Addition of evenamide, a glutamate release inhibitor, to patients with treatment resistant schizophrenia on an antipsychotic is effective and associated with long-term efficacy: Results of a Phase 2 study

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Preclinical

Key Preclinical Findings

- **Evenamide is a sodium channel blocker**, devoid of biological activity at >130 CNS targets up to high concentrations (10μM)
- Evenamide has demonstrated dose-dependent glutamate release attenuation
- Behavioral results from preclinical models of psychosis indicate evenamide antagonizes worsening induced by NMDAr antagonists (PCP, MK-801, Ketamine)
- Evenamide as a monotherapy reverses the PPI deficit induced by glutamate dysregulation due to ketamine. Combination of ineffective doses of clozapine and evenamide fully rescues PPI **(Figure 1)**
- Inhibition of abnormal activity in glutamatergic networks translates into normalization of glutamate levels (**Figure 2**)
- The preferential blockade of the Na channel in its inactivated state translates into the modulation of sustained repetitive firing without inducing impairment of the normal neuronal excitability (**Figure 3**)

Figure 1

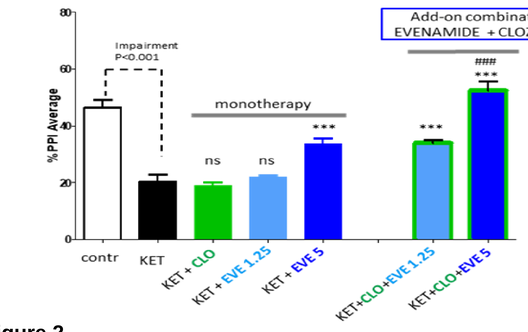


Figure 2

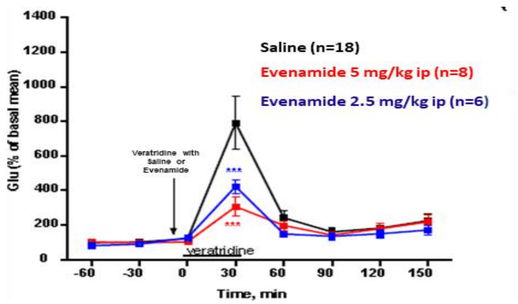
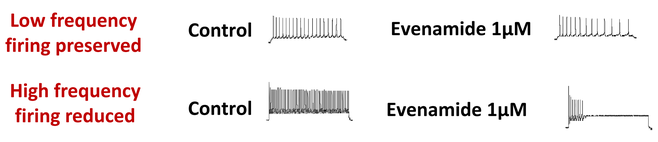


Figure 3

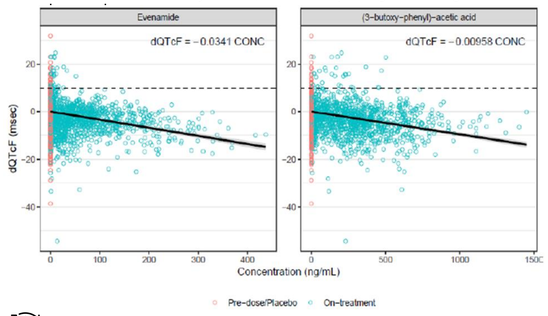


Anand et al 2018, ECNP

Phase I

NW-3509/010/I/2019

- Randomized, 4-way cross-over study to assess the effect of single doses of evenamide (NW-3509) of 30 and 60 mg compared to moxifloxacin on the **QT/QTc interval** in healthy subjects in 56 **healthy volunteers**
- **NO effects on QTc** (PK/QTc analyses), Holter measurements, or ECG (HR, PR, QRS) abnormalities at doses of 30 and 60 mg
- **NO evidence of QTcF prolongation**
- **NO occurrences of clinically relevant conduction abnormalities**, arrhythmias, or morphologic changes were



Evenamide – ADME Summary

- **Absorption** – Rapid (Tmax 1-2 hour post-dose), half-life (2-4 hours)
- **Distribution** – Protein binding 94.2% (humans), rapid entry in brain (rat)
- **Metabolism** – Extensive (>20 components, largely by CYP2D6), one major metabolite (3-BPAA) which is inert
- **Excretion** – renal <1%, faecal excretion <1.5%, metabolites cleared by conjugation, glucuronidation

NW-3509/002/II/2015

- This 4-week, Phase 2a, double-blind, placebo-controlled, randomized, multi-national study
- Tolerability, safety and preliminary evidence of efficacy of evenamide (15-25 mg bid) as an add-on to aripiprazole or risperidone in 89 patients with chronic schizophrenia
- **Patients** treated with evenamide **showed improvement** on the symptoms of schizophrenia assessed by the Positive and Negative Syndrome Scale (PANSS)
- The **proportions of patients showing improvement from baseline to endpoint were substantially higher for evenamide** vs. placebo on the CGI-C (55.3% vs 35.9%) and on the PANSS Positive Symptoms sub-scale (74.5% vs 43.6 %).

PANSS Positive and Total; MMRM by Visit (mITT Population Excluding 3 Outliers)

		Evenamide (N=47)	Placebo (N=37)	DIFF vs Placebo		
	Day	LS Mean (SE)	LS Mean (SE)	LS Mean	95% CI	P-value
PANSS Positive	8	-1.28 (0.25)	0.01 (0.27)	-1.29	(2.009,0.580)	0.0006
	15	-1.47 (0.30)	-0.46 (0.33)	-1.01	(1.893,0.131)	0.0250
	22	-2.25 (0.39)	-1.10 (0.42)	-1.15	(2.290,0.009)	0.0482
	28	-2.03 (0.43)	-0.65 (0.47)	-1.38	(2.640,0.119)	0.0324
PANSS Total	8	-2.63 (0.67)	-0.13 (0.72)	-2.51	(4.419,0.593)	0.0109
	15	-4.23 (0.87)	-1.43 (0.94)	-2.80	(5.315,0.282)	0.0298
	22	-4.81 (1.12)	-2.78 (1.22)	-2.04	(5.305,1.231)	0.2181
	28	-4.58 (1.20)	-2.36 (1.33)	-2.21	(5.753,1.325)	0.2166

NW-3509/008/II/2019

- 4-week, randomized, double-blind, placebo-controlled, study designed to evaluate the safety, tolerability, including effects on EEG recordings, and preliminary efficacy of 2 fixed oral doses of evenamide of 7.5 mg and 15 mg bid as add-on to atypical antipsychotics in patients with chronic schizophrenia
- No evidence of any seizurogenic activity for evenamide based on interpretations of EEG, as well as assessment of the Seizure Checklist
- No patient treated with study medication experienced an EEG abnormality that would be indicative of seizure-like activity; and no seizure-like symptoms were identified for patients treated with evenamide in the assessment of the Seizure Checklist.
- No effects of evenamide 7.5 or 15 mg BID were noted on physical or neurological examinations, standard eye examinations, EPS (assessed by ESRS-A), suicidality (assessed by the C-SSRS), or depressive symptoms (assessed by the CDSS).

Phase II

NW-3509/014/II/2019 + **NW-3509/015/II/2019** **[*ongoing*]**

- **Study 014** → 6-week, randomized, open-label, rater-blinded, international study
- **Study 015** → 46-week, long-term extension
- Safety, tolerability and preliminary efficacy
- 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 antipsychotic (other than clozapine)

Long-term, 1-year, interim results for the first 100 patients randomized in Study 014

1. Key efficacy measures (N=97; LOCF)

Visit	PANSS Responder Rate #	PANSS* Mean Rating (Change)	CGI-S* Mean Rating (Change)	LOF* Mean Rating (Change)
Baseline	-	79.7	4.6	18.1
Week-6	16.5%	70.2 (-9.5*) [-11.9%]	3.9 (-0.7*)	19.0 (+1.0*)
6-Months	39.2%	67.1 (-12.6*) [-15.9%]	3.7 (-0.9*)	19.7 (+1.6*)
1-Year	**47.4%**	**65.1 (-14.6*) [-18.3%]**	**3.5 (-1.1*)**	**19.9 (+1.8*)**

At least 20% improvement from Baseline on PANSS Total score *p-value <0.001 (paired t-test)

2. Key safety assessment (N=100)

- Most common TEAEs → pyrexia and insomnia, each experienced by 3 patients
- No clinically important new/worsening abnormalities on → vital signs, ECG, laboratory tests, physical/neurological/eye exams, EPS (ESRS-A) or depression (CDSS)

3. Key findings and conclusions (N=97; LOCF)

- **Statistically significant improvement** in PANSS total score, CGI-S, and LOF (*p<0.001; paired t-test; LOCF)
- Through **1-year,** all efficacy scales show **gradually increasing and sustained improvement**:
- **Add-on of evenamide** to all antipsychotics (APs) was **well tolerated**, with a low incidence of (TEAEs).
- **97%** of patients completed 6-week treatment period, with **90%** continuing in long-term extension.

Phase III

NW-3509/008A/II/2020 [*ongoing*]

- **Phase II/III**, international, 4-week, double-blind, placebo-controlled, international study
- Enrollment target N=260
- **Evenamide/matching placebo added on to antipsychotic in** outpatients with chronic schizophrenia not responding adequately to their current therapy
- **Safety**, **tolerability** and preliminary **efficacy**
- Fixed add-on dose of evenamide of **30 mg *bid*** and placebo

New Evenamide TRS Study [Q4 2023]

- Phase III, potentially pivotal, double-blind, placebo-controlled, international study
- 12-week initial treatment period + 40-week extension
- 2 doses of evenamide
- Patients with treatment-resistant schizophrenia (TRIPP criteria) not responding adequately to their current antipsychotic treatment – "standard of care"

Summary Of Subjects Who Have Received Evenamide
Cut off date 31-January-2023

Treatment	Non-Therapeutic studies	Therapeutic studies
Evenamide Dose	1-60 (mg/day)	
Evenamide (a)	103	352
Placebo	76 (b)	136

(a) Total unique exposures to evenamide.
(b) In crossover study 010, subjects are counted for each treatment period

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2023 Congress of the Schizophrenia International Research Society (SIRS) | 11-15 May, 2023 | Toronto, Canada

Evenamide, a new chemical entity, benefits patients with treatment-resistant schizophrenia (TRS) when used as an add-on to antipsychotics: final results from a Phase II, international, randomized study

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[1]R&D department, Anand Pharma Consulting AG, St. Moritz, Switzerland; [2] R&D department, Newron Pharmaceuticals SpA, Bresso, Italy;
[3] NeurWrite LLC, Morristown, USA

Background

1. **TRS** may occur in up to 20% of first-episode patients, while another ~20% develop it within 5 years of starting antipsychotic (AP) treatment
2. Findings from neurochemistry, neuro-metabolism, and functional imaging in TRS patients indicate **abnormalities in glutamatergic neurotransmission**
3. **Evenamide**, a selective inhibitor of voltage-gated sodium channels, which is devoid of biological activity at >130 CNS targets, **normalizes glutamate release** without affecting basal levels
4. **Evenamide**, as monotherapy and as add-on to APs, **attenuates worsening** induced by amphetamine, scopolamine, phencyclidine, MK-801, or ketamine **in animal models of schizophrenia**

AIM

Present **encouraging**, group-blinded, **final efficacy and safety results** from a Phase-II clinical trial evaluating **evenamide** as add-on therapy for patients with TRS

Methods

1. This is a **6-week**, **randomized**, open-label, **rater-blinded**, **international** study to evaluate the **safety**, tolerability and **preliminary** evidence of **efficacy** of evenamide (7.5, 15 and 30 mg bid, po) in **patients with TRS** on a stable dose of an antipsychotic, other than clozapine.
2. Efficacy was assessed on the PANSS, CGI-S/C, and Strauss-Carpenter Level of Functioning (LOF) scale, while tolerability was assessed based on treatment-emergent adverse events (TEAEs), Vital Signs, ECG, EPS (ESRS-A) and all other safety measures.
3. A total of 161 patients were randomly assigned to treatment in Study 014, with a **minimum of 50 in each of the 3 treatment groups.**
4. Efficacy and safety assessments were conducted at 1 to 2-week intervals. Change from baseline was analyzed for the PANSS, CGI-S, and LOF using a paired t-test.
5. Completers continuing assigned doses for an **additional 46 weeks in Study 015.**

Key inclusion criteria

1. TRS defined as significant clinical symptoms despite adequate doses of 2 standard antipsychotic medications (other than clozapine) from 2 different chemical classes, including at least 1 atypical antipsychotic, for at least 6 weeks of treatment

2. Moderately to severely ill (**CGI-S of 4, 5 or 6**)

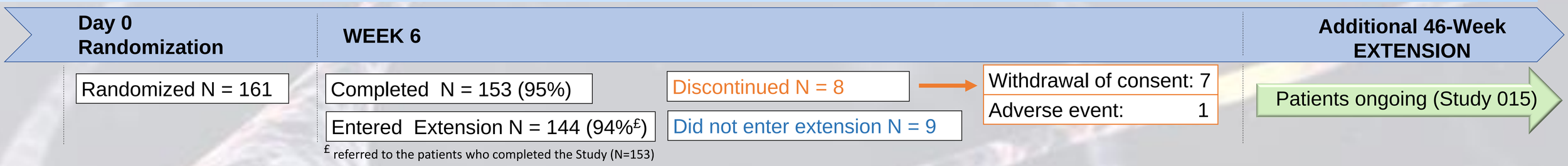
3. PANSS total score of **70-90** and predominant positive symptoms (score of 4 or more on at least 2 core symptoms and a PANSS Positive total score ≥ 20)

4. Functional deficits (**GAF ≤50**)

5. Monotherapy at a stable dose with any antipsychotic (other than clozapine)

Results

Study 014 – Patient disposition



£ referred to the patients who completed the Study (N=153)

Demographic and baseline characteristics (mITT, N=156)

Characteristic	Statistic	Total N=156
Age (years)	Mean (SD)	37.8 (9.77)
Duration of illness (years)	Mean (SD)	6.8 (3.09)
BMI (kg/m2)	Mean (SD)	25.1 (5.02)
Sex – Male	n (%)	109 (69.87)
Race – Asian	n (%)	153 (98.08)
Most common background APs		
Risperidone	n (%)	88 (56.4)
Olanzapine	n (%)	43 (27.6)

Summary of Efficacy (mITT, N=156)

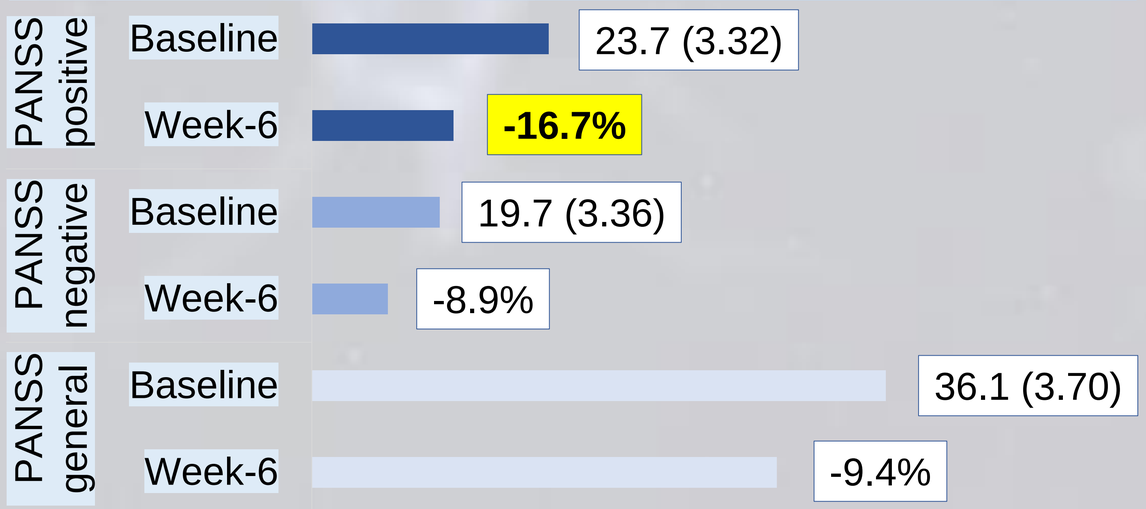
Scale	Baseline Mean (SD)	Week 6 Mean change (SD) [% change]
PANSS Total Score	79.5 (5.03)	-9.5 (7.10)* [-11.9%]
CGI-S	4.5 (0.70)	-0.7 (0.70)*
CGI-C #	-	3.0 (0.74)
Strauss-Carpenter LOF	17.9 (4.05)	+1.3 (2.70)*
MSQ +	4.0 (0.78)	+0.9 (1.06)

* p-value <0.001 (LOCF, paired t-test) # Mean rating at Endpoint (Week 6 or early d/c)
+ Medication Satisfaction Questionnaire

Safety Summary (N=160) and most common TEAEs (> 1.5%)

Patients	No. of patient (%)
With at least one TEAE	41 (25.5)
Pyrexia	*4 (2.5)*
Dizziness	*3 (1.9)*
Blood creatine phosphokinase increased	*3 (1.9)*
With at least one treatment-related TEAE	15 (9.3)
With any TEAE leading to Study discontinuation	1 (0.6)

PANSS subscales analysis: Mean (SD) and % change from Baseline



Key Findings and Conclusions

Statistically significant improvement in PANSS total score, CGI-S, and Strauss-Carpenter LOF (*p<0.001; paired t-test; LOCF)

Improvement was observed in all **PANSS subscales (including negative symptoms), with the positive subscale** showing highest level of improvement

Add-on of evenamide to all APs was **well tolerated**, with low incidence of TEAEs and no pattern of abnormalities on other safety measures. Moreover, **95%** of patients completed 6-week treatment period, with **94%£** of the completers continuing in long-term extension.

This trial is the first international trial of an NCE AP used as an add-on to a single AP in patients with TRS. Results may change the management of future TRS patients.

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Evenamide, as an add-on to antipsychotics, benefits patients with treatment-resistant schizophrenia (TRS): 1-year interim results from the first 100 patients in an ongoing international randomized study

Ravi Anand[1], Rodolfo Giuliani[2], Alessio Turolla[2], Giovanni Chinellato[2], Richard Hartman[3]

[1]R&D department, Anand Pharma Consulting AG, St. Moritz, Switzerland; [2] R&D department, Newron Pharmaceuticals SpA, Bresso, Italy; [3] NeurWrite LLC, Morristown, USA

Background

1. **TRS** develops in **~30%** of patients **in about 5 years** from starting treatment with antipsychotics (APs), resulting in increased morbidity, suicidality, and mortality
2. Findings from neurochemistry, neuro-metabolism, and functional imaging in TRS patients indicate **abnormalities in glutamatergic neurotransmission**
3. **Evenamide**, a selective inhibitor of voltage-gated sodium channels, is devoid of biological activity at >130 CNS targets**,** and **normalizes glutamate release** without affecting basal levels
4. **Evenamide**, as monotherapy and as add-on to antipsychotics, **attenuates worsening** induced by amphetamine, scopolamine, phencyclidine, MK-801, or ketamine **in animal models of schizophrenia**

AIM

Provide group-blinded, **1-year treatment, interim efficacy and safety results** from the first Phase-II clinical trial evaluating a glutamate release inhibitor (evenamide) as add-on therapy for patients with TRS

Methods

1. Study 014 is a **6-week, randomized, rater-blinded, international** study with completers continuing assigned doses for an **additional 46 weeks** (Study 015).
2. Patients were initially randomized to 7.5 or 15 mg bid; the Independent Safety Monitoring Board (ISMB) allowed randomization to 30 mg bid after reviewing safety data from the first 50 patients.
3. Efficacy ratings (PANSS, CGI-C/S, and Level of Functioning [LOF] scale) were performed by a **psychiatrist blinded to the evenamide dose.**
4. Data were analyzed as a single evenamide group, using **paired t-test** to assess **changes from baseline to endpoint** (Week 52)

Key inclusion criteria

1. TRS defined as significant clinical symptoms despite adequate doses of 2 standard antipsychotic medications (other than clozapine) from two different chemical classes, including at least 1 atypical antipsychotic, for at least 6 weeks of treatment

2. Moderately to severely ill (**CGI-S of 4 to 6**)

3. PANSS total score of **70-90** and predominant positive symptoms (score of 4 or more on at least 2 core symptoms and a PANSS Positive total score ≥ 20)

4. Functional deficits (**GAF ≤50**)

5. Monotherapy at a stable dose with any antipsychotic (other than clozapine)

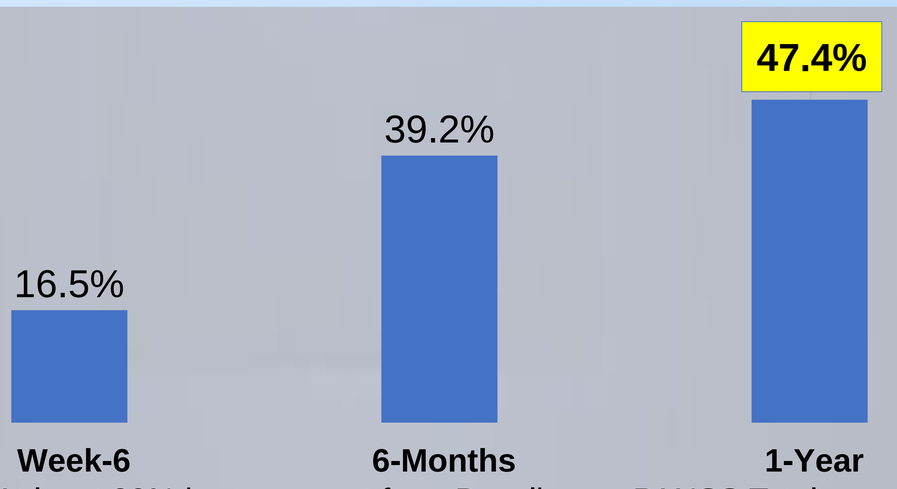
Results

Patient disposition

Day 0 Randomization	WEEK 6		WEEK 30 6-MONTH	WEEK 52 1-YEAR
Randomized N = 100	Completed N = 97	Discontinued N = 3	Completed N = 85	Completed N = 77
	Entered Extension N = 90	Did not enter extension N = 7	Discontinued N = 5	Discontinued N = 8

Total discontinued:	16
Withdrawal of consent:	10
Lost to follow-up:	4
Adverse event:	2

PANSS Responder Rate # (N=97; LOCF)

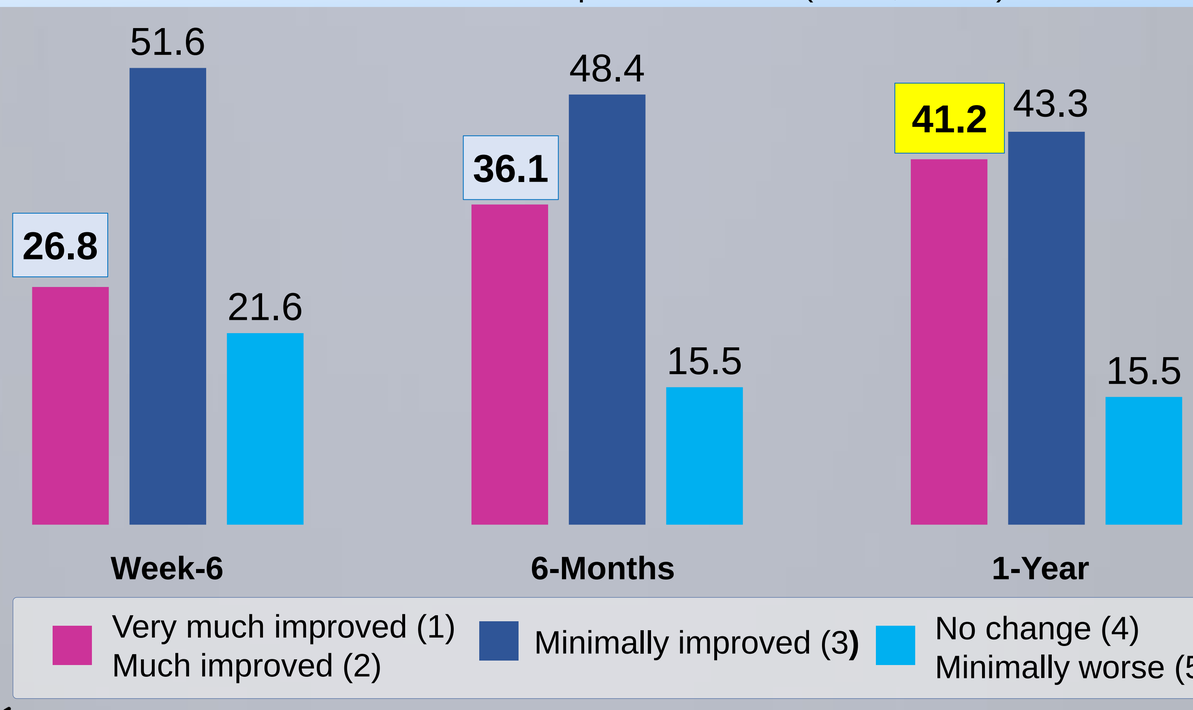


At least 20% improvement from Baseline on PANSS Total score

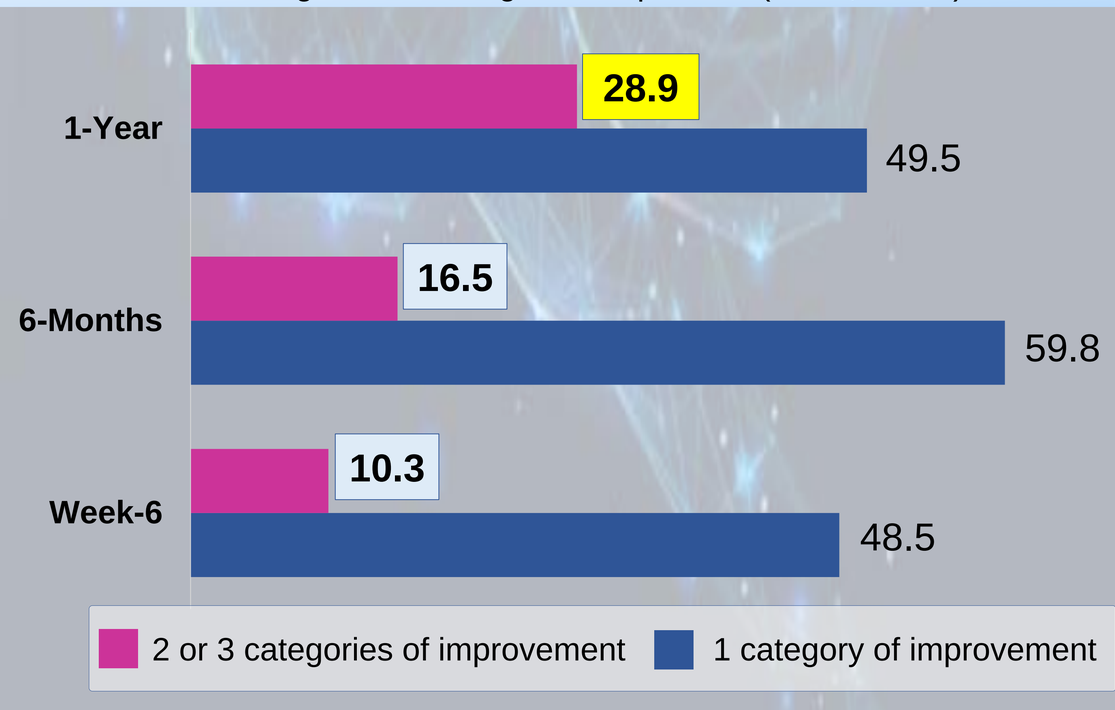
Mean ratings of PANSS, CGI-S and LOF over time (N=97; LOCF)

Visit	PANSS	CGI-S	LOF
	Mean Rating (Change) [%]	Mean Rating (Change)	Mean Rating (Change)
Baseline	79.7	4.6	18.1
Week-6	70.2 (-9.5*) [-11.9%]	3.9 (-0.7*)	19.0 (+1.0*)
6-Months	67.1 (-12.6*) [-15.9%]	3.7 (-0.9*)	19.7 (+1.6*)
1-Year	**65.1 (-14.6*) [-18.3%]**	**3.5 (-1.1*)**	**19.9 (+1.8*)**

CGI-C from Baseline - Responder Rate % (N=97; LOCF)



CGI-S categories of change - % of patients (N=97; LOCF)



Key Findings and Conclusion

Statistically significant improvement at all 3 timepoints in PANSS total score, CGI-S, and Strauss Carpenter LOF (*p<0.001; paired t-test; LOCF)

Through **1-Year,** all efficacy scales show **gradual and sustained improvement**

Add-on of evenamide to all APs was **well tolerated**, with low incidence of treatment-emergent adverse events (TEAEs). **97%** of patients completed 6-week treatment period, with **90%** continuing in long-term extension.

This trial is the first international trial of an NCE AP used as an add-on to a single AP in patients with TRS. Results may change the management of future TRS patients.

Demographic and baseline characteristics

- Age (years) - Mean [SD] → 37.6 [10.1]
- Gender (% males) → 69%
- Duration of illness (years) – Mean [SD] → 6.7 [2.7]
- Background AP→ risperidone (56%), olanzapine (29%), others (15%)

Safety summary

- Most common TEAEs → pyrexia, insomnia, and upper respiratory tract infection each experienced by 3 patients
- No clinically important new/worsening abnormalities on → vital signs, ECG, laboratory tests, physical/neurological/eye exams, EPS (ESRS-A) or depression (CDSS)

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