# SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

## Corporate presentation

BIO CEO & Investor Conference, New York, February 13-14, 2017

Newron
Pharmaceuticals

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# Investment Highlights


1. Diversified Portfolio of Innovative CNS Product Candidates
2. Xadago® - Commercialized in 11 Countries with Clear Path to US Registration
3. Sarizotan for Rett Syndrome in Late Stage Development
4. Evenamide - a Novel Mechanism to Address Schizophrenia
5. Multiple Catalysts on the Horizon
6. Management Team with Proven Track Record



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# Successful Track Record in CNS Product Development

## NOVEL CNS PRODUCT CANDIDATES

### Xadago®

…(safinamide) commercialized in 11 European markets for Parkinson's disease (PD); in late stage regulatory approval for US market

Newron receives milestone and royalty payments from sales of safinamide in PD

### Sarizotan

Developing Sarizotan for Rett syndrome, an orphan disease, in a potentially pivotal trial ongoing

Opportunity to commercialize Sarizotan for Rett syndrome directly

### Evenamide

…(NW-3509) Phase IIa trial results met study objectives of good tolerability, safety, and preliminary evidence of efficacy

Ready for Phase IIb / out-licensing for schizophrenia

**… INNOVATION**
**in rare diseases**

# Innovative Clinical Pipeline with Multiple Near Term Catalysts

| PRODUCTS | | Phase I | Phase II | Phase III | Market | Commercial Rights |
|---|---|---|---|---|---|---|
| Xadago® (safinamide)[1] | Adjunctive therapy in PD | | | | | Zambon |
| | Adjunctive therapy in PD | | | | | US WorldMeds |
| | Adjunctive therapy in PD | | | | | Meiji Seika |
| Evenamide (NW-3509)[1] | Schizophrenia | | | | | Newron |
| Sarizotan[2] | Rett syndrome (Orphan drug status) | | | | | Newron |
| Ralfinamide[1] | Orphan indication in neuropathic pain | | | | | Newron |

## Expected Milestones

**Xadago®:**
further EU launches expected;
PDUFA date: March 21, 2017

**Evenamide:**
Full Phase IIa results in March 2017; ready for Phase IIb / out - licensing

**Sarizotan:**
potentially pivotal study commenced July 2016; results HY1 2018; commercialization 2018

Ongoing search for strategically relevant assets to in-license

1 Safinamide, NW-3509 and Ralfinamide all developed from Newron's ion channel based research
2 Sarizotan was licensed from Merck KGaA

# Newron Leadership Team

**STEFAN WEBER**
CEO

- 30 years of experience
- Previously worked at: Lohmann Group, Girindus and Biofrontera

**RAVI ANAND**
CMO

- >30 years of experience
- Previously worked at: Roche (CH), Sandoz (US), Novartis and Organon (NL)

**ROBERTO GALLI**
Vice President Finance

- 20 years of experience
- Previously worked at: Coopers & Lybrand and PricewaterhouseCoopers

**MARCO CAREMI**
EVP Business Development

- >35 years of experience
- Previously worked at: Schwarz Pharma and Schering-Plough

**DENNIS DIONNE**
Vice President, Commercial Affairs

- >26 years of experience
- Previously worked at: Novartis and Johnson & Johnson

**NON-Executive Chairman of the Board of Directors**

**ULRICH KÖSTLIN**:
Former Executive at
Bayer Schering Pharma AG

**STEPHEN GRAHAM**
Executive Director, Clinical Development

- 30 years of experience
- Previously worked at: Boots Pharmaceuticals, Sandoz/ Novartis and Forest Laboratories/ Forest Research Institute

# Xadago®: 1st New Chemical Entity Approved in US or Europe in a Decade for Parkinson's Disease



## A progressing disorder, no cure available yet

- PD 2nd most common chronic progressive neurodegenerative disorder in the elderly
- Affecting 1-2% of individuals aged ≥ 65 years worldwide

## First PD therapy working through dual mechanism


### EARLY PD PATIENTS – add-on dopamine agonist

- Significant improvement of
  - UPDRS III - motor function, regulatory endpoint (mean change, responder rate)
  - Quality of life (PDQ-39, EQ5D)
  - Reduction of number of interventions
- Benefits seen after 6 and 18 months
- Delay levodopa

### MID- TO LATE-STAGE PD PATIENTS – add-on dopamine replacement

- Significant improvement of
  - ON Time/OFF Time – regulatory endpoint
  - UPDRS II – activities of daily living
  - UPDRS III – motor function
  - UPDRS IV – treatment complications
  - CGI (clinical global impression) – severity and improvement
  - GRID HAMD (depression)
- Additional ON Time without any increase in any dyskinesia
- Dyskinesia significantly improved
- Benefits seen after 6 and 24 months

Sources:
Parkinson's Disease – Global Drug Forecast and Market Analysis – Event-Driven Update -GlobalData, June 2015
Parkinson's Disease Foundation: Statistics on Parkinson's
Treatment of Advanced Parkinson's Disease, Varanese et al., 2010, NCBI



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# Xadago® (Safinamide) Approved and Launched in Europe for the Treatment of Parkinson's Disease

## EU MARKETING AUTHORIZATION (RECEIVED FEBRUARY 2015)

- Both dopaminergic and non-dopaminergic mechanisms
- Sustained efficacy for 2 years for ON Time, OFF Time and UPDRS III
- "Very much/much improved" in Clinical Global Impression
- Significant improvement in activities of daily living (UPDRS III)
- Well tolerated
- No drug interactions; no age, gender or race restrictions
- No dietary restrictions
- No requirement for laboratory tests, ECG, or any other examination

## ANTICIPATED PATH TO US APPROVAL

- FDA agrees no additional evaluation of abuse liability or dependence / withdrawal effects in humans is required
- NDA re-submitted Sept 2016:
  Class II re-submission – 6 month review
- FDA set PDUFA date: March 21, 2017

# Significant Commercial Opportunity in Safinamide (Xadago®)

**US**



US WorldMeds

Re-submitted to US FDA in September 2016;
PDUFA date: March 21, 2017

**EU**



Zambon 1906

**Latin America**

Launched in Germany, UK, Italy, Spain and other EU territories, plus Switzerland

**Japan**



meiji

Confirmatory Phase II/III and long-term Phase III studies initiated

**Australia/New Zealand**

Seqirus
A CSL Company

Partner to submit application for regulatory approval

- Milestone and royalty revenues to Newron since 2012
- Long period of market exclusivity (patent life: 2029 in EU, 2031 in the US)
- Peak sales potential $450m - $700m+ (analyst estimates)


**20** to **30** percent in early stage

**70** to **80** percent in mid to late stage

**>$4 Billion** worldwide market

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# Rett Syndrome: Severe Neuro-developmental Orphan Disease with No Specific Treatment Options

- 95-97% of patients have 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%)
- 25% of sudden deaths in RTT linked to cardio-respiratory abnormalities
- Focus on symptom management
- Estimated 36,000 patients in US and EU combined

# Sarizotan: Targeting Respiratory Disturbances in Rett Syndrome Patients

- First RTT 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; clear commercialization strategy
- Orphan drug designation in EU and US
- Potentially pivotal STARS study initiated July 2016

## EFFECTS OF 14-DAY TREATMENT WITH SARIZOTAN IN RTT FEMALE MICE ($MECP2^{R168X/+}$)

Apnea in MeCP2-deficient mice


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

# STARS: First International Phase III Potentially Pivotal Study in RTT

- Randomized, double blind, placebo-controlled, 6 months' treatment study under US IND
- Will enroll minimally 129 RTT patients, 13 years or older who experience at least 10 apnea episodes of >10 sec/ hour as verified by a validated device over at least 3 hours of recording time while patient is awake and at home
- Primary endpoint: percent reduction in number of objectively defined clinically significant (>10 sec) apnea episodes over an extended period of time
- Centres of excellence in the United States, Italy and India
- Study protocol designed in accordance with regulatory authorities in the United States, Europe and Canada
- Study enrolling
- Expected completion HY1/2018

# Sarizotan Market Opportunity Commercialization by Newron

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

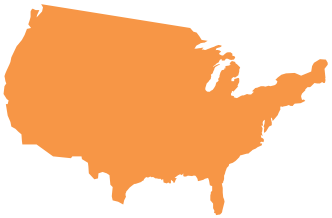
- Fostering partnership and collaborations with Rett advocacy, thought leaders & governing payers
- Global survey to quantify the ways in which patient “respiratory breathing abnormalities” affect daily life
- Meets Health Technology Assessment (HTA) requirements, including European Network of countries requiring information for treatment access

Goals

- Identify gaps & unmet need for improving disease management
- Align economic & clinical outcomes
- Create awareness to breathing abnormality burden
- Optimize market uptake, access, reimbursement
- Build Newron leadership

Rare pediatric disease voucher possibility

**US 16,000 patients**



**Orphan exclusivity**
**7.5** years post approval

**EU 20,000 patients**

**Orphan exclusivity**
**12** years post approval

Sources:
- RettSyndrome.org Foundation
- National Institute of Health – NINDS
- US Census Bureau, 2012
- Eurostat Census, 2011

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

- Onset of disease occurs in early adulthood affecting 1% of the population worldwide
  - Need for life-long treatment
- Disease characterized by either positive or negative symptoms or both:
  - Hallucinations, delusions, paranoia and disorganized speech (positive)
  - Progressive deterioration of cognition and behavior & presence of negative symptoms such as apathy, lack of emotion, socially inappropriate behavior and lack of ability to feel contentment
- High rates of suicide, multiple physical illnesses and lower life expectancy

- Efficacy of current treatment options insufficient
  - Typicals (e.g. haloperidol) less effective against negative symptoms and can cause neurological side effects
  - Efficacy limited and wanes over 18 months; 60-70% of patients switch but without additional benefit


Source: FiercePharma, 2011

# Evenamide (NW-3509): Novel MOA to Benefit Poorly Responding Schizophrenia Patients

- First-in-class voltage-gated sodium channel (VGSC) blocker for add-on treatment in schizophrenia, schizo-affective and bipolar disorders
  - Small molecule, orally available, rapid onset of action, high availability in the brain
- Unique mechanism of action (MoA):
  - Selectively blocks VGSCs in a voltage- and use-dependent manner – no effect on dopaminergic, serotonergic, histaminergic neurotransmission
  - Modulates sustained repetitive firing without impairment of normal neuronal excitability
  - Reduces stimulated glutamate release
- Benefit shown in models of positive symptoms, aggression, cognition (schizophrenia), negative symptoms, mania, depression, obsessive behavior
- IND approval from FDA as FIRST ADD-ON TO ANTIPSYCHOTICS for patients with positive symptoms schizophrenia
  - Improvement of symptoms in patients not responding to current treatments
- Well-tolerated in Phase I study
  - Exposure increased with dose; exposure achieved overlaps with plasma levels in animals at doses proven to be efficacious
- Encouraging preliminary phase IIa data in early 2017:
  - Good tolerability, safety and preliminary evidence of efficacy
- Composition of matter – USPTO, 2013 - patent life 2028 plus extension

# Unique MOA Demonstrated

## NW-3509, a selective Voltage-Gated Sodium Channel (VGSC) Blocker

**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 naive sodium channels expressed in rat cortical neurons

$K_{rest}$ (µM)

25

$K_{inact}$ (µM)

0.4

### High frequency firing

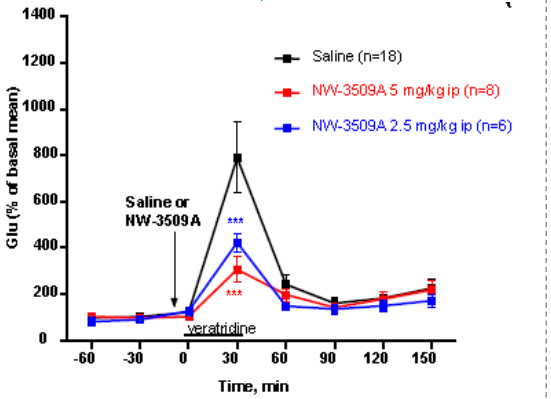
Control

NW-3509 1µM

### Low frequency firing

Control

NW-3509 1µM

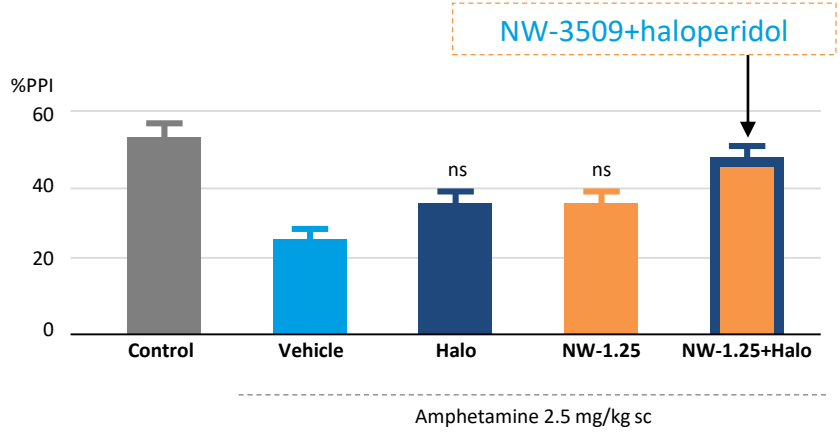


# Amphetamine-Induced Prepulse Inhibition (PPI) Deficit Model
# NW-3509 Augments the Effect of Typical and Atypical Antipsychotics

## Typical

Add-on with non-active dose of **haloperidol**

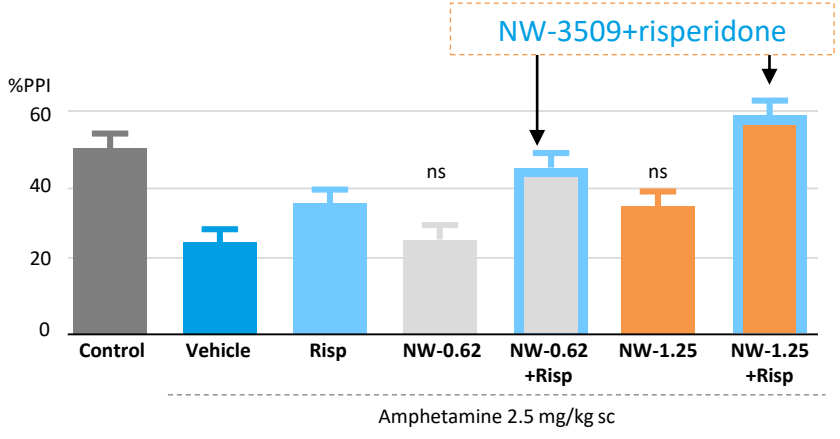
MED 1.25 mg/kg *po* (+ haloperidol 0.05 mg/kg *ip*)




## Atypical

Add-on with non-active dose of **risperidone**

MED 0.62 mg/kg *po* (+ risperidone 0.05 mg/kg *ip*)




Amph (2.5 mg/kg sc) and NW-3509A (1.25 or 0.62 mg/kg po) were administered 5 min before PPI session. Haloperidol and risperidone were administered ip 30 min before PPI session at 0.05 mg/kg.
Statistics: Tukey's multiple comparison test *p<0.05, ***p<0.001 vs Vehicle+Amp (n=6-18 rats per group) (Studies performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari- USCLA)

# Phase IIa Study: Preliminary Validation of a Novel Treatment Concept

- Evenamide as add-on treatment in positive symptoms of schizophrenia
  - Patients with stable and adequate dose of standard therapy, experiencing break-through symptoms
- Double-blind, placebo-controlled, randomized, 4-week in/outpatient study in US and India in 89 patients receiving Evenamide 15-25 mg/ twice daily or placebo, in addition to their current antipsychotic
- Endpoints: Symptoms of schizophrenia, as assessed by
  - Positive and Negative Syndrome Scale (PANSS),
  - Strauss-Carpenter Level of Functioning scale,
  - Clinical Global Impression - Change from baseline (CGI-C) and CGI - Severity of illness (CGI-S)
- Evenamide met study objectives of good tolerability, safety and showed preliminary evidence of efficacy
  - No side-effects which are associated with dopamine-blocking antipsychotics
  - Consistent pattern of benefit on all efficacy measures assessed
  - Preliminary results warrant further investigation in larger and longer trials
- Detailed results at 16th International Congress on Schizophrenia Research - March 2017
- Ready for Phase IIb / out-licensing

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