# Glutamate modulation as adjunctive therapy in patients with schizophrenia not adequately responding to second-generation antipsychotics: clinical benefits of evenamide in a phase 3, international, randomized, double-blind, placebo-controlled trial

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## INTRODUCTION

**Treatment of schizophrenia remains an open challenge**, with **30-60%** of **patients failing to adequately benefit** from treatment with second-generation antipsychotics (SGAs)

Patients with **limited or no benefit from APs** seem to have **glutamatergic, but not dopaminergic dysfunction**, as suggested by neuroimaging and neurochemistry studies[1]

**Evenamide (NW-3509)** is a **new chemical** entity, highly selective and state-dependent blocker of **voltage-gated sodium channel** that **normalizes excessive glutamate** release without affecting its basal levels

Evenamide, as a result of its ability to **attenuate ventral hippocampus hyperexcitability**, is able to downregulate the hyperdopaminergic state, **rescuing social deficits** and **recognition memory impairment** in the **MAM** animal model of schizophrenia[2]

**Add-on treatment** with evenamide was associated with **long-term clinically important benefits** in patients with **treatment-resistant schizophrenia** in a pilot, open-label, rater-blinded 1-year study[3,4]

## STUDY 008A[5]

- **Evenamide 30 mg *bid*** or **placebo (1:1)** , **add-on** to SGAs (including clozapine)
- **Key selection criteria:**
  1. **Outpatients** with chronic schizophrenia, not responding adequately to SGAs despite **therapeutic plasma concentrations** (assessed for eligibility)
  2. **PANSS** total score **70-85; CGI-S** moderately to severely ill (**4-6**)
  3. Score **≥4** on at least 2 **core symptoms** (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) and score **≥20** on core symptoms + grandiosity, hostility and excitement
  4. **NO** other primary psychiatric diagnosis or severe/unstable comorbidities
- **PANSS and CGI-S/C** assessed by **2 trained psychiatrists blinded to each other** ratings

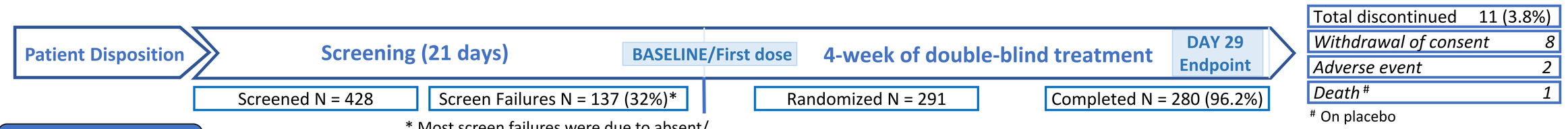
**KEY EFFICACY MEASURES**
- PANSS
- CGI-S/C

**SAFETY MEASURES**
- Adverse Events
- Vital signs, labs, ECG
- EEG, seizure checklist
- Physical/neurological/eye exams
- C-SSRS, CDSS, ESRS-A

Phase 3
International
Randomized
Double blind
Placebo controlled
4-Week

## AIM

Determine the **efficacy** and **safety** of **evenamide 30 mg *bid*** as **add-on to SGA** (including clozapine) in poorly responding patients




## RESULTS

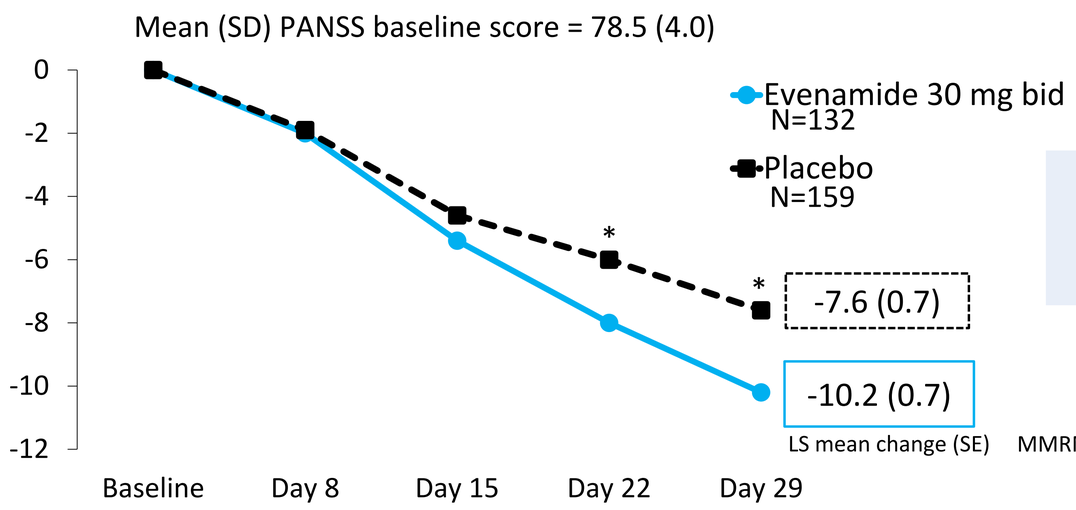
### 1. Demographic and Disease characteristics (Safety pop N=291)

71.1% males | Asian ~40%; White ~60% | Age (mean) 40.3 years

| Characteristic | Mean (SD) |
|---|---|
| Duration of illness (years) | 12.5 (10.7) |
| Duration of current episode (months) | 10.7 (21.3) |
| Number of psychiatric hospitalizations | 3.1 (7.1) |
| Failed AP attempts* | 2.3 (1.2) |

* Including current AP medication; multiple attempts with the same molecule have been counted as one

### 2. Primary efficacy results – PANSS change from baseline (ITT N=291)



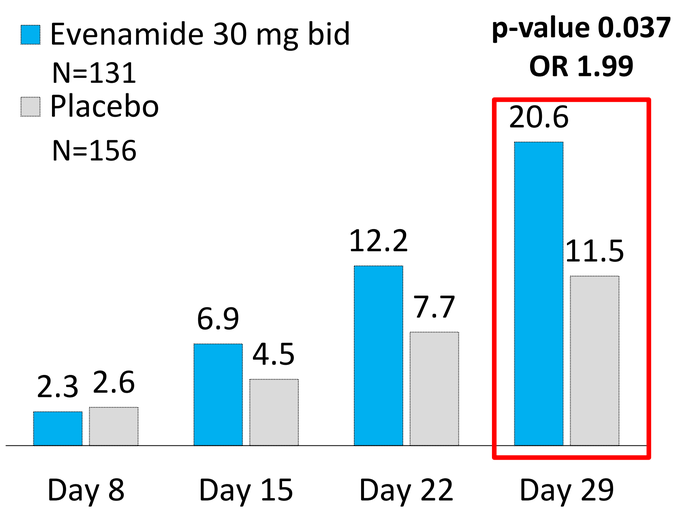

**Endpoint Treatment Difference**:
LS mean (SE) = -2.5 (0.9)
**p-value = 0.006**

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

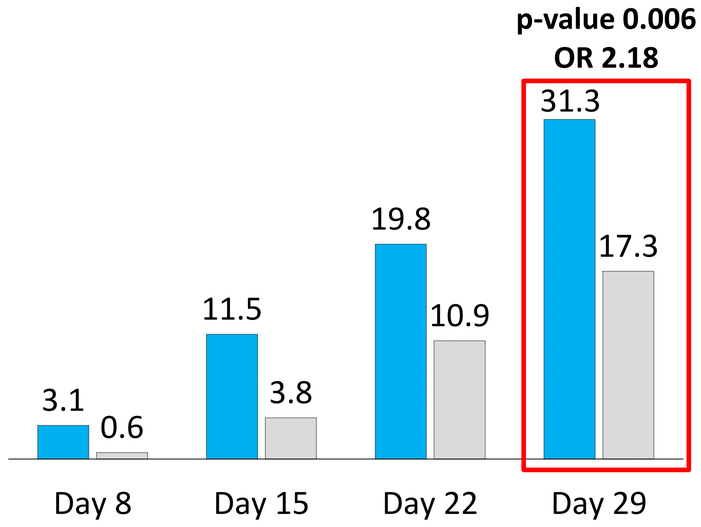
| Scale | Visit | Evenamide 30 mg bid N=132 | Placebo N=159 | Drug-placebo difference |
|---|---|---|---|---|
| CGI-S | Baseline – mean (SD) | 4.4 (0.6) | 4.5 (0.6) | - |
| | Day 29 – LS mean change (SE) | -0.6 (0.1) | -0.5 (0.1) | **-0.16 (0.08)** |
| | **p-value [CI]** | **0.037 [-0.3, -0.0]** | |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

### 4. PANSS, CGI-C Responder Analyses (mITT N=287; OC)

**PANSS Responder Analysis**
Proportion of patients improved by ≥20% from baseline




**CGI-C Responder Analysis**
Proportion of patients rated at least "much improved"




### 5. Summary of Safety results (Safety pop N=291)

Most common TEAE on Evenamide (≥1.5%) (EVE vs PBO)
Headache: 2.3% vs 2.5% | Vomiting: 2.3% vs 0.6% | Nasopharyngitis: 2.3% vs 0.6% | Somnolence: 1.5% vs 3.1% | Diarrhea: 1.5% vs 0%

## KEY FINDINGS AND CONCLUSIONS

Results for the **primary** (PANSS total) and **key secondary** (CGI-S) **efficacy endpoint** showed a **statistically significant improvement at Day 29** for evenamide compared to placebo. Significance on sensitivity analyses confirmed the robustness of these findings. Moreover, a **significantly higher proportion of responders** (based on PANSS and CGI-C) on evenamide vs placebo was observed at Day 29 suggesting a steady and continuous improvement

The **very low drop-out rate (<4%)**, **only 0.7% due to adverse events**, **similar incidence of TEAEs between evenamide and placebo** (~25%), and **absence** of pattern of **abnormal findings** on any **safety measure** suggest that **evenamide 30 mg bid is well tolerated**

This is the **first** randomized, double-blind, placebo-controlled trial **demonstrating the clinically relevant improvements** associated with glutamatergic modulation by evenamide added on to an SGA in patients with schizophrenia not adequately responding to AP

**Find out more here!**

**References**: [1] Demjaha et al., 2012; [2] Uliana et al., 2025; [3] Anand R, et al., 2023; [4] Anand R et al., 2024; [5] Anand R, et al., 2025