National Academies Workshop
Novel Target in Mood Disorders and Psychosis

M1/M4 Muscarinic Targets for Psychotic Disorders

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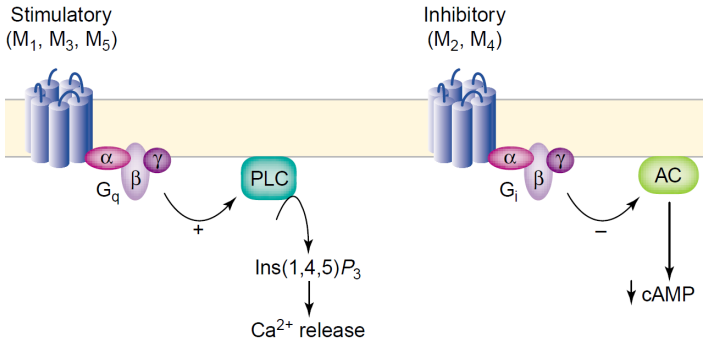
SCHOOL OF **MEDICINE**

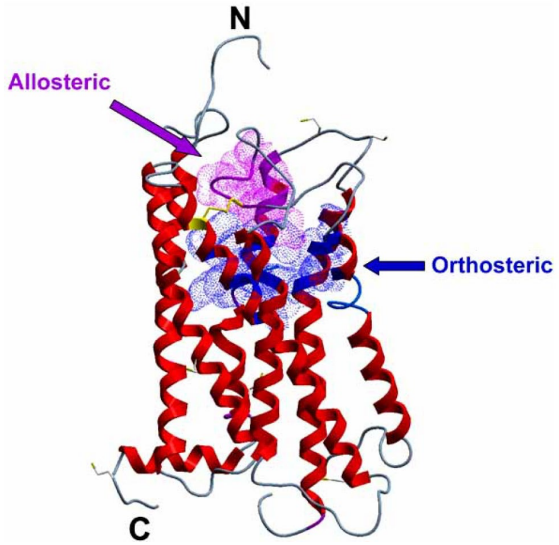
Disclosures

- Chief Clinical Advisor; Chair, Scientific Advisory Board – Karuna Therapeutics
- Consultant – BioXcel Therapeutics
- Clinical Advisor – Perception Neuroscience

Muscarinic Receptors

- Two different types of acetylcholine receptors
  - Nicotinic: ion channel-linked
  - Muscarinic: G-protein-coupled
- 5 different subtypes of muscarinic receptors
- All 5 show significant expression in brain
- M1-4 expressed in peripheral tissue
- M1 and M4 implicated in neuropsychiatric disorders

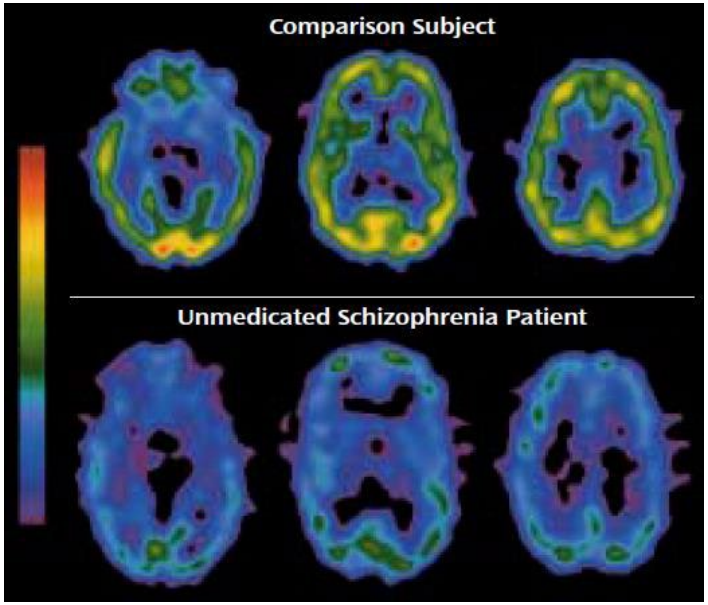




Multiple Lines Of Evidence Point To M1/M4 As Potential Targets For Schizophrenia

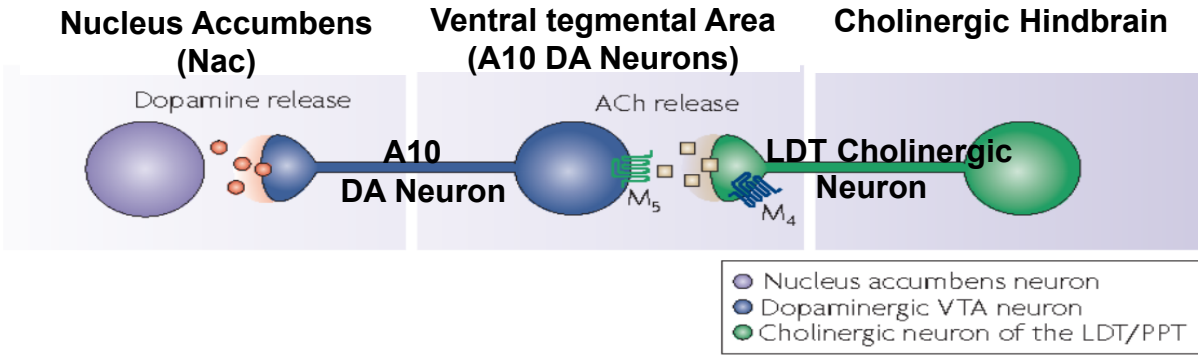
Rationale

- Antagonist (scopolamine) produces cognitive deficit, hallucinations and delusions[1]
- M1/M4 agonists demonstrated efficacy in animal models of psychosis and cognition[2]
- M1/M4 knockout mice indicate the role of the receptors is cognition and psychosis[3]
- Decreased M1/M4 expression in postmortem studies[4]
- SPECT imaging showed decreased muscarinic availability in schizophrenia[5]

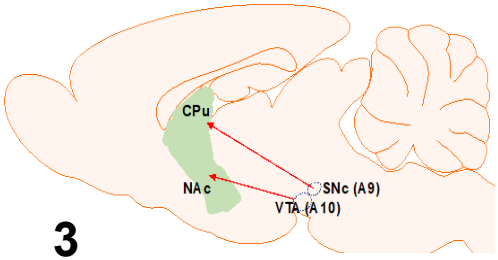


1. Ellis et al., *Int. J. Neuropsychopharm.* (2006) 9, 175.
2. Brady et al., *JPET* (2008) 327, 941.
3. Wess et al., *Nat Rev Drug Disc* (2007) 6, 721.
4. Dean et al., *Mol Psych (*1996) 1, 54.
5. Weinberger et al., *Am J Psych* (2003) 160, 118

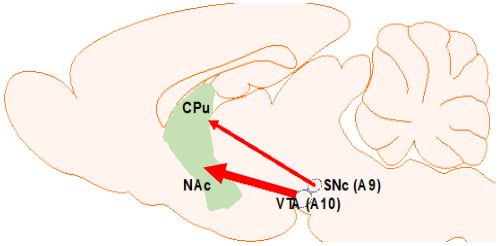
M_4 Auto-receptor Agonism Selectively Modulates A10 VTA Meso-Limbic DA Neurons and not Motoric A9 Tracks



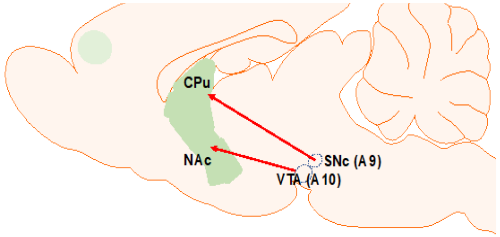
1 **Basal State**



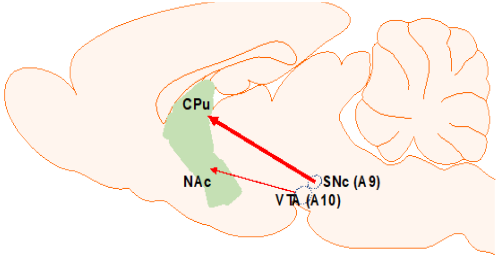
2 **Psychosis**

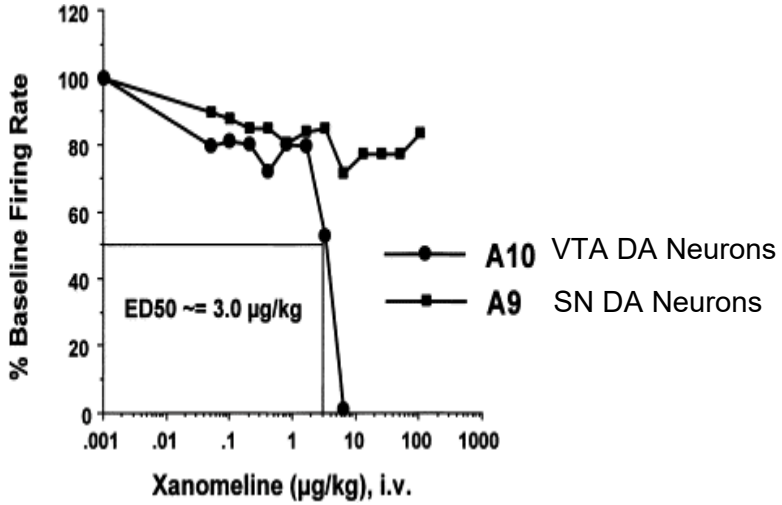


3 **Conventional Antipsychotics**



4 **M_4 Agonism**





[1] Shannon et al. 2000, Schizophre Res 42: 249-59; [2] White and Yang 1983, Life Sci 32: 983-93. [3] Valenti et al. 2011, J Neuro 31: 123330-8; [4] Hand et al. 1987, Brain Res 415: 257-69

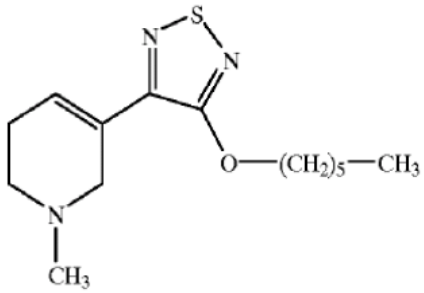
Muscarinic Receptor Compounds in Development

- Karuna M1/M4 preferencing agonist (KarXT – xanomeline-trospium) – Phase 3 for schizophrenia
- Cerevel M4 PAM (CVL-231) - Phase 1B for schizophrenia
- Acadia M1 PAM (Acadia-319) – Phase 1
- Sosei Group re-acquired muscarinic agonist platform from Abbvie (M1, M4, M1/4)
- Lundbeck M4 PAM

Xanomeline: An M1/M4-Preferring Agonist

Xanomeline

- M_1/M_4 preferring agonist developed by Eli Lilly
- Efficacy in human trials for psychotic & cognitive symptoms of AD and total symptoms of SZ
- Efficacy in 12 animal models (3 different species) of schizophrenia[1-5]
- Licensed from Lilly to Karuna



Receptor	EC50 (nM)[6]
M_1	7.6
M_2	125
M_3	67
M_4	20
M_5	508

1. Shannon et al. Schizophrenia Research (2000) 42: 249–259.
2. Stanhope et al. JPET (2001) 299: 782–792.
3. Mirza et al. CNS Drug Reviews (2003) 9: 159-186.
4. Thompson et al. Psychopharmacology (2010) 208: 401–416.
5. Berak et al. Int J Neuropsychopharmacol. (2011) Jan 7:1-14.
6. NIMH Psychoactive Drug Screening Program

Early Evidence of Xanomeline Antipsychotic Efficacy

- **Alzheimer's Disease**

Phase 2, 6-month, multi-dose, placebo-controlled trial of xanomeline (N=343)

– Dose-dependent, significant improvement in psychotic symptoms *(Bodick et al Arch of Neurology, 1997)*

- **Schizophrenia**

Exploratory, 4-week double-blind placebo-controlled trial in treatment refractory patients (N=20)

– Significant effects on PANSS total, BPRS total scores and cognitive tests *(Shekhar et al Am J Psychiatry, 2008)*

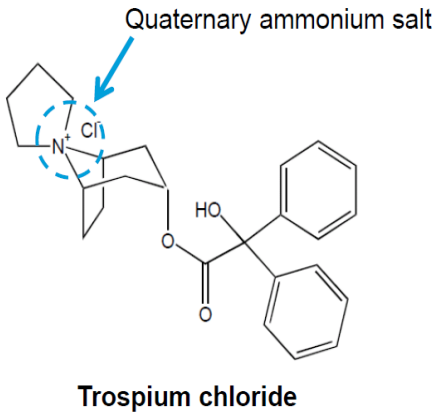
- **Safety/Tolerability**

In both studies, high rates of pro-cholinergic side effects – nausea, vomiting, diaphoresis, diarrhea - led to the discontinuation of development of xanomeline as a single agent

Trospium Chloride:
A Peripherally Restricted Pan-Muscarinic Antagonist

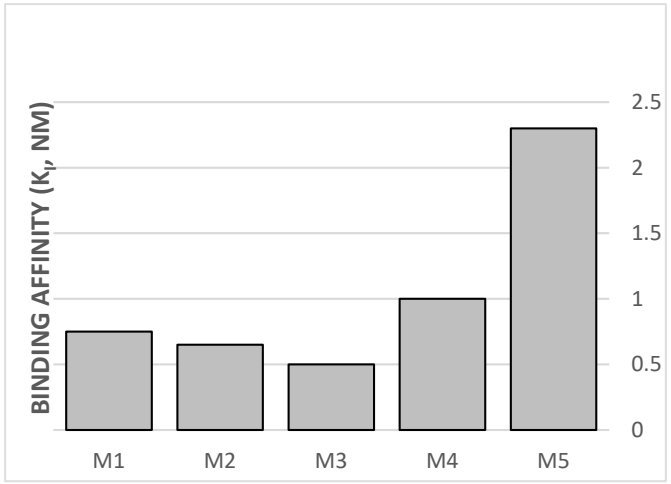
Trospium chloride

- Approved for OAB and off patent
- Minimal/no CNS penetration
- Majority of compound excreted as unchanged parent compound
- Insignificant activity at cytochrome P450s (xanomeline is metabolized in the liver)
- Side effects limited to anticholinergic effects (5-10% constipation and dry mouth)
- 18.5 hr plasma half-life leads to favorable PK profile for combination product



Trospium chloride

Trospium M1-5 receptor binding affinity



1. Hedges SS, *Br J Pharmacology* 2006
2. Napier CM, Gupta P, *Neurourol Urondyn,* 2002
3. Sanctura label

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia

Stephen K. Brannan, M.D., Sharon Sawchak, R.N., Andrew C. Miller, Ph.D., Jeffrey A. Lieberman, M.D., Steven M. Paul, M.D., and Alan Breier, M.D.

ABSTRACT

BACKGROUND

The muscarinic receptor agonist xanomeline has antipsychotic properties and is devoid of dopamine receptor–blocking activity but causes cholinergic adverse events. Trospium is a peripherally restricted muscarinic receptor antagonist that reduces peripheral cholinergic effects of xanomeline. The efficacy and safety of combined xanomeline and trospium in patients with schizophrenia are unknown.

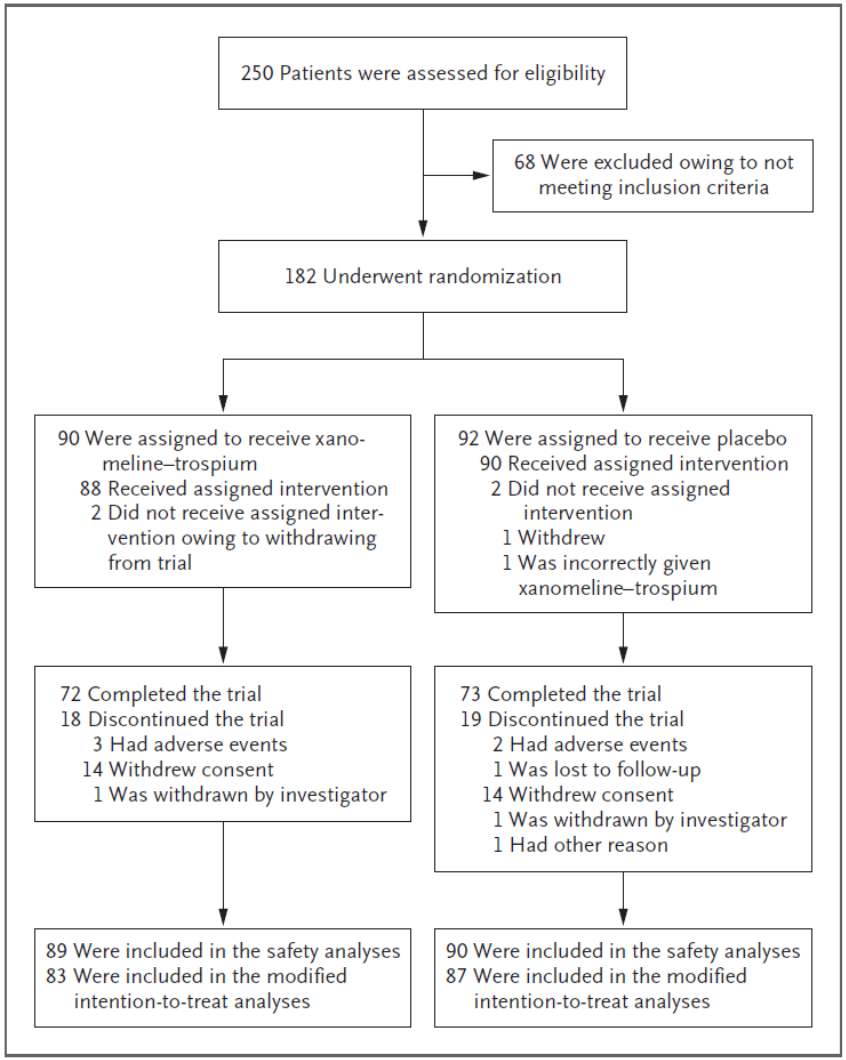
METHODS

In this double-blind, phase 2 trial, we randomly assigned patients with schizophrenia in a 1:1 ratio to receive twice-daily xanomeline–trospium (increased to a maximum of 125 mg of xanomeline and 30 mg of trospium per dose) or placebo

From Karuna Therapeutics, Boston (S.K.B., S.S., A.C.M., S.M.P.); Columbia University Vagelos College of Physicians and Surgeons, New York (J.A.L.); and Indiana University School of Medicine, Indianapolis (A.B.). Address reprint requests to Dr. Paul at Karuna Therapeutics, 33 Arch St., Suite 3110, Boston, MA 02110, or at steve@karunatx.com.

N Engl J Med 2021;384:717-26.
DOI: 10.1056/NEJMoa2017015

Consort Diagram: Patient Flow



SK Brannan et al., *N Engl J Med* 2021;384:717-726.

Characteristics of the Patients at Baseline (ITT Population)

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Xanomeline–Trospium (N=90)	Placebo (N=92)
Age — yr	43.4±10.1	41.6±10.1
Male sex — no. (%)	72 (80)	68 (74)
Race — no. (%)†		
Black	67 (74)	70 (76)
White	20 (22)	17 (18)
Other	3 (3)	5 (5)
Non-Hispanic or non-Latino ethnic group — no. (%)†	71 (79)	79 (86)
Body-mass index‡	28.1±5.0	29.6±5.4
PANSS score§		
Total	97.7±9.7	96.6±8.3
Positive symptom subscore	26.4±3.4	26.3±3.2
Negative symptom subscore	22.6±4.4	22.8±4.6
Marder negative symptom subscore	22.3±4.7	22.3±5.0
Score on the CGI-S scale¶	5.0±0.6	4.9±0.6

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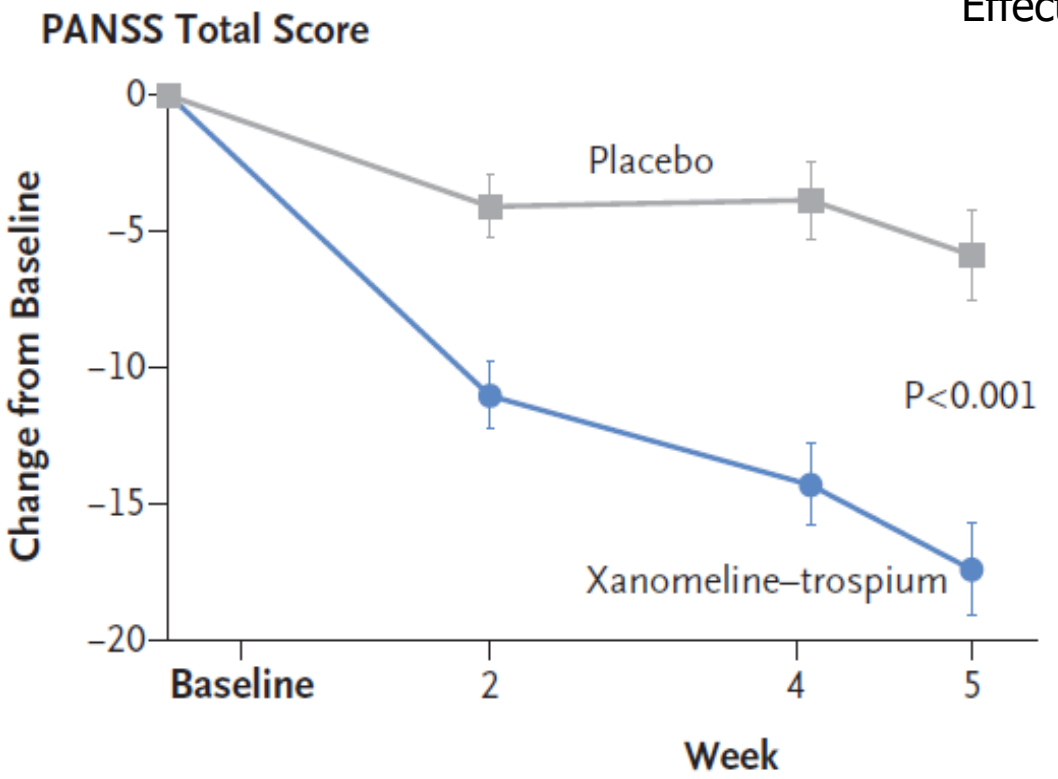
Primary Efficacy End Point

Effect Size = 0.75



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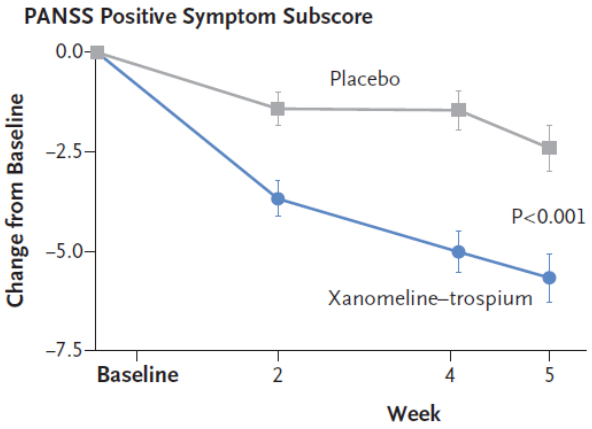
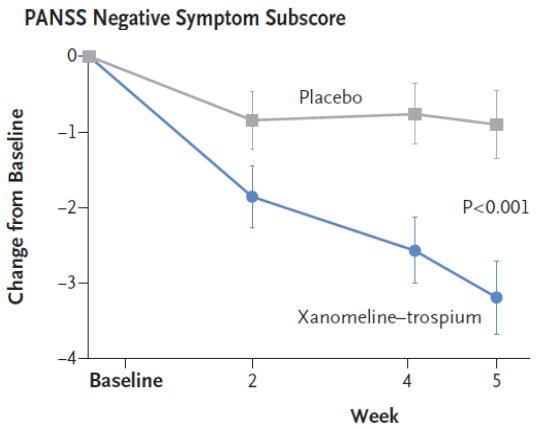
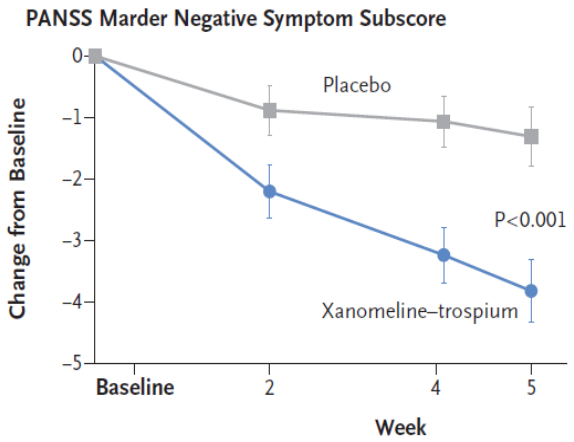
Secondary Efficacy End points: PANSS subscales







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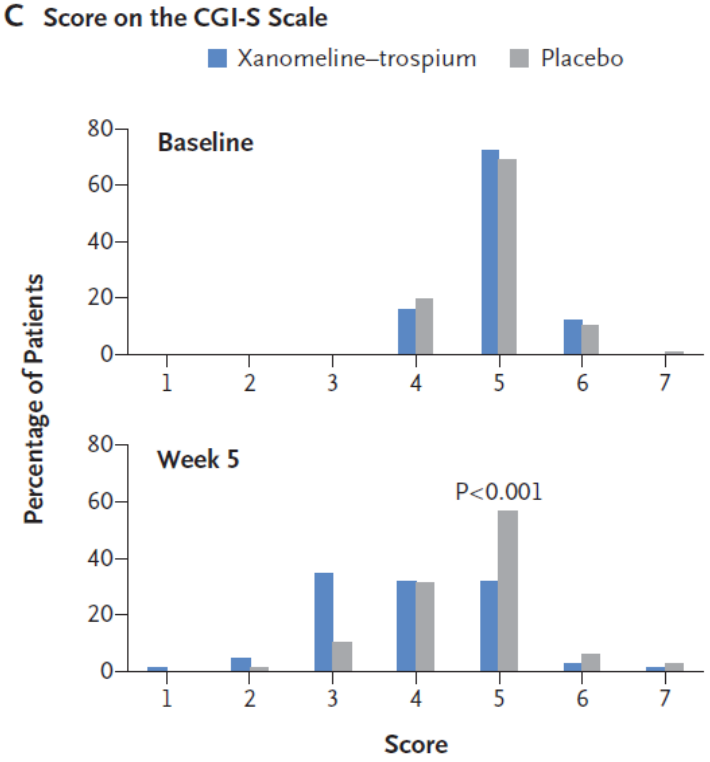
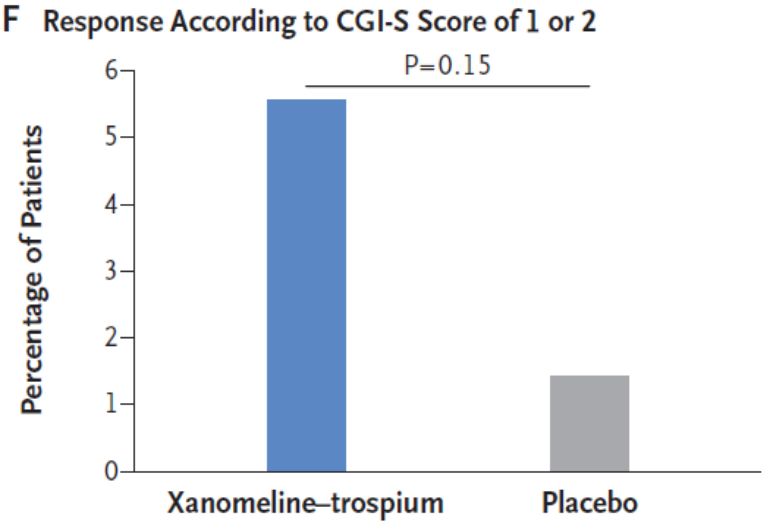
Secondary Efficacy End Points:
CGI-S[1] frequency counts and responder analysis at week 5





[1]CGI-S scoring: 1 = normal, no illness; 7 = extremely ill

SK Brannan et al., *N Engl J Med* 2021;384:717-726.

Effects on Cognition

Exploratory End Point

- Exploratory endpoint analyses show non-significant results in cognition for xanomeline-trospium relative to placebo (Figure 1).
- *Post-hoc* subgroup analysis of composite scores stratified by baseline impairment (Figure 2)

Fig. 1 Cognitive results*

Cognitive test	Statistic (X-T vs. placebo)	Value
Composite Score	**p-value**	**0.11**
	Cohen's d	**0.24**
Detection	p-value	0.07
	Cohen's d	0.28
Pediatric Groton Maze Learning	p-value	0.47
	Cohen's d	0.11
Identification	p-value	0.40
	Cohen's d	0.13
International Shopping List	p-value	0.35
	Cohen's d	0.14
One-Back Speed	p-value	0.35
	Cohen's d	0.16
One-Back Accuracy	p-value	0.92
	Cohen's d	-0.02

Fig. 2 Composite score analysis stratification by baseline impairment

Statistic (X-T vs. placebo)	Impairment Median Split		Impairment Tertile Split*		
	High	Low	Highest	Middle	Lowest
p-value	0.03	0.53	0.02	0.52	0.87
Cohen's d	0.56	0.13	0.83	0.19	0.04

*Data presented at 33rd ECNP Congress (Sept. 12 – 15, 2020)

Adverse Events (Safety Population)

Variable	Xanomeline–Trospium (N=89)	Placebo (N=90)
Any adverse event — no (%)	48 (54)	39 (43)
Serious adverse event — no. (%)†	1 (1)	0
Severe adverse event — no. (%)‡	1 (1)	1 (1)
Adverse event leading to discontinuation of the active drug or placebo — no. (%)	2 (2)	2 (2)
Adverse events occurring in ≥2% of the patients in the xanomeline–trospium group — no. (%)		
Constipation	15 (17)	3 (3)
Nausea	15 (17)	4 (4)
Dry mouth	8 (9)	1 (1)
Dyspepsia	8 (9)	4 (4)
Vomiting	8 (9)	4 (4)
Headache	6 (7)	5 (6)
Somnolence	5 (6)	4 (4)
Akathisia	3 (3)	0
Dizziness	3 (3)	3 (3)
Increased weight	3 (3)	4 (4)
Tachycardia	3 (3)	2 (2)
Sedation	2 (2)	2 (2)
Diarrhea	2 (2)	4 (4)
Increased γ-glutamyltransferase level	2 (2)	0
Agitation	2 (2)	1 (1)
Insomnia	2 (2)	2 (2)
Decreased appetite	2 (2)	0
Hyperhidrosis	2 (2)	1 (1)
Mean change from baseline in body weight at wk 5 — kg	1.5±2.8	1.1±3.5
Mean change from baseline in score on Simpson–Angus Scale at wk 5§	−0.1±0.7	−0.1±0.8
Mean change from baseline in score on Barnes Akathisia Rating Scale at wk 5¶	−0.1±1.0	0.0±0.7

SK Brannan et al., *N Engl J Med* 2021;384:717-726.

Summary

- Xanomeline is a M1/M4 preferencing agonist with early evidence of antipsychotic efficacy, but high levels of pro-cholinergic adverse events
- In a phase 2 trial, xanomeline–trospium demonstrated:
  - Significant antipsychotic efficacy (PANSS total score: effect size 0.75)
  - Improved safety profile, lower rates of cholinergic adverse events, all rated mild/moderate:
    – Most common AEs were pro/anticholinergics: Nausea 17%, constipation 17%
  - Overall, well tolerated – AEs related study discontinuations: xanomeline-trospium N=2, placebo N=2

<u>Key Questions</u>:

- Are both M1 and M4 receptor agonism required for efficacy?
- Are non-dopaminergic downstream pathways also important for efficacy?
- Will phase 2 results be replicated in phase 3? Those studies are underway.
- Will cognitive enhancement be demonstrated in prospective trials with baseline stratification for high cognitive test scores?

Acknowledgments

- Stephen K. Brannan
- Steven M. Paul
- Andrew C. Miller
- Sharon Sawchak
- Jeffrey A. Lieberman
- Korie Handwerger
- Sara Kavanagh

Funding sources: Karuna Therapeutics, Wellcome Trust (phase 1 studies)