

KarXT for Schizophrenia

Draft Background and Scope

July 5, 2023

Background

Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. The symptoms are typically separated into three general categories: positive (delusions, hallucinations, disorganized speech, thought and behavior); negative (poor motivation, lack of pleasure and enjoyment, lack of speech, lack of social interaction), and cognitive (impaired executive function, attention, and memory). These symptoms can negatively impact everyday functioning (e.g., attending work or school, socializing, personal care, etc.).¹ The underlying cause of schizophrenia is unknown. It typically presents in adolescence or young adulthood and continues through the individual's entire life. Males typically present earlier than females.²

Researchers estimate that schizophrenia affects about 3.9 million people in the United States (US) and 24 million people worldwide.³ Black Americans are diagnosed with schizophrenia at about twice the rate of White Americans and have worse outcomes.⁴ The annual economic burden is estimated to be approximately \$343 billion in the United States alone.³ The majority of these costs are societal, not medical.

Current medical treatments primarily target positive symptoms. Unfortunately, effective therapy comes with significant side effects such as weight gain leading to diabetes and hypertension, agitation, movement disorders (tardive dyskinesia and Parkinsonism), sedation, a flat affect, elevated prolactin levels, and sexual side effects. Many patients find the side effects to be worse than the benefits of treatment and decide to stop therapy, leading to relapse of symptoms, hospitalization, and poor long-term recovery.¹ Current guidelines recommend psychosocial interventions in addition to medical therapy in order to target negative and cognitive symptoms. These may include cognitive behavioral therapy, supported employment services, self-management skills training, cognitive remediation, and others.⁵

Most current therapies (typical and atypical antipsychotics) block the dopamine D2 receptor with the newer atypical antipsychotic medications also modulating serotonin levels.⁶

KarXT (Karuna Therapeutics) is a novel combination therapy with one drug (xanomeline) that targets CNS muscarinic receptors (M1 and M4 receptor agonists) and a second drug (trospium) that reduces the peripheral side effects of muscarinic receptor activation. A new drug application (NDA) for KarXT is expected in the third quarter of 2023.⁷

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Anosognosia, the patient's lack of awareness about their psychiatric condition, is a major obstacle to treatment and a source of frustration for caregivers. Patients have challenges advocating for themselves and are often estranged from family members who might otherwise advocate for them.

We heard that the real goals of therapy should revolve around re-integration of the patient into the community: back to school, back to work, and re-establishing relationships with friends and family.

The side effects of currently available therapies are severe including significant weight gain and movement disorders. Patients often weigh the benefits and harms of therapy and make a conscious choice to stop their medications. However, this routinely leads to relapse and the associated complications of suicide, incarceration, or involuntary hospitalization. The best medication for a person living with schizophrenia is the medication that they are willing to take.

There are many barriers to high quality care for patients living with schizophrenia. These include, but are not limited to our fragmented healthcare system, a shortage of trained mental health providers, and stigma (self, societal, and provider).

The impact of the disease on caregivers is enormous. They often sacrifice their own education, time with family and friends, and vacation to help the person who they are caring for. This impacts the caregivers' work productivity, finances, and social relationships.

We heard great hope that KarXT's novel mechanism of action would lead to better outcomes, and especially to fewer side effects and thus greater acceptance by patients over the long term. However, we also heard caution, as prior drugs that had promised markedly fewer side effects ended up offering little, if any benefits compared to the many other drugs used to treat schizophrenia.

In addition, we heard hope that KarXT might address the negative and cognitive symptoms associated that are an integral part of the symptoms experienced by patients living with schizophrenia, but not addressed by current drugs.

The themes that we heard echo those described in the summary of the FDA’s Voice of the Patient series “Reimagine Schizophrenia: Transforming How We Are Treated, Function, and Thrive.”⁸ The major themes from the meeting included the devastating and chronically disabling impact that the disease has on patients and their loved ones, the many barriers standing in the way of successful treatment, and the desire for more effective treatments with fewer side effects.

Report Aim

This project will evaluate the health and economic outcomes of KarXT for schizophrenia. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER’s [grey literature policy](#)).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the intervention and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Populations

The population of focus for this review is adults with an established diagnosis of schizophrenia who are not considered to have treatment-resistant schizophrenia.

Data permitting, we intend to assess evidence on treatment for schizophrenia for groups stratified by:

- Age
- Race/ethnicity
- Sex

Interventions

The intervention of interest will be:

- xanomeline / trospium (KarXT) (Karuna Therapeutics)

Comparators

Data permitting, we intend to compare KarXT to standard care including relevant oral second-generation antipsychotics such as olanzapine, aripiprazole, and risperidone.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
 - Minimize symptoms of schizophrenia
 - Positive (e.g., Positive and Negative Syndrome Scale [PANSS])
 - Negative (e.g., PANSS)
 - Cognitive (e.g., Cambridge Neuropsychological Test Automated Battery [CANTAB])
 - Relapse
 - Hospitalization
 - Quality of life
 - Improvement in functioning (e.g., community integration, ability to work, attend school, live independently)
 - Treatment-emergent adverse events
 - Extrapyramidal symptoms
 - Brain fog

- Sedation and somnolence
- Anticholinergic side effects
- Long-term complications of antipsychotic use
 - Weight gain
 - Need for treatment of diabetes
 - Need for treatment of hypertension
 - Cardiovascular disease (e.g., stroke)
 - Tardive dyskinesia
 - Gynecomastia, galactorrhea, or low libido due to prolactin elevation
- Other adverse events including:
 - Serious adverse events
 - Adverse events leading to discontinuation of therapy
- Other Outcomes
 - Caregiver impact
 - Caregiver quality of life
 - Caregiver health
 - Caregiver productivity

Timing

Evidence on intervention effectiveness and harms will be derived from studies with a duration of at least three weeks.

Settings

All relevant settings will be considered, including inpatient, outpatient/clinic, and home settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of KarXT relative to current standard of care that includes second-generation antipsychotics. In the intervention arm of the model, patients will start treatment on KarXT. If KarXT treatment is discontinued, a patient will then be modeled to switch to a market basket of second-generation antipsychotics (including but not limited to aripiprazole, risperidone, and olanzapine), and then will subsequently switch to clozapine if the market basket of second-generation antipsychotics is discontinued. In the comparator arm of the model, patients will start treatment on aripiprazole based on feedback from numerous clinical experts that aripiprazole was the most tolerated second-generation antipsychotic and represented substantial market share. If aripiprazole treatment is discontinued in the comparator arm, a patient will then be modeled to switch to a market basket of second-generation antipsychotics (including but not limited to aripiprazole, risperidone, and olanzapine), and then will subsequently switch to clozapine if the market basket of second-generation antipsychotics is discontinued.

The model structure will be based in part on a literature review of prior published models of schizophrenia.⁹⁻¹² The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, impacts of the intervention outside of the health care system will be considered in a separate modified societal perspective analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than \$200,000 per QALY, and/or when the result crosses the threshold of \$100,000-\$150,000 per QALY gained.

The target population will consist of adults with an established diagnosis of schizophrenia who are not considered to have treatment-resistant schizophrenia at the model start. The model may consist of two phases, including an acute phase modeled by an upfront decision tree and a subsequent maintenance phase represented by a Markov model. The upfront decision tree would track the cohort of patients through the acute relapse and assess for response to the treatments administered during the acute phase. Each relapse will be modeled for a duration of three months, and thus the first phase of the model would be three months long. From the first phase of the model, patients could then transition to the second phase of the model on the treatment that they responded to during the first phase of the model. The second phase of the model will be a lifetime Markov model that will track the cohort of patients following the acute relapse and throughout the maintenance phase with health states for stable, relapse, and death over cycles of three months long. Treatment-emergent adverse events that are expected to be different between the intervention and comparator arms will be tracked in the model, as data allow. We will continue to engage experts on the relevance of including both the acute and maintenance phase in our modeling efforts, or if our economic modeling efforts should focus solely on the maintenance phase.

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.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. 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. Quality of life weights will be applied to each health state, including quality of life decrements for relapses and treatment-emergent adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and treatment-emergent adverse events. In addition, productivity impacts and other indirect costs will be included in a separate analysis if available data allow. Pairwise comparisons will be made between the two modeled arms, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per case of diabetes averted.

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. More information on ICER's methods for estimating potential budget impact can be found [here](#).

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's [Value Assessment Framework](#)). These services are ones that would not be directly affected by KarXT (e.g., hospitalization for relapse), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of schizophrenia beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Marder SR, Cannon TD. Schizophrenia. *N Engl J Med*. 2019;381(18):1753-1761.
2. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *Lancet*. 2022;399(10323):473-486.
3. Kadakia A, Catillon M, Fan Q, et al. The Economic Burden of Schizophrenia in the United States. *J Clin Psychiatry*. 2022;83(6).
4. Merritt CC, Halverson TF, Elliott T, Jarskog LF, Pedersen CA, Penn DL. Racial disparities and predictors of functioning in schizophrenia. *Am J Orthopsychiatry*. 2023;93(3):177-187.
5. Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry*. 2020;177(9):868-872.
6. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry*. 1996;153(4):466-476.
7. Karuna Therapeutics. Karuna Therapeutics Reports First Quarter 2023 Financial Results and Provides General Business Updates. <https://investors.karunatx.com/news-releases/news-release-details/karuna-therapeutics-reports-first-quarter-2023-financial-results>. Published 2023. Accessed.
8. Schizophrenia and Psychosis Action Alliance AffSP, Mental Health America, National Alliance on Mental Illness, National Council for Mental Wellbeing. Reimagine Schizophrenia: Transforming How We Are Treated, Function and Thrive. Report on the Externally-Led Patient-Focused Drug Development Meeting on Schizophrenia. In: Food and Drug Administration, ed2022.
9. Zhou J, Millier A, Toumi M. Systematic review of pharmacoeconomic models for schizophrenia. *J Mark Access Health Policy*. 2018;6(1):1508272.
10. Davies A, Vardeva K, Loze JY, L'Italien G J, Sennfalt K, Baardewijk M. Cost-effectiveness of atypical antipsychotics for the management of schizophrenia in the UK. *Curr Med Res Opin*. 2008;24(11):3275-3285.
11. Beard SM, Maciver F, Clouth J, R  ther E. A decision model to compare health care costs of olanzapine and risperidone treatment for schizophrenia in Germany. *Eur J Health Econ*. 2006;7(3):165-172.
12. Furiak NM, Ascher-Svanum H, Klein RW, et al. Cost-effectiveness model comparing olanzapine and other oral atypical antipsychotics in the treatment of schizophrenia in the United States. *Cost Eff Resour Alloc*. 2009;7:4.