# SUCCESS IN CNS DRUG DEVELOPMENT – INNOVATION IN RARE DISEASES

R&D Day
October 31, 2018
New York City

Newron
Pharmaceuticals

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# Agenda


10.00 WELCOME

10.05 NEWRON COMPANY HIGHLIGHTS – STEFAN WEBER, CEO

10.15 INTRODUCTION TO GUEST SPEAKERS – RAVI ANAND, CMO

10.20 NATURAL HISTORY OF AWAKE BREATHING DYSFUNCTION AND EMERGING DATA - DANIEL GLAZE, MD

10.50 Q&A

11.00 NEWRON'S RETT SYNDROME DEVELOPMENT PROGRAM – RAVI ANAND, CMO

11.25 SPECTRUM OF TREATMENT RESISTANT SCHIZOPHRENIA: NEW THERAPEUTIC MECHANISMS – JOHN KANE, MD

11.55 Q&A

12.05 NEWRON'S SCHIZOPHRENIA DEVELOPMENT PROGRAM – RAVI ANAND, CMO

12.30 Q&A

12.45 LUNCH

# Company Highlights


Diversified portfolio of innovative CNS products/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. $60m (June 30, 2018)
- Access to long term loan facility of up to $46m

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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
- $42m received to date

## Sarizotan

Undergoing potentially pivotal development in Rett syndrome – an orphan disease

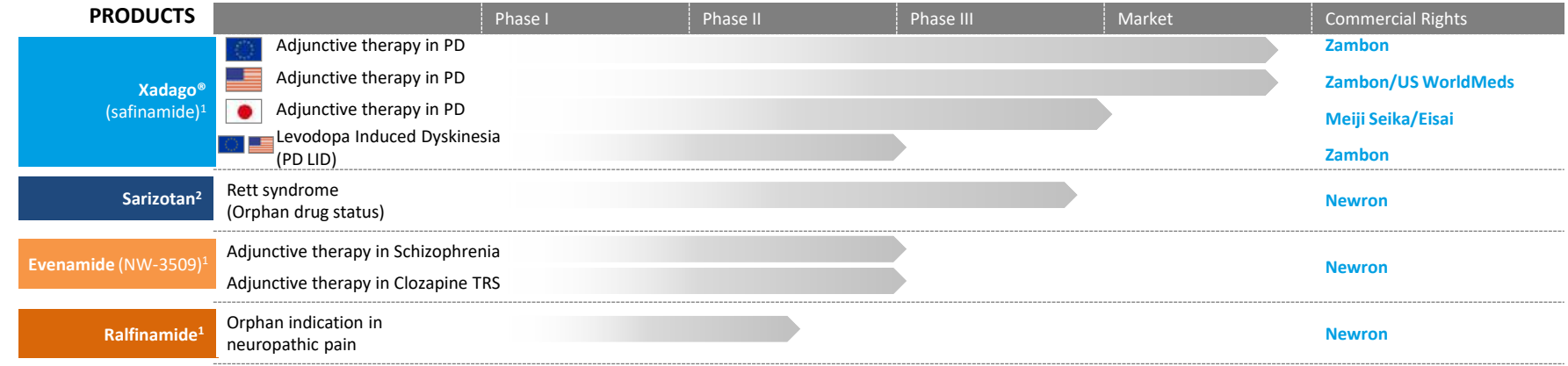
Newron will commercialize Sarizotan for Rett syndrome in the US and – if viable – in key EU territories

## 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

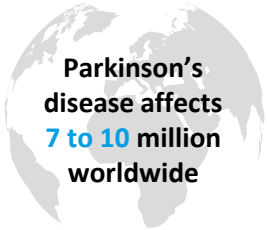
**Sarizotan:**
Potentially pivotal study commenced; results expected QIII 2019; own commercialization

**Evenamide:**
Start of potentially pivotal studies in H1 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 are 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**

Application for regulatory approval filed for Australia

- 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

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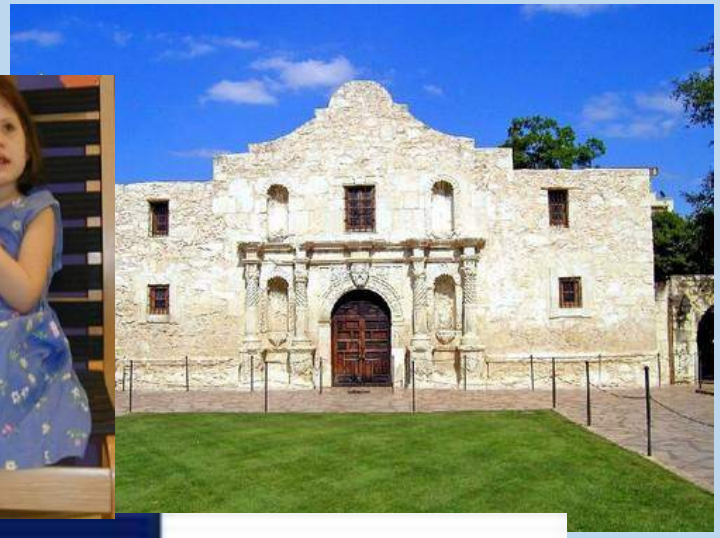
# HOWDY!





# Rett Syndrome: Natural History of Awake Breathing Dysfunction and Emerging Data

Daniel G. Glaze, MD
Medical Director, The Blue Bird Circle Rett Center
Professor Departments of Pediatrics and Neurology
Baylor College of Medicine
Houston, Texas

# A Progressive Syndrome of Autism, Dementia, Ataxia, and Loss of Purposeful Hand Use in Girls: Rett's Syndrome: Report of 35 Cases

Bengt Hagberg, MD,* Jean Aicardi, MD,† Karin Dias, MD,‡ and Ovidio Ramos, MD†

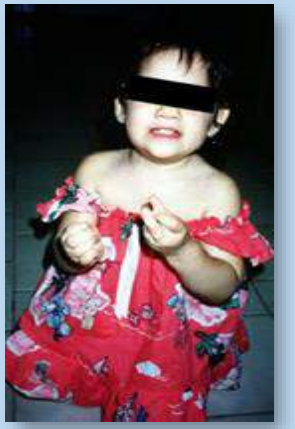
Thirty-five patients, exclusively girls, from three countries had a uniform and striking progressive encephalopathy. After normal general and psychomotor development up to the age of 7 to 18 months, developmental stagnation occurred, followed by rapid deterioration of higher brain functions. Within one-and-a-half years this deterioration led to severe dementia, autism, loss of purposeful use of the hands, jerky truncal ataxia, and acquired microcephaly. The destructive stage was followed by apparent stability lasting through decades. Additional insidious neurological abnormalities supervened, mainly spastic parapareses, vasomotor disturbances of the lower limbs, and epilepsy. Prior extensive laboratory investigations have not revealed the cause. The condition is similar to a virtually overlooked syndrome described by Rett in the German literature. The exclusive involvement of females, correlated with findings in family data analyses, suggests a dominant mutation on one X chromosome that results in affected girls and nonviable male hemizygous conceptuses.

Hagberg B, Aicardi J, Dias K, Ramos O: A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann Neurol 14:471–479, 1983

# Andreas Rett

# Rett Syndrome

- Initial apparently normal development
- Period of regression:
  - Loss of spoken communication and purposeful hand use skills
  - Gait abnormalities
  - Stereotypic hand movements
  - Autistic-like features



# Rett Syndrome

- 95% due to mutations in MECP2 Gene (X chromosome)
- Relatively long life expectancy
- **No approved or effective medications addressing core symptoms**

# Rett Syndrome

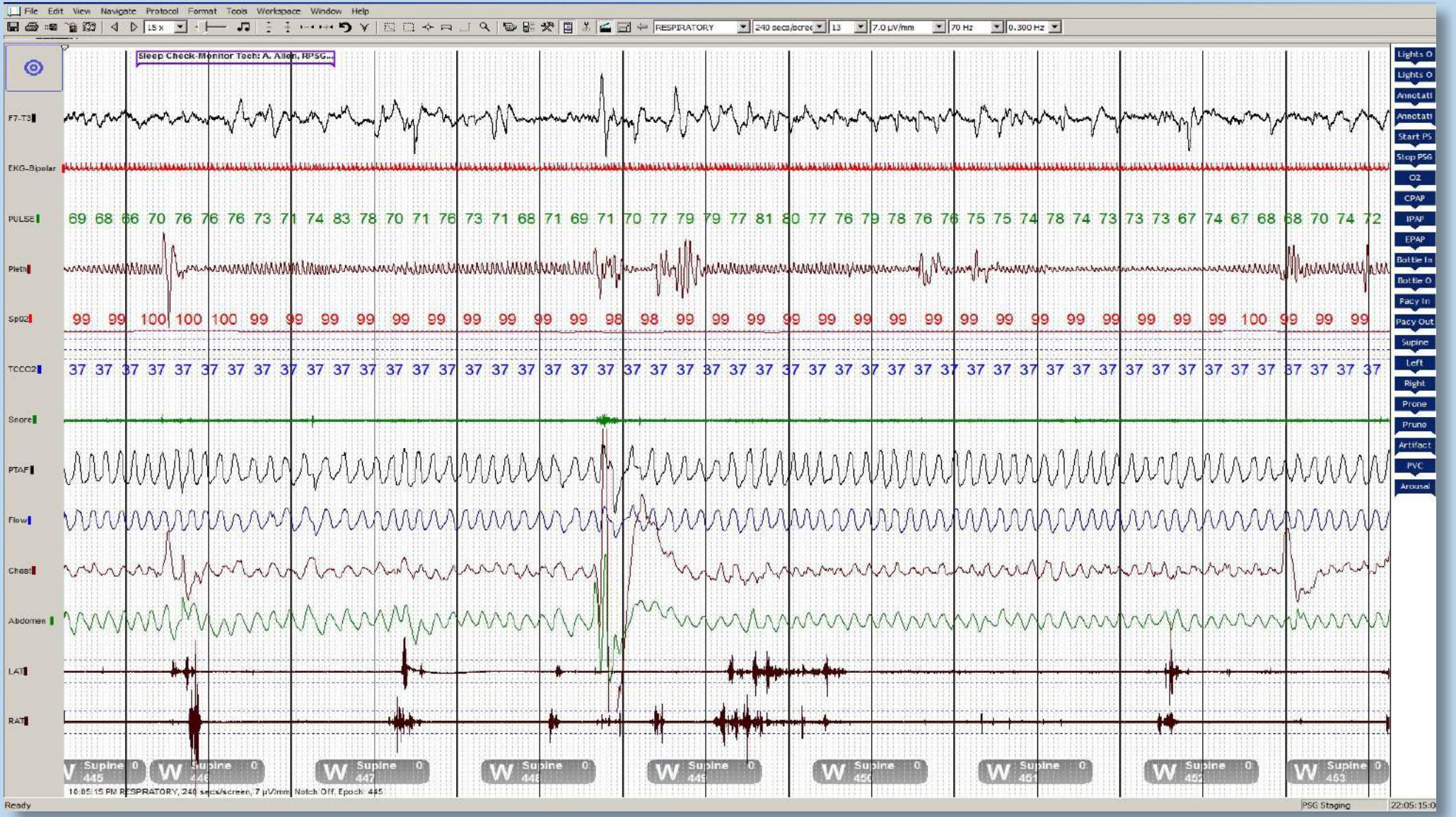
- Waxing and Waning: GI Dysfunction; Seizures; Awake Breathing Dysfunction
- Andreas Rett and Hagberg (1983): 66% “Episodic Hyperpnea”
- Breathing Dysfunction: Awake, exacerbated by stress, Cyanosis

Hyperventilation: Shallow, Fast Forceful

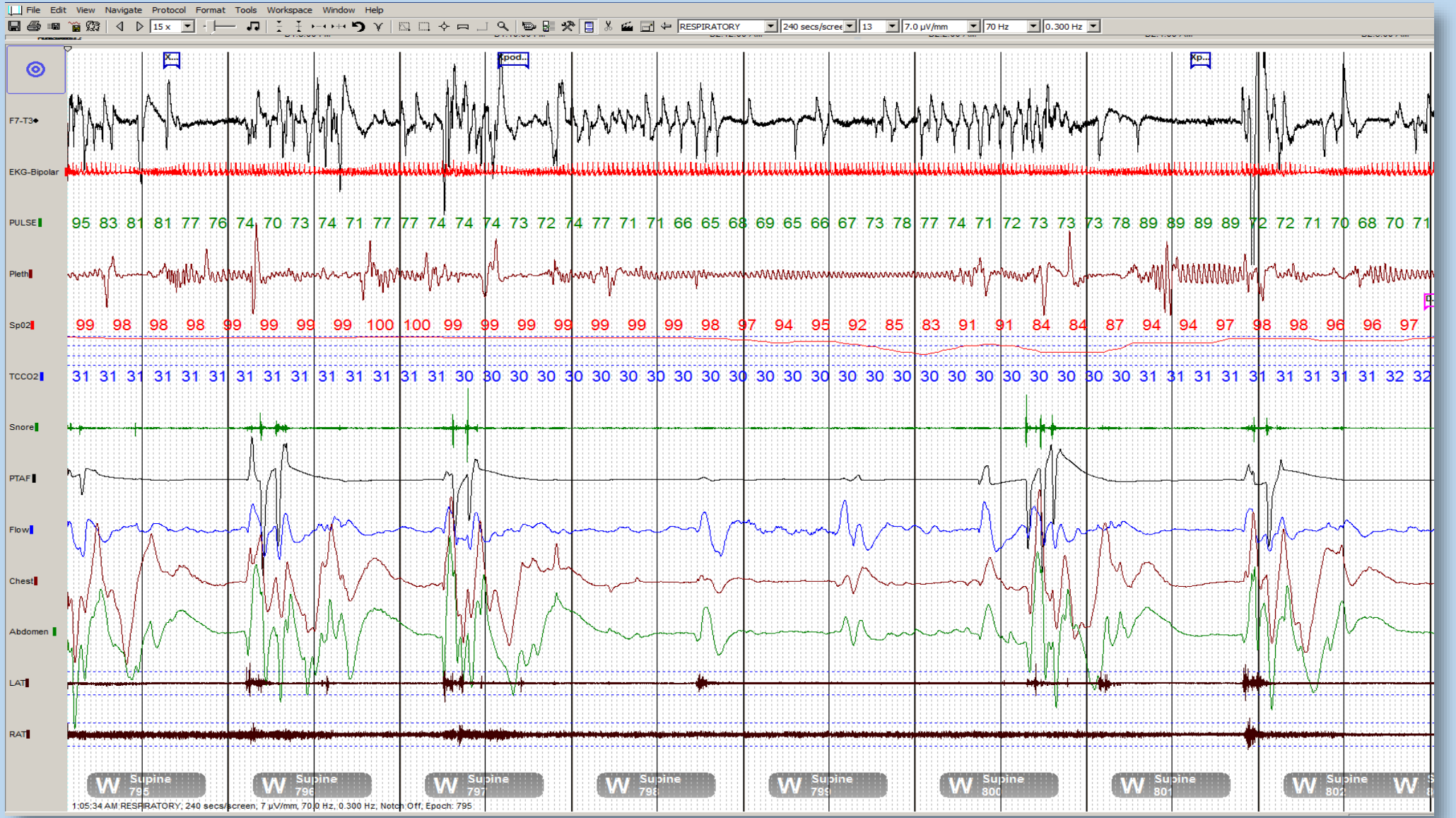
Breath holding: Apnea, Valsalva

Air Swallowing: Bloating

# Awake, typically developing adolescent



# Awake in RTT: Disorganized breathing



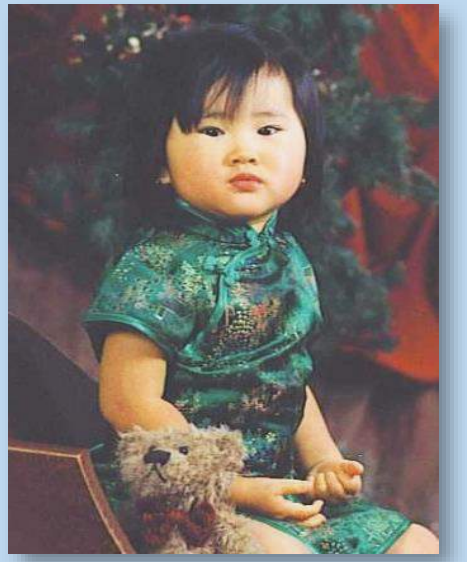
# NATURAL HISTORY STUDY


# RTT: Course of Awake Breathing Dysfunction
(Tarquinio et al 2018)

- Rett Syndrome Natural History Study
- Rare Disease Clinical Research Network
- Multicenter USA: 2006-2015
- Clinical Diagnosis (Typical, Atypical)
- MECP2 Mutational Status
- Evaluations: Every 6-12 Months
- Clinical Characteristics, Severity

# RTT: Course of Awake Breathing Dysfunction

- Enrollment: 1185 with RTT
- 985 > one visit
- 778 (of 922) Typical RTT Longitudinal F/U
- Median age diagnosis: 2.7 yr.
- Mean age recruitment: 10.2 yr. (0.7-66.5 yr.)
- Longitudinal F/U: Mean 5.5 yr. (3.2-9 yr.); 5 visits (median)



# RTT: Course of Awake Breathing Dysfunction

- At recruitment:
  - 51.5% Hx HV
  - 67.1% Hx BH
  - 47.2% Hx Air Swallowing
- Median age onset HV/BH: 3.0 yr (2-4 yr)

  75% BH/HV By Age 8.7 yr
- Highly variable (Age): Peak 6-11 yr

# RTT: Course of Awake Breathing Dysfunction

## Breathing dysfunction over time

| Age Group(years) | BH (%) | HV (%) |
|---|---|---|
| < 5 | 52.6 | 39.6 |
| **5-<10** | **65.4** | **50.6** |
| 10-<15 | 62.6 | 46.2 |
| 15-<20 | 57.1 | 45.7 |
| >20 | **51.3** | **33.8** |

- BH -Breath holds
- HV -Hyperventilation

# RTT: Course of Awake Breathing Dysfunction

- At recruitment those with no history BH/HV (428)

  70% developed HV; 83% BH; 59% Air Swallowing

- Lifetime Burden: >90%
- Point Prevalence at Annual visits:

  HV: 53.8%-68.3%

  BH: 76.6%-84.3%

  Air Swallowing: 49.2%-68.3%

# RTT: Course of Awake Breathing Dysfunction

- Detection:
  - In 25% physicians detected BH/HV not recognized by caretakers
  - In 4-7% physicians did not observe BH/HV reported by caretakers
- During 6-12 Month Period 10-20% undergo spontaneous remission
- During 6-12 Month Period 10-20% Onset of BH/HV
- Day-to-day variation unknown

# RTT: Course of Awake Breathing Dysfunction

- Severe: 20-40% (Peak age 7-10 yr.)
- Pattern over the lifespan
  - 3% Free of Awake Breathing Dysfunction
  - 60% Continuous Awake Breathing Dysfunction:
    Prone to severe HV/BH over the lifespan
  - 37% Relapsing/Remitting Course
- Worse age 3-12 years
- > Age 12 years rarely severe

# RTT: Course of Awake Breathing Dysfunction

MECP2 Mutation

- Of those with Awake Breathing Dysfunction:
  **96.8% positive**
- Not associated with specific mutation
- HV/BH occurred earlier in those with any MECP2 mutation (VS none)
- Onset BH delayed in those in milder mutation group

# RTT: Course of Awake Breathing Dysfunction

Clinical Severity:

- Clinical Severity Score (Higher values, greater clinical severity):

16.5 (no BH/HV) versus 22.0 ( with any BH/HV) p=.001

- Motor Behavior Assessment (Higher values > clinical severity)

34.5 (no BH/HV) versus 46.0 (any BH/HV) p = .001

# BH/HV Severity - 42.3% at some point had > 50% time with BH/HV

## Associated with:

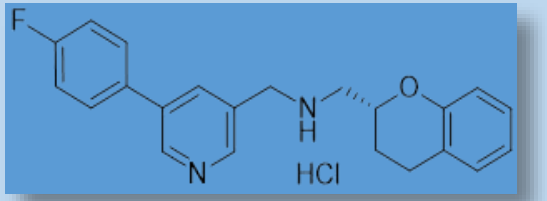
- Poorer ambulation and hand use
- Seizures, hand movements, Dystonia
- Autonomic Dysfunction
- QOL (Physical Health)
- QTc Prolongation

## Not associated:

- Race, Ethnicity, SES
- MECP2 Mutation Status,
- Age of DX RTT/Onset BH/HV
- Communication
- Frequency of hospitalizations
- Parental QOL

# RTT: Awake Breathing Dysfunction

Newron, a biotech company headquartered in Milan with offices in the US, is developing:




**Sarizotan hydrochloride** (licensed from Merck KgA) for the treatment of apnea in patients with RTT Syndrome. (phase III trial ongoing; **STARS**)

**Sarizotan** has demonstrated profound efficacy in reducing the respiratory abnormalities noted in mice models of Rett Syndrome.

**The doses** (2-10mg BID) used in the STARS trial were selected to match/exceed the exposures associated with efficacy in multiple RTT mice models.

# RTT: Course of Awake Breathing Dysfunction

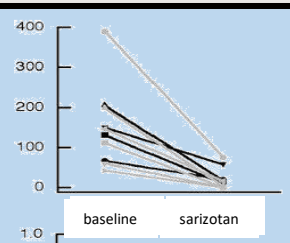
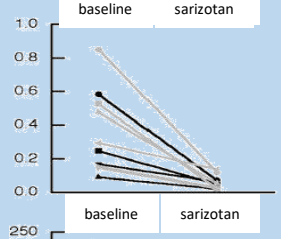
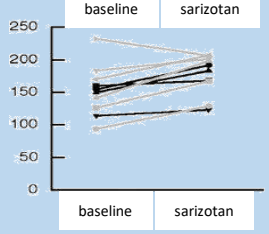
- **Sarizotan:** significantly improves breathing in the RTT/MECP2 Mouse Model
- **Sarizotan**: well tolerated in over 1,800 adults

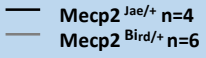
  Doses of 1-200 mg/day

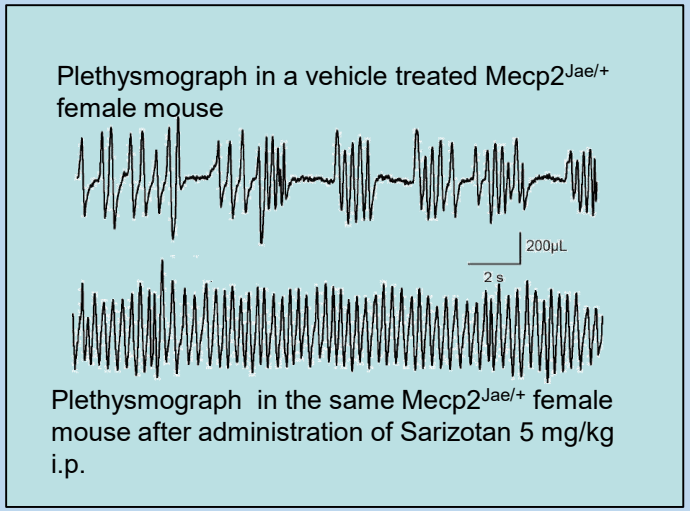
  Have been treated with sarizotan for 6 months
- *There was no evidence of any significant adverse events, increase in serious adverse events, dropouts due to adverse events, vital signs/lab/ECG abnormalities, or mortality in patients treated with sarizotan versus placebo*

# Sarizotan reduced respiratory arrythmia in pre-clinical studies

Acute treatment: Effects of single administration of Sarizotan (5 mg/kg ip) in RTT female mice (Mecp2 $^{Jae/+}$ + Mecp2 $^{Bird/+}$ )

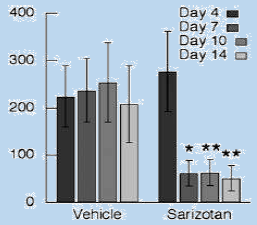
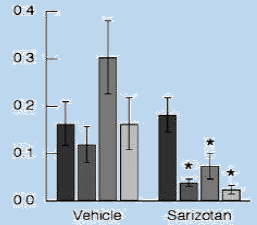
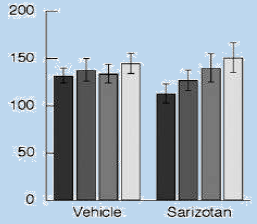
| Outcomes definition and units | Mean baseline data in vehicle treated RTT mice | Mean data in sarizotan treated RTT mice | Data from individual mice | Change vs baseline |
|---|---|---|---|---|
| **Apnea Incidence** (number apneas per hour ) | 143 ± 31 | 20 ± 8 |  | **↓ by 86% (p=0.001)** |
| **Irregularity score** (variance) | 0.34 ± 0.07 | 0.06 ± 0.01 |  | **↓ by 82% (p= 0.0001)** |
| **Respiratory Frequency** (breaths per minute) | 153 ± 12 | 177 ± 10 |  | **↑ by 16% (p = 0.012)** |




Incidence of apnea and irregularity were significantly reduced by sarizotan at 20 mins compared to vehicle

# Sarizotan reduced respiratory arrythmia in pre-clinical studies

| Outcomes definition and units | results | Change vs control (vehicle treated) group |
|---|---|---|
| **Apnea Incidence** (number apneas per hour ) |  | **↓ by 73.9% on Day 7 (p < 0.05)<br>↓ by 75% on Day 10 (p < 0.01)<br>↓ by 75.6% on Day 14 (p < 0.01)** |
| **Irregularity score** (variance) |  | **significant decrease (p<0.05)** |
| **Respiratory Frequency** (breaths per minute) |  | **ns** |

- 14-day treatment with Sarizotan (13.8 ± 1.9 mg/kg per day) was effective in improving respiration in Mecp2$^{R168X/+}$ female mice.

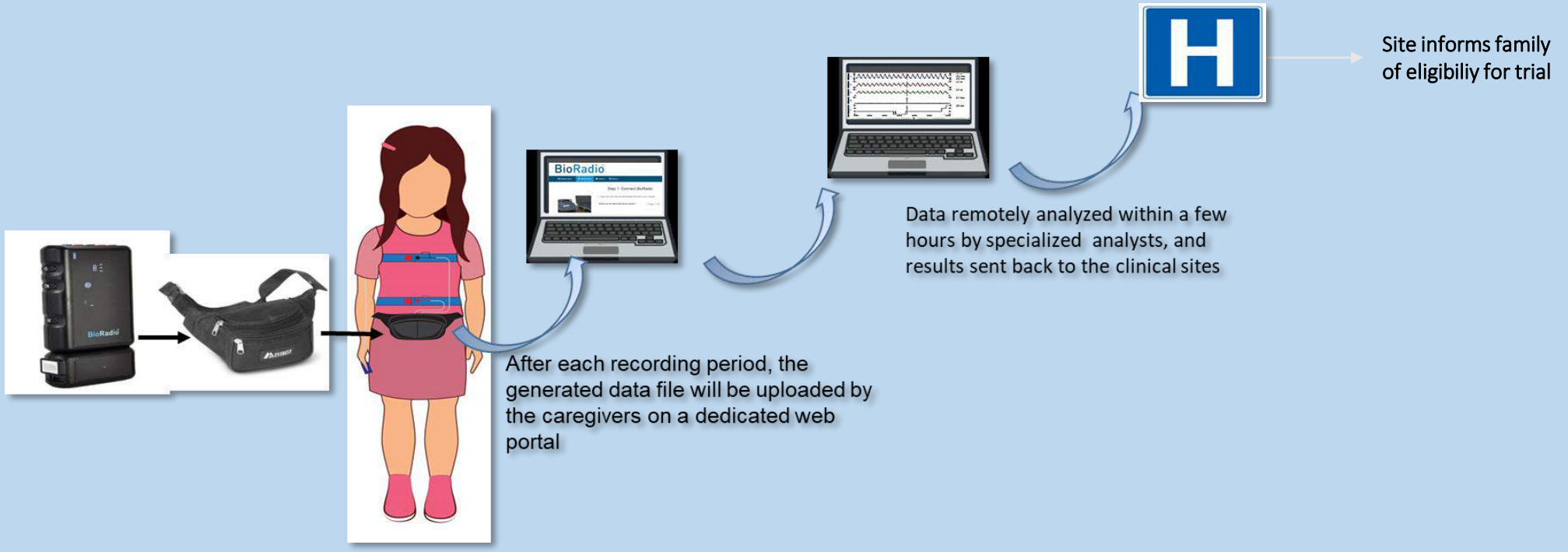
A crossover design was used so that half of the Mecp2$^{R168X/+}$ female mice (n=4) received vehicle (1.25% DMSO + 0.1% saccharin) in their drinking water and half (n=4) received sarizotan (0.0625 mg/ml). At the end of 14 days, the treatment was reversed.
30 min monitoring of respiratory pattern with plethysmography performed on the 4th, 7th, 10th and 14th day of vehicle or sarizotan. *p=<0.05, **p=<0.01 vs corresponding day receiving vehicle.

Chronic treatment: Effects of 14-day treatment with Sarizotan in RTT female mice (Mecp2$^{R168X/+}$)

# STARS - Sarizotan Treatment of Apneas in Rett Syndrome (RTT)

A randomized, double-blind, placebo-controlled, six-month study evaluating the efficacy, and safety of sarizotan in patients with Rett syndrome with respiratory symptoms in at least 129 patients.

# BioRadio™ in clinic test recording & data upload




- Recording performed at home for 6 hours/day during awake time on 3 consecutive days (up to 18 hrs of recording) in each of the first 3 weeks of the screening period.
- Data transmitted daily from device/computer to data monitoring center who review for completeness, movements, duration and number of apneas/hyperventilation, oxygen saturation.
- Investigator informed as soon as analyses confirm eligibility criteria (i.e. >10 apnea epsidoes of 10 secs or longer per hour have been recorded)
- Same procedure repeated post randomization on any 3 days in the week prior to each scheduled clinic visit at Weeks 2, 8, 16, and 24

# Respiratory abnormalities do not decline with age

- Data from first 102 patients
- Patients who experience at least 10 episodes of apnea of ≥10 sec duration per hour meet the entry criterion for STARS
- More RTT patients qualified for randomization in the older age range

| | | Age range (years) | | | |
|---|---|---|---|---|---|
| | | **< 13 Y** | **13-18 Y** | **> 18 Y** | Total (c) |
| | | N (%) | N (%) | N (%) | N |
| **Screened** | (a) | 75 (50.3 %) | 39 (26.2 %) | 35 (23.5 %) | 149 |
| **Screen failed** | (b) | 28 (59.6 %) | 11 (23.4 %) | 8 (17.0 %) | 47 |
| **Randomized** | (b) | 47 (62.7 %) | 28 (71.8 %) | 27 (77.1 %) | 102 |

*(a) % are calculated by row: N/Total screened; (b) % are calculated by column: N/Total screened in the age group; (c) Excluding 13 subject in screening phase at DLP*

# STARS: Apnea and Hyperventilation in RTT

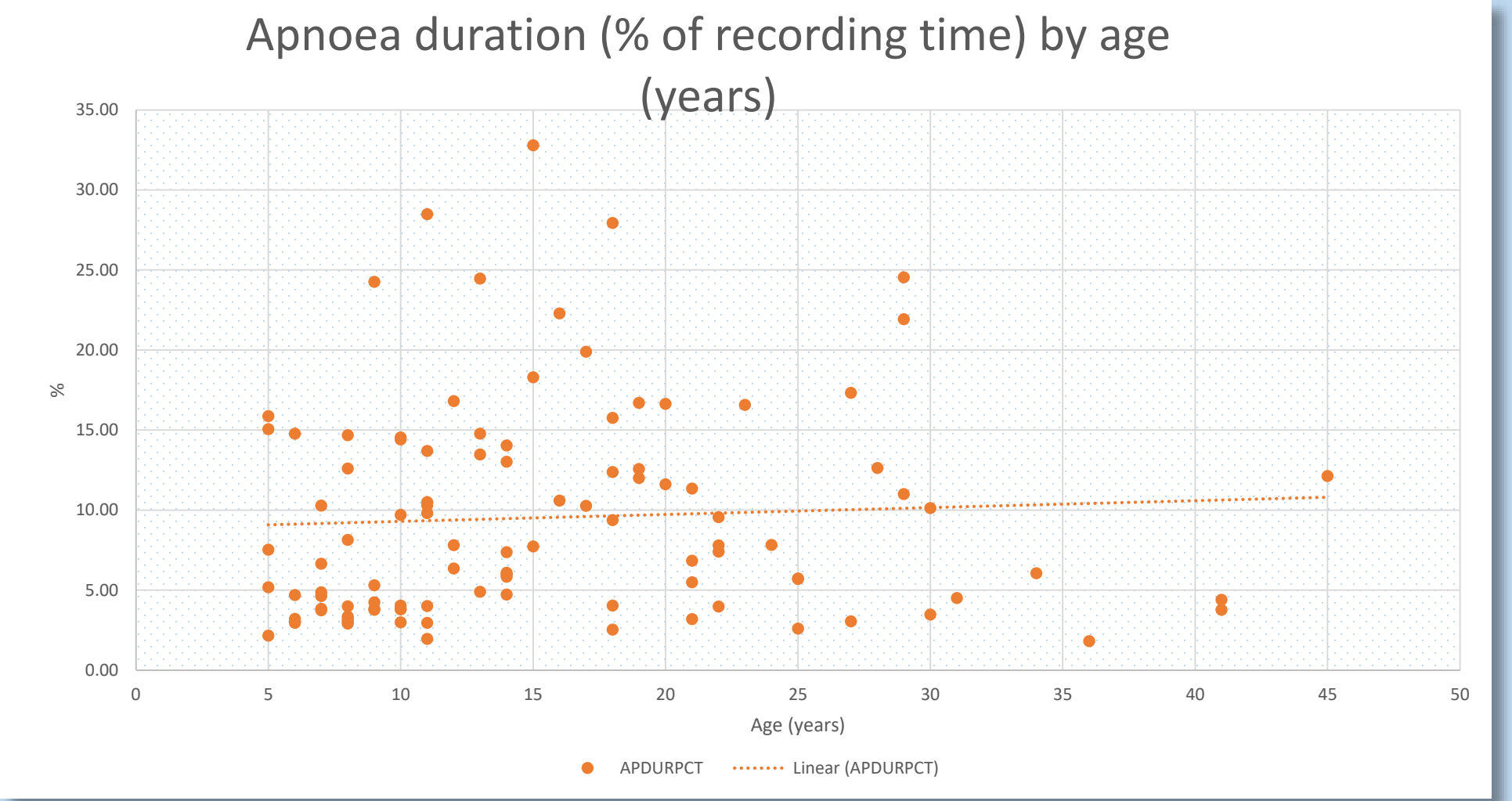
| | Apnea (> 10 secs) | | Hyperventilation | |
|---|---|---|---|---|
| **Statistics** | Episodes/h | Duration in min./h (Total) | Episodes/h | Duration in min./h (Total) |
| **N** | 102 | 102 | 102 | 102 |
| **Mean** | 22.2 | 5.7 | 14.2 | 5.0 |
| **Std Dev** | 13.5 | 4.0 | 16.1 | 6.4 |
| **Min** | 4.5 | 1.1 | 0 | 0 |
| **Max** | 62.2 | 19.7 | 74.4 | 33.1 |
| **Median** | 19.5 | 4.6 | 9.0 | 2.7 |

- Entry criterion was >10 apnea episodes of at least 10 secs per hr

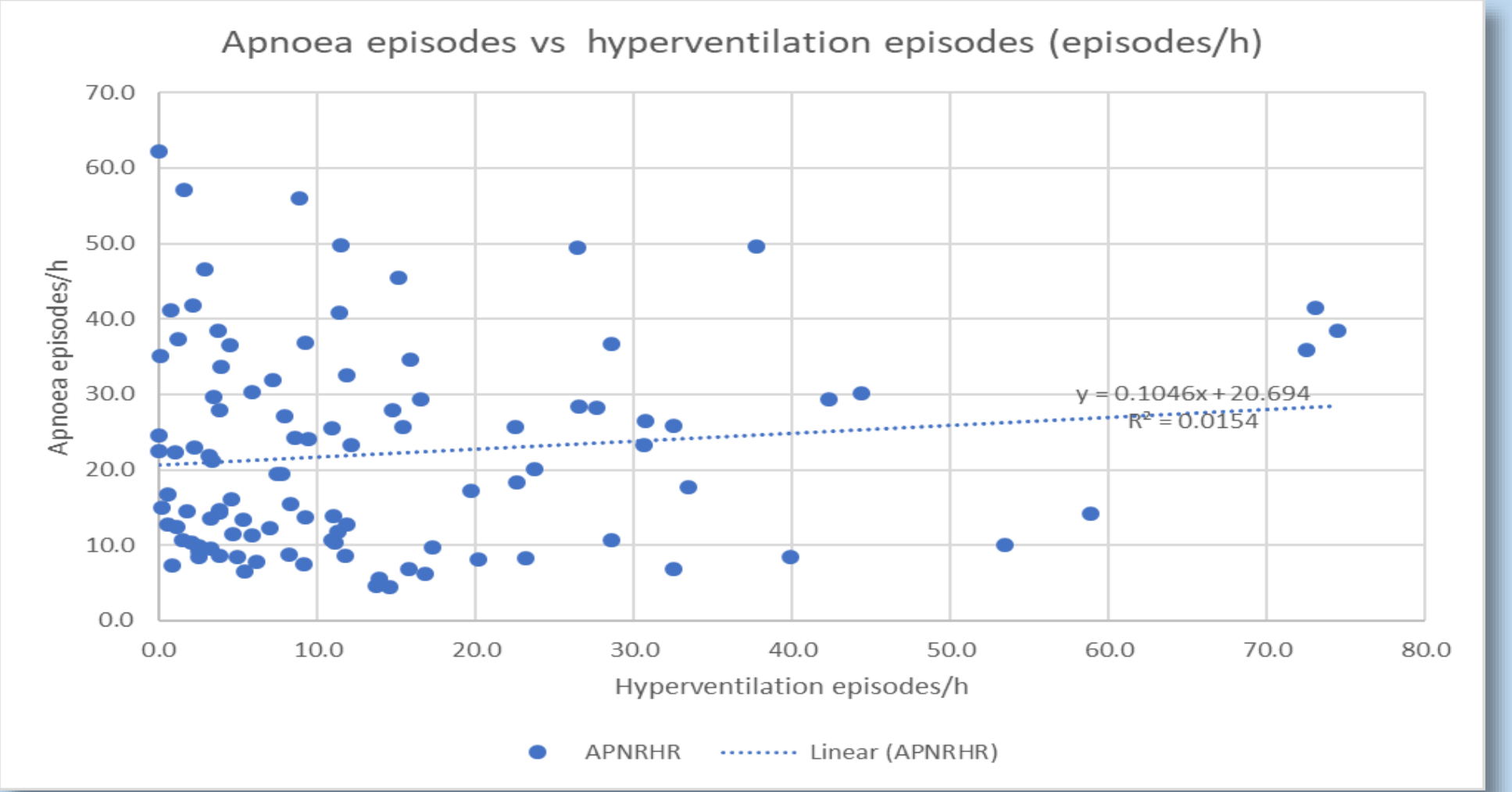
# STARS: Abnormal breathing and oxygen desaturation significant

| | Abnormal breathing | | SpO2 (<90%) | |
|---|---|---|---|---|
| **Statistics** | Episodes/h | Duration in min./h (Total) | Episodes/h | Duration in min./h (Total) |
| **N** | 102 | 102 | 102 | 102 |
| **Mean** | 36.3 | 10.8 | 4.2 | 6.9 |
| **Std Dev** | 22.3 | 7.9 | 4.3 | 9.7 |
| **Min** | 8.2 | 2.1 | 0 | 0 |
| **Max** | 114.5 | 42.4 | 24.6 | 48.7 |
| **Median** | 32.3 | 8.8 | 3.2 | 2.7 |

# Apnoea duration by age



# Relationship of Apnea to Hyperventilation in RTT Patients



# RTT: Course of Awake Breathing Dysfunction

**Summary: Natural History Study**

- Very common among RTT Individual; Variable; Age dependent
- Severe Awake Breathing Dysfunction present in 40%
- Severe Awake Breathing Dysfunction associated with worsening of Core Symptoms

# RTT: Course of Awake Breathing Dysfunction

**Summary: Natural History Study**

- Severe Awake Breathing Dysfunction associated with Long QTc Interval and may contribute to Unexpected Sudden Death
- Sudden death with no preceding symptoms has been reported in 22–26% of deaths of Rett syndrome patients compared to 2.3% in the general population of the same age (Byard, 2005)
- There is no effective treatment
- There have been no systematic attempts to quantitate these abnormalities, their time course, the associated effects on SpO2 saturation

# STARS: Course of Awake Breathing Dysfunction

- 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** (e.g. >10 episodes of >10 sec duration per hour) minimally 10% of their time is spent without breathing
- Oxygen saturation goes below 90% 4.2 -24 times per hr, duration may last a long as **48 minutes/hr**
- Contrary to some suposition there is no relationship between hyperventilation and apnea.

# STARS: Course of Awake Breathing Dysfunction

- Provides a objective means of evaluating breathing dysfunction in the home enviroment over a long period of wakefulness
- Provides quantitative as well as qualitative assessment of breathing dysfunction in RTT
- Key question is whether reduction in apnea will improve patient performance

# Thanks to the girls and women & their families!

# SARIZOTAN TREATMENT OF APNEA IN PATIENTS WITH RETT SYNDROME (STARS)

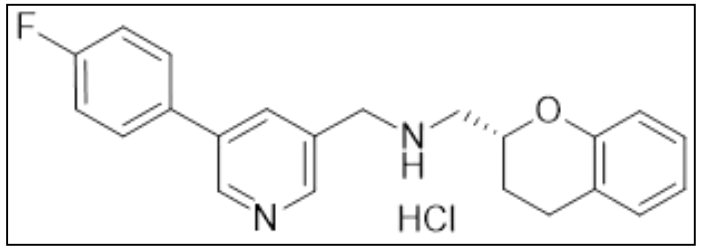
## *NEW FINDINGS FROM AN INTERNATIONAL, 6-MONTH, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III TRIAL (STARS)*

Ravi Anand, CMO

Newron Pharmaceuticals

# NEWRON AND SARIZOTAN

- Newron is developing:
  - Sarizotan hydrochloride (licensed from Merck KgA) for the treatment of apnea in patients with RTT Syndrome (phase II trial ongoing




  - Sarizotan exhibits high affinity for 5-HT1A (full agonist), D2 (partial agonist/antagonist), D3 (agonist/antagonist) and D4 (full agonist) receptors
  - *In vivo* pharmacology studies demonstrate that sarizotan has strong 5-HT1A agonism (1-3 mg/kg po). Antagonism at D2 receptors (16-20 mg/kg po). Weak D2 agonist activity ( >>10 mg/kg po)
  - Initially developed as an antipsychotic and for treatment-associated dyskinesias in Parkinson's disease; preclinical pharmacological studies provided evidence for other possible neurological and psychiatric indications

# Rett syndrome and respiration

- Rett Syndrome (RTT), an X-linked dominant neurodevelopmental disorder caused by mutations in *MECP2* (95% of cases), primarily affects females with prevalence of 1 in 10,000.
- Although the most common symptoms include seizures (60-70%), severe intellectual impairment and autistic behaviours (61%), stereotypies (>90%), and other movement disorders (30-50%), respiratory abnormalities (70%) [hyperventilation (26%), apneas (32%) and breath-holds (60%)], during waking hours (onset 3 to 5 years: peak 5 to 15 years) are the most striking feature of RTT.
- The symptoms of hyperventilation and apneas are worsened by anxiety and agitation.
- Apneas can lead to cyanosis, loss of consciousness, and progress to cardiorespiratory uncoupling which may lead to cardiorespiratory homeostasis/ prolonged QT syndrome; sudden death, anxiety and fearfulness, gastrointestinal reflux, contribute to scoliosis, and may influence normal development of the brain in younger patients.
- Sudden death with no preceding symptoms has been reported in 22–26% of deaths of Rett syndrome patients compared to 2.3% in the general population of the same age (Byard, 2005)

# Respiratory dysfunction; Natural History Study Data

- **Natural history sudies; 1205 participants, followed for 9 years (Tarquino, 2018): similar data from (Mackay, 2017)**
  - 922 classic RTT patients with MECP2 mutations were recruited (0.7-66.5 years): median age of recruitment 6.8 years
  - Over the 9 years, 52 patients died, most due to cardiorespiratory issues
  - Respiratory symptoms: median age of onset 3.0 y: peak at 6-11 years.
  - Onset (breath-holding or hyperventilation) in majority of girls was by 4 years of age: 75% developed hyperventilation by 8.7 years and breath-holding by 5.6 y
  - Parents reported: hyperventilation in 51.6%, breathholding in 67.1%, and air-swallowing in 47.2%
- Most importantly the studies indicate that 50% of patients have partial, and 15% have terminal remission of respiratory dysfunction based on caregiver/physician reports in the last 6 months before the visit.
  - *The above statement was based purely on caregiver feedback without any objective measurement of respiration*
- Only one study to date used a RIP device to measure respiration in 10 RTT patients, for a limited time, in the hospital
  - *Hospital visits worsen apnea in RTT patients, and measurements at home for longer periods of time are required*

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# Data from Natural History Study suggests a decrease in breathing dysrhythmia over time

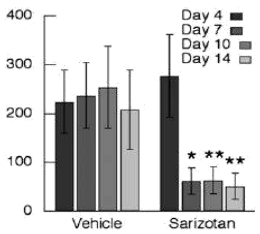
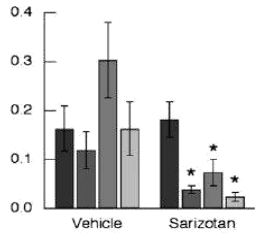
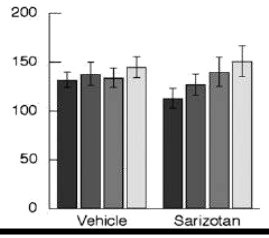
**Breathing dysrythmia over time**

| Age Group(years) | BH (%) | HV (%) |
|---|---|---|
| < 5 | 52.6 | 39.6 |
| **5-<10** | **65.4** | **50.6** |
| 10-<15 | 62.6 | 46.2 |
| 15-<20 | 57.1 | 45.7 |
| >20 | 51.3 | 33.8 |

- BH -Breath holds
- HV -Hyperventilation

# Sarizotan reduced respiratory arrythmia in pre-clinical studies (2)

**Chronic treatment: Effects of 14-day treatment with Sarizotan in RTT female mice (Mecp2$^{R168X/+}$)**

| Outcomes definition and units | results | Change vs control (vehicle treated) group |
|---|---|---|
| **Apnea Incidence** (number apneas per hour ) |  | **↓ by 73.9% on Day 7 (p < 0.05)<br>↓ by 75% on Day 10 (p < 0.01)<br>↓ by 75.6% on Day 14 (p < 0.01)** |
| **Irregularity score** (variance) |  | **significant decrease (p<0.05)** |
| **Respiratory Frequency** (breaths per minute) |  | **ns** |

- 14-day treatment with Sarizotan (13.8 ± 1.9 mg/kg per day) was effective in improving respiration in Mecp2$^{R168X/+}$ female mice.

A crossover design was used so that half of the Mecp2$^{R168X/+}$ female mice (n=4) received vehicle (1.25% DMSO + 0.1% saccharin) in their drinking water and half (n=4) received sarizotan (0.0625 mg/ml). At the end of 14 days, the treatment was reversed.
30 min monitoring of respiratory pattern with plethysmography performed on the 4th, 7th, 10th and 14th day of vehicle or sarizotan. *p=<0.05, **p=<0.01 vs corresponding day receiving vehicle.

# Selection of doses for RTT patients based on PK/PD data from RTT mice

Effective plasma concentrations in mice (respiratory symptoms), corresponding human doses, and estimate of the doses to be used in RTT patients

| Effective doses in RTT mice [a] | Plasma levels in mice at effective doses [b] | Single dose in humans (HV) [c] that approximates exposures in RTT mice | Corresponding plasma levels in humans (HV) [c] | Estimated dose for RTT girls of 25-50 kg body weight |
|---|---|---|---|---|
| **5 mg/kg** (acute study) | $C_{max}$ (ng/ml) **269** | **2 mg** **(0.028 mg/kg)** | $C_{max}$ (ng/ml) **170.5 (108 – 274)** | **0.7 – 1.4 mg** |
| | AUC (ng/ml/h) **1070** | | AUC (ng/mlxh) **497.9 (304.2-1224)** | |
| **14 mg/kg/day** (long-term study) | $C_{max}$ (ng/ml) **753** | **10 mg** **(0.137 mg/kg)** | $C_{max}$ (ng/ml) **488 (410-721)** | **3.4 – 6.85 mg** |
| | AUC (ng/ml/h) **2996** | | AUC (ng/mlxh) **2775 (1997- 3731)** | |

(a) Effective doses in RTT mice are taken from *Abdala et al., Am J Respir Cell Mol Biol. 2014 Jun;50(6):1031-9*

(b) Plasma levels at the effective doses are extrapolated from ***TK study EMD 128130-PKM 15-98***

(c) Doses and plasma levels in healthy volunteers (HV) are taken from ***study EMR 62225 – 021*** and ***study EMD 128 130-001***

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# Overview of Sarizotan safety data

- Doses selected for the STARS trial will be associated with Cmax >488 and AC >2775ng/hr/mL that were associated with efficacy in multiple RTT mice models.
- Highest projected Cmax at 10mg in RTT patients is 0.017μM (unbound fraction): no effect likely on hERG (IC50 1.95 μm), or APD/QT prolongation (60 μm).
- Doses of 2-10mg BID were well tolerated in over 1800 adult subjects who received sarizotan at doses of 1-200mg/day in clinical trials in healthy volunteers – 23 studies, patients with schizophrenia – 1 study, or Parkinson's Disease – 4 studies
- Greater than 1800 patients have been treated with sarizotan for 6 months, > 400 for 1 year, >200 for 2 years, >150 for 3 years) at doses of 1 – 200 mg/day.
- *There was no evidence of any significant treatment-related adverse outcomes and no increase in SAEs, discontinuations due to AEs, vital signs/lab/ECG abnormalities, or mortality in patients treated with sarizotan versus placebo*

# STARS sites – international, multi-centre trial

14 sites Worldwide

5 in US (Texas, Chicago, Alabama, Chicago, San Diego, St Paul Minnesota),

1 UK (London)

2 in Italy (Siena and Milan),

5 India (Kolkata, New Delhi, Mumbai (2), Kochi), 1 UK (London), 1 AUS (Perth)

1 Australia (Perth)

# STARS - Sarizotan Treatment of Apneas in Rett Syndrome (RTT)

- The sarizotan protocol (STARS) and program has been discussed and approved by Health Authorities in UK, Germany, Sweden, Spain, Canada, CHMP, and US.
- STARS is a randomized, double-blind, placebo-controlled, six-month study evaluating the efficacy, and safety of sarizotan in patients with Rett syndrome with respiratory symptoms in at least 129 patients.
- STARS includes:
  - Females and males ≥ 4 years, body weight ≥ 10 kg meeting RTT consensus clinical criteria (Neul et al, 2010), confirmed by MECP2 mutations (Xq28)
  - Patients meet all of the following criteria related to breathing abnormalities:
    - ≥10% of the time should be with abnormal breathing
    - Has at least 10 episodes of breathing dysrhythmia, defined by episodes ≥10 seconds of breath holding (apnea), per hour during cardiorespiratory monitoring (performed with home/ambulatory monitoring system - BioRadio™).

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# EFFICACY OUTCOMES

## PRIMARY

- **PERCENT REDUCTION IN THE NUMBER OF APNEA EPISODES (EACH ≥ 10 SECONDS) PER HOUR.**
  - Primary efficacy variable to be calculated from data from home cardiorespiratory monitoring using BioRadio™ (sent by WiFi /Internet)
  - Measurements to be performed for 6-hr per day, during time awake, on any 3 days during the week:
    - *Screening*: Weeks 1, 2 and 3 – evaluation for I/E criteria
    - *Initial Treatment Period*: Weeks 2, 8, 16 and **24** - in week prior to visit
    - *Extension Treatment Period:* Weeks 24, 32, 40 and 48 - in week prior to visit
  - Data from all 3 days with complete (up to 6-hr) recording in the week prior to each visit will be averaged and used in calculating the value for the primary efficacy outcome

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# EFFICACY OUTCOMES (2)

## Key Secondary

- **Caregiver-rated Impression of Change (CIC)**:
  - Caregiver to rate how much the patient's illness has improved or worsened relative to the baseline state using 7-point scale ( 1 = very much improved to 7 = very much worse, with 4 = no change);
  - Ratings, performed in consultation with the Investigator, to be based on changes in the following domains: **Respiratory Symptoms , Activities, Communication, Behavior** and **Participation**

## Other Secondary

- **Respiratory Measures** (from home monitoring using BioRadio):
  - Percent time spent with breathing dysrhythmia (% time apnea + % time hyperventilation )per hour;
  - Number of hyperventilation episodes(≥10 seconds each) per hour
  - Oxygen saturation (# of episodes of oxygen desaturation below 90% per hour)
  - *Respiratory Distress Index* – breath-holding + hyperventilation + oxygen saturation < 90%
  - Incidence of breathing dysrhythmia
- **Heart beat variables**: heart rate
- **Motor-Behavioral Assessment Scale**
- **Clinical Global Impression of Change**(CGI-C) – clinician-rated change from baseline
- **Caregiver Top 3 Concerns** (severity of each rated using 100-mm Visual Analogue Scale)
- **Rett syndrome Clinical Severity Scale** (RCSS)

# Determining respiratory dysfunction for eligibility

- This is the **first large scale prospective clinical trial** to use **objective measurement** of respiration
  - At screening, feedback/observation from parents will be used to determine eligibility to start screening process of patients after signing of the ICF.
  - Parents and patients instructed on the correct use of the BioRadio™ system for home monitoring of cardiorespiratory parameters
  - Patients monitored at home using the device for 6 hours/day during awake time on any 3 days (up to 6 hr/day) in each of the first 3 weeks of the screening period.
  - Data collected are transmitted via the Internet to the central data monitoring center (Vivonoetics) to confirm correct use of the device, and determine if patient meets respiratory selection criteria.
  - Patients who experience at least 10 episodes of apnea of ≥10 sec duration per hour) during the 4-week screening period, meet the entry criterion for the number of episodes of apnea
  - Measurements must confirm at least 10% of time with abnormal breathing

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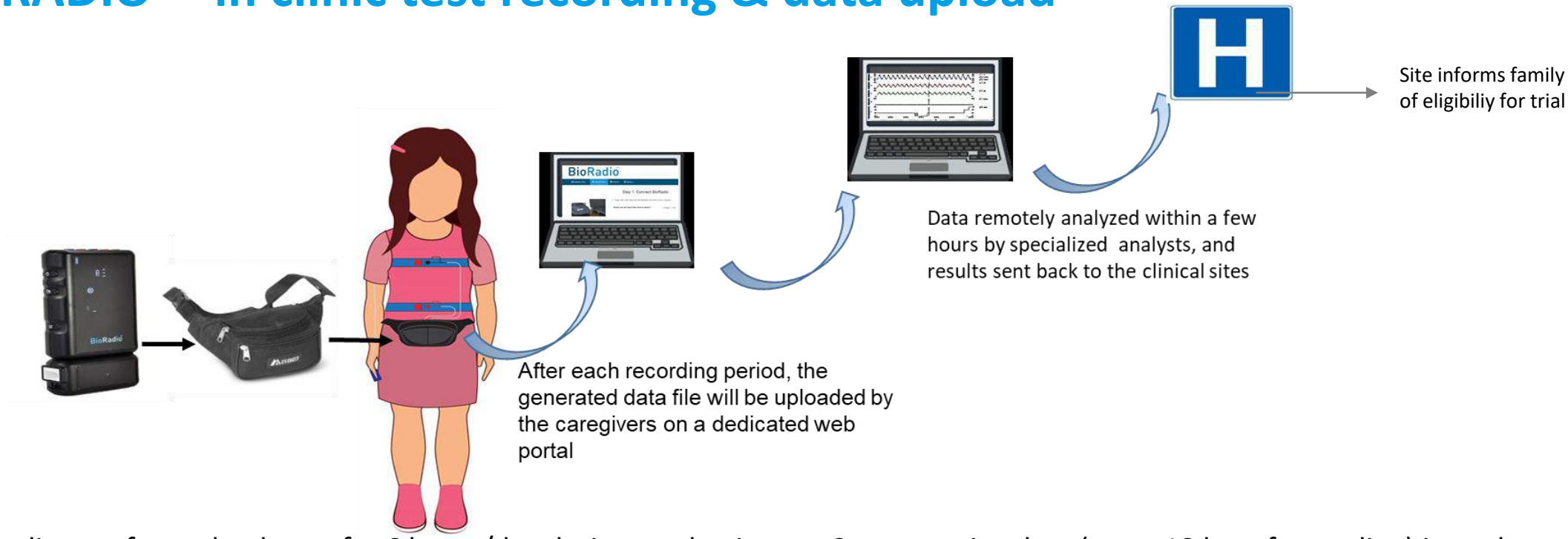
# BIORADIO™ in clinic test recording & data upload




- Recording performed at home for 6 hours/day during awake time on 3 consecutive days (up to 18 hrs of recording) in each of the first 3 weeks of the screening period.
- Data transmitted daily from device/computer to data monitoring center who review for completeness, movements, duration and number of apneas/hyperventilation, oxygen saturation.
- Investigator informed as soon as analyses confirm eligibility criteria (i.e. >10 apnea epsidoes of 10 secs or longer per hour have been recorded)
- Same procedure repeated post randomization on any 3 days in the week prior to each scheduled clinic visit at Weeks 2, 8, 16, and 24

# STARS UPDATE

- **Recruitment Status**
  - All investigators informed of extension of recruitment to end Nov
  - There are 182 patients screened (as of Oct 24)
  - 116 randomized,  9 in screening (including 4 BioRadio qualified)
  - 57 screen failures  (41 failed based on bio-radio performance)
  - 71 patients have completed the first 6 months, and 63 have continued into the open label extension.
  - 14 patients have discontinued from double-blind treatment (7 due to AE, 6 Withdrawn consent, 1 other – caregiver decision) and 16 have discontinued from open-label treatment.

- **Timeline LPLV 3Q 2019**

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# STARS: BASELINE CHARACTERISTICS

# Respiratory abnormalities do not decline with age

- Data from first 102 patients
- Patients who experience at least 10 episodes of apnea of ≥10 sec duration per hour meet the entry criterion for STARS
- More RTT patients qualified for randomization in the older age range

| | | Age range (years) | | | |
|---|---|---|---|---|---|
| | | **< 13 Y** | **13-18 Y** | **> 18 Y** | Total (c) |
| | | N (%) | N (%) | N (%) | N |
| **Screened** | (a) | 75 (50.3 %) | 39 (26.2 %) | 35 (23.5 %) | 149 |
| **Screen failed** | (b) | 28 (59.6 %) | 11 (23.4 %) | 8 (17.0 %) | 47 |
| **Randomized** | (b) | 47 (62.7 %) | 28 (71.8 %) | 27 (77.1 %) | 102 |

*(a) % are calculated by row: N/Total screened; (b) % are calculated by column: N/Total screened in the age group; (c) Excluding 13 subject in screening phase at DLP*

# Most common associated conditions in RTT patients increase with age

| | | Age range (years) | | | |
|---|---|---|---|---|---|
| | | **< 13 Y** (N=47) | **13-18 Y** (N=28) | **> 18 Y** (N=27) | Total (N=102) |
| | | n (%)* | n (%)* | n (%)* | n (%)* |
| **Nervous system disorders** | Seizure/epilepsy | 33 (70.2 %) | 23 (82.1 %) | 27 (100 %) | 84 (82.3 %) |
| **Gastrointestinal disorders** | Constipation/Bowel | 20 (42.6 %) | 18 (64.3 %) | 22 (81.5 %) | 60 (58.5 %) |
| | Gastroesophageal condition | 13 (27.7 %) | 13 (46.4 %) | 19 (70.4 %) | 46 (45.0 %) |
| **Musculoskeletal and connective tissue disorders** | Scoliosis | 8 (17.0 %) | 14 (50.0 %) | 19 (70.4 %) | 41 (40.2 %) |

# Abnormal breathing and oxygen desaturation significant

| | Abnormal breathing | | SpO2 (<90%) | |
|---|---|---|---|---|
| **Statistics** | Episodes/h | Duration in min./h (Total) | Episodes/h | Duration in min./h (Total) |
| **N** | 102 | 102 | 102 | 102 |
| **Mean** | 36.3 | 10.8 | 4.2 | 6.9 |
| **Std Dev** | 22.3 | 7.9 | 4.3 | 9.7 |
| **Min** | 8.2 | 2.1 | 0 | 0 |
| **Max** | 114.5 | 42.4 | 24.6 | 48.7 |
| **Median** | 32.3 | 8.8 | 3.2 | 2.7 |

# Respiratory abnormalities, Rett syndrome, and new learnings from the STARS clinical trial

- The natural history studies point to the fact that respiratory symptoms start early in these patients (minimum 0.7 years: median 3 years), quickly become prominent and dramatic, and wane over time
- There have been no systematic attempts to quantitate these abnormalities, their time course, the associated effects on SpO2 saturation
- Natural history studies suggest that up to 50% of patients experience remission from respiratory abnormalities and these are unlikely to be present in older patients
- 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** (e.g. >10 episodes of >10 sec duration per hour) minimally 10% of their time is spent without breathing
- Oxygen saturation goes below 90% 4.2 times per hr, duration may last a long as **48 minutes/hr**
- Contrary to some suposition there is no relationship between hyperventilation and apnea.
- Key question is whether reduction in apnea will improve patient performance
- 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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# Spectrum of Treatment Resistant Schizophrenia: New Therapeutic Mechanisms

John M. Kane, M.D.

Professor and Chairman
Department of Psychiatry
The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

# Defining treatment-resistant schizophrenia

- National and international treatment guidelines are broadly aligned on the definition of treatment-resistant schizophrenia (TRS)[1-3]

| Guideline | Prior antipsychotic treatment failures | Treatment duration | Failure criteria |
|---|---|---|---|
| APA (2004)[1] | ≥2 failures, ≥1 atypical antipsychotic | ≥6 weeks | Little or no symptomatic response to a trial of adequate duration and dose (therapeutic range) |
| NICE (2014)[2] | ≥2 sequential failures, ≥1 non-clozapine atypical antipsychotic | 4–6 weeks | Illness has not responded adequately, despite established adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration |
| WFSBP (2012)[3] | ≥2 failures, ≥2 different chemical classes, ≥1 atypical antipsychotic | 2–8 weeks | No significant improvement in psychopathology and/or target symptoms; assured treatment adherence |

**Common definition of TRS: No significant improvement in target symptoms after treatment with ≥2 different antipsychotics (at an adequate dose and duration)**

APA=American Psychiatric Association; TRS=treatment-resistant schizophrenia;
NICE=National Institute for Health and Care Excellence; WFSBP=World Federation of Societies of Biological Psychiatry

1. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56; 2. National Institute for Health and Care Excellence. nice.org.uk/guidance/cg178;
3. Hasan et al. World J Biol Psychiatry 2012;13:318–378

# Prevalence of treatment resistance within schizophrenia

More than 21 million people worldwide are affected by schizophrenia[1]

Over 60 different types of atypical and typical antipsychotic treatments for schizophrenia are used globally, with 15–40 being available in any single country[2]

Despite the variety of antipsychotics available, a considerable proportion of patients suffering from schizophrenia remain severely ill and resistant to treatment[3]

At the onset of illness, rates of primary treatment resistance have been shown to be up to 23%[4]

Overall, 10–30% of patients have little or no response to antipsychotic medications, and up to an additional 30% of patients have partial responses to treatment[3]

1. World Health Organization. who.int/mediacentre/factsheets/fs397/en/; 2. Bruijnzeel et al. Asian J Psychiatr 2014;11:3–7;
3. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56; 4. Lally et al. Psychol Med 2016;46(15):3231–3240

# Burden of TRS

- TRS has severe clinical and economic impacts on patients, families, and society as a whole

## Patient burden[1,2]

- Worse disease course; poorer scores on measures of psychopathology, psychosocial functioning, and cognitive performance
- Adverse treatment effects
- Comorbidities
- Suicidal ideation

## Caregiver burden[3]

- Many hours spent care-giving; caregiver burden in a study of patients with psychoses[a] included approximately half a full-time working week spent on care-related activities
- Mental health problems
- Reduced productivity
- Strain on relationships

## Social burden[1,2,4]

Higher rates of:

- Unemployment
- Homelessness
- Aggressive behaviour
- Substance abuse

## Economic burden[2,3]

- Longer/more frequent hospitalisations
- Higher healthcare resource utilisation
- Absenteeism
- Costs to families and carers

[a]This study was not specific to TRS, and included a total of 107 patients; 81 patients (76%) had a diagnosis of schizophrenia, while 26 patients (24%) had other forms of psychotic disorder

TRS=treatment-resistant schizophrenia

1. Iasevoli et al. Prog Neuropsychopharmacol Biol Psychiatry 2016;65:34–48; 2. Kennedy et al. Int Clin Psychopharmacol 2014;29(2):63–76;
3. Flyckt et al. Int J Soc Psychiatry 2011;59(2):137–146; 4. Jones & Castle. S Afr Psychiatry Rev 2006;9:17–23

# TRRIP working group consensus criteria for assessment and definition of TRS

| The optimum requirements put forward by the TRRIP working group include:[1] | |
|---|---|
| | Prospective evaluation of treatment using a standardised rating scale (e.g., PANSS, BPRS, SANS, SAPS) |
| | At least moderate disease severity and <20% symptom reduction during a prospective trial or observation of ≥6 weeks |
| | At least moderate functional impairment measured using a validated scale (e.g., SOFAS) |
| | An illness duration of ≥12 weeks |
| | Information about past treatment response to be gathered from patient/carer reports, staff and case notes, pill counts, and dispensing charts |
| | ≥2 prior treatments with different antipsychotics, of ≥6 weeks at a therapeutic dosage (equivalent to ≥600 mg of chlorpromazine per day); ≥1 prior treatment utilises a long-acting injectable antipsychotic (for ≥4 months) |
| | ≥80% of prescribed doses taken; adherence should be assessed using at least two sources; trough antipsychotic serum levels measured on ≥2 occasions separated by ≥2 weeks |

BPRS=Brief Psychiatric Rating Scale; PANSS=Positive and Negative Syndrome Scale; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SOFAS=Social and Occupational Functioning Scale; TRS=treatment-resistant schizophrenia

1. Howes et al. Am J Psychiatry 2016;174(3):216–229

# Clinical and pathophysiological heterogeneity within TRS

**Observed response to antipsychotic treatment**

**Initial response, but treatment resistance develops over time**

**Antipsychotic re-challenge in previous responders is associated with attenuated response[1]**

**30–60%** of patients eventually become resistant or only partially responsive to treatment[2,3]

**No initial response**

**10–23%** of patients have TRS from illness onset[2-4]

Patients who do not improve early are unlikely to respond later[5]

**TRS may represent separate schizophrenia subtypes,[6,7] with different neurobiology, psychopathology and clinical course[8,9]**

TRS=treatment-resistant schizophrenia

1. Agid et al. Neuropsychopharmacology 2014;39:S373–S374; 2. Lally et al. Psychol Med 2016;46(15):3231–3240; 3. Lieberman. J Clin Psychiatry 1999;60(Suppl 12):9–12; 4. Demjaha et al. Psychol Med 2017 [Epub]; 5. Samara et al. Am J Psychiatry 2015;172(7):617–629; 6. Gillespie et al. BMC Psychiatry 2017;17:12; 7. Farooq et al. Schizophr Bull 2013;39(6):1169–1172; 8. Iasevoli et al. Prog Neuropsychopharmacol Biol Psychiatry 2016;65:34–48; 9. Mouchlianitis et al. Lancet Psychiatry 2016;3(5):451–463

# Results of a longitudinal study: predictors for TRS

- A ten-year longitudinal, population-based study followed 323 first-episode psychosis patients
- Data were collected on severity of symptoms, antipsychotic treatment, and treatment adherence, to determine the presence, course, and predictors of treatment resistance

**74 patients (23%) were treatment-resistant**

**62 were treatment-resistant from illness onset**

Predictors for treatment resistance from onset included:

- Diagnosis of schizophrenia
- Younger age at onset
- Presence of negative symptoms
- Longer duration of untreated psychosis

**12 had a delayed onset of treatment resistance**

Patients with a delayed onset of treatment resistance had:

- A diagnosis of schizophrenia
- An older age at onset by approximately 4 years
- Developed treatment resistance, on average, 5 years after initial treatment, and after 4 hospital admissions

50 of the 74 patients who were treatment-resistant received clozapine:

- 14 responded to clozapine
- 12 were clozapine-resistant
- For 24 patients, either a suboptimal trial, or insufficient data prevented a clozapine response from being determined

TRS=treatment-resistant schizophrenia

1. Demjaha et al. Psychol Med 2017;47(11):1981–1989

# Summary

Treatment guidelines internationally are broadly aligned on the definition of TRS[1-3]

- TRS is commonly defined as no significant improvement in target symptoms after treatment with ≥2 different antipsychotics (at an adequate dose and duration)

TRS is highly prevalent and has severe clinical and economic impacts on patients, families, and society as a whole[4-7]

TRRIP consensus guidelines have been published for the identification and terminology of TRS, with the aim of facilitating more consistent research[8]

Patients with TRS may have different clinical paths to resistance[9,10]

Risk factors for TRS differ from schizophrenia that responds to $D_2$ antagonists, and include younger age at first diagnosis, rural living, previous suicide attempts, and inpatient status at the onset of psychosis[11]

TRS=treatment-resistant schizophrenia

1. Hasan et al. World J Biol Psychiatry 2012;13:318–378; 2. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56; 3. National Institute for Health and Care Excellence. nice.org.uk/guidance/cg178;
4. Iasevoli et al. Prog Neuropsychopharmacol Biol Psychiatry 2016;65:34–48; 5. Kennedy et al. Int Clin Psychopharmacol 2014;29(2):63–76; 6. Flyckt et al. Int J Soc Psychiatry 2011;59(2):137–146;
7. Jones & Castle. S Afr Psychiatry Rev 2006;9:17–23; 8. Howes et al. Am J Psychiatry 2016;174(3):216–229; 9. Lally et al. Psychol Med 2016;46(15):3231–3240;
10. Lieberman. J Clin Psychiatry 1999;60(Suppl 12):9–12; 11. Wimberley et al. Lancet Psychiatry 2016;3(4):358–366

# The neurobiology of TRS

- It has been suggested that TRS may constitute one or more distinct subtypes of schizophrenia,[1,2] with different underlying neurobiology[3]
- Research has generated several hypotheses regarding the underlying neurobiology[4-6]

TRS=treatment-resistant schizophrenia

1. Gillespie et al. BMC Psychiatry 2017;17:12; 2. Farooq et al. Schizophr Bull 2013;39(6):1169–1172;
3. Iasevoli et al. Prog Neuropsychopharmacol Biol Psychiatry 2016;65:34–48; 4. Howes & Kapur. Br J Psychiatry 2014;205(1):1–3;
5. Suzuki et al. Psychiatry Res 2015;227(2–3):278–282; 6. Šagud. Psychiatr Danub 2015;27(3):319–326

# Biological hypotheses for TRS

One hypothesis suggests that patients who respond to $D_2$ antagonists show a hyperdopaminergic profile, whilst patients with TRS show a normodopaminergic profile[1]

Another hypothesis is that the development of dopamine supersensitivity psychosis (DSP) leads to treatment resistance[2]

Other hypotheses suggest that TRS could be associated with abnormalities in other systems (e.g., glutamate neurotransmission, and the immune system)[3]

TRS=treatment-resistant schizophrenia

1. Howes & Kapur. Br J Psychiatry 2014;205(1):1–3; 2. Suzuki et al. Psychiatry Res 2015;227(2–3):278–282; 3. Šagud. Psychiatr Danub 2015;27(3):319–326

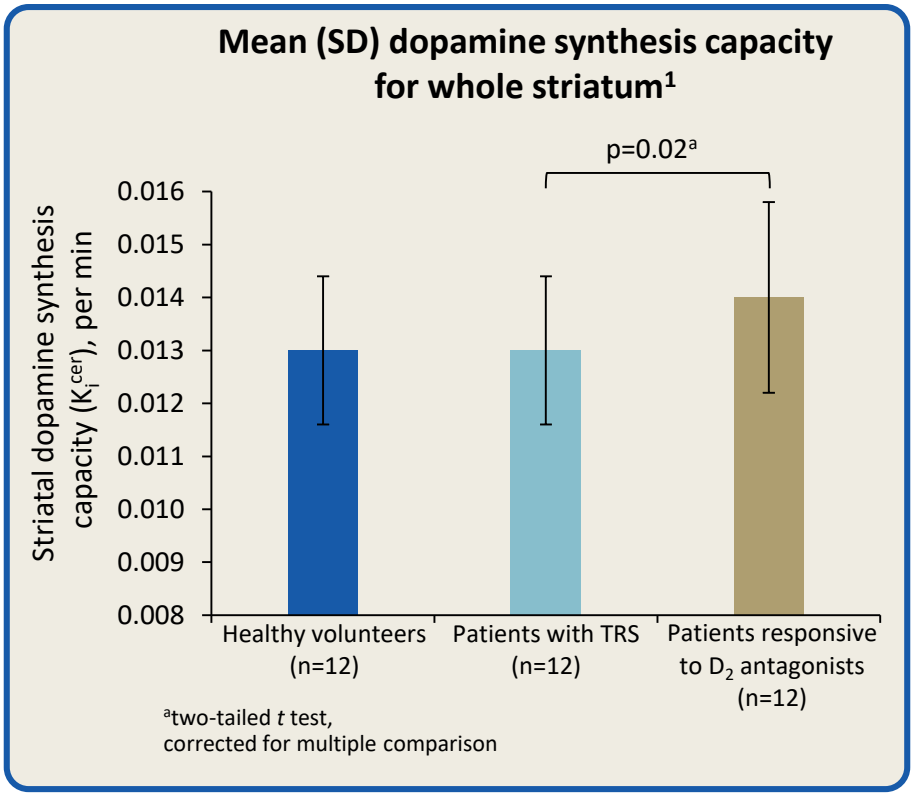
# Hyperdopaminergic profile hypothesis

| | |
|---|---|
| **Hyperdopaminergic (type A) profile:[1]** | The type A profile is characterised by elevated striatal dopamine synthesis and release capacity[1], along with a higher density of dopaminergic synapses[2] |
| | Patients with the type A profile show a good response to dopamine $D_2$ blocking antipsychotics[1,3,4] |
| **Normodopaminergic (type B) profile:[1]** | The type B profile does not exhibit elevated striatal dopamine synthesis and release capacity,[1] and dopaminergic synapse density does not differ from controls[2] |
| | Patients with the type B profile do not respond to dopamine $D_2$ blocking drugs[1,3,4] |

1. Howes & Kapur. Br J Psychiatry 2014;205(1):1–3; 2. Roberts et al. Synapse 2009;63(6):520–530;
3. Demjaha et al. Am J Psychiatry 2012;169(11):1203–1210; 4. Abi-Dargham et al. Proc Natl Acad Sci USA 2000;97(14):8104–8109

# Dopamine synthesis capacity in TRS

- Data suggest that patients with TRS may:[1]
  - Have a normal dopamine synthesis capacity
- By contrast, patients who respond to $D_2$ antagonists exhibit increased capacity for dopamine synthesis[1]

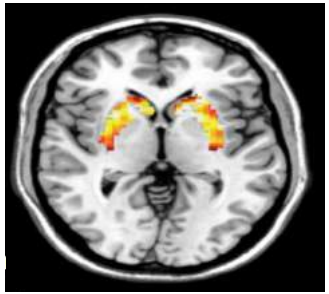



PET=positron emission tomography; SD=standard deviation; TRS=treatment-resistant schizophrenia

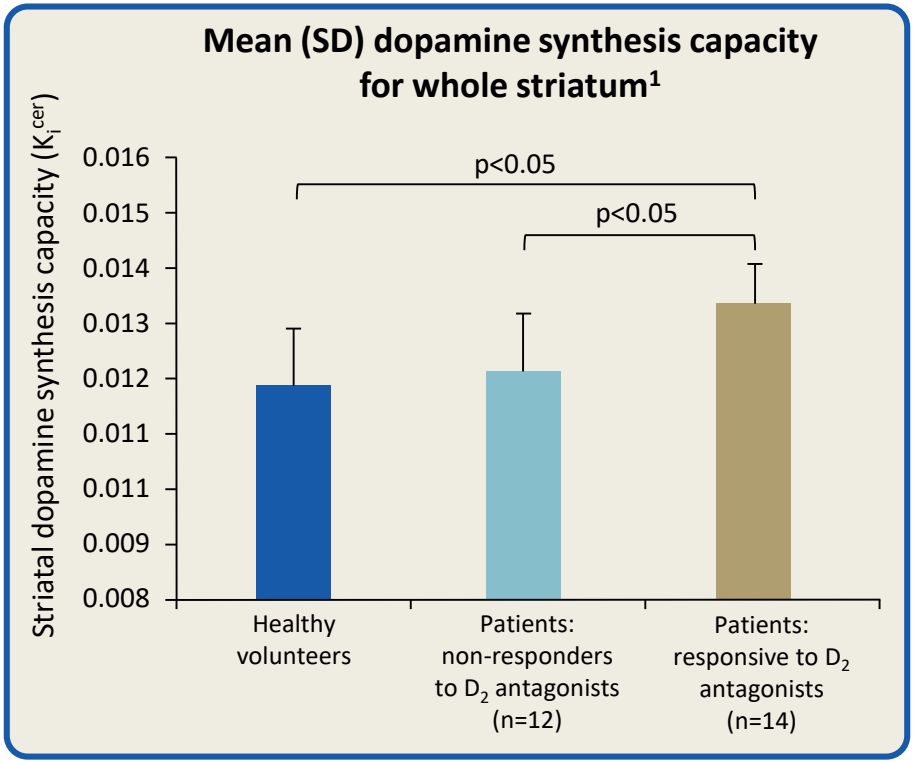
1. Demjaha et al. Am J Pyschiatry 2012;169(11):1203–1210

# Dopamine synthesis capacity predicts non-response in first-episode drug-naïve patients

- Dopamine synthesis capacity is unaltered in treatment non-responders from first episode



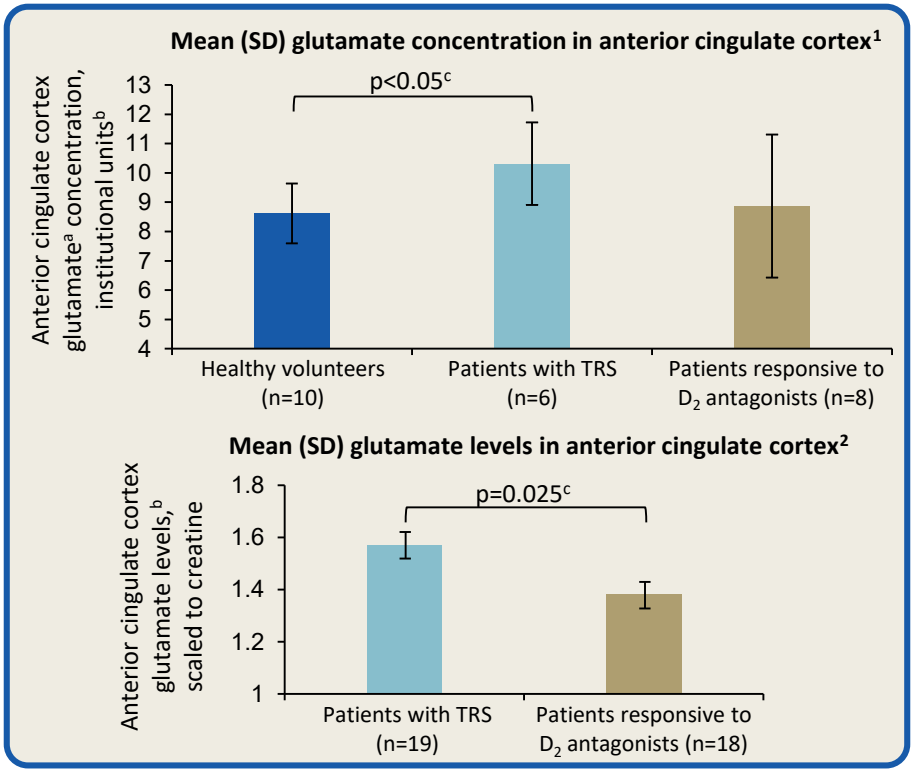
SD=standard deviation; TRS=treatment-resistant schizophrenia




1. Jauhar et al. Submitted

# Other hypotheses: glutamate abnormalities in TRS

- Other neurotransmitter systems may also be implicated in TRS, including glutamate[1,2]
- Data show that glutamate levels are significantly higher in patients with TRS compared to healthy volunteers,[1] and compared to patients with schizophrenia who were responsive to $D_2$ antagonists[2]
- Measures of glutamate function might provide a means of stratifying patients with psychosis according to their response to treatment[2]




[a]Glutamate concentration estimates are likely to include some contamination by glutamine; [b]as measured by proton magnetic resonance spectroscopy; [c]two-tailed *t* test

SD=standard deviation; TRS=treatment-resistant schizophrenia

1. Demjaha et al. Biol Psychiatry 2014;75(5):e11–e13; 2. Mouchlianitis et al. Schizophr Bull 2016;42(3):744–752

# Other hypotheses for TRS

**Neurodegeneration[1]**

Reduced grey-matter volume in TRS may represent accelerated disease course and/or different underlying pathophysiology[1]

**Brain connectivity[2,3]**

Reduced connectivity in the ventromedial prefrontal cortex,[2] ventral striatum,[3] and substantia nigra[3] in TRS may suggest different pathophysiology

**Substance misuse[4]**

Patients with substance use disorder may have a more severe and drug-resistant expression of schizophrenia[4]

**Neuroinflammation[5,6]**

Elevated microglial activity may be predictive of those at risk of psychosis,[5] whilst cortisol and inflammatory biomarkers at onset of psychosis may predict TRS[6]

**Genetic polymorphisms[7]**

Variation in the brain-derived neurotrophic factor gene has been associated with treatment resistance[7]

TRS=treatment-resistant schizophrenia

1. Anderson et al. Int J Neuropsychopharmacol 2015;18(7):pyv016; 2. Alonso-Solís et al. Schizophr Res 2015;161(2–3):261–268;
3. White et al. Neuropsychopharmacology 2016;41(5):1274–1285; 4. Picci et al. Psychiatry Res 2013;210(3):780–786; 5. Bloomfield et al. Am J Psychiatry 2016;173(1):44–52;
6. Mondelli et al. Schizophr Bull 2015;41(5):1162–1170; 7. Zhang et al. Schizophr Res 2013;146(1–3):285–288

# Summary – (ii)

Studies show that dopamine synthesis capacity,[1] and dopaminergic synapse density,[2] are higher in patients who respond to $D_2$ antagonists than in patients with TRS, who do not significantly differ from controls

Animal and human studies show upregulation of $D_2$ receptors following long-term treatment with APs;[3-5] the resulting dopamine supersensitivity means patients need increasing dosages of AP[6]

Elevated glutamate levels and inflammatory biomarkers (IL-6) have been detected in patients with TRS,[7-10] and may help to identify those at risk for psychosis,[9] and to stratify patients by their response to treatment[8]

Genetic polymorphisms and substance abuse may also be involved in TRS;[11,12] patients with substance use disorder may be at risk for a more severe and treatment-resistant expression of schizophrenia[12]

Confirmation of TRS as one or more distinct subtypes of schizophrenia, and the ability to identify treatment resistance at disease outset, would take the field one step closer to personalised treatment[13]

AP=antipsychotic; DSP=dopamine supersensitivity psychosis; IL=interleukin; TRS=treatment-resistant schizophrenia

1. Howes & Kapur. Br J Psychiatry 2014;205(1):1–3; 2. Roberts et al. Synapse 2009;63(6):520–530; 3. Tarazi et al. J Pharmacol Exp Ther 2001;297(2):711–717;
4. Tarazi et al. Neuropsychopharmacology 1997;17(3):186–196; 5. Silvestri et al. Psychopharmacology (Berl) 2000;152(2):174–180;
6. Suzuki et al. Psychiatry Res 2015;227(2–3):278–282; 7. Demjaha et al. Biol Psychiatry 2014;75(5):e11–e13; 8. Mouchlianitis et al. Schizophr Bull 2016;42(3):744–752;
9. Bloomfield et al. Am J Psychiatry 2016;173(1):44–52; 10. Mondelli et al. Schizophr Bull 2015;41(5):1162–1170; 11. Zhang et al. Schizophr Res 2013;146(1–3):285–288;
12. Picci et al. Psychiatry Res 2013;210(3):780–786; 13. Gillespie et al. BMC Psychiatry 2017;17(1):12

# Current treatment for TRS: clozapine

- Clozapine is the only pharmacological treatment approved for use in treatment-resistant schizophrenia (TRS),[1] and is recommended as a third-line treatment in clinical guidelines from the APA,[2] NICE,[3] and WFSBP[4]

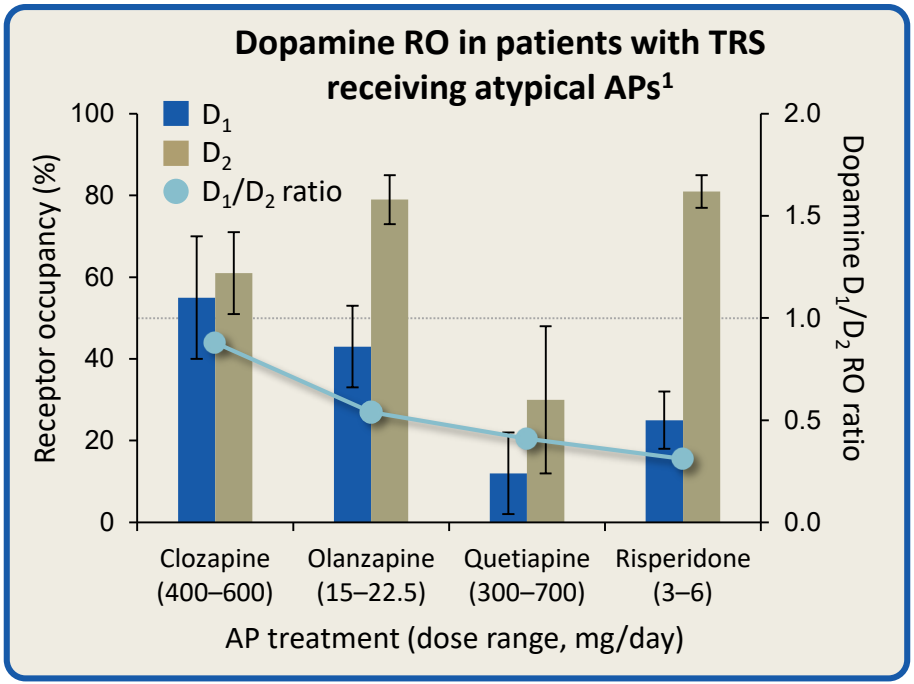
| Guidelines | Basic use | Specific clinical features |
|---|---|---|
| APA[2] | If psychotic symptoms persist after two antipsychotic trials, then clozapine should be given strong consideration | • Persistent hostility<br>• Persistent aggressive behaviour<br>• Persistent suicidal ideation<br>• Tardive dyskinesia |
| NICE[3] | If there is an inadequate response after two sequential trials, with different antipsychotics, then clozapine should be offered | • No specific clinical features listed |
| WFSBP[4] | If there have been ≥2 failures (from ≥2 different chemical classes) then clozapine should be introduced as the treatment of choice | • Persistent positive or negative symptoms<br>• Severe cognitive dysfunction<br>• Recurrent affective symptoms and suicidal behaviour<br>• Bizarre behaviours<br>• Deficits in vocational/social functioning<br>• Poor quality of life |

APA=American Psychiatric Association; NICE=National Institute for Health and Care Excellence; WFSBP=World Federation of Societies of Biological Psychiatry

1. Stroup et al. Am J Psychiatry 2016;173(2):166–173; 2. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56;
3. National Institute for Health and Care Excellence. nice.org.uk/guidance/cg178; 4. Hasan et al. World J Biol Psychiatry 2012;13:318–378

# Receptor profile of clozapine compared to other APs

- Positron emission tomography with radioligands was used to investigate striatal dopamine $D_1$ and $D_2$ receptor occupancies in patients with refractory schizophrenia receiving atypical APs (clozapine, olanzapine, quetiapine, or risperidone)[1]
- Clozapine has similar dopamine $D_1$ and $D_2$ receptor occupancy (ratio close to 1 at therapeutic doses)[1]
- Other antipsychotics all have significantly higher occupancy at the dopamine $D_2$ receptor than at the dopamine $D_1$ receptor (i.e., the $D_1/D_2$ RO ratio is <1)[1]

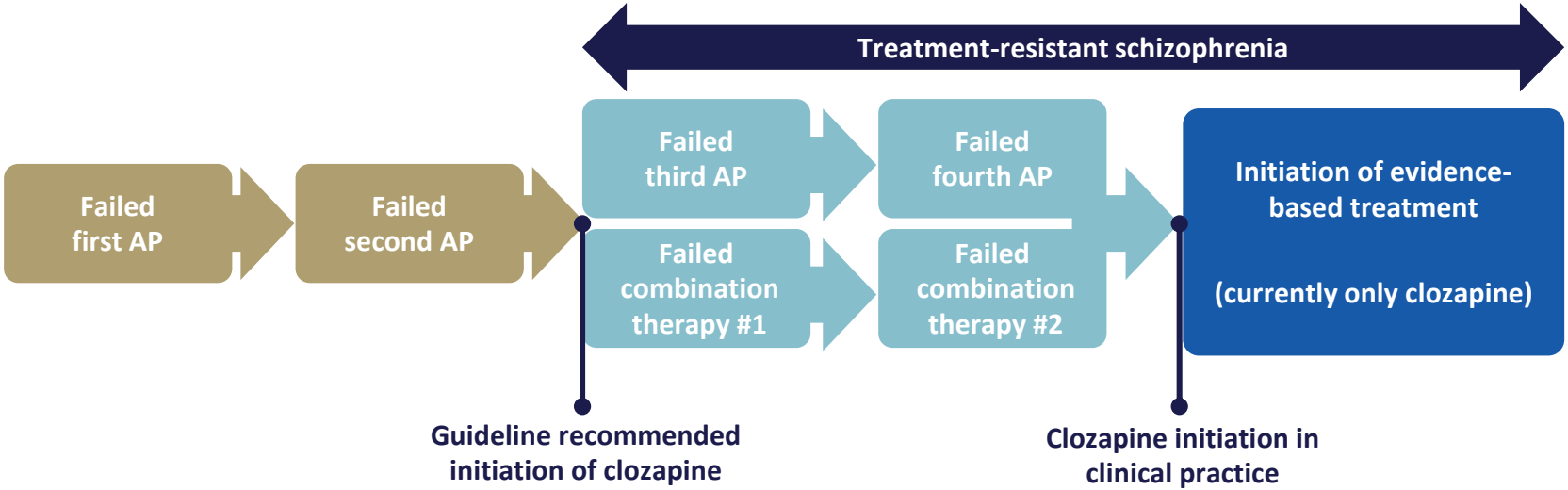



[a]The study included 25 patients with schizophrenia who were receiving ongoing treatment with an atypical antipsychotic for at least 14 days before the study
AP=antipsychotic; RO=receptor occupancy; TRS=treatment-resistant schizophrenia

1. Tauscher et al. Am J Psychiatry 2004;161(9):1620–1625

# Delays in prescribing clozapine

- Although guidelines recommend starting clozapine after two AP treatment failures, its introduction is often delayed by several years[1,2]




AP=antipsychotic

1. Howes et al. Br J Psychiatry 2012;201(6):481–485; 2. Najim et al. Psychiatr Danub 2013;25(Suppl 2):165–170

# Other pharmacological strategies for TRS

Due to the lack of approved options for TRS, psychiatrists often try other pharmacological strategies before initiating clozapine[1-3]

These strategies include:

- Increasing the antipsychotic dose[1,2]
- Combination therapy and augmentation strategies[1-3]
- Treatment switching (multiple antipsychotics used sequentially)[2]

TRS=treatment-resistant schizophrenia

1. Howes et al. Br J Psychiatry 2012;201(6):481–485; 2. Dold & Leucht. Evid Based Ment Health 2014;17(2):33–37;
3. Thompson et al. J Psychopharmacol 2016;30(5):436–443

# Antipsychotic dose increase

A study of lurasidone showed that increasing the dose to 160 mg/day resulted in superior efficacy among patients who failed to respond to the initial 80 mg/day dose after two weeks of treatment; however, the increased dose was associated with a higher incidence of some adverse events[1]

Although high-dose[a] olanzapine (25–45 mg/day) has shown similar efficacy to clozapine in patients with TRS,[1] metabolic side effects are a limitation, and olanzapine 50 mg/day may be associated with a higher rate of anticholinergic effects[2] and weight gain compared with clozapine[2,3]

Among several randomised clinical studies, there was no superiority of high-dose medication compared with the standard dose for the majority of patients[4]

High-dose AP treatment is not recommended as a general treatment option for TRS[4]

[a]High-dose treatment is defined as a dose higher than that recommended in the drug prescribing information

AP=antipsychotic; TRS=treatment-resistant schizophrenia

1. Loebel et al. J Clin Psychiatry 2016;77(12):1672–1680; 2. Meltzer et al. J Clin Psychiatry 2008;69(2):274–285;
3. Kelly et al. Ann Clin Psychiatry 2003;15(3–4):181–186; 4. Dold & Leucht. Evid Based Ment Health 2014;17(2):33–37

# Antipsychotic combination therapy

Combination therapy for the treatment of schizophrenia is a widely used strategy in clinical practice[1]

Risks of metabolic side effects and all-cause discontinuation may be increased significantly by administering AP combinations. Therefore, efficacy, drug interactions, and occurrence of adverse events require close monitoring[1]

There is insufficient evidence to recommend combination therapies, and current treatment guidelines recommend the use of AP monotherapies[2,3]

AP=antipsychotic

1. Dold & Leucht. Evid Based Ment Health 2014;17(2):33–37; 2. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56;
3. Hasan et al. World J Biol Psychiatry 2012;13:318–378

# Antipsychotic switching

Medication should be switched preferentially to an antipsychotic with a different receptor binding profile from that of the previous antipsychotic[1]

In studies in which the control group stayed on the previous treatment, the superiority of switching strategies was low[1]

Insufficient evidence exists for clear pharmacotherapeutic recommendations with regard to switching strategies[1-3]

The chance of responding to antipsychotic treatment declines substantially (from 75% to 17%) after the first trial in patients with first-episode schizophrenia[4]

Only 7–9% of patients improve with subsequent treatments after two antipsychotic failures[5]

1. Dold & Leucht. Evid Based Ment Health 2014;17(2):33–37; 2. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56;
3. Hasan et al. World J Biol Psychiatry 2012;13:318–378; 4. Agid et al. Eur Neuropsychopharmacol 2013;23(9):1017–1022;
5. Kinon et al. Psychopharmacol Bull 1993;29(2):309–314

# Non-pharmacological treatments for TRS

Non-pharmacological treatments for TRS are also available, including psychosocial interventions, electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS)[1-3]

Psychosocial interventions, such as cognitive behavioural therapy, can improve the symptoms of schizophrenia, when integrated with pharmacological treatments, although there are varying degrees of evidence available[1]

ECT as add-on to pharmacological treatment for patients with TRS may be appropriate[1,3,4]

A meta-analysis demonstrated an overall response to clozapine plus ECT of 66%[5]

However, negative perceptions of ECT limit its use[6]

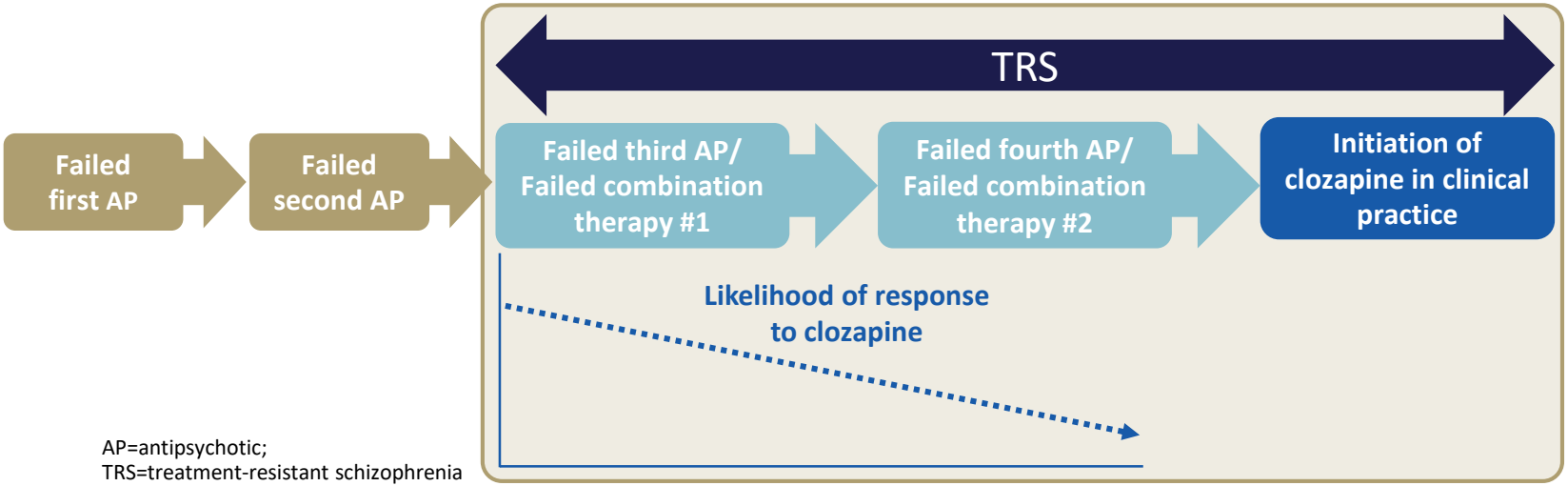
rTMS may improve negative symptoms in patients with TRS, although there is a limited evidence base[3]

ECT=electroconvulsive therapy; rTMS=repetitive transcranial magnetic stimulation; TRS=treatment-resistant schizophrenia

1. Lehman et al. Am J Psychiatry 2004;161(2 Suppl):1–56; 2. National Institute for Health and Care Excellence. nice.org.uk/guidance/cg178;
3. Hasan et al. World J Biol Psychiatry 2012;13:318–378; 4. National Institute for Health and Care Excellence. nice.org.uk/guidance/ta59;
5. Lally et al. Schizophr Res 2016;171(1–3):215–224; 6. Payne & Prudic. J Psychiatr Pract 2009;15(5):369–390

# Early recognition of TRS

- Earlier identification of TRS has particular importance because prompt and effective pharmacological intervention can change the course of the illness, significantly improving prognosis[1,2]
- This is due largely to the fact that repeated psychotic relapse, which may reflect a period of disease progression,[3] increases the likelihood of non-response to subsequent antipsychotic treatment,[3] as well as the time to functional recovery[4]




AP=antipsychotic;
TRS=treatment-resistant schizophrenia

1. Stroup et al. Am J Psychiatry 2016;173(2):166–173; 2. Schooler et al. J Clin Psychiatry 2016;77(5):628–634;
3. Emsley et al. BMC Psychiatry 2013;13:50; 4. Kane. J Clin Psychiatry 2007;68 (Suppl 14):27–30;
5. Nielsen et al. J Clin Psychopharmacol 2012;32(5):678–683; 6. Yoshimura et al. Psychiatry Res 2017;250:65–70

# Summary

Clozapine is currently the only available treatment for TRS, but many patients receiving clozapine fail to achieve an adequate response[1-4]

Psychiatrists and patients may be reluctant to use clozapine due to the need for regular blood tests,[5] as well as safety and tolerability concerns[6]

Psychiatrists may try several non-evidence-based treatment strategies before trialling clozapine in patients with TRS;[7] clozapine treatment is often delayed[8,9]

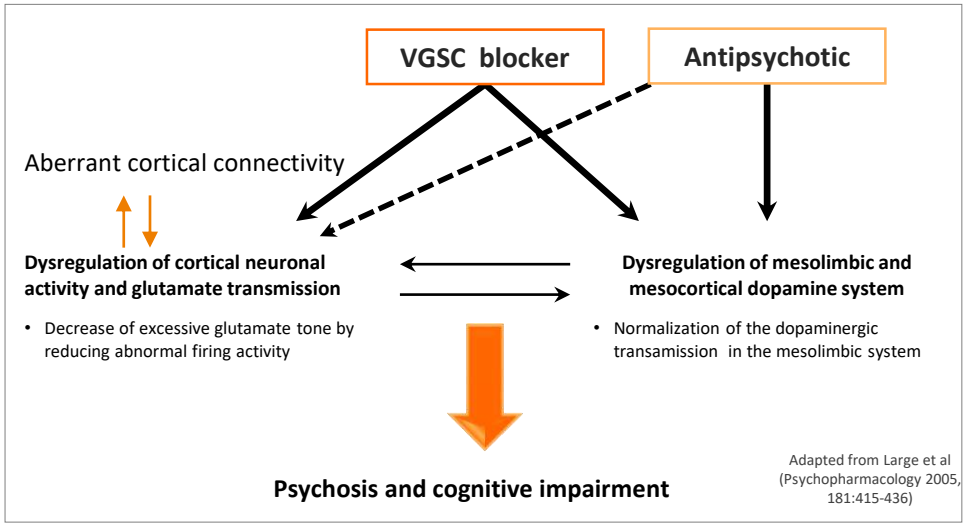
No new drugs have been approved for TRS in the last three decades[10,11]

**There is a need for novel therapies for TRS**

1. Strassnig & Harvey. CNS Spectr 2014;19(Suppl 1):16–23; 2. Kane et al. Arch Gen Psychiatry 1988;45(9):789–796;
3. Meltzer et al. Psychopharmacology (Berl) 1989;99 Suppl:S68–72; 4. Meltzer. Br J Psychiatry Suppl 1992;(17):46–53; 5. Gee et al. Acta Psychiatr Scand 2014;130:16–24;
6. Clozaril® Prescribing information, 2014; 7. Dold & Leucht. Evid Based Ment Health 2014;17:33–37; 8. Howes et al. Br J Psychiatry 2012;201:481–485;
9. Najim et al. Psychiatr Danub 2013;25(Suppl 2):165–170; 10. Schooler et al. J Clin Psychiatry 2016;77(5):628–634; 11. Stroup et al. Am J Psychiatry 2016;173(2):166–173

# Novel Mechanism of Action: Synergy with other Antipsychotics

- Current antipsychotic drugs target the dysregulation of mesolimbic and mesocortical dopamine systems
- The aberrant electrical connectivity in schizophrenia that leads to abnormal cortical neuronal activity and glutamate transmission is not affected by existing drugs
- 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 symptoms in schizophrenia**

# Evenamide does not bind to the principal FGA / SGA targets

| receptor | EVENAMIDE % binding at 10 µM |
|---|---|
| D1 | 5 |
| D2L / D2S | -8 / 3 |
| D3 | 3 |
| 5-HT1A | 11 or 19 (two studies) |
| 5-HT2A | 10 |
| 5-HT2C | 17 |
| 5-HT6 | 8 |
| 5-HT7 | 35 |
| α1 adrenoceptor | 14 |
| α2 adrenoceptor | 14 |
| Histamine H1 | 7 |
| Muscarinic M1 | 5 |
| Muscarinic M2 | 3 |
| Muscarinic M3 | 1 |
| Muscarinic M4 | 2 |
| NMDAr (all sites) | 0 |

binding >50% (at 10 uM) was found for these three receptors out of >130 targets tested in total

| | |
|---|---|
| sigma 1 | 88 |
| sigma 2 | 63 |
| Imidazoline I2 peripheral | 54 (IC50 =8.19µM) |

| Drug class | Second-generation antipsychotics | | | | | | | | First-generation antipsychotics | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Receptor | AMI | ARI | ASE | CLO | OLA | PALI | RIS | QUE | SER | ZIP | HAL | PER |
| $D_2$ | 1.3[b] | 0.66[a,b] | 1.3[b] | 210 | 20 | 2.8 | 3.77 | 770 | 2.7 | 2.6 | 2.6 | 1.4[b] |
| 5-$HT_{1A}$ | >10,000[c] | 5.5[a,b] | 2.5[b] | 160 | 610 | 480 | 190 | 300 | 2,200 | 1.9[a,b] | 1,800 | 421 |
| 5-$HT_{2A}$ | 2,000[c] | 8.7[b] | 0.06[b] | 2.59 | 1.5 | 1.2 | 0.15 | 31 | 0.14 | 0.12 | 61 | 5[b] |
| 5-$HT_{2C}$ | >10,000[c] | 22[b] | 0.03[b] | 4.8 | 4.1 | 48 | 32 | 3,500 | 6.0 | 0.9 | 4,700 | 132[b] |
| $\alpha_1$ | 7,100[c] | 26[b] | 1.2[b] | 6.8 | 44 | 10 | 2.7 | 8.1 | 3.9 | 2.6 | 17 | 10 |
| $\alpha_2$ | 1,600[c] | 74[a] | 1.2[b] | 158 | 280 | 80 | 8 | 80 | 190 | 154 | 600 | 500 |
| $H_1$ | >10,000[d] | 30[b] | 1.0[b] | 3.1 | 0.08 | 3.4 | 5.2 | 19 | 440 | 4.6 | 260 | 8 |
| $M_1$ | N/A | 6,780[b] | 8128[b] | 1.4[b] | 2.5[b] | >10,000[b] | >10,000[b] | 120[b] | 5,000 | 300[b] | >10,000[b] | 1,500 |
| $M_2$ | N/A | 3,510[b] | 4.5[b] | 204[b] | 622[b] | >10,000[b] | >10,000[b] | 630[b] | N/A | >3,000[b] | >10,000[b] | N/A |
| $M_3$ | N/A | 4,680[b] | 4,67[b] | 109[b] | 126[b] | >10,000[b] | >10,000[b] | 1,320[b] | 2,692[b] | >1,300[b] | >10,000[b] | 1,848[b] |
| $M_4$ | N/A | 1,520[b] | 5.09[b] | 27[b] | 350[b] | >10,000[b] | >10,000[b] | 660[b] | N/A | >1,600[b] | >10,000[b] | N/A |

**Notes:** Adapted with permission from Correll CU, From receptor pharmacology to improved outcomes: individualizing the selection, dosing, and switching of antipsychotics, *Eur Psychiatry*, 2010;25(Suppl 2):S12–S21, Copyright © 2010, Elsevier Masson SAS. All rights reserved.[79] Data represented as the equilibrium constant (Ki; nM), ie, nanomolar amount of the antipsychotic needed to block 50% of the receptors in vitro. Therefore, a lower number denotes stronger receptor affinity and binding. [a]Partial agonism. [b]Data from cloned human brain receptors. [c]Data extracted from rat. [d]Data extracted from guinea pig.
**Abbreviations:** AMI, amisulpride; ARI, aripiprazole; ASE, asenapine; CLO, clozapine; HAL, haloperidol; OLA, olanzapine; PALI, paliperidone; PER, perphenazine; QUE, quetiapine; RIS, risperidone; SER, sertindole; ZIP, ziprasidone; N/A, not applicable.

| Receptor | Haloperidol | Clozapine | Quetiapine | Olanzapine | Risperidone | Ziprasidone |
|---|---|---|---|---|---|---|
| Dopamine D1 | 15 | 53 | 390 | 10 | 21 | 9.5 |
| Dopamine D2 | 0.82 | 36 | 39 | 2.1 | 0.44 | 2.8 |
| Dopamine D3 | 2.5 | 22 | >500 | 17 | 13 | 28 |
| 5-$HT_{1A}$ | 2600 | 710 | >830 | 7100 | 21 | 37 |
| 5-$HT_{1B/1D}$ | | | | | | |
| 5-$HT_{2A}$ | 28 | 4.0 | 82 | 1.9 | 0.39 | 0.25 |
| 5-$HT_{2C}$ | 1500 | 5.0 | 1500 | 2.8 | 6.4 | 0.55 |
| 5-$HT_{2D}$ | | | | | | |
| 5-$HT_6$ | 6600 | 9.5 | 33 | 10 | 2400 | n.t. |
| 5-$HT_7$ | 80 | 21 | 290 | 120 | 1.6 | 4.9 |
| $\alpha_1$-Adrenoceptor | 7.3 | 3.7 | 4.5 | 7.3 | 0.69 | 1.9 |
| $\alpha_2$-Adrenoceptor | 1600 | 51 | 1100 | 140 | 1.8 | 390 |
| Histamine $H_1$ | >730 | 17 | 21 | 5.6 | 88 | 510 |
| Muscarinic $M_1$ | 570 | 0.98 | 56 | 2.1 | >5000 | >10000 |

Receptor bindings are presented as Ki values (nmol/L).
Data from Horacek J. Novel antipsychotics and extrapyramidal side effects. Theory and reality. Pharmacopsychiatry 2000;33:34–42; and Schmidt AW, Lebel LA, Howard HR Jr, Zorn SH. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425:197–201.

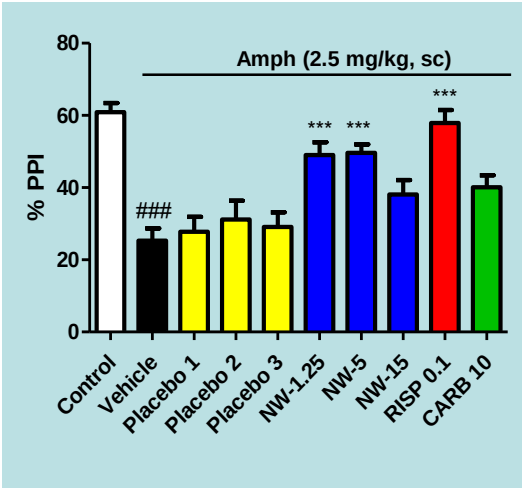
# Evenamide is active in a wide range of schizophrenia and psychiatric animal models as monotherapy and as add-on to existing antipsychotics

| | | Monotherapy | Add-On |
|---|---|---|---|
| **Information Processing Deficit** | Pre-pulse inhibition (PPI) disrupted by | | |
| | • dopamine activation (amphetamine -rat) | ✓ | ✓ |
| | • NMDA antagonists (MK-801, PCP, -rat) | ✓ | |
| | • natural stimuli (sleep deprivation -rat) | ✓ | |
| | • Ketamine in rat | ✓ | ✓ |
| | Pre-pulse inhibition spontaneous deficit (C57 mice) | ✓* | ✓ |
| **Negative Symptoms** | PCP-induced deficit in Social Interaction in the rat | ✓ | ✓ |
| | Saccharin preference test (anhedonia) [Prenatal Poly(I:C) Exposure -mice] | ongoing | |
| | Three-chamber sociability test [Prenatal Poly(I:C) Exposure -mice] | ongoing | |
| | Forced swimming test (avolition) [Prenatal Poly(I:C) Exposure -mice] | ongoing | |
| **Psychosis and Mania** | Amphetamine induced hyperactivity in mice | ✓ | ✓ |
| | Amphetamine plus Chlordiazepoxide induced hyperactivity in mice | ✓ | ✓ |
| | PCP induced hyperactivity in mice (add-on to clozapine) | ongoing | ✓ |
| **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) | ✓ | |

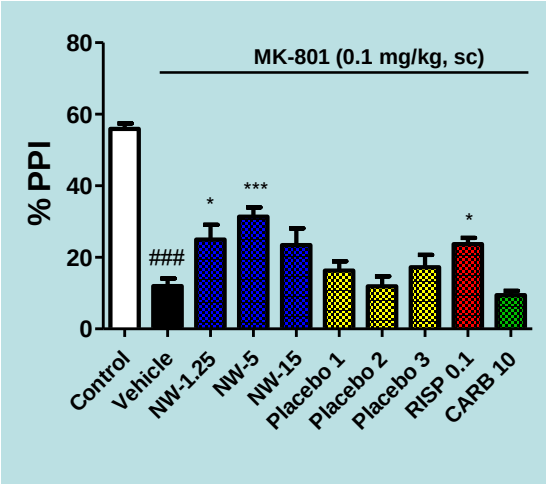
*Trend; Blank cells = not evaluated

# Evenamide as a monotherapy reverses the PPI deficit induced by Amphetamine or MK-801 in rats

**PPI DEFICIT INDUCED BY AMPHETAMINE**



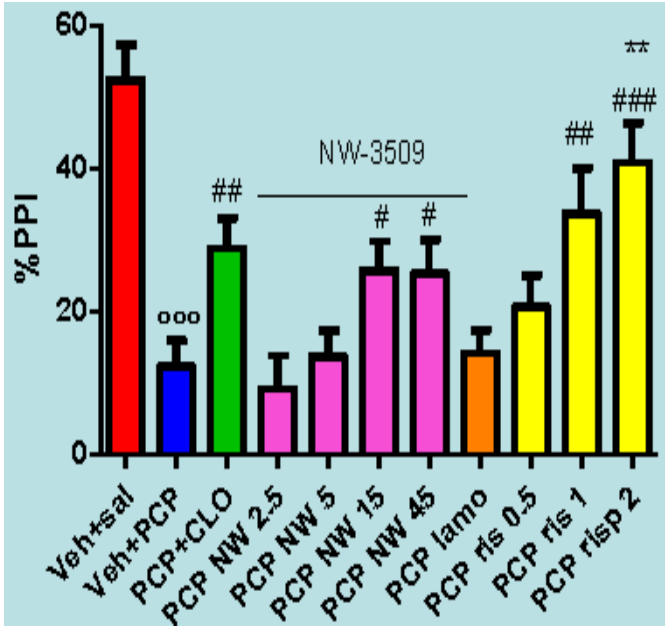

**PPI DEFICIT INDUCED BY MK-801**




- Evenamide minimal effective dose: 1.25mg/kg *po*
- Study conducted under double-blind conditions with three placebo controls
- Amphetamine (2.5mg/kg, sc) or MK-801 (0.1mg/kg, sc), injected 5 min before PPI session
- Evenamide and placebo administered immediately before Amphetamine or MK-801
- Risperidone (0.1mg/kg, ip) and carbamazepine (10mg/kg, ip), used as standard controls, administered 30 min before testing
- Statistics of Amph study: Tukey's test $p<0.001$ vs vehicle + Amph; $p<0.001$ vs control (n=23-24 rats per group)
- Statistics of MK-801 study: Tukey's test $p<0.05$, $p<0.0001$ vs vehicle + MK-801; $p<0.001$ vs control (n=27-47 rats

Note: Studies performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari - USCLA

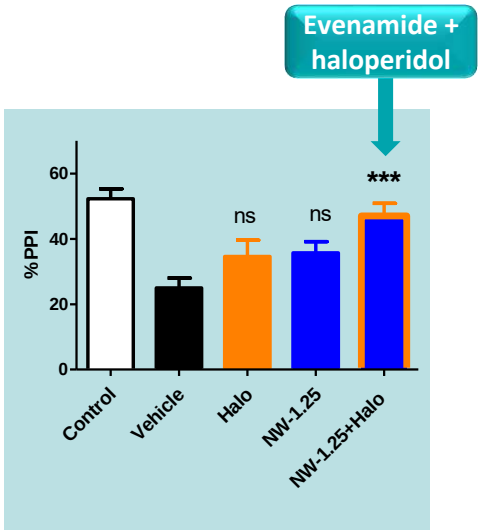
# Similar to Clozapine, Evenamide as monotherapy attenuates PCP-induced PPI deficit in rats (Lamotrigine not effective)




- Evenamide minimal effective dose: 15mg/kg po
- Evenamide was administered 5 min before PPI session
- PCP (5mg/kg ip) was administered 15 min before PPI session
- N=10 rats per group
- Statistics:
  - One-way ANOVA $p<0.001$ vs Vehicle + Saline,
  - Tukey's post hoc test $p<0.01$ vs Vehicle + PCP
  - Unpaired t-test $p<0.05$, $p<0.01$, $p<0.001$ vs Vehicle + PCP
- CLO=Clozapine (5mg/kg ip), NW=Evenamide (po doses), lamo=Lamotrigine (10mg/kg ip), risp=Risperidone (ip doses)

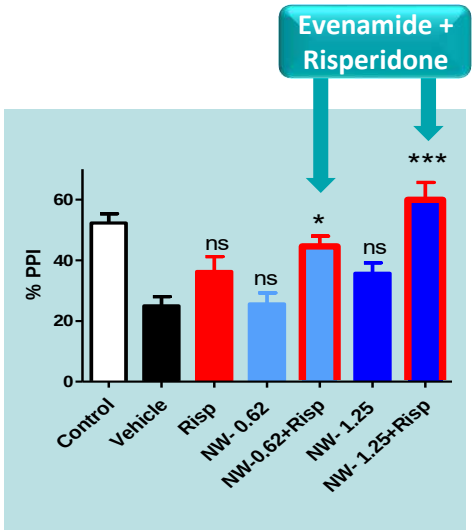
# Evenamide as an add-on augments the effect of typical and atypical antipsychotics in Amphetamine-induced PPI deficit

**ADD-ON WITH INACTIVE DOSE OF HALOPERIDOL**




*Evenamide 1.25mg/kg po + haloperidol 0.05mg/kg ip*

**ADD-ON WITH INACTIVE DOSE OF RISPERIDONE**




*Evenamide 0.62mg/kg po +risperidone 0.05 mg/kg ip*

- Amphetamine (2.5mg/kg sc) and Evenamide (1.25 or 0.62mg/kg po) were administered 5 min before PPI session
- Haloperidol and risperidone were administered ip 30 min before PPI session at 0.05mg/kg
- Statistics: Tukey's multiple comparison test $p<0.05$, $p<0.001$ vs Vehicle +Amphetamine (n=6-18 rats per group)

Note: Studies performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari - USCLA

# The biological effects of evenamide are mediated by Na+ channel blockade

**Selectively blocks VGSCs in a voltage-and use-dependent manner**

Inhibition of native sodium channels expressed in rat (neonatal) cortical neurons

$K_{rest}$ (µM)

23

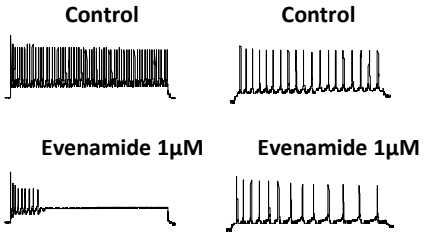
$K_{inact}$ (µM)

0.98

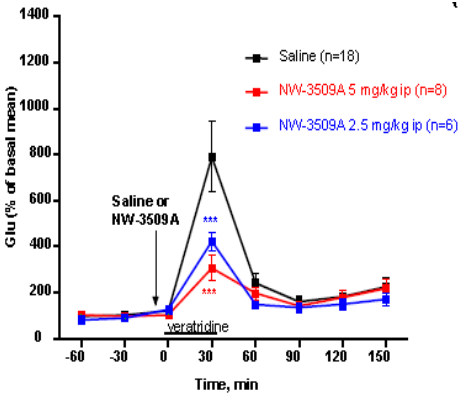
**Modulates sustained repetitive firing without inducing impairment of the normal neuronal excitability**

High frequency firing

Low frequency firing



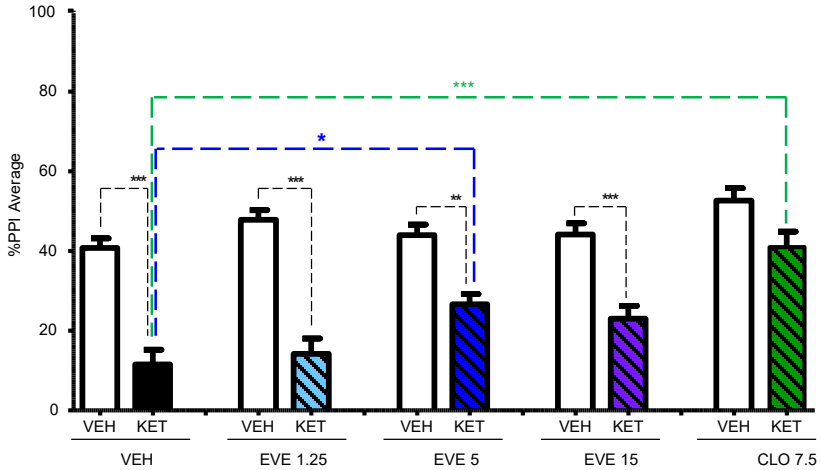

**Inhibits Glutamate Release**



# Unique MoA demonstrated: Evenamide (NW-3509) is a 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 stimulated glutamate release without modifying the basal levels
- In radioligand binding assays, Evenamide has shown less than 20% inhibition against a panel of >130 receptors, ion channels, transporters and kinases when tested at 10µM (plasma concentration at max human dose of 30mg is 0.3uM)
- No effect of Evenamide on dopamine, serotonin, norepinephrine and their metabolites levels after acute treatment (2.5mg/kg po) in rat PFC, NAc and Striatum
- Evenamide has no significant activity against other ion channels, such as voltage-gated Ca2+ channels and NMDA receptor channels up to high concentrations (IC50 >>100µM) when tested with the electrophysiology patch clamp technique

# Similar to Clozapine, Evenamide monotherapy attenuates Ketamine-induced PPI deficit in rats




KET: Ketamine: 6 mg/kg, SC, 45 min before testing; EVE: Evenamide 1.25-5-15 mg/kg, PO, 5 min before testing; CLO: Clozapine 7.5 mg/kg, IP, 30 min before testing

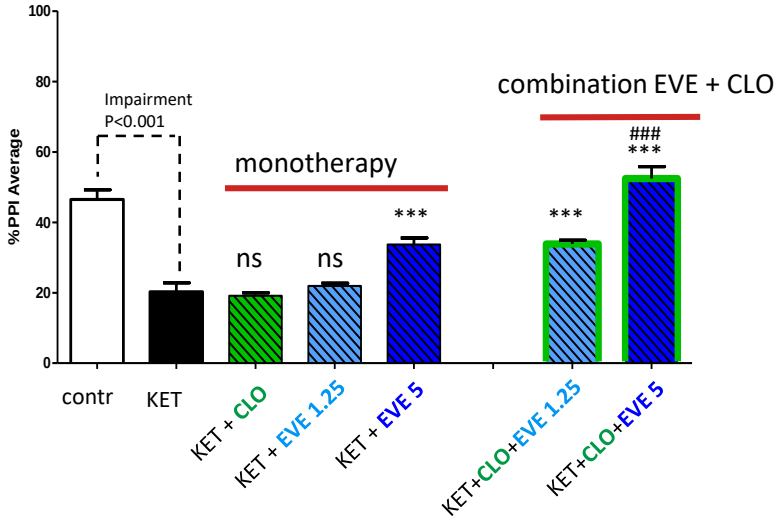
Statistics: 3-way, repeated-measure ANOVA; *, P<0.05; **, P<0.01; ***, P<0.001 for all comparisons indicated by dotted lines (Tukey's post-hoc test). (n=34/group)

*Studies performed by Dr. Bortolato, Univ. Utah*

- Ketamine significantly (p<0.0001) impaired PPI by 72%
- Evenamide at a dose of 5 mg/kg, p.o. significantly (p=0.02) attenuated by 52% the impairment of PPI by ketamine
- Clozapine at a dose of 7.5 mg/kg, i.p also significantly attenuated this impairment

These results confirm that **evenamide produces its effect by antagonizing glutamate dysfunction**

# The combination of ineffective doses of Clozapine and Evenamide significantly reduces Ketamine-induced deterioration of PPI




KET: Ketamine: 10 mg/kg, SC, 45 min before testing
EVE: Evenamide 1.25 - 5 mg/kg, PO, 5 min before testing
CLO: Clozapine 3 mg/kg, IP, 30 min before testing

Statistics: 3-way, repeated-measure ANOVA; ***P<0.001 vs KET; ### P<0.001 vs EVE 5 (Tukey's post-hoc test) (n=16/group)

*Studies performed by Dr. Bortolato, Univ. Utah*

- Significant attenuation of KET detrimental effect by EVE 5mg/kg monotherapy (reconfirms the previous study)
- Significant attenuation of KET detrimental effect by the combination of inactive dose of EVE 1.25mg/kg + inactive CLO 3mg/kg;
- Full reversal produced by the combination of EVE 5mg/kg + inactive CLO 3mg/kg; this combination is also significantly different from EVE 5mg/kg alone

# Clinical: Study 002 – Results Support Preliminary Evidence of Efficacy

**Mean Values and Changes from Baseline to Endpoint (Day 28) for the PANSS Total Score, LOF Total Score and CGI-S (mITT Population)**

| Value at Day 28/EOS [Mean (SD)] | Evenamide (N=48) | | | Placebo (N=39) | | | |
|---|---|---|---|---|---|---|---|
| **Scale** | **n** | **Value** | **Change** | **n** | **Value** | **Change** | **p-Value (b)** |
| PANSS Total | 46 | 58.3 (9.1) | -4.5 (9.0) | 37 | 60.3 (10.2) | -2.3 (7.4) | 0.1470 |
| PANSS Positive | 47 | 13.0 (3.6) | -2.3 (3.0) | 39 | 14.0 (3.8) | -1.2 (2.6) | 0.0459 |
| LOF Total | 48 | 22.8 (3.2) | 0.72 (3.3) | 39 | 21.0 (4.4) | 0.31 (3.1) | -- |
| CGI-S | 47 | 3.1 (0.7) | -0.3 (0.6) | 39 | 3.2 (0.8) | -0.2 (0.7) | -- |

| Proportion of Responders [n/n (%)] at Day 28 | | | | | |
|---|---|---|---|---|---|
| **Scale** | **Responder Criterion** | **N** | **NW-3509** | **N** | **Placebo** |
| PANSS Positive | Change from baseline less than 0 (reduction in score = improvement) | 47 | 35/47 (74.5)* | 39 | 17/39 (43.6) |
| CGI-C | Rating of 1, 2 or 3 (very much, much or minimally improved, respectively) | 47 | 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

# Study 004: Study Design

| | |
|---|---|
| Design: | A phase IIb/III, prospective, randomized, double-blind, parallel-group, multi-center, 8-week study to determine the efficacy, safety, and tolerability of add-on treatment with Evenamide (15 or 30 mg BID) or placebo in patients with treatment-resistant schizophrenia (TRS) not responding adequately to clozapine |
| Centers/countries: | 450 patients (150/group), 30 centers in Canada, Europe, India, Latin America and US |
| Population: | • Male and female (not of CBP) outpatients with chronic schizophrenia (DSM-5) with a TRS diagnosis of at least 2 yrs., despite an adequate trial with a dose of clozapine of at least 300 mg/day for 8 weeks, and a plasma clozapine concentration of at least 300 ng/ml.<br>• Total score of at least 20, and a score of 4 (moderate) or more on at least 2 of the 4 core symptoms of psychosis (conceptual disorganization, hallucinatory behaviour, suspiciousness and unusual thought content - derived from the BPRS); CGI-S of moderately to severely ill (score of 4 – 6); GAF < 41. |
| Screening period: | 3-21 days; patients meeting all selection criteria at screening and baseline will be randomized to treatment and receive their first dose in the clinic on Day 1. |
| Initial treatment period: | Return for scheduled visits on Days 8, 15, 36, and 57 (endpoint) |
| Extension treatment period: | separate 44-week open-label extension study (Study 006); to maintain the blind, all patients will start at a dose of 15 mg BID Evenamide, and have their dose titrated. |

# EVENAMIDE: A HIGHLY ATYPICAL ANTIPSYCHOTIC IN THE TREATMENT OF SCHIZOPHRENIA

Ravi Anand, CMO

Newron
Pharmaceuticals

# 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

Newron Pharmaceuticals

# Current antipsychotics (5HT2/D2 antagonists) and their role in patients with chronic treatment-responsive schizophrenia

## THE CATIE STUDY INDICATES SIGNIFICANT DISSATISFACTION WITH CURRENT ANTIPSYCHOTICS:

- NIMH Sponsored study randomized 1493 treatment responsive US patients with schizophrenia at 57 US (universities, State mental health agencies, Veterans hospitals, private clinics and academic sites to first (perphenazine) and second (quetiapine, risperidone ziprasidone) generation antipsychotics at therapeutic doses for 18 months in Phase 1 of the study.
- >50% of patients discontinued their medication due to dissatisfaction with their effects within 6 months; by 18 months over 74% (1061 of 1432 patients) had discontinued their assigned medication.
- Minimal differences between drugs in improvement in psychopathology based on PANSS, CGI, QLSS
- Overall , study suggests no superiority in efficacy of second compared to first generation antipsychotics

## THE CUTLASS STUDY CONFIRMS CATIE STUDY RESULTS

- Non-commercial randomized 56-week study in 227 patients with schizophrenia and related illnesses showing inadequate response or side-effects in 14 NHS trusts
- Pragmatic prescription (choice of managing psychiatrist) of either FGAs or SGAs (other than clozapine)
- Primary outcome, the Quality Of Life Scale indicated trend for preference for first generation antipsychotics
- No systematic benefits between FGA and SGA

Newron Pharmaceuticals

# Current antipsychotics and their benefits in treatment-resistant schizophrenia (TRS)

- At least 30 % of all schizophrenic patients develop resistance to antipsychotic drugs with 5-years of starting treatment
- Development of treatment-resistance, unlike TD , is not influenced by the of use of first- or second-generation antipsychotics
- Clozapine, launched in the US in 1989 is the only drug to have demonstrated unequivocal efficacy in a randomized controlled trial in patients with TRS
- Failure to show efficacy in TRS patients noted for olanzapine, risperidone, quetiapine, sertindole, amisulpiride , haloperidol, chlorpromazine, ziprasidone, perphenazine
- Al of the above drugs acts by blocking D2 receptors in addition to various species of serotoninergic, alpha-adrenergic, histaminergic, cholinergic receptors.
- Other mechanisms that have failed to show benefit in TRS patients include selective antagonism of D1, 5-HT2, D3, D1/D2, 5-HT1A, receptors
- The changes in presynaptic dopamine transmission usually seen in schizophrenia are absent in TRS, therefore D2 antagonism is unlikely to benefit patients with TRS
- Very recent results wit AF 35700, a low D2 but potent $D_1$, $5\text{-}HT_{2A}$, and $5\text{-}HT_6$ receptor antagonist in a 10-week, well-controlled, randomized study with 964 TRS patients confirms that modulation of monoaminergic systems does not benefit TRS patients
- Higher glutamate levels have been noted in the anterior cingulate glutamate cortex with normal dopaminergic functioning in TRS patients indicating that the persistence of symptoms in TRS may be associated with abnormal high glutamate levels; clozapine reduces central glutamate levels
- Evenamide, by inhibiting glutamate release due to its sodium channel blockade, has shown similar benefits as clozapine, and also when added to clozapine in situations where clozapine shows sub-optimal response

Newron Pharmaceuticals

# Current antipsychotics and their benefits in patients with first episode of psychosis (FEP)

- Treatment close to the onset of the first psychotic episode improves outcomes for patients with schizophrenia and may lower suicide risk in these patients (Craig et al, 2004,Yuen et al, 2014, Kane et al, 2016)
- Over 80 % of FEP patients respond well to treatment and more than 50 % achieve remission in studies suggesting favorable long-term prognosis
- However, a prospective observational analysis of a population based cohort of individuals aged 16–30 years with FEP using data from the US DHHS Multi-Payer Claims Database (MPCD) suggests 'real-world' experience differs and causes serious concerns when reviewing data for mortality and severe morbidity
- Schoenbaum et al ( 2017) identified 154322 subjects with a FEP in 207-2010; subjects with continuous insurance prior to and at least 1 year later were 14910, while those with an additional ICD-9 diagnoses in the year after the FEP and had commercial insurance were 1357 in the ages of 16-30
- **108 deaths occurred in the 16-30 year-old patients, i.e. 24 times higher than age-matched controls, and 89 times the US general population;**
- All patients took psychotropic medication; repeat prescriptions for antipsychotics were for 40% of patients.

Newron Pharmaceuticals

# Current antipsychotics and their benefits in patients with schizophrenia

- Available antipsychotics benefit acute/ sub-acute exacerbations of psychosis, and help reduce risk of relapse
- CATIE results indicate high discontinuation rates for FGA and SGA with no superiority for SGA while CUTLASS results low improvement in QoL with these drugs with some preference for FGA
- Many patients with FEP show early worsening in the community; chronic schizophrenia patients show dissatisfaction and no improvement in cognition, negative symptoms, or functioning demonstrated

Possible reasons for the limited benefits of FGA and SGA include:

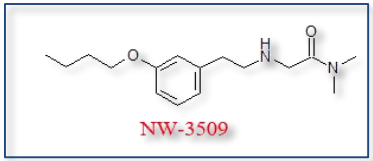
- All FGA and SGA have same/similar mechanism of action, e.g. D2,D1, 5HT2 blockade antagonism as well as effects on other serotoninergic, dopaminergic, cholinergic, alpha-adrenergic receptors
- Chronic blockade of dopaminergic receptors in mesolimbic structures may lead to upregulation of receptors and loss of efficacy/worsening (super-sensitivity psychosis)
- Drugs without dopamine blockade show no efficacy in acute patients; lack of glutamate modulation limits benefits of these drugs to these patients
- These findings suggest that the effective resolution of psychopathology may require effects on other targets/mechanisms especially effects on cortical activity and glutamate modulation

Newron Pharmaceuticals

# Discovery of Evenamide (NW-3509)

- Newron's ion channel program (2003-2006) performed to discover novel small-molecule blockers of sodium channels yielded several chemical structures using a SAR program that demonstrated activity in models of epilepsy and pain
- The phenethylamine derivative **NW-3381** **showed** good pharmacological activity in several models of epilepsy, pain, psychiatric disorders following oral administration, not explained by its poor pharmacokinetic profile (bioavailability 0.3%; T ½ <15 min)


- Except by the possible formation of an active metabolite after oral administration (PK profile of NW-3509 indicated an improvement in bioavailability (17%) and T ½ (42 min)




- The chemical variation of one substituent led to the synthesis of **NW-3509**

# Evenamide is active in a wide range of schizophrenia and psychiatric animal models as a monotherapy and as an add-on to existing antipsychotics

| | |
|---|---|
| **Information Processing Deficit** | ▪ **Pre-pulse inhibition (PPI) disrupted by dopamine activation (amphetamine -rat)** |
| | ▪ **Pre-pulse inhibition (PPI) disrupted by NMDA antagonists (ketamine , MK-801, PCP, -rat)** |
| | ▪ *Pre-pulse inhibition (PPI) disrupted by ketamine (add-on to clozapine ongoing- rat)* |
| | ▪ *Pre-pulse inhibition (PPI) disrupted by natural stimuli (sleep deprivation -rat)* |
| | ▪ *Pre-pulse inhibition spontaneous deficit (C57 mice)* |
| **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** |
| | ▪ *PCP induced hyperactivity in mice (add-on to clozapine ongoing)* |
| **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)** |

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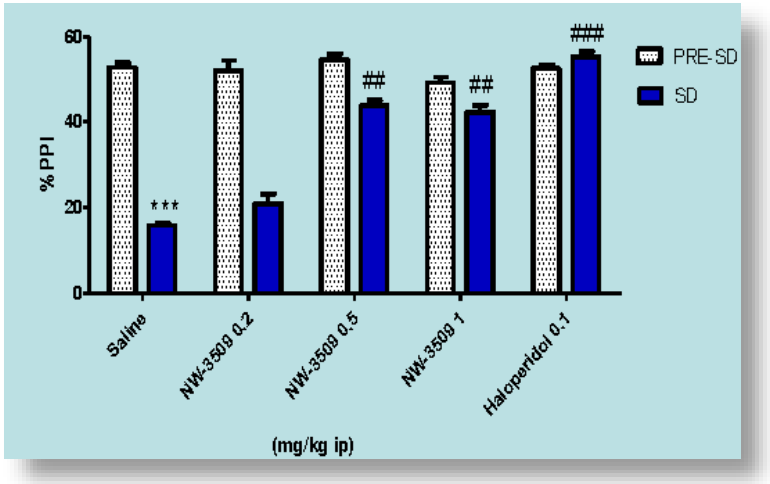
# Evenamide as a monotherapy reverses the PPI deficit induced by stress in sleep deprived rats

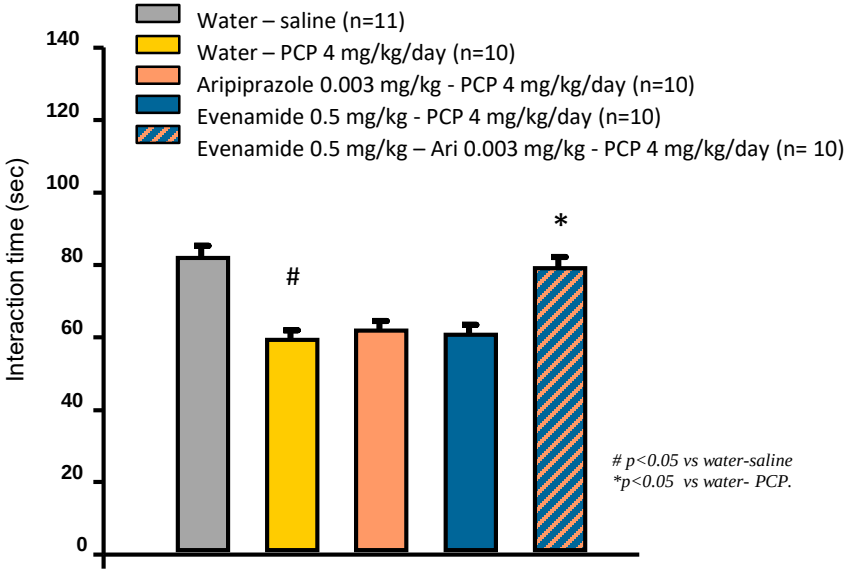
- Evenamide reverses PPI disrupted by natural highly stressful stimuli: the sleep deprivation (SD) procedure (72hr REM SD) in rats




- Evenamide minimal effective dose: 0.5mg/kg ip
- Evenamide administered 5 min before PPI test
- P<0.001 vs saline PRE-SD, p<0.01, p<0.001 vs saline SD
- N=8-18 rats per group

Note: Studies performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari - USCLA

# Combination of ineffective doses of Evenamide and Aripiprazole reverses the PCP-induced social interaction deficit




| Evenamide dose (mg/kg po) | Evenamide Mean plasma concentration at the time of test (15 min after administration) (ng/ml) |
|---|---|
| 1<br>*Monotherapy Active* | 19.13 |
| 0.5<br>*Add-On Active* | 9.19 |

- Separately neither Evenamide 0.5mg/kg nor aripiprazole 0.003mg/kg show a significant attenuation of PCP-induced social interaction deficits
- The combination of inactive doses of both compounds significantly reverses this deficits. The time spent by PCP treated rats in interacting is reinstated to the level of the control-saline treated rats

# Unlike other existing therapies, Evenamide has demonstrated efficacy in reversing PPI-induced deficit induced by a variety of pharmacological and natural stimuli

## COMPARATIVE EFFECT OF EVENAMIDE VERSUS SODIUM CHANNEL BLOCKERS AND ANTIPSYCHOTIC DRUGS

| Compound | Minimal Effective Doses on Different PPI Deficit Models | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Amphetamine (2.5mg/kg sc) rat** | **MK-801 (0.2mg/kg ip) rat** | **PCP (5mg/kg ip) rat** | **Ketamine (6-10 mg/kg sc) rat** | **Sleep deprivation (72hr) rat** | **Spontaneous deficit in C57 mice** | **Sedative effect (effect on startle)** |
| **Evenamide** | 1.25-2.5mg/kg po (monotherapy) 0.62-1.25mg/kg po (add-on) | 1.25-5mg/kg po (monotherapy) | 15mg/kg po (monotherapy) | 5mg/kg po monotherapy 1.25mg/kg po (add-on) | 0.5mg/kg ip (monotherapy) | 10mg/kg po (add-on) | No effect up to 45mg/kg po |
| **Lamotrigine** | Not active [1,2] | 10mg/kg ip | Not active at 10mg/kg ip | Not active[7] | NA | NA | No effect at 10mg/kg ip |
| **Carbamazepine** | Not active at 10mg/kg ip | Not active at 10mg/kg ip / Not Active [3] | NA | 50 mg/kg (in mice) | NA | NA | No effect at 10mg/kg ip |
| **Haloperidol** | 0.1mg/kg ip | Not active at 0.1mg/kg ip | Not active [4] | Not active[7] | 0.1mg/kg ip | 0.3-1mg/kg ip | Effect at 0.1-0.3mg/kg ip |
| **Risperidone** | 0.1mg/kg ip | 0.1mg/kg ip | 1mg/kg ip | Not active[7] | 1mg/kg ip | NA | Effect at 0.1-0.3mg/kg ip |
| **Clozapine** | Active on apomorphine [5] | Active [5,6] | 5mg/kg ip | 7.5 mg/kg ip | 5mg/kg ip | NA | No effect at 5mg/kg ip |

NA = Not Available

When internal data not available, data from published literature is indicated: 1. Ong et al 2005; 2. Brody et al 2003; 3. Umeda et al 2006; 4. Suemaru et al 2004; 5. Frau et al 2007; 6. Levin et al 2007; 7. Cilia et al 2007

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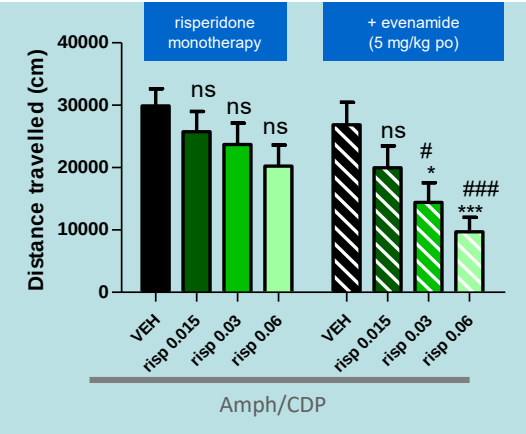
# Add-on: Evenamide augments the effect of antipsychotics in hyperactivity models

**Mania model: amph/CDZ hyperactivity**

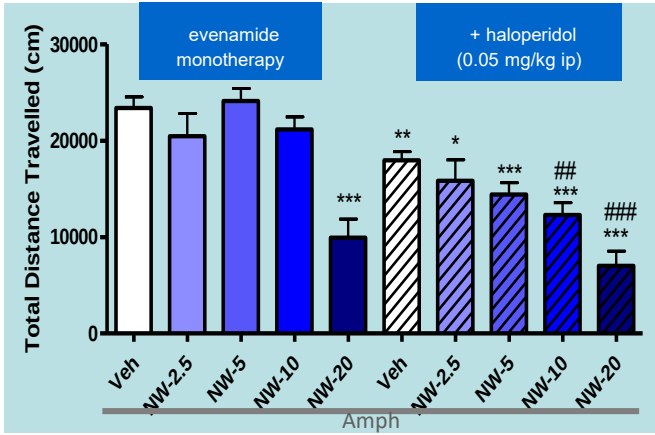
**Add-on with risperidone**
**MED 5 mg/kg *po* (+risperidone 0.03 mg/kg *ip*)**




One-way ANOVA, Bonferroni's post-hoc test *p<0.05; ***p<0.001 versus Amph/CDP vehicle; Two-way ANOVA, Bonferroni's post-hoc test #p <0.05; ###p<0.001 vs Amph/CDP+NW-3509A. n=14-15 mice per group.

**Psychosis model: amphetamine hyperactivity**

**Add-on with haloperidol**
**MED 10 mg/kg *po* (+haloperidol 0.05 mg/kg *ip*)**




Two-way ANOVA. Bonferroni's multiple comparison tests *p<0.05; **p<0.01 and ***P<0.001 versus vehicle (veh) ; ##p<0.01 and ###p<0.001 versus amph+haloperidol. n=10-40 mice per group

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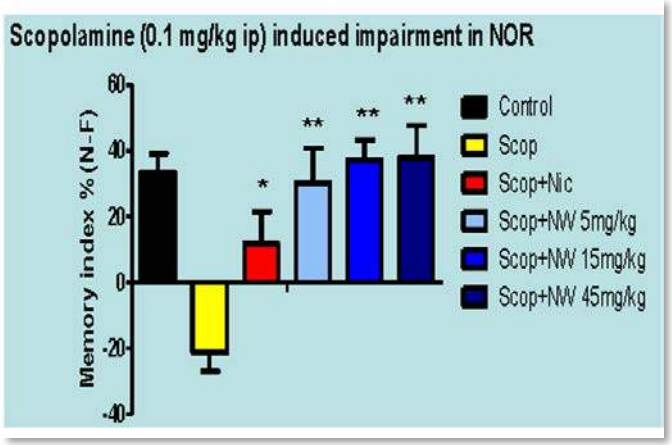
# Effects of Evenamide on short and long-term memory tests

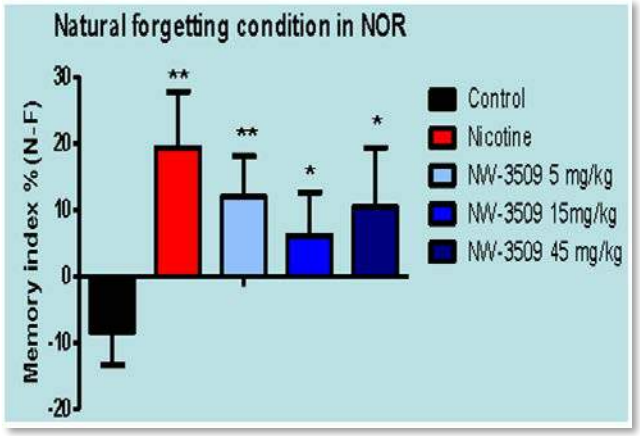
## Novel Object Recognition (NOR) test in rat
## Minimal effective dose 5 mg/kg po

**EFFECT ON SCOPOLAMINE-INDUCED AMNESIA - 1 H ITI**




- 1 H ITI : 1 hr interval between sample trial (2 equal objects) and choice trial (familiar + novel object)
- Scopolamine 0.1 mg/kg ip administration 30 min before sample trial
- Nicotine 0.4 mg/kg sc administration 20 min before sample trial
- Evenamide po administration 15 min before sample trial

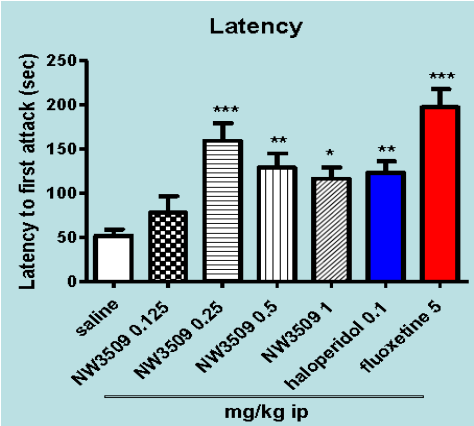
**EFFECT ON NATURAL FORGETTING – 24 H ITI**




- 24 H ITI : 24 hr interval between sample trial (2 equal objects) and choice trial (familiar + novel object)
- Nicotine 0.4 mg/kg sc administration 20 min before both sample and choice trial
- Evenamide po administration 15 min before both sample and choice trial

# Effects of Evenamide in a model of Impulse Control disorder

**Resident Intruder test in mice.**
Minimal Effective dose 0.25 mg/kg *ip*




- Minimal effective dose is 0.25mg/kg ip
- Both resident and intruder mice (CD1) were isolated for 4-8 weeks
- N= 15-30 mice per group
- *p<0.05, **p<0.01, ***p<0.001 versus saline group Tukey's test

Studies performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari - USCLA

- Significant effect on <u>latency to the first attack</u>
- No significant effect of Evenamide on the other two parameters tested: duration and number of attacks
- Unlike haloperidol, Evenamide had no effect on baseline locomotor activity at any dose

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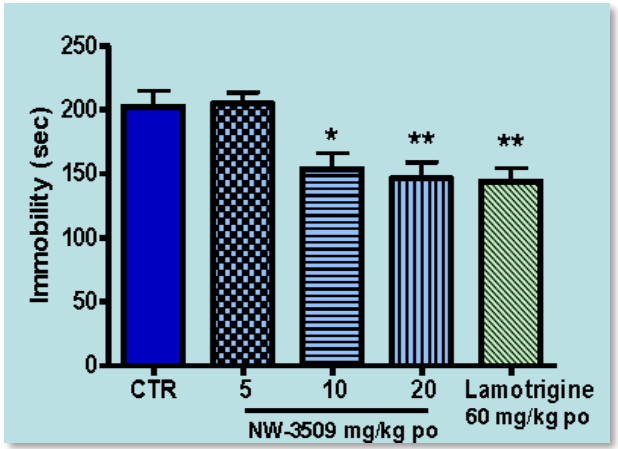
# Effect of Evenamide in animal models of mood disorders

## Depression Model: TST

Minimal effective dose 10 mg/kg po

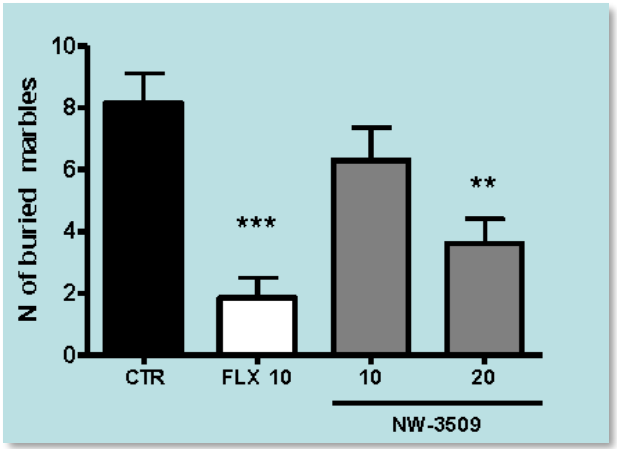



- The Tail Suspension Test (TST) is an animal model widely used and predictive of potential anti-depressant drugs
- C57Bl/6J male mice suspended by the tail after a while stop struggling and stay immobile. Immobility behaviour is an index of depression/despair-like status (the total time of immobility (sec) during a 6 min period of test was calculated).

Studies performed by Dr Bortolato, Dept. of Pharm. Sciences, Univ. Cagliari - USCLA

## OCD model: marble burying test

Minimal effective dose 20 mg/kg po




- CD1 mice placed individually in a cage containing a number of glass marbles spontaneously tend to bury the glass marbles present
- Several compounds which attenuate anxiety, depression, psychosis or obsessive-compulsive disorder reduce the number of marbles buried
- Therefore the test has predictive validity for anti-anxiety and anti-OCD potential compounds

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# Estimated human doses expected to affect the target and to produce *in vivo* activity

| Target / model | Technique /administration | concentrations active on the target * | Plasma Levels Cmax (µM) ** | Minimal Effective Dose (mg/kg po) *** | Projected Minimal Effective Dose (mg) in humans, (rat dose x HED factor x 60 kg) **** |
|---|---|---|---|---|---|
| **Na channels** (cortical neurons neonatal rat) | Patch Clamp electrophysiology | **0.98 µM** | **0.075 µM** (21 ng/ml) | 1.4 | **13.4** |
| **Na channels** Human recombinant CNS subtypes (Nav1.1, Nav1.2, Nav1.3, Nav1.6) | Automated electrophysiology | **1.49-1.96 µM** | **0.12-0.15 µM** 36.2-41.8 ng/ml | 2.4-2.75 | **23 – 26.4** |
| **Inhibition of glutamate release** | In vivo microdyalisis- local administration | **1 µM** | **0.077 uM** (21.4 ng/ml) | 1.4 | **13.4** |
| **PPI (Amph) (rat)** | Add-on to haloperidol | | **0.07 µM** 19 ng/ml | 1.25 | **12** |
| **PPI (Amph) (rat)** | Add-on to risperidone | | **0.03 µM** 10 ng/ml | 0.62 | **6** |
| **Social Interaction (rat)** | Add-on to aripiprazole | | **0.033 µM** 9.19 ng/ml (measured) | 0.5 | **4.8** |

* These concentrations are taken from experimental results and are assumed to be needed in the brain

** Estimated plasma concentrations are based on brain/plasma ratio of 13 as measured in rat PK study

*** Doses corresponding to the estimated plasma levels are extrapolated from PK study in the rat

**** HED (human equivalent dose) factor (rat) = 0.16

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# Evenamide is not selective for voltage-gated sodium channel (VGSC) subtypes

## Recombinant human sodium channel subtypes

- Evenamide inhibits multiple Nav subtypes
  - low µM potency in the inactivated state and high resting/inactivated safety ratios (>>10) were observed against human recombinant sodium subtypes (Nav1.1 – 8)

| Sodium channels (human recombinant) | Tonic Block (Kr µM) | **Affinity for the Inactivated-State (Ki)** |
|---|---|---|
| Nav1.1 | 33.33 | **1.92** |
| Nav1.2 | 35.01 | **1.49** |
| Nav1.3 | 39.39 | **1.96** |
| Nav1.4 | 32.91 | **1.85** |
| Nav1.5 | 36.03 | **0.82** |
| Nav1.6 | 23.63 | **1.65** |
| Nav1.7 | 16.80 | **1.21** |
| Nav1.8 | 25.73 | **1.85** |

- *Data obtained with an automated electrophysiology assay (ChanTest) on CHO cells expressing different human recombinant sodium channel subtypes.*
- *Ki values have been calculated using $IC_{50}$ data from the resting and depolarized condition applied to equation $1/IC_{50dep}=h/Kr + (1-h)/Ki$. (Kr= $IC_{50}$ for the block of the resting/closed state; $IC_{50dep}$= $IC_{50}$ for the block of the channel in the depolarized condition, h and (1-h) are the fractions of channels present at the rest and depolarized potentials, respectively)*

# STUDY 002: Multiple Dose Study in Patients with Chronic Schizophrenia

4-week, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and preliminary evidence of efficacy in minimally 90 patients (3:1 ratio modified later to 1:1) treated with a dose range of evenamide or placebo. Dose increase dependent on tolerability:

- Level 1: 15 mg BID (or placebo) on Day 1, Level 2: 20 mg BID (or placebo) on Day 8, Level 3: 25 mg BID (or placebo) on Day 15.

**Centers/countries:** 5 sites (US: 2 - 60 pts; India: 3 -29 pts).

**Population:**

- Patients on risperidone (2 mg/day or higher) or aripiprazole (10 mg/day or higher) who are still symptomatic, despite ≥ 4 weeks of treatment at a stable dose, and diagnosed ≥ 2 years ago; current symptoms present for at least one month
- Total PANSS <80; Clinical Global Impression - Severity (CGI-S) rating of mildly, moderately, or moderately severely ill (score of 3, 4 or 5). Patients with 1 or more core positive symptoms (hallucinations, delusions, excitement, suspiciousness/persecution and hostility) rated moderately severe or higher, or rating of moderate on more than 2 of these items, were excluded

**Objectives:**

- ***Primary*** – Safety and tolerability.
- ***Secondary*** – Efficacy (PANSS positive, PANSS total, CGI-S and CGI-C, Level of Functioning [LOF])

**Safety Monitoring Board:** Comprised of 3 independent members (2 psychiatrists, 1 statistician), who also provided oversight of Study 001

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# Study 002: Demographics and baseline characteristics

- **No. of Patients:** 89 (Evenamide – 50; Placebo – 39)
- **Age:** 43.9 (11.2)* years
- **Gender:** 86.5% male
- **Weight:** 83.7 (18.4) kg
- **BMI:** 27.8 ( 5.17) kg/$m^2$
- **Duration of Schizophrenia:** 217.6 (131.3) months
- **No. of Hospitalizations for Schizophrenia:** 2.9 (5.5)
- **PANSS Total Score:** 62.9 (7.4)
- **CGI-Severity:** 3.4 (0.5)
- **Concomitant Antipsychotics (percentage of patients):**
  - Risperidone – 78.7%
  - Aripiprazole – 21.3%

- * Numbers for all continuous measures represent mean (standard deviation)

# Study 002: Summary of safety

- **9 subjects discontinued** the study prematurely: 8 (16.0%) evenamide, 1 (2.6%) placebo;
- **2 (both on evenamide) of these 9 subjects discontinued for AEs**: atrial fibrillation and seizure (both SAEs)
  - **Atrial fibrillation** – highest plasma concentration of evenamide in this patient [91.3 ng/mL] was ~11 fold less than that producing cardiac effects in animals
  - **Seizure** – highest plasma concentration of evenamide in this patient [74.8 ng/mL] was ~16-40 fold less than that associated with seizures in animals
- **No effect on ECG** (performed 15 times in the 27-day study)
  - Change from Baseline at Day 28 (NW-3509 vs. placebo): QTcB: 0.24 vs. 0.14 ms; QTcF: -3.18 vs. -5.35 ms
- **Most frequently reported AEs** in Nervous System and Psychiatric Disorders (NW-3509 vs. placebo)
  - Nervous System: Somnolence (16.0% vs. 12.8%), Headache (6.0% vs. 0)
  - Psychiatric Disorders: Insomnia (10.0% vs. 2.6%), Nightmare (4.0% vs 0), Abnormal dreams (evenamide - 1 patient, placebo - 1 patient), Anxiety (evenamide – 1 patient) and Depression (evenamide – 1 patient)
- **No evidence of AEs usually associated with antipsychotics:**
  - no EPS, sedation, sexual dysfunction, prolactin increase or weight gain
  - no clinically relevant changes in VS, labs

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# Study 002 – Efficacy (1)

**PANSS Positive Scale Total Score: Statistical Analysis of Change from Baseline using MMRM by Visit (mITT Population)**

| | Change from Baseline | | | | Difference: NW-3509 vs. Placebo | | |
|---|---|---|---|---|---|---|---|
| | NW-3509 (N=48) | | Placebo (N=39) | | | | |
| Visit | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean (SE) | (95% CI) | p-value (a) |
| Day 8 | 46 | -1.26 (0.245) | 38 | -0.04 (0.263) | -1.22 (0.350) | (-1.92, -0.52) | 0.0008 |
| Day 15 | 44 | -1.47 (0.310) | 38 | -0.59 (0.331) | -0.88 (0.446) | (-1.76, 0.01) | 0.0528 |
| Day 22 | 42 | -2.27 (0.404) | 38 | -1.30 (0.430) | -0.97 (0.584) | (-2.14, 0.19) | 0.0993 |
| Day 28/Endpoint | 47 | -2.06 (0.439) | 39 | -0.87 (0.478) | -1.19 (0.643) | (-2.47, 0.09) | 0.0678 |

(a) p-value for difference between evenamide and placebo groups from ANCOVA (LOCF) analysis with region and treatment as fixed effects, and baseline value as covariate.

**PANSS Positive Scale Total Score: Proportion of patients rated as improved[(a)] from baseline (mITT population)**

| | Evenamide (N=48) | | Placebo (N=39) | | |
|---|---|---|---|---|---|
| **Visit** | n | n/n (%) | n | n/n (%) | p-Value (b) |
| Day 8 | 46 | 28/46 (60.9) | 38 | 11/38 (28.9) | 0.0044 |
| Day 15 | 44 | 29/44 (65.9) | 38 | 14/38 (36.8) | 0.0143 |
| Day 22 | 42 | 31/42 (73.8) | 38 | 20/38 (52.6) | 0.0638 |
| Day 28/Endpoint | 47 | 35/47 (74.5) | 39 | 17/39 (43.6) | 0.0043 |

(a) Improvement = Any improvement in PANSS Positive Score compared to baseline; (b) p-value for Fisher's Exact chi-square test.

# Study 002 – Efficacy (2)

**CGI-C: Proportion of patients rated as improved(a) from baseline (mITT population)**

| | Evenamide (N=48) | | Placebo (N=39) | | |
|---|---|---|---|---|---|
| **Visit** | **n** | **n/n (%)** | **n** | **n/n (%)** | **p-Value (b)** |
| Day 8 | 46 | 15/46 (32.6) | 38 | 6/38 (15.8) | 0.0845 |
| Day 15 | 44 | 21/44 (47.7) | 38 | 8/38 (21.1) | 0.0198 |
| Day 22 | 42 | 24/42 (57.1) | 38 | 14/38 (36.8) | 0.012 |
| Day 28/Endpoint | 47 | 26/47 (55.3) | 39 | 14/39 (35.9) | 0.0855 |

(a) Improvement = Rating of 1, 2 or 3 (very much, much or minimally improved, respectively); (b) p-value for Fisher's Exact chi-square test.

# Evenamide: Regulatory interactions and Phase III clinical development plan

Discussed with Health Authorities in:

- Spain, Denmark, Sweden, Germany, UK (CHMP), US FDA - End of Phase II , Canada (scheduled for Nov. 5th)

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**

# Study 003: Study design

A Phase IIb/III, prospective, randomized, double-blind, placebo-controlled, parallel-group, multi-center, 6-week study to evaluate the efficacy, safety, and tolerability of three add-on fixed doses of Evenamide (7.5, 15 and 30 mg BID) or placebo in patients with established schizophrenia not responding adequately to their current single atypical antipsychotic medication.

**Patients/centers/countries:** 520 patients (130/group) ~30 centers in Canada, Europe, India, Latin America and North America

- **Population:**
  - Male/female (not of CBP) outpatients, age ≥ 18 Y, chronic schizophrenia (DSM-5) on a stable dose of an atypical antipsychotic (min. 4 weeks prior to screening);
  - Total score ≥ 20, and a score of 4 (moderate) or more on at least 2 of 4 core symptoms of psychosis (conceptual disorganization, hallucinatory behaviour, suspiciousness and unusual thought content);
  - CGI-S of moderately to severely ill (4-6); functional deficits (GAF < 50)
  - Patient has achieved remission or "good response" to any antipsychotic within past 5 years

Screening 3-21 days; patients meeting all selection criteria at screening and baseline will be randomized to treatment and receive their first dose in the clinic on Day 1. Return for scheduled visits on Days 8, 15, 29 and 43 (endpoint)

**Extension (Study 005):** Separate 46-week, double-blind, placebo-controlled, extension; continue double-blind treatment on same dose/treatment.

# 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
- Possibility to contact high clozapine prescribers only
  - 80% of the CTRS patients in 10 US states, selected VA, state, city hospitals and prison system
- Similar prevalence estimated for EU, Japan and Canada

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# Study 004: Study design

A phase IIb/III, prospective, randomized, double-blind, parallel-group, multi-center, 8-week study
to determine the efficacy, safety, and tolerability of add-on treatment with Evenamide (15 or 30 mg BID) or placebo in patients with treatment-resistant schizophrenia (TRS) not responding adequately to clozapine.

**Patients/centers:** 450 patients (150/group), 30 centers in Canada, Europe, India, Latin America and US

- **Population:**
  - Male/female (not of CBP) outpatients with chronic schizophrenia (DSM-5) with a TRS diagnosis of at least 2 yrs, despite an adequate trial of clozapine (≥ 12 wks, with a dose of ≥ 300 mg/day for 8 weeks), and a plasma clozapine concentration of ≥ 300 ng/ml
  - Total score ≥ 20, and a score of 4 (moderate) or more on at least 2 of 4 core symptoms of psychosis (conceptual disorganization, hallucinatory behaviour, suspiciousness and unusual thought content);
  - CGI-S of moderately to severely ill (4 – 6); functional deficits (GAF < 41).

Screening 3-21 days; patients meeting all selection criteria at screening and baseline will be randomized to treatment and receive their first dose in the clinic on Day 1. Return for scheduled visits on Days 8, 15, 36, and 57 (endpoint).

**Extension (Study 006):** Separate 44-week open-label extension study; to maintain the blind in Study 004, all patients will have Evenamide dose titrated.