KarXT for Schizophrenia

Final Evidence Report

March 11, 2024

Prepared for

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

March 19, 2025: New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review 12 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. No public comments were received. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

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Jeffrey A. Tice served as the lead author for the report. Avery McKenna and Abigail Wright led the systematic review and authorship of the comparative clinical effectiveness section of this report with assistance from Finn Raymond. Melanie D. Whittington developed the cost-effectiveness model and authored the corresponding sections of the report. Marina Richardson conducted analyses for the budget impact model. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Kelsey Gosselin, Becca Piltch, Grace Ham, Anna Geiger, and Yamaya Jean for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include Karuna Therapeutics. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About New England CEPAC

The New England Comparative Effectiveness Public Advisory Council – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. NE CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The NE CEPAC Panel is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about NE CEPAC is available at: https://icer.org/who-we-are/people/independent-appraisal-committees/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

Expert Reviewers

Anissa Abi-Dargham, MD
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Dr. Anissa Abi-Dargham received monetary value such as consulting fees or honoraria in excess of $5,000 from Sunovion Pharmaceuticals.

Andrew Davies
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Andrew Davies received monetary value for services such as consulting fees or honoraria in excess of $5,000 from Broadstreet HEOR, Tolley Health Economics, Cogentia, Icon plc, AstraZeneca, Lilly, Gilead, and Pfizer.

Stephen R. Marder, MD
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Dr. Stephen Marder receives monetary value in excess of $5,000 from Boehringer Ingelheim, Merck, and Karuna, and received manufacturer support in the clinical area of this meeting from Boehringer Ingelheim.

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S&PAA receives <25% funding from health care companies, including from Karuna Therapeutics.

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2023/11/Schizophrenia_Stakeholder-List_112823.pdf

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
BPRS	Brief Psychiatric Rating Scale
CDR	Clinical trial Diversity Rating
CGI-S	Clinical global impressions – severity
CNS	Central nervous system
EPS	Extrapyramidal symptoms
eVLY	Equal-value life year
FDA	Food and Drug Administration
HBPB	Health Benefit Price Benchmark
HIDI	Health Improvement Distribution Index
Kg	Kilogram
LAI	Long-acting injectable
LY	Life year
Mg	Milligram
n	Number
N	Total number
NE	Not estimated
NDA	New drug application
NMA	Network meta-analysis
NR	Not reported
PANSS	Positive and Negative Syndrome Scale
QALY	Quality-adjusted life year
SD	Standard deviation
US	United States
VAF	Value Assessment Framework

Executive Summary

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 symptoms (delusions, hallucinations, disorganized speech, thought and behavior); negative symptoms (poor motivation, lack of pleasure and enjoyment, lack of speech, lack of social interaction), and cognitive (impaired executive function, attention, and memory).[1] The underlying cause of schizophrenia is unknown, but it is thought to be a neurodevelopmental brain disorder influenced by genetic and environmental factors.[2,3]

Researchers estimate that schizophrenia affects about 3.9 million people in the United States (US) and 24 million people worldwide.[4] Black Americans are diagnosed with schizophrenia at about twice the rate of White Americans and have worse outcomes.[5] The annual economic burden is estimated to be approximately $343 billion in the United States alone.[4] The majority of these costs are societal, not medical.

Most pharmacological therapies for patients with schizophrenia (typical and atypical antipsychotics) block the dopamine D2 receptor. In addition, the newer atypical antipsychotic medications also modulate serotonin levels.[6] Current guidelines recommend psychosocial interventions in addition to pharmacological 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.[7]

KarXT (Karuna Therapeutics) is an oral therapy taken twice daily. It combines one drug (xanomeline) that targets central nervous system (CNS) muscarinic receptors (M1 and M4 receptor agonists) with a second drug (trospium) that reduces the peripheral side effects of muscarinic receptor activation. Karuna Therapeutics submitted a new drug application (NDA) for KarXT on September 28, 2023.[8]

In meta-analyses of the three placebo-controlled randomized trials, KarXT significantly improved the total Positive and Negative Syndrome Scale (PANSS) score and the proportion of patients with at least a 30% improvement in the PANSS score over five weeks in patients hospitalized for acute worsening of their schizophrenia. There were no differences in weight gain or discontinuation rates between KarXT and placebo.

As there were no head-to-head trials with other antipsychotic medications, we performed network meta-analyses with acute trials of three commonly used second-generation antipsychotic medications (aripiprazole, olanzapine, risperidone). There were no significant differences between KarXT and the three antipsychotics in change from baseline PANSS score or the percentage of patients with at least a 30% improvement in PANSS score. The change in weight was significantly

less for KarXT compared with olanzapine and risperidone, but not with aripiprazole. Similarly, KarXT was significantly more likely to be discontinued in the acute setting compared with olanzapine and risperidone, but not with aripiprazole.

The major source of uncertainty is the lack of data on the efficacy of KarXT for longer than five weeks. In addition, KarXT has a new mechanism of action, which may lead to unanticipated adverse events over the long run. The initial data suggest that weight gain may not be an important side effect of KarXT, but this needs to be confirmed over time. Similarly, we have no data on the incidence of tardive dyskinesia and other long-term movement disorder side effects. The hope is that KarXT will represent a safer and effective therapy for long-term maintenance of patients living with schizophrenia, but we have no data yet on the prevention of relapse, return to work and school, or improvements in relationships with friends and family.

For the evidence ratings, we assumed that KarXT will be used for maintenance therapy in patients who respond to KarXT in the acute setting. The patients in the EMERGENT trials were not considered to have treatment resistant schizophrenia, so patients will have additional therapeutic options available.

KarXT significantly improved the total PANSS score and the proportion of patients with a response compared with placebo in the acute setting. KarXT side effects generally were those anticipated given the mechanisms of action of its two component medications. Importantly, we have no data on the efficacy and side effect profile of KarXT beyond five weeks. Given the lack of data on the long-term benefits and harms of KarXT, which has a novel mechanism of action and thus the possibility of unanticipated long term adverse events,[9] we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with no therapy.

Treatment with second-generation antipsychotics can result in serious long-term adverse effects including metabolic syndrome and tardive dyskinesia. A safer antipsychotic may be preferable to use initially even if it has lower efficacy; this is seen in practice where patients are frequently only treated with clozapine after they have not received benefit from other less effective antipsychotic medications. Our evidence ratings below take into account choices between KarXT and other antipsychotics where those same antipsychotics could be used as later line therapy if KarXT is insufficiently effective or causes significant side effects.

There are no trials directly comparing KarXT with aripiprazole. In our indirect comparisons in the acute setting, there were no significant differences between the two therapies in change in PANSS, PANSS response, weight gain, or discontinuation rates. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks in the hospital for the treatment of an acute exacerbation. Given no evidence for superiority in the acute setting and the lack of long-term data,

we find the evidence to be insufficient (I) to judge the comparative clinical effectiveness of KarXT compared with aripiprazole.

There are no trials directly comparing KarXT with olanzapine or risperidone. In our indirect comparisons in the acute setting, there were no significant differences between KarXT and these two therapies in change in PANSS, PANSS response, or discontinuation rates. KarXT was associated with significantly lower weight gain, which may translate into fewer cases of metabolic syndrome, diabetes, and their cardiovascular complications over the longer term. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks in the hospital for the treatment of an acute exacerbation. Given the lack of long-term data, we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with both olanzapine and risperidone.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
KarXT	No antipsychotic therapy	P/I
KarXT	Aripiprazole	I
KarXT	Olanzapine	P/I
KarXT	Risperidone	P/I

I: insufficient, P/I: promising but inconclusive

Making the highly favorable assumption that KarXT does not increase the risk of metabolic syndrome and associated consequences beyond that seen in the general population, our analyses suggest that treatment with KarXT results in less time with diabetes and in greater QALYs, greater life years, and greater evLYs. Under this assumption, the health benefit price benchmark (HBPB) range for KarXT is between $16,000 and $20,000 per year. The HBPB range for KarXT would be lower if KarXT is found to be associated with a risk of metabolic syndrome. In contrast, we assumed no reduction in the risk of tardive dyskinesia with KarXT compared with other second-generation antipsychotic medications. If KarXT does not cause tardive dyskinesia, its HBPB range would increase.

Policy Recommendations

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for people living with schizophrenia are introduced in a way that will help improve comprehensive care for people with schizophrenia and reduce health inequities, particularly for Black Americans.

To address these concerns:

Manufacturers:

- Set the price for KarXT in fair alignment with added benefits for patients.

Private payers:

- Improve outcomes by allowing for longer inpatient stays and by assuring that case managers are available to help people find appropriate housing and support following hospitalization.

- Expand the options for collaborative care to provide high quality care by facilitating telehealth and other methods for primary care clinicians and non-physician mental health providers to collaborate with psychiatrists and Board-certified psychiatric pharmacists.

Medicaid and Medicare:

- Ensure that patients being discharged from inpatient care have adequate case management and support for housing and care in the community.

State and Federal Policymakers:

- Create policies that require greater attention to the needs of people with schizophrenia who are in prison.

If KarXT receives FDA approval, payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Given the significant uncertainty that remains about the long-term effectiveness of KarXT, and its presumed high cost in relation to available generic treatment options, it is reasonable for payers to use limited prior authorization as a component of coverage.

1. 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 symptoms (delusions, hallucinations, disorganized speech, thought and behavior); negative symptoms (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.).[10] The underlying cause of schizophrenia is unknown, but it is thought to be a neurodevelopmental brain disorder influenced by genetic and environmental factors.[2,3] It typically presents in adolescence or young adulthood and continues through the individual's entire life. Males usually present earlier than females.[11]

Researchers estimate that schizophrenia affects about 3.9 million people in the United States (US) and 24 million people worldwide.[4] Black Americans are diagnosed with schizophrenia at about twice the rate of White Americans and have worse outcomes.[5] The annual economic burden is estimated to be approximately $343 billion in the United States alone.[4] 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 metabolic syndrome, agitation, movement disorders (tardive dyskinesia and Parkinsonism), sedation, a flat affect, and sexual side effects. Metabolic syndrome has various definitions but is felt to be a syndrome of insulin resistance that can include hypertension, diabetes, abnormal lipids, and increased fat in the liver; metabolic syndrome increases the risk of cardiovascular disease.[12] Many patients find the side effects to outweigh the benefits of treatment and decide to stop therapy, leading to recurrence of symptoms, hospitalizations, and poor long-term recovery.[10] Current guidelines recommend psychosocial interventions in addition to pharmacological 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.[7]

Most therapies for patients with schizophrenia (typical and atypical antipsychotics) block the dopamine D2 receptor. In addition, the newer atypical antipsychotic medications also modulate serotonin levels.[6]

KarXT (Karuna Therapeutics) is a novel combination therapy with one drug (xanomeline) that targets central nervous system (CNS) muscarinic receptors (M1 and M4 receptor agonists) and a

second drug (trospium) that reduces the peripheral side effects of muscarinic receptor activation. Karuna Therapeutics submitted a new drug application (NDA) for KarXT on September 28, 2023.[8]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Xanomeline-trospium (KarXT)	Selective M1/M4 muscarinic receptor agonist	Oral	125/30 mg twice daily

mg: milligram

2. Patient and Caregiver Perspectives

We conducted two focus groups (one with people living with schizophrenia and one with caregivers) and reviewed the literature to understand patient and caregiver perspectives. We received additional public comments from seven individuals living with schizophrenia. For people living with schizophrenia, the goal for treatment should be recovery. This is defined as being able to attend school and/or have a steady job, have relationships with friends and family members, and be a productive member of the community.

Although recovery is possible, people living with schizophrenia and their caregivers face multiple obstacles to treatment and care. The first barrier many people face is getting the correct diagnosis. Multiple hospital stays and misdiagnosis are common (ADHD, depression, anxiety, drug-induced psychosis, etc.). For many people the time from symptom onset to a diagnosis of schizophrenia is years.

Once a person is diagnosed, there are many barriers to high quality care. These include, but are not limited to, our fragmented healthcare system, a shortage of trained mental health providers who are willing to treat people with the disease, and stigma surrounding schizophrenia. Another major barrier, which occurs in over 50% of people with schizophrenia, is anosognosia. This is a lack of awareness and acceptance about their disease. People with anosognosia do not believe that they have schizophrenia. This leads to people not seeking or adhering to treatment and is a major source of frustration for caregivers.

Due to anosognosia, cognitive deficits, and other sequalae of disease, people with schizophrenia often have challenges advocating for themselves. Those without family members who can do so are at a risk of not receiving proper treatment.

Even with medication, individuals highlighted that their challenging symptoms are not all well managed. Many individuals mentioned that they needed to try many different drugs (more than 20 for one individual) over many years (a decade for another individual) before finding one that worked well enough. Individuals highlighted many burdensome side effects of even the drugs that worked best for them including restlessness, sedation, weight gain, lethargy, and suppressed emotions. These side effects also often interfered with the quality of their day-to-day life and limited their ability to participate in activities they enjoy. Because of this, people with schizophrenia often discontinue their medication, which may lead to suicide, incarceration, or involuntary hospitalization. When considering the best medications for a person with schizophrenia, it is always the one they are willing to take.

People living with schizophrenia told us that they live in fear of saying or doing the wrong thing which could lead to exclusion from school, loss of jobs, and loss of friends. They expressed how painful it is to live with the loneliness that comes with isolation from other people. They expressed how sometimes it is challenging to accomplish basic daily tasks such as bathing, getting dressed, and accomplishing simple household chores.

The impact of the disease on caregivers can be enormous. They described the challenges of finding adequate care and the toll of trying multiple treatments that did not work. Caregivers emphasized the unpredictable nature of schizophrenia and described the "revolving door" of watching their loved ones go through hospitalizations, jails and prisons, and periods of homelessness. The illness often disrupts all aspects of their lives. They sacrifice their own education, employment, finances, sleep, and time with family and friends to care for their loved one. They also must cope with the effects of stigma related to schizophrenia and described isolation as a result.

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

We heard great hope that KarXT's novel mechanism of action would result in fewer side effects and better treatment of negative and cognitive symptoms than current medications, leading to greater acceptance by patients over the long term. However, we also heard caution, as prior drugs have made similar claims and not lived up to their promise.

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."[13] 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.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on KarXT for the treatment of schizophrenia are detailed in Section D of the Supplement.

Scope of Review

We reviewed the clinical effectiveness of KarXT compared to three second-generation oral antipsychotics (aripiprazole, risperidone, and olanzapine) for the treatment of schizophrenia. The three comparators were chosen because they are three of the most frequently prescribed antipsychotic medications and to represent a range of side effect profiles and effectiveness. We searched for evidence on patient-important outcomes such as changes in symptom severity, weight gain, quality of life, improvement in functioning, extrapyramidal symptoms, discontinuation, and anticholinergic side effects.

We evaluated the comparative clinical effectiveness of the acute treatment of KarXT to placebo through direct evidence from randomized control trials (RCTs), and, where data was available, to aripiprazole, olanzapine, and risperidone through indirect comparisons by conducting Bayesian network meta-analyses (NMAs). Outcomes not included in the NMA are described qualitatively. Due to the lack of available long-term data for KarXT at the time of this review, we were unable to compare the long-term efficacy and safety of KarXT to the three comparators and thus we qualitatively described the long-term efficacy and safety data for the comparators. The full scope of the review is described in Supplement Section D1.

Evidence Base

Direct Evidence: KarXT versus Placebo in the Acute Setting

Our search identified 12 references related to one Phase II (EMERGENT-1) and two Phase III (EMERGENT-2 & 3) randomized, placebo controlled trials.[14-25] At the time of the posting of this review, EMERGENT-1 and -2 have been published in peer-reviewed journals, while data for EMERGENT-3 were abstracted from conference posters and presentations. We also received data from Karuna Therapeutics to inform our clinical trial diversity ratings and network meta-analyses.[26]

Across EMERGENT-1, -2, and -3, 690 adult patients with schizophrenia who were hospitalized and experiencing an acute exacerbation of symptoms were randomized to receive either KarXT 125/30 mg or placebo for five weeks. Patients were eligible for enrollment if they had a DSM-5 diagnosis of schizophrenia, were experiencing an acute exacerbation or relapse of symptoms requiring

hospitalization, a Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120, and a clinical global impression – severity (CGI-S) score of ≥4. They could not have been hospitalized for more than 30 days during the 90 days prior to screening, have any primary DSM-5 diagnosis other than schizophrenia, or have a history of treatment-resistant schizophrenia, defined as inadequate response to two prior courses of treatment. Baseline characteristics for the EMERGENT trials are provided in Table 3.1. They are notable for the high proportion of Black or African American patients enrolled in the trials compared to the trials included in this review that studied aripiprazole, risperidone, and olanzapine in the acute setting.

The primary outcome of the three studies was the change from baseline in the PANSS score compared to placebo at week five. Secondary outcomes include change from baseline in the PANSS positive score, PANSS negative score, CGI-S score, and weight change. Due to the similarities across the study designs, inclusion criteria, and outcomes of the EMERGENT trials, we conducted random-effects meta-analyses to describe the results. Details of the meta-analyses can be found in Supplement Section D2.

Table. 3.1. Overview of Key Studies for KarXT[15,19]

Study Name		EMERGENT-1		EMERGENT-2		EMERGENT-3	
Duration (weeks)		5		5		5	
Arms		KarXT	Placebo	KarXT	Placebo	KarXT	Placebo
N		90	92	126	126	125	131
Age, mean (SD)		43.4 (10.1)	41.6 (10.1)	45.6 (10.4)	46.2 (10.8)	43.6 (11.4)	42.6 (12.2)
Sex, n (%)	Male	72 (80.0)	68 (73.9)	95 (75.4)	95 (75.4)	87 (69.6)	104 (79.4)
	Female	18 (20.0)	24 (26.1)	31 (24.6)	31 (24.6)	38 (30.4)	27 (20.6)
Baseline PANSS, mean (SD)	Total	97.7 (9.7)	96.6 (8.3)	98.3 (8.9)	97.9 (9.7)	97.3 (8.9)	96.7 (8.9)
	Positive	26.4 (3.4)	26.3 (3.2)	26.8 (3.7)	26.7 (4.0)	26.9 (3.7)	26.4 (3.3)
	Negative	22.6 (4.4)	22.8 (4.6)	22.9 (4.0)	22.9 (3.8)	22.6 (3.2)	22.0 (3.7)
Baseline CGI-S, mean (SD)		5.0 (0.6)	4.9 (0.6)	5.1 (0.6)	5.1 (0.6)	5.1 (0.7)	5.0 (0.6)
Race, n (%)	Asian	2 (2.2)	2 (2.2)	2 (1.6)	1 (0.8)	1 (0.8)	0 (0)
	Black or African American	67 (74.4)	70 (76.1)	97 (77.0)	92 (73.0)	79 (63.2)	77 (58.8)
	White	20 (22.2)	17 (18.5)	26 (20.6)	31 (24.6)	45 (36.0)	53 (40.5)
	Other	1 (1.1)	3 (3.3)	1 (0.8)	2 (1.6)	0 (0)	0 (0)
Non-Hispanic / Non-Latino Ethnic Group, n (%)		71 (79)	79 (86)	NR	NR	NR	NR

CGI-S: clinical global impressions – severity, n: number, N: total number, NR: not reported, PANSS: positive and negative syndrome scale, SD: standard deviation

Indirect Evidence: KarXT versus Other Second-Generation Antipsychotics in the Acute Setting

As direct evidence of KarXT compared to aripiprazole, olanzapine, and risperidone was not available, we conducted indirect comparisons to these second-generation antipsychotics by performing NMAs that evaluated: PANSS response (defined as a ≥30% improvement in total score); PANSS total, positive, and negative scores; CGI-S score; weight gain; all-cause discontinuation; and discontinuation due to adverse events.

We identified 33 studies that met our inclusion criteria for our NMA network including three placebo-controlled trials for KarXT, four for aripiprazole, 13 for olanzapine, eight for risperidone, and five head-to-head trials.[15,19,20,27-55] All the trials in our network enrolled individuals with a diagnosis of schizophrenia who were hospitalized for an acute exacerbation of symptoms. The trials lasted between three and eight weeks.

The results for PANSS response, PANSS total score, weight gain, and all-cause discontinuation are described below. The results for PANSS positive and negative scores, CGI-S score, and discontinuation due to adverse events can be found in Supplement Section D2. Three sensitivity analyses were conducted: 1) including only studies that had patients hospitalized for the duration of the study, 2) excluding studies deemed as outliers on baseline PANSS, and 3) excluding trials published prior to 2009. These results can be found in Supplement Tables D2.15-20. Individual networks for each outcome can be found in Supplement Section D2. The study design and baseline characteristics of the included studies can be found in Supplement Section D3.

3.2. Results

Clinical Benefits: Acute Treatment

PANSS Total Score

The PANSS is a widely used measure to assess symptom severity for people living with schizophrenia. A complete definition can be found in Supplement Section A1. NMA input data for the PANSS outcomes can be found in Supplement Tables D2.3-6.

Direct Evidence

In a meta-analysis of the EMERGENT-1, -2, and -3 trials, the change from baseline in PANSS total for KarXT compared to placebo was -9.67 (95% CI: -12.25, -7.1). Individual trial results are reported in Supplement Table D2.3.

Indirect Evidence

All the antipsychotics had significant reductions in PANSS total score compared to placebo. KarXT had similar reductions compared to placebo as the other antipsychotic medications. No comparisons between the antipsychotics were statistically significant (see Table 3.2). Similar trends were observed for the PANSS positive and negative subscales (see Supplement Tables D2.11-12).

Table 3.2. Change from Baseline in PANSS Total Score

KarXT				
-1.4 (-7.64, 4.82)	**Aripiprazole**			
0.89 (-4.7, 6.48)	2.29 (-1.5, 6.12)	**Olanzapine**		
-1.73 (-7.63, 4.09)	-0.33 (-5.01, 4.31)	-2.63 (-6.29, 0.97)	**Risperidone**	
-9.78 (-14.83, -4.74)	**-8.38 (-12.04, -4.68)**	**-10.67 (-13.11, -8.24)**	**-8.05 (-10.99, -5.03)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0. Individual trial data can be found in Supplement Table D2.3.

PANSS Response

Direct Evidence

In a meta-analysis of the three trials, the PANSS response, defined as a ≥30% improvement on total PANSS score, was observed in more patients receiving KarXT than placebo (relative risk: 1.96; 95% CI: 1.46, 2.66). Individual trial results can be found in Supplement Table D2.6.

Indirect Evidence

All four antipsychotics had statistically significantly greater PANSS response rates compared to placebo. The comparisons between the four antipsychotic medications were not statistically significant (see Table 3.3).

Table 3.3. PANSS Response

KarXT				
1.48 (0.91, 2.47)	**Aripiprazole**			
1.22 (0.78, 1.98)	0.83 (0.55, 1.24)	**Olanzapine**		
1.03 (0.62, 1.8)	0.7 (0.44, 1.14)	0.85 (0.56, 1.29)	**Risperidone**	
2.03 (1.4, 3.06)	**1.37 (1.01, 1.88)**	**1.66 (1.28, 2.17)**	**1.96 (1.36, 2.83)**	**Placebo**

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Individual trial data can be found in Supplement Table D2.6.

NMA results for PANSS positive, PANSS negative, and CGI-S can be found in Supplement Tables D2.11 – 2.13. Additional data on the PANSS response thresholds (>20%, >40%, >50%), PANSS

Marder Factor scores for positive and negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression for KarXT can be found in Supplement Tables D3.8 and D3.9.

Harms: Acute Treatment

Weight Gain

Direct Evidence

In a meta-analysis of the three trials, weight change was -0.37 kg (95% CI: -1.19, 0.46) compared to placebo. In EMERGENT-1, there was slightly more weight gain in the KarXT arm (1.5 kg gained) compared to placebo (1.1 kg gained) at week five. However, there was less weight gain observed in those receiving KarXT than placebo in EMERGENT-2 (1.4 kg versus 2.5 kg) and EMERGENT-3 (1.4 kg versus 2 kg). Across the three trials, approximately 5.3% of patients receiving KarXT and 11.4% receiving placebo reported a weight gain ≥7%, which is a commonly reported threshold in acute trials of treatments for schizophrenia.[22] Given the variability across trials and the small number of patients, this may represent a chance finding.

Indirect Evidence

Indirect comparisons for weight change show KarXT had numerically less weight gain than placebo and aripiprazole, but the differences were not statistically significant. KarXT had significantly less weight gain compared to olanzapine and risperidone, although the credible intervals are wide (Table 3.4).

Table 3.4. Change from Baseline in Weight, kg

KarXT				
-0.64 (-1.88, 0.59)	**Aripiprazole**			
-2.86 (-3.97, -1.82)	**-2.23 (-3.12, -1.39)**	**Olanzapine**		
-2.06 (-3.29, -0.87)	**-1.43 (-2.51, -0.36)**	0.8 (-0.06, 1.7)	**Risperidone**	
-0.37 (-1.34, 0.58)	0.26 (-0.52, 1.04)	**2.49 (2.02, 3)**	**1.69 (0.96, 2.43)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0. Individual trial data can be found in Supplement Table D2.8.

Discontinuation

Direct Evidence

In a meta-analysis of the three trials, discontinuation rates were similar in patients receiving KarXT and those receiving placebo (relative risk 1.19; 95% CI: 0.93, 1.53). In EMERGENT-1, all-cause

discontinuation was comparable between KarXT (20%) and placebo (21%), with 15% of patients in each arm withdrawing their consent. Discontinuation rates were numerically higher in the KarXT arm compared to placebo for EMERGENT-2 (25% versus 21%) and EMERGENT-3 (37% versus 29%). Specific reasons for discontinuation can be found in Supplement Tables D3.10 and D3.11.

Indirect Evidence

KarXT had higher all-cause discontinuation than the three comparators and placebo, but the only comparisons that were statistically significant were with olanzapine and risperidone (see Table 3.5). Similar trends were observed with discontinuations due to adverse events, but none of the comparisons were statistically significant (see Supplement Table D2.14).

Table 3.5. All-cause Discontinuation

KarXT				
1.39 (1, 1.94)	**Aripiprazole**			
1.67 (1.21, 2.29)	1.2 (0.99, 1.44)	**Olanzapine**		
1.58 (1.14, 2.2)	1.14 (0.91, 1.42)	0.95 (0.78, 1.15)	**Risperidone**	
1.19 (0.89, 1.59)	0.86 (0.72, 1.01)	**0.71 (0.63, 0.81)**	**0.75 (0.65, 0.88)**	**Placebo**

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Individual trial data can be found in Supplement Table D2.9.

Other Patient-Important Harms

We sought information on additional patient important outcomes including quality of life, improvement in functioning, caregiver impact, brain fog, sedation & somnolence, anticholinergic side effects, gynecomastia (breast tissue enlargement), galactorrhea (milk leaking from nipples), and low libido (sex drive). These outcomes were not consistently reported across the trials (Supplement Table D3.6) and therefore we were unable to make any indirect comparisons. Extrapyramidal symptoms (unintentional muscle movements) and prolactin elevation were more commonly reported, and the comparisons are described below.

Extrapyramidal Symptoms

Overall, extrapyramidal symptoms (EPS) were reported by 3.2% of patients receiving KarXT compared to 0.9% receiving placebo in EMERGENT-1, -2, and -3. This category of symptoms included akathisia, dyskinesia, dystonia, and extrapyramidal disorder. Tardive dyskinesia was not reported by any patients. Treatment-related EPS was reported by 1.5% of patients in the KarXT group and 0.3% of patients in the placebo group.[23] EPS was measured differently across comparator trials. Available data includes extrapyramidal syndrome, extrapyramidal disorder, EPS-related adverse events, akathisia, parkinsonism, and dyskinesia. Consistent with previously

published systematic reviews of acute trials, higher rates of EPS were reported in patients receiving risperidone or aripiprazole compared to olanzapine.[56] See Supplement Table D3.7 for details.

Prolactin Elevation

Across the EMERGENT trials, changes in prolactin levels from baseline were similar with a small increase in the KarXT arms (0.75 ± 16.45 ng/L) and a small decrease in the placebo arms (-1.38 ± 16.49 ng/L).[22] Prolactin change is reported in six risperidone, six olanzapine, three aripiprazole, and one olanzapine versus aripiprazole trial. Among the comparator trials that report this outcome, increases in prolactin levels were seen most frequently in those receiving risperidone whereas a reduction in prolactin was observed in those receiving aripiprazole. The results for olanzapine were inconsistent across trials. (Supplement Table D3.15) This is consistent with previously published systematic reviews.[56]

Commonly Reported Adverse Events

Common treatment-related adverse events across the EMERGENT trials are reported in Table 3.6 below. These are in line with the expected side effects of muscarinic receptor activation (nausea, vomiting, and diarrhea) and the common side effects of trospium (constipation, headache, dizziness). Hypertension and tachycardia were more common in the KarXT arm, but it is uncertain if these will lead to long-term harm. Additional safety data can be found in Supplement Tables D3.12-D3.14.

Table 3.6. Pooled Treatment-Related Adverse Events in EMERGENT trials[22]

Adverse Event, %	KarXT (n= 340)	Placebo (n= 343)
Nausea	17.1%	3.2%
Constipation	15.0%	5.2%
Dyspepsia	12.1%	2.3%
Vomiting	10.9%	0.9%
Hypertension	5.9%	1.2%
Dry Mouth	5.0%	1.5%
Tachycardia	4.7%	2.0%

Clinical Benefits and Harms: Long-term Treatment

The long-term efficacy and safety of KarXT is currently being evaluated in a 53-week outpatient open-label extension study enrolling participants from EMERGENT-2 and -3 (EMERGENT-4), a 56-week outpatient open-label study enrolling participants with stable schizophrenia (EMERGENT-5), and a 52-week open label extension trial of ARISE (ARISE-2) evaluating KarXT as adjunctive therapy for people with inadequately controlled symptoms of schizophrenia. At the time of the posting of

this report, data from these three trials were not available. Details of these trials can be found in Supplement Table D4.1.

The long-term efficacy and safety of aripiprazole, olanzapine, and risperidone were assessed using previously published systematic reviews and their FDA prescribing information.

In their respective FDA prescribing information packets, oral aripiprazole, olanzapine, and risperidone have black box warnings of increased mortality in elderly patients who have dementia-related psychosis. Aripiprazole has an additional black box warning of increased suicidal thoughts and behaviors in those taking antidepressants. Warnings about neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension, seizures, leukopenia, neutropenia, and agranulocytosis are highlighted for all three antipsychotics.[57-59]

Schneider-Thoma et al. 2022[60] evaluated the efficacy and tolerability of antipsychotics for the maintenance treatment of schizophrenia in individuals with stable symptoms. No clear differences in relapse rates of rehospitalization, remission, quality of life, or improvement in functioning among aripiprazole, olanzapine, and risperidone or any of the other antipsychotics were observed. Olanzapine had significantly greater weight gain compared to placebo (mean difference: 2.13; 95% CI: 1.47, 2.79) whereas aripiprazole had less weight gain than placebo (mean difference: -0.39; 95% CI: -1.32, 0.54), although this was not statistically significant. Few events of tardive dyskinesia were reported resulting in wide credible intervals and comparisons across antipsychotics could not be made reliably.

Leucht et al. 2023[61] evaluated the long-term efficacy of first- and second-generation antipsychotics in adults living with schizophrenia or related disorders who were acutely ill and followed for at least six months. The primary focus of the systematic review and NMA was to assess overall symptom change through the PANSS, Brief Psychiatric Rating Scale (BPRS), or other relevant scales. A greater reduction in symptoms, less all-cause discontinuation, and greater weight gain was observed in olanzapine compared to aripiprazole. Aripiprazole and risperidone had lower prolactin levels than olanzapine. Compared to olanzapine, aripiprazole had a similar risk for akathisia whereas risperidone had a higher risk.

Further detail on both analyses can be found in Supplement Section D5.

Subgroup Analyses and Heterogeneity

We sought evidence on subgroups effects for race/ethnicity, sex, and age. For KarXT, EMERGENT-1 reported there was no difference in incidence of adverse events by age (<44 versus ≥44 years old) or in weight gain by sex or age (Supplement Table D3.16 and D3.17).[20] Subgroup data were not available for EMERGENT-2 or -3. Few comparator trials reported subgroup analyses. None of the head-to-head, aripiprazole, or risperidone trials reported efficacy outcomes by race/ethnicity, sex,

or age. Two trials for olanzapine reported changes in PANSS total score by age, gender, and race and found no significant differences. Four trials reported prolactin level changes by sex. Due to the limited number of trials reporting subgroup data, no efficacy comparisons can be made across antipsychotics. Further details on these subgroup analyses can be found in Supplement Section D6.

Evaluation of Clinical Trial Diversity

Table 3.8. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older adults)
EMERGENT-1	Fair	Fair	NE
EMERGENT-2	Fair	Fair	NE
EMERGENT-3	Fair	Fair	NE

NE: Not Estimated

We evaluated the demographic diversity of the clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[62] Table 3.8 presents clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) on the key trials in our report. Details on each of the demographic categories are provided below. Additional details on the CDR tool, including the scoring and rating of each trial, are provided in Supplement D1 and ICER's updated Value Assessment Framework (VAF).

Race and Ethnicity: There is a higher prevalence of diagnosis of schizophrenia in Black or African American adults than other racial/ethnic groups. The EMERGENT trials enrolled predominately Black or African American adults living with schizophrenia (61% - 75%), followed by White adults (20% - 38%), and Asian adults (0.4% - 2.2%). The percentage of Hispanic or Latino participants ranged from 10% - 18% in the trials, reflecting good representation of this ethnic group. Although there was good representation of Black or African American adults, the EMERGENT trials enrolled very few Asian adults leading to a rating of "fair" for racial/ethnic diversity.

Sex: Lifetime prevalence of schizophrenia is slightly higher among men (2.0%) compared to women (1.7%).[63] Approximately 75% of the enrolled patients in EMERGENT-1, -2 and -3 were male leading to an underrepresentation of women across the three trials.

Age: The prevalence of schizophrenia in older adults was 1.4% and the KarXT trials did not enroll participants over the age of 65 years.[64] Thus, we were not able to evaluate the representation of older adults.

Uncertainty and Controversies

The major source of uncertainty is the lack of data on patients taking KarXT for longer than five weeks. This uncertainty concerns both efficacy and harms. KarXT has a new mechanism of action,

which may lead to unanticipated adverse events over the long run. The initial data suggest that weight gain may not be an important side effect of KarXT, but this needs to be confirmed over time. Similarly, we have no data on the incidence of tardive dyskinesia and other long-term movement disorder side effects. Finally, it is unclear whether the GI (gastrointestinal) side effects (nausea, constipation) will impact long term discontinuations or non-adherence with KarXT. The hope is that KarXT will represent a safer and effective therapy for long-term maintenance of patients living with schizophrenia, but we have no data on the prevention of relapse, return to work and school, or improvements in relationships with friends and family.

There are concerns that trials of medications for schizophrenia conducted more than 15 years ago had larger impacts on symptoms than trials today, perhaps reflecting differences over time in the patients admitted to the hospital for acute worsening of their symptoms. We conducted sensitivity analyses eliminating trials conducted more than 15 years ago, which did not change our findings. However, this issue remains an area of uncertainty and controversy.

Another source of uncertainty is the lack of a long-acting injectable form of KarXT. We did not compare oral KarXT to long-acting injectables (LAIs), as this would not be an appropriate comparison, but it will be an important clinical question in the maintenance phase.

There is hope that KarXT may improve the cognitive and negative symptoms better than currently available antipsychotic medications as xanomeline was initially developed to improve cognitive function in patients with dementia. However, these symptoms can only be fairly evaluated in the maintenance phase of therapy. We heard from experts that controlling the positive symptoms in a patient who is acutely psychotic will confound any assessment of changes in cognitive function and negative symptoms. When patients are actively hallucinating, their cognitive function will be impaired and they will often have difficulties interacting with others. When hallucinations are controlled, cognitive function and negative symptoms may improve. However, this improvement is primarily due to the impact on positive symptoms rather than direct improvements in cognitive function or a reduction in negative symptoms.

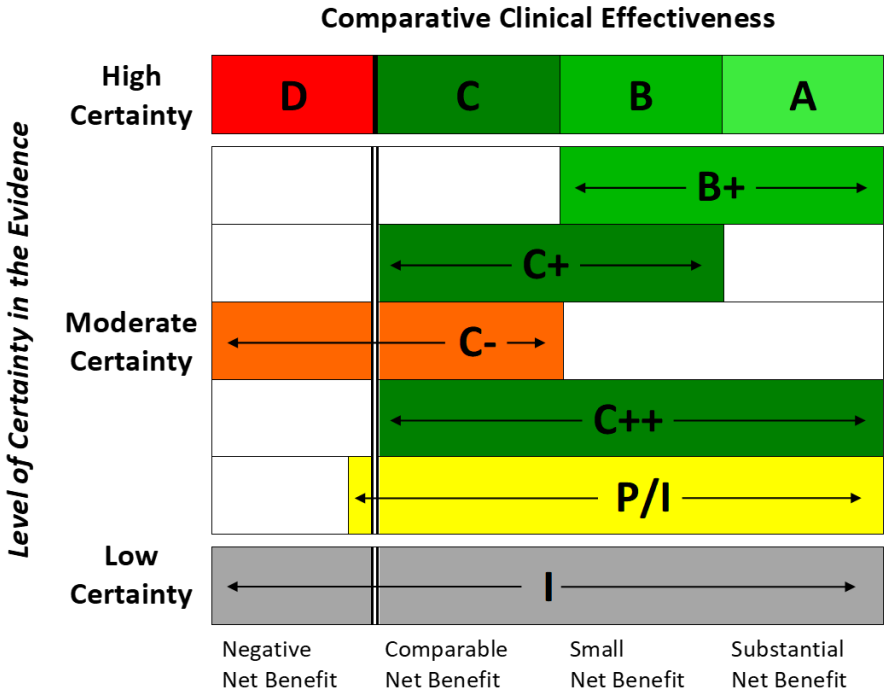
Some experts expressed eagerness to use KarXT either as the first therapy in patients with a new diagnosis (due to the hope of better tolerability and long-term adherence) or as an add on to patients with effective control with a current medication, but bothersome side effects, in the hope that the dose of the effective drug could be lowered to reduce the side effects while maintaining good control of symptoms. Unfortunately, there are no data currently available to support those potential uses of KarXT.

Finally, there are concerns about the generalizability of the findings of the randomized trials of KarXT to the population of people living with schizophrenia. Studies suggest that as many as 80% of patients with schizophrenia would be excluded from current randomized trial designs.[65]

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

If approved, KarXT will not be used solely in the inpatient setting. For the evidence ratings, we assumed that KarXT will be used for maintenance therapy in patients who respond well to KarXT in the acute setting as is being studied in the EMERGENT-4 and EMERGENT-5 trials. The patients in the EMERGENT trials were not considered to have treatment resistant schizophrenia, so patients will have additional therapeutic options available.

In the three trials of KarXT in the acute setting, the new therapy significantly improved the total PANSS score and the proportion of patients with a response compared with placebo. The discontinuation rate in the KarXT group was similar to that of the placebo group, although there were more side effects in the KarXT group; KarXT side effects generally were those anticipated given the mechanisms of action of its two component medications. Importantly, we have no data on the efficacy and side effect profile of KarXT beyond five weeks. Given the lack of data on the long term benefits and harms of KarXT, which has a novel mechanism of action and thus the possibility of unanticipated long term adverse events,[9] we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with no therapy.

Treatment with second-generation antipsychotics can result in serious long-term adverse effects including metabolic syndrome and tardive dyskinesia. A safer antipsychotic may be preferable to use initially even if it has lower efficacy; this is seen in practice where patients are frequently only treated with clozapine after they have not received benefit from other less effective antipsychotic medications. Our evidence ratings below take into account choices between KarXT and other antipsychotics where those same antipsychotics could be used as later line therapy if KarXT is insufficiently effective or causes significant side effects.

There are no trials directly comparing KarXT with aripiprazole. In our indirect comparisons in the acute setting, there were no significant differences between the two therapies in change in PANSS, PANSS response, weight gain, or discontinuation rates. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks in the hospital for the treatment of an acute exacerbation. Given no evidence for superiority in the acute setting and the lack of long term data, we find the evidence to be insufficient (I) to judge the comparative clinical effectiveness of KarXT compared with aripiprazole.

There are no trials directly comparing KarXT with olanzapine. In our indirect comparisons in the acute setting, there were no significant differences between the two therapies in change in PANSS, PANSS response, or discontinuation rates. KarXT was associated with significantly lower weight gain than olanzapine and no weight gain compared with placebo, which may translate into fewer cases of metabolic syndrome, diabetes, and their cardiovascular complications over the longer term. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks in the hospital for the treatment of an acute exacerbation. Given the lack of long term data, we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with olanzapine.

There are no trials directly comparing KarXT with risperidone. In our indirect comparisons in the acute setting, there were no significant differences between the two therapies in change in PANSS, PANSS response, or discontinuation rates. KarXT was associated with significantly lower weight gain than risperidone and no weight gain compared with placebo, which may translate into fewer cases of metabolic syndrome, diabetes, and their cardiovascular complications over the longer term. However, we have no data on the efficacy and side effect profile of KarXT beyond five weeks

in the hospital for the treatment of an acute exacerbation. Given the lack of long term data, we rate the net health benefit of KarXT as promising, but inconclusive (P/I) compared with risperidone.

Table 3.9. Evidence Ratings

Treatment	Comparator	Evidence Rating
KarXT	No antipsychotic therapy	P/I
KarXT	Aripiprazole	I
KarXT	Olanzapine	P/I
KarXT	Risperidone	P/I

I: insufficient, P/I: promising but inconclusive

New England CEPAC Votes

Table 3.5. New England CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Is the currently available evidence adequate to demonstrate that the net health benefit of KarXT is superior to that of aripiprazole?	2	10
Is the currently available evidence adequate to demonstrate that the net health benefit of KarXT is superior to that of olanzapine and/or risperidone?	7	5

A majority of the panel voted that the currently available evidence is not adequate to demonstrate the net health benefit of KarXT is superior to that of aripiprazole, while a slight majority of the panel voted that the currently available evidence is adequate to demonstrate that the net health benefit of KarXT is superior to that of olanzapine and/or risperidone. While deliberating, panel members discussed the lack of currently available long-term data, acknowledging that emerging data is forthcoming. Panel members emphasized the need for investment into research, highlighting that patients benefit from a variety of treatment options for schizophrenia.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

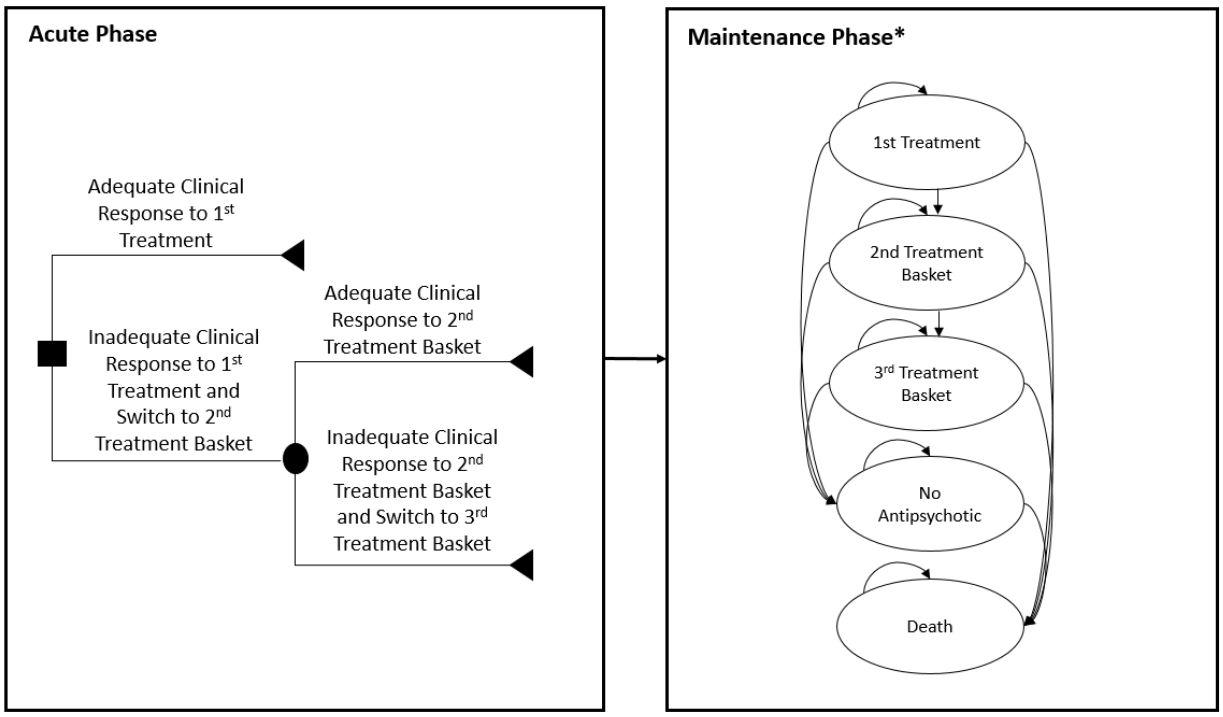
The primary aim of this analysis was to estimate the lifetime cost-effectiveness from the health care sector perspective of KarXT relative to current standard of care that includes second-generation antipsychotics. To achieve this, a two-phase decision analytic model with an upfront decision tree representing an acute psychosis event and a lifetime Markov model representing the maintenance period was developed. Costs and outcomes were discounted at 3% per year. Productivity impacts, caregiver impacts, and criminal justice impacts were considered in a scenario analysis using a modified societal perspective.

The modeled population included adults with schizophrenia who were not considered to have treatment-resistant schizophrenia at the model start. We developed a *de novo* decision analytic model, informed by key clinical trials and prior relevant economic models.[66-68] In the intervention arm of the model, adults with schizophrenia started on KarXT. In the comparator arm of the model, adults with schizophrenia started on aripiprazole because it was believed to have the fewest side effects among currently approved second-generation antipsychotics. If the initially modeled treatment (i.e., KarXT in the intervention arm or aripiprazole in the comparator arm) was discontinued, the modeled adult with schizophrenia switched to a second treatment market basket that was 51% risperidone and 49% olanzapine based on market share data.[69] Risperidone and olanzapine were selected to represent the second treatment market basket as they are widely used, represent a range of effectiveness and side effect profiles for second-generation antipsychotics, and allowed for the second modeled treatment to be consistent between the intervention and comparator arms. If the second modeled treatment (i.e., market basket of risperidone and olanzapine for both the intervention and comparator arm) was discontinued, the modeled adult with schizophrenia switched to a third treatment market basket that was 36% risperidone, 34% olanzapine, and 30% clozapine. Clozapine was included in the third treatment market basket in alignment with evidence suggesting treatment-resistant schizophrenia occurs in approximately 30% of individuals diagnosed with schizophrenia and is an appropriate treatment for those individuals if they discontinued at least two prior antipsychotics.[1] All adults with schizophrenia stayed on treatment with an antipsychotic over their lifetime, except for 18.2% of the alive population who stopped treatment 20 years after the model start in alignment with evidence suggesting that 81.8% of adults with schizophrenia are still on treatment twenty years after starting.[70]

The model consisted of two phases, including an acute phase modeled by an upfront decision tree and a subsequent maintenance phase represented by a Markov model. Figure 4.1 depicts the model schematic. The upfront decision tree modeled the cohort of adults with schizophrenia

through an acute psychosis event and assessed for adequate clinical response (defined by a 30% improvement in Positive and Negative Syndrome Scale [PANSS]) to the treatment(s) administered during the acute phase. From the acute phase of the model, members of the modeled cohort transitioned to the maintenance phase of the model on the treatment that they were on at the end of the acute phase. The maintenance phase of the model was a lifetime Markov model that modeled a cohort of adults with schizophrenia following the acute psychosis event and throughout the maintenance period while recording relapses, treatment-emergent adverse events, treatment switching, treatment stopping, and death over cycles of three months long. All members of the modeled cohort started in the acute phase of the model experiencing an inpatient acute psychosis event in alignment with the clinical evidence for KarXT. Adults with schizophrenia remained in the model until they died due to either disease-specific (i.e., schizophrenia, diabetes, or cardiovascular disease) or all-cause mortality.

Figure 4.1. Model Structure



*For each of the alive health states depicted in the schematic, there were sub-health states for no metabolic syndrome, metabolic syndrome, diabetes, cardiovascular disease, and diabetes and cardiovascular disease. Metabolic syndrome, diabetes, and cardiovascular disease were considered irreversible. Separately, relapses were recorded as an event within each of the health states.

Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, total costs, and years with diabetes over a lifetime time horizon. Additional information on the methods can be found in Section E of the Supplemental Materials.

Changes to the economic evaluation between the Draft Report and the revised Evidence Report included adjustments to the modified societal perspective scenario analysis. In this revised Evidence Report, indirect costs associated with diabetes and cardiovascular disease were also included in the modified societal perspective scenario analysis. This update resulted in changes to the incremental cost-effectiveness ratios from the modified societal perspective.

4.2. Key Model Assumptions and Inputs

Our model includes several assumptions stated in Table 4.1. Additional model assumptions can be found in Section E of the Supplemental Materials.

Table 4.1. Key Model Assumptions

Assumption	Rationale
While receiving KarXT, members of the modeled cohort were not at an increased risk of developing metabolic syndrome beyond that of the general population.	There was no significant difference in weight gained between patients treated with KarXT and patients treated with placebo reported in the KarXT clinical trials. Without evidence on the risk of metabolic syndrome for adults with schizophrenia who are not on an antipsychotic, we assumed the same risk of metabolic syndrome as the general population.
The starting population did not have metabolic syndrome, diabetes, or cardiovascular disease.	The entire population treated was eligible for the potential benefit of KarXT not increasing the risk of metabolic syndrome or its associated long-term consequences.
In the acute phase, members of the modeled cohort discontinued a treatment and switched to the subsequent treatment in the sequence due to inadequate clinical response.	While experiencing an inpatient acute psychosis event, adults with schizophrenia are likely continuously treated until they respond adequately, and thus we assumed that treatment response is the primary trigger of treatment switching in the acute phase. This is a simplifying structural assumption in the acute phase only and is aligned with other published economic models.[68] All individuals exited the acute phase on a treatment.
In the maintenance phase, members of the modeled cohort discontinued a treatment and switched to the subsequent treatment in the sequence due to inefficacy, side effects, or their own decision.	While receiving treatment in the maintenance phase, members of the modeled cohort could discontinue a treatment if it was not working adequately, adverse events occurred, or for some other personal reason. Lacking these reasons, members of the modeled cohort continued their current treatment. Discontinuation was based on treatment-specific discontinuation probabilities and were not directly linked to certain events recorded in the model.
Members of the modeled cohort stayed on treatment over their lifetime, except for a small proportion of the population that stopped antipsychotic treatment at twenty years.	Schizophrenia requires lifelong treatment. Based on evidence from a study with 20-year follow up, only 18.2% of adults with schizophrenia are not using antipsychotics twenty years after treatment start.[70] Therefore, we modeled that 18.2% of the surviving population would stop antipsychotic treatment

	(irrespective of the treatment they were on) at 20 years after the start of the model, and the remaining modeled population would stay on treatment over the lifetime time horizon.

Key model inputs are presented in Table 4.2, with an exhaustive list of model inputs and their respective sources available in Section E of the Supplemental Materials. Treatment effectiveness for KarXT was estimated by way of an effect on achieving adequate clinical response in the acute phase, and on experiencing relapses, developing metabolic syndrome (and associated long-term consequences), and discontinuation in the maintenance phase.

Table 4.2. Key Treatment-Specific Model Inputs

Parameter	Input	Source
Adequate Clinical Response in Acute Phase		
KarXT	53%	ICER's NMA on acute phase probability of 30% improvement in PANSS
Aripiprazole	36%	
Olanzapine*	43%	
Risperidone*	51%	
Three-Month Probability of Relapse in Maintenance Phase		
KarXT	10.5%	Assumed the mid-point between the range of the other second-generation anti-psychotics
Aripiprazole	12.7%	Davies et al., 2008[67]
Olanzapine	8.2%	
Risperidone	12.7%	
Clozapine	8.9%	
No Antipsychotic	41.0%	Davies et al. 2008[67] & Schneider-Thoma et al., 2022[60]
Three-Month Probability of Developing Metabolic Syndrome in Maintenance Phase		
KarXT	0.7%	Assumed the same as no antipsychotic use due to findings from ICER's NMA suggesting no significant difference in weight gained between KarXT and placebo
Aripiprazole	3.8%	Park et al., 2014[66], Davies et al., 2008[67]
Olanzapine	9.1%	
Risperidone	5.5%	
Clozapine	11.2%	
No Antipsychotic	0.7%	Li et al., 2022[71]

Parameter	Input	Source
Three-Month Probability of Discontinuation in Maintenance Phase		
KarXT	5.9%	The relative risk of KarXT to olanzapine from ICER's NMA on acute phase discontinuation, hospital sensitivity analysis was applied to the olanzapine three-month probability of discontinuation
Aripiprazole	5.4%	Fisher et al., 2014[72]
Olanzapine*	4.0%	
Risperidone*	4.0%	
Net Drug Price Per Year		
KarXT	$20,000	Placeholder[69]
Aripiprazole	$40	REDBOOK
Olanzapine	$150	
Risperidone	$62	
Clozapine	$1,336	

NMA: network meta-analysis, PANSS: Positive and Negative Syndrome Scale

*Inputs are for the second treatment market basket. Patients stay on treatment over their lifetime and thus they do not discontinue the third treatment basket unless they are part of the 18.2% of the modeled population that stops treatment twenty years after the model start.

4.3. Results

Base-Case Results

Treatment with KarXT results in less time with diabetes and greater QALYs, greater life years, and greater evLYs. Using a placeholder annual cost of $20,000 per year, the intervention costs (i.e., costs to acquire KarXT) are greater, but there are fewer non-intervention costs (e.g., costs associated with relapses, diabetes, cardiovascular disease, etc.) resulting from fewer relapses and treatment-emergent adverse events. Table 4.3 reports the base-case model outcomes for each arm of the model.

Table 4.3. Results for the Base-Case, Lifetime Time Horizon

Treatment	KarXT Cost	Total Cost	Years With Diabetes	QALYs	Life Years	evLYs
KarXT*	$42,000	$350,000	4.00	10.39	16.25	10.41
Aripiprazole	$0	$326,000	4.40	10.25	16.18	10.25

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Assuming a KarXT placeholder price of $20,000 per year.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Year Without Diabetes
KarXT*	$163,000	$347,000	$146,000	$60,000

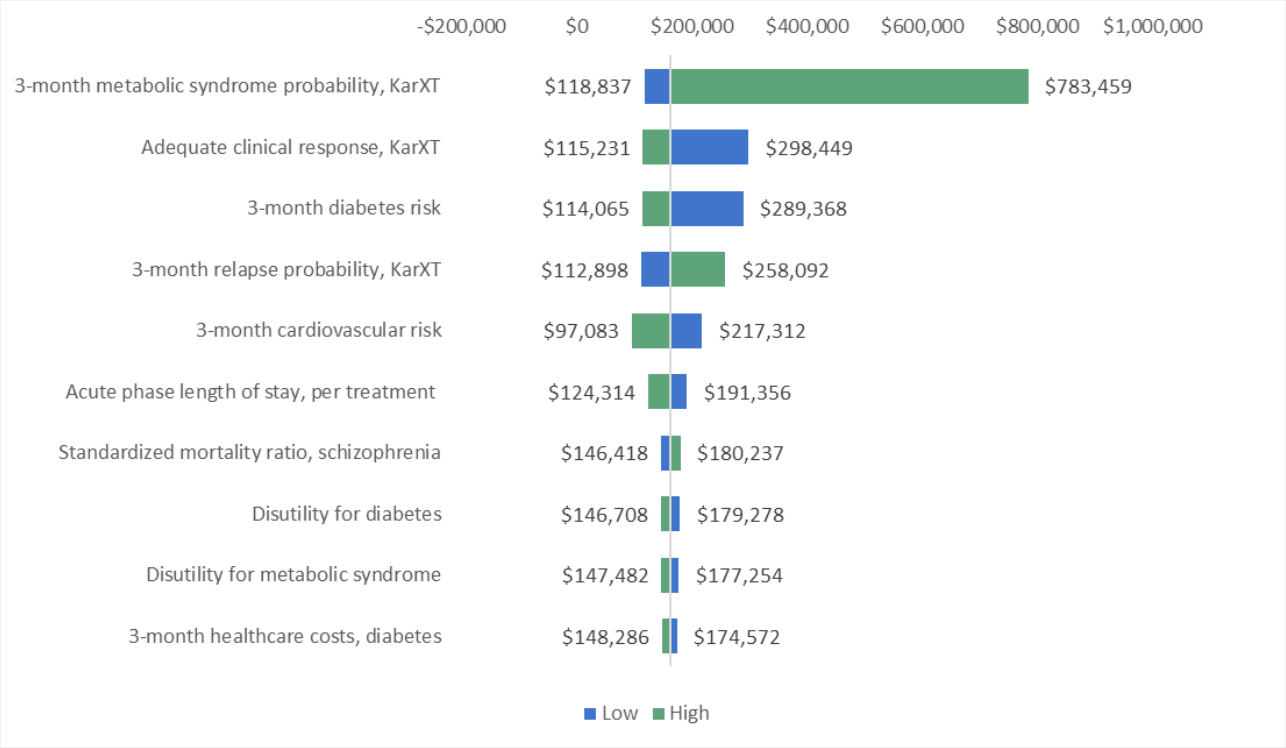
evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

Sensitivity Analyses

Figure 4.2 reports the inputs with the most influence on the incremental cost-effectiveness ratio. The parameter with the greatest influence on the cost-effectiveness of KarXT was the probability of developing metabolic syndrome while on KarXT.

Figure 4.2. Tornado Diagram



*Assuming a KarXT placeholder price of $20,000 per year.

Tables 4.5 and 4.6 present the probability of KarXT being cost-effective at common thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively. At the assumed placeholder price for KarXT, 40% of the 1,000 iterations within the probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios beneath $150,000 per evLY gained.

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
KarXT*	5%	18%	34%	51%

evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

Table 4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
KarXT*	6%	23%	40%	55%

evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

Additional sensitivity analysis result tables can be found in the Supplement.

Scenario Analyses

Table 4.7 reports the incremental cost per evLY gained for the base-case and three scenario analyses assuming a placeholder price of $20,000 per year for KarXT. Cost-effectiveness stayed nearly the same from the modified societal perspective due to the limited differential effects of KarXT compared with other antipsychotic medications on societal-level factors. Cost-effectiveness improved in the optimistic scenario that assumed that while an adult with schizophrenia was treated with KarXT, they were at a 0% risk of developing tardive dyskinesia. Cost-effectiveness worsened in the scenario that assumed KarXT was associated with a risk of developing metabolic syndrome (i.e., half the risk of metabolic syndrome for aripiprazole).

Table 4.7. Scenario Analysis Results

Treatment	Base-Case Results ($/evLY)	Modified Societal Perspective ($/evLY)	No Risk of Tardive Dyskinesia When on KarXT ($/evLY)	Small Risk of Metabolic Syndrome When on KarXT ($/evLY)
KarXT*	$146,000	$142,000	$67,000	$253,000

evLY: equal-value life year

*Assuming a KarXT placeholder price of $20,000 per year.

Additional scenario analysis findings can be found in Section E of the Supplemental Materials.

Threshold Analyses

Tables 4.8 and 4.9 report the threshold prices at $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively.

Table 4.8. QALY-Based Threshold Analysis Results

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
KarXT	$12,000	$15,600	$19,100	$22,600

QALY: quality-adjusted life year

Table 4.9. evLY-Based Threshold Analysis Results

	Unit Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
KarXT	$12,400	$16,400	$20,300	$24,300

evLY: equal-value life year

Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results and performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the manufacturer for external verification around the time of publishing the draft report. Finally, we compared results to other cost-effectiveness models in this therapy area.

Uncertainty and Controversies

While appraising the methods and interpreting the findings, the objective of the analysis should be remembered. The objective of this portion of the assessment is to estimate the cost-effectiveness of KarXT. Our objective is not to estimate the most cost-effective sequence of treatments for the management of schizophrenia, but rather isolate the costs and consequences specific to KarXT. In order to do this, it was important to have a lifetime time horizon to capture the potential long-term benefits of KarXT of reducing metabolic syndrome and its lifetime consequences. This lifetime time horizon required treatment switches to be modeled, but to achieve our intended objective, the treatment switches were the same across both arms of the economic model. Relatedly, our objective is not to model the reality of an individual patient's life. We appreciate each individual's treatment sequence and treatment experience differs and there are important patient-level

considerations that should be considered in provider-patient decision making. However, the objective of this portion of the assessment is to determine the cost-effectiveness and health benefit price benchmark for a population, based on average effects, not individual effects or experiences.

Further, the findings from this portion of the assessment should not be used to estimate the overall burden of schizophrenia and should not be interpreted as a comprehensive societal perspective. For example, the cost-effectiveness findings for KarXT did not differ dramatically between the health care system perspective and the modified societal perspective based on the available data and model structure. This is not to suggest that there isn't an enormous societal impact of schizophrenia. Rather this suggests that, as modeled, KarXT doesn't dramatically influence the net societal impacts that were modeled in the modified societal perspective.

There is no evidence for KarXT in the maintenance phase, although if KarXT is approved, it will likely be used in the maintenance phase and the maintenance phase could represent the vast majority of the time that a patient is on treatment. Therefore, we had to make numerous assumptions around the effectiveness of KarXT in the maintenance phase based on the short-term acute phase data that are available for KarXT and evidence for other second-generation antipsychotics in the maintenance phase. Our modeled inputs for KarXT in the maintenance phase were relatively similar to the other second-generation antipsychotics except for the assumed effect of KarXT on developing metabolic syndrome. In the maintenance phase, we assumed KarXT would not be associated with any increased risk of developing metabolic syndrome and associated consequences outside the risk experienced by the general population. This assumption is a key driver of the cost-effectiveness of KarXT and thus it has been varied extensively in sensitivity and scenario analyses.

4.4 Summary and Comment

Making the highly favorable assumption that KarXT does not increase the risk of metabolic syndrome beyond that seen in the general population, our analyses suggest that treatment with KarXT results in less time with diabetes and in greater QALYs, greater life years, and greater evLYs. Under this assumption, at a placeholder price of $20,000 per year, the incremental cost-effectiveness ratios are around the upper bounds of commonly used thresholds. The parameter with the greatest influence on the cost-effectiveness of KarXT was the probability of developing metabolic syndrome in the maintenance phase while on KarXT. KarXT would be less cost-effective if it is found to be associated with a risk of metabolic syndrome. In contrast, we assumed no reduction in the risk of tardive dyskinesia with KarXT compared with other second-generation antipsychotic medications. If KarXT does not cause tardive dyskinesia, its cost-effectiveness would become more favorable.

5. Contextual Considerations and Potential Other Benefits

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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	People living with schizophrenia are at higher risk for suicide compared to the general population (relative risk: 9.76; 95%CI: 7.6-12.55).[73] **Those with schizophrenia have a life expectancy that is 15 years shorter than the general population in the US.[74]** Cardiovascular health and side effects from current medications are a key contributor to this premature death.[73]
Magnitude of the lifetime impact on individual patients of the condition being treated	People living with schizophrenia have reduced academic achievement, significant reductions in long term employment, and often have disruptions in relationships with friends and family.[13]

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	It is unclear if KarXT can make a significant impact on patients' ability to achieve major life goals compared with currently available therapies.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	It is unclear if KarXT can make a significant impact on caregivers quality of life or their ability to achieve major life goals compared with currently available therapies.
Patients' ability to manage and sustain treatment given the complexity of regimen	KarXT offers no significant advantages compared with existing oral therapies and may be less efficacious than existing long acting injectable medications.
Society's goal of reducing health inequities	Schizophrenia appears to disproportionately affects racial minority populations, and significant disparities exist in prevalence, disease control, and rates of complications. ICER calculated the Health Improvement Distribution Index, looking at the relative proportion of any health gains from treatment of schizophrenia for the following groups with a higher prevalence of schizophrenia than the general US population (see Supplement A1): • Black / African American = 2.3 However, there is some uncertainty about whether the higher rates of diagnosis of schizophrenia in Black people in the US represents

Potential Other Benefit or Disadvantage	Relevant Information
	true higher prevalence or a tendency for psychosis to be attributed to affective psychotic disorders (such as bipolar mania) in a White population and to schizophrenia in a Black population.
Other	KarXT is a drug with a new mechanism of action that may allow treatment of people who did not benefit from and/or tolerate existing treatments.

New England CEPAC Votes

At the public meeting, the New England CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for Schizophrenia, on the basis of the following contextual considerations:

Table 5.3. New England CEPAC Votes on Contextual Considerations Questions

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	0	0	2	3	7
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	0	1	11

A majority of the panel agreed that treatments for schizophrenia should be given high priority when considering the acuity of need for treatment based on short-term risk of death or progression to permanent disability. Seven panel members voted for very high priority, three panel members voted for high priority, and two panel members voted for average priority. The panel heard testimony from clinical and patient experts highlighting the importance of intervening in the early stages of psychosis and schizophrenia, as it determines long-term trajectory. Considering how schizophrenia affects various areas of life, eleven panel members voted that given the magnitude of the lifetime impact on individual patients, very high priority should be given to any treatment. One panel member voted for high priority.

What are the relative effects of KarXT versus clinically-guided management using second generation antipsychotics on the following outcomes that inform judgment of the overall long-term value for money of KarXT?

5.4. New England CEPAC Votes on Potential Other Benefits or Disadvantages Questions

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	3	7	2
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	2	7	3
Patients' ability to manage and sustain treatment given the complexity of regimen	0	4	7	1	0
Society's goal of reducing health inequities	1	0	2	9	0

Seven panel members voted that KarXT would have a minor positive effect on patients' ability to achieve major life goals related to education, work, or family life, while two panel members voted for major positive effect and three panel members voted no difference. The panel expressed their concern with the lack of data in the evidence but agreed that there is a need for some form of treatment as schizophrenia highly impacts people's lives.

A majority of the panel voted that KarXT versus clinically-guided management using second generation antipsychotics has a minor positive effect on caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life. The panel heard from patient and clinical experts about the social, emotional, and financial impact of this disease on caregivers, such as wage loss and the full-time commitment needed for care. The panel had seven votes for minor positive effect, three for major positive effect, and two for no difference.

A majority of the panel voted that KarXT has no difference on patients' ability to manage and sustain treatment given the complexity of regimen. The panel had seven votes for no difference, four votes for minor negative effect, and one for minor positive effect. The panel discussed how taking medicine twice a day may be challenging but not entirely a barrier to patients' ability to complete treatment.

A large majority of the panel voted that KarXT would have a minor positive effect on society's goal of reducing health inequities, while two voted for no difference and one voted for major negative effect. The panel discussed how schizophrenia exhibits a higher prevalence among Black Americans and other minority groups, such as immigrant populations. As schizophrenia disproportionately affects marginalized populations, the panel expressed how treating schizophrenia in its early stages may reduce health inequities to those highly impacted.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with KarXT are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for KarXT

Annual Prices Using…	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
QALYs Gained	$16,000	$19,000
evLYs Gained	$16,000	$20,000

evLY: equal value life year, QALY: quality-adjusted life year

New England CEPAC Votes

Table 6.2. New England CEPAC Votes on Long-Term Value for Money at Current Prices

Question	Yes	No
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with KarXT versus aripiprazole?		

Long-term value for money votes were not taken at the public meeting because a net price for KarXT was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of KarXT compared to current standard of care that includes second-generation antipsychotics for adults with an established diagnosis of schizophrenia. In alignment with the cost-effectiveness analysis, the comparator arm of the model, was represented by aripiprazole because it was believed to have the fewest side effects among currently approved second-generation antipsychotics. We used an annual placeholder price ($20,000), and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) in our estimates of budget impact.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs for the prevalence of schizophrenia for US adults (1.8%),[4,75] the average projected US adult population size over five years (2023-2027; 269,529,814),[76] and the percentage of adults with schizophrenia estimated to be receiving antipsychotic medication (71.3%).[77] Applying these sources results in estimates of 3,459,146 eligible adults with schizophrenia in the US. For the purposes of this analysis, we will assume that 20% of these individuals would initiate treatment in each of the five years, or 691,829 adults with schizophrenia per year.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $735 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplemental Section F.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated potential budget impact for KarXT compared to current standard of care. At KarXT's placeholder price of $20,000 annually, the average annual budget impact per patient treated, per year, was $2,060 in Year one with cumulative net annual costs increasing to $21,570 in Year five.

Figure 7.1. Cumulative Annual Per-Patient Treated Budget Impact of KarXT (Using a Placeholder Price) Compared to Current Standard of Care in Adults with an Established Diagnosis of Schizophrenia

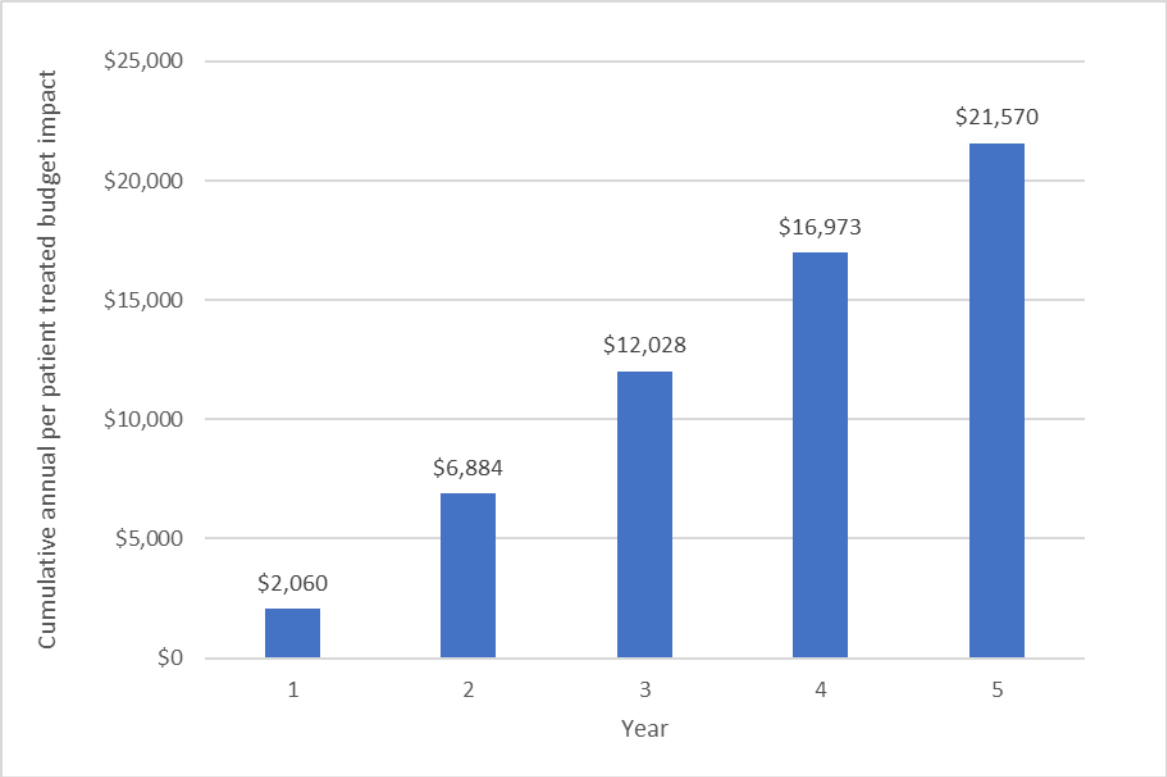
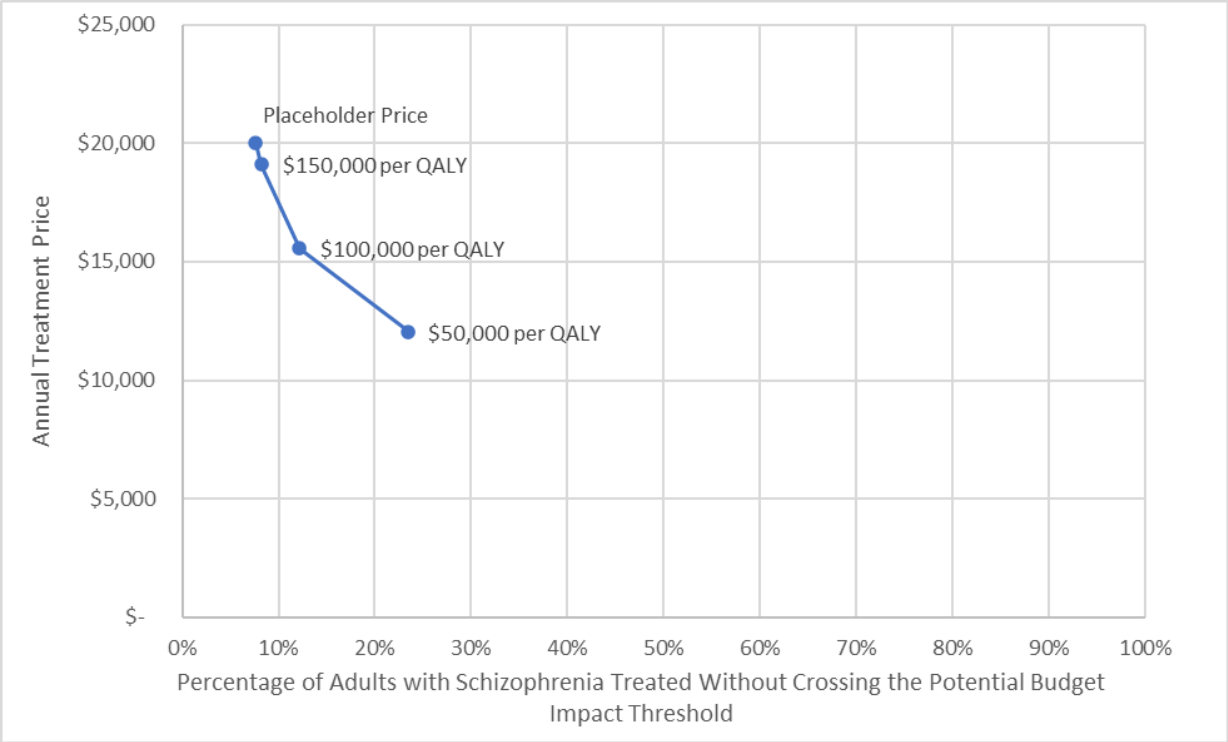


Figure 7.2 illustrates the potential budget impact of KarXT at a placeholder price of $20,000 annually. At the placeholder price, approximately 8% of adults living with schizophrenia who are eligible for treatment could be treated with KarXT without crossing the ICER potential budget impact threshold of $735 million per year. At prices to reach thresholds of $150,000, $100,000, and $50,000 per QALY ($19,102, $15,569, and $12,035), approximately 8%, 12%, and 24% of adults living with schizophrenia who are eligible for treatment, respectively, could be treated over five years without reaching the ICER potential budget impact threshold of $735 million per year.

Figure 7.2. Potential Budgetary Impact of KarXT (Using a Placeholder Price) in Adults with an Established Diagnosis of Schizophrenia



QALY: quality-adjusted life year

Access and Affordability Alert

ICER is not issuing an access and affordability alert for KarXT. The actual price of KarXT is unknown. The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

8. Policy Recommendations

Following the New England CEPAC's deliberation on the evidence, a policy roundtable discussion was moderated by Dr. Steve Pearson around how best to apply the evidence on the use of KarXT. The policy roundtable members included two patient advocates, two clinical experts, two payers, and one representative from the drug maker. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in Supplement Section G.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for people living with schizophrenia are introduced in a way that will help improve comprehensive care for people with schizophrenia and reduce health inequities, particularly for Black Americans.

Safe, and effective comprehensive treatment for schizophrenia remains a significant unmet health care need for all Americans, and Black Americans suffer disproportionately, since they are diagnosed with schizophrenia at twice the rate of other races, and they have worse clinical outcomes once diagnosed. Efforts are needed, therefore, to ensure that new treatments like KarXT serve as a stimulus to improve all aspects of care for people living with schizophrenia.

Clinical experts and patients at the ICER public meeting highlighted numerous factors leading to health inequities and poor care for many individuals. The failure of broader societal safety nets for individuals, families and other caregivers affected by this condition is pervasive. High costs for medications can also create significant barriers to access and adherence. Funding should target an expansion of inpatient beds and allow lengths of stay that ensure that patients have sufficient time to be stabilized on a therapy that works for them prior to discharge. Too many patients are discharged with limited support and instead need access to humane, supervised housing to ensure a smooth transition. Outpatient care should not be limited to medical management but should instead include increased combination approaches using non-pharmacological interventions including cognitive remediation therapy, compliance therapy, social skills training, social group therapy, and supported employment therapy.

To address these significant and numerous concerns, individual stakeholders should take the following actions:

Manufacturers:

- Set the price for KarXT in fair alignment with added benefits for patients.

Private payers:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access, especially for lower income people and families.

- Improve outcomes by allowing for longer inpatient stays and by assuring that case managers are available to help people find appropriate housing and support following hospitalization.

- Expand the options for collaborative care to provide high quality care by facilitating telehealth and other methods for primary care clinicians and non-physician mental health providers to collaborate with psychiatrists and Board-certified psychiatric pharmacists.

Medicaid and Medicare:

- Improve payment and resources for clinicians caring for people with schizophrenia.

- Ensure that patients being discharged from inpatient care have adequate case management and support for housing and care in the community.

State and Federal Policymakers:

- Create policies that require greater attention to the needs of people with schizophrenia who are in prison.

- Require collaboration among providers and insurers at the state or regional level to develop dashboards for tracking access and outcomes of people living with schizophrenia. Measurement with public scrutiny will be important for driving improvement across the wide range of services needed to help people living with schizophrenia.

Clinical specialty societies should take the following actions:

- Develop and disseminate educational materials and create measurable goals to ensure that Black Americans receive care consistent with current best practices.

Payers

Recommendation 1

If KarXT receives FDA approval, payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Given the significant uncertainty that remains about the long-term effectiveness of KarXT, and its presumed high cost in relation to available generic treatment options, it is reasonable for payers to use limited prior authorization as a component of coverage. Prior authorization criteria should be based on the FDA label, clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers. It should be fully compliant with the January 17, 2024 Centers for Medicare and Medicaid Services (CMS) Interoperability and Prior Authorization Final Rule.

We heard that prior authorization serves as a deterrent for patients in rural areas who often travel long distances to visit a pharmacy. If they are unable to pick up their prescription due to prior authorization delays, they may be less likely to come in to pick up prescriptions in the future.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: Cornerstones of 'fair' drug coverage: appropriate cost sharing and utilization management policies for pharmaceuticals.

Manufacturers

Recommendation

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of KarXT for people living with schizophrenia, while there is considerable hope associated with the promise of the drug, there also remains substantial uncertainty regarding its longer-term safety and effectiveness. Launch pricing should reflect these considerations.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial patient benefit, manufacturers should be allowed to increase pricing in accordance with benefit. This is particularly true for KarXT, which has only been studied in five-week trials, but may be used by patients for decades.

Researchers/Regulators

Recommendation

Conduct research that directly compares real-world treatment options and engages patients at the beginning of the study design phase.

The FDA requirement of five-week placebo controlled trials for approval is inadequate. Multiple stakeholders expressed concerns about the lack of information directly comparing new treatments and the need for active comparator trials. Since manufacturers have little incentive to conduct head-to-head trials, federal agencies (PCORI, NIMH) should work with patients and clinical researchers to design and fund be head-tohead trials of drugs to treat schizophrenia, including KarXT. Patients and caregivers should be engaged at the earliest stages of research to ensure optimal study design in terms of target populations, comparators, and outcome measures that matter to patients. Appropriate head-to-head trials with follow-up of at least 12 months would help to inform decision making by patients and clinicians.

The NIH should increase funding for basic and translational research focused on schizophrenia.

NIH funding for schizophrenia has been steady since about 2008, while funding for other neurologic disorders has increased substantially. Given the tremendous economic costs to society from schizophrenia, more research dollars should be allocated to promising approaches to prevent, diagnose, and treat the disease.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Acute phase**:** The phase of schizophrenia when a person experiences an increase in distressing symptoms.

Maintenance phase: The phase of treatment when antipsychotic drug regimens are administered to limit the frequency and severity of relapses and maximize the effects of treatment on symptoms.

Treatment resistant schizophrenia: Nonresponse to at least two sequential antipsychotic trials of sufficient dose, duration, and adherence.[78]

Assessments of Symptoms and Severity in Schizophrenia/Outcomes in Schizophrenia Research

Positive and Negative Syndrome Scale (PANSS): One of the most widely used measures of symptom severity in schizophrenia clinical research. The 30-item clinician-administered rating scale is used to evaluate the presence, absence, and severity of positive, negative, and general psychopathology symptoms. Each subscale (positive, negative, and general psychopathology) is rated with 1 to 7 points ranging from absent to extreme, with scores ranging from 7-49 for the positive and negative subscales and 16-112 for the general psychopathology scale. The strengths of the PANSS include its structured interview, reliability, availability of detailed anchor points, and validity.[79]

PANSS Positive Symptom Subscale: Seven items on the PANSS scale that quantify positive symptoms, which refer to an excess or distortion of normal functions (e.g., hallucinations and delusions).[80]

PANSS Negative Symptom Subscale: Seven items on the PANSS scale that quantify negative symptoms, which represent a diminution or loss of normal functions (e.g., lack of emotional expression, lack of motivation, etc.).[80]

PANSS Categorical Response: Prespecified percentage improvements in PANSS total score between baseline and endpoint used to assess response to antipsychotic treatment (e.g., >30% improvement in PANSS total score from baseline to an endpoint).[16]

Clinical Global Impressions-Severity (CGI-S): The CGI-S asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" This rating is based upon observed and reported symptoms, behavior, and function in the past seven days. Scores range from one to seven with a higher score reflecting a worse disease state.[81]

Criteria for Diagnosing Schizophrenia

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): A diagnostic tool published by the American Psychiatric Association that serves as the principal authority for psychiatric diagnoses. To receive a diagnosis of schizophrenia, an individual would have to present with more than two positive, negative, or cognitive symptoms. One of the symptoms must be either delusion, hallucination, or disorganized speech. Additionally, greater than one area of dysfunction of daily function, interpersonal relationships, or self-care must be present (e.g., social isolation, difficulty maintaining employment, impaired self-care, etc.). The duration of the symptoms must be at least one month and the duration of the dysfunctions must last at least 6 months.[81]

Other

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits (Section 5). For the calculation for the HIDI, we used population estimates of adults aged 18-65 with a diagnosis of schizophrenia spectrum disorders from the Mental and Substance Use Disorders Prevalence Study.[63] Results are in Table A1.1 below.

Table A1.1. ICER Health Improvement Distribution Index (HIDI)

Subgroup	HIDI
Asian, non-Hispanic	*
Black / African American, non-Hispanic	2.3
Hispanic	0.6
White, non-Hispanic	0.7

* No data available

A2. Potential Cost-Saving Measures in Schizophrenia

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for schizophrenia (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. During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with schizophrenia that could be reduced, eliminated, or made more efficient. No suggestions have been received.

B. Patient Perspectives: Supplemental Information

B1. Methods

We gathered feedback on the experiences of people living with schizophrenia by reviewing the FDA's Voice of the Patient series "Reimagine Schizophrenia: Transforming How We Are Treated, Function, and Thrive."[13] Then we spoke with representatives from two organizations that support patients with schizophrenia and their families: the National Alliance on Mental Health and the Schizophrenia & Psychosis Action Alliance. Finally, we spoke with five people living with schizophrenia and five caregivers for people living with schizophrenia. A summary of what we heard is included in Section 2 of the main report.

C. Clinical Guidelines

The American Psychiatric Association Practice Guideline. 2020.[7]

The American Psychiatric Association (APA) issued guidance on the treatment of patients with schizophrenia in 2020. The guideline includes recommendations on the assessment of a treatment plan, pharmacotherapy, and psychosocial interventions. It is recommended that individuals receive a comprehensive initial assessment and psychiatric evaluation to inform a person-centered treatment plan. The plans should include both pharmacological and nonpharmacological treatments. The APA recommends the use of antipsychotic medication for the initial treatment of schizophrenia and the continuation of medication when symptoms have improved. Monitoring is recommended for evaluating the effectiveness and side effects. Clozapine is recommended for individuals living with treatment-resistant schizophrenia or for those that have risk of suicide or suicide attempts. Long-acting injectable formulations are encouraged when acceptable to patients. Alongside pharmacotherapy, the APA recommends coordinated specialty care (CSC) programs for those experiencing first episode psychosis and cognitive behavioral therapy for psychosis, psychoeducation, and supported employment services.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

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 for effect modification of treatment for schizophrenia in the following subgroups:

- 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. We are not considering long-acting preparations, as we heard of important differences between the populations most commonly receiving oral and long-acting preparations.

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, home, and unhoused settings.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on KarXT for schizophrenia followed established best research methods.[82,83] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[84] The PRISMA guidelines include a checklist of 27 items (see Table D1). During the scoping phase, we identified one network meta-analysis from Huhn et al. (2019) for the acute treatment of schizophrenia.[56] We abstracted data from this network meta-analysis and conducted an updated literature search for new evidence published since the last search alongside a new search for evidence on KarXT. Additionally, we conducted a targeted search for literature reviews on relevant treatments in the maintenance phase.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and APA PsychInfo for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data.

Table D1.2. Search Strategy: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and APA PsychInfo 1967 - 2023 for KarXT

#	Search Terms
1	exp schizophrenia/
2	('Schizophrenia' or 'Schizophrenias' or 'Schizophrenic Disorders' or 'Disorder, Schizophrenic' or 'Disorders, Schizophrenic' or 'Schizophrenic Disorder').ti,ab.
3	1 or 2
4	('LY246708' or 'Xanomeline' or 'Xanomeline-Trospium' or 'Xanomeline; Trospium Chloride' or 'Karuna-Xanomeline-Trospium' or 'KarXT').ti,ab.
5	3 and 4
6	(animals not (humans and animals)).sh.
7	5 NOT 6
8	(addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR guideline OR interactive tutorial).pt
9	7 NOT 8
10	limit 9 to English language
11	Remove duplicates from 10

Table D1.3. Search Strategy: EMBASE for KarXT

#	Search Terms
1	'schizophrenia'/exp
2	'chronic schizophrenia' OR 'schizophrenic' OR 'schizophrenic language' OR 'schizophrenic syndrome' OR 'schizophrenia':ti,ab
3	#1 or #2
4	'ly246708' OR 'xanomeline' OR 'xanomeline-trospium' OR 'xanomeline; trospium chloride' OR 'karuna-xanomeline-trospium' OR 'xanomeline/trospium' OR 'karxt':ti,ab
5	#3 and #4
6	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
7	#5 NOT #6
8	#7 AND [english]/lim
9	#8 AND [medline]/lim
10	#8 NOT #9
11	#10 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
12	#10 NOT #11

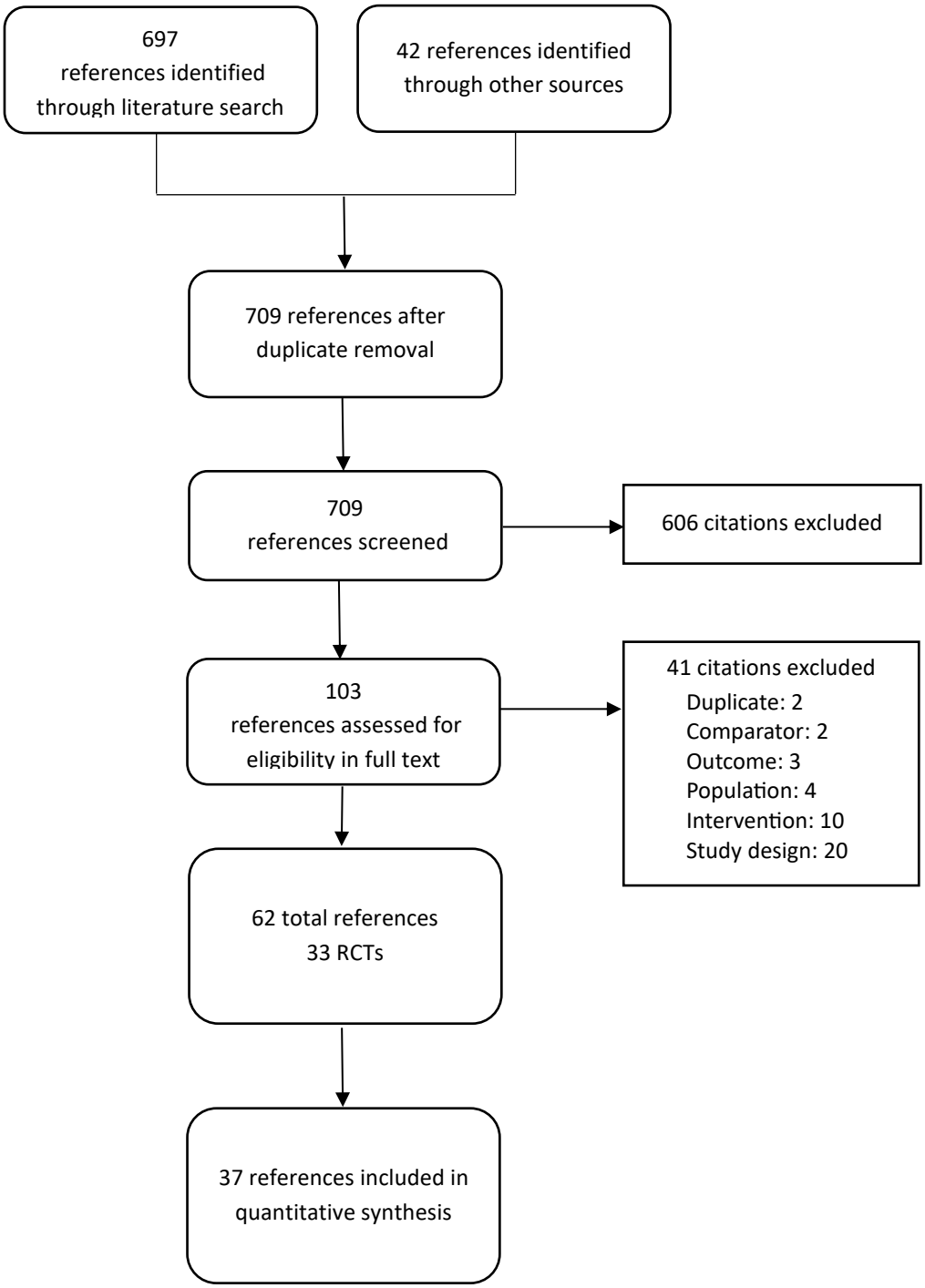
Table D1.4. Search Strategy: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and APA PsychInfo 1967 - 2023. (Key Second-Generation Antipsychotics updated since 2019 Network Meta-Analysis[56])

#	Search Terms
1	(Aripiprazole or Olanzapine or Risperdal or Risperidone).mp.
2	exp schizophrenia/ or schizo$.mp. or hebephreni$.mp. or oligophreni$.mp. or psychotic$.mp. or psychosis.mp. or psychosis.mp.
3	1 AND 2
4	3 AND (clinical trial, phase iii or clinical trial, phase iv or randomized controlled trial).pt.
5	4 NOT (addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt
6	limit 5 to ed=20171108-20230809

Table D1.5. Search Strategy: EMBASE (Key Second-Generation Antipsychotics updated since 2019 Network Meta-Analysis[56])

#	Search Terms
1	(Aripiprazole or Olanzapine or Risperdal or Risperidone):ti,ab
2	'schizophrenia'/exp or (schizo$ OR hebephreni$ OR oligophreni$ OR psychotic$ OR psychosis OR psychoses):ti,ab
3	#1 AND #2
4	#3 AND ('phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de)
5	#4 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' OR 'case report' OR 'cohort analysis' OR 'comment' OR 'congresses' OR 'consensus development conference' OR 'cross-sectional study' OR 'duplicate publication' OR 'editorial' OR 'guideline' OR 'in vitro' OR 'interview' OR 'lecture' OR 'legal cases' OR 'legislation' OR 'letter' OR 'news' OR 'newspaper article' OR 'note' OR 'observational study' OR 'patient education handout' OR 'periodical index' OR 'personal narratives' OR 'portraits' OR 'practice guideline' OR 'review' OR 'retrospective study' OR 'short survey' OR 'video audio media')/it
6	#5 AND [medline]/lim
7	#5 NOT #6
8	#7 AND [2017-11-08]/sd

Figure D1. PRISMA flow Chart Showing Results of Literature Search for KarXT and Key Second-Generation Antipsychotics



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias or each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[85,86]

Risk of Bias Assessment

We examined the risk of bias for each randomized control trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[87,88] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: Positive and Negative Syndrome Scale (PANSS) Total Score and All-cause Discontinuation. See Table D1.6. and D1.7.

Additionally, as part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for KarXT using ClinicalTrials.gov. Search terms included "xanomeline-trospium," and "KarXT." We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Table D1.6. Risk of Bias Assessment: PANSS Total Score

Studies	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
KarXT[15,25]						
EMERGENT-1	Low	Low	Low	Low	Low	Low
EMERGENT-2	Low	Low	Low	Low	Low	Low
EMERGENT-3	Not Evaluable*					
Risperidone[28,34,36,39-41,46,55]						
Casey 2008	Low	Low	Low	Low	Low	Low
Downing 2014	Low	Some Concern	Low	Low	Low	Some Concern
Geffen 2012	Low	Low	Low	Low	Low	Low
Durgam 2014	Low	Low	Low	Low	Low	Low
Potkin 2007c	Low	Low	Low	Low	Low	Low
Lieberman 2015	Low	Low	Low	Low	Low	Low
Walling 2019	Low	Low	High	Low	Low	High
Higuchi 2019	Some Concern	Low	Low	Low	Low	Some Concern
Olanzapine[27,30,33,37,43-45,48,50,51,53,54]						
Egan 2013	Low	Low	Low	Low	Low	Low
Schmidt 2012	Low	Low	Some Concern	Low	Low	Some Concern
Shen 2014	Low	Low	High	Low	Low	High
Bugarski Kirola 2014	Low	Low	Low	Low	Low	Low
Beasley 1996b	Not Evaluable*					
Davidson 2007	Low	Low	Low	Low	Low	Low
ENLIGHTEN-1 2020	Low	Low	Low	Low	Low	Low
Kane 2007b	Low	Low	Low	Low	Low	Low
Marder 2007c	Low	Low	Low	Low	Low	Low
Meltzer 2011	Low	Low	Low	Low	Low	Low
Kinon 2011	Low	Low	Low	Low	Low	Low
Landbloom 2017	Low	Low	Low	Low	Low	Low
Corrigan 2004	Low	Low	Low	Low	Low	Low

Aripiprazole[31,35,49,89]						
McEvoy 2007b	Low	Low	Low	Low	Low	Low
Durgam 2015	Low	Low	Low	Low	Low	Low
Correll 2016	Low	Low	Low	Low	Low	Low
Cutler 2006	Low	Low	Low	Low	Low	Low
Head-to-Head[29,32,38,42,52]						
Fleischhacker 2009	Low	Low	Low	Low	Low	Low
McQuade 2004	Low	Some Concerns	High	Low	Low	High
Chen 2018	High	Some Concerns	High	Low	Low	High
Sacchetti 2008	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
Jindal 2013	Low	Some Concerns	High	Low	Low	High

*Risk of Bias was not assessed for non-peer reviewed publications (EMERGENT-3) and trials that did not measure PANSS (Beasley 1996b)

Table D1.7. Risk of Bias Assessment: All-cause Discontinuation

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
KarXT[15,25]						
EMERGENT-1	Low	Low	Low	Low	Low	Low
EMERGENT-2	Low	Low	Low	Low	Low	Low
EMERGENT-3	Not Evaluable*					
Risperidone[28,34,36,39-41,46,55]						
Casey 2008	Low	Low	Low	Low	Low	Low
Downing 2014	Low	Low	Low	Low	Low	Low
Geffen 2012	Low	Low	Low	Low	Low	Low
Durgam 2014	Low	Low	Low	Low	Low	Low
Potkin 2007c	Low	Low	Low	Low	Low	Low
Lieberman 2015	Low	Low	Low	Low	Low	Low
Walling 2019	Low	Low	Low	Low	Low	Low
Higuchi 2019	Some Concern	Low	Low	Low	Low	Some Concern

Olanzapine[27,30,33,37,43-45,47,48,50,51,54]						
Egan 2013	Low	Low	Low	Low	Low	Low
Schmidt 2012	Not Evaluable*					
Shen 2014	Low	Low	Low	Low	Low	Low
Bugarski Kirola 2014	Low	Low	Low	Low	Low	Low
Beasley 1996b	Low	Low	Low	Low	Low	Low
Davidson 2007	Low	Low	Low	Low	Low	Low
ENLIGHTEN-1 2020	Low	Low	Low	Low	Low	Low
Kane 2007b	Low	Low	Low	Low	Low	Low
Marder 2007c	Low	Low	Low	Low	Low	Low
Meltzer 2011	Low	Low	Low	Low	Low	Low
Kinon 2011	Low	Low	Low	Low	Low	Low
Landbloom 2017	Low	Low	Low	Low	Low	Low
Corrigan 2004	Low	Low	Low	Low	Low	Low
Aripiprazole[31,35,49,89]						
McEvoy 2007b	Low	Low	Low	Low	Low	Low
Durgam 2015	Low	Low	Low	Low	Low	Low
Correll 2016	Low	Low	Low	Low	Low	Low
Cutler 2006	Low	Low	Low	Low	Low	Low
Head-to-Head[38,52]						
Fleischhacker 2009	Low	Low	Low	Low	Low	Low
McQuade 2004	Not Evaluable*					
Chen 2018	Not Evaluable*					
Sacchetti 2008	Low	Low	Low	Low	Low	Low
Jindal 2013	Not Evaluable*					

*Risk of Bias was not assessed for non-peer reviewed publications (EMERGENT-3) and trials that did not measure discontinuation (Schmidt 2012, McQuade 2004, Chen 2018, Jindal 2013)

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[62] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5 below. Representation for each demographic category was evaluated relative to the disease prevalence, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.10. We did not evaluate the subgroup of adults ≥65 as the trials enrolled a patient population between the ages of 18 and 65.

Table D1.8. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

Table D1.9. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.10. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity. For this review one trial (EMERGENT-3) was multinational (i.e., enrolled patients from the US and other countries). We were unable to obtain US subgroup data on this trial, thus, these trials were rated on race/ethnicity using the full sample (including both US and non-US participants). The participants in EMERGENT-3 were enrolled both in the U.S. (81.2%) and Ukraine (18.8%).

Lifetime prevalence estimates for sex and the White, Black/African American, and Hispanic/Latino racial/ethnic populations were derived from the Mental and Substance Use Disorders Prevalence Study conducted by Ringeisen et al. in 2023.[63] Prevalence data for Asian, American Indian or Alaskan Native, and Native Hawaiian or Pacific Islander populations were not available and thus we used an estimate of 6.3% which reflects the population estimate of Asian Americans from the US 2022 Census.[90] Data from the Global Burden of Disease Database was used for the prevalence estimate of adults ≥65 who are living with schizophrenia.[64]

Results

Table D1.11. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence	39.27%	31.73%	6.3%	11.67%	--	--	1.3%	0.3%
US Participants Only								
EMERGENT-1	20.3%	75.3%	2.2%	17.6%	--	--	0%	1.1%
PDRR	0.5	2.4	0.4	1.5	--	--	--	--
Score	2	3	1	3	9	Fair	--	--
US Participants Only								
EMERGENT-2	22.6%	75%	1.2%	9.9%	--	--	0%	0%
PDRR	0.6	2.4	0.2	0.9	--	--	--	--
Score	2	3	1	3	9	Fair	--	--
All Participants								
EMERGENT-3	38.3%	60.9%	0.4%	12.5%	--	--	0%	0%
PDRR	1.0	1.9	0.1	1.1	--	--	--	--
Score	3	3	1	3	10	Fair	--	--

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.12. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence	52.4%	47.6%	--	--	1.4%	--	--
EMERGENT-1	76.9%	23.1%	--	--	NC	NC	NC
PDRR	1.5	0.5	--	--	NC	NC	NC
Score	3	2	5	Fair	NC	NC	NC
EMERGENT-2	75.4%	24.6%	--	--	NC	NC	NC
PDRR	1.4	0.5	--	--	NC	NC	NC
Score	3	2	5	Fair	NC	NC	NC
EMERGENT-3	74.6%	25.4%	--	--	NC	NC	NC
PDRR	1.4	0.5	--	--	NC	NC	NC
Score	3	2	5	Fair	NC	NC	NC

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

D2. Network Meta-Analysis (NMA), Meta-Analysis & Additional Clinical Results

NMA Methods

We assessed the feasibility of conducting an indirect treatment comparison of the efficacy and safety of KarXT, aripiprazole, olanzapine, and risperidone by evaluating differences in study population, study design, and outcome assessments of key trials. The outcomes of interest were change from baseline in PANSS score (total, positive, and negative), CGI-S score, weight change, PANSS response, all-cause discontinuation, and discontinuation due to adverse events.

Using a previously published NMA (Huhn 2019[56]) assessing efficacy and tolerability of antipsychotics for the acute treatment of schizophrenia and an updated systematic literature review, we sought trials with a duration of three to eight weeks that enrolled patients with a diagnosis of schizophrenia experiencing an acute exacerbation of symptoms that reported data for our outcomes of interest. We identified 33 trials that met our inclusion criteria (Figure D2.1).

For the comparators, we included studies that had dosages either equal to or higher than the recommended dose in their respective FDA labels (aripiprazole: 10-30 mg, olanzapine: 10-20 mg, risperidone: 4-8 mg). When trials had multiple arms with eligible dosages for a drug, we pooled the data. We excluded study arms for antipsychotics outside the scope of our review. We did not include trials that enrolled patients with schizoaffective disorder or first episode psychosis.

We conducted three sensitivity analyses: 1) including only studies that had patients hospitalized for the duration of the study for CGI-S, all-cause discontinuation, and discontinuation due to adverse events, 2) excluding three studies (ENLIGTHEN 2020, Jindal 2018, and Burgarski Kirola 2014)[27,42,51] deemed as outliers on baseline PANSS for the PANSS total and PANSS negative outcomes, and 3) excluding ten trials published prior to 2009 for the PANSS total outcome. [28,30-33,39,43,48,49,52]

PANSS response, all-cause discontinuation, and discontinuation due to adverse events were evaluated as dichotomous outcomes. We conducted random-effects Bayesian NMAs using a binomial likelihood with log link. The input was the number of patients with an event and total number of patients and the output was relative risk. Change from baseline in PANSS total, positive, and negative scores, CGI-S, and weight gain were analyzed as continuous outcomes. We conducted random-effects Bayesian NMAs using a normal likelihood with identity link. The input was mean change from baseline and standard error with an output of relative mean difference. In instances where standard error was not available, we calculated it from other data (e.g., standard deviation) or made assumptions based on similar trials. We evaluated model fit for all outcomes and also conducted fixed-effects models to compare model fit (Tables D2.1 & D2.2). Due to the heterogeneity of the included trials in the network, the results of the random-effects NMA are

described in the main report. We also examined inconsistencies in loops of evidence using a random-effects meta-analysis that used direct evidence only. These results were consistent with the NMA results.

Model Fit

Table D2.1. Model Fit for Random-Effects Models

Outcome	Dbar	DIC	Unconstrained Datapoints	I^2
PANSS Total	62.83	115.66	63	1%
PANSS Positive	47.6	84.56	47	3%
PANSS Negative	45.28	84.42	45	3%
PANSS Response	34.56	61.22	32	10%
CGI-S	45.78	76.7	43	8%
Weight Change	42.05	78.09	42	2%
All-cause Discontinuation	58.75	98.33	58	3%
Discontinuation due to Adverse Events	61.47	100.03	58	7%

CGI-S: clinical global impressions scale, Dbar: posterior distribution for the deviance, DIC: deviance information criterion, I^2: fraction of variance due to heterogeneity, PANSS: positive and negative syndrome scale

Table D2.2. Model Fit for Fixed-Effects Models

Outcome	Dbar	DIC	Unconstrained Datapoints	I^2
PANSS Total	110.21	145.22	63	44%
PANSS Positive	63.3	91.33	47	28%
PANSS Negative	83.35	109.35	45	47%
PANSS Response	45.22	65.17	32	31%
CGI-S	51.36	76.35	43	18%
Weight Change	77.25	101.26	42	47%
All-cause Discontinuation	64.73	98.69	58	13%
Discontinuation due to Adverse Events	67.28	99.88	58	15%

CGI-S: clinical global impressions scale, Dbar: posterior distribution for the deviance, DIC: deviance information criterion, I^2: fraction of variance due to heterogeneity, PANSS: positive and negative syndrome scale

NMA Network Diagrams

Figures D2.1 – 8 represent the NMA network diagrams for each outcome. A thicker line signifies more trials comparing each antipsychotic.

Figure D2.1. Overall Network Diagram (33 Trials)

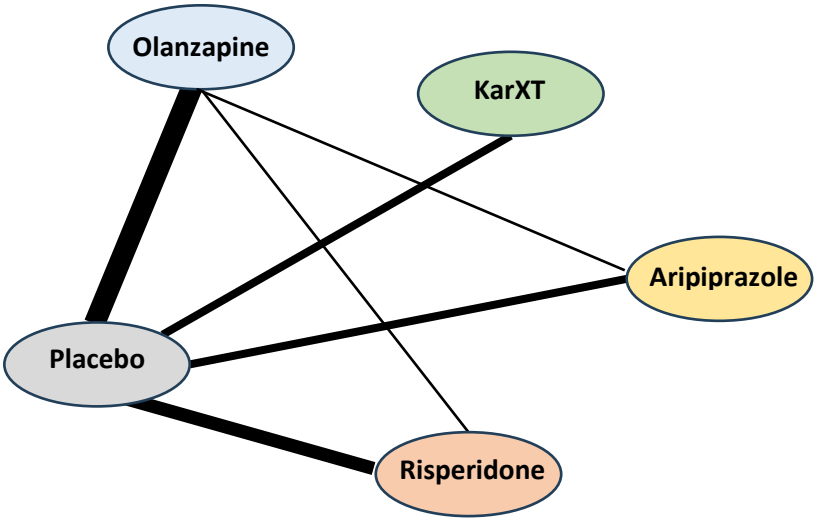


Figure D2.2. PANSS Total Network Diagram (32 Trials)

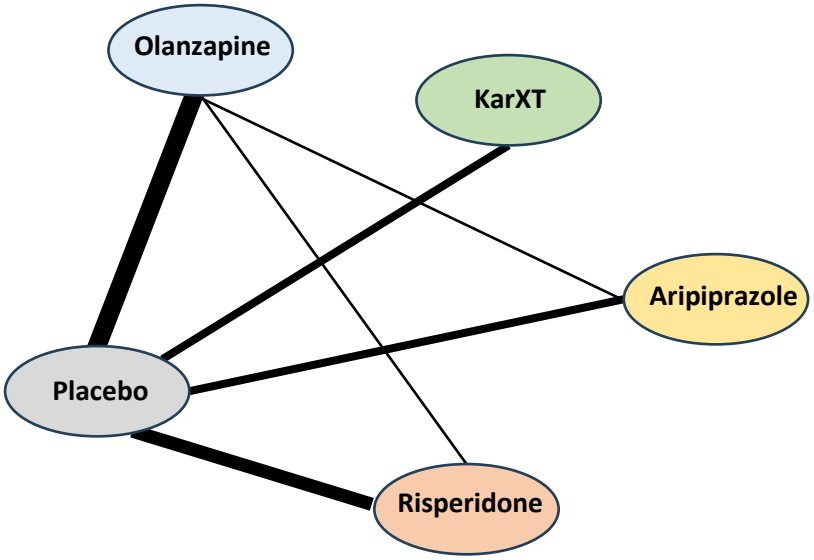


Figure D2.3. PANSS Positive Network Diagram (24 Trials)

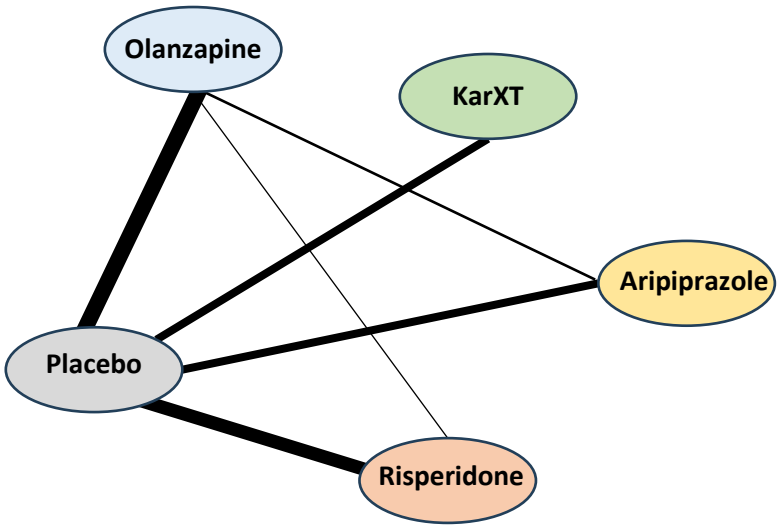


Figure D2.4. PANSS Negative Network Diagram (23 Trials)

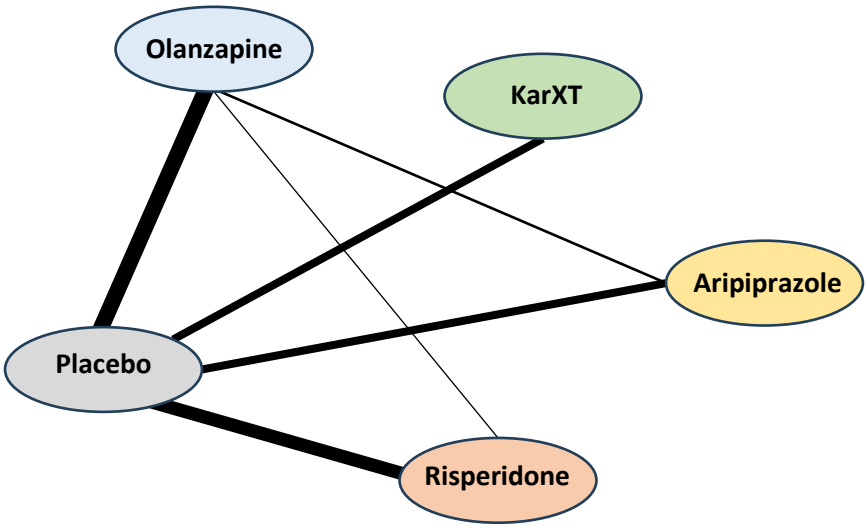


Figure D2.5. PANSS Response Network Diagram (16 Trials)

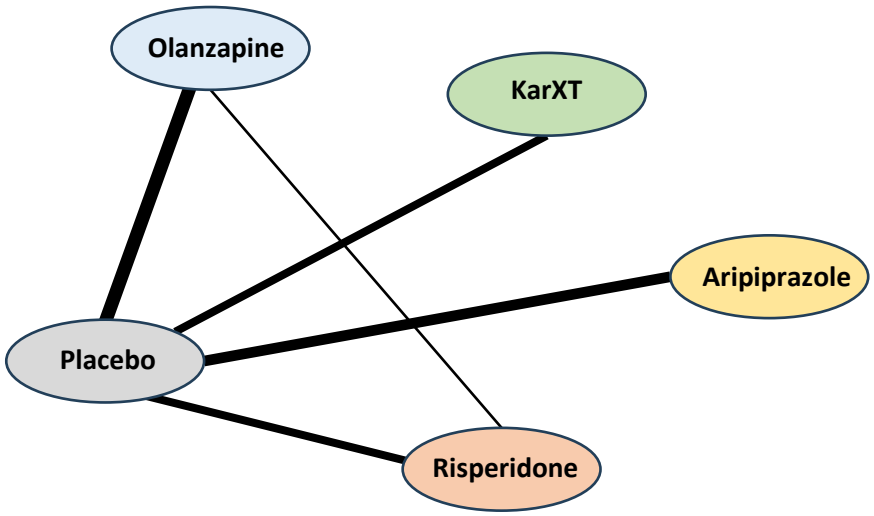


Figure D2.6. CGI-S Network Diagram (22 Trials)

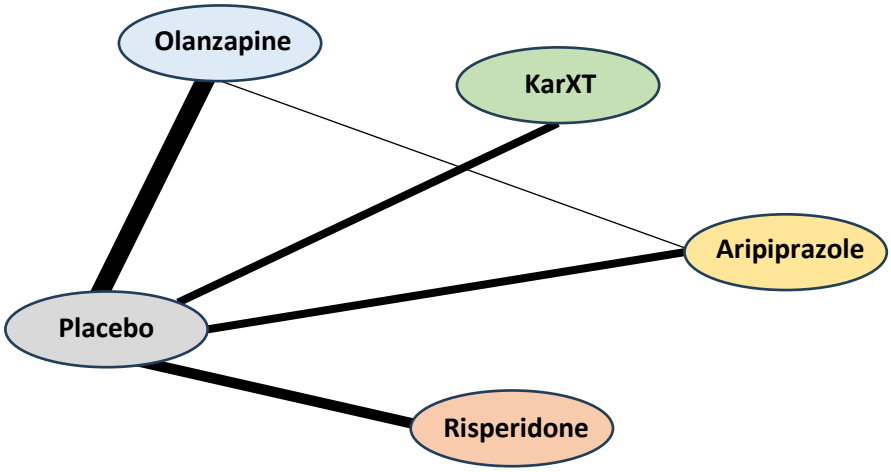


Figure D2.7. Weight Change Network Diagram (22 Trials)

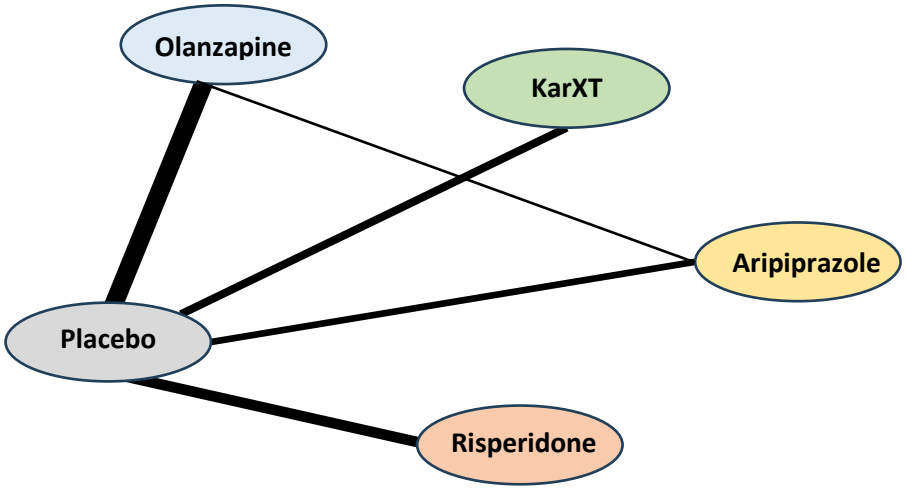


Figure D2.8. All-Cause Discontinuation Network Diagram (29 Trials)

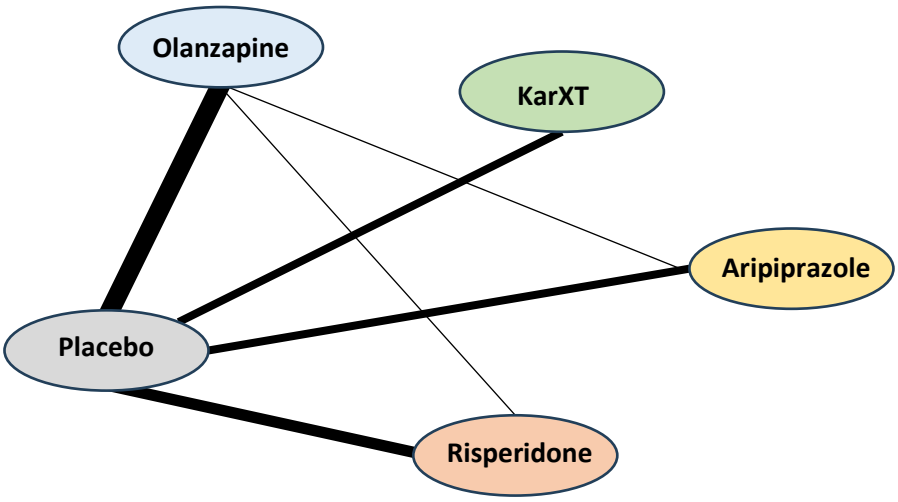
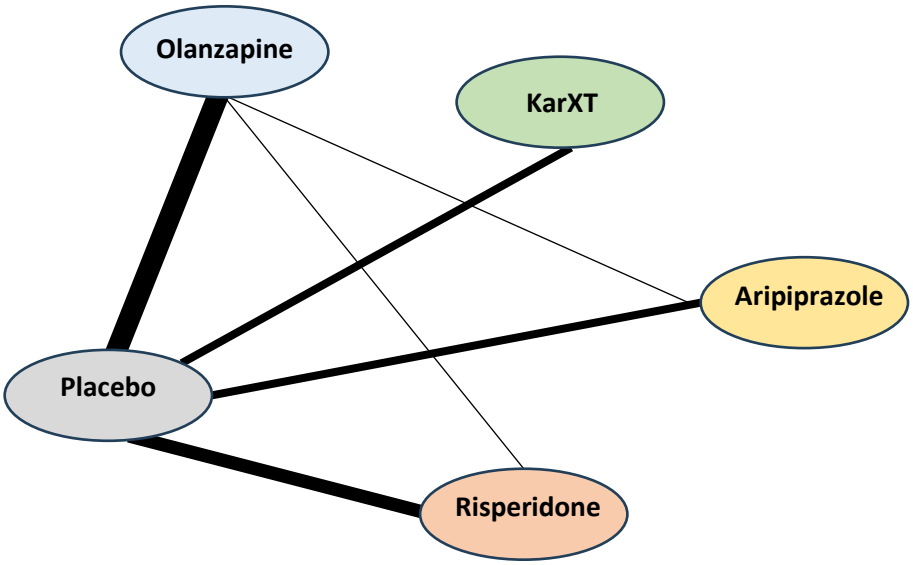


Figure D2.9. Discontinuation due to Adverse Event Network Diagram (29 Trials)



NMA Input tables

Table D2.3. Input Data for NMA: PANSS Total Score (Number of Trials: 32)[15,19,27-46,48-55,89]

Study Name	Name	Patient Number	Mean Difference	Standard Error
EMERGENT-1	KarXT	83	-17.4	1.8
EMERGENT-1	Placebo	87	-5.9	1.7
EMERGENT-2	KarXT	117	-21.2	*1.6*
EMERGENT-2	Placebo	119	-11.6	*1.6*
EMERGENT-3	KarXT	114	-20.6	*1.5*
EMERGENT-3	Placebo	120	-12.2	*1.5*
Casey 2008	Risperidone	116	-15.7	SD :14.9
Casey 2008	Placebo	114	-5.3	SD :16.3
Downing 2014	Risperidone	124	-16.6	*1.3*
Downing 2014	Placebo	253	-7.9	*1.3*
Geffen 2012	Risperidone	91	-9.4	95% CI: -14.9, -3.8
Geffen 2012	Placebo	93	NR	NR
Durgam 2014	Risperidone	138	-26.9	1.6
Durgam 2014	Placebo	148	-11.8	1.5
Potkin 2007c	Risperidone	59	-10.9	NR
Potkin 2007c	Placebo	62	-5.3	NR
Lieberman 2015	Risperidone	75	-13.4	1.72
Lieberman 2015	Placebo	80	-7.4	1.68
Walling 2019	Risperidone	26	-19.1	2.9
Walling 2019	Placebo	63	-10.8	1.9
Higuchi 2019	Risperidone	64	-7.1	2.4
Higuchi 2019	Placebo	129	-2.5	1.7
Egan 2013	Olanzapine	45	-17	*2.9*
Egan 2013	Placebo	78	-12.7	*2.3*
Schmidt 2014	Olanzapine	81	-22.9	*1.9*
Schmidt 2014	Placebo	55	-6.3	*1.9*
Shen 2014	Olanzapine	71	-14.7	2.4
Shen 2014	Placebo	71	-2.7	2.44
Bugarski Kirola 2014	Olanzapine	61	-14.9	2.13
Bugarski Kirola 2014	Placebo	79	-11.9	1.9
Davidson 2007	Olanzapine	126	-18.1	SD:20.3
Davidson 2007	Placebo	120	-2.8	SD:20.9
ENLIGHTEN-1 2020	Olanzapine	132	-22.8	1.3
ENLIGHTEN-1 2020	Placebo	133	-17.5	1.3
Kane 2007b	Olanzapine	128	-19.9	SD:19
Kane 2007b	Placebo	126	-4.1	SD: 23.3
Marder 2007c	Olanzapine	105	-18.4	SD:19.9
Marder 2007c	Placebo	105	-8	SD: 21.5

Study Name	Name	Patient Number	Mean Difference	Standard Error
Meltzer 2011	Olanzapine	121	-28.7	1.9
Meltzer 2011	Placebo	114	-16	2.1
Kinon 2011	Olanzapine	62	-20.68	3.08
Kinon 2011	Placebo	122	-14.6	2.2
Landbloom 2017	Olanzapine	35	-21.6	2.32
Landbloom 2017	Placebo	60	-16.2	1.71
Corrigan 2004	Olanzapine	93	-31.5	NR
Corrigan 2004	Placebo	85	-12.6	NR
McEvoy 2007b	Aripiprazole	103	-15.04	NR
McEvoy 2007b	Aripiprazole	103	-11.73	NR
McEvoy 2007b	Aripiprazole	97	-14.44	NR
McEvoy 2007b	Placebo	107	-2.33	NR
Durgam 2015	Aripiprazole	150	-21.2	1.4
Durgam 2015	Placebo	149	-14.3	1.5
Correll 2016	Aripiprazole	50	-20.97	2.93
Correll 2016	Placebo	93	-17.28	2.19
Cutler 2006	Aripiprazole	94	-11.3	NR
Cutler 2006	Placebo	88	-5.3	NR
Fleischhacker 2009	Olanzapine	344	-29.5	NR
Fleischhacker 2009	Aripiprazole	347	-24.6	NR
McQuade 2004	Olanzapine	161	-30.6	NR
McQuade 2004	Aripiprazole	156	-28.5	NR
Chen 2018	Olanzapine	32	-20.91	NR
Chen 2018	Risperidone	25	-11.79	NR
Sacchetti 2008	Risperidone	20	-32.1	*SD: 22.1*
Sacchetti 2008	Olanzapine	20	-34.4	*SD: 15.5*
Jindal 2013	Aripiprazole	26	-45.31	SD: 11.94
Jindal 2013	Olanzapine	27	-40.93	SD: 5.4

CI: confidence interval, NR: not reported, SD: standard deviation

Note: Italicized data has been digitized

Table D2.4. Input Data for NMA: PANSS Positive Score (Number of Trials: 24)[15,19,27,28,30,31,35-37,39-42,44,46,49-55,89]

Study Name	Name	Patient Number	Mean difference	Standard Error
EMERGENT-1	KarXT	83	-5.6	0.6
EMERGENT-1	Placebo	87	-2.4	0.6
EMERGENT-2	KarXT	117	-6.8	*0.5*
EMERGENT-2	Placebo	119	-3.9	*0.5*
EMERGENT-3	KarXT	114	-7.1	*0.5*
EMERGENT-3	Placebo	120	-3.6	*0.5*
Casey 2008	Risperidone	116	-5.3	SD: 4.8

Study Name	Name	Patient Number	Mean difference	Standard Error
Casey 2008	Placebo	114	-2	SD: 5.2
Geffen 2012	Risperidone	91	-4.7	95% CI: -6.7, -2.6
Geffen 2012	Placebo	93	NR	NR
Durgam 2014	Risperidone	138	-9.5	0.5
Durgam 2014	Placebo	148	-4.1	0.5
Potkin 2007c	Risperidone	59	-5.1	NR
Potkin 2007c	Placebo	62	-2.5	NR
Lieberman 2015	Risperidone	75	-4.8	0.5
Lieberman 2015	Placebo	80	-2.3	0.5
Walling 2019	Risperidone	26	-7.1	0.9
Walling 2019	Placebo	63	-4.1	0.6
Higuchi 2019	Risperidone	64	-2.9	0.8
Higuchi 2019	Placebo	129	-0.6	0.5
Egan 2013	Olanzapine	45	-5.6	95% CI: -7.4, -3.8
Egan 2013	Placebo	78	-4.2	95% CI: -5.6, -2.9
Schmidt 2012	Olanzapine	81	-7.4	0.65
Schmidt 2012	Placebo	55	-2.6	0.71
Shen 2014	Olanzapine	71	-4.97	0.78
Shen 2014	Placebo	71	-1.86	0.79
Bugarski Kirola 2014	Olanzapine	61	*-5.4*	*1.4*
Bugarski Kirola 2014	Placebo	79	*-3.7*	*1.3*
ENLIGHTEN-1 2020	Olanzapine	132	*-7.5*	*0.5*
ENLIGHTEN-1 2020	Placebo	133	*-5.6*	*0.4*
Meltzer 2011	Olanzapine	121	-9.3	0.7
Meltzer 2011	Placebo	114	-5.4	0.7
Kinon 2011	Olanzapine	62	-7.34	0.96
Kinon 2011	Placebo	122	-4.9	0.69
Corrigan 2004	Olanzapine	93	-9.4	NR
Corrigan 2004	Placebo	85	-3	NR
McEvoy 2007b	Aripiprazole	103	-4.98	NR
McEvoy 2007b	Aripiprazole	103	-3.81	NR
McEvoy 2007b	Aripiprazole	97	-4.51	NR
McEvoy 2007b	Placebo	107	-1.1	NR
Durgam 2015	Aripiprazole	150	-7.2	0.4
Durgam 2015	Placebo	149	-5.3	0.5
Correll 2016	Aripiprazole	50	-7.58	0.95
Correll 2016	Placebo	93	-5.7	0.71
Cutler 2006	Aripiprazole	94	-4.2	NR
Cutler 2006	Placebo	88	-2.3	NR
Sacchetti 2008	Risperidone	20	-12.3	SD:7.6
Sacchetti 2008	Olanzapine	20	-11.3	SD:7.2
Jindal 2013	Aripiprazole	26	-12.27	SD:4.06

Study Name	Name	Patient Number	Mean difference	Standard Error
Jindal 2013	Olanzapine	27	-11.52	SD: 2.68

CI: confidence interval, NR: not reported, SD: standard deviation

Note: Italicized data has been digitized

Table D2.5. Input Data for NMA: PANSS Negative Score (Number of Trials: 23)[15,19,28,30,31,35-37,39-42,44,46,49-55,89]

Study Name	Name	Patient Number	Mean Difference	Standard Error
EMERGENT-1	KarXT	83	-3.2	0.5
EMERGENT-1	Placebo	87	-0.9	0.5
EMERGENT-2	KarXT	117	-3.4	*0.5*
EMERGENT-2	Placebo	119	-1.6	*0.5*
EMERGENT-3	KarXT	114	-2.7	*0.5*
EMERGENT-3	Placebo	120	-1.8	*0.5*
Casey 2008	Risperidone	116	-3.6	SD:4.6
Casey 2008	Placebo	114	-1.3	SD:4.6
Geffen 2012	Risperidone	91	-2	95% CI: -3.4, -0.6
Geffen 2012	Placebo	93	NR	NR
Durgam 2014	Risperidone	138	-5.1	0.4
Durgam 2014	Placebo	148	-2	0.4
Potkin 2007c	Risperidone	59	-1.05	NR
Potkin 2007c	Placebo	62	-0.6	NR
Lieberman 2015	Risperidone	75	-0.4	0.5
Lieberman 2015	Placebo	80	-0.3	0.5
Walling 2019	Risperidone	26	-2.5	0.8
Walling 2019	Placebo	63	-1.3	0.5
Higuchi 2019	Risperidone	64	-1.7	0.6
Higuchi 2019	Placebo	129	-0.9	0.5
Egan 2013	Olanzapine	45	-3.1	95% CI: -4.5, -1.6
Egan 2013	Placebo	78	-2.9	95% CI: -4.0, -1.8
Schmidt 2012	Olanzapine	81	-4.5	0.46
Schmidt 2012	Placebo	55	-1.8	0.51
Shen 2014	Olanzapine	71	-1.97	0.71
Shen 2014	Placebo	71	2.23	0.73
ENLIGHTEN-1 2020	Olanzapine	132	*-4.4*	*0.4*
ENLIGHTEN-1 2020	Placebo	133	*-3.9*	*0.4*
Meltzer 2011	Olanzapine	121	-6.2	0.5
Meltzer 2011	Placebo	114	-3.6	0.5
Kinon 2011	Olanzapine	62	-4.46	0.72
Kinon 2011	Placebo	122	-3.07	0.52
Corrigan 2004	Olanzapine	93	-8.1	NR
Corrigan 2004	Placebo	85	-4.2	NR

Study Name	Name	Patient Number	Mean Difference	Standard Error
McEvoy 2007b	Aripiprazole	103	-3.52	NR
McEvoy 2007b	Aripiprazole	103	-2.65	NR
McEvoy 2007b	Aripiprazole	97	-3.33	NR
McEvoy 2007b	Placebo	107	0.08	NR
Durgam 2015	Aripiprazole	150	-4.2	0.3
Durgam 2015	Placebo	149	-3	0.4
Correll 2016	Aripiprazole	50	-4.37	0.68
Correll 2016	Placebo	93	-4.03	0.51
Cutler 2006	Aripiprazole	94	-2.7	NR
Cutler 2006	Placebo	88	-1.3	NR
Sacchetti 2008	Risperidone	20	-5.2	*SD: 4.9*
Sacchetti 2008	Olanzapine	20	-6.4	*SD: 3.3*
Jindal 2013	Aripiprazole	26	-13.19	SD: 2.65
Jindal 2013	Olanzapine	27	-11.85	SD: 2.01

CI: confidence interval, NR: not reported, SD: standard deviation

Note: Italicized data has been digitized

Table D2.6. Input Data for NMA: PANSS Response (Number of Trials: 16)[16-18,27,28,31,35,36,43,46,48,49,51-53,89]

Study	Arm	Responders	Sample Size
EMERGENT-1	KarXT	*32*	83
EMERGENT-1	Placebo	*10*	87
EMERGENT-2	KarXT	*54*	117
EMERGENT-2	Placebo	*32*	119
EMERGENT-3	KarXT	*44*	114
EMERGENT-3	Placebo	26	120
Casey 2008	Risperidone	26	116
Casey 2008	Placebo	8	114
Durgam 2014	Risperidone	60	138
Durgam 2014	Placebo	28	148
Lieberman 2015	Risperidone	30	75
Lieberman 2015	Placebo	18	80
Schmidt 2014	Olanzapine	62	93
Schmidt 2014	Placebo	26	99
Bugarski Kirola 2014	Olanzapine	19	61
Bugarski Kirola 2014	Placebo	25	79
ENLIGHTEN-1 2020	Olanzapine	*71*	132
ENLIGHTEN-1 2020	Placebo	*51*	133
Kane 2007b	Olanzapine	*67*	128
Kane 2007b	Placebo	*38*	126
Marder 2007c	Olanzapine	*48*	105

Study	Arm	Responders	Sample Size
Marder 2007c	Placebo	*36*	105
McEvoy 2007b	Aripiprazole	122	303
McEvoy 2007b	Placebo	28	107
Durgam 2015	Aripiprazole	45	150
Durgam 2015	Placebo	29	149
Correll 2016	Aripiprazole	*30*	50
Correll 2016	Placebo	*47*	93
Cutler 2006	Aripiprazole	*40*	94
Cutler 2006	Placebo	*29*	88
Sacchetti 2008	Risperidone	9	20
Sacchetti 2008	Olanzapine	13	20

CI: confidence interval, NR: not reported, SD: standard deviation

Note: Italicized data has been digitized or calculated

Table D2.7. Input Data for NMA: CGI-S (Number of Trials: 22)[15,19,27,28,30,31,35-41,44,45,47,49-51,54,89]

Study Name	Name	Patient Number	Mean Difference	Standard Error
EMERGENT-1	KarXT	83	-1	0.1
EMERGENT-1	Placebo	87	-0.3	0.1
EMERGENT-2	KarXT	117	-1.2	*0.1*
EMERGENT-2	Placebo	119	-0.7	*0.1*
EMERGENT-3	KarXT	114	-1.1	*0.1*
EMERGENT-3	Placebo	120	-0.6	*0.1*
Casey 2008	Risperidone	116	-0.76	0.9
Casey 2008	Placebo	114	-0.25	0.9
Geffen 2012	Risperidone	91	-0.67	95% CI: -1.02, -0.33
Geffen 2012	Placebo	NR	NR	NR
Durgam 2014	Risperidone	138	-1.5	0.1
Durgam 2014	Placebo	148	-0.7	0.1
Potkin 2007c	Risperidone	59	-0.75	NR
Potkin 2007c	Placebo	62	-0.28	NR
Higuchi 2019	Risperidone	64	-0.4	0.1
Higuchi 2019	Placebo	129	0	0.1
Egan 2013	Olanzapine	45	-0.8	95% CI: -1.2, -0.5
Egan 2013	Placebo	78	-0.9	95% CI: -1.1, -0.6
Shen 2014	Olanzapine	71	-0.87	0.13
Shen 2014	Placebo	71	-0.25	0.13
Bugarski Kirola 2014	Olanzapine	61	-0.96	0.14
Bugarski Kirola 2014	Placebo	79	-0.68	0.12
Beasley 1996b	Olanzapine	66	-1	SD: 1.1
Beasley 1996b	Placebo	66	-0.3	SD: 1.2
ENLIGHTEN-1 2020	Olanzapine	132	-1.3	0.08

Study Name	Name	Patient Number	Mean Difference	Standard Error
ENLIGHTEN-1 2020	Placebo	133	-0.8	0.09
Meltzer 2011	Olanzapine	121	-1.5	0.1
Meltzer 2011	Placebo	114	-1.1	0.1
Kinon 2011	Olanzapine	62	-0.99	0.16
Kinon 2011	Placebo	122	-0.77	0.11
Landbloom 2017	Olanzapine	35	-1.1	0.14
Landbloom 2017	Placebo	58	-1	0.11
Corrigan 2004	Olanzapine	93	-1.6	NR
Corrigan 2004	Placebo	85	-0.8	NR
McEvoy 2007b	Aripiprazole	103	-0.65	NR
McEvoy 2007b	Aripiprazole	103	-0.51	NR
McEvoy 2007b	Aripiprazole	97	-0.64	NR
McEvoy 2007b	Placebo	107	-0.18	NR
Durgam 2015	Aripiprazole	150	-1.4	0.1
Durgam 2015	Placebo	149	-1	0.1
Correll 2016	Aripiprazole	50	-1.3	0.16
Correll 2016	Placebo	93	-1.05	0.12
Cutler 2006	Aripiprazole	94	-0.6	NR
Cutler 2006	Placebo	88	-0.3	NR
Fleischhacker 2009	Olanzapine	344	-1.42	NR
Fleischhacker 2009	Aripiprazole	347	-1.25	NR

CI: confidence interval, NR: not reported, SD: standard deviation

Note: Italicized data has been digitized

Table D2.8. Input Data for NMA: Weight Change (Number of Trials: 22)[14,15,27,28,32,33,35,36,39,43,44,46-51,53-55,89]

Study Name	Name	Patient Number	Mean Difference	Standard Error
EMERGENT-1	KarXT	89	1.5	SD: 2.8
EMERGENT-1	Placebo	90	1.1	SD: 3.5
EMERGENT-2	KarXT	126	1.36	SD: 3.31
EMERGENT-2	Placebo	125	2.49	SD: 6.92
EMERGENT-3	KarXT	125	1.41	SD: 3.37
EMERGENT-3	Placebo	128	2	SD: 3.08
Casey 2008	Risperidone	96	2.27	NR
Casey 2008	Placebo	81	0.59	NR
Durgam 2014	Risperidone	140	2	SD: 3.2
Durgam 2014	Placebo	151	0.5	SD: 2.9
Potkin 2007c	Risperidone	47	1.6	NR
Potkin 2007c	Placebo	54	0.15	NR
Lieberman 2015	Risperidone	82	3	SD: 3.69
Lieberman 2015	Placebo	85	0.8	SD: 3.46

Study Name	Name	Patient Number	Mean Difference	Standard Error
Walling 2019	Risperidone	36	2.7	SD: 3
Walling 2019	Placebo	74	1	SD: 2.6
Schmidt 2012	Olanzapine	81	*1.8*	*0.2*
Schmidt 2012	Placebo	55	NR	NR
Shen 2014	Olanzapine	77	5.34	SD: 5.09
Shen 2014	Placebo	77	1.3	SD: 4.58
Bugarski Kirola 2014	Olanzapine	62	2.6	NR
Bugarski Kirola 2014	Placebo	80	0.6	NR
Beasley 1996b	Olanzapine	69	3.5	SD: 3.9
Beasley 1996b	Placebo	68	NR	NR
Davidson 2007	Olanzapine	115	2.2	SD: 3.94
Davidson 2007	Placebo	110	-0.8	SD: 4.24
ENLIGHTEN-1 2020	Olanzapine	133	2.38	SD: 3.65
ENLIGHTEN-1 2020	Placebo	134	0.24	SD: 2.76
Kane 2007b	Olanzapine	123	1.3	SD: 2.8
Kane 2007b	Placebo	119	-0.7	SD: 2.4
Marder 2007c	Olanzapine	90	2.7	SD: 4.4
Marder 2007c	Placebo	94	0.4	SD: 3.6
Meltzer 2011	Olanzapine	122	4.1	SD: 4.3
Meltzer 2011	Placebo	116	0.6	SD: 2.7
Kinon 2011	Olanzapine	62	1.37	0.26
Kinon 2011	Placebo	122	0.19	0.19
McEvoy 2007b	Aripiprazole	105	0.46	NR
McEvoy 2007b	Aripiprazole	105	-0.17	NR
McEvoy 2007b	Aripiprazole	98	0.31	NR
McEvoy 2007b	Placebo	107	-0.64	NR
Durgam 2015	Aripiprazole	152	0.7	SD: 2.9
Durgam 2015	Placebo	153	0.1	SD: 2.9
Correll 2016	Aripiprazole	50	0.3	SD: 2.7
Correll 2016	Placebo	93	0.2	SD: 2.3
McQuade 2004	Olanzapine	161	2.9	NR
McQuade 2004	Aripiprazole	156	-0.2	NR

NR: not reported, SD: standard deviation

Note: Italicized data has been digitized

Table D2.9. Input Data for NMA: All-cause Discontinuation (Number of Trials: 29) [14,15,27,28,30,31,33-41,43-52,54,55,89]

Study	Arm	Responders	Sample Size
EMERGENT-1	KarXT	18	90
EMERGENT-1	Placebo	19	92

Study	Arm	Responders	Sample Size
EMERGENT-2	KarXT	*32*	126
EMERGENT-2	Placebo	*26*	126
EMERGENT-3	KarXT	*46*	125
EMERGENT-3	Placebo	*38*	131
Casey 2008	Risperidone	61	120
Casey 2008	Placebo	70	119
Downing 2014	Risperidone	46	142
Downing 2014	Placebo	124	295
Geffen 2012	Risperidone	20	91
Geffen 2012	Placebo	37	93
Durgam 2014	Risperidone	39	140
Durgam 2014	Placebo	72	151
Potkin 2007c	Risperidone	34	59
Potkin 2007c	Placebo	41	60
Lieberman 2015	Risperidone	15	82
Lieberman 2015	Placebo	19	85
Walling 2019	Risperidone	11	36
Walling 2019	Placebo	14	74
Higuchi 2019	Risperidone	*14*	64
Higuchi 2019	Placebo	*48*	129
Egan 2013	Olanzapine	9	47
Egan 2013	Placebo	21	83
Shen 2014	Olanzapine	37	77
Shen 2014	Placebo	49	77
Bugarski Kirola 2014	Olanzapine	18	62
Bugarski Kirola 2014	Placebo	22	80
Beasley 1996b	Olanzapine	*35*	69
Beasley 1996b	Placebo	*46*	68
Davidson 2007	Olanzapine	40	128
Davidson 2007	Placebo	76	123
ENLIGHTEN-1 2020	Olanzapine	14	133
ENLIGHTEN-1 2020	Placebo	23	134
Kane 2007b	Olanzapine	38	128
Kane 2007b	Placebo	69	127
Marder 2007c	Olanzapine	60	110
Marder 2007c	Placebo	73	110
Meltzer 2011	Olanzapine	39	123
Meltzer 2011	Placebo	45	116
Kinon 2011	Olanzapine	22	62
Kinon 2011	Placebo	49	122
Landbloom 2017	Olanzapine	11	46

Study	Arm	Responders	Sample Size
Landbloom 2017	Placebo	41	101
Corrigan 2004	Olanzapine	24	93
Corrigan 2004	Placebo	22	87
McEvoy 2007b	Aripiprazole	63	106
McEvoy 2007b	Aripiprazole	74	106
McEvoy 2007b	Aripiprazole	63	100
McEvoy 2007b	Placebo	78	108
Durgam 2015	Aripiprazole	*38*	152
Durgam 2015	Placebo	*58*	153
Correll 2016	Aripiprazole	12	50
Correll 2016	Placebo	27	93
Cutler 2006	Aripiprazole	41	94
Cutler 2006	Placebo	44	88
Fleischhacker 2009	Olanzapine	77	348
Fleischhacker 2009	Aripiprazole	104	355
Sacchetti 2008	Risperidone	5	25
Sacchetti 2008	Olanzapine	5	25

Note: Italicized data has been digitized or calculated

Table D2.10. Input Data for NMA: Discontinuation due to adverse event (Number of Trials: 29)

14,15,25,27,28,30,31,33-41,43-49,51,52,54,55,89

Study	Arm	Responders	Sample Size
EMERGENT-1	KarXT	2	89
EMERGENT-1	Placebo	2	90
EMERGENT-2	KarXT	10	126
EMERGENT-2	Placebo	6	126
EMERGENT-3	KarXT	8	125
EMERGENT-3	Placebo	7	128
Casey 2008	Risperidone	17	120
Casey 2008	Placebo	13	119
Downing 2014	Risperidone	12	142
Downing 2014	Placebo	33	295
Geffen 2012	Risperidone	8	91
Geffen 2012	Placebo	4	93
Durgam 2014	Risperidone	13	140
Durgam 2014	Placebo	22	151
Potkin 2007c	Risperidone	4	60
Potkin 2007c	Placebo	7	62
Lieberman 2015	Risperidone	3	82
Lieberman 2015	Placebo	0	85

Study	Arm	Responders	Sample Size
Walling 2019	Risperidone	3	36
Walling 2019	Placebo	4	74
Higuchi 2019	Risperidone	*1*	64
Higuchi 2019	Placebo	*8*	129
Egan 2013	Olanzapine	0	47
Egan 2013	Placebo	0	83
Shen 2014	Olanzapine	5	77
Shen 2014	Placebo	11	77
Bugarski Kirola 2014	Olanzapine	5	62
Bugarski Kirola 2014	Placebo	2	80
Beasley 1996b	Olanzapine	*4*	69
Beasley 1996b	Placebo	*7*	68
Davidson 2007	Olanzapine	5	128
Davidson 2007	Placebo	5	123
ENLIGHTEN-1 2020	Olanzapine	3	133
ENLIGHTEN-1 2020	Placebo	7	134
Kane 2007b	Olanzapine	9	128
Kane 2007b	Placebo	9	127
Marder 2007c	Olanzapine	8	110
Marder 2007c	Placebo	5	110
Meltzer 2011	Olanzapine	8	123
Meltzer 2011	Placebo	10	116
Kinon 2011	Olanzapine	6	62
Kinon 2011	Placebo	4	122
Landbloom 2017	Olanzapine	1	46
Landbloom 2017	Placebo	10	101
Corrigan 2004	Olanzapine	7	93
Corrigan 2004	Placebo	3	87
McEvoy 2007b	Aripiprazole	11	106
McEvoy 2007b	Aripiprazole	3	106
McEvoy 2007b	Aripiprazole	5	100
McEvoy 2007b	Placebo	6	108
Durgam 2015	Aripiprazole	14	152
Durgam 2015	Placebo	17	153
Correll 2016	Aripiprazole	3	50
Correll 2016	Placebo	5	93
Cutler 2006	Aripiprazole	4	94
Cutler 2006	Placebo	6	88
Fleischhacker 2009	Olanzapine	18	348
Fleischhacker 2009	Aripiprazole	37	355
Sacchetti 2008	Risperidone	0	25

Study	Arm	Responders	Sample Size
Sacchetti 2008	Olanzapine	1	25

Note: Italicized data has been digitized or calculated

Additional Clinical Results

PANSS Positive

Direct Evidence

A greater reduction in the PANSS positive score in KarXT compared to placebo was observed across the three trials (relative mean difference: -3.2; 95% CI: -4.04, -2.36). Individual trial results are reported in Table D2.4.

Indirect Evidence

Compared to placebo, risperidone had the greatest reduction in PANSS positive score although all antipsychotics had statistically significant reductions (Table D2.11).

Table D2.11. Change from baseline in PANSS Positive Score

KarXT				
-0.67 (-2.51, 1.2)	**Aripiprazole**			
-0.16 (-1.83, 1.56)	0.52 (-0.89, 1.92)	**Olanzapine**		
0.27 (-1.44, 1.97)	0.94 (-0.61, 2.45)	0.42 (-0.92, 1.72)	**Risperidone**	
-3.2 (-4.61, -1.79)	**-2.53 (-3.74, -1.34)**	**-3.05 (-4, -2.11)**	**-3.47 (-4.42, -2.5)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0. Individual trial data can be found in Supplement Table D2.4.

PANSS Negative

Direct Evidence

Patients receiving KarXT had significantly greater reductions in PANSS negative scores compared to placebo in EMERGENT-1 (-2.3 points; p<0.001) and EMERGENT-2 (-1.8 points; p=0.0055). A reduction of 3.5 points compared to placebo was observed in EMERGENT-3 but this was not significant (p=0.12).

Indirect Evidence

All the antipsychotics had significant reductions in the PANSS negative score compared to placebo with no statistically significant differences between the antipsychotic treatments (Table D2.12).

Table D2.12. Change from baseline in PANSS Negative Score

KarXT				
0.27 (-1.67, 2.2)	**Aripiprazole**			
0.33 (-1.46, 2.13)	0.06 (-1.32, 1.46)	**Olanzapine**		
-0.22 (-2.06, 1.57)	-0.5 (-2.04, 1.01)	-0.55 (-1.88, 0.72)	**Risperidone**	
-1.66 (-3.2, -0.14)	**-1.94 (-3.12, -0.75)**	**-1.99 (-2.95, -1.07)**	**-1.44 (-2.4, -0.45)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0. Individual trial data can be found in Supplement Table D2.5.

Clinical Global Impressions – Severity (CGI-S) Scale

Direct Evidence

A greater reduction in CGI-S was observed in patients receiving KarXT compared to placebo (mean difference: -0.57; 95% CI -0.73, -0.41).

Indirect Evidence

All the treatments had statistically significant decreases in CGI-S score compared to placebo. KarXT had greater reductions numerically compared to aripiprazole and olanzapine, but these results were not statistically significant (Table D2.13).

Table D2.13. Change from baseline in CGI-S Score

KarXT				
-0.23 (-0.52, 0.04)	**Aripiprazole**			
-0.14 (-0.4, 0.1)	0.09 (-0.12, 0.3)	**Olanzapine**		
-0.01 (-0.27, 0.26)	0.23 (-0.02, 0.48)	0.14 (-0.07, 0.35)	**Risperidone**	
-0.57 (-0.78, -0.36)	**-0.33 (-0.52, -0.15)**	**-0.42 (-0.55, -0.29)**	**-0.56 (-0.72, -0.4)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0. Individual trial data can be found in Supplement Table D2.7.

Discontinuation due to adverse events

Direct Evidence

Discontinuation due to *treatment-emergent* adverse events for EMERGENT-1 was 2% in both arms whereas rates were higher in the KarXT arm compared to placebo for EMERGENT-2 (7.1% versus 5.6%) and EMERGENT-3 (6.4% versus 5.5%). Results for discontinuation due to *any* adverse events were similar for EMERGENT-1 and 2.[15] This data is not yet publicly available for EMERGENT-3 and so data on file provided from the manufacturer was used in this indirect comparison.

Indirect Evidence

KarXT had numerically greater but not significantly greater rates of discontinuation due to any adverse events from aripiprazole, olanzapine, risperidone, and placebo (Table D2.14).

Table D2.14. Discontinuation Due to Adverse Event

KarXT				
1.19 (0.48, 3.12)	**Aripiprazole**			
1.58 (0.66, 3.81)	1.33 (0.73, 2.24)	**Olanzapine**		
1.49 (0.61, 3.64)	1.25 (0.63, 2.36)	0.94 (0.55, 1.66)	**Risperidone**	
1.34 (0.62, 3)	1.13 (0.67, 1.85)	0.85 (0.6, 1.26)	0.91 (0.6, 1.38)	**Placebo**

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Individual trial data can be found in Supplement Table D2.10.

Additional data on reasons for discontinuations (i.e., due to lack of efficacy or withdrawing consent) are available in Supplement Tables D3.10 – 3.11.

Cognition

Cognition was evaluated as an exploratory outcome in the EMERGENT trials. For EMERGENT-1, effects on cognition were evaluated using the Cogstate Brief Battery scale which included domains such as attention, processing speed, execution, and working memory. EMERGENT-2 and -3 used the Cambridge Neuropsychological Test Automated Battery (CANTAB), which assesses domains such as attention, verbal memory, and executive function. Using the modified intent-to-treat population, an analysis of an overall sample and a sample of patients who were considered cognitively impaired at baseline were assessed for the three trials.

In EMERGENT-1, a significant difference in the Cogstate Brief Battery Scale was observed for the cognitively impaired sample (least square mean [LSM] difference 0.5; p=0.03) but not the overall sample (LSM difference: 0.18; p=0.16).[21] Similarly, for EMERGENT-2 and -3, a significant difference was observed at week five for the cognitively impaired sample (LSM difference: 0.29; p<0.01), but not the overall sample (LSM difference: 0.06; p=0.33).[21]

Cognition was not consistently measured in the trials of aripiprazole, olanzapine, and risperidone and therefore is not described.

NMA Sensitivity Analyses

Hospital Duration

Among the 33 trials included in the overall network, 14 trials required patients to remain in hospital for the study duration. For the remaining 19 trials, seven required ≥2 weeks in hospital, six required ≥3 weeks, three required ≥4 weeks, one required hospitalization until day four, and two studies did not specify the required duration. We conducted sensitivity analyses on the CGI-S, all-cause discontinuation, and discontinuation due to adverse events outcomes using the 14 trials requiring hospitalization for study duration.

By removing trials that allowed patients to be discharged during the trial duration, significant changes in CGI-S in aripiprazole and risperidone were not observed compared to placebo. KarXT had similar reductions in CGI-S compared to the other antipsychotics in this analysis compared to the overall sample (Table D2.15). No significant differences in all-cause discontinuation or discontinuation due to adverse events in any of the antipsychotic comparisons versus each other or placebo were observed in this sample (Tables D2.16-17).

Table D2.15. Change from Baseline in CGI-S Score – Hospital Sensitivity

KarXT				
-0.26 (-0.75, 0.22)	**Aripiprazole**			
-0.2 (-0.65, 0.22)	0.06 (-0.35, 0.44)	**Olanzapine**		
-0.17 (-0.82, 0.48)	0.09 (-0.57, 0.77)	0.03 (-0.58, 0.68)	**Risperidone**	
-0.57 (-0.89, -0.24)	-0.31 (-0.66, 0.05)	**-0.36 (-0.63, -0.07)**	-0.4 (-0.97, 0.17)	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0.

Table D2.16. All-cause Discontinuation – Hospital Sensitivity

KarXT				
1.34 (0.9, 1.99)	**Aripiprazole**			
1.46 (0.94, 2.17)	1.09 (0.79, 1.43)	**Olanzapine**		
1.45 (0.86, 2.39)	1.08 (0.68, 1.68)	0.99 (0.62, 1.6)	**Risperidone**	
1.19 (0.85, 1.64)	0.88 (0.7, 1.1)	0.81 (0.63, 1.07)	0.82 (0.55, 1.22)	**Placebo**

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D2.17. Discontinuation due to adverse events – Hospital Sensitivity

KarXT				
0.82 (0.14, 5.14)	**Aripiprazole**			
0.78 (0.12, 3.91)	0.96 (0.2, 3.18)	**Olanzapine**		
1.13 (0.14, 7.37)	1.37 (0.17, 8.43)	1.44 (0.22, 9.6)	**Risperidone**	
1.32 (0.36, 4.73)	1.61 (0.44, 5.37)	1.69 (0.59, 6.06)	1.18 (0.28, 5.69)	**Placebo**

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

PANSS Outliers

We conducted sensitivity analyses for the PANSS total and PANSS negative outcomes by removing three trials (ENLIGTHEN 2020, Jindal 2018, and Burgarski Kirola 2014)[27,42,51] that had baseline PANSS scores that were deemed to be outliers.

By removing these three trials, the comparisons between aripiprazole versus olanzapine and olanzapine versus risperidone show statistically significant differences in the PANSS total score. All other results reflect similar trends to the overall sample (Table D2.18). No significant differences were observed in the PANSS negative outcome in this analysis compared to the overall network (Table D.19).

Table D2.18. Change from Baseline in PANSS Total – Outlier Sensitivity

KarXT				
-2.03 (-7.34, 3.2)	**Aripiprazole**			
2.69 (-2.11, 7.3)	**4.71 (1.1, 8.25)**	**Olanzapine**		
-1.34 (-6.25, 3.37)	0.68 (-3.45, 4.73)	**-4.03 (-7.2, -0.89)**	**Risperidone**	
-9.76 (-13.89, -5.66)	**-7.73 (-11, -4.41)**	**-12.44 (-14.66, -10.11)**	**-8.41 (-10.83, -5.85)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0.

Table D2.19. Change from Baseline in PANSS Negative – Outlier Sensitivity

KarXT				
-0.08 (-2.05, 1.88)	**Aripiprazole**			
0.53 (-1.24, 2.34)	0.61 (-0.98, 2.25)	**Olanzapine**		
-0.21 (-2, 1.56)	-0.13 (-1.73, 1.46)	-0.74 (-2.08, 0.55)	**Risperidone**	
-1.67 (-3.16, -0.17)	**-1.59 (-2.86, -0.31)**	**-2.2 (-3.19, -1.24)**	**-1.46 (-2.4, -0.49)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0.

Trial Year Sensitivity: Removal of trials prior to 2009

Ten of the 32 trials (32%) included in the NMA examining PANSS total outcome were published prior to 2009. Of the 10 trials, two trials evaluated risperidone, four evaluated olanzapine, two evaluated aripiprazole, and two were head-to-head trials.[28,30-33,39,43,48,49,52] We conducted a sensitivity analysis removing these 10 trials from NMA examining the change from baseline in PANSS total score. Results reflect similar trends to the overall sample with small numerical changes and large credible intervals (Table D2.20).

Table D2.20. Change from Baseline in PANSS Total – Trial Year Sensitivity

KarXT				
-2.56 (-9.99, 4.75)	**Aripiprazole**			
-1.03 (-7.2, 5.18)	1.51 (-3.54, 6.72)	**Olanzapine**		
-2.06 (-8.57, 4.32)	0.49 (-5.71, 6.69)	-1.02 (-5.66, 3.45)	**Risperidone**	
-9.77 (-15.08, -4.47)	**-7.22 (-12.28, -2.04)**	**-8.73 (-11.91, -5.59)**	**-7.71 (-11.29, -4)**	**Placebo**

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0.

KarXT Meta-Analysis

Meta-Analysis Methods

The EMERGENT trials had similar study designs, enrollment criteria, and reported outcomes. To report the direct evidence of KarXT and placebo, we conducted both pairwise fixed-effects and random-effects meta-analyses for eight outcomes of interest using trial data from EMERGENT 1, 2, and 3. The random-effects results are presented in the main report. Continuous outcomes are reported as related mean differences and 95% credible intervals. Binomial outcomes are reported as relative risks and 95% credible intervals. Results for PANSS total, PANSS positive, PANSS negative, and CGI-S outcomes are similar to the results recently presented in an abstract at the 2023 NEI conference.[23]

Table D2.21. Fixed and Random Effect Meta-Analyses Results

Pairwise Fixed-Effects Meta-Analyses		
Continuous Outcomes	**Estimate (95% CI)**	**I^2 (heterogeneity)**
PANSS total	-9.67 (-12.25, -7.10)	0%
PANSS positive	-3.20 (-4.04, -2.36)	0%
PANSS negative	-1.67 (-2.47, -0.87)	0.66%
CGI-S	-0.57 (-0.73, -0.41)	0%
Weight gain	-0.34 (-0.89, 0.21)	51.56%
Binomial Outcomes	**Estimate (95% CI)**	**I^2 (heterogeneity)**
PANSS 30	1.98 (1.55, 2.54)	41.20%

Continuous Outcomes	Estimate (95% CI)	I^2 (heterogeneity)
All-cause discontinuation	1.19 (0.92, 1.53)	0%
Discontinuation due to AEs	1.34 (0.70, 2.58)	0%
Pairwise Random-Effects Meta-Analyses		
Continuous Outcomes	**Estimate (95% CI)**	**I^2 (heterogeneity)**
PANSS total	-9.67 (-12.25, -7.10)	0%
PANSS positive	-3.20 (-4.04, -2.36)	0%
PANSS negative	-1.67 (-2.47, -0.86)	0.66%
CGI-S	-0.57 (-0.73, -0.41)	0%
Weight gain	-0.37 (-1.19, 0.46)	51.58%
Binomial Outcomes	**Estimate (95% CI)**	**I^2 (heterogeneity)**
PANSS 30	1.96 (1.46, 2.66)	41.20%
All-cause discontinuation	1.19 (0.93, 1.53)	0%
Discontinuation due to AEs	1.34 (0.70, 2.58)	0%

CGI-S: clinical global impressions – severity I^2: fraction of variance due to heterogeneity, PANSS: positive and negative syndrome scale

Note: Continuous outcomes are relative mean difference and 95% credible intervals. Binomial outcomes are relative risks and 95% credible intervals.

D3. Evidence Tables

Table D3.1. Study Design of Key Trials of KarXT and Comparators

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
KarXT				
EMERGENT-1[15] **NCT03697252**	Phase 2, randomized, double-blinded, placebo-controlled, multicenter, inpatient study N = 182 Population: Adults with a DSM-5 diagnosis of schizophrenia who are in an acute exacerbation phase. Duration: 5 weeks	**Arm I:** Oral xanomeline 50 mg/trospium 20 mg (KarXT 50/20 mg) BID on days 1-2 followed by KarXT 100/20 mg BID on days 3-7. Dose is increased to KarXT 125/30 mg BID on days 8-34 unless experiencing adverse events. (n=90) Dosing must not change after Visit 7 of the study (at 21 ± 2 days of dosing) and may be decreased for tolerability reasons no more than once during the study. **Arm II:** Placebo capsules (n=92)	**Inclusion** - 18 to 60 years old - Requires hospitalization for acute exacerbation or relapse of symptoms - PANSS total score 80-120 - CGI-S score of ≥4 **Exclusion** - Any primary DSM-5 disorder other than schizophrenia - Moderate to severe substance abuse disorder - Psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening - History of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months	Change From Baseline in PANSS Total Score [week 5]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
EMERGENT-2[25] **NCT04659161**	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, inpatient study N = 252 Population: Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia Duration: 5 weeks	**Arm I:** Oral xanomeline 50 mg/trospium 20 mg (KarXT 50/20 mg) BID on days 1-2 followed by KarXT 100/20 mg BID on days 3-7. Dose is increased to KarXT 125/30 mg BID on days 8-34 unless the experiencing adverse events. (n=126) Dosing must not change after Visit 7 of the study (at 21 ± 2 days of dosing) and may be decreased for tolerability reasons no more than once during the study. **Arm II:** Placebo capsules (n=126)	**Inclusion** - 18 to 65 years old - Requires hospitalization for acute exacerbation or relapse of symptoms - PANSS total score 80-120 - CGI-S score of ≥4 **Exclusion** - Any primary DSM-5 disorder other than schizophrenia - Moderate to severe substance abuse disorder - Psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening - History of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months	Change From Baseline in PANSS Total Score [week 5]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
EMERGENT-3[14] **NCT04738123**	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, inpatient study. N = 256 Population: Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia Duration: 5 weeks	**Arm I:** Oral xanomeline 50 mg/trospium 20 mg (KarXT 50/20 mg) BID on days 1-2 followed by KarXT 100/20 mg BID on days 3-7. The dose is increased to KarXT 125/30 mg BID on days 8-34 unless experiencing adverse events. (n=125) Dosing must not change after Visit 7 of the study (at 21 ± 2 days of dosing) and may be decreased for tolerability reasons no more than once during the study. **Arm II:** Placebo capsules (n=131)	**Inclusion** - 18 to 65 years old - Requires hospitalization for acute exacerbation or relapse of symptoms - PANSS total score 80-120 - CGI-S score of ≥4 **Exclusion** - Any primary DSM-5 disorder other than schizophrenia - Moderate to severe substance abuse disorder - Psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening - History of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months	Change From Baseline in PANSS Total Score [week 5]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Risperidone				
Casey 2008[28]	Randomized, double-blind, fixed-dose, placebo-controlled, parallel-group study. N = 589 Population: Adult patients with an acute exacerbation of schizophrenia Duration: 6 weeks	**Arm I:** Oral bifeprunox 5 mg once daily (n=115) **Arm II:** Oral bifeprunox 10 mg once daily (n=120) **Arm III:** Oral bifeprunox 20 mg once daily (n=115) **Arm IV:** Oral risperidone 6 mg once daily (n=120) **Arm V:** Oral placebo once daily (n=119)	**Inclusion** - 18 to 65 years old at screening - PANSS score between 70 and 120 - Baseline score of ≥4 on at least two of key PANSS items - A CGI-S score of ≥4 **Exclusion** - Current psychiatric diagnosis other than schizophrenia - Current diagnosis or history of substance abuse or alcohol abuse within 6 months - Treatment resistant schizophrenia	Change from baseline in PANSS total score [week 5]
Downing 2014[34]	Phase 2, multicenter, randomized, double blind, parallel, fixed-dose study. N= 1013 Population: Adult patients with schizophrenia who had experienced an exacerbation of symptoms Duration: 6 weeks	**Arm I:** LY2140023 40 mg, orally, BID (n=292) **Arm II:** LY2140023 80 mg, orally, BID (n=280) **Arm III:** Placebo capsules or tablets, orally, BID (n=295) **Arm IV:** Risperidone 2 mg, orally, BID (n=142)	**Inclusion** - Experienced an exacerbation of their illness 2 weeks prior leading to a need for intensification of psychiatric care - Antipsychotic treatment naive or not treatment resistant **Exclusion** - Any other current Axis I psychiatric diagnoses in addition to schizophrenia - A diagnosis of substance abuse - History of one or more seizures	Change from baseline in the PANSS total score [week 5]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Geffen 2012[40]	Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study. N = 363 Population: Adults diagnosed with chronic schizophrenia Duration: 6 weeks	**Arm I**: BL-1020 10 mg/day (n=90) **Arm II:** BL-1020 20-30 mg/day (n=89) **Arm III:** Risperidone 2-8 mg/day (n=91) **Arm IV:** Placebo, daily (n=93)	**Inclusion** - 18 to 65 years old at screening - Acute exacerbation within 30 days - PANSS total score ≥70 and ≥4 on 2 key PANSS items - CGI-S rating of ≥4 **Exclusion** - Treatment resistant - Tardive dyskinesia (past or present) - Clozapine use within 3 years	PANSS total score [week 6]
Durgam 2014[36]	Phase IIb, multinational, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study N = 732 Population: Adult patients with acute exacerbation of schizophrenia Duration: 9 weeks (1 week washout period, 6 weeks of double-blind treatment, 2-week safety period)	**Arm I:** Placebo (n=151) **Arm II:** Cariprazine 1.5 mg/d (n=145) **Arm III:** Cariprazine 3.0 mg/d (n=146) **Arm IV:** Cariprazine 4.5 mg/d (n=147) **Arm V:** Risperidone 4.0 mg/d (n=140)	**Inclusion** - 18 to 60 years old - At least 1 psychotic episode requiring hospitalization, antipsychotic medication change, or intervention during the preceding year - PANSS total score of 80-120 range - A score ≥4 on at least 2 of 4 PANSS positive symptoms - CGI-S rating ≥4 **Exclusion** - Patients with treatment-resistant schizophrenia - Patients experiencing a first episode of psychosis	Change from baseline in PANSS total [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Potkin 2007[39]	Double-blind, double-dummy, 3-arm, fixed-dose, placebo- and risperidone-controlled trial N = 182 Population: Patients with acute schizophrenia. Duration: 6 weeks	**Arm I:** 5 mg sublingual asenapine BID and oral placebo BID (n=60) **Arm II:** 3 mg oral risperidone BID and sublingual placebo BID (n=60) **Arm III:** Oral and sublingual placebo BID (n=62)	**Inclusion** - ≥18 years old - CGI-S score ≥4 - PANSS total score ≥60 - Baseline score ≥4 on ≥2 items of the PANSS positive subscale **Exclusion** - A diagnosis of residual-type schizophrenia, schizophreniform disorder, or schizoaffective disorder - A score >2 on any item of the Abnormal Involuntary Movement Scale	Change from baseline in PANSS total score [week 6]
Lieberman 2015[46]	Phase II, randomized, double-blind, placebo- and active-controlled, multicenter trial N = 335 Population: Acutely psychotic adults with schizophrenia Duration: 4 weeks	**Arm I:** ITI-007 60 mg taken orally once daily in the morning (n=84) **Arm II:** ITI-007 120 mg taken orally once daily in the morning (n=84) **Arm III:** Placebo taken orally once daily in the morning (n=85) **Arm IV:** Risperidone 4 mg taken orally once daily in the morning (n=82)	**Inclusion** - 18 to 55 years of age - Experiencing an acute exacerbation of psychosis defined as a score of ≥40 on the 18-item Brief Psychiatric Rating Scale with a score of ≥4 on ≥2 of the positive symptom items - The current acute episode starting ≤4 weeks of screening **Exclusion** - Treatment-naïve or treatment-resistant - Schizoaffective disorder/bipolar disorder/acute mania/major depression with psychotic features	Change from baseline in PANSS total score [week 4]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Walling 2019[55]	Phase II, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study N = 259 Population: Patients with an acute exacerbation of schizophrenia Duration: 4 weeks	**Arm I:** PF-02545920 5 mg every 12 hours (n=74) **Arm II:** PF-02545920 15 mg every 12 hours (n=74) **Arm III:** Risperidone 3 mg every 12 hours (n=37) **Arm IV:** Placebo every 12 hours (n=74)	**Inclusion** - Patients aged 18 to 65 years - Experiencing an acute exacerbation of schizophrenia <4 weeks' duration - PANSS-derived Brief Psychiatric Rating Scale score of ≥45 at screening and ≥4 on ≥2 of the 4 core items - CGI-S score of ≥4 at screening and baseline **Exclusion** - Dystonic reactions to ≥3 prior antipsychotics - History of treatment-resistant schizophrenia	Change from baseline in the total PANSS score [4 weeks]
Higuchi 2019[41]	Phase III, randomized, double-blind, double-dummy, parallel-controlled, adjustable dose, non-inferiority, and multicenter study N = 460 Population: Hospitalized patients with schizophrenia Duration: 6 weeks	**Arm I:** Lurasidone tablets 40 mg/d (n=125) **Arm II:** Lurasidone tablets 80 mg/d (n=129) **Arm III:** Risperidone tablets 4 mg/d (n=64) **Arm IV:** Placebo tablets (n=129)	**Inclusion** - Aged between 18 and 65 years - PANSS total score ≥ 70 and ≤ 120 - Score ≥ 4 on the CGI-S **Exclusion** - History of alcohol abuse/alcoholism or drug abuse/dependence within the last 6 months	Mean Change from Baseline in PANSS Total Scores [6 weeks]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Olanzapine				
Egan 2013[37]	Phase IIa, Randomized, Multicenter, Double-Blind, Active Comparator- and Placebo-Controlled Study N = 216 Population: Acutely psychotic inpatients with schizophrenia Duration: 4 weeks	**Arm I:** MK-8998 6 mg capsules with matching placebos, taken orally twice daily (n=86) **Arm II:** Olanzapine 5 mg tablets with matching placebos, taken orally twice daily (n=47) **Arm III:** Placebo tablets matching olanzapine tablets and MK-8998 capsules, taken orally twice daily (n=83)	**Inclusion** - Patient's age is 18 to 55 - Diagnosed with schizophrenia for over 1 year - Acute exacerbation of psychotic symptoms ≥3 days and ≤6 weeks **Exclusion** - History of treatment-resistant schizophrenia - History of alcohol/drug dependence	Mean Change from Baseline in the PANSS [4 weeks]
Schmidt 2012[53]	Multicenter, double-blind, randomized, placebo- and active-controlled, parallel-group, dose–response study N = 498 Population: Patients with schizophrenia who were experiencing an exacerbation of their illness. Duration: 12 weeks	**Arm I:** JNJ-37822681 10 mg, BID (n=100) **Arm II:** JNJ-37822681 20 mg, BID (n=104) **Arm III:** JNJ-37822681 30 mg, BID (n=100) **Arm IV:** Olanzapine 15 mg, once-daily (n=93) **Arm V:** Placebo for 6 weeks followed by olanzapine (15 mg, once-daily) for the remaining 6 weeks (n=101)	**Inclusion** - Aged between 18 and 65 years - Diagnosed with schizophrenia for at least 1 year - An acute exacerbation of disease for less than 6 months - PANSS total score 70-120 **Exclusion** - Antipsychotic naïve patients - A history of lack of response to antipsychotic therapy - Had used clozapine for treatment resistance or reduction of suicidal risk	Change in PANSS total score from baseline [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Shen 2014[54]	Randomized, double-blind, placebo-controlled, comparator-referenced, multicenter parallel-group trial. N = 289 Population: Adult subjects with acute exacerbation of schizophrenia Duration: 6 weeks	**Arm I:** 200 mg/day vabicaserin (n=82) **Arm II:** 400 mg/day vabicaserin (n=77) **Arm III:** olanzapine 15 mg/day (n=77) **Arm IV:** placebo (n=77)	**Inclusion** - PANSS total score ≥70 and ≤120 - PANSS Positive Symptoms Subscale score ≥20, and scores of ≥4 on at least 2 of the 4 key PANSS items - CGI-S score ≥4 **Exclusion** - Known history of resistance to antipsychotic treatment - Current diagnosis or history of substance dependence	Change in Central Rated PANSS Positive Subscale [week 6]
Bugarski Kirola 2014[27]	Multicenter, randomized, double-blind, double-dummy, placebo-and active-controlled, parallel group phase II/III study N = 301 Population: Patients with acute exacerbation of schizophrenia Duration: 4 weeks	**Arm I:** Bitopertin 10mg orally daily (n=80) **Arm II:** Bitopertin 30mg orally daily (n=79) **Arm III:** Olanzapine 15mg orally daily (n=63) **Arm IV:** Placebo orally daily (n=79)	**Inclusion** - 18 to 65 years of age - Acute exacerbation beginning within the previous 8 weeks - PANSS total score of 80-120 including a score of ≥4 on ≥2 of the key PANSS items - CGI-S score of ≥4 at screening **Exclusion** - Current or previous treatment with clozapine - A primary movement disorder	Change in PANSS total score [4 weeks]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Beasley 1996b[47]	Randomized, double-blind, placebo-controlled study N = 271 Population: Patients met the DSM-III-R criteria for schizophrenia with an acute exacerbation Duration: 6 weeks	**Arm I:** Olanzapine 2.5, 5, or 7.5 mg/day (n=65) **Arm II:** Olanzapine 7.5, 10, 0r 12.5 mg/day (n=64) **Arm III:** Olanzapine 12.5, 15, or 17.5 mg/day (n=69) **Arm IV:** Haloperidol 10, 15, 20 mg/day (n=69) **Arm V:** Placebo daily (n=68)	**Inclusion** - Age 18 and 65 - BPRS-Anchored total score of 24 **Exclusion** - Substance-use disorder active within 3 months of study entry - Patients with Parkinson's disease or myasthenia gravis	Change in BPRS-positive score [week 6]
Davidson 2007[33]	Multicenter, double-blind, randomized, placebo- and active-controlled, parallel group, dose-response study N = 618 Population: Adults experiencing an acute episode of schizophrenia Duration: 6 weeks	**Arm I:** paliperidone ER 3 mg oral once daily **Arm II:** paliperidone ER 9 mg oral once daily **Arm III:** paliperidone ER 15 mg oral once daily **Arm IV:** olanzapine 10 mg oral once daily **Arm V:** placebo once daily	**Inclusion** - ≥18 years old - PANSS total score between 70 and 120 - Diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year prior to screening **Exclusion** - History of tardive dyskinesia - History of unresponsiveness to antipsychotics	Change in PANSS total score [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
ENLIGHTEN-1 2020[51]	Phase III, double-blind, randomized, active- and placebo-controlled study N = 403 Population: adult subjects with acute exacerbation of schizophrenia Duration 4 weeks	**Arm I:** OLZ/SAM 20 mg/10 mg orally once daily **Arm II:** olanzapine 20 mg orally once daily **Arm III:** placebo orally once daily	**Inclusion** - Age 18 to 70 years - PANSS total score ≥80 with a score ≥4 on ≥3 of the PANSS items - CGI-S score of ≥4 at screening **Exclusion** - A psychiatric hospitalization for ≥30 days during the 90 days - First antipsychotic treatment within the past 12 months - Received clozapine within 6 months prior to screening - History of treatment resistance	Change in PANSS total score [week 4]
Kane 2007b[43]	Multicenter, double-blind, randomized, placebo- and active-controlled, parallel-group, dose-response study. N = 628 Population: Adult patients experiencing an acute episode of schizophrenia Duration: 6 weeks	**Arm I:** paliperidone ER 6 mg orally once daily (n=123) **Arm II:** paliperidone ER 9 mg orally once daily (n=122) **Arm III:** paliperidone ER 12 mg orally once daily (n=130) **Arm IV:** olanzapine 10 mg orally once daily (n=128) **Arm V:** placebo orally once daily (n=127)	**Inclusion** - ≥18 years of age - PANSS total score 70-120 - Diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year **Exclusion** - History of unresponsiveness to antipsychotics - History of tardive dyskinesia	Change in PANSS total score from baseline to end point [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Marder 2007c[48]	Multicenter, double-blind, randomized, parallel-group study N = 444 Population: Adult patients with acute schizophrenia Duration: 6 weeks	**Arm I:** once-daily oral paliperidone ER 6 mg (n=112) **Arm II:** once-daily oral paliperidone ER 12 mg (n=112) **Arm III:** once-daily oral olanzapine 10 mg (n=110) **Arm IV:** once-daily oral placebo (n=110)	**Inclusion** - ≥18 years of age - PANSS total score of 70 –120 - Diagnosis of schizophrenia for 1 year **Exclusion** - History of unresponsiveness to antipsychotics - History of tardive dyskinesia - Diagnosis of substance dependence within the previous 6 months	Change in PANSS total score from baseline to end point [week 6]
Meltzer 2011[50]	Randomized, double-blind, prospective, multicenter, parallel-group study N = 478 Population: Recently admitted acutely ill adult inpatients with schizophrenia with an acute exacerbation of psychotic symptoms Duration: 6 weeks	**Arm I:** lurasidone, 40 mg once daily (n=119) **Arm II:** lurasidone, 120 mg once daily (n=118) **Arm III:** olanzapine, 15 mg once daily (n=122) **Arm IV:** placebo, once daily (n=114)	**Inclusion** - Hospitalized patients 18–75 years of age - Illness duration of at least 1 year - Hospitalized for ≤2 weeks - PANSS total score ≥80 with a score ≥4 on ≥2 of the PANSS items - CGI-S score ≥4	Change from baseline in PANSS total score [week 6]
Kinon 2011[44]	Phase 2, multicenter, randomized, double-blind, parallel, placebo- and active-controlled study N = 669 Population: Adult patients with acutely exacerbated schizophrenia	**Arm I:** LY2140023 monohydrate 5 mg twice daily **Arm II:** LY2140023 monohydrate 20 mg twice daily **Arm III:** LY2140023 monohydrate 40 mg	**Inclusion** - Age 18 to 65 years - Brief Psychiatric Rating Scale total score, extracted from PANSS, of ≥45 - A minimum score of 4 on the CGI-S scale **Exclusion** - Ever having active suicidal ideation	Change in PANSS total score [week 4]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
	Duration: 4 weeks	twice daily **Arm IV:** LY2140023 monohydrate 80 mg twice daily **Arm V:** placebo twice daily **Arm VI:** placebo (AM) and 15 mg of olanzapine (PM) daily		
Landbloom 2017[45]	Randomized, double-blind, double-dummy, fixed-dose trial N = 360 Population: Adult subjects with an acute exacerbation of schizophrenia Duration: 6 weeks	**Arm I:** asenapine 2.5 mg bid (n=97) **Arm II:** asenapine 5 mg bid (n=113) **Arm III:** placebo (n=101) **Arm IV:** olanzapine 15 mg once daily (n=46)	**Inclusion** - Aged ≥18 years - PANSS total score ≥70 with a score ≥4 on at ≥2 items in the PANSS positive subscale - CGI-S score ≥4 - An acute exacerbation of schizophrenia (duration of ≤8 weeks) **Exclusion** - BMI <18.5 or >40.0 kg/m^2 - Clozapine use within 12 weeks before baseline for treatment-resistant schizophrenia	Difference in least squares mean change from baseline [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Corrigan 2004[30]	Multinational, multicenter, randomized, double-blind, placebo- and olanzapine-controlled trial N = 467 Population: Hospitalized adults with schizophrenia Duration: 6 weeks	**Arm I:** Sonepiprazole 1.5 mg/day (n=96) **Arm II:** Sonepiprazole 10 mg/day (n=99) **Arm III:** Sonepiprazole 60 mg/day (n=91) **Arm IV:** Olanzapine 15 mg/day (n=93) **Arm V:** Placebo daily (n=87)	**Inclusion** - Age 18–65 years - score of at least 60 on the PANSS - Patients who had never received antipsychotic therapy and those who were relapsing after chronic treatment **Exclusion** - History of failure to respond to standard antipsychotic treatments at therapeutic doses - History of drug or alcohol use	Mean change from baseline in the PANSS total score [6 weeks]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Aripiprazole				
McEvoy 2007b[49]	Multicenter, double-blind, placebo-controlled randomized trial Population: Adults with schizophrenia diagnosis experiencing acute relapse Duration: 6 weeks N = 420	**Arm I:** Aripiprazole 10 mg once daily (n=106) **Arm II:** Aripiprazole 15 mg once daily (n=106) **Arm III:** Aripiprazole 20 mg once daily (n=100) **Arm IV:** Placebo (n=108)	**Inclusion** - 18 years or older - Acute exacerbation of symptoms that required inpatient hospitalization - PANSS Total score of ≥60 and a score of at ≥4 on ≥2 of the 4 key items - Prior responsiveness to antipsychotic medication **Exclusion** - History of significant substance abuse disorder within 3 months	Mean change from baseline in PANSS Total score [week 6]
Durgam 2015[35]	Phase III multinational, fixed-dose, double-blind, placebo- and active controlled randomized trial Population: Adults with schizophrenia diagnosis experiencing acute psychotic episode Duration: 9 weeks (1 week washout, 6 weeks of double-blind treatment, 2 weeks safety follow-up) N = 617	**Arm I:** Cariprazine 3 mg once daily (n=155) **Arm II:** Cariprazine 6 mg once daily (n=157) **Arm III:** Aripiprazole 10 mg once daily (n=152) **Arm IV:** Placebo (n=153)	**Inclusion** - 18 to 60 years old - Diagnoses for ≥ 1 year and had ≥ 1 psychotic episode that required hospitalization or change in antipsychotic medication - Duration of current episode must be <2 weeks - CGI-S score of ≥4, PANSS total score of ≥80-≤120, and score ≥4 on at least 2 of the PANSS positive symptoms **Exclusion** - Substance abuse/dependence or suicide attempt (past 2 years) - Treatment resistance - BMI <18 or >40	Mean change from baseline in PANSS Total score [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Correll 2016[89]	Phase II multicenter, double-blind, flexible-dose, placebo- and active-controlled randomized trial Population: Adults with a schizophrenia diagnosis experiencing an acute exacerbation of symptoms Duration: 6 weeks N = 459	**Arm I:** Brexipiprazole 0.25 mg once daily (n=42) **Arm II**: Brexipiprazole 1 ± 0.5 mg once daily (n=89) **Arm III:** Brexipiprazole 2.5 ± 0.5 mg once daily (n=90) **Arm IV:** Brexipiprazole 5 ± 1.0 mg once daily (n=93) **Arm V:** Aripiprazole 15 ± 5 mg once daily (n=50) **Arm VI**: Placebo (n=95)	**Inclusion** - Aged 18 to 65 - PANSS total score ≥80 together with a CGI-S score ≥4 **Exclusion** - First episode of schizophrenia - DSM-IV-TR Axis I diagnosis other than schizophrenia - Substance abuse or dependence in the previous 180 days - Clinically significant medical condition.	Mean change from baseline in PANSS Total score [week 6]
Cutler 2006[31]	Multicenter, double-blind, placebo-controlled randomized trial Population: Adults with a schizophrenia diagnosis experiencing an acute relapse Duration: 6 weeks N = 367	**Arm I:** Aripiprazole 2 mg once daily (n=93) **Arm II:** Aripiprazole 5 mg once daily (n=92) **Arm II:** Aripiprazole 10 mg once daily (n=94) **Arm IV:** Placebo (n=88)	**Inclusion** - 18 years and older - Worsening of schizophrenia within the previous 3 months and required inpatient hospitalization - PANSS Total score of >60 and a score of at least 4 on >2 of key PANSS items - Responsiveness to antipsychotic medication in the past 2 years **Exclusion** - DSM-IV diagnosis of schizoaffective disorder - Clinical history or current presentation consistent with delirium, dementia, amnesic or other cognitive disorder, or bipolar disorder - Significant substance abuse disorder within the previous 3 months	Mean change from baseline in PANSS Total score [week 6]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
			- Hospitalization more than 14 days for the current acute episode	
Head-to-Head				
Fleischhacker 2009[38]	Multicenter, double-blind randomized trial Population: Adults with schizophrenia diagnosis experiencing acute relapse requiring hospitalization Duration: 6 weeks (+ 46-week extension study) N = 703	**Arm I:** Aripiprazole 15 to 30 mg daily (n=355) **Arm II:** Olanzapine 10 to 20 mg daily (n=348)	**Inclusion** - 18 and 65 years old - Had demonstrated a previous response to antipsychotic drugs - Had been treated as outpatients for at least one continuous 3-month period during the past 12 months **Exclusion** - DSM-IV diagnosis of any other psychiatric disorder - History of substance abuse - Significant risk of suicide - Recent treatment with a long-acting antipsychotic	Mean change from baseline in PANSS total score [week 6] and percentage of patients showing significant weight gain (≥7%) from baseline [week 26]
McQuade 2004[32]	Double-blind, parallel-group randomized trial Population: Adults with schizophrenia diagnosis experiencing acute relapse Duration: 26 weeks N= 317	**Arm I:** Aripiprazole 15 to 30 mg daily (n=156) **Arm II:** Olanzapine 10 to 20 mg daily (n=161)	**Inclusion** - 18 years and older with DSM-IV diagnosis of schizophrenia in acute relapse and requiring hospitalization - Had been treated as an outpatient for at least 1 continuous 3-month period during the past 12 months **Exclusion** - Hospitalized for >14 days immediately prior to screening - Patients who had failed to respond to clozapine, or who were likely to require concomitant therapy	Incidence of significant weight gain (≥7%) [week 26]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Chen 2018[29]	Open-label and naturalistic randomized controlled trial Population: Adults with diagnosis of schizophrenia experiencing a relapse Duration: 12 weeks N = 111	**Arm I:** Olanzapine 10 - 20 mg daily (n=53) **Arm II:** Risperidone 4 -6 mg daily (n=28) **Arm III:** Paliperidone 6 - 12 mg daily (n=30)	**Inclusion** - 18 to 65 years old - Hospitalized with diagnosis of schizophrenia - No major systemic illnesses based on physical examinations and laboratory test results - Baseline PANSS total score ≥60 **Exclusion** - Participants not taking any antipsychotics in the previous one month - History of clozapine treatment in the previous 3 months - Patients receiving long-acting antipsychotic injections in the preceding 6 months of enrollment	PANSS score at weekly time points [up to week 12]
Sacchetti 2008[52]	Flexible-dose, parallel-group, rate-blind, quasi-naturalistic randomized trial Population: Adults with DSM-IV-TR diagnosis of schizophrenia hospitalized for severe psychotic symptoms Duration: 8 weeks N = 75	**Arm I:** Risperidone 4 mg BID (8 mg total) (n=25) **Arm II:** Olanzapine 20 mg once daily (n=25) **Arm III:** Quetiapine 800 mg once daily (n=25)	**Inclusion** - 18 and 65 years old - Total score of ≥70 on the PANSS - No exposure to depot antipsychotics in the previous 6 weeks. **Exclusion** - Current DSM-IV-TR axis I comorbid disorders - History of substance-abuse related disorders in the preceding 6 months - Concomitant severe, unstable physical illnesses	Improvement from baseline in PANSS total score in the per protocol population and the number of completers who experienced ≥ 40% improvement on the same scale [week 8]

Trial	Study Design	Treatment Arms (mean dosage)	Inclusion/Exclusion Criteria	Primary Outcome
Jindal 2013[42]	Randomized, double-blind controlled trial Population: Adults with ICD-10 diagnosis of schizophrenia who are acutely hospitalized Duration: 6 weeks N = 60	**Arm I:** Aripiprazole 10 mg/day. Dose was increased up to 20 mg/day as needed. (n=30) **Arm II:** Olanzapine 10 mg/day. Dose was increased up to 20 mg/day as needed. (n=30)	**Inclusion** - 18 to 65 years old - Hospitalized with a diagnosis of schizophrenia according to ICD-10 classification of Mental and Behavioral disorders **Exclusion** - Comorbid medical/psychiatric disorder, history of seizure disorder, substance abuse/dependence	Percentage of patients showing clinical improvement (defined as 40% reduction in the BPRS total score as compared to baseline) [week 6]

BID: two times a day, BMI: body mass index, BPRS: Brief Psychiatric Rating Scale, CGI-S: Clinical Global Impression Scale - Severity, DSM-III-R: The Diagnostic and Statistical Manual of Mental Disorders Third Edition, DSM-IV: The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, DSM-IV-TR: The Diagnostic and Statistical Manual of Mental Disorders Text Revision Fourth Edition, DSM-5: The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, ICD-10: International Classification of Diseases Tenth Revision, mg: milligram, mg/d: milligrams per day, n: number, OLZ/SAM: combination of olanzapine and samidorphan , PANSS: The Positive and Negative Syndrome Scale

Table D3.2. Baseline Characteristics[15,19,25-55,89]

Study Name	Weeks	Arms (mean dosage)	N	Age, mean (SD)	Sex, n (%)		Duration of schizophrenia, mean (SD), years	Past Psychiatric Hospitalizations, mean (SD)	Baseline weight, mean (SD), kg	BMI, mean (SD)
					Male	Female				
KarXT										
EMERGENT-1	5	KarXT 125/30 mg	90	43.4 (10.1)	72 (80.0)	*18 (20.0)*	NR	NR	NR	28.1 (5.0)
		Placebo	92	41.6 (10.1)	68 (73.9)	*24 (26.1)*	NR	NR	NR	29.6 (5.4)
EMERGENT-2	5	KarXT 125/30 mg	126	45.6 (10.4)	95 (75.4)	31 (24.6)	NR	NR	NR	30.2 (5.4)
		Placebo	126	46.2 (10.8)	95 (75.4)	31 (24.6)	NR	NR	NR	29.1 (5.4)
EMERGENT-3	5	KarXT 125/30 mg	125	43.6 (11.4)	87 (69.6)	38 (30.4)	NR	NR	NR	NR
		Placebo	131	42.6 (12.2)	104 (79.4)	27 (20.6)	NR	NR	NR	NR
Risperidone										
Casey 2008	6	Risperidone 6mg	116	41.1 (8.6)	94 (81)	22 (19)	NR	NR	88.2 (NR)	NR
		Placebo	114	40.8 (9.4)	88 (77)	26 (23)	NR	NR	87.2 (NR)	NR
Downing 2014	6	Risperidone 4 mg	142	40.3 (11.1)	87 (61.3)	*55 (38.7)*	15.2 (10.4)	7.4 (5.7)	82.7 (21.9)	NR
		Placebo	295	39.8 (11.4)	181 (61.4)	*114 (38.6)*	14.5 (10.7)	8.0 (9.4)	81.4 (20.8)	NR
Geffen 2012	6	Risperidone 8mg	91	34.2 (10.3)	65 (71.4)	*26 (28.6)*	8.3 (8.9)	NR	60.9 (13.2)	22.6 (4.02)
		Placebo	93	35.2 (10.3)	56 (60.2)	*37 (39.8)*	9.3 (8.9)	NR	61.4 (15.9)	23.4 (5.7)
Durgam 2014	6	Risperidone 4mg	140	36.5 (11.1)	98 (70.0)	*42 (30.0)*	12.3 (9.9)	6.3 (8.1)	75.1 (18.2)	25.8 (4.8)
		Placebo	151	36.0 (10.8)	101 (66.9)	*50 (33.1)*	11.6 (9.7)	5.6 (5.7)	74.4 (18.6)	25.2 (4.5)

Study Name	Weeks	Arms (mean dosage)	N	Age, mean (SD)	Sex, n (%)		Duration of schizophrenia, mean (SD), years	Past Psychiatric Hospitalizations, mean (SD)	Baseline weight, mean (SD), kg	BMI, mean (SD)
					Male	Female				
Potkin 2007c	6	Risperidone 6mg	59	43 (22-61)*	36 (61.0)	*23 (39.0)*	NR	NR	85 (57-162)*	NR
		Placebo	62	42 (22-68)*	49 (79.0)	*13 (21.0)*	NR	NR	90 (55-150)*	NR
Lieberman 2015	4	Risperidone 4mg	82	40.7 (9.3)	73 (89.0)	*9 (11.0)*	15.2 (9.4)	NR	NR	NR
		Placebo	85	40.5 (9.8)	65 (76.5)	*20 (23.5)*	16.7 (10.4)	NR	NR	NR
Walling 2019	4	Risperidone 3mg Q12H	36	41.3 (10.9)	25 (69.0)	11 (31)	16 (2-38)*	NR	83.8 (16.9)	28.1 (5.0)
		Placebo	74	41.2 (10.9)	56 (76.0)	18 (24)	15.5 (0.4-47)*	NR	83.9 (18.8)	27.6 (5.5)
Higuchi 2019	6	Risperidone 4 mg	64	45.6 (NR)	*114* (59.1)	*79* (40.9)	69.1% > 10 years	NR	NR	NR
		Placebo	129					NR	NR	NR
Olanzapine										
Egan 2013	4	Olanzapine 15mg	47	36.1 (10.3)	24 (51.1)	*23 (48.9)*	10.7 (9.7)	8.4 (7.6)	NR	NR
		Placebo	83	36.4 (8.5)	53 (63.9)	*30 (36.1)*	11.2 (7.3)	6.9 (5.5)	NR	NR
Schmidt 2012	6	Olanzapine 15mg	93	38.6 (10.8)	49 (53)	44 (47)	10.7 (7.9)	NR	71.3 (15.1)	24.7 (4.7)
		Placebo	99	38 (10.5)	59 (60)	40 (40)	10.9 (8.5)	NR	73.3 (14.2)	25.3 (4.6)
Shen 2014	6	Olanzapine 15mg	71	40.1 (10.5)	46 (64.8)	25 (35.2)	NR	NR	92.1 (27.3)	NR
		Placebo	71	39.6 (10.4)	52 (73.3)	19 (26.8)	NR	NR	86.0 (21.3)	NR
Bugarski Kirola 2014	4	Olanzapine 15mg	62	40.3 (12.4)	46 (74.2)	16 (25.8)	13.9 (11.1)	NR	NR	NR
		Placebo	80	37.8 (11.5)	58 (72.5)	22 (27.5)	12.5 (9.6)	NR	NR	NR

Study Name	Weeks	Arms (mean dosage)	N	Age, mean (SD)	Sex, n (%)		Duration of schizophrenia, mean (SD), years	Past Psychiatric Hospitalizations, mean (SD)	Baseline weight, mean (SD), kg	BMI, mean (SD)
					Male	Female				
Beasley 1996b	6	Olanzapine 2.5-7.5mg	65	36 (10)	*60* (92.3)	*5 (7.7)*	NR	NR	NR	NR
		Olanzapine 7.5-12.5mg	64	37 (10)	*56* (87.5)	*8 (12.5)*	NR	NR	NR	NR
		Olanzapine 12.5-17.5mg	69	36 (10)	*54* (78.3)	*15 (21.7)*	NR	NR	NR	NR
		Placebo	68	35 (8)	*62* (91.2)	6 (8.8)	NR	NR	NR	NR
Davidson 2007	6	Olanzapine 10 mg	126	36.5 (10.2)	*96* (76)	*30* (24)	NR	NR	75.3 (20.8)	25.8 (7.3)
		Placebo	120	37.3 (10.9)	*83* (69)	*37* (31)	NR	NR	75.8 (19.3)	25.8 (5.7)
ENLIGHTEN-1	4	Olanzapine 20 mg	133	41.5 (10.9)	81 (60.9)	*52 (39.1)*	NR	NR	82.2 (19.3)	27.5 (5.4)
		Placebo	134	41.1 (10.6)	78 (58.2)	*56 (41.8)*	NR	NR	76.6 (15.9)	25.9 (4.8)
Kane 2007b	6	Olanzapine 10 mg	128	36.3 (11.2)	*60* (47)	*68* (53)	NR	NR	71.7 (19.5)	NR
		Placebo	126	37.9 (10.9)	*65* (52)	*61* (48)	NR	NR	71.2 (16.3)	NR
Marder 2007c	6	Olanzapine 10 mg	105	40.5 (11.0)	*84* (80)	*21* (20)	NR	NR	89.7 (23.2)	NR
		Placebo	105	42.3 (10.7)	*82* (78)	*33* (32)	NR	NR	89.7 (20.3)	NR
Meltzer 2011	6	Olanzapine 15 mg	122	38.3 (10.2)	95 (78)	*27 (22)*	13.2 (10.9)	NR	76.0 (20.1)	26.0 (6.1)
		Placebo	114	37.0 (11.3)	88 (77)	*26 (23)*	12.6 (9.6)	NR	75.2 (18.6)	25.8 (5.4)
Kinon 2011	4	Olanzapine	62	41.7 (12.3)	*34* (54.8)	*28 (45.2)*	15.0 (10.8)	NR	73.9 (17.9)	NR
		Placebo	122	38.9 (11.3)	*70* (57.4)	*52 (42.6)*	12.5 (10.2)	NR	73.0 (13.4)	NR
Landbloom 2017	6	Olanzapine 15 mg	46	40.8 (11.2)	*28 (60.1)*	18 (39.1)	NR	NR	NR	NR

Study Name	Weeks	Arms (mean dosage)	N	Age, mean (SD)	Sex, n (%)		Duration of schizophrenia, mean (SD), years	Past Psychiatric Hospitalizations, mean (SD)	Baseline weight, mean (SD), kg	BMI, mean (SD)
					Male	Female				
		Placebo	101	41.4 (12.1)	*54 (53.5)*	47 (46.5)	NR	NR	NR	NR
Corrigan 2004	6	Olanzapine 15 mg	93	36.8 (19-61)*	59 (63.4)	34 (36.6)	12.3 (0-12)*	NR	NR	NR
		Placebo	87	37.2 (19-59)*	63 (72.4)	24 (27.6)	14.2 (1-12)*	NR	NR	NR
Aripiprazole										
McEvoy 2007b	6	Aripiprazole 10 mg	106	40.0 (1.1)†	82 (77)	24 (23)	NR	NR	82.9 (2.0)†	NR
		Aripiprazole 15 mg	106	40.0 (1.1)†	79 (75)	27 (25)	NR	NR	81.5 (1.9)†	NR
		Aripiprazole 20 mg	100	40.4 (1.1)†	82 (82)	18 (18)	NR	NR	86.7 (2.4)†	NR
		Placebo	108	41.2 (1.1)†	83 (77)	25 (23)	NR	NR	84.1 (1.9)†	NR
Durgam 2015	6	Aripiprazole 10mg	152	39.3 (10.8)	94 (61.8)	58 (38.2)	12.4 (8.9)	7.5 (9.4)	79.5 (17.1)	NR
		Placebo	153	38.2 (11.3)	97 (63.4)	56 (36.6)	12.5 (9.7)	7.2 (9.4)	78.3 (18.4)	NR
Correll 2016	6	Aripiprazole 15 +/- 5 mg	50	40.8 (11.0)	34 (68.0)	16 (32.0)	NR	NR	NR	24.7 (4.8)
		Placebo	93	38.8 (11.5)	56 (60.2)	37 (39.8)	NR	NR	NR	26.4 (5.4)
Cutler 2006	6	Aripiprazole 2 mg	93	40.7	74 (79.6)	19 (20.4)	NR	NR	NR	NR
		Aripiprazole 5 mg	92	40.9	70 (76.1)	22 (23.9)	NR	NR	NR	NR
		Aripiprazole 10 mg	94	40	72 (76.6)	22 (23.4)	NR	NR	NR	NR
		Placebo	88	42.9	72 (81.8)	16 (18.2)	NR	NR	NR	NR
Head-to-head Trials										
Fleischhacker 2009	6	Olanzapine 10-20mg	348	37.3 (18-65)*	196 (56)	152 (44)	NR	NR	74.5 (42.2-130)*	25.6 (15.1-44.8)*

Study Name	Weeks	Arms (mean dosage)	N	Age, mean (SD)	Sex, n (%)		Duration of schizophrenia, mean (SD), years	Past Psychiatric Hospitalizations, mean (SD)	Baseline weight, mean (SD), kg	BMI, mean (SD)
					Male	Female				
		Aripiprazole 15 - 30mg	355	35.9 (18-64)*	203 (57)	152 (43)	NR	NR	75.9 (41-146.5)*	25.9 (14.8-41.5)*
McQuade 2004	6	Olanzapine 10-20mg	161	38.2 (0.87)†	115 (71)	46 (29)	NR	NR	81.7 (1.67)†	27.7 (0.59)†
		Aripiprazole 15-30mg	156	38.6 (0.85)†	114 (73)	42 (27)	NR	NR	81.3 (1.77)†	27.6 (0.53)†
Chen 2018	12	Olanzapine	53	35.6 (11.26)	33 (62.3)	*20 (37.7)*	8.96 (9.72)	NR	NR	NR
		Risperidone	28	35.04 (9.85)	18 (64.3)	*10 (35.7)*	7.24 (6.92)	NR	NR	NR
Sacchetti 2008	8	Risperidone	25	43 (13)	10 (40)	15 (60)	10 (2-20)*	NR	70 (14)	NR
		Olanzapine	25	35 (11)	18 (72)	7 (28)	7 (1-15)*	NR	68 (15)	NR
Jindal 2018	6	Aripiprazole 12.5 (10-20)	30	NR	19 (63.3)	11 (36.7)	NR	NR	NR	NR
		Olanzapine 11 (10-20)	30	NR	15 (50.0)	15 (50.0)	NR	NR	NR	NR

%: percent, #: number, BMI: body mass index, mg: milligram, N: number, NR: not reported, SD: standard deviation

Note: Italicized data has been calculated

*Range

†Standard Error

‡Reports in ranges, majority of participants between 18-38 years

Table D3.3. Baseline Characteristics, Race and Ethnicity[15,19,27-55,89]

Study Name	Weeks	Arms (mean dosage)	N	Race, n (%)						Ethnicity, n (%)	
				White	Black or African American	Asian	American Indian or Alaska Native	Native Hawaiian or Other Pacific Islander	Other	Hispanic or Latino	Non-Hispanic / Non-Latino
KarXT											
EMERGENT-1	5	KarXT 125/30 mg	90	20 (22.2)	67 (74.4)	2 (2.2)	NR	NR	1 (1.1)	NR	71 (79)
		Placebo	92	17 (18.5)	70 (76.1)	2 (2.2)	NR	NR	3 (3.3)	NR	79 (86)
EMERGENT-2	5	KarXT 125/30 mg	126	26 (20.6)	97 (77.0)	2 (1.6)	NR	NR	1 (0.8)	NR	NR
		Placebo	126	31 (24.6)	92 (73.0)	1 (0.8)	NR	NR	2 (1.6)	NR	NR
EMERGENT-3	5	KarXT 125/30 mg	125	45 (36.0)	79 (63.2)	1 (0.8)	NR	NR	0 (0)	NR	NR
		Placebo	131	53 (40.5)	77 (58.8)	0 (0)	NR	NR	0 (0)	NR	NR
Risperidone											
Casey 2008	6	Risperidone 6 mg	116	43 (37)	54 (47)	2 (2)	2 (2)	NR	5 (5)	12 (10)	NR
		Placebo	114	50 (44)	51 (45)	2 (2)	0 (0.0)	NR	0 (0)	11 (10)	NR
Downing 2014	6	Risperidone 4 mg	142	93 (65.5)	47 (33.1)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	9 (6.3)	133 (93.7)
		Placebo	295	183 (62.0)	102 (34.6)	1 (0.3)	1 (0.3)	2 (0.7)	6 (2.0)	13 (4.4)	282 (95.6)
Geffen 2012	6	Risperidone 8 mg	91	25 (27.5)	3 (3.3)*	63 (69.2)	NR	NR	NR	NR	NR
		Placebo	93	26 (28)	3 (3.2)	64 (68.8)	NR	NR	NR	NR	NR
Durgam 2014	6	Risperidone 4 mg	140	67 (47.9)	35 (25.0)	37 (26.4)	NR	NR	1 (0.7)	NR	NR
		Placebo	151	80 (53.0)	34 (22.5)	36 (23.8)	NR	NR	1 (0.7)	NR	NR

Study Name	Weeks	Arms (mean dosage)	N	Race, n (%)						Ethnicity, n (%)	
				White	Black or African American	Asian	American Indian or Alaska Native	Native Hawaiian or Other Pacific Islander	Other	Hispanic or Latino	Non-Hispanic / Non-Latino
Potkin 2007c	6	Risperidone 6 mg	59	25 (42.0)	26 (44.0)	NR	NR	NR	8 (14.0)	NR	NR
		Placebo	62	20 (32.0)	32 (52.0)	NR	NR	NR	10 (16.0)	NR	NR
Lieberman 2015	4	Risperidone 4 mg	82	16 (19.5)	64 (78.0)	2 (2.4)	NR	NR	0	NR	80 (97.6)
		Placebo	85	17 (20.0)	65 (76.5)	1 (1.2)	NR	NR	2 (2.4)	NR	81 (95.3)
Walling 2019	4	Risperidone 3 mg Q12H	36	11 (30.6)	24 (66.7)	0 (0)	NR	NR	1 (2.8)	NR	NR
		Placebo	74	21 (28.4)	52 (70.3)	0 (0)	NR	NR	1 (1.4)	NR	NR
Higuchi 2019	6	Risperidone 4 mg	64	NR	NR	NR	NR	NR	NR	NR	NR
		Placebo	129	NR	NR	NR	NR	NR	NR	NR	NR
Olanzapine											
Egan 2013	4	Olanzapine 15 mg	47	46 (97.9)	NR	NR	NR	NR	NR	NR	NR
		Placebo	83	83 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
Schmidt 2012	6	Olanzapine 15 mg	93	76 (82)	2 (2)	11 (12)	NR	NR	4 (4)	NR	NR
		Placebo	99	82 (83)	2 (2)	12 (12)	NR	NR	3 (3)	NR	NR
Shen 2014	6	Olanzapine 15 mg	71	19 (26.8)	47 (66.2)	4 (5.6)	1 (1.4)	NR	0 (0)	0 (0)	NR
		Placebo	71	17 (23.9)	48 (67.6)	3 (4.3)	0 (0)	NR	0 (0)	1 (1.4)	NR
	4	Olanzapine 15 mg	62	39 (62.9)	22 (35.5)	1 (1.6)	NR	NR	0 (0)	NR	NR

Study Name	Weeks	Arms (mean dosage)	N	Race, n (%)						Ethnicity, n (%)	
				White	Black or African American	Asian	American Indian or Alaska Native	Native Hawaiian or Other Pacific Islander	Other	Hispanic or Latino	Non-Hispanic / Non-Latino
Bugarski Kirola 2014		Placebo	80	45 (56.3)	30 (37.5)	3 (3.8)	NR	NR	2 (2.5)	NR	NR
Beasley 1996b	6	Olanzapine 2.5 - 7.5 mg	65	*42* (64.6)	*17* (26.2)	NR	NR	NR	NR	NR	NR
		Olanzapine 7.5 - 12.5 mg	64	*46* (71.9)	*13* (20.3)	NR	NR	NR	NR	NR	NR
		Olanzapine 12.5 - 17.5 mg	69	*54* (78.3)	*11* 15.9)	NR	NR	NR	NR	NR	NR
		Placebo	68	*48* (70.6)	*14* (20.6)	NR	NR	NR	NR	NR	NR
Davidson 2007	6	Olanzapine 10 mg	126	*60* (48)	*29* (23)	*30* (24)	NR	NR	*7* (6)	NR	NR
		Placebo	120	*61* (51)	*26* (22)	*28* (23)	NR	NR	*6* (5)	NR	NR
ENLIGHTEN1	4	Olanzapine 20 mg	133	99 (74.4)	33 (24.8)	0 (0)	NR	NR	1 (0.8)	NR	NR
		Placebo	134	91 (67.9)	38 (28.4)	3 (2.2)	NR	NR	2 (1.5)	NR	NR
Kane 2007b	6	Olanzapine 10 mg	128	*111* (87)	NR	*1* (1)	NR	NR	*16* (13)	NR	NR
		Placebo	126	*106* (84)	NR	*1* (1)	NR	NR	*19* (15)	NR	NR
Marder 2007c	6	Olanzapine 10 mg	105	*44* (42)	*56* (53)	*4* (4)	NR	NR	*1* (1)	NR	NR
		Placebo	105	*50* (48)	*53* (50)	0 (0)	NR	NR	*2* (2)	NR	NR
Meltzer 2011	6	Olanzapine 15 mg	122	41 (34)	44 (36)	30 (25)	NR	NR	7 (6)	17 (14)	NR
		Placebo	114	36 (32)	41 (36)	27 (24)	NR	NR	10 (9)	16 (14)	NR
Kinon 2011	4	Olanzapine	62	*57* (91.9)	*3* (4.8)	0 (0)	NR	NR	NR	*2* (3.2)	NR
		Placebo	122	*112* (91.8)	*2* (1.6)	0 (0)	NR	NR	NR	*8* (6.6)	NR

Study Name	Weeks	Arms (mean dosage)	N	Race, n (%)						Ethnicity, n (%)	
				White	Black or African American	Asian	American Indian or Alaska Native	Native Hawaiian or Other Pacific Islander	Other	Hispanic or Latino	Non-Hispanic / Non-Latino
Landbloom 2017	6	Olanzapine 15 mg	46	29 (63.0)	16 (34.8)	0 (0)	0 (0)	0 (0)	1 (2.2)	NR	NR
		Placebo	101	74 (73.3)	27 (26.7)	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
Corrigan 2004	6	Olanzapine 15 mg	93	33 (35.5)	13 (14.0)	28 (30.1)	NR	NR	19 (20.4)	NR	NR
		Placebo	87	25 (28.7)	17 (19.5)	26 (29.9)	NR	NR	19 (21.8)	NR	NR
Aripiprazole											
McEvoy 2007b	6	Aripiprazole 10 mg	106	NR	NR	NR	NR	NR	NR	NR	NR
		Aripiprazole 15 mg	106	NR	NR	NR	NR	NR	NR	NR	NR
		Aripiprazole 20 mg	100	NR	NR	NR	NR	NR	NR	NR	NR
		Placebo	108	NR	NR	NR	NR	NR	NR	NR	NR
Durgam 2015	6	Aripiprazole 10mg	152	99 (65.1)	33 (21.7)	NR	NR	NR	4 (2.6)	NR	NR
		Placebo	153	93 (60.8)	42 (27.5)	NR	NR	NR	6 (3.9)	NR	NR
Correll 2016	6	Aripiprazole 15 +/- 5 mg	50	34 (68.0)	NR	NR	NR	NR	16 (32.0)	NR	NR
		Placebo	93	58 (62.4)	NR	NR	NR	NR	35 (37.6)	NR	NR
Cutler 2006	6	Aripiprazole 2 mg	93	47 (50.5)	41 (44.1)	NR	NR	NR	5 (5.4)	NR	NR
		Aripiprazole 5 mg	92	39 (42.4)	48 (52.2)	NR	NR	NR	5 (5.4)	NR	NR
		Aripiprazole 10 mg	94	52 (55.3)	40 (42.6)	NR	NR	NR	2 (2.1)	NR	NR
		Placebo	88	39 (44.3)	43 (48.9)	NR	NR	NR	6 (6.8)	NR	NR

Study Name	Weeks	Arms (mean dosage)	N	Race, n (%)						Ethnicity, n (%)	
				White	Black or African American	Asian	American Indian or Alaska Native	Native Hawaiian or Other Pacific Islander	Other	Hispanic or Latino	Non-Hispanic / Non-Latino
Head-to-head Trials											
Fleischhacker 2009	6	Olanzapine 10-20 mg	348	313 (90)	18 (5)	NR	NR	NR	17 (5)	NR	NR
		Aripiprazole 15-30 mg	355	326 (92)	13 (4)	NR	NR	NR	16 (5)	NR	NR
McQuade 2004	6	Olanzapine 10-20 mg	161	NR	NR	NR	NR	NR	NR	NR	NR
		Aripiprazole 15-30 mg	156	NR	NR	NR	NR	NR	NR	NR	NR
Chen 2018	12	Olanzapine	53	NR	NR	NR	NR	NR	NR	NR	NR
		Risperidone	28	NR	NR	NR	NR	NR	NR	NR	NR
Sacchetti 2008	8	Risperidone	25	NR	NR	NR	NR	NR	NR	NR	NR
		Olanzapine	25	NR	NR	NR	NR	NR	NR	NR	NR
Cheng 2019	8	Risperidone	157	NR	NR	NR	NR	NR	NR	NR	NR
		Olanzapine	158	NR	NR	NR	NR	NR	NR	NR	NR
		Aripiprazole	162	NR	NR	NR	NR	NR	NR	NR	NR
Jindal 2018	6	Aripiprazole 12.5mg	30	NR	NR	NR	NR	NR	NR	NR	NR
		Olanzapine 11.01mg	30	NR	NR	NR	NR	NR	NR	NR	NR

mg: milligram, N: number, NR: not reported, Q12H: every 12 hours

Note: Italicized data has been calculated

*Black or African American and other

Table D3.4. Baseline PANSS and CGI-S[15,19,27-55,89]

Study Name	Weeks	Arms (mean dosage)	N	Baseline PANSS, mean (SD)			Baseline CGI-S, mean (SD)
				Total	Positive	Negative	
KarXT							
EMERGENT-1	5	KarXT 125/30 mg	90	97.7 (9.7)	26.4 (3.4)	22.6 (4.4)	5.0 (0.6)
		Placebo	92	96.6 (8.3)	26.3 (3.2)	22.8 (4.6)	4.9 (0.6)
EMERGENT-2	5	KarXT 125/30 mg	126	98.3 (8.9)	26.8 (3.7)	22.9 (4.0)	5.1 (0.6)
		Placebo	126	97.9 (9.7)	26.7 (4.0)	22.9 (3.8)	5.1 (0.6)
EMERGENT-3	5	KarXT 125/30 mg	125	97.3 (8.9)	26.9 (3.7)	22.6 (3.2)	5.1 (0.7)
		Placebo	131	96.7 (8.9)	26.4 (3.3)	22.0 (3.7)	5.0 (0.6)
Risperidone							
Casey 2008	6	Risperidone 6 mg	116	90.9 (11.6)	24 (NR)	22.9 (NR)	4.6 (NR)
		Placebo	114	92.1 (12.2)	24.4 (NR)	23.1 (NR)	4.54 (NR)
Downing 2014	6	Risperidone 4 mg	142	84.0 (16.2)*	NR	NR	NR
		Placebo	295	84.3 (14.8)	NR	NR	NR
Geffen 2012	6	Risperidone 8mg	91	99.5 (12.1)	28.9 (3.1)	23.1 (4.2)	5.0 (0.6)
		Placebo	93	98.5 (11.4)	28.9 (3.2)	23.3 (4.5)	5.0 (0.6)
Durgam 2014	6	Risperidone 4 mg	140	98.1 (SE: 0.8)	25.4 (SE: 0.3)	25.2 (SE: 0.4)	4.8 (0.1)†
		Placebo	151	97.3 (SE: 0.8)	25.4 (SE: 0.3)	25.2 (SE: 0.4)	4.9 (0.1)†
Potkin 2007c	6	Risperidone 6 mg	59	92.18 (NR)	24.70 (NR)	21.86 (NR)	4.6 (NR)
		Placebo	62	92.43 (NR)	24.12 (NR)	23.1 (NR)	4.6 (NR)
Lieberman 2015	4	Risperidone 4 mg	82	86.1 (12.2)	24.2 (4.1)	20.7 (5.1)	NR

Study Name	Weeks	Arms (mean dosage)	N	Baseline PANSS, mean (SD)			Baseline CGI-S, mean (SD)
				Total	Positive	Negative	
		Placebo	85	86.3 (13.1)	24.6 (4.6)	19.8 (4.8)	NR
Walling 2019	4	Risperidone 3 mg Q12H	36	97.4 (15.1)	NR	NR	NR
		Placebo	74	97.2 (14.9)	NR	NR	NR
Higuchi 2019	6	Risperidone 4 mg	64	NR	NR	NR	NR
		Placebo	129	NR	NR	NR	NR
Olanzapine							
Egan 2013	4	Olanzapine 15 mg	47	96.4 (11.2)	23.8 (3.5)	25.2 (4.5)	4.9 (0.5)
		Placebo	83	96.0 (12.9)	24.2 (4.2)	25.4 (4.5)	4.9 (0.5)
Schmidt 2012	6	Olanzapine 15 mg	93	91.0 (11.2)	NR	NR	NR
		Placebo	99	90.2 (10.4)	NR	NR	NR
Shen 2014	6	Olanzapine 15 mg	71	94.5 (11.7)	26.5 (4.5)	21.5 (4.9)	5.11 (0.6)
		Placebo	71	94.7 (10.2)	25.7 (4.1)	21.9 (5.1)	5.08 (0.7)
Bugarski Kirola 2014	4	Olanzapine 15 mg	62	63.0 (9.5)	NR	NR	4.9 (0.6)
		Placebo	80	65.1 (8.7)	NR	NR	4.8 (0.6)
Beasley 1996b	6	Olanzapine 2.5 - 7.5 mg	65	NR	NR	NR	4.9 (0.8)
		Olanzapine 7.5 - 12.5 mg	64	NR	NR	NR	5.1 (0.9)
		Olanzapine 12.5 -17.5 mg	69	NR	NR	NR	5.0 (0.8)
		Placebo	68	NR	NR	NR	4.9 (0.8)
Davidson 2007	6	Olanzapine 10 mg	126	93.3 (12.2)	27.8 (4.7)‡	23.5 (6.0)‡	NR

Study Name	Weeks	Arms (mean dosage)	N	Baseline PANSS, mean (SD)			Baseline CGI-S, mean (SD)
				Total	Positive	Negative	
		Placebo	120	93.9 (12.7)	28.3 (4.9)	23.0 (5.4)	NR
ENLIGHTEN1	4	Olanzapine 20 mg	133	100.6 (12.1)	NR	NR	5.1 (0.7)
		Placebo	134	102.7 (11.9)	NR	NR	5.1 (0.7)
Kane 2007b	6	Olanzapine 10 mg	128	93.0 (10.7)	NR	NR	NR
		Placebo	126	94.1 (10.7)	27.0 (4.2)	23.4 (5.2)	NR
Marder 2007c	6	Olanzapine 10 mg	105	94.9 (12.4)	29.4 (4.7)	22.4 (4.9)	NR
		Placebo	105	93.6 (11.7)	28.1 (4.4)	22.7 (5.0)	NR
Meltzer 2011	6	Olanzapine 15 mg	122	96.3 (12.2)	NR	NR	4.9 (0.7)
		Placebo	114	95.8 (10.8)	NR	NR	4.9 (0.7)
Kinon 2011	4	Olanzapine	62	99.6 (10.0)	25.1 (4.1)	26.2 (4.7)	4.9 (0.6)
		Placebo	122	97.6 (12.1)	24.1 (4.1)	26.1 (4.9)	4.8 (0.7)
Landbloom 2017	6	Olanzapine 15 mg	46	92.7 (10.5)	NR	NR	4.8 (0.6)
		Placebo	101	93.4 (11.2)	NR	NR	4.8 (0.6)
Corrigan 2004	6	Olanzapine 15 mg	93	24 (NR)	NR	NR	5 (NR)
		Placebo	87	23.8 (NR)	NR	NR	5.1 (NR)
Aripiprazole							
McEvoy 2007b	6	Aripiprazole 10 mg	106	92.7 (1.9)†	24.5 (0.5)†	23.4 (0.7)†	4.8 (0.1)†
		Aripiprazole 15 mg	106	93.2 (2.1)†	24.6 (0.6)†	23.3 (0.7)†	4.8 (0.1)†
		Aripiprazole 20 mg	100	92.5 (2.1)†	24.3 (0.5)†	23.5 (0.7)†	4.7 (0.1)†

Study Name	Weeks	Arms (mean dosage)	N	Baseline PANSS, mean (SD)			Baseline CGI-S, mean (SD)
				Total	Positive	Negative	
		Placebo	108	92.3 (2.1)†	24.3 (0.5)†	22.6 (0.7)†	4.6 (0.1)†
Durgam 2015	6	Aripiprazole 10 mg	152	NR	NR	NR	NR
		Placebo	153	NR	NR	NR	NR
Correll 2016	6	Aripiprazole 15 +/- 5 mg	50	97.1 (10.7)	25.9 (3.7)	23.9 (4.2)	4.9 (0.7)
		Placebo	93	97.5 (9.9)	25.6 (3.5)	24.9 (4.5)	5.0 (0.6)
Cutler 2006	6	Aripiprazole 2 mg	93	90.8	24.3	21.6	4.6
		Aripiprazole 5 mg	92	92.2	24.5	22.9	4.7
		Aripiprazole 10 mg	94	90	24.3	21.7	4.7
		Placebo	88	90.9	24.6	22.1	4.7
Head-to-head Trials							
Fleischhacker 2009	6	Olanzapine 10-20 mg	348	NR	NR	NR	NR
		Aripiprazole 15-30 mg	355	NR	NR	NR	NR
McQuade 2004	6	Olanzapine 10-20 mg	161	NR	NR	NR	NR
		Aripiprazole 15-30 mg	156	NR	NR	NR	NR
Chen 2018	12	Olanzapine	53	89.85 (22.29)	NR	NR	NR
		Risperidone	28	94.39 (23.40)	NR	NR	NR
Sacchetti 2008	8	Risperidone	25	96.0 (20.5)	25.0 (7.3)	23.2 (8.2)	NR
		Olanzapine	25	98.5 (20.0)	24.7 (7.8)	25.3 (9.2)	NR
Jindal 2018	6	Aripiprazole 12.5 mg	30	107.96 (14.08)	27.61 (5.39)	30.46 (4.67)	NR

Study Name	Weeks	Arms (mean dosage)	N	Baseline PANSS, mean (SD)			Baseline CGI-S, mean (SD)
				Total	Positive	Negative	
		Olanzapine 11.01 mg	30	99.59 (11.94)	24.96 (4.71)	28.4 (4.8)	NR

CGI-S: The Clinical Global Impressions Scale – Severity, mg: milligram, N: number, NR: not reported, PANSS: Positive and Negative Syndrome Scale, Q12H: every 12 hours, SD: standard deviation

*Efficacy-Evaluable ITT Population

†Standard Error

‡PANSS Marder Factor Scores

Table D3.5. KarXT Additional Baseline Characteristics[16-18,21]

Study Name	Weeks	Arms	N	Baseline cognition, mean (SD)		Cognitively Impaired, n	Baseline Marder Factor, mean (SD)				
				CogState Battery score	CANTAB		Positive symptoms	Negative symptoms	Disorganized thoughts	Uncontrolled hostility/ excitement	Anxiety/ depression
EMERGENT-1	5	KarXT	90	-1.0 (1.0)*	NR	23	30.8 (3.8)	22.3 (4.6)	22.1 (4.0)	9.7 (2.9)	12.4 (2.8)
		Placebo	92	1.3 (0.96)*	NR	37	30.6 (3.5)	22.4 (5.1)	22.3 (4.1)	9.5 (2.5)	11.9 (3.1)
EMERGENT-2	5	KarXT	126	NR	0.1 (0.7)†	69†	31.0 (4.0)	22.8 (5.1)	21.8 (4.01)	10.0 (3.4)	12.6 (3.4)
		Placebo	126	NR	0.1(0.6)†	65†	30.8 (4.0)	22.5 (4.7)	21.8 (3.8)	10.0 (3.2)	12.5 (3.2)
EMERGENT-3	5	KarXT	125	NR	REF	REF	30.5 (3.8)	22.0 (3.7)	22.0 (3.50)	10.1 (3.2)	12.3 (3.3)
		Placebo	131	NR	REF	REF	30.4 (3.6)	21.9 (4.2)	21.6 (3.92)	10.1 (3.1)	12.6 (3.3)

CANTAB: Cambridge Neuropsychological Test Automated Battery, N: number, NR: not reported, REF: reference, SD: standard deviation

*KarXT n=60, Placebo n=65

†EMERGENT-2 and EMERGENT-3 mixed populations (KarXT n=152, Placebo n=160)

Table D3.6. KarXT and Comparator Patient Important Outcomes[14,15,27-55,89]

Intervention	Study	Quality of Life	Improvement in Functioning*	Caregiver Impact	Treatment-Emergent Adverse Events				
					Extrapyramidal Symptoms	Brain Fog	Sedation & Somnolence	Anticholinergic Side Effects	Sexual/ Hormonal Dysfunction
KarXT	EMERGENT-1	-	-	-	X	-	X	X	-
	EMERGENT-2	-	-	-	X	-	-	X	-
	EMERGENT-3	-	-	-	X	-	-	X	-
Risperidone	Casey 2008	-	-	-	X†	-	-	X	-
	Downing 2014	-	-	-	X‡	-	X	X	-
	Geffen 2012	-	X§	-	X#	-	-	X	-
	Durgam 2014	-	-	-	X†‡	-	X	X	-
	Potkin 2007c	-	-	-	X¤	-	X	X	-
	Lieberman 2015	-	-	-	X†¤	-	X	X	-
	Walling 2019	-	X**	-	X‡	-	X	X	-
	Higuchi 2019	-	-	-	X	-	-	-	-
Olanzapine	Egan 2013	-	-	-	X¤	-	X	-	-
	Schmidt 2012	-	X##	-	-	-	-	-	-
	Shen 2014	-	-	-	-	-	X	X	-
	Bugarski Kirola 2014	-	-	-	X†	-	X	X	-
	Beasley 1996b	-	-	-	X†¤	-	X	X	-
	Davidson 2007	-	-	-	X‡¤	-	X	X	-
	ENLIGHTEN-1 2020	-	-	-	X‡#¤	-	X	X	-
	Kane 2007b	-	X‡‡	-	X‡#¤	-	X	-	X§§
	Marder 2007c	-	X‡‡	-	X‡#¤	-	X	X	X##
	Meltzer 2011	-	-	-	X†‡¤	-	X	X	-
	Kinon 2011	-	-	-	X¤	-		-	-
	Landbloom 2017	-	-	-	X†‡¤	-	X	-	-
	Corrigan 2004	-	-	-	X¤	-	X	-	-
Aripiprazole	McEvoy 2007b	-	-	-	X	-	X	X	-

Intervention	Study	Quality of Life	Improvement in Functioning*	Caregiver Impact	Treatment-Emergent Adverse Events				
					Extrapyramidal Symptoms	Brain Fog	Sedation & Somnolence	Anticholinergic Side Effects	Sexual/ Hormonal Dysfunction
	Durgam 2015	X¤¤	-	-	X†¤	-		X	-
	Correll 2016	-	-	-	X†‡#	-	X	X	-
	Cutler 2006	-	-	-	X	-	X	X	-
Head-to-head	**Fleischhacker 2009**	-	-	-	X***	-	X***	-	-
	McQuade 2004	-	-	-	X†‡#	-	X	-	-
	Chen 2018	-	-	-	-	-	-	-	-
	Sacchetti 2008	-	-	-	X¤	-	-	-	-
	Jindal 2013	-	-	-	X†	-	X	-	X†††

AE: adverse event, AIMS: abnormal involuntary movement scale, BARS: Barnes Akathisia Rating Scale, EPS: Extrapyramidal Symptoms, SAS: The Simpson-Angus Scale

Note: Anticholinergic side effects include constipation, dry mouth, and dyspepsia

Sexual / Hormonal dysfunction includes galactorrhea, gynecomastia, amenorrhea, anorgasmia, impotence, and abnormal sexual function

*e.g., community integration, ability to work, attend school, live independently

†Akathisia

‡Extrapyramidal disorder or extrapyramidal symptoms

§Strauss-Carpenter Level of Functioning Scale

#Movement disorder related adverse events including parkinsonism, dystonia, dyskinesia, hyperkinesia, or hypertonia

¤Extrapyramidal rating scale (SAS, AIMS, or BARS)

**Global Assessment of Function

††Nurses' Observation Scale for Inpatient Evaluation

‡‡Personal and Social Performance Scale

§§Galactorrhea, gynecomastia, abnormal sexual function, amenorrhea, anorgasmia

##Impotence and abnormal sexual function

¤¤Schizophrenia Quality of Life Scale Revision 4

***At week 52

†††Amenorrhea

Table D3.7. KarXT and Comparator Extrapyramidal Symptoms Outcomes[15,23,26-55,89]

Study Name	Arms (mean dosage)	N	Extrapyramidal Syndrome, n (%)	Akathisia, n (%)	Parkinsonism, n (%)	Dyskinesia, n (%)
KarXT						
Pooled EMERGENT Data	KarXT 125/30 mg	340	2 (0.6)¤	2 (0.6)	NR	1 (0.3)
	Placebo	343	0	1 (0.3)	NR	0
Risperidone						
Casey 2008	Risperidone 6 mg	120	NR	6 (5)	NR	NR
	Placebo	119	NR	0 (0)	NR	NR
Downing 2014	Risperidone 4 mg	142	0	NR	NR	NR
	Placebo	295	3 (1)	NR	NR	NR
Geffen 2012	Risperidone 8 mg (2-8 mg)	91	NR	14 (15.4)	9 (9.9)	NR
	Placebo	93	NR	1 (1.1)	1 (1.1)	NR
Durgam 2014	Risperidone 4 mg	140	18 (12.9)	12 (8.6)	NR	NR
	Placebo	151	7 (4.6)	7 (4.6)	NR	NR
Potkin 2007c	Risperidone 6 mg	59	NR	NR	NR	NR
	Placebo	60	NR	NR	NR	NR
Lieberman 2015	Risperidone 4 mg	82	NR	6 (7.3)	NR	NR
	Placebo	85	NR	2 (2.3)	NR	NR
Walling 2019	Risperidone 3 mg Q12H	36	NR	1 (2.8)	NR	NR
	Placebo	74	NR	1 (1.4)	NR	NR
Higuchi 2019	Risperidone 4 mg	64	*20* (30.8)	*9* (13.8)	15 (23.3)	NR
	Placebo	129	*23* (18.2)	*6* (4.5)	11 (8.8)	NR
Olanzapine						
Egan 2013	Olanzapine 15 mg	47	NR	NR	NR	NR
	Placebo	83	NR	NR	NR	NR
Schmidt 2012	Olanzapine 15 mg	93	NR	NR	NR	NR
	Placebo	101	NR	NR	NR	NR
Shen 2014	Olanzapine 15 mg	77	NR	NR	NR	NR
	Placebo	77	NR	NR	NR	NR

Study Name	Arms (mean dosage)	N	Extrapyramidal Syndrome, n (%)	Akathisia, n (%)	Parkinsonism, n (%)	Dyskinesia, n (%)
Bugarski Kirola	Olanzapine 15 mg	62	NR	2 (3.2)	NR	NR
	Placebo	80	NR	5 (6.3)	NR	NR
Beasley 1996b	Olanzapine 12.5 -17.5 mg	69	NR	5 (7.2)	NR	NR
	Placebo	68	NR	1 (1.5)	NR	NR
Davidson 2007	Olanzapine 10 mg	128	4 (3)*	NR	NR	NR
	Placebo	123	3 (2)*	NR	NR	NR
ENLIGHTEN-1	Olanzapine 20 mg	133	NR	6 (4.5)	6 (4.5)	1 (0.8)
	Placebo	134	NR	11 (8.2)	14 (10.4)	2 (1.5)
Kane 2007b	Olanzapine 10 mg	128	2 (2)*	NR	NR	NR
	Placebo	126	1 (1)*	NR	NR	NR
Marder 2007c	Olanzapine 10 mg	109	2 (2)*	NR	NR	NR
	Placebo	106	4 (4)*	NR	NR	NR
Meltzer 2011	Olanzapine 15 mg	122	NR	9 (7.4)	6 (4.9)	NR
	Placebo	116	NR	1 (0.9)	2 (1.7)	NR
Kinon 2011	Olanzapine	62	NR	NR	NR	NR
	Placebo	122	NR	NR	NR	NR
Landbloom 2017	Olanzapine 15 mg	46	2 (4.3)†	1 (2.2)	NR	NR
	Placebo	101	7 (6.9)†	5 (5.0)	NR	NR
Corrigan 2004	Olanzapine 15 mg	93	NR	NR	6 (7)‡	NR
	Placebo	87	NR	NR	4 (5)‡	NR
Aripiprazole						
McEvoy 2007b	Aripiprazole 10 mg	105	4 (4)	10 (10)	NR	NR
	Aripiprazole 15 mg	105	3 (3)	6 (6)	NR	NR
	Aripiprazole 20 mg	98	2 (2)	5 (5)	NR	NR
	Placebo	107	6 (6)	3 (3)	NR	NR
Durgam 2015	Aripiprazole 10 mg	152	NR	11 (7.2)	*8* (5)	NR
	Placebo	153	NR	7 (4.6)	*5* (3)	NR
Correll 2016	Aripiprazole 15 +/- 5 mg	50	6 (12)§	2 (4)	3 (6.0)	0 (0)
	Placebo	95	13 (13.7)§	4 (4.2)	7 (7.4)	1 (1.1)

Study Name	Arms (mean dosage)	N	Extrapyramidal Syndrome, n (%)	Akathisia, n (%)	Parkinsonism, n (%)	Dyskinesia, n (%)
Cutler 2006	Aripiprazole 2 mg	93	*1* (1.1)#	0 (0)	NR	NR
	Aripiprazole 5 mg	91	*3* (3.3)#	0 (0)	NR	NR
	Aripiprazole 10 mg	94	*8* (8.5)	2 (2.1)	NR	NR
	Placebo	87	*3* (3.4)	1 (1.1)	NR	NR
Head-to-Head						
Fleischhacker 2009	Olanzapine 10-20 mg	346	4 (1)	21 (6)	NR	NR
	Aripiprazole 15 – 30 mg	349	20 (6)	33 (9)	NR	NR
McQuade 2004	Olanzapine 10-20 mg	161	NR	NR	NR	NR
	Aripiprazole 15-30 mg	156	NR	NR	NR	NR
Chen 2018	Olanzapine	53	NR	NR	NR	NR
	Risperidone	28	NR	NR	NR	NR
Sacchetti 2008	Risperidone	25	NR	NR	1 (4.0)	NR
	Olanzapine	25	NR	NR	0 (0)	NR
Jindal 2018	Aripiprazole 12.5 mg	30	NR	2 (7.7)	NR	NR
	Olanzapine 11.01 mg	30	NR	0 (0)	NR	NR

Mg: milligram, N: number, NR: not reported, Q12H: every 12 hours
Italicized data has been calculated
*Extrapyramidal disorder
†Extrapyramidal symptoms, standardized MedDRA
‡Treatment emergent-EPS, primarily parkinsonism
§All EPS events
#EPS-related adverse events
¤Extrapyramidal disorder (n=1) and dystonia (n=1)

Table D3.8. KarXT Additional Categorical Response Outcomes[16-18]

Trials	Week	Arms (mean dosage)	N	PANSS Threshold >20%			PANSS Threshold >40%			PANSS Threshold >50%		
				Event #, (%)	P value	NNT	Event #, (%)	P value	NNT	Event #, (%)	P value	NNT
EMERGENT-1	5	KarXT 125/30 mg	83	*49* (59)	<0.0001	3	*20* (24.1)	0.006	7	*13* (15.7)	0.047	11
		Placebo	87	*20* (23)			*7* (8)			*5* (5.7)		

Table D3.8. KarXT Additional Categorical Response Outcomes[16-18]

EMERGENT-2	5	KarXT 125/30 mg	117	*63* (53.8)	0.0036	6	*39* (33.3)	0.015	8	*20* (17.1)	0.22	17
		Placebo	119	*42* (35.3)			*23* (19.3)			*13* (10.9)		
EMERGENT-3	5	KarXT 125/30 mg	114	*65* (57)	0.0078	6	*25* (21.9)	0.08	12	*15* (13.2)	0.158	18
		Placebo	120	*47* (39.2)			*16* (13.3)			*9* (7.5)		

#: number, N: number, NNT: number needed to treat, PANSS: positive and negative syndrome scale
Italicized data has been calculated

Table D3.9. KarXT Marder Factor Outcomes[16-18]

Trials		**EMERGENT-1**		**EMERGENT-2**		**EMERGENT-3**	
Week		**5**		**5**		**5**	
Arms		**KarXT**	**Placebo**	**KarXT**	**Placebo**	**KarXT**	**Placebo**
N		83	87	117	119	114	120
Marder Factor, Positive symptom	**LSM Change (95% CI)**	-5.65 (-6.82, -4.48)	-2.55 (-3.66, -1.43)	-6.8 (NR)	-3.99 (NR)	-6.60 (NR)	-3.96 (NR)
	LSM Difference (95% CI)	-3.10 (-4.62, -1.59)		-2.82 (NR)		-2.64 (NR)	
	p value	<0.0001		0.0003		0.0002	
	Cohen's d	0.63		0.524		0.564	
Marder Factor, Negative symptom	**LSM Change (95% CI)**	-3.85 (-4.88, -2.83)	-1.32 (-2.29, -0.35)	-4.18 (NR)	-1.98 (NR)	-3.48 (NR)	-2.66 (NR)
	LSM Difference (95% CI)	-2.53 (-3.85, -1.22)		-2.2 (NR)		-0.82 (NR)	
	p value	0.0002		0.0022		0.1957	
	Cohen's d	0.59		0.442		0.194	
Marder Factor, Disorganized thoughts	**LSM Change (95% CI)**	-3.69 (-4.56, -2.82)	-1.56 (-2.39, -0.73)	-4.36 (NR)	-2 (NR)	-3.86 (NR)	-2.49 (NR)
	LSM Difference (95% CI)	-2.13 (-3.27, -1.00)		-2.36 (NR)		-1.37 (NR)	
	p value	0.0003		<0.0001		0.0103	
	Cohen's d	0.58		0.581		0.389	
Marder Factor, Uncontrolled hostility/excitement	**LSM Change (95% CI)**	-1.20 (-1.96, -0.45)	0.32 (-0.39, 1.03)	-1.73 (NR)	-0.57 (NR)	-2.34 (NR)	-0.65 (NR)
	LSM Difference (95% CI)	-1.52 (-2.49, -0.56)		-1.15 (NR)		-1.69 (NR)	

	p value	0.0022		0.0116		0.0003	
	Cohen's d	0.48		0.363		0.551	
Marder Factor, Anxiety/depression	**LSM Change (95% CI)**	-3.34 (-4.11, -2.57)	-1.22 (-1.95, -0.49)	-4.03 (NR)	-2.61 (NR)	-4.15 (NR)	-2.94 (NR)
	LSM Difference (95% CI)	-2.12 (-3.11, -1.13)		-1.42 (NR)		-1.57 (NR)	
	p value	<0.0001		0.0026		0.0031	
	Cohen's d	0.66		0.443		0.452	

CI: confidence interval, LSM: least squares method, N: number, NR: not reported

Table D3.10. Discontinuation and Adverse Events[14,15,19,25-55,89]

Trials	Week	Arms	N	All-cause Discontinuation, n (%)	Discontinued due to AE, n (%)	Discontinued due to lack of efficacy, n (%)	Discontinued by withdrawing consent, n (%)	Discontinued, other, n (%)	Any AE, n (%)	Serious AE, n (%)
KarXT										
EMERGENT-1	5	KarXT 125/30 mg	89	18 (20)	3 (3.3)	NR	14 (15.6)	0	48 (54)	*1* (1)
		Placebo	90	19 (21)	2 (2.2)	NR	14 (15.2)	1 (1.1)	39 (43)	*0 (0)*
EMERGENT-2	5	KarXT 125/30 mg	126	*32* (25)	10 (7.9)	NR	13 (10.3)	9 (7.1)	95 (75.4)*	2 (1.6)*
		Placebo	125	*26* (21)	6 (4.8)	NR	11 (8.8)	6 (4.8)	73 (58.4)*	2 (1.6)*
EMERGENT-3	5	KarXT 125/30 mg	125	*46* (37)	8 (6.4)	NR	35 (28.0)	3 (2.4)	88 (70.4)*	1 (0.8)*
		Placebo	128	*38* (29)	7 (5.4)	NR	22 (16.8)	9 (6.9)	64 (50)*	0 (0)*
Risperidone										
Casey 2008	6	Risperidone 6 mg	120	61 (51)	17 (14)	8 (7)	21 (18)	16 (13.3)	107 (89)*	*19* (16)
		Placebo	119	70 (59)	13 (11)	27 (23)	21 (18)	9 (7.6)	101 (85)*	*11* (9)

Trials	Week	Arms	N	All-cause Discontinuation, n (%)	Discontinued due to AE, n (%)	Discontinued due to lack of efficacy, n (%)	Discontinued by withdrawing consent, n (%)	Discontinued, other, n (%)	Any AE, n (%)	Serious AE, n (%)
Downing 2014	6	Risperidone 4 mg	142	46 (32.4)	12 (8.4)†	10 (7)	18 (12.7)	6 (4.2)	82 (57.7)	NR
		Placebo	295	124 (42)	33 (11.2)†	48 (16.3)	26 (8.8)	17 (5.7)	177 (60)	NR
Geffen 2012	6	Risperidone 8 mg	91	20 (22)	8 (8.8)	4 (4.4)	1 (1.1)	8 (8.6)	80 (87.9)*	3 (3.3)
		Placebo	93	37 (39.8)	4 (4.3)	18 (19.4)	8 (8.6)	7 (7.7)	64 (68.8)*	6 (6.5)
Durgam 2014	6	Risperidone 4 mg	140	39 (27.9)	13 (9.3)	10 (7.1)	15 (10.7)	1 (0.7)	95 (67.9)*	3 (2.1)
		Placebo	151	72 (47.7)	22 (14.6)	33 (21.9)	14 (9.3)	3 (2)	100 (66.2)*	7 (4.6)
Potkin 2007c	6	Risperidone 6 mg	59	34 (57.6)	4 (6.8)	16 *(27)*	NR	14 *(23)*	*53* (90)	*4* (7)
		Placebo	60	41 (68.3)	7 (11.7)	18 *(30)*	NR	16 *(26)*	*47* (79)	*6* (10)
Lieberman 2015	4	Risperidone 4 mg	82	15 (18)	3 (4)	3 (4)	8 (10)	1 (1)	NR	1 *(1.2)*
		Placebo	85	19 (22)	0	8 (9)	6 (7)	5 (6)	NR	1 *(1.1)*
Walling 2019	4	Risperidone 3 mg Q12H	36	11 (30.6)	3 (8.3)	0 (0)	5 (13.9)	3 (8.3)	23 (63.9)	2 (5.6)
		Placebo	74	14 (18.9)	4 (5.4)	5 (6.7)	5 (6.7)	0	52 (70.3)	1 (1.4)
Higuchi 2019	6	Risperidone 4 mg	64	14 (21.5)	1 (1.5)	NR	NR	NR	NR	2 (3.1)
		Placebo	129	48 (37.1)	8 (6.1)	NR	NR	NR	NR	10 (7.6)
Olanzapine										
Egan 2013	4	Olanzapine 15 mg	47	9 (19.1)	0 (0)	4 *(9)*	2 *(4)*	3 *(6)*	23 (48.9)	0
		Placebo	83	21 (25.3)	0 (0)	15 *(18)*	6 *(7)*	0	31 (37.3)	1 (1.2)

Trials	Week	Arms	N	All-cause Discontinuation, n (%)	Discontinued due to AE, n (%)	Discontinued due to lack of efficacy, n (%)	Discontinued by withdrawing consent, n (%)	Discontinued, other, n (%)	Any AE, n (%)	Serious AE, n (%)
Schmidt 2012	6	Olanzapine 15 mg	93	NR	NR	NR	NR	NR	NR	NR
		Placebo	101	NR	NR	NR	NR	NR	NR	NR
Shen 2014	6	Olanzapine 15 mg	77	37 (*48.1*)	5 (*6.5*)	9 *(11.7)*	20 *(26)*	3 *(3.9)*	64 *(83.1)**	4 (5.2)
		Placebo	77	49 (*64*)	11 (*14.3*)	13 *(16.9)*	19 *(25)*	6 *(7.8)*	64 *(83.1)**	7 (9.1)
Bugarski Kirola 2014	4	Olanzapine 15 mg	62	18 (29)	5 (8.1)	1 (1.6)	11 (17.7)	1 (1.6)	37 (59.7)	2 (3.2)‡
		Placebo	80	22 (27.5)	2 (2.5)	9 (11.3)	10 (12.5)	1 (1.3)	47 (58.8)	6 (7.5)‡
Beasley 1996b	6	Olanzapine 2.5-7.5mg	65	38 (58.5)	*5* (7.7)	*22* (33.8)	*7* (10.8)	*4 (6.2)*	NR	NR
		Olanzapine 7.5-12.5mg	64	38 (59.4)	*1* (1.6)	*24* (37.5)	*7* (10.9)	*6 (9.4)*	NR	NR
		Olanzapine 12.5-17.5mg	69	*35* (50.7)	*4* (5.8)	*18* (26.1)	*7* (10.1)	*6 (8.6)*	NR	NR
		Placebo	68	*46* (67.6)	*7* (10.3)	*32* (47.1)	*2* (2.9)	*5 (7.4)*	NR	NR
Davidson 2007	6	Olanzapine 10 mg	128	40 (31)	5 (4)	16 (13)	11 (9)	8 (6)	92 (72)	*8* (6)
		Placebo	123	76 (62)	5 (4)	54 (44)	13 (11)	4 (3)	74 (60)	*9* (7)
ENLIGHTEN-1	4	Olanzapine 20 mg	133	14 (10.5)	2 (1.5)	2 (1.5)	9 (6.8)	1 (0.8)	73 (54.9)	1 (0.8)
		Placebo	134	23 (17.2)	7 (5.2)	8 (6)	8 (6)	0	60 (44.8)	0
Kane 2007b	6	Olanzapine 10 mg	128	38 (30)	9 (7)	19 (15)	5 (4)§	5 (*3.9*)	81 (63)	*3* (2)
		Placebo	127	69 (54)	9 (7)	51 (40)	7 (6)§	2 (2)	79 (63)	*3* (2)

Trials	Week	Arms	N	All-cause Discontinuation, n (%)	Discontinued due to AE, n (%)	Discontinued due to lack of efficacy, n (%)	Discontinued by withdrawing consent, n (%)	Discontinued, other, n (%)	Any AE, n (%)	Serious AE, n (%)
Marder 2007c	6	Olanzapine 10 mg	110	60 (55)	8 (7)	24 (22)	17 (15)§	*11 (10)*	79 (72)	*12* (11)
		Placebo	110	73 (66)	5 (5)	39 (35)	17 (15)§	*12 (11)*	82 (77)	*11* (10)
Meltzer 2011	6	Olanzapine 15 mg	123	39 (31.7)	8 (6.5)	8 (6.5)	19 (15.4)	*4 (3.3)*	100 (82.0)	NR
		Placebo	116	45 (38.8)	10 (8.6)	18 (15.5)	12 (10.3)	*5 (4.3)*	84 (72.4)	NR
Kinon 2011	4	Olanzapine	62	*22 (35.5)*	6 (9.7)	8 (12.9)	6 (9.7)§	2 (3.2)	37 (59.7)*	0
		Placebo	122	*49 (40.2)*	4 (3.3)	33 (27.0)	6 (4.9)§	*6 (4.9)*	54 (44.3)*	0
Landbloom 2017	6	Olanzapine 15mg	46	11 (23.9)	2(4.3)#	0 (0)	3 (6.5)	7 (15.2)	25 (54.3)	1 (2.2)
		Placebo	101	41 (39.8)	18 (17.8)#	13 (12.6)	6 (5.8)	12 (12.0)	62 (61.4)	8 (7.9)
Corrigan 2004	6	Olanzapine 15 mg	93	24 (25.8)	7 (7.5)	4 (4.3)	11 (11.8)	2 (2.2)	60 (65)*	2 (2.2)
		Placebo	87	22 (25.3)	3 (3.4)	15 (17.4)	4 (4.6)	0	51 (60)*	0
Aripiprazole										
McEvoy 2007b	6	Aripiprazole 10 mg	106	63 (59.4)	11 (10.4)	5 (4.7)	18 (17.0)	29 (27.4)	67 (64)	3 (2.8)
		Aripiprazole 15 mg	106	74 (69.8)	3 (2.8)	8 (7.5)	24 (22.6)	39 (36.8)	76 (72)	10 (9.4)
		Aripiprazole 20 mg	100	63 (63.0)	5 (5.0)	11 (11.0)	18 (18)	29 (29)	72 (74)	4 (4)
		Placebo	108	78 (72.2)	6 (5.5)	11 (10.2)	13 (12.0)	48 (44.4)	66 (62)	8 (7.4)
Durgam 2015	6	Aripiprazole 10 mg	152	38 (25.0)	14 (9.2)	8 (5.3)	15 (9.9)	1 (0.7)	100 (65.8)*	4 (2.6)
		Placebo	153	58 (37.9)	17 (11.1)	20 (13.1)	17 (11.1)	4 (2.6)	102 (66.7)*	2 (1.3)

Trials	Week	Arms	N	All-cause Discontinuation, n (%)	Discontinued due to AE, n (%)	Discontinued due to lack of efficacy, n (%)	Discontinued by withdrawing consent, n (%)	Discontinued, other, n (%)	Any AE, n (%)	Serious AE, n (%)
Correll 2016	6	Aripiprazole 15 +/- 5 mg	50	12 (24.0)	3 (6)	4 (8.0)	4 (8.0)	0	NR	NR
		Placebo	95	27 (28.4)	5 (5.3)	8 (8.4)	13 (13.7)	1 (1.1)	NR	NR
Cutler 2006	6	Aripiprazole 2 mg	93	42 (45.2)	2 (2.2)	22 (23.7)	17 (18.3)	1 (1.1)	*66* (71)*	*9* (9.7)
		Aripiprazole 5 mg	92	45 (48.9)	1 (1.1)	13 (14.1)	26 (28.3)	5 (5.4)	*59* (65)*	*4* (4.4)
		Aripiprazole 10 mg	94	41 (43.6)	4 (4.3)	14 (14.9)	21 (22.3)	2 (2.1)	*66* (70)	*10* (10.6)
		Placebo	88	44 (50.0)	6 (6.8)	20 (22.7)	16 (18.2)	2 (2.3)	*59* (68)	*7* (8)
Head-to-Head										
Fleischhacker 2009	6	Olanzapine 10-20 mg	348	77 (22.1)	18 (5.2)	25 (7.2)	30 (8.6)	4 (1.2)	NR	NR
		Aripiprazole 15-30 mg	355	104 (29.3)	37 (10.4)	30 (8.5)	25 (7.0)	12 (3.4)	NR	NR
McQuade 2004	6	Olanzapine 10-20 mg	161	NR	NR	NR	NR	NR	NR	NR
		Aripiprazole 15-30 mg	156	NR	NR	NR	NR	NR	NR	NR
Chen 2018	6	Olanzapine	53	NR	NR	NR	NR	NR	NR	NR
		Risperidone	28	NR	NR	NR	NR	NR	NR	NR
Sacchetti 2008	8	Risperidone	25	5 (20.0)	0	0	3 (12.0)	2 (8.0)	1 (4.0)¤	0
		Olanzapine	25	5 (20.0)	1 (4.0)	0 (0)	2 (8.0)	2 (8.0)	4 (16.0)¤	0
Jindal 2018	6	Aripiprazole 12.5 mg	30	NR	NR	NR	NR	NR	NR	NR
		Olanzapine 11.01 mg	30	NR	NR	NR	NR	NR	NR	NR

AE: adverse event, mg: milligram N: number, NR: not reported, Q12H: every 12 hours
Italicized data has been digitized or calculated.
*Treatment emergent adverse events
†Pooled discontinuation due to adverse event, physician decision, and subject decision
‡Includes 2 week follow up period
§Participants choice
#Pooled AE & AE leading to worsening of schizophrenia
¤Of moderate intensity
**Treatment-related adverse events

Table D3.11. KarXT Additional Discontinuation and Adverse Events[14,15,19,25,26]

Trial	Week	Arms	N	Discontinued due to TEAE, n (%)	Withdrawn by investigator, n (%)	Lost to follow-up, n (%)	Progressive disease, n (%)	No reason collected, n (%)
EMERGENT-1	5	KarXT	89	2 (2)	1 (1.1)	0	NR	NR
		Placebo	90	2 (2)	1 (1.1)	1 (1.1)	NR	NR
EMERGENT-2	5	KarXT	126	9 (7.1)	0	0	0	0
		Placebo	125	7 (5.6)	0	0	1 (0.8)	1 (0.8)
EMERGENT-3	5	KarXT	125	8 (6.4)	0	0	NR	NR
		Placebo	128	7 (5.5)	0	0	NR	NR
Pooled Safety	5	KarXT	340	*19* (5.6)	NR	NR	NR	NR
		Placebo	343	*16* (4.7)	NR	NR	NR	NR

N: number, NR: not reported, TEAE: treatment emergent adverse event
Italicized data has been calculated

Table D3.12. KarXT Safety Outcomes[14,15,25]

Intervention	**KarXT**					
Study	**EMERGENT-1**		**EMERGENT-2**		**EMERGENT-3**	
Duration, weeks	**5**		**5**		**5**	
Arms	**KarXT**	**Placebo**	**KarXT**	**Placebo**	**KarXT**	**Placebo**
N	89	90	126	125	125	128

Experienced Weight Gain	**%**	3.4	4.4	NR	NR	NR	NR
Weight Gain, kg	**Mean Change (SD)**	1.5 (2.8)	1.1 (3.5)	1.36 (3.31)	2.49 (6.92)	1.41 (3.37)	2 (3.08)
Weight Gain ≥ 7%	**Event n (%)**	2 (2.2)	5 (5.6)	6 (6.4)	13 (13)	5 (6.4)	12 (13)
Body Mass Index, kg/m^2	**Mean Change (SD)**	0.5 (1.0)	0.4 (1.2)	NR	NR	NR	NR
Simpson-Angus Scale*	**Mean Change (SD)**	−0.1 (0.7)	−0.1 (0.8)	0.0 (0.61)	-0.1 (0.70)	-0.1 (0.56)	-0.1 (0.36)
Barnes Akathisia Rating Scale†	**Mean Change (SD)**	−0.1 (1.0)	0.0 (0.7)	-0.1 (1.09)	-0.2 (0.98)	-0.1 (0.75)	-0.1 (0.88)
Total Cholesterol, mg/dL	**Mean Change (SD)**	0.8 (27.71)	-4.9 (27.04)	-0.1 (0.91)	-0.1 (1.21)	NR	NR
Glucose, mg/dL	**Mean Change (SD)**	9.8 (32.23)	12.5 (41.56)	0.7 (2.66)	0.5 (1.77)	NR	NR
Triglycerides, mg/dL	**Mean Change (SD)**	13.4 (51.88)	-5.7 (75.86)	0.2 (1.22)	0.0 (1.03)	NR	NR
Mean Change in Orthostatic Blood Pressure	**Systolic, mmHg (SD)**	-0.4 (11.9)	-1.0 (11.3)	NR	NR	NR	NR
	Diastolic, mmHg (SD)	-0.9 (7.8)	-1.3 (10.4)	NR	NR	NR	NR
Mean Change in Supine Blood Pressure	**Systolic, mmHg (SD)**	-3.9 (14.5)	-0.2 (12.3)	*1.4* (NR)	*0.47* (NR)	*2.34* (NR)	*0* (NR)
	Diastolic, mmHg (SD)	-1.4 (9.3)	0.5 (10.3)	*2.64* (NR)	*0.7* (NR)	*3.2* (NR)	*0.22* (NR)
Mean Change in Standing Blood Pressure	**Systolic, mmHg (SD)**	-4.3 (14.8)	-1.2 (12.0)	NR	NR	NR	NR
	Diastolic, mmHg (SD)	-2.3 (9.6)	-0.8 (8.3)	NR	NR	NR	NR
Patients with Treatment-Emergent Increased Liver Function	**ALT > 3X ULN, n (%)**	0	1 (1.1)	NR	NR	NR	NR
	AST > 3X ULN, n (%)	0	1 (1.1)	NR	NR	NR	NR
	GGT > 2X ULN, n (%)	2 (2.2)	1 (1.1)	NR	NR	NR	NR
	ALP > 2X ULN, n (%)	0	0	NR	NR	NR	NR
	TB > 2X ULN, n (%)	0	0	NR	NR	NR	NR

Mean Change in QT Interval Measurement	**Aggregate, msec (SD)**	-20.7 (33.5)	-9.6 (32.4)	NR	NR	NR	NR
	QTcF, msec (SD)	-2.7 (22.0)	-3.8 (17.5)	-8.8 (18.88)	-5.5 (16.10)	NR	NR

Italicized data has been digitized or calculated

ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, kg: kilogram, kg/m^2: kilogram per square meter, mg/dL: milligrams per deciliter, mmHg: millimeters of mercury, msec: millisecond, N: number, NR: not reported, QT: measurement used in electrocardiogram looking at changes in heart rhythm, QTcF: corrected QT interval by Fridericia, SD: standard deviation, TB: hepatic tuberculosis, ULN: upper limit normal

Table D3.13. KarXT Adverse Events[14,15,19,22]

Intervention		KarXT							
Trial		EMERGENT-1		EMERGENT-2		EMERGENT-3		Pooled Safety	
Arms		KarXT	Placebo	KarXT	Placebo	KarXT	Placebo	KarXT	Placebo
N		89	90	126	125	125	128	340	343
Treatment Emergent Adverse Events, n (%)	Constipation	15 (17)	3 (3)	27 (21.4)	13 (10.4)	16 (12.8)	5 (3.9)	*58* (17.1)	*21* (6.1)
	Nausea	15 (17)	4 (4)	24 (19.0)	7 (5.6)	24 (19.2)	2 (1.6)	*63* (18.5)	*13* (3.8)
	Dry mouth	8 (9)	1 (1)	NR	NR	NR	NR	*17* (5.0)	*5* (1.5)
	Dyspepsia	8 (9)	4 (4)	24 (19.0)	10 (8.0)	20 (16.0)	2 (1.6)	*52* (15.3)	*16* (4.7)
	Vomiting	8 (9)	4 (4)	18 (14.3)	1 (0.8)	20 (16.0)	1 (0.8)	*46* (13.5)	*6* (1.7)
	Headache	6 (7)	5 (6)	17 (13.5)	15 (12.0)	14 (11.2)	15 (11.7)	*37* (10.9)	*35* (10.2)
	Somnolence	5 (6)	4 (4)	NR	NR	NR	NR	NR	NR
	Akathisia	3 (3)	0 (0)	NR	NR	NR	NR	NR	NR
	Dizziness	3 (3)	3 (3)	11 (8.7)	4 (3.2)	2 (1.6)	1 (0.8)	15 (4.4)[‡]	6 (1.7)[‡]
	Increased weight	3 (3)	4 (4)	NR	NR	NR	NR	NR	NR
	Tachycardia	3 (3)	2 (2)	NR	NR	NR	NR	16 (4.7)[‡]	7 (2.0)[‡]
	Sedation	2 (2)	2 (2)	NR	NR	NR	NR	NR	NR
	Diarrhea	2 (2)	4 (4)	7 (5.6)	4 (3.2)	7 (5.6)	1 (0.8)	NR	NR
	Increased y-glutamyltransferase Level	2 (2)	0 (0)	NR	NR	NR	NR	NR	NR
	Agitation	2 (2)	1 (1)	NR	NR	NR	NR	NR	NR
	Insomnia	2 (2)	2 (2)	3 (2.4)	6 (4.8)	7 (5.6)	10 (7.8)	NR	NR
	Decreased appetite	2 (2)	0 (0)	NR	NR	NR	NR	NR	NR
	Hyperhidrosis	2 (2)	1 (1)	NR	NR	NR	NR	NR	NR
	Hypertension	NR	NR	12 (9.5)	1 (0.8)	8 (6.4)	2 (1.6)	*21* (6.2)[†]	*4* (1.2)[†]
	Gastroesophageal Reflux Disease	NR	NR	8 (6.3)	0 (0)	5 (4.0)	1 (0.8)	9 (2.6)[‡]	1 (0.3)[‡]
	Abdominal discomfort / pain	NR	NR	7 (5.6)	4 (3.2)	2 (1.6)	3 (2.3)	16 (4.7)[‡]	5 (1.5)[‡]
	Vision blurred	NR	NR	NR	NR	NR	NR	8 (2.4)[‡]	6 (1.7)[‡]
Serious Adverse Events, n*	Suicidal Ideation	NR	NR	2	0	NR	NR	2	0
	Increased Psychosis	1	0	NR	NR	NR	NR	1	0
	Worsening of Schizophrenia Symptoms	NR	NR	0	1	NR	NR	0	1

Intervention		KarXT							
Trial		EMERGENT-1		EMERGENT-2		EMERGENT-3		Pooled Safety	
	Gastroesophageal Reflux Disease	NR	NR	NR	NR	1	0	1	0
	Appendicitis	NR	NR	0	1	NR	NR	0	1

MedDRA: Medical Dictionary for Regulatory Activities, N: number, NR: not reported

Note: Italicized data has been digitized or calculated

*A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, led to inpatient hospitalization or prolongation of hospitalization, or caused persistent or clinically significant disability or incapacity.

†Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension.

‡Treatment-related adverse event

Table D3.14. KarXT and Comparator Adverse Events[14,15,27-55,89]

Intervention	Adverse Events (>10% in Active Arm and Greater than Placebo)
KarXT	Nausea, Constipation, Dyspepsia, Vomiting, Headache, Dizziness, Hypertension
Aripiprazole	Headache, Insomnia, Akathisia, Nausea, Somnolence, Constipation, Lightheadedness, Agitation, Anxiety, Diarrhea, Vomiting, Back Pain, Abdominal discomfort
Risperidone	Weight Gain, Parkinsonism, Akathisia, Muscle Rigidity, Insomnia, Anxiety, Nausea, Dyspepsia, Constipation, Headache, Tremor, Sedation, Fatigue
Olanzapine	Weight Gain, Parkinsonism, Akathisia, Insomnia, Somnolence/Sedation, Agitation, Tachycardia, Dyspepsia, Constipation, Tremor, Diarrhea, Dry mouth, Nausea

Table D3.15. Comparators Prolactin Change from Baseline[22,27-55,89]

Trials	Week	Arms	N	Prolactin change, ng/mL, mean (SD)
KarXT				
Pooled Data	5	KarXT 125/30 mg	340	0.75 ng/L (16.45)
		Placebo	343	-1.38 ng/L (16.49)
Risperidone				
Casey 2008	6	Risperidone 6 mg	120	27.81 (NR)
		Placebo	119	-0.96 (NR)

Trials	Week	Arms	N	Prolactin change, ng/mL, mean (SD)
Downing 2014	6	Risperidone 4 mg	142	50.90 (NR) µg/L
		Placebo	295	NR
Geffen 2012	6	Risperidone 8 mg (2-8 mg)	91	45.74 (44.96)
		Placebo	93	-3.39 (22.31)
Durgam 2014	6	Risperidone 4 mg	140	*male: 11.79 (NR), female: 54.87 (NR)*
		Placebo	151	*male: -7.69 (NR), female: -19.23 (NR)*
Potkin 2007c	6	Risperidone 6 mg	59	*59.34 (NR) µg/L*
		Placebo	60	*-5.9 (NR) µg/L*
Lieberman 2015	4	Risperidone 4 mg	82	*699. 65 (NR) mcIU/mL*
		Placebo	85	*35.34 (NR) mcIU/mL*
Walling 2019	4	Risperidone 3 mg Q12H	36	NR
		Placebo	74	NR
Higuchi 2019	6	Risperidone 4 mg	64	NR
		Placebo	129	NR
Olanzapine				
Egan 2013	4	Olanzapine 15 mg	47	NR
		Placebo	83	NR
Schmidt 2012	6	Olanzapine 15 mg	93	NR
		Placebo	101	NR
Shen 2014	6	Olanzapine 15 mg	77	NR
		Placebo	77	NR
Bugarski Kirola 2014	4	Olanzapine 15 mg	62	NR
		Placebo	80	NR
Beasley 1996b	6	Olanzapine 2.5-7.5 mg	65	0.1 ± 0.3 nmol/L
		Olanzapine 7.5-12.5 mg	64	0.2 ± 0.3 nmol/L
		Olanzapine 12.5-17.5 mg	69	0.2 (0.3) nmol/L
		Placebo	68	0.1 (0.2) nmol/L
Davidson 2007	6	Olanzapine 10 mg	128	male: -1.5 (NR), female: -3.3 (NR)
		Placebo	123	Male: -2.1 (NR), Female: -6.3 (NR)
ENLIGHTEN-1	4	Olanzapine 20 mg	133	NR
		Placebo	134	NR
Kane 2007b	6	Olanzapine 10 mg	128	NR
		Placebo	127	NR

Trials	Week	Arms	N	Prolactin change, ng/mL, mean (SD)
Marder 2007c	6	Olanzapine 10 mg	110	male: 4.0 (NR), female: 5.9 (NR)
		Placebo	110	male: 0.4 (NR), female: 5.0 (NR)
Meltzer 2011	6	Olanzapine 15 mg	123	5.0 (12.2)
		Placebo	116	-2.5 (16.9)
Kinon 2011	4	Olanzapine	62	1.59 (2.34)
		Placebo	122	-9.43 (1.73)
Landbloom 2017	6	Olanzapine 15 mg	46	-138.0 (65.25)
		Placebo	101	-349.9 (46.55)*
Corrigan 2004	6	Olanzapine 15 mg	93	NR
		Placebo	87	NR
Aripiprazole				
McEvoy 2007b	6	Aripiprazole 10 mg	106	-20.54 (NR)
		Aripiprazole 15 mg	106	-22.09 (NR)
		Aripiprazole 20 mg	100	-22.08 (NR)
		Placebo	108	-13.34 (NR)
Durgam 2015	6	Aripiprazole 10 mg	152	-20.6 (32.2)
		Placebo	153	-16.9 (37.2)
Correll 2016	6	Aripiprazole 15 +/- 5 mg	50	male: -6.94 (10.42), female: -15.5 (30.94)
		Placebo	95	male: -3.47 (10.32), female: -27.57 (53.42)
Cutler 2006	6	Aripiprazole 2 mg	93	NR
		Aripiprazole 5 mg	92	NR
		Aripiprazole 10 mg	94	NR
		Placebo	88	NR
Head-to-Head				
Fleischhacker 2009	6	Olanzapine 10-20 mg	348	-12.3 (NR)
		Aripiprazole 15-30 mg	355	-22.2 (NR)
McQuade 2004	6	Olanzapine 10-20 mg	161	NR
		Aripiprazole 15-30 mg	156	NR
Chen 2018	6	Olanzapine	53	NR
		Risperidone	28	NR
Sacchetti 2008	8	Risperidone	25	NR
		Olanzapine	25	NR
Jindal 2018	6	Aripiprazole 12.5 mg (10-20 mg)	30	NR
		Olanzapine 11.01 mg (10-20 mg)	30	NR

µg/l: micrograms per liter, mg: milligram, n: number, ng/mL: nanograms per milliliter, nmol/L: nanomoles per liter,
NR: not reported, Q12H: every 12 hours SD: standard deviation
Note: Italicized data has been digitized
*Unit note provided

Table D3.16. EMERGENT-1 Incidence and Severity of Treatment-emergent AEs by Age[20]

Trial	EMERGENT-1			
Subgroup	**Median Split Age <44 y**		**Median Split Age ≥44 y**	
Arms	KarXT	Placebo	KarXT	Placebo
N	43	46	46	44
Any AE, n (%)	23 (53.5)	24 (52.2)	25 (54.3)	15 (34.1)
Any Mild AE, n (%)	22 (51.2)	19 (41.3)	19 (41.3)	13 (29.5)
Any Moderate AE, n (%)	6 (14.0)	10 (21.7)	9 (19.6)	3 (6.8)
Any Severe AE*, n (%)	1 (2.3)	1 (2.2)	0	0

AE: adverse event, n: number, y: years
*A severe AE was defined as any event that was incapacitating or caused an inability to perform normal activities of daily living.

Table D3.17. EMERGENT-1 Mean Change in Body Weight by Age and Sex[20]

Trial	EMERGENT-1							
Subgroup	**Median Split Age <44 y**		**Median Split Age ≥44 y**		**Male**		**Female**	
Arms	KarXT	Placebo	KarXT	Placebo	KarXT	Placebo	KarXT	Placebo
N	43	46	46	44	37	39	6	7
Mean change in body weight, kg (SD)	1.2 (2.8)	0.3 (3.8)	1.7 (2.9)	1.9 (3.1)	1.4 (3)	1.0 (3.8)	1.6 (2.3)	1.4 (2.8)

Kg: kilogram, N: number, SD: standard deviation, y: years

Table D3.18. ENLIGHTEN-1 Change from Baseline in PANSS Total Score in Key Subgroups[51]

Trial	ENLIGHTEN-1						
Arms	Olanzapine vs Placebo						
Subgroup	Age (years)		Sex		Race		
	<55	≥55	Male	Female	White	Black	Other
N	229	36	158	107	188	71	6
LS Mean Difference (95% CI)	-7.7 (-11.5, -3.8)	10.6 (1.0, 20.2)	-4.9 (-9.5, -3.0)	6.0 (-11.8, -0.1)	-8.0 (-12.0, -4.0)	4.8 (-2.9, 12.4)	-12.4 (-36.7, 11.8)

CI: confidence interval, LS: least squares, n: number

Table D3.19. Bugarski-Kirola et al. 2014 PANSS total score change from baseline by various demographic features (ITT population)[27]

Trial	Bugarski-Kirola et al. 2014											
Subgroup	Age, years				Sex				Race*			
	18-40		41-65		Male		Female		White		Black	
Arms	OLZ	Placebo	OLZ	Placebo	OLZ	Placebo	OLZ	Placebo	OLZ	Placebo	OLZ	Placebo
N	61	79	61	79	61	79	61	79	61	79	61	79
Mean change from baseline (SE)	-14.80 (3.05)	-12.99 (2.39)	-15.50 (2.88)	-10.16 (3.05)	-14.42 (2.35)	-13.43 (2.1)	-16.65 (4.81)	-9.25 (4.26)	-13.37 (2.78)	-8.35 (2.59)	-17.87 (3.52)	-17.59 (2.99)
Mean difference (SE)	-1.81 (3.874)		-5.35 (4.198)		-0.99 (3.149)		-7.40 (6.419)		-5.03 (3.796)		-0.28 (4.617)	
p value	0.641		0.206		0.754		0.259		0.188		0.952	

ITT: intent to treat, N: number, OLZ: olanzapine, p: probability, PANSS: Positive and Negative Syndrome scale, SE: standard error

*Data for patients of Asian (n=5) and 'other' (n=3) races not included due to small patient numbers

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Trial	Study Design	Treatment Arms	Inclusion & Exclusion Criteria	Outcomes [Timepoint]
EMERGENT-4 NCT04659174 **Estimated primary completion:** 12/23	Phase 3, multicenter, 53-week, outpatient, open-label extension (OLE) study N=350 **Population:** Subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies	**Arm I:** Fixed combination of xanomeline 125 mg and trospium chloride 30 mg twice daily [BID].	**Inclusion** -Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study - Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009. **Exclusion** - Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and Columbia-Suicide Severity Rating Scale (C-SSRS).	**Primary [week 53]:** - Incidence of treatment-emergent adverse events (TEAEs) **Secondary [week 53]:** - Incidence of serious TEAEs and TEAEs leading to withdrawal - Change From Baseline in PANSS Total Score, PANSS Positive Score, PANSS Negative Score, PANSS Marder Negative symptom factor score, CGI-S - Percentage of PANSS responders (a 30% change in PANSS total score)
EMERGENT-5 NCT04820309 **Estimated study completion:** 12/23	Phase 3, multicenter, 56-week, outpatient, open-label (OL) study N=400 **Population:** De novo subjects with Diagnostic and Statistical Manual-Fifth Edition (DSM-5) schizophrenia.	**Arm I:** Fixed combination of xanomeline 125 mg and trospium chloride 30 mg twice daily [BID]	**Inclusion** - Adult aged 18 to 65 years old at screening with primary diagnosis of schizophrenia based on the DSM-5 criteria. - Has not required an increase in level of care due to symptom exacerbation within 8 weeks and is psychiatrically stable in the opinion of investigator. - PANSS total score ≤80 at screening and Baseline - CGI-S score of ≤4 at screening and Baseline - At screening, or anytime 30 days prior, has received an oral antipsychotic medication daily at a dose and frequency consistent with the drug label. - Off lithium therapy for at least 2 weeks and must have discontinued all oral antipsychotic medications.	**Primary [week 53]:** - Incidence of TEAEs **Secondary [week 53]:** - Incidence of serious TEAEs and TEAEs leading to withdrawal - Change From Baseline in PANSS Total Score, PANSS Positive Score, PANSS Negative Score, PANSS Marder Negative symptom factor score, CGI-S - Percentage of PANSS

Trial	Study Design	Treatment Arms	Inclusion & Exclusion Criteria	Outcomes [Timepoint]
			- Subjects taking a LAI antipsychotic could not have received a dose of medication for at least 12 weeks **Exclusion** - Any primary DSM-5 disorder other than schizophrenia within 12 months before screening - Subject has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months or a positive urine drug screen (UDS) for a substance other than cannabis at screening or baseline. - Subjects cannot currently (within 5 half-lives before Day 0) be receiving monoamine oxidase inhibitors, anticonvulsants, tricyclic antidepressants, centrally active anticholinergics, or any other psychoactive medications other than daily antipsychotic maintenance therapy -Subject has a history of treatment resistance to schizophrenia medications within the past 12 months or having received clozapine within the past 3 years	responders (a 30% change in PANSS total score)
ARISE NCT05145413 **Estimated study completion:** 02/24	Phase 3, 6-week, randomized, double-blind, placebo-controlled, multicenter, outpatient study N=400 **Population:** Subjects with schizophrenia with an inadequate response to their current atypical antipsychotic treatment.	**Arm I:** KarXT 50 mg/20 mg BID KarXT 75mg/20 mg BID KarXT 100mg/20 mg BID KarXT 125mg/30 mg BID. **Arm II:** Placebo capsules	**Inclusion** - Adult ages 18 to 55 years old with primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 criteria - Currently being treated with monotherapy risperidone, paliperidone, aripiprazole, quetiapine, ziprasidone or lurasidone and has been taking this treatment with the same dosing regimen for at least 8 weeks - At least 1 previous inadequate response to above antipsychotics that was dosed appropriately for at least 6 weeks - Not required psychiatric hospitalization, incarceration in prison, acute crisis intervention, or	**Primary [week 6]:** - Change From Baseline in PANSS Total Score **Secondary [week 6]:** - Change from Baseline in Personal Social Performance (PSP), CGI-S, PANSS Marder Positive symptom factor score, PANSS Marder Negative symptom factor score - Categorical response defined as the proportion of subjects achieving a ≥

Trial	Study Design	Treatment Arms	Inclusion & Exclusion Criteria	Outcomes [Timepoint]
			other increase in the level of care due to symptom exacerbation within 8 weeks and is psychiatrically stable - To be eligible for randomization, subjects will need 80% adherence with their prescribed antipsychotic dosing using AiCure technology and pill count during the Screening period. - PANSS total score ≥ 70 at Screening and randomization - CGI-S scale with a score ≥ 4 at Screening and randomization - PANSS Marder Positive symptom factor ≥ 4 on two items, at Screening and randomization - Subjects with ≤ 20-point decrease in PANSS Total score between Visit 1 and Visit 3 - BMI must be within 18 to 40 kg/m^2 **Exclusion** - Any primary DSM-5 disorder other than schizophrenia within 12 months before screening - History of moderate to severe alcohol use disorder or substance use disorder (other than nicotine or caffeine) within the past 12 months - History of inadequate response to schizophrenia medications - History of symptom instability - >3 psychiatric hospitalizations over the last 12 months or 2 over the last 6 months - Current APD is other than aripiprazole, risperidone, paliperidone, or their LAI versions, quetiapine, ziprasidone or lurasidone -Olanzapine is not permitted - Subjects who are newly diagnosed or are experiencing their first treated episode of schizophrenia	30% improvement in PANSS total score - Preference of Medication (POM)

Trial	Study Design	Treatment Arms	Inclusion & Exclusion Criteria	Outcomes [Timepoint]
ARISE-2 NCT05304767 Estimated study completion: 11/25	Phase 3, multicenter, 52-week, outpatient, open-label extension (OLE) study. N = 280 **Population:** Subjects with schizophrenia who previously completed the treatment period of the ARISE Study.	**Arm I:** Fixed dose of xanomeline 125 mg and trospium chloride 30 mg, orally, twice daily [BID]	**Inclusion** - Subject is aged ≥18 to <60 years old who completed the treatment period of ARISE Study - Subject has been compliant with the procedures in ARISE Study - Subject has been compliant with their background antipsychotic drug in ARISE Study **Exclusion** - Subject answers "Yes" to "suicidal ideation" Item 4 or Item 5 on the C-SSRS	**Primary [week 54]:** - Incidence of treatment-emergent adverse events (TEAEs) **Secondary [week 54]:** - Incidence of serious treatment-emergent adverse events (TEAEs) - Incidence of TEAEs leading to discontinuation of study drug

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies) APD: antipsychotic drugs, BID: twice a day, BMI: body mass index, CGI-S: Clinical Global Impressions scale, C-SSRS: Columbia Suicide Severity Rating Scale, DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, kg/m^2: kilograms by meters squared, LAI: long-acting injectable, mg: milligram, N: number, OLE: open label extension, OL: open label, PANSS: Positive and Negative Syndrome Scale, TEAE: treatment emergent adverse event

D5. Previous Systematic Reviews and Technology Assessments

We identified three previously conducted systematic literature reviews (SLR) and no health technology assessments (HTA). The three SLRs are briefly summarized below.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019;394(10202):939-951.[56]

Huhn et al. conducted a network meta-analysis of 402 placebo-controlled and head-to-head randomized controlled trials with data for 53,463 adults with acute symptoms of schizophrenia or related disorders. The NMA compared the effectiveness of 32 antipsychotics using the primary outcome of change in overall symptoms measured with standardized rating scales, eight secondary efficacy measures, and eight safety outcomes. The effect size estimates suggested that all antipsychotic drugs reduced overall symptoms of schizophrenia more than placebo, significant for all but six drugs, with standardized mean differences ranging –0.89 and –0.03 (median –0.42). However, when comparing antipsychotics to each other, there were few significant differences between the individual antipsychotics on change in overall symptoms. Only clozapine, amisulpride, zotepine, olanzapine, and risperidone were significantly more efficacious in reducing overall symptoms when compared to other antipsychotics. For safety outcomes, antipsychotics very often scored worse than placebo, with each drug having a different side-effect profile. The older first-generation antipsychotics included in the review were more often associated with extrapyramidal side effects and prolactin elevation, whereas many of the newer antipsychotics were seen to produce more weight gain and sedation. Lastly, it was recommended that when choosing an antipsychotic, clinicians consider the patient's treatment pathway, preferences, and which outcomes are most important to them.

Leucht S, Schneider-Thoma J, Burschinski A, et al. Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: systematic review and network meta-analysis. *World Psychiatry.* 2023;22(2):315-324.[61]

Although most trials evaluating antipsychotics for acute phases of schizophrenia last only a few weeks, patients typically take antipsychotics for much longer in the maintenance phase of treatment. To examine the long-term effects of antipsychotic drugs in acutely ill patients living with schizophrenia, Leucht et al. performed a systematic literature review and network meta-analysis. The study included randomized, blinded trials of at least six months on all second-generation and 18 first-generation antipsychotics of any formulation (including long acting injectables). There were 45 studies included with 11,238 participants and a mean study duration of 42 weeks. The primary outcome of this analysis was the change in overall symptoms of schizophrenia; secondary outcomes included all-cause discontinuation, change in positive and negative symptoms, weight gain, and more. Olanzapine was more efficacious than several other first- and second-generation

antipsychotics in reducing overall symptoms, with varied standardized mean differences reflecting small changes (0.12 versus risperidone) and moderate changes (0.37 versus ziprasidone). The results for secondary outcomes, change in positive and negative symptoms, were similar to those for overall symptoms. Olanzapine was associated with the lowest all-cause discontinuation rate; however, it was also associated with higher weight gain than all other antipsychotics. Overall, olanzapine was observed to be more efficacious than a number of other antipsychotics in the long-term treatment of acutely ill patients with schizophrenia, with risperidone and amisulpride being considered the best alternatives. However, olanzapine's superior efficacy must be balanced with its risk for weight gain. A key limitation of this study is that most of the trials included lasted only six weeks whereas these drugs usually need to be taken much longer for the maintenance treatment of schizophrenia.

Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *The Lancet.* 2022;399(10327):824-836.[60]

Schneider et al. performed a systematic literature review and network meta-analysis to assess the efficacy and tolerability of antipsychotics as maintenance treatment for non-treatment-resistant patients with schizophrenia. This review included randomized controlled trials lasting at least 12 weeks that recruited adult participants with schizophrenia or schizoaffective disorder who were non-treatment resistant and had stable symptoms. Trials must have included either a second-generation antipsychotic (oral or long-acting injectable) or one of 19 more utilized first-generation antipsychotics as an active treatment arm. The primary outcome of this review was the number of participants who experienced a relapse of symptoms. This was analyzed by a random-effects Bayesian network meta-analysis. Data for the primary outcome was taken from 100 studies with 16,812 participants that looked at 30 antipsychotics. Results showed that all antipsychotics had less risk of relapse compared with placebo, with all but three comparisons being statistically significant. Although there was no clear evidence for the superiority of any of antipsychotic for relapse prevention, olanzapine, paliperidone, and risperidone ranked among the more efficacious drugs. Given the uncertainty of differences between antipsychotics for relapse prevention, the choice of antipsychotics for maintenance treatment should be guided mainly by an individual patient's tolerability, needs, and preferences.

D6. Heterogeneity and Subgroups

For olanzapine, ENLIGHTEN 2020 reported change from baseline in PANSS total score by age (<55, ≥55), gender, and race.[51] There was no significant difference in PANSS score by gender. Black individuals had numerically greater increases in PANSS score compared to White individuals or individuals categorized as "other" race, although the credible intervals are wide and overlapping.

The ≥55 years of age group had increase in PANSS score compared to placebo (LS mean difference: 10.6 [95% CI: 1.0, 20.2]) compared to the <55 group (LS mean difference: -7.7 [95% CI: -11.5, -3.8]). In Burgarski-Kirola et al. 2014, significant differences in change in PANSS total score were not observed in subgroup analyses for race, sex, and age.[27]

Four trials reported changes in prolactin levels by sex. One risperidone trial (Durgam et al. 2014[36]) and one olanzapine trial (Marder et al. 2007[48]) report females receiving the active treatment had greater increases in prolactin levels compared to males and both females and males receiving placebo report decreases in prolactin. One olanzapine trial (Davidson et al. 2007[33]) and one aripiprazole trial (Correll et al. 2016[89]) reported a decrease in prolactin levels for both males and females receiving active treatment with a numerically greater decrease in females. See Supplement Table D3.15 for more detail.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	☐	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	X	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

4. Adapted from Sanders et al[91]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[92]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population for the economic evaluation included adults with schizophrenia who were not considered to have treatment-resistant schizophrenia at the model start. All members of the modeled cohort started in the acute phase of the model experiencing an inpatient acute psychosis event in alignment with the clinical evidence for KarXT. Table E2 describes the baseline population characteristics. Age and sex influence the general population mortality risk and utility estimates. None of the schizophrenia-specific inputs are age- or sex-dependent. We assumed the starting population did not have metabolic syndrome, diabetes, or cardiovascular disease and thus the entire population treated was eligible for the potential benefit of KarXT not increasing the risk of metabolic syndrome.

Table E2. Base-Case Model Cohort Characteristics

	Value	Primary Source
Mean Age at Baseline, years	44 years	EMERGENT 3[14]
Percent Female, %	30.4%	
Percent with Metabolic Syndrome, %	0%	Assumption

Treatment Strategies

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- xanomeline/trospium (KarXT) (Karuna Therapeutics)

Comparators

The comparator for KarXT was aripiprazole. Aripiprazole was selected as the comparator because it is believed to have the fewest side effects among the other second-generation antipsychotics.

The model allowed for treatment switching and stopping. If the initially modeled treatment (i.e., KarXT in the intervention arm or aripiprazole in the comparator arm) was discontinued, a modeled adult with schizophrenia switched to a second treatment market basket that was 51% risperidone and 49% olanzapine based on market share data.[69] Risperidone and olanzapine were selected to represent the second treatment market basket as they are widely used, represent a range of effectiveness and side effect profiles for second-generation antipsychotics, and allowed for the second modeled treatment to be consistent between the intervention and comparator arms. If the second modeled treatment (i.e., market basket of risperidone and olanzapine for both the intervention and comparator arm) was discontinued, the modeled adult with schizophrenia switched to a third treatment market basket that was 36% risperidone, 34% olanzapine, and 30% clozapine. Clozapine was included in the third treatment market basket in alignment with evidence suggesting treatment-resistant schizophrenia occurs in approximately 30% of individuals diagnosed with schizophrenia and is an appropriate treatment for those individuals if they discontinued at least two prior antipsychotics.[1] All members of the modeled cohort stayed on treatment with an antipsychotic over their lifetime, except for 18.2% of the alive population who stopped treatment twenty years after the model start in alignment with evidence suggesting that 81.8% of adults with schizophrenia are still on treatment twenty years after starting.[70]

E2. Model Inputs and Assumptions

Our model includes several assumptions stated in Table E3.

Table E3. Model Assumptions

Assumption	Rationale
While receiving KarXT, members of the modeled cohort were not at an increased risk of developing metabolic syndrome beyond that of the general population.	There was no significant difference in weight gained between patients treated with KarXT and patients treated with placebo reported in the KarXT clinical trials. Without evidence on the risk of metabolic syndrome for adults with schizophrenia who are not on an antipsychotic, we assumed the same risk of metabolic syndrome as the general population.
The starting population did not have metabolic syndrome, diabetes, or cardiovascular disease.	The entire population treated was eligible for the potential benefit of KarXT not increasing the risk of metabolic syndrome or its associated long-term consequences.
In the acute phase, members of the modeled cohort discontinued a treatment and switched to the subsequent treatment in the sequence due to inadequate clinical response.	While experiencing an inpatient acute psychosis event, adults with schizophrenia are likely continuously treated until they respond adequately, and thus we assumed that treatment response is the primary trigger of treatment switching in the acute phase. This is a simplifying structural assumption in the acute phase only and is aligned with other published economic models.[68] All individuals exited the acute phase on a treatment.
In the acute phase, the length of the hospitalization for the acute psychosis event was one month, two months, or three months based on if one, two, or three separate treatments were administered, respectively.	If members of the modeled cohort did not have an adequate response to a treatment, they switched to another treatment after a certain period of time. In the acute phase of this model, that period of time was one month. Switching treatments thus extended the time hospitalized with the acute psychosis event.
In the maintenance phase, members of the modeled cohort discontinued a treatment and switched to the subsequent treatment in the sequence due to inefficacy, side effects, or their own decision.	While receiving treatment in the maintenance phase, adults with schizophrenia could discontinue a treatment if it was not working adequately, adverse events occurred, or for some other personal reason. Lacking these reasons, adults with schizophrenia continued their current treatment. Discontinuation was based on treatment-specific discontinuation probabilities and were not directly linked to certain events recorded in the model.
Members of the modeled cohort stayed on treatment over their lifetime, except for a small proportion of the population that stopped antipsychotic treatment after twenty years.	Schizophrenia requires lifelong treatment. Based on evidence from a study with 20-year follow up, only 18.2% of adults with schizophrenia are not using antipsychotics twenty years after starting treatment.[70] Therefore, we modeled that 18.2% of the surviving population would stop antipsychotic treatment (irrespective of the treatment they were on) at 20 years after the start of the model, and the remaining

	modeled population would stay on treatment over the lifetime time horizon.

Model Inputs

Key model inputs included clinical response, relapse rates, treatment-emergent adverse events, quality of life, treatment discontinuation, treatment stopping, and costs. Probabilities, adverse events, costs, and other inputs differed to reflect varying effectiveness between interventions. Treatment effectiveness for KarXT was estimated by way of an effect on achieving adequate clinical response in the acute phase, and on experiencing relapses, developing metabolic syndrome (and associated long-term consequences), and discontinuation in the maintenance phase. Because KarXT evidence is limited to only five weeks, published data on the maintenance use of other second-generation antipsychotic drugs was used wherever possible to populate the model during the maintenance phase. Quality of life weights were applied to each health state, including quality of life decrements for relapses and treatment-emergent adverse events. The model included direct medical costs, including but not limited to costs related to drug acquisition, condition-related care, and treatment-emergent adverse events. In addition, productivity impacts, caregiver time spent caregiving, and criminal justice impacts were included in the modified societal perspective scenario analysis.

Clinical Inputs

Clinical inputs included the percent achieving adequate clinical response in the acute phase. In the maintenance phase, the clinical inputs included the probability of relapse, treatment-emergent adverse events, long-term consequences of treatment-emergent adverse events, discontinuation, and mortality.

Adequate Clinical Response

All members of the modeled cohort started in the acute phase of the model while experiencing an inpatient acute psychosis event at the start of the model. In the acute phase of the model, members of the modeled cohort were treated and assessed for an adequate clinical response to treatment, defined as a 30% improvement in PANSS. If an individual did not achieve an adequate clinical response to the first treatment in the model, they switched to the second treatment in the sequence after one month on the first treatment (i.e., one month since the model started). If an individual did not achieve an adequate clinical response to the second treatment in the sequence after one month on the second treatment (i.e., two months since the model started), they switched to the third treatment. After the three-month acute phase, members of the modeled cohort entered the maintenance phase of the model on the treatment that they were on at the end of the

acute phase. Table E4 reports the probability of achieving an adequate clinical response for each treatment.

Table E4. Adequate Clinical Response

Treatment	Value	Source	Notes
KarXT	53% (33%, 72%)	ICER's NMA on acute phase probability of 30% improvement in PANSS	The relative risk point estimates from ICER's NMA were applied to the placebo probability of adequate clinical response of 26%.
Aripiprazole	36% (18%, 57%)		
Olanzapine*	43% (31%, 55%)		
Risperidone*	51% (32%, 70%)		

NMA: network meta-analysis, PANSS: Positive and Negative Syndrome Scale

*Inputs are for the second treatment market basket. The modeled adults with schizophrenia stay on the third treatment basket over their lifetime and thus they do not discontinue the third treatment basket unless they are part of the 18.2% of the modeled population that stops treatment at twenty years.

Maintenance Phase Relapse Inputs

After the acute phase of the model, members of the modeled cohort could experience a relapse based on the treatment-specific probabilities reported in Table E5. No evidence exists for KarXT in the maintenance phase. Because KarXT was not significantly different from the other second-generation antipsychotics in terms of adequate clinical response in the acute phase, as evidenced by ICER's network meta-analysis, we assumed KarXT's probability of relapse in the maintenance phase would be similar to that of the other second-generation anti-psychotics.

Table E5. Maintenance Phase Relapse Probabilities

Treatment	Three-Month Probability of Relapse	Source	Notes
KarXT	10.5% (7%, 15%)	Davies et al., 2008[67]	Assumed the mid-point between the range of second-generation anti-psychotics.
Aripiprazole	12.7% (8%, 18%)		Adjusted the annual estimates from Davies et al. to 3-month probabilities
Olanzapine	8.2% (5%, 12%)		
Risperidone	12.7% (8%, 18%)		
Clozapine	8.9% (6%, 13%)		
No Antipsychotic	41.0% (26%, 57%)	Davies et al. 2008[67] & Schneider-Thoma et al., 2022[60]	Estimated using olanzapine's probability of relapse from Davies et al. and the effectiveness of olanzapine versus placebo on relapse from Schneider-Thoma et al.

Treatment-Emergent Adverse Events

The maintenance phase of the model also tracked treatment-emergent adverse events, primarily metabolic syndrome and its long-term consequences. Other health economic models in schizophrenia have also included extrapyramidal symptoms (EPS) and hyperprolactinemia (HPRL) as treatment-emergent adverse events.[66,67] However, EPS and HPRL have not been major drivers of the cost-effectiveness of past treatments for schizophrenia and KarXT-specific evidence for these adverse events is lacking; therefore, EPS and HPRL were not tracked in this model. In a scenario analysis, we included tardive dyskinesia. Table E6 reports the treatment-specific three-month probabilities for developing metabolic syndrome. In alignment with other economic models, metabolic syndrome was considered irreversible and would be associated with consequences even after the period of medication administration.

Table E6. Treatment-Emergent Adverse Events

Treatment	Three-Month Probability of Metabolic Syndrome	Source	Notes
KarXT	0.7% (0%, 4%)	Li et al. 2022[71] & ICER's NMA on acute phase absolute weight gain	Assumed the same point estimate as no antipsychotic use due to findings from ICER's NMA suggesting no significant difference in weight gained between KarXT and placebo
Aripiprazole	3.8% (2%, 5%)	Park et al., 2014[66], Davies et al., 2008[67]	Adjusted the 18-week estimates from Park et al. to three-month probabilities, applied aripiprazole's relative risk to olanzapine from Davies et al. to the olanzapine estimate from Park et al.
Olanzapine	9.1% (6%, 13%)		
Risperidone	5.5% (4%, 8%)		
Clozapine	11.2% (7%, 16%)		
No Antipsychotic	0.7% (0%, 1%)	Li et al., 2022[71]	Assumed the same as the general population, calculated based on the reported 14-year incidence of metabolic syndrome among the US general population.

NMA: network meta-analysis, US: United States

Members of the modeled cohort who developed metabolic syndrome were at an increased risk of developing diabetes or cardiovascular disease. The model also tracked these long-term consequences associated with metabolic syndrome. The per-cycle risks of developing diabetes and cardiovascular disease if an individual has metabolic syndrome are reported in Table E7. Diabetes and cardiovascular disease were modeled as independent conditions. A member of the modeled cohort could have neither of the conditions, one of the conditions, or both of the conditions.

Table E7. Long-Term Consequences of Metabolic Syndrome

	Three-Month Risk of Developing	Source	Notes
Diabetes	1.2% (0%, 4%)	Park et al., 2014[66]	Adjusted the annual estimates from Park et al. to three-month probabilities
Cardiovascular Disease	0.5% (0%, 3%)		

Treatment with KarXT may be associated with other minor adverse events (e.g., gastrointestinal events). This model did not track these events as they are unlikely to have a large impact on cost or consequences.

Treatment Discontinuation

In the maintenance phase of the model, members of the modeled cohort could discontinue a treatment and switch to the subsequent treatment in the sequence due to inefficacy, side effects, or their own decision. Lacking these reasons, patients continued their current treatment. Discontinuation was assumed to occur at the end of the cycle. Table E8 reports the treatment-specific discontinuation inputs that were used for each model cycle for the first and second modeled treatments.

Table E8. Treatment Discontinuation

Treatment	Three Month Probability of Discontinuation	Source	Notes
KarXT	5.9% (4%, 8%)	Fisher et al., 2014[72] & ICER's NMA on acute phase discontinuation, hospital sensitivity analysis	The relative risk of KarXT to olanzapine from ICER's NMA was applied to the olanzapine three-month probability of discontinuation
Aripiprazole	5.4% (3%, 8%)	Fisher et al., 2014[72]	Adjusted the annual estimates from Fisher et al. to three-month probabilities
Olanzapine*	4.0% (3%, 6%)		
Risperidone*	4.0% (3%, 6%)		

NMA: network meta-analysis

*Inputs are for the second treatment market basket. The modeled adults with schizophrenia stay on treatment over their lifetime and thus they do not discontinue the third treatment basket unless they are part of the 18.2% of the modeled population that stops treatment at twenty years.

Mortality

In the maintenance phase, mortality was tracked over the lifetime time horizon. All-cause mortality from the general population served as the underlying risk of mortality, and condition-specific mortality was added on to the general population risk of mortality to estimate the total mortality risk. Table E9 reports the standardized mortality ratios that were used to estimate the condition-specific mortality probabilities. These standardized mortality ratios were multiplied by the general population risk of mortality. From there, the schizophrenia-specific, diabetes-specific, and cardiovascular disease-specific mortality probabilities were isolated by removing the general population risk of mortality. The competing risks for mortality (i.e., due to all-cause, schizophrenia, diabetes, or cardiovascular disease) result in a potential for double counting. We attempted to reduce this potential for double counting while still modeling an independent (i.e., separate from schizophrenia-specific mortality) risk of mortality associated with diabetes and cardiovascular disease.

Table E9. Standardized Mortality Ratios

	Standardized Mortality Ratio vs. the General Population	Source	Notes
Schizophrenia	2.34 (1.51, 3.34)	Brown et al., 2000[93]	Removed the deaths due to diabetes and cardiovascular disease to avoid double counting
Diabetes	2.19 (1.42, 3.13)	Leibson et al., 2005[94]	Risk of death from diabetes and cardiovascular disease is assumed to be in addition to the risk of death from schizophrenia
Cardiovascular Disease	1.67 (1.08, 2.39)	Nabi et al., 2010[95]	

Health State Utilities

Health state utilities were derived from publicly available literature. Age-adjusted utility estimates from the general population served as the foundation for the utility estimates. Utility decrements due to schizophrenia, relapse, and treatment-emergent adverse events were applied. Table E10 reports these disutilities that were applied for the duration of the model cycle(s) during which the

event(s) are present. Metabolic syndrome, diabetes, and cardiovascular disease were considered irreversible and thus the disutility continued even if antipsychotic treatment stopped.

Table E10. Disutilities

Parameter	Disutility	Notes	Source
Stable Schizophrenia without Adverse Events	-0.081 (-0.04, -0.13)	Calculated by subtracting the mean utility value for schizophrenia with mild symptoms (0.80) from the age-adjusted utility estimates for the general population	Aceituno et al., 2020[96]
Relapse	-0.460 (-0.41, -0.51)	Calculated by subtracting the mean utility value for schizophrenia with severe symptoms (0.34) from the mean utility value for schizophrenia with mild symptoms (0.80); applied for a duration of three months (i.e., one model cycle)[68]	
Metabolic Syndrome without Diabetes or Cardiovascular Disease	-0.06 (-0.03, -0.09)	Based on a time trade-off assessment study investigating impact of treatment-emergent adverse events for schizophrenia	Matza et al., 2014[97]
Diabetes	-0.100 (-0.07, -0.14)		
Cardiovascular Disease	-0.100 (-0.07, -0.14)	Assumed to be the same as the disutility for schizophrenia with diabetes based on other studies suggesting the disutility for CHD was similar to or equal to that of diabetes	Park et al., 2014[66] & Matza et al., 2014[97]

Cost Inputs

All costs used in the model were adjusted to 2022 US dollars.

Drug Costs

A price is not yet known for KarXT and thus a placeholder price was used in the economic model. IPD Analytics estimates an annual price of approximately $20,000 per year. Therefore, we used an annual price of $20,000 per year as a placeholder price in our economic model.[69]

All of the other drugs included in our model have generic equivalents available. For approved drugs with generic equivalents available, we used the lowest cost generic wholesale acquisition cost (WAC) as the estimate of the net price in alignment with ICER's reference case. Table E11 reports the modeled dose, WAC per dose, net price per dose, and net price per year. Given all drugs are administered orally, no administration costs were modeled.

Table E11. Drug Costs

Drug	Dose	WAC per Dose	Net Price per Dose	Net Price per Year
Aripiprazole	15 mg once daily	$0.11	$0.11	$40
Risperidone	4 mg once daily	$0.17	$0.17	$62
Olanzapine	20 mg once daily	$0.41	$0.41	$150
Clozapine	400 mg once daily	$3.66	$3.66	$1,336

mg: milligram, WAC: wholesale acquisition cost

Non-Drug Costs

Other Direct Medical Costs

In addition to drug costs, the model tracked direct medical costs related to schizophrenia and related to treatment-emergent adverse events. In the acute phase, the model tracked the cost of the hospitalization for the acute psychosis event. The length of the initial acute hospitalization was one month, two months, or three months based on if they were treated with one, two, or three separate treatments, respectively. The number of treatments the received in the acute phase was based on the model inputs for adequate clinical response. The acute hospitalization was monetized using the daily cost of an inpatient visit of $1,075 per day.[98] Table E12 reports the schizophrenia-related health care utilization and unit costs that the model tracked in the maintenance phase.

Table E12. Schizophrenia-Related Healthcare Utilization and Unit Costs

Utilization	Number of Units	Source	Unit Cost	Source
Physician visit (CPT 99215)	1 visit per month	Park et al., 2014[66]	$185 per visit	Physician Fee and Lab Schedule 2023[99]
Mental health clinic visit (CPT 90834)	1 visit per month		$102 per visit	
Group intervention	0.5 hours per month		$88 per hour	Park et al., 2014[66]
Inpatient visit	11 days per relapse		$1,075 per day	HCUP, 2020[98]
ED visit	1 visit per relapse		$526 per visit	Karaca & Moore, 2020[100]

Table E12. Schizophrenia-Related Healthcare Utilization and Unit Costs

Physician visit (CPT 99215)	1 additional visit per relapse		$185 per visit	Physician Fee and Lab Schedule 2023[99]
Mental health clinic visit (CPT 90834)	2 additional visits per relapse		$102 per visit	
Hospital treatment	1.25 days per relapse		$877 per day	Park et al., 2014[66]
Home care	3 hours per relapse		$122 per hour	
Group intervention	2 additional hours per relapse		$88 per hour	

HCUP: healthcare cost and utilization project

Table E13 reports the treatment-emergent adverse event costs the model tracked in the maintenance phase. Diabetes and cardiovascular disease were considered irreversible and thus the costs would continue even if antipsychotic treatment stopped.

Table E13. Treatment-Emergent Adverse Event Costs

Parameter	Three-Month Cost	Source	Notes
Diabetes	$3,099 ($2,006, $4,427)	Habib, 2023[101]	Subtracted out all-cause health care costs, inflated to 2022 US dollars, and adjusted to three-month cycle.
Cardiovascular Disease	$3,946 ($2,554, $5,636)	Nichols et al., 2010[102]	Subtracted out all-cause health care costs, inflated to 2022 US dollars, and adjusted to three-month cycle.

US: United States

Productivity Impact

The societal perspective accounted for the patient productivity impact of schizophrenia. To model the impact of schizophrenia on an individual's productivity, we assumed each relapse was associated with 65 days of missed work for the 37% of patients living with schizophrenia who work.[103,104] Assuming a day of missed work was eight hours of missed work per day, we monetized the time missed from work using an average hourly wage of $33.82 as reported by the Bureau of Labor Statistics.[105] We also incorporated the productivity impact of diabetes and cardiovascular disease for those patients who developed diabetes or cardiovascular disease. Patients living with diabetes received an additional indirect cost of $3,323 per year.[106,107] Patients living with cardiovascular disease received an additional indirect cost of $7,516 per year.[106,108]

Caregiver Impact

The societal perspective accounted for the uncompensated time spent caregiving for a patient living with schizophrenia. Sixty-five percent of patients living with schizophrenia have a caregiver.[109] Among patients with a caregiver, the caregiver spends on average 39.7 hours per week (or 516 hours per model cycle) providing uncompensated care.[110] We monetized the time spent caregiving using an average hourly wage of $33.82 as reported by the Bureau of Labor Statistics.[105]

Criminal Justice Impact

The societal perspective accounted for the criminal justice impact of schizophrenia. The direct cost to the criminal justice system from 2,877 psychiatric hospitalizations was $21,145,992 (in 2013 US dollars).[111] This equates to $7,350 per psychiatric hospitalization (in 2013 US dollars). This number was inflated to 2022 US dollars ($8,590 of direct cost to the criminal justice system per psychiatric hospitalization) and was used to monetize the criminal justice impact of a relapse.

E3. Results

Table E14. Undiscounted Clinical Outcomes, Base Case

	KarXT Arm	Aripiprazole Arm
Years on First Treatment	2.32	1.73
Years on Second Treatment	4.13	3.68
Years on Third Treatment	16.49	17.41
Years Off Treatment	1.20	1.18
Number of Relapses	12.07	12.10
Years with Metabolic Syndrome	9.98	10.38
Years with Diabetes	7.21	7.80
Years with Cardiovascular Disease	3.72	4.04

E4. Sensitivity Analyses

Table E15. Tornado Diagram Inputs* and Results, Incremental Cost per QALY Gained

	Lower Input CE Ratio	Upper Input CE Ratio	Lower Input	Upper Input
3-month metabolic syndrome probability, KarXT	$119,000	$783,000	0%	4%
Adequate clinical response, KarXT	$298,000	$115,000	33%	72%
3-month diabetes risk	$289,000	$114,000	0%	4%
3-month relapse probability, KarXT	$113,000	$258,000	7%	15%
3-month cardiovascular risk	$217,000	$97,000	0%	3%
Acute phase length of stay, per treatment	$191,000	$124,000	15	51
Standardized mortality ratio, schizophrenia	$146,000	$180,000	1.51	3.34
Disutility for diabetes	$179,000	$147,000	-0.07	-0.14
Disutility for metabolic syndrome	$177,000	$147,000	-0.03	-0.09
3-month healthcare costs, diabetes	$175,000	$148,000	$2,006	$4,427

CE: cost-effectiveness

*Assuming a KarXT placeholder price of $20,000 per year.

Table E16. Results of Probabilistic Sensitivity Analysis

The probabilistic incremental cost-effectiveness ratios are similar to the deterministic estimates but are slightly less favorable due to the non-linear distributions assumed for some key model inputs such as the probability of metabolic syndrome for KarXT.

	KarXT*	Aripiprazole
Costs	$341,000	$315,000
QALYs	10.60 (9.21, 12.05)	10.46 (9.00, 11.94)
evLYs	10.61 (9.24, 12.06)	10.46 (9.00, 11.94)
Incremental CE Ratio ($/QALY)		$189,000
Incremental CE Ratio ($/evLY)		$173,000

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

E5. Scenario Analyses

Scenario Analysis 1

Table E17 and E18 report results from the modified societal perspective scenario analysis. In this scenario, patient productivity losses, caregiver time spent caregiving, and costs to the criminal justice system were included. Caregiver time spent caregiving was greater for KarXT-treated patients due to the longer duration of caregiving requirements. Productivity losses and costs to the criminal justice system were marginally lower for KarXT-treated patients due to the marginally

fewer relapses that occurred due to the marginally longer time on antipsychotic treatment and the fewer years with diabetes and cardiovascular disease.

Table E17. Model Outcomes for the Modified Societal Perspective Scenario Analysis

Treatment	Total Health System Costs	Lost Productivity	Caregiver Time	Criminal Justice Costs	Total Societal Costs
KarXT*	$350,000	$82,000	$737,000	$70,000	$1,240,000
Aripiprazole	$326,000	$85,000	$734,000	$71,000	$1,217,000

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Assuming a KarXT placeholder price of $20,000 per year.

Table E18. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective Scenario Analysis

Treatment	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Year Without Diabetes
KarXT*	$158,000	$337,000	$142,000	$58,000

evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

Scenario Analysis 2

Table E19 and E20 report results from the scenario analysis that assumed that while a patient was treated with KarXT, they were at a 0% risk of developing tardive dyskinesia. There is currently no KarXT evidence to support this assumption; however, we presented this as a scenario analysis to suggest what the cost-effectiveness of KarXT could look like if KarXT was not associated with any risk of tardive dyskinesia. In contrast, while adults with schizophrenia were on any other second-generation antipsychotic, they were at a 0.5% risk[112] of developing tardive dyskinesia every model cycle. For those who developed tardive dyskinesia, they were assigned a disutility of -0.21[97] and a cycle cost of $3,260[113] for every remaining cycle. Tardive dyskinesia effects were not included in the base case due to the lack of evidence linking extrapyramidal symptoms to tardive dyskinesia and no evidence for KarXT on tardive dyskinesia.

Table E19. Model Outcomes for the Tardive Dyskinesia Scenario Analysis

Treatment	Total Cost	Years With Diabetes	QALYs	Life Years	evLYs
KarXT*	$386,500	4.00	9.81	16.25	9.83
Aripiprazole	$368,700	4.40	9.57	16.18	9.57

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Assuming a KarXT placeholder price of $20,000 per year.

Table E20. Incremental Cost-Effectiveness Ratios for the Tardive Dyskinesia Scenario Analysis

Treatment	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Year Without Diabetes
KarXT*	$73,000	$260,000	$67,000	$45,000

evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

Scenario Analysis 3

Table E21 and E22 report results from the scenario analysis that assumed that while a patient was treated with KarXT, they were at a 1.9% risk of developing metabolic syndrome rather than the 0.7% (i.e., same risk as general population) risk modeled in the base case. A 1.9% risk is still half the risk of developing metabolic syndrome for aripiprazole, which had the lowest modeled risk of metabolic syndrome among the other modeled second generation antipsychotics. There is currently no KarXT evidence on developing metabolic syndrome; however, we made the optimistic assumption that it would not be associated with an increased risk of metabolic syndrome beyond that observed in the general population. We present this as a scenario analysis to show the sensitivity of the cost-effectiveness to KarXT's effect on the subsequent development of metabolic syndrome.

Table E21. Model Outcomes for the Scenario Analysis Assuming a Risk of Metabolic Syndrome Among Patients Treated with KarXT

Treatment	Total Cost	Years With Diabetes	QALYs	Life Years	evLYs
KarXT*	$353,000	4.15	10.34	16.22	10.35
Aripiprazole	$327,000	4.40	10.25	16.18	10.25

evLYs: equal-value life years, QALYs: quality-adjusted life years

*Assuming a KarXT placeholder price of $20,000 per year.

Table E22. Incremental Cost-Effectiveness Ratios for the Scenario Analysis Assuming a Risk of Metabolic Syndrome Among Patients Treated with KarXT

Treatment	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Year Without Diabetes
KarXT*	$280,000	$630,000	$253,000	$107,000

evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). We also

conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

The model used to generate the cost-effectiveness estimates was based on previously published models and was adapted based on stakeholder guidance.[66-68] It incorporated the acute phase model from Beard et al. with the maintenance phase model in Davies et al. and Park et al. Some key adaptations in our model were a lifetime time horizon to capture the potential lifelong benefits of preventing/delaying metabolic syndrome, using market baskets for the modeled treatment 2 and 3 rather than a single specific treatment because our goal was not to estimate the most cost-effective sequence, and having members of the modeled cohort stay on antipsychotic treatment over their lifetime except for the small proportion of people that stop treatment. As part of our model validation efforts, we adapted our model to be nearly identical in model assumptions and in model inputs as what was used in Park et al. and the findings were comparable. In the paper by Park and colleagues, two of the sequences they modeled were ziprasidone to risperidone to clozapine and separately olanzapine to risperidone to clozapine. They reported an incremental difference in cost of -$12,000 (comparing the ziprasidone as first line to the olanzapine as first line) and an incremental difference in QALYs of 0.06. In our model adaptation, we calculated an incremental difference in cost of -$10,000 and an incremental difference in QALYs of 0.06.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with KarXT.

The potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs for the prevalence of schizophrenia for US adults (1.8%),[4,75] the average projected US adult population size over five years (2023-2027; 269,529,814),[76] and the percentage of adults with schizophrenia estimated to be receiving antipsychotic medication (71.3%).[77] Applying these sources results in estimates of 3,459,146 eligible adults with schizophrenia in the US. For the purposes of this analysis, we will assume that 20% of these individuals would initiate treatment in each of the five years, or 691,829 adults with schizophrenia per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[114,115] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact were calculated, we compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.

G. Supplemental Policy Recommendations

Payers

Drug-Specific Coverage Criteria: KarXT

Many people living with schizophrenia have suboptimal control of their symptoms with current therapies and / or experience intolerable side effects. KarXT, with its novel mechanism of action offers hope to these patients. However, lack of long-term data, the potential for side effects, and the expected high annual price for KarXT compared to current generic antipsychotic therapies, will likely lead many payers to develop prior authorization criteria or step therapy criteria for KarXT.

None of these utilization management tools, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for KarXT.

Coverage Criteria

- **Age:** The clinical trials of KarXT enrolled patients ages 18 to 65 years. There is no *a priori* reason to exclude patients over the age of 65 years, though they may be at higher risk for side effects from KarXT. However, it would be reasonable to restrict the use of KarXT to adults until studies have demonstrated the efficacy and safety of KarXT in adolescents.

- **Clinical eligibility**: Patients should have a documented diagnosis of schizophrenia. Although the clinical trials of KarXT were restricted to patients with a diagnosis of schizophrenia hospitalized for acute exacerbation of psychotic symptoms, clinicians will not stop therapy as patients transition back to the outpatient setting. Therefore, KarXT use should not be limited to the inpatient setting and will likely be initiated for many patients in the outpatient setting. Some payers may choose to include wording in clinical criteria that patients started on KarXT in the inpatient setting will be allowed to continue therapy.

  KarXT should not be used in combination with other antipsychotic medications at this time due to the risk for additive anti-cholinergic side effects and unknown efficacy. However, coverage criteria should be rapidly updated once data from the 4ARISE trial studying KarXT as an adjunct treatment are available.

- **Exclusion criteria**: Payers are likely to include many if not all the exclusion criteria from the clinical trials to ensure that patients are not at significant risk of serious side effects.

    - Patients who are pregnant or lactating or planning to become pregnant
    - Patients with significant liver disease

- Patients at high risk for urinary retention, gastric retention, or acute angle glaucoma

- **Dose:** Dosing of KarXT is typically initiated at 50 mg xanomeline plus 20 mg trospium twice daily for two days and then increased to 100 mg xanomeline plus 20 mg trospium. If there is an inadequate clinical response after 7 days, the dose may be increased to 125 mg xanomeline and 30 mg trospium. Dose reductions may be required based on side effects.

- **Duration of coverage and renewal criteria**: No coverage limits or renewal criteria are needed.

- **Provider restrictions**: Schizophrenia is a serious illness and, in the ideal world, initial drug treatment should be managed by psychiatrists. KarXT can have significant side effects that require expertise in management. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects. However, given the current provider shortage of psychiatrists, payers should consider allowing all providers to prescribe KarXT if they indicate that they are in consultation with a psychiatrist or a Board-certified psychiatric pharmacist. In general, generalist physicians do not initiate new treatments for patients with schizophrenia, though they may assume the responsibility for routine refilling of prescriptions once a patient is on stable therapy.

Step Therapy for Initial Treatment

Payers should only require step therapy for KarXT when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.

Clinical experts and patient representatives stated that delayed and restricted access to treatment due to step therapy requirements for patients with schizophrenia is common. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients, including poor adherence. That said, the studies of KarXT excluded patients who had never received treatment for schizophrenia, and there are more than 20 drugs with FDA approval for the treatment of schizophrenia, most of which are generic. These treatments have many years of safety data available, and their risks are well understood. Thus, clinical experts felt it would not be unreasonable for payers to require at least one therapeutic trial of a second generation antipsychotic drug at adequate dosing and duration prior to covering KarXT to treat patients living with schizophrenia. If patients do not receive adequate benefit, and/or if they experience significant weight gain or have other adverse effects from initial treatment, KarXT would be a reasonable second or third-line agent.

If long-term studies confirm that KarXT has equivalent efficacy to second generation antipsychotics without the weight gain and metabolic side effects common to existing treatments, payers should consider moving KarXT to a preferred position on their formulary if the drug is priced within reasonable cost-effectiveness ranges, even if that price is higher than the price for generic

treatment options. In particular, patients with pre-existing diabetes or cardiovascular disease should be able to bypass any step therapy should long-term studies confirm the safety of KarXT.

H. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on February 9th, 2024. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Two speakers did not submit summaries of their public comments.

A video recording of all comments can be found here, beginning at minute 00:00:20. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Lisa Guardiola, NAMI South Suburbs of Chicago
Vice President

Hello and my name is Lisa Guardiola. I am very excited to be here and to give my testimony. Just a little about myself I am 52 years old and was formally diagnosed with Schizophrenia in 2004. I am 20 years in my mental health recovery journey and I work for a mental health provider in the southern suburbs of Chicago as a Community Outreach and Education trainer.

I have been successful in my mental health recovery in that I have been working for the past 9 years bring about mental health literacy and breaking the stigma that surrounds mental illness through my work that I do.

My journey has not been without its pitfalls along the way. One of the things that is most important in my recovery is to take my medication every day. With that said, taking medication has not been without its pitfalls.

I have had my share of side effects from medications that I have been prescribed. During my first hospitalization I was prescribed medication where I experienced multiple side effects.

I was so lethargic and slept most of my days away but had trouble staying asleep at night. I gained 90 pounds in 6 months and often felt weighted down resulting in a shuffled walk due to stiff muscles.

All of these side effects were awful but the worst side effect was that the medication raised my prolactin levels. My breasts began to swell and lactate. I was mortified!

When I visited my primary care physician about my concerns, she asked me if I thought I was pregnant. I answered that, “Not unless the immaculate conception has happened.”

You see, I was not sexually active and had not been so for a least a year prior to my hospitalization. It was still early in my treatment process as I had only been on this medication for 8 months since my discharge.

I was still grappling with managing my symptoms of delusions and auditory hallucinations. I still had grandiose thoughts that I was a direct decedent of Mary Magdalene and that angels were talking to me. I was still learning how to determine what was reality.

I am telling you this story because medication side effects not only affect one physically but mentally as well.

Not only did the physical side effect make it difficult to function they also took a toll on my self-esteem. I felt self-conscious about my weight. I felt guilty that my mobility and lethargy made it difficult for me to work or focus. I was scared that I was pregnant without being sexually active.

It is important that those who develop and prescribe medications are aware that these medications affect those taking them both physically and mentally. Especially for those of us that are new to our recovery process.

It is my wish that there will be a day when the medications I am prescribed will have no or minimal side effects. I don’t know if any medications could make my symptoms and side effects go away completely. That would be a miracle. If my symptoms could be put in complete remission that would be wonderful. But even a medication that helped more with the above symptoms and side effects would be valuable. Also, it would be nice to have medications that help people in taking their medications. For example, if there were more medications that we could take once a month or every other month, instead of every day, to manage symptoms.

Thank you for allowing me to provide this public comment. I hope that my lived experience of living with schizophrenia and taking medications has given you insight into how these medications affect those who they are prescribed. I am honored that I was given this opportunity and I hope that my story will help in developing new medications in the future.

No conflicts to disclose.

Paulie VonEdWærd-Benjamin, Earth Star, Heart Root
Tarot Reader

Greetings everyone! We are pleased and honored to be here. We are Paulie VonEdWærd-Benjamin, someone who has lived with psychotic conditions such as schizophrenia most of our adult life. During our life, we've been diagnosed bipolar disorder, then schizophrenia, and finally, schizoaffective disorder. These are along with a few other diagnoses over the years at various times that were more general.

(Please note: We (I) use plural pronouns, sometimes even when referring to ourself.)

Schizophrenia and schizoaffective disorder have affected our life in more ways than We can count. Looking back 30 years on when We were first diagnosed as bipolar, the main reason for that being We were too afraid to speak about the voices we were hearing and some of the delusions we were having due to public stigmas. These days there is more information available from doctors, and more support from fellow patients via peer support forums. However, a very important thing that's being done more in the medical community now for conditions such as schizophrenia is involving the patients more in their own treatment.

This is a huge evolution but it still has a ways to go. For example the last time we were admitted to a psychiatric hospital it was a rushed procedure. Not all of the people involved were taking their time to find out what our personal stance was on the symptoms we were experiencing, and instead it felt still like the mentality of "just get them through the system". This is not the fault of the people working within the system (We were at the ER!). This is simply because it is a system evolving from where people with mental and brain conditions are treated like we should just be taken care of, and that our own opinion does not necessarily matter as much as the professionals.

So now, patients' opinions matter much more when speaking to their therapist, but they are still left out of many areas of the research and decision-making process when it comes to the corporate pharmaceutical level. However, organizations like Karuna Therapeautics are taking steps to involve patients, or at least the opinions of patients, from some of the earliest stages of research.

Humanity now has technology that enables us to make predictive analysis based even sometimes just on someone's written or oral account of their symptoms. In this way, specific behaviors, habits and coping and managing strategies can all be taken into account when trying to diagnose a patient and figure out the best treatment for them. Not just the best treatment available from a professional standpoint, but from the patient's standpoint, too.

Of course, we still have a ways to go. We are here speaking for KarXT because of this need for involving patients more. This is the mentality that will, in our opinion, lead to much more success in the future. Patients are standing up for themselves now more when it comes to what their doctors are telling them by asking for specific treatments, and that their medical support team takes into

account several variables from their personal life that might help in their treatment. Now more than ever, information and support resources are readily available over the Internet – and while much of that does need the usual "large grain of salt", it doesn't change the fact that it's easier for people to support themselves.

Allowing patients the ability to have more input into the overall process of treatment is not just about respect, but We believe can also help with predictive long-term effects and management of treatment. Especially those of us who have suffered for years and, for lack of a better term, we've had to "make do" with what works for us when the system fails. Much of our own personal development towards healthier living comes from our fellow patients and peers! It would be grand if more companies treated our lived experiences with as much respect.

For example, although We do currently take medication, overall our experience with pharmaceutical treatments has been negative. Primarily because We feel they suppress our emotions too much, or that We cannot fully express ourself because We feel too mentally numb. Our current treatment has worked best so far, but this is after 20+ years of being on and off multiple medications. And the number one thing that helps outside of that is what We practice based on our own personal experiences with our conditions. We can only dream of what our treatment would have been like 30 years ago had a system been in place to cater to our own personal reactions to medications instead of just what was generally acceptable.

We hope you will take into account that having a patient focused drive in research and development – not just clinical trials – with more patient involvement from as early on as possible will be more effective because it is actually done with the people who are living with this every day. We're the only ones with a truly subjective and unique – as all people are – perspective on our conditions.

Thank you.

No conflicts to disclose.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the February 9th, 2024 Public meeting of KarXT for Schizophrenia.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Sarah Emond, MPP, President and CEO, ICER	**Grace Ham, BS**, Program and Events Coordinator, ICER
Yamaya Jean, MA, Program Manager, ICER	**Avery McKenna, BS**, Research Lead, ICER
Becca Piltch, MPP, Program Manager, ICER	**Steven Pearson, MD, MSc**, Special Advisor, ICER
Finn Raymond, BS, Research Assistant, ICER	**David Rind, MD, MSc**, Chief Medical Officer, ICER
Jeff Tice, MD, Professor of Medicine, University of California, San Francisco	**Mel Whittington, PhD, MS**, Senior Fellow Center for the Evaluation of Value and Risk in Health (CEVR), Tufts Medical Center
Abigail Wright, PhD, MSc, Research Lead, ICER	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC*	
Rob Aseltine, PhD, Professor and Chair, UConn Health	**Marthe Gold, MD, MPH,** Senior Research Scholar, New York Academy of Medicine
Megan Golden, JD, CEO, Mission: Cure	**Rebecca Kirch, JD**, EVP Policy and Programs, National Patient Advocate Foundation
Stephen Kogut, PhD, MBA, RPh, Professor of Pharmacy Practice, University of Rhode Island College of Pharmacy	**Donald Kreis, MS, JD**, Patient Advocate, New Hampshire Office of the Consumer Advocate
Tara Lavelle, PhD, Assistant Professor, Tufts Medical Center	**Stephanie Nichols, PharmD, MPH, BCPP, FCCP**, Associate Professor, University of New England
Brian O'Sullivan, MD, Professor of Pediatrics, Geisel School of Medicine, Dartmouth	**Jeanne Ryer, MSc, EdD,** Director, NH Citizens Health Initiative
Jason Schwartz, PhD, Associate Professor of Health Policy, Yale School of Public Health	**Jason Wasfy, MD,** Associate Professor, Harvard Medical School and Mass General Hospital

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Kristin Khalaf Gillard, PharmD, PhD, Executive Director, Health economics and outcomes research, Karuna Therapeutics	*Dr. Gillard is a full-time employee of Karuna Therapeutics.*
Tony Grillo, PharmD, Vice President, Express Scripts	*Dr. Grillo is a full-time employee of Express Scripts.*
Steven Lamberti, MD, Professor of Psychiatry, University of Rochester Medical Center	*No conflicts to disclose.*
Arundati Nagendra, PhD, Director of Research and Scientific Affairs, Schizophrenia & Psychosis Action Alliance	*S&PAA receives <25% funding from healthcare companies, including from Karuna Therapeutics.*
Marc Pomper, Caregiver	*No conflicts to disclose.*
Marina Sehman, PharmD, CSP, Director, Clinical Pharmacy, IPD Analytics	*Dr. Sehman is a full-time employee of IPD Analytics.*
Vinod Srihari, MD, Professor of Psychiatry; Director, Specialized Treatment Early in Psychosis Program, Yale School of Medicine	*No conflicts to disclose.*

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