Glutamate modulation by evenamide produces statistically significant and clinically relevant improvement in patients with treatment-resistant schizophrenia

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BACKGROUND

- **Modulation of monoamines**, effective in acute exacerbations of schizophrenia, **failed** to produce **statistically significant or clinically relevant benefits** in patients with **inadequate response** or **treatment-resistant schizophrenia** (TRS)[1,2]
- The **absence of benefit of augmentation therapy** with antipsychotics[3] (5-HT/DA modulators) for the management of schizophrenia has led to an increasing interest for **therapeutic agents** with **novel mechanisms of action** (e.g. muscarinic modulators, glutamate transmission modulators, etc.), which, in some cases, have proved efficacy in acutely ill patients but **did not demonstrate benefits in patients with poor/no response** (e.g. KarXT)[4]

- **Evenamide**, a selective inhibitor of **voltage-gated sodium channels, normalizes excessive glutamate release** without affecting its basal levels. By acting at the site of dysfunction, evenamide normalizes hyperactive hippocampal neurons and consequently reduces hyperdopaminergic firing in the VTA
- Evenamide has been shown to be **effective in animal models of psychosis** including the **MAM model**, in which it was able to rescue cognitive deficits and social impairments, suggesting its potential for improving cognitive and negative symptoms. The effects of evenamide persist beyond its presence in the brain in MAM rats, suggesting potential for neuronal plasticity[5]

AIM

Present **new results** underlining the **clinical meaningfulness** of **evenamide in patients with inadequate response or TRS** from **Studies 014/015** and **Study 008A**

METHODS

Study 014/015 [6,7]	Study 008A [8]
Phase II, **1-year** (6-week + 46-week), randomized, open-label, rater-blinded, international study	**Phase III**, **4-week**, randomized, double-blind, **placebo-controlled**, international study
Safety, tolerability, and preliminary efficacy of fixed doses of evenamide of **7.5 mg bid**, **15 mg bid**, and **30 mg bid add-on** to AP	Efficacy, safety, and tolerability of **evenamide 30 mg bid** vs placebo bid **add-on** to SGA including clozapine
Patients with **TRS** on a stable therapeutic dose of a single antipsychotic (other than clozapine)	Outpatients with chronic schizophrenia **not responding adequately** to a therapeutic dose of an atypical AP
PANSS total 70-90; **CGI-S 4-6**; predominant positive symptoms	**PANSS total 70-85**; **CGI-S 4-6**; predominant positive symptoms
N=**161** patients randomized, N=121 (**75%**) completed at 1-year	N=**291** patients randomized, N=280 (**96%**) completed the trial

RESULTS

1. Proportion of patients no longer meeting protocol TRS severity criteria
Study 014/015 (mITT N=156; OC)

Severity criteria	Week-6 N=152 n(%)	6-Month N=131 n(%)	1-Year N=120 n(%)
1. PANSS ≥ 70	72 (47.3)	84 (64.1)	84 (70.0)
2. Core items* ≥ 20	60 (39.4)	76 (58.0)	80 (66.7)
3. CGI-S ≥ 4	52 (34.2)	66 (50.4)	76 (63.3)
4. Score ≥ 4 on at least 2 core symptoms of psychosis#	75 (49.3)	87 (66.4)	87 (72.5)
All Combined	40 (26.3)	51 (38.9)	66 (55.0)

*P1=delusions; P2=conceptual disorganization; P3=hallucinatory behavior; P4=excitement; P6=suspiciousness; P7=hostility; G9=unusual thought content
P2=conceptual disorganization; P3=hallucinatory behavior; P6=suspiciousness; G9=unusual thought content

2. Proportion of patients achieving remission
Study 014/015 (mITT N=156; OC)

Remission criteria	Definition	Maintenance period required	n (%) of patients meeting remission criteria
Lieberman et al., 1993 (adapted)	P1, P2, P3, P6, G5 ≤ 3 CGI-S maximum mildly ill CGI-C at least much improved	8 weeks	43 (27.6)
Andreasen et al., 2005	P1, P2, P3, N1, N4, N6, G5, G9 ≤ 3	24 weeks	39 (25.0)

P1=delusions; P2=conceptual disorganization; P3=hallucinatory behavior; P6=suspiciousness; N1=blunted affect; N4=passive social withdrawal; N6=lack of spontaneity; G5=mannerism and posturing; G9=unusual thought content

3. Proportion of patients meeting composite responder definitions
Study 014/015 (mITT N=156; OC)

Responder criteria	Week-6 N=156 n (%)	6-Month N=156 n (%)	1-Year N=156 n (%)
PANSS≥20% improvement from baseline, PANSS<63 **AND** CGI-S ≤3	16 (10.3)	31 (19.9)	50 (32.1)
PANSS≥20% improvement from baseline, PANSS<63 **OR** CGI-S ≤3	22 (14.1)	41 (26.3)	56 (35.9)
PANSS≥20% improvement from baseline, CGI-S at least 1-category improvement, CGI-C at least "much improved"	22 (14.1)	36 (23.1)	46 (29.5)

4. Proportion of patients meeting composite responder definitions
Study 008A (mITT N=287; OC)

Responder criteria	Evenamide W4 N=131 n (%)	Placebo W4 N=156 n (%)	p-value
PANSS≥20% improvement from baseline, PANSS<63 **AND** CGI-S ≤3	19 (14.5)	14 (9.0)	0.147
PANSS≥20% improvement from baseline, PANSS<63 **OR** CGI-S ≤3	26 (19.8)	18 (11.5)	0.054
PANSS≥20% improvement from baseline, CGI-S at least 1-category improvement, CGI-C at least "much improved"	21 (16.0)	11 (7.0)	0.019

Percentages are calculated as n (Observed cases) / N (mITT population)

KEY FINDINGS AND CONCLUSIONS

- **Study 014/015** demonstrated clinically relevant **long-term benefits of evenamide** when used as **add-on** to first- and second-generation antipsychotics in **patients with TRS**. **At 1-year, more than 50% of enrolled patients** did not meet **anymore protocol TRS severity criteria** and approximately the **25% of them** achieved **remission** based on literature criteria
- **Study 008A** was associated with **statistically significant, clinically important improvements** in **inadequately responding** patients on SGA (including **clozapine**)
- **Modulation of glutamatergic system** with **evenamide** is a promising **novel therapeutic approach** for patients with **inadequate or no response to antipsychotics**

References: [1]Bugarski-Kirola et al., 2022; [2]Kane et al., 2022; [3]Galling et al., 2017; [4]Bristol Meyer Squibb press release 22 April 2025; [5]Uliana et al., 2025; [6]Anand et al., 2023; [7]Anand et al., 2024; [8] Anand et al., 2025

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