Evenamide Phase 3 Program:
Study 023 (ENIGMA-TRS 1) evaluates the efficacy of add-on glutamate modulation in patients with documented treatment-resistant schizophrenia

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Treatment-resistant schizophrenia (TRS)

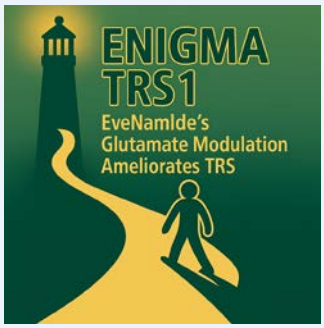
1. Treatment-resistance to antipsychotics (TRS) occurs in **~30%** of patients with schizophrenia. **Clozapine**, the only drug approved for TRS, is **highly underutilized** (5-15%) due to its unfavourable safety and tolerability profile
2. Increasing evidence indicate **abnormal glutamatergic activity** in TRS, rather than increased dopamine synthesis

Evenamide

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

2. 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 a SGA in an international, **randomized**, **double-blind**, **placebo-controlled**, 4-week trial[3].



- III Phase 3 - Potentially pivotal
- International
- Randomized
- Double-blind
- Placebo-controlled
- Add-on
- Primary Endpoint: Week 12
  Duration: 52 Weeks (1 Year)

AIM

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

Study 023 (ENIGMA-TRS 1)

Enrollment start: June 2025
Enrollment completion (projected): June 2026

Screening - 42 days

Prospective confirmation period

Plasma levels of background AP to confirm compliance

- Informed consent
- MINI
- BPRS, CGI, GAF
- CDSS, C-SSRS

Double-blind treatment of 52 weeks

Baseline	12 weeks	26 weeks	52 weeks
	Pivotal Study Endpoint	**Long-Term Endpoint - 1**	**Long-Term Endpoint - 2**
	Primary Efficacy Endpoint PANSS Total: Change from baseline Key Secondary Endpoint CGI-S: Change from baseline	Second (Long-term) Efficacy and Safety Endpoint PANSS Total: Change from baseline	Third (1-year) Efficacy and Safety Endpoint PANSS Total: Change from baseline

Open-Label Extension

Patients receiving background APs at stable therapeutic dose

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**

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

KEY GENERAL FEATURES

- **Independent Eligibility Committee** will determine if patients meet TRRIP criteria for TRS and other protocol selection criteria
- **Compliance to background AP** assessed prior to randomization through plasma levels
- **Placebo switch-over**: 50% patients on placebo switched to evenamide from Week 12

ENIGMA-TRS PROGRAM

ENIGMA-TRS 1 (023)	ENIGMA-TRS 2 (022)
600 patients randomized 1:1:1	**400** patients randomized 1:1
Evenamide 15 mg, 30 mg and **placebo (bid)**	**Evenamide 15 mg** and **placebo (bid)**
52-week double-blind treatment	**12-week** double-blind treatment
60-80 centers in **EU, Asia, Canada, LATAM**	40 centers in **USA + selected countries**

ENIGMA-TRS PROGRAM UPDATES

- **10 Investigator's meetings** performed to date, involving **18 countries**
- **First patients randomized** and receiving treatment in the study

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)

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

CONCLUSIONS

Results from these studies will determine whether the **addition of evenamide to APs** is associated with significant and **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., 2023; [2] Anand et al., 2024; [3] Anand et al., 2025