u>The analysis is speculative which is not reflected in the tone of the document</u>** I was surprised, to say the least, that ICER has taken the position that such a review is even possible in the first place. As stated in the document, this was written with no data information about the long-term effectiveness or tolerability. To me that makes absolutely no sense because of the long-term nature of the illness. While I suppose this ship has sailed, I am puzzled that the document does not really inform the reader that this analysis is speculative. While there are caveats throughout, there is no cogent discussion tackling why this was done in the first place. There should be a more transparent limitations section, in my opinion, and ICER might want to provide some examples as to how optimal understanding of antipsychotics can take years after approval (see later section). Likewise, the limitations of the current treatments are somewhat woodenly recited and there is no sense of urgency that it has taken drug development over 50 years to come up with a non-dopaminergic treatment of schizophrenia that seems every bit as effective as current therapies. ICER may wish to mention other disease areas (hypertension; AIDS; cancer, MS) where the introduction of different mechanisms of treatment has provided dramatic	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.

	benefits to patients in ways that were not, and could not, be fully understood at the time of FDA approval.	
2.	**<u>The uncertainty assumptions are skewed to unknown risks and ignore unknown benefits</u>** The documents tone emphasizes fear of unknown problems , for example, just looking at one page in the executive summary, we find on page 2 of the executive summary: • *"The major source of uncertainty is the lack of data on the efficacy of KarXT for longer than five weeks."* Page ES2 Paragraph 2, 1st sentence followed by • *"…In addition, KarXT has a new mechanism of action, which may lead to unanticipated adverse events over the long run"* ES2 Paragraph 2 second sentence. Two paragraphs later this is repeated almost verbatim from paragraph 2 • *Given the lack of data on the long-term benefits and harms of KarXT, which **has a novel mechanism of action and thus the possibility of unanticipated long term adverse events*** [emphasis added].." Page ES2, paragraph 4 Any statement of lack of evidence is followed by negative inferences only • *"Given no evidence for superiority in the acute setting and the lack of long-term data, we find the evidence to be insufficient (I) to judge the comparative clinical effectiveness of KarXT compared with aripiprazole."* [page ES2 bottom of last paragraph] • *Making the **highly favorable assumption*** [emphasis added] *that KarXT does not increase the risk of metabolic syndrome and associated consequences beyond that seen in the general population.."* Page ES3 1st sentence of paragraph 2 • *In contrast, **we assumed no reduction in the risk of tardive dyskinesia with KarXT*** [emphasis added] *compared with other second-generation antipsychotic medications.* ES3 towards the end of paragraph 2	Long experience with treatments has taught everyone in medicine that unanticipated harms are common and unanticipated benefits are rare. If you review our evidence ratings and figure 3.1 in the report, you will see that the uncertainties capture both large benefits and some harms. We think this is appropriate.
3.	I agree with the ICER review that there are unknown efficacy and safety risks associated with KarXT. I disagree with the tone and feel that there is a rigging of assumptions biased against KarXT. Here is what I mean. For better or worse, you have embarked on an analysis of an investigational medication without even having the complete data set needed for an FDA review for its approval. Because of this, assumptions are made. But in fairness, if you are embarking on assumptions (some might say speculation) why do these assumptions seem to stack against KarXT? Would it not be a better approach to be dispassionate about this, drop the dramatic tone and provide what if scenarios, some including unanticipated problems and other anticipated strengths. Why was tardive dyskinesia a secondary analysis whereas lack of metabolic risk was grudgingly put into the model? It seems to me that, if	Please see our responses above explaining why tardive dyskinesia was not included in the base case and justifying the timing of our review. In the trial data we do have, KarXT was still associated with extrapyramidal symptoms (3.2% in the KarXT arm and 1% in the placebo arm). Because extrapyramidal symptoms still occurred with KarXT treatment, there was no evidence to suggest that there would be a benefit of KarXT on tardive dyskinesia. Despite this not being a strong indicator that KarXT would not cause tardive

	anything, a stronger theoretical case can be made that KarXT will not cause TD and that to be fair the document should add it to the primary model. For tardive dyskinesia risk, it would seem very appropriate for the authors to review and summarize / cite the preclinical literature that in my opinion is a strong indicator that KarXT will not cause tardive dyskinesia within the limits of signal detection in clinical populations.	dyskinesia, we present a scenario assuming KarXT would not be associated with any tardive dyskinesia.
4.	**<u>Unknown value is as important as unknown risks</u>** There is a similar bias that the long-term efficacy assumption of equivalence to current antipsychotics is a best case for KarXT. Why warn the reader that long-term relapse prevention might not be as effective as current antipsychotics without mentioning the possibility be better for relapse prevention? My reaction to the tone of the draft report is that it comes across as biased with a kind of rigged "Heads I Win, Tails is a Tie" feel to the assumptions review. To me, the tone makes me wonder about why ICER chose to review KarXT right now. There is no way that any new psychiatric treatment can realistically show its true value at the time of approval, let alone before approval. It makes me wonder whether ICER is signaling its opposition to innovation in a disease like schizophrenia despite the known problems with current therapies. To me, this draft's tone and biased assumptions ignores the enormous *potential* value of KarXT.	Most imagined therapies do not work. This is why we require clinical trials before administering therapies rather than administering them until they have been proven to be ineffective or harmful.
5.	**<u>Examples of antipsychotics whose value unfolded over time</u>** As the ICER report correctly reminds us, the risks of any new treatment might not be understood right away and might therefore lead to overvaluation of relative safety benefits of the new treatment relative to its predecessors. The classic example in treatment of schizophrenia is the long lag time between the introduction of first-generation antipsychotics ("neuroleptics") and tardive dyskinesia. But I will conclude this commentary by providing examples of antipsychotics whose benefits were not known at the time of approval. • <u>Clozapine for treatment-resistant symptoms</u> Clozapine was initially considered to be equivalent to the other neuroleptics and only after it was approved did it become apparent that it had unique efficacy for treatment-resistant schizophrenia. To state the obvious, an imaginary IICER evidence review of clozapine at an equivalent time as KarXT is now would miss clozapine's future. • <u>Lower relapse risk associated with olanzapine and risperidone relative to first generation</u> The first post-clozapine atypical antipsychotics were risperidone and olanzapine. Both risperidone and olanzapine were shown to be more effective for relapse prevention than first generation medications	We agree that there is the potential for unexpected long term benefits. If substantial new evidence becomes available, ICER may decide to update its assessment using the new evidence. In addition, ICERs models are available online so that manufacturers and payers can update them with new information in addition to inputs tailored to their specific populations and costs. Clinicians in the field who we spoke with pointed more frequently to other therapies initially touted as being effective with fewer or no side effects only to be found to have significant side effects with longer follow-up.

	such as haloperidol. This efficacy finding was not anticipated or understood until some time after their respective FDA approval. • <u>The specific benefits of some antipsychotics for bipolar depression came after approval</u> At the time quetiapine was approved for schizophrenia, to my knowledge no one would have thought that it might specific efficacy for bipolar depression. But it did, and eventually opened up a new therapeutic class of treatment for bipolar depression.	
6.	**<u>Summary and some recommendations</u>** It seems that if this document invokes unknown safety risks as a potential unknown risk associated with KarXT (and I think it should), the document should also consider the possibility that KarXT will provide additional efficacy in ways that we can't predict. My recommendation to you as ICER authors is to provide examples of how future value may occur in ways that are unknown at the time of the immediate review, and that it seems likely that a new, non-dopaminergic MOA might provide benefits related to persistent symptoms, relapse prevention, other symptom domains, subgroups, in ways that are not predictable with of course the caveat that the current analysis cannot include these as estimates but this certainly is a potential future value that needs to be recognized.	We agree and we believe that we have highlighted the hope that KarXT may improve cognitive function and reduce negative symptoms, which would be a major leap forward for patients and their caregivers. Unfortunately, without any data supporting these hopes, they cannot be incorporated into our analyses except as hopes.

#	Comment	Response/Integration
Patient/Patient Groups		
Institute for Patient Access		
1.	**A Health Care Framework Ignores the Larger Societal Costs of Schizophrenia** Schizophrenia is associated with many societal costs, including disproportionate rates of incarceration, lost educational opportunities, lost economic opportunities, lower productivity, premature mortality and caregiver burden. While acknowledging they exist, the base case analysis ignores these societal costs. Consequently, the report underestimates KarXT's value. As the draft evidence report notes, the majority of the $343 billion in economic costs "are societal, not medical." According to Kadakia et al. (2022), the direct health care costs from this disease are a bit more than $62 billion, while the total societal costs are nearly $281 billion.[10] The breakdown of these societal costs include a $112.3 billion annual burden on caregivers, $61.6 billion in unemployment and lost productivity costs, and $35 billion in law enforcement, homeless and income support costs. The higher premature mortality rates impose another $77.9 billion annually in economic burden. By ignoring more than four-fifths of schizophrenia's costs, the analysis significantly underestimates KarXT's potential benefits. In fact, an accurate understanding of the treatment's cost effectiveness cannot be obtained within the constraints of ICER's current methodological approach. Unless the final report incorporates societal considerations into the base case analysis, the evaluation will underestimate KarXT's value.	Importantly, our objective is not to assess the comprehensive societal burden of schizophrenia as a condition, but rather isolate the costs and effects associated with KarXT (a potential treatment for schizophrenia). We do not deny the extensive societal costs and impacts of schizophrenia, and a comprehensive societal burden analysis of schizophrenia is important research. However, that is not the objective of this analysis. This analysis is estimating the incremental impact of KarXT (as compared to other second-generation antipsychotics) on costs (health care sector and societal) and outcomes (health care sector and societal). In alignment with this objective, this analysis is treatment-specific and is not a comprehensive disease-level analysis. This comment says we are significantly underestimating KarXT's potential benefits but does not state which benefits we are underestimating. We are not incorporating all of the schizophrenia-related societal-level costs and health outcomes within our model because that is not necessary for our objective. Rather we are incorporating the societal-level costs and health outcomes that we can reasonably say KarXT impacts as compared to other second-generation antipsychotics because that is necessary for our objective.
2.	**Relegating Societal Costs to a Scenario Analysis Does Not Address the Problem** Incorporating societal cost considerations into a scenario analysis does not solve this fundamental problem. Instead, it relegates most of the costs that patients bear	The findings from the modified societal perspective scenario analysis are nearly identical to the base-case analysis from the health care sector perspective. Therefore, even if the modified societal perspective was the base-case, the findings would be nearly identical.

	to a secondary analysis. Even if this secondary analysis were accurately estimated, the more comprehensive assessment of the medicine's cost effectiveness is portrayed as a less important estimate. The base case estimates, which account for only a portion of the costs, will inevitably drive subsequent discussions about value, coverage and access.	This assessment follows ICER's value assessment framework and reference case for when the modified societal perspective scenario analysis is presented as a co-base-case.
3.	**The Scenario Analysis Excludes Many Potential Benefits for Patients** For the societal cost scenario, the report makes assumptions about KarXT's long-term efficacy, side effects and adherence because that data does not yet exist (a topic discussed further below). These assumptions are mostly biased toward undervaluing KarXT; consequently, there are concerns regarding how the scenario analysis evaluated societal costs. The draft evidence report summarizes the results of the societal costs scenario, which accounted for productivity losses, caregiver time spent caregiving, and the costs to the criminal justice system, by stating > Caregiver time spent caregiving was greater for KarXT-treated patients due to the longer duration of caregiving requirements. Productivity losses and costs to the criminal justice system were marginally lower for KarXT-treated patients due to the marginally fewer relapses that occurred due to the marginally longer time on antipsychotic treatment. These conclusions raise several concerns. The above quote from the draft evidence report indicates that the authors are assuming KarXT will reduce the amount of premature mortality from schizophrenia – that is why the assessment states that more caregiver time is spent caring for patients due to "longer duration of caregiving requirements." Despite assuming that there are reduced mortality benefits (i.e., a reduction in the annual economic costs of nearly $78 billion caused by higher premature mortality), these benefits are not considered in the societal cost scenario. From a patient perspective, improved mortality is perhaps the most valuable benefit an effective	Keeping people alive longer without significantly improving their schizophrenia does undoubtedly mean an increase in caregiving time. There is no evidence that KarXT is more effective than the other second-generation antipsychotic drugs on managing schizophrenia. If a treatment cured schizophrenia or dramatically alleviated symptoms of disease, we would agree that the caregiver impact would go down even with life extension. However, KarXT is not a cure for schizophrenia and does not dramatically alleviate symptoms of schizophrenia, but rather potentially reduces weight gain and subsequent development of diabetes and cardiovascular disease. In the revised Evidence Report, we now include indirect costs associated with diabetes and cardiovascular disease within the modified societal perspective scenario analysis. In the Evidence Report, Supplemental Table E17 reports the disaggregated societal-level costs that were included in the analysis. The caregiver costs between the intervention and comparator arm are different by less than a half percent.

	medication can offer. The exclusion of these mortality benefits grossly underestimates the societal benefits from KarXT. Other assumptions are also troubling. For instance, the authors simply assume that the additional caregiving requirements from a longer lifespan are larger than any potentially reduced caregiving requirements because patients' schizophrenia is better controlled. This random assumption drives the results but is not grounded in actual data. Should this assumption prove wrong, a definite possibility, then the arbitrary assumptions of the report may have supported unnecessary obstacles that make it more difficult for patients to access medication that could benefit them. From a patient perspective, the implication of these assumptions is troubling. Since the analysis ignores the reduced premature mortality benefits, while also assuming that longer lifespans impose a greater burden on caregivers, the draft evidence report assumes that longer lifespans for schizophrenia patients are a net cost. This conclusion is clearly wrong and inappropriate. The final report should, at bare minimum, change these assumptions to correctly account for the benefits that reduced premature mortality provides.	
4.	**Arbitrary Assumptions Drive the Evaluation's Health Care Perspective Results** Misguided assumptions used in the health care sector analysis also plague the draft evidence report. The analysis relies heavily on poorly founded assumptions because the timing of the review is premature. The FDA has only accepted KarXT's new drug application as of September 28, 2023. Consequently, only data from the drug's clinical trials are available. The trial data is promising. Thus far, KarXT has been effective in reducing schizophrenia symptoms with minimal adverse events.[11] As with all new drugs, however, more research is needed. Over time, this data will become available, enabling a better understanding of the medicine's impact, particularly with respect to the longer-term cognitive benefits and potential side effects	The timing is not premature unless you believe that the timing of FDA approval is premature. Decisions about drug pricing, negotiated rebates, and coverage policy happen at the time of FDA approval. The only time that an analysis of comparative clinical efficacy and cost effectiveness/value can have an impact is if it is available at about the time of FDA approval. We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness

	of KarXT. But this lack of data, which is to be expected at this stage of the drug development process, severely limits the validity of any cost-effectiveness analysis. There is simply not enough data to derive meaningful results.	research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. We also question your assertion that KarXT has minimal adverse effects. The discontinuation rates due to adverse effects were quite high in just the 5 weeks of available clinical trial data.
5.	To overcome this obstacle, the draft evidence report makes assumptions regarding fundamental clinical outcomes, such as KarXT's impact on diabetes, tardive dyskinesia (TD) and adherence. For example, the analysis assumes that the "three-month probability of relapse in the maintenance phase" of the drug is the average of the other medications used as comparators. Like the caregiver assumptions used in the societal costs section, this assumption meaningfully alters the results. In this case, the assumption biases the cost-effectiveness results toward the average impact of the current medicines. There is no reason to believe that the relapse probability is the average of the comparator medicines.	No evidence exists on the impact of KarXT on relapse. However, KarXT evidence that does exist on adequate clinical response was not statistically different from the other second generation antipsychotics. Therefore, we made a reasonable assumption that the relapse probability is the average of the comparator medicines. We discussed this assumption with stakeholders and varied it widely in sensitivity analyses. As for other assumptions that were required, we used the data that we did have available, along with evidence from other antipsychotics and stakeholder feedback, to make reasonable and evidence-based assumptions. We then varied these model inputs and assumptions widely.
6.	As another example, the report makes disconcerting assumptions regarding TD. KarXT has a novel mechanism of action, and one potential benefit expected from this novel mechanism is a lower rate of TD. The draft evidence report acknowledges that there is insufficient data with respect to TD and uses that lack of data as an excuse to ignore the potential benefits from reducing its incidence. Assuming away one of KarXT's potential benefits could be particularly troubling should the expectation of lower TD incidence be fulfilled once sufficient time to evaluate this benefit has passed.	Please see our response to Karuna Therapeutic's first comment that includes our rationale for why tardive dyskinesia was not included in the base-case analysis.

7.	The amount of misinformation these assumptions introduce into the report are currently unknown. Consequently, whether the draft evidence report's estimated cost effectiveness of KarXT accurately reflects the medicine's actual cost effectiveness is unknown. The data availability problem will not be resolved prior to publishing the final report based on the current publication schedule. This constraint justifies a delay in publishing any cost-effectiveness analysis until more data regarding the medication's benefits and side effects (particularly the long-term benefits and side effects) has been published.	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.
8.	**QALYs Are Inappropriate Metrics for Evaluating Mental Illness** There are well known flaws with the QALY that create serious accuracy concerns when applied to mental illnesses such as schizophrenia. The QALY metric attempts to create a consistent standard from which the value of medications can be judged. This standard incorporates quality-of-life considerations and mortality impacts into one value. One of several problems plaguing the QALY metric is that many quality-of-life considerations are difficult to accurately measure. While this problem can affect many diseases, it is especially significant for diseases, such as mental health disorders, where improvements are often subjective. The QALY is a significantly less reliable measure when applied to medications that provide patients with subjective improvements in health outcomes because the calculation requires impacts to be transparent and easily observable. Unlike diseases such as cancer, meaningful improvements for patients living with schizophrenia are often subtle and difficult to quantify. The inability to easily measure potential improvements does not mean that patients are not experiencing meaningful benefits. Patients with schizophrenia can	We are uncertain why you feel that quality of life measurements are particularly inaccurate when applied to a condition like schizophrenia that has enormous impacts on quality of life. The notion that impacts need to be "transparent and easily observable" is incorrect and mischaracterizes how quality of life is assessed.

	often experience significant improvements in their quality of life even though researchers may find it difficult to measure these improvements. This reality indicates that the QALY methodology is likely providing an inaccurate assessment of KarXT's quality-of-life improvements.	
9.	**Conclusion** As indicated in the draft evidence report, around 3.9 million people are living with schizophrenia – a disproportionate share being African American. Cost-effectiveness evaluations that provide inaccurate estimates can erect unnecessary barriers that make it more difficult for patients to access medicines that are potentially efficacious for them. Worse, given the demographic realities, these barriers will disproportionately harm minorities and could widen health care disparities. Considering these costs, IfPA urges ICER to delay the final report until sufficient data exists to perform an accurate assessment. At the very least, the final report should include societal costs, which include the benefits from reduced premature mortality, in the base case analysis. Further, the societal costs should ensure that patients longer lifespans are not considered a cost but the undeniable benefit that they are. Finally, the analysis should recognize the weakness of the QALY measure when evaluating mental illnesses.	Please see above comments.
Don Kreis – Patient Advocate		
1.	As you know, I am a member of the New England Comparative Effectiveness Public Advisory Council (CEPAC), in my personal capacity as a representative of the patient/family advocacy community. Because I plan to participate in the New England CEPAC's February 9 virtual public meeting concerning KarXT for Schizophrenia, I have reviewed ICER's draft evidence report on this treatment. This letter responds to ICER's invitation for public comments on the draft report by today's deadline. I offer my comments as an interested lay person who has no background in medicine, scientific research, or economics. My interest in the subject of drug pricing arises out of my experience raising a daughter who has cystic fibrosis. As such, I have no prior experience with schizophrenia or its treatment, either directly or through a loved one. Accordingly, my suggestions about the draft report on KarXT are offered with	Thank you for sharing your comments.

	the sole purpose of improving the clarity of the document from the perspective of concerned laypeople of goodwill who want emerging treatments for a serious disease like schizophrenia to be widely available and fairly priced. My comments here are intended to express no opinion on the merits of the report. Please be assured that I approach the February 9 virtual public meeting, and the questions the New England CEPAC will vote on at that meeting, with an open mind and heart.	
2.	Page 1 – The "Background" section of the draft report makes the very salient point that "Black Americans are diagnosed with schizophrenia at about twice the rate of White Americans and have worse outcomes." Later in the report, at pages 28-29 of the section on "Contextual Considerations and Potential Other Benefits," the draft report refers to "uncertainty about whether the higher rates of diagnosis of schizophrenia in Black people in the US represents true higher prevalence or a tendency for psychosis to be attributed to affective psychotic disorders (such as bipolar mania) in a White population and to schizophrenia in a Black population." This strikes me as a startling and significant hypothesis that merits a somewhat more detailed discussion in the report, given that ICER recognizes the reduction of health inequities as an important societal goal that is germane to the report's ultimate conclusions. It would, for example, be helpful to have more insight into the basis of the referenced uncertainty. Put simply, if Black Americans are being misdiagnosed in large numbers with schizophrenia then the widespread use of KarXT in that population would be both wasteful and harmful, whereas it most assuredly would advance society's goal of reducing health inequities if KarXT is widely available to a racial minority that truly suffers from schizophrenia at a significantly higher rate than the general population.	Thank you for acknowledging the importance of this issue. However, we feel that a more detailed exploration of these issues is beyond the scope of the report. They remain important and should receive their due during the public deliberations of the report. It is worth noting that it may not be a misuse of KarXT if the diagnosis is different, but still involves psychosis. Psychiatrists commonly use medications approved for treatment of schizophrenia to manage psychotic symptoms of other diseases such as bipolar disorder.
3.	Page 3 – The section on "Patient and Caregiver Perspectives" includes an interesting and obviously important observation that anosognosia – lack of awareness and acceptance of the disease – occurs in more than half of people with schizophrenia and thus serves as a significant barrier to high quality care. The draft report notes that "[w]hen considering the best medicatyions for a person with schizophrenia, it is always the one they are willing to take." Missing, however, is any insight from patients and caregivers about whether KarXT would make any difference or, perhaps, whether no treatment can ever overcome this barrier.	Thank you. This is a huge issue in the care of patients living with schizophrenia and their caregivers as eloquently described by Dr. Considine in his comments above. Given the paucity of experience with KarXT, we were unable to obtain any clear guidance from patients and caregivers about whether KarXT will help to overcome this barrier.
4.	Page 5 – The abbreviation "RCT" appears on this page, but nowhere in the draft report (e.g., in the list of acronyms and abbreviation) is it explained that RCT means "randomized control trial." Obviously, every medical researcher on the	Thank you. We have corrected this oversight in our revised report.

	planet knows what an RCT is, but it is probably not in the common lexicon of the patient and caregiver community for schizophrenia.	
5.	Page 9 – The discussion labeled "Harms: Acute Treatment" notes that, across three trials of KarXT, 5.3 percent of patients receiving the drug and 11.4 percent of patients receiving the placebo reported a weight gain of greater than seven percent, identified as a commonly reported threshold in acute trials of schizophrenia treatments. Perhaps related to the discussion of metabolic syndrome, below, it seems counter-intuitive that treatment with a placebo would trigger any weight gain unless it is normal and expected for all schizophrenia patients to experience weight gain of that magnitude over any random five-week period in their lives. Perhaps I am the only reader who finds this perplexing. Also, it would appear (at least to someone whose graduate training is in law and journalism) that this disparity – 5.3 percent vs. 11.4 percent – is inconsistent with the observation at page 20 that "[t]here was no significant difference in weight gained between patients treated with KarCT and patients treated with placebo reported in the KarXT clinical trials."	We agree that the findings that you point to are perplexing. In part, that is why we highlighted that in one trial, patients receiving KarXT gained more weight than those in the placebo group, while in the other two, the opposite was the case. The differences are small and not statistically significant, suggesting that they are due to chance given the relatively small number of patients in each trial. KarXT does not appear to lead to weight gain in the short term compared with placebo. However, both olanzapine and risperidone do lead to significant weight gain compared to placebo and, in our indirect analyses, compared to KarXT. Furthermore, the weight changes does not reflect maintenance therapy. Rather these are weight changes during a period when the patients were acutely psychotic and hospitalized and weight changes could be a response to hospitalization with access to food or to changes related to treatment (or lack thereof) of the patient's acute psychosis.
6.	Page 10 – I respectfully suggest brief parenthetical explanations of "gynecomastia," "galactorrhea," and "[e]xtrapyramidal symptoms," given that these are among the listed "Other Patient-Important Harms" and there will be patients reading the final report.	Thank you. We have addressed your concerns.
7.	Page 14 – Two seemingly important assertions on this page would, I think, benefit from elaboration or perhaps a clearer explanation. A sentence I cannot understand is: "We heard from experts that controlling the positive symptoms in a patient who is acutely psychotic will confound any assessment of changes in cognitive function and negative symptoms." A sentence that arguably cries out for elaboration (based on insights from the cited authority) is: "Studies suggest that as many as 80% of patients with schizophrenia would be excluded from current randomized trial designs."	Thank you. We have elaborated on the potential bias in interpreting changes in cognitive function and negative symptoms in the setting of treatment focused on poorly controlled positive symptoms. We provided the citation for the issues of generalizability of data from RCTs to the larger population of patients living with schizophrenia and feel that suffices given the scope of our review.
8.	Page 16 – At this point in the "Summary and Comment" section, there is much discussion of the incidence of	Thank you for pointing out this oversight. We have added a brief explanation of the

	"metabolic syndrome" in schizophrenia patients as a serious adverse effect of existing treatments. The report should explain what "metabolic syndrome" is, even though the term is presumably a well-known one among those who treat, or live with, schizophrenia. A forthright and explicit description of what metabolic syndrome is would communicate to schizophrenia patients, and their loved ones, that ICER well understands what is obviously a significant and unwelcome reality for those struggling to overcome this disease.	components of the metabolic syndrome to the 3rd paragraph of the Background section.
9.	Page 23 – Section 4.3 of the report, describing the "Base-Case Results" of the long-term cost effectiveness analysis, is obviously a key element of the draft report. It would, therefore, be desirable if this discussion were as comprehensible as possible to people who are not healthcare economists and, potentially, primed to be skeptical about ICER assessments of cost effectiveness. I fear this sentence will be completely opaque to such readers: "Using a placeholder annual cost of $20,000 per year, the intervention costs are greater, but there are fewer non-intervention costs resulting from fewer relapses and treatment-emergent adverse events." The final report should explain why ICER selected a placeholder price of $20,000, and what "fewer non-intervention costs" means. (In other words, "intervention" vs. "non-intervention" costs are, arguably, jargon – deployed at a critical juncture in the draft report.) Moreover – and here I forthrightly confess I might just be a victim of my own brain fog – I do not understand why the draft employs a placeholder cost of $20,000 while Table 4.3 lists the cost of KarXT as $42,000.	Thank you for highlighting this. We have added detail to this section to define intervention costs and non-intervention costs. We also provide examples of what these costs are. We have also added "Lifetime Time Horizon" to the title of Table 4.3. The placeholder cost of $20,000 is per one year of treatment, whereas the $42,000 reported in Table 4.3 is the total KarXT cost over the entire lifetime time horizon.
10.	Page 26 – I have no suggestions about this section of the draft report, labeled "Uncertainties and Controversies." Rather, I want to single it out for praise as a lucid explanation of the distinction between the lived experience of any individual patient versus average population-wide effects versus the "enormous societal impact of schizophrenia."	Thank you for sharing this.
Partnership to Improve Patient Care		
1.	**The EQ-5D is an inappropriate PRO tool to use in this assessment as it is insensitive to changes in QOL in mental health.** The generic EQ-5D is a tool known to be insensitive to changes in quality of life (QOL) for psychiatric conditions. In general, generic preference-based measures do not correlate well with symptoms for psychiatric conditions or with clinician-assessed outcomes. This can be challenging for economic evaluation since interventions typically target positive symptom reduction that would be missed by measures such as the EQ–5D.[12] A	As modeled, the value of KarXT is not driven by improvements in mental health status, but rather fewer years with diabetes or cardiovascular disease. As evidenced by the Tornado Diagram in Figure 4.2, the schizophrenia specific utility estimates are not key drivers of the findings. Rather the utility estimates for diabetes, cardiovascular disease, and metabolic syndrome are key drivers of the findings.

	specific example of this is a study of chronic schizophrenia using measures of psychopathology and functioning to establish change in which the EQ–5D did not have a significant correlation with negative symptoms, disorganization, depression, excitement and general symptoms.[13] These points have also been found in subsequent studies on the use of generic preference based measures in most areas of mental health.[14] As a general rule, disease specific tools, are stronger and do a better job reporting true patient outcomes. PIPC would recommend these always be used over the EQ-5D, but for this assessment specifically, the EQ-5D is a particularly poor choice.	
2.	**ICER's assessment presents a dangerous oversimplification of a complex disease.** ICER chooses to drastically simplify the disease by over-categorizing many health states into only two – with and without severe symptoms. There are many problems with over-categorizing of diseases by using too few health states, which PIPC has pointed out to ICER in the past. If ICER's actual goal is to show true efficacy of a treatment, this practice hinders that goal. If a treatment is represented by movement of patients from a worse state to a better state, if the number of states is small – or classification too crude - the number of people transitioning between states may result in an underestimate of the true effect of the treatment. Doing so tends to rely on the assumption of a similar distribution of severity within states as the distribution of severity across states. This over-categorization of outcomes has been shown to lead to underestimation of treatment effects.[15,16]	Each arm of the model has twenty health states: 1. Treatment 1, no metabolic syndrome 2. Treatment 1, metabolic syndrome 3. Treatment 1, diabetes 4. Treatment 1, cardiovascular disease 5. Treatment 1, diabetes and cardiovascular disease 6. Treatment 2, no metabolic syndrome 7. Treatment 2, metabolic syndrome 8. Treatment 2, diabetes 9. Treatment 2, cardiovascular disease 10. Treatment 2, diabetes and cardiovascular disease 11. Treatment 3, no metabolic syndrome 12. Treatment 3, metabolic syndrome 13. Treatment 3, diabetes 14. Treatment 3, cardiovascular disease 15. Treatment 3, diabetes and cardiovascular disease 16. No treatment, no metabolic syndrome 17. No treatment, metabolic syndrome 18. No treatment, diabetes 19. No treatment, cardiovascular disease 20. No treatment, diabetes and cardiovascular disease Further, within each health state, relapses are tracked. The modeled health states are selected to capture the areas of treatment benefit and the structure we took achieves this.

3.	**ICER's modified societal perspective calculations seem to rely on illogical assumptions.** Before getting into the weeds on this topic, it should be noted that ICER should always, particularly in the case of a disease with deep societal implications like schizophrenia, be using the societal perspective as its base case versus the health care perspective. In ICER's draft assessment, it chose to use a health care perspective as its base case and then presented a modified societal perspective. The report suggests that the modified societal perspective estimates of cost-effectiveness of KarXT are close to identical to that of the base-case. The argument for this is that the "*the cost savings resulting from productivity gains and fewer criminal justice encounters [are] being offset by additional time required of the caregiver*." This is illogical, as the source of any reduction in criminal costs and increase in productivity would be a patient spending more time in milder disease states, which would also indicate lower caregiver needs. This inconsistency calls into question the validity of ICER's data, and PIPC would urge ICER to work more closely with the patient groups representing individuals with schizophrenia to understand more clearly the burden of disease as well as the societal and caregiver impact.	Actually, we heard from stakeholders that a reduction in relapses (which results in fewer criminal justice encounters and fewer days of missed work) actually likely increases caregiver impact because caregiver time required is typically lower during a relapse because they are hospitalized. Please see our response to the third comment from the Institute for Patient Access for additional detail related to the modified societal perspective.
4.	**ICER must move away from the assumption that all patients are average.** ICER continues to conduct its assessments to show benefit to the "average" patient. Ultimately this does not provide valid information to help inform decision making in a way that provides high quality patient care. A population average is not a proxy measure that represents all patients. An average doesn't represent all patients – even as a proxy. An average patient acts as a proxy solely for a handful of patients who happen to land in the middle of a random distribution of patients. These patients are not the majority, they aren't the most needy, and they aren't even those for whom the intervention itself would necessarily be most effective. If ICER wishes to provide helpful information with the aim of informing a decision-maker as to what value a new therapy might have for any patients, it should focus on producing an estimate – or a range of estimates - for as many of that wide range of patients, or patient types, as is possible. It is well established that generating and reporting of differential value assessment estimates across subgroups leads to substantial health gains, both through treatment selection and	ICER does not think patients are average. ICER thinks drugs sold in the US have an average price. ICER evaluates drugs, not people.

	coverage.[17,18] If ICER is to take seriously its role of informing health policy decision makers about the value of new therapies, it needs to move away from the assumption that all patients are the same, and the value to each can be determined by the estimation of the average value to a patient archetype.	
Schizophrenia & Psychosis Action Alliance		
1.	Upon review of ICER's Draft Report for KarXT in schizophrenia, the **Schizophrenia & Psychosis Action Alliance (S&PAA) continues to have significant concerns about the quality, accuracy, and transparency of ICER's methodology, as detailed below. Moreover, as detailed on pages 2-3, we are dismayed by ICER's dismissal of the societal costs and lived experience perspectives of those with schizophrenia.** S&PAA has had continuous interactions with ICER since June 2023 and has provided public comments on the Draft Scope, as well as private comments on the Model Analysis Plan, and an earlier version of the Draft Report. Much of the feedback below has been summarized to ICER in previous communications but has been left unaddressed without justification about ICER's decision-making process. Given that ICER is not subject to peer review, this lack of transparency is deeply concerning.	We thank you for your written feedback throughout our review process. We believe that we did share our justification for decisions during our two calls with your team, following our modeling analysis plan and following your early review of our draft report. This response to comments document also serves as a formal written process for ICER to further explain our rationale for decisions. In addition, when we choose not to follow a recommendation or agree with a particular comment, it does not mean we are not being transparent.
2.	**First, we reiterate our stance that this review is being conducted prematurely. This undermines almost every single aspect of this report, resulting in a model that lacks rigor and accurate data on pivotal inputs.** The only currently available data for KarXT are for short-term clinical trials limited to hospitalized patients experiencing acute psychotic episodes. Despite not having long-term data, ICER has created a lifetime model including relapse, adherence, adverse events, and maintenance treatment for KarXT. This approach is problematic given that KarXT employs a novel mechanism of action and such projections cannot be scientifically justified without comprehensive long-term data. Throughout the draft report, there are multiple references to the lack of available data necessary to reach conclusions about the cost-effectiveness of KarXT. As examples, the Background section states that the *"major source of uncertainty is the lack of data on the efficacy of KarXT for longer than five weeks."* The Comparators section discloses, "*Due to the lack of available long-term data for KarXT at the time of this review, we were unable to compare the long-term efficacy and safety of KarXT*	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.

	to the three comparators". The report also states, "*there is hope that KarXT may improve the cognitive and negative symptoms better than currently available antipsychotic medications… However, these symptoms can only be fairly evaluated in the maintenance phase of therapy*." Negative and cognitive symptoms are potentially transformative treatment targets of KarXT that have not been adequately addressed by current antipsychotic medications.	
3.	Per ICER's own report, these are stark limitations that compromise the quality of the model. Regardless, ICER concludes, *"given the lack of long-term data, we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with both olanzapine and risperidone."* ICER's rating of the net health benefit as "promising but inconclusive" is significant because it impacts how policymakers, insurers, and healthcare providers may perceive the value and effectiveness of a new treatment. Insurance companies often rely on ICER's evaluations when determining coverage policies, and a rating that suggests uncertainty can lead to restrictive measures such as limited coverage, stringent prior authorization processes, or prohibitive guideline adjustments for this medication. Consequently, this premature analysis, conducted in the absence of complete clinical data, could inadvertently underestimate KarXT's long-term effectiveness, and limit patient access to a potentially life-altering treatment.	Please see comment above.
4.	**Second, we have concerns about the comprehensiveness and quality of the references throughout this report.** While a systematic literature review was conducted for the Network Meta-Analysis (NMA), outdated trials were included. For example, 69% (n=22) of 32 studies used to input data for the primary outcome (PANSS) were published more than 15 years ago, in 2008 or earlier. Some citations used for other outcomes in the NMA are from the 1990s. Publications from the 1990s and 2000s do not reflect the current standard of care, and it is likely that increased awareness, expanded mental health support teams, and newer agents make these trial publications less relevant to current decision making. Moreover, some of the references are from studies conducted outside of the US, which may not be applicable to a US-based model due to differences in regulatory environments, healthcare systems, or population health profiles. ICER has not justified their inclusion of older and potentially non-representative publications in their NMA.	This statement is factually incorrect. Only 10 of the 32 trials (32%) in the NMA examining PANSS total outcome were published on or before 2008, not 22. There were no trials in this analysis prior to 2004. The one trial published prior to 2000 (in 1996) was only included in the NMAs examining weight gain and all-cause discontinuation. Furthermore, our NMA was conducted as an update to a highly regarded NMA published in 2019 in The Lancet:[10] we added more recently published trials to that NMA. To evaluate the impact of including older trials in our NMA, we conducted sensitivity analyses where we removed trials published on, or prior to, 2008 from the NMA of the total PANSS score. (See Supplement Table D2.20 in the Evidence Report) There were no notable differences in the summary estimate, though, as expected when including fewer trials, the credible intervals were wider signaling less precision in the estimates.

		Nine out of 33 trials (27%) in the NMAs were conducted exclusively outside of the US (28% in the analysis examining PANSS total, specifically). The baseline characteristics were similar to those conducted exclusively within the US and there were no differences in the study design that suggested potential effect modification.
5.	**Third, ICER's societal scenario model is overly reductive and insufficiently supported.** ICER selected productivity, caregiver impacts, and criminal justice impacts as the key outcomes, and concluded that "*cost-effectiveness stayed nearly the same from the modified societal perspective due to the cost savings resulting from productivity gains and fewer criminal justice encounters being offset by additional time required of the caregiver*." In dialogues with ICER, they have indicated that the limited data on KarXT only permits the inference that this medication might offer a more favorable side effect profile compared to existing antipsychotics, rather than a marked difference in symptom alleviation, and that this would not have a substantial impact on the societal costs associated with schizophrenia. As such, they have not invested their resources in thoroughly exploring the potential societal impact of KarXT. We strongly oppose this approach. Especially in the context of extrapolation and assumptions made throughout the rest of this report, ICER could feasibly explore the consequences of a more tolerable side effect profile on productivity, caregiver burden, and other metrics of societal costs[1,2]. They have opted not to do so, as further indicated by the sparse references for this section of the report. As such, included costs are vastly underestimated and lack elaboration or justification, as described below.	In the revised Evidence Report, we now include indirect costs associated with diabetes and cardiovascular disease within the modified societal perspective scenario analysis.
6.	**Productivity impacts are underestimated.** The impact of schizophrenia on productivity was modeled by assuming that each relapse results in 65 missed workdays for 37% of employed people with schizophrenia, with the financial cost calculated using an average hourly wage of $33.82. This approach fails to account for the potential increase in the employment rate among those with schizophrenia who could return to work or increase their productivity given more effective symptom management and fewer side effects. Notably, the majority of people with schizophrenia express a desire to work, despite facing high unemployment rates. Moreover, the model does not consider the economic burden of disability benefits (e.g., SSI/SSDI) provided to individuals with schizophrenia, nor does it address the prevalence of part-time employment, underemployment, and the associated loss of productivity in this population.	In the revised Evidence Report, we now include indirect costs associated with diabetes and cardiovascular disease within the modified societal perspective scenario analysis. There is no evidence to suggest KarXT would differentially impact the other things mentioned within this comment compared with other treatments.
7.	**Similarly, caregiver cost estimates lack breadth and depth.** The current methodology primarily focuses on uncompensated caregiving hours, overlooking extensive costs	Importantly, the objective of this analysis is not to provide an accurate reflection of the true economic and social burden of

	borne by caregivers[2–7]. These include not only out-of-pocket expenses related to hospitalization and daily care needs but also substantial financial burdens associated with major life events and legal matters[8]. Moreover, there is a notable omission of lost productivity costs for caregivers, who often sacrifice their employment opportunities or face reduced working hours to provide care. A more inclusive and realistic approach should be adopted to quantify these often substantial yet overlooked economic and personal sacrifices made by caregivers, and the impact of fewer side effects on caregiver burden. This would provide a more accurate reflection of the true economic and social burden of schizophrenia on caregivers.	schizophrenia on caregivers. Rather, our objective is to isolate the effect of KarXT. There is no KarXT evidence to suggest that KarXT meaningfully differentially impacts caregiver costs or alleviates the burden on caregivers compared with other treatments.
8.	**Criminal justice impacts are confusing and underestimate costs.** ICER appears to have calculated costs to the criminal justice system resulting from psychiatric hospitalizations associated with schizophrenia. Given the number of people who are incarcerated with schizophrenia, such a calculation would make more sense to use within the primary model should all appropriate settings have been included. The societal scenario should include not just psychiatric hospitalization costs, but costs related to long-term incarceration and legal fees, as well as services provided by police, sheriffs, deputies, judicial staff, and institutions (e.g., local and county jails; paid legal guardians). This approach disregards several known societal costs of schizophrenia, including supportive housing services and the cost of homelessness. If, as stated in informal discussions, ICER considers a detailed societal scenario analysis to be unnecessary, this stance should be overtly stated in the report and no such analysis should be conducted.	Given the lack of evidence that KarXT is more effective at managing schizophrenia than other second-generation antipsychotics, KarXT would not have a dramatic effect on societal costs that are downstream of schizophrenia management like the ones mentioned in this comment.
9.	**It is worse to conduct a cursory review of societal costs and then conclude that KarXT is unlikely to have a meaningful societal impact than it is to conduct no analysis at all.** Moreover, the *Patient and Caregiver Perspectives* section, along with focus group data from those with schizophrenia and their caregivers, is ineffectively integrated into the model's overall inputs. It lacks depth, as well as connection to established literature on the lived experience of schizophrenia, reflecting a perfunctory acknowledgment of these perspectives by ICER rather than a substantive inclusion. The *Contextual Considerations* section similarly fails to convey the full extent of the schizophrenia's impact due to insufficient detail. Additionally, the scarcity of data prevents the completion of three out of four *Potential Other Benefits and Disadvantages* sections, a predicament resulting from ICER's premature review process.	KarXT is unlikely to have effect on societal costs independent of the analysis of societal costs. The evidence suggests that KarXT is unlikely to be more effective than other antipsychotic therapies and thus it will not have net differences in societal outcomes compared with other therapies. Furthermore, the importance of the *Patient and Caregiver Perspectives*, *Contextual Considerations,* and the *Potential Other Benefits and Disadvantages* sections are to highlight factors that can't be incorporated into the economic model. They are intended to support voting council deliberations by highlighting important perspectives that aren't in the

		model to ensure that they are front and center in the deliberations.
10.	We emphasize that ICER has asked for feedback from our patient advocacy group throughout this review process, ostensibly to show that they are invested in capturing the lived experience perspective. Our community has engaged in good faith that ICER will seriously consider their perspectives, including by participating in focus groups and sharing personal and painful stories with ICER staff. **ICER's manner of engagement has involved requesting lived experience input for an extended period of time, only to later provide a cursory summary of these perspectives while implying that a comprehensive societal scenario analysis is not merited. This does an injustice to those with schizophrenia and their caregivers, and has been a drain on our small non-profit's financial and personnel resources.** At best, this method of engagement is unhelpful for our population. At worst, it is harmful and undermines ICER's credibility in our eyes.	We acknowledge that engagement on ICER's review can be time-consuming for organizations and are appreciative that S&PAA has volunteered your time, effort, and network to ensure community-wide participation. We believe the lived experience of individuals with schizophrenia provides important context for our modeling decisions, even when qualitative information from group interviews may not directly impact the model inputs. Because we believe this qualitative information is incredibly valuable to both the interpretation of the evidence and public deliberation of our findings, we have provided an in-depth summary of the lived experience with schizophrenia in the Patient and Caregiver Perspectives section. This section is intentionally placed toward the beginning of the report in order to frame the report content and allow the reader and appraisal committee to interpret ICER's analysis through the lens of the community's lived experience. Please keep in mind, however, that ICER is not trying to write a comprehensive report about schizophrenia; we are trying to assess a particular new therapy for schizophrenia. Choices about a societal perspective reflect issues with the therapy's ability to affect societal implications of schizophrenia not a statement about the importance of these implications.
11.	**Third, the model does not reflect the reality of the medication experience for those with schizophrenia.** We have previously summarized feedback regarding the structure of the model analytic plan, including concerns about extrapolation of short-term data, use of outdated data, choice of comparators, consideration of common comorbid conditions that may impact cost, adverse events and side effects, and oversimplification of health states. ICER has not explained their decision-making process in regard to these concerns. We highlight our most pressing concerns below.	Our objective is not to model the reality of an individual patient's life. We appreciate each individual's treatment sequence and treatment experience differs and there are important patient-level considerations that should be considered in provider-patient decision making. However, the objective of this portion of the assessment is to determine the cost-effectiveness and health benefit price benchmark for a

		population, based on average effects, not individual effects or experiences.
12.	**Short-term data for pivotal data inputs have been over-extrapolated.** Given that QALYs are primarily derived from the maintenance phase of this lifetime model, the assumptions around efficacy, tolerability, and relapse rates in the maintenance phase (based on 5-week data only) introduce large uncertainty in the results. Assuming that relapse rates are likely to be midpoint of comparator rates presents some risk, as this is likely to be a pivotal input to the model. We recommend that scenarios be explored with alternative assumptions, such as relapse rates for KarXT at 5%, 10%, 15%. Alternatively, ICER may choose to wait until maintenance data is available for KarXT and simply present an acute model at this time. Otherwise, ICER risks reaching incorrect conclusions about cost-effectiveness.	These inputs were varied extensively in sensitivity analyses. Stakeholders did not believe that, if approved, KarXT would only be prescribed in the acute setting and thus we did not model KarXT as only utilized in the acute setting. However, we did include the acute setting in the model to leverage the acute data that we did have available. Most models in this space do not include the acute setting.
13.	**ICER has not justified their choice of comparators (aripiprazole, risperidone, and olanzapine).** Comparators should not be selected based on prescribing patterns or because they are second- generation antipsychotics, as ICER has done. Prescription patterns are not based on the clinical profile of the products and may not reflect optimal treatments in terms of clinical effectiveness and tolerability. Moreover, the distinction between first- and second-generation antipsychotics (FGAs and SGAs) is complicated and may not be the most meaningful way to approach this analysis[9]. We previously proposed that ICER should group comparator antipsychotic medications by tolerability (side effect) and efficacy profiles as has generally been suggested by research experts[10,11].	We respectfully disagree and we did justify our choice in the draft scope, final scope, and in the draft report. We spoke with many experts as well as the companies involved and consistently were told that aripiprazole, risperidone, and olanzapine were the appropriate comparators representing a mix of drugs typically used including those with lower side effects, but lower efficacy and those with greater side effects and greater efficacy. Our choice was reinforced by the data on prescribing patterns in the US.
14.	**The health states included in the model (stable without adverse events, metabolic syndrome without diabetes or cardiovascular disease, diabetes, cardiovascular disease, relapse, death) fail to reflect the full spectrum of schizophrenia experiences.** The model's current extremes—either an ideal condition without adverse events or a severe relapse requiring hospitalization—oversimplify the reality of the illness. The term "stable" encompasses a wide range, from individuals who manage symptoms effectively and live independently to those who, despite controlled positive symptoms, struggle with negative symptoms, cognitive impairments, and dependency on disability support and caregiving[12–14]. The "relapse" state should also be differentiated into “acute” and “chronic” to capture that some individuals experience brief hospitalizations, while others face prolonged inpatient care, homelessness, or incarceration, all of which have profound implications for healthcare costs[15]. We strongly urge ICER to include more granular health states to accurately	The model is looking at incremental differences between the intervention arm and the comparator arm. There is no evidence to suggest KarXT impacts these more granular states differently than the comparator so inclusion of this granularity would not influence the incremental findings.

	model the economic burdens and relevant outcomes for schizophrenia.	
15.	**The proposed model fails to consider the effects of reduced weight gain on life expectancy for individuals with schizophrenia.** Given that weight gain and its related health complications are among the leading predictors of premature mortality in this population —where death occurs approximately 15 years earlier than in the general population[17]—this oversight could significantly affect the accuracy of the model's long-term outcomes and cost projections.	The model does include an increased risk of death for both diabetes and cardiovascular disease.
16.	**The placeholder price of $20,000/year is high.** Wholesale acquisition costs for other branded products are $17,028/year (Rexulti)[18], $16,532/year (Vraylar)[19], $18,830/year (Calypta)[20]. The mean of these branded treatments is $17,463. Unless Karuna has told ICER that $20,000 is the expected price, the base case would be more credible if it were based on real-world comparators on the market. Given that this model already makes a slew of assumptions, the addition of anything credible is important. This is a simple update that could make this report more credible for stakeholders.	The placeholder price is merely a placeholder based on analyst estimates. It is used so we can perform certain analyses. The manufacturer had multiple opportunities to suggest that ICER use a different placeholder price.
17.	**Core model assumptions made by ICER are questionable.** As one example, ICER writes on page 20 that "*without evidence on the risk of metabolic syndrome for adults with schizophrenia who are not on an antipsychotic, we assumed the same risk of metabolic syndrome as the general population*." However, there is evidence that those with schizophrenia are at increased risk of metabolic syndrome even if they are antipsychotic-naïve, as indicated by recent literature[21].	We made a favorable assumption for KarXT as it relates to metabolic syndrome. That is, making the assumption suggested here would make the analysis of KarXT **less** favorable. We did vary this widely in sensitivity and scenario analyses.
18.	**ICER inaccurately states that the proposed model considers "all relevant settings" but only includes inpatient, outpatient/clinic, home, and unhoused settings.** Those with schizophrenia dwell in varied settings that are both a consequence of treatment effectiveness and directly impact healthcare and societal costs. These include emergency rooms[22], homeless shelters or the street[23], jails and prisons[24], and supported living facilities such as group or nursing homes[25]. At the very least, ICER should transparently state that they are not able to consider all relevant settings in which people with schizophrenia receive care.	This statement reflects the PICOTS in the scope: that we will consider studies in any of these settings. We found no studies of KarXT for any of these other settings. We look forward to additional data in the future that may address these important gaps in the evidence base for a more complete evaluation of the clinical and economic benefits and harms of KarXT compared with currently available therapies.
19.	**The full spectrum of healthcare services for schizophrenia is not included.** This includes case management, emergency room visits, pharmacy costs, physical healthcare visits, assertive community treatment, crisis response teams, family psychoeducation, group therapy, home care, and others. ICER acknowledges some of these treatments in the clinical guidelines provided by the American Psychiatric Association in	We included physician visits, mental health clinic visits, group interventions, inpatient visits, ED visits, hospital treatment, and home care as part of our healthcare utilization cost buckets.

	Appendix C, but these are not included in the actual model. The comprehensive nature of these costs is crucial to include given that the services received by those with schizophrenia after a relapse are more expensive and greater in magnitude than when one is stable.	Please see our comments above related to this being an incremental model (KarXT as compared to other second generation antipsychotics) and KarXT was assumed to perform similarly to other second generation antipsychotics as it relates to schizophrenia and other schizophrenia-related symptoms.
20.	**The proposed model neglects the full scope of psychiatric and medical comorbidities that occur with schizophrenia.** Common psychiatric comorbidities, such as anxiety, depression, and substance use disorders, which are all costly mental health conditions, are not included in this model[26]. Moreover, ICER has only included treatment-emergent health effects (e.g., weight gain) in their model, and underlying comorbidities that are not linked to treatment[27]. The consequence of neglecting these conditions is that ICER is underestimating healthcare and societal costs. For example, nearly half of those with schizophrenia (47%) are estimated to have substance use disorders, which significantly drives up healthcare and societal costs[26].	We are only modeling the incremental effects of KarXT. There is no evidence to suggest that KarXT has a differential impact on substance use compared with other therapies for schizophrenia.
21.	**Years with diabetes is the only key medical model outcome included in the model.** Although diabetes is one of the leading causes of mortality in schizophrenia and can be a side effect of antipsychotic medication use[28], this is a limited perspective of schizophrenia. ICER has not provided a clear justification as to why they have included only diabetes as the key medical outcome as opposed to other comorbid illnesses that are important in this same regard such as obesity, hypertension, and hyperlipidemia[29].	This is because KarXT may have an incremental effect on years with diabetes.
22.	**We urge ICER not to list any "low-value services" in their report.** We strongly advise that no services in this area should be reduced or eliminated at this time. The complex nature of schizophrenia, existing barriers to care, and the heterogenous presentation of individuals throughout their lifetimes require real-time shared decision- making and personalized approaches to care. Until more refined diagnostic and prognostic approaches are available to target treatments accurately, it is irresponsible to suggest any treatment is superior to another and limit access to any treatment in any way for any given individual.	We typically do not include low-value services unless they are suggested in submissions, which none were for this review. The purpose of this section is not to limit access to services but instead to highlight when resources are not used effectively or providing patients with quality care. For example, we could see this as an opportunity to emphasize that a system that incarcerates people with schizophrenia rather than providing better wrap-around services and treatment is likely an inefficient use of societal resources.

23.	We have strong concerns about the scientific rigor and neutrality of ICER's current approach, which may do a grave disservice to a community that needs significant help and support. For these reasons, we have serious concerns about the impact of ICER's proposed approach to the cost-effectiveness model, **as it does not reflect the lived experience of those with schizophrenia and their caregivers and may result in barriers to access to a potentially life-altering medication option for our community.** If ICER is sincere about their mission to encourage fair access, support continued innovations, and remove barriers to how care is delivered to those in need, we urge them to delay their timeline in order to fully address the feedback provided by stakeholders, to genuinely include the societal perspective, and to increase the transparency of their modeling process.	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.
The STARR Coalition		
1.	We are very excited about the possibility of a true novel treatment for (arguably) one of the most devastating of all mental illnesses, schizophrenia. In this case, the new treatment is for a condition that faces far greater barriers than any other condition, as schizophrenia has more stigma and fewer champions than almost any other illness. Given that, it is our opinion that any pricing discussions on any novel mechanism for schizophrenia adds yet another hurdle in the innovation and investment in researching novel mechanisms and should be undertaken with that in mind.	We recommend a fair price for medications based on how well they work, and 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, 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/info on this question, see this ICER.org blog: https://icer.org/news-insights/commentaries/overpriced-drugs-can-harm-more-patients-than-they-help/
2.	Suggested Revision 1: Use the existing data on KarXT to extrapolate and populate the pricing model, noting the limitations in the assessment. KarXT relies on novel	We did use the existing data on KarXT for PANSS and weight gain directly into the model. The only mid-point was used for

	mechanisms for treatment and is therefore not comparable to the existing second-generation anti-psychotics. In the cases where there is not enough data or the existing data on KarXT was "promising but inconclusive (P?I)", the assumptions are based on a "mid-point between the range of the other second-generation anti-psychotics." Preliminary evidence does not support the assumption that KarXT would fall at the mid-point of the existing anti-psychotics, making this a faulty assumption.	evidence on relapse rates. No evidence exists on the impact of KarXT on relapse. However, KarXT evidence that does exist on adequate clinical response was not statistically different from the other second-generation antipsychotics. Therefore, we made a reasonable assumption that the relapse probability is the average of the comparator medicines. We discussed this assumption with stakeholders and varied it widely in sensitivity analyses.
3.	Suggested Revision 2: Use the existing data on KarXT which suggests that TD would NOT be a side effect for inclusion in the pricing model, noting the limitations in the assessment. Consideration of the incidence of tardive dyskinesia (TD) and other long-term movement disorder side effects is listed as an 'uncertainty' and less weight is given this important side effect of existing anti-psychotics. Data from 2019 suggests that total health care costs were significantly greater for patients with TD than for those without TD and patients diagnosed with TD demonstrate significantly higher health care utilization and costs compared with non-TD patients.[1] There is no evidence that suggests that KarXT will cause TD in the long-term and therefore should be noted and assumed in the model.	Please see our response to Karuna Therapeutic's first comment that includes our rationale for why tardive dyskinesia was not included in the base-case analysis.
4.	Suggested Revision 3: Caregiver costs should be given adequate consideration in the model. Aside from the fact that the true burden of caring for a loved one with schizophrenia can hardly be calculated, there must be significant weight given to the caregiver burden, possibly equal to the cost of the annual QALY or evLY.	Caregiver costs were included in the modified societal perspective scenario analysis.
5.	Suggested Revision 4: Build cost assumptions based on present-day data, encompassing the significant increases in the cost of living and inflationary adjustments.	All costs used in the economic model were inflated to 2022 US dollars following the practices for inflation in ICER's reference case.

1. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019;394(10202):939-951.