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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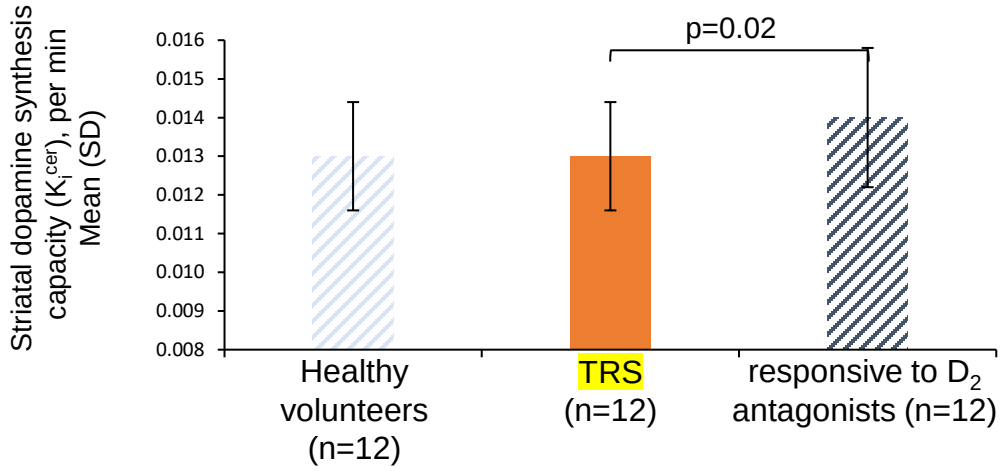
NEUROCHEMICAL CHANGES IN APS RESPONDERS, TRS, AND HEALTHY CONTROLS

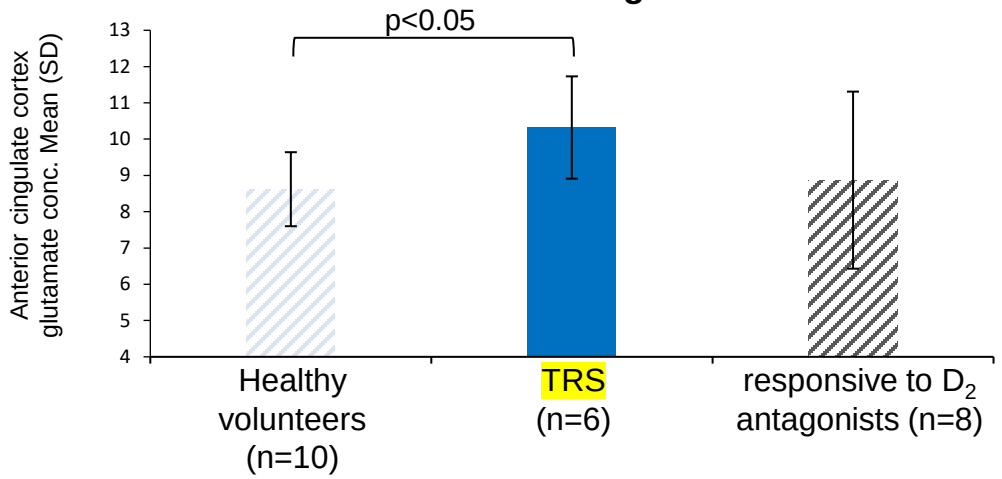
- Patients with TRS and non-responders from first episode have a normal **dopamine** synthesis capacity[1,3]
- By contrast, patients who respond to D_2 antagonists exhibit increased capacity for **dopamine** synthesis[1,3]

- **Glutamate** levels are significantly higher in patients with TRS compared to healthy volunteers[1], and compared to patients with schizophrenia who were responsive to D_2 antagonists[2]

Dopamine synthesis capacity (whole striatum)[1]



Glutamate conc. in anterior cingulate cortex[1]



1. Demjaha et al. Am J Pyschiatry 2012;169(11):1203–1210;
2. Mouchlianitis et al. Schizophr Bull 2016;42(3):744–752;
3. Jauhar et al. Mol Psychiatry 2019;24 (10):1502-1512

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Evenamide reverses schizophrenia-related dysfunction in a neurodevelopmental animal model

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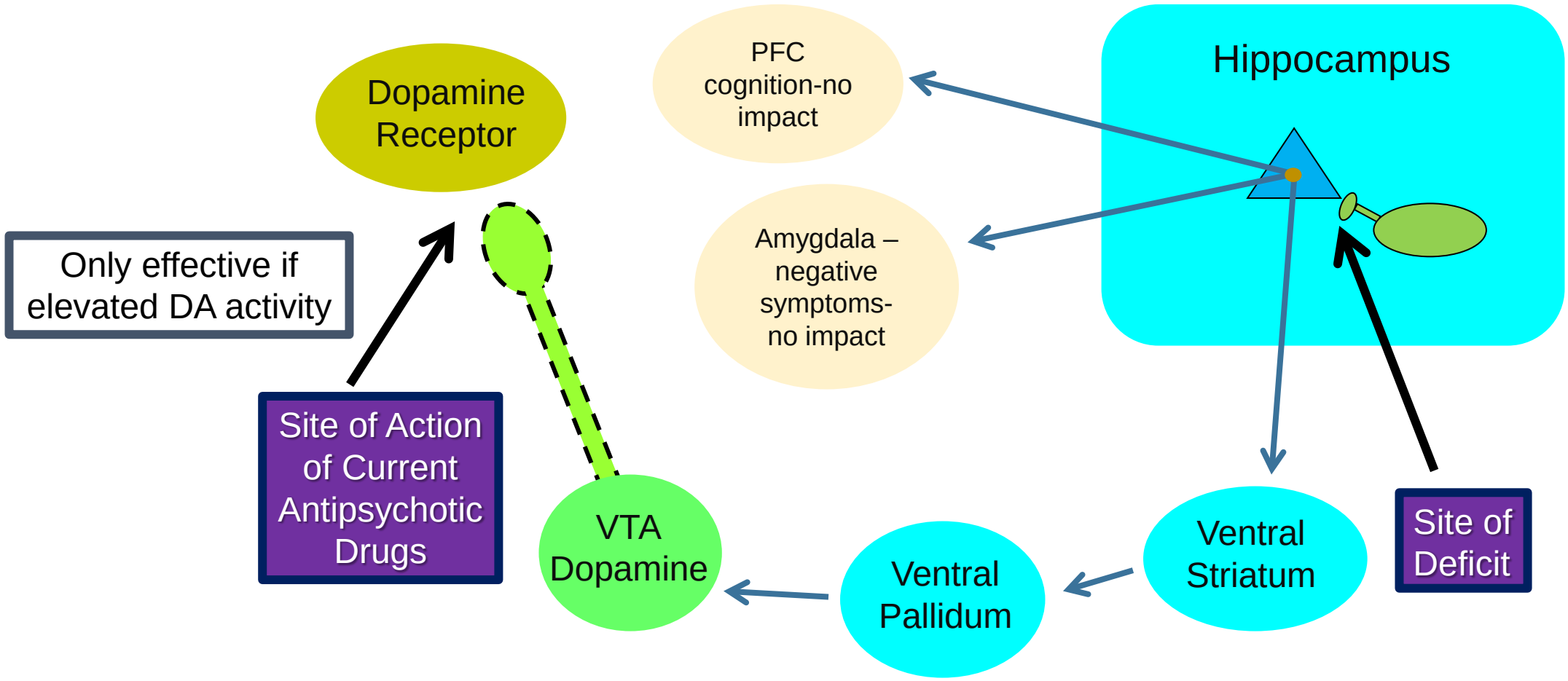
Neuropsychopharmacology (2025) | Cite this article

1. *Evenamide's efficacy in downregulating the hyperdopaminergic state, social deficits, and recognition memory impairment may result from its* ***ability to attenuate vHipp hyperexcitability***

2. *Evenamide is* ***capable of addressing positive, cognitive, and negative symptoms of schizophrenia***

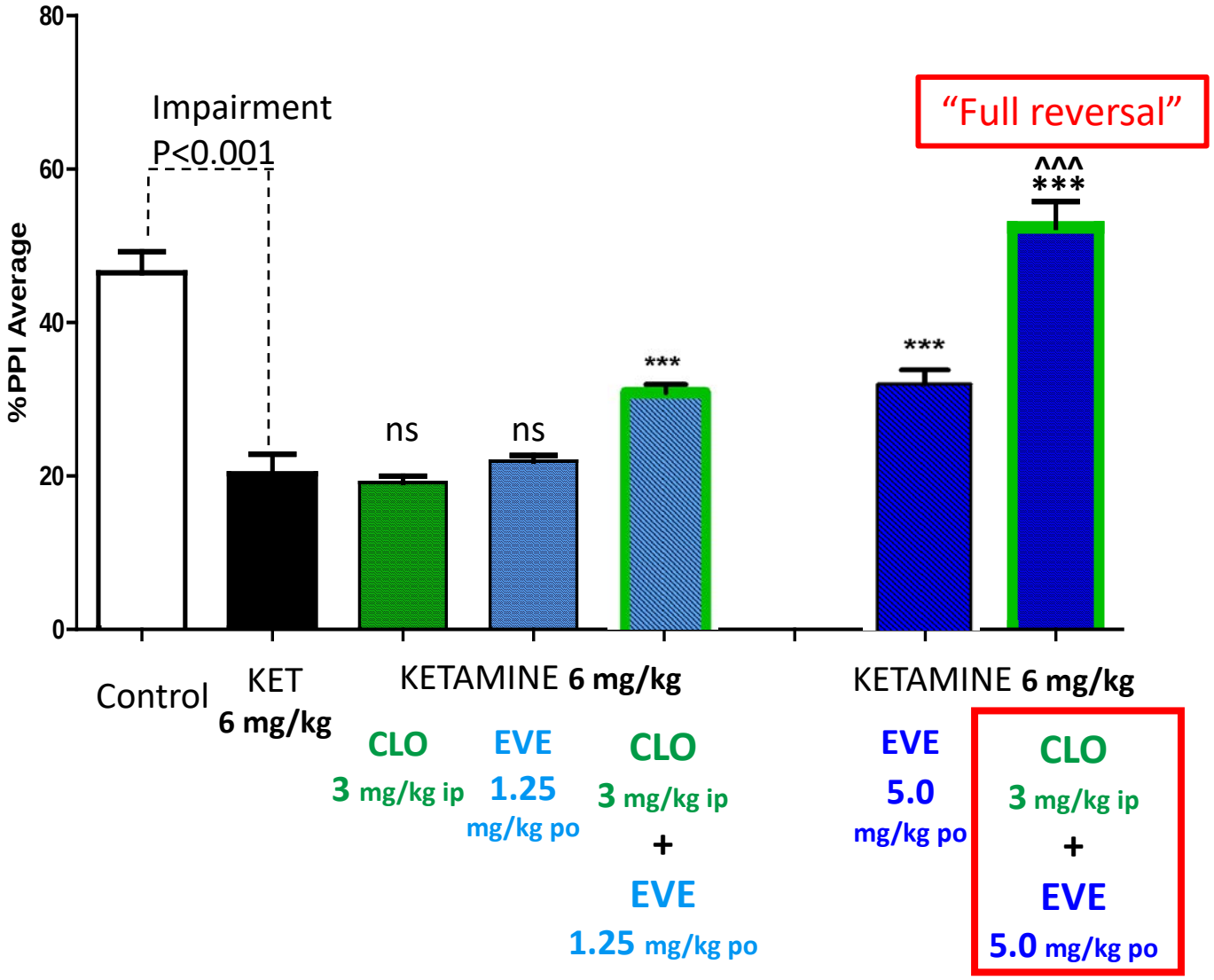
3. ***Sustained effects of evenamide*** *suggest that its impact may extend* ***beyond its peak plasma*** *concentration. This could indicate that evenamide may induce a* ***circuit-level plasticity***

ANTIPSYCHOTIC DRUG ACTION



A better approach would be to treat the site of pathology

KETAMINE-INDUCED DETERIORATION OF PPI IS RESCUED BY A COMBINATION OF INEFFECTIVE DOSES OF CLOZAPINE AND EVENAMIDE



Statistics: 3-way, repeated-measure ANOVA;
***P<0.001 vs KET; ^^^ P<0.001 vs EVE 5 (Tukey's post-hoc test) (n=16/group)

Evenamide + FGAs/SGAs

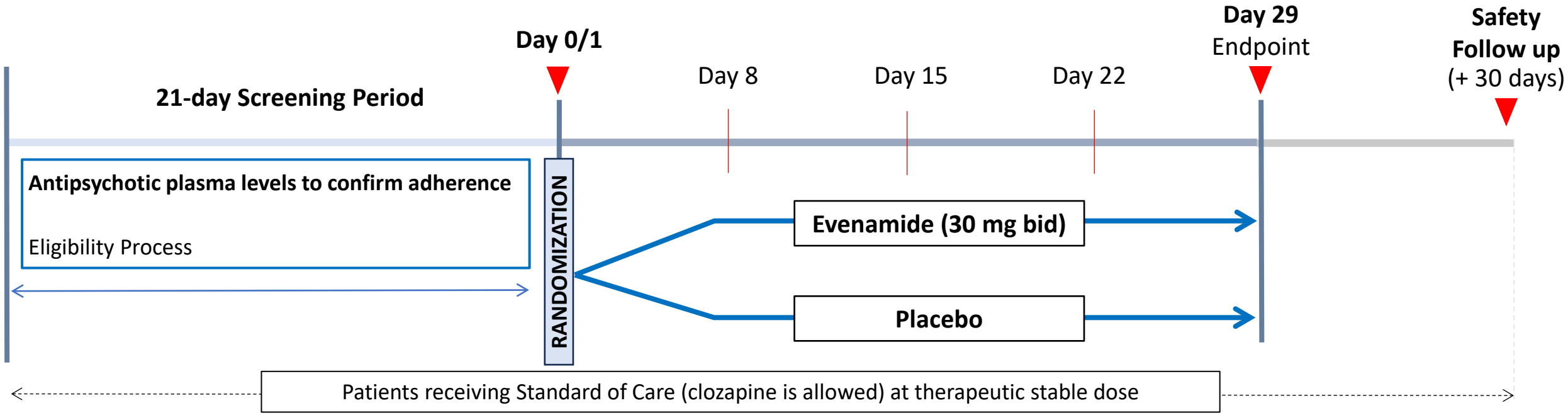
1. Combination of ineffective doses of evenamide with antipsychotics (APs) was associated with improvement in animal models of psychosis

2. Potential to benefit:
positive, negative and cognitive symptoms

STUDIES WITH EVENAMIDE IN HUMAN SUBJECTS

Phase 1	Phase 2				Phase 3
001, 007, 010, 011 N=115	**002 N=89**	**008 N=138**	**014 - TRS N=161**	**015 - TRS (OLE)**	**008A N=291**
US, UK, GER	**US; India**	**US; India**	**India; Sri Lanka; Italy**		**EU; LATAM; Asia 11 countries**
Randomized Placebo 1-60 mg *od*	Double-blind Placebo 15-25 mg *bid*	Double blind Placebo 7.5 and 15 mg *bid*	Open label 7.5/15/30 mg *bid*		Double-blind Placebo 30 mg *bid*
Single dose	4-week	4-week	6-week	46-week	4-week
Key findings	**Key findings**				**Key findings**
No abnormal, QTc, laboratory, safety or tolerability findings	**Progressive improvement** up to 1-year across all efficacy measures **NO safety abnormalities** detected (EEG, EPS, Labs, ECG etc)				**Demonstration of Efficacy and Safety**

STUDY 008A – OUTPATIENT STUDY IN INADEQUATELY RESPONDING PATIENTS WITH CHRONIC SCHIZOPHRENIA



Key study features

Double-blind, randomized (1:1)
Evenamide 30 mg BID vs Placebo
Add-on treatment to SGAs*
11 Countries; **45** sites
Europe, India, and LATAM

Key selection criteria

Outpatients still symptomatic despite ≥ 4 weeks of AP treatment at a stable dose

Total PANSS: 70 to 85; CGI-S: 4 to 6

Score of ≥ 4 (moderate) on at least 2 of the 4 core symptoms of psychosis#

Key outcome measures

PANSS Total score
CGI of Severity
CGI of Change
Strauss-Carpenter LOF
Medication Satisfaction Questionnaire (MSQ)

* Aripiprazole, cariprazine, clozapine, olanzapine, paliperidone, quetiapine, risperidone,
# P2 Conceptual disorganization, P3 Hallucinatory behavior, P6 Suspiciousness and G9 Unusual thought content

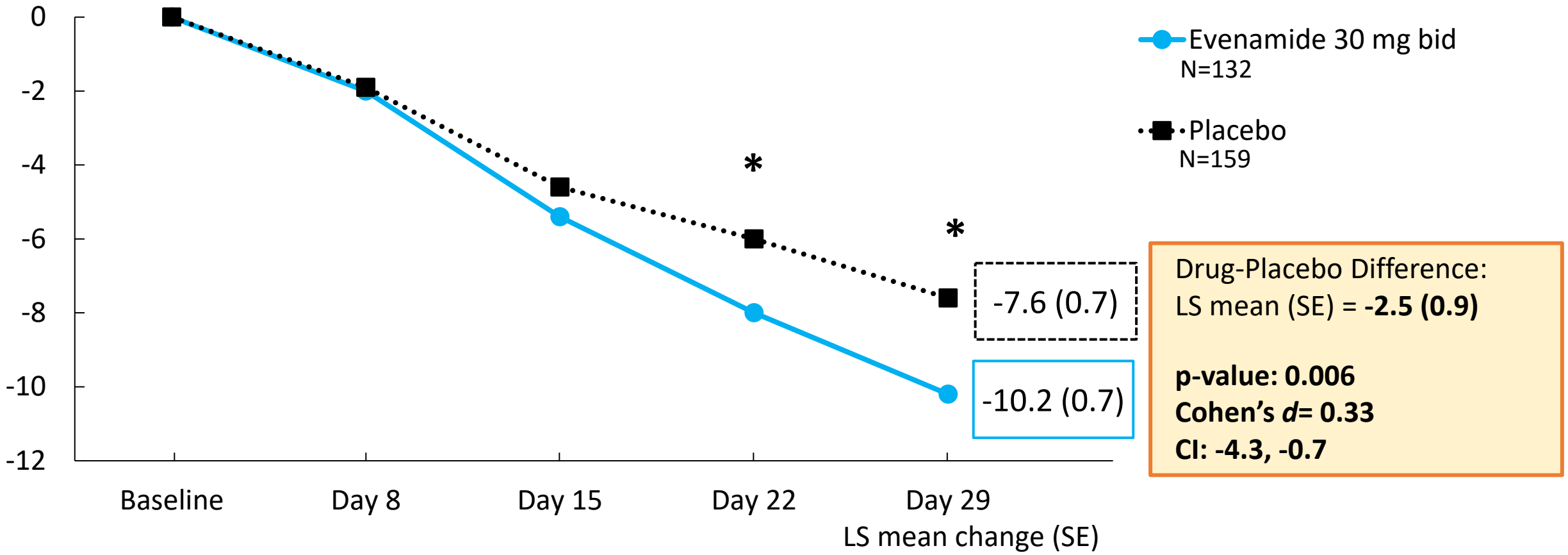
SUMMARY OF DISPOSITION AND ADVERSE EVENTS

	Evenamide 30 mg bid n (%)	Placebo n (%)
Screened	-	-
Randomized	**132**	**159**
Completed Day 29	**126 (95.5)**	**154 (96.9)**
Adverse dropout*	*2 (1.5)*	*1 (0.6)*
Withdrawal of consent	4 (3.0)	4 (2.5)
Most frequent adverse events		
Nasopharyngitis	3 (2.3)	1 (0.6)
Headache	3 (2.3)	4 (2.5)
Vomiting	3 (2.3)	1 (0.6)
Somnolence	2 (1.5)	5 (3.1)

* Placebo: 1 death; Evenamide: 1 sinus bradycardia; 1 vomiting

Randomized by region: Europe N=116 (39.9%); Asia N=112 (38.5%); Latin America N=63 (21.6%)

PANSS TOTAL SCORE TO DAY 29; ITT POPULATION
PRIMARY ESTIMAND - TREATMENT POLICY; MMRM



Drug-Placebo Difference:
LS mean (SE) = **-2.5 (0.9)**

p-value: 0.006
Cohen's *d*= 0.33
CI: -4.3, -0.7

Significant results were also obtained using the mITT population; N=287
CI= 95% confidence interval; SD=standard deviation; LS mean=least squares mean; SE=standard error; *P value <0.05

PANSS and CGI-S/C were assessed by 2 independent raters, blinded to each other's ratings

PRIMARY AND KEY SECONDARY EFFICACY ENDPOINTS MEAN CHANGE FROM BASELINE TO DAY 29 - ITT POPULATION - PRIMARY ESTIMAND - TREATMENT POLICY; MMRM

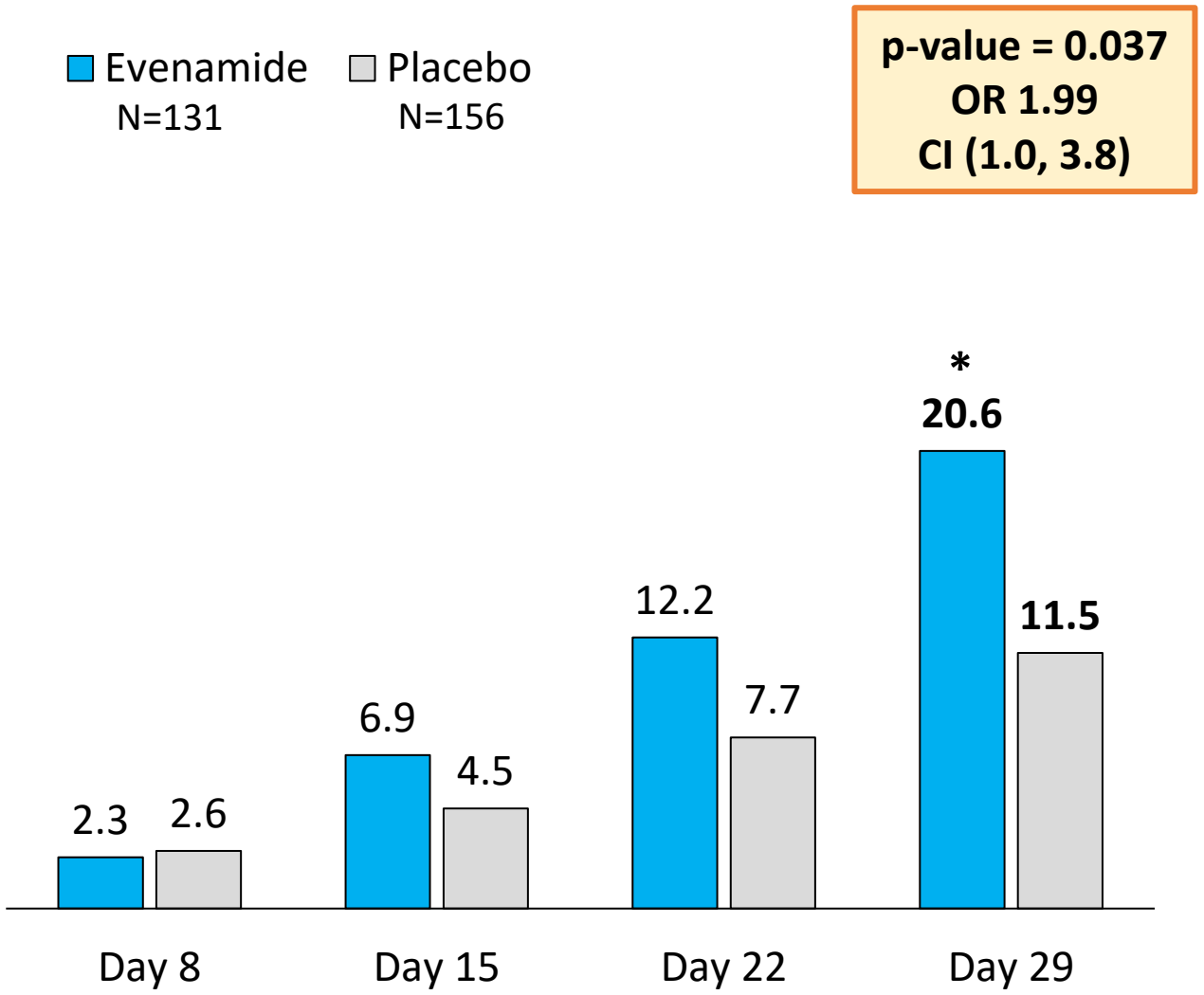
Scale	Visit	Evenamide 30 mg bid N=132	Placebo N=159	LS mean difference (SE) p-value [CI]
CGI of Severity (CGI-S)	Baseline – mean (SD)	4.4 (0.6)	4.5 (0.6)	**-0.16 (0.08)* 0.037 [-0.3, -0.0]**
	Day 29 – LS mean (SE)	-0.6 (0.1)	-0.5 (0.1)	
Positive symptoms	Baseline – mean (SD)	22.5 (2.5)	22.1 (2.5)	**-1.16 (0.4)* 0.001 [-1.9, -0.5]**
	Day 29 – LS mean (SE)	-4.7 (0.4)	-3.6 (0.4)	
Negative symptoms	Baseline – mean (SD)	20.3 (3.5)	20.3 (3.3)	**-0.63 (0.3)* 0.016 [-1.1, -0.1]**
	Day 29 – LS mean (SE)	-1.9 (0.3)	-1.3 (0.3)	
General psychopatology	Baseline – mean (SD)	35.6 (3.6)	36.2 (3.9)	-0.59 (0.44) 0.184 [-1.5, 0.3]
	Day 29 – LS mean (SE)	-2.9 (0.5)	-2.3 (0.4)	

* p-value <0.05; Significant results were also obtained using the mITT population (N=287)

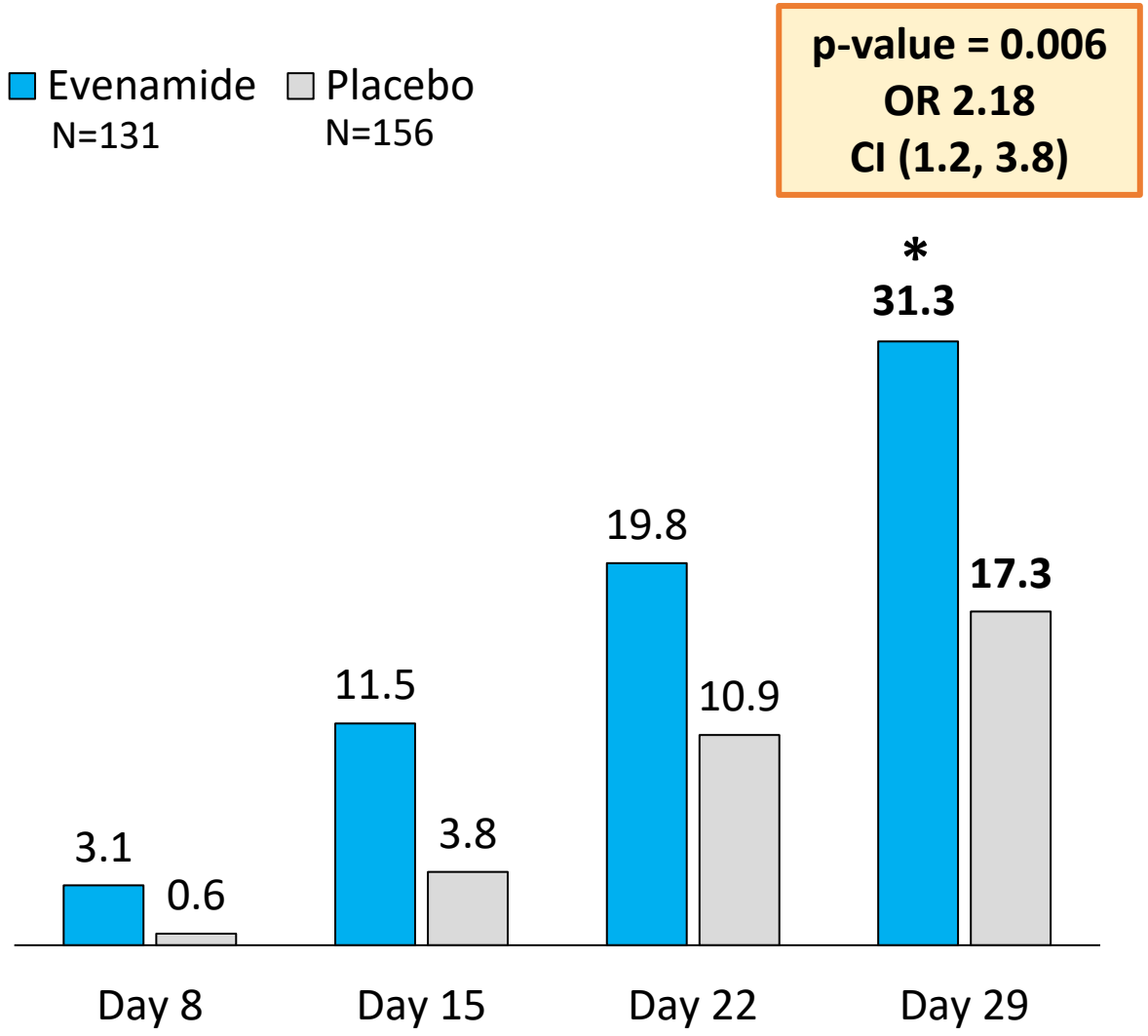
CI= 95% confidence interval; SD=standard deviation; LS mean=least squares mean; SE=standard error

RESPONDER ANALYSES - PROPORTION OF PATIENTS (%) - MITT; OC

PANSS improving ≥20% from baseline



CGI-C rating of at least "much improved"



CI=95% confidence interval; OR=odds ratio;
Percentages are calculated as number of observed patients at each visit meeting responder definition divided by N under mITT population in each group

EVALUATION OF PRIMARY AND KEY SECONDARY EFFICACY ENDPOINTS

SENSITIVITY ANALYSES

Endpoint Measure	Analysis Model	p-value
Primary PANSS Total score	Primary Estimand Treatment Policy MMRM	**0.006**
	Supportive Estimand Hypothetical	**0.002**
	WOCF ANCOVA	**0.008**
	MI ANCOVA	**0.006**
	Tipping point ANCOVA	**0.004**
Key secondary CGI-S	Primary Estimand Treatment Policy MMRM	**0.037**
	MI ANCOVA	**0.014**

MMRM=Mixed Model Repeated Measures; WOCF=Worst Observation Carried Forward; MI=Multiple Imputation; ANCOVA=Analysis of Covariance

PANSS MEAN CHANGE FROM BASELINE BY CURRENT ANTIPSYCHOTIC MEDICATION; ITT; OC

Antipsychotic	Evenamide 30 mg bid N=132		Placebo N=159	
	n (%)	PANSS change from baseline (SD)	n (%)	PANSS change from baseline (SD)
Risperidone	**51 (38.6)**	**-8.8 (6.5)**	**63 (39.6)**	**-7.3 (7.4)**
Olanzapine	**32 (24.2)**	**-13.4 (8.6)**	**32 (20.1)**	**-7.9 (6.5)**
Clozapine	**19 (14.4)**	**-7.3 (6.2)**	**17 (10.7)**	**-4.4 (4.4)**
Paliperidone	**15 (11.4)**	**-7.9 (9.5)**	**24 (15.1)**	**-5.5 (8.4)**
Aripiprazole	11 (8.3)	-11.9 (9.6)	14 (8.8)	-11.8 (10.9)
Quetiapine	2 (1.5)	-2.5 (13.4)	7 (4.4)	-4.9 (3.8)
Cariprazine	2 (1.5)	-3.5 (7.8)	2 (1.3)	-5.5 (3.5)

SD=standard deviation

PANSS RESPONSE OF PATIENTS WHO FAILED 1 VS ≥2 ANTIPSYCHOTICS - (ITT; OC)

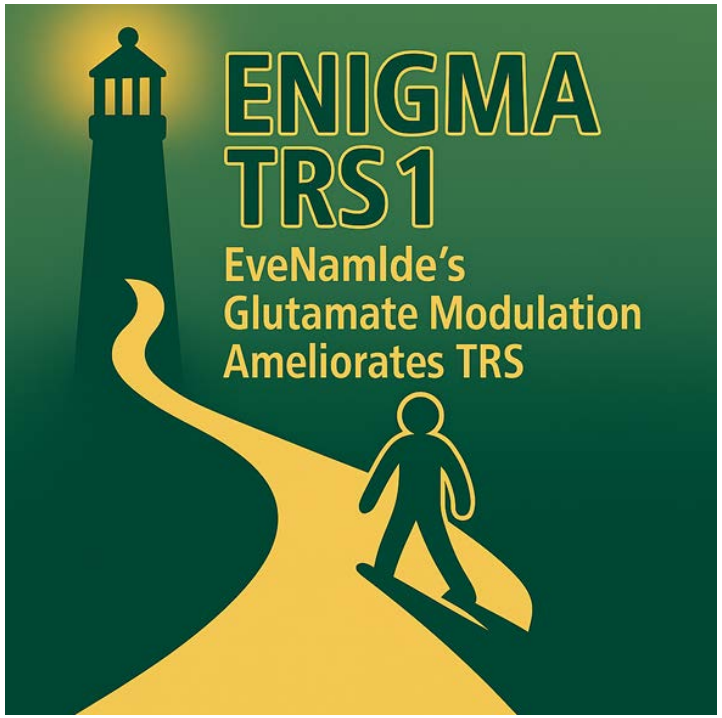
Antipsychotic attempts*	Stat	PANSS Change Day 29 Mean (SD)		
		Evenamide N=127	**Placebo N=154**	**EVE-PBO p-value**
1	n (%)	38 (29.9)	50 (32.5)	**-4.1 0.0122#**
	Mean change (SD)	-8.9 (6.5)	-4.8 (6.4)	
≥2	n (%)	89 (70.1)	104 (67.5)	**-2.4 0.0311#**
	Mean change (SD)	-10.5 (8.3)	-8.3 (7.7)	

*These are attempts failed for 'any reason'. Multiple attempts with the same molecule at different doses have been counted as one

p-value calculated using mixed model linear regression

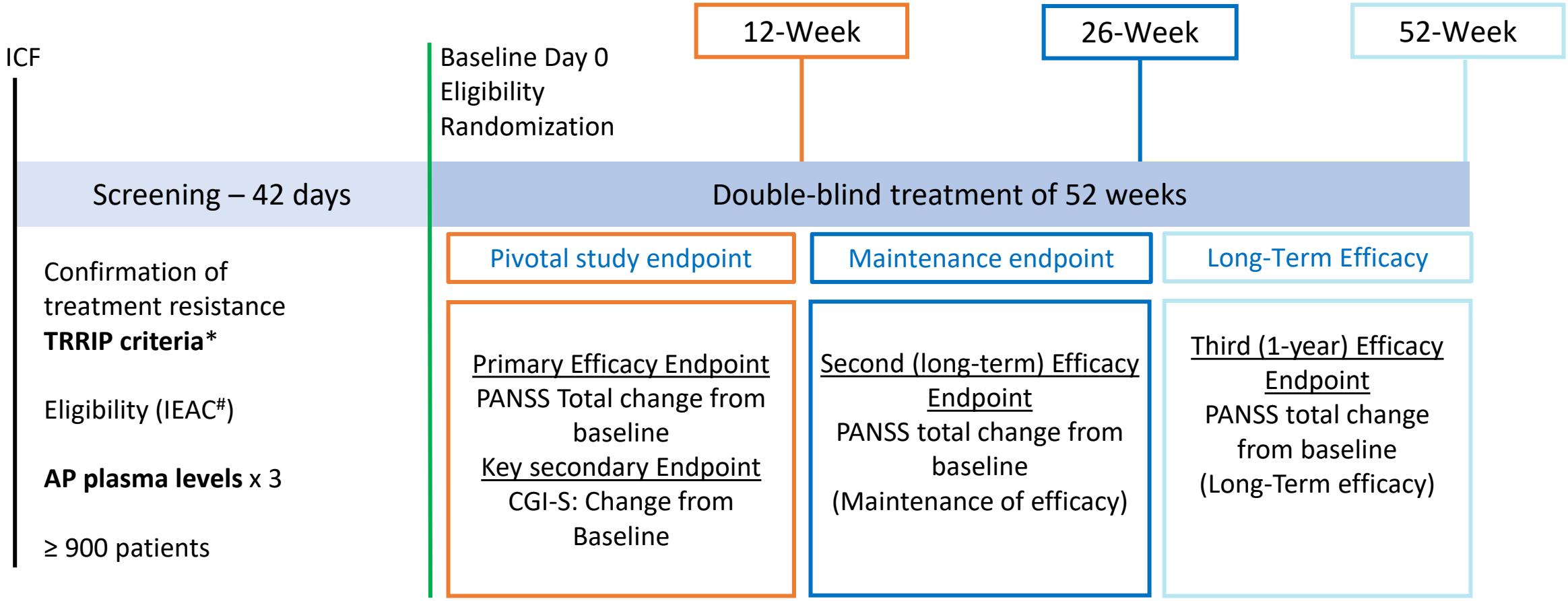
Evenamide Study NW-3509/023/III/2024

(**ENIGMA-TRS 1**)



A Phase III, 52-week, prospective, randomized, double-blind, placebo-controlled, parallel-group, multi-center study, with a primary efficacy endpoint at 12 weeks, to determine the efficacy, safety, and tolerability of fixed doses of 15 mg bid and 30 mg bid of evenamide as add-on in patients with documented treatment-resistant schizophrenia, which is not adequately controlled by a stable therapeutic dose of the patient's current antipsychotic medication(s)

Evenamide Phase 3 TRS Study – **ENIGMA-TRS 1**



* TRRIP Working Group Howes et al., 2017

\# Independent Eligibility Assessment Committee

≥ 600 patients randomized to:
200 (15 mg bid) : 200 (30 mg bid) : 200 (placebo)

Thank you