cerevel

CVL-231

A Novel Positive Allosteric Modulator of the Cholinergic M4 Receptor for the Treatment of Schizophrenia

SIRS 2021 Pharmaceutical Pipeline Session
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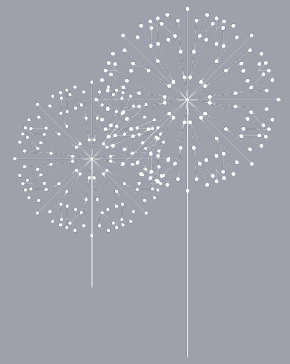
Disclosures

I am an employee of Cerevel Therapeutics, LLC.



Cerevel's M4 PAM is a Potential Next Generation Antipsychotic

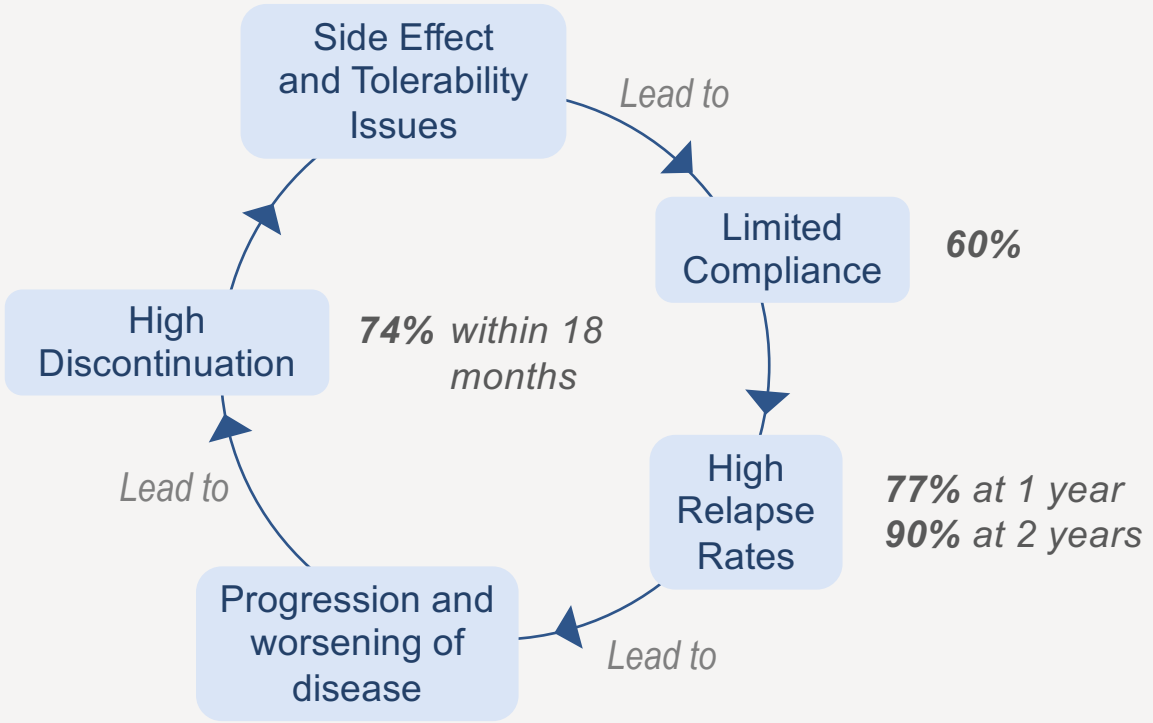
Opportunity for Innovation in Schizophrenia

- Current Standard of Care Uses Same Mechanism of Action (MOA) as Therapies from the 1950s
- Large Patient Population:
  - ~21 M Patients Worldwide
  - 2.7 million Americans had schizophrenia in 2017 *(0.5% -1.0% of U.S. population)*

Potential New Standard of Care

- First in Class Therapy with Novel MOA
- M4 Selective
- Targeted Muscarinic Activity
- Improved Tolerability

Significant Need for New Treatment Option



Debilitating side effects of atypicals often lead to discontinuation and relapse, driving a vicious cycle of disease progression

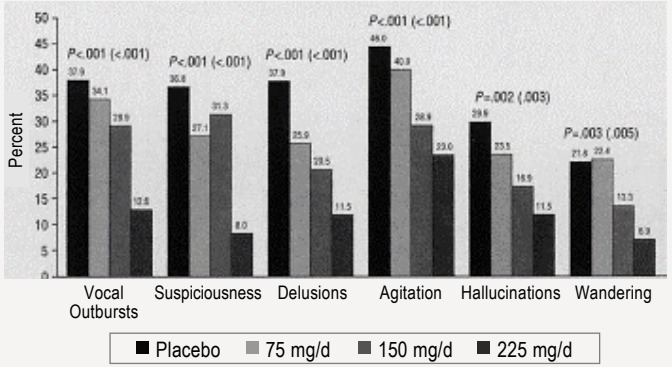
Source: World Health Organization, DRG Market Research

Xanomeline Clinical Data:
Compelling Activity, Limited by Side Effect Profile

Xanomeline (Non-selective M1/M4 Preferring Agonist) Impacted Symptoms…

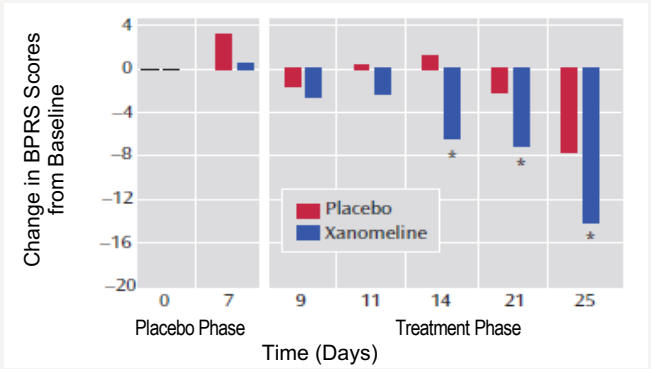
1997 Phase 2 in Alzheimer's Disease

Statistically significant impact on agitation and other psychosis-related endpoints in Alzheimer's patients[2]



2008 Phase 2 in Schizophrenia

Statistically significant impact on total BPRS and PANSS scores in schizophrenia patients[1]



…But Development Was Limited by GI Side Effects

Adverse Events

Event	Placebo (n=87)	Dose† Low (n=85)	Dose† Medium (n=83)	Dose† High (n=87)	Total (N=342)	P‡
Sweating	4 (4.6)	12 (14.1)	38 (45.8)	66 (75.9)	120 (35.1)	<.001
Nausea	17 (19.5)	24 (28.2)	29 (34.9)	45 (51.7)	115 (33.6)	<.001
Vomiting	8 (9.2)	11 (12.9)	33 (39.8)	37 (42.5)	89 (26.0)	<.001
Dyspepsia	7 (8.0)	20 (23.5)	23 (27.7)	21 (24.1)	71 (20.8)	.007
Chills	1 (1.1)	8 (9.4)	22 (26.5)	32 (36.8)	63 (18.4)	<.001
Chest Pain	1 (1.1)	5 (5.9)	13 (15.7)	10 (11.5)	29 (8.5)	.004
Increased salivation	0 (0)	2 (2.4)	6 (7.2)	21 (24.1)	29 (8.5)	<.001
Syncope	4 (4.6)	3 (3.5)	11 (13.3)	11 (12.6)	29 (8.5)	.03
Fecal incontinence	0 (0)	4 (4.7)	1 (1.2)	6 (6.9)	11 (3.2)	.04
Nausea and vomiting	2 (2.3)	0 (0)	1 (1.2)	7 (8.0)	10 (2.9)	.009
Dysphagia	1 (1.1)	0 (0)	2 (2.4)	6 (6.9)	9 (2.6)	.03

Xanomeline's high rate of nausea, vomiting and dyspepsia is likely driven by non-selective muscarinic agonism

* Only events statistically significant at P< .05 are given. Values are number (percentage) of patients unless otherwise indicated.
† Low-dose group received 25 mg of xanomeline tartrate 3 times a day; medium, 50 mg 3 times a day; high, 75 mg 3 times a day.
‡ Pearson χ^2 test.

These studies as well as a convergence of preclinical evidence that M4 activation showed antipsychotic potential provided the impetus for initiating a selective M4 receptor program (originally at Pfizer)

Source: 1. Shekhar et al. Am J Psychiatry, Vol 165, Aug 2008. N=20. 2 active and 3 placebo-arm patients discontinued the study, none due to adverse events.
2. Bodick et al. Arch Neurol, Vol 54, Apr 1997. N = 343. 52% of patients in high-dose arm discontinued treatment due to adverse events.

M4 Receptor Activation Reduces Dopamine in the Striatum

M4 auto-receptor activation prevents additional Ach release

Cholinergic Neuron

M4 Auto-Receptor

CVL-231 enhances M4 auto-receptor activation in the presence of Ach

CVL-231 (PAM)

Dopaminergic tone is reduced ***without*** direct antagonistic activity on post-synaptic dopamine receptors

Acetylcholine (Ach)

Dopamine

Nicotinic Receptors

Nucleus Accumbens

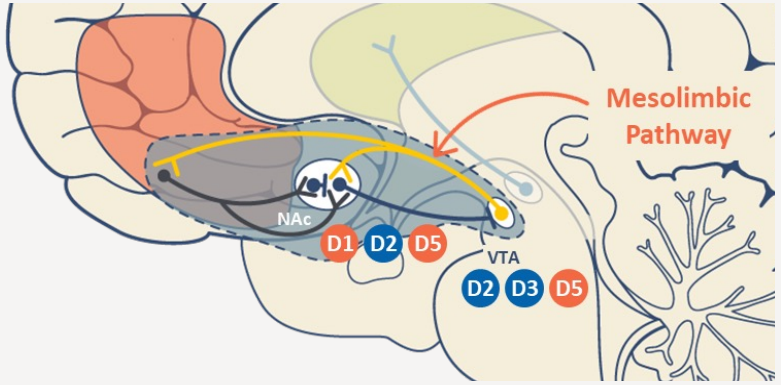
Dopamine Neuron

Originates from Ventral Tegmental Area (VTA)

In the absence of Ach, dopamine output decreases, which ***dampens hyperdopaminergic activity*** in striatum

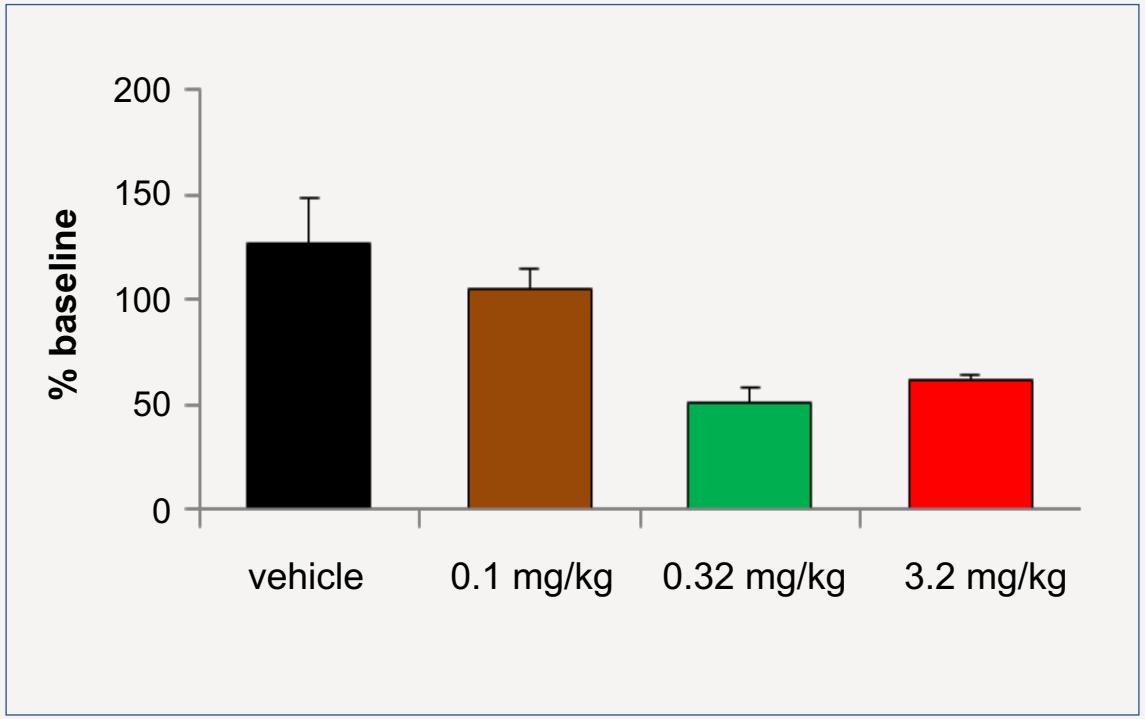
Decreased Psychosis

Schizophrenia symptoms driven by ***overactivity of the dopaminergic*** mesolimbic pathway

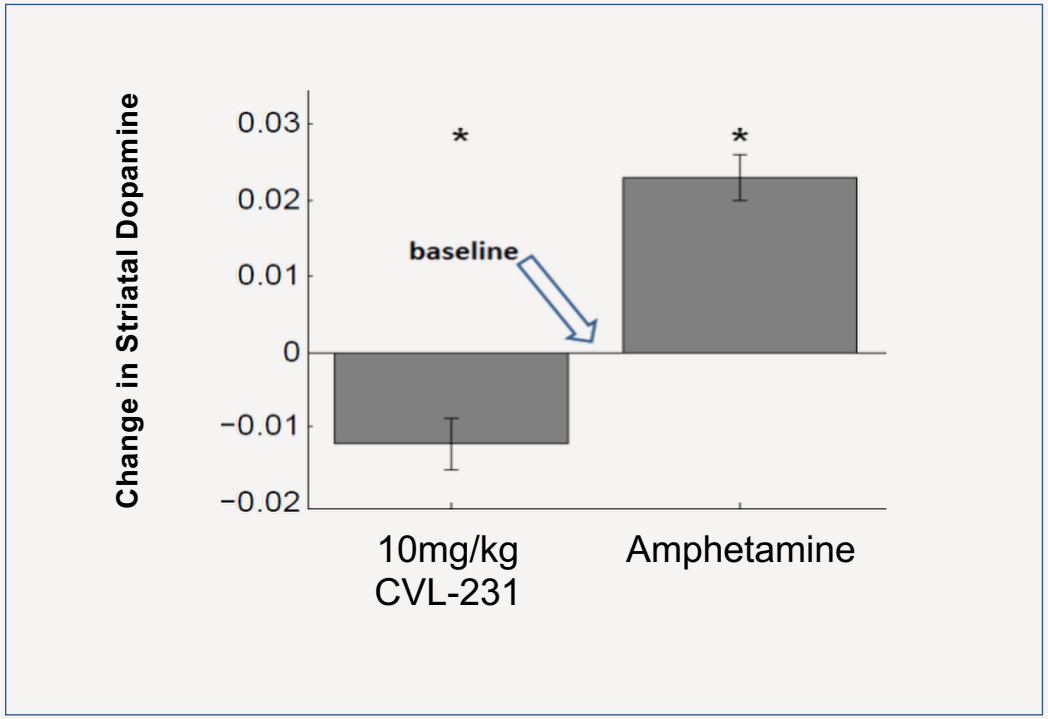


Rationale for Antipsychotic Activity Associated with CVL-231

CVL-231 Attenuates Striatal Ach Release from Cholinergic Interneurons

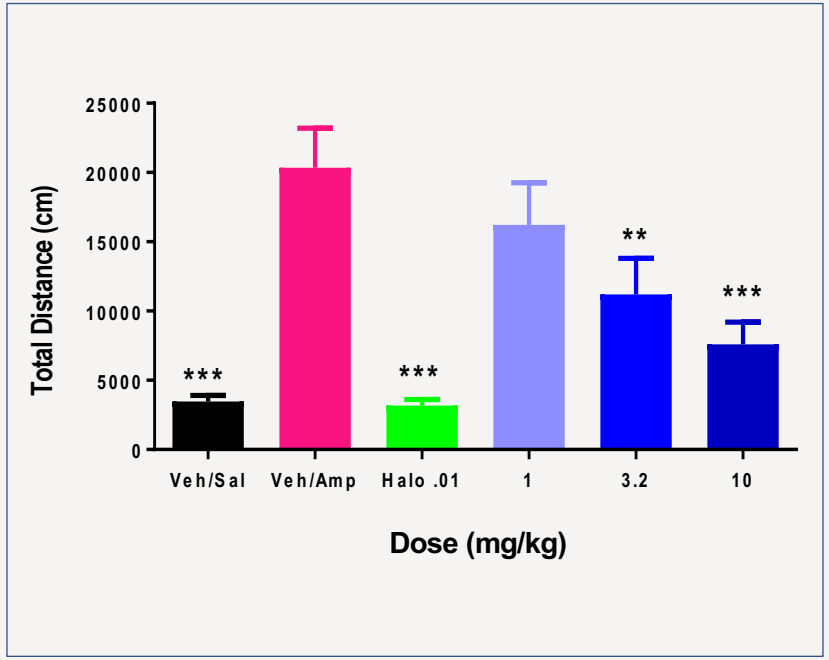


This Results in a Subsequent Attenuation of Striatal DA Release (Fiber photometry)

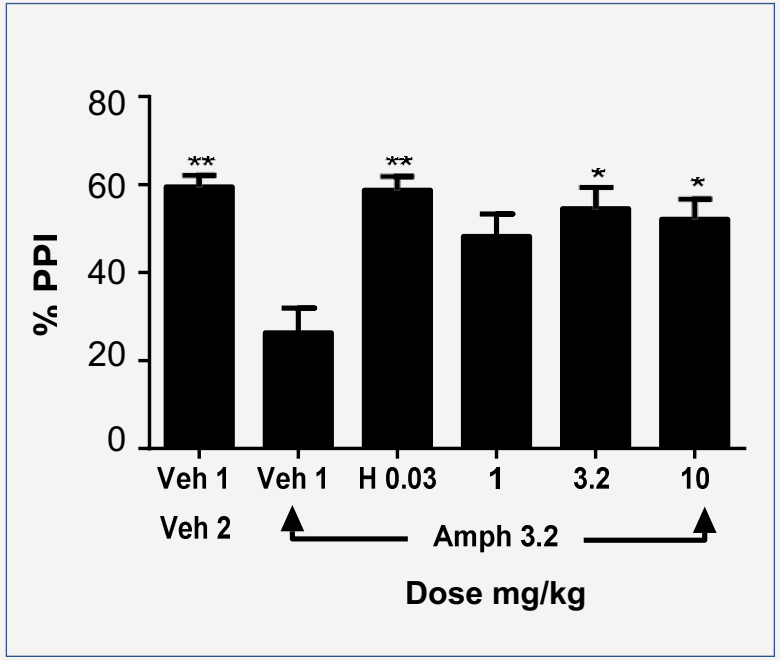


Rationale for Antipsychotic Activity Associated with CVL-231

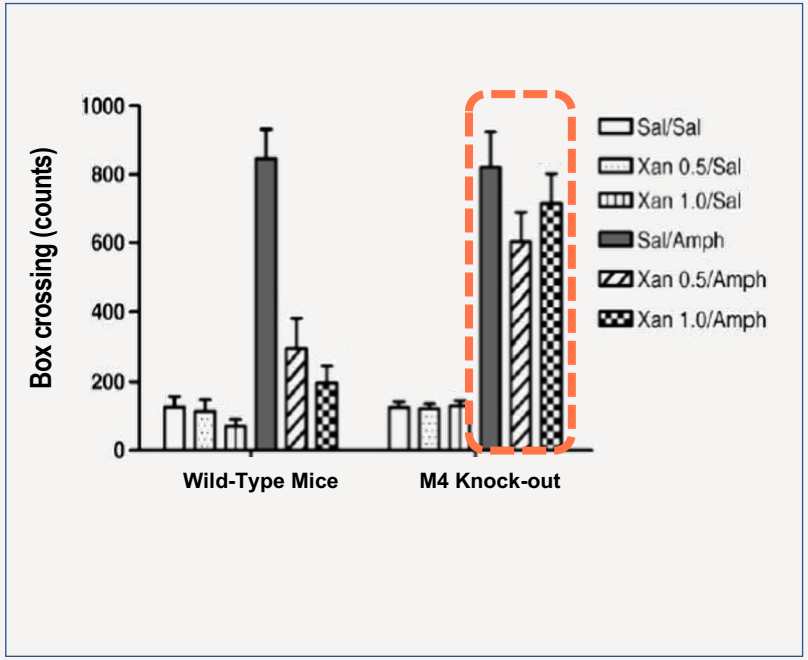
Reduction in DA translates into a reduction in Amphetamine stimulated locomotor activity



Reduction in DA translates into Antipsychotic Activity as evidenced in the Amphetamine-disrupted prepulse inhibition model



Xanomeline had no antipsychotic effect in M4 knock-out mice



Source: Woolley, et al. European Journal of Pharmacology 603 (2009)

CVL-231 Single Ascending Dose Trial Design

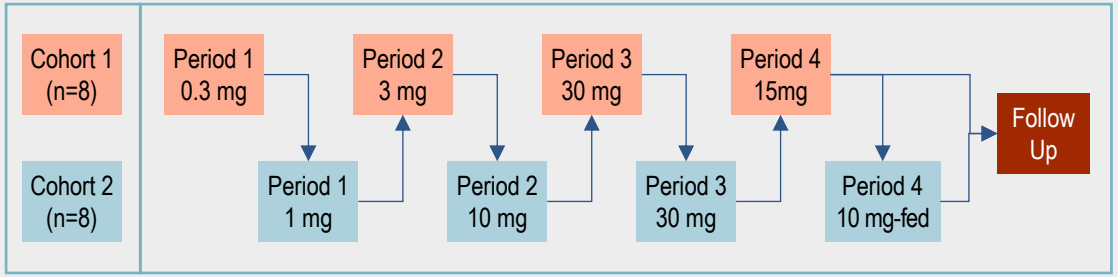
Methods

- A phase 1, randomized, double-blind, sponsor-open, placebo-controlled, first-in-human study to evaluate the safety, tolerability, and pharmacokinetics of single ascending oral doses of CVL-231 in healthy subjects was conducted. Single oral doses of CVL-231 (0.3-30 mg) were evaluated in the study, with a minimum 14 day washout between doses.
- Safety, tolerability and PK of CVL-231 were evaluated following single ascending oral doses in a double-blind (investigator and subject), sponsor-open, 4-period crossover trial in healthy volunteers (NCT03217604)
- Standard laboratory measures, ECGs, vital signs and treatment emergent adverse events (TEAEs) were monitored to evaluate the safety and tolerability of single doses of CVL-231

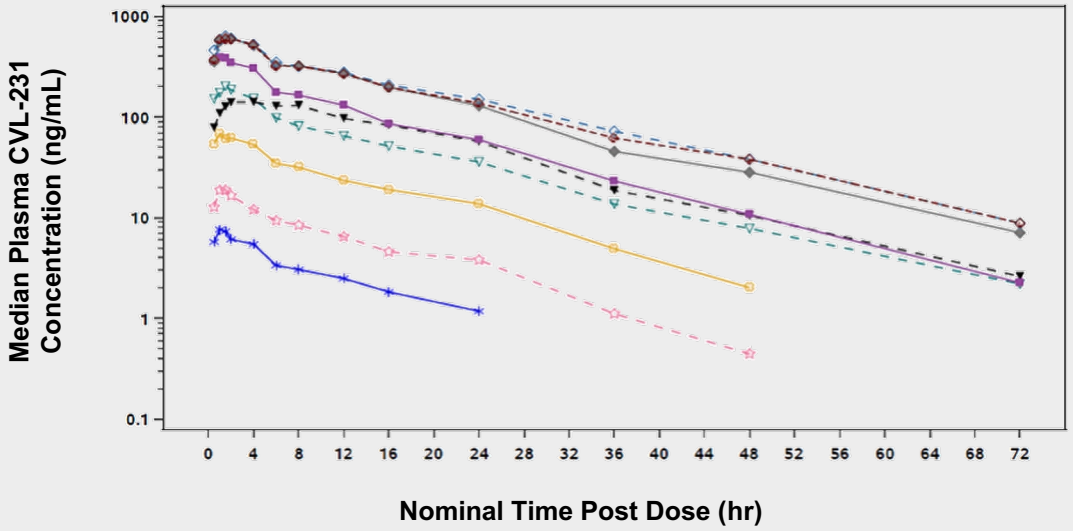
Demographic Characteristics *All subjects (N=17)*

Gender	**Male** 17	**Female** 0
Age (years)	**Mean (SD)** 37.71 (10.15)	**Range** 19-52
Race	**White** 16	**Not reported** 1
Weight (kg)	**Mean (SD)** 74.0 (10.76)	**Range** 56.0-91.0
BMI (kg/m^2)	**Mean (SD)** 24.1 (2.90)	**Range** 18.1-28.8

Study Design: 4-period crossover design



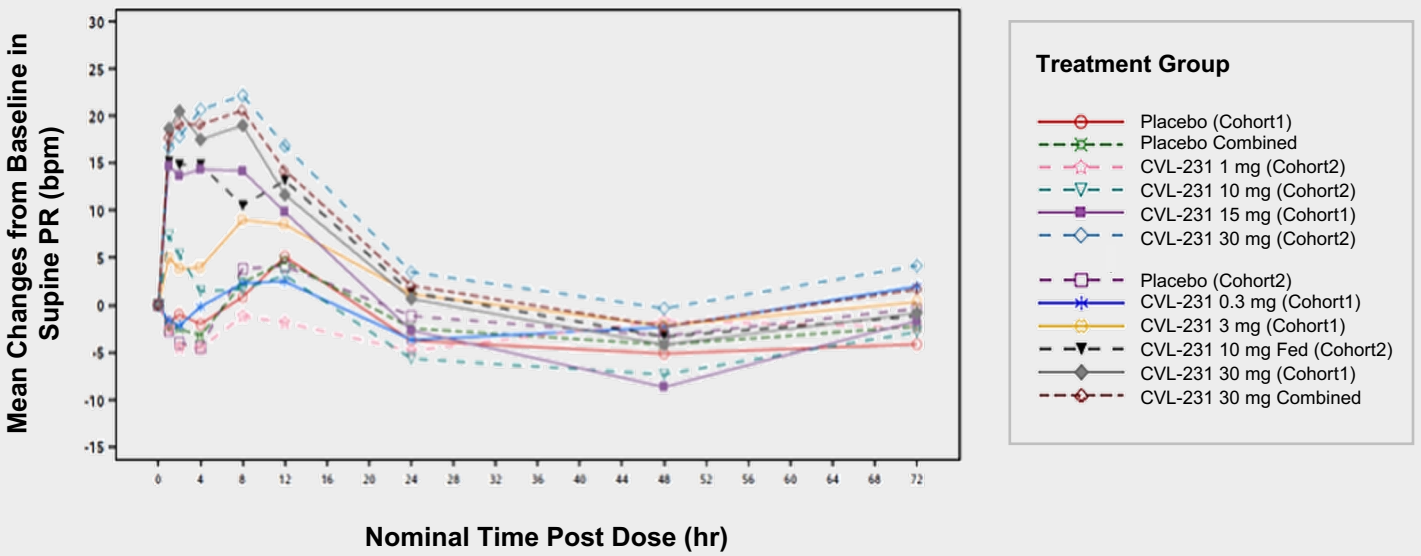
Median plasma concertation profiles following single oral doses



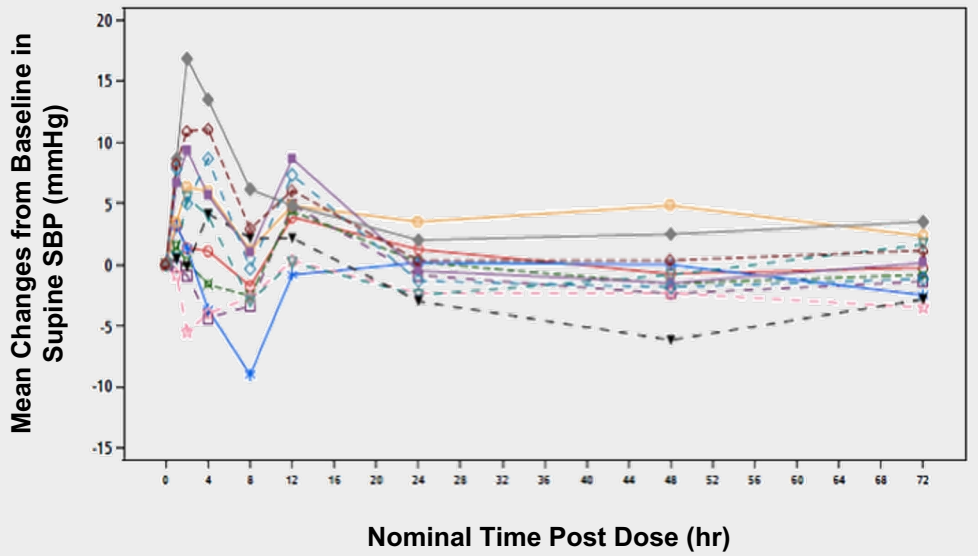
CVL-231 Single Ascending Dose Trial Design

- CVL-231 was observed to be generally safe and the observed adverse event profile in healthy volunteers following single ascending doses up to 30 mg supported progression to the multiple ascending dose study
- Increase in exposures was dose proportional. Food reduced Cmax by 30% and had no impact on AUC
- Observed t1/2 ranged from 9.4-12.2 hrs
- Dose related increases in Systolic BP, diastolic BP and pulse rate (& heart rate)

Supine Pulse Rate



Supine Systolic BP



CVL-231 Single Ascending Dose Trial Design

- Most of the AEs were mild in severity and self limiting. There were no SAEs.
- One subject was discontinued for reasons unrelated to safety or tolerability.
- Most frequently reported treatment-emergent AEs: fatigue, dizziness, headache and dry mouth.
- There were no clinically significant findings in the clinical laboratory, vital signs or physical examinations. Additionally, there were no withdrawal symptoms on discontinuation of treatment.
- There were three (3) cardiovascular AEs of moderate severity: 2 sinus tachycardia and 1 orthostatic hypotension, all observed at the 30 mg dose level, all resolved within the same day

Incidence of Treatment-Emergent Adverse Events All-Causality (Treatment-Related) in > 3 subjects

* *Subjects were counted only once per treatment per event*

Event	Placebo (N=16)	0.3 mg (N=6)	1 mg (N=6)	3 mg (N=6)	10 mg (N=6)	10 mg fed (N=6)	15 mg (N=6)	30 mg (N=12)
Fatigue	2 (1)	0	0	0	0	1 (1)	3 (3)	3 (3)
Dizziness	1 (1)	0	0	0	0	1 (1)	3 (3)	3 (3)
Headache	1 (1)	1 (1)	1 (1)	0	0	0	1 (1)	2 (2)
Dry Mouth	1 (1)	0	0	0	0	0	2 (2)	3 (3)
Back Pain	1	0	1 (1)	0	0	0	0	2 (1)
Sinus Tachycardia	0	0	0	0	0	0	0	3 (3)

Important Insights on Side Effects of M4 PAM

Results of a Phase 1 SAD trial indicated CVL-231 was generally safe with asymptomatic transient effects on heart rate and blood pressure

Phase 1 SAD Trial (N=17)

Tested doses up to 30 mg

No SAEs

Most frequently reported treatment-emergent AEs: fatigue, dizziness, headache and dry mouth

Moderate treatment-emergent transient increases in blood pressure and pulse rate observed

Cardiovascular effects were asymptomatic and transient in nature

Insights

Preclinical studies show heart rate effects attenuated with repeat dosing

Data from other compounds also suggest that increased heart rate may attenuate over time with repeat dosing

Tolerability may be differentiated in schizophrenia patients

CVL-231-SCH-001 Ongoing Phase 1b Multiple Ascending Dose Trial

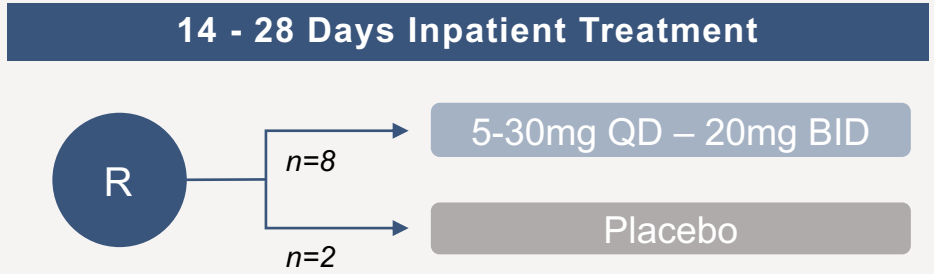
Part A: Safety and tolerability – Patients with stable symptoms of schizophrenia

Multiple Ascending Dose

Up to 5 Cohorts (n=10 each)

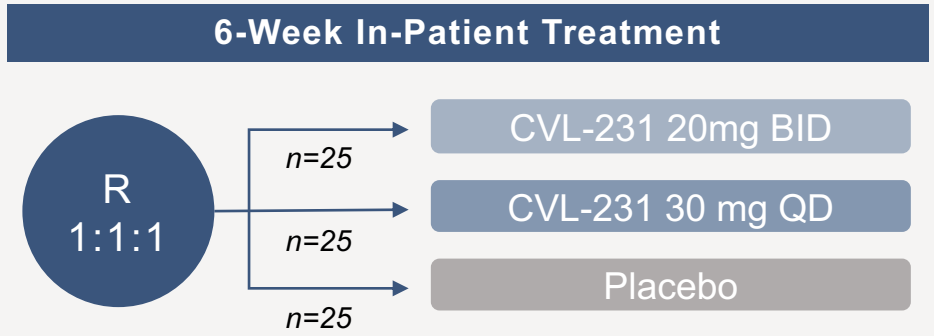
Primary Objective
- Safety & tolerability

Secondary Objective
- PK



Part B: Pharmacodynamics – Patients with schizophrenia experiencing an acute exacerbation of psychosis

Exploratory PD Assessment
- Positive and Negative Syndrome Scale (PANSS)*
- Clinical Global Impression – Severity Scale (CGI-S)*
- Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding test*



Methodically designed to identify optimal PK and PD for Phase 2 trial

* Not powered for statistical significance

Backup

M4 Receptors: Auto receptor highest expression in Striatum

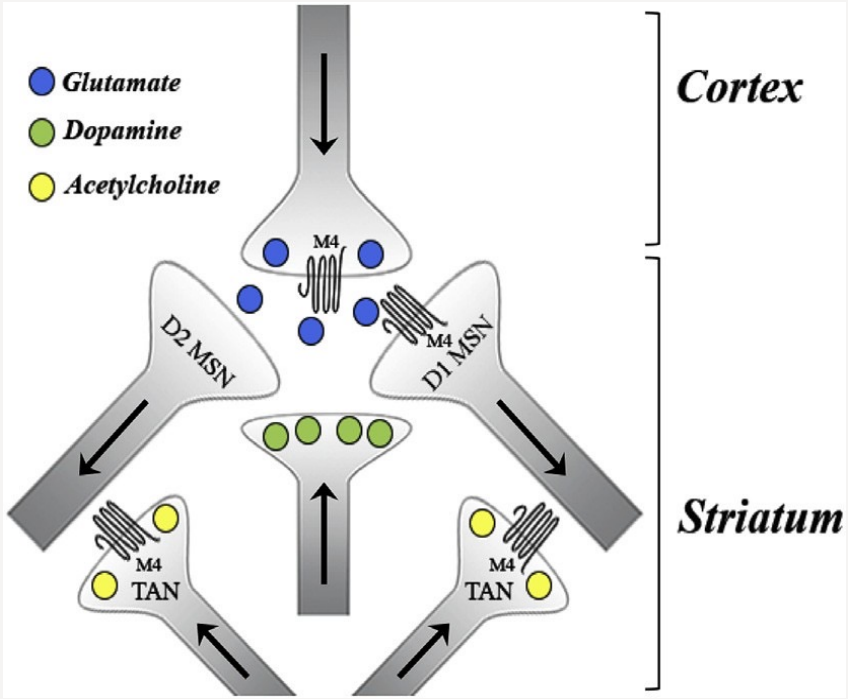
- Predominant source of Ach in the striatum is from cholinergic interneurons (TANs)
- Synapse onto D1 direct and indirect medium spiny neurons (MSN) to modulate glutamatergic output

TABLE VI. Densities of M4 MRs (B_{max}, fmol/mg tissue, mean ± SD) in AD (n = 16) vs. control (n = 18) brains

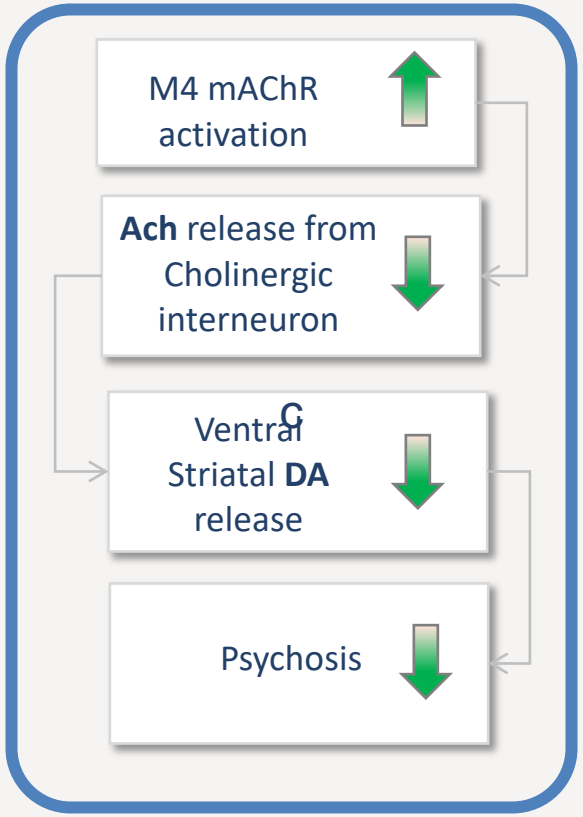
Brain area	Controls	AD	% change	p[1]
Frontal cortex				
Layers I–III	200 ± 141	221 ± 142	+11	NS[2]
Layer IV	189 ± 150	195 ± 138	+3	NS
Layers V	174 ± 140	184 ± 130	+6	NS
Layer VI	162 ± 129	174 ± 114	+7	NS
Temporal cortex				
Layers I–III	140 ± 54	143 ± 52	+2	NS
Layer IV	143 ± 60	132 ± 47	−8	NS
Layer V	137 ± 55	124 ± 41	−9	NS
Layer VI	128 ± 46	113 ± 30	−12	NS
Visual cortex				
Layers I–III	159 ± 61	140 ± 72	−12	NS
Layer IVc	128 ± 56	111 ± 78	−13	NS
Layer V	165 ± 48	126 ± 67	−24	NS
Layer VI	156 ± 36	120 ± 56	−23	NS
Entorhinal cortex				
Layers I–III	133 ± 67	124 ± 82	−7	NS
Layer IV–VI	119 ± 58	118 ± 75	−1	NS
Hippocampus				
Subiculum, pyramidalis	134 ± 72	137 ± 91	−2	NS
CA_1, pyramidalis	143 ± 62	138 ± 83	−3	NS
CA_3, pyramidalis	128 ± 46	122 ± 69	−5	NS
Dentate gyrus, hilus	102 ± 43	103 ± 53	+1	NS
Dentate gyrus, molecular	146 ± 47	143 ± 78	−2	NS
Striatum				
Caudate	333 ± 93	300 ± 184	−10	NS
Putamen	418 ± 82	451 ± 165	+8	NS

[1]Two-tailed Student's t test.
[2]Not statistically significant

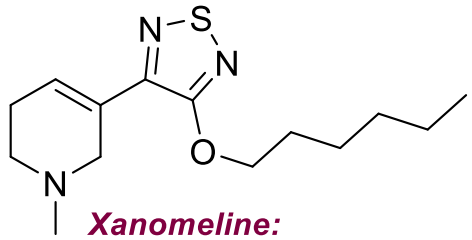
Synapse. 1997 Aug;26(4):341-50.



E.P. Lebois et al. / Neuropharmacology 136 (2018)



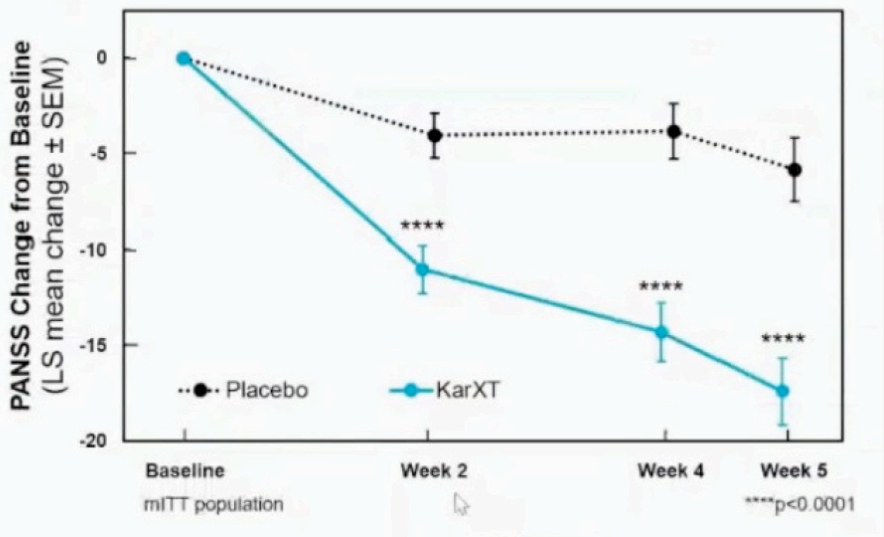
Clinical Confidence in Rationale: M1/M4 agonist Xanomeline Demonstrated Efficacy in Alzheimer's Disease and Schizophrenia



Xanomeline:

- Xanomeline, an M1/M4 preferred muscarinic orthosteric agonist, has demonstrated pro-cognitive and anti-psychotic efficacy **in the clinic**
- Development halted due to classic cholinergic adverse events (AE's)
- Activation of M2, M3, and more recently M1, have been linked to cholinergic AE's

Efficacy of KarXT (xanomeline + trospium) in Schizophrenia Patients with Acute psychosis



Effect of xanomeline on behaviours in AD patients

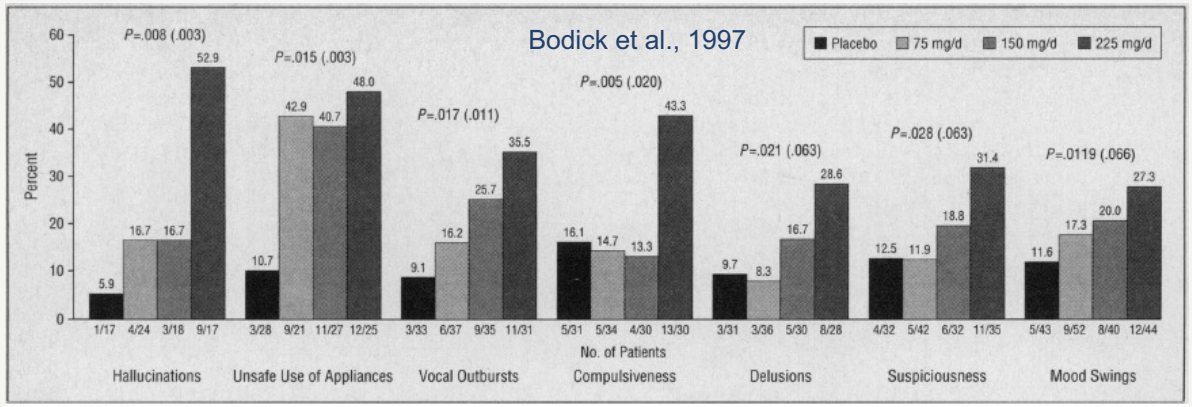
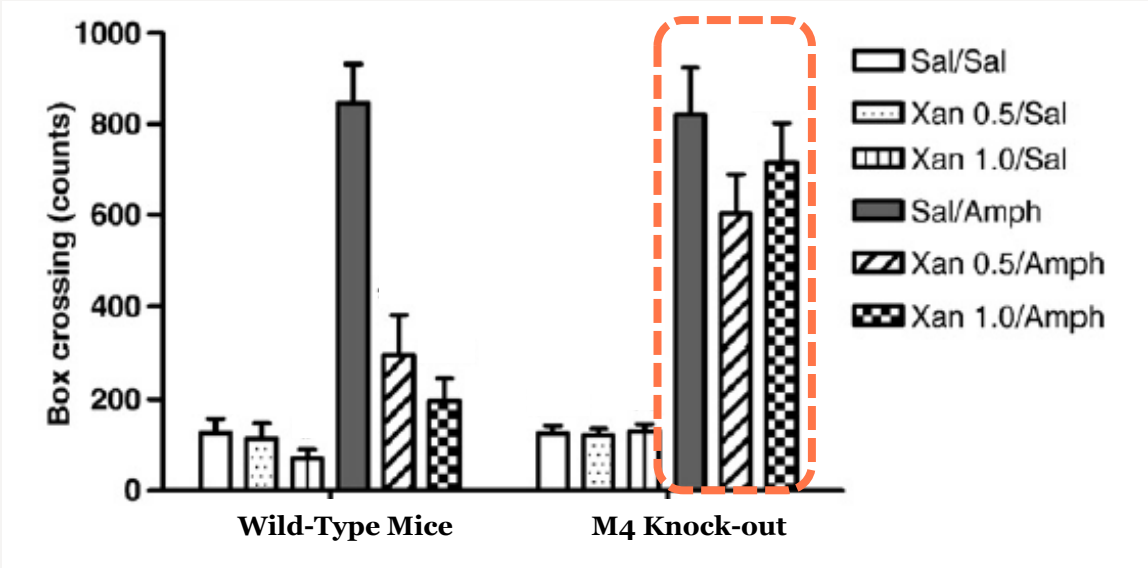


Figure 4. *Alzheimer's Disease Symptomatology Treatment. Percentage of patients with symptom at baseline, stopped while receiving treatment. The P values are for dose response and 225 mg/d of xanomeline tartrate vs placebo (in parentheses).*

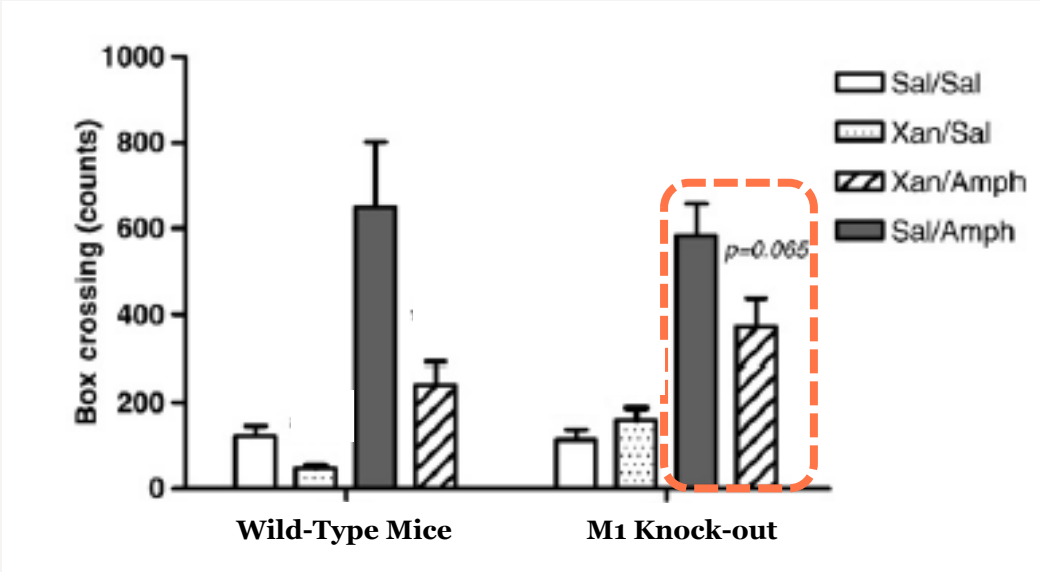
Preclinical Evidence: M4 Modulation Drives Antipsychosis

No Effect of Xanomeline in M4 Knock-out Mouse Model



Xanomeline had no effect on amphetamine-induced hyperactivity in M4 knock-out mice

Reduction in Hyperactivity in M1 Knock-out Mice



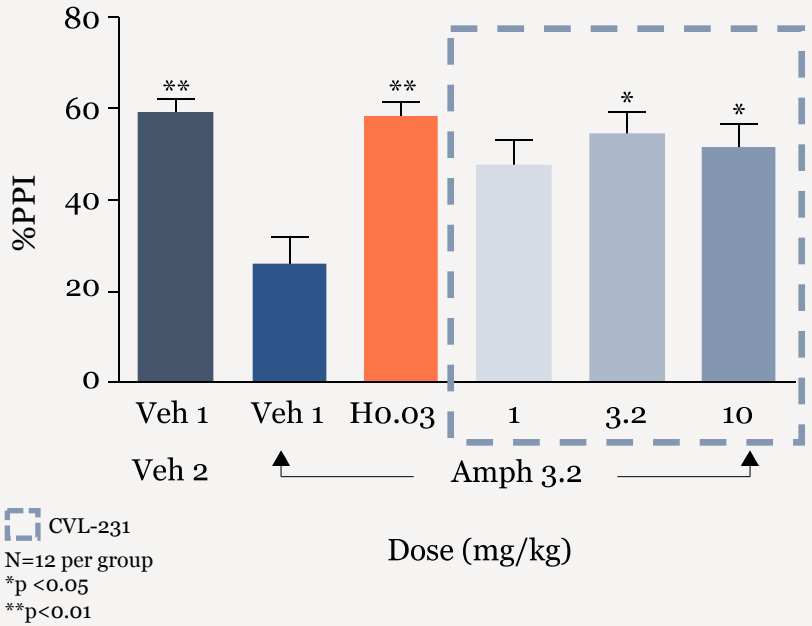
Xanomeline reduced hyperactivity in M1 knock-out mice

In mouse studies, M4 receptors drive the antipsychotic activity of xanomeline

Source: Woolley, et al. European Journal of Pharmacology 603 (2009)

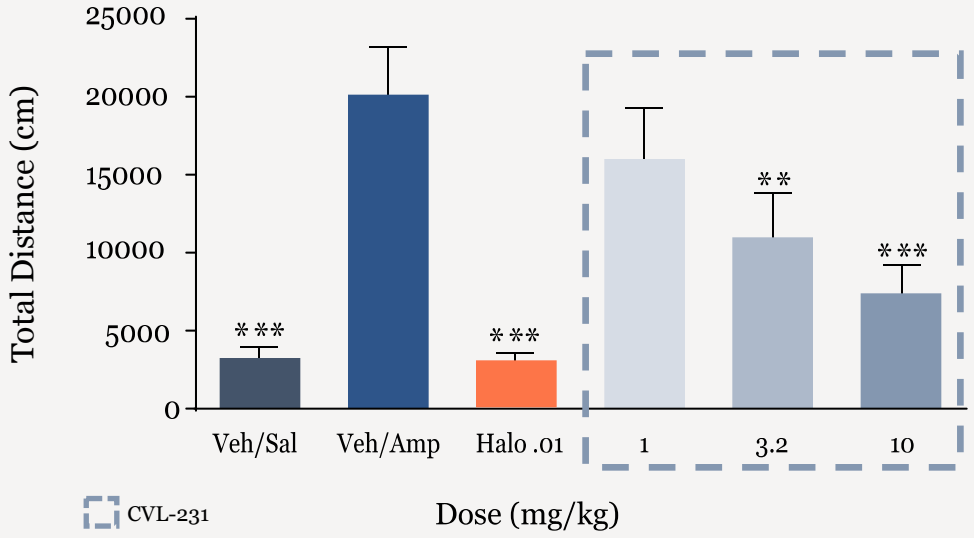
M4 PAM Preclinical Data in Psychosis

CVL-231 showed similar effect to haloperidol in reversing amphetamine-disrupted Pre-pulse Inhibition (PPI) in rats



N=12 per group
*p <0.05
**p<0.01

CVL-231 showed dose-dependent reductions on amphetamine-induced locomotion in rats



N=10 per group
**p <0.01
***p<0.001

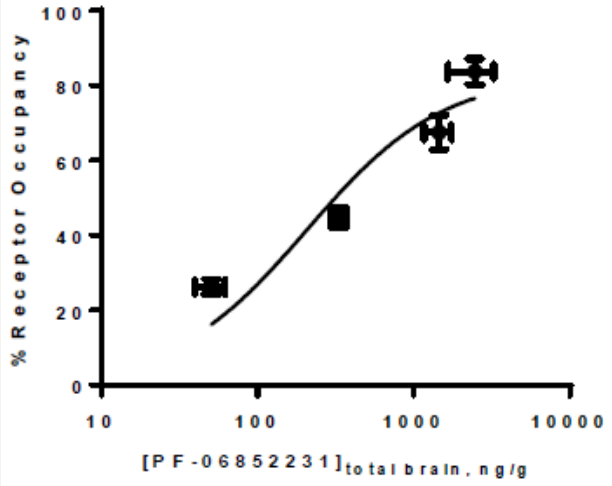
In multiple rodent models of psychosis, CVL-231 demonstrated antipsychotic activity consistent with xanomeline and atypical antipsychotics

Source: Cerevel studies.

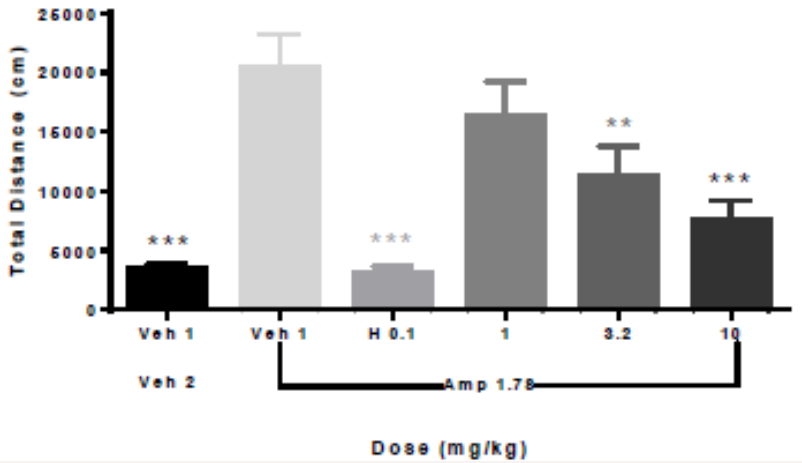
CVL-231 is a Muscarinic M4 Receptor Partial Allosteric Modulator (PAM) for Psychosis

CVL-231, M4 PAM, can regulate neurotransmitter imbalance, and is being developed for treatment of psychosis in neurodegenerative diseases

CVL-231 Inhibits [^{3}H]M4 PAM Binding in Mouse Striatum Receptor Occupancy Versus Total Brain Concentration



Total Distance Traveled Post-Amphetamine: Effect of CVL-231 and Haloperidol on Amphetamine-Stimulated Locomotor Activity in C57BL/6J Mice



Potential to reduce "SLUDGE" effects of pan-muscarinic activation:
Salivation, **L**acrimation, **U**rination, **D**iaphoresis(Sweating), **G**astrointestinal upset and **E**mesis

Cerevel's M4 PAM is a Potential Next Generation Antipsychotic

M4 PAM (CVL-231)

Potential New Standard of Care

First-in-Class Therapy with Novel MOA

M4 Selective

Targeted Muscarinic Activity

Improved Tolerability

Opportunity for Innovation in Schizophrenia

Current Standard of Care Uses Same Mechanism of Action (MOA) as Therapies from the 1950s

Large patient population

~21M
Patients Worldwide

2.7 million Americans
(0.5% -1.0% of U.S. population)
had schizophrenia in 2017

Significant need for new treatment option

Debilitating side effects of atypicals often lead to discontinuation and relapse, driving a vicious cycle of disease progression

Source: World Health Organization, DRG Market Research