Results From a Phase 4, Open-Label, Multicenter, Two-Cohort, Two-Period, Slow-Titration and Food Effect Trial to Assess the Safety and Efficacy of Xanomeline and Trospium Chloride in Schizophrenia

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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]
- In the clinical development program, xanomeline/trospium (X/T) was administered as a twice daily (BID) dosing of X/T on an empty stomach (≥1 hour before a meal or ≥2 hours after a meal)[1]
- In pharmacokinetic studies, dosing with food has been shown to reduce trospium bioavailability, potentially impacting tolerability of X/T
- In the 5-week EMERGENT clinical trials of X/T in adults with schizophrenia, the most common peripheral treatment-emergent adverse events (TEAEs) due to xanomeline generally resolved with continued treatment,[2] suggesting that acclimation to xanomeline may occur
- It is hypothesized that this acclimation may mitigate the reductions in trospium bioavailability associated with food intake
- Here, data are presented from a 2-cohort, 2-period trial assessing the safety and efficacy of X/T for 4 weeks when taken on an empty stomach followed by 4 weeks of treatment administered within 30 minutes of a meal

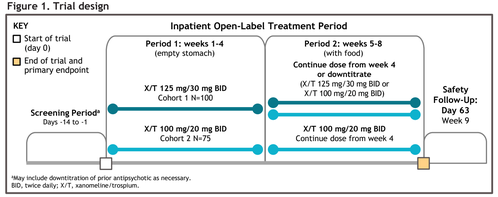
Objective

- To examine the safety and efficacy of X/T after 4 weeks of BID treatment on an empty stomach with a slower uptitration schedule than that used in the registrational trials, followed by participants being allowed to take food within 30 minutes of taking their stable dose

Methods

- This trial was an inpatient, 2-cohort, multicenter, phase 4 trial (NCT06572449) that included two 4-week periods of open-label treatment with X/T (**Figure 1**)
  - The trial enrolled adults aged 18-65 years with a confirmed DSM-5 diagnosis of schizophrenia, stable symptoms, a Positive and Negative Syndrome Scale (PANSS) total score ≤80, and a Clinical Global Impression-Severity (CGI-S) score ≤4
  - All participants were washed out of their prior antipsychotic before starting X/T
  - Food intake was left to the discretion of the participant; food quantity was not consistent or tracked
- X/T was dosed as follows
  - During period 1, participants began BID treatment on an empty stomach for 4 weeks
    - Days 1-7 (week 1), cohorts 1 and 2: xanomeline/trospium chloride 50 mg/20 mg
    - Days 8-14 (week 2), cohorts 1 and 2: xanomeline/trospium chloride 100 mg/20 mg
    - Days 15-28 (weeks 3-4)
      - Cohort 1: xanomeline/trospium chloride 125 mg/30 mg, unless the participant was continuing to experience TEAEs from the previous dose. All participants who were increased to the maximum dose in period 1 had the option to return to the 100 mg/20 mg dose for the remainder of the treatment period depending on tolerability as assessed by the investigator
      - Cohort 2: remained on xanomeline/trospium chloride 100 mg/20 mg
  - During period 2, treatment continued for 4 more weeks, during which participants continued on the same dose but received treatment within 30 minutes of a meal or snack
- Incidence of TEAEs and changes in PANSS total and CGI-S scores were assessed
  - Safety was assessed in all treated participants who received ≥1 dose of trial medication; adverse events were assessed in each time period and defined as new events occurring in that time period
    - TEAEs were assessed in each time period and defined as new events or worsening of an event occurring in that time period
    - TEAEs were counted as per the start date of the event; eg, TEAEs that started in period 1 and continued into period 2 were counted only once in period 1 and not in period 2
  - Efficacy analyses were performed in participants who completed the day 56 efficacy assessment
  - All analyses were performed using data pooled from cohorts 1 and 2
  - All data were summarized descriptively
- Pharmacokinetic samples were drawn on day 22 and day 43

Figure 1. Trial design



Results

Baseline demographics

- The overall pooled safety population consisted of 173 participants (maximum dose 100 mg/20 mg, n=83; maximum dose 125 mg/30 mg, n=83) (**Table 1**)
  - Most participants were male, Black or African American, and not Hispanic or Latino
  - Mean±standard deviation PANSS total and CGI-S scores at baseline were 64.1±10.8 and 3.2±0.7, respectively
  - Note: 7 participants terminated within 1 week of starting treatment and were excluded from the maximum dose analysis

Table 1. Demographics and baseline characteristics (safety population)

Parameter	Max Dose 100 mg/20 mg (n=83)	Max Dose 125 mg/30 mg (n=83)	Overall (N=173[a])
Age, years, mean±SD	43.9±11.6	44.8±11.4	44.6±11.5
Sex, n (%)			
Male	61 (73.5)	61 (73.5)	126 (72.8)
Female	22 (26.5)	22 (26.5)	47 (27.2)
Race, n (%)			
Asian	0	1 (1.2)	1 (0.6)
Black or African American	64 (77.1)	61 (73.5)	128 (74.0)
White	18 (21.7)	21 (25.3)	42 (24.3)
Not reported/unknown	1 (1.2)	0	2 (1.2)
Ethnicity			
Hispanic or Latino	15 (18.1)	16 (19.3)	32 (18.5)
Not Hispanic or Latino	66 (79.5)	67 (80.7)	139 (80.3)
Not reported	2 (2.4)	0	2 (1.2)
Weight, kg, mean±SD	86.7±15.0	87.0±17.5	87.1±16.2
Body mass index, kg/m², mean±SD	29.0±4.8	29.4±5.8	29.3±5.3
PANSS total score, mean±SD	62.3±10.7	65.9±10.7	64.1±10.8
CGI-S score, mean±SD	3.2±0.7	3.3±0.8	3.2±0.7

[a]7 participants terminated within 1 week of starting treatment and were excluded from the max dose analysis.
CGI-S, Clinical Global Impression-Severity; Max, maximum; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Safety and tolerability

- A total of 64.2% and 39.0% of participants reported ≥1 TEAE in period 1 (without food) and period 2 (with food), respectively (**Table 2**)
  - No serious adverse events were reported
  - A total of 6 TEAEs (3 each in periods 1 and 2) led to trial medication discontinuation; 4 were deemed related to trial medication
  - The incidence of new onset TEAEs, including anticholinergic and procholinergic TEAEs, were lower in period 2
- The most common TEAEs (incidence of ≥5%) were (**Table 3**):
  - Period 1: nausea (22.5%), dyspepsia (15.6%), headache (15.0%), constipation (12.7%), vomiting (11.6%), and gastroesophageal reflux disease (8.7%)
  - Period 2: vomiting (7.8%), nausea (5.8%), and dyspepsia (5.2%)
    - All TEAEs were mild or moderate in intensity during period 1 and period 2
  - There were few reports of TEAEs of weight increased (n=6), somnolence (n=2), and extrapyramidal disorder (n=1)

Table 2. Overall summary of safety and tolerability by period (safety population)

Variable, n (%)	Period 1 Weeks 1-4 (n=173)	Period 2 Weeks 5-8 (n=154)	Overall[b] (N=173)
≥1 TEAE[a]	111 (64.2)	60 (39.0)	127 (73.4)
≥1 serious TEAE	0	0	0
≥1 TEAE leading to discontinuation of trial medication	3 (1.7)	3 (1.9)	6 (3.5)
≥1 procholinergic TEAE	52 (30.1)	19 (12.3)	64 (37.0)
≥1 anticholinergic TEAE	61 (35.3)	14 (9.1)	71 (41.0)
≥1 AESI	1 (0.6)	0	1 (0.6)

[a]Incidence of new onset TEAEs. [b]Number of unique individuals overall; a participant who may have experienced a TEAE in period 1 may have experienced a new TEAE in period 2.
AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.

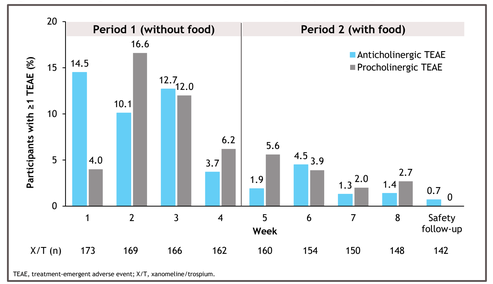
- The incidence of the most commonly occurring TEAEs decreased in period 2 (weeks 5-8) (**Table 3**)
- The percentage of participants who experienced ≥1 anticholinergic or procholinergic TEAE did not increase when X/T was taken with food (**Figure 2**)

Table 3. TEAEs reported in ≥5% of participants by period and intensity (safety population)

Preferred Term, n (%)	Period 1 Weeks 1-4 (n=173)				Period 2 Weeks 5-8 (n=154)				Overall (N=173)
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	
Nausea	31 (17.9)	8 (4.6)	0	39 (22.5)	7 (4.5)	2 (1.3)	0	9 (5.8)	47 (27.2)
Dyspepsia	23 (13.3)	4 (2.3)	0	27 (15.6)	7 (4.5)	1 (0.6)	0	8 (5.2)	35 (20.2)
Vomiting	17 (9.8)	3 (1.7)	0	20 (11.6)	10 (6.5)	2 (1.3)	0	12 (7.8)	30 (17.3)
Headache	26 (15.0)	0	0	26 (15.0)	4 (2.6)	0	0	4 (2.6)	29 (16.8)
Constipation	19 (11.0)	3 (1.7)	0	22 (12.7)	3 (1.9)	0	0	3 (1.9)	25 (14.5)
GERD	13 (7.5)	2 (1.2)	0	15 (8.7)	0	0	0	0	15 (8.7)
Dizziness	8 (4.6)	0	0	8 (4.6)	3 (1.9)	0	0	3 (1.9)	12 (6.9)
Abdominal discomfort	8 (4.6)	0	0	8 (4.6)	1 (0.6)	0	0	1 (0.6)	9 (5.2)

GERD, gastroesophageal reflux disease; TEAE, treatment-emergent adverse event.

Figure 2. Percentage of participants with ≥1 anticholinergic or procholinergic TEAE by week



TEAE, treatment-emergent adverse event; X/T, xanomeline/trospium.

- First onset of nausea and vomiting largely occurred during the first 4 weeks of X/T administration (**Figure 3**)

Efficacy

- PANSS total score decreased over periods 1 and 2 in the overall population; mean±standard error of the mean (SEM) changes from baseline (CFB) were -2.7±0.4 and -4.8±0.6 at the end of periods 1 and 2, respectively (**Figure 4A**)
  - No differences were observed in those who received a maximum dose of xanomeline/trospium chloride 100 mg/20 mg or 125 mg/30 mg
- CGI-S score decreased over period 1 (mean±SEM CFB: -0.2±0.1) with no further change over period 2 (mean±SEM CFB: -0.3±0.1) in the overall population (**Figure 4B**)

Figure 3. Duration and incidence of vomiting and nausea

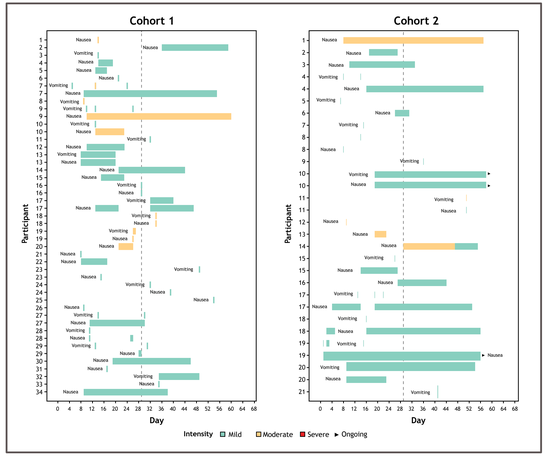
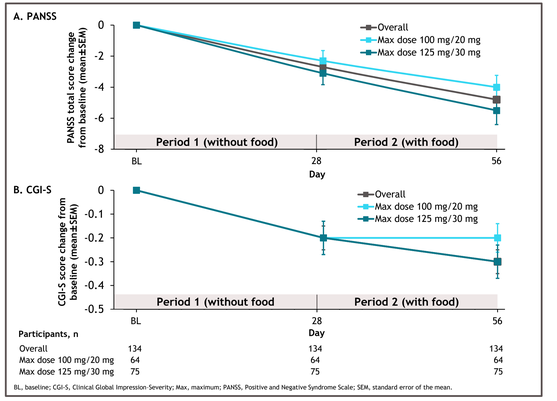


Figure 4. Efficacy measures: change from baseline to end of period 1 and period 2



BL, baseline; CGI-S, Clinical Global Impression-Severity; Max, maximum; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Pharmacokinetics

- Dose-normalized area under the curve and maximum concentration of trospium decreased by 34.5% and 43.4%, respectively, when taken with food compared with fasting (**Table 4**); in previous trials, maximum concentration and area under the curve were reduced 70%-75% and 85%-90%, respectively, when taken with a high-fat meal compared with a fasted state[1]
- No clinically significant differences were observed in xanomeline exposures under the same conditions

Table 4. Dose-normalized PK parameter summary

PK Parameter	Trospium		Xanomeline	
	Day 22 (Period 1; Empty Stomach)	Day 43 (Period 2; With food)	Day 22 (Period 1; Empty Stomach)	Day 43 (Period 2; With Food)
Dose-normalized $AUC_{0\text{-}12h,ss}$ (h·pg/mL/mg)[a]	940.7 (85.5%, n=145)	596.3 (102.5%, n=124)	390.1 (100.2%, n=144)	362.6 (89.1%, n=128)
Dose-normalized $AUC_{0\text{-}12h}$ ratio[b]	65.5% (90% CI: 58.5%-73.3%)		91.5% (90% CI: 82.3%-101.8%)	
Dose-normalized $C_{max,ss}$ (10^{-3}·h/mL)[a]	170.2 (105.1%, n=153)	92.5 (141.8%, n=137)	63.3 (118.4%, n=155)	57.1 (105.9%, n=139)
Dose-normalized $C_{max,ss}$ ratio[b]	56.6% (90% CI: 48.9%-65.4%)		88.0% (90% CI: 77.8%-99.6%)	

[a]Data reported as geometric mean (CV%, N=number of subjects included). [b]Data reported as geometric mean of day 43/day 22 (range with a 90% CI). Geometric mean ratio and its 90% CI were derived by taking the exponent of the period estimate, which came from a mixed effect model with log-transformed AUC value as the dependent variable, periods (day 22 and day 43) as the fixed effect, and subjects treated as random effect in the model.
$AUC_{0\text{-}12h,ss}$, area under the curve 0-12 hours at steady state; CI, confidence interval; $C_{max,ss}$, maximum concentration at steady state; CV, coefficient of variation; PK, pharmacokinetic.

Conclusions

- An open-label trial examined X/T tolerability and efficacy in adults with schizophrenia who slowly titrated to the target dose of X/T during the initial 4 weeks of treatment on an empty stomach before switching to dosing with food
- No new safety signals or increases in the incidence and/or severity of adverse events were observed when switched to dosing with food
- Treatment with X/T was not associated with adverse events often observed with antipsychotic use
- Results suggest that administering X/T with food may be well tolerated with maintained efficacy after a 4-week period of acclimation
- The decrease in trospium exposure was less than expected when taken with food; however, food requirements were not specified in this trial

References

1. Cobenfy. Prescribing information. Bristol Myers Squibb; 2024.
2. Kaul I, et al. *J Clin Psychiatry*. 2025;86(1):24m15497.

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Declaration of interests

JH, RD, AG, RS, RT, and **KK** are employees of Bristol Myers Squibb. **ACM** was an employee of Bristol Myers Squibb at the time the study was conducted and is currently a consultant to Bristol Myers Squibb. **DPW** has received research support from AbbVie, Acadia, Alkermes, Allergan, Avanir, BMS, Cerevel, Indivior, IntraCellular, J & JRPD, Karuna, Lupin, Lundbeck, Neurocrine, Novartis, Noven, Pfizer, Roche, Sage, Sunovion, and Takeda; and has received research support and served as a consultant for Biogen, Boehringer Ingelheim, Janssen, Lyndra, and Otsuka. **KJ** is the medical director of CenExel—iResearch Georgia, an independent research organization that conducts investigator-initiated and industry-sponsored pharmaceutical trials, including the one presented here; she has no financial ties to the sponsor of the current investigation.

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