SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

29th Annual Piper Jaffray Healthcare Conference

Lotte New York Palace, November 29, 2017

Newron
Pharmaceuticals

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Company Highlights

1. **Diversified Portfolio of Innovative CNS Product Candidates**
2. **Xadago® - Commercialized in 12 European Countries, launched in US in July 2017**
3. **Sarizotan for Rett Syndrome in Late Stage Development**
   - **Pivotal Phase III data expected QIII/2018**
4. **Evenamide - a Novel Mechanism / Treatment Paradigm for Schizophrenia**
   - **PoC demonstrated; HA review of potentially pivotal studies' design ongoing**
5. **Multiple Catalysts on the Horizon**
6. **Management Team with Proven Track Record**

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

Successful Track Record in CNS Product Development

NOVEL CNS PRODUCT CANDIDATES

Xadago® (safinamide)

Commercialized in 12 European markets and the US for Parkinson's disease ("PD")

- Newron receives milestone and royalty payments from sales of safinamide in PD
  - €36m received to date

Sarizotan

Undergoing potentially pivotal development for Rett syndrome – an orphan disease

- Newron will commercialize Sarizotan for Rett syndrome

Evenamide (NW-3509)

Phase IIa trial demonstrated PoC

- Preparations for potentially pivotal studies ongoing

… INNOVATION
in rare diseases

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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 / Eisai
	Levodopa Induced Dyskinesia (PD LID)					Zambon
Sarizotan[2]	Rett syndrome (Orphan drug status)					Newron
Evenamide (NW-3509)[1]	Adjunctive Schizophrenia					Newron
	Adjunctive Clozapine TRS					
Ralfinamide[1]	Orphan indication in neuropathic pain					Newron

Expected Milestones

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

Sarizotan:
Potentially pivotal study commenced; results expected QIII/2018; own commercialization

Evenamide:
Start of potentially pivotal studies in 2018

Ongoing search for strategically relevant assets to in-license

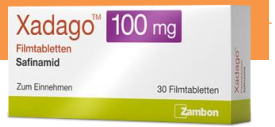
1 Safinamide, Evenamide and Ralfinamide all developed from Newron's ion channel based research
2 Sarizotan was licensed from Merck KGaA

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

A progressing disorder, no cure available yet

- Parkinson's Disease: 2nd most common chronic progressive neurodegenerative disorder in the elderly
- Affecting 1-2% of individuals aged ≥ 65 years worldwide

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®: Label Expansion Study in Patients with Levodopa Induced Dyskinesia (PD LID)

- Newron and its partner Zambon, together with academic and regulatory experts, are designing a potentially pivotal efficacy study to evaluate the effects of Xadago® (safinamide) in patients with levodopa induced dyskinesia (PD LID)
- Discussions with the EU and US regulators on study design, based upon previously reported clinical and pre-clinical data for PD LID (>200 patients, 2 year treatment duration); expected to be finalized by QII/2018
- Participating centers in US, Europe and RoW
- The study is expected to start in 2018, with data read-out expected in 2019

Significant Commercial Opportunity in Xadago® (Safinamide)

US / Canada

VALEO PHARMA®

US WorldMeds

Launched in US in July 2017

EU

Zambon 1906

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

Latin America

Japan / Asia

meiji Eisai

Confirmatory Phase II/III and long-term Phase III studies initiated 2015, results exp. QI/19

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 up to $700m+ (analyst estimates)

20% to **30%** 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 Approved 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
- Global potentially pivotal STARS study ongoing

EFFECTS OF ACUTE ADMINISTRATION WITH SARIZOTAN IN RTT 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 International Phase III, Potentially Pivotal, Study in RTT

- Global, randomized, double blind, placebo-controlled, 6 months treatment study under US IND
- Centers of excellence in the United States, Italy, UK, Australia and India
- Registration program approved by FDA, CHMP and HPB (Canada)
- Target enrollment of 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
- Study enrolling
- Top line results expected QIII / 2018

Sarizotan Market Opportunity and Commercialization Strategy by Newron "Breathing is everything"

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

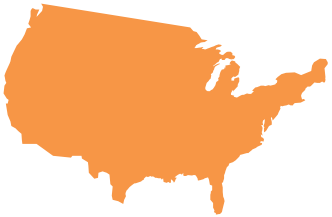
- Fostering partnership and collaborations with Rett advocacy, thought leaders & governing payers
- Global survey to quantify the ways in which patient "respiratory breathing abnormalities" affect daily life
- Meets Health Technology Assessment (HTA) requirements, including European Network of countries requiring information for treatment access
- International Experts advocated timely approach as critical for management of patients, at 5th EU Rett Congress, Nov. 2017

Goals

- 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

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

Schizophrenia Market Opportunity – No Effective Treatment that Reduces Burden of Disease in Last 20 Years

- Onset of disease occurs in early adulthood affecting 1% of the population worldwide
  - Disease onset in 20s, need for life-long treatment
  - Globally, over 4m patients
- Disease characterized by positive, negative, and cognitive symptoms:
  - Hallucinations, delusions, paranoia, hostility and irritability (positive)
  - High rates of suicide, incarceration, multiple physical illnesses and lower life expectancy
- Personal cost: homelessness, suicide, violence, jail, poor quality of life
- Cost to society (direct cost US, only): $63bln. p.a.

- Efficacy of current treatment options insufficient
  - Efficacy of typicals and atypicals limited and wanes over 18 months; 64-82% of patients switch but without additional benefit
  - No effect on 50% suicide attempt rate (but clozapine)
- 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

Limited Effectiveness of Current Antipsychotics in Treating Schizophrenia

- Findings From 3 Major Non-Commercial (CATIE , CUTLASS, and EUFEST) studies reveal significant dissatisfaction with all current antipsychotics:
  - Approximately 74% of patients discontinue first or second generation antipsychotic medication (CATIE, CUTLASS) within 18 months due to inadequate efficacy/ intolerance
  - Median time to discontinuation ranges from 3.5 (ziprasidone)- 9.2 (olanzapine) months (CATIE)
  - Minimal marked differences between treatments (except clozapine) in extent of improvement in psychopathology as measured by PANSS, CGI, QLSS

POSSIBLE REASONS INCLUDE:

- All these drugs have same/ similar mechanism of action, e.g. 5HT2/D2 antagonism with effects at other receptors of no relevance for efficacy
- Effective resolution of psychopathology requires effects on other targets / mechanisms
- Chronic blockade of dopaminergic receptors in mesolimbic structures may lead to upregulation of receptors and loss of efficacy/ worsening

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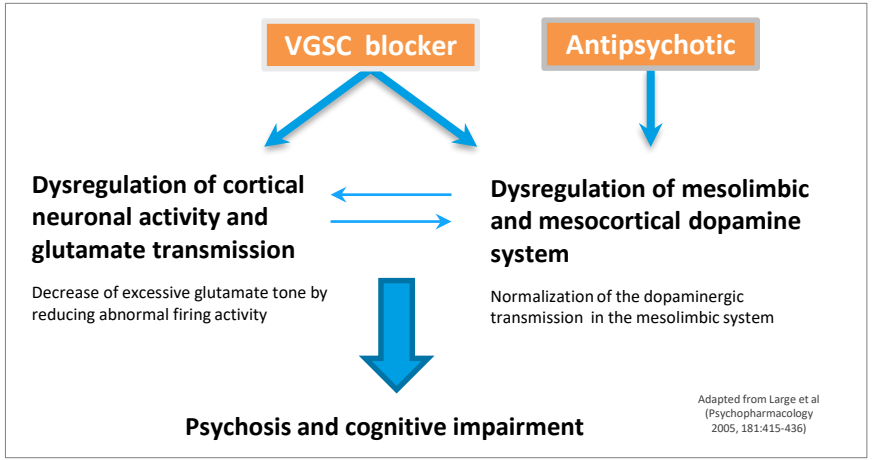
Evenamide (NW-3509)'s novel MoA: Synergistic with Marketed Antipsychotics

- Evenamide 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 and modulate these major neurotransmitter systems that have been associated with positive symptoms in schizophrenia
  - 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



Unique MOA Demonstrated

Evenamide, a selective Voltage-Gated Sodium Channel (VGSC) Blocker, shows no effect on >130 CNS receptors, enyzmes, 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

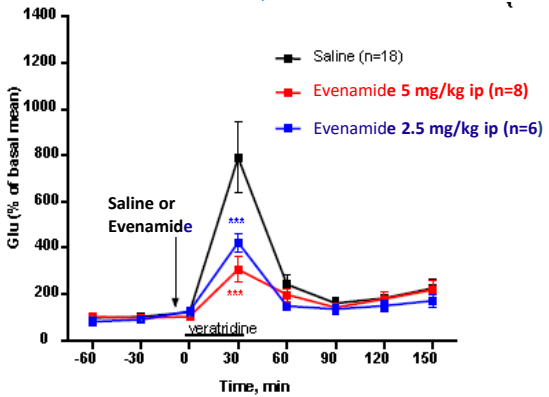
Control

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)	✓	

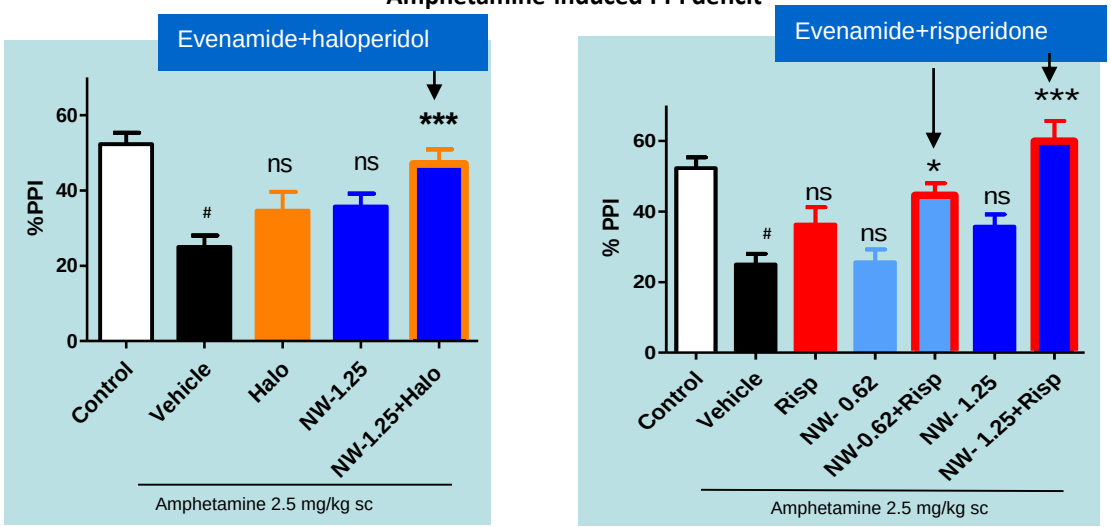
*Trend
Blank cells = not evaluated

Add-on: Evenamide augments the effect of typical and atypical antipsychotics in positive symptom models

Add-on with non-active dose of **haloperidol**
MED 1.25 mg/kg *po* (+haloperidol 0.05mg/kg *ip*)

Add-on with non-active dose of **risperidone**
MED 0.62 mg/kg *po* (+risperidone 0.05 mg/kg *ip*)

Amphetamine-induced PPI deficit



Tukey's multiple comparison test *p<0.05, ***p<0.001 vs Vehicle+Amp (n=6-18 rats per group)

Add-on activity showed in other models

- ✓ Pre-pulse inhibition spontaneous deficit (C57 mice)
- ✓ Amphetamine hyperactivity in mice
- ✓ Amphetamine plus Chlordiazepoxide induced hyperactivity in mice
- ✓ PCP- induced deficit in Social Interaction in the rat

Evenamide – PoC study in patients with schizophrenia - overview

- 4-week, placebo-controlled, add-on study of evenamide (15-25mg BID/day) study in patients on stable doses of aripripazole or risperidone showing signs of worsening;
- Results support hypothesis that evenamide's glutamatergic mechanism will improve symptoms of psychosis in patients not responding to D2/5HT2 blockade of standard antipsychotics
- Physiological modelling predicted that mean plasma concentrations of >20 ng/ml would be efficacious: this was confirmed in this study at doses of 15-25 mg bid
- Scientific Advisory Board meeting (July 12, 2017);
  - US and EU schizophrenia experts reviewed preclinical, safety and efficacy data
  - Fully endorsed above conclusions: unique mechanism needs exploration in other indications
  - Strongly recommend study in clozapine failures
- Positive scientific advice meetings with D, DK, E, S, UK; upcoming meetings with CHMP, FDA, HPB (Canada)

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Evenamide – PoC study: Principal results, PANSS Positive Scale

Visit	Mean Value				Mean Change from Baseline			
	Evenamide (N=48)		Placebo (N=39)		Evenamide (N=48)		Placebo (N=39)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	48	14.8 (2.77)	39	14.7 (2.81)	--	--	--	--
Day 8	46	13.7 (2.49)	38	14.9 (2.87)	46	-1.2 (1.59)	38	0.1 (1.84)
Day 15	44	13.5 (3.06)	38	14.3 (2.96)	44	-1.4 (2.43)	38	-0.5 (1.81)
Day 22	42	12.6 (3.41)	38	13.6 (3.23)	42	-2.3 (3.03)	38	-1.2 (2.61)
Day 28	47	13.0 (3.60)	39	14.0 (3.79)	47	-1.9 (3.15)	39	-0.7 (3.08)

Day 28	Change from Baseline				Difference: Evenamide vs. Placebo		
	Evenamide (N=48)		Placebo (N=39)				
	n	LS Mean (SE)	n	LS Mean (SE)	LS Mean (SE)	(95% CI)	p-value
MMRM	47	-2.06 (0.439)	39	-0.87 (0.478)	-1.19 (0.643)	(-2.47, 0.09)	**0.0678**
ANCOVA (LOCF)	48	-2.31 (0.445)	39	-1.03 (0.477)	-1.28 (0.632)	(-2.54, -0.02)	**0.0459**
ANCOVA (OC)	43	-2.51 (0.454)	38	-1.03 (0.475)	-1.48 (0.641)	(-2.76, -0.20)	**0.0237**

Evenamide – PoC study: Effect on additional efficacy measures

Proportion of Responders [n/n (%)] at Day 28					
Scale	**Responder Criterion**	**N**	**Evenamide**	**N**	**Placebo**
PANSS Positive	Change from baseline less than 0 (reduction in score = improvement)	50	35/47 (74.5)*	39	17/39 (43.6)
CGI-C	Rating of 1, 2 or 3 (very much, much or minimally improved, respectively)	50	26/47 (55.3) (*)	39	14/39 (35.9)

*p < 0.05 vs. placebo, Fisher's Exact chi-square test; (*) p<0.1 vs. placebo

	Mean Value at Day 28				**Mean Change from Baseline**			
	NW-3509 (N=48)		**Placebo (N=39)**		**NW-3509 (N=48)**		**Placebo (N=39)**	
Scale	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
PANSS Total	47	57.8 (9.66)	39	59.3 (10.81)	47	-5.1 (9.67)	39	-3.7 (9.65)
LOF Total	48	22.79 (3.189)	39	20.95 (4.359)	47	0.72 (3.321)	39	0.31 (3.130)
CGI-S	47	3.1 (0.68)	39	3.2 (0.77)	47	-0.3 (0.60)	39	-0.2 (0.74)

- All efficacy measures showed superior benefit compared with standard of care at every assessment in the study

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Evenamide – Applicability in Clozapine Resistant Treatment Resistant Schizophrenia (TRS), an “Orphan” Indication

- ~ 30%* patients continue to be psychotic, with unresolved symptoms, such as delusions, hostility, grandiosity, and hallucinations, after they have completed treatment with at least two adequate trials antipsychotic medications at therapeutic doses from different chemical classes
- Outcomes/service utilization data indicate treatment-resistant schizophrenia 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
- Despite similarities; olanzapine and quetiapine do not show efficacy in TRS
- No drug other than clozapine has shown efficacy in these patients
- Clozapine is the only drug with an FDA indication for TRS and for reducing suicidal behavior
- 30% of (TRS) patients on clozapine do not respond adequately, or develop resistance to its effects
- NIMH/ FDA/ ECNP/ EMA have raised this as an issue of grave concern

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Rationale for use of Evenamide in Clozapine failures

Glutamate system in (TRS) patients

- Studies suggest treatment-resistance (TRS) may be differentiated by abnormalities in brain glutamate concentrations not seen in treatment-responsive patients; this suggests a categorical difference rather than one of severity
- Case studies, small placebo-controlled studies, meta-analyses, suggest benefit of lamotrigine as add-on treatment, in clozapine resistant TRS; however there is considerable variability among trials.
- The benefits of lamotrigine are most likely due to antagonism of glutamate release
- 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

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“Orphan” Drug Market Opportunity Of Evenamide

Add On Therapy For Treatment Resistant Schizophrenia (TRS) Who Are NOT Responding Adequately To Clozapine

Description		Total
Patients with Schizophrenia in US		2.4M
TRS patients (20-50%) after 5-10 years	30%	600K
Current users of Clozapine		70K
Clozapine resistant schizophrenia (30%)		21K

- Physician prescribers (US) identified through National Registry
- Targeted launch to known clozapine prescribers only
  - 80% of the CTRS patients in 10 US states, selected VA, state, city hospitals and prison system cover 80%
- Similar prevalence estimated for EU, Japan and Canada

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Next Steps

Completing with CHMP, FDA, HPB (Canada) to obtain concurrance on planned development of Evenamide

- Orphan Designation: placebo-controlled, add-on therapy trial in Treatment Resistent Schizophrenia (TRS) not responding to clozapine (**18 months to completion**)
- Pivotal Study: placebo-controlled study to demonstrate efficacy and safety/tolerability of three fixed doses of Evenamide as add-on to antipsychotics in patients experiencing worsening of symptoms of schizophrenia (**18 months to completion)**

Submissions relating to Orphan/PRIME/Fast track designation

- Briefing books/Meeting requests to be submitted by year end
- Designation decisions expected by QII 2018
- Start of studies in 2018

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Multiple Catalysts on the Horizon

Recent Accomplishments

March 2017	Encouraging PIIa data for Evenamide in Schizophrenia patients	✓
March 2017	FDA approves Xadago® for Parkinson's Disease patients	✓
April 2017	Xadago® launched in Portugal for Parkinson's Disease	✓
May 2017	Expansion of sarizotan STARS study to include patients under 13 years	✓
July 2017	Xadago® launched in US for Parkinson's Disease	✓

Expected Milestones

QI 2018	Potential Orphan Designation for Evenamide in Clozapine resistant TRS patients	
Mid-2018	Pivotal Phase III Rett Syndrome data for sarizotan	
2018	Initiate pivotal study for Xadago® in Parkinson's Disease patients with PD LID	
2019	Japan Phase II/III Xadago® results in Parkinson's Disease	
2019	Pivotal Phase IIb/III and Orphan Designation TRS Evenamide data	
2019	Potential approvals for sarizotan in Rett syndrome	
2019	Potential approvals for Xadago® in Japan	

Company Highlights

1. **Diversified Portfolio of Innovative CNS Product Candidates**
2. **Xadago® - Commercialized in 12 European Countries, launched in US in July 2017**
3. **Sarizotan for Rett Syndrome in Late Stage Development**
   - **Pivotal Phase III data expected QIII/2018**
4. **Evenamide - a Novel Mechanism / Treatment Paradigm for Schizophrenia**
   - **PoC demonstrated; HA review of potentially pivotal studies' design ongoing**
5. **Multiple Catalysts on the Horizon**
6. **Management Team with Proven Track Record**

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