SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

Stefan Weber, CEO

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Newron Pharmaceuticals

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Company Highlights

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 stage development
- Evenamide – changing the treatment paradigm for schizophrenia

Significant near-term value drivers

Management team with proven track record

Fully funded beyond key value inflexion points

- Cash balance of abt. € 51m (June 30, 2018)
- Access to long term loan facility of up to € 40m

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Leadership Team with Significant Expertise

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

LARRY ALPHS
Deputy Chief Medical Officer

- 35 years of experience
- Previously worked at: Sandoz, Knoll, Novartis, Pfizer Group Janssen (J&J group)

Successful Track Record in CNS Product Development

Xadago® (safinamide)

Commercialized by partner in 14 European markets and the US for Parkinson's disease ("PD")

Newron receives milestone and royalty payments from sales of safinamide in PD
- €34m received to date

Sarizotan

Undergoing potentially pivotal development in Rett syndrome – an orphan disease

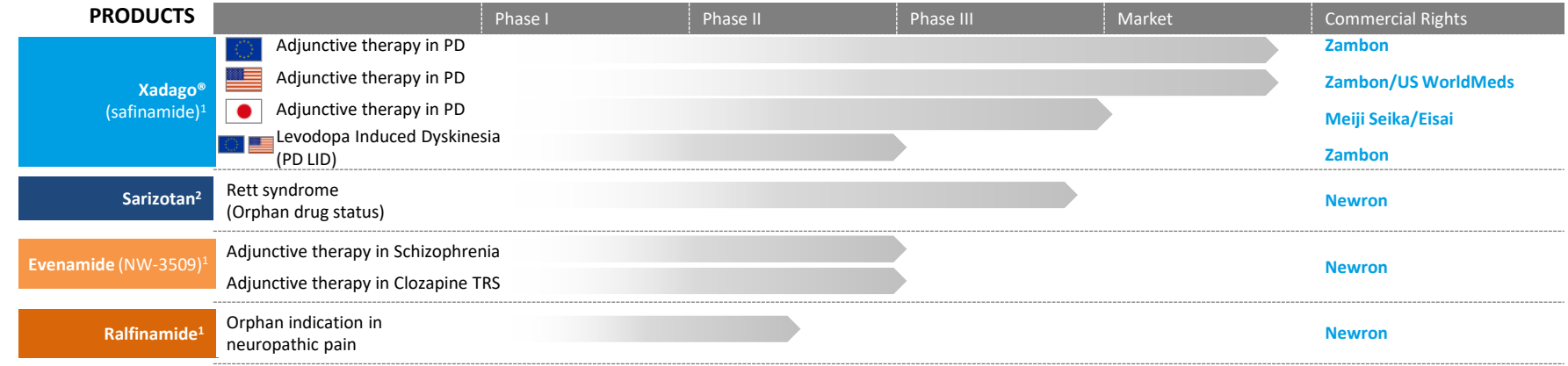
Newron will commercialize Sarizotan for Rett syndrome in the US and – if viable – in key EU territories

Evenamide (NW-3509)

Phase IIa trial demonstrated PoC

Preparations for potentially pivotal studies ongoing, opportunities for commercialization by Newron (Clozapine TRS population) and partnering (major indication)

Innovative Clinical Pipeline with Multiple Near-Term Catalysts



Expected Milestones

Xadago®:
Further launches expected
Study in patients with Levodopa Induced Dyskinesia (PD LID) expected to start end 2018/early 2019

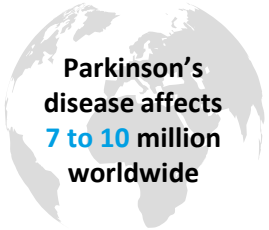
Sarizotan:
Potentially pivotal study commenced; results expected QIII 2019; own commercialization

Evenamide:
Start of potentially pivotal studies in QII 2019

Ongoing search for strategically relevant assets to in-license

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

Xadago®: 1st 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

- 2nd 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

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

- Newron and partner Zambon have completed designing a potentially pivotal study to evaluate Xadago® in patients with levodopa induced dyskinesia (PD LID)
- There is prior evidence of Xadago's benefit in this area of high unmet need
- Advanced discussions with US regulators on study design ongoing
- Participating centers in US and Europe
- Study expected to start end of 2018/early 2019

Significant Commercial Opportunity in Xadago® (Safinamide)

US / Canada

Launched in US in July 2017
Application for regulatory approval filed for Canada

EU

Latin America

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

Israel

Application for regulatory approval filed

Japan / Asia

Phase II/III completed in Jan. 18; application for regulatory approval filed in Oct. 2018

Australia /New Zealand

Regulatory approval for Australia in Oct. 2018

- Parkinson's disease affects 7 to 10 million people worldwide
- Long period of Xadago® market exclusivity (patent life: 2029 in EU, 2031 in the US)
- Milestone and royalty revenues to Newron since 2012

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; clear commercialization strategy
- Orphan drug designation in EU and US
- Rare Pediatric Disease Priority Review Voucher Program

EFFECTS OF ACUTE ADMINISTRATION WITH SARIZOTAN IN RETT FEMALE MICE (MECP2R168X/+). BENEFIT PERSISTS IN LONG LASTING TREATMENTS (14-DAYS-MECP2$^{R168X/+}$)

Apnea in MeCP2-deficient mice

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

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 ≥ 4 years, body weight ≥ 10 kg meeting RTT consensus clinical criteria, confirmed by MECP2 mutations
  - Patients meet all criteria related to breathing abnormalities:
    - ≥10% of the time with abnormal breathing
    - At least 10 episodes of breathing dysrhythmia (≥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
- Primary endpoint:
  - Percent reduction in number of apnea episodes/hour
    - Primary efficacy variable to be calculated from data from home cardiorespiratory monitoring
  - Measurements to be performed for 6-hr per day, during time awake, on any 3 days during the week
    - Weeks 2, 8, 16 and 24
- Enrolment close to completion
- Results expected QIII 2019

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Natural history study and new learnings from the STARS clinical trial

- 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 a long as **48 minutes/hr**
- Definitive data will be available late next year, however anecdotal data from investigators suggest that greater awareness of surroundings, increased attempt at non-verbal communication, greater alertness noted in patients who experience some improvement in apnea'

Rett families are doing a heroic job in providing care for these patients and the STARS investigators have pioneered the first quantitative methods for evaluating respiration in RTT patients

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Sarizotan Market Opportunity and Commercialization Strategy

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

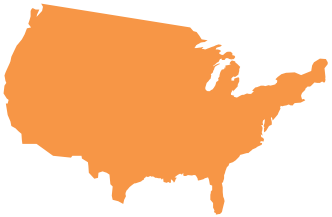
- Partnerships and collaborations with Rett advocacy, thought leaders & governing payers
- Global survey to quantify the ways in which patient “respiratory breathing abnormalities” affect daily life
- Meets Health Technology Assessment (HTA) requirements
- International Experts advocated timely approach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

US 16,000 patients



Orphan exclusivity
7.5 years post approval

EU 20,000 patients

Orphan exclusivity
12 years post approval

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

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

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

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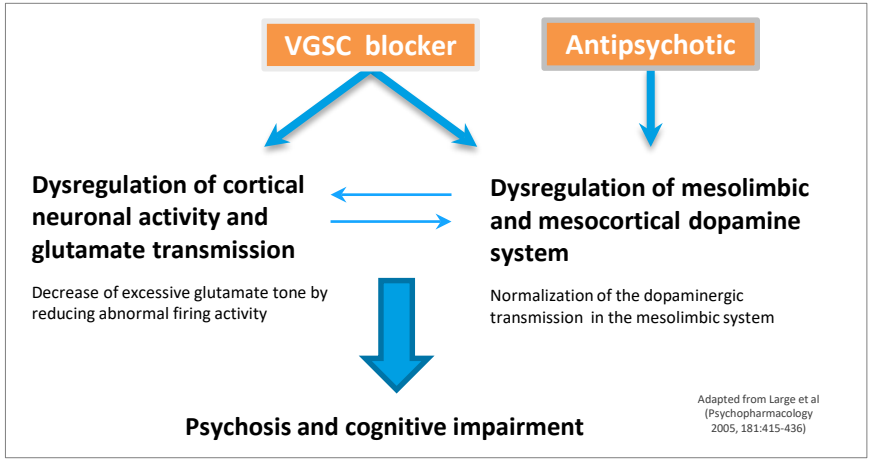
Evenamide Novel MoA: Synergistic with Marketed Antipsychotics

- 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 aripriprazole
- 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} (µM)

25

K_{inact} (µM)

0.4

High frequency firing

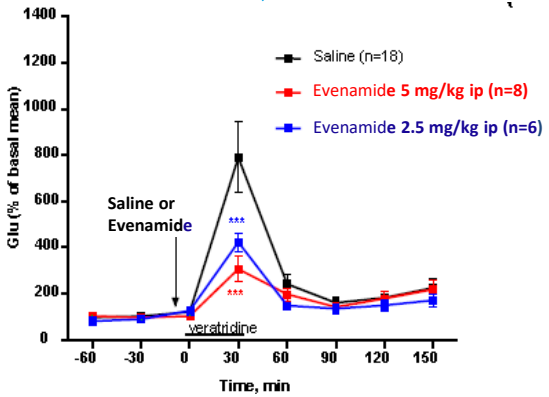
Control

Evenamide 1µM

Low frequency firing

Control

Evenamide 1µM



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
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 (ongoing)	✓	
Negative Symptoms	PCP-induced deficit in Social Interaction in the rat	✓	✓
	Saccharin preference test (anhedonia) in prenatal poly:IC exposed mice (ongoing)	✓	
	Three-chamber sociability test in prenatal poly:IC exposed mice (ongoing)	✓	
	Forced swimming test (avolition) in prenatal poly:IC exposed mice (ongoing)	✓	
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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Evenamide: Overview of PoC Study in Patients with Schizophrenia

- 4-week, placebo-controlled, add-on study of evenamide (15-25mg BID/day) in 89 patients on stable doses of aripripazole 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: Applicability in Clozapine Resistant Treatment Resistant Schizophrenia (TRS)

- 30% of TRS patients on clozapine do not respond adequately to this treatment, or develop resistance to its effects
- Outcomes/service utilization data indicate TRS is a categorically different illness to treatment-responsive schizophrenia
  - 10-20% of patients already show symptoms of resistance in first episode
- TRS is associated with some of the highest rates of hospitalization and costs to society - $34bln. in direct healthcare costs in the United States
- No drug other than clozapine has shown efficacy in these patients
- NIMH/ FDA/ ECNP/ EMA have raised this as an issue of grave concern
- Evenamide antagonizes (in vivo)
  - effect of ketamine (glutamate antagonist) on PPI
  - effects of MK-801 and PCP (glutamate releasers)
- Results with Evenamide in animal models of schizophrenia mimic effects of clozapine

EVENAMIDE: REGULATORY INTERACTIONS AND PHASE III CLINICAL DEVELOPMENT PLAN

Discussed with Health Authorities in:

- Spain, Denmark, Sweden, Germany, UK, CHMP, US, Canada: end of Phase II

All Health Authorities accepted pharmacokinetics, metabolism, toxicology, safety pharmacology, human safety, and efficacy data from Study 002
Indications, selection criteria, study designs, dose-range, safety/efficacy measures agreed on Phase III
Efficacy program will be comprised of 2 populations:

- **Non-treatment resistant patients**: chronic schizophrenics experiencing inadequate benefit for symptoms of their psychosis, on current atypical antipsychotic monotherapy (risperidone, aripripazole, 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 would lead to approval of 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 HI 2019 – appr. 18 months to results

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CONTACT DETAILS

NEWRON
STEFAN WEBER – CEO
+39 02 6103 46 26
pr@newron.com

UK/EUROPE
JULIA PHILLIPS / NATALIE GARLAND-COLLINS, FTI CONSULTING
+44 20 3727 1000
scnewron@fticonsulting.com

SWITZERLAND
MARTIN MEIER-PFISTER, IRF COMMUNICATIONS
+41 43 244 81 40
martin.meier-pfister@irfcom.ch

GERMANY/EUROPE
ANNE HENNECKE, MC SERVICES
+49 211 52925222
anne.hennecke@mc-services.eu

USA
PAUL SAGAN, LAVOIEHEALTHSCIENCE
+1 617 374 8800, EXT. 112
psagan@lavoiehealthscience.com