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 1-year, open-label trial

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

Current management of patients with schizophrenia with antipsychotics (APs) is associated with **30%** of patients becoming **treatment resistant**

Preclinical, neurometabolic and mechanistic studies suggest that treatment-resistant schizophrenia (**TRS**) is characterized by **excessive glutamatergic** but **normal dopaminergic transmission**

Evenamide, a NCE structurally unrelated to any existing/in development AP, is a highly selective **sodium channel blocker** which **attenuates excessive glutamate release** without affecting basal glutamate levels

Evenamide has demonstrated **efficacy in animal models** of psychosis ameliorating behavioral disturbances induced by sleep deprivation, dopaminergic, cholinergic, and glutamatergic antagonists

Study 014/015 Methods

Phase 2, **international**, **1-year, randomized, open-label, rater-blinded** trial to evaluate the **tolerability and efficacy** of **evenamide as add-on** in patients with **TRS** not responding to their current AP

1. Key inclusion criteria according to the study protocol
   - **TRS** defined as **"***persistent significant clinical symptoms despite at least two failed attempts of treatment with antipsychotics (other than clozapine), including at least one atypical antipsychotic, for an adequate period of time at therapeutic doses"*
   - **PANSS** total score of **70-90** with predominant positive symptoms
   - Moderately to severely ill (**CGI-S** of **4-6**)
   - Global Level of Functioning (**GAF**) **≤ 50**
   - **Monotherapy** at a stable dose with any AP (except clozapine)
2. Patients were randomized equally to **7.5,15 or 30 mg *bid*** of evenamide
3. Efficacy ratings (PANSS, CGI-C/S, and Strauss-Carpenter LOF) 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** (1 year)

Patient Disposition

Day 0 Randomization	WEEK 6		WEEK 30 6-MONTH	WEEK 52 1-YEAR
Randomized N = 161*	Completed N = 153 (95%)	Entered Extension N = 144 (94% £)	Completed N = 132 (92%#)	Completed N = 121 (84%#)
	Discontinued N = 8	Did not enter extension N = 9	Discontinued N = 12	Discontinued N = 11

* One patient not dosed

£ of Week-6 completers

# of patients entered in study 015

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

Results

Demographic and baseline characteristics (Safety population N=160)

Characteristic	Statistic	Total N=160
Age (years)	Mean (SD)	37.7 (9.71)
Sex – Male	n (%)	111 (69.38)
Race – Asian	n (%)	157 (98.13)
Duration of illness (years)	Mean (SD)	6.8 (3.09)
BMI (kg/m^2)	Mean (SD)	25.1 (5.16)
Most common background AP		
Risperidone	n (%)	88 (55.0)
Olanzapine	n (%)	42 (26.3)
Trifluoperazine	n (%)	9 (5.6)
Aripiprazole	n (%)	8 (5.0)

Safety Summary (N=160) and most common TEAEs (≥ 2.5%)

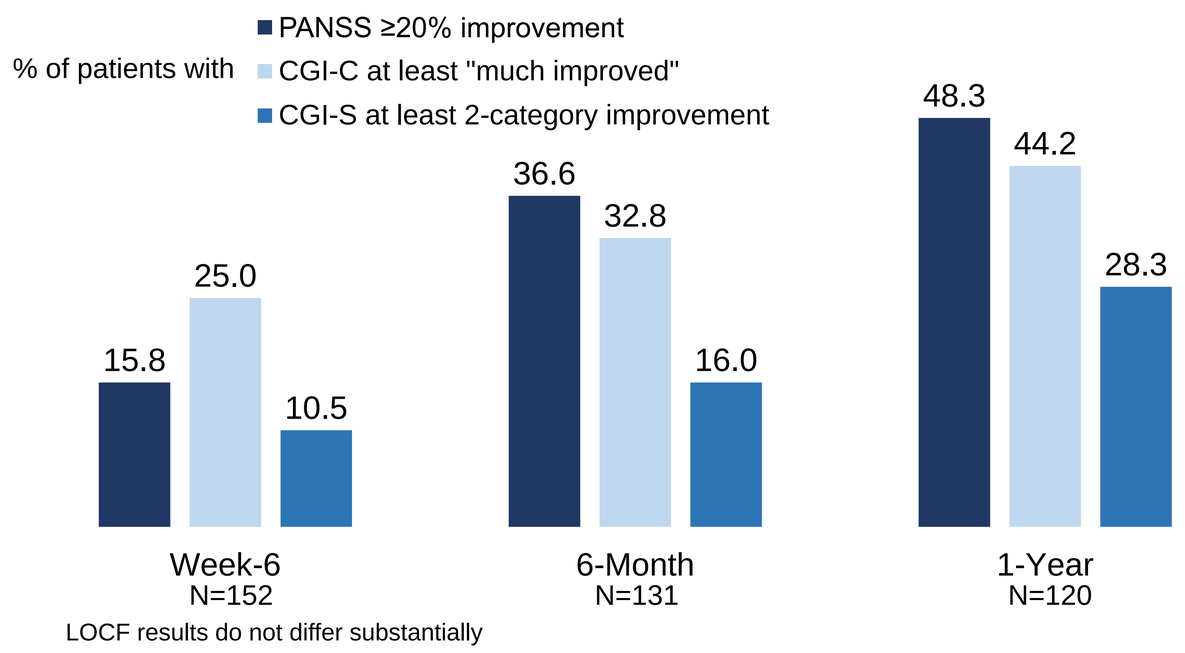
Patients with	No. of patients (%)
Treatment emergent adverse events (TEAE)	65 (40.6)
Blood creatine phosphokinase increased	*6 (3.8)*
Dizziness	*4 (2.5)*
Insomnia	*4 (2.5)*
Pyrexia	*4 (2.5)*
Treatment-related TEAE	22 (13.8)
Adverse dropout	3 (1.9)
Serious Adverse Event (SAE)	1 (0.6)
Death	1 (0.6)

Efficacy results (mITT N=156; OC)

Scale	Statistics	Visit			
		Baseline	Week-6 (N=152)	6-Month (N=131)	1-Year (N=120)
PANSS	Mean/mean change (%)	79.5	-9.5 (-11.9) *	-12.8 (-16.1) *	-15.9 (-20.0) *
CGI-S	Mean/mean change	4.5	-0.7 *	-1.0 *	-1.1 *
LOF	Mean/mean change	17.9	+1.3 *	+2.2 *	+ 2.5 *
CGI-C	Mean rating	NA	3.0	2.8	2.7

* p-value <0.001; paired t test; LOCF results do not differ substantially

Responder Analysis (mITT N=156; OC)



Key Findings and Conclusion

Add-on of evenamide to APs was **well-tolerated**, with no detected pattern of ECG, laboratory, EPS or CNS abnormalities, and **low** incidence of **adverse drop-outs** (1.9%)

Absence of psychotic relapses during the 1-year treatment period in TRS population

Gradual, **sustained**, and **long-lasting improvement** across all efficacy measures up to and including 1-year on mean change from baseline and on responders rates

Although this is an open-label study, and the vast majority of patients is from India, the fact that the improvement is continued and sustained till 1 year of treatment indicates that it is unlikely related only to a placebo effect

These data support the hypothesis that patients with TRS may have an excess of glutamatergic transmission, and advocate the role of glutamate release inhibition in the therapy of patients not responding to 5HT2/D2 modulators

These encouraging results have expedited the conduct of a potentially pivotal, phase 3, randomized, double-blind, placebo-controlled, international study of evenamide as add-on treatment in patients with TRS

CMO Ravi Anand, MD - **Email** ravi@anand.ch **Disclosure**: R. Anand, MD is a consultant to Newron Pharmaceuticals SpA

Treatment with evenamide for 1 year in TRS patients not benefitting to current antipsychotics is associated with sustained, clinically important benefit: Results from a prospective, pilot, 1-year, randomized, open-label trial

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

Background

1. **Treatment-resistant schizophrenia (TRS)** occurs in ~**30%** of patients, and is associated with high morbidity, mortality, suicidality, frequent hospitalizations, and increased costs for families and society
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, devoid of biological activity at >130 CNS targets, **normalizes excessive glutamate release** without affecting its 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 highly encouraging, final, 1-year, efficacy and safety results from a Phase 2 clinical trial evaluating evenamide as add-on therapy in patients with TRS

Methods

1. Study 014: **6-week**, **randomized**, open-label, **rater-blinded**, **multinational** 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 AP (other than clozapine)
2. Study 015: **46-week** open-label **extension** to Study 014, with patients continuing on their assigned dose of evenamide
3. Key efficacy assessments → Positive and Negative Syndrome Scale **(PANSS),** Clinical Global Impression Scale of Severity/Change (**CGI-S/C)**, and Strauss-Carpenter Level of Functioning Scale **(LOF)**
4. Key safety measures → Treatment-emergent adverse events (**TEAEs**), **Vital Signs, ECG, Laboratory Tests, ESRS-A**
5. Change from baseline analyzed for the PANSS, CGI-S, and LOF using a paired t-test

Key inclusion criteria

1. TRS: *persistent significant clinical symptoms despite at least two failed attempts of treatment with antipsychotics (other than clozapine), including at least one atypical antipsychotic, for an adequate period of time at therapeutic doses*

2. PANSS total score of **70-90** with predominant positive symptoms:

- **Core items ≥ 20** (P1, P2, P3, P4, P6, P7, G9)
- Score of **4 or more** on at least 2 **core symptoms** of psychosis (P2, P3, P6, G9)

3. Moderately to severely ill (**CGI-S of 4 to 6**)
4. Global Level of Functioning (**GAF**) **≤** 50
5. **Monotherapy** at a stable dose with any antipsychotic (other than clozapine)

Patient Disposition

Day 0 Randomization	WEEK 6		WEEK 30 6-MONTH	WEEK 52 1-YEAR
Randomized N = 161*	Completed N = 153 (95%)	Entered Extension N = 144 (94% £)	Completed N = 132 (92%#)	Completed N = 121 (84%#)
	Discontinued N = 8	Did not enter extension N = 9	Discontinued N = 12	Discontinued N = 11

Total discontinued:	**31**
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Adverse event:	2
Death:	1

*One patient not dosed

£ of Week-6 completers

# of patients entered in study 015

Results

Demographic and baseline characteristics (Safety population N=160)

Characteristic	Statistic	Total N=160
Age (years)	Mean (SD)	37.7 (9.71)
Sex – Male	n (%)	111 (69.38)
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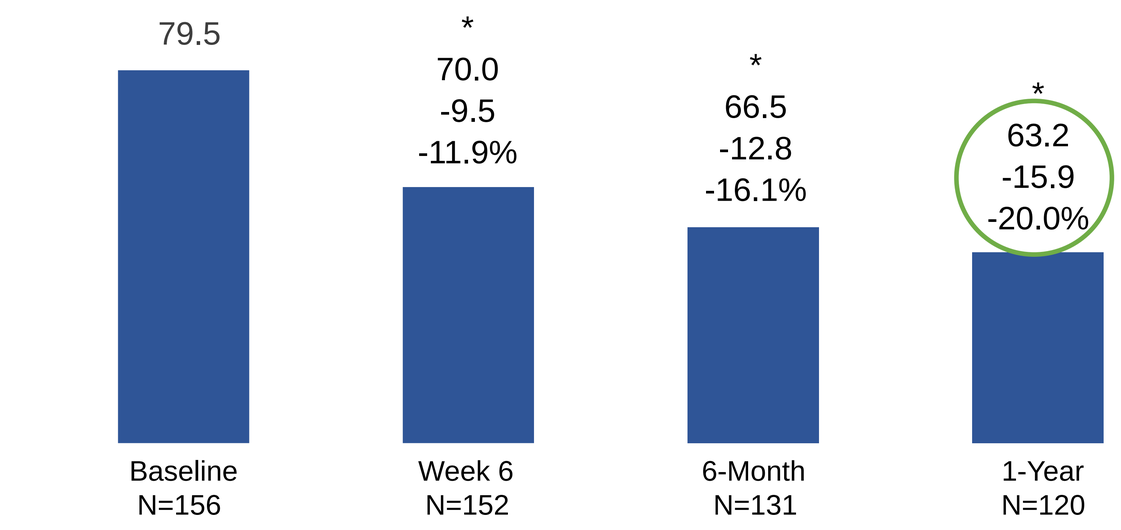
Safety Summary (N=160) and most common TEAEs (≥ 2.5%)

Patients with	No. of patients (%)
TEAE	65 (40.6)
Blood creatine phosphokinase increased	*6 (3.8)*
Dizziness	*4 (2.5)*
Insomnia	*4 (2.5)*
Pyrexia	*4 (2.5)*
Treatment-related TEAE	22 (13.8)
Adverse dropout	3 (1.9)
Serious Adverse Event (SAE)	1 (0.6)
Death	1 (0.6)

Mean change from baseline on PANSS total score (mITT N=156; OC)



* p-value <0.001; paired t test; LOCF results do not differ substantially, i.e. change (%) at 1-year: -14.6 (-18.3)

Mean change from baseline on CGI-S/LOF, mean rating on CGI-C (mITT N=156; OC)

Scale	Statistic	Visit			
		Baseline	Week-6 (N=152)	6-Month (N=131)	1-Year (N=120)
CGI-S	Mean/mean change	4.5	-0.7 *	-1.0 *	-1.1 *
LOF	Mean/mean change	17.9	+1.3 *	+2.2 *	+ 2.5 *
CGI-C	Mean rating	NA	3.0	2.8	2.7

* p-value <0.001; paired t test; LOCF results do not differ substantially

Clinically significant responder rates are showed on a dedicated poster

Key Findings and Conclusion

The **low rate of dropouts** during the 1-year period, in particular for adverse events (1.9%), indicates **good tolerability** of evenamide at all doses. No pattern of adverse events related to either the 7.5 mg bid, or 15 mg bid, or 30 mg bid dose of evenamide was observed

Statistically significant improvement in PANSS total, CGI-S, and Strauss-Carpenter LOF for all three doses of evenamide (*p<0.001; paired t-test; OC/LOCF) up to 1 year

Complete **absence of psychotic relapses** throughout the 1-year treatment period

This is the first international 1-year trial of a drug acting on the glutamate system as an add-on to a single AP in patients with TRS. These data demonstrate the unique and multi-domain benefits of glutamate modulation when added to APs

Positive and encouraging results from this study have expedited the conduct of a potentially pivotal, international, Phase 3, randomized, double-blind, placebo-controlled trial of evenamide as add-on to APs in patients with TRS

CMO Ravi Anand, MD - **Email** ravi@anand.ch **Disclosure**: R. Anand, MD is a consultant to Newron Pharmaceuticals SpA

Addition of evenamide for 1 year to antipsychotics in TRS patients results in increasing clinically important benefit to an extent that a substantial proportion no longer meet international criteria for treatment resistance

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

Treatment-resistant schizophrenia (TRS) develops in **~30%** of patients within about **5 years** from starting treatment with antipsychotics (APs), resulting in increased morbidity, suicidality, and mortality

The combination of more APs has not been shown to be beneficial for patients with TRS, as all act through modulation of dopaminergic and serotoninergic transmission

Increasing evidence suggests that **abnormalities in glutamatergic neurotransmission** characterize TRS, rather than excess of dopamine synthesis

Evenamide, a selective inhibitor of voltage-gated sodium channels, is devoid of biological activity at >130 CNS targets**, normalizes excessive glutamate release** without affecting basal levels, and demonstrated **benefits in animal models of psychosis** as monotherapy and as an add-on to APs

AIM

Present long-term (1 year), efficacy results from a clinical trial with evenamide as add-on therapy in patients with TRS

Methods

1. Study 014/015 is a **Phase 2**, **1-year, randomized, open-label rater-blinded, international** trial in patients with TRS not responding to a therapeutic dose of an AP
2. Patients were randomized equally to 7.5,15 or 30 mg *bid* of evenamide
3. Efficacy ratings (PANSS, CGI-C/S, and Strauss-Carpenter LOF scale) were performed by a **psychiatrist blinded to the evenamide dose**
5. **Responder rates**, **maintenance of response**, and **conversion** of TRS patients to a **responsive state** were assessed

Key inclusion criteria

1. TRS: *persistent significant clinical symptoms despite at least two failed attempts of treatment with antipsychotics (other than clozapine), including at least one atypical antipsychotic, for an adequate period of time at therapeutic doses*

2. PANSS total score of **70-90** with predominant positive symptoms:

- **Core items ≥ 20** (P1, P2, P3, P4, P6, P7, G9) *****
- Score of **4 or more** on at least 2 **core symptoms** of psychosis (P2, P3, P6, G9) #

3. Moderately to severely ill (**CGI-S of 4 to 6**)
4. Global Level of Functioning (**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 = 161*	Completed N = 153 (95%)	Entered Extension N = 144 (94% £)	Completed N = 132 (92%#)	Completed N = 121 (84%#)
	Discontinued N = 8	Did not enter extension N = 9	Discontinued N = 12	Discontinued N = 11

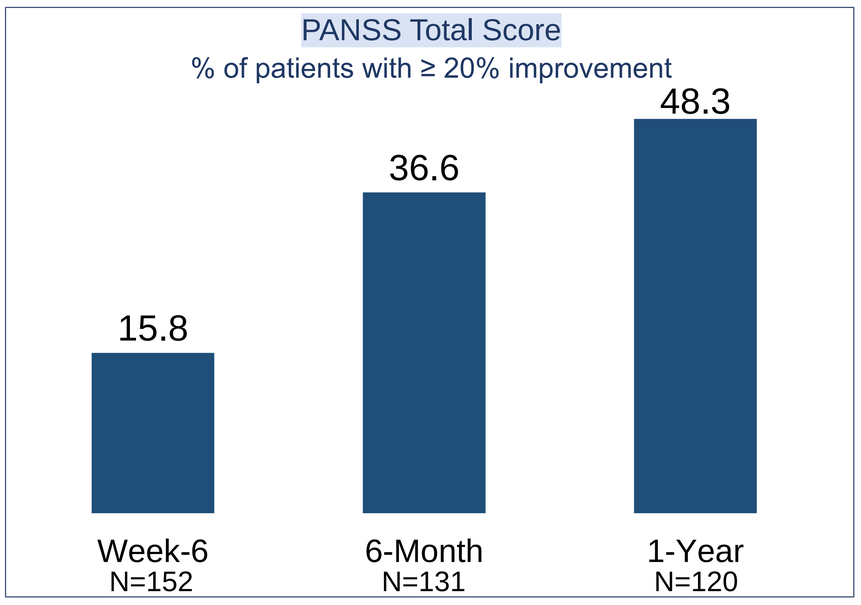
* One patient not dosed

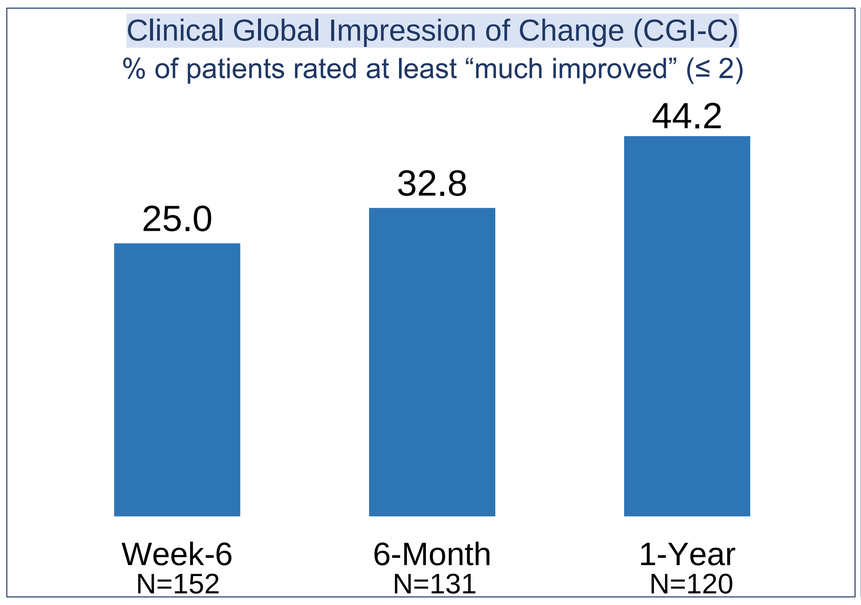
£ of Week-6 completers

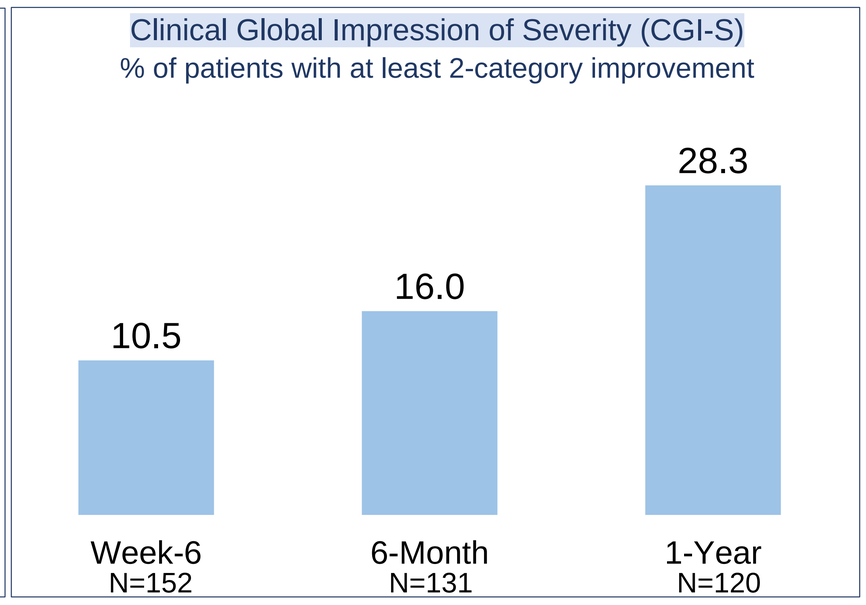
# of patients entered in study 015

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

Responder analysis (mITT N=156; OC)







LOCF results do not differ substantially

Proportion of patients no longer meeting protocol TRS severity criteria

Severity Criteria	Visit	Week-6		6-Month		1-Year	
	Stat	LOCF	OC	LOCF	OC	LOCF	OC
	N	156	152	156	131	156	120
1. PANSS ≥ 70	n (%)	72 (46.1)	72 (47.3)	93 (59.6)	84 (64.1)	99 (63.5)	84 (70.0)
2. Core items* ≥ 20	n (%)	60 (38.4)	60 (39.4)	83 (53.2)	76 (58.0)	93 (59.6)	80 (66.7)
3. CGI-S ≥ 4	n (%)	52 (33.3)	52 (34.2)	73 (46.7)	66 (50.4)	89 (57.1)	76 (63.3)
4. Score ≥ 4 on at least 2 core symptoms of psychosis#	n (%)	75 (48.1)	75 (49.3)	96 (61.5)	87 (66.4)	104 (66.7)	87 (72.5)
All Combined	n (%)	40 (25.6)	40 (26.3)	57 (36.5)	51 (38.9)	76 (48.7)	66 (55.0)

Maintenance of response (PANSS ≥ 20% improvement)

Timepoint of response «onset»	Stat	Week-6 N=152	Week-18 N=139	6-Month N=131	Week-42 N=123	1-Year N=120
Week-6	n (%)	24 (15.8%)	21 (87.5%)	16 (66.7%)	16 (66.7%)	14 (58.3%)
Week-18	n (%)	-	35 (25.2%)	26 (74.3%)	26 (74.3%)	25 (71.4%)
6-Month	n (%)	-	-	48 (36.6%)	45 (93.8%)	44 (91.7%)

% based on the N of observed patients at the corresponding visit
All other % are based on the n of responders observed at the timepoint of response «onset»

Key Findings and Conclusion

1 **Add-on of evenamide** to APs was **well tolerated**, with no pattern of ECG, labs, EPS or CNS abnormalities, in addition to a **low** incidence of **adverse dropouts** (1.9%), and a **high completion rate** at 1 year

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

3 **Increase up to and including 1 year** in the proportion of patients with a **clinically meaningful improvement** on PANSS (≥ 20%), CGI-C (at least much improved), and CGI-S (≥ 2-category)

4 **Conversion of TRS patients into a responsive state:** ~50% of patients at 1 year no longer met the protocol severity criteria used to select TRS patients for the study

5 These data demonstrate the unique, multi-domain and long-lasting effects of evenamide, a glutamate modulator, used as add-on to a single AP in patients with TRS.
If confirmed, results may change the management of patients with TRS.

Encouraging results of this study have expedited the conduct of a potentially pivotal, phase 3, international, randomized, double-blind, placebo-controlled, study of evenamide as add-on treatment in patients with TRS according to TRRIP criteria

CMO Ravi Anand, MD - **Email** ravi@anand.ch **Disclosure**: R. Anand, MD is a consultant to Newron Pharmaceuticals SpA

Design of a potentially pivotal, phase 3, international, randomized, double-blind, placebo-controlled clinical trial evaluating evenamide as add-on treatment for treatment-resistant schizophrenia (TRS) patients

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

Study Rationale

Currently available antipsychotics (APs) fail to benefit a large part of patients living with schizophrenia, with **30-60%** showing **no**, and another **10-30%** showing **inadequate response** to AP medication

Treatment-resistant schizophrenia (TRS) is associated with increased risk for hospitalization, morbidity, suicidality, and reduced life expectancy by up to 20 years

Clozapine, despite being the **only drug approved for TRS**, is not widely used due to severe **side-effects** (i.e., agranulocytosis, neutropenia, extreme weight gain) **blood-monitoring** requirements, and **poor response** (30% of TRS patients do not benefit from clozapine)

Findings from neurochemistry, neuro-metabolism, and functional imaging in TRS patients indicate **abnormalities in glutamatergic neurotransmission**, which are not targeted by current APs

Evenamide, a voltage-gated sodium channel blocker, which **normalizes excessive glutamate release** without affecting basal levels, is associated with **benefit in animal models** of schizophrenia

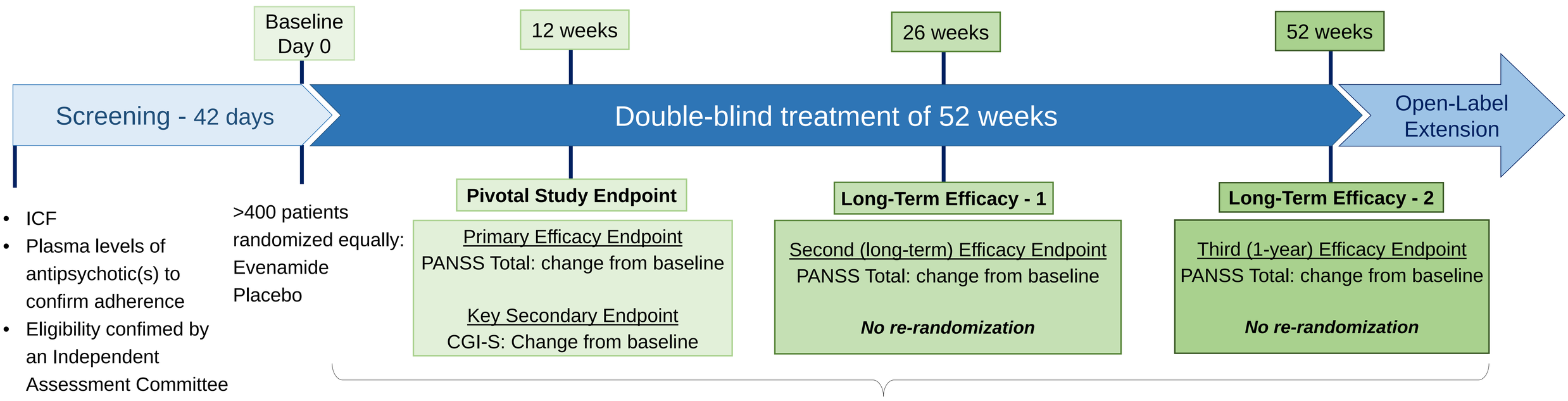
Preliminary evidence of efficacy in **patients with TRS** stabilized on a **single AP** has been demonstrated in a pilot, phase II, 6-week study with a 46-week extension, where increasing benefits were noted across all efficacy measures up to 1 year of treatment (**Study 014/015**)

Study design

International | **Randomized** | **Double-blind** | **Placebo-controlled** | **52 weeks**

AIM

Evaluate the **efficacy** and tolerability of evenamide as **add-on** treatment in patients with documented **TRS** not benefiting from their current AP treatment



- Plasma levels of antipsychotic(s) to confirm adherence
- Plasma levels of evenamide for PK assessment

Key inclusion criteria

1. DSM-5-TR diagnosis of schizophrenia, confirmed by **MINI**
2. Confirmation of **TRS** according to **TRRIP working group criteria** (Howes et al., 2017)
3. Currently receiving **"standard of care"**: 1 or 2 AP at a stable therapeutic dose for at least 6 weeks prior to screening. Adherence confirmed by measuring plasma levels
4. Mildly to severely ill on Clinical Global Impression - Severity of illness (**CGI-S 3 to 6**)
5. **BPRS** total score **>45**, with score of **at least 18** on P2, P3, P4, P5, P6, P7, G9 and **at least** a score of "**5**" on at least one or "**4**" on at least two of the **4 core items** (P2, P3, P6, G9)
6. Positive and Negative Syndrome Scale (**PANSS**) total **≥ 70** (at Baseline)

Efficacy Evaluations

- **PANSS total:** mean change from baseline (*primary*)
- **CGI-S:** mean change from baseline (*key secondary*)
- **CGI-C:** mean rating at endpoint
- **PANSS Positive:** mean change from baseline
- Quality of Life (**Q-LES-Q-SF**) and Personal and Social Performance (**PSP**) scale
- **PANSS Negative** and **MSQ** (*tertiary*)
- **Cognitive** assessments (*long term*)

Regions in which TRS study may be performed

North America
Central and South America
EU + UK
Asia

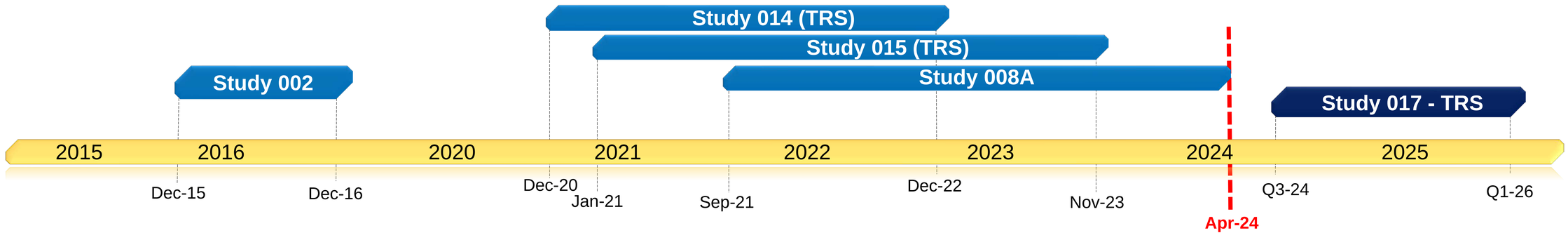
Results and Conclusions

Positive results from this study would change the current management of patients with TRS, indicating that modulation of excessive glutamatergic transmission by evenamide should be advocated for TRS patients with inadequate response to their AP treatment

Safety Measures

- Adverse events/ vital signs/ ECG/ laboratory evaluations
- Physical/ neurological/ eye examinations
- Calgary Depression Scale for Schizophrenia (**CDSS**)
- Columbia-Suicide Severity Rating Scale (**C-SSRS**)
- Extrapyramidal symptom rating scale (**ESRS-A**)
- Assessment of potential withdrawal effects

Phase 2/3 Evenamide Program Summary



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