Efficacy of Xanomeline and Trospium Chloride Across Symptom Domains in Adults With Schizophrenia: Pooled Analysis of Data From the Phase 3 EMERGENT-2 and EMERGENT-3 Clinical Trials

Psych Congress 85

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*At the time the analysis was conducted

Background

- The dual M_1/M_4 preferring muscarinic receptor agonist xanomeline in combination with the peripherally restricted pan muscarinic antagonist trospium chloride was approved for the treatment of schizophrenia in adults by the U.S. Food and Drug Administration in 2024[1]
- Xanomeline and trospium chloride (X/T) demonstrated significant improvement in PANSS total score compared with placebo in the pivotal EMERGENT-2 (NCT04659161) and EMERGENT-3 (NCT04738123) phase 3 trials[2,3]
- The Positive and Negative Syndrome Scale (PANSS) Marder 5 factors is a derivation of the PANSS that uses factor analysis to classify PANSS items into 5 dimensions and is intended to highlight distinct underlying processes in schizophrenia[4,5]
- Here, we present a post hoc efficacy analysis of PANSS Marder 5-factor scores of data pooled from the pivotal EMERGENT-2 and EMERGENT-3 trials

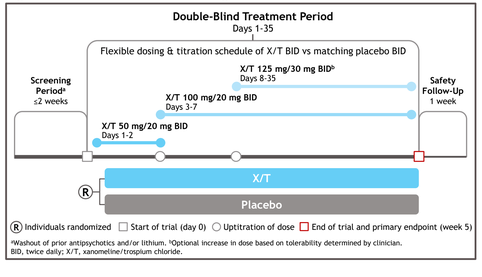
Objective

- To evaluate the efficacy of X/T compared with placebo on PANSS Marder 5-factor scores from the pooled pivotal EMERGENT-2 and EMERGENT-3 clinical trials

Methods

- EMERGENT-2 and EMERGENT-3 were randomized, double-blind, placebo-controlled, inpatient trials of adults with schizophrenia (**Figure 1**)
  - Trials enrolled participants aged 18 to 65 years with a primary diagnosis of schizophrenia and recent worsening of positive symptoms warranting hospitalization, baseline PANSS total score 80-120, and baseline Clinical Global Impression–Severity score ≥4
  - Eligible participants were randomized 1:1. Oral X/T dosing started at 50 mg/20 mg BID and increased to a maximum of 125 mg/30 mg BID
- Data from EMERGENT-2 and EMERGENT-3 were pooled, and efficacy analyses were performed using the modified intent-to-treat (mITT) analysis set, defined as all randomized individuals who received ≥1 dose of trial medication as well as one baseline and ≥1 postbaseline PANSS assessment
- The difference in change from baseline for PANSS Marder factor scores was estimated using mixed model for repeated measures (MMRM). The model included treatment group (X/T or placebo), visit, and the interaction between treatment groups and visit as fixed factors. Age, sex, study, and baseline PANSS scores were included as covariates

Figure 1. Phase 3 EMERGENT trials design



Results

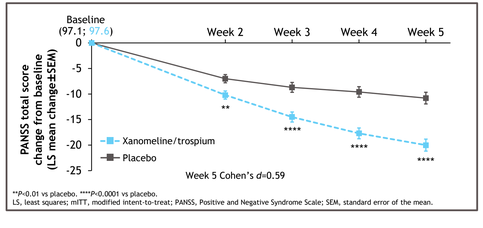
- Overall, 231 participants who received X/T and 239 participants who received placebo met mITT population criteria and were included in the analysis
- Baseline characteristics were similar in the X/T and placebo groups (**Table 1**)
- X/T was associated with larger reductions in PANSS total score from baseline to week 5 compared with placebo (least squares mean [LSM]: -20.0 vs -10.8; LSM difference=-9.2; $P<0.0001$, Cohen's $d=0.59$; **Figure 2**)
  - Week 2: X/T resulted in a LSM difference of -3.2 points in PANSS total score compared with placebo (-10.2 vs -7.0; $P<0.01$)
- Improvements with X/T compared with placebo persisted across PANSS Marder positive, negative, uncontrolled hostility, disorganized thought, and depression/anxiety factors ($P<0.0001$ for all; **Figure 3**)
  - The individual items that make up each Marder factor showed greater improvement with X/T compared with placebo at week 5, except for difficulty in abstract thinking, a component of the PANSS Marder disorganized thought factor, in which score change from baseline was equivalent in both groups

Table 1. Baseline demographics (pooled EMERGENT-2 and EMERGENT-3 population)

Characteristic[a]	X/T (n=251)	Placebo (n=253)
Age, years, mean±SD	44.6±11.0	44.4±11.7
Sex, n (%)		
Male	182 (72.5)	196 (77.5)
Female	69 (27.5)	57 (22.5)
Race, n (%)		
Asian	3 (1.2)	1 (0.4)
Black or African American	176 (70.1)	166 (65.6)
White	71 (28.3)	83 (32.8)
Other	1 (0.4)	2 (0.8)
Not reported	0	1 (0.4)
Time since diagnosis, years, mean±SD	21.3±11.0	19.8±12.4
PANSS total score, mean±SD	97.6±8.8	97.1±9.1
PANSS Marder positive score, mean±SD	30.8±3.9	30.6±3.8
PANSS Marder negative score, mean±SD	22.4±4.5	22.2±4.5
PANSS Marder uncontrolled hostility score, mean±SD	10.1±3.3	10.1±3.2
PANSS Marder disorganized thought score, mean±SD	21.9±3.8	21.7±3.8
PANSS Marder depression/anxiety score, mean±SD	12.4±3.4	12.6±3.2
CGI-S score, mean±SD	5.1±0.6	5.0±0.6

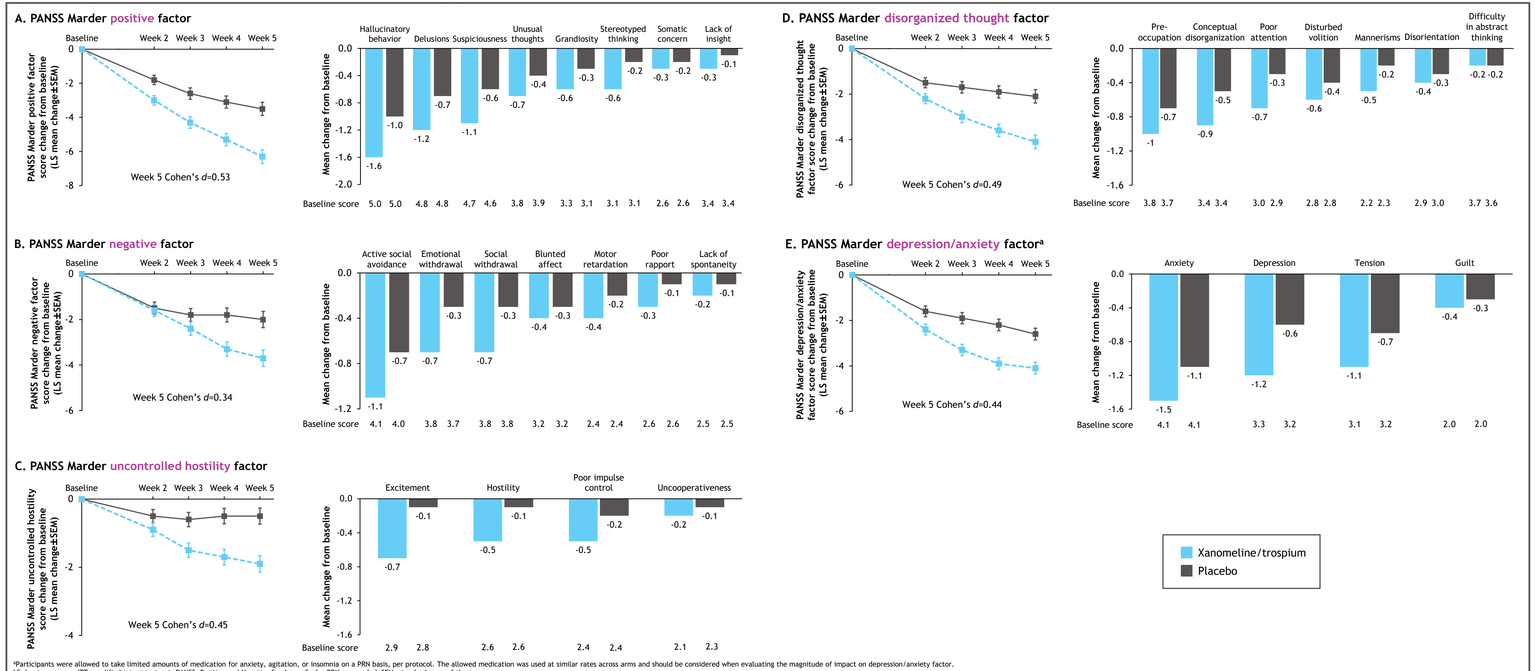
[a]Age, sex, and race data are from the safety population, defined as all participants who received ≥1 dose of trial medication. Time since diagnosis, PANSS, and CGI-S data are from the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication and ≥1 postbaseline PANSS assessment (X/T n=231, placebo n=239).
CGI-S, Clinical Global Impression–Severity; ITT, intent-to-treat; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; X/T, xanomeline/trospium chloride.

Figure 2. Change in PANSS total score from baseline (mITT population)



**P<0.01 vs placebo. ****P<0.0001 vs placebo.
LS, least squares; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Figure 3. Change in PANSS Marder factor scores from baseline to week 5 (mITT population)



[a]Participants were allowed to take limited amounts of medication for anxiety, agitation, or insomnia on a PRN basis, per protocol. The allowed medication was used at similar rates across arms and should be considered when evaluating the magnitude of impact on depression/anxiety factor.
LS, least squares; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; PRN, as needed; SEM, standard error of the mean.

Conclusions

- X/T is an approved treatment for adults with schizophrenia with agonist activity at M_1/M_4 muscarinic receptors and no direct D_2 receptor activity[1,6]
- In the pivotal EMERGENT-2 and EMERGENT-3 trials, X/T was associated with improvement in PANSS total score at week 5 compared with placebo[2,3]
- Post hoc analysis of pooled pivotal trial data demonstrated a consistent benefit with X/T compared with placebo across symptoms as assessed by PANSS Marder positive, negative, uncontrolled hostility, disorganized thought, and depression/anxiety factors
- These results support a broad symptom efficacy of X/T in the treatment of schizophrenia

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Acknowledgments

- The authors thank the participants and families who made the trials possible and the clinical study teams that participated
- These trials were supported by Karuna Therapeutics, a Bristol Myers Squibb company
- All authors contributed to and approved the poster; writing and editorial assistance were provided by Isaac Dripps, PhD, and Paula Stuckart of Apollo Medical Communications, part of Helios Global Group, which was funded by Bristol Myers Squibb

Declaration of interests

JMK has been a consultant for or received honoraria from Alkermes, Allergan, Boehringer-Ingelheim, Bristol Myers Squibb, Cerevel, Click Therapeutics, Dainippon Sumitomo, Eli Lilly, H. Lundbeck, Intracellular Therapies, Janssen Pharmaceuticals, Johnson and Johnson, Karuna, LB Pharmaceuticals, Mapi Pharma, Maplight, Merck, Minerva, Neurocrine, Newron, NW Pharmatech, Otsuka, Reviva, Roche, Sunovion, Takeda, and Teva. He has received grant support from Janssen, Lundbeck, Otsuka, and Sunovion. He has participated in advisory boards for Alkermes, Dainippon Sumitomo, Intracellular Therapies, Lundbeck, Neurocrine, Otsuka, Pierre Fabre, Takeda, and Teva. He is a shareholder in Health Rhythms, LB Pharmaceuticals, Inc., MedinCell, North Shore Therapies, and Vanguard Research Group. **TH** has participated in speaker's bureaus for Alkermes, ITCI, Neurocrine, and Teva. **LS** is a member of speaker's bureaus for Axsome, Bristol Myers Squibb, and Johnson and Johnson, and has participated in advisory boards for Boehringer-Ingelheim and Bristol Myers Squibb. **JA**, **ME**, and **PN** are employees of Bristol Myers Squibb. **AC** was an employee of Bristol Myers Squibb at the time the analysis was conducted.

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Presented at the Psych Congress, September 17-21, 2025, San Diego, CA, USA

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