KarXT for Schizophrenia: Effectiveness and Value

Public Meeting — February 9th, 2024

Meeting materials available at:

https://icer.org/assessment/schizophrenia-2024/#overview

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

AN ICER PROGRAM
NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

Patient Experts

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.*

Clinical Experts

Steve Lamberti, MD, Professor of Psychiatry; Academic Chief of the Community Division, University of Rochester

- *No conflicts to disclose.*

Vinod Srihari, MD, Professor of Psychiatry; Director, STEP Program, Yale School of Medicine

- *No conflicts to disclose.*

Why are we here today?

The first symptom I really noticed was the paranoia…that led to delusional thinking and I started to hear a voice…thought that newscasters and radio announcers were talking to me personally and sending me messages through the television and through songs being played on the radio. That made it really difficult because I couldn't enjoy the things I wanted to do – I'm an artistic person…so I wasn't able to enjoy my life anymore and over time it progressively got worse.

Person Living with Schizophrenia

Why Are We Here Today?

- What happens the day these treatments receive FDA approval?
- Questions about:
  - What are the risks and benefits?
  - How do new treatments fit into the evolving landscape?
  - What are reasonable prices and costs to patients, the health system, and the government?
  - What lessons are being learned to guide our actions in the future?

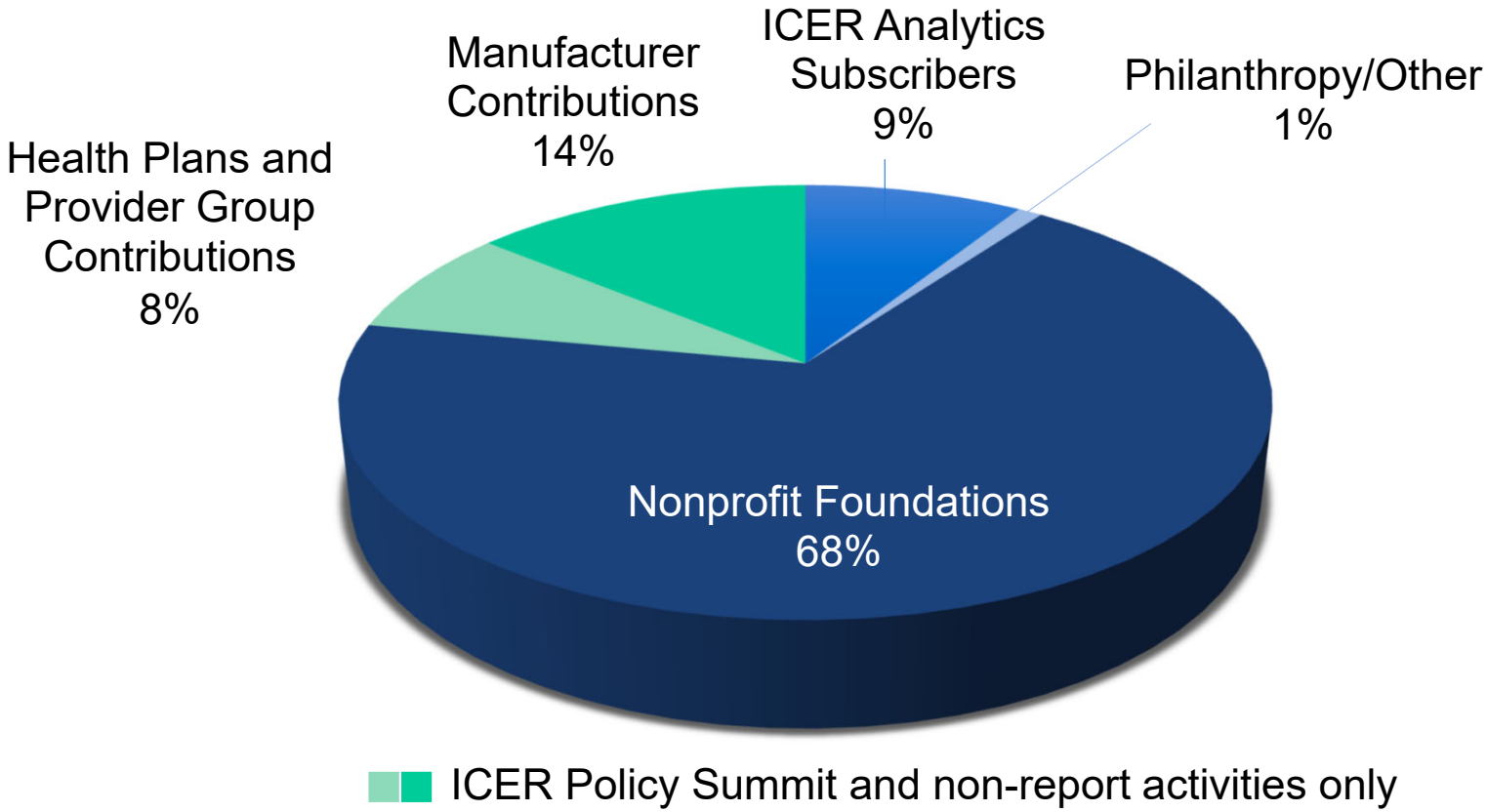
The Impact on Rising Health Care Costs for Everyone

https://khn.org/news/article/diagnosis-debt-investigation-100-million-americans-hidden-medical-debt/

Organizational Overview

- New England Comparative Effectiveness Public Advisory Council (New England CEPAC)
- Institute for Clinical and Economic Review (ICER)

Funding 2024



How Was the ICER Report Developed?

- Scoping with guidance from patients, clinical experts, manufacturers, and other stakeholders
- Internal ICER evidence analysis and cost-effectiveness modeling done by Tufts Medical Center
- Public comment and revision
- Expert reviewers
  - **Anissa Abi-Dargham, MD**, Distinguished Professor and Chair, Stony Brook University
  - **Andrew Davies, MSc**, Director, Stockbridge Economic Appraisal Ltd
  - **Stephen R. Marder, MD**, Professor, Semel Institute at UCLA
  - **Arundati Nagendra, PhD**, Director of Research and Scientific Affairs, Schizophrenia & Psychosis Action Alliance
- How is the evidence report structured to support New England CEPAC voting and policy discussion?

Value Assessment Framework: Long-Term Value for Money

Agenda (ET)

10:00 AM	Meeting Convened and Opening Remarks
10:20 AM	Presentation of the Clinical Evidence
11:00 AM	Presentation of the Economic Model
11:40 AM	Public Comments and Discussion
12:05 PM	Lunch Break
12:50 PM	New England CEPAC Deliberation and Vote
1:50 PM	Break
2:00 PM	Policy Roundtable Discussion
3:30 PM	Reflections from New England CEPAC
4:00 PM	Meeting Adjourned

Presentation of the Clinical Evidence

Jeffrey A. Tice, MD

Professor of Medicine

University of California, San Francisco

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Key Collaborators

- **Avery McKenna, BS,** Associate Research Lead, ICER
- **Abigail Wright, PhD, MSc,** Research Scientist, ICER
- **Finn Raymond, BS,** Research Assistant, ICER

Disclosures:

Financial support was provided by ICER to the University of California, San Francisco.

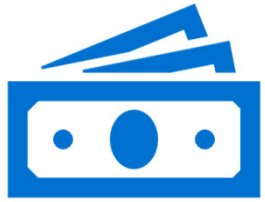
No conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

Background: Schizophrenia

Schizophrenia is a serious mental illness that affects how a person **thinks**, **feels**, and **acts**

Schizophrenia affects **3.9 million** people in the U.S. and **24 million** people worldwide

Black Americans are diagnosed at **twice** the rate of White Americans and have **worse** outcomes



Economic burden is **$343 billion** annually in the US with most being **societal**, not medical

Categories of Symptoms

Positive

- Delusions
- Hallucinations
- Disorganized speech, thought, and behavior

Negative

- Poor motivation
- Lack of pleasure and enjoyment
- Lack of speech
- Lack of social interaction

Cognitive

- Impaired executive function, attention, and memory

Discussions with People Living with Schizophrenia

Impact of Disease on Daily Life

- Day-to-day tasks are challenging
- Difficulty keeping a job or staying in school
- Maintaining personal relationships: isolation and loneliness
- Painful positive symptoms: voices saying bad things about self
- Stigma

Challenges with Current Medications

- Time to find the right one
- Symptoms not all managed
- Burdensome side effects (e.g., sedation, weight gain, lethargy)

Hope for New Therapies

- Fewer complications / less emotional suppression
- All symptom classes improved

Schizophrenia
Treatment Options

Pharmacologic

- First-generation antipsychotics
- Second-generation antipsychotics
- Long-acting injectable antipsychotics

Non-pharmacologic

- Cognitive behavioral therapy
- Cognitive remediation therapy
- Compliance therapy
- Social skills training
- Individual counseling
- Interactive / Social group therapy

KarXT

- New mechanism of action: not through dopamine receptor
- Xanomeline originally developed to improve cognitive function

Scope of Review

- Comparative clinical effectiveness of KarXT
  - Comparators: Aripiprazole, olanzapine, risperidone
  - Acute phase: Systematic review and network meta-analysis (NMA)
  - Maintenance: Previously published NMAs

Clinical Evidence

Key Clinical Trials: The EMERGENT Program

- **Design:** Three 5-week inpatient RCTs
- **Population:** Adults with schizophrenia hospitalized for worsening symptoms

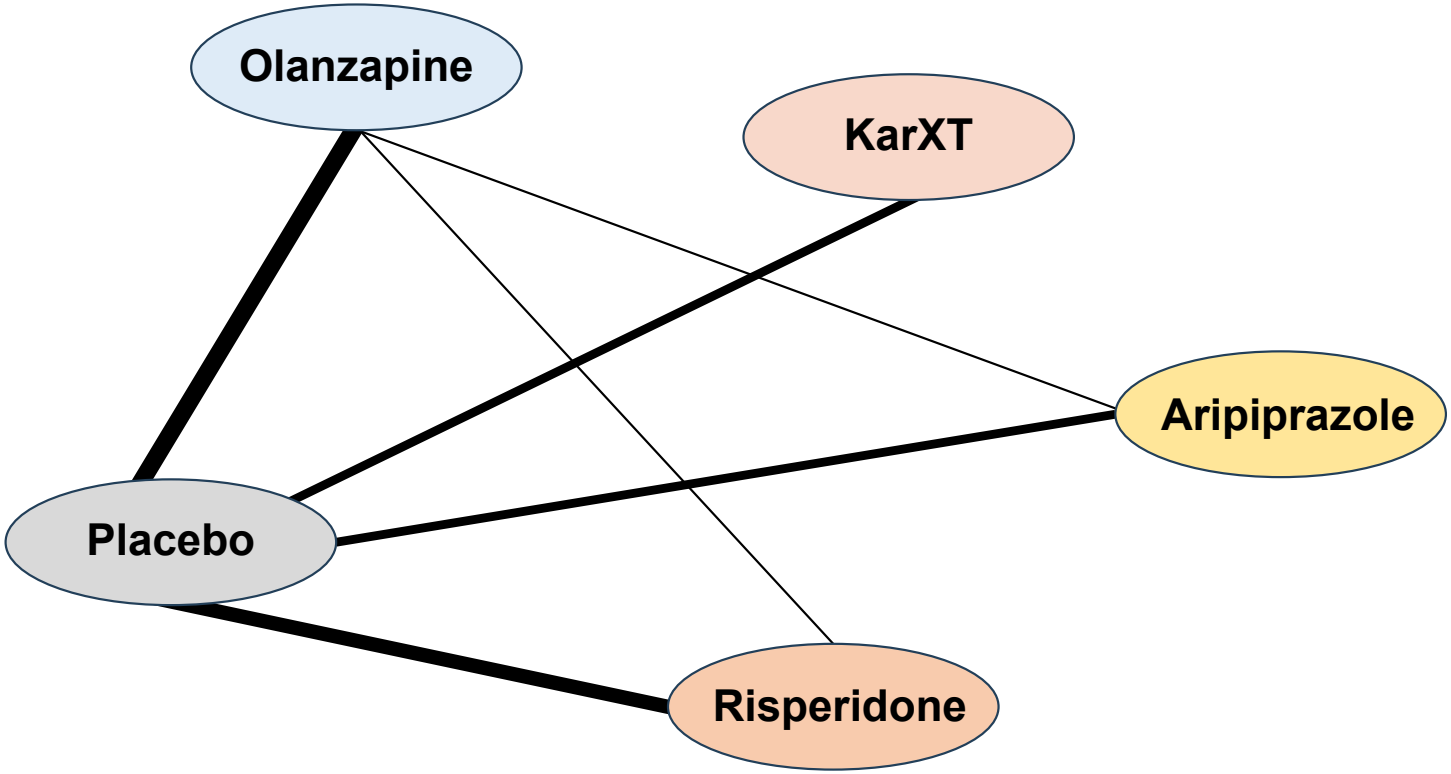
Baseline Characteristic		KarXT (n=340)	Placebo (n=343)
Age (years), mean ± SD		44.3 ± 10.8	43.7 ± 11.3
Male, n (%)		254 (74.7)	262 (76.4)
Race, n (%)	**Asian**	4 (1.2)	3 (0.9)
	Black	225 (71.7)	235 (68.5)
	White	92 (27.1)	99 (28.9)

Pooled baseline characteristics from the safety population of the EMERGENT trials.

NMA Overview

- **Population:** Adults with schizophrenia experiencing an acute exacerbation
- **Key Outcomes**
  - Positive and Negative Syndrome Scale (PANSS) scores
  - PANSS response (≥30% improvement)
  - Weight gain
  - Discontinuation
- **Duration:** 3 – 8 weeks
- **Model:** Bayesian random-effects

NMA Network: 33 trials



PANSS Response (≥30% improvement)

Indirect Evidence: NMA

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.

Short-Term Weight Change, kg

Indirect Evidence: NMA

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 that the 95% credible interval does not contain 0.

All-Cause Discontinuation

Indirect Evidence: NMA

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.

Patient-Important Harms

	KarXT (n=340)	**Placebo** (n=343)
Extrapyramidal Symptoms,* %	3.2	0.9
Prolactin Change from Baseline, mean ± SD	0.75 ± 16.45 ng/L	-1.38 ± 16.49 ng/L
Commonly Reported Adverse Events, n (%)		
Nausea	63 (18.5)	13 (3.8)
Constipation	58 (17.1)	21 (6.1)
Dyspepsia	52 (15.3)	16 (4.7)
Vomiting	46 (13.5)	6 (1.7)

n: number, ng/L: nanograms per liter, SD: standard deviation

*Akathisia, dyskinesia, dystonia, and extrapyramidal disorder

Controversies and Uncertainties

Long-term Data

- Lack of long-term data: uncertainties, particularly given novel mechanism

Symptom Improvement

- Uncertainty of impact on cognitive and negative symptoms

Generalizability

- Trials of hospitalized individuals experiencing acute worsening of symptoms
- Trials with high percentage of Black Americans (~75% at US sites)

Potential Other Benefits and Contextual Considerations

- New mechanism of action: Muscarinic receptor agonist
- 10-fold higher risk of suicide and markedly shorter life expectancy that the general population (15 years)
- Schizophrenia disproportionately affects the Black population

Public Comments Received

NMA network includes outdated trials

Caution about cognitive data given short-term data

Report is premature given no data on maintenance

Summary

- PANSS score and PANSS response
  - KarXT significantly better than placebo
  - No significant differences between KarXT and the three comparators
- Weight gain over 5 weeks
  - KarXT significantly less than olanzapine and risperidone
  - No significant differences between KarXT and aripiprazole or placebo
- Discontinuation rates
  - KarXT significantly higher discontinuation rates than olanzapine and risperidone
  - Numerically, but not statistically higher than aripiprazole and placebo

ICER Evidence Ratings for Maintenance Phase

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

Questions?

Presentation of the Economic Evidence

Melanie D. Whittington, PhD, MS

Center for the Evaluation of Value and Risk in Health

Tufts Medical Center

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Key Review Team Members

- **Marina Richardson, PhD,** Associate Director, HTA Methods and Health Economics, ICER

Disclosures:

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

Objective

Estimate the lifetime cost-effectiveness of KarXT compared to current standard of care that includes second-generation antipsychotics for the treatment of schizophrenia.

Treatments Modeled

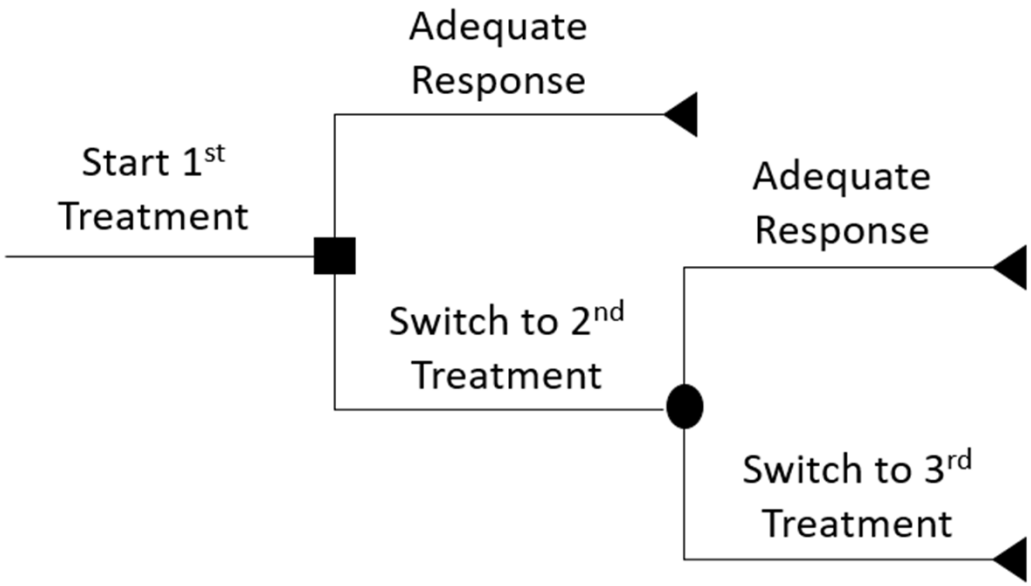
- **Intervention**: xanomeline / trospium (KarXT)
- **Comparator**: aripiprazole

- The model allowed for treatment switching
  - Second treatment: basket of risperidone and olanzapine
  - Third treatment: basket of risperidone and olanzapine and clozapine

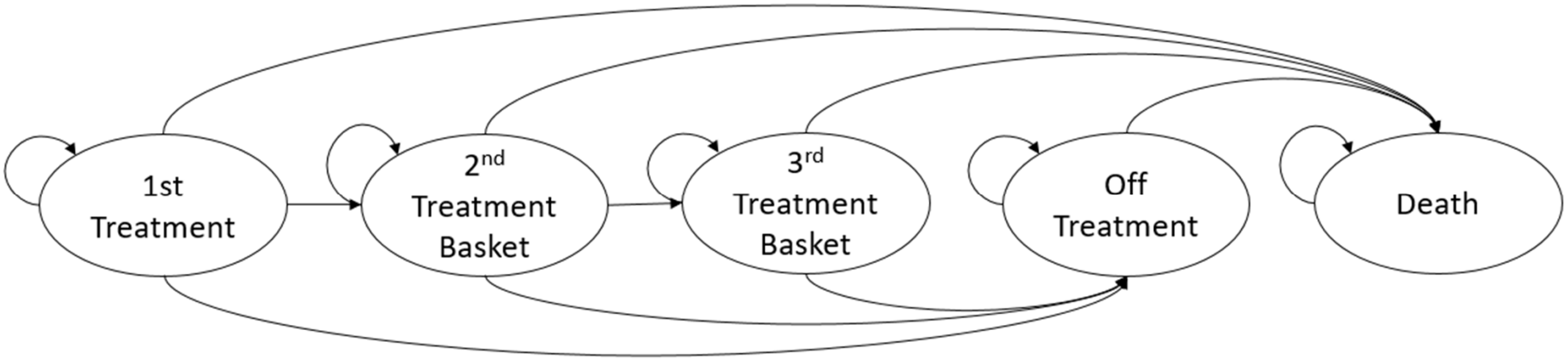
Methods Overview

- **Model:** Upfront decision tree followed by a Markov model
- **Setting:** United States
- **Perspective:** Health Care Sector and Modified Societal
- **Time Horizon:** Lifetime
- **Discount Rate:** 3% per year (costs and outcomes)
- **Cycle Length:** 3 months
- **Outcomes:** Costs, life years, quality-adjusted life years, equal-value life years, years with diabetes

Model Schematic – Acute Phase



Model Schematic – Maintenance Phase



Key Model Assumptions

- KarXT was not associated with a risk of developing metabolic syndrome beyond that of the general population
- No metabolic syndrome, diabetes, or cardiovascular disease at baseline
- On treatment over the lifetime time horizon, except for small proportion that stops treatment at 20 years

Acute Phase – Adequate Clinical Response

Treatment	Adequate Clinical Response*
KarXT	53%
Aripiprazole	36%
Olanzapine	43%
Risperidone	51%

*Defined as a 30% improvement in the Positive and Negative Syndrome Scale

Maintenance Phase – Relapse

Treatment	Three-Month Probability of Relapse
KarXT	10.5%
Aripiprazole	12.7%
Olanzapine	8.2%
Risperidone	12.7%
Clozapine	8.9%
No Antipsychotic	41.0%

Metabolic Syndrome

Treatment	Three-Month Probability of Developing Metabolic Syndrome
KarXT	0.7%
Aripiprazole	3.8%
Olanzapine	9.1%
Risperidone	5.5%
Clozapine	11.2%
No Antipsychotic	0.7%

Maintenance Phase - Treatment Discontinuation

Treatment	Three-Month Probability of Discontinuing
KarXT	5.9%
Aripiprazole	5.4%
Olanzapine (second basket)	4.0%
Risperidone (second basket)	4.0%

Drug Costs

- KarXT, placeholder price of $20,000 per year

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

mg: milligram

Societal Considerations

Societal Factor	Value
Productivity	65 days of missed work per relapse $3,323 per year with diabetes $7,516 per year with cardiovascular disease
Criminal Justice	$8,590 per relapse
Caregiver	39.7 hours per week

Results

Base-Case Results

Drug	Total Cost	Years With Diabetes	QALYs	Life Years	evLYs
KarXT*	$350,000	4.00	10.39	16.25	10.41
Aripiprazole	$327,000	4.40	10.25	16.18	10.25

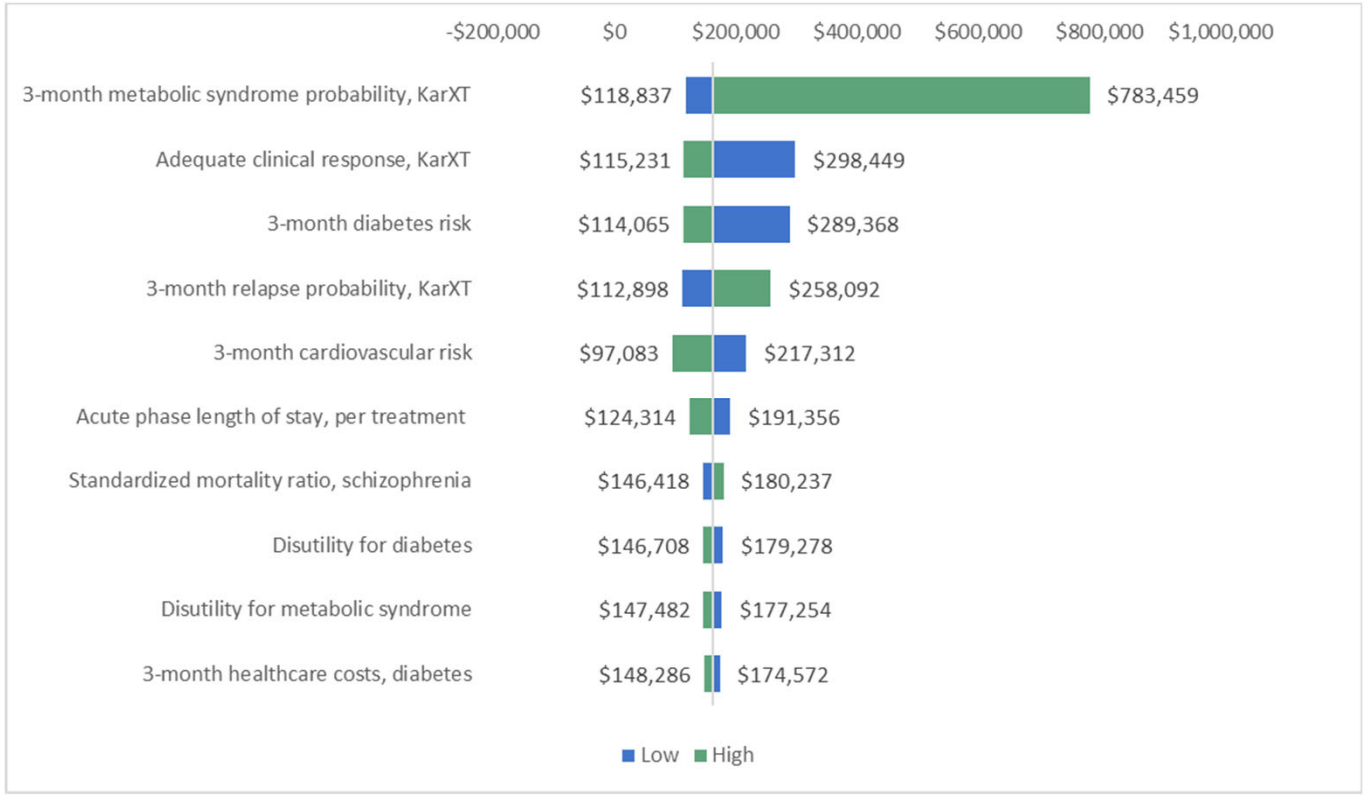
evLYs: equal value life years, QALYs: quality-adjusted life years
*Assuming a KarXT placeholder price of $20,000 per year

Base-Case Incremental Results

Drug	Cost per QALY	Cost per evLY	Cost per Year Without Diabetes
KarXT*	$163,000	$146,000	$60,000

evLYs: equal value of life years, QALYs: quality-adjusted life years
*Assuming a KarXT placeholder price of $20,000 per year

One-Way Sensitivity Analyses



Probabilistic Sensitivity Analysis

Health Outcome	Cost-Effective at $50,000	Cost-Effective at $100,000	Cost-Effective at $150,000
Per QALY Gained	5%	18%	34%
Per evLY Gained	6%	23%	40%

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

Scenario Analyses

Scenario	Cost per evLYG
Base-Case	$146,000
Modified Societal Perspective	$142,000
No Risk of Tardive Dyskinesia when on KarXT	$67,000
Small Risk of Metabolic Syndrome When on KarXT	$253,000

evLYG: equal value life year gained

Health Benefit Price Benchmarks

Intervention	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
KarXT	$16,000	$20,000

Limitations

- Not an estimate of the overall societal burden of schizophrenia
- No direct evidence for KarXT in the maintenance phase

Public Comments Received

Include tardive dyskinesia in the base-case

Make third treatment basket clozapine only

Societal perspective lacks breadth and depth

Conclusions

- Assuming KarXT is not associated with metabolic syndrome, KarXT produces less time with diabetes and more QALYs, life years, and evLYs
- At a placeholder price of $20,000 per year, the cost-effectiveness is near the upper bounds of common thresholds
  - Would be less favorable if associated with a risk of metabolic syndrome
  - Would be more favorable if not associated with tardive dyskinesia

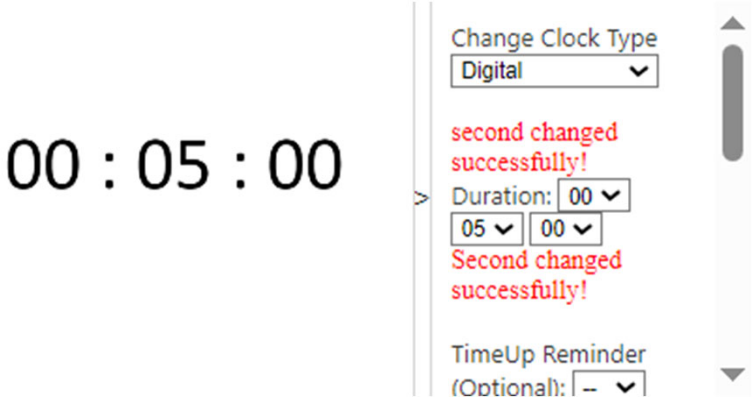
Questions?

Manufacturer Public Comment and Discussion

Ken Kramer, VP, Medical Affairs Karuna

Conflicts of Interest:

- *Ken Kramer collaborated with Lumanity to directly compose public comments.*



Public Comment and Discussion

Arundati Nagendra, Ph.D., Director of Research & Scientific Affairs, Schizophrenia & Psychosis Action Alliance

Conflicts of Interest:

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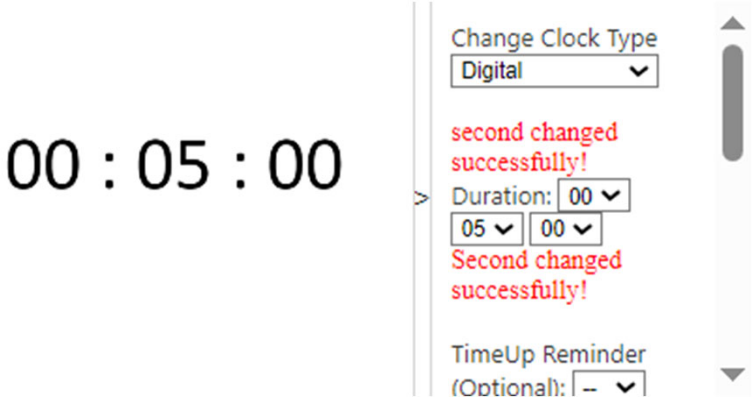
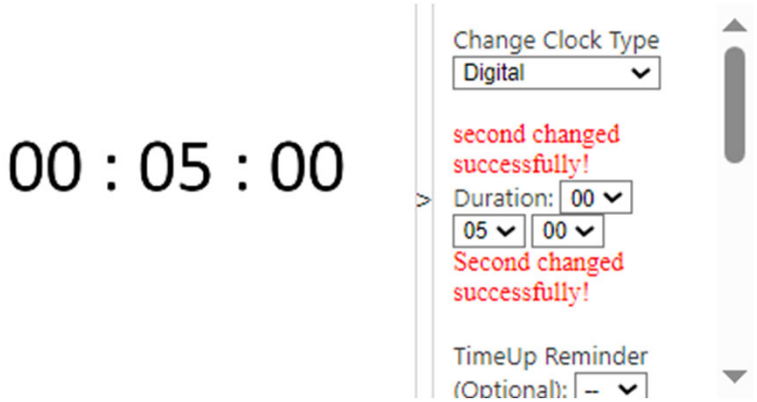


Lisa Guardiola, Individual Living With Schizophrenia
Vice President, NAMI South Suburbs of Chicago

Conflicts of Interest:

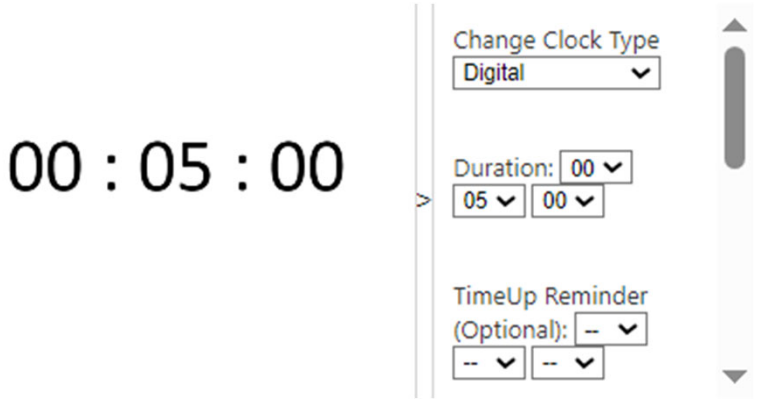
- *No conflicts to disclose.*



Paulie VonEdwaerd-Benjamin, Individual Living with Schizophrenia
Tarot Reader, Earth Star, Heart Root

Conflicts of Interest:

- *No conflicts to disclose.*



Lunch

Meeting will resume at 12:50pm EST

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Voting Questions

Clinical Evidence Questions

Patient Population for All Questions: Adults with an established diagnosis of schizophrenia who are not considered to have treatment-resistant schizophrenia.

Antipsychotic Therapy for All Questions: Therapy is being used for maintenance treatment and the comparator therapy and other second-generation antipsychotic treatments are available as next-line treatments if the chosen therapy is ineffective or is discontinued for adverse effects.

slido

1. Is the currently available evidence adequate to demonstrate that the net health benefit of KarXT is superior to that of aripiprazole?

ⓘ Start presenting to display the poll results on this slide.

slido

2. Is the currently available evidence adequate to demonstrate that the net health benefit of KarXT is superior to that of olanzapine and/or risperidone?

ⓘ Start presenting to display the poll results on this slide.

Contextual Considerations and Potential Other Benefits or Disadvantages

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:

slido

3. Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability

ⓘ Start presenting to display the poll results on this slide.

slido

4. Magnitude of the lifetime impact on individual patients of the condition being treated

ⓘ Start presenting to display the poll results on this slide.

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?

slido

5. Patients’ ability to achieve major life goals related to education, work, or family life

ⓘ Start presenting to display the poll results on this slide.

slido

6. Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life

ⓘ Start presenting to display the poll results on this slide.

slido

7. Patients’ ability to manage and sustain treatment given the complexity of regimen

ⓘ Start presenting to display the poll results on this slide.

slido

8. Society’s goal of reducing health inequities

ⓘ Start presenting to display the poll results on this slide.

9. Other - Drug with new mechanism of action that may allow treatment of people who did not benefit from and/or tolerate existing treatments.*

*Evidence report stipulated this as a Contextual Consideration and Potential Other Benefit, but we will not be voting on this question since it's self-evident if KarXT is approved.

Long-Term Value for Money Question

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?

slido

9. What is the long-term value for money of treatment at current pricing with KarXT versus aripiprazole?

ⓘ Start presenting to display the poll results on this slide.

Break

Meeting will resume at 2:00pm EST

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Policy Roundtable

Policy Roundtable

Participant	Conflict of Interest
Kristin Khalaf Gillard, PharmD, PhD, Executive Director, HEOR, 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, URMC	*No conflicts to disclose.*
Arundati Nagendra, PhD, Director of Research & 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, STEP Program, Yale University	*No conflicts to disclose.*

New England CEPAC Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around March 11, 2024
  - Includes description of NE CEPAC votes, deliberation, policy roundtable discussion
    - Materials available at: https://icer.org/assessment/schizophrenia-2024/#overview

Adjourn

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