# DEVELOPING UNIQUELY DIFFERENTIATED DRUGS FOR CNS TARGETS

## Full Year Results 2020 and Outlook 2021

## Tuesday, March 16, 2021, 3:00 pm CET

Newron
Pharmaceuticals

# FULL YEAR RESULTS 2020 AND OUTLOOK 2021 TELEPHONE CONFERENCE

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**Speakers:**

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# 2020 - Execution on strategy (1/2)

## Evenamide - schizophrenia

- All evenamide pre-clinical studies requested by the US Food and Drug Administration (FDA) have been completed with no toxicity concerns identified
- Despite the COVID-19 pandemic, Newron successfully completed enrolment for explanatory study 008 with evenamide in patients with schizophrenia, with results expected end of March 2021
- Newron remains on track to initiate its pivotal Phase III program in Q3 2021
- Newron continues to evaluate potential options for partnering/co-developing evenamide

# 2020 - Execution on strategy (1/2)

## Xadago®/safinamide – Parkinson's disease

- Newron notes that Supernus Pharmaceuticals acquired US rights to Xadago®/safinamide, effective June 2020
- Agreement signed with Zambon for potentially pivotal study with safinamide in patients suffering from Levodopa-induced dyskinesia (PD LID)

## Corporate

- Newron continues to evaluate opportunities to broaden its pipeline of treatments for central and peripheral nervous system diseases
- Newron received third tranche of EUR 7.5 million under its financing agreement with the European Investment Bank (EIB)

# Company Highlights

Unique portfolio of innovative CNS product candidates

- Xadago® for Parkinson's disease – Global approvals validate Newron's development capabilities from research to market
- Evenamide – New concept in treating inadequate/non-response in schizophrenia
- Ongoing search for strategically relevant assets

Significant near-term value drivers for both candidates

Management team with extensive experience and proven track record in drug development and commercialization

Fully funded beyond key value inflection points

- Cash balance of approx. € 31.3 million (Dec. 31, 2020)
- Access to long term funding facility of up to € 15 million (European Investment Bank)
- Royalty income, R&D tax credit

Newron
Pharmaceuticals

# DEVELOPING UNIQUELY DIFFERENTIATED DRUGS FOR CNS TARGETS

## Xadago® (safinamide)

Commercialized by partners in 15 European markets, the US, Canada and other markets for Parkinson's disease ("PD")

Newron receives milestone and royalty payments from sales of safinamide in PD; > € 55 million received to date

## Evenamide (NW-3509)

Phase IIa trial demonstrated efficacy; potential first mechanistically validated treatment for poor/non-responding patients with schizophrenia

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

# Innovative Clinical Pipeline with 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 | | | | | Zambon/Supernus |
| | Adjunctive therapy in PD | | | | | Meiji Seika/Eisai |
| | Levodopa Induced Dyskinesia (PD LID) | | | | | Zambon/Supernus |
| Evenamide (NW-3509)[1] | Adjunctive therapy in Schizophrenia | | | | | Newron |
| | Adjunctive therapy in Clozapine TRS | | | | | |
| Ralfinamide[1] | Orphan indication in neuropathic pain | | | | | Newron |

## Expected Milestones

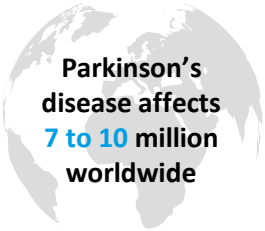
**Xadago®:**
Further launches expected
Study in patients with Levodopa Induced Dyskinesia (PD LID) expected to start 2021

**Evenamide:**
Potentially pivotal studies expected to start mid-2021

Ongoing search for strategically relevant assets

1 Safinamide, Evenamide and Ralfinamide all developed from Newron's ion-channel based research

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



**Parkinson's disease affects 7 to 10 million worldwide**

**A progressive 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

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

- Zambon previously discussed with the US Food and Drug Administration (FDA) the design of a potentially pivotal efficacy study to evaluate the effects of Xadago®/safinamide in patients with PD LID
  - Intention is to perform the study in the US, Europe and Asia/Australia
- Given Newron's experience in the development of Xadago, Newron to conduct the study
  - Zambon remains associated with the study
- Newron and Zambon to share study cost, equally, in return, Newron to qualify for a one-time milestone payment and a greater share of royalties should the study lead to a label extension
- Evidence indicating Xadago's anti-dyskinetic effect:
  - Mechanism, i.e. glutamate release inhibition
  - LID models in rats and monkeys
  - PD patient data: significant reduction of dyskinesia in 223 dyskinetic (Dyskinesia Rating Scale) PD patients in a 2-year, placebo-controlled study
- Agreement executed March 2021
  - LID label represents "substantial additional benefit to patients" (Supernus Pharma)
- Study expected to start 2021

# Significant Commercial Opportunity in Xadago® (Safinamide)

**US / Canada**

Launched in US in 2017
Launched in Canada in 2019

**EU** **Latin America**

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

**Israel**

Launched in 2021

**Japan / Asia**

Launched in 2019

**Australia /New Zealand**

Launched in Australia in 2019

- 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

# Schizophrenia: No Effective Treatment for the Last 20 Years to Reduce Burden of Disease

**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

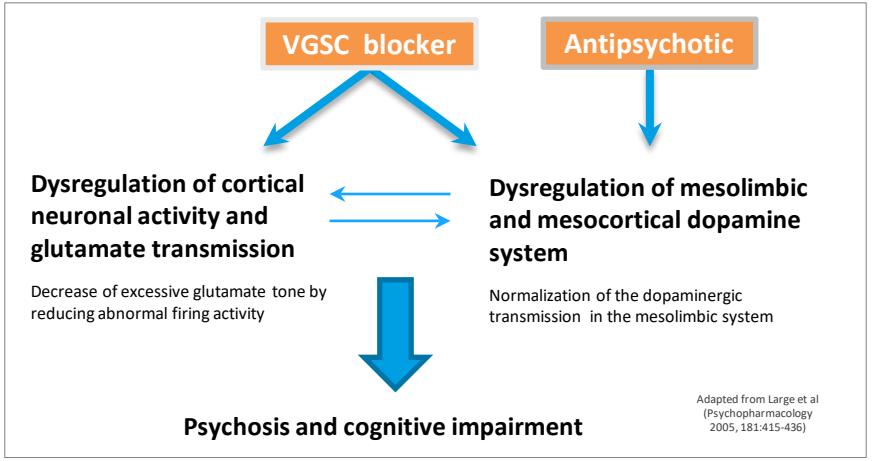
**Onset of disease occurs in early adulthood affecting 1% of the population worldwide**

- Most patients with schizophrenia demonstrate reduced response to typical and atypical antipsychotics after few years of treatment
- 64-82% of chronically treated patients switch treatments but without additional benefits, no significant reduction in side-effects
- 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
- New data indicate far worse prognosis than current concepts:
  - Outcome after one year for young US patients on treatment following first episode: 24 times greater mortality than age matched (16-30 years old) controls (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**

Inhibition of native sodium channels expressed in rat cortical neurons

$K_{rest}$ (µM)

25

$K_{inact}$ (µM)

0.4

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

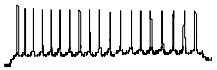
High frequency firing

Control

Evenamide 1µM

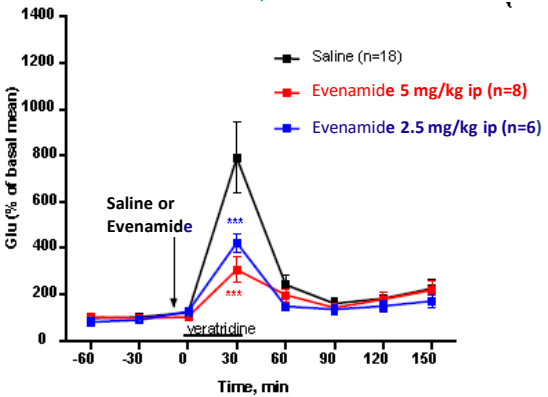
Low frequency firing

Control



Evenamide 1µM

**Inhibits Glutamate Release**



# 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 | ✓ | ✓ |
| **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

# Evenamide: Proof of Concept in Patients with Schizophrenia Demonstrated

- 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

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

Newron aims to complete additional informative studies, requested by the FDA, to allow for its Phase III to commence in mid-2021, with results expected 18 months after initiation

- Preclinical part of safety work has been successfully completed; no toxicity issues reported; submitted to FDA, already
- First clinical safety study initiated in July 2020
  - Four-week, randomized, double-blind placebo-controlled study
  - To evaluate safety (tolerability and EEG effects) and preliminary efficacy of 7.5 mg and 15 mg BID
  - Outpatients suffering from chronic schizophrenia being treated with one of the leading anti-psychotics
  - 13 study centers in the US and India
  - Enrollment completed (Jan. 21, 2021), 138 patients randomized
  - Results expected by end of March 2021

# Evenamide: Regulatory Interactions and Phase III Clinical Development Plan

Phase III 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 quetiapine) **– 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

# NEWRON LISTING PROFILE AS OF DECEMBER 31, 2020

- Newron is listed at
  - SIX since December 2006 and
  - Dusseldorf Stock Exchange (XETRA) since June 2019
- Newron issues ordinary shares (nominal value 0.20€), only
- Number of outstanding shares as of Dec. 31, 2020: 17,845,345
  - Senior managers and Directors hold 100,140 shares (0.6%)
- Number of outstanding derivative holding as of Dec. 31, 2020: 2,353,740
  - Senior managers and Directors hold 1,017,597 call options (5.7%)
  - EIB holds 504,481 warrant (2.8%). Strike price equal to EUR 9.25

Additional info can be found in Corporate Governance section of 2020 annual report: https://www.newron.com/investors/reports-and-presentation/year/2020

# ANALYSTS AND MOST RECENT INFO ON SHAREHOLDINGS

## Sell-side analyst coverage:

Jefferies — Lucy Codrington/Peter Welford

Kempen — René Wouters

Baader — Bruno Bulic

## Further coverage:

RX Securities, valuationLab, Edison

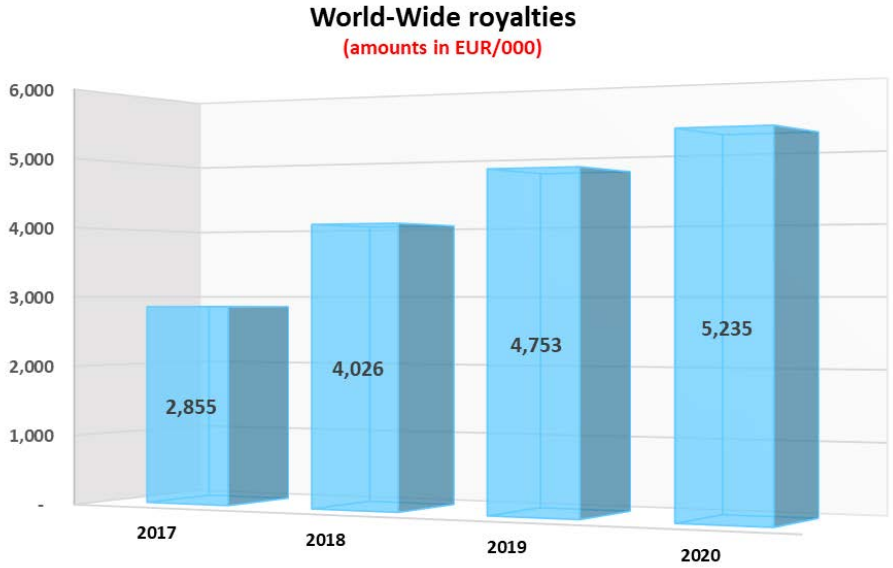
## Disclosed* material shareholders (>3%)

Zambon > 4%

*: to the best of Newron' knowledge https://www.six-exchange-regulation.com/en/home/publications/significant-shareholders.html?companyId=NEWRONPH

# GROUP CONSOLIDATED FINANCIALS (IFRS) FY 2020 – INCOME STATEMENT

| EUR/000 | 2020 | 2019 |
|---|---|---|
| Licence income | 23 | 2,284 |
| **Royalties** | **5,235** | 4,754 |
| **Research and development expenses** | **(14,853)** | (17,440) |
| Marketing and advertising expenses | (331) | (634) |
| General and administrative expenses | (8,140) | (9,865) |
| **Operating loss** | **(18,066)** | **(20,899)** |
| **Net loss** | **(20,998)** | **(20,207)** |
| Net loss per share - in EUR | (1.18) | (1.13) |

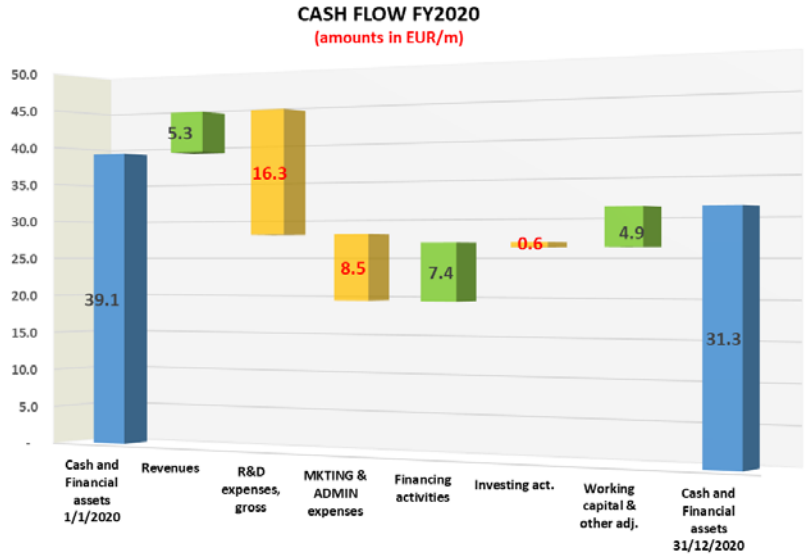



- Royalties increased by 10%; effective June 2020, Supernus Pharmaceuticals Inc. acquired the CNS portfolio of US WorldMeds, including the US rights to Xadago®
- R&D expenses are exposed net by Italian R&D Tax Credit (2020 equal to 1,4m€)
- Delta between Operating and Net loss mainly related to EIB interests on 25m€ loan

# GROUP CONSOLIDATED FINANCIALS (IFRS) FY 2020 – BALANCE SHEET AND CASH FLOW STATEMENTS

| EUR/000 | 2020 | 2019 |
|---|---|---|
| **Non-current assets** | **13,324** | 14,797 |
| Current assets | 6,624 | 6,328 |
| **Cash and other financial ass.** | **31,250** | 39,163 |
| | | |
| Total shareholders' equity | 17,246 | 36,798 |
| **Non-current liabilities** | **27,060** | 17,895 |
| Current liabilities | 6,892 | 5,595 |

- Non-current assets include 12.5m€ of R&D tax credit
  - ✓ The amount Management expect to use in 2021 (3.4m€) has been reclassified in Current assets
- Cash, other financial assets and EIB facility are sufficient to finance Newron' development activities beyond 2022
- Non-current liabilities includes: i) the EIB loan accounted for amortized cost; ii) the Lease liabilities and iii) the Employees severance indemnity




- Opening and year-end position, includes both Cash and Other current financial assets
- R&D expenses are gross of R&D tax credit
- Working capital includes: i) adjustments for non-monetary items; ii) R&D tax credit effect for the year and iii) accruals of EIB interests

# AGM APRIL 13, 2021 – 10.30 AM CET - NEWRON PREMISES

## AGENDA

1. Approval of the financial statements as at December 31st, 2020. Related and consequent resolutions.

# Company Highlights

Unique portfolio of innovative CNS product candidates

- Xadago® for Parkinson's disease – Global approvals validate Newron's development capabilities from research to market
- Evenamide – New concept in treating inadequate/non-response in schizophrenia
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- Royalty income, R&D tax credit

# Q&A

Newron
Pharmaceuticals

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