

July 24, 2023

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Submitted electronically at: [publiccomments@icer.org](mailto:publiccomments@icer.org)

**Re: Draft Scoping Document for KarXT in Schizophrenia**

Dear Dr. Rind:

Cerevel Therapeutics appreciates the opportunity to submit comments in response to ICER's draft scoping document for the review of the health and economic outcomes of KarXT for the treatment of schizophrenia. Cerevel is a company dedicated to unraveling the mysteries of the brain to treat neuroscience diseases. We have a diversified pipeline of five clinical-stage investigational therapies and several preclinical compounds with the potential to treat a range of devastating conditions. Most notable for the purposes of this letter, Cerevel is developing emraclidine for the treatment of both schizophrenia and Alzheimer's Disease Psychosis. Similar to KarXT, emraclidine does not bind to D2 receptors the way current antipsychotics do.

With our commitment to patients and innovation in mind, we submit the following comments. We are hopeful that this evaluation will ultimately foster greater patient access to needed innovative treatments for schizophrenia.

**Schizophrenia Burden and Unmet Need:** Schizophrenia is a serious, complex, and debilitating illness. It is one of the top 20 causes of disability worldwide and is disproportionately present in certain vulnerable communities.<sup>1,2</sup> Schizophrenia is characterized by three symptomatic categories: (1) negative symptoms, which include loss of motivation, activity, or emotion;<sup>1</sup> (2) positive symptoms, which involve changes to a person's behavior or thoughts and include hallucinations, delusions, thought disorders, and movement disorders;<sup>3</sup> and (3) cognitive symptoms, which are associated with attention, concentration, and memory problems.<sup>1, 4, 5</sup>

People living with schizophrenia face a disease burden that includes reduced quality of life, increased medical costs, higher rates of serious comorbidities, fewer opportunities for employment, increased suicide risk and increased mortality. The impact of schizophrenia on individuals' lives and livelihoods is evidenced by high rates of qualification, through income and disability, for public insurance; Medicare and Medicaid pay for nearly 90% of all schizophrenia healthcare costs.<sup>6</sup>

Untreated and undertreated illness also has immense societal ramifications, placing tremendous pressure on caregivers, government programs, and society. Direct healthcare costs of treating schizophrenia represent only 18% of the total economic burden of this disease. Indirect costs, mainly driven by unpaid, informal caregiving, represent 73%.<sup>1</sup> Indirect non-medical costs including homelessness (\$24.7 billion), incarceration (\$14.5 billion), law enforcement and judicial system costs (\$2.3 billion), social security disability income (\$5.1 billion) and substance abuse are equally significant.<sup>7,3</sup>

**Current Treatment:** Oral antipsychotic drugs are the cornerstone of treatment for schizophrenia and can be effective at addressing the positive symptoms of the illness. However, lack of innovation in this space means patients are still being treated with drugs whose essential mechanism of action (MoA) has not changed since they were discovered in the 1950s – and patients are still grappling with side effects caused by these older medicines that may limit longer term effectiveness.<sup>8</sup>

Typical, or first generation, antipsychotics act as antagonists at D2 receptors. Although effective as antipsychotics, they often lead to motor-related side effects. Atypical, or second-generation antipsychotics, interfere with signaling at D2 receptors via partial blockade or partial agonism, but also target serotonergic systems. They are often

characterized by metabolic side effects and significant and rapid weight gain. These medications also fail to address the root cause of the illness.

The problematic side effects inherent in both classes of drugs can contribute to poor treatment adherence, relapse, treatment switches, and eventually, treatment resistance.<sup>9</sup> Adherence is such a large concern with antipsychotics that both Medicare and Medicaid provider programs reward physicians who are able to improve medication adherence in patients with schizophrenia.<sup>10,11</sup>

**Impactful Innovation:** New research is evaluating muscarinic acetylcholine receptors as a potential new class of molecules that work differently from existing antipsychotics due to their more precise targeting of relevant pathways and receptors. Muscarinic receptor activation is hypothesized to target the pathology upstream, at the source rather than targeting problematic downstream D2 receptors. It is hypothesized that avoidance of dopamine and serotonin will manifest as improved tolerability and reduced side effects, which should facilitate better adherence, leading to better effectiveness, ultimately improving long-term outcomes.

The emerging science and data support the development of new MOAs such as muscarinic modulators to address the problem of burdensome side effects while providing robust efficacy on psychotic symptoms. Additional studies will be needed to specifically address negative symptoms and cognitive impairment associated with schizophrenia.

Scientific advancement in the treatment of schizophrenia will necessarily be iterative. We recommend ICER recognize the importance of this scientific process and the positive impact new therapies could have on the treatment of this devastating disease. Novel MoAs have the potential to improve on the side effect profiles of current therapies, offering patients new options to tailor treatments and having a potentially profound impact on families, caregivers, and society. Economic evaluations should appropriately assess and value the full impact of innovation in this space - a therapeutic area that has been stagnant for decades - to support access to novel treatments and encourage continued scientific progress towards increasingly better therapeutic options.

#### **Comments on Elements of the PICOTS Framework:**

*ICER's base cost-effectiveness model should apply a societal perspective to measure KarXT's full value.* As noted above, the costs of schizophrenia to society are large, with indirect costs representing almost four times the direct medical costs (which are primarily paid by public payers). As such, schizophrenia may appropriately be thought of as a public health condition. In the scoping document, ICER acknowledges that a societal perspective is appropriate “when the societal costs of care are large relative to direct health care costs”, which is clearly the case with schizophrenia. As such, we believe a societal perspective is most appropriate for the cost-effectiveness model.

*Newer, branded comparator drugs should be included in cost-effectiveness model.* The three comparator drugs ICER suggests using in the cost-effectiveness model are all currently available in generic form, however many newer, single-source branded products are widely used and accepted as “current standard of care” and “relevant oral second-generation antipsychotics,” citing ICER’s requirement for appropriate comparators. Therefore, we suggest ICER include one or more branded comparators.

*Clarification on intervention arm of the cost-effectiveness model.* The scoping document states that, in the cost-effectiveness model, “patients will start treatment on KarXT.” Please clarify if this means incident, new-to-therapy patients. Since it is not yet clear whether KarXT will be approved and used as first line therapy, and since most health plans currently require patients to fail at least one generic antipsychotic before coverage for a new, branded product, ICER should consider including such a “step” in their model to reflect current, real-world utilization of antipsychotics. We also urge ICER to assess whether its modeling around the use of clozapine is reflective of clinical practice. We recognize that the American Psychiatric Association guidelines recommend clozapine after “no response to two trials of antipsychotic medication,”<sup>12</sup> however, patient reports indicate it can be extremely difficult to access the drug due to its REMS program.<sup>13</sup>

*ICER's cost-effectiveness model should adjust efficacy outcomes for medication adherence.* Efficacy data from clinical trials may not represent real world outcomes, as nonadherence with antipsychotics has been reported to be as high as 50%.<sup>14</sup> Among patients with schizophrenia, medication side effects are highly prevalent and significantly associated with medication nonadherence and increased healthcare resource use.<sup>15</sup> Innovative medications with

fewer or more tolerable side effects may help patients adhere to their treatment regimen, ultimately increasing effectiveness and reducing relapse, decreasing hospitalizations and reducing healthcare costs. In addition to adherence, more tolerable side effect profiles may decrease medication switching and increase the number of patients willing to initiate therapy or remain on treatment.<sup>16</sup>

Medication adherence has also frequently been shown to be affected by medication dosing frequency, with fewer daily doses associated with better adherence in numerous illnesses<sup>17,18,19,20</sup> including mental health conditions<sup>21</sup> and schizophrenia.<sup>22</sup> An additional study found that twice versus once daily dosing of risperidone for schizophrenia (controlling total daily dose) was associated with a 56% higher risk of rehospitalizations in one-year follow-up.<sup>23</sup> It is recommended that ICER incorporate the impact of antipsychotic dosing frequency on medication adherence which, in turn, impacts clinical outcomes.

Failure to account for medication adherence will over-estimate the real-world effectiveness of antipsychotics and fail to capture down-stream effects on relapse, hospitalization, survival, and costs.

*ICER's cost-effectiveness model should account for increased mortality for people with schizophrenia and those who are sub-optimally treated.* People with schizophrenia have substantially higher all-cause mortality versus the general population (RR=2.94, 95% CI: 2.75-3.13), with a decreased life expectancy of 15 to 20 years.<sup>24,25</sup> Suicide, comorbid illness, poor living conditions, reduced access to care, and substance abuse have been identified as modifiable risk factors contributing to this decline. Use of antipsychotics versus non-use has been shown to be associated with a reduction of all-cause mortality in patients with schizophrenia (RR=0.71, 95% CI: 0.59-0.84).<sup>14</sup> Since psychotic symptoms typically start in late adolescence or early adulthood, the impact of successful treatment on life years saved could be substantial. Since ICER is proposing a lifetime time horizon for the cost-effectiveness analysis, survival, and survival benefits of antipsychotic treatment (including impact of adherence and persistence) should not be overlooked.

*Additional costs associated with caregiving should be included.* Cerevel commends ICER's intention to consider caregiver outcomes, but additional costs associated with both paid and unpaid caregiving should also be included in the model. While some of the indirect value of caregiving may be captured in productivity loss estimates, many caregivers, who may otherwise not work outside the home, contribute an average of 86 hours per week caring for a patient with schizophrenia.<sup>26</sup> Costs associated with this informal caregiving have been reported to be the greatest contributor to excess indirect costs, at an estimated \$112.3 billion in 2019,<sup>27</sup> and should be included.

Not all caregiving costs are indirect. As states implement Medicaid Consumer-Directed Personal Assistance Programs, many informal caregivers are now being compensated for the care they provide, resulting in direct medical costs to Medicaid agencies. Also, since the Medicaid program pays for nursing facility services, including long term care (LTC), a majority of the 2.9% of LTC admissions with a diagnosis of schizophrenia<sup>28</sup> are also directly paid by state Medicaid programs. Direct nursing care costs should be incorporated in the model.

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Cerevel expresses gratitude to ICER for the opportunity to participate in the review of KarXT and appreciates your consideration of our comments. We would be happy to answer any questions or to provide any additional information of interest to ICER.

Sincerely,



Christopher Zacker, RPh, PhD  
Director, Global Value & Access

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July 26, 2023

*Comments regarding the Institute for Clinical and Economic Review planned assessment of the comparative clinical effectiveness and value of xanomeline tartrate/trospium chloride (KarXT, Karuna Therapeutics) for the treatment of schizophrenia*

To date, all available antipsychotics for the treatment of schizophrenia are associated with at least some postsynaptic dopamine D2 receptor blockade in the striatum (1). Although this is thought to reduce the intensity and frequency of hallucinations and delusions, it is also implicated in the production of drug-induced parkinsonism, akathisia, and ultimately tardive dyskinesia. The latter is often irreversible and has been a long-standing iatrogenic movement disorder that has plagued patients (2). Other adverse events, tolerability challenges, and safety concerns, including metabolic dysregulation and the development of diabetes mellitus have ultimately limited the choice of treatments for patients with schizophrenia, including for the most used second-generation antipsychotics – risperidone, olanzapine, and aripiprazole (3). Medications that would treat schizophrenia that are devoid of drug-induced movement disorders, metabolic disturbances, hyperprolactinemia, or prolongation of the ECG QT interval would be welcome.

In a five-week study conducted with acutely exacerbated inpatients with schizophrenia, published in the New England Journal of Medicine, xanomeline/trospium combination showed improvements in Positive and Negative Syndrome Scale (PANSS) scores vs placebo, with a robust effect size and with no clinically relevant metabolic, endocrine, or motor adverse effects (4). In 2 subsequent clinical trials whose results await formal publication, xanomeline-trospium combination was associated with similarly clinically meaningful and statistically significant improvement in PANSS scores and with a similar adverse event profile (5, 6). Of importance is the proposed mechanism of action – xanomeline targets muscarinic M1 and M4 receptors, ultimately reducing excess dopamine signaling to that specific part of the striatum thought responsible for the positive symptoms of schizophrenia and without affecting the dorsal striatum, thus avoiding motoric adverse effects (7).

Presently there is no data regarding the maintenance use of xanomeline-trospium combination for the reduction of risk of relapse. An assumption is that the robust effect sizes observed in the acute studies could translate to robust effect sizes for long-term use. Importantly, in addition to a beneficial impact on risk reduction for relapse, there is no mechanistic pathway for the

development of tardive dyskinesia, and it appears that xanomeline-trospium combination is not associated with clinically relevant weight gain or metabolic disturbances so that the risk of development of diabetes mellitus is not increased. The management of these risks is paramount for a disorder that is lifelong and that requires treatment of indefinite duration.

The hope is to be able to treat people with schizophrenia with agents that work well, are better tolerated, and lead to improved outcomes. Having different mechanisms of action also opens the door to rational polypharmacy and potential synergy for those patients in whom clinical response has thus far been suboptimal.



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### **Comments regarding assessment of Novel Schizophrenia treatment.**

1. First of all, it seems that the selection of Karuna's KarXT for this assessment is somewhat arbitrary and I am curious why this was done. There are many new therapies being brought to market on a regular basis that do not receive this attention from ICER. While I applaud the concept of assessing new drugs independent of FDA to provide HCPs and patients another perspective on value and benefit, this exercise should be applied to either all new therapies or none, or perhaps ICER should formulate and articulate a policy in this regard. Otherwise, it appears to an outside unbiased observer that there may be some sort of inappropriate influence behind this project, particularly given that I am not aware of any prior ICER assessments of yet-to-be-approved drugs. Please provide more details on this issue, either in a direct reply to me or to all interested parties on your website or some subsequent publication. Please address not only the background for this project but also ICER's intent and policy for conducting similar assessments in the future.
2. Since it seems you are principally interested in whether this new mechanism medication results in longer patient compliance periods, due to possible more favorable side effect profile, ultimately resulting in fewer relapses and associated consequences, it seems that it will be difficult to assess this in any meaningful way when one only has access to the largely short-term clinical data of a yet to be approved drug. Also, I am curious about what agreements have been put in place between Karuna and ICER to allow ICER access to this proprietary data in advance on an FDA approval (or subsequent to). Assessment of the ability of a medication to maintain a patient on therapy relative to alternative treatments can only be reasonably assessed over an extended time period. Typically, these types of assessments are only done once the product being evaluated has been in clinical use by the public for a long enough period to gather useful prescription data that can be used to assess real world compliance experience.
3. Further to the above point, I note that ICER intends to use as comparators oral forms of olanzapine, aripiprazole and risperidone. However, you do not discuss other formulations or methods of administration etc. these comparators will be assessed. As you well know, most manufacturers of these later atypical psychotics have recognized the compliance issue for many years and have worked to develop "depo" formulations of these products that largely address the compliance/discontinuation issue by being implanted in the patient and administering continuous dosing for periods of as long as 9 months. If you are going to do any sort of reasonable compliance comparison with KarXT, you should be comparing it to these implants as the "standard of care"
4. Because of the points above, I would encourage ICER to rethink conducting this proposed assessment at this time as I do not think it will produce any useful, valid or relevant data to address the central question of interest.



July 26, 2023

Ms. Kelsey Gosselin  
Program Manager  
Institute for Clinical and Economic Review (ICER)  
(Sent via electronic mail)

Dear ICER Review Team,

Karuna Therapeutics, Inc. welcomes the opportunity to provide comments on the published draft background and scoping document, “KarXT for Schizophrenia”, dated July 5, 2023. While we recognize ICER faces notable challenges in the comparison of an entirely novel agent to earlier generations of drugs within a given class (e.g., significant unmet need in a sizeable, heterogenous patient population), Karuna has six (6) principal recommendations concerning the proposed scope for this assessment, as follows:

- (1) Designated comparators for the KarXT Comparative Value Analyses should be expanded to include olanzapine and risperidone, since these agents are as commonly used today as aripiprazole. Each agent should be compared with KarXT and these additional two oral second-generation antipsychotics (SGAs) should be compared with KarXT on a pairwise (and not pooled) basis to improve the generalizability of findings.
- (2) As data for KarXT currently are limited to hospitalized patients experiencing acute relapse, the final scope of the Clinical Evidence Review and Comparative Value Analyses should clarify how data from the three KarXT RCTs will be generalized to patients who are not experiencing relapse and/or initiating treatment in other settings.
- (3) Karuna recommends that ICER conduct scenario analyses examining the comparative value of KarXT vs comparators in patients who are of normal weight, overweight, and obese, respectively, when treatment is initiated to model the impact of AEs on treatment adherence and downstream outcomes.
- (4) While relapse and rehospitalization are important real-world clinical outcomes in patients with schizophrenia, data for KarXT currently are limited to three short-term, acute treatment RCTs in hospitalized subjects admitted for treatment of relapse; the final scoping document should clarify how data from these trials will be used to characterize relapse and rehospitalization in patients assumed to receive KarXT will be characterized in the comparative value analysis in the absence of any data specific to KarXT.
- (5) Karuna recommends that ICER further clarify and include in the scope of its Comparative Value Analyses how the long-term incidence and impact of adverse events, including their impact on adherence/persistence, will be captured in the model.
- (6) Karuna supports consideration of expanded measures of disease impact for schizophrenia, but is concerned about the absence of such data for individual agents. If expanded measures of disease impact are included in the model, Karuna recommends that these be characterized using the established relationship between societal impact and changes in key schizophrenia outcomes similar for KarXT and the comparators.

- (1) Designated comparators for the KarXT Comparative Value Analyses should be expanded to include olanzapine and risperidone, since these agents are as commonly used today as aripiprazole. Each of these agents should be compared with KarXT and these additional two oral second-generation antipsychotics (SGAs) should be**

**compared with KarXT on a pairwise (and not pooled) basis to improve the generalizability of findings.**

ICER stated that it would compare KarXT to aripiprazole exclusively in its Comparative Value Analysis. However, rates of utilization today for both olanzapine and risperidone are higher than those of aripiprazole<sup>1</sup>. Moreover, while aripiprazole may be better tolerated than risperidone and olanzapine, the latter two drugs may have better efficacy than aripiprazole. Therefore, while not fully representative of the class, it is recommended that all three agents be included as comparators in the Comparative Value Analysis for KarXT. Furthermore, KarXT should be compared to each on a pairwise basis because the adverse event profiles and costs of these three agents differ, and possibly also their efficacy. If ICER ultimately decides not to include olanzapine and risperidone as comparators in its Comparative Value Analyses, Karuna strongly recommends that scenario analyses are conducted in which each of these agents is considered as an alternative comparator. Additional pairwise analyses of the comparative value of KarXT versus olanzapine and risperidone would enhance the generalizability of findings from this evaluation and the extent to which it can inform coverage, reimbursement, and utilization management decisions.

**(2) As data for KarXT currently are limited to hospitalized patients experiencing acute relapse, the final scope of the Clinical Evidence Review and Comparative Value Analyses should clarify how data from the three KarXT RCTs will be generalized to patients who are not experiencing relapse and/or initiating treatment in other settings.**

While many patients with schizophrenia begin a new medication regimen in outpatient settings while not experiencing acute relapse, data for KarXT currently are limited to Karuna's three completed RCTs, all of which limited enrollment to patients who were treated for acute relapse in the inpatient setting. Notably, similar inclusion criteria have been used in placebo-controlled RCTs for other antipsychotic agents. These patients may differ in any number of potentially important respects from patients who might initiate KarXT in another setting. As an example, it is expected that rates of adherence and persistence would be lower for patients in outpatient settings compared with those who are hospitalized. Karuna recommends the final scoping document clarify how data from the three KarXT RCTs (as well as data for the comparators) will be generalized to patients who initiate treatment outside of inpatient settings.

**(3) Karuna recommends that ICER conduct scenario analyses examining the comparative value of KarXT vs comparators in patients who are normal weight, overweight, and obese, when treatment is initiated, to model the impact of AEs on treatment adherence and downstream outcomes.**

ICER acknowledges in its Draft Scoping Document that weight gain in patients receiving current antipsychotic medications is often associated with diabetes, hypertension, and other physiologic and psychological morbidities. It can also adversely affect treatment adherence/persistence and, thus, risk of relapse and hospitalization. Additionally, weight gain has been reported to be a key reason for medication discontinuation among patients receiving antipsychotics. As initial body weight may be a significant predictor of weight gain with current antipsychotic medications, and excess body weight may increase risk of diabetes and cardiovascular disease (CVD), Karuna recommends that ICER undertake scenario analyses examining the comparative value of KarXT vs. its designated comparators in patients who are of normal weight, overweight, and obese, respectively, when treatment is initiated.

**(4) While relapse and rehospitalization are important real-world clinical outcomes in patients with schizophrenia, data for KarXT currently are limited to three short-term, acute treatment RCTs in hospitalized subjects admitted for treatment of relapse. The final scoping document should clarify how relapse and rehospitalization**

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<sup>1</sup> Source: Data on file, IQVIA NPA and APLD, May 2023

**in patients assumed to receive KarXT will be characterized in the comparative value analysis in the absence of any data specific to KarXT.**

Data for KarXT are currently limited to three RCTs in study subjects hospitalized for relapse at trial entry and all patients also remained in hospital for the duration of acute treatment (i.e., 5 weeks). By definition, these patients cannot be at risk of rehospitalization. In the absence of information on rates of relapse and rehospitalization in patients receiving KarXT, any assumption regarding event rates that may be observed in other patients, in other settings, would be speculative. It is recommended that ICER clarify in the Comparative Value Analyses how relapse and rehospitalization will be characterized in patients assumed to receive KarXT in the absence of any data specific to KarXT and its novel MOA.

**(5) Karuna recommends that ICER further clarify and include in the scope of its Comparative Value Analyses how the long-term incidence and impact of adverse events, including their impact on adherence/persistence, will be captured in the model.**

Karuna agrees with ICER's inclusion of diabetes as an outcome of focus in the Comparative Value Analyses, but recommends that the clinical and economic burden of other common treatment-related AEs also be included. For instance, weight gain may adversely affect patient QoL even if it does not result in diabetes or a CV event. Tardive dyskinesia may substantially diminish patient QoL and, require costly, novel therapies for treatment, increasing healthcare costs. Moreover, patients who experience weight gain and other treatment-related AEs, as ICER notes in the Draft Scoping Document, more often discontinue their medication. Therefore, Karuna recommends that the Final Scoping Document provide greater clarity about how ICER will characterize both the incidence and clinical and economic consequences of treatment-related AEs during long-term follow-up in the model, for KarXT as well as the designated comparators, including how treatment adherence/persistence may be adversely impacted.

**(6) Karuna supports consideration of expanded measures of disease impact for schizophrenia, but is concerned about the absence of such data for individual agents. If expanded measures of disease impact are included in the model, Karuna recommends that these be characterized using the established relationship between societal impact and changes in key schizophrenia outcomes similar for KarXT and the comparators.**

ICER has designated improvements in functioning (e.g., community integration, ability to work, attend school, and live independently) and caregiver impact as important outcomes. Karuna agrees with ICER's desire to incorporate such outcomes into its value framework, as they may provide important considerations in therapeutic decision making. However, productivity and caregiver burden were not included as measures in KarXT RCTs, and evidence on these included measures is limited in designated comparators' RCTs. Thus, it is unlikely that ICER would be able to differentiate the impact of KarXT versus the comparators with respect to such outcomes. In the absence of data, Karuna recommends that ICER assume similar impacts for KarXT and the SGA comparators for these expanded measures of disease impacts.

Thank you again for this opportunity to provide comments on the draft scoping document. We look forward to continuing the engagement with ICER throughout the duration of this assessment. If you have any questions, please feel free to reach out.

Sincerely,

Judith C. Kando, Pharm.D., BCPP  
Interim Head of Medical Affairs  
Karuna Therapeutics

July 26, 2023

Steven D. Pearson, MD, MSc, FRCP  
President  
Institute for Clinical and Economic Review  
One State Street, Suite 1050  
Boston, MA 02109 USA

**Re: ICER to assess xanomeline tartrate/trospium chloride for the treatment of schizophrenia**

Dear Dr. Pearson:

Thank you for the opportunity to provide comments on the draft scoping document for the assessment of xanomeline tartrate/trospium chloride for the treatment of schizophrenia released on July 5, 2023. At this time, we would like to provide feedback.

**1. Population:**

The draft scope mentions “Data permitting, we intend to assess evidence on treatment for schizophrenia for groups stratified by: Age, Race/ethnicity, and Sex”

Individuals with schizophrenia require long-term antipsychotic treatment to prevent recurrent relapses and clinical decline [1]. Multiple relapses lead to longer recovery times and reduced chances of regaining previous health levels [2]. Strong predictors of relapses include non-adherence to medication, prior relapse, substance abuse, and psychiatric hospitalization [3-5]. Poor premorbid adjustment, early disease onset, longer illness duration, and untreated psychosis also contribute to poorer long-term outcomes [6]. Other factors, such as disease duration, treatment history, antipsychotic exposure, and previous relapses, should be considered in stratification.

**Recommendation:**

ICER should provide a clinical rationale why age, race/ethnicity and sex are the only variables planned to be stratified in the scoping document. This scope should encompass all relevant important subgroups, supported by evidence without limiting to age, race/ethnicity or sex.

**2. Interventions**

The scoping document has mentioned the intervention of interest is xanomeline tartrate/trospium, which is a novel treatment for schizophrenia.

SEP-363856 is a trace-amine associated receptor 1 (TAAR1) agonist with 5-HT1A receptor agonist activity with FDA Breakthrough Therapy Designation, for the treatment of schizophrenia [8] which is a novel non-D2 receptor binding drug with available safety and efficacy results [7].

**Recommendation:**

ICER should provide a more detailed clinical and policy rationale for only considering xanomeline tartrate/trospium.

### 3. Comparators

The scoping document mentions three comparators (aripiprazole, risperidone, and olanzapine) in a market basket approach.

Ideally, treatment decisions and pathways rely on several factors, including the severity or acuity of the illness, previous treatment response, and tolerability, as well as the careful consideration of medication efficacy and adverse effect profiles, all within the context of patient preferences and adherence [9]. The approach's selection of aripiprazole as the comparator lacks clinical and empirical evidence, relying solely on feedback from experts. In the comparator arm, the model assumes aripiprazole's continued inclusion in the market basket even after its discontinuation. Also, it is important to consider that in the included treatment trial, there could be patients who had prior antipsychotic failure including the treatments mentioned in the market basket.

#### **Recommendation:**

It would be helpful to provide more information on the specific reasons for selecting aripiprazole as an appropriate as the comparator; the rationale for selecting the specific market basket of second-generation antipsychotics should be explained and clarification for including aripiprazole in the market basket despite prior discontinuation by patients in comparator arm. Data permitting, all relevant comparators for the group of patients under consideration should be considered in this assessment.

### 4. Scope of comparative value analysis

The scoping document mentioned the economic evaluation approach. The model includes two phases: an upfront decision tree (acute phase) and followed by a lifetime Markov model.

There are several limitations in this approach such as:

1. Simplified representation: The model oversimplifies schizophrenia treatment by an acute phase and a maintenance phase, ignoring disease heterogeneity and variations in individual patient experiences. A more nuanced representation may be necessary to account for different subtypes, treatment responses, and disease trajectories.
2. Relapse duration: Fixed relapse duration of three months may not accurately reflect the variability observed in real-world clinical practice.
3. Transition criteria: Undefined transition criteria from acute to maintenance phase. Relying solely on treatment response may overlook tolerability, patient preferences, and long-term goals. A more personalized, patient-centered approach is needed, considering a broader range of factors for transitions.
4. The model approach lacks information to address the risk of comorbidities (obesity, diabetes, metabolic syndrome, etc.) and their impact on life-expectancy in schizophrenia patients. These conditions are linked to treatment choices and significantly increase mortality risk (2-3 fold) in this population [10 -12].

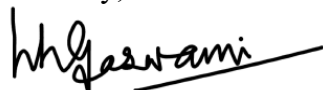
#### **Recommendation:**

A potentially better approach that presents the suggestions as flexible options based on feasibility and available data for a more robust approach:

1. Individualized patient modeling: Ideally, customizing the model to reflect the unique characteristics, treatment history, and preferences of each patient would enhance accuracy. If feasible and supported by data availability, incorporating schizophrenia-specific risk equations that account for individual and disease characteristics could improve prediction of comorbidity risks.
2. Longitudinal data integration: Long-term observational studies offer valuable insights into schizophrenia's natural and treatment responses, improving its ability to capture real-world complexities. If possible, integrating real-world data from diverse patient populations with longitudinal follow-up could strengthen the model's validity.
3. Enhanced treatment considerations: If feasible, and supported by data, expanding the model to include a broader range of treatment options, adjunctive therapies, and psychosocial interventions would better reflect the evolving landscape of schizophrenia treatment. Also, considering the evaluation of weight and metabolic outcomes is crucial due to its impact on patient health, treatment decisions, healthcare costs, and overall well-being. This could lead to a more comprehensive evaluation of treatment efficacy, safety, and cost-effectiveness.
4. Address limitations and assumptions: It is important to explicitly state and justify assumptions, discuss potential limitations and their impact on the model results, acknowledging uncertainties or data gaps and their potential impact on the validity of the findings would enhance transparency and reliability.
5. Discuss generalizability: Address the model's findings' applicability to the target population and real-world clinical practice. Highlight how the new model overcomes limitations of previous approaches based on a literature review.
6. Consider external validation if possible: If feasible, plans for external validation of model's output against real-world data would provide evidence of its accuracy and reliability.
7. Provide additional information on data sources: Providing detailed information on data sources (xanomeline tartrate/trospium trials, network-meta-analyses, and the best available published data on second-generation antipsychotics), including quality relevance to the target population, and potential limitations or biases, would increase transparency and reliability.

Thank you again for this opportunity to provide comments and we look forward to continuing this engagement throughout the assessment period. If you have any questions, please feel free to reach out.

Sincerely,



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## Comments on KarXT for Schizophrenia - Draft Scoping Document

**Author:** Jonathan M. Meyer, MD, Voluntary Clinical Professor - Department of Psychiatry, University of California, San Diego

**Disclosures:** In the past 24 months Dr. Meyer has served on advisory boards for two companies involved in the development of muscarinic agonists for schizophrenia: Karuna; Cerevel.

**Nature of comments:** Potential other benefits and disadvantages and contextual considerations

Below is a short list of concerns inherent to the proposed analysis that related primarily to paucity of data covering certain important areas crucial to modeling psychiatric outcomes, and to the unique challenges related to model development with a novel mechanism of action (MOA).

**1. Efficacy comparisons:** While some nonresistant schizophrenia patients respond better to D<sub>2</sub> receptor (D<sub>2</sub>R) antagonist antipsychotics (APs) than to D<sub>2</sub>R partial agonist APs, use of a D<sub>2</sub>R partial agonist (aripiprazole) as the starting comparator is not unreasonable considering that meta-analyses find limited efficacy differences among direct D<sub>2</sub>R modulating agents, but substantial tolerability difference.<sup>1</sup> The bigger concern relates to the attempt to model differential outcomes between any D<sub>2</sub>R modulating agent and one with a novel MOA in the absence of any KarXT trials with an active comparator arm (whether designed as a head-to-head comparison, or where the D<sub>2</sub>R modulating agent was employed solely for assay sensitivity).

When a specific reason can be pinpointed (as opposed to ‘patient’s decision’), studies such as the CATIE Schizophrenia Trial indicate that approximately 60% of AP switches are related to inefficacy, and 40% to tolerability.<sup>2</sup> Here are some issues raised by the absence of comparative data between KarXT and D<sub>2</sub>R modulating agent:

**a. Efficacy and intolerability:** There is sufficient data to model the extent to which switching or nonadherence is driven by D<sub>2</sub>R or non-D<sub>2</sub> related adverse effects (AEs) regardless of the MOA. One important consideration in evaluating AEs is to separate central nervous system (CNS) anticholinergic effects from peripheral anticholinergic AEs for one primary reason: CNS anticholinergic AEs are not only unpleasant (e.g. sedation) and thus lead to nonadherence or switching, but they directly induce deleterious measurable cognitive effects and thus impact function even when patients do not discontinue the offending agent.<sup>3</sup> The patient may thus be harmed by remaining on the strongly anticholinergic AP.

Another confounding element is the extent to which any AE may be tolerated if the trade-off is differential efficacy. The effect sizes for the 3 registrational trials (Emergent-1, 2 and 3) are greater than those for D<sub>2</sub>R modulating APs approved in the last 20 years, but the extent to which this is the product of the novel MOA or other study design factors is unknown, especially given the lack of comparator arms.

**b. Overall symptom efficacy:** Assuming that one could adequately model treatment inefficacy related to intolerability, any attempt to impute relative acute or long-term efficacy for KarXT versus D<sub>2</sub>R modulating APs appears problematic based on the absence of long-term relapse/maintenance studies for KarXT. With the novel MOA for KarXT it does not seem reasonable at this stage to assume KarXT’s effect on relapse in the maintenance phase will directly parallel the acute phase data as the non-D<sub>2</sub> MOA may capture a subgroup of patients that are not classically treatment resistant,<sup>4</sup> but who

euphemistically represent the “walking wounded,” a cohort of suboptimal responders who derive some limited benefit from D<sub>2</sub>R modulation, but who remain moderately symptomatic. Two double-blind, randomized studies indicate that these individuals achieve greater symptomatic response when switched to clozapine.<sup>5,6</sup> It thus remains an open question whether another non-D<sub>2</sub> strategy might also benefit this population of schizophrenia patients. That KarXT might display differential response characteristics is a valid and testable hypothesis, one with great implications for patients and payors, but the extent of this value cannot be modeled in the absence of data, and it might be significantly underestimated if assumptions are driven solely by use of the extant clinical trials data, studies that typically do not include patients with a history of inadequate response.

**c. QALYs and cognition, negative symptoms:** These also represent important aspects of KarXT’s putative differential effect related to its MOA as noted in preclinical models,<sup>7,8</sup> but ones for which there is a paucity of clinical data. A poster presented in 2022 suggested potential cognitive benefit for KarXT (Harvey PD, et al. *The Potential of M<sub>1</sub> Agonists to Treat Cognitive Impairment: Evidence From a Phase 2 Study of KarXT in Schizophrenia (EMERGENT-1)*); poster presented at the Schizophrenia International Research Society 2022 Annual Congress, April 6-10, 2022, Florence, Italy), but such data need replication and confirmation of differential functional outcomes versus existing APs. The same can be said for negative symptom impact.

- 2. The value of adjunctive treatment:** Although AP monotherapy is a laudable goal, and initial models should focus on monotherapy comparisons, preclinical models indicate that KarXT will compliment and augment the efficacy of existing D<sub>2</sub>R modulating agents.<sup>9</sup> These findings not only demand that one explore the value of an agent that can **be rationally combined with existing APs**, but account for the fact that this strategy is so promising that phase 3 adjunctive trials of KarXT are ongoing. (It is worth noting that the MOA of KarXT may be interfered with by more strongly anticholinergic APs such as olanzapine, high dose quetiapine, or clozapine, and these agents are not included in the adjunctive program.) In performing such modeling, one must acknowledge that polypharmacy is quite common,<sup>10,11</sup> often driven by the search for greater efficacy in managing the positive symptoms of schizophrenia. Some AP combinations involve the additive benefits of greater D<sub>2</sub> blockade, are thus may not be ideal but are not entirely irrational; however, other combinations are completely irrational and reflect ignorance of AP pharmacodynamics. The classic example involves the combination of D<sub>2</sub>R partial agonist APs with antagonist APs, especially using doses of the partial agonists that substantially interfere with the antagonist actions at the D<sub>2</sub>R.<sup>12</sup>

KarXT’s presynaptic modulation of dopamine release, and its ability to avoid motoric effects in the striatum thus represent an enormous potential value to manage inadequate treated positive psychotic symptoms. As discussed above, there is a significant subgroup of suboptimal responders who are technically not treatment resistant, and thus often not the focus of clinical trials or clinical attention. Before embarking on any models of KarXT’s value it would be important ascertain to what extent these patient might benefit from a presynaptic muscarinic agonist MOA added to their D<sub>2</sub>R modulating AP. A monotherapy-focused model might thereby underestimate the true potential of this novel MOA beyond the avoidance of certain D<sub>2</sub>-related AEs and other tolerability advantages.

This is especially true given the comfort level of psychiatric prescribers for AP combination therapy, and particularly for those patients in whom a long-acting injectable (LAI) AP forms the foundation of their AP regimen, but where the level of response from the LAI is deemed insufficient. In many instances clinicians would not want to lose the value of an LAI, but would welcome the means to rationally add another agent that provides something other than more D<sub>2</sub>R modulation.

**Summary:** The proposed modeling project proposed is absolutely necessary, but the overarching concern is that there may be inadequate data to serve as reliable inputs to address a number of important issues (e.g. long-term response/relapse) and unique issues posed by the emergence of a novel MOA for schizophrenia treatment in the form of muscarinic agonism (e.g. differential activity versus D<sub>2</sub>R modulating APs, adjunctive use). Given the enormous amount of work that this project entails, one wonders whether the current attempt might be premature, and rest too heavily on assumptions and inference, instead of data.

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July 26, 2023

Submitted electronically to [publiccomments@icer.org](mailto:publiccomments@icer.org)

**RE: ICER Draft Background and Scope: KarXT for Schizophrenia**

Otsuka America Pharmaceutical, Inc. (Otsuka) appreciates the opportunity to submit comments on the Institute for Clinical and Economic Review’s (ICER’s) draft scoping document for its review of KarXT for schizophrenia.<sup>1</sup>

Otsuka and its affiliates oversee research and development and commercialization activities for innovative products in North America. At Otsuka, our driving philosophy is to defy limitation, so others can too. We seek to serve those with unmet medical needs in three important treatment areas: nephrology, neuroscience, and digital therapeutics. Otsuka is proud to be at the forefront of the research and development of new therapies designed to help patients with agitation associated with dementia due to Alzheimer’s disease, mental illness, and complex kidney disease. We respect the value within every mind—whether it’s a grand idea that changes the world, a simple human connection that changes someone’s life, or something in between.

We offer questions and comments on each section of the Draft Scoping Document below.

**A. Background**

We encourage ICER to revise this section and elaborate on potential causes of certain outcomes and the presence of adverse events and side effects. For example, ICER should clarify that the “worse outcomes” of certain populations may be due to documented treatment differences among historically marginalized groups. In addition, not all “effective therap[ies]” have the same side effects, and some populations may be more vulnerable to certain types of side effects. The presence (or absence) of shared decision-making may also affect both outcomes and patients’ willingness to adhere to prescribed therapies. In addition, we generally recommend using the term “Black/African Americans” (rather than just “Black Americans”).

**B. Scope of Clinical Evidence Review**

**Comparators.** Please clarify if only generic second-generation antipsychotics will be included or if branded drugs will also be included. Otsuka suggests including all oral therapies for the treatment of schizophrenia in the market basket of second line therapies. Please also confirm that ICER’s review will be limited to oral antipsychotics and exclude long-acting injectables (LAIs) in the “market basket” of second line therapies. Given that LAIs only comprise a small portion of the market and are typically used as a second-line therapy and the KarXT therapy is an oral therapy, we do not recommend including them as comparators.

**Populations.** Has ICER considered which social determinants of health to include in the model that may affect its assessment of the stratified groups?

**Outcomes.** Will negative symptoms be measured with the Positive and Negative Syndrome Scale (PANSS) negative symptom score or the PANSS Marder negative symptom score?

Please explain how the following outcomes will be measured: (1) quality of life, (2) improvement in functioning (e.g., community integration, ability to work, ability to care for dependents, attend school, live independently), (3) brain fog, and (4) burden on caregivers of patients with schizophrenia. Please also explain whether and to what extent there will be an opportunity to assess and incorporate patient objectives and preferences.

### **C. Potential Other Benefits and Contextual Considerations**

Please explain what “Other” contextual considerations ICER will include in the protocol.

### **D. Scope of Comparative Value Analyses**

**Model Structure.** The model consists of a three-month acute phase and a maintenance phase, but most acute schizophrenia trials only have six weeks’ data.<sup>ii</sup> To reduce the need to generate assumptions on extrapolated data, ICER should shorten the acute phase to six weeks.

**Market Basket.** The description of the economic model does not clarify whether the “market basket” will be measured using composite endpoints or using each comparator’s own data. Otsuka encourages the use of composite endpoints, calculated based on each comparator’s market share. If, however, each comparator’s own data is used, we recommend assigning patients to separate market basket drugs based on market share, rather than evenly splitting them among comparators.

**Comparator Arm.** The draft indicates that a patient whose “aripiprazole treatment is discontinued in the comparator arm” will be modeled to a “market basket of second-generation of antipsychotics,” which would also include “aripiprazole.” We are concerned that including the same drug for both lines of treatment are inconsistent with treatment guidelines and could diminish any positive effects from the drug. Otsuka recommends that ICER structure the model to ensure that the model does *not* include the same drugs for both first- and second-line therapies (e.g. remove aripiprazole from the market basket of second line therapy for the aripiprazole arm in the model).

**Life Expectancy.** When establishing life expectancy for the second phase of lifetime maintenance in the Markov model, ICER should use a life expectancy that is based on patients with schizophrenia specifically, which tends to be shorter than the general population.<sup>iii</sup>

**Relapse.** Otsuka encourages ICER to ensure that a consistent definition of relapse is used across trials, since the relapse data are used to determine health states and transition probabilities.

**Caregiver Impact.** Please provide more details about how the impact on caregivers will be assessed in the model. Because caregiver costs drive the indirect health care costs, we expect these to have a significant impact on ICER’s results. We note, however, that these types of costs are not consistently reported in the literature, and it will be important to distinguish the costs of professional caregivers (e.g., nurses) from those of informal caregivers (e.g., family members).<sup>iv</sup>

**Adherence Rates.** We recommend that ICER develop the model to address lower adherence rates among adult patients with schizophrenia on atypical antipsychotics as well as the decline in adherence across the course of therapy. It may be possible to capture this in the Markov model. In addition, please explain whether the model be able to evaluate the impact of: (1) twice-daily (i.e., BID) dosing and adherence, and (2) patient preferences.

**Best Available Data Used to Populate the Model.** Please explain whether real-world evidence for specific drugs will be used to support the model, or if ICER will rely solely on clinical trial data.

**Health Outcomes – Cardiovascular Disease.** We recommend including cases of cardiovascular (CV) disease averted as a health outcome. CV disease complications (e.g., stroke) were listed in the “Scope of Clinical Evidence Review” section, but we want to ensure that it is specifically addressed here. Schizophrenia itself as well as treatment-associated metabolic effects (e.g., weight gain) are associated with increased risk of CV disease, which can lead to a high economic burden and will likely affect cost and utility in the model.<sup>v</sup> We encourage that ICER use the Framingham risk equation to predict the long-term incidence of CV events.<sup>vi</sup>

**Health Outcomes – Diabetes.** Otsuka also encourages ICER to consider the use of the ARIC risk equation to estimate the incidence of diabetes.<sup>vii</sup>

\* \* \* \* \*

Otsuka appreciates the opportunity to comment on the proposed changes to the Kar-XT Scoping Document. If you have any questions about these comments, please contact Heidi Waters, PhD, Senior Director Policy Research, at Heidi.Waters@otsuka-us.com.

Sincerely,

Kaan Tunceli, PhD

Vice President, Global Value & Real World Evidence

Otsuka Pharmaceutical Development & Commercialization, Inc.

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<sup>i</sup> *ICER to Assess Treatment for Schizophrenia*, ICER (July 5, 2023), <https://icer.org/news-insights/press-releases/icer-to-assess-treatment-for-schizophrenia/#:~:text=BOSTON%2C%20July%205%2C%202023%20%E2%80%93,for%20the%20treatment%20of%20schizophrenia>; *KarXT for Schizophrenia: Draft Background and Scope*, ICER (July 5, 2023), [https://icer.org/wp-content/uploads/2023/06/Schizophrenia\\_Draft-Scope\\_for-publication\\_070523.pdf](https://icer.org/wp-content/uploads/2023/06/Schizophrenia_Draft-Scope_for-publication_070523.pdf).

<sup>ii</sup> See, e.g., Stefan Leucht et al., *Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis*, 382 *Lancet* 951-52 (Sept. 2013); Toby Pillinger et al., *Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis*, 7 *Lancet Psychiatry* 64-77 (Jan. 2020) available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029416/>.

<sup>iii</sup> See Thomas M. Lauren et al., *Life expectancy and cardiovascular mortality in persons with schizophrenia*, 25 *Current Op. Psychiatry* 83-88 (Mar. 2012).

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<sup>iv</sup> Cecilia Brain et al., *Experiences, attitudes, and perceptions of caregivers of individuals with treatment-resistant schizophrenia: a qualitative study*, 18 *BMC Psychiatry* 253 (Aug. 2018), available at <https://bmcp psychiatry.biomedcentral.com/articles/10.1186/s12888-018-1833-5>; Csilla Csoboth, *The humanistic and economic burden of providing care for a patient with schizophrenia*, 61 *Int'l J. Soc. Psychiatry* 754-61 (Dec. 2015).

<sup>v</sup> See Charles H. Hennekens et al., *Schizophrenia and increased risks of cardiovascular disease*, 150 *Am. Heart J.* 1115-21 (Dec. 2005); Benjamin Kearns et al., *Schizophrenia Treatment with Second-Generation Antipsychotics: A Multi-Country Comparison of the Costs of Cardiovascular and Metabolic Adverse Events and Weight Gain*, 17 *Neuropsychiatric Disease Treatment* 125-137 (Jan. 2021), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7829121/>.

<sup>vi</sup> See Johanna A. Damen et al., *Performance of the Framingham risk models and pooled cohort equations for predicting 10-year risk of cardiovascular disease: a systematic review and meta-analysis*, 17 *BMC Med.* 109 (June 2019), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6563379/>.

<sup>vii</sup> See Maria Ines Schmidt et al., *Identifying individuals at high risk for diabetes: The Atherosclerosis Risk in Communities study*, 28 *Diabetes Care* 2013-18 (Aug. 2005), available at <https://diabetesjournals.org/care/article/28/8/2013/23777/Identifying-Individuals-at-High-Risk-for>.



## Schizophrenia & Psychosis Action Alliance's Response to ICER Schizophrenia Draft Scope

Wednesday, July 26<sup>th</sup>, 2023

**Introduction.** The Schizophrenia & Psychosis Action Alliance (S&PAA) appreciates the opportunity to support ongoing and future clinical effectiveness reviews for the care of individuals diagnosed with schizophrenia, conducted by the Institute for Clinical and Economic Review (ICER). We value ICER's stated commitment to increasing population-level access to health interventions. This emphasis is especially important for those living with schizophrenia and their loved ones, given that lack of access to high-quality care is one of the key drivers of the horrific outcomes seen in those with schizophrenia, such as a life expectancy that is 15-20 years earlier than that of the general population<sup>1</sup>.

Our current systems both neglect and abuse those with schizophrenia, and we welcome ICER's efforts to encourage fair access, support continued innovations, and remove barriers to how care is delivered to those in need. S&PAA believes that the work that ICER has elected to undertake can have impacts well beyond the determination of value for this single product. 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 a way for any given individual. Additionally, forcing someone to take the wrong treatment to prove it is wrong often takes months harming this vulnerable population further. As the American Psychiatric Association (APA) guidelines for treating schizophrenia state, "*the choice of an antipsychotic agent depends on many factors that are specific to an individual patient.*"<sup>2</sup>

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. Our primary concern is that the proposed modeling approach may create additional barriers to access to life-altering medications for schizophrenia. As ICER approaches "the value" of a single treatment in schizophrenia, it is critical that findings are presented in the context of the significant limitations of this population-level approach, available data, and disease understanding to avoid introducing further harm, healthcare access issues, and associated injustice to this vulnerable population.

The following comments are made in this context, and we look forward to continued dialogue throughout the evaluation process.

### **Comments on the Background**

It is critical for ICER to describe the most up-to-date knowledge about schizophrenia. For example, while it is somewhat accurate that "*the underlying cause of schizophrenia is unknown,*" the etiology of this illness has been widely explored. A more accurate statement would be that "*schizophrenia is known to be strongly influenced by genetic and environmental factors, and is considered a neurodevelopmental brain disease, but mechanisms involved in disease pathology are unknown*"<sup>3,4</sup>. Additionally, the most recent comprehensive US-based lifetime prevalence estimate for schizophrenia is 1.8% and should be used as an up-to-date citation<sup>5</sup>.

### **Comments on the Model Approach**

**1. The base case model must include societal costs to reflect the lived experience of those with schizophrenia and their caregivers.** In ICER's 2023 value assessment framework, it is stated that societal costs in models will be included when such costs are large, presenting a "modified societal perspective as a co-base case". This aligns with the draft scope background and real-world evidence confirming **the majority of annual economic costs of schizophrenia are societal, not medical.** Using only the healthcare system perspective and focusing only on direct medical costs will severely underestimate the immense burden of schizophrenia in terms of lost productivity and under/unemployment, disability, supportive housing and services, homelessness, justice system and legal costs and outcomes, and the multifaceted caregiver costs<sup>6-13</sup>.



To put specific numbers to this, a recent study we conducted<sup>7</sup> showed that the annual excess total cost of schizophrenia is \$280 billion (B) but only 9.7% of this amount (\$27B) results from direct healthcare costs. The remainder of the total direct costs of schizophrenia (\$62B) comprise supportive housing and homelessness, justice system involvement, and social security/disability. The indirect costs of schizophrenia are more than 3.5 times higher than the direct costs, including unpaid caregiver wages, nonemployment and reduced wages, life expectancy, quality of life, and caregiver burden. The indirect costs for unpaid caregiver wages, alone, are higher than the direct costs. These numbers are underestimated based on more recent research that shows higher prevalence (e.g., 1.2% vs. 0.8%) and caregiver costs (e.g., out-of-pocket)<sup>5,6</sup>.

ICER's approach must incorporate all costs and impacts to represent the true burden of schizophrenia, determine treatment impacts, and avoid causing further misconceptions and associated harm to our community.

**2. The current health states in the lifetime Markov model (stable, relapse, and death) are an inappropriate representation of the illness experience for those with schizophrenia, as they do not account for levels of symptom severity, associated outcomes, and costs.** Stability within schizophrenia is not a clearly defined health state, as the majority of those who are “stable” with schizophrenia still have residual positive, negative and/or cognitive symptoms<sup>14-16</sup>. Residual symptoms affect quality of life and treatment adherence and are associated with different levels of healthcare and societal costs and outcomes. In particular, cognitive and negative symptoms of schizophrenia are strong predictors of social and community functioning<sup>17,18</sup> and finding and sustaining employment<sup>19-22</sup>. Unfortunately, these cognitive and negative symptoms of schizophrenia are relatively untouched by current antipsychotic medications and tend to show relative stability or worsen over time<sup>14-16</sup>. Consequently, “stable” includes someone whose symptoms are controlled and who is working and living independently, but “stable” also includes someone whose positive symptoms are minimized, with negative symptoms and cognitive impairments, who cannot work, is on disability, and requires significant caregiver support. The economic burden and outcomes of these two “stable” individuals are vastly different.

To address this oversimplification, ICER can divide “stable” into symptom profiles as outlined in Table 1. “Relapse” should also be separated into “acute” and “chronic” health states to capture that some individuals require short-term hospitalization while others need long-term stays on inpatient units, are homeless or end up in jail or prisons, which significantly affects mental healthcare costs<sup>23</sup>. Moreover, individuals often move rapidly from stability to relapse<sup>24,25</sup>, which should be accounted for in modeling. Using extant literature, these health states can be linked to the healthcare system and societal costs.

ICER should provide more granular health states that reflect the lived experience of schizophrenia as outlined in Table 1.

**3. The “settings” listed by ICER (inpatient, outpatient/clinic, and home settings) are insufficient.** Those with schizophrenia dwell in many settings that are both a consequence of treatment effectiveness and directly impact healthcare and societal costs. These include homeless shelters or the street<sup>26</sup>, jails and prisons<sup>27</sup>, and supported living facilities such as group or nursing homes<sup>28</sup>.

Health states should account for setting as outcomes, with associated costs in the health states included in the model.

**4. Schizophrenia is defined by several population characteristics associated with adherence to guide health state transitions.** Non-adherence is associated with poor functional outcomes, including psychiatric hospitalizations, use of emergency services, poorer mental functioning, high levels of suicidal ideation, poorer life satisfaction, greater substance use, more alcohol-related problems, and associated impacts such as arrests and victimizations<sup>29</sup>. Population characteristics, treatment efficacy, and treatment side effects all influence adherence. The following population characteristics affect adherence: symptom severity and stability<sup>30</sup>, anosognosia<sup>31,32</sup> and serious and lasting side effects<sup>33</sup>.

We suggest that ICER use the outlined population characteristics and associated assumptions for adherence levels to guide health state transitions.

**5. The proposed models neglect psychiatric and medical comorbidities with schizophrenia.** Common psychiatric comorbidities include an increased prevalence of anxiety (e.g., estimated at 15% for panic disorder, 29% for post-traumatic stress disorder, and 23% for obsessive-compulsive disorder), depression (50%), and substance use disorders (47%)<sup>34</sup>. ICER has neglected to include any of these costly mental health conditions in their proposed model. Moreover, ICER has only included treatment-emergent health effects (e.g., weight gain) in their model. Thus, it is unclear whether the model will include underlying comorbidities that are not linked to treatment, which also contribute to healthcare and societal costs<sup>35</sup>. Relatedly, while it is known that diabetes is one of the leading causes of mortality in schizophrenia and can be a side effect of antipsychotic medication use<sup>36</sup> there are other comorbid illnesses that are also important in this same regard, such as obesity, hypertension, and hyperlipidemia<sup>37</sup>. Given this, we wonder why ICER is using only the number of averted diabetes cases as an output rather than other treatment-emergent medical illnesses.

ICER should ensure that all long-term comorbidities present in schizophrenia are included in the model, and account for the fact that some medical comorbidities are transient, some cease upon discontinuation of medication, and some are irreversible. Moreover, a sub-analysis should be conducted on those with co-occurring substance use disorders as this common (47%)<sup>34</sup> and significantly increases costs.

**6. Comparators should not be selected based on prescribing patterns or because they are second-generation antipsychotics.** 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. Specifically, APA treatment guidelines state *“An evidence-based ranking of FGAs and SGAs or an algorithmic approach to antipsychotic selection is not possible because of the significant heterogeneity in clinical trial designs, the limited numbers of head-to-head comparisons of antipsychotic medications, and the limited clinical trial data for a number of the antipsychotic medications. By the same token, it is not possible to note a preference for either SGAs or FGAs.”*<sup>38</sup>

ICER should group comparator antipsychotic medications by tolerability (side effect) and efficacy profiles as has generally been suggested by research experts<sup>39,40</sup>.

**7. It is inappropriate to consider any treatment for schizophrenia a low-value service.** S&PAA is highly concerned with any attempt to determine low-value services for this particular population. Schizophrenia is a chronic, lifelong disease and relapses can occur throughout its progression. Therefore, hospitalizations are an important part of the continuum of care and offer the opportunity to keep people in recovery by adjusting medications and dosages, and preventing suicide completions. Moreover, our health system has arbitrary limitations on the ability for any given service to be appropriately and equally implemented across the population. For example, Medicare limits the lifetime maximum of inpatient psychiatric days to 190 days. The service is not low value, rather the arbitrary restriction on expert care for this manageable neurodevelopmental condition is low value. Additionally, despite mental health parity requirements, this population still does not have full access to healthcare services required to receive evidence-based care. As our payor systems have significant limits (e.g., either by not having enough covered providers, limiting the number of psychiatric beds a facility can have, or limiting access to those beds), those who can afford specific services or who have advocates receive better services. Thus, any data based on our current system that suggests a service as low value is biased against those who are more disadvantaged (e.g., socioeconomically or without a support network)

We strongly advise that no services be reduced, eliminated, or made more efficient at this time. High-value services should be promoted.

The Schizophrenia & Psychosis Action Alliance thanks ICER for considering our input and looks forward to continued discussion throughout this process.

**Table 1. Health States Suggestions**

	Majority setting	Treatment adherence	Healthcare costs <sup>a</sup>	Supportive housing costs	Caregiver costs <sup>b</sup>	Employment <sup>c</sup>	Justice System costs <sup>d</sup>
No or mild symptoms	Independent OR supportive housing	High	Moderate	Low	Low	Moderate	Low
Residual positive symptoms	Independent OR supportive housing	Moderate	Moderate	Moderate <sup>g</sup>	Moderate	High	Moderate
Residual negative symptoms	Independent OR supportive housing	Moderate	Moderate	Moderate	Moderate	High	Low
Residual cognitive symptoms	Independent OR supportive housing	Moderate	Moderate	Moderate	Moderate	High	Low
Moderate/severe symptoms	Supportive housing OR long-term care OR homeless OR incarcerated	Low	High (type of cost varies by setting)	High <sup>h</sup>	High	High	Moderate
Acute relapse	Hospital OR long-term care OR homeless OR incarcerated	Low	High (type of cost varies by setting)	High <sup>e,f</sup>	High	High	High
Chronic relapse	Supportive housing OR Long-term care OR Homeless OR prison or jail	Low	High (type of cost varies by setting)	High <sup>e,f</sup>	Moderate	High	High
Death	NAP <sup>i</sup>	NAP <sup>i</sup>	NAP <sup>i</sup>	NAP <sup>i</sup>	NAP <sup>i</sup>	NAP <sup>i</sup>	NAP <sup>i</sup>

- a. Healthcare costs include outpatient care, visits, medication, other treatments; ER visits; inpatient care; home healthcare)
- b. Caregiver costs include cost of unpaid labor, higher health care costs, work absenteeism, and out-of-pocket costs spent on caregiving
- c. Employment costs include reduced wages among the employed, lack of employment, supportive income from the Social Security Administration (i.e., SSI/SSDI)
- d. Justice system interactions include: services provided by police, sheriffs, deputies; by judicial staff; by institutions (e.g., local and county jails; paid legal guardians), and legal fees
- e. Homeless remediation costs include: homeless shelters, street outreach activities, crisis response center visits)
- f. Incarceration costs include: Labor and time for correctional staff as well as shelter, security, food, and other necessities provided in the facility
- g. Supportive residential services (e.g., rent, support staff)
- h. Residential costs and all costs associated with providing care while in the facility
- i. Not applicable

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Re: Comments on Draft Scope of ICER's Assessment of KarXT for Schizophrenia

To Whom This Concerns:

I am writing to submit comments and suggested refinements to ICER's Draft Scope of the KarXT Assessment.

The STARR Coalition is a non-profit organization that advocates for patient access to every available treatment option, including new, cutting-edge treatments for mental illnesses. We do this by supporting stakeholders involved in mental health clinical research and working to ensure that clinical research is a familiar and trusted part of the community healthcare ecosystem.

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.

That said, here are specific comments on the draft scope of the assessment:



- [Response to paragraph 3, page 7] “Key model inputs will include clinical response, relapse rates, treatment-emergent adverse events, quality of life, treatment discontinuation, and costs. Probabilities, adverse events, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using evidence from the KarXT randomized controlled trials for assessing clinical response in the acute phase and network meta-analysis evidence to support assumptions on KarXT’s effect on reducing relapses and reducing treatment-emergent adverse events in the maintenance phase. **Best available published data on the long-term use of second-generation antipsychotic drugs will be used wherever possible to populate the model during the maintenance phase.**
  - KarXT is a 3<sup>rd</sup> generation treatment, not comparable to 2<sup>nd</sup> gen meds; according to this paragraph, the ICER assessment will be using non-comparable treatment data to model the maintenance phase of KarXT.
    - A suggested revision would be to use the (albeit limited) existing data on KarXT to estimate and populate the model of the maintenance phase and note the limitations in the assessment.
  - How is KarXT’s cognitive function benefit evaluated in the pricing model?
    - A suggested revision would be to assign a value to the cognitive function benefits and include this in the assessment.
  
- [Response to paragraph 4, page 7-8] “The health outcomes of KarXT will be evaluated in terms of life-years gained, quality-adjusted life years (QALYs) gained, equal value of life years gained (evLYG), and cases of diabetes averted”:
  - A suggested revision to “cases of diabetes averted” might be to assess metabolic parameters, increase in glucose, and weight gain, as it could impact diabetes.
  - The health outcome evaluation needs to include KarXT’s increased cognitive functionality. A suggested revision would be to assign a value to the cognitive function benefits and include this in the health outcomes assessment.





- [Response to paragraph 2, page 8] “*In separate analyses*, we will explore the **potential health care system budgetary impact** of treatment over a *five-year time horizon*, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.”
  - “In a separate analyses” – ‘analyses’ is plural - does that mean that ICER isn’t going to include potential health care system budgetary impact in THIS evaluation of KarXT?
  - “five-year time horizon” is too short a time frame. A suggested revision would be to include ten-year and twenty-five-year time frames.
  - “This budgetary impact analysis will indicate the **relation between treatment prices** and level of use for a given potential budget impact,” – no treatment price has been established, so any evaluation of the treatment price would be premature.  
Furthermore, there is no comparable treatment, as this is a completely novel mechanism for schizophrenia, so there is no comparable treatment available that could be used to determine a price. If KarXT is anywhere as good as the PII data indicates, this treatment is **INVALUABLE**.

Please include me and The STARR Coalition in future correspondence regarding this assessment as well as any other assessments of mental health treatments.

Respectfully,

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