SIRS
Schizophrenia International Research Society

Newron
Pharmaceuticals

STUDY 008A: *ADD-ON TREATMENT WITH EVENAMIDE IN PATIENTS WITH CHRONIC SCHIZOPHRENIA NOT RESPONDING ADEQUATELY TO THEIR CURRENT ANTIPSYCHOTIC*

Results of a potentially pivotal, phase 2/3, international, randomized, double-blind, placebo-controlled trial

Ravi Anand, MD

Anand Pharma Consulting (APC)

Consultant Chief Medical Officer Newron Pharmaceuticals SpA

SIRS 2024 – 6th April 2024 – Florence, Italy

AUTHOR DISCLOSURES

Commercial Interest	**Relationship(s)**
Newron Pharmaceuticals SpA	Chief Medical Officer, Consultant
AbbVie, Acadia, BiolineRx, Domain, Enkam, Erydel, Forest, Janssen, Hoffman La Roche, Lundbeck, Noema, Ono, Pfizer, UCB, Sigma–Tau, Shire, Takeda, Teva	Consultant

EVENAMIDE – EFFICACY IN PSYCHIATRIC ANIMAL MODELS

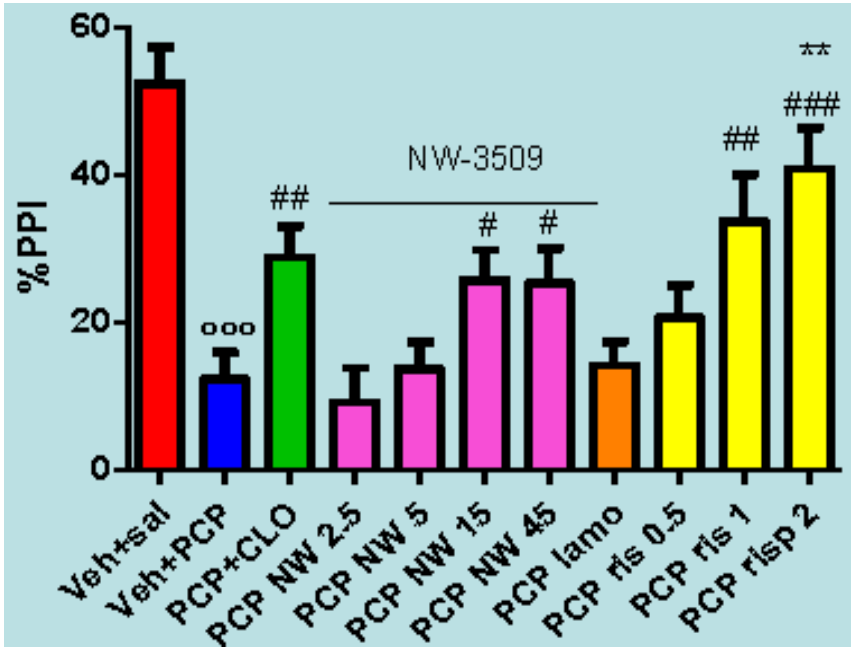
- Evenamide is a voltage gated sodium channel (VGSC) modulator devoid of any interaction with any other CNS target (>130 tested), and it attenuates stimulated release of glutamate
- It is active as a monotherapy and add–on to ineffective doses of first–or–second generation antipsychotics, attenuating abnormal behaviours in different animal models

	Monotherapy	Add-On
Information Processing Deficit - Pre-Pulse Inhibition (PPI)		
PPI disrupted by dopamine activation (amphetamine -rat)	✓	✓ (haloperidol, risperidone)
PPI disrupted by NMDA antagonists (Ketamine, MK-801, PCP, -rat)	✓	✓ (clozapine)
PPI disrupted by stressful stimuli (sleep deprivation -rat)	✓	
Pre-pulse inhibition spontaneous deficit (C57 mice)	✓	✓ (haloperidol)
Psychosis and Mania		
Amphetamine plus Chlordiazepoxide induced hyperactivity in mice	✓	✓ (risperidone)
Negative Symptoms		
PCP-induced deficit in Social Interaction in the rat	✓	✓ (aripiprazole)
Cognitive Impairment		
Novel object recognition in the rat: short term scopolamine impairment	✓	
Novel object recognition in the rat: long term 24 hr natural forgetting	✓	
Impulse Control		
Resident–Intruder test in mice (aggression / Impulsivity)	✓	
MAM Model - development disruption model	Ongoing	

Blank cells = not evaluated

EVENAMIDE AS A MONOTHERAPY REVERSES THE PPI DEFICIT INDUCED BY DYSREGULATION OF THE GLUTAMATE NEUROTRANSMISSION DUE TO PCP OR MK-801 ADMINISTRATION

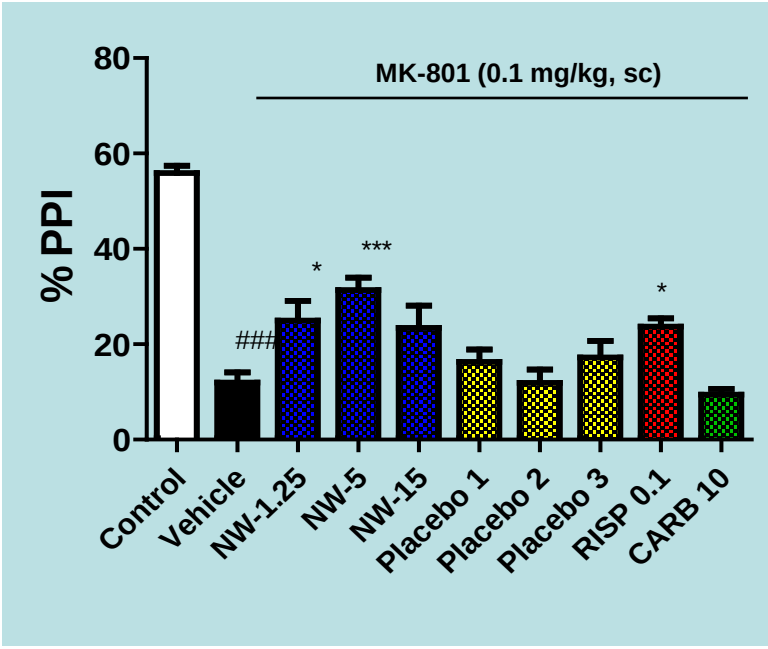
PPI DEFICIT INDUCED BY PCP



Study performed by Scottish Biomedical, Glasgow, UK

- Evenamide was administered 5 min before PPI session
- PCP (5mg/kg ip) was administered 15 min before PPI session
- N=10 rats per group
- Statistics:
  - °°° one-way ANOVA p<0.001 vs Vehicle + Saline,
  - ** Tukey's post hoc test p<0.01 vs Vehicle + PCP
  - #, ##, ### Unpaired t-test p<0.05, p<0.01, p<0.001 vs Vehicle + PCP
- CLO=Clozapine (5mg/kg ip), NW=Evenamide (po doses), lamo=Lamotrigine (10mg/kg ip), risp=Risperidone (ip doses)

PPI DEFICIT INDUCED BY MK-801

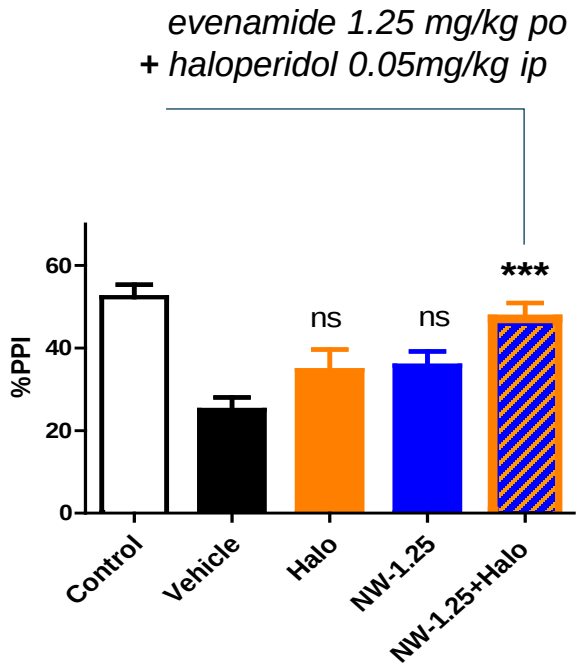


Study performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari - USCLA

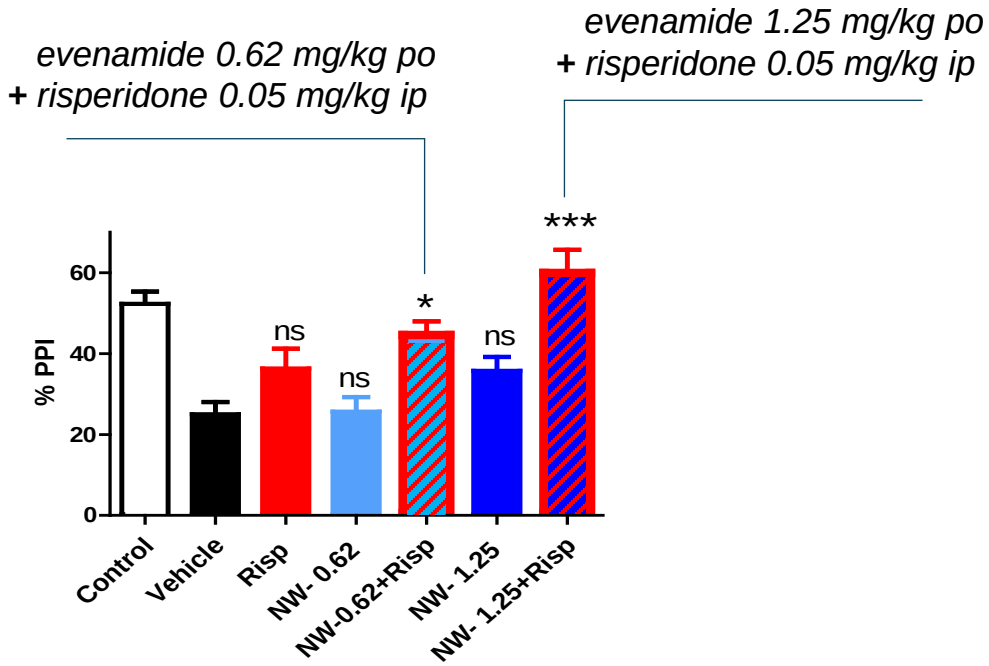
- Study conducted under double-blind conditions with three placebo controls
- MK-801 (0.1mg/kg, sc), injected 5 min before PPI session
- Evenamide and placebo administered immediately before MK-801
- Risperidone (0.1mg/kg, ip) and carbamazepine (10mg/kg, ip), used as standard controls, administered 30 min before testing
- Statistics: *, *** Tukey's test p<0.05, p<0.0001 vs vehicle + MK-801; ### p<0.001 vs control (n=27-47 rats per group)

EVENAMIDE AS ADD-ON IN AMPHETAMINE-INDUCED PPI DEFICIT

Evenamide augments the effect of Typical and Atypical Antipsychotics in amphetamine-induced Pre-Pulse Inhibition (PPI) deficit



Add-on with inactive dose of haloperidol



Add-on with inactive dose of risperidone

PHASE 2/3 COMPLETED AND PLANNED CLINICAL STUDIES WITH EVENAMIDE ADD-ON TREATMENT TO ANTIPSYCHOTICS

Study 002	Study 014 - TRS	Study 015 - TRS	Study 008A	Study 017 - TRS
Phase 2 US; India	Phase 2 India; Sri Lanka; Italy	Phase 2 India; Sri Lanka; Italy	Phase 2/3 EU; LATAM; Asia	Phase 3 EU; US; LATAM; Asia
Randomized, DB, PBO-controlled	Randomized, OL, fixed doses of evenamide (7.5, 15, 30 mg bid)	OL extension to Study 014	Randomized, DB, PBO-controlled	Randomized, DB, PBO-controlled
Safety Preliminary efficacy	Safety Preliminary efficacy	Long-term safety Preliminary efficacy	Efficacy Safety	Efficacy Safety
4-week	6-week	Additional 46-week	4-week	1-year
PANSS Positive Scale p-value 0.0043 CGI-C responder rate p–value 0.0855	Progressive and sustained improvement up to 1–year across all efficacy measures (e.g. PANSS, CGI–S/C) No pattern of safety abnormalities detected (ECG, Labs, metabolic syndrome, sexual dysfunction etc)		Results are expected by end of April 2024	Planned

DB=Double blind; PBO=Placebo; OL= open label

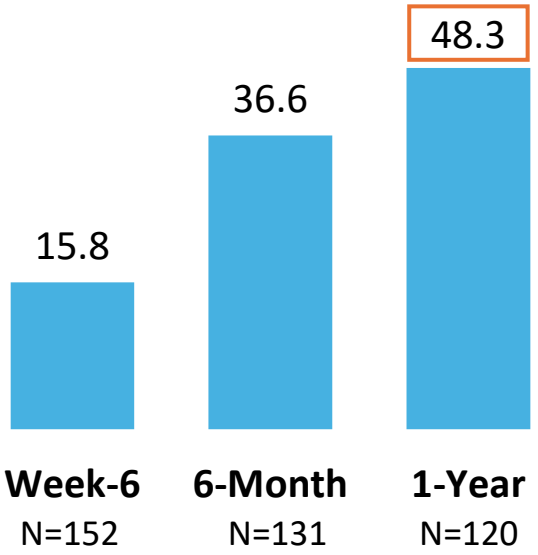
STUDIES 014/015 TRS – LONG–TERM EFFICACY RESULTS UP TO 1–YEAR OC; mITT N=156

- Progressive and sustained improvement up to 1–year of treatment with evenamide at all doses (7.5, 15 and 30 mg *bid*)
- Benefits across all efficacy measures (PANSS total and subscales, CGI–S, CGI–C and LOF^)

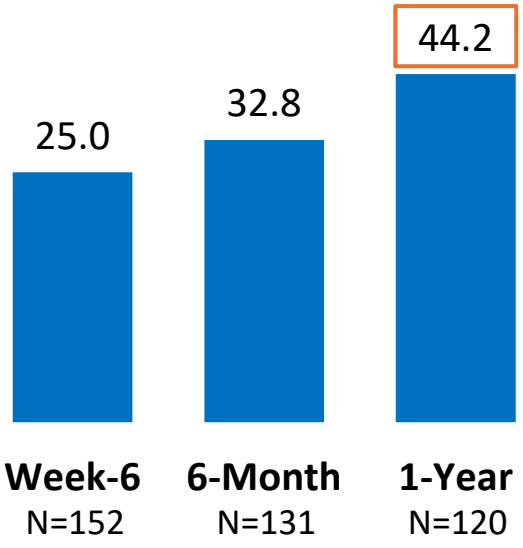
Mean change from baseline on PANSS total, CGI–S, LOF

Scale	Baseline N=156	Week–6 N=152	6–Month N=131	1–Year N=120
	Mean	Mean change (%) from baseline		
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
LOF	17.9	+1.3	+2.2	+2.5

PANSS total score – Responder rate
% of patients with ≥20% improvement*



CGI–C – Responder rate
% of patients rated at least «much improved»



*Rosenheck et al., 1997; Meltzer et al., 2008

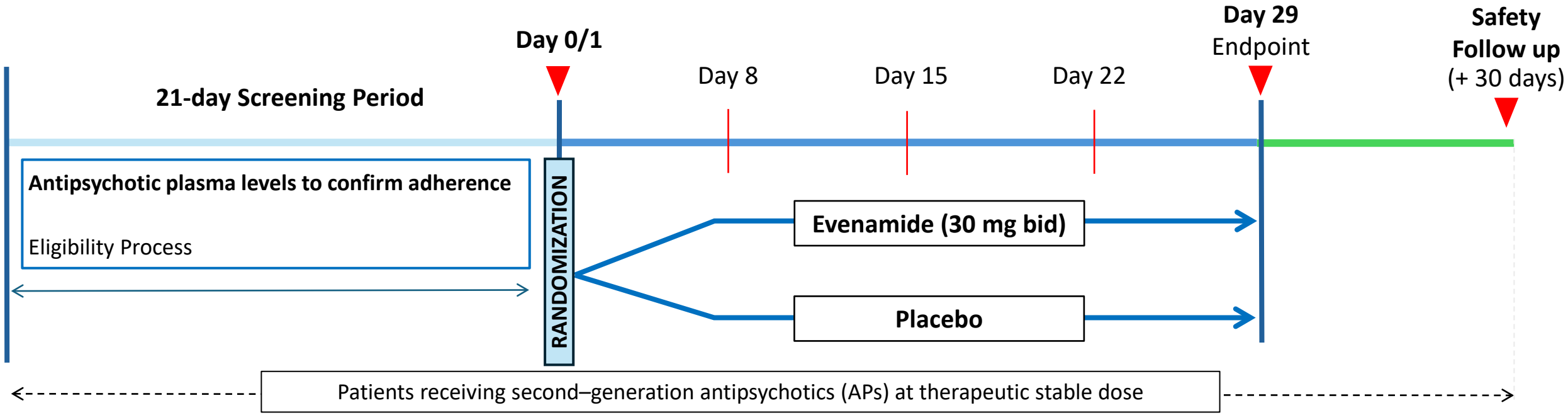
Results obtained using Last Observation Carried Forward (LOCF) do not differ substantially; ^ Strauss and Carpenter, 1977

EVENAMIDE STUDY 008A

EVENAMIDE IN PATIENTS WITH CHRONIC SCHIZOPHRENIA
NOT RESPONDING ADEQUATELY TO SECOND-GENERATION ANTIPSYCHOTICS

A Phase II/III, 4-week, international, randomized, double-blind, placebo-controlled, add-on study

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

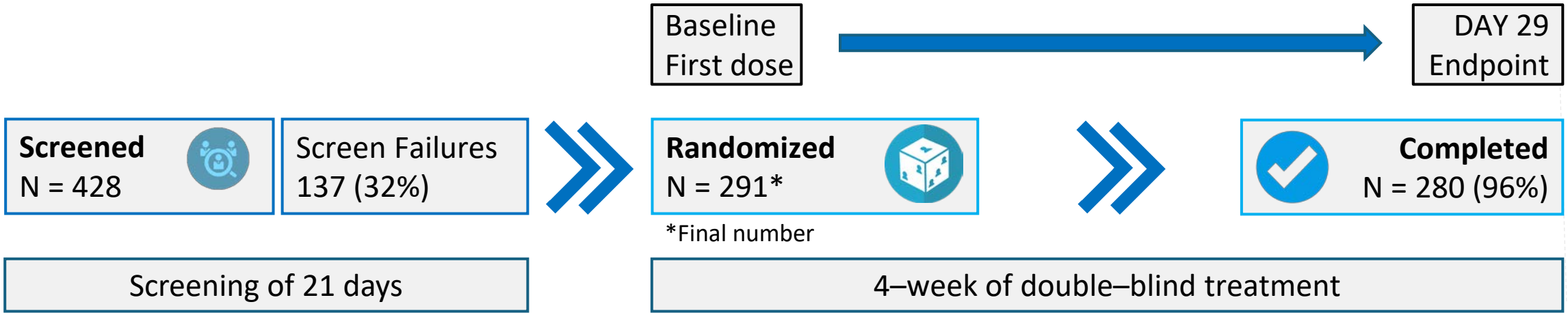
STUDY 008A – ISSUES IMPACTING ON AVAILABILITY OF RESULTS

- Entry in the screening period was terminated on 30 November 2023
- Randomization was terminated on 28 December 2023 (LPI N=290)
- An Investigator in Argentina, contacted by the caregiver, informed that a patient, who was in screening, wanted to participate (investigations were ongoing for suspected appendicitis)
- This created a dilemma as randomization had been completed, however, for ethical reasons, Sponsor decided to let the patient participate
- Unfortunately, patient took another 3 weeks to recover and start double-blind treatment
- Original date for results was March 2024, but because of patient number 291 who entered the study > 1 month late, these results are now due in late April 2024

STUDY 008A – CHALLENGES IN SUBJECT SELECTION

- Identifying patients on antipsychotic monotherapy (70% at most sites on antipsychotic polypharmacy)
- Non-compliance with background AP; results from AP plasma assessments during screening indicated:
  - No AP detected;
  - AP plasma levels do not reflect the dose administered;
  - AP different from the one prescribed by Investigator;
  - More than 1 AP detected (antipsychotic polypharmacy)
- Likelihood of non-compliance with the protocol: frequency and length of visits; multiple study assessments
- Delays in reporting of antipsychotic levels by central laboratory led to patients terminating screening

STUDY 008A – PATIENT DISPOSITION



Total Screen Failures*	137 (32.0%)
Did not meet entry criteria	84 (61.3%)
Withdrawal of consent	30 (21.9%)
Other	19 (13.9%)
Lost to follow–up	2 (1.5%)
Pretreatment Event/Adverse Event	2 (1.5%)

Total Discontinued	11
Withdrawal of consent	8
Adverse event[$]	2
Death*	1

[$] 1 Sinus bradycardia; 1 vomiting
* Suspected suicide/accidental fall
Blind not broken

* Screen failure rate was similar across regions (Asia, Europe, and LATAM)

STUDY 008A – PATIENT CHARACTERISTICS BY REGION

Region	Randomized (% completers)	Antipsychotic daily dose (mg)		Demographic and disease characteristics				Baseline values	
		Risperidone Use	Risperidone dose equivalent #	Sex	Age	Age at diagnosis *	Duration of illness (years) ^	PANSS Total	CGI-S
	n (%)	n (%)	Mean (min–max)	n (%) males	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Asia	112 (99.1%)	**70 (62.5%)**	**6.6 (1.5–16.3)**	87 (77.7)	**36.1 (10.3)**	**29.8 (9.5)**	**7.4 (5.6)**	77.1 (4.2)	4.3 (0.4)
Latin America	63 (93.7%)	29 (43.0%)	5.4 (1.4–32.6)	43 (68.3)	43.6 (14.1)	27.5 (11.6)	17.1 (12.7)	78.5 (3.6)	4.8 (0.5)
Europe	116 (94.8%)	15 (12.9%)	5.8 (1.4–16.3)	77 (66.4)	42.6 (11.4)	28.8 (9.7)	14.9 (11.2)	79.9 (3.6)	4.6 (0.6)
Total Population	**291**	**114 (39.2%)**	**6.3 (1.4–32.6)**	**207 (71.1)**	**40.3 (12.1)**	**28.9 (10.1)**	**12.5 (10.7)**	**78.5 (4.0)**	**4.5 (0.6)**

Leucht et al, 2020; Gardner et al, 2010
* Derived using date of diagnosis of schizophrenia and date of birth
^ Derived using date of diagnosis and date of randomization

STUDY 008A – DEMOGRAPHIC CHARACTERISTICS OF PATIENTS CONCOMITANTLY TREATED WITH MOST COMMON ANTIPSYCHOTICS (>10%)

Antipsychotic	Patients	Daily dose *	Risperidone dose equivalent # Daily doses	Demographic and disease characteristics		Baseline values	
				Age	Duration of illness (years)	PANSS Total	CGI-S score
	n (%)	Mode (min–max) in mg	Mean (min–max) in mg	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Risperidone	114 (39.2)	6 (2–16)	5.9 (2–16)	38.9 (10.7)	10.9 (9.7)	77.6 (4.1)	4.4 (0.5)
Olanzapine	64 (22.0)	10 (7.5–45)	**6.6 (3.1–18.6)**	40.9 (14.1)	11.6 (10.3)	79.3 (3.8)	4.5 (0.6)
Paliperidone	39 (13.4)	12 (3–12)	3.4 (1.4–9.3)	41.3 (9.9)	14.0 (8.2)	79.3 (3.2)	4.6 (0.6)
Clozapine ^	36 (12.4)	300 (100–750)	4.4 (1.5–11.3)	40.8 (13.1)	**17.4 (13.4)**	78.9 (4.3)	4.5 (0.7)

* Doses of patients taking depot APs 45 (15.5%) were converted into oral daily doses

Leucht et al, 2020; Gardner et al, 2010; ^ Mean (SD) plasma level: 528.6 (355.6) ng/mL

EXPERIENCE GAINED DURING PERFORMANCE OF AN ADD–ON INTERNATIONAL STUDY IN NON–TRS PATIENTS

- Risperidone is the most used background antipsychotic overall: the usage was higher in Asia
- The risperidone dose equivalents of background APs show some variability, with higher doses prescribed in Asia
- Demographic characteristics (i.e., age, gender, race, duration of illness) show some differences across regions
- Severity of current episode similar across regions (PANSS total and CGI-S)
- Major challenges in the patient selection worldwide:
  - Patients on AP polypharmacy (~20% worldwide and across decades Gallego et al., 2012), although no AP medication is approved as adjunctive treatment
  - Poor compliance with prescribed AP based on AP plasma levels: need to perform this in clinical trials to differentiate between patients who are psychotic due to non compliance and poor responders
- Study 008A has some unique features: positive results may lead to a new treatment paradigm for patients with schizophrenia

Final study results are awaited soon

SIRS
Schizophrenia International Research Society

Newron
Pharmaceuticals

GLUTAMATE MODULATION BY EVENAMIDE AS AN ADD-ON TO TRS PATIENTS NOT RESPONDING TO CURRENT ANTIPSYCHOTICS IS ASSOCIATED WITH CLINICALLY IMPORTANT IMPROVEMENT ACROSS OUTCOME MEASURES

Results from a pilot, phase II, 1-year, open-label trial in patients with treatment resistant schizophrenia (TRS)

Ravi Anand, MD

Anand Pharma Consulting (APC)

Consultant Chief Medical Officer Newron Pharmaceuticals SpA

SIRS 2024 - Pharmaceutical Pipeline - 4th April 2024 - Florence, Italy

AUTHOR DISCLOSURES

Commercial Interest	**Relationship(s)**
Newron Pharmaceuticals SpA	Chief Medical Officer, Consultant
AbbVie, Acadia, BiolineRx, Domain, Enkam, Erydel, Forest, Janssen, Hoffman La Roche, Lundbeck, Noema, Ono, Pfizer, UCB, Shire, Sigma-Tau, Takeda, Teva	Consultant

AGENDA

- Evenamide Background
- Study 014/015: Open-label 1-year results in patients with TRS
- Design of a potentially pivotal 1-year study in TRS

EVENAMIDE BACKGROUND

EVENAMIDE – MECHANISM OF ACTION

- Evenamide is a highly selective inhibitor of voltage-gated sodium channels (VGSCs)
- Reduces excessive glutamate release without any effect on basal levels of glutamate
- Devoid of biological activity at >130 CNS targets [receptors, transporters, enzymes, channels (except for Na+ channels) where other antipsychotics show activity]
- Effective in animal models of inadequate response to antipsychotics, mania: both as monotherapy and add-on therapy
- Reduces glutamate antagonists (ketamine, PCP, MK-801) induced worsening in PPI not attenuated by clozapine
- Benefits also noted in animal models of negative symptoms when used as monotherapy or add-on

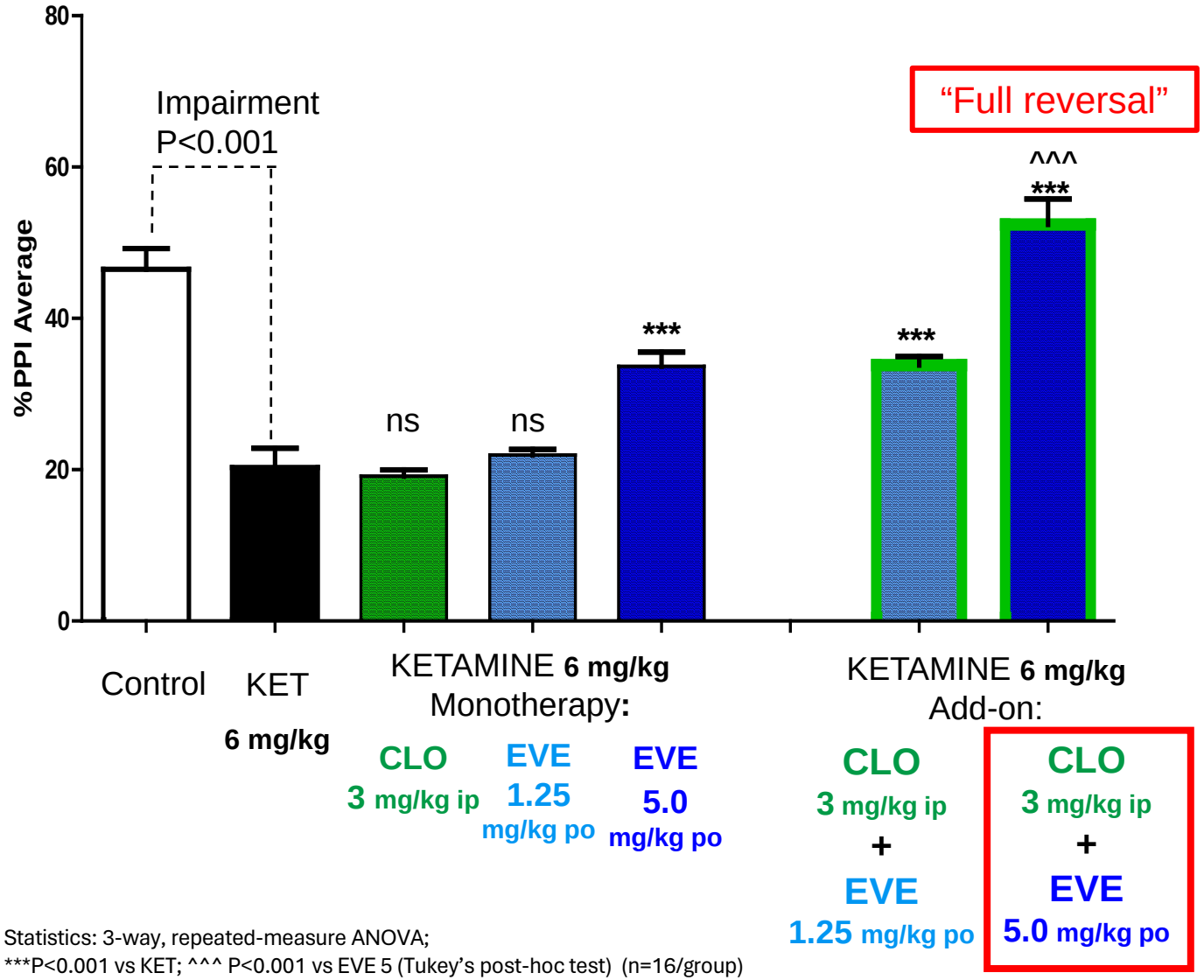
EVENAMIDE – EFFICACY IN PSYCHIATRIC ANIMAL MODELS

Evenamide is active as a monotherapy and add-on to ineffective doses of first-or-second generation antipsychotics, attenuating abnormal behaviours in different animal models

	Monotherapy	Add-On
Information Processing Deficit - Pre-Pulse Inhibition (PPI)		
PPI disrupted by dopamine activation (amphetamine -rat)	✓	✓ (haloperidol, risperidone)
PPI disrupted by NMDA antagonists (Ketamine, MK-801, PCP, -rat)	✓	✓ (clozapine)
PPI disrupted by stressful stimuli (sleep deprivation -rat)	✓	
Pre-pulse inhibition spontaneous deficit (C57 mice)	✓	✓ (haloperidol)
Psychosis and Mania		
Amphetamine plus Chlordiazepoxide induced hyperactivity in mice	✓	✓ (risperidone)
Negative Symptoms		
PCP-induced deficit in Social Interaction in the rat	✓	✓ (aripiprazole)
Cognitive Impairment		
Novel object recognition in the rat: short term scopolamine impairment	✓	
Novel object recognition in the rat: long term 24 hr natural forgetting	✓	
Impulse Control		
Resident–Intruder test in mice (aggression / Impulsivity)	✓	
MAM Model - development disruption model	Ongoing	

Blank cells = not evaluated

KETAMINE-INDUCED DETERIORATION OF PPI IS RESCUED BY 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

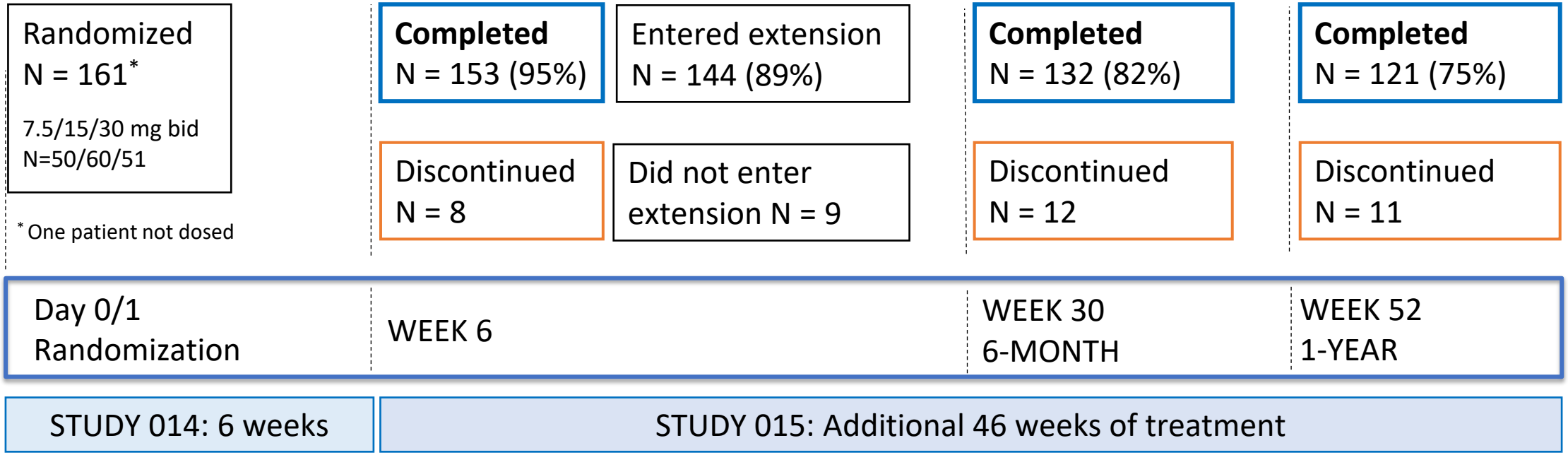
EVENAMIDE STUDY 014/015

PILOT, PHASE 2, OPEN-LABEL RESULTS WITH EVENAMIDE IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA (TRS)

STUDY 014/015 – KEY FEATURES

- Six-week, open-label, randomized, rater-blinded, parallel group study, option to enter extension up to 1 year to evaluate tolerability and preliminary efficacy of adjunctive 7.5, 15, 30 mg BID
- Patients with confirmed treatment resistant schizophrenia (TRS) non-responding to their current antipsychotic medication (except clozapine)
- PANSS scores 70-90; CGI-S 4 to 6
- Score of 4 or more on at least 2 of the PANSS core symptoms of psychosis: P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P6 (Suspiciousness/Persecution) and G9 (Unusual Thought Content)
- Total score ≥ 20 on the PANSS symptom items (combined): P1 (Delusions), P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P4 (Excitement), P6 (Suspiciousness/Persecution), P7 (Hostility), G9 (Unusual thought content)
- 161 patients randomized in 12 sites in India, Sri Lanka, Italy; Enrolment/performance of the study was impacted by the Covid-19 pandemic
- Key efficacy measures (PANSS total, CGI-S, CGI-C, LOF)

STUDY 014/015 – PATIENT DISPOSITION BY STUDY AND DURATION



Continuation rate into extension (Study 015) → 144/153 (94%)

Completion rate of Study 015 alone → 121/144 (84%)

Total Discontinued	**31**
Withdrawal of consent	23
Lost to follow-up	5
Adverse event	2
Death	1

DEMOGRAPHICS, BASELINE AND DISEASE CHARACTERISTICS – SAFETY POPULATION

Characteristic	Statistics	Total N=160
Age (years)	mean (SD)	37.7 (9.71)
Sex (% of males)	n (%)	111 (69.4)
Race		
Asian population	n (%)	157 (98.1)
White	n (%)	3 (1.9)
Duration of illness (years)	mean (SD)	6.8 (3.1)
Duration of current episode (months)	mean (SD)	7.9 (4.9)
PANSS total – baseline	mean (SD)	79.5 (5.0)
PANSS positive – baseline	mean (SD)	23.7 (3.3)
CGI-S – baseline	mean (SD)	4.5 (0.6)
BMI (kg/m^2)	mean (SD)	25.1 (5.2)
CDSS* baseline score	mean (SD)	0.6 (1.3)

* Calgary Depression Scale for Schizophrenia

BACKGROUND MOST COMMONLY PRESCRIBED CURRENT ANTIPSYCHOTIC MEDICATIONS – SAFETY POPULATION N=160

Antipsychotic	n (%) of patients N=160	Daily dose Mode [min-max] in mg
Risperidone	88 (55.0)	8 [2-12]
Olanzapine	42 (26.3)	20 [10-40]
Trifluoperazine	11 (6.9)	10 [10-20]
Aripiprazole	8 (5.0)	20 [20-45]
Other *	11 (6.9)	-

AP class	Statistics	Total N=160
SGAs	n (%)	144 (90.0)
FGAs	n (%)	16 (10.0)

* (5) haloperidol; (2) paliperidone; (2) quetiapine; (1) amisulpride; (1) blonanserin

STUDY 014/015

SAFETY AND EFFICACY RESULTS AT 1-YEAR

SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs) AT 1 YEAR SAFETY POPULATION N=160

Number of subjects with	7.5 mg bid N=50	15 mg bid N=60	30 mg bid N=50	Total N=160
At least one TEAE	23 (46.0%)	18 (30.0%)	24 (48.0%)	65 (40.6%)
At least one Serious TEAE*	0	1 (2.0%)	1 (2.0%)	2 (1.3%)
At least one treatment-related TEAE	8 (16.0%)	7 (11.7%)	7 (11.7%)	22 (13.8%)
Any TEAE leading to study discontinuation (ADOs)^	1 (2.0%)	1 (1.7%)	1 (2.0%)	3 (1.9%)

* Excluding medication errors; (1) dilutional hyponatremia followed by an acute symptomatic seizure - more than 20 days out of IP (15 mg *bid*), (1) sudden death after approximately six months of treatment - improvement from baseline ≥ 20%, no other TEAEs (30 mg *bid*)

^ (1) flu-like symptoms (7.5 mg *bid*), (1) somnolence (15 mg *bid*), (1) insomnia (30 mg *bid*)

MOST COMMON (≥2.5%) TEAE BY PREFERRED TERM – SAFETY POPULATION N=160

Preferred Term	7.5 mg bid N=50	15 mg bid N=60	30 mg bid N=50	Total N=160
Medication error (investigator mistake in dispensing kit) *	0	0	7 (14.0%)	7 (4.3%)
Blood creatine phosphokinase increased	2 (4.0%)	2 (3.3%)	2 (4.0%)	6 (3.8%)
Dizziness	2 (4.0%)	0	2 (4.0%)	4 (2.5%)
Insomnia	1 (2.0%)	2 (3.3%)	1 (2.0%)	4 (2.5%)
Pyrexia	2 (4.0%)	1 (1.7%)	1 (2.0%)	4 (2.5%)

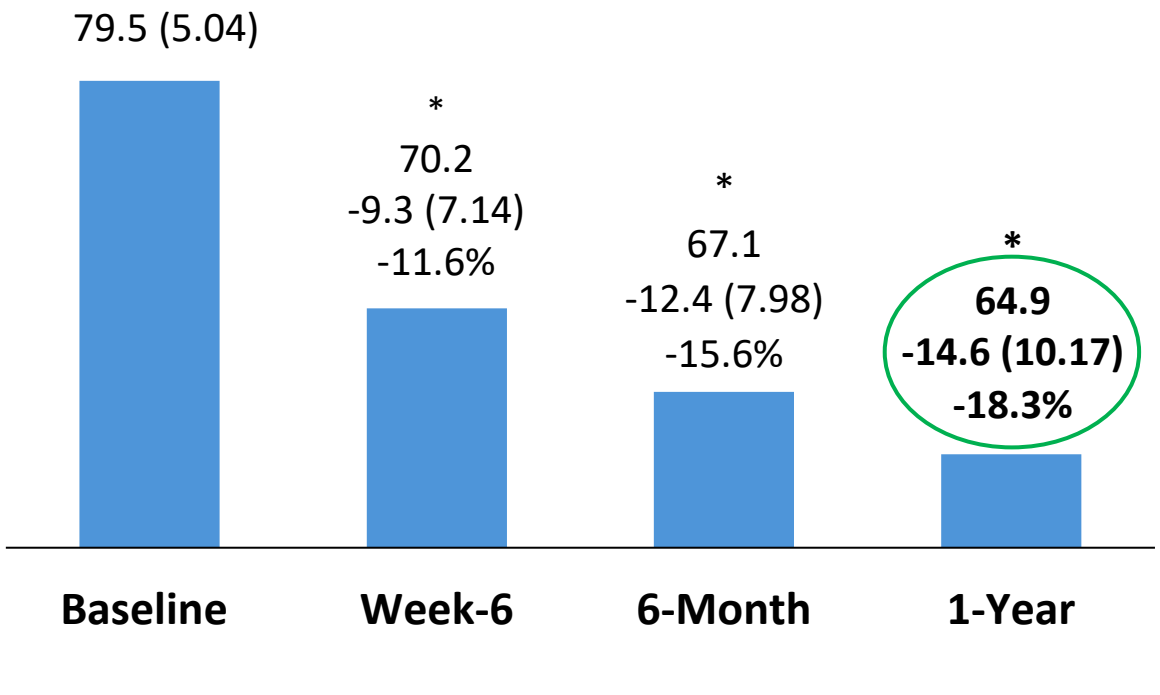
* No sign and symptoms or adverse events associated with any of the medication errors

OTHER SAFETY MEASURES

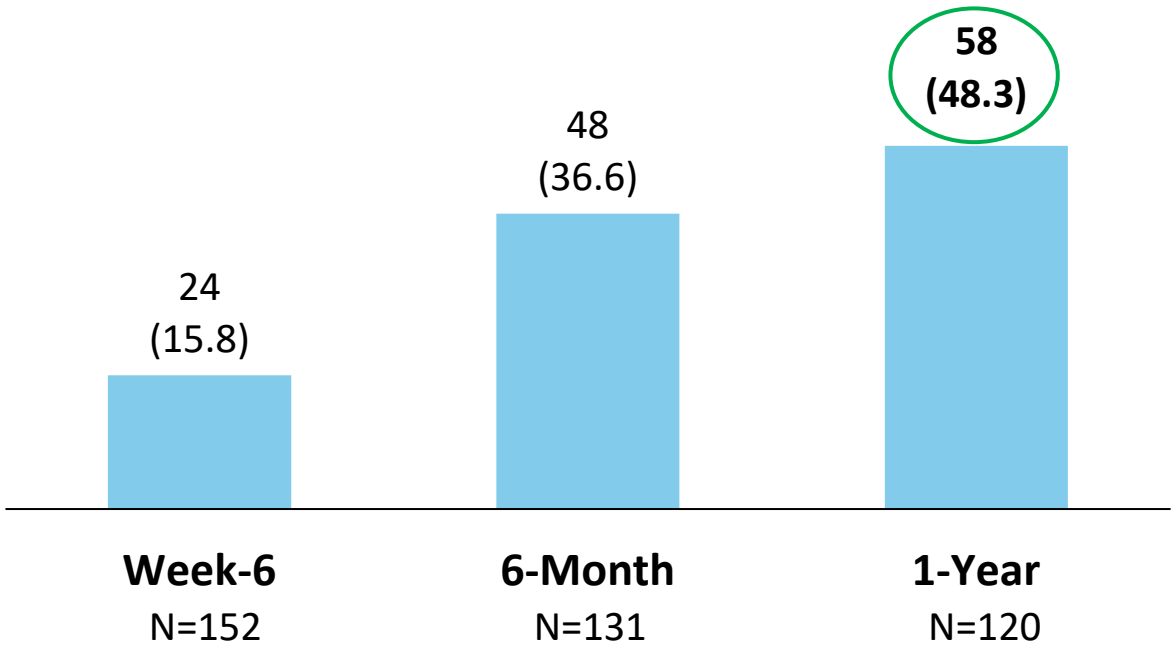
No pattern of abnormalities on: vital signs, physical/neurological/eye examination, extrapyramidal symptoms (EPS), depressive symptoms, laboratory examinations, ECG, sexual dysfunction, metabolic syndrome, endocrine abnormalities

LONG-TERM UP TO 1-YEAR EFFICACY RESULTS; mITT N=156

PANSS mean change from baseline (SD)
% change from baseline
LOCF



PANSS Responder Analysis
n (%) of patients with ≥20% improvement from baseline #
OC



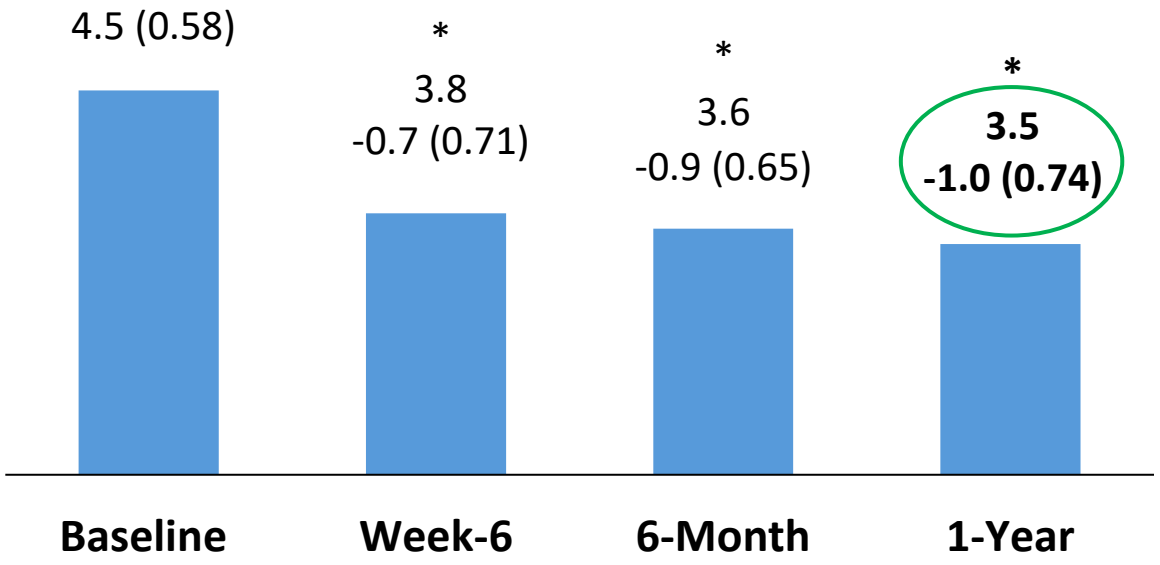
* p-value vs baseline < 0.001, paired t-test, LOCF

Rosenheck et al., 1997; Meltzer et al., 2008

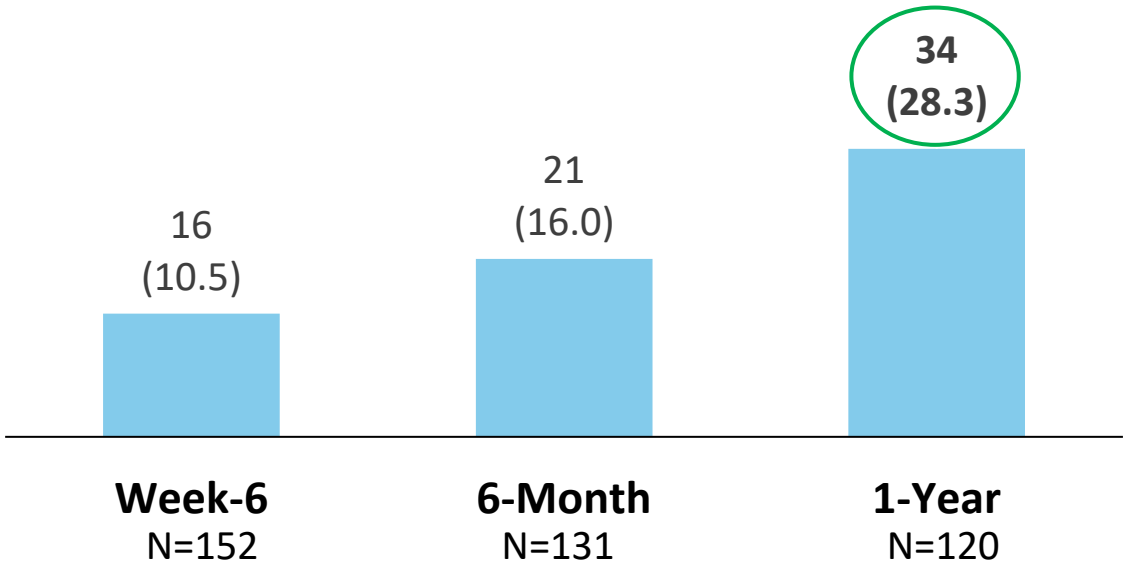
Results obtained using LOCF and OC do not differ significantly

LONG-TERM – UP TO 1-YEAR EFFICACY RESULTS; mITT N=156

CGI-S mean change from baseline (SD)
LOCF



CGI-S Responder Analysis
n (%) of patients with ≥2 categories of improvement
OC

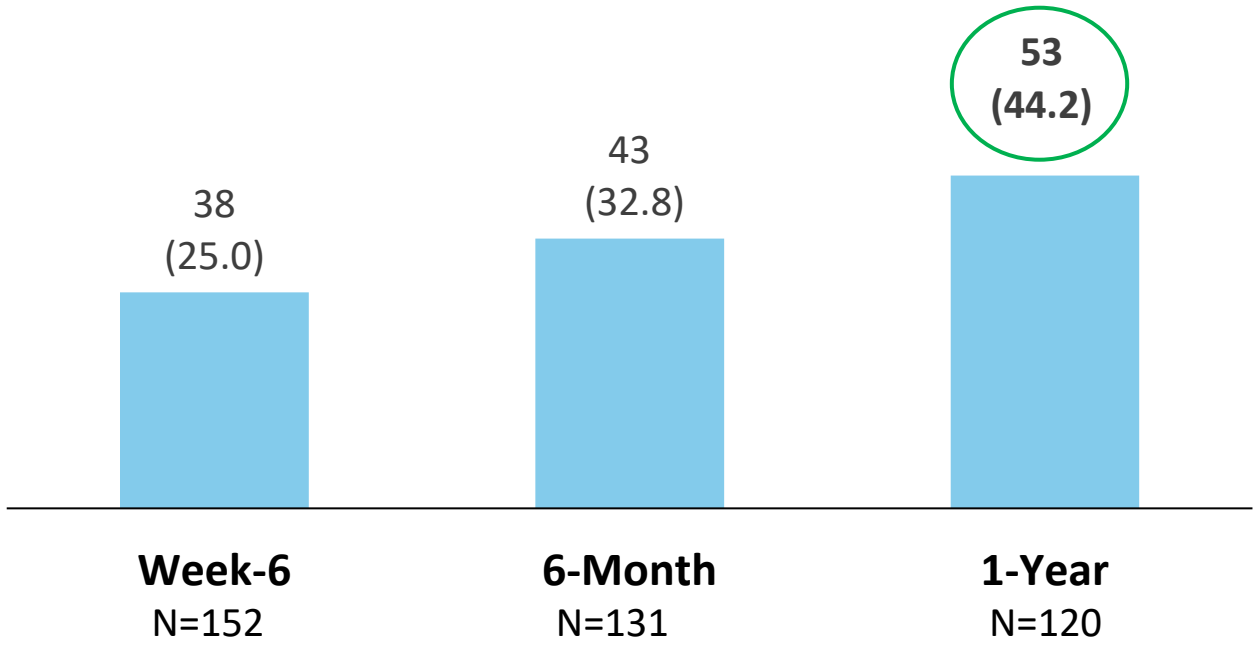


* p-value vs baseline < 0.001, paired t-test, LOCF

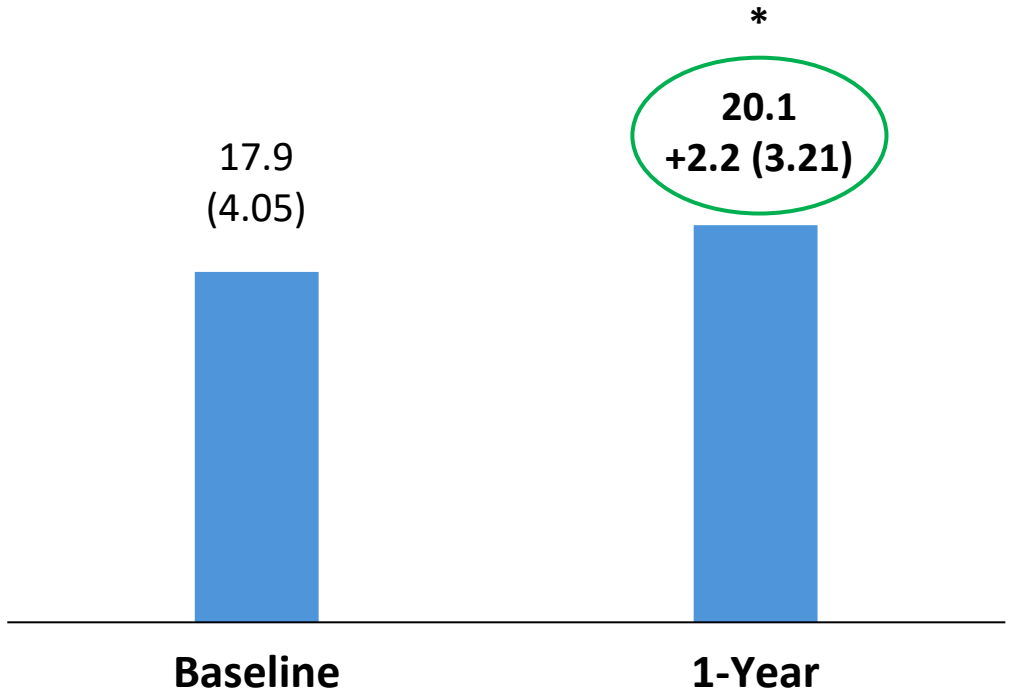
Results obtained using LOCF and OC do not differ significantly

LONG-TERM – UP TO 1-YEAR EFFICACY RESULTS; mITT N=156

CGI-C Responder Analysis
n (%) of patients rated at least "much improved"
OC



LOF# mean change from baseline (SD)
LOCF



Strauss-Carpenter Level of Functioning Scale
* p-value vs baseline < 0.001, paired t-test

Results obtained using LOCF and OC do not differ significantly

PATIENTS NO LONGER MEETING SEVERITY CRITERIA FOR TRS

Selection criteria for severity of symptoms:

1. PANSS total score ≥ 70
2. CGI-S of moderately ill to severely ill (score 4-6)
3. Total score ≥ 20 on the combined total of the PANSS symptom items: P1 (Delusions), P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P4 (Excitement), P6 (Suspiciousness/Persecution), P7 (Hostility), and G9 (Unusual thought content)
4. Score of 4 or more on at least 2 of the PANSS core symptoms of psychosis: P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P6 (Suspiciousness/Persecution) and G9 (Unusual Thought Content)

AN ANALYSIS WAS PERFORMED TO DETERMINE THE PROPORTION OF PATIENTS NO LONGER MEETING EACH OF THESE CRITERIA AT 1-YEAR

PATIENTS NO LONGER MEETING SEVERITY CRITERIA FOR TRS (mITT; OC)

Severity Criteria	Stats	Week-6 N=152	6-Month N=131	1-Year N=120
1. PANSS < 70	n (%)	72 (47.3)	84 (64.1)	84 (70.0)
2. CGI-S < 4	n (%)	52 (34.2)	66 (50.4)	76 (63.3)
3. Core items* < 20	n (%)	60 (39.4)	76 (58.0)	80 (66.7)
4. Score ≥ 4 in maximum 1 core symptom #	n (%)	75 (49.3)	87 (66.4)	87 (72.5)
All Combined	n (%)	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)

LOCF results do not differ substantially

CRITERIA FOR REMISSION IN PATIENTS WITH SCHIZOPHRENIA

ORIGINAL REQUIREMENTS

Lieberman et al., 1993

- Score ≤3 on SADS-C+PD* items: suspiciousness, severity of delusions, hallucinations, **impaired understandability, bizarre behavior**
- CGI-S of maximum “mildly ill” (i.e. score ≤3)
- CGI-C at least “much improved” (i.e. score ≤2)
- **Maintenance** for ≥ **8 weeks**

Andreasen et al., 2005

- Score **≤3** «mild» on PANSS items: P1= delusions - P2= conceptual disorganization - P3= hallucinatory behaviour - N1=Blunted affect - N4=Passive/apathetic social withdrawal - N6=Lack of spontaneity and flow of conversation - G5= Mannerism and posturing - G9=Unusual thought content
- **Maintenance** of this level of response for ≥ **6 months**

PROPOSED ADAPTATIONS

- SADS **Impaired understandability** → replaced with PANSS **P2** conceptual disorganization
- SADS **Bizarre behavior** → replaced with PANSS **G5** Mannerism and posturing

*Schedule for Affective Disorders and Schizophrenia - Change Version with Psychosis and Disorganization items

STUDY 014/015 – PROPORTION OF PATIENTS WHO MEET PROPOSED REMISSION CRITERIA FROM LITERATURE (mITT)

Method	Criteria	Maintenance requirement	n (%) of patients meeting remission criteria N=156
Lieberman et al, 1993	P1, P2, P3, P6, G5 ≤ 3 CGI-S «mildly ill»; CGI-C «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%)**

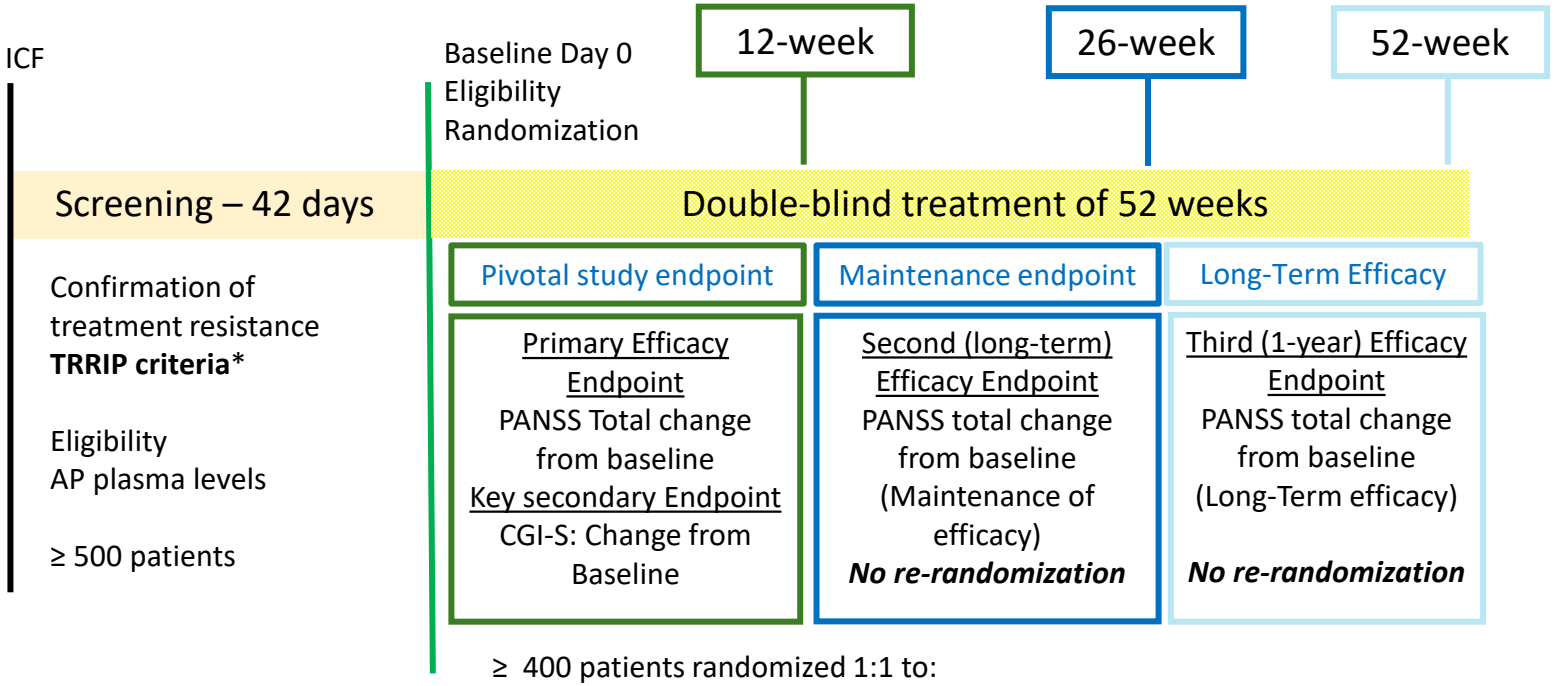
P1= delusions - P2= conceptual disorganization - P3= hallucinatory behaviour - N1=Blunted affect - N4=Passive/apathetic social withdrawal - N6=Lack of spontaneity and flow of conversation - G5= Mannerism and posturing - G9=Unusual thought content

LONG-TERM TREATMENT WITH EVENAMIDE: KEY OBSERVATIONS

- Well-tolerated: only three (3) adverse dropouts (i.e. flu-like symptoms, somnolence, insomnia)
- No pattern of laboratory, ECG, vital signs abnormalities, no complaints of EPS, sedation, weight gain, sexual dysfunction, and endocrine abnormalities
- No psychotic relapses during 1-year of treatment in TRS population
- Gradual, sustained, and long-lasting improvement measured by PANSS, CGI-C and CGI-S and LOF
- Most of the subjects who responded at week 6 maintained the response at 6-month and 1 year
- Half (~50%) of the patients no longer met operational criteria for severity at 1-year
- One-fourth (~25%) of the patients met the criteria for remission according to Liberman et al., 1993 and Andreasen et al., 2005
- Onset of clinical important response observed even at 1-year (late responders) is rare in TRS patients

PHASE 3, PLACEBO-CONTROLLED, 1-YEAR STUDY IN PATIENTS WITH TRS

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 evenamide as add-on in patients with documented treatment-resistant schizophrenia (TRS), which is not adequately controlled by a stable therapeutic dose of the patient's current antipsychotic medication(s)



* TRRIP Working Group Howes et al., 2017

Key Selection Criteria

- Treatment resistance (**TRS**) according to **TRRIP** working group (Howes et al., 2017)
- Antipsychotic treatment as per '**Standard of Care**', minimally one oral or depot antipsychotic at a stable therapeutic dose
- **BPRS** total score ≥ 45 at Screening
- **Prominent positive** symptoms as measured by the BPRS
- **CGI-S** rating of mildly ill to severely ill (score of 3 to 6)
- Antipsychotic (AP) **plasma levels** tested at screening and throughout the study to confirm adherence to the background AP therapy and evenamide therapy

Thank you