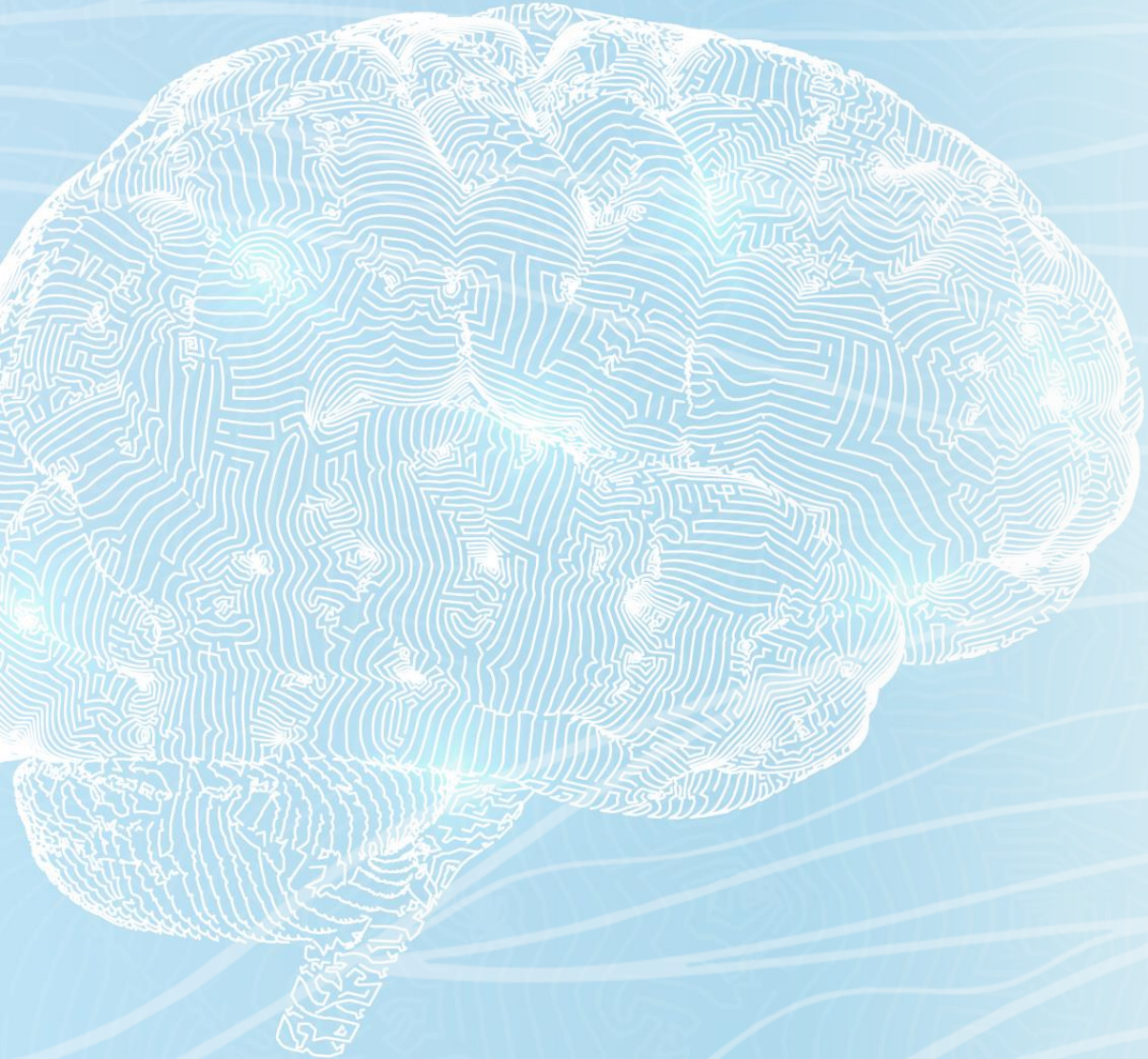


KARUNA THERAPEUTICS

KarXT (a new mechanism antipsychotic based on xanomeline), is superior to placebo in patients with schizophrenia: Phase 2 clinical trial results

STEPHEN BRANNAN, M.D.

ORAL PIPELINE SESSION

ASCP 2020 ANNUAL MEETING

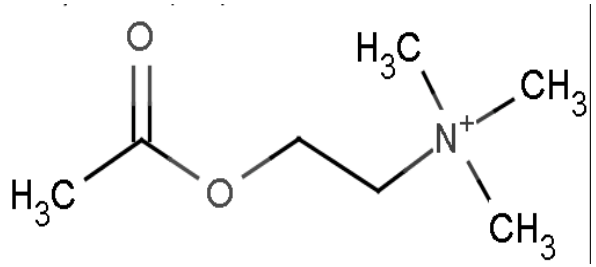
Disclosures/COI

The presenter, Stephen Brannan, M.D.,
is a full-time employee of Karuna Therapeutics

Xanomeline is a selective M1/M4 muscarinic receptor agonist

ACETYLCHOLINE

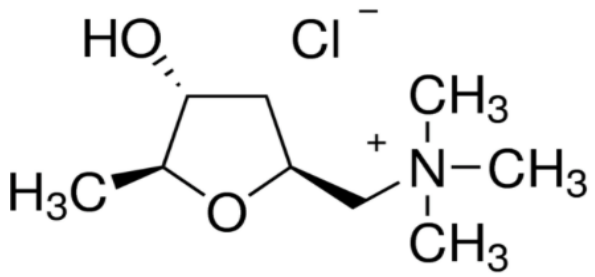
First identified neurotransmitter (Loewi,1921)



Ubiquitous to both central (CNS) and peripheral sympathetic & parasympathetic systems.

MUSCARINE

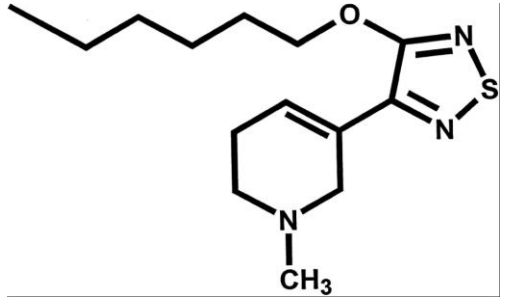
First isolated from the mushroom *Amanita muscaria*



Five muscarinic receptor subtypes: M1-M5, found both in central (CNS) and peripheral (PNS) synapses

XANOMELINE

Selective M1/M4 muscarinic receptor agonist synthesized in the 1990s



Signal of antipsychotic efficacy in Alzheimer's disease and schizophrenia shown in the 1990s

What is KarXT?

Rationale for Combining Xanomeline with the Peripheral Anticholinergic Trospium

xanomeline tartrate

(M1/M4 muscarinic *agonist*)

- Human antipsychotic proof-of-concept in double-blind, placebo-controlled trials in schizophrenia and Alzheimer's disease
- Eli Lilly discontinued Alzheimer's disease program due to muscarinic AEs
- Licensed to Karuna Therapeutics
- Karuna Therapeutics approach: mitigate muscarinic AEs

KarXT

Combination of
xanomeline + trospium

KarXT designed to provide xanomeline antipsychotic efficacy while mitigating peripheral cholinergic Adverse events (AEs)

KarXT

Phase 1 trials established
PK and safety/tolerability

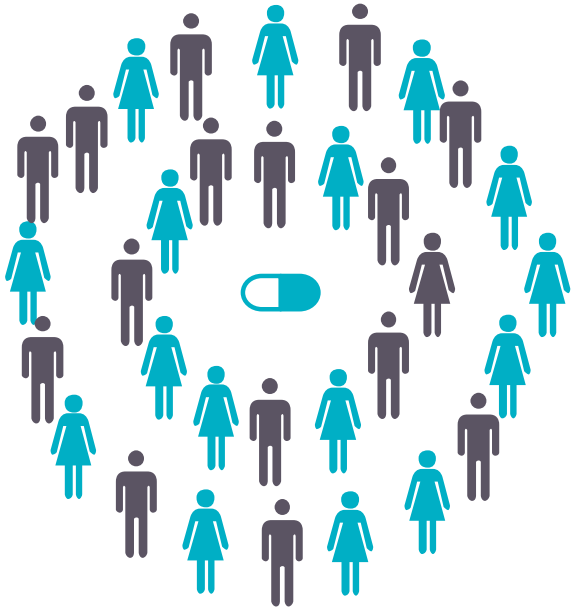
trospium chloride

(peripheral anticholinergic approved for overactive bladder)

- Peripheral anticholinergic properties offset muscarinic AEs
- Does not cross the blood- brain-barrier, so no central anticholinergic effects
- No known metabolic overlap with xanomeline

Phase 2 RCT in Schizophrenia Design Overview

- Randomized, double-blind, placebo-controlled, five week, inpatient trial
- Enrolled 182 patients with schizophrenia in acute psychotic exacerbation (N=90 on KarXT, N=92 on Placebo)
- Patients were washed out of any antipsychotic drugs prior to randomization
- Flexible dose, two-arm trial with 1:1 randomization to KarXT or placebo, with a five-week treatment period
- Ascending up-titration schedule with final dose determined by tolerability
  - Days 1-2: 50/20 KarXT BID (50 mg xanomeline/20 mg trospium)
  - Days 3-7: 100/20 KarXT BID
  - Days 8-35: 100/20 KarXT BID with optional increase to 125/30 KarXT BID



Prespecified Efficacy Outcomes

Overview of PANSS & CGI-Severity Results

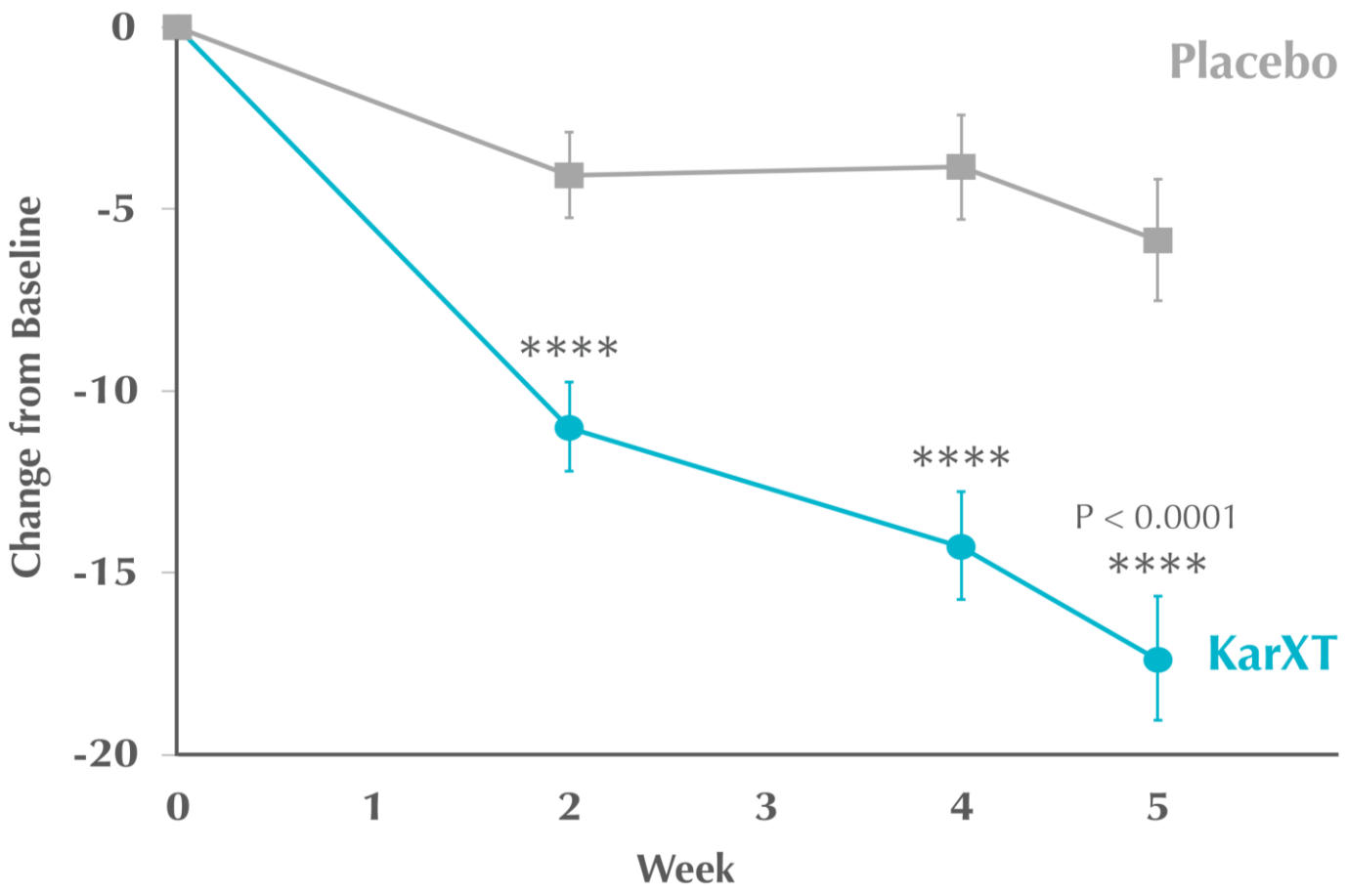
Primary Outcome	**Change from baseline in PANSS total score for KarXT vs placebo treated patients (MMRM for mITT)**	p< 0.0001 KarXT vs placebo
Key Secondary #1	Change from baseline in PANSS-positive	p< 0.0001 KarXT vs placebo
Key Secondary #2	Change from baseline in CGI-Severity	p< 0.001 KarXT vs placebo
Key Secondary #3	Change from baseline in PANSS-negative	p< 0.001 KarXT vs placebo
Key Secondary #4	Change from baseline in PANSS Marder negative	p< 0.001 KarXT vs placebo
Key Secondary #5	Proportion responders defined as CGI-S of ≤ 2	p=0.15 KarXT vs placebo

Patient Disposition: ITT Population

	Placebo	KarXT
Randomized	92	90
Completed	73 (79.3%)	72 (80.0%)
Discontinued	19 (20.7%)	18 (20%)
Reason for discontinuation…		
Consent withdrawn	14	14
Adverse Event	2	3*
Investigator decision	1	1
Lost to follow-up	1	0
Other	1	0

- Overall 80% completion for both KarXT and placebo patients
- Three AE discontinuations (3.3%) in KarXT group
  - 2 worsening of psychosis*
  - Elevated GGT
  - *One of these discontinuations occurred in a subject who left prior to taking study drug

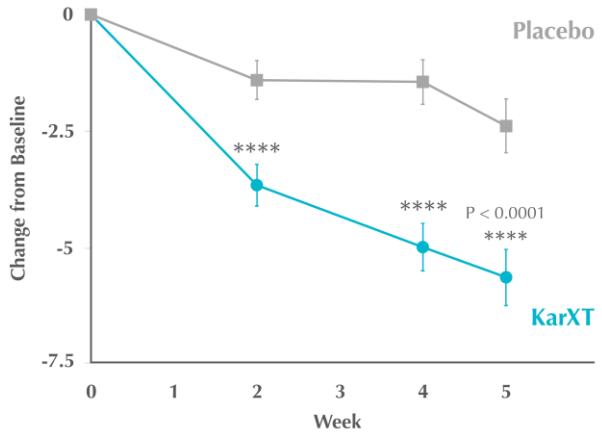
Statistically Significant and Clinically Meaningful Improvement on Primary Endpoint: Change in PANSS Total Score over 5 Weeks



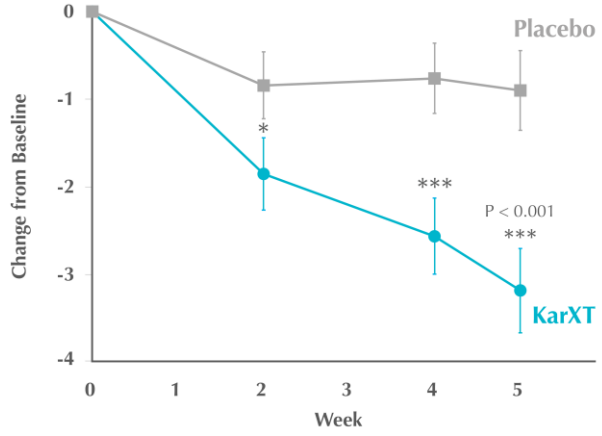
- 11.6-point improvement at week 5 for KarXT compared with placebo (-17.4 vs. -5.9 points, p<0.0001)
- Statistical separation at every assessed time point
- Cohen's d effect size of 0.75

Statistically Significant and Clinically Meaningful Improvement on Secondary Endpoints: PANSS Positive, Negative, Marder, and CGI-S

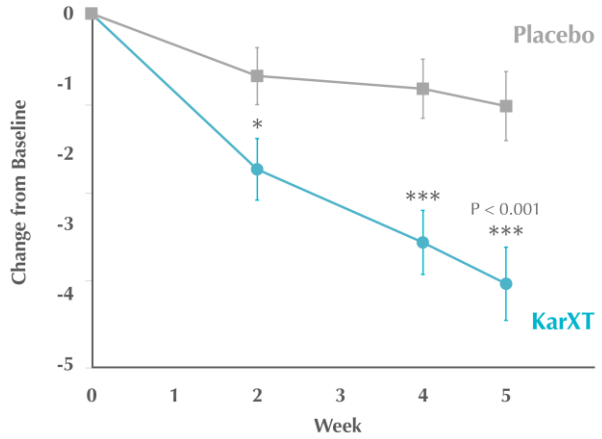
A. $PANSS_P$



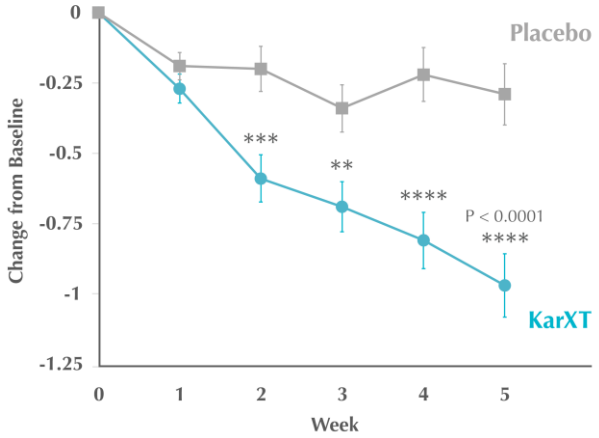
B. $PANSS_N$



C. PANSS Marder Negative

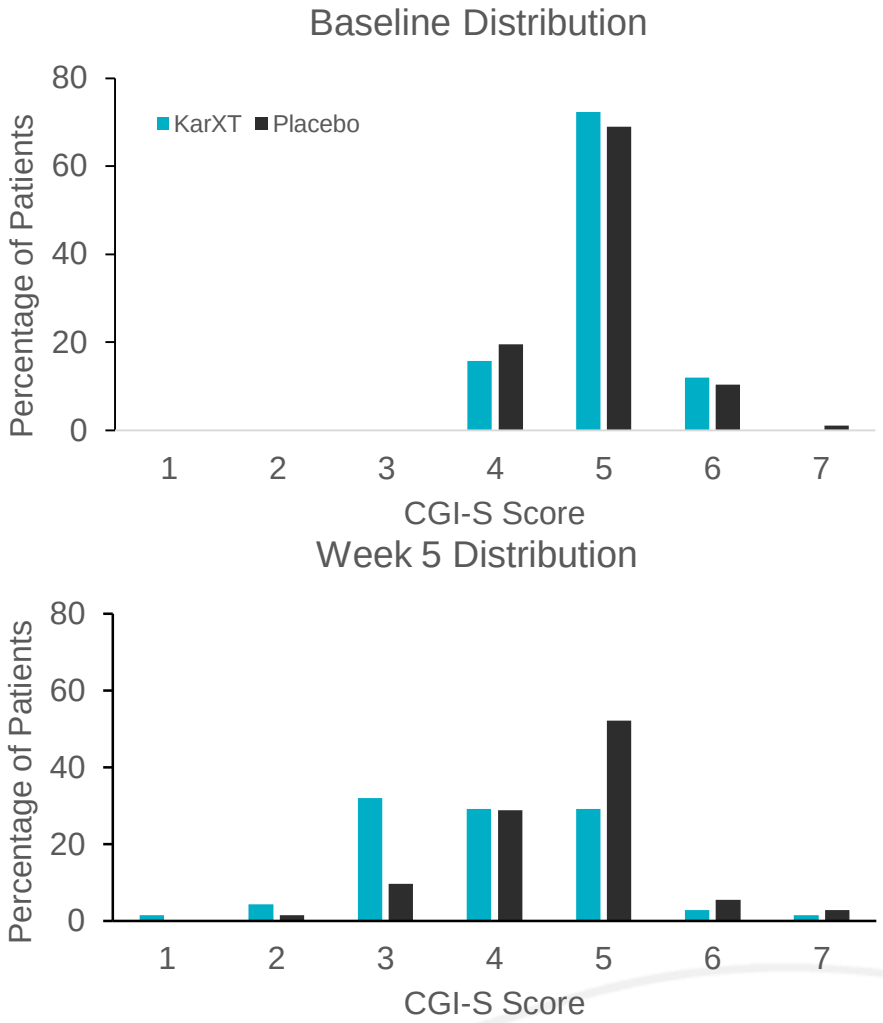


D. CGI-S



- Statistical separation at every assessed time point for secondary endpoints 1-4:
  - PANSS positive subscore
  - CGI-S score
    - Note that Panel D is not the prespecified analysis
  - PANSS negative subscore
  - PANSS Marder negative factor score
- Prespecified secondary endpoint 5 was responder analysis, defined as % of CGI-S responders (endpoint CGI-S score of 1 or 2)
  - Percentage of responders for KarXT compared with placebo: 5.6% vs.1.4%, p=0.151

Statistically Significant and Clinically Meaningful Improvement on Clinical Global Impression-Severity (CGI-S): Categorical Analyses



- *Shifts in CGI-S scores from baseline :*
  P<0.001 at endpoint using non-parametric comparison of KarXT vs. placebo (Mann-Whitney Wilcoxon test)
  - This was the prespecified endpoint analysis
  - Statistical separation at every assessed time point (week 2, 4 and 5)
- At baseline:
  - Percentage of patients with scores 5 or 6 for KarXT compared to placebo: 84% vs 80%
- At endpoint:
  - Percentage of patients with scores rated 5-7 for KarXT compared to placebo: 33% vs. 60%
  - Percentage of patients rated mildly ill or better (scores rated 1, 2, or 3) for KarXT compared to placebo: 38% vs. 11%

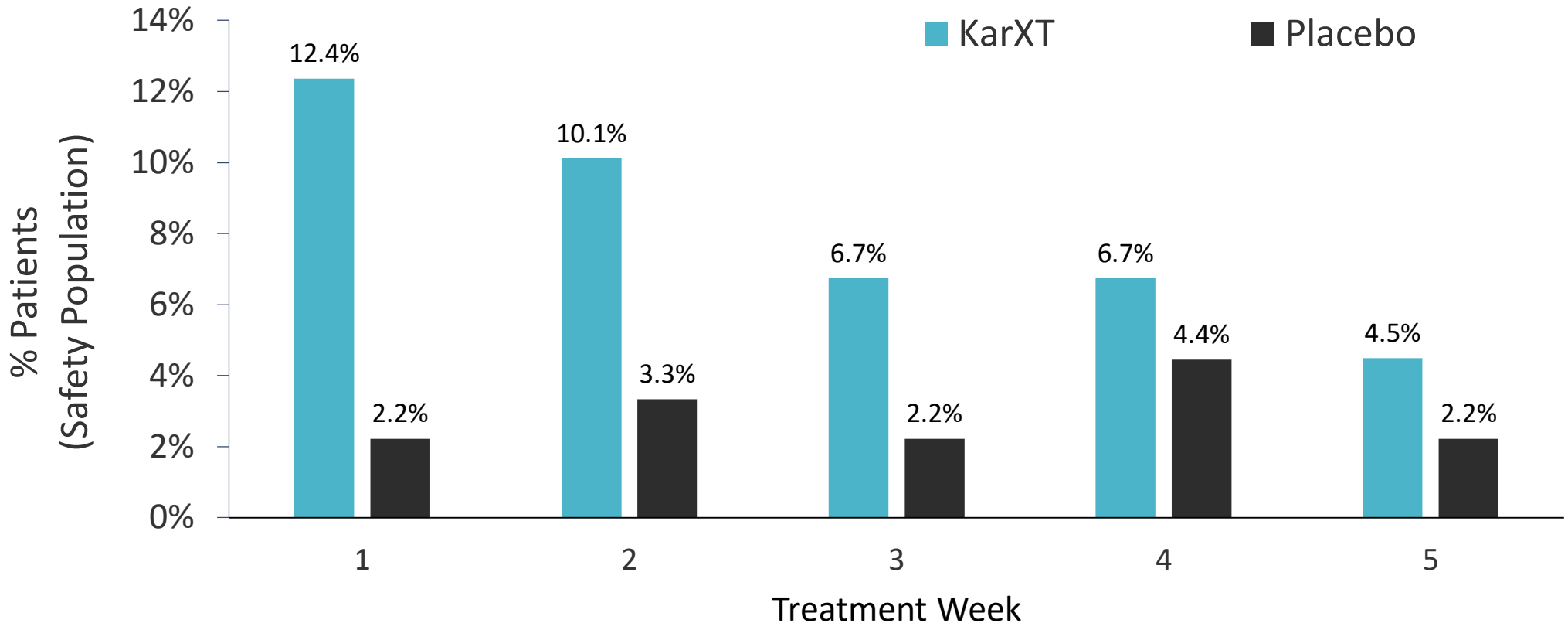
CGI-S score legend: 1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = extremely ill

Adverse Events (≥5%) over Course of Study

Safety population	Placebo (N=90)	KarXT (N=89)
Any AE (N,%)	39 (43.3%)	48 (53.9%)
AEs ≥ 5%		
Constipation	3 (3.3%)	15 (16.9%)
Nausea	4 (4.4%)	15 (16.9%)
Dry mouth	1 (1.1%)	8 (9.0%)
Dyspepsia	4 (4.4%)	8 (9.0%)
Vomiting	4 (4.4%)	8 (9.0%)
Headache	5 (5.6%)	6 (6.7%)
Somnolence	4 (4.4%)	5 (5.6%)

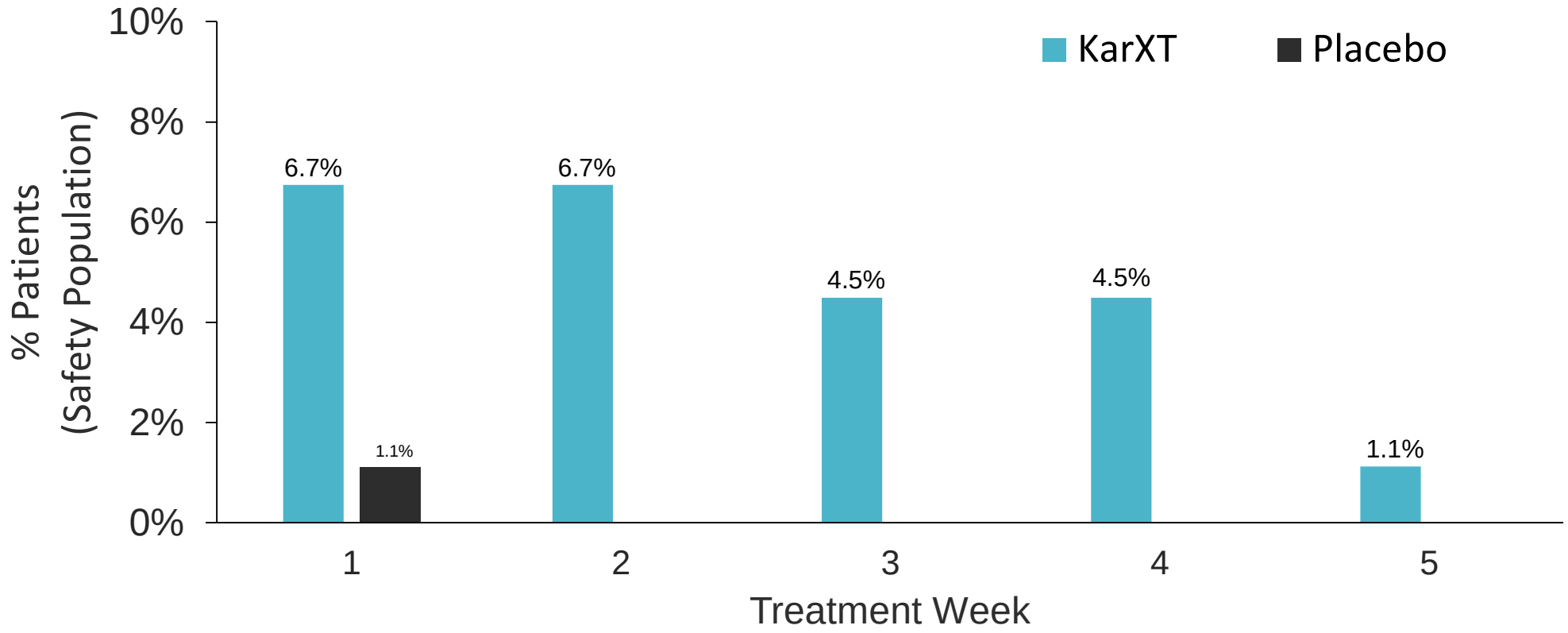
- Safety population received ≥1 dose study medication
- One serious adverse event on KarXT for worsening of psychosis
- Please see accompanying poster for listing AEs ≥ 2% cutoff criteria

Rates of AEs Related to Muscarinic Receptor Agonism (Nausea and Vomiting) Decreased over Time in KarXT-Treated Patients



- Bars represent % of subjects with muscarinic AE ≥ 5% (nausea or vomiting) as an AE at any point in that study week interval (safety population N=89 KarXT and N=90 placebo)
- All were mild or moderate and none caused withdrawal from study

Rates of A *Peripheral* Anticholinergic AE (Dry Mouth) Decreased over Time in KarXT-Treated Patients



- Bars represent % of subjects with dry mouth as an AE at any point in that study week interval (safety population: N=89 for KarXT and N=90 placebo group).
- All were rated mild or moderate and none caused withdrawal from study
- Constipation showed less of a downward trend

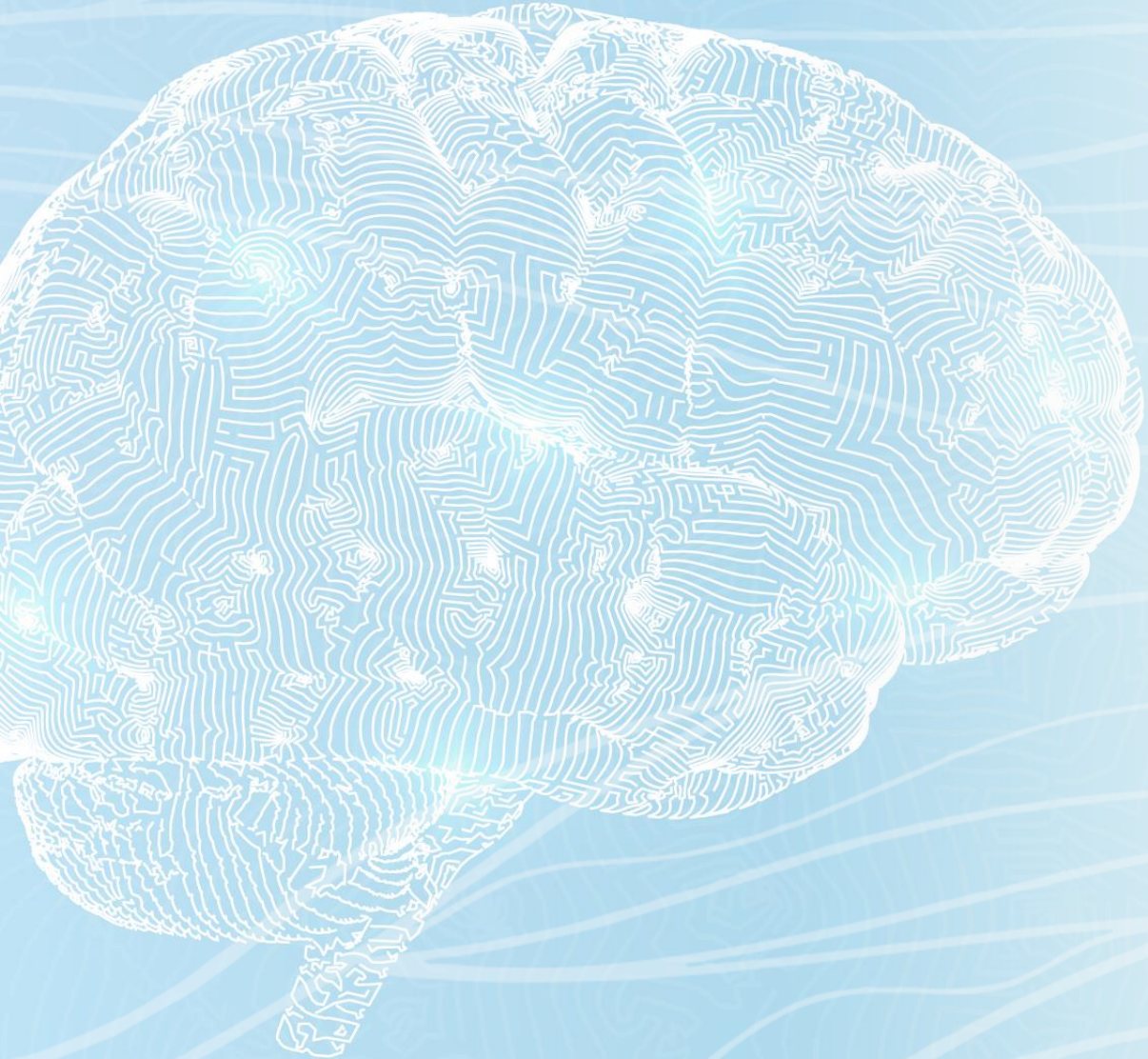
Summary of Safety and Tolerability

- **Overall adverse event rate for KarXT compared with placebo (54% vs.43%)**
  - Overall discontinuation rate similar for KarXT and placebo (20% vs. 21%)
    - TEAE discontinuation rate the same for KarXT vs placebo (2.2% vs. 2.2%)
    - One SAE in KarXT group for worsening psychosis
  - 91% of patients escalated to 125/30 dose of KarXT (vs. 97% who escalated on placebo)
- **AE profile differed from available antipsychotics**
  - Most common adverse events: constipation, nausea, dry mouth, dyspepsia, and vomiting
    - All of these mild or moderate in severity
    - No discontinuations associated with any of the above AEs
  - AEs associated with currently available antipsychotics:
    - Weight gain and metabolic changes similar to placebo
    - EPS similar to placebo

data from safety population

Phase 2 study showed robust antipsychotic efficacy and favorable safety/tolerability of KarXT in hospitalized patients with schizophrenia

- **KarXT showed early (2 weeks) & sustained (entire 5 weeks) separation from placebo arm**
  - On the primary efficacy measure (PANSS total)
  - On four of five secondary outcome measures
- **Safety profile consistent with prior work with KarXT combination**
  - All but one Treatment-Emergent AE rated mild or moderate
  - Most cholinergic and anticholinergic AEs decreased over the course of the study
- **Potential to offers patients a novel MOA antipsychotic that may have different efficacy or tolerability profile than currently available antipsychotic options**
- **These results support Phase 3 development of KarXT for treatment of schizophrenia**



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