Success in the mechanism-based development of evenamide for patients with inadequate response or treatment-resistant schizophrenia

Ravi Anand[1], Alessio Turolla[2], Giovanni Chinellato[2], Francesca Sansi[2], Richard Hartman[3]
[1]Anand Pharma Consulting AG, St. Moritz, Switzerland; [2] Newron Pharmaceuticals SpA, Bresso, Italy; [3] NeurWrite LLC, Morristown, USA
CMO Ravi Anand, MD - **Email** ravi@anand.ch; **Disclosure**: R. Anand is a consultant to Newron Pharmaceuticals SpA

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BACKGROUND

- **Schizophrenia** is a **chronic mental health disorder**, in which both **dopaminergic** and **glutamatergic abnormalities** are believed to be responsible for symptoms impacting **cognition, behavior, and emotions**
- **Unmet medical needs** remain for this disease, with **30-60%** of patients experiencing **inadequate benefit** from antipsychotics (APs) and **30%** developing **treatment-resistant schizophrenia (TRS)**
- Increasing evidence revealed **excessive glutamatergic rather than dopaminergic activity** in patients with **limited/no response to AP**
- **Evenamide**, a selective **inhibitor** of **voltage-gated sodium channels**, **normalizes excessive glutamatergic activity** in the **hippocampus** and **downregulates** the **hyperdopaminergic** state in the **VTA**, reversing schizophrenia-related cognitive and social dysfunctions in the MAM animal model[1]

AIM

Present clinical results obtained with evenamide as add-on to APs in patients with TRS and poor responders from two phase II/III studies

STUDIES 014/015 [2,3]

- **Phase II, 1-year** (6-week + 46-week), randomized, open-label, rater-blinded, international study
- Safety, tolerability, and preliminary efficacy of fixed **add-on doses** of **evenamide of 7.5 mg bid**, **15 mg bid**, and **30 mg bid**
- Patients with **TRS** on a stable therapeutic dose of a single AP (**other than clozapine**)
- Key inclusion criteria: **PANSS total 70-90**; **CGI-S 4-6**; **predominant positive symptoms**

Key efficacy results (mITT N=156) – Statistic: Mean/mean change (%)

Scale	Baseline	Week-6 N=152	6-Month N=131	1-Year N=120
PANSS Total	79.5	-9.5 (-11.9)	-12.8 (-16.1)	-15.9 (-20.0)
CGI-S	4.5	-0.7	-1.0	-1.1

Responder analyses (mITT N=156) – Statistic: n (%)

Scale	Week-6 N=152	6-Month N=131	1-Year N=120
PANSS ≥20% improvement	24 (15.4)	48 (34.0)	59 (41.8)
CGI-C at least "much improved"	38 (24.4)	43 (30.5)	53 (37.6)
CGI-S ≥2 categories of improvement	16 (10.3)	21 (14.9)	34 (24.1)

OVERALL SUMMARY OF SAFETY

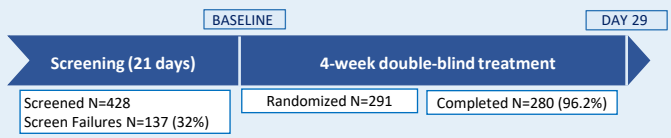
Absence of pattern of abnormal findings on vital signs, ECG (>5000), lab exams, metabolic abnormalities, sexual dysfunction, EPS, suicidality, or depressive symptoms. **No evidence of seizurogenic activity** based on EEG (>1000) and Seizure Checklist (>4000)

Most frequent TEAEs on evenamide (>1.5%) vs placebo

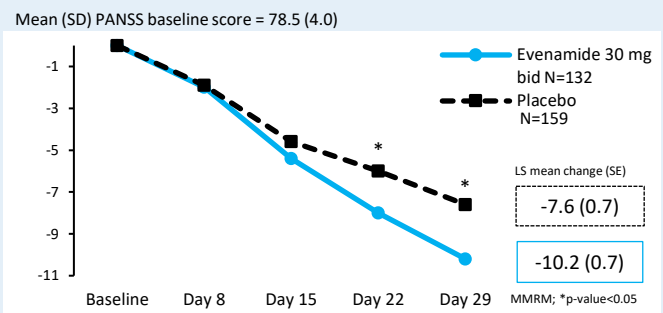
Preferred Term	Evenamide	Placebo
Somnolence	3.7%	4.9%
Headache	3.2%	2.5%
Insomnia	2.4%	2.5%
Vomiting	1.7%	0.8%

STUDY 008A [4]

- **Phase III**, 4-week, randomized, double-blind, **placebo-controlled**, international study
- **Efficacy**, safety, and tolerability of **evenamide 30 mg bid** (vs placebo bid) as an **add-on to SGAs** including clozapine
- Outpatients with chronic schizophrenia **not responding adequately** to an atypical AP at therapeutic plasma concentration
- Key inclusion criteria: **PANSS total 70-85**; **CGI-S 4-6; predominant positive symptoms**



Primary efficacy results – PANSS mean change from baseline (ITT N=291)



Endpoint Treatment Difference: LS mean (SE) = -2.5 (0.9); **p-value = 0.006**

Key secondary efficacy results – CGI-S change from baseline (ITT N=291)

Scale	Visit	Evenamide 30 mg bid N=132	Placebo N=159	Drug-placebo difference
CGI-S	Baseline – mean (SD)	4.4 (0.6)	4.5 (0.6)	
	Day 29 – LS mean change (SE)	-0.6 (0.1)	-0.5 (0.1)	**-0.16 (0.08)**
	p-value [CI]	**0.037 [-0.3, -0.0]**		

Responder analyses: PANSS and CGI-C (mITT N=287)

Improvement category	Visit and Statistics	Evenamide 30 mg bid N=131	Placebo N=156
PANSS ≥20% improvement	n (%) Day 29	20.6%	11.5%
	Odds Ratio (p-value)	**1.99 (0.037)**	
CGI-C at least "much improved"	n (%) Day 29	31.3%	17.3%
	Odds Ratio (p-value)	**2.18 (0.006)**	

KEY FINDINGS AND CONCLUSIONS

- Pilot open-label **studies 014/015** in **TRS patients** indicated that **add-on** treatment with **evenamide** was associated with **progressive and long-lasting improvements up to 1-year** of treatment
- Double-blind, placebo-controlled **study 008A** in **inadequate responders** was associated with **statistically significant benefits**, compared to placebo, observed across all efficacy scales (**PANSS/CGI-S/CGI-C**), both in terms of **mean change from baseline** as well as on the **responder analyses**
- These results indicate that **glutamate modulation** can provide **additional benefits** and address unmet needs in patients with **poor AP response or TRS**
- The **phase-III program ENIGMA-TRS** has been initiated to confirm the benefits of glutamate modulation in patients with documented **TRS** (see poster **PS01-0225**)

References: [1] Uliana et al., 2025; [2] Anand et al., 2023; [3] Anand et al., 2024; [4] Anand et al., 2025