

Novel findings from a neurodevelopmental animal model of schizophrenia support long-term clinical benefits of evenamide in treatment-resistant schizophrenia

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BACKGROUND

Emerging evidences suggest that the **hippocampus** is the **primary site** of dysfunction in **schizophrenia**¹, and **hippocampal hyperexcitability** is thought to play a key role in its pathophysiology

Targeting the hippocampus could **improve negative symptoms** and **cognitive impairment**, in addition to **positive symptoms**, avoiding safety concerns associated with 5HT2/D2 blockade e.g., metabolic dysfunction, EPS, cardiovascular issues

EVENAMIDE

Blocks voltage-gated sodium channels (**VGSC**) in a state-dependent manner, **reducing neuronal hyperexcitability** while **leaving basal neuron function unaffected**

Normalizes glutamate release induced by aberrant VGSC activity, without affecting glutamate basal levels

Benefits numerous animal models of psychosis, as monotherapy and add-on to antipsychotics (e.g., clozapine, haloperidol, and risperidone)

Evenamide in the MAM model: Key pre-clinical findings

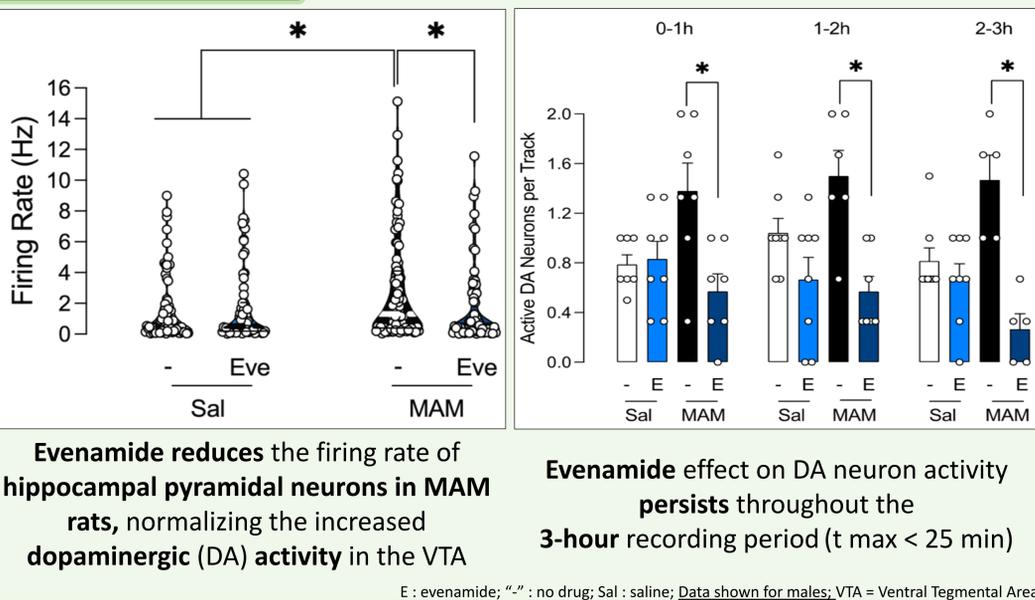
Uliana et al., 2025²

- **Pregnant rats** administered with methylazoxymethanol acetate (**MAM**), a **DNA alkylating agent**, or saline (control)
- Pups of **MAM-treated rats** resemble **symptoms of schizophrenia**, with **increased activity in the hippocampus** and **cognitive and social deficits**
- **Evenamide** (or saline) **was administered**, and effects were assayed using electrophysiology and behavioral assessment

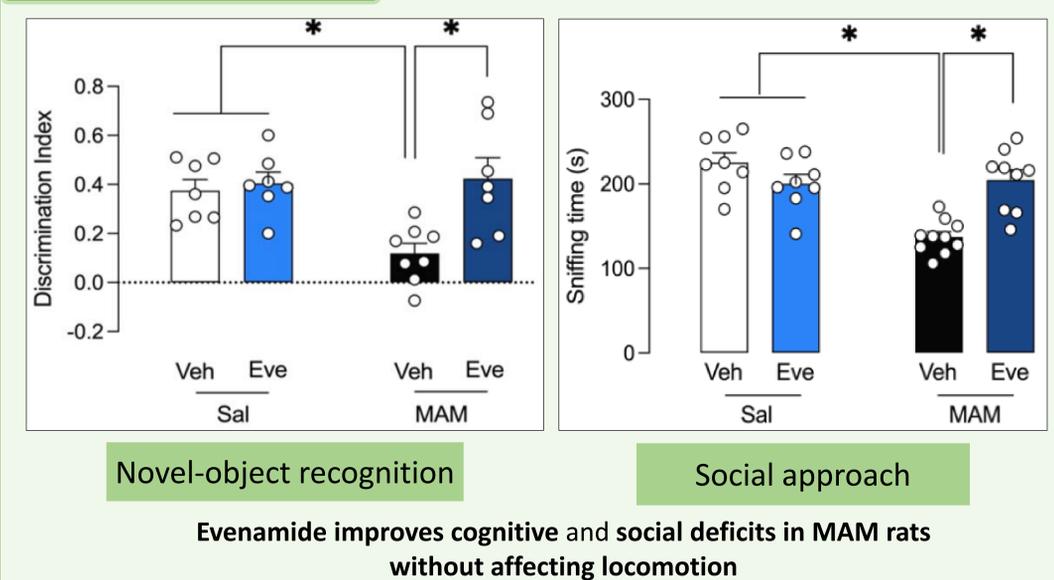
AIM

To present **clinical findings** from **phase 2/3 trials** with **evenamide** and **interpret** them based on pre-clinical results from the **MAM model**

1) Electrophysiology



2) Behavioral Assessment

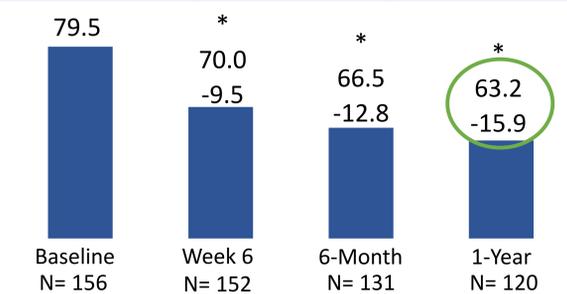


Evenamide in patients with schizophrenia: Key findings

Study 014/015 – Patients with treatment-resistant schizophrenia (TRS)³

- International
- Randomized
- Open Label
- Add-on evenamide 7.5-30 mg bid
- 1-year

PANSS total score mean change from baseline (mITT N=156; OC)

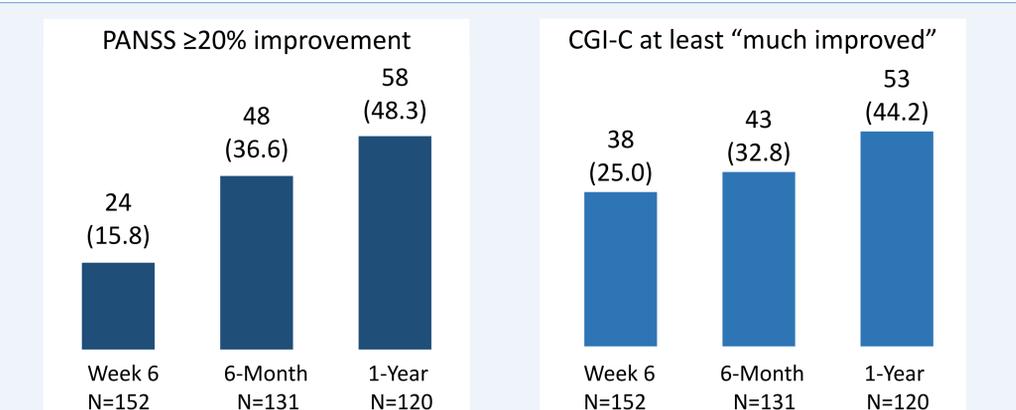


CGI-S mean change from baseline (mITT N=156; OC)

Mean score/mean change (SD)			
Baseline (N=156)	Week 6 (N=152)	6-Month (N=131)	1-Year (N=120)
4.5 (0.6)	-0.7 (0.7)*	-1.0 (0.6)*	-1.1 (0.7)*

* p-value < 0.001; paired t test; LOCF results do not differ substantially

Responder Analyses – n (%) (mITT N=156; OC)

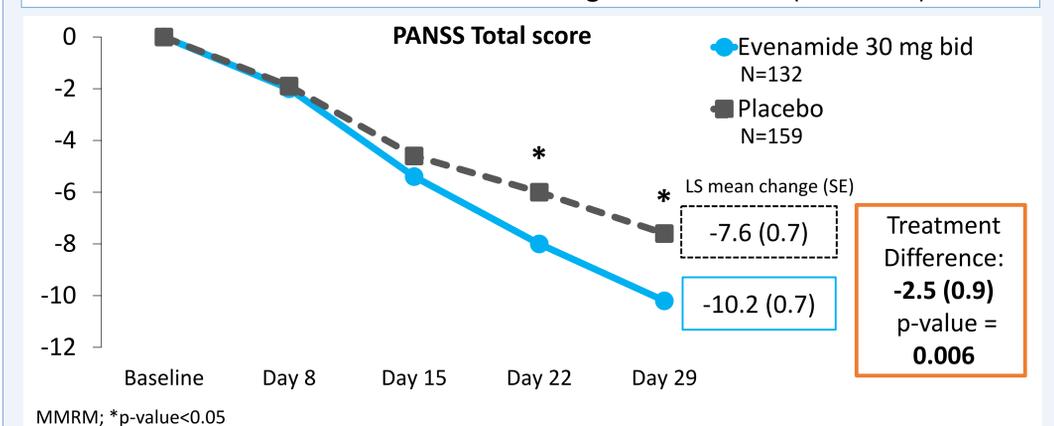


Benefits of evenamide, noted at Week 6, 6-Month, and 1-Year, suggest that the increased number of responders at 6-Month and 1-Year may result from changes in **circuit-level plasticity**, as suggested by findings in the MAM model

Study 008A – Patients with inadequate response to antipsychotics⁴

- International
- Randomized
- Double blind
- Placebo controlled
- Add-on evenamide 30 mg bid vs placebo
- Therapeutic plasma level of background AP
- 4 weeks

PANSS Total and Subscales mean change from baseline (ITT N=291)



Efficacy Endpoint	Evenamide 30 mg bid (N=132)	Placebo (N=159)	Drug-placebo difference; p-value
PANSS Positive	-4.7 (0.4)	-3.6 (0.4)	-1.16 (0.4); 0.001
PANSS Negative	-1.9 (0.3)	-1.3 (0.3)	-0.63 (0.3); 0.016
CGI-S	-0.6 (0.1)	-0.5 (0.1)	-0.16 (0.08); 0.037

LS mean change (SE)

- **Efficacy in positive symptoms** may be associated with hippocampal regulation of downstream VTA dopaminergic system
- **Efficacy in negative symptoms** may be mediated by connections to the prefrontal cortex/amygdala
- Evenamide is also likely to benefit **social functioning and life engagement**⁵ consistently with MAM behavioral results and likely to be explained by its action in the ventral **hippocampus**

Also see poster S10!

CONCLUSIONS

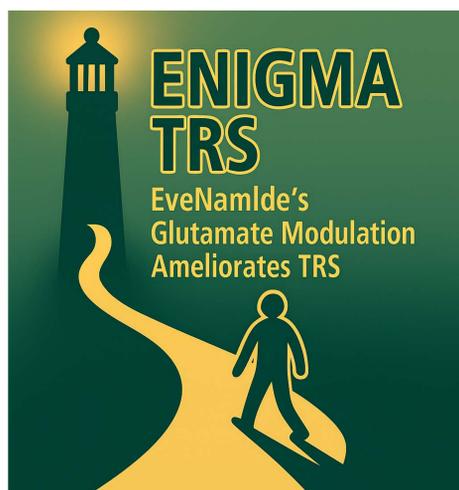
Evenamide, by **normalizing glutamatergic activity** directly at the **hippocampus**, may lead to **sustained and long-lasting benefits** on symptoms of schizophrenia including **negative and cognitive symptoms**

Novel add-on glutamate modulation with evenamide in treatment-resistant schizophrenia: updates from the phase 3, potentially pivotal, ENIGMA-TRS program

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 **Phase 3 - Potentially pivotal**

 **International (> 20 countries)**

 **Randomized**

 **Double-blind**

 **Placebo-controlled**

 **Add-on**

 **Primary Endpoint: 12 Weeks Duration: 1 year**

BACKGROUND

 Among people living with schizophrenia, **30%** of them develop **treatment-resistant schizophrenia (TRS)**, which is associated with **higher risk for morbidity, mortality, and hospitalization**¹

 **Clozapine is currently the only treatment approved for TRS, with limited usage (5-15%)** due to safety and tolerability concerns²

EVENAMIDE

 Voltage-gated sodium channel (VGSC) blocker that **normalizes** aberrant hippocampal **glutamatergic** activity and **reduces** the downstream **hyperdopaminergic** state³

 Clinical trials (**Study 014/015**^{4,5} and **008A**⁶) demonstrated **statistically significant** and **clinically important** benefits with evenamide add-on to antipsychotics (AP) in patients with TRS and inadequate response to antipsychotics

AIM

To present the key design features of the potentially pivotal ENIGMA-TRS program (Study 023 and 022)

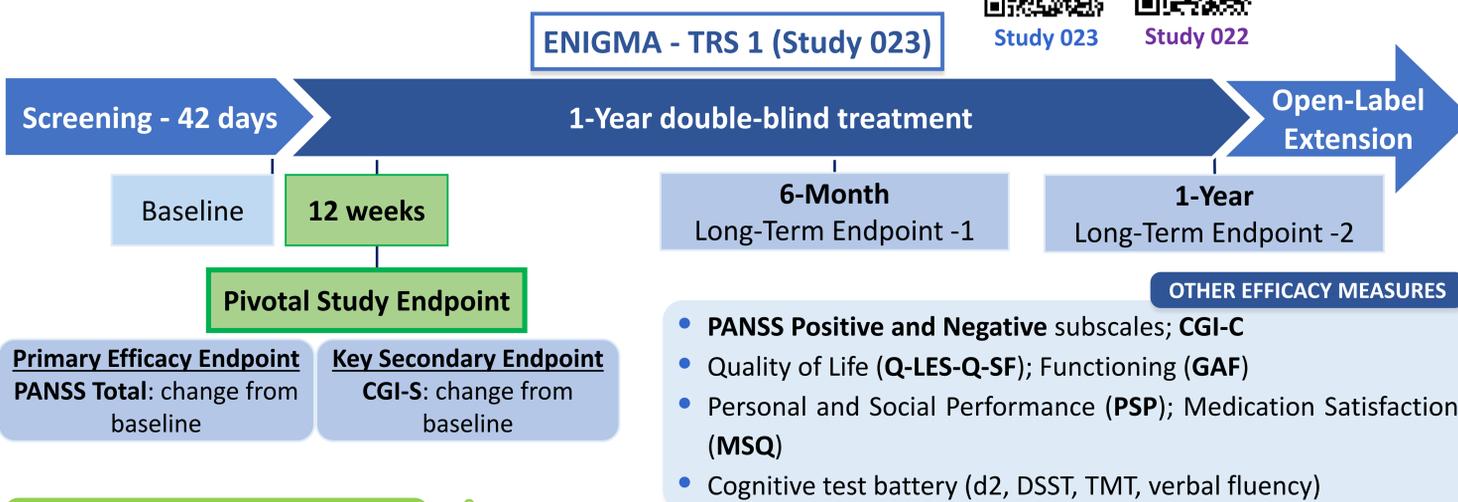


Study 023



Study 022

Scan for details!



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
~100 centers in EU, Asia, Canada, LATAM	~40 centers in USA, LATAM, and Asia

OTHER EFFICACY MEASURES

- PANSS Positive and Negative subscales; CGI-C
- Quality of Life (Q-LES-Q-SF); Functioning (GAF)
- Personal and Social Performance (PSP); Medication Satisfaction (MSQ)
- Cognitive test battery (d2, DSST, TMT, verbal fluency)

KEY INCLUSION CRITERIA

1. DSM-5-TR diagnosis of **schizophrenia**, confirmed by MINI
2. Confirmation of TRS according to **TRRIP working group criteria**⁷
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 either as primary or secondary 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 a score of **at least "5"** on at least one or **"4"** on at least two of the **4 core items** (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) and score of **at least 18** on the 4 core items + 3 additional positive items (grandiosity, hostility, and excitement)
6. Positive and Negative Syndrome Scale (**PANSS**) total ≥ 70 (at Baseline)
7. Global Assessment of Functioning (**GAF**) ≤ 50

*Study 022: CGI-S (3-7)

KEY EXCLUSION CRITERIA

1. Improvement from screening to baseline of $\geq 20\%$ on BPRS or **1 point** on CGI-S
2. Diagnosis of **schizophreniform disorder, schizoaffective disorder, or other primary psychiatric disorder**; **Depressive symptoms** as assessed by **CDSS score of 7 or more**
3. Suicidal risk based on evaluation of C-SSRS
4. Substance use disorder (caffeine, nicotine, and THC allowed if not causing toxic psychosis)
5. Advanced, **severe or unstable disease** of any type that may **interfere** with the **study evaluations** (e.g. liver or kidney disease, severe uncontrolled asthma, malignancy)

KEY 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

- Trial design features of the **ENIGMA-TRS program** described above have been implemented to **standardize patients' selection** and **ratings** across all the sites involved
- Results from the **ENIGMA-TRS program** will determine whether the **addition of evenamide to Standard of Care** is associated with **clinically important benefits** in patients with TRS
- Statistically significant results from these studies would support the **need for glutamate modulation** for the treatment of patients with TRS added on to their antipsychotic treatment



METHODOLOGICAL CHALLENGES

Identification of appropriate standardized criteria for selection of patients with TRS

Confirmation of resistance to antipsychotics rather than non-compliance

Independent confirmation of treatment resistance

Minimizing rating variability on efficacy scales (PANSS, CGI-S/C) across ~100 sites

Retention in a double-blind placebo-controlled study lasting 1-year



SALIENT STUDY DESIGN FEATURES

Adoption of **TRRIP consensus criteria**, at least **2 failed AP attempts of ≥ 6 weeks** in duration including 1 SGA⁷

Confirmation of **adherence** to background AP assessed prior to randomization and during the trial through **plasma levels**

An **Independent Eligibility Assessment Committee (IEAC)** will determine if the patient meets the TRRIP criteria for TRS

Standardization of rating practices through implementation of a **rater training program**

Placebo Switchover: Up to ~50% of patients randomized to **placebo** will be **gradually switched to evenamide** from Week 12 onwards

References:

¹Nucifora et al., 2020, Neurobiol Dis.; ²Warnez et al., 2014, BMC Psychiatry; ³Uliana et al., 2025, Neuropsychopharmacology; ⁴Anand et al., 2025, Int J Neuropsychopharmacol; ⁵Anand et al., 2023, Int J Neuropsychopharmacol; ⁶Anand et al., 2025, Neuropharmacology; ⁷Howes et al., 2017, Am J Psychiatry.



Unique benefits of evenamide on social functioning and life engagement in patients with treatment-resistant schizophrenia or inadequate response to second-generation antipsychotics

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BACKGROUND

Available antipsychotics (AP) for schizophrenia primarily act on **dopamine/serotonin receptors** and benefit **positive** symptoms, failing to improve **negative** or **cognitive** symptoms of schizophrenia

Evenamide, a new drug under development, **normalizes hippocampal hyperglutamatergic** activity and, consequently, **reduces hyperdopaminergic** firing in the **VTA** (Ventral Tegmental Area), with benefits demonstrated on cognitive and social dysfunctions in the MAM animal model of schizophrenia¹

Pre-clinical studies showed benefits of evenamide in **animal models of psychosis**, when used both as **monotherapy** and as **add-on with first- and second-generation antipsychotics (FGA/SGA)**

Clinical trials (**Studies 014/015^{2,3} and 008A⁴**) demonstrated **statistically significant** and **clinically important benefits** with evenamide as add-on to AP in patients with **treatment-resistant schizophrenia (TRS)** and **inadequate response to AP**



Anand et al., 2026
Scan for details!



AIM

Present **post-hoc analyses** from **Study 014/015 and 008A** to show preliminary **benefits of evenamide** on **social functioning and life engagement**

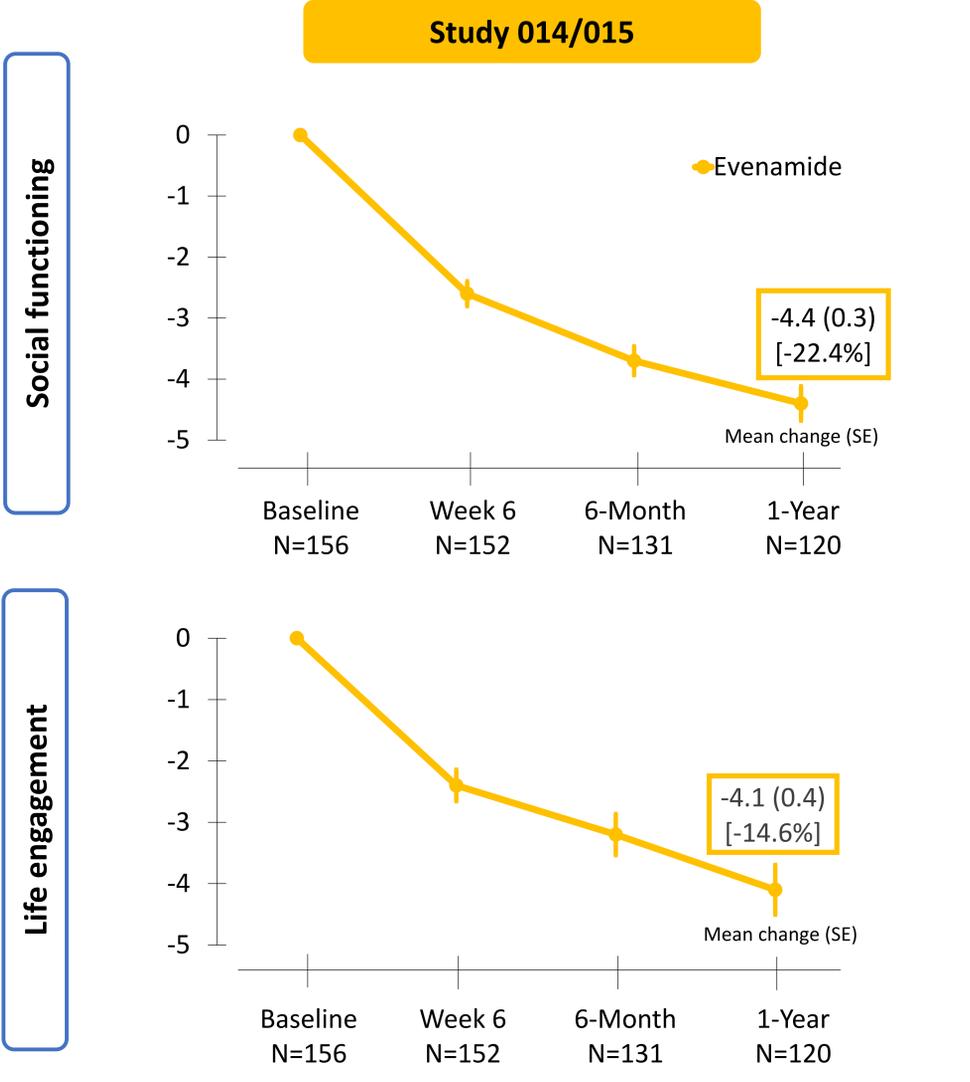


METHODS

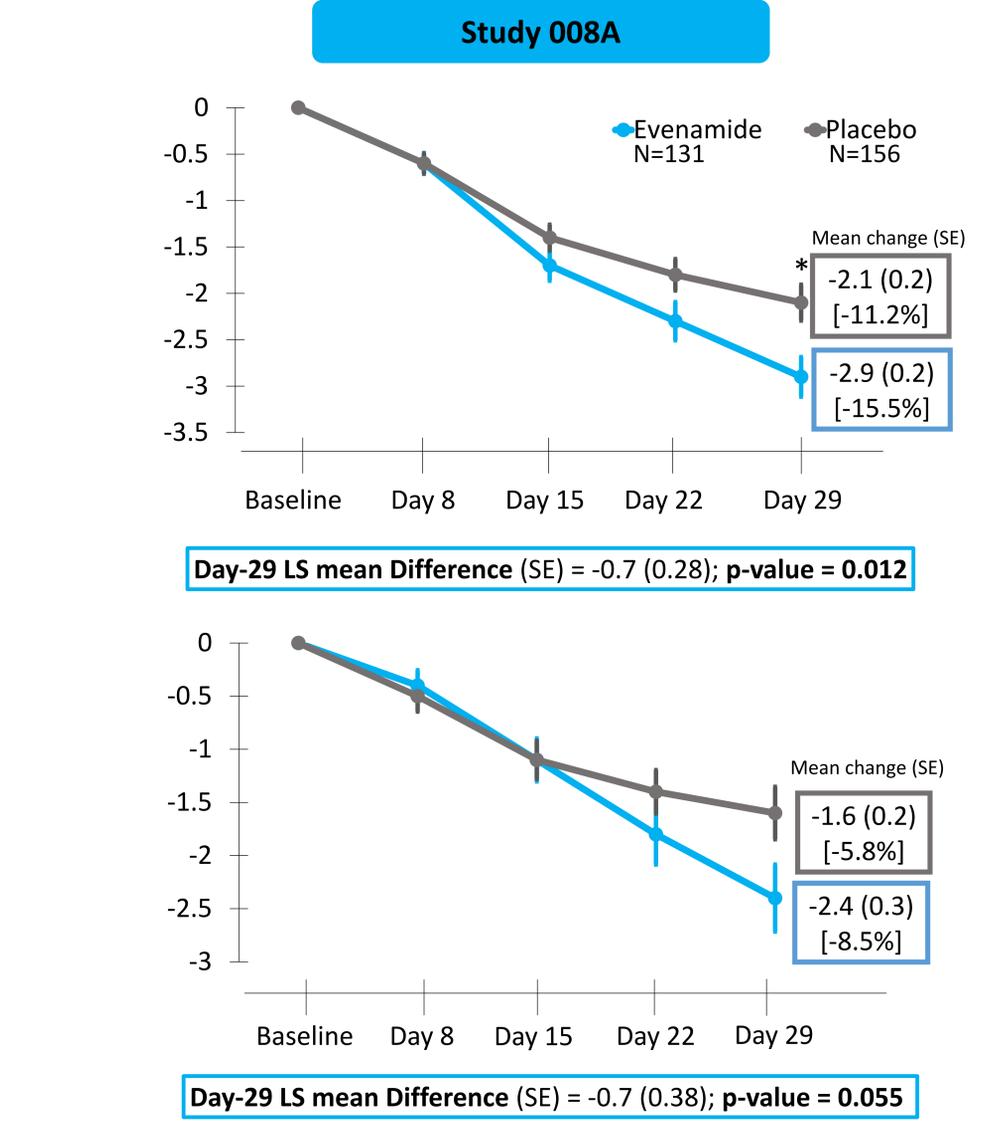
Study 014/015	Study 008A
Phase 2, N = 161, 3 countries	Phase 3, N = 291, 11 countries
1-year	4-week
Randomized, open-label	Randomized, double-blind, placebo-controlled
Long-term efficacy and safety of evenamide (7.5-30 mg bid) add-on to an AP (no clozapine)	Efficacy and safety of evenamide 30 mg bid add-on to an SGA (including clozapine)
Patients with TRS	Patients with inadequate response to SGA

RESULTS

Mean change from baseline on PANSS subdomains of **Social Functioning[#]** and **Life Engagement[§]** (mITT, OC)⁵



Study 014/015 showed **benefits up to and including 1 year** in **patients with TRS** in both **social functioning** and **life-engagement** PANSS subdomains



Study 008A showed a statistically significant evenamide-placebo difference on **Social Functioning PANSS subdomain** in inadequate responders to AP. A greater improvement (borderline significant) with evenamide compared to placebo was also observed on **Life Engagement subdomain**

[#] Social functioning (Purnine et al., 2000): P3,P6,N2, N4,N7,G16

[§] Life engagement (Ismail et al., 2024): N1,N2,N3,N4,N5,N6,G6,G7,G13,G15,G16

TAKE HOME MESSAGES

- **Evenamide as add-on** is associated with a **long-term** (1 Year, **Study 014/015**) **improvement** in **Social Functioning** and **Life Engagement** subdomains of the PANSS
- The trend observed over the **4-week period** of **Study 008A** is **promising**, as it suggests a **continued, positive effect of evenamide compared to placebo** (SGA) on **Social Functioning and Life Engagement** domains, which may **further increase over a longer treatment period**
- By modulating **hippocampal hyperglutamatergic activity**, **evenamide** was associated with **statistically significant benefits** on both **positive and negative symptoms of schizophrenia** (PANSS subscales)⁴. If positive, results from the ongoing ENGIMA-TRS program will support the use of evenamide as a new treatment option for patients living with TRS

¹Uliana et al., 2025, *Neuropsychopharmacology*; ²Anand, et al., 2025 *IntJNeuropsychopharmacology*; ³Anand et al., 2023 *IntJNeuropsychopharmacology*; ⁴Anand et al., 2025 *Neuropharmacology*; ⁵Anand et al., 2026 *Ther. Adv. Psychopharmacol.*