



Corporate Overview



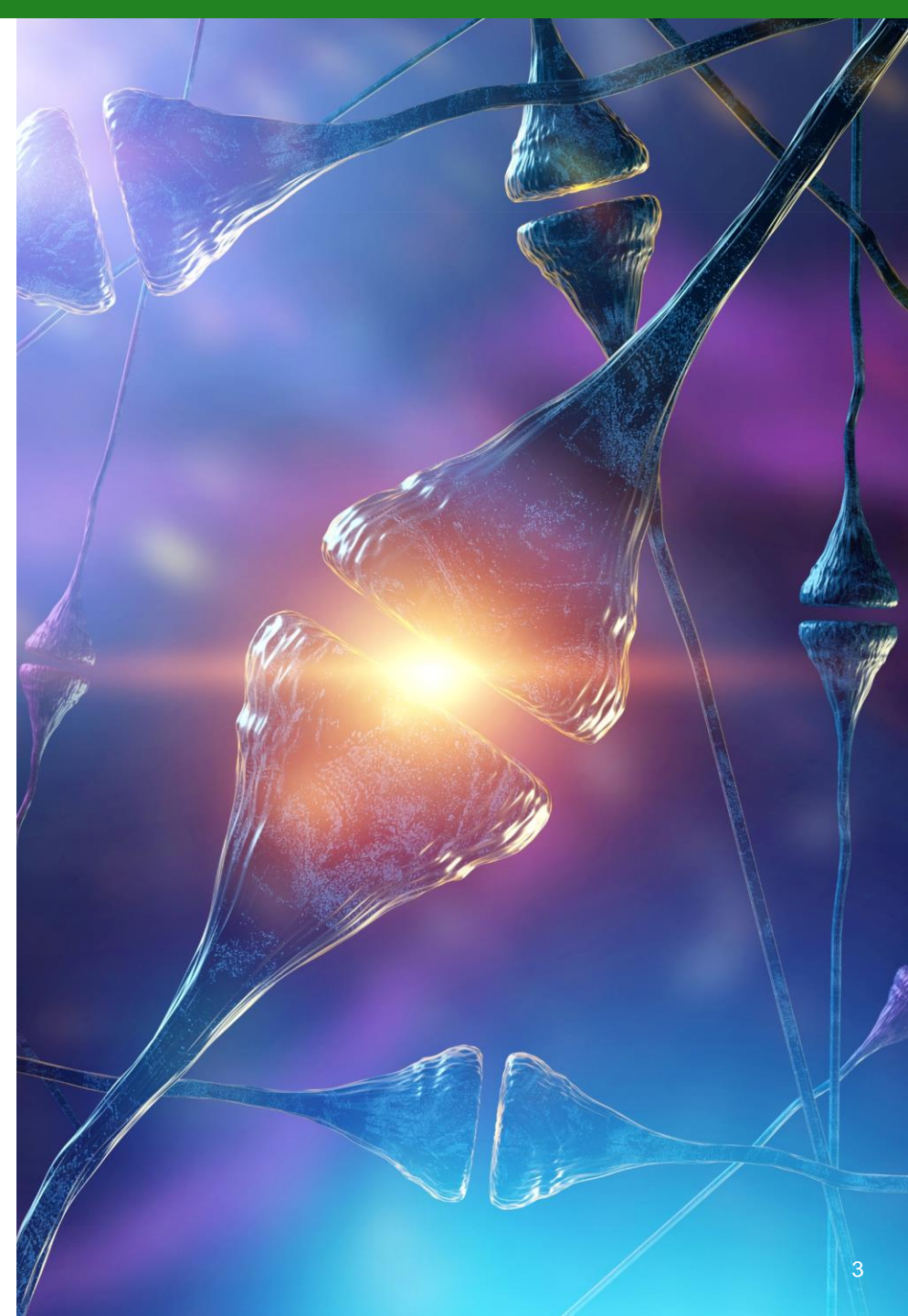
AVENUE THERAPEUTICS, INC. | NASDAQ: ATXI | November 2022

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Executive Summary

- Avenue Therapeutics is a specialty pharmaceutical company that seeks to develop and commercialize therapies to treat central nervous system (CNS) conditions
- Our portfolio includes two clinical stage programs, both of which we believe have significant market potential:
 - **IV Tramadol** (Phase 3) for acute postoperative surgical pain
 - **BAER-101** (Phase 1b) for epilepsy and acute anxiety
- Our clinical development strategy are designed to deliver near-term milestones that could build near-term value
- Potential to continue to expand pipeline through additional acquisitions in the rare / CNS disease spaces




Our clinical stage assets address large unmet patient and market needs in the CNS therapeutic space

Pipeline Asset	BAER-101	IV Tramadol	
Indication	Epilepsy and acute anxiety	Post operative pain	
Mechanism	Selective GABA-A 2, 3 receptor positive allosteric modulator	Opioid agonist & inhibitor of norepinephrine & serotonin re-uptake	
Key therapeutic value proposition	A safer and more tolerable benzodiazepine	Fills in the gap in acute care space between IV acetaminophen/NSAIDS and conventional narcotics	
Comparable companies and transactions	Cerevel Therapeutics (Market cap ~\$4.4B ^{**})	Cadence Pharmaceuticals (acquired by Mallinckrodt for \$1.4B in March 2014)	

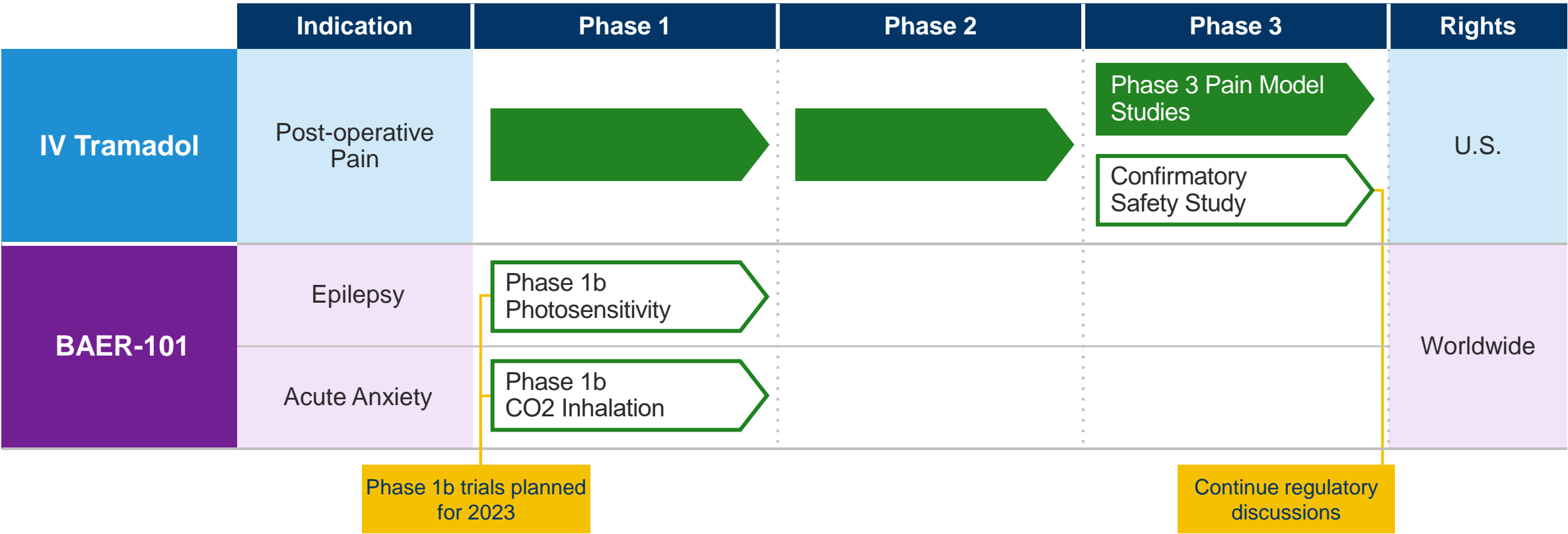
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Growing CNS portfolio

Our pipeline has potential near-term value inflection points



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BAER-101

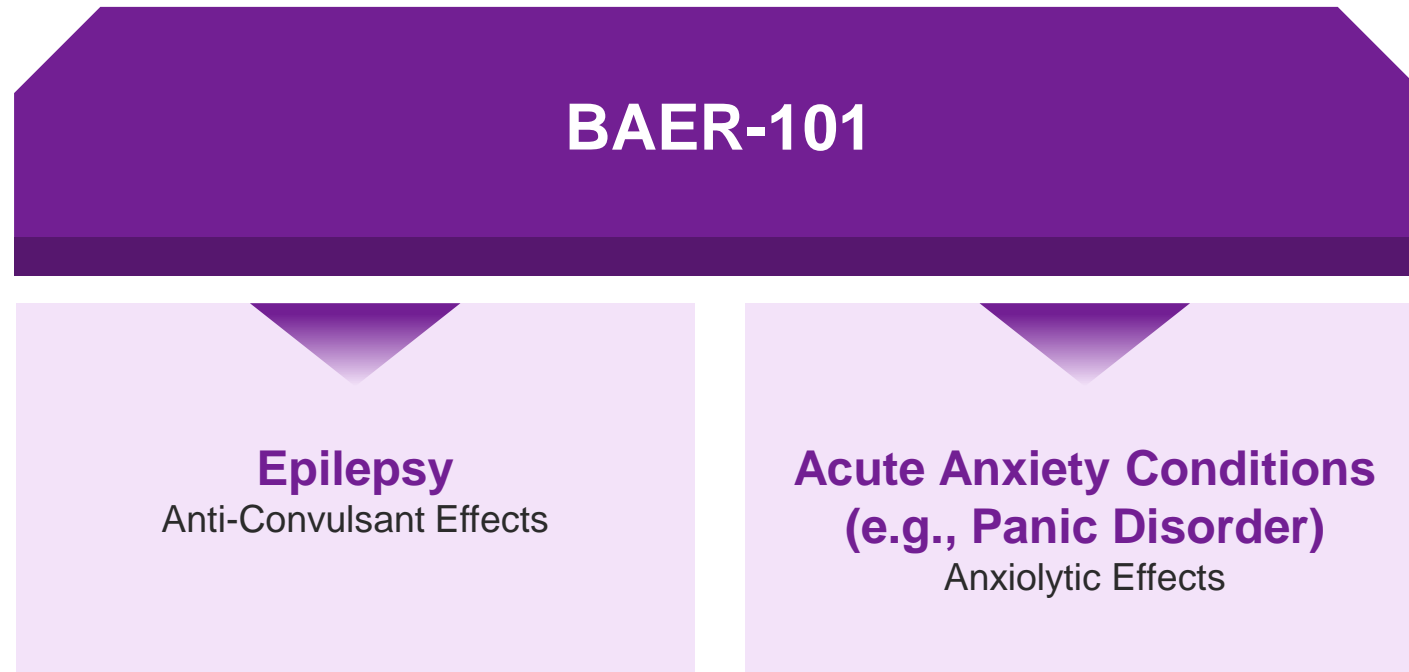
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IV Tramadol

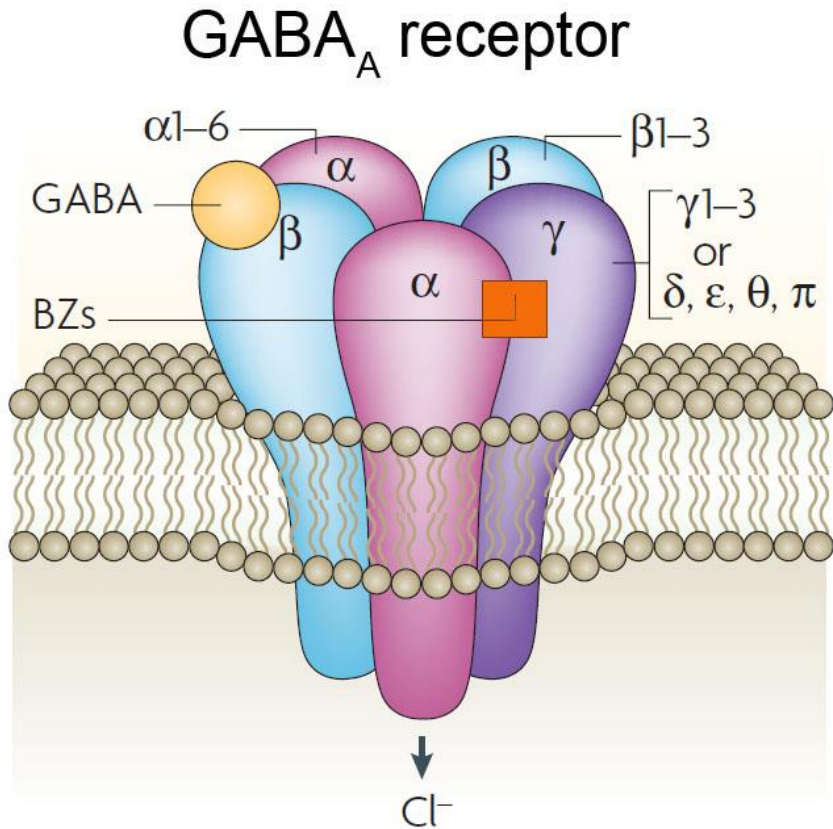
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**Acquire CNS Rare
Disease Assets**

BAER-101 is being developed for epilepsy and acute anxiety



BAER-101 is a selective GABA α receptor agonist that produces anticonvulsant and anxiolytic activity



- GABA receptors are the major inhibitory neurotransmitter receptors in the mammalian brain
- GABA receptors have three major subunits α β γ , which are organized into a pentameric structure
- Each subunit has multiple subtypes (e.g., $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 5$), and these have different dominant functions

BAER-101 targets GABA $\alpha 2$ and $\alpha 3$ subtypes more than $\alpha 1$ and $\alpha 5$, which should have important clinical consequences

BAER-101 may have a more tolerable side effect profile compared to nonselective benzodiazepines due to greater GABA subtype selectivity

Predicted effect of targeting GABA_A subtypes

Therapeutic Effect		GABA _A subtypes			
		α1	α2	α3	α5
Positive	Anti-convulsant	✓✓	✓✓	✓✓	
	Anxiolysis		✓✓	✓✓	
	Analgesia		✓✓	✓	✓✓
	Muscle Relaxation		✓✓	✓✓	
Negative	Sedation	✓✓			
	Cognitive Impairment	✓✓			✓✓
	Tolerance	✓✓			✓
	Addiction	✓✓	✓		

Benzodiazepines

- Benzodiazepines (BZDs) are **non-selective** agonists of the alpha subunits α1, α2, α3 and α5
- BZDs have an extensive adverse event profile that can limit the dose and its effectiveness: somnolence, sedation, cognitive impairment, overuse, misuse and addiction

VS

BAER-101

- BAER-101 is a **selective agonist** at the α2 and α3 subunits
- The goal of BAER-101 is to provide anticonvulsant and anxiolytic activity by minimizing adverse events and risk of tolerance and abuse

Epilepsy and acute anxiety patients are prescribed benzodiazepines, but have significant unmet needs for therapies with improved safety profiles

Epilepsy

Acute Anxiety Conditions

U.S. Prevalence

3 - 4M patients (~65M patients worldwide)

~6M patients (~360M patients with any anxiety condition worldwide)

Disease

Epilepsy is a chronic disease that manifests as recurrent seizures from abnormal electrical discharge in the brain

Panic disorder is a common form of an **acute anxiety disorder** manifesting as frequent panic attacks unrelated to specific situations

Treatment

Use of one or more anti-epileptic drugs (e.g., benzodiazepines are a class of anti-epileptic drugs that are used to treat seizures)

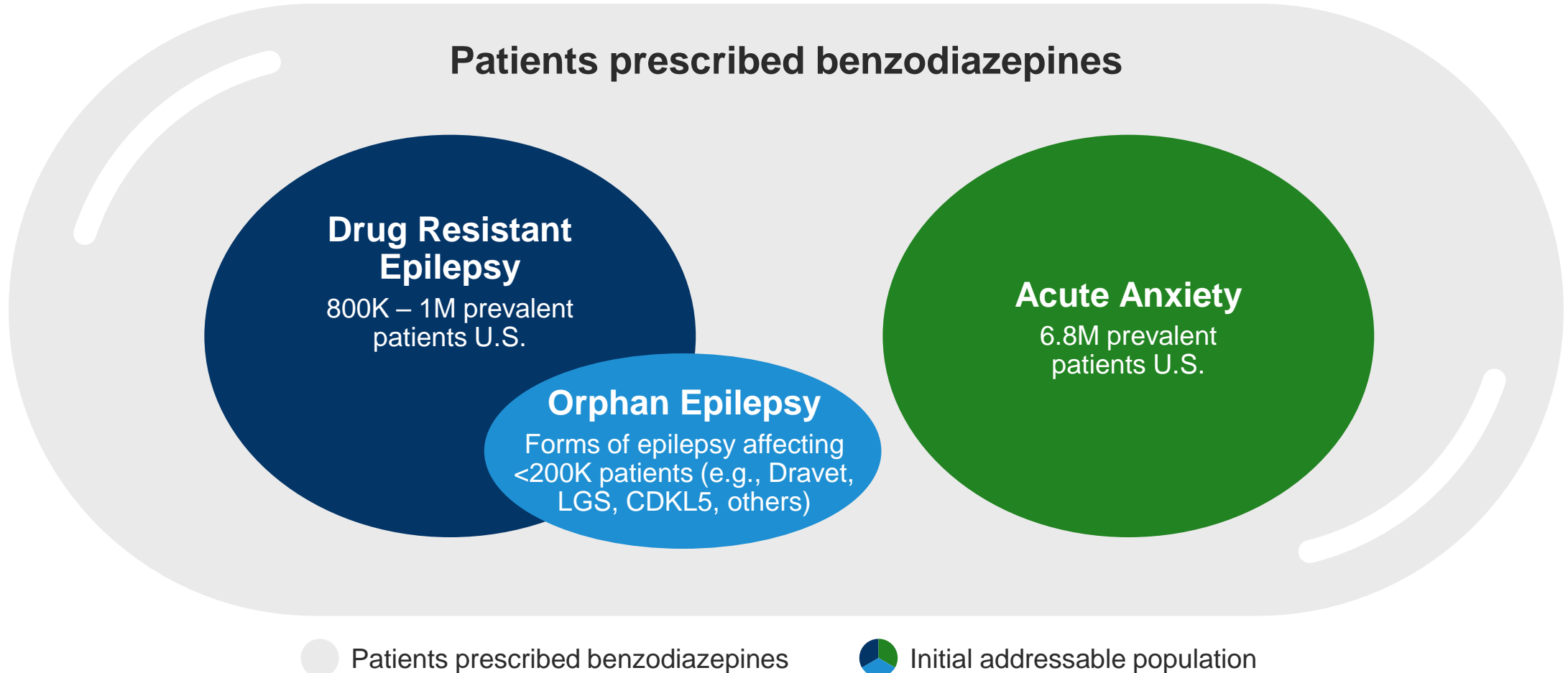
Combination of cognitive behavioral therapy and pharmacotherapy (e.g., benzodiazepines, tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors)

Unmet Need

Benzodiazepines are effective, but **not well tolerated due to significant side effects** including sedation, cognitive impairment, ataxia and addiction

BAER-101 can target the large market of patients prescribed BZDs by targeting drug resistant epilepsy, orphan epilepsy, or acute anxiety

Addressable market



BAER-101 has a compelling profile to address this market

**Selective
in vitro profile**

**Preclinical
disease model
efficacy**

**Preclinical
disease model
safety and
reduced abuse
liability**

**High receptor
occupancy**

**Safety
in humans
demonstrated
in clinical
trials in
>700 patients**

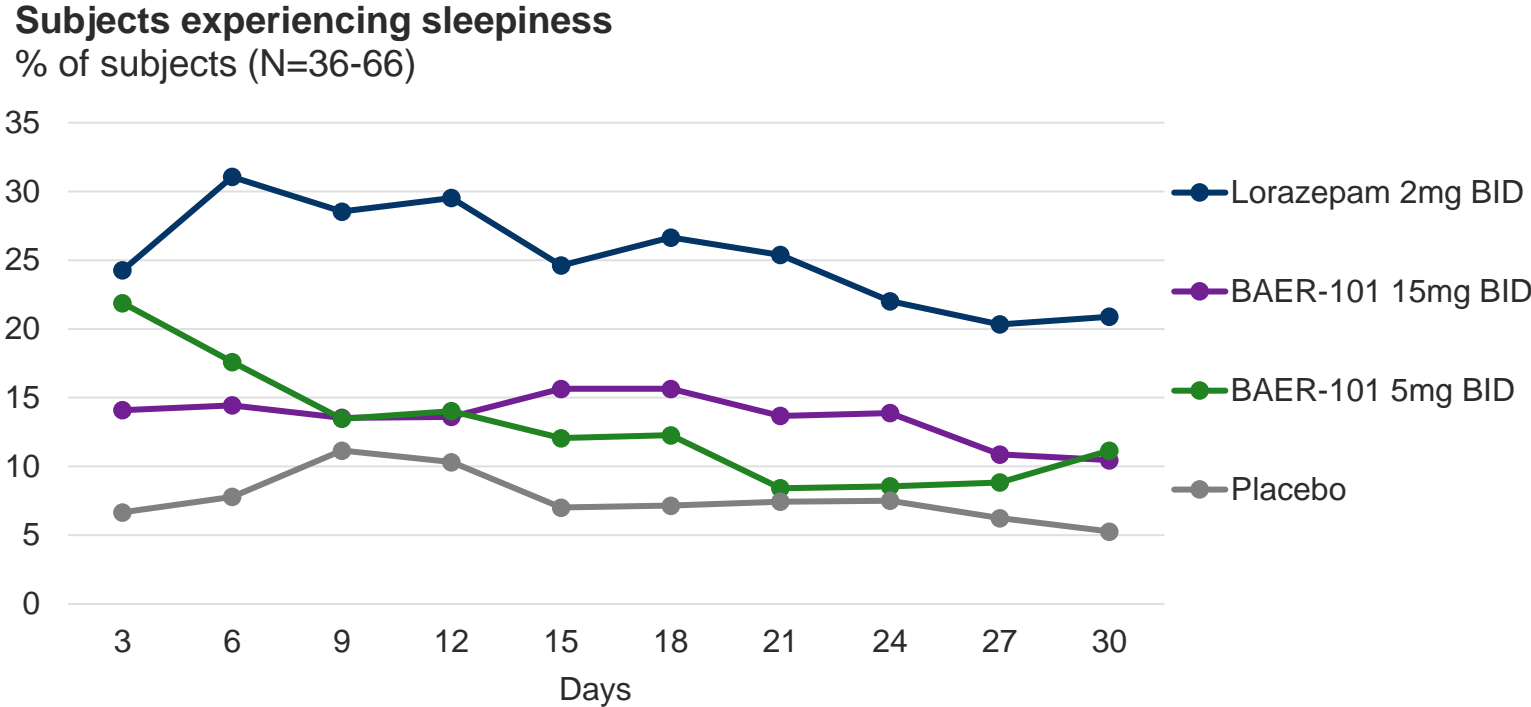
**BAER-101 was licensed from AstraZeneca (where it was called AZD7325)
in December 2019 with an extensive preclinical and clinical package**

AstraZeneca completed 10 clinical studies and demonstrated safety across trials at selected doses

- BAER-101/AZD7325 was tested in over 700 subjects (healthy volunteers and patients)
- Side effects were mild or moderate with the most common side effects being dizziness and somnolence
- In two Phase 2 studies, BAER-101 was tested in patients with generalized anxiety disorder (GAD), but missed the primary endpoint
 - A sub analysis of the data with removal of dropouts and non-compliant patients (as measured by drug plasma levels), showed a dose-related anxiolytic signal and a correlation between average exposure and efficacy
 - Further, Cerevel's darigabat (a similar molecule) also missed the primary endpoint in the truncated GAD study and showed promising results in two Phase 1b studies in epilepsy and acute anxiety
- BAER-101 was also tested in a human abuse liability study where risk abuse with BAER-101 appeared lower than lorazepam (a BZD)

Clinical studies demonstrate positive sedation and cognition effects

Example: subset analysis from Phase 2 generalized anxiety study



Compared to the benzodiazepine lorazepam, two dosing regimens of BAER-101 led to less sedation as captured by the measurement of sleepiness

We plan to initiate two Phase 1b studies that have the potential to translate well into later development programs

Epilepsy: Photosensitivity Study

- The epilepsy photosensitivity model is a clinical translational model that provides proof-of-principle for antiepileptic activity in early clinical development
- Testing new antiepileptic drugs in this clinical model can provide data that translates well into larger and other epilepsy populations

WARNING!

The following contains bright, flashing lights and/or imagery that may cause discomfort and/or seizures for those with photosensitivity epilepsy.
Viewer discretion is advised.

Acute Anxiety: Hypercapnia CO2 Inhalation Model

- The CO2 inhalation challenge is a clinical translational model well-established in both healthy volunteers and in patients with panic disorder that provides proof-of-principle for anxiolytic activity in early clinical development
- The model is sensitive to drugs used to treat anxiety disorders (including benzodiazepines & SSRIs) and emerging new treatments with novel mechanisms



BAER-101 is differentiated from others in the class

Differentiation vs other selective GABA α therapies

Company	Asset	Selectivity	Phase	Indications
Avenue Therapeutics	BAER-101	α 2/3-preferring	Phase 1	Epilepsy and panic disorder
Cerevel (Nasdaq: CERE)	darigabat	α 2/3/5-preferring	Phase 2	Epilepsy and panic disorder
Engrail Therapeutics	ENX101	α 2/3/5-preferring	Phase 1b	Epilepsy
Saniona (OMX: Sanion)	SAN711	α 3-preferring	Phase 1	Migraine and pain
RespireRx (OTC: RSPI)	KRM-II-81	α 2/3-preferring	Preclinical	TBD

- BAER-101 is selective to the α 2/3 receptor subunits and BAER-101 does not have high activity with the α 5 subunit
- Furthest along GABA α compound in clinical development is darigabat from Cerevel, which targets the α 5 subunit in addition to the α 2/3 receptor subunits
 - Targeting the α 5 receptor subunit is associated with tolerance development and this is potentially detrimental to developing a clinically effective drug for chronic use as resistance to the drug can occur over time. In addition, the α 5 receptor subunit is also associated with sedation
 - BAER-101, unlike darigabat, is less likely to lead to treatment resistance and sedation

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BAER-101

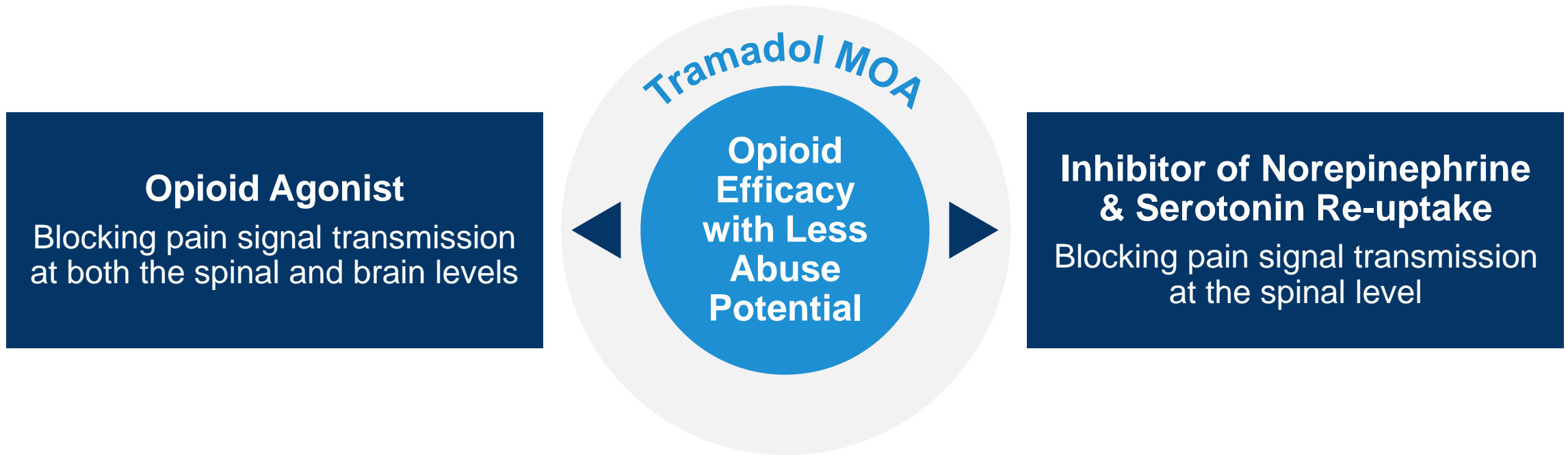
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IV Tramadol

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Acquire CNS Rare
Disease Assets

Tramadol has a unique dual mechanism of action among IV analgesics



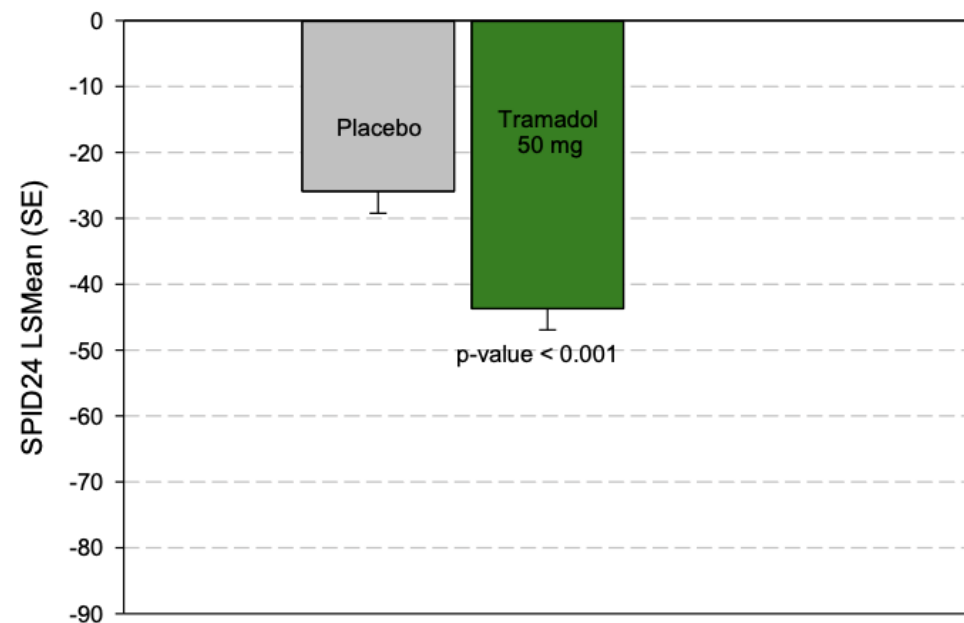
Schedule IV versus Conventional Narcotics (Schedule II)

**IV Tramadol has been safely used in Europe for 30 years –
Approximately 370 million doses were administered in Europe from 2010 to 2019**

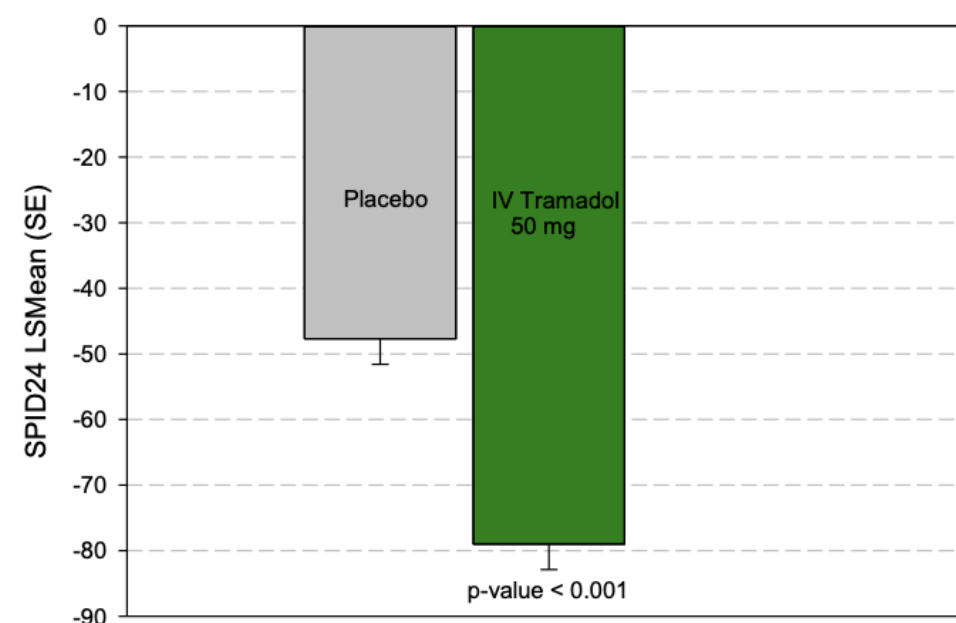
Safety and efficacy profiles have been demonstrated in two Phase 3 trials in over 700 patients

Both pain relief study models show benefit of Tramadol over placebo

Study AVE-901-102 (Bunionectomy) SPID24



Study AVE-901-103 (Abdominoplasty) SPID24



p-value is comparing IV tramadol to placebo.

IV Tramadol 50 mg achieved primary endpoint and all key secondary endpoints

Regulatory history and now a path forward for IV Tramadol NDA

2019

December 2019: We submitted a New Drug Application (“NDA”) for IV Tramadol and received a Complete Response Letter (CRL) from the FDA in October 2020.

2021

February 2021: We addressed the manufacturing issue identified in the CRL and resubmitted the NDA for IV Tramadol.

June 14, 2021: We announced that we had received a second CRL from the FDA regarding our NDA for IV Tramadol. While efficacy and safety endpoints were met in clinical trials, the FDA expressed a desire for additional safety data related to opioid stacking, which was not directly addressed in the two Phase 3 trials.

2022

August 9, 2022: We met with the FDA to discuss a study design to address the agency’s concern regarding opioid stacking, when rescue medicine is required in addition to IV tramadol, for patients with acute pain in the hospital monitored post surgical clinical setting.

We received the meeting minutes, and the FDA stated that the proposed new study design appears reasonable and seems to address many of their concerns.

The Company intends to continue the dialogue with the FDA and submit a detailed protocol to gain alignment on a single safety study – the outcomes of this study could form the basis for resubmission of the NDA for IV tramadol

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BAER-101

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IV Tramadol

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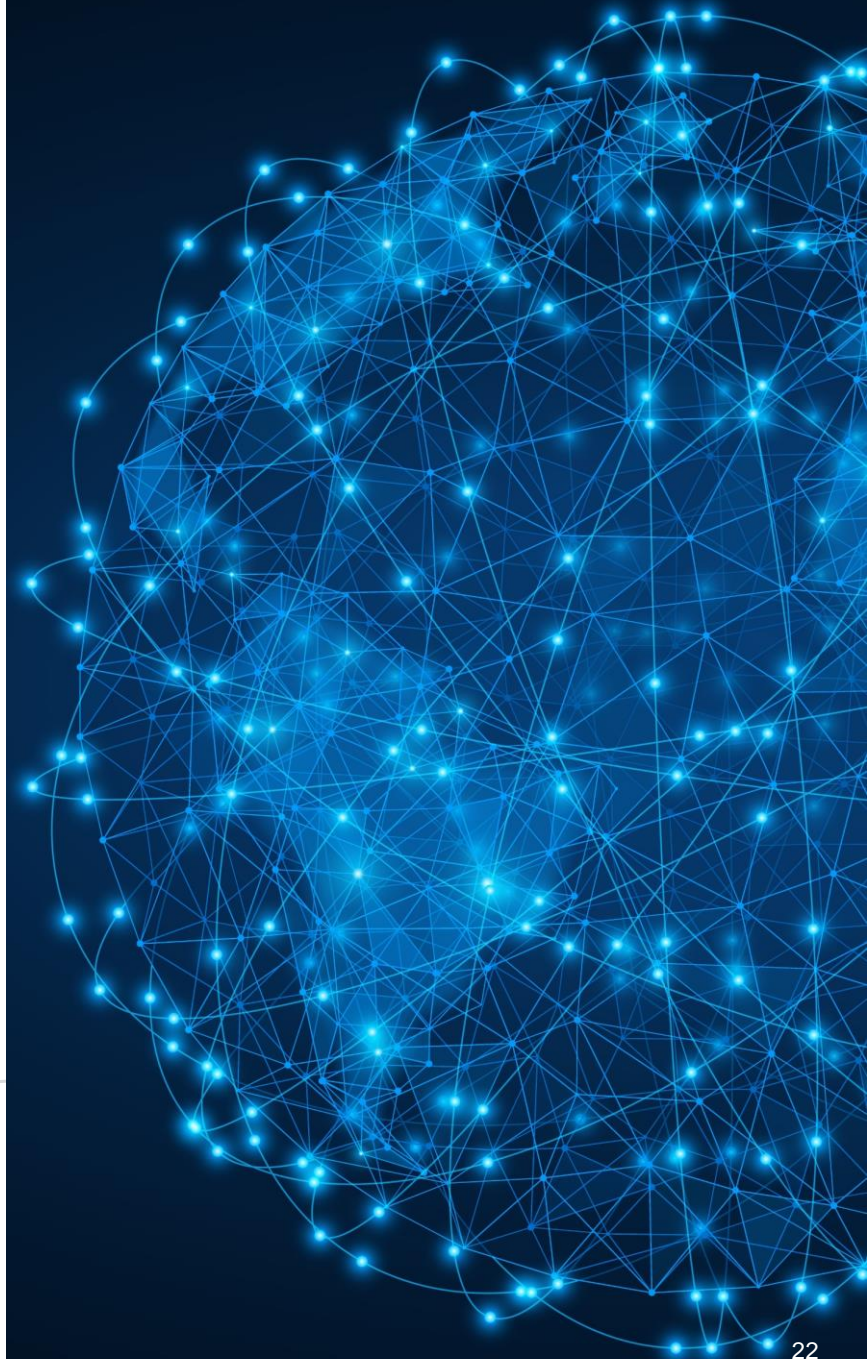
**Acquire CNS Rare
Disease Assets**

We are searching the world for first-rate CNS / rare disease assets with these characteristics

**Imaging and
Biomarker
Driven
Endpoints**

**Feasible
Clinical
Development
Programs with
Reasonable
Costs**

**Clinical Stage
with Human
Data**



We are led by an experienced management team and board of directors

Management



Alexandra MacLean MD
CEO



David Jin
Interim CFO



Michael Ryan
VP Clinical Operations &
Program Management



Board of Directors

Lindsay Rosenwald MD
CEO, Fortress Biotech

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Neil Herskowitz
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Curtis Oltmans
Chief Legal Officer, Fulcrum
Therapeutics

Faith Charles
Partner, Thompson Hine LLP

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