Evenamide, a glutamate release modulator, as add-on to second-generation antipsychotics in treatment-resistant schizophrenia: updates from ENIGMA-TRS 1, a phase 3, potentially pivotal, international, randomized, double-blind, placebo-controlled trial

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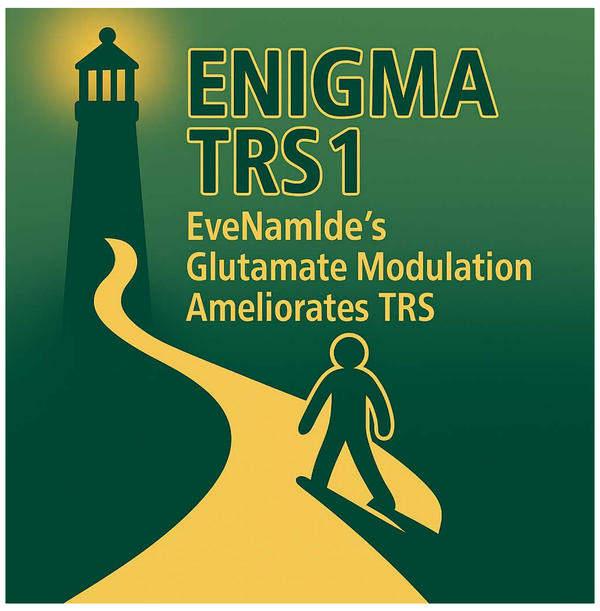


Phase 3 - Potentially pivotal

International

Randomized

Double-blind

Placebo-controlled

Add-on

Primary Endpoint: 12 Weeks
Duration: 52 Weeks

Aim

Evaluate the efficacy and safety of evenamide as add-on treatment to antipsychotics (including clozapine) in patients with documented TRS

Treatment-resistant schizophrenia (TRS)

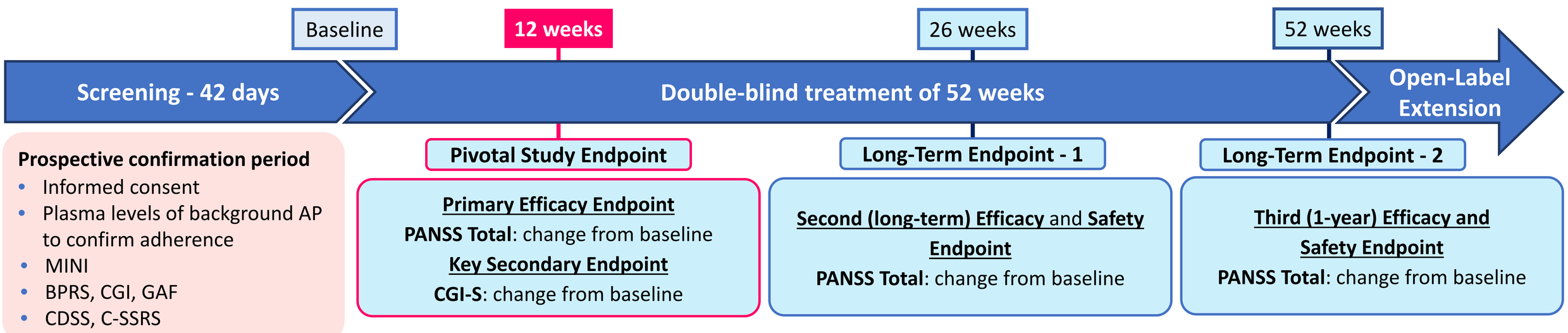
1. Treatment-resistant schizophrenia (TRS) develops in **30%** of patients. **Clozapine**, the only drug approved for TRS, is **highly underutilized** (5-15%) due to its unfavourable safety profile
2. Increasing evidence indicate **excessive glutamatergic activity** in TRS, rather than increased dopamine synthesis

Evenamide

Evenamide **normalizes excessive glutamate release** by blocking voltage-gated sodium channels. It demonstrated **benefits in animal models** of psychosis, mania, aggressiveness

Previous phase 2-3 clinical findings:

- **Long-term** benefits as **add-on** in **TRS** patients in an **open-label**, **rater-blinded**, **1-year** trial[1,2]
- **Statistically significant** and **clinically meaningful improvements** in patients with schizophrenia not adequately benefitting from an SGA in an international, **randomized**, **double-blind**, **placebo-controlled**, 4-week trial[3]



Prospective confirmation period

- Informed consent
- Plasma levels of background AP to confirm adherence
- MINI
- BPRS, CGI, GAF
- CDSS, C-SSRS

Patients receiving background APs at stable therapeutic dose

SALIENT FEATURES

- **Independent Eligibility Assessment Committee** will determine if patients meet protocol selection criteria
- **Confirmation of adherence** to background AP assessed **prior to randomization** through **plasma levels**
- **Placebo switch-over:** 50% of patients on placebo switched to evenamide from Week 12

Enrollment start: June 2025
Enrollment completion: June 2026
~600 patients randomized **1:1:1** on evenamide **15 mg bid/30 mg bid/placebo**
~ 20 countries; ~ 70-80 sites

KEY INCLUSION CRITERIA

1. DSM-5-TR diagnosis of **schizophrenia**, confirmed by **MINI**
2. Confirmation of **TRS** according to **TRRIP working group criteria** (Howes et al., 2017)
3. Currently receiving **"Standard of care"**: 1 or more AP (only SGAs allowed as primary AP) at a stable therapeutic dose for at least 6 weeks prior to screening. **Clozapine** is allowed as primary AP.
4. Clinical Global Impression - Severity of illness (**CGI-S**) of mildly to severely ill (**3-6**)
5. Brief Psychiatric Rating Scale (**BPRS**) total score **≥ 45**, with score of **at least 18** on P2, P3, P4, P5, P6, P7, G9 and a score of **at least** "**5**" on at least one or "**4**" on at least two of the **4 core items** (P2, P3, P6, G9)
6. Positive and Negative Syndrome Scale (**PANSS**) total **≥ 70** (at Baseline)
7. Global Assessment of Functioning (**GAF**) **≤ 50**

EFFICACY MEASURES

- **PANSS total** and subscales; **CGI-S/C**
- Quality of Life (**Q-LES-Q-SF**)
- Personal and Social Performance (**PSP**)
- Medication Satisfaction Questionnaire (**MSQ**)
- Functioning (**GAF**)
- Cognition (d2, DSST, TMT, verbal fluency)

KEY EXCLUSION CRITERIA

1. Improvement from screening to baseline of **≥20% on BPRS** or **1 point on CGI-S**
2. Diagnosis of schizophreniform disorder, schizoaffective disorder, or **other primary psychiatric disorder**
3. Depressive symptoms as assessed by **CDSS** score of **7** or more
4. Substance use disorder
5. **Suicidal risk** based on evaluation of C-SSRS

SAFETY MEASURES

- Adverse events/ vital signs/ ECG/ laboratory tests
- Physical/ neurological/ eye examinations
- Calgary Depression Scale for Schizophrenia (**CDSS**)
- Columbia-Suicide Severity Rating Scale (**C-SSRS**)
- Extrapyramidal symptom rating scale (**ESRS-A**)
- Assessment of potential withdrawal effects

ENIGMA-TRS PROGRAM UPDATES

- **10 Investigator's meetings** performed to date, involving **18 countries**
- **First patients randomized** and receiving treatment in the study
- **US** centers will follow **FDA requirements**

KEY FINDINGS

Results from the ENIGMA-TRS program will determine whether **addition of evenamide to Standard of Care** is associated with **clinically important benefits** in patients with **TRS**. Positive results would support the **need for glutamate modulation** for the optimal treatment of patients with TRS

References: [1]Anand et al., 2024; [2] Anand et al., 2023; [3] Anand et al., 2025

Mechanism of action of antipsychotics and its impact on tolerability and safety

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BACKGROUND

- Three **second generation antipsychotics** (SGAs) have been recently approved: **Lumateperone**, **Cariprazine**, and **KarXT**
- **Evenamide** (NW-3509) is a new chemical entity, highly selective and state-dependent blocker of voltage-gated sodium channels that **normalizes excessive glutamate release** without affecting its basal levels
- Due to differences in the design of the studies (performed in in/outpatients, selected countries or globally, monotherapy or add-on therapy), **it is difficult to make a definitive statement** about their **relative efficacy**. However, **these issues should not impact on safety and tolerability**

AIM

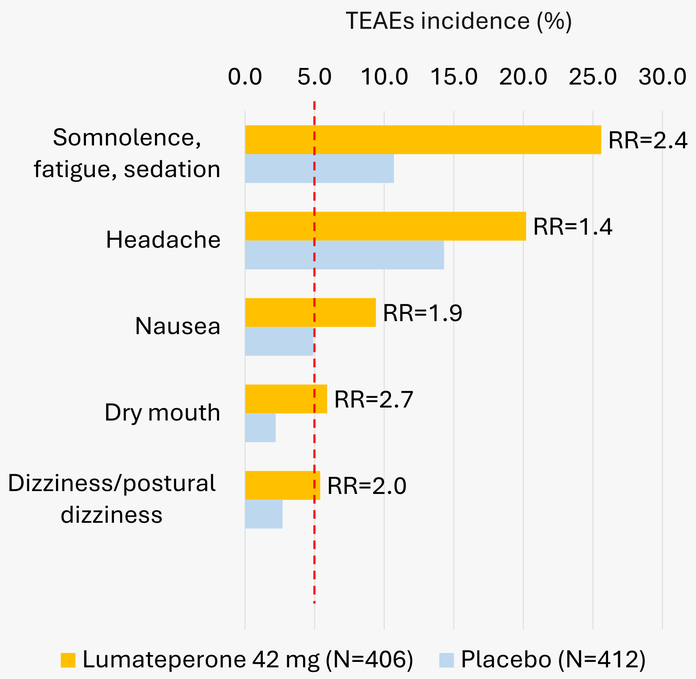
Assessing the **impact of mechanisms of action** (MoA) of **Lumateperone**, **Cariprazine**, **KarXT** and **Evenamide** on **safety and tolerability**

METHODS

Review of published Phase III data (pivotal studies) in schizophrenia of **4-6 week** in duration. **Evenamide** was administered as **add-on therapy** to concurrent APs while **Cariprazine, Lumateperone** and **KarXT** were administered as **monotherapy**. Data are presented as **relative risk (RR)** vs placebo (PL).

RESULTS

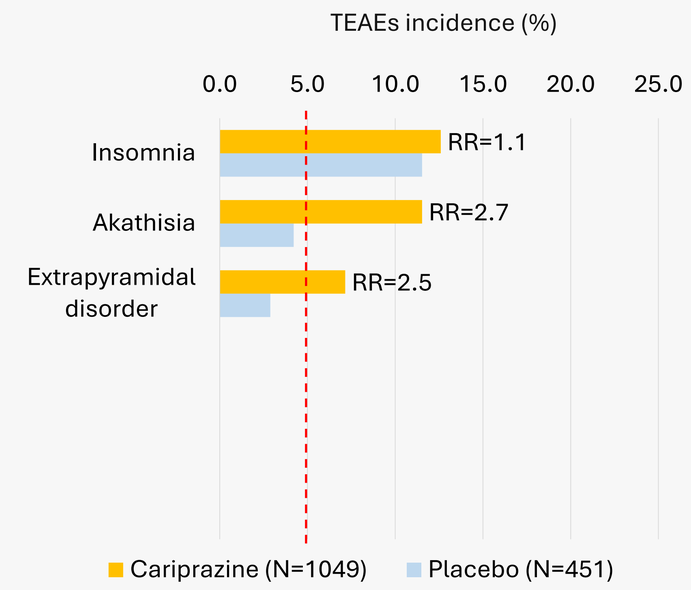
LUMATEPERONE (D1, D2, D4, 5HT2A antagonist, indirect glutamate modulator) (1)



Lumateperone (1)
TEAE ≥ 5% of patients treated with lumateperone 42 mg and RR > 1 vs placebo

(1) Phase 3 studies ITI-007-005, ITI-007-301, ITI-007-302 (NDA 209500 Multi-disciplinary Review and Evaluation)

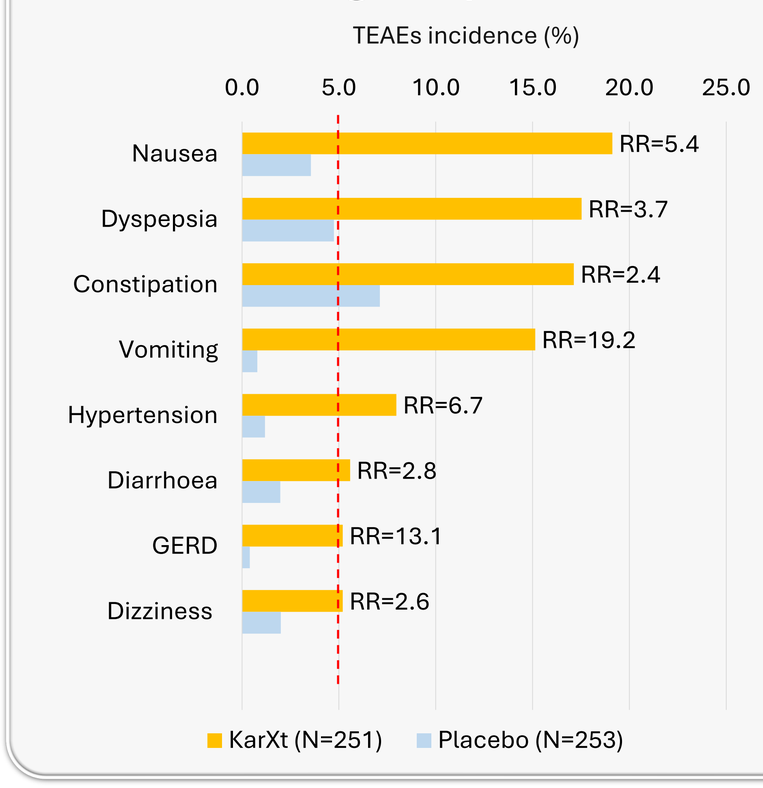
CARIPRAZINE (D2, D3, and 5-HT1A receptors partial agonist, 5-HT2B, 5-HT2A receptors antagonist) (2)



Cariprazine (2)
TEAE ≥ 5% of patients treated with Cariprazine (1.5 to 9 mg) and RR > 1 vs placebo

(2) Phase 3 studies RGH-MD-16, RGH-MD-04, and RGH-MD-05; Canadian Journal of Health Tecnologies (CADTH)

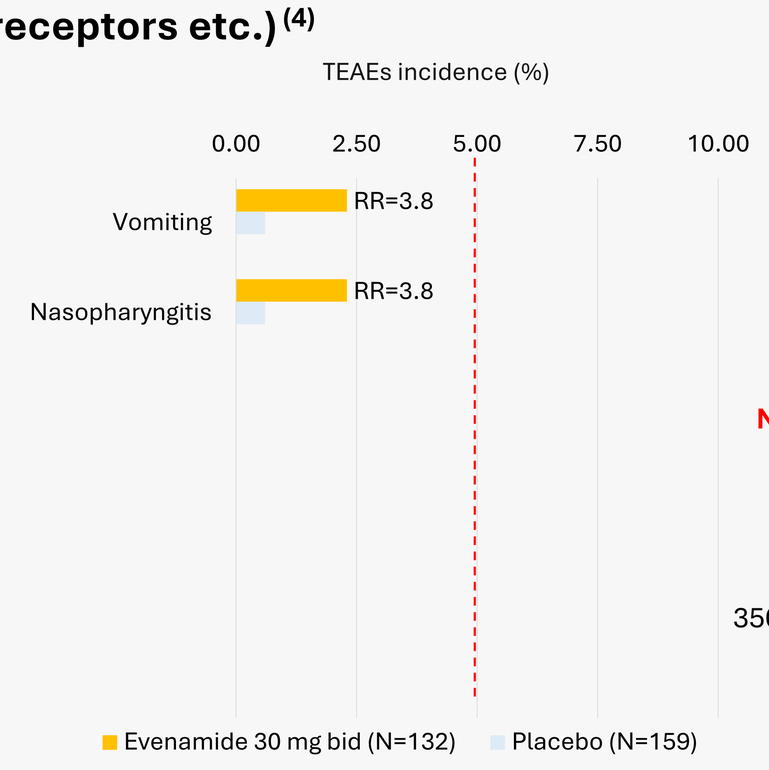
XANOMELINE/TROSPIUM [KarXT] (xanomeline is M1-M4 muscarinic receptors agonist, trospium is a peripheral muscarinic antagonist) (3)



KarXT (Xanomeline-Trospium (3)
TEAE ≥ 5% of patients treated with KarXT (125/30 mg bid) and RR > 1 vs placebo

(3) KarXT: Emergent-2, Emergent-3 (Kaul I et al 2024, and ICER 2024, KarXT for Schizophrenia)

EVENAMIDE (blocks selectively VGSCs, modulates the release of glutamate, and is devoid of any significant activity at over >130 CNS targets including D2, 5HT, Musc. receptors etc.) (4)



Evenamide (4)
TEAE ≥ 2% of patients treated with evenamide 30 mg bid (as add-on to SGA) mg and RR > 1 vs placebo (Phase 3 study 008A)

No TEAEs ≥ 5% occurred on evenamide

(4) Evenamide: NW-3509/008A/II/2020 (Anand et al 2025)

KEY FINDINGS

MoAs influence the type and pattern of AEs associated to the antipsychotics (APs):

- **Lumateperone**'s side effects reflect muscarinic, serotoninergic and autonomic adverse effects consistent with its multiple neurotransmitter affinities although muscarinic activity was not reported.
- **Cariprazine**'s side effects reflect dopamine antagonism (e.g. akathisia, extra-pyramidal side-effects, restlessness), muscarinic (constipation) and serotoninergic activity (headache, insomnia).
- **KarXT** profile is highly influenced by its cholinergic activities (e.g. vomiting, gastroesophageal reflux, hypertension, nausea, dyspepsia, dizziness, constipation, and diarrhoea).
- **Evenamide**'s new MoA may contribute to its safety and tolerability profile, as evidenced by the relative risk (RR) of AEs in this clinical trial (study 008A), where evenamide administered at the dose of 30 mg bid as add-on therapy to concurrent SGAs (including clozapine) was associated with autonomic side effects (vomiting and nasopharyngitis) with low incidence (< 5%).

CONCLUSION

Recently, there was an increasing attitude to treat inadequate response to a single AP with a combination therapy of two or more APs to achieve better efficacy. This approach increases the risk of developing AEs related to different MoAs. Evenamide, based on its tolerability and safety profile, could be used as add-on without increasing the risk for AEs.