



# SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

Annual Media and Analyst Conference  
Zurich, March 2, 2017



# Disclaimer

## RESTRICTED SCOPE; EXCLUSION OF LIABILITY; CONFIDENTIALITY

This document has been prepared by Newron Pharmaceuticals S.p.A. ("Newron") solely for your information. The information contained herein has not been independently verified. No representation or warranty, express or implied, is made as to, and no reliance should be placed on, the fairness, accuracy, completeness or correctness of the information or opinions contained herein. Newron does not undertake any obligation to up-date or revise any information contained in this presentation. None of Newron, its advisors or any of their respective representatives or affiliates shall have any liability whatsoever (in negligence or otherwise) for any loss howsoever arising from any use of this document or its contents or otherwise arising in connection with this document.

This copy of the presentation is strictly confidential and personal to the recipient. It may not be (i) used for any purpose other than in connection with the purpose of this presentation, (ii) reproduced or published, (iii) circulated to any person other than to whom it has been provided at this presentation.

## FORWARD-LOOKING STATEMENTS

This document contains forward-looking statements, including (without limitation) about (1) Newron's ability to develop and expand its business, successfully complete development of its current product candidates and current and future collaborations for the development and commercialisation of its product candidates and reduce costs (including staff costs), (2) the market for drugs to treat CNS diseases and pain conditions, (3) Newron's anticipated future revenues, capital expenditures and financial resources, and (4) assumptions underlying any such statements. In some cases these statements and assumptions can be identified by the fact that they use words such as "will", "anticipate", "estimate", "expect", "project", "intend", "plan", "believe", "target", and other words and terms of similar meaning. All statements, other than historical facts, contained herein regarding Newron's strategy, goals, plans, future financial position, projected revenues and costs and prospects are forward-looking statements.

By their very nature, such statements and assumptions involve inherent risks and uncertainties, both general and specific, and risks exist that predictions, forecasts, projections and other outcomes described, assumed or implied therein will not be achieved. Future events and actual results could differ materially from those set out in, contemplated by or underlying the forward-looking statements due to a number of important factors. These factors include (without limitation) (1) uncertainties in the discovery, development or marketing of products, including without limitation negative results of clinical trials or research projects or unexpected side effects, (2) delay or inability in obtaining regulatory approvals or bringing products to market, (3) future market acceptance of products, (4) loss of or inability to obtain adequate protection for intellectual property rights, (5) inability to raise additional funds, (6) success of existing and entry into future collaborations and licensing agreements, (7) litigation, (8) loss of key executive or other employees, (9) adverse publicity and news coverage, and (10) competition, regulatory, legislative and judicial developments or changes in market and/or overall economic conditions.

Newron may not actually achieve the plans, intentions or expectations disclosed in forward-looking statements and assumptions underlying any such statements may prove wrong. Investors should therefore not place undue reliance on them. There can be no assurance that actual results of Newron's research programmes, development activities, commercialisation plans, collaborations and operations will not differ materially from the expectations set out in such forward-looking statements or underlying assumptions.

## NO OFFER OR INVITATION; NO PROSPECTUS

This document does not contain or constitute an offer or invitation to purchase or subscribe for any securities of Newron and no part of it shall form the basis of or be relied upon in connection with any contract or commitment whatsoever.

This document is not a prospectus within the meaning of art. 652a of the Swiss Code of Obligations or article 32 of the SIX Swiss Exchange Listing Rules. In making a decision to purchase or sell securities of Newron, investors must rely (and they will be deemed to have relied) solely on their own independent examination of Newron.

The securities of Newron have not been registered under the US Securities Act of 1933 as amended (the "Securities Act") and may not be offered or sold in the United States unless registered under the Securities Act or pursuant to an exemption from such registration. Newron does not intend to register any securities it may offer under the Securities Act.

This document is only being distributed to and is only directed at (1) persons who are outside the United Kingdom or (2) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order"), (3) high net worth companies, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order, or (4) qualified investors, pursuant to article 100 of Legislative decree 58/98, as amended (all such persons in (1) to (4) above together being referred to as "relevant persons"). Any person who is not a relevant person should not act or rely on this document or any of its contents.

## ACCEPTANCE OF DISCLAIMER

By accepting this document, you acknowledge and agree to each of the foregoing disclaimer.

# 2016 - Year of fundamental progress



## Xadago® (safinamide):

Launch by Zambon for patients with Parkinson's disease in 10 additional European territories  
U.S. FDA

- Re-submitted NDA for Xadago® is complete, class 2 response to CRL
- PDUFA date March 21, 2017

*Seqirus and Zambon partner for Xadago® in AUS/NZ*

## Evenamide (NW-3509):

Phase IIa study design presentation at 5th Biennial Schizophrenia International Research Society Conference  
*Encouraging preliminary results of Phase IIa study*

*Detailed Phase IIa study results: 16th ICOSR, March 24-28*

## Sarizotan:

IND approval for Sarizotan for treatment of Rett syndrome by FDA  
STARS trial design presentation at U.S. Rett Syndrome Symposium  
Initiation of

- international burden of disease study in Rett syndrome
- STARS potentially pivotal study for patients with Rett syndrome

## Corporate:

CHF 26.8 million private placement and exercise of 2015 option  
Dennis Dionne appointed Vice President Commercial Affairs



## 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**

# 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
<b>Xadago®</b> (safinamide) <sup>1</sup>	Adjunctive therapy in PD					<b>Zambon</b>
	Adjunctive therapy in PD					<b>US WorldMeds</b>
	Adjunctive therapy in PD					<b>Meiji Seika</b>
<b>Evenamide (NW-3509)<sup>1</sup></b>	Schizophrenia					<b>Newron</b>
<b>Sarizotan<sup>2</sup></b>	Rett syndrome (Orphan drug status)					<b>Newron</b>
<b>Ralfinamide<sup>1</sup></b>	Orphan indication in neuropathic pain					<b>Newron</b>

## 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 2019



Ongoing search for strategically relevant assets to in-license

<sup>1</sup> Safinamide, NW-3509 and Ralfinamide all developed from Newron's ion channel based research

<sup>2</sup> 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)



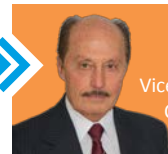
**ROBERTO  
GALLI**  
Vice President  
Finance

- 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



# 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

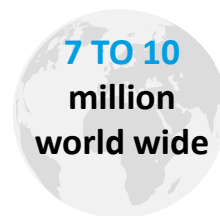
# Significant Commercial Opportunity in Safinamide (Xadago®)

US	EU	Latin America	Japan	Australia/New Zealand
  Re-submitted to US FDA in September 2016; PDUFA date: March 21, 2017	  Launched in Germany, UK, Italy, Spain and other EU territories, plus Switzerland		  Confirmatory Phase II/III and long-term Phase III studies initiated	  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

# 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<sup>R168X/+</sup>)

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)

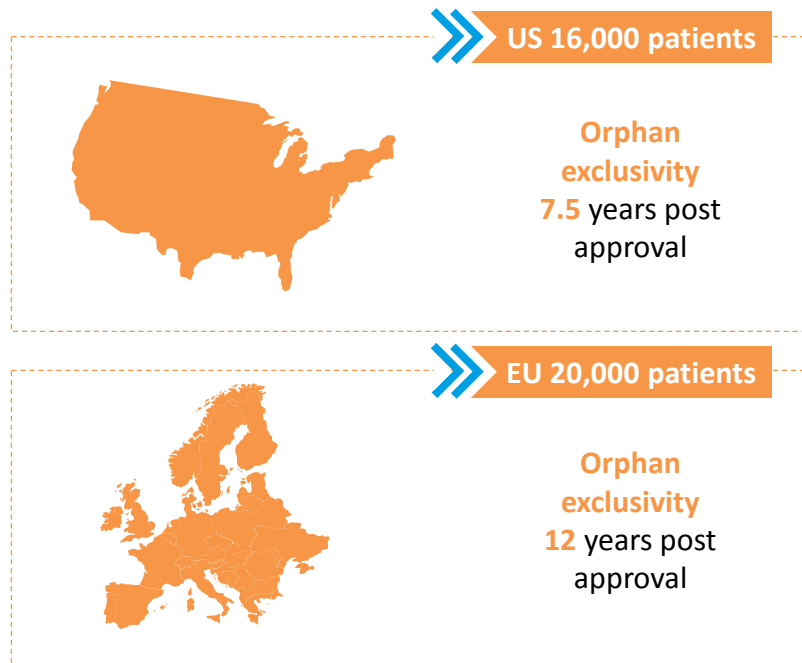
→ "burden of illness"

- 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



### Sources:

- RettSyndrome.org Foundation
- US Census Bureau, 2012
- National Institute of Health – NINDS
- 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
  - High rates of suicide, multiple physical illnesses and lower life expectancy
- Efficacy of current treatment options insufficient
  - Typical (e.g. haloperidol) worsen negative symptoms and cause neurological side effects
  - Efficacy limited and wanes over 18 months; 60-70% of patients switch but without additional benefit
  - No effect on suicidality



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 no longer 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

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

25

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

0.4

High frequency firing

Control



NW-3509 1 $\mu\text{M}$

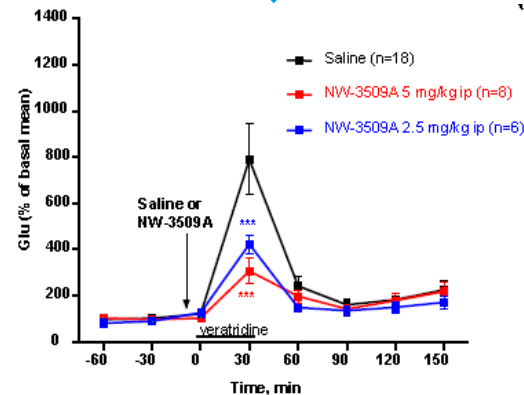


Low frequency firing

Control



NW-3509 1 $\mu\text{M}$



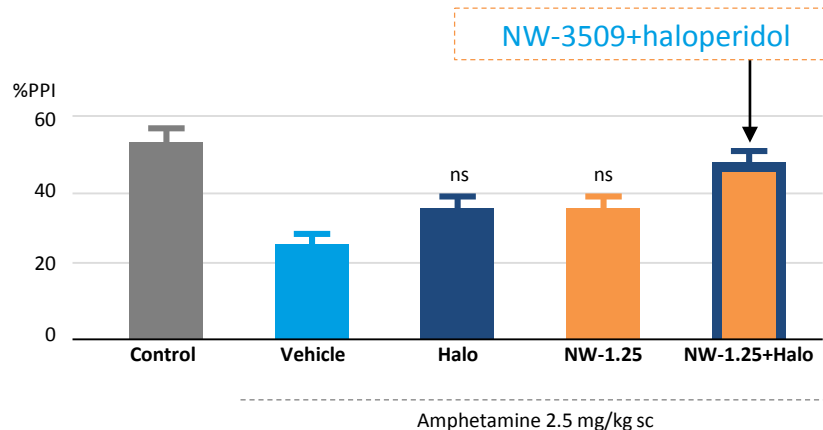
# Amphetamine-Induced Prepulse Inhibition (PPI) Deficit Model

## NW-3509 Augments the Effect of Typical and Atypical Antipsychotics

### Typical

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

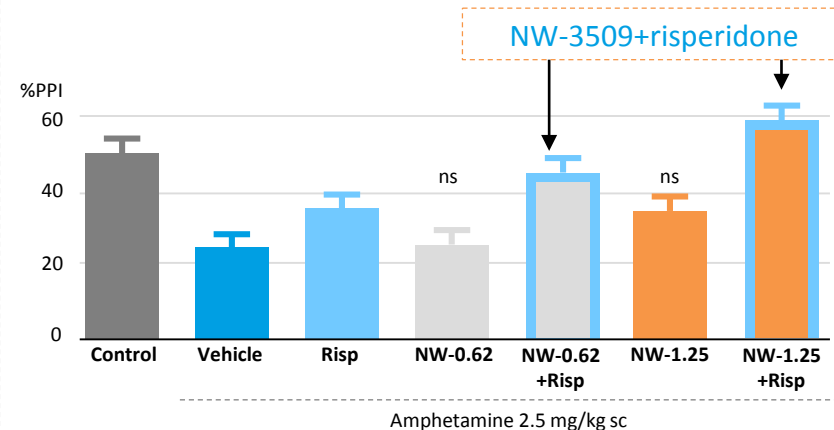
MED 1.25 mg/kg *po* (+ haloperidol 0.05 mg/kg *ip*)



### 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+Amph ( $n = 6-18$  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

## Investment Highlights

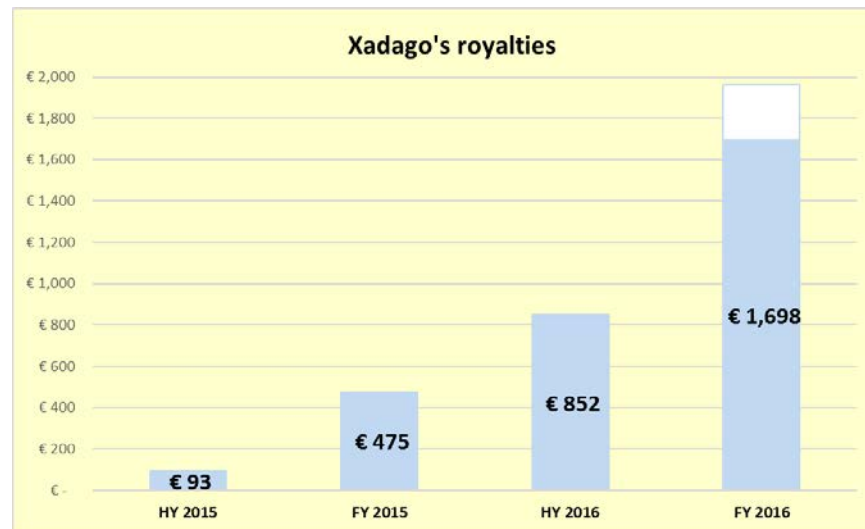
---



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**

## Group Consolidated Financials (IFRS) 2016 – Income statement

€/000	2016	2015
Licence income	3,039	1,800
<b>Royalties</b>	<b>1,698</b>	<b>475</b>
Other income	1,989	105
<b>Research and development expenses</b>	<b>(12,398)</b>	<b>(18,449)</b>
Marketing and advertising expenses	(513)	(53)
General and administrative expenses	(9,140)	(8,278)
<b>Operating loss</b>	<b>(15,325)</b>	<b>(24,400)</b>
Financial result, net	121	(583)
Income tax	(33)	2,167
<b>Net loss</b>	<b>(15,237)</b>	<b>(22,816)</b>
Net loss per share - EUR	(1.04)	(1.66)



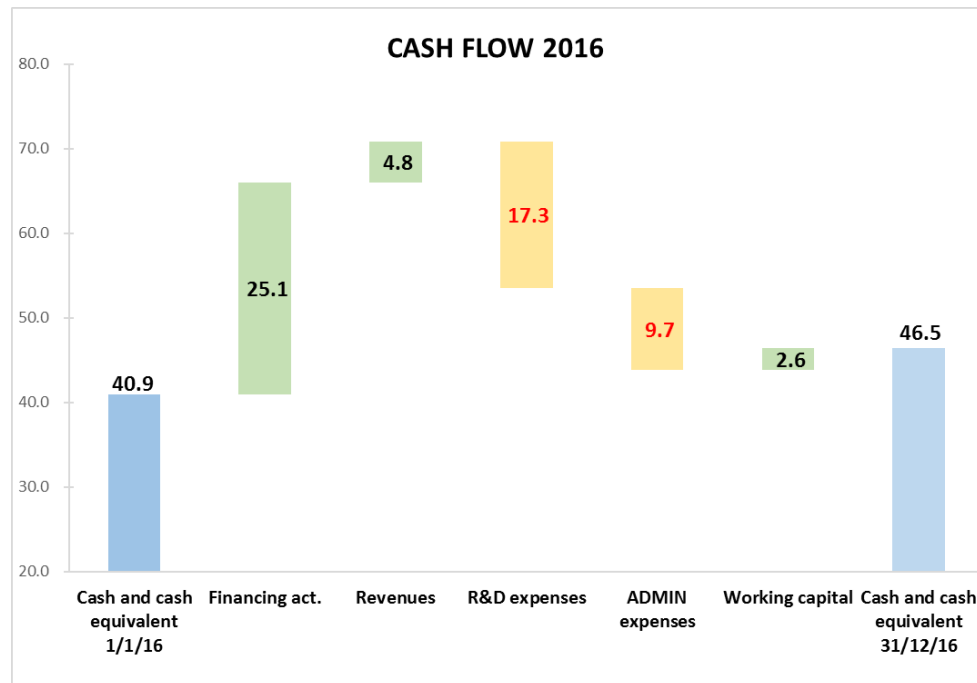
- Royalties are ramping up despite AIFA (Italian authority) imposing a ceiling for 2016 and 2017 sales (currently under negotiation) – **in white the 2Q 2016 impact**
- Gross R&D expenses are increasing (sarizotan and evenamide clinical studies and related activities)
  - 2016 amount reduced by R&D tax credit income (4.9m€); 2015 amount included 6.7m€ write-off

# Group Consolidated Financials (IFRS) 2016

## Balance sheet and Cash flow statements

€/000	2016	2015
Non-current assets	451	406
Current assets	9,672	3,043
Cash and cash equivalent	46,468	40,931
Total shareholders' equity	49,747	37,112
Non current liabilities	199	755
Current liabilities	6,645	6,513

- Current assets include 6.9m€ of R&D tax credit
  - ✓ To be offset during the following years with against certain contributions and taxes (also income taxes)
  - ✓ Companies can accrue R&D tax credit on qualifying R&D expenses until 2020





## AGENDA

Approval of the financial statements as at December 31<sup>st</sup>, 2016. Related and consequent resolutions;

Appointment of the Board of Directors for the financial years 2017, 2018 and 2019 and, therefore, until the approval of the financial statements as of December 31<sup>st</sup>, 2019, as follows:

- Ulrich Köstlin in quality of Chairman of the Board and non-executive director
- Stefan Weber, in quality of executive director
- Patrick Langlois in quality of non-executive director
- Bo Jesper Hansen in quality of non-executive director
- Robert Leslie Holland in quality of non-executive director
- Luca Benatti in quality of non-executive director and,
- Donald deBethizy in quality of non-executive director.

Determination of the remuneration of the Board of Directors. Related and consequent resolutions

**Shareholders will be called to express their vote on each individual candidate**

Please check Newron's web-site for additional info regarding the shareholders' meeting

# Q&A