# EndeavourRx LLC

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Advanced Treatments for Disruption of Neurological Signaling

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# NON-SOLICITATION AND FORWARD-LOOKING STATEMENT

#### (continued)

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- Company Profile
- Neuromodulators
  - AMPAkines
  - GABAkines
- Organization
- Financial Status



#### **RespireRx Group– Key Assets**

# **RespireRx Group**



# **Underlying Science**

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#### **Neurotransmission**



- Neurons communicate through a process of neurotransmission in which they release chemical neurotransmitters that bind to specific receptors on adjacent neurons.
- RespireRx is developing drugs to modify neurotransmission in those disorders with alterations in neurotransmission

### **EndeavourRx - Neuromodulators**

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#### Neuromodulators Can Enhance Synaptic Transmission

- Neurons communicate by releasing chemical neurotransmitters that bind to specific receptors on the adjacent neuron.
- Neuromodulators do not act directly at the neurotransmitter binding site and have no intrinsic activity of their own but instead act at accessory sites that enhance or reduce the actions of neurotransmitters.
- Neuromodulators offer the possibility of developing "kinder and gentler" neuropharmacological drugs with greater pharmacological specificity and reduced side effects



#### **AMPAkines**

- Extensive safety database in Phase 1 and 2
- Significant improvement in cognition/attention in subjects experiencing sleep deprivation
- In three Phase 2 studies, CX717 and CX1739 restored breathing in humans and, in other studies, in animals, after impairment due to opioids without affecting opioid analgesia
- In a Phase 2 study, CX717 successfully produced rapid, statistically significant improvement in adult patients with ADHD
- Extensive preclinical data demonstrating significant improvement in motor function after spinal cord injury. A DOD funded Phase 2 study is about to begin at Shirley Ryan AbilityLab

#### Ampakines Reduce Opioid-Induced Respiratory Depression (OIRD) in Phase 2A Clinical Trials

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\* Approximately 15 and 10 mg/kg on a weight basis, respectively; comparable to animal doses

Validation of Doses for Target Engagement Prophylactic for Chronic Pain Patients Taking Opioids

# **CX717** Maintains the Analgesic Properties of Opioids While Antagonizing Respiratory Depression

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Delivery of a electrical stimulation to finger

- Alfentanil reduced the pain sensitivity (produced analgesia)
- Analgesia was unaffected by CX717



Data are expressed as the pain sensitivity, normalized to the Baseline measurement.

N = 15 and 16 per group. CX717 dose is 1200mg.

### **CX717 Significantly Improves ADHD**

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**Phase 2 Study of CX717 in Adult ADHD**: Randomized, double-blind, multi-center, 2-period crossover study that compared 2 doses of CX717 (200 or 800 mg BID) with placebo. Statistically significant effects were observed with 800 mg as early as week 1.

# **Ampakines – Spinal Injury – Bladder Function**



#### AMPAkine + Acute Intermittent Hypoxia (AIH) Vastly Improve Motor Neuron Firing

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- 1. All is used in SCI patients as an adjunct therapeutic treatment to improve motor functions, including respiration and walking due to its rapid triggering of neuroplasticity
- 1. AMPAkines have been shown to enhance neuroplasticity and increase neurotrophic growth factor (NGF)



8 weeks following surgery, AMPAkine (15 mg/kg) increases amplitude in electrical recordings taken from rat phrenic nerves

#### Next Step: Phase 2 Clinical Trial-CX1739 in the Treatment of SCI Funded by \$1.8 million Dept of Defense Grant to SRAL

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#### Blinded, Placebo-controlled, Escalating-dose Study Evaluating CX1739 in Patients with Spinal Cord Injury

#### Primary Objectives

- 1. Evaluate the safety of acute and multiple daily doses of CX1739 in patients with SCI
- 2. Evaluate the efficacy of CX1739 in improving bladder function and respiration

#### Secondary Objectives

- 1. Evaluate the effect of acute and multiple BID doses of CX1739 on motor function and recovery, with and without AIH in patients with SCI
- 2. Assess the impact of CX1739 on SCI EDGE outcomes measures as appropriate

RespireRx and now EndeavourRX are working with academic collaborators including the University of Florida and The Shirley Ryan AbilityLab to advance the development of CX1739 for the treatment of spinal cord injury. Above clinical trial funded by a \$1.8 million grant from the Department of Defense

#### GABAkines

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#### **Animal Models**

- Epilepsy in thirty-three animal models, KRM-II-81 was superior or equivalent to standard treatment
- KRM-II-81 (three studies) dramatically reduced epileptic activity in brain tissue removed from patients with untreatable epilepsy
- Pain in twelve animal models of our GABAkines, seven of which were with KRM-II-81, the GABAkines were superior or equivalent to standard treatment
- KRM-II-81 does not produce side effects associated with standard drugs, such as sedation, tolerance, dependence, withdrawal, etc.
- Also active in animal models of anxiety and depression

#### Superior Anti-convulsant Efficacy of KRM-II-81 over Standard of Care



Model System	Species	Efficacy	Reference
CHEMICAL SEIZURE			
PROVOCATION MODELS			
Pentylenetetrazol – clonic seizures	Rat	= Diazepam	Witkin et al., 2018
Pentylenetetrazol – clonic seizures	Mouse	= Diazepam	Knutson et al., 2020
Pentylenetetrazol – tonic seizures	Mouse	= Diazepam	Knutson et al., 2020
Pentylenetetrazol – lethality	Mouse	= Diazepam	Knutson et al., 2020
Pentylenetetrazol – seizure threshold	Rat	<mark>&gt; Diazepam</mark>	Witkin et al., 2018
Cocaine – clonic seizures	Mouse	> Diazepam	Knutson et al., 2020
4-Aminopyridine – clonic seizures	Mouse	> Diazepam	Knutson et al., 2020
4-Aminopyridine – tonic seizures	Mouse	> Diazepam	Knutson et al., 2020
4-Aminopyridine – lethality	Mouse	= Diazepam	Knutson et al., 2020
NMDA – clonic seizures	Mouse	> Diazepam	Knutson et al., 2020
NMDA – lethality	Mouse	> Diazepam	Knutson et al., 2020
Picrotoxin – clonic seizures	Mouse	= Diazepam	Knutson et al., 2020
Picrotoxin – tonic seizures	Mouse	<mark>&gt; Diazepam</mark>	Knutson et al., 2020
Picrotoxin – lethality	Mouse	> Diazepam	Knutson et al., 2020
Strychnine – clonic seizures	Mouse	> Diazepam	Knutson et al., 2020
Strychnine – tonic seizures	Mouse	> Diazepam	Knutson et al., 2020
Strychnine – lethality	Mouse	<mark>&gt; Diazepam</mark>	Knutson et al., 2020
Pilocarpine – clonic seizures	Mouse	= Diazepam	Knutson et al., 2020
Pilocarpine – lethality	Mouse	= Diazepam	Knutson et al., 2020
ELECTRICAL SEIZURE PROVOCATION MODELS			
6Hz stimulation – 44mA	Mouse	ND	Witkin et al., 2018
Electroconvulsive Shock	Mouse	= Diazepam	Witkin et al., 2018

#### Superior Anti-convulsant Efficacy of KRM-II-81 over Standard of Care



Model System	Species	Efficacy	Reference	
SEIZURE SENSITIZATION				
Corneal kindling	Mouse	>Tpm	Witkin et al., 2020	
Amygdala kindling-ADT	Rat	<mark>&gt; Diazepam</mark>	Witkin et al., 2018	
Amygdala kindling-ADD	Rat	= Diazepam	Witkin et al., 2018	
Amygdala kindling-Seizure Severity	Rat	= Diazepam	Witkin et al., 2018	
Pentylenetetrazol kindling – Fully kindled	Mouse	= Diazepam	Knutson et al., 2020	
Pentylenetetrazol kindling - Expression	Mouse	= Diazepam	Knutson et al., 2020	
Pentylenetetrazol kindling - Development	Mouse	> Diazepam	Knutson et al., 2020	
Cocaine kindling-– Fully kindled	Mouse	> Diazepam	Knutson et al., 2020	
Cocaine kindling- Expression	Mouse	<mark>&gt; Diazepam</mark>	Knutson et al., 2020	
Cocaine kindling- Development	Mouse	<mark>&gt; Diazepam</mark>	Knutson et al., 2020	
PHARMACORESISTANT MODELS				
Mesial temporal lobe epilepsy	Mouse	<mark>&gt;Ltg, Val</mark>	Witkin et al., 2020	
Ltg-insensitive kindling	Rat	<mark>&gt;Ltg, Tpm</mark>	Witkin et al., 2020	
Kainate-induced chronic epilepsy	Rat	>Ltg, Lev	Witkin et al., 2020	
HUMAN EPILEPTIC TISSUE				
Picrotoxin stimulation	Human	Active	Witkin et al., 2018	
4-Aminopyridine stimulation	Human	Active	Witkin et al., 2018	
4-Aminopyridine stimulation	Human	Active	Unpublished	

### **Translational Results Predict Human Efficacy**



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#### KRM-II-81 Reduces Epileptiform Activity in Cortical Slices from Juvenile Epileptic Patients



Electrical recordings were made from epileptic brain tissues removed from juvenile patients with pharmaco-resistant epilepsy. Data presented with the approval of the parents

\*Reference - Witkin et al, Brain Res. 1722 (2019) 146356

# **Chronic Pain – Neuropathic and Inflammatory**



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Compound	Pain model	Species	Comparators	References
KRM-II-81	Acetic and lactic-acid-induced writhing, nesting and locomotion	ICR mice	Morphine	Lewter et al. (2017)
KRM-II-18B	Acetic and lactic-acid-induced writhing, nesting and locomotion	ICR mice	Morphine	Lewter et al. (2017)
KRM-II-81	Lactic-acid and ICSS behavior	Sprague Dawley rats	Ketorolac and diazepam	Moerke et al. (2019)
MP-III-024	Zymosin A-induced mechanical hyperalgesia	C57BL/6 mice	Gabapentin	Fischer et al., 2017
KRM-II-81	Formalin-induced tactile hyperalgesia	Sprague-Dawley rats	Tramadol and diazepam	(Witkin et al. (2019)
KRM-II-81	L5/6 nerve ligation – induced tactile hyperalgesia	Sprague-Dawley rats	Gabapentin	(Witkin et al. (2019)
KRM-II-81	L5/6 nerve ligation – senitization training - induced tactile hyperalgesia	Sprague-Dawley rats	Gabapentin	(Witkin et al. (2019)
KRM-II-81	Chemotherapy-induced thermal hyperalgesia	C57BL/6 mice	Gabapentin	Biggerstaff et al. (2020)
KRM-II-81	Chemotherapy-induced tactile hyperalgesia	C57BL/6 mice	Gabapentin	Biggerstaff et al. (2020)
HZ-166	Zymosin A-induced mechanical hyperalgesia	C57BL/6 mice	Gabapentin	Di Lio et al. (2011)
HZ-166	Chronic constriction injury	C57BL/6 mice	Gabapentin	Di Lio et al. (2011)
HZ-166	Inflammotory bladder pain	Neonatal Sprague- Dawlev rats	No	Kannampalli et al. (2017)



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# **Portfolio Development Status**

	Preclinical	Phase 1	Phase 2	Phase 3
Neuromodulators				
AMPAkines				
CX717/1739 - ADHD				
CX1739 - Spinal Cord Injury				
CX1739 – Central Sleep Apnea and OIRD (possibly RespireRx)				
CX1942 – soluble follow-up compound				
GABAkines KRM-II-81 – Preclinical Toxicology				

### **Biopharma VC Deals**

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Source: PitchBook • Geography: Global • As of September 30, 2024 Note: Determined as the highest phase of a trial that started prior to the round closing. Data combines trials between phases to the highest phase.

#### Biopharma VC deal value (\$B) by highest phase

80



Source: PitchBook • Geography: Global • As of September 30, 2024 Note: Determined as the highest phase of a trial that started prior to the round closing. Data combines trials between phases to the highest phase.

- From 2022 to 2024, Phase 2 companies consistently captured the most deals and the highest deal sizes.
- Phase 3 assets saw declining investments levels dropping from \$4.2 billion in 2021 to \$1.7 billion in 2024
- Companies advancing through mid-stage trials are better positioned to secure licensing deals or acquisitions

Phase 4

 In 2025, VCs are expected to prioritize companies advancing to Phase 2 and beyond

#### WHAT TO DO? RE-STRUCTURE ASSETS

# **RespireRx Group**



# WHY IS RESPIRERX FORMING SUBSIDIARIES?

#### \$18

#### Difficulties with Fund Raising

- Phase 4 80
- RespireRx assets not well recognized due to weak balance sheet liabilities >> assets
- RespireRx not current with its SEC financial filings
- Reliance on government grants
- On a macro-level average time between funding rounds increased 50% from 1.6 years in 2021 to 2.2 years in 2024\*\*
- Phase 3 failures such as Alzheimer drugs produced overall decline in biopharma investments\*\*

#### Subsidiary visibility and more

- Individual asset valuations/modeling
- Separation of research and development risks across entities
- Cleaner balance sheets
- Allows for investor selectivity
- Each financing round allows for separate capital market valuations
- \*\* Source: PitchBook Geography: Global As of September 30, 2024

# WILL IT WORK?

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### **Individual and Group Value Proposition**





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