



# SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

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## Company Highlights

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### Diversified portfolio of innovative CNS product candidates

- Xadago® for Parkinson's disease – validation of Newron's development approach – from research to market
- Sarizotan for Rett syndrome – in late Phase III development
- Evenamide – Re-defining the treatment of poor/non-response in schizophrenia

### Significant near-term value drivers

### Management team with proven track record

### Fully funded beyond key value inflexion points

- Cash balance of about € 39.4m (June 30, 2019)
- Access to long term funding facility of additional up to € 30m (European Investment Bank)



# Successful Track Record in CNS Product Development

## Xadago® (safinamide)

Commercialized by partner in 15 European markets and the US for Parkinson's disease ("PD")



Newron receives milestone and royalty payments from sales of safinamide in PD  
– €40m received to date

## Sarizotan

Close to completion of Phase III program in Rett syndrome (orphan disease)



Newron will commercialize Sarizotan for Rett syndrome in the US and – if viable – in key EU territories

## Evenamide (NW-3509)

Phase IIa trial demonstrated PoC



Ready for Phase III program in two indications. Opportunities for commercialization by Newron (Clozapine TRS population) and partnering (major indication)

# Innovative Clinical Pipeline with Multiple Near-Term Catalysts

PRODUCTS	Phase I	Phase II	Phase III	Market	Commercial Rights
<b>Xadago®</b> (safinamide) <sup>1</sup>	Adjunctive therapy in PD				<b>Zambon</b>
	Adjunctive therapy in PD				<b>Zambon/US WorldMeds</b>
	Adjunctive therapy in PD				<b>Meiji Seika/Eisai</b>
	Levodopa Induced Dyskinesia (PD LID)				<b>Zambon</b>
<b>Sarizotan<sup>2</sup></b>	Rett syndrome (Orphan drug status)				<b>Newron</b>
<b>Evenamide (NW-3509)<sup>1</sup></b>	Adjunctive therapy in Schizophrenia				<b>Newron</b>
	Adjunctive therapy in Clozapine TRS				
<b>Ralfinamide<sup>1</sup></b>	Orphan indication in neuropathic pain				<b>Newron</b>

## Expected Milestones

### Xadago®:

Further launches expected  
 Study in patients with Levodopa Induced Dyskinesia (PD LID) expected to start in 2019

### Sarizotan:

Potentially pivotal study commenced; results expected QIV 2019; own commercialization

### Evenamide:

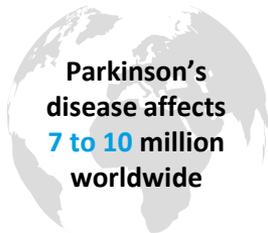
Potentially pivotal studies expected to start in 2020

Ongoing search for strategically relevant assets to in-license

<sup>1</sup> Safinamide, Evenamide and Ralfinamide all developed from Newron's ion channel based research

<sup>2</sup> Sarizotan was licensed from Merck KGaA

# Xadago®: 1<sup>st</sup> New Chemical Entity Approved in a Decade for Parkinson's Disease



Parkinson's  
disease affects  
7 to 10 million  
worldwide

## A progressing disorder, no cure available yet

- 2<sup>nd</sup> most common chronic progressive neurodegenerative disorder in the elderly
- Affecting 1-2% of individuals aged ≥ 65 years worldwide
  - 20% to 30% in early stage
  - 70% to 80% percent in mid to late stage
  - >\$4 billion worldwide market



## Fast and sustained efficacy, well tolerated

MID- TO LATE-STAGE PD PATIENTS –  
add-on to L-Dopa dopamine replacement

- Significant improvement of
  - ON Time/OFF Time – regulatory endpoint
  - UPDRS II – activities of daily living
  - UPDRS III – motor function
  - CGI (clinical global impression) – severity and improvement
- Additional ON Time without any increase in any dyskinesia





## Xadago®: New Label Study in Patients with Levodopa Induced Dyskinesia

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- Newron and partner Zambon have completed designing a potentially pivotal study to evaluate Xadago® in patients with levodopa induced dyskinesia (PD LID)
- Study to be performed in Europe and US
- Supportive evidence of Xadago's anti-dyskinetic effect:
  - Mechanism, i.e. glutamate release inhibition
  - LID models
  - PD patient data: significant benefit on DRS (Dyskinesia Rating Scale) in 223 dyskinetic PD patients in a 2 year-placebo-controlled study
- Study design agreed upon with FDA
- Study expected to start in 2019

# Significant Commercial Opportunity in Xadago® (Safinamide)

**US / Canada**



VALEO PHARMA



Launched in US in 2017  
Launched in Canada in 2019

**EU**



Zambon

Launched in Germany, UK, Italy, Spain and other EU territories, and Switzerland; regulatory approval for Brazil and Colombia, application for regulatory approval filed for Mexico

**Israel**



MEDISON  
Delivering Innovative Healthcare

Application for regulatory approval filed

**Japan / Asia**



meiji Eisai

Phase II/III completed in Jan. 18; application for regulatory approval filed

**Australia / New Zealand**



Seqirus  
A CSL Company

Launched in Australia in 2019

➤ Parkinson's disease affects 7 to 10 million people worldwide

➤ Milestone and royalty revenues to Newron since 2012

➤ Long period of Xadago® market exclusivity (patent life: 2029 in EU, 2031 in the US)

# Rett Syndrome: A Severe Neuro-Development Orphan Disease



**25% of sudden deaths in Rett syndrome may be due to cardio-respiratory abnormalities**

- Estimated 36,000 patients in US and EU combined
- Focus on symptom management

## ➤➤ No Approved Treatment Options

### Spontaneous mutations in the X-linked MeCP2 gene

- Disease manifests almost exclusively in females with one affected X-chromosome
- Normal development until 6-18 months of age, then loss of skills and ability for social interaction
- Respiratory abnormalities, motor and severe intellectual impairment, sleep abnormalities and seizures in most patients (70-90%)

# Sarizotan: Targeting Respiratory Disturbances in Rett Syndrome Patients

- First Rett syndrome drug candidate targeting respiratory disturbances as primary efficacy outcome
- Deficits in serotonergic transmission due to the MeCP2 mutation in the mid-brain nucleus underlie the respiratory abnormalities in MeCP2 deficit mice
- Sarizotan, a full agonist at the serotonergic 5HT1A receptor, has demonstrated dramatic improvement of respiration in genetic (MeCP2) mouse model of RTT
- Development path/regulatory requirements for approval agreed upon with FDA/EMA/HPB
- Orphan drug designation in EU and US

EFFECTS OF ACUTE ADMINISTRATION WITH SARIZOTAN IN RETT FEMALE MICE (MECP2<sup>R168X/+</sup>). BENEFIT PERSISTS IN LONG LASTING TREATMENTS (14-DAYS-MECP2<sup>R168X/+</sup>)

Apnea in MeCP2-deficient mice



Apnea in MeCP2-deficient mice treated with Sarizotan 5.0 mg/kg



Ref: **Abdala AP, Lioy DT, Garg SK, Knopp SJ, Paton J F, Bissonnette JM.** Effect of Sarizotan, a 5-HT<sub>1A</sub> and D<sub>2</sub>-Like Receptor Agonist, on Respiration in Three Mouse Models of Rett Syndrome. *American Journal of Respiratory Cell and Molecular Biology*, 50(6): 1031-1039.



## STARS: First Ever Global Phase III Study in Rett Syndrome

- Protocol/program discussed and approved by HA in UK, Germany, Sweden, Spain, Canada, CHMP, and US
- Randomized, double-blind, placebo-controlled, six-month study evaluating efficacy and safety of sarizotan in at least 129 Rett syndrome patients with respiratory symptoms
  - Females and males  $\geq 4$  years, body weight  $\geq 10$  kg meeting RTT consensus clinical criteria, confirmed by MECP2 mutations
  - Patients meet all criteria related to breathing abnormalities:
    - $\geq 10\%$  of the time with abnormal breathing
    - At least 10 episodes of breathing dysrhythmia ( $\geq 10$  seconds of breath holding, apnea)/hour during cardiorespiratory monitoring (home/ambulatory monitoring system - BioRadio™)
- 14 Centers of excellence in the United States, Italy, UK, Australia and India
- Efficacy endpoints are focused on improvement of respiration and overall status
  - Reduction in number of apnea episodes/hour
  - Caregiver rating of top 3 concerns (Top 3)
  - Clinician rating of change in overall status (CGI-C)
  - Caregiver rating of change in overall status (CIC)
  - Motor behavior assessment scale (MBAS)
- Enrollment completed
- Results expected QIV 2019

## > Natural history study and new learnings from the STARS clinical trial

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- The **natural history study** points to the fact that respiratory symptoms start early in these patients (minimum 0.7 years: median 3 years), quickly become prominent and dramatic, but wane over time; they are correlated with worsening of the core symptoms and with Long QTc interval
    - but there has been no systematic attempts to quantitate these breathing abnormalities, their time course, the associated effects on SpO2 saturation
  - **STARS data suggest** that the proportion of patients with respiratory abnormalities **does not decline with age**
  - Quantitative recordings for over 18 hours in the home setting **indicate that up to 70% of patients evaluated experience clinical significant apnea**
  - Oxygen saturation goes below 90% 4.2 times per hr, duration may last as long **as 48 minutes/hr**
  - Definitive data will be available QIV/2019; anecdotal data from investigators suggest that greater awareness of surroundings, increased attempt at non-verbal communication, greater alertness was noted in patients who experience some improvement in apnea
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# Sarizotan Market Opportunity and Commercialization Strategy

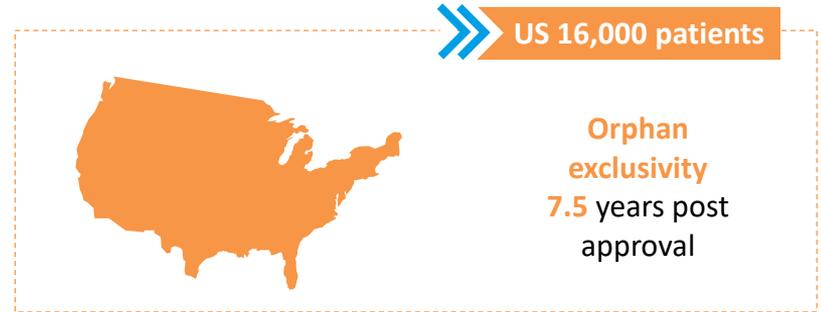
Initiation of a Health Economic Outcome Research Study (HEOR)  
→ "burden of illness"

- Partnerships and collaborations with Rett advocacy, thought leaders & governing payers
- Global survey to quantify the ways in which patient "respiratory breathing abnormalities" affect daily life
- Meets Health Technology Assessment (HTA) requirements
- International Experts advocated timely approach as critical for management of patients

## Goals

- Align economic & clinical outcomes
- Create awareness to breathing abnormality burden
- Optimize market uptake, access, reimbursement
- Build Newron leadership

Rare Pediatric Disease Priority Review Voucher Program



Small team ~ 25-30 medical liaison managers required to commercialize sarizotan in US and Europe

# Schizophrenia: No Effective Treatment that Reduces Burden of Disease in Last 20 Years



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

## Globally over 4 million patients

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

## » Efficacy of current treatment options is insufficient

Onset of disease occurs in early adulthood affecting 1% of the population worldwide

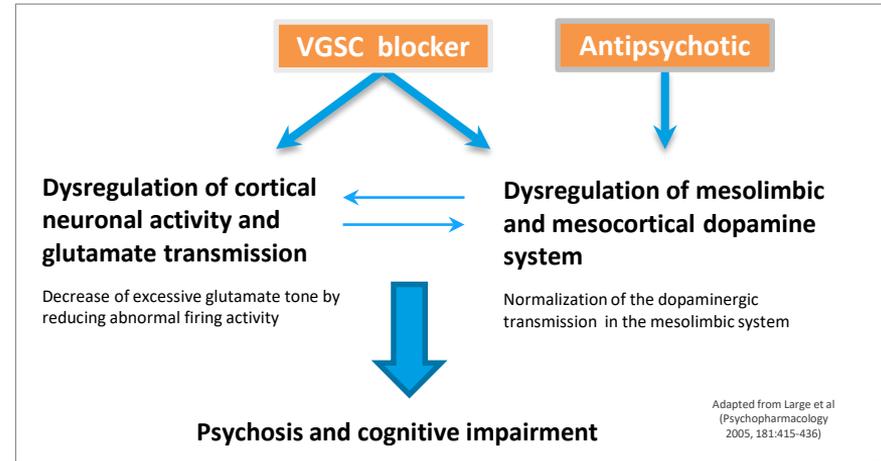
- Efficacy of typicals and atypicals limited and wanes over 18 months; severe side effects; 64-82% of patients switch but without additional benefits
- Treatment-resistant schizophrenia (TRS)
  - Min. 30% of patients after 3-5 years are TRS: only clozapine shows efficacy
  - 30-50% of these patients show resistance to clozapine; no therapeutic option left
- Outcomes for 1-year treated young US first episode patients: 24 times greater mortality than age matched (16-30 year olds) controls despite use of antipsychotics (40%) and mental health services (Schoenbaum, 2017)



## Evenamide Novel MoA: Synergistic with Marketed Antipsychotics

- Evenamide, a Voltage-Gated Sodium Channels (VGSC) blocker has the potential to target the abnormal neuronal activity and glutamate transmission in patients with schizophrenia
- Evenamide may add to or synergize with antipsychotic drugs to bring about a combined therapeutic effect on glutamate and dopamine systems
  - Effects seen in combination with haloperidol, risperidone and aripiprazole
- Composition of matter – USPTO, 2013 – patent life 2028 plus extension

**Voltage-Gated Sodium Channels (VGSC) blockers may act synergistically with antipsychotics in schizophrenia therapy**





# Evenamide's Unique MOA Demonstrated

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

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

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

Inhibits Glutamate Release

Inhibition of native sodium channels expressed in rat cortical neurons

$K_{rest}$  ( $\mu\text{M}$ )

25

$K_{inact}$  ( $\mu\text{M}$ )

0.4

High frequency firing

Control

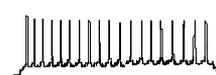


Evenamide 1 $\mu\text{M}$

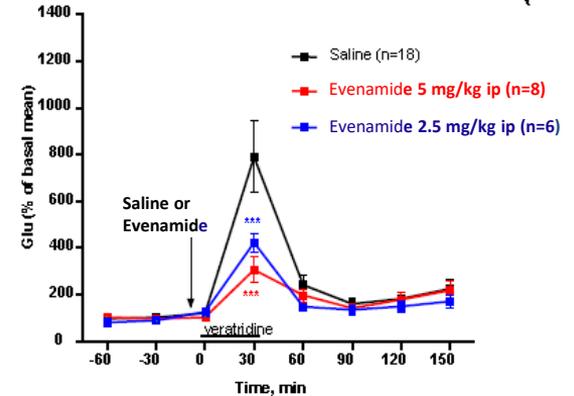


Low frequency firing

Control



Evenamide 1 $\mu\text{M}$



# Evenamide is Active in a Wide Range of Schizophrenia and Psychiatric Animal Models as a Monotherapy and as an Add-on to Existing Antipsychotics

		Monotherapy	Add-on
<b>Information Processing Deficit</b>	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	✓	✓
<b>Negative Symptoms</b>	PCP-induced deficit in Social Interaction in the rat	✓	✓
	<i>Saccharin preference test (anhedonia) in prenatal poly:IC exposed mice (ongoing)</i>	✓	
	<i>Three-chamber sociability test in prenatal poly:IC exposed mice (ongoing)</i>	✓	
	<i>Forced swimming test (avolition) in prenatal poly:IC exposed mice (ongoing)</i>	✓	
<b>Psychosis and Mania</b>	Amphetamine induced hyperactivity in mice	✓	✓
	Amphetamine plus Chlordiazepoxide induced hyperactivity in mice	✓	✓
<b>Cognitive Impairment</b>	Novel object recognition in the rat: short term scopolamine impairment	✓	
	Novel object recognition in the rat: long term 24 hr natural forgetting	✓	
<b>Impulse Control and Mood Symptoms</b>	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





## Evenamide: PoC in Patients with Schizophrenia Demonstrated

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- 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 day 8)
    - **Significant improvement of**
      - PANSS positive, both mean change AND responder rate
      - CGI-C
    - **Superior benefit on**
      - PANSS total
      - LOF total
      - CGI-S
  - Glutamatergic MoA seems to improve symptoms of psychosis in patients not responding to D2/5HT2 blockade
-

# ➤ EVENAMIDE: REGULATORY INTERACTIONS AND PHASE III CLINICAL DEVELOPMENT PLAN

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All Health Authorities (Spain, Denmark, Sweden, Germany, UK, CHMP, US, Canada) in agreement with proposed Phase III plan

Newron expects new explanatory studies requested by health authority to be completed, aiming at Phase III start in 2020

Efficacy program will be comprised of two pivotal studies in specific populations:

- **Non-treatment resistant patients:** chronic schizophrenics experiencing inadequate benefit for symptoms of their psychosis, on current atypical antipsychotic monotherapy (risperidone, aripiprazole, paliperidone, olanzapine, or quietapine) – **Planned Study 003**
- **Treatment resistant schizophrenia:** Patients whose psychotic symptoms are not responding adequately to treatment with clozapine - **Planned Study 004**

Positive results of both studies would meet efficacy criteria for both indications

Positive result of study 004 only would lead to approval of clozapine-resistant population only

Positive result of study 003 only would lead to need for another similarly designed study

Start of Phase III program expected 2020 – appr. 18 months to results



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