COMMITTED TO CNS DRUG DEVELOPMENT

INNOVATIVE TREATMENTS TO IMPROVE QUALITY OF LIFE

Evenamide TRS Study 014/015: 6-month results

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January 3, 2023

Newron
Pharmaceuticals

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COMPANY HIGHLIGHTS

Unique portfolio of innovative CNS product candidates

- **Xadago®** for Parkinson's disease – Global approvals validate Newron's development capabilities from research to market
- **Evenamide** – New concept in treating inadequate/non-response in schizophrenia
- Ongoing search for strategically relevant assets

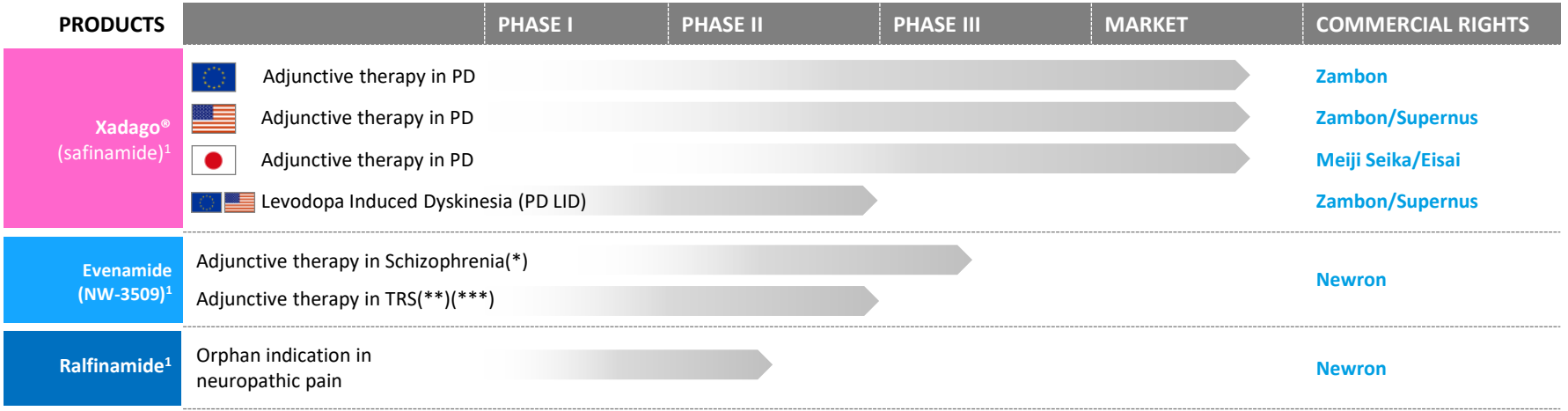
Management team with extensive experience and proven track record in drug development and commercialization

Significant near-term value drivers for leading candidate

Fully funded beyond key value inflection points

- Cash balance of € 28.4 million (June 30, 2022)
- Royalty income, R&D tax credit: approx. €16m (2 yrs.)
- Cash reach 2024

INNOVATIVE CLINICAL PIPELINE WITH NEAR-TERM CATALYSTS



EXPECTED MILESTONES

Xadago®

Preparations for study in patients with Levodopa Induced Dyskinesia (PD LID) ongoing, study expected to start 2023

Evenamide

*Minimally 260 pts phase II/III study (008A) started Sept 2021, results expected in 2023
**Safety, tolerability and preliminary efficacy, six-week, randomized, rater-blinded study in TRS patients (study 014, 161 patients). Results from interim assessment of first 100 patients available since June 2022, final results expected in QI 2023
***Further pivotal study in TRS to initiate in 2023

Ongoing search for strategically relevant assets

DIFFERENTIATION OF EVENAMIDE IN SCHIZOPHRENIA

- Large market
- Unique MoA and positioning
  - **First add-on drug**
    - Change a non-responder into a responder
    - No need to change current therapy, minimizing risk of patient relapse
    - Ease-of-use for patients & physicians
  - **First/only TRS drug since/beyond clozapine**
    - 30-50% of total population
    - Opportunity to keep niche indication within TRS for commercialization

- Positive results from phase II Study 002 in non-TRS patients
- 1 of 2 pivotal studies (non-TRS) ongoing
- Pilot study in TRS patients ongoing, 4 weeks and 6 months interim results available
- Chance for early market access
- Exclusivity: 2033 (COMP) and beyond (10 yrs exclusivity post approval in the EU)

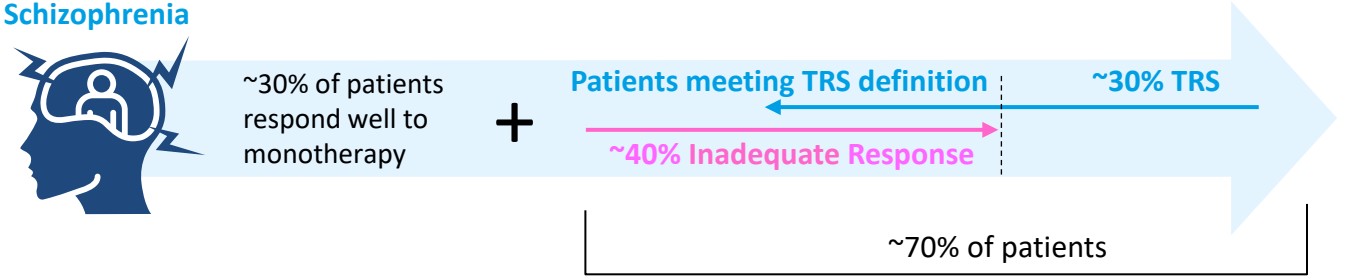
ENORMOUS MEDICAL NEED FOR 20 MILLION PATIENTS WORLDWIDE

VAST MARKET OPPORTUNITY
(anti-psychotics market >$23bn)

- 1% prevalence of disease
- Disease onset in 20s, need for life-long treatment
- **Cost to society** (direct cost US only): $63bn p.a.

Over 30 antipsychotics available, but all provide short-term and insufficient relief of some of the symptoms

Most patients with schizophrenia demonstrate reduced control of positive symptoms by typical and atypical antipsychotics after first few years of treatment



Major shortcomings of current antipsychotics:

- No effective drugs to eliminate symptoms, reduce progression, limit disability, suicide or early mortality
- All available options target D2/5HT2, but not glutamate, shown lately to be the major abnormality in poor/non-responders

EVENAMIDE – THE COMMERCIAL OPPORTUNITY

- **Large Market Opportunity**
- **NO direct competition as evenamide can be added to all antipsychotics**
- **Promise to change treatment management paradigm in schizophrenia**

- First **add-on** antipsychotic to be approved for **inadequately responding** patients
  - Up to 70% of Chronic schizophrenia, non-TRS population, every (on average) 18 months (CATIE study), due to loss of efficacy and side effects of current antipsychotic medication
  - Add-on therapy with **no dose-limiting side effects** a key advantage for patients and prescribers
- **First drug for treatment of TRS** since clozapine (1989)
  - >30% of schizophrenia population (with upside to 50%)
  - Strong HTA value story to support pricing and coverage
- No antipsychotic has demonstrated benefit as add-on to clozapine, thus **evenamide would be the only option** (Abt. 30k C-TRS patients in each key territory)

EVENAMIDE'S UNIQUE MOA DEMONSTRATED

Selectively blocks native sodium channels, showing no off-target effect on >130 other CNS receptors, enzymes, transporters, etc.

Selectively blocks VGSCs in a voltage-and use-dependent manner

Inhibition of native sodium channels expressed in rat cortical neurons

K_{rest} (µM)

25

K_{inact} (µM)

0.4

Modulates sustained repetitive firing without inducing impairment of the normal neuronal excitability

High frequency firing

Control

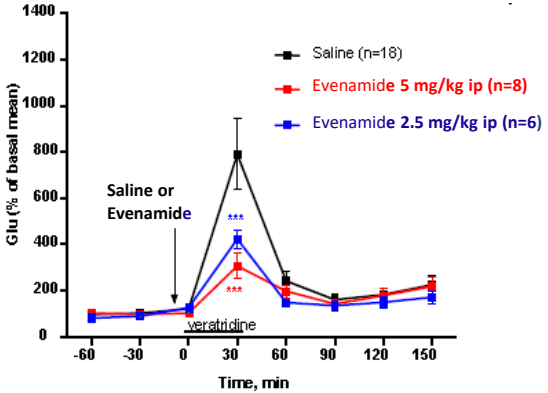
Evenamide 1µM

Low frequency firing

Control

Evenamide 1µM

Inhibits Glutamate Release



MONOTHERAPY AND ADD-ON EFFECT OF EVENAMIDE DEMONSTRATED IN ANIMAL MODELS RELEVANT TO SCHIZOPHRENIA

		MONOTHERAPY	ADD-ON
Information Processing Deficit	Pre-pulse inhibition (PPI) disrupted by dopamine activation (amphetamine -rat)	✓	✓
	Pre-pulse inhibition (PPI) disrupted by NMDA antagonists (MK-801, PCP, -rat)	✓	
	Pre-pulse inhibition (PPI) disrupted by natural stimuli (sleep deprivation -rat)	✓	
	Pre-pulse inhibition spontaneous deficit (C57 mice)	✓*	✓
	Pre-pulse inhibition (PPI) disrupted by Ketamine in rat	✓	✓
Negative Symptoms	PCP-induced deficit in Social Interaction in the rat	✓	✓
Psychosis and Mania	Amphetamine induced hyperactivity in mice	✓	✓
	Amphetamine plus Chlordiazepoxide induced hyperactivity in mice	✓	✓
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 and Mood Symptoms	Resident–Intruder test in mice (Impulsivity)	✓	
	Tail suspension test in mice (Depression)	✓	
	Marble burying test in mice (Obsessive Compulsive Disorders)	✓	

*Trend
Blank cells = not evaluated

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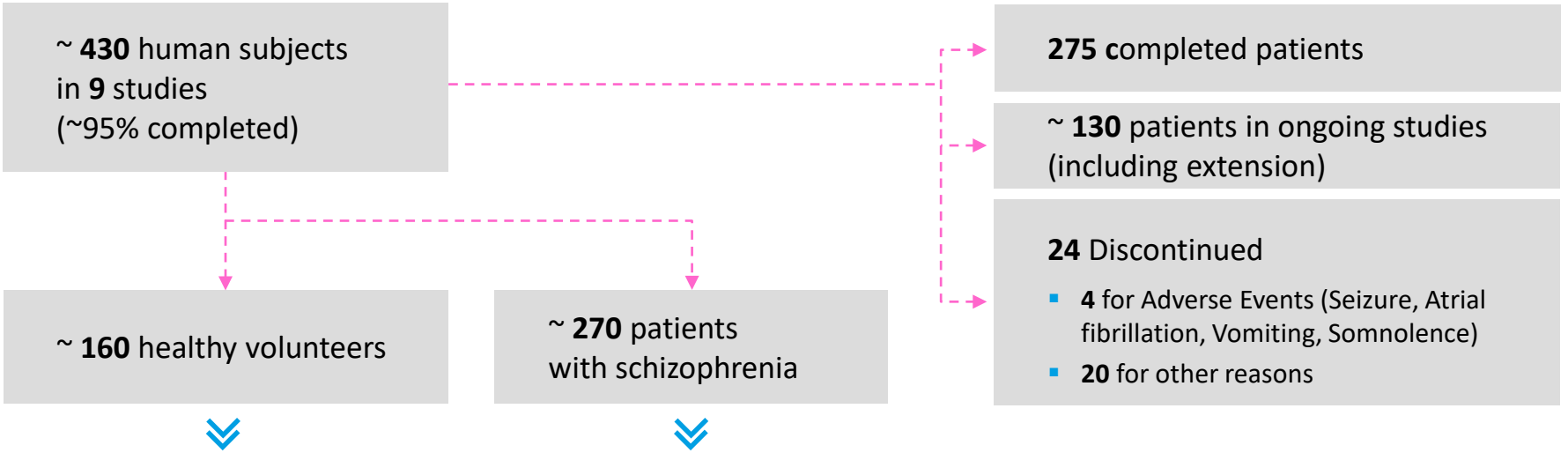
DISPOSITION OF SUBJECTS EXPOSED TO EVENAMIDE AND MOST FREQUENT (>3%) TREATMENT EMERGENT ADVERSE EVENTS



Most frequent (>3%) AEs:

Headache → 7.5%
Dizziness → 6.3%
Abdominal pain/discomfort → 3.1%

Most frequent (>3%) AEs:

Somnolence → 5.5%
Headache → 3.7%
Insomnia → 3.3%

CONCLUSIONS ON SAFETY

Single doses of **60 mg** of evenamide in healthy volunteers, and multiple doses of 7.5 to 30 mg bid in patients with schizophrenia receiving antipsychotics, were **well tolerated**

To date, >400 subjects have been treated in Phase I-III trials **without any evidence of EPS, metabolic syndrome, sexual disfunction, significant CNS events, or laboratory abnormalities**

TQT study in HVs indicated that evenamide is **devoid of risks of QTc prolongation** (evenamide maximal increase was <6 msec; placebo 7.6 msec) or arrhythmias

The emerging, favourable safety profile of evenamide indicates it **could be added to any current AP** in patients with schizophrenia without any risk of drug-drug interaction or additional toxicity

EVENAMIDE: EFFICACY DEMONSTRATED IN PATIENTS WITH SCHIZOPHRENIA (NON-TRS, STUDY 002)

- 4-week, placebo-controlled, add-on study of evenamide (15-25mg BID/day) in 89 patients on stable doses of aripiprazole or risperidone showing signs of worsening when compared to standard of care, at every assessment during the study (starting from Day 8)
  - **Significant improvement of**
    - PANSS positive, both mean change AND responder rate
    - CGI-C
  - **Superior benefit on**
    - PANSS total
    - LOF total
    - CGI-S
- Evenamide's glutamatergic MoA seems to improve symptoms of psychosis in patients not responding to first- or second-generation antipsychotics

EVENAMIDE: REGULATORY INTERACTIONS

Health Authorities (Spain, Denmark, Sweden, Germany, UK, CHMP, US, Canada) consulted on Phase III plan

Newron providing additional informative studies suggested by the FDA prior to allowing Newron to initiating its Phase III development program

- Preclinical part of safety work has been successfully completed; no toxicity issues reported; submitted to FDA, already
- First 4-week clinical safety (EEG) study completed in March 2021 (Study 008); 138 patients: no safety issues
- Following recent discussions with FDA, Newron will address the remaining FDA issues once full data from study 014 are available

ONGOING PHASE II EXPLORATORY SAFETY AND EFFICACY STUDY IN TRS PATIENTS

PHASE II

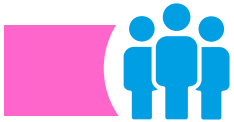
Safety and efficacy

- **Six-week, open-label,** randomized, rater-blinded, parallel group study, option to enter extension up to 12 months
- To evaluate tolerability and preliminary efficacy of adjunctive 7.5, 15, 30 mg BID
- TRS patients with PANSS scores ≥ 70 and ≤90; CGI-S 4 to 6, non-responders to their current antipsychotic medication
- **161 patients** randomized in 12 study centers in India, Sri Lanka, Italy
- Primary efficacy outcome measures mean change in PANSS total score
- 90% completed 6-week treatment period
- Of first 100 patients randomized,
  - 97 completed 6-weeks of treatment
  - 90 continued in extension study 015
  - 85 completed 6-month treatment period
- Promising interim analysis results of the first 100 TRS patients (June 2022: https://www.newron.com/investors/reports-and-presentation/year/2022)
- **Final results of study 014: Q1 2023**
- **Final results of study 015: Q1 2024**

ONGOING EXPLORATORY STUDY IN TRS PATIENTS (STUDY 014) INTERIM ASSESSMENT

OBJECTIVE

- Provide data on safety and preliminary evidence of benefit to Independent Safety Monitoring Board to allow assessment of risk-benefit for evenamide



ANALYSIS POPULATION

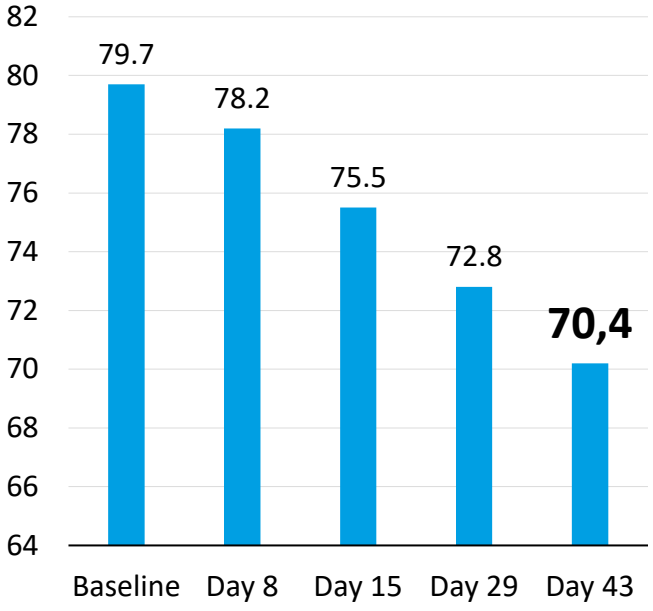
- First 100 patients randomized completing 6-weeks and 6 months in Studies 014/015

KEY CHARACTERISTICS

- Results based on M-ITT/LOCF
- No unblinding by dose groups (raters are blinded to dose)
- Descriptive statistics
- Safety: disposition, Serious Adverse Events
- Efficacy Measures: PANSS, CGI-S/C, LOF
- Medication Satisfaction Questionnaire (MSQ)

EFFICACY: PANSS TOTAL SCORE BY VISIT AND CHANGE FROM BASELINE

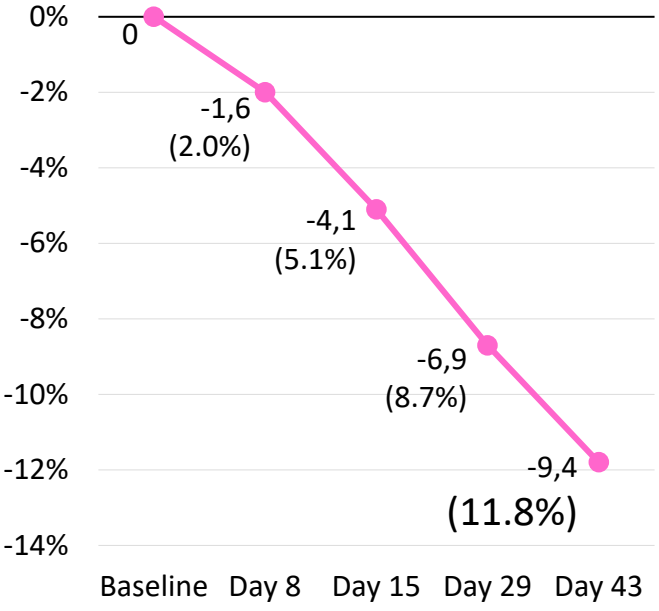
PANSS TOTAL SCORE



Effect further improved by > 30%

Week 30

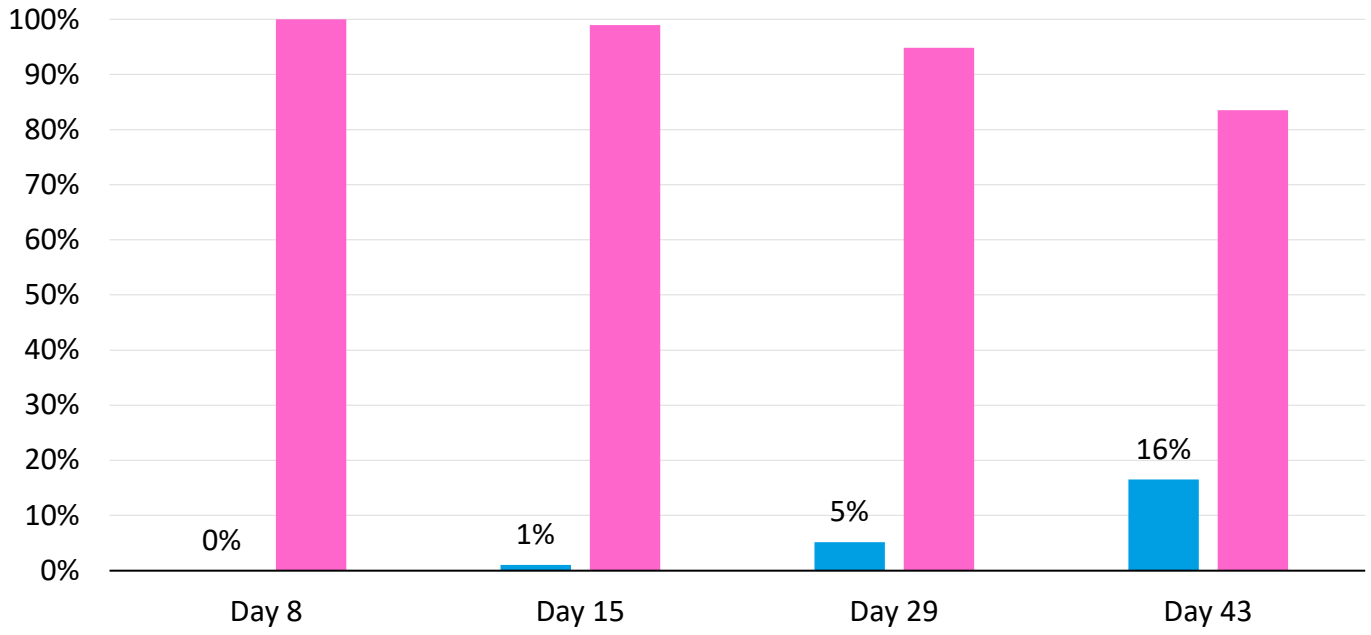
CHANGE FROM BASELINE



Effect further improved by > 30%

Week 30

EFFICACY: PANSS TOTAL SCORE RESPONDER RATE



Responders: Improvement ≥20% on PANSS total score

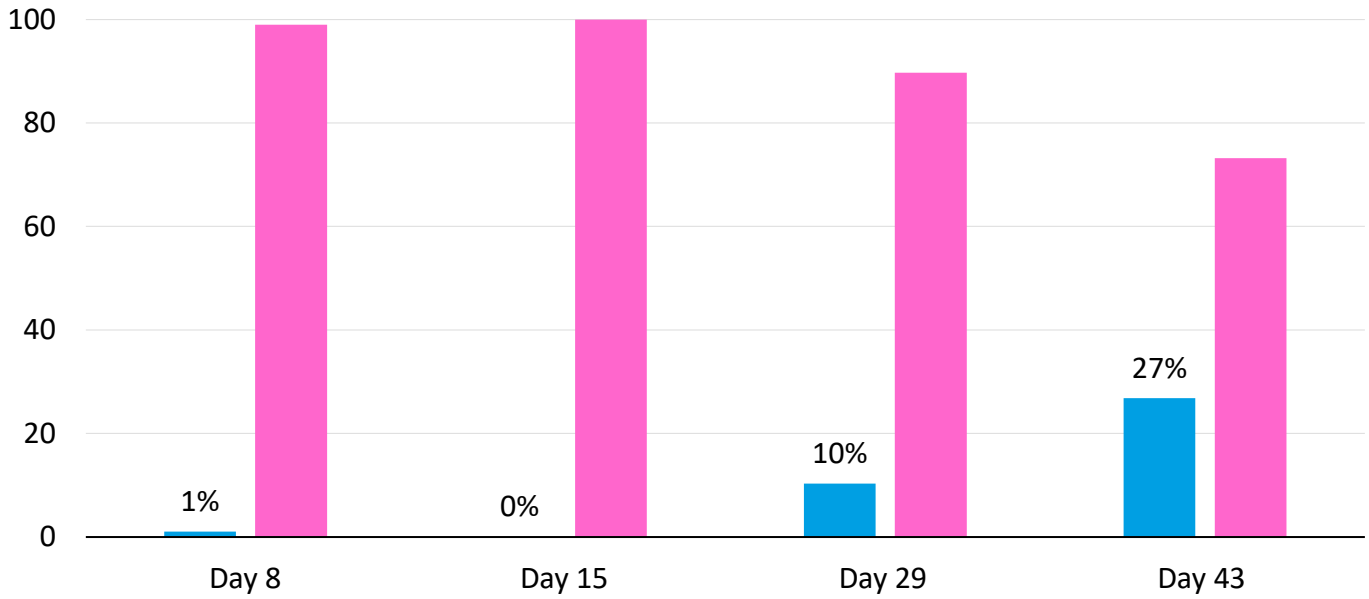
Responders more than doubled

Week 30

EFFICACY: CGI-S & CGI-C OVER TIME

	CGI-S		CGI-C
Visit	Mean Rating	Mean Change from Baseline	Mean Rating
Baseline	4.6	–	–
Day 8	4.5	-0.1	3.8
Day 15	4.3	-0.3	3.5
Day 29	4.0	-0.5	3.2
Day 43	3.9	**-0.7**	**3.0**
6-Month	**Change further improved by > 25%**		**Rating further improved by ~10%**

EFFICACY: CGI-C RESPONDER RATE



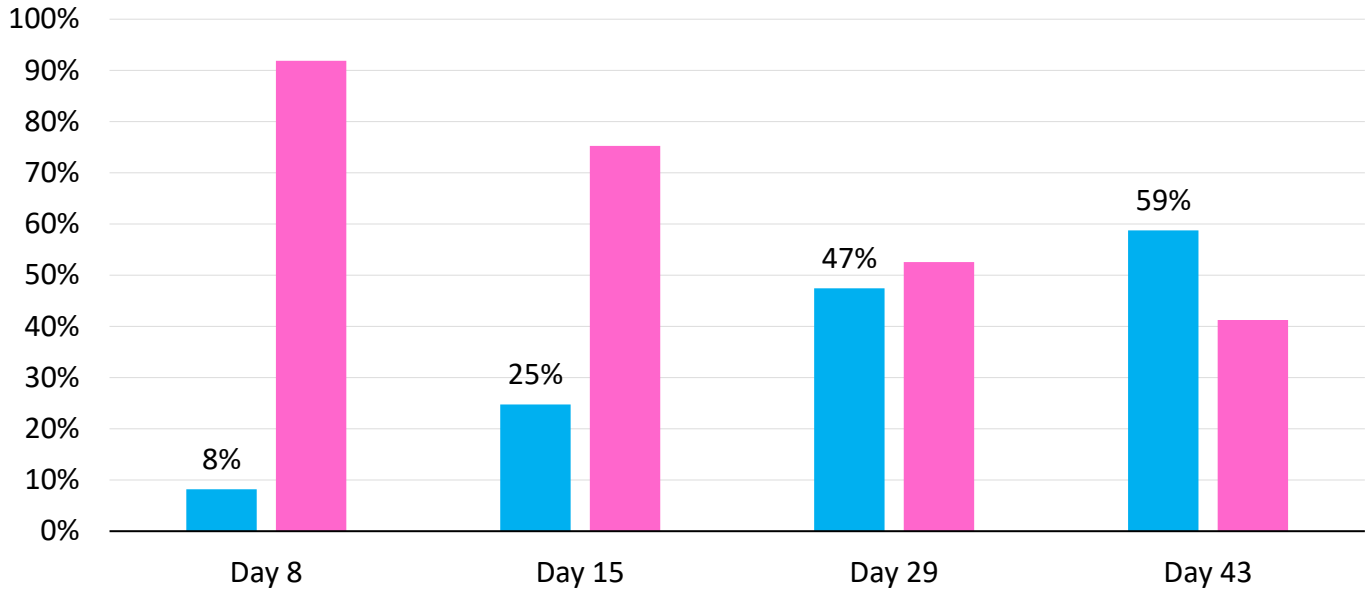
Responders further improved by > 10%

Week 30

Responders: Very much improved | Much improved

Non-Responders: Minimally improved | No change | Minimally worse | Much worse | Very much worse

EFFICACY: CGI-S RESPONDER RATE



Responders further increased by ~20%

Week 30

Responders: Any improvement on CGI-S

INTERIM EFFICACY ASSESSMENT – 6-MONTH VERSUS 6 WEEKS

FIRST 100 PATIENTS RANDOMIZED IN STUDY 014 FOLLOWED OVER TIME

Item	6-week	30-week** (compared to 6 weeks)
Completers	97	85
Adverse Drop-Outs	1	2 (+1)
PANSS Total – Mean change from baseline	-9.4	Further improved by > 30%
PANSS Total – Responders rate*	16.3%	More than doubled
CGI-C – Mean rating	3.0	Further improved by ~10%
CGI-C – Responders rate^	26.8%	Further increased by > 10%
CGI-S – Mean change from baseline	-0.7	Further improved by > 25%
CGI-S – Improvement rate§	58.2%	Further increased by ~20%

* Improvement ≥20% on PANSS total score
^ Rating of much improved or very much improved on CGI-C
§ Any improvement on CGI-S
** Compared with results at Week 6, exact numbers not shown due to potential conflict with publication; will be disclosed at 31st European Congress of Psychiatry taking place March 25-28, 2023, in Paris, France

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CONCLUSIONS

Add-on of evenamide to all antipsychotics was well tolerated with few new adverse events

97% completed 6-week treatment period with 90% continuing in extension study

PANSS total, CGI-S, LOF, and MSQ show **gradual improvement** over time at doses used; possible that higher doses (30 mg bid) would show greater benefit

This indicates the treating psychiatrists rating of the CGI-C is based on recognition of benefits of evenamide that are based on the symptoms assessed in the PANSS

CGI-C ratings, performed by the same psychiatrist who rated the PANSS, indicated a high concordance in the proportion of patients rated as 'clinically significant responders' on both measures

The improvement in LOF and MSQ at Day 43 was indicative of an overall improvement in functioning, and a greater patient satisfaction with background medication + evenamide compared to background medication alone, respectively

NEWRON HAS INITIATED THE FIRST OF TWO PIVOTAL STUDIES

PHASE IIB/III

Safety and efficacy study (study 008A, **non-TRS**), started Sept 6th, 2021

- **Four-week,** randomized, double-blind, placebo-controlled study
- To evaluate efficacy and safety (tolerability and EEG effects) of **adjunctive 30 mg BID**
- Outpatients suffering from chronic schizophrenia being treated with one of the leading antipsychotics
- **Total 260 patients** to be enrolled at study centers in Europe, Asia and Latin America
- **Results expected in 2023**

PHASE III

Safety and efficacy study in **TRS** patients to start in 2023 (study 003)

- **Ten-week**, randomized, double-blind parallel group study
- To evaluate efficacy, safety, and tolerability of adjunctive 15 or 30 mg BID
- **Outpatients with treatment-resistant schizophrenia (TRS)** not responding adequately to their monotherapy treatment with atypical antipsychotics (including clozapine)
- **Minimum 450 patients** to be randomized in approximately 40 centers in Europe, Asia, North America (US, if FDA approves), Central America, and South America
- Study completion in 18 months from start

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