# Advancing Novel Therapies in Neuropsychiatry

## Introducing CLE-905, a Potent Dual M1/M4 Receptor Agonist in Development for Treatment of Schizophrenia and Additional Psychiatric Disorders

**7th Neuropsychiatric Drug Development Summit**

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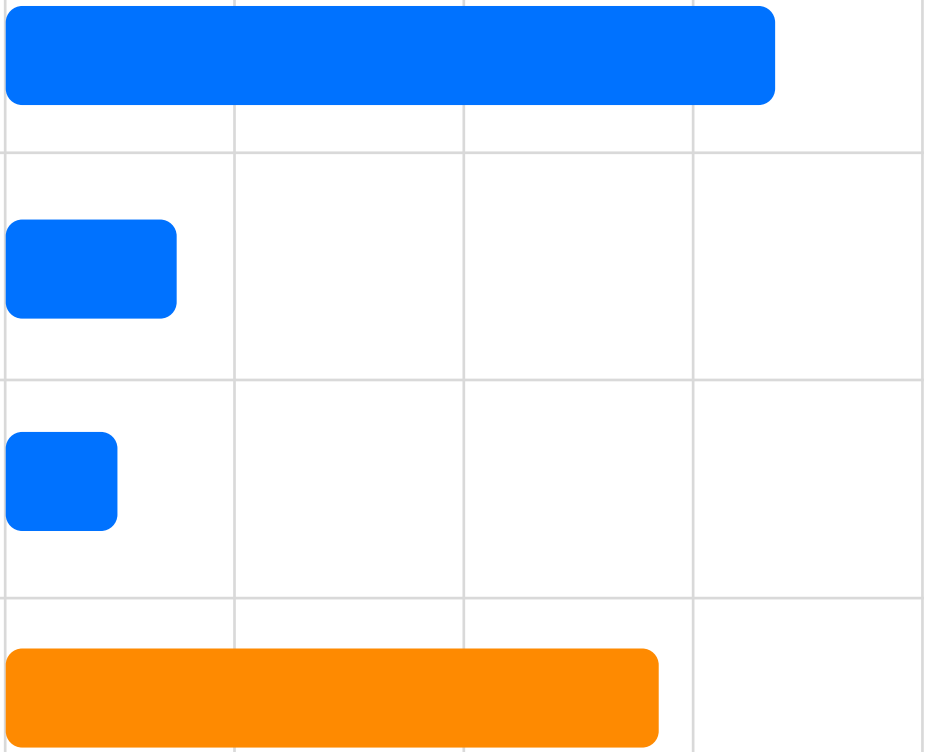
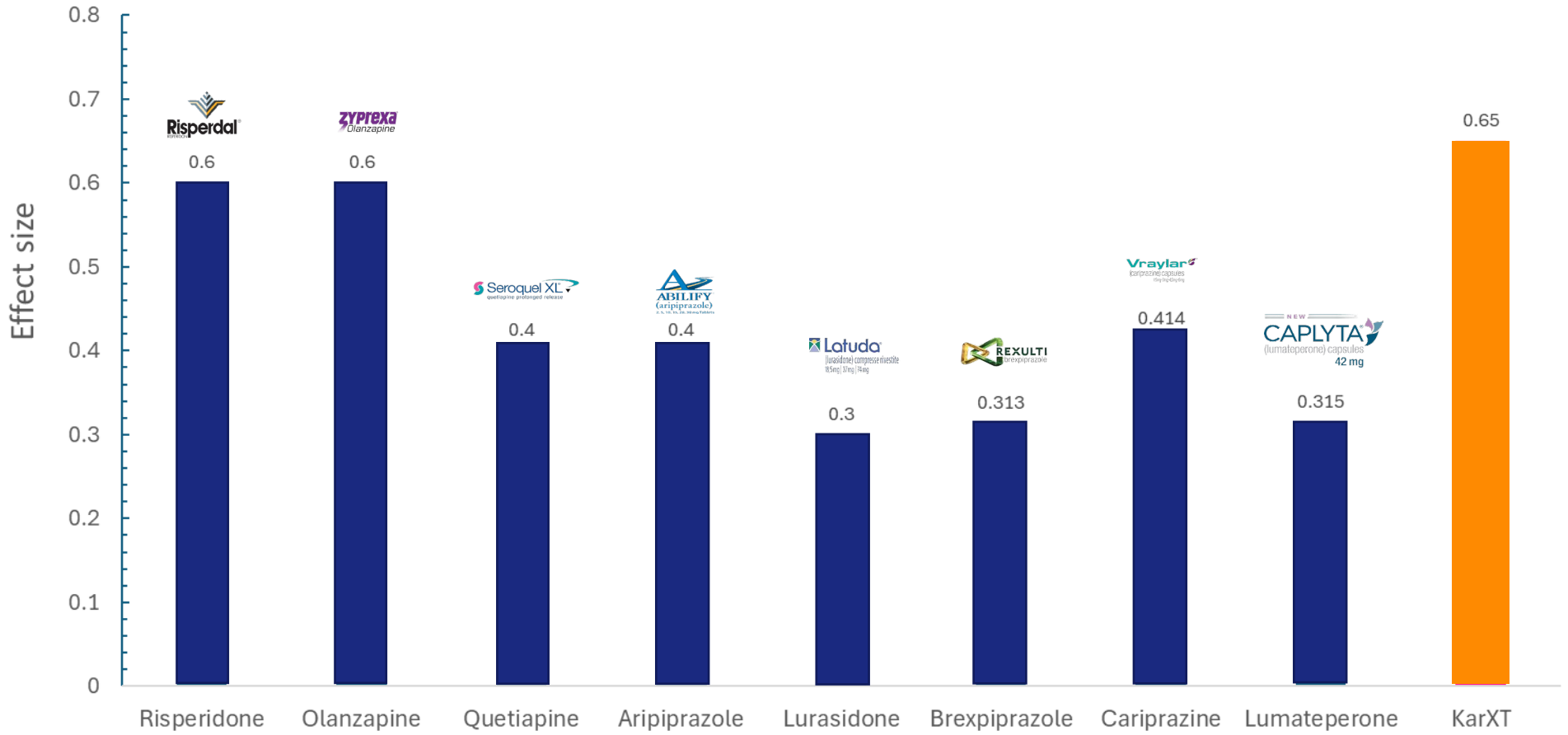
# A Broad Pipeline of Promising MoAs for Psychiatric and Neurological Conditions

| | Program | Indication | Preclinical | Phase 1 | Phase 2 | Phase 2b |
|---|---|---|---|---|---|---|
| Psychiatry | **CLE-100**<br>NMDA antagonist (Oral esketamine) | **Major Depressive Disorder**<br>Patients with inadequate response to previous anti-depressants | | | | |
| Psychiatry | **CLE-905**<br>M1/M4 muscarinic agonist | **Schizophrenia**<br>**& Additional Psychiatric Disorders** | | | | |
| Psychiatry | **CLE-901**<br>NMDA antagonist | **Bipolar Depression**<br>**Major Depressive Disorder** | | | | |
| Neuro-Derm | **CLE-400**<br>Potent α2-adrenergic agonist (Detomidine) | **Notalgia Paresthetica**<br>A neuropathic itch indication | | | | |



# M1/M4 Dual Agonism Has Demonstrated Superior Efficacy in Schizophrenia Compared to Leading Atypical Antipsychotics




Source: 1. Risperdal. Prescribing information. Janssen Pharmaceuticals, Inc.; 2022. 2. Zyprexa. Prescribing information. Eli Lilly and Company; 2021. 3. Seroquel. Prescribing information. AstraZeneca; 2009. 4. Abilify. Prescribing information. Otsuka Pharmaceutical Co., Ltd.; Latuda. Prescribing information. Sunovion Pharmaceuticals Inc.; 2022. 6. Rexulti. Prescribing information. Otsuka Pharmaceutical Co., Ltd.; 2021. 7. Vraylar. Prescribing information. Allergan; 2022. 8. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc.; 2022. 9. Li JA, et al. *Biol Psychiatry*. 2016;79(12):952-961. 10. Lybalvi. Prescribing information. Alkermes, Inc.; 2021. 11. Seroquel XR. Prescribing information. AstraZeneca; 2022. 12. Leucht S, et al. *Lancet*. 2013;382(9896):951-962.13. Correll CU, et al. *Schizophr Res*. 2016;174(1-3):82-9 Marder S, et al. *Eur Neuropsychopharmacol*. 2019;29(1):127-136. 15. Correll CU, et al. *JAMA Psychiatry*. 2020;77(4):349-358. 16. Kane JM, et al. *International Clinical Psychopharmacology*. 2021;36:244-250.

*KarXT data is pooled from EMERGENT 1-3.

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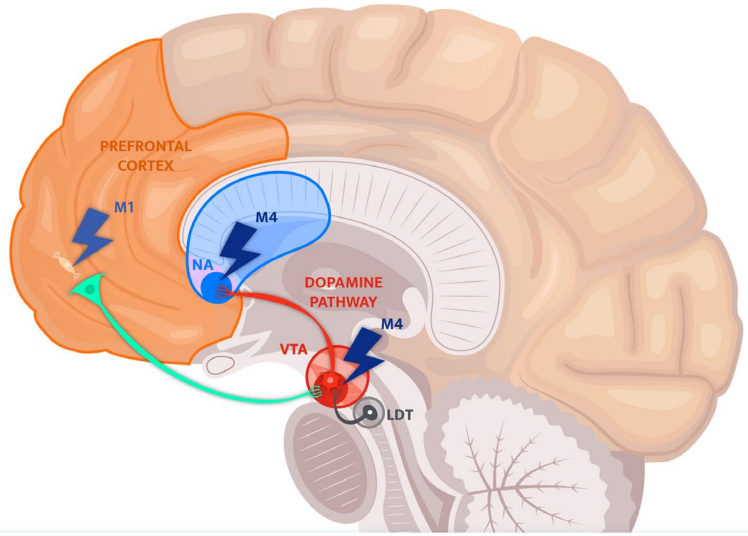
# Differentiation of Muscarinic Activators

| Type of Muscarinic Activation | Subtype Selectivity | Does Not Rely on Endogenous Ach | M1 Activity | Current Clinical Evidence |
|---|---|---|---|---|
| **M4 PAM** | ✓ Selective over M1,2,3,5 | ✗ | ✗ | • Emraclidine demonstrated positive results in Phase 1b in schizophrenia , ongoing Phase 2. |
| **M4 Selective Agonist** | ✓ Selective over M1,2,3,5 | ✓ | ✗ | • NBI-1117568 demonstrated positive results in Phase 2 in schizophrenia, lack of dose response. |
| **M1/M4 Dual Agonist** | ✓ Selective over M2,3,5 | ✓ | ✓ | • KarXT demonstrated positive results in 3 pivotal studies in schizophrenia.<br>• Highest effect size across symptom domains<br>• Ongoing studies in DRP |

- Preliminary clinical data suggests that M4 receptors have antipsychotic effect in schizophrenia. Data from ongoing and future studies is needed to confirm the initial findings
- Clinical data to date confirm that M1/M4 dual agonism is particularly effective against psychosis.

# M1/M4 Dual Agonism: Additional Antipsychotic Benefits

- M4 receptors are located at both ends of the mesostriatal dopamine pathways which play a central role in psychosis, and their activation reduces dopamine release.
- Activating prefrontal cortex M1 receptors is expected to reduce cortical stimulation of mesostriatal dopamine activity further reducing psychosis.
- Clinical data to date show that M1/M4 dual agonism is particularly effective against psychosis.




Striatum

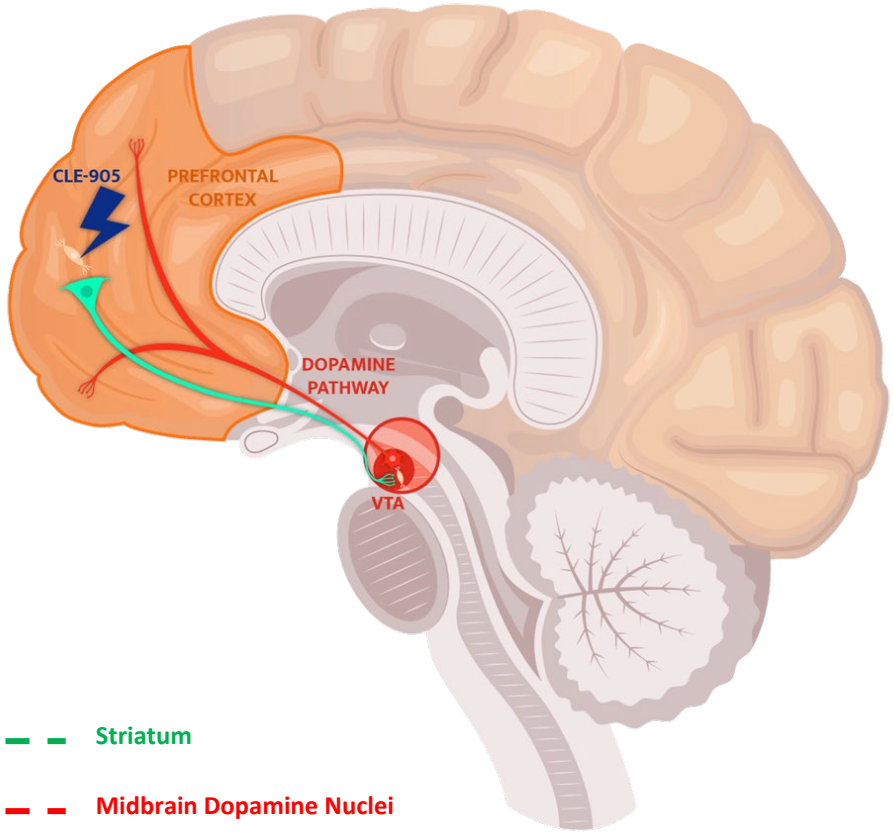
Midbrain Dopamine Nuclei

**Dual antipsychotic mechanisms of M1/M4 promises enhanced efficacy against psychosis.**

References: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 5th ed. Cambridge University Press; 2021. Paul et al. (2024) Biological Psychiatry, in press.

# M1 Agonism: Potential Additional Broad Benefits Beyond Psychosis

- Cortical dysfunction is associated with cognitive, behavioral and psychological symptoms of dementia (e.g. psychosis, agitation) and cognitive impairment associated with schizophrenia.
- Insufficient mesocortical dopamine activity and dysfunction of glutamatergic systems are thought to play key roles in negative and cognitive symptoms of schizophrenia.
- Stimulation of M1 receptors increases dopaminergic activity in the prefrontal cortex (PFC) and has the potential to treat non-positive symptoms
- M1 activators have been shown to improve cognition in various preclinical models.
- Preclinical data suggest that M1 activation is well positioned to treat cortical dysfunction.



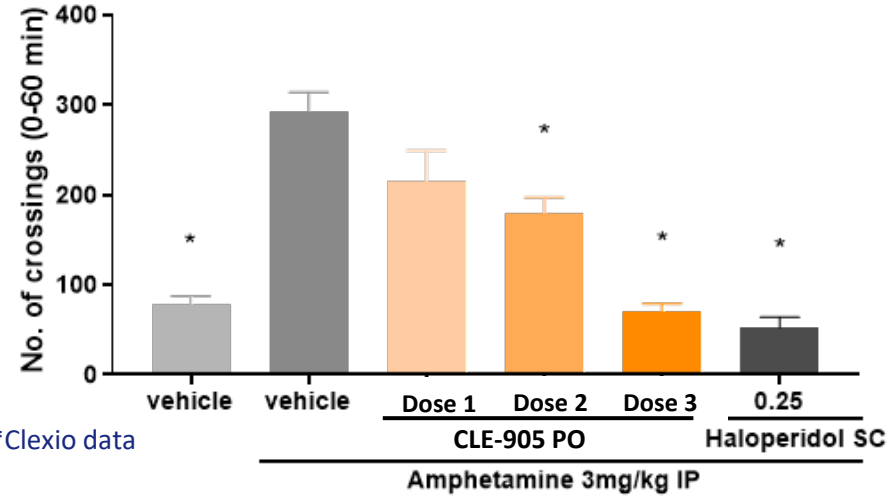

References: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 5th ed. Cambridge University Press; 2021. Paul et al. (2024) Biological Psychiatry, in press.

**Dual M1/M4 agonism has clinical potential across multiple neuropsychiatric indications and symptom domains.**

# CLE-905 Has Potent Effects in Multiple Preclinical Psychosis Models

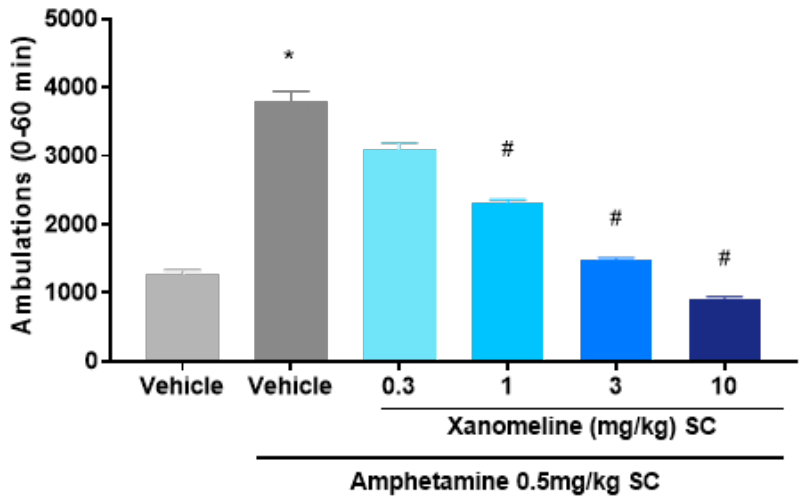
## Amphetamine-induced Hyperactivity in Rats

**CLE-905 Oral***




*Clexio data

**Xanomeline S.C ****




**Both CLE-905 and Xanomeline attenuated amphetamine-induced hyperactivity in a dose-dependent manner:**

- CLE-905 reduces amphetamine-induced hyperlocomotion with **ED50 = 0.1 mg/kg po**
- Xanomeline was effective in this model with an ED50 of about **1 mg/kg sc**

- CLE-905 also demonstrated robust dose-dependent effects in pre-pulse inhibition and conditioned avoidance psychosis models.

**Adopted from: "The Muscarinic Receptor Agonist Xanomeline Has an Antipsychotic-Like Profile in the Rat" K. J. STANHOPE, et.al THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS Vol. 299, No. 2

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# CLE-905: A Very Potent Dual M1/M4 Muscarinic Agonist

## Dual M1/M4 Agonism

- Very potent agonist of M1 and M4 receptors (single digit nM EC50)
- Dual M1/M4 muscarinic agonist antipsychotic activity confirmed using selective M1 and M4 antagonists in psychosis model.
- Significant opportunity for additional indications

## Molecule Properties

- No off-target activity (98 panel)
- High CNS penetration
- Low protein binding
- High bioavailability
- Excellent molecule properties reduce peripheral exposure and the potential for cholinergic adverse effects.

## Efficacy

- Antipsychotic activity confirmed in several psychosis models.
- Pro-cognitive activity confirmed in several learning and memory models
- Central target engagement confirmed by EEG in rodent model

## Patient Compliance

- Designed for once daily dosing
- Very good fit for LAI: High potency and expected low daily dose to achieve efficacy

# CLE-905 Overview

## CLE-905 Is A Novel And Differentiated Agonist With A Competitive Benefit-Risk Profile

Potent & Functionally Selective Dual M1/M4 Agonist Potentially Engaging Several Disease-related Brain Circuits to Achieve Greater Potential Benefits Across All Schizophrenia Symptom Domains

CLE-905 Preclinical Data Support Broad Benefits In Psychosis, Cognitive And Mood Disorders.

Differentiated ADME Properties Support Minimal Peripheral Exposure and Decreased Potential for Cholinergic Adverse Effects.

Convenient Once Daily for Optimal Patient Compliance

## Development Status

- Ongoing IND Enabling Studies
- Targeted to Reach The Clinic In 2025

# Contact Us

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