Antihostility Effects of Xanomeline and Trospium Chloride in Subjects With Schizophrenia: Post Hoc Pooled Analyses of EMERGENT-1, EMERGENT-2, and EMERGENT-3 Trials

Psych Congress 93

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Plain Language Summary

- In this analysis, X/T showed an antihostility effect compared with placebo in adults experiencing a short-term worsening of schizophrenia
- The improvement in symptoms of hostility observed with X/T occurred independently of confounding factors such as resolving psychosis or the presence of sedation
- Importantly, X/T reduced hostility most among those who had the highest levels of baseline hostility
  - Individuals with high baseline hostility have a higher potential for aggressive behavior and violence

Conclusions

- This post hoc analysis of data pooled from the short-term EMERGENT trials demonstrates that X/T has a specific antihostility effect compared with placebo in adults experiencing an acute exacerbation of schizophrenia
- X/T demonstrated specific improvement in symptoms of hostility that was observed independent of change in other positive symptoms of schizophrenia or the presence of somnolence/sedation
- The results of this post hoc analysis suggest that X/T may be an effective treatment for hostility in adults with schizophrenia
- Increased antihostility efficacy was observed for X/T in participants with the highest level of baseline hostility
  - As these individuals represent an especially at-risk group for aggressive behaviors, nonadherence with treatment, and the potential for violence, a specific antihostility effect is an important consideration during clinical decision-making[2]

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Background

- In addition to hallucinations and delusions, people with schizophrenia may exhibit hostility, which is associated with aggressive and violent behavior during acute exacerbations[1]
- Hostility is a significant risk factor for medication nonadherence/discontinuation rates, which, in turn, is a predictor of relapse and rehospitalization[2]
- In previous research, the specific antihostility effects of several atypical antipsychotics have been demonstrated[1,2]
- The dual M_1/M_4 preferring muscarinic receptor agonist xanomeline in combination with the peripherally restricted trospium chloride (X/T) has been approved for the treatment of schizophrenia in adults by the U.S. Food and Drug Administration[3,4]
- The efficacy, safety, and tolerability of X/T in adults with schizophrenia has previously been characterized[5,6]; however, the specific antihostility effects of X/T have yet to be established

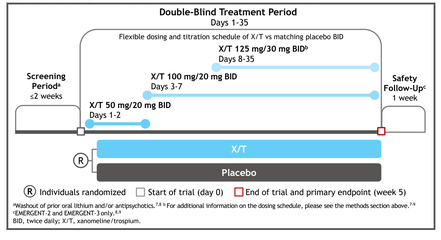
Objective

- To assess the efficacy of X/T in reducing hostility in participants with schizophrenia in a post hoc analysis of pooled data from the EMERGENT-1, EMERGENT-2, and EMERGENT-3 clinical trials

Methods

- Individual participant data were extracted and pooled from 3 short-term, similarly designed 5-week, randomized, double-blind, placebo-controlled, inpatient trials: EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123)[5] (**Figure 1**)
  - Eligible participants were aged 18-60 (EMERGENT-1) and 18-65 years (EMERGENT-2 and EMERGENT-3) experiencing acute exacerbation of psychotic symptoms[5]
  - Participants received placebo or X/T titrated over 7 days to 125 mg/30 mg twice daily[5]
    - Starting dose was twice daily 50 mg xanomeline/20 mg trospium for 2 days and then 100 mg/20 mg BID for 5 days. Dosing was titrated upward to 125 mg/30 mg BID on day 8 unless the subject was continuing to experience adverse events from the previous dose of 100 mg/20 mg BID. All subjects who were increased to xanomeline/trospium chloride 125 mg/30 mg BID, depending on clinical response and tolerability, had the option to return to 100 mg/20 mg BID for the remainder of the treatment period. Most participants (X/T, 82.5%; placebo, 96.0%) ended the trials at the highest dose[5]
  - The primary endpoint was change from baseline in Positive and Negative Syndrome Scale (PANSS) total score to week 5[5]
  - Secondary efficacy outcome measures included change from baseline in PANSS positive subscale, PANSS negative subscale, PANSS Marder negative factor, and Clinical Global Impression-Severity scores[5]
- In this post hoc analysis, mean change in the PANSS positive subscale hostility item (P7) score was assessed
  - To address pseudospecificity, results were adjusted for positive symptom change and somnolence
  - The least squares means between X/T and placebo were calculated using 3 different mixed models for repeated measures. The first model included terms for treatment (X/T or placebo), visit, interaction between treatment and visit, age, sex, trial, and baseline P7. The second model included the interaction between visit and other PANSS positive symptoms (P1, P2, P3 , P5, P6, and G9). The third model also includes the occurrence of an adverse event of hypersomnia, hypersomnolence, sedation, or somnolence

Figure 1.Trial design for EMERGENT-1, EMERGENT-2, and EMERGENT-3[7-9]



[a]Washout of prior oral lithium and/or antipsychotics.[7,8,9] For additional information on the dosing schedule, please see the methods section above.[7-9] [b]EMERGENT-2 and EMERGENT-3 only.[8,9] [c]BID, twice daily; X/T, xanomeline/trospium.

Results

Baseline demographics and characteristics

- Baseline demographics and characteristics were generally well balanced between the treatment groups[5]
- Mean age was 44.6 and 44.4 years for adults treated with X/T and placebo, respectively; most participants were male and Black[5] (**Table 1**)

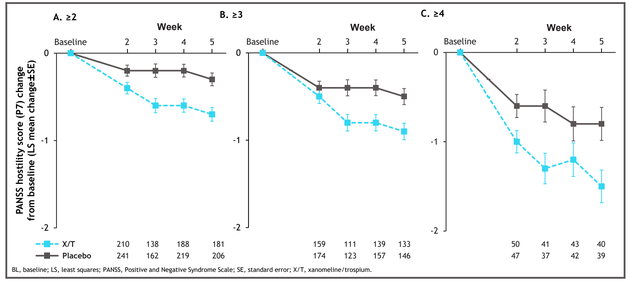
Table 1. Baseline demographics and characteristics[5]

Characteristic	X/T (n=314)	Placebo (n=326)
Age, years, mean±SD	44.6±10.7	43.7±11.3
Sex, n (%)		
Male	233 (74.2)	250 (76.7)
Female	81 (25.8)	76 (23.3)
Race, n (%)		
Asian	4 (1.3)	2 (0.6)
Black or African American	225 (71.7)	221 (67.8)
Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.3)
White	83 (26.4)	98 (30.1)
Other	1 (0.3)	4 (1.2)
Ethnicity, n (%)		
Hispanic or Latino	47 (15.0)	34 (10.4)
Not Hispanic or Latino	265 (84.4)	291 (89.3)
Not reported	2 (0.6)	1 (0.3)
Country, n (%)		
United States	295 (93.9)	300 (92.0)
Ukraine	19 (6.1)	26 (8.0)
Weight, kg, mean±SD	88.9±18.5	87.3±18.6
BMI, kg/m^2, mean±SD	29.2±5.5	28.9±5.4
PANSS total score, mean±SD	97.5±9.0	97.0±8.9
PANSS positive subscale score, mean±SD	26.6±3.6	26.4±3.4
PANSS negative subscale score, mean±SD	22.7±3.8	22.6±4.0
PANSS Marder negative factor, mean±SD	22.4±4.5	22.3±4.6
CGI-S score, mean±SD	5.1±0.6	5.0±0.6

BMI, body mass index; CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; X/T, xanomeline/trospium.

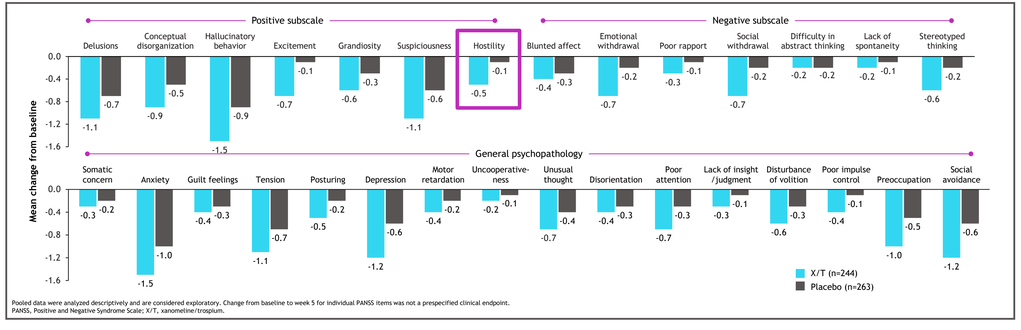
- Within the PANSS positive subscale, the individual item constituting the uncontrolled hostility factor showed greater improvement with X/T than placebo at week 5 (**Figure 2**)
- In individuals with baseline PANSS hostility scores noted below, improvement in hostility item P7 from baseline to week 5 was greater among those receiving X/T than those receiving placebo at the following timepoints (**Figure 3**)
  - ≥2 or ≥3: weeks 3, 4, and 5
  - ≥4: weeks 2, 3, and 5
- This improvement was maintained when adjusted for
  - Other PANSS positive symptoms (**Figure 4**)
    - ≥2 or ≥3: weeks 3 and 5
    - ≥4: weeks 2, 3, and 5
  - Other PANSS positive symptoms and somnolence (**Figure 5**)
    - ≥2 or ≥3: weeks 3 and 5
    - ≥4: weeks 2, 3, and 5

Figure 3. LS mean change from BL in participants with PANSS hostility (P7) ≥2, ≥3, or ≥4



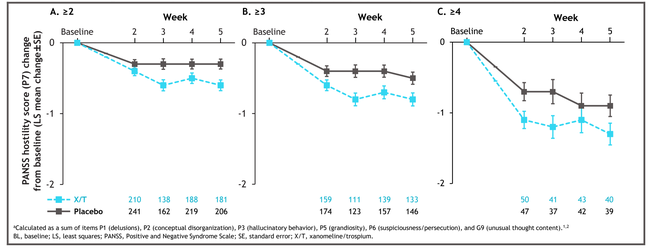
BL, baseline; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error; X/T, xanomeline/trospium.

Figure 2. Pooled acute EMERGENT trials: PANSS item change from baseline to week 5



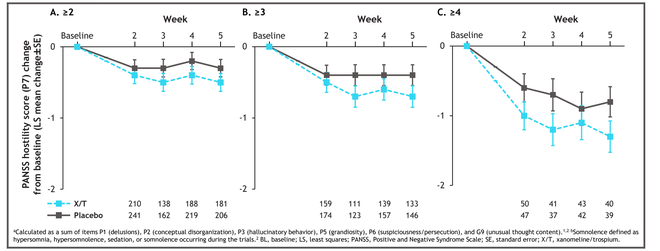
Pooled data were analyzed descriptively and are considered exploratory. Change from baseline to week 5 for individual PANSS items was not a prespecified clinical endpoint.
PANSS, Positive and Negative Syndrome Scale; X/T, xanomeline/trospium.

Figure 4. LS mean change from BL in participants with PANSS hostility (P7) ≥2, ≥3, or ≥4 adjusted for other PANSS positive symptoms[a]



[a]Calculated as a sum of items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P5 (grandiosity), P6 (suspiciousness/persecution), and G9 (unusual thought content).[1,2] BL, baseline; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error; X/T, xanomeline/trospium.

Figure 5. LS mean change from BL in participants with PANSS hostility (P7) ≥2, ≥3, or ≥4 adjusted for other PANSS positive symptoms and somnolence/sedation[b]



[a]Calculated as a sum of items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P5 (grandiosity), P6 (suspiciousness/persecution), and G9 (unusual thought content).[1,2] [b]Somnolence defined as hypersomnia, hypersomnolence, sedation, or somnolence occurring during the trials.[2] BL, baseline; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error; X/T, xanomeline/trospium.

Limitations

- This is a post hoc analysis and participants were not specifically selected because they were hostile or aggressive
- The small sample size limits the statistical power to detect differences. No formal power calculations were performed, and analyses were descriptive rather than inferential
- Participants provided informed consent for the placebo-controlled clinical trials, and so may not be entirely representative of the population with schizophrenia routinely presenting for treatment at a hospital or clinic
- The short duration of the included trials preclude any discussion of enduring or long-term therapeutic effects of X/T

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Acknowledgments

- The authors thank the participants and families who made the trials possible and the clinical study team 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 Helen French, PhD, and Shannon Davis of Apollo Medical Communications, part of Helios Global Group, which was funded by Bristol Myers Squibb

Declaration of interests

LC has received fees for consulting with AbbVie/Allergan, Acadia, Adamas, AdhereTech, Alkermes, Alumis, Angelini, Astellas, Autobahn, Avanir, Axsome, Biogen, BioXcel, Bristol Myers Squibb, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Draig Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, Immune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, MedAvante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, and Wells Fargo, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research. LC has also served as a speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Bristol Myers Squibb, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Neopharm, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, Vanda, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies. LC has a small number of shares of common stock in Bristol Myers Squibb, Eli Lilly, J & J, Merck, and Pfizer, purchased >10 years ago, and stock options in Reviva. LC has received royalties/publishing income from Taylor & Francis (Editor-in-Chief, Current Medical Research and Opinion, 2022–date), Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), and Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics, through Spring 2025). **SV, JA,** and **PN** are employees of Bristol Myers Squibb. **RNM** and **AC** were employees of Bristol Myers Squibb at the time the analysis was conducted.