Symptom Stability During Treatment Transition to Xanomeline and Trospium Chloride: Post Hoc Analysis of an Inpatient Trial in Schizophrenia

Psych Congress 100

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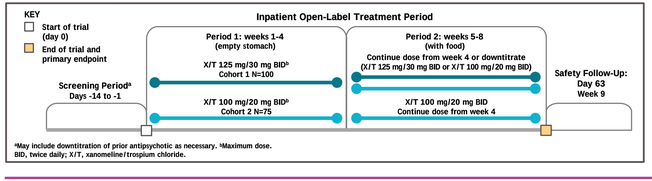
Background

- Switching from one antipsychotic regimen to another is common in people with schizophrenia; up to 50% of people with schizophrenia switch within 6 to 24 months in real-world analyses[1]
  - Lack of tolerability and lack of efficacy are most often cited as reasons for switching therapy[2-4]
- There is no standard guidance for switching antipsychotics; switching strategies include abrupt switch, taper switch, cross-taper switch, and plateau taper switch[5]
- Risk of relapse is a concern when discontinuing therapy, regardless of how long the person may have been on treatment previously[6,7]
- In light of the novel mechanism of action of xanomeline and trospium chloride (X/T), a trial of X/T requiring washout of prior antipsychotic drugs (pAPD) provided an opportunity to examine safety and disease symptom stability during this transition

Methods

- In this poster, we describe an inpatient, 2-cohort, multicenter, phase 4 trial (NCT06572449) that includes two 4-week periods of open-label 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 tapered off their stable medication prior to starting X/T
- X/T was dosed as follows
  - During period 1, participants began twice daily 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 treatment-emergent adverse events (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 received at the end of period 1 but received treatment within 30 minutes of a meal or snack. Participants in cohort 1 could downtitrate to a dose of xanomeline/trospium chloride 100 mg/20 mg in the event of intolerable side effects or at investigator discretion
- Incidence of TEAEs and change in PANSS total score were assessed
  - Efficacy analyses were performed in participants who completed the day 56 efficacy assessment
  - 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
  - All analyses were performed using data pooled from cohorts 1 and 2
  - All data were summarized descriptively

Figure 1. Trial design



[a]May include downtitration of prior antipsychotic as necessary. [b]Maximum dose.
BID, twice daily; X/T, xanomeline/trospium chloride.

Results

Baseline demographics

- The overall pooled safety population consisted of 173 participants (Table 1)
  - Most participants were male, Black or African American, and not Hispanic or Latino
  - Mean±standard deviation (SD) PANSS total and CGI-S scores at baseline were 64.1±10.8 and 3.2±0.7, respectively

Table 1. Demographics and baseline characteristics (safety population)

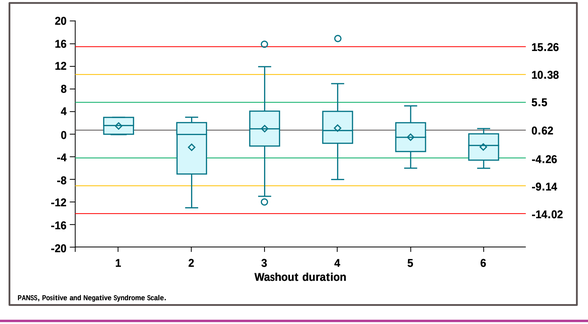
Parameter	Overall (N=173)
Age, years, mean±SD	44.6±11.5
Sex, n (%)	
Male	126 (72.8)
Female	47 (27.2)
Race, n (%)	
Asian	1 (0.6)
Black or African American	128 (74.0)
White	42 (24.3)
Not reported/unknown	2 (1.2)
Ethnicity	
Hispanic or Latino	32 (18.5)
Not Hispanic or Latino	139 (80.3)
Not reported	2 (1.2)
Weight, kg, mean±SD	87.1±16.2
Body mass index, kg/m², mean±SD	29.3±5.3[a]
PANSS total score, mean±SD	64.1±10.8
CGI-S score, mean±SD	3.2±0.7

[a]N=172.
CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Efficacy

- Mean±SD PANSS total scores were stable from screening (63.4±10.9) to baseline (64.1±10.7) and independent of washout duration (r=0.05) (Figure 2); median (min, max) washout duration was 3 (1, 6) days
  - Note: Period between screening and baseline was a maximum of 14 days; participants had to discontinue all pAPD ≥3 days prior to the baseline visit

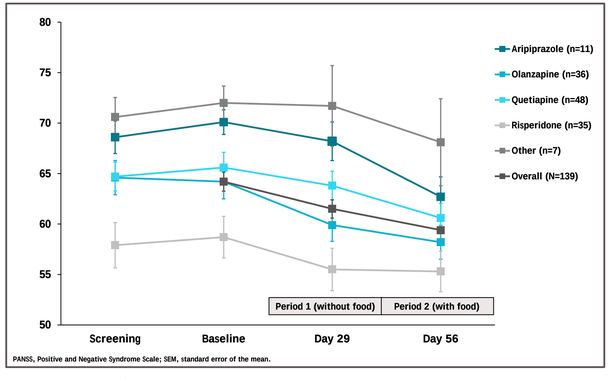
Figure 2. Change from screening to baseline in PANSS total by washout duration



PANSS, Positive and Negative Syndrome Scale.

- Mean±standard error of the mean (SEM) changes from screening to baseline in PANSS total score for individuals previously on (Figure 3):
  - Aripiprazole (n=11): 1.5±1.5
  - Quetiapine (n=48): 0.9±0.9
  - Olanzapine (n=36): -0.4±0.5
  - Risperidone (n=35): 0.8±0.6
- PANSS total score decreased over periods 1 and 2; mean±SEM changes from baseline were -2.7±0.5 and -4.8±0.6 at the end of periods 1 and 2, respectively, in the overall population (Figure 3)

Figure 3. Efficacy measures: PANSS total score from screening through day 56



PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

Safety and tolerability

- A total of 73.4% of participants reported ≥1 TEAE (Table 2)
  - No serious adverse events were reported
  - A total of 6 TEAEs lead to trial medication discontinuation; 4 were deemed related to trial medication
- Peak incidence of nausea (Table 3) and vomiting (Table 4) was generally observed at days 3-7 (EMERGENT-1,2,3) or week 2 (food effect trial) at first introduction of the xanomeline/trospium chloride 100 mg/20 mg dose
  - Incidence of nausea and vomiting reduced with continued treatment and titration to the 125 mg/30 mg dose

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

Variable, n (%)	Overall (N=173)
≥1 TEAE[a]	127 (73.4)
≥1 serious TEAE	0
≥1 TEAE leading to discontinuation of trial medication	6 (3.5)
≥1 procholinergic TEAE	64 (37.0)
≥1 anticholinergic TEAE	71 (41.0)
≥1 AESI	1 (0.6)

[a]Incidence of new onset TEAEs.
AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.

Table 3. Incidence of nausea by week (safety population)

	Incidence of Nausea (%)			
	Week 1	Week 2	Week 3	Week 4
	50 mg/20 mg	100 mg/20 mg	Maximum Dose	
Pooled (N=173)	1.7	12.4	7.8	3.1
Maximum dose, 100 mg/20 mg (n=83)	3.6	14.5	7.3	3.8
Maximum dose, 125 mg/30 mg (n=83)	0	10.8	8.4	2.4

Table 4. Incidence of vomiting by week (safety population)

	Incidence of Vomiting (%)			
	Week 1	Week 2	Week 3	Week 4
	50 mg/20 mg	100 mg/20 mg	Maximum Dose	
Pooled (N=173)	1.7	7.7	3.0	3.1
Maximum dose, 100 mg/20 mg (n=83)	2.4	10.8	6.1	3.8
Maximum dose, 125 mg/30 mg (n=83)	1.2	4.8	0	2.4

Conclusions

- Switching antipsychotics is common among individuals with schizophrenia
- Overall, increases in PANSS total scores from screening to baseline were not seen when switching individuals from pAPD to X/T
- These data suggest that stable individuals can be safely transitioned from pAPD to X/T without destabilization of schizophrenia symptoms
- Despite a slower titration than used in the EMERGENT clinical trials, nausea and vomiting were most commonly observed at the xanomeline/trospium chloride 100 mg/20 mg dose, which then resolved with continued treatment

References

1. Martin A, et al. *Adv Ther*. 2022;39(9):3933-3956.
2. Roussidis A, et al. *Ann Gen Psychiatry*. 2013;12(1):42.
3. Fee R, et al. *J Manag Care Spec Pharm*. 2024;30(7):698-709.
4. Hugenholtz GW, et al. *Pharmacopsychiatry*. 2005;38(3):122-124.
5. Buckley PF, et al. *J Clin Psychiatry*. 2008;69(suppl 1):4-17.
6. Alvarez-Jimenez M, et al. *Schizophr Res*. 2012;139(1-3):116-128.
7. Emsley R, et al. *BMC Psychiatry*. 2013;13:50.

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Declaration of interests

All authors are employees of Bristol Myers Squibb.

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