SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

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Stefan Weber, CEO
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Investment Highlights

1. Diversified Portfolio of Innovative CNS Product Candidates
2. Xadago® - Commercialized in 12 European Countries, US launch announced for July 2017
3. Sarizotan for Rett Syndrome in Late Stage Development
4. Evenamide - a Novel Mechanism / Treatment Paradigm for 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 12 European markets for Parkinson’s disease (PD); approved for commercialization in the US, launch upcoming (July)
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
Newron will commercialize Sarizotan for Rett syndrome

**Evenamide**
...(NW-3509) Phase IIa trial results met study objectives of good tolerability, safety, and preliminary evidence of efficacy
Ready for confirmatory efficacy / safety study by Newron or in conjunction with a partner

... INNOVATION in rare diseases
Innovative Clinical Pipeline with Multiple Near Term Catalysts

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<td>Orphan indication in neuropathic pain</td>
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<td>Newron</td>
<td>Newron</td>
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**Expected Milestones**

- **Xadago®:** Further EU launches expected; US launch expected July 2017
- **Evenamide:** Start of confirmatory efficacy / safety study alone or with a partner
- **Sarizotan:** Potentially pivotal study commenced July 2016; results HY1 2018; commercialization 2019

**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

ULRICH KÖSTLIN:
Former Executive at Bayer Schering Pharma AG

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

STEPHEN GRAHAM
Executive Director, Clinical Development

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

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

Fast and sustained efficacy, well tolerated

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

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
**Significant Commercial Opportunity in Safinamide (Xadago®)**

- **US / Canada**
  - FDA-Approved in March 2017
  - Launch expected in July 2017

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

- **Latin America**
  - Confirmatory Phase II/III and long-term Phase III studies initiated

- **Japan / Asia**
  - Partner to submit application for regulatory approval

- **Australia/New Zealand**

**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 up to $700m+ (analyst estimates)**

**7 TO 10 million world wide**

- 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 may be due 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 (MECP2R168X/+)**

- 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

- International, randomized, double blind, placebo-controlled, 6 months’ treatment study under US IND
- Will enroll minimally 129 RTT patients, 6 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, UK, Australia and India
- Study protocol designed in accordance with regulatory authorities in the United States, Europe and Canada
- Study enrolling
- Expected completion 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

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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 positive, negative or cognitive symptoms:
  - Hallucinations, delusions, paranoia, hostility and irritability (positive)
  - Progressive deterioration of cognition and behavior & presence of negative symptoms
  - High rates of suicide, incarceration, 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 of typicals and atypicalss limited and wanes over 18 months; 60-70% of patients switch but without additional benefit
  - No effect on suicidality

Source: FiercePharma, 2011

VAST MARKET OPPORTUNITY
(anti-psychotics market >$23bn)
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 ADD-ON TO ANTIPSYCHOTICS for patients with schizophrenia
  - Improvement of symptoms in patients worsening on standard treatment they had benefited from

- Well-tolerated in Phase I study
  - Exposure increased with dose; exposure achieved overlaps with plasma levels in animals at doses proven to be efficacious

- Phase IIa data in early 2017:
  - Consistent evidence of efficacy, good tolerability and safety

- Composition of matter – USPTO, 2013 - patent life 2028 plus extension
**Unique MOA Demonstrated**

**Evenamide, a selective Voltage-Gated Sodium Channel (VGSC) Blocker**

<table>
<thead>
<tr>
<th>Selectively blocks VGSCs in a voltage-and use-dependent manner</th>
<th>Modulates sustained repetitive firing without inducing impairment of the normal neuronal excitability</th>
<th>Inhibits Glutamate Release</th>
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</table>

- **Inhibition of native sodium channels expressed in rat cortical neurons**
  - $K_{\text{rest}}$ (µM)
    - 25
  - $K_{\text{inact}}$ (µM)
    - 0.4

- **High frequency firing**
  - Control

- **Low frequency firing**
  - Control

- **NW-3509 1µM**

![Graph showing Glu (% of basal level) over time](chart.png)

- Saline (n=16)
- NW-3509 5 mg/kg ip (n=6)
- NW-3509 2.5 mg/kg ip (n=6)
Amphetamine-Induced Prepulse Inhibition (PPI) Deficit Model
Evenamide Augments the Effect of Typical and Atypical Antipsychotics

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)

<table>
<thead>
<tr>
<th>Typical</th>
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<th>Atypical</th>
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<tr>
<td>Add-on with non-active dose of <strong>haloperidol</strong> MED 1.25 mg/kg po (+ haloperidol 0.05 mg/kg ip)</td>
<td></td>
<td>Add-on with non-active dose of <strong>risperidone</strong> MED 0.62 mg/kg po (+ risperidone 0.05 mg/kg ip)</td>
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<tr>
<td>Control</td>
<td>Vehicle</td>
<td>Halo</td>
</tr>
<tr>
<td>%PPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>ns</td>
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Phase IIa Study: Clinical Validation of a Novel Treatment Concept

- Evenamide as add-on treatment
  - For patients with schizophrenia on 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)
- Detailed results presented at 16th International Congress on Schizophrenia Research March 25, 2017
- Evenamide met study objectives of good tolerability, and safety
- Evenamide demonstrated consistent evidence of efficacy on key measures
  - Primary measure: Significant improvement on PANSS positive (mean change and responders)
  - Near Significant increase in CGI-C responders
  - No side-effects that are associated with dopamine-blocking antipsychotics
  - Greater improvement on all efficacy measures at every time point compared to standard of care
- Ready for confirmatory efficacy / safety study or partnering
NEXT STEPS

Meetings with regulatory authorities to obtain feedback on plans for development of Evenamide

Design and conduct of adequate and well-controlled study to demonstrate efficacy and safety/tolerability of fixed doses of Evenamide as add-on to antipsychotics in patients experiencing worsening of symptoms of schizophrenia

Global, 12-week study requiring approx. 360 patients randomized (1:1:1) to Evenamide (15 and 30 mg BID) or placebo

- Male and female (not of childbearing potential) outpatients; ages 18-55 yrs
- Diagnosis of schizophrenia (DSM-5) ≤ 6 yrs prior; current symptoms present ≤ 6 mo.
- PANSS total score >70; CGI-S – mildly ill or greater; score of 13 or higher on the following core symptoms of psychosis: hallucinatory behavior, delusions, suspicious/persecution, unusual thought content (on PANSS)
- Receiving a stable dose (> 4 weeks prior to screening) of an oral atypical antipsychotic (risperidone, olanzapine, lurasidone, ziprasidone, paliperidone, or aripiprazole)
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