ORIGINAL RESEARCH

Xanomeline and Trospium Chloride Versus Placebo for the Treatment of Schizophrenia: A Post Hoc Analysis of Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed

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Purpose: Describe xanomeline and trospium chloride efficacy and safety/tolerability for the treatment of schizophrenia using number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

Methods: Categorical data were extracted from the three 5-week, randomized, double blind, placebo controlled EMERGENT-1, EMERGENT-2, and EMERGENT-3 clinical trials of xanomeline/trospium in adults with schizophrenia experiencing acute psychosis. Efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression–Severity (CGI-S), and categorical response criteria. Safety and tolerability were assessed using rates of discontinuation and treatment-emergent adverse events (TEAEs). NNT, NNH, and LHH values were calculated for each individual study as well as pooled.

Results: In data from the acute EMERGENT trials, NNT estimates were significant for xanomeline/trospium vs placebo for the pre-specified treatment response threshold of ≥30% reduction from baseline in PANSS total score at Week 5 (NNT=5 [95% CI, 4–8]). NNT estimates for response thresholds of ≥20% and ≥40% reduction from baseline in PANSS total score and ≥1- and ≥2-point decrease from baseline in CGI-S score were <10, indicating a clinically relevant therapeutic benefit of xanomeline/trospium over placebo. Estimates of NNH vs placebo for the most common TEAEs were >10, with the exception of nausea and vomiting; however, rates of discontinuations due to TEAEs of nausea, dyspepsia, or vomiting were low (NNH=49 [95% CI, 28–182]). LHH indicated an overall benefit of xanomeline/trospium vs placebo for all assessed outcomes. In indirect comparisons based on published data from trials of available antipsychotics approved for schizophrenia, xanomeline/trospium exhibited comparable or more robust NNT estimates vs placebo and was the least likely agent to be associated with weight gain or somnolence/sedation.

Conclusion: In the 5-week EMERGENT clinical trials, NNT, NNH, and LHH assessments demonstrated a favorable benefit-risk profile for xanomeline/trospium.

Trial Registration: ClinicalTrials.gov identifiers: NCT03697252, NCT04659161, NCT04738123.

Keywords: antipsychotic, xanomeline and trospium chloride, KarXT, schizophrenia, number needed to treat, number needed to harm

Introduction

The limitations of available antipsychotic medications are well known, and new treatments with broader efficacy and improved tolerability are an area of significant unmet need for individuals living with schizophrenia. Xanomeline and trospium chloride, formerly known as KarXT, has been assessed in three clinical trials of adults with acute exacerbations of schizophrenia and is an approved treatment for this population and an investigational therapy for psychosis in Alzheimer's disease.[1–4] A novel mechanism of action distinguishes xanomeline/trospium from previously approved

antipsychotics: xanomeline is a dual M_1/M_4 preferring muscarinic receptor agonist without any binding affinity to the dopamine D_2 receptor.[5–7] Xanomeline is combined with the peripherally restricted pan-muscarinic receptor antagonist trospium to reduce unwanted cholinergic side effects elicited by xanomeline activity in the periphery.[8,9]

The clinical development program assessing the efficacy and safety of xanomeline/trospium in schizophrenia included three 5-week, randomized, double-blind, placebo-controlled trials of nearly identical design: the Phase 2 EMERGENT-1 (NCT03697252)[1] and Phase 3 EMERGENT-2 (NCT04659161)[2] and EMERGENT-3 (NCT04738123)[3] trials. The primary endpoint of change from baseline to Week 5 in Positive and Negative Syndrome Scale (PANSS) total score with xanomeline/trospium vs placebo was met in all three trials, demonstrating statistically significant improvement in symptoms of schizophrenia with xanomeline/trospium compared with placebo. Consistent with the activity of xanomeline and trospium at muscarinic receptors, the most common side effects observed with treatment were primarily gastrointestinal, such as constipation and nausea, mild to moderate in intensity, and transient. Notably, xanomeline/trospium was not associated with clinically meaningful adverse events (AEs) commonly observed with currently available antipsychotics, including extrapyramidal movement disorders, hyperprolactinemia, weight gain, metabolic side effects, or somnolence/sedation.[10,11] Based on the results of the acute EMERGENT trials, the US Food and Drug Administration (FDA) awarded xanomeline/trospium approval for the treatment of schizophrenia in adults in September 2024.

Evidence-based medicine metrics such as number needed to treat (NNT) and number needed to harm (NNH) can aid physicians in assessing the clinical relevance of results from clinical trials.[12] NNT and NNH are measures of effect size and indicate how many patients would need to be treated with one intervention (such as a medication) instead of the comparator (such as another medication or placebo) to encounter one additional outcome of interest. NNT and NNH can also be used to quantify benefit vs risk by calculating the ratio of NNH to NNT (likelihood to be helped or harmed [LHH]). In general, a LHH >1 would mean the likelihood to be helped is greater than the likelihood to be harmed. For a LHH <1, the reverse is true. For a LHH to be meaningful, the efficacy outcome and adverse outcome must be clinically relevant for the person being treated. In this analysis, NNT, NNH, and LHH estimates were calculated for xanomeline/ trospium vs placebo and indirectly compared with available oral, first-line, second-generation antipsychotics approved for the treatment of schizophrenia, including aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone, based on previously published data for these agents.

Methods
Trial Design

The pivotal EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials were nearly identical 5-week, randomized, double-blind, placebo-controlled trials of xanomeline/trospium in adults with schizophrenia experiencing acute psychosis.[1–3] Briefly, the trials enrolled participants aged 18–60 years (EMERGENT-1) and 18–65 years (EMERGENT-2 and EMERGENT-3) with a confirmed diagnosis of schizophrenia based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition,[13] a PANSS total score of 80–120 (higher scores reflect greater symptom severity),[14] and a recent worsening of psychosis requiring hospitalization. Enrolled participants were randomized 1:1 to receive twice-daily treatment with placebo or xanomeline/trospium starting at a dose of 50-mg xanomeline/20-mg trospium chloride and titrating up to a maximum dose of 125-mg xanomeline/30-mg trospium chloride over a period of 7 days.

All trials were conducted in accordance with the principles of the Declaration of Helsinki, the International Council of Harmonization guidelines for Good Clinical Practice, and regulations of the countries in which the trials took place.[1–3] Protocols were approved by centralized institutional review boards in the United States (EMERGENT-1, Copernicus Group, Cary, NC; EMERGENT-2 and EMERGENT-3, WCG IRB, Puyallup, WA) and local ethics committees at trial sites in Ukraine, and all participants submitted informed consent prior to enrollment. Trials followed guidelines for the Consolidated Standards of Reporting Trials (CONSORT).

Outcomes

Efficacy data were extracted from the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials. In the trials, PANSS assessments were made at Weeks 2, 3 (EMERGENT-2 and EMERGENT-3 only), 4, and 5. Clinical Global Impression–Severity (CGI-S) scores were assessed weekly at Weeks 1 through 5. Data were collected for participants classified as responders at endpoint (Week 5 or early termination [using a last observation carried forward approach]) as assessed using both PANSS total and CGI-S score response criteria thresholds: PANSS total score reductions from baseline to endpoint of ≥20%, ≥30%, ≥40%, and ≥50% and CGI-S score of ≤2 (not at all ill or borderline ill) or ≤3 (not at all ill, borderline ill, or mildly ill) at endpoint.[15] Additionally, data were collected for participants who achieved a decrease from baseline in CGI-S score of ≥1, ≥2, or ≥3 points. The denominator for all efficacy outcome measures was the number of participants who had a baseline and ≥1 post-baseline PANSS assessment (the modified intention-to-treat [mITT] population).

Safety and tolerability data were extracted from the three pivotal EMERGENT trials including specific outcomes of clinical interest occurring at any point during the double-blind treatment period. Data were collected for the following safety and tolerability outcomes: discontinuations due to treatment-emergent AEs (TEAEs); dose reductions due to TEAEs; both discontinuations and dose reductions due to a TEAE of nausea, dyspepsia, or vomiting; TEAEs occurring in ≥5% of participants; TEAEs relevant to indirect comparisons with other second-generation antipsychotics, including ≥7% weight increase, akathisia, and somnolence/sedation; participants exhibiting shifts at any time in electrocardiogram QTc interval from <450 msec to ≥450 msec, in total cholesterol from <240 mg/dL to ≥240 mg/dL, in fasting glucose from <126 mg/dL to ≥126 mg/dL, or in fasting triglycerides from <200 mg/dL to ≥200 mg/dL; plasma prolactin values of ≥17 ng/mL (men) and ≥25 ng/mL (women); and plasma prolactin values of ≥34 ng/mL (men) and ≥50 ng/mL (women). Prolactin was assessed in EMERGENT-2 and EMERGENT-3 only. The denominator for AE analyses was the number of randomized participants who received ≥1 dose of trial drug (safety population). The denominator for weight and laboratory variables was the number of participants who had a baseline and ≥1 post-baseline value for a variable while on treatment, and in the case of shifts, met the defined starting threshold.

Data Analysis

NNT estimates, with their respective 95% CIs, were calculated for xanomeline/trospium vs placebo using previously published formulas (Box 1) and pooled when all data elements were available for each trial.[16] NNH estimates, with their respective 95% CIs, were also calculated for xanomeline/trospium vs placebo and pooled using all available data.

LHH was calculated for xanomeline/trospium to illustrate potential trade-offs for efficacy and tolerability outcomes, specifically response (≥30% reduction from baseline in the total PANSS score at endpoint [Week 5 or early termination]) vs discontinuation from the trial because of a TEAE; discontinuation from the trial because of an AE of nausea, dyspepsia, or vomiting; dose reduction because of an AE; dose reduction because of an AE of nausea, dyspepsia, or

Box 1 Formulae Used for Calculating NNT, NNH, and LHH

Absolute risk increase (ARI)= (incidence on medication)–(incidence on placebo)= f_1 - f_2

- 95% confidence interval (CI) calculated by:

  Lower bound of the $CI = ARI - z\sqrt{\frac{f_1(1-f_1)}{n_1} + \frac{f_2(1-f_2)}{n_2}}$, where z=1.96 for a 95% CI

  Upper bound of the $CI = ARI + z\sqrt{\frac{f_1(1-f_1)}{n_1} + \frac{f_2(1-f_2)}{n_2}}$, where z=1.96 for a 95% CI

- NNT (or NNH)=1/ARI, and rounded up to the next highest whole number (NNT and NNH are estimates of effect size, with lower numbers being more robust; thus, rounding down could potentially exaggerate the effect size estimate)

- The CI for the NNT (or NNH) calculated by taking the reciprocal of the lower and upper bounds of the CI for the ARI

- LHH=NNH/NNT

Note: Reprinted from Citrome L, Juday T, Frech F, Atkins N Jr. Lemborexant for the treatment of insomnia: direct and indirect comparisons with other hypnotics using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Clin Psychiatry.* 2021;82:20m13795.[16]

Abbreviations: LHH, likelihood to be helped or harmed; NNH, number needed to harm; NNT, number needed to treat.

vomiting; weight gain ≥7%; somnolence/sedation AEs; akathisia AEs; and all AEs occurring in ≥5% of participants receiving xanomeline/trospium and at a rate at least twice that observed in the placebo group (nausea, constipation, dyspepsia, vomiting, hypertension, dry mouth, tachycardia). When a NNH estimate is a negative number (ie, when the rate of the AE is higher with placebo than with xanomeline/trospium), the LHH calculation is uninterpretable. In such instances, we took the customary approach to impute a value of 1000 for the NHH to quantify LHH.[17,18]

If the 95% CI for the NNT or NNH estimate included "infinity" the result was considered not statistically significant at the *P*<0.05 threshold, and the notation "ns" was used rather than displaying two non-continuous domains of numbers ranging to infinity or negative infinity. The terms "statistically significant" and "non-statistically significant" were used descriptively rather than inferentially. In general, data pooling increases the sample size and narrows the 95% CI, leading to more precise estimates of effect size and these results are included in the body of this report; the results from the individual studies are included in the Supplementary Appendix, including baseline characteristics (Tables S1a, S1b, and S1c), efficacy outcomes (Tables S2a, S2b, and S2c), and safety/tolerability outcomes (Tables S3a, S3b, S3c, S4a, S4b, and S4c). Additional pooled data can also be found in Tables S2d, S3d, and S4d.

Indirect comparisons with other agents used to treat schizophrenia were possible because similar analyses have been performed with most second-generation antipsychotics, including all currently available branded single-agent oral products.[19–22]

Results

Participants

A total of 683 participants (xanomeline/trospium, n=340; placebo, n=343) were included in the pooled safety population; there were no meaningful differences in demographics and baseline characteristics between treatment groups (Table 1; see Supplementary Appendix for the demographics and baseline characteristics from the individual studies). Efficacy outcomes were examined in the mITT population (xanomeline/trospium, n=314; placebo, n=326).

Table 1 Demographics and Baseline Characteristics (Safety Population)

Characteristic	Xanomeline/trospium (n=340)	Placebo (n=343)
Age, years, mean±SD	44.3±10.75	43.7±11.33
Sex, n (%)		
Male	254 (74.7)	262 (76.4)
Female	86 (25.3)	81 (23.6)
Race, n (%)		
Asian	4 (1.2)	3 (0.9)
Black	242 (71.2)	235 (68.5)
Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.3)
White	92 (27.1)	99 (28.9)
Not reported/missing/unknown/other	1 (0.3)	5 (1.5)
Ethnicity, n (%)		
Hispanic or Latino	50 (14.7)	37 (10.8)
Not Hispanic or Latino	288 (84.7)	305 (88.9)
Not reported/missing/unknown/other	2 (0.6)	1 (0.3)
Country, n (%)		
United States	319 (93.8)	316 (92.1)
Ukraine	21 (6.2)	27 (7.9)
Weight, kg, mean±SD	88.6±18.70	87.2±18.44
Body mass index, kg/m^2, mean±SD	29.1±5.47	28.9±5.32

Abbreviation: SD, standard deviation.

Efficacy

The majority of the NNT estimates for xanomeline/trospium compared with placebo were low (<10). NNT for the outcome measure of ≥30% reduction from baseline to Week 5 in PANSS total score was 5 (95% CI, 4–8); the NNT for outcomes of ≥20% and ≥40% reduction from baseline to Week 5 in PANSS total score were similar, at 5 (95% CI, 4–7) and 8 (95% CI, 6–16), respectively (Table 2; see Supplementary Appendix for results from the individual studies). NNT for xanomeline/trospium compared with placebo for the outcomes of CGI-S score of ≤3 (representing severities of not at all ill, borderline ill, or mildly ill)[15] was 8 (95% CI, 5–14) and <10 for CGI-S decreases from baseline of both ≥1 and ≥2 points. Only the highest threshold outcomes, ie, ≥50% reduction from baseline to Week 5 in PANSS total score, ≥3-point decrease from baseline to Week 5 in CGI-S score, and endpoint CGI-S score of ≤2 (not at all ill or borderline ill) yielded NNT estimates >10.

Tolerability

Xanomeline/trospium NNH estimates based on TEAEs and laboratory or metabolic endpoints were generally high (>10). The proportions of participants who discontinued treatment due to a TEAE were low and similar between xanomeline/trospium and placebo groups (5.6% vs 4.7%), and the NNH compared with placebo was not significant (Table 3; see Supplementary Appendix for results from the individual studies). The NNH estimates for nausea and vomiting were <10; however, the NNH estimate based on discontinuation due to a TEAE of nausea, dyspepsia, or vomiting was 49, and the NNH estimate based on dose reductions due to the same TEAEs was 170 and non-significant compared with placebo. NNH estimates for all the other most common TEAEs were ≥10. NNH estimates based on metabolic and clinical laboratory outcomes either exceeded 10 or the event rate was higher with placebo than with xanomeline/trospium, resulting in negative NNH values (Table 4).

Likelihood to Be Helped or Harmed

LHH is a ratio of NNT to NNH and reflects the relative benefit vs risk of harm associated with treatment. LHH estimates for the most common TEAEs in the acute EMERGENT trials and those of special interest vs treatment response (defined as ≥30% reduction from baseline in PANSS total score) are presented in Table 5. LHH was >1 for all AEs, indicating that

Table 2 NNT Based on PANSS Total and CGI-S Score Criteria (mITT Population)

Percent Reduction in PANSS Total Score from Baseline to Endpoint	Xanomeline/trospium (n=314), n (%)	Placebo (n=326), n (%)	NNT (95% CI)
≥20%	176 (56.1)	109 (33.4)	5 (4–7)
≥30%	130 (41.4)	68 (20.9)	5 (4–8)
≥40%	84 (26.8)	46 (14.1)	8 (6–16)
≥50%	48 (15.3)	27 (8.3)	15 (9–50)
Point Reduction in CGI-S Score From Baseline to Endpoint			
≥1	197 (62.7)	133 (40.8)	5 (4–7)
≥2	90 (28.7)	44 (13.5)	7 (5–12)
≥3	20 (6.4)	4 (1.2)	20 (13–46)
CGI-S Score at Endpoint			
≤2	18 (5.7)	6 (1.8)	26 (15–107)
≤3	90 (28.7)	48 (14.7)	8 (5–14)

Abbreviations: CI, confidence interval; CGI-S, Clinical Global Impression–Severity; mITT, modified intent-to-treat; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale.

Table 3 NNH Based on TEAE (Safety Population)

Event	Xanomeline/trospium (n=340), n (%)	Placebo (n=343), n (%)	NNH (95% CI)
Trial drug discontinuation due to a TEAE	19 (5.6)	16 (4.7)	109 (ns)
Trial drug discontinuation due to a TEAE of nausea, dyspepsia, or vomiting	7 (2.1)	0	49 (28–182)
Dose reduction due to a TEAE	8 (2.4)	1 (0.3)	49 (27–284)
Dose reduction due to a TEAE of nausea, dyspepsia, or vomiting	2 (0.6)	0	170 (ns)
TEAE occurring in ≥5% of participants:			
Nausea	63 (18.5)	13 (3.8)	7 (6–10)
Constipation	58 (17.1)	21 (6.1)	10 (7–17)
Dyspepsia	52 (15.3)	16 (4.7)	10 (7–17)
Vomiting	46 (13.5)	6 (1.7)	9 (7–13)
Headache	37 (10.9)	35 (10.2)	148 (ns)
Hypertension	21 (6.2)	4 (1.2)	20 (13–46)
Dry mouth	17 (5.0)	5 (1.5)	29 (17–111)

Abbreviations: CI, confidence interval; NNH, number needed to harm; ns, not significant; TEAE, treatment-emergent adverse event.

Table 4 NNH Based on Shift in QTc Interval, Weight, Metabolic Variables, and Prolactin (Safety Population)

Variable	Xanomeline/trospium, n/N (%)	Placebo, n/N (%)	NNH (95% CI)
Shifts of ECG QTc interval at any time from <450 msec to ≥450 msec	1/314 (0.3)	0/315	314 (ns)
Weight gain of ≥7% from baseline at LOCF endpoint	14/269 (5.2)	31/278 (11.2)	−17 (−10 to −72)
Total cholesterol at LOCF endpoint ≥240 mg/dL	27/279 (9.7)	29/296 (9.8)	−835 (ns)
Fasting glucose at LOCF endpoint ≥126 mg/dL	11/280 (3.9)	11/297 (3.7)	445 (ns)
Fasting triglyceride value at LOCF endpoint ≥200 mg/dL	15/279 (5.4)	16/295 (5.4)	−2111 (ns)
Plasma prolactin value at LOCF endpoint (males) ≥17 ng/mL ≥34 ng/mL	28/142 (19.7) 12/142 (8.5)	27/158 (17.1) 4/158 (2.5)	38 (ns) 17 (9 to 137)
Plasma prolactin value at LOCF endpoint (females) ≥25 ng/mL ≥50 ng/mL	15/58 (25.9) 6/58 (10.3)	13/47 (27.7) 7/47 (14.9)	−56 (ns) −22 (ns)

Abbreviations: CI, confidence interval; ECG, electrocardiogram; LOCF, last observation carried forward; NNH, number needed to harm; ns, not significant.

Table 5 Likelihood to Be Helped or Harmed

Event	NNH	NNT for Response[a]	LHH (NNH/NNT)
Trial drug discontinuation due to a TEAE	109	5	21.8
Trial drug discontinuation due to a TEAE of nausea, dyspepsia, or vomiting	49	5	9.8
Dose reduction due to a TEAE	49	5	9.8
Dose reduction due to a TEAE of nausea, dyspepsia, or vomiting	170	5	34.0
Weight gain ≥7%	−17	5	200

(Continued)

Table 5 (Continued).

Event	NNH	NNT for Response[a]	LHH (NNH/NNT)
TEAE			
Nausea	7	5	1.4
Constipation	10	5	2.0
Dyspepsia	10	5	2.0
Vomiting	9	5	1.8
Hypertension	20	5	4.0
Dry mouth	29	5	5.8
Somnolence/sedation	83	5	16.6
Akathisia	68	5	13.6
Tachycardia	38	5	7.6

Note: [a]Based on NNT for a ≥30% reduction from baseline in PANSS total score at endpoint.
Abbreviations: LHH, likelihood to be helped or harmed; NNH, number needed to harm; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale; TEAE, treatment-emergent adverse event.

a response is expected to occur more often than any single harm. Regarding discontinuations, the LHH estimate of 21.8 for trial drug discontinuation due to a TEAE suggests that a response is nearly 22× more likely to occur than a discontinuation due to a TEAE. The trend toward greater likelihood of a response vs TEAE remains, albeit to a lesser degree, when considering discontinuation due to a TEAE of nausea, dyspepsia, or vomiting (LHH=9.8). Among the most common TEAEs reported in the acute EMERGENT trials (listed in Table 3) and those of somnolence/sedation, akathisia, and tachycardia, nausea was the most likely to be encountered but was still less common than a response (LHH=1.4); somnolence/sedation was the least likely to occur (LHH=16.6). Weight gain was a highly uncommon event, approximately 200× less likely to occur than a treatment response.

Indirect Comparisons

Indirect comparisons of effect size indicate a NNT vs placebo for xanomeline/trospium that is comparable to, or more robust than, other oral, first-line, second-generation agents that are approved by the US Food and Drug Administration for schizophrenia and for which similar data are available (Figure 1). NNT estimates for currently available antipsychotics were calculated using data collected from the pivotal trials of each compound that informed product labeling.[20–29] In the published analyses, response was defined as ≥30% reduction from baseline in PANSS total score in the trials of xanomeline/trospium, asenapine, cariprazine, lumateperone, lurasidone, paliperidone, quetiapine extended release, and one of the three pivotal trials of ziprasidone, and as ≥30% reduction from baseline in PANSS total score or a CGI-S score of 1 or 2 for aripiprazole and brexpiprazole.[20–29] Although CIs overlap across agents, the NNT estimate of 5 places xanomeline/trospium within the lower range of values (ie, a more robust effect size) calculated for currently available antipsychotics (Figure 1).

A heat map for NNH for the outcomes often observed with antipsychotic use of weight gain ≥7%, somnolence/sedation, and akathisia for xanomeline/trospium and oral, first-line, second-generation antipsychotics vs placebo is shown in Table 6. NNH estimates calculated from placebo-controlled trials in adults with acutely exacerbated schizophrenia symptoms[20–29,31–34] were <10 for somnolence/sedation for lumateperone and quetiapine extended release and ≥7% for weight gain for olanzapine and quetiapine immediate release. In this indirect comparison, xanomeline/trospium was one of only three interventions, including aripiprazole and paliperidone, to exhibit a low risk (NNH ≥20) for all three of the outcomes in question. Xanomeline/trospium was the only agent that showed no difference from placebo in terms of weight gain ≥7%, and it displayed relatively high NNH estimates of 83 and 68 for somnolence/sedation and akathisia, respectively.
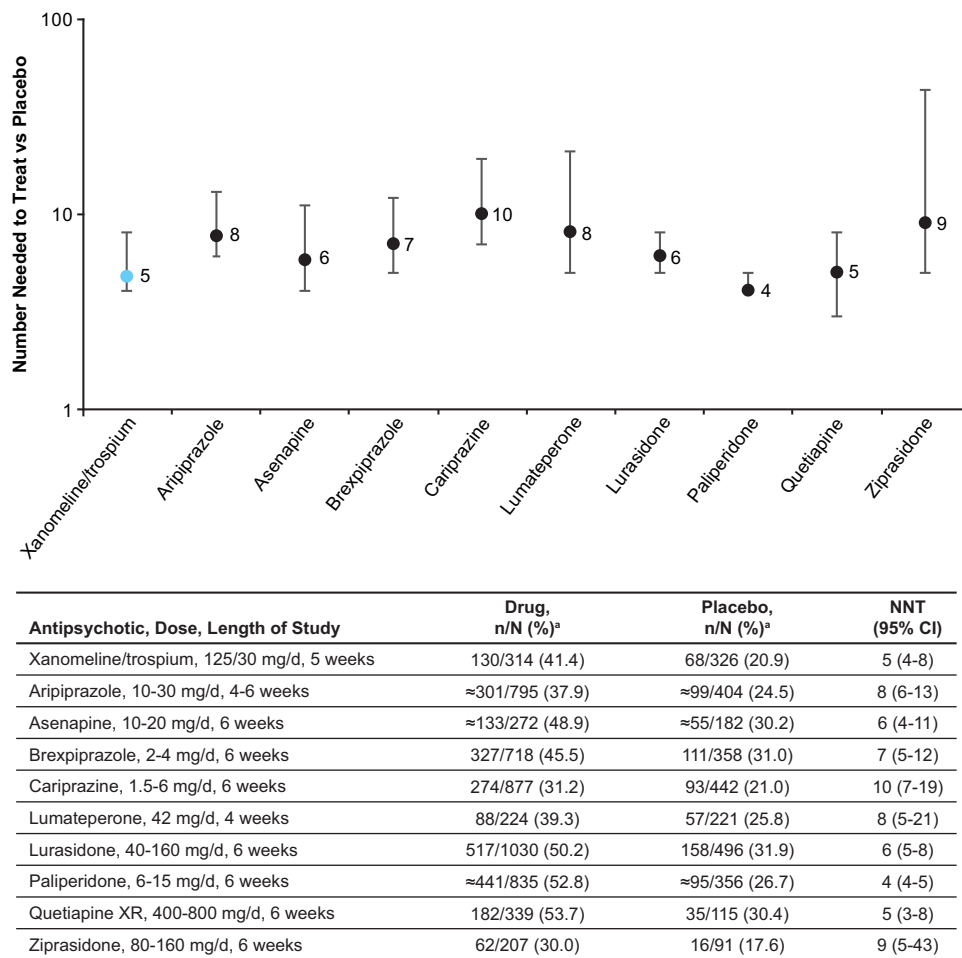
Figure 1 Indirect comparisons of efficacy vs placebo.

Notes: [a]Response defined as ≥30% reduction from baseline in PANSS total score (xanomeline/trospium, asenapine,[24,25] cariprazine,[21] lumateperone,[22] lurasidone,[26] paliperidone,[29] quetiapine XR,[28] and 1 of the 3 pivotal trials of ziprasidone)[23] and as ≥30% reduction from baseline in PANSS total score or a CGI-S score of 1 (very much improved) or 2 (much improved; aripiprazole,[27] brexpiprazole).[20] Data are not available for the pivotal trials of risperidone, olanzapine, quetiapine immediate release, or iloperidone. Figure adapted from Citrome L, Durgam S, Edwards JB, et al. Lumateperone for the treatment of schizophrenia: number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Clin Psychiatry*. 2023;84(2):22r14631.[30]

Abbreviations: CGI-S, Clinical Global Impression–Severity; CI, confidence interval; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale; XR, extended release.

Antipsychotic, Dose, Length of Study	Drug, n/N (%)[a]	Placebo, n/N (%)[a]	NNT (95% CI)
Xanomeline/trospium, 125/30 mg/d, 5 weeks	130/314 (41.4)	68/326 (20.9)	5 (4–8)
Aripiprazole, 10–30 mg/d, 4–6 weeks	≈301/795 (37.9)	≈99/404 (24.5)	8 (6–13)
Asenapine, 10–20 mg/d, 6 weeks	≈133/272 (48.9)	≈55/182 (30.2)	6 (4–11)
Brexipiprazole, 2–4 mg/d, 6 weeks	327/718 (45.5)	111/358 (31.0)	7 (5–12)
Cariprazine, 1.5–6 mg/d, 6 weeks	274/877 (31.2)	93/442 (21.0)	10 (7–19)
Lumateperone, 42 mg/d, 4 weeks	88/224 (39.3)	57/221 (25.8)	8 (5–21)
Lurasidone, 40–160 mg/d, 6 weeks	517/1030 (50.2)	158/496 (31.9)	6 (5–8)
Paliperidone, 6–15 mg/d, 6 weeks	≈441/835 (52.8)	≈95/356 (26.7)	4 (4–5)
Quetiapine XR, 400–800 mg/d, 6 weeks	182/339 (53.7)	35/115 (30.4)	5 (3–8)
Ziprasidone, 80–160 mg/d, 6 weeks	62/207 (30.0)	16/91 (17.6)	9 (5–43)

Discussion

The inferential statistics used in registrational clinical trials provide a method for distinguishing a probable outcome different from a chance finding but do not necessarily reflect the outcome's clinical relevance. The clinical relevance of a treatment outcome can be appraised using NNT and NNH effect sizes expressed in clinically intuitive "patient units" that provide measures of a therapy's relative advantages vs risks. Outside of the clinic, NNT and NNH are also of potential use to regulators assessing benefit: risk ratios during the drug approval process.[35] When interpreting these metrics, lower values represent a greater treatment benefit than higher values for NNT estimates for the outcome of a response vs placebo, and estimates of <10 are preferable.[12] NNH estimates ≥10 are generally preferred, although lower values may be acceptable for AEs that are mild or moderate, short-lived, do not result in treatment discontinuation, or do not pose a serious health risk.

Here, NNT estimates with xanomeline/trospium for most efficacy outcomes were <10, suggesting the efficacy demonstrated in the acute EMERGENT trials is clinically relevant. NNT was >10 for the efficacy outcomes of ≥50% reduction from baseline to Week 5 in PANSS total score, ≥3-point decrease from baseline to Week 5 in CGI-S score, and endpoint CGI-S score of ≤2, three outcomes that could be considered unusually robust for a 5-week clinical trial. Equally notable is the relative absence of side effects associated with currently available antipsychotics used to treat schizophrenia, such as weight gain/metabolic abnormalities, sedation/somnolence, akathisia, elevation in prolactin, or

Table 6 Heat Map of Indirect Comparisons of Acute Tolerability

	NNH		
	Weight Gain ≥7%	**Somnolence/Sedation**	**Akathisia**
Xanomeline/trospium	No difference	83	68
Aripiprazole	21	34	31
Asenapine sublingual	35	17	26
Brexpiprazole	17	50	112
Cariprazine (to 6 mg/d)	34	65	15
Iloperidone	10	16	No difference
Lumateperone	122	8	No difference
Lurasidone	67	11	11
Olanzapine	6	10	25
Paliperidone	35	42	40
Quetiapine immediate release	6	15	No difference
Quetiapine extended release	22	7	188
Risperidone (to 8 mg/d)	18	13	15
Ziprasidone	16	13	72

Notes: Red: higher risk (NNH <10). Yellow: intermediate risk (NNH 10–19). Green: lower risk (NNH ≥20).
Abbreviation: NNH, number needed to harm.

prolongation of the electrocardiogram QT interval, as quantified by the NNH estimates reported here. The most common AEs with xanomeline/trospium reported in the acute EMERGENT trials were primarily gastrointestinal, mild or moderate in intensity, and transient.[1–3] Gastrointestinal symptoms are a major factor in non-adherence with other types of medications and even moderate symptoms could potentially interfere with xanomeline/trospium adherence.[36] Here, two TEAEs, nausea and vomiting, had NNH estimates <10 in our analyses; however, the NNH for discontinuation due to a TEAE vs placebo was 109 (not significant) and the NNH for discontinuation due specifically to a TEAE of nausea, dyspepsia, or vomiting vs placebo remained high at 49, suggesting the TEAEs that occurred were manageable or of low enough intensity so as not to interfere with treatment.

LHH is the ratio of NNT to NNH and provides a measure of the relative likelihood of encountering a therapeutic benefit versus an undesirable event or harm. Xanomeline/trospium LHH estimates were >1 for all outcomes measured, meaning that a therapeutic benefit was more likely to be encountered than an adverse outcome. LHH estimates for individual TEAEs range from 1.4 for nausea, one of the most common TEAEs observed in the clinical trials, to 16.6 for somnolence/sedation, a common and bothersome side effect of many available antipsychotics.[10,11] The LHH of 200 for clinically significant weight gain (≥7% body weight gain) provides a significant contrast with the relatively high risk of clinically significant weight gain associated with many second-generation antipsychotics.[10,11] Taken together, in the present analysis xanomeline/trospium demonstrates the dual attributes of treatment benefit and acceptable tolerability, which to date have been an area of considerable unmet need in schizophrenia. Most available antipsychotics rely on a similar mechanism of antagonism or partial agonism of dopamine D_2 receptors and, as a result, exhibit overlapping limitations in efficacy and safety. Xanomeline/trospium, in contrast, is a potent agonist of muscarinic M_1/M_4 receptors and exhibits no direct dopamine D_2 receptor activity.[37,38] The novel mechanism may underlie the advantageous benefit to risk profile observed here.

Using indirect comparisons, the xanomeline/trospium NNT estimate of 5 for response over placebo positions this agent among the more efficacious of oral, first-line, second-generation antipsychotics. These findings parallel efficacy analyses based on treatment effect size using standardized mean difference for the continuous measures: in clinical trials,

the PANSS total score effect size of 0.65 (in standard deviation units) for xanomeline/trospium compares favorably to the median effect size of 0.42 reported in a meta-analysis of 32 antipsychotics.[10,39] Additionally, xanomeline/trospium demonstrated improved tolerability vs the comparators. Tolerability is a major concern in schizophrenia treatment, and side effects contribute to a medication non-adherence rate of approximately 50%.[40,41] Among the most common side effects is weight gain, and approximately half of individuals using antipsychotics are considered overweight/obese.[42] Weight gain is a source of reduced quality of life and places people treated with antipsychotics at increased risk of cardiovascular morbidity and mortality.[43,44] Somnolence/sedation is another side effect observed with nearly all anti-psychotics and may impair social and work-related functioning.[10,11] Motor side effects are reported by approximately 22% of people treated with second generation antipsychotics,[45] may become both serious and chronic, and contribute to poor health outcomes.[46–48] In the present analysis, xanomeline/trospium is the only treatment that does not differ from placebo in terms of NNH for ≥7% weight gain and has the highest NNH estimate for somnolence and/or sedation in comparison with available second-generation antipsychotics. While the risk of akathisia with xanomeline/trospium was greater than placebo, the NNH estimate of 68 suggests this risk is low. Overall, the combination of a favorable efficacy profile and low side effect risk distinguishes xanomeline/trospium from comparator agents in these indirect analyses.

This study has several limitations. First, as is necessary in calculating NNT and NNH, the results reported here are restricted to dichotomous outcomes, with the inherent loss of precision that could otherwise be retained with the use of effect size measures such as Cohen's *d* for continuous variables. Second, the short duration of the clinical trials prevents examination of NNH for AEs that may manifest after prolonged treatment. Third, the applicability of these results beyond the research environment is uncertain; individuals living with schizophrenia in the general population typically differ from those individuals who meet the strict inclusion and exclusion criteria for participation in clinical trials; also, participants discontinue clinical trials for myriad and complex reasons and as such the NNH estimates of discontinuation due to AEs may not accurately reflect tolerability in a clinical setting. Moreover, this trial enrolled participants from the United States and Ukraine, which may limit the generalizability of the current findings in other countries. However, recent analyses demonstrated persistent efficacy of xanomeline/trospium across a broad range of demographic and baseline subgroups in the EMERGENT trials.[39] In addition, NNH and NNT estimates should be interpreted in the context of the underlying percentages because similar estimates may derive from quite different clinical scenarios. For example, a NNT estimate of 10 may result from comparing responder rates of 80% vs 90% or 10% vs 20%. Lastly, indirect comparisons of NNT, NNH, and LHH with other antipsychotics must be regarded with caution due to differences in study design, including trial population characteristics and treatment dosing and duration, as well as when the studies were conducted. Trials of several of the agents included in our analyses employed 6- or 4-week treatment periods as opposed to the 5 weeks used in the EMERGENT clinical program.

Conclusion

Xanomeline/trospium is an efficacious agent for the treatment of schizophrenia with an effect size vs placebo comparable to, or in some instances more robust than, currently available antipsychotics. The favorable safety profile is particularly noteworthy in that xanomeline/trospium exhibits a low risk for motor adverse effects and has the least likelihood to be associated with weight gain or somnolence/sedation among other first-line agents FDA approved for the treatment of schizophrenia.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, LC, upon reasonable request.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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