# Corporate Overview

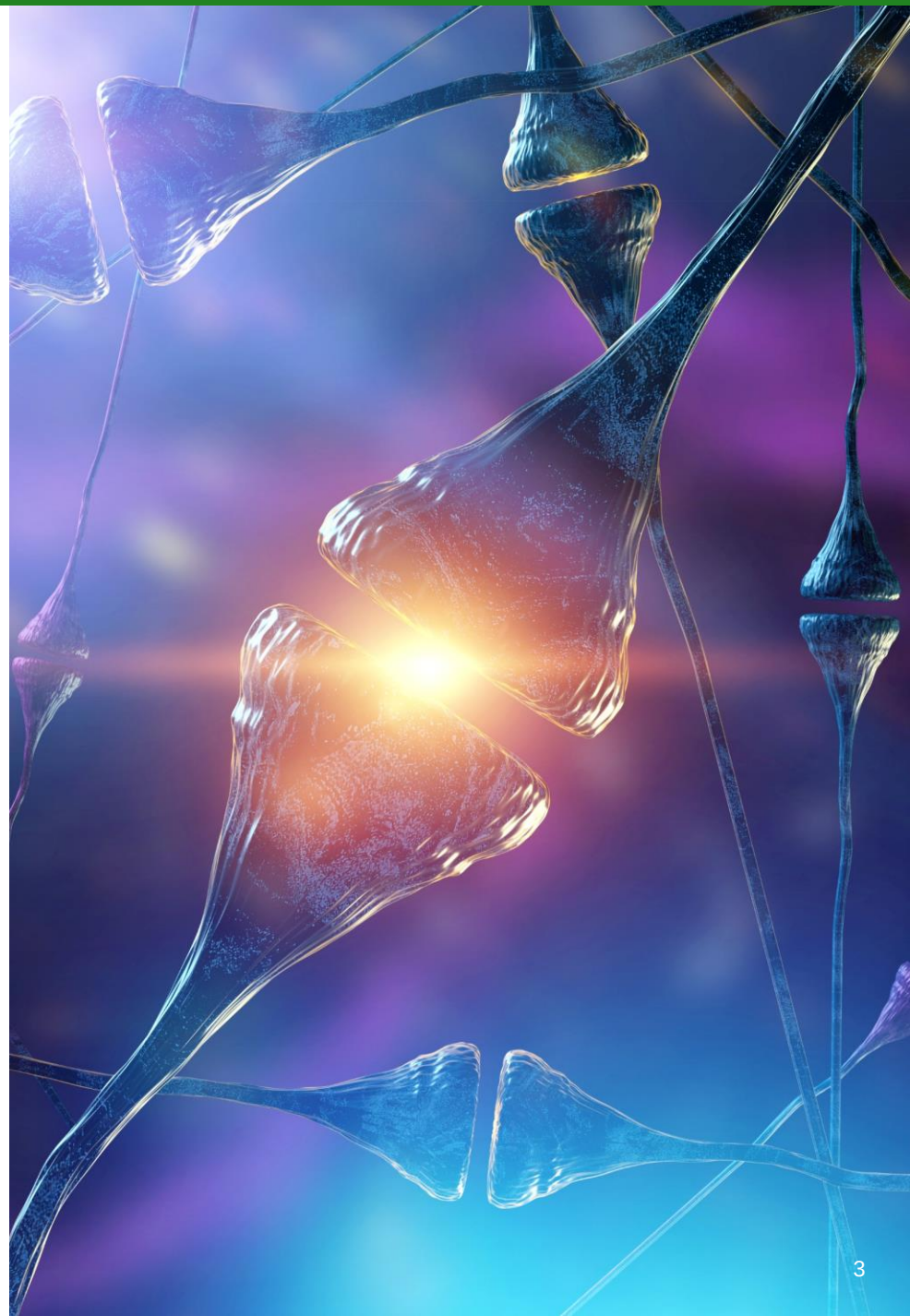
AVENUE THERAPEUTICS

# Forward looking statement

This presentation contains predictive or “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. All statements other than statements of current or historical fact contained in this presentation, including statements that express our intentions, plans, objectives, beliefs, expectations, strategies, predictions or any other statements relating to our future activities or other future events or conditions are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “will,” “should,” “would” and similar expressions are intended to identify forward-looking statements. These statements are based on current expectations, estimates and projections made by management about our business, our industry and other conditions affecting our financial condition, results of operations or business prospects. These statements are not guarantees of future performance and involve risks, uncertainties and assumptions that are difficult to predict. Therefore, actual outcomes and results may differ materially from what is expressed or forecasted in, or implied by, the forward-looking statements due to numerous risks and uncertainties. Factors that could cause such outcomes and results to differ include, but are not limited to, risks and uncertainties arising from: expectations for increases or decreases in expenses; expectations for the clinical and pre-clinical development, manufacturing, regulatory approval, and commercialization of our pharmaceutical product candidate or any other products we may acquire or in-license; our use of clinical research centers and other contractors; expectations for incurring capital expenditures to expand our research and development and manufacturing capabilities; expectations for generating revenue or becoming profitable on a sustained basis; expectations or ability to enter into marketing and other partnership agreements; expectations or ability to enter into product acquisition and in-licensing transactions; expectations or ability to build our own commercial infrastructure to manufacture, market and sell our product candidate; acceptance of our products by doctors, patients or payors; our ability to compete against other companies and research institutions; our ability to secure adequate protection for our intellectual property; our ability to attract and retain key personnel; availability of reimbursement for our products; estimates of the sufficiency of our existing cash and cash equivalents and investments to finance our operating requirements, including expectations regarding the value and liquidity of our investments; the volatility of our stock price; expected losses expectations for future capital requirements; ability to successfully integrate Baergic Bio in the Company’s operations; and those risks discussed in our filings which we make with the SEC. Any forward-looking statements speak only as of the date on which they are made, and we undertake no obligation to publicly update or revise any forward-looking statements to reflect events or circumstances that may arise after the date of this presentation, except as required by applicable law. Investors should evaluate any statements made by us in light of these important factors. The information contained herein is intended to be reviewed in its totality, and any stipulations, conditions or provisos that apply to a given piece of information in one part of this presentation should be read as applying mutatis mutandis to every other instance of such information appearing herein.

# 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 ~$4.9B**) | Cadence Pharmaceuticals (acquired by Mallinckrodt for $1.4B in March 2014) |

+ = **Growing CNS portfolio**

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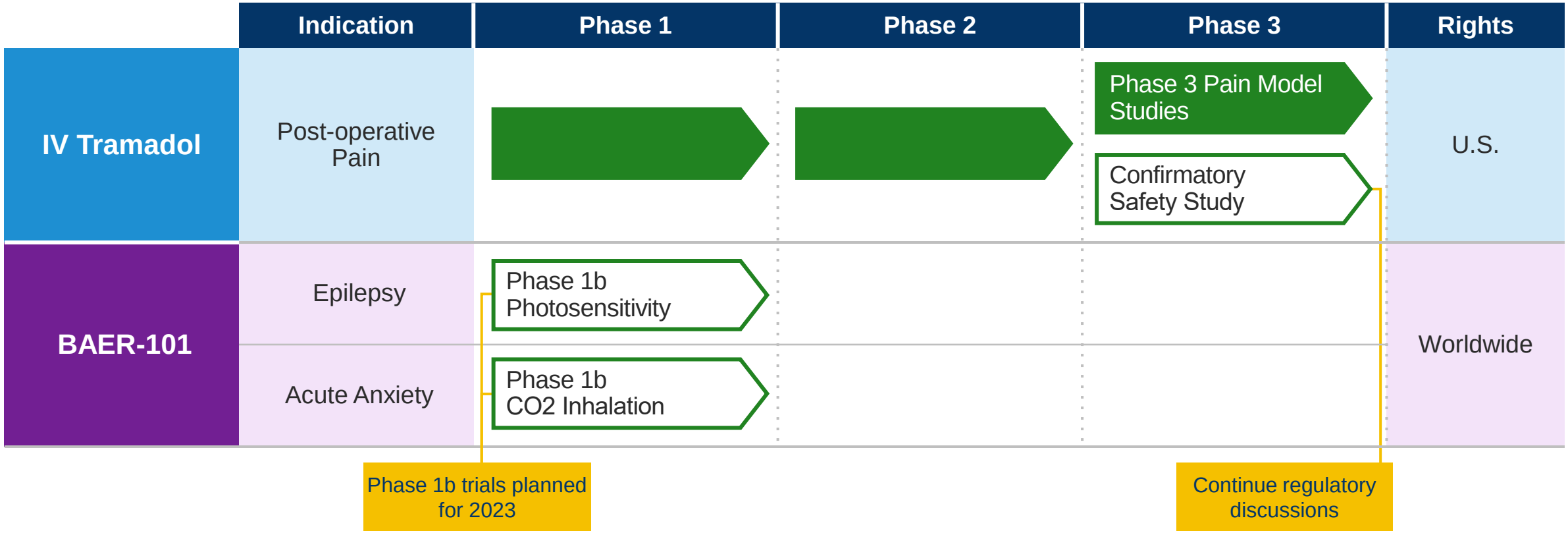
*** Market cap as of Dec 30, 2022*

# 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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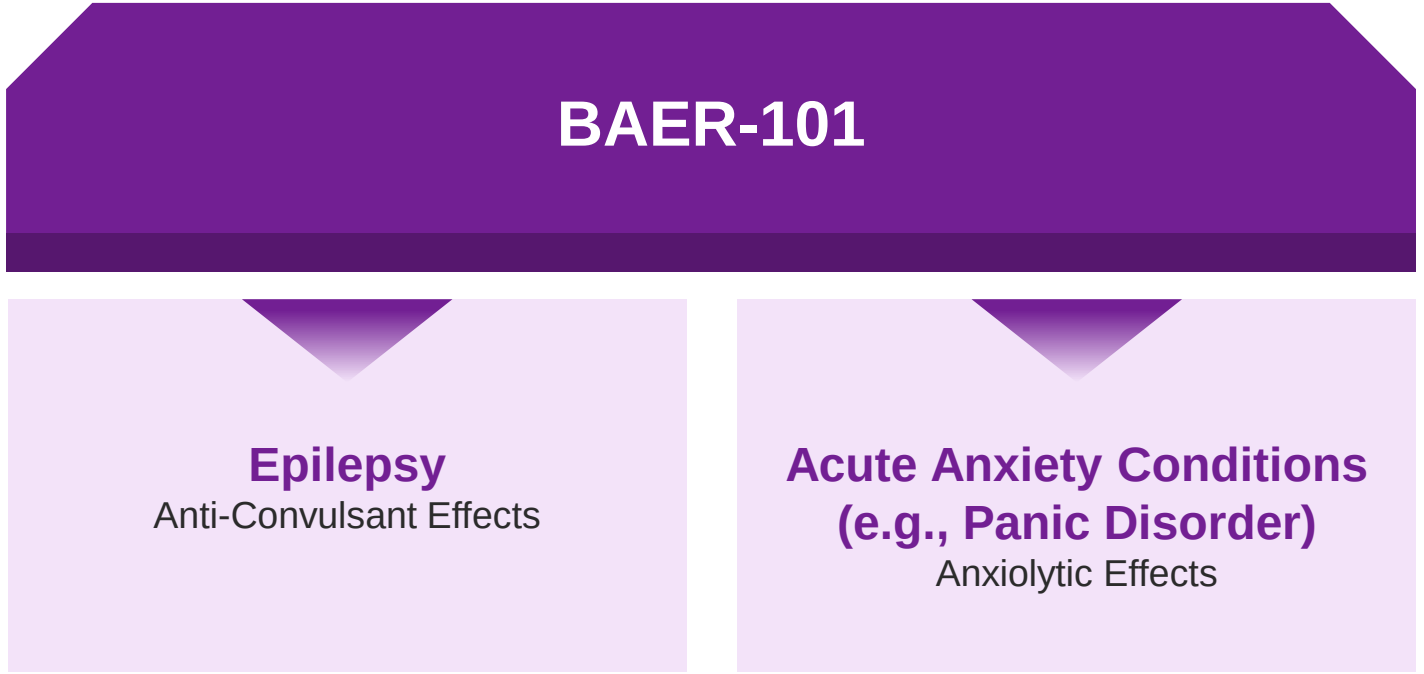
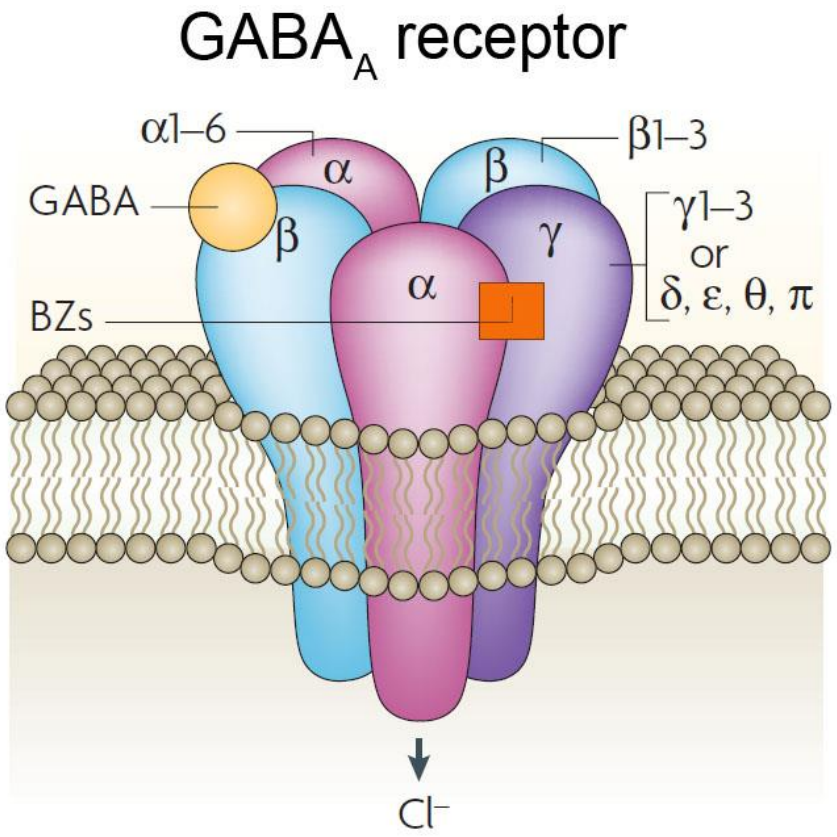
**Acquire CNS Rare Disease Assets**

# BAER-101 is being developed for epilepsy and acute anxiety



# BAER-101 is a selective GABAα 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., α1, α2, α3, α5), and these have different dominant functions

**BAER-101 targets GABA α2 and α3 subtypes more than α1 and α5, which should have important clinical consequences**

*Source: Jacob et al., Nature Reviews Neuroscience, 2008*

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

## Predicted effect of targeting $GABA_{\alpha}$ 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

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*Source: Jacob et al., Nature Reviews Neuroscience, 2008; Luo, Y., & Balle, T. Basic and Clinical Pharmacology & Toxicology, 2022; McKernan, et al., Nature Neuroscience, 2000; Möhler, H., Journal of Neurochemistry, 2007*

# 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 | |

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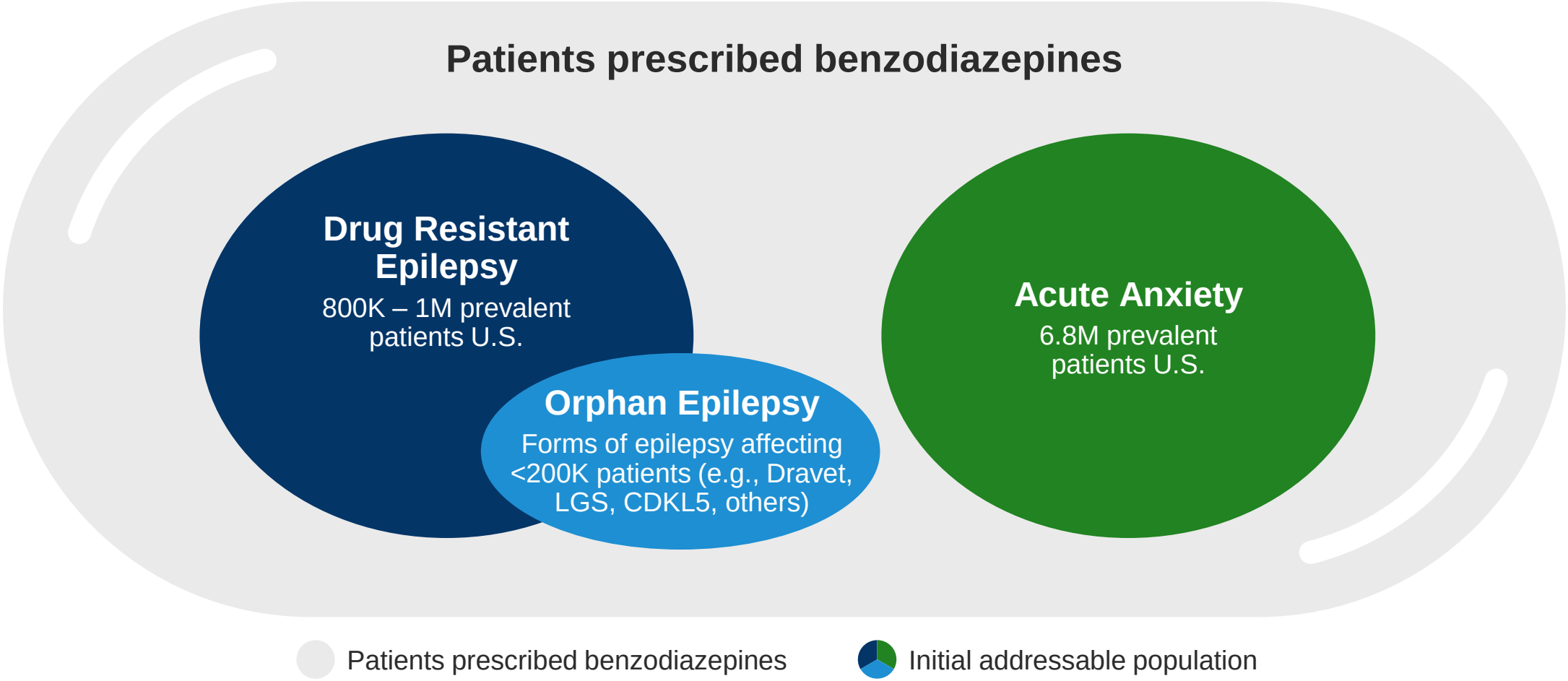
*Source: CDC.gov; Kalilani L et al. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018 Dec; ADAA.org; Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet, 2021*

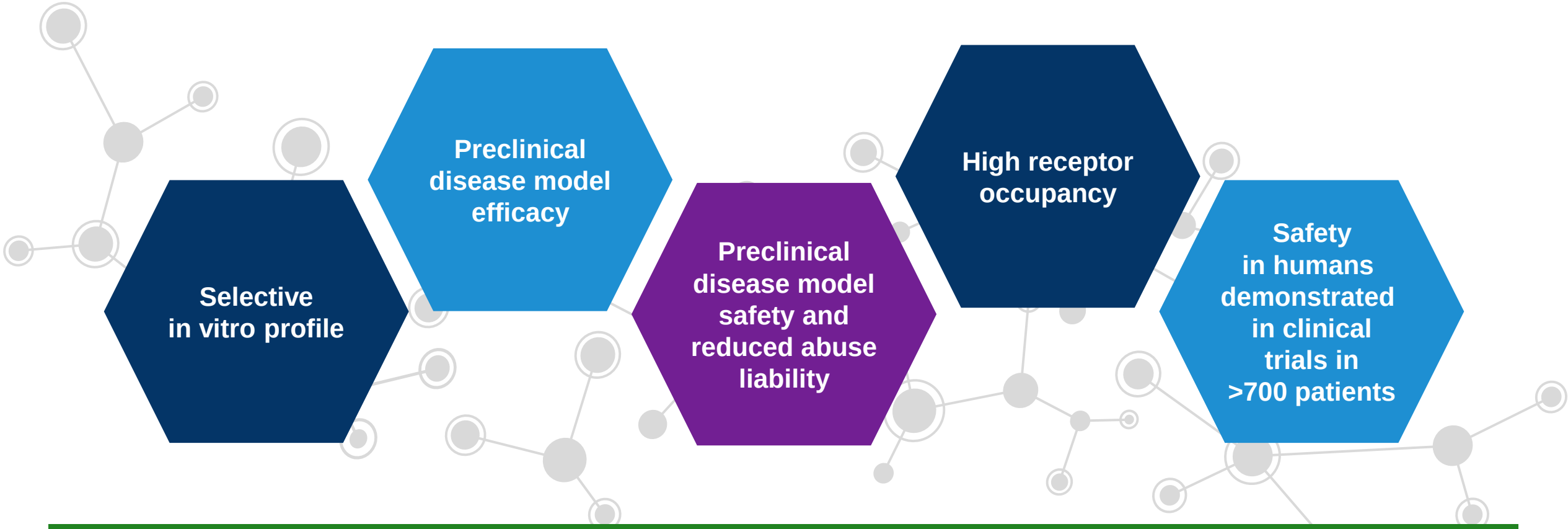
# BAER-101 can target the large market of patients prescribed BZDs by targeting drug resistant epilepsy, orphan epilepsy, or acute anxiety

## Addressable market




*Source: CDC.gov; Grand View Research, Polaris Market Research; Kalilani L et al. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018 Dec; NORD; LGS Foundation; NIH.gov; ADAA.org*

# BAER-101 has a compelling profile to address this market




**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)

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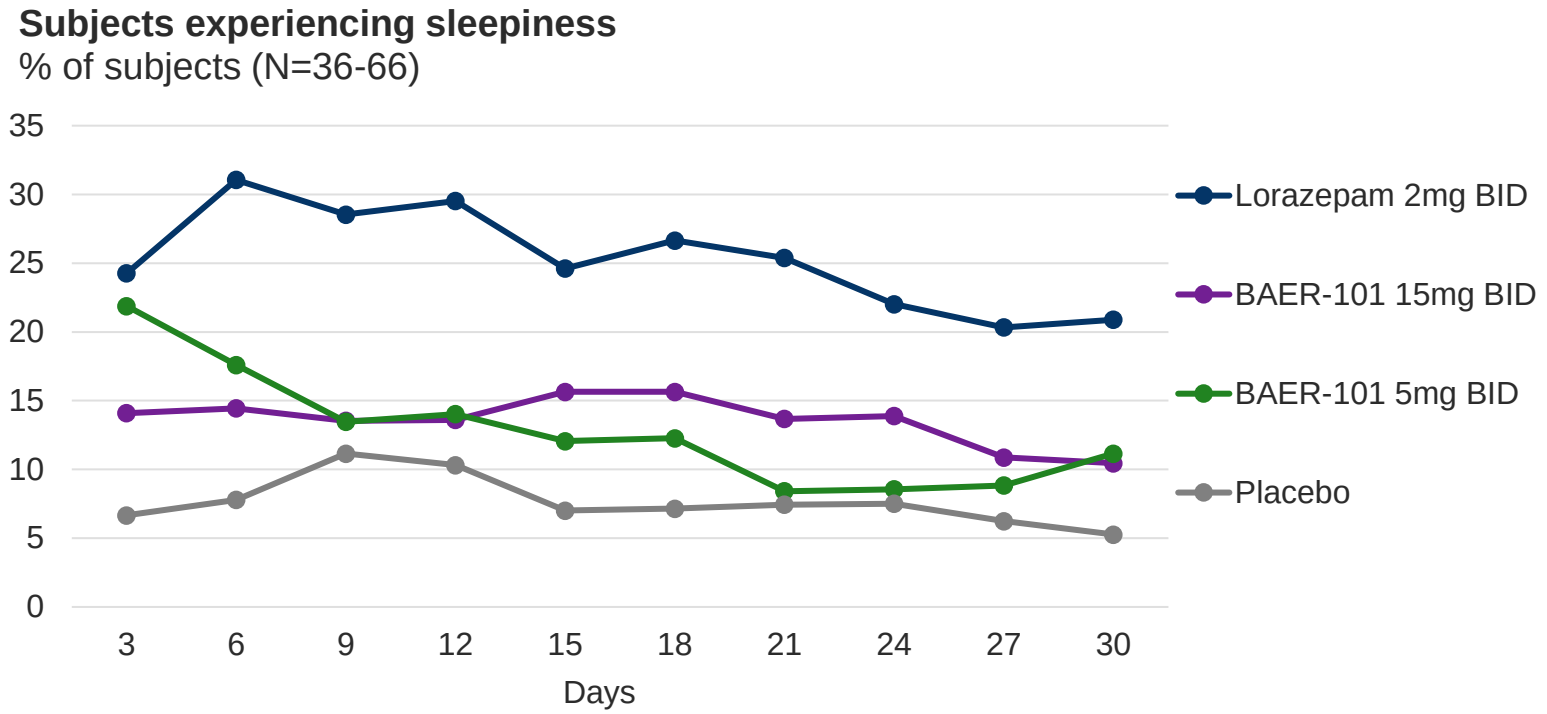
*Note: BAER-101 was previously known as AZD7325*

# 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**

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*Note: BAER-101 was previously known as AZD7325 when tested in these preclinical models*

# 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 GABAα therapies

| Company | Asset | Selectivity | Phase | Indications |
|---|---|---|---|---|
| **Avenue Therapeutics** | **BAER-101** | **α2/3-preferring** | **Phase 1** | **Epilepsy and panic disorder** |
| **Cerevel** (Nasdaq: CERE) | darigabat | α2/3/5-preferring | Phase 2 | Epilepsy and panic disorder |
| **Engrail Therapeutics** | ENX101 | α2/3/5-preferring | Phase 1b | Epilepsy |
| **Saniona** (OMX: Sanion) | SAN711 | α3-preferring | Phase 1 | Migraine and pain |
| **RespireRx** (OTC: RSPI) | KRM-II-81 | α2/3-preferring | Preclinical | TBD |

- BAER-101 is selective to the α2/3 receptor subunits and BAER-101 does not have high activity with the α5 subunit
- Furthest along GABAα compound in clinical development is darigabat from Cerevel, which targets the α5 subunit in addition to the α2/3 receptor subunits
  - Targeting the α5 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 α5 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

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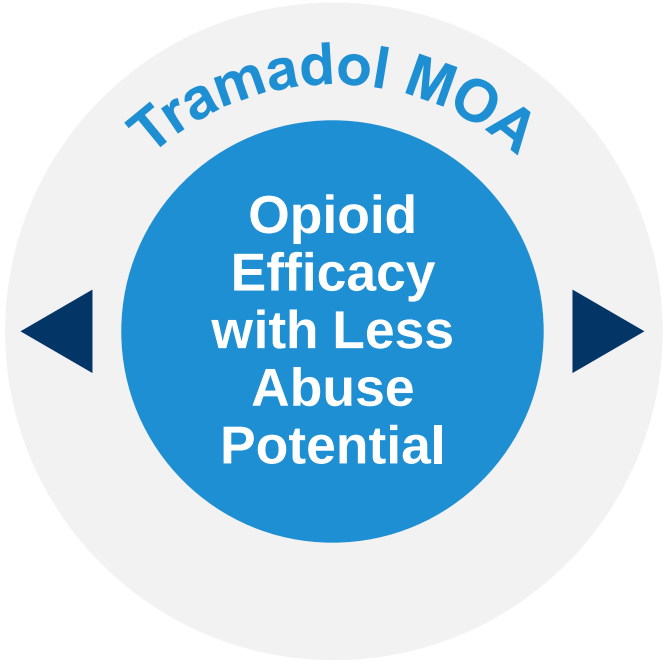
# Tramadol has a unique dual mechanism of action among IV analgesics

**Opioid Agonist**

Blocking pain signal transmission at both the spinal and brain levels




**Inhibitor of Norepinephrine & Serotonin Re-uptake**

Blocking pain signal transmission at the spinal level

**Schedule IV** versus Conventional Narcotics (Schedule II)

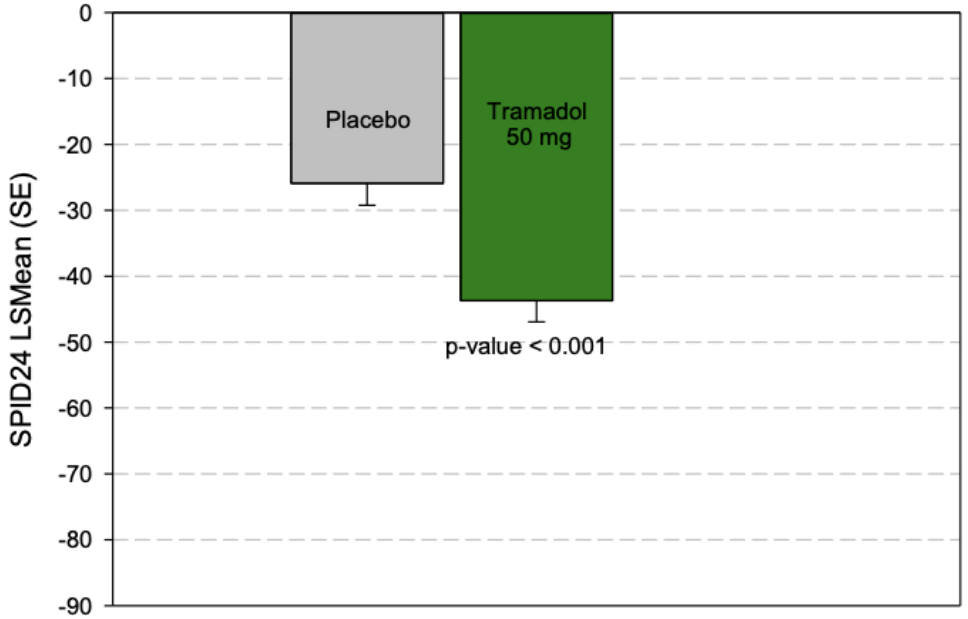
**IV Tramadol has been safely used in Europe for 30 years – Approximately 370 million doses were administered in Europe from 2010 to 2019**

*Note: Schedule IV substances are defined as drugs with a low potential for abuse and low risk of dependence. Schedule II substances are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence.*
*Source: https://www.dea.gov/drug-information/drug-scheduling*

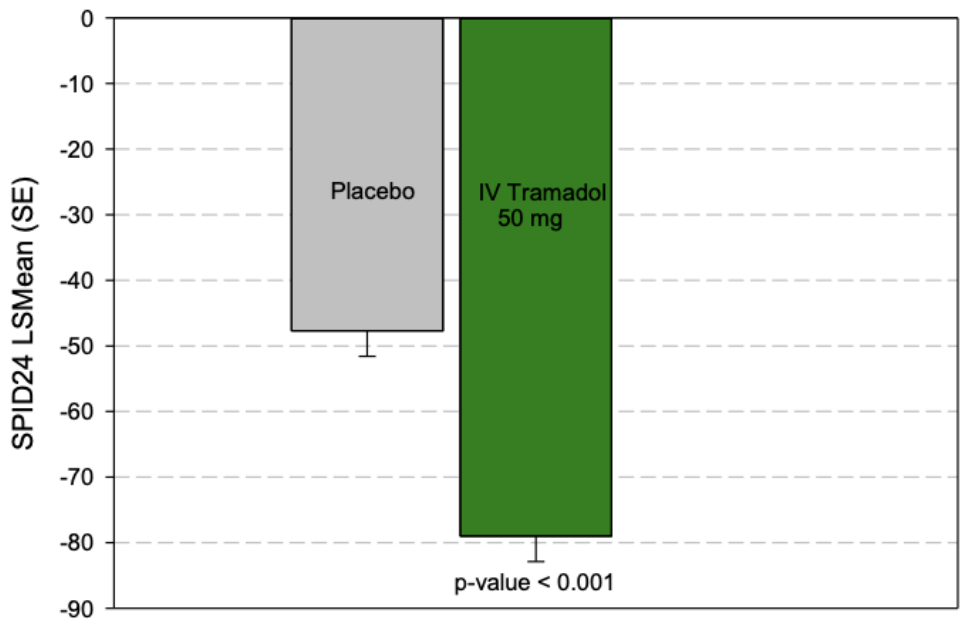
# Safety and efficacy profiles have been demonstrated in two Phase 3 trials in over 700 patients

**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**

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# 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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*Additional details on the history of regulatory interactions, decisions, and meetings between Avenue and the FDA are available in our public filings with the Securities and Exchange Commission*

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Acquire CNS Rare Disease Assets

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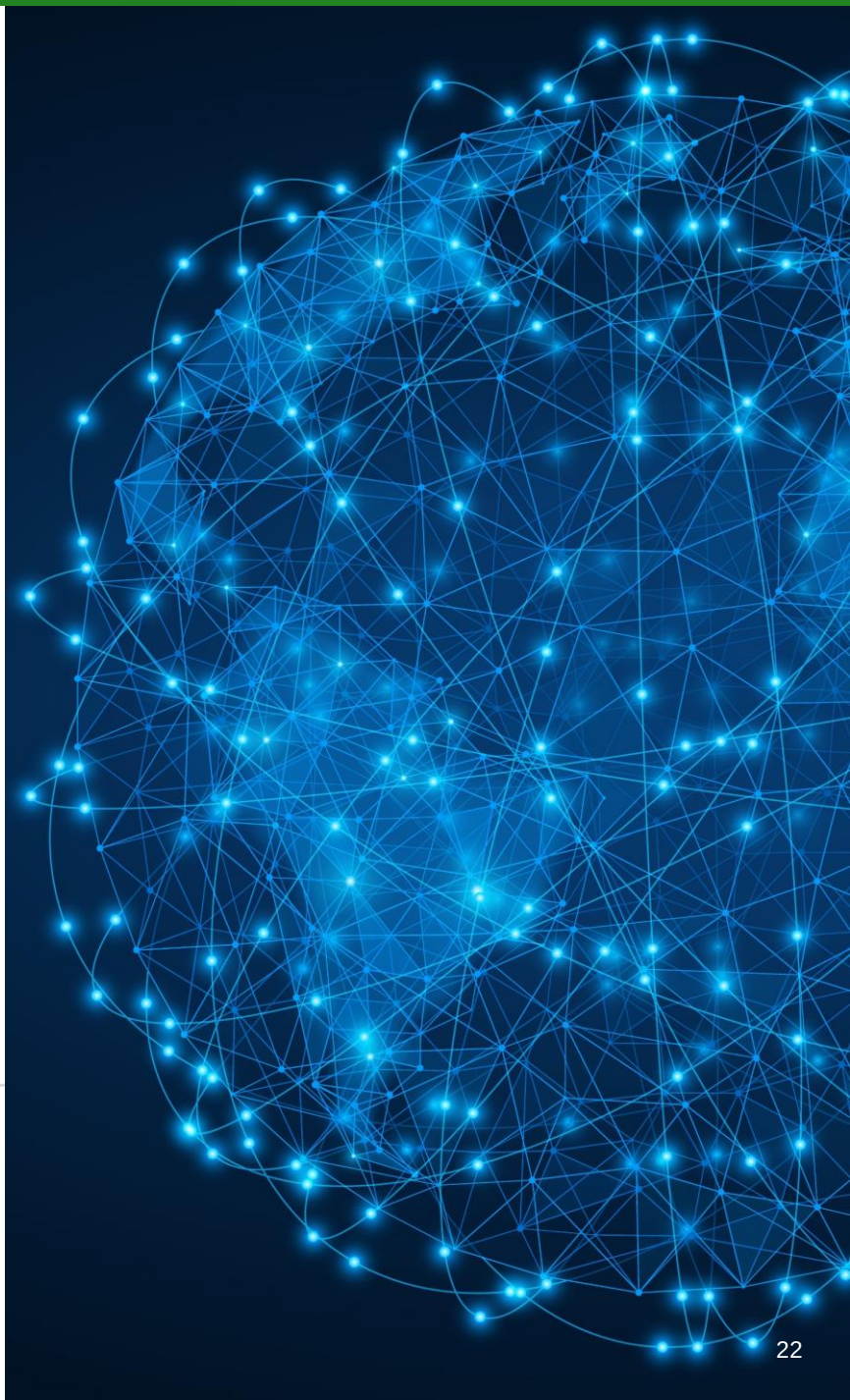
# We are searching the world for first-rate CNS / rare disease assets with these characteristics

**Imaging and Biomarker Driven Endpoints**

**Feasible Clinical Development Programs with Reasonable Costs**

**Clinical Stage with Human Data**



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

## Management

**Alexandra MacLean MD**
CEO

MERCK
Medtronic
FORTRESS BIOTECH
COVIDIEN
IMBRIUM THERAPEUTICS
PURDUE

**David Jin**
Interim CFO

FORTRESS BIOTECH
BARINGS
sorrento THERAPEUTICS
B RILEY
IQVIA

**Michael Ryan**
VP Clinical Operations & Program Management

FORTRESS BIOTECH
Indevus Pharmaceuticals, Inc.
endo

## Board of Directors

**Lindsay Rosenwald MD**
CEO, Fortress Biotech

**Jay Kranzler MD PhD**
CEO, Urica Therapeutics

**Neil Herskowitz**
Founder, ReGen Capital

**Curtis Oltmans**
Chief Legal Officer, Fulcrum Therapeutics

**Faith Charles**
Partner, Thompson Hine LLP

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