The M1/M4 agonist xanomeline, in combination with the peripheral anticholinergic trospium, is effective for acute treatment of schizophrenia: results of a Phase 2 RCT comparing KarXT vs placebo

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BACKGROUND

KarXT (xanomeline-trospium) is a non-dopaminergic investigational antipsychotic that preferentially activates muscarinic receptors in the CNS

- KarXT is a combination of xanomeline and trospium, an FDA-approved peripheral anticholinergic drug that does not cross the blood-brain barrier

xanomeline
(muscarinic receptor agonist)

Antipsychotic efficacy in double-blind, placebo-controlled trials in schizophrenia and Alzheimer's disease (Eli Lilly)[1, 2]

Eli Lilly discontinued development due to pro-cholinergic adverse events (e.g., nausea, vomiting)

Exclusively licensed to Karuna

KarXT
xanomeline + trospium

Maintains efficacy of xanomeline while mitigating its associated pro-cholinergic AEs[1]

trospium
(muscarinic receptor antagonist)

Generic drug approved for overactive bladder

Does not meaningfully cross the blood brain barrier, limiting effects to peripheral tissues

No known metabolic overlap with xanomeline

- KarXT efficacy, safety, and tolerability was tested in a Phase 2 trial in acutely psychotic patients with schizophrenia **(EMERGENT-1/KAR-004; clinicaltrials.gov ID: NCT03697252)**
  - KarXT showed robust efficacy across the primary endpoint and key secondary endpoints (e.g., Fig. 1, additional details in Ref. 2)
  - Favorable safety and tolerability profile (e.g., Table 2), including no clinically meaningful weight gain or EPS (additional details in Ref. 2)
- Additional EMERGENT-1 analysis provided here provide further insight into the clinical meaningfulness of KarXT efficacy and that underscore the transient nature of KarXT-associated pro-cholinergic and anti-cholinergic AEs

METHODS

Trial Overview:

- Randomized, double-blind, placebo-controlled, 5-week, multi-site, in-patient trial
- 182 participants; any previous antipsychotics washed out prior to 1:1 randomization to KarXT or placebo
- KarXT flexibly dosed to a maximum of 125 mg xanomeline/30 mg trospium BID based on tolerability

Outcome Measures:

- Pre-specified efficacy analyses (week 5, KarXT vs. placebo):
  - Least-squares mean (LSM) change from baseline in PANSS-total, PANSS-positive, PANSS-negative, PANSS Marder negative
  - CGI-S score frequency counts, percentage of patients with CGI-S score 1 or 2
- *Post hoc* efficacy analyses (responders per study week, KarXT vs. placebo):
  - ≥ 30% reduction from baseline in PANSS total score, scale: 0-6 (0-180 range)
  - ≥ 2 point reduction from baseline in CGI-S
- Safety and tolerability:
  - Adverse events rates, laboratory findings, EPS rating scales

Analyses:

- All efficacy analyses employed the modified intent-to-treat (mITT) population, defined as all randomized participants who received at least one dose of study medication and had a baseline and at least one post-baseline PANSS-Total assessment (KarXT: n = 83; pbo: n = 87)
- Treatment effects for pre-specified analyses presented here were calculated using a mixed-effects model for repeated measures (MMRM) with no imputation for missing data
- Treatment effects for *post hoc* analyses presented here were calculated using a logistic regression model with missing data imputed using last observation carried forward (LOCF) methodology
- All safety and tolerability analyses employed descriptive statistics in the safety population, defined as all participants who received at least one dose of study medication (KarXT: n = 89; pbo: n = 90)

RESULTS

Key baseline demographics and symptom scores

Table 1 – Key Demographics and Baseline Characteristics (mITT population)[1]

	KarXT (n = 83)	Placebo (n = 87)
Mean age (years) ± SD	43.7 ± 10.0	41.8 ± 10.0
Gender, male (%)	80.7	73.6
Race (% non-white)	77.1	80.4
Mean Baseline PANSS Total Score ± SD	97.3 ± 9.3	96.6 ± 8.4
Mean Baseline CGI-S Score	5.0 ± 0.5	4.9 ± 0.6

[1]Plus-minus values are mean ± SD

Pre-specified primary endpoints and key secondary efficacy endpoints

- KarXT treatment was associated with statistically significant superior efficacy compared with placebo at week 5 on the following:
  - PANSS-Total primary endpoint (11.6-point treatment difference in least-squares mean change from baseline, p < 0.001; Cohen's d = 0.75)

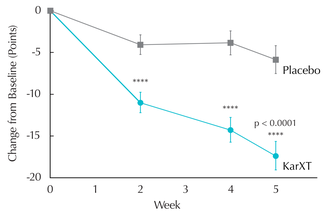


Fig. 1 – At week 5, the LSM change from baseline on PANSS-Total score in the KarXT arm compared to the placebo arm was -17.4 vs. -5.9 points; ****p < 0.001.

  - Four out five pre-specified secondary outcome measures: PANSS-positive subscore, PANSS-negative subscore, and PANSS Marder negative factor (Ref. 1) and CGI-S frequency counts (all p < 0.001). The percentage of participants who achieved a CGI-S score of 1 or 2 was not statistically different between treatment arms (p = 0.151)

Post hoc efficacy analyses: PANSS–Total and CGI–S responses as a function of trial week

PANSS-Total response: ≥ 30% improvement

- Significant treatment effect for KarXT vs. placebo at every assessed time point; response was measured as percentage of participants who achieved a ≥ 30% improvement from baseline in PANSS-Total score
- At endpoint (week 5), 38.6% of participants in the KarXT arm were responders, compared to 11.5% of participants in the placebo arm (OR = 4.83, 95% CI = 2.2-10.7, p = 0.0001)

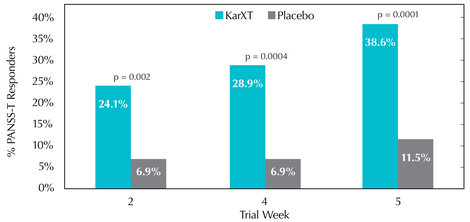


Fig. 2 – Percentage of participants who achieved ≥ 30% improvement from baseline in PANSS-Total score as a function of study week.

CGI-S response: ≥ 2-point improvement

- Treatment effect favors KarXT vs. placebo at every assessed time point, with statistical significance reached at week 4 and sustained through week 5
- At endpoint (week 5), 28.9% of participants in the KarXT arm were responders, compared to 8.0% of participants in the placebo arm (OR = 4.99, 95% CI = 2.0-12.6, p = 0.0006)

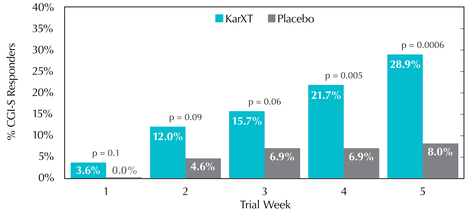


Fig. 3 – Percentage of participants who achieved ≥ 2-point improvement from baseline in CGI-S score as a function of study week.

Safety and tolerability overview

- Overall rates of TEAEs similar in KarXT and placebo arms (54% vs. 43%); AE-related discontinuations similar in KarXT and placebo arms (n = 2 per arm)
- 91% of participants in KarXT titrated to highest dose (vs. 97% on placebo); 4% titrated back down (vs. 1% on placebo)
- Majority of most common TEAEs pro-cholinergic or anti-cholinergic

Table 2 – Most Common Adverse Events – Number (Percent) of Participants

Treatment-Emergent AEs ≥ 5% in KarXT arm	KarXT (n = 89)	Placebo (n = 90)
Constipation	15 (16.9%)	3 (3.3%)
Nausea	15 (16.9%)	4 (4.4%)
Dry mouth	8 (9.0%)	1 (1.1%)
Dyspepsia	8 (9.0%)	4 (4.4%)
Vomiting	8 (9.0%)	4 (4.4%)
Headache	6 (6.7%)	5 (5.6%)
Somnolence	5 (5.6%)	4 (4.4%)

- All AEs that occurred at > 5% in the KarXT arm were rated mild or moderate; no associated treatment discontinuations

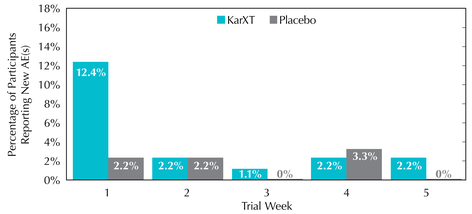
Table 3 – Severity of Key Pro-cholinergic and Anti-cholinergic AEs – Number (Percent) of Total Events

	KarXT		Placebo	
	Mild	Moderate	Mild	Moderate
Constipation	12/16 (75%)	4/16 (25%)	2/3 (67%)	1/3 (33%)
Nausea	13/15 (86.7%)	2/15 (13.3%)	3/4 (75%)	1/4 (25%)
Dry mouth	6/8 (75%)	2/8 (25%)	1/1 (100%)	0/1 (0%)
Vomiting	5/8 (62.5%)	3/8 (37.5%)	3/4 (75%)	1/4 (25%)

Onset of key pro-cholinergic and anti-cholinergic AEs

A. Pro-cholinergic AE onset (nausea, vomiting)

- Most onset in KarXT arm during first week; proportion of participants with nausea and vomiting similar in KarXT and placebo arms after first week



B. Anti-cholinergic AE onset (dry mouth, constipation)

- Most onset in KarXT and placebo arms in first week; lower proportion of participants with dry mouth and constipation in KarXT arm after first week

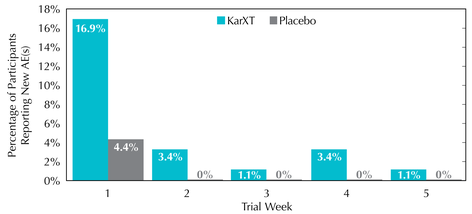


Fig. 4 – Percentage of participants with newly reported key AEs as a function of trial week. (A) pro-cholinergic (nausea, vomiting), (B) anti-cholinergic (dry mouth, constipation).

Duration of key pro-cholinergic and anti-cholinergic AEs

- Majority of pro-cholinergic AEs in the KarXT arm were transient in nature, lasting ≤ 1 day for vomiting and < 7 days for nausea
- Majority of anti-cholinergic AEs (dry mouth; constipation) in the KarXT arm lasted < 2 weeks
- Non-normal duration distributions of nausea and constipation duration, with broad range for both KarXT and placebo
- Overall, AE duration appeared similar in KarXT and placebo arms; mean/median durations provided for context

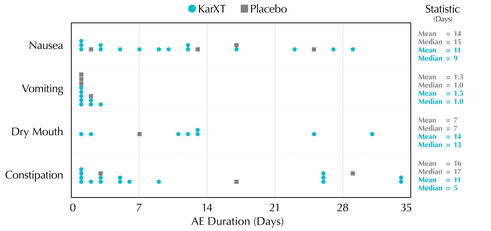


Fig. 5 – Individual event duration for key pro-cholinergic (nausea, vomiting) and anti-cholinergic (dry mouth, vomiting) AEs. Duration was calculated as (AE end date-AE start date) +1, except for two instances that were ongoing at the end of the trial, wherein duration was imputed using each participants end of study date instead of AE end date.

CONCLUSIONS

Post hoc analyses of EMERGENT-1 data:

Provide additional support for and insight into the clinical meaning of the robust efficacy seen in primary analyses of KarXT in acutely psychotic patients with schizophrenia

- Differential efficacy of KarXT in both PANSS-T and CGI-S responder analyses; rapid separation from placebo and significant treatment difference reached before endpoint

Emphasize KarXT tolerability in patients with schizophrenia

- Most common AEs were pro-cholinergic and anti-cholinergic in nature; all were mild-to-moderate in severity and not associated with treatment discontinuation
- Key pro-cholinergic and anti-cholinergic AEs mostly appeared in the first week of treatment and lasted < 2 weeks (most vomiting lasted ≤ 1 day)

Results support Phase 3 development of KarXT in acutely psychotic patients with schizophrenia

REFERENCES

(1) Kavoussi, R, Miller, AC, Brannan, SK, and Breier A. (2017). Poster presented at ASCP annual meeting.

(2) Brannan,SK, Sawchak S, Miller, AC, Paul, SM, and Breier A. (2020). Poster presented at ASCP annual meeting.

* **Author disclosures:**
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