Corporate Overview

AVENUE THERAPEUTICS

Forward looking statement

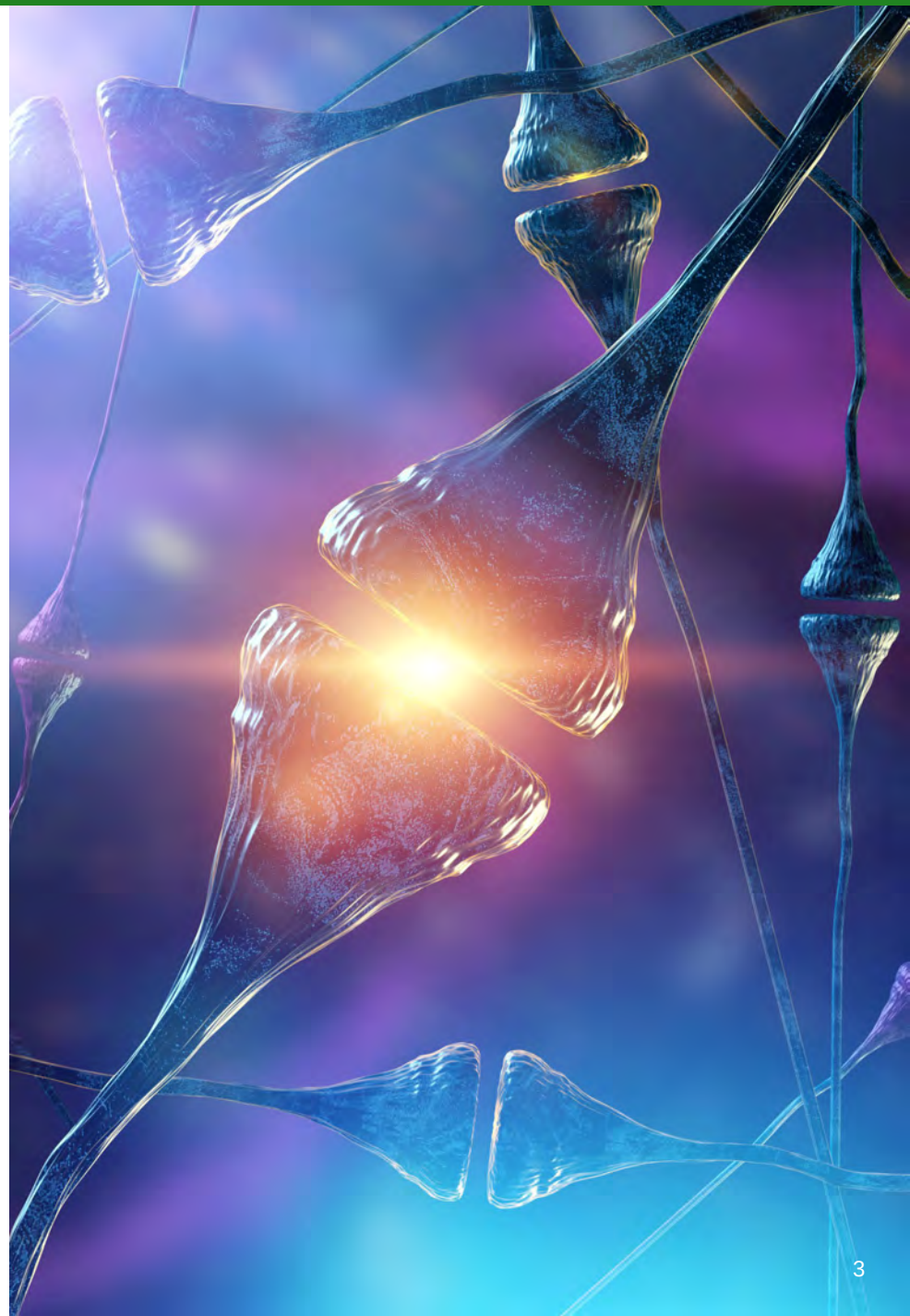
This presentation contains predictive or “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. All statements other than statements of current or historical fact contained in this presentation, including statements that express our intentions, plans, 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 candidates 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 candidates; 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; 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 focused on the development and commercialization of therapies for the treatment of rare and neurologic diseases

- In February 2023, we executed a license with AnnJi Pharmaceutical for AJ201; this business development effort brings a cutting-edge asset into Avenue's pipeline that is the lead molecule in the clinic to treat Spinal and Bulbar Muscular Atrophy (Kennedy's Disease), a debilitating rare neuromuscular disorder

- We expect that our diversified portfolio of three assets, with AJ201 leading the way, will deliver for investors in the near term, and patients in the longer term:
  - **AJ201** (Phase 1b/2a) for Spinal and Bulbar Muscular Atrophy (SBMA)
  - **IV Tramadol** (Phase 3) for acute postoperative surgical pain
  - **BAER-101** (Phase 1b) for epilepsy and acute anxiety



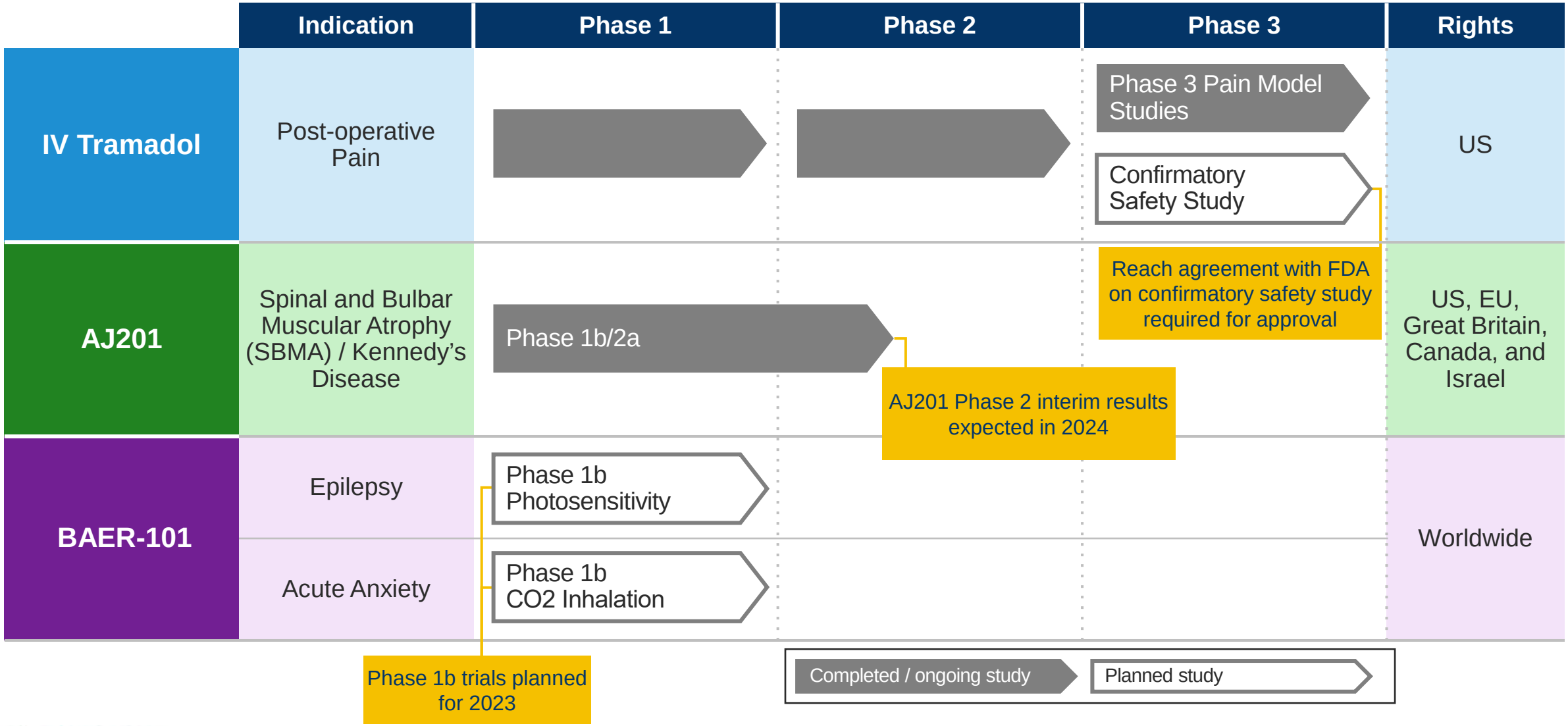
Our clinical stage assets address large unmet patient and market needs in the neurologic therapeutic space

Pipeline Asset	AJ201		IV Tramadol		BAER-101	
Indication	Spinal and Bulbar Muscular Atrophy (Kennedy's Disease)	+	Post operative pain	+	Epilepsy and acute anxiety	=
Mechanism	Activation of Nrf1 / Nrf2 and promotion of AR degradation		Opioid agonist & inhibitor of norepinephrine & serotonin re-uptake		Selective GABA-A 2, 3 receptor positive allosteric modulator	
Key therapeutic value proposition	No FDA approved therapies exist for SBMA patients		Fills in the gap in acute care space between IV acetaminophen/NSAIDS and conventional narcotics		A safer and more tolerable benzodiazepine	
Comparable companies and transactions	Reata Pharma (Market cap $3.1B*)		Cadence Pharmaceuticals (acquired by Mallinckrodt for $1.4B in March 2014)		Cerevel Therapeutics (Market cap ~$4.3B*)	

Growing neuro portfolio

*Note: * Market cap as of March 1st, 2023*

Our pipeline has potential near-term value inflection points



1

AJ201

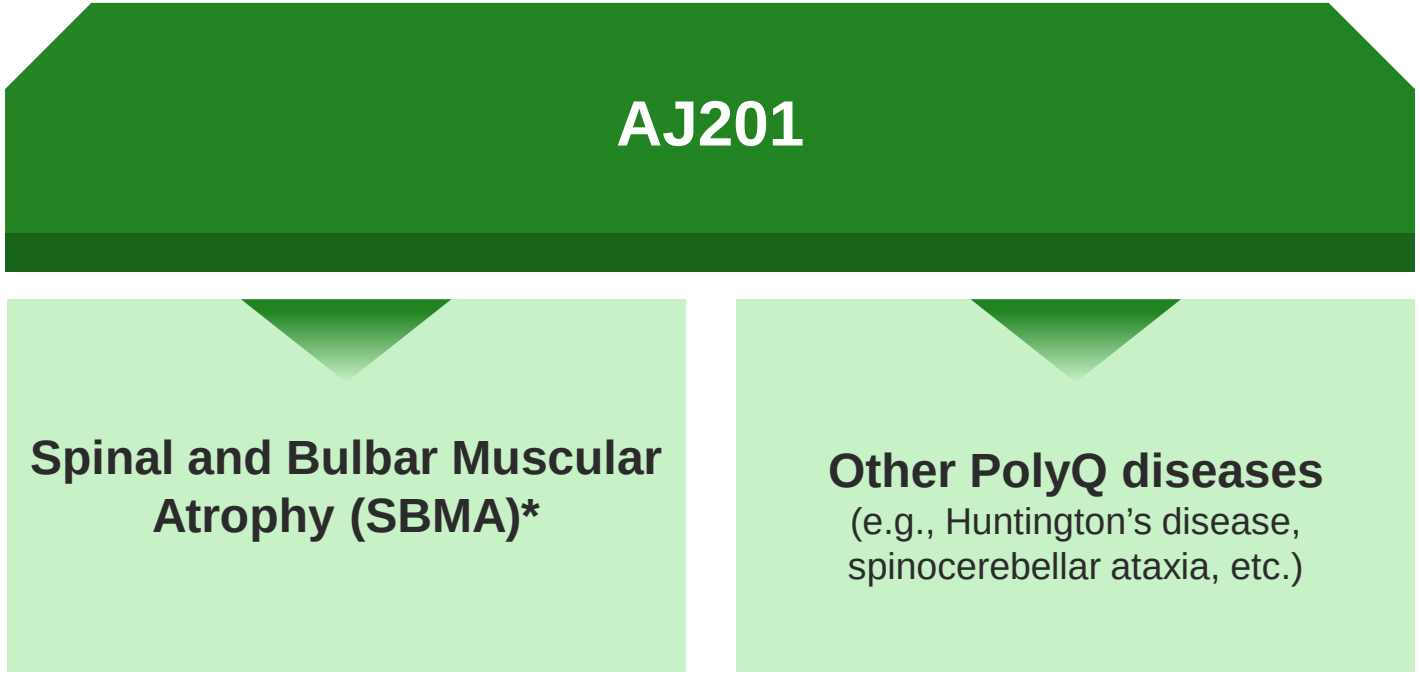
2

IV Tramadol

3

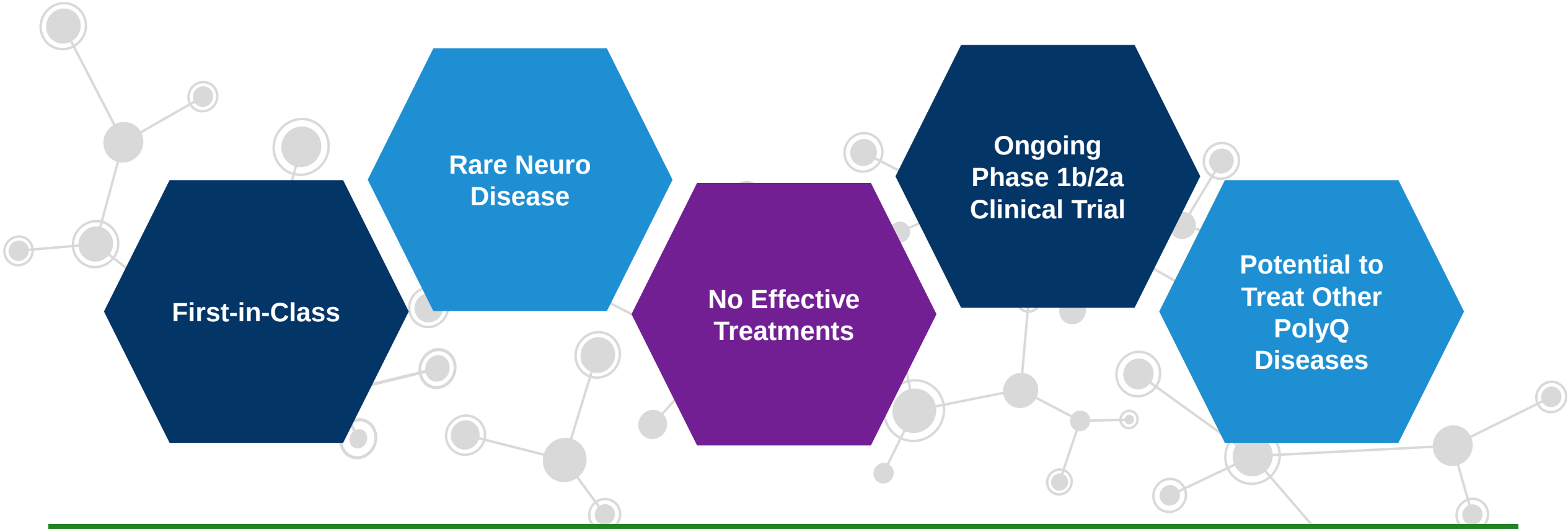
BAER-101

AJ201 is being developed for Spinal and Bulbar Muscular Atrophy and may address other PolyQ diseases



Note: Spinal and Bulbar Muscular Atrophy is also known as Kennedy's disease

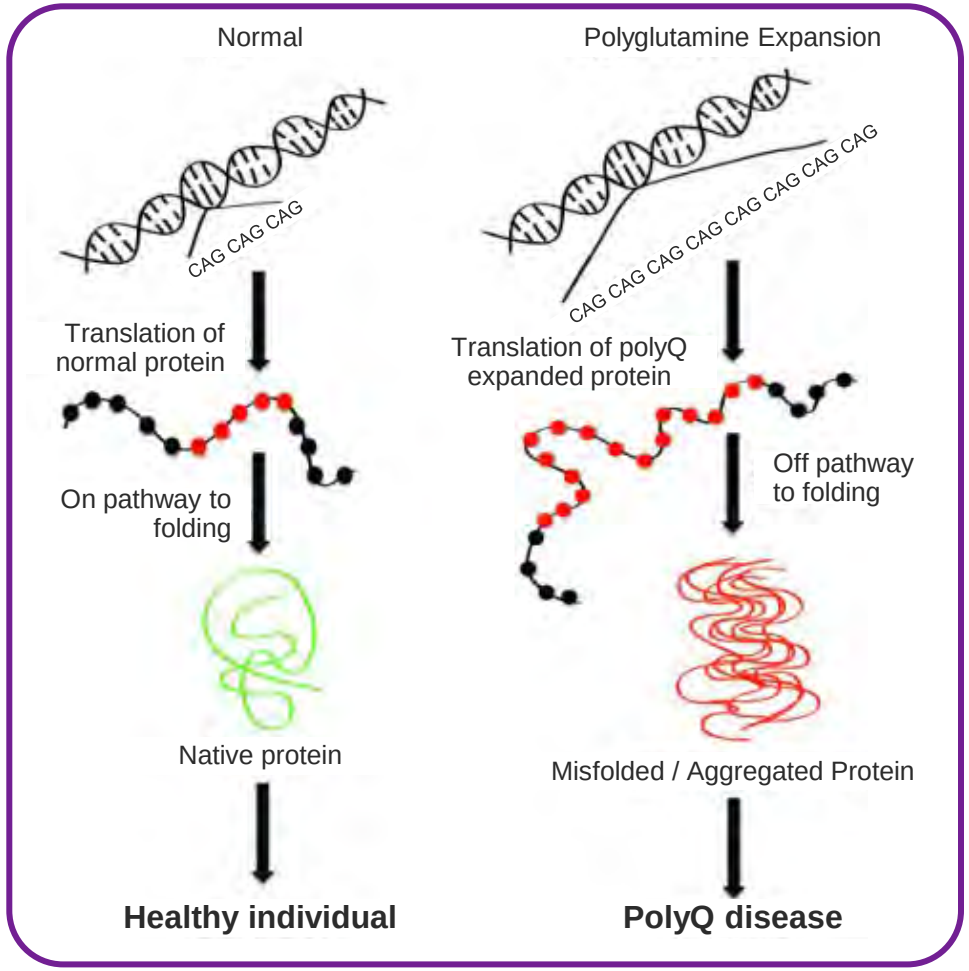
AJ201 adds a cutting-edge asset to Avenue's neurologic asset portfolio



AJ201 was licensed from AnnJi Pharmaceutical in Q1 2023 with an impressive preclinical and clinical package

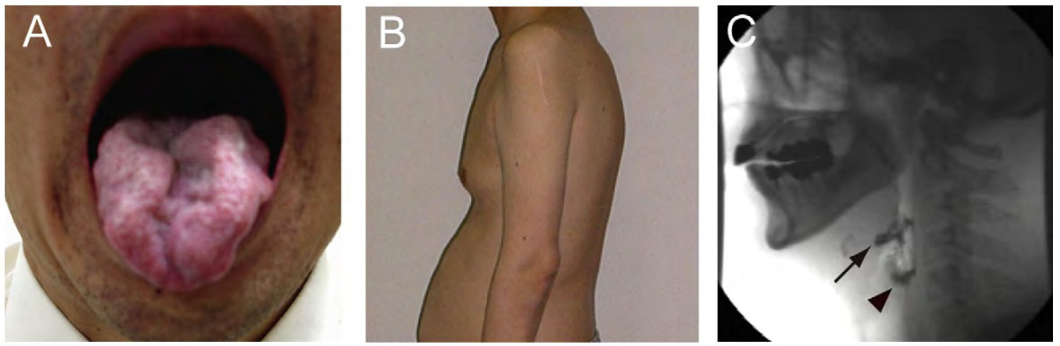
AVENUE THERAPEUTICS

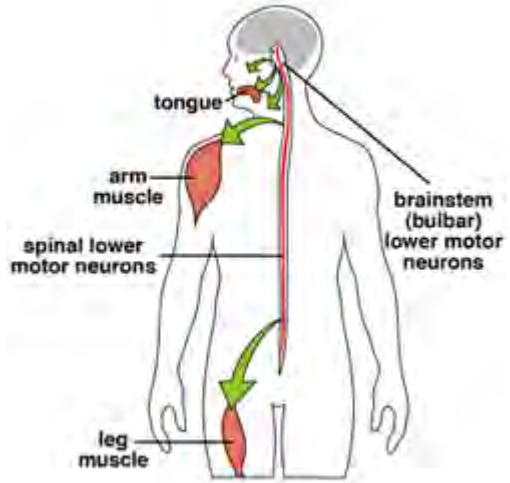
SBMA is a polyglutamine (PolyQ) disease, which is characterized by mutant protein aggregation and progressive neurodegeneration



- At least nine neurodegenerative diseases (NDD) are caused by the expansion of CAG repeats encoding polyglutamine (polyQ) tracts in affected genes, resulting in aggregation of the mutant proteins in brain and other tissues
- Misfolded / aggregated protein causes toxicity as well as nerve and muscle death
- PolyQ diseases include:
  - Huntington's disease (HD)
  - Dentato-rubro-pallido-luysian atrophy (DRPLA)
  - Six types of spinocerebellar ataxias ((SCAs) 1, 2, 3, 6, 7 and 17)
  - Spinal and Bulbar Muscular Atrophy (SBMA)

SBMA affects multiple organ systems with symptoms worsening over time



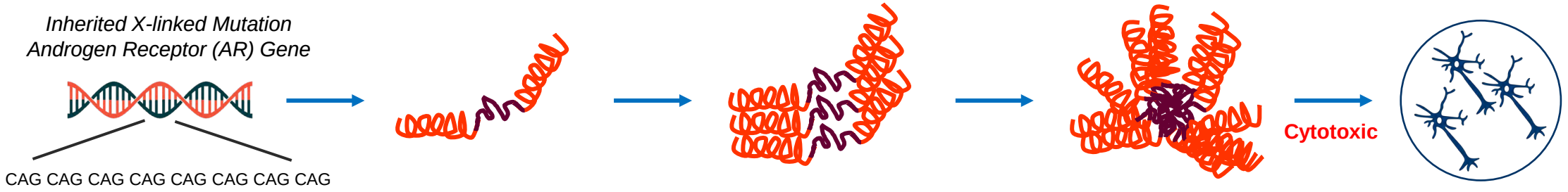


- SBMA is an X-linked polyQ disease, which results in only men developing the full spectrum of symptoms
- Although there is a range of cited prevalence rates in the literature, a recent study used genetic analysis to estimate disease prevalence of 1:6,887 males[1].
- Age of onset of the disease ranges from 18-64
- Weakening of the bulbar muscles affects chewing, speech and swallowing; SBMA also affects muscles in the limbs, leading to difficulty walking and injury caused by falling
- No FDA approved treatment for SBMA exists; patients are currently managed with physical therapy, steroids, and pain management

Source: 1) M. Zanovello et al., Oxford University Press on behalf of the Guarantors of Brain. 2023.

AJ201 is a pleiotropic small molecule that may treat SBMA by enhancing mutant protein degradation and decreasing neuroinflammation

SBMA disease pathway



Polyglutamine Expansion
>38 repeats

Misfolded
polyQ AR protein

Accumulation of misfolded
polyQ AR protein

Protein aggregation and
deposition

Neuron damage & muscle
degeneration

AJ201 potential therapeutic activity

Mutant Androgen Receptor (AR) Degradation

Nrf1 Pathway Activation

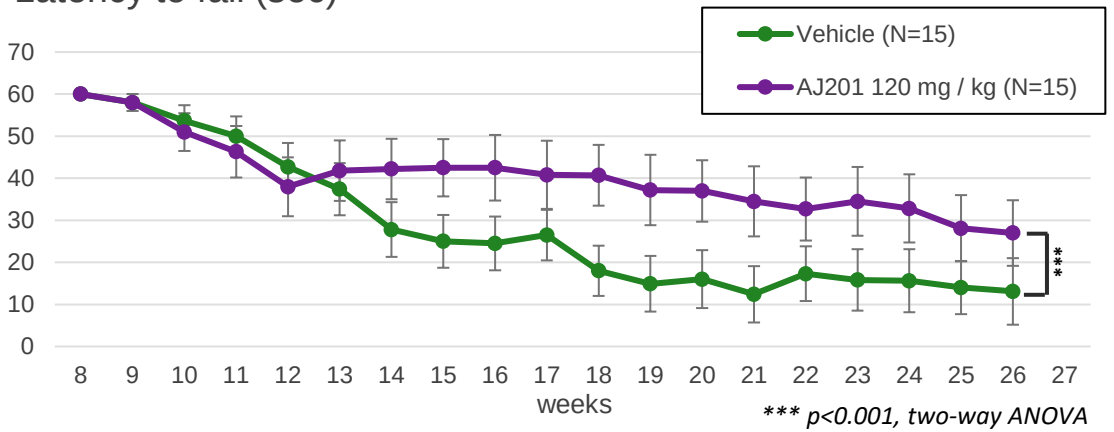
Nrf2 Pathway Activation

Source: Bott et al., Hum Mol Genet. 2016

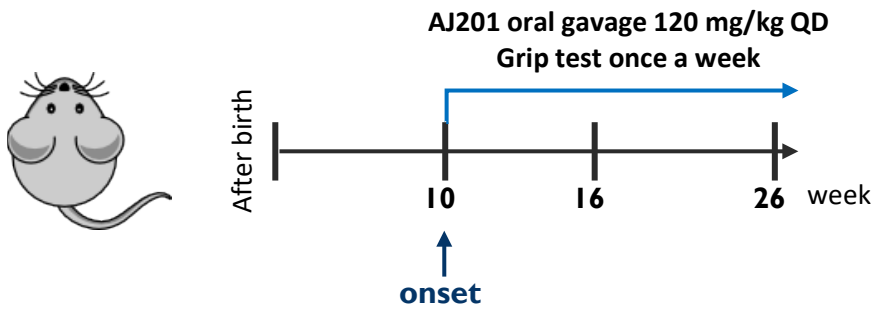
The development of AJ201 is supported by preclinical efficacy data in SBMA models

AJ201 led to improved motor function in symptomatic animals compared with vehicle control

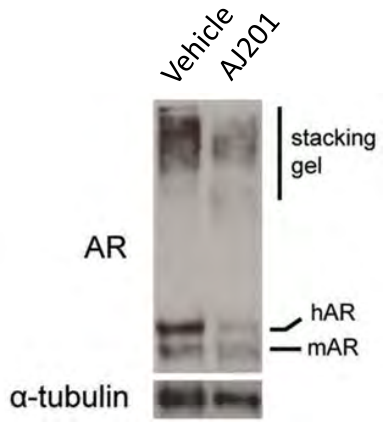
Grip test in SBMA disease mouse model (AR97Q)
Latency to fall (sec)

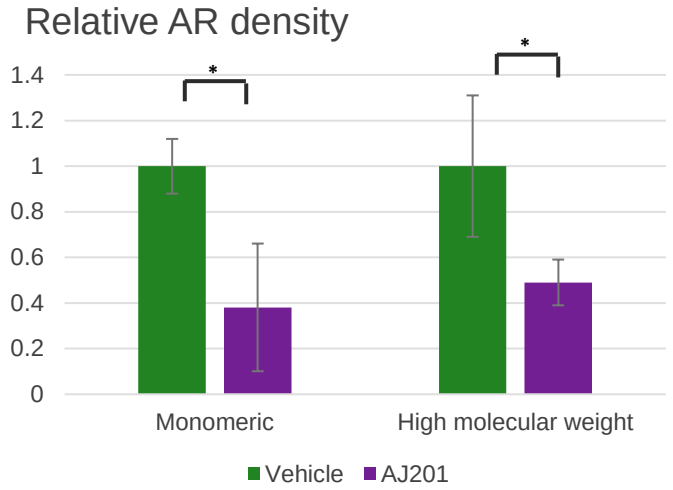


*** p<0.001, two-way ANOVA

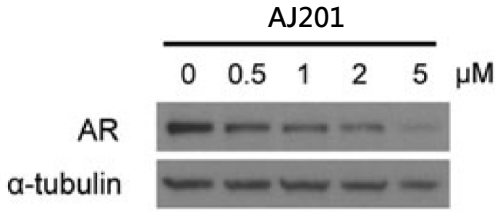


AJ201 reduced levels and accumulation of the mutant AR protein in mouse muscle tissues





AJ201 enhanced degradation of mutant AR in SBMA patient fibroblasts



Source: Bott et al., Hum Mol Genet. 2016

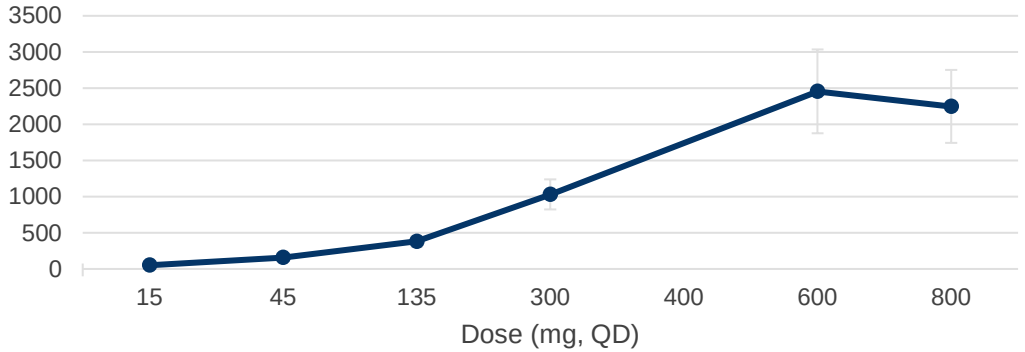
The Phase 1 SAD and MAD in healthy volunteers showed a favorable pharmacokinetic and safety profile

SAD and MAD* study overview

- A total of 72 subjects enrolled; no subjects were withdrawn due to safety concerns
- Well-tolerated with no serious adverse events (SAEs)
- Treatment-emergent AEs observed: 84% mild, 15% moderate, and 0.5% severe
- No significant food effect on drug absorption
- Dose-proportional exposure over 40 folds of dose range from 15 mg to 600 mg; drug absorption plateaued above 600 mg; No drug accumulation over repeated daily treatment

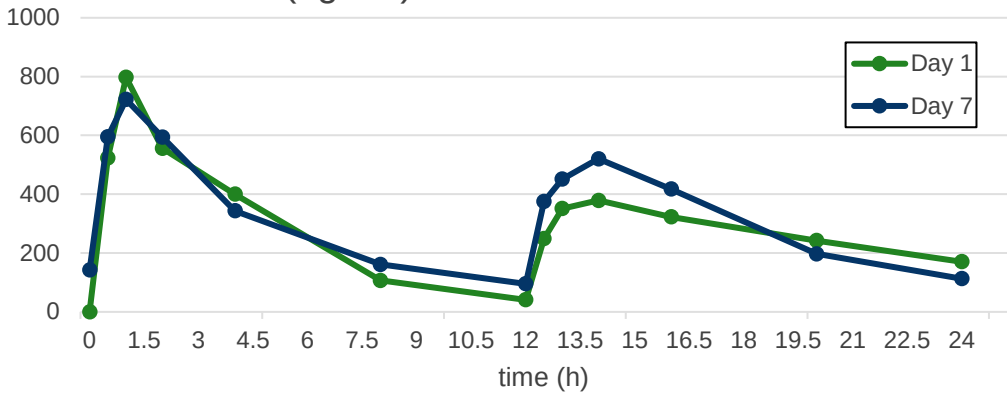
SAD cohorts

$AUC_{0\text{-last}}$ (hr*ng/mL)



MAD cohort 9

Plasma AJ201 (ng/mL)



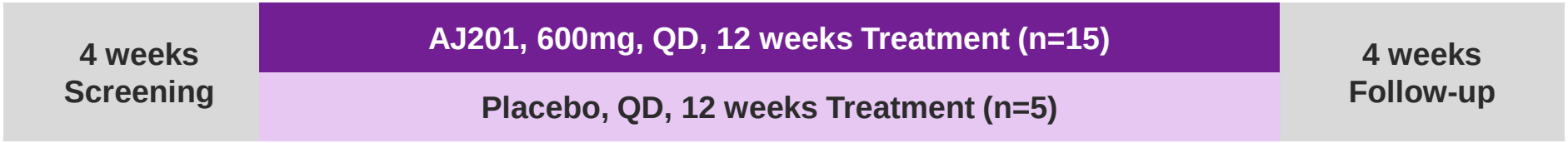
* Single ascending dose (SAD) and multiple ascending dose (MAD)

Phase 1b/2a study of AJ201 in SBMA patients is expected to read out top-line data in 2024

Phase 1b/2a multicenter double blind randomized clinical trial overview

Primary Objective	Assessing the safety, tolerability of AJ201 in subjects with clinically and genetically defined SBMA
Secondary Objective	Assessing the pharmacokinetics (PK), and pharmacodynamics (PD) of AJ201 in skeletal muscles
Exploratory Objective	To evaluate the proposed clinical assessments in subjects with SBMA as potential clinical outcome measures for future Phase II and III efficacy studies
Enrollment	20 early SBMA patients of ≥18 years old in the US
Regimen	Oral administration of 600 mg once daily for 12 weeks with 4 weeks follow-up
Six sites	Stanford University (Dr. John Day), University of California, Irvine (Dr. Tahseen Mozaffar), National Institutes of Health (Dr. Chris Grunsiech), Mayo Clinic Jacksonville (Dr. Bjorn Oskarsson), Mayo Clinic Rochester (Dr. Eric Sorenson), Washington University in St. Louis (Dr. Alan Pestronk)

Phase 1b/2a study design



Hypothesis: AJ201 reduces the levels of mutant AR proteins and activate antioxidant response in muscles. This might translate into clinical benefits in SBMA patients in future efficacy study of longer treatment duration and larger population

AVENUE THERAPEUTICS

AJ201 is the lead clinical program targeting SBMA

Product	Developer	MoA	Preclinical	Phase I	Phase II	Phase III	Approved
Leuprorelin	Takeda	Gonadotropin releasing hormone stimulants					*Japan only & Limited efficacy*
AJ201	**AnnJi**	**Activation of Nrf1 / Nrf2 and promotion of AR degradation**					
NIDO361	Nido Biosciences	AR BF3 modulator					
AAV-miRNA	University of Pennsylvania	Gene therapy to knockdown mutant AR					

AJ201 has orphan disease designations to enable a robust market presence

Orphan drug status granted

Indication	US FDA	EMA
SBMA	✓	✓
Huntington's disease	✓	
Spinocerebellar ataxia	✓	

Intellectual property overview

- Orphan drug designation (ODD) provides 7 years of market exclusivity in the US and 10 years in the EU
- Patents to provide market protection for other PolyQ diseases through 2040

1

AJ201

2

IV Tramadol

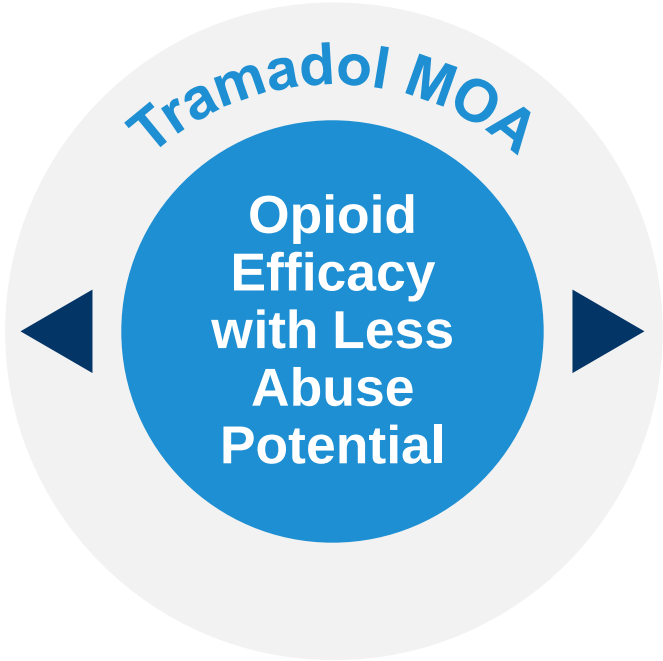
3

BAER-101

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)

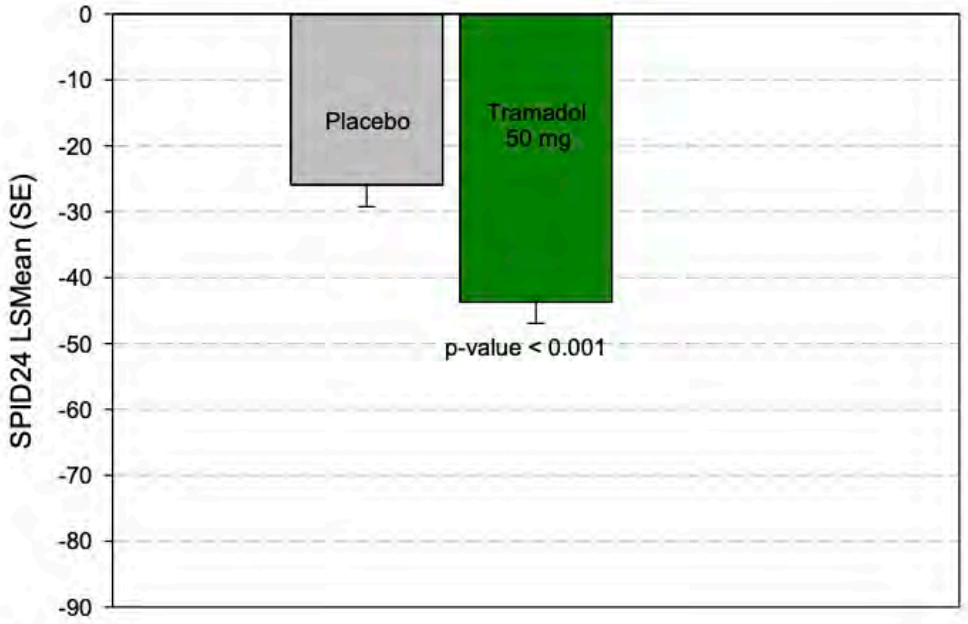
IV Tramadol has been safely used in Europe for 30 years – Approximately 370 million doses were administered in Europe from 2010 to 2019

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

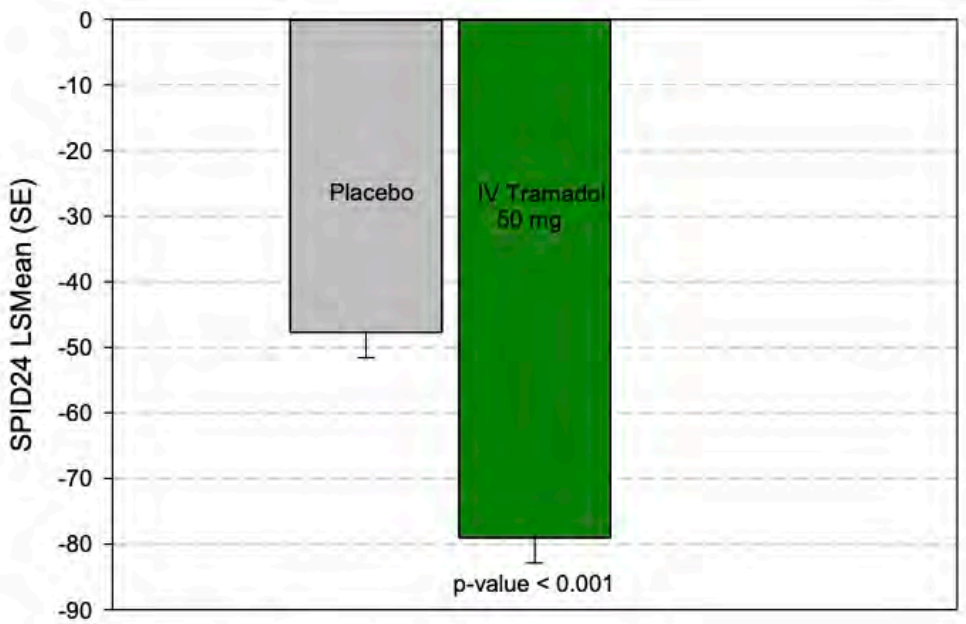
Safety and efficacy profiles have been demonstrated in two Phase 3 trials in over 700 patients

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

AVENUE THERAPEUTICS

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

AVENUE THERAPEUTICS

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

1

AJ201

2

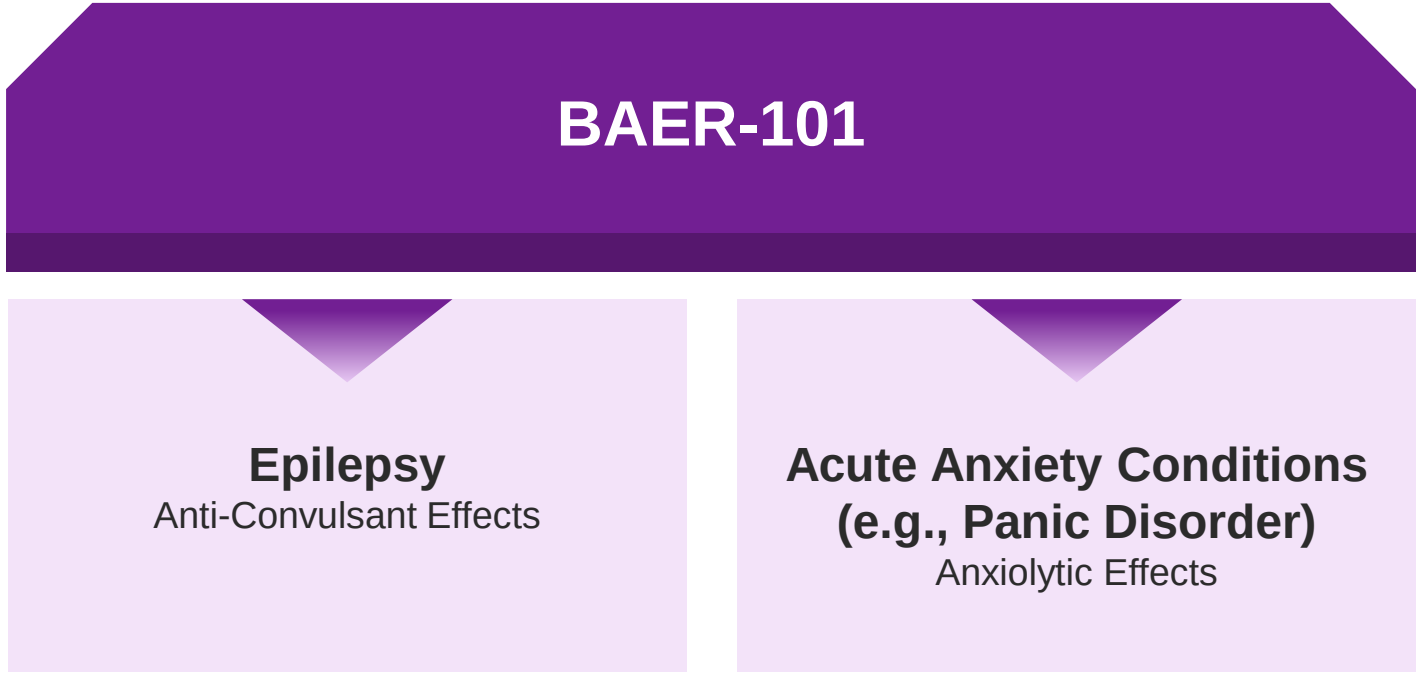
IV Tramadol

3

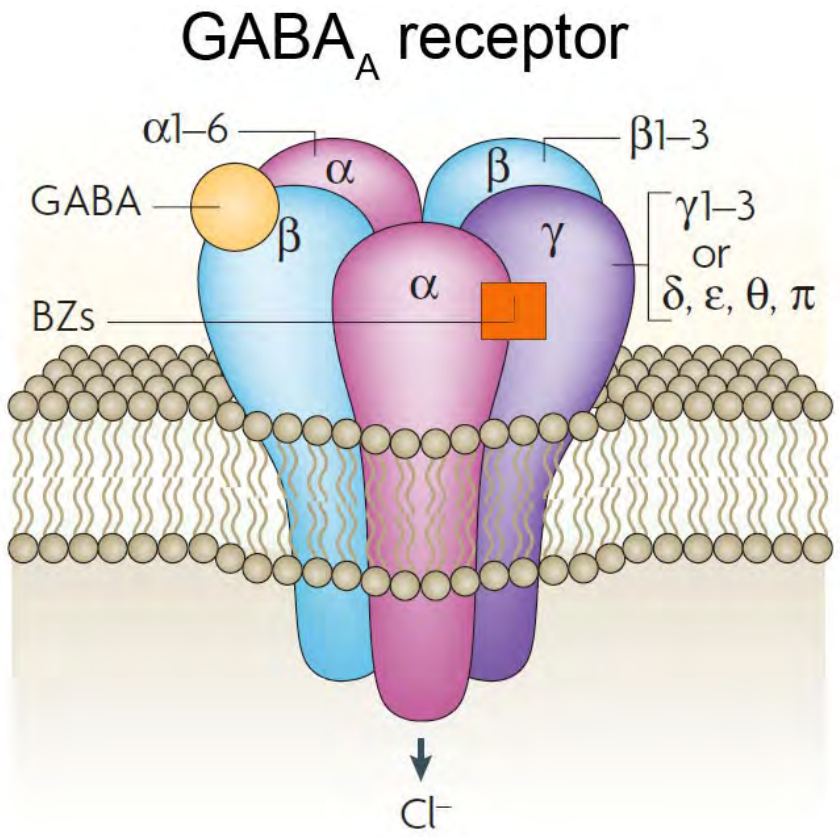
BAER-101

AVENUE THERAPEUTICS

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

AVENUE THERAPEUTICS

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

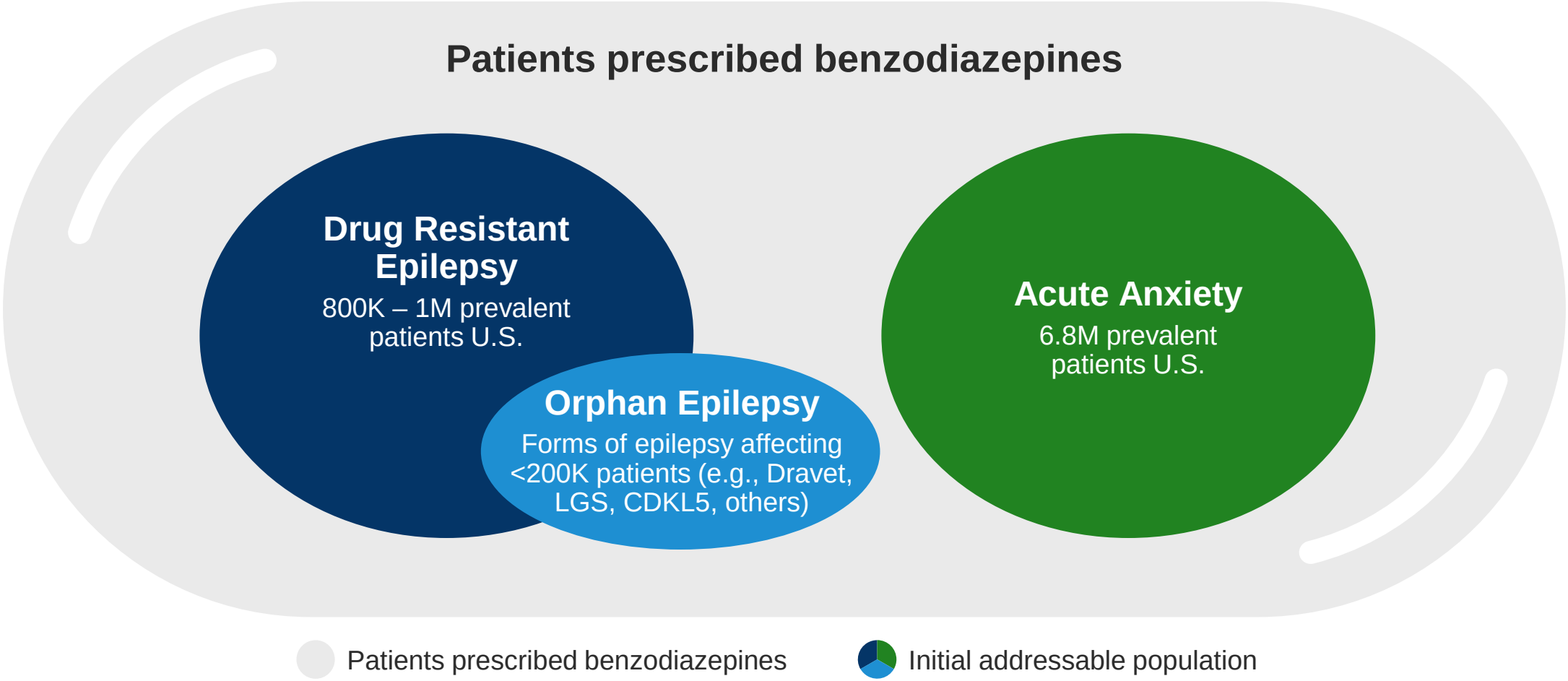
	Epilepsy	Acute Anxiety Conditions
U.S. Prevalence	3 - 4M patients (~65M patients worldwide)	~6M patients (~360M patients with any anxiety condition worldwide)
Disease	**Epilepsy** is a chronic disease that manifests as recurrent seizures from abnormal electrical discharge in the brain	**Panic disorder** 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	

AVENUE THERAPEUTICS

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

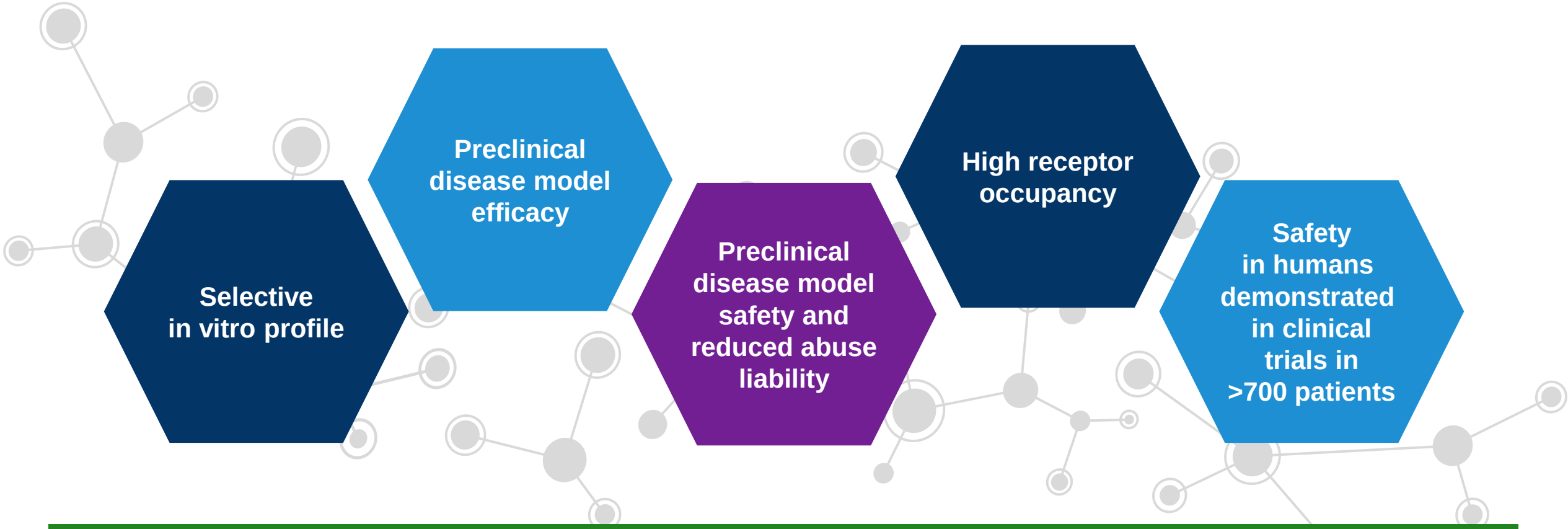
BAER-101 can target the large market of patients prescribed BZDs by targeting drug resistant epilepsy, orphan epilepsy, or acute anxiety

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

AVENUE THERAPEUTICS

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

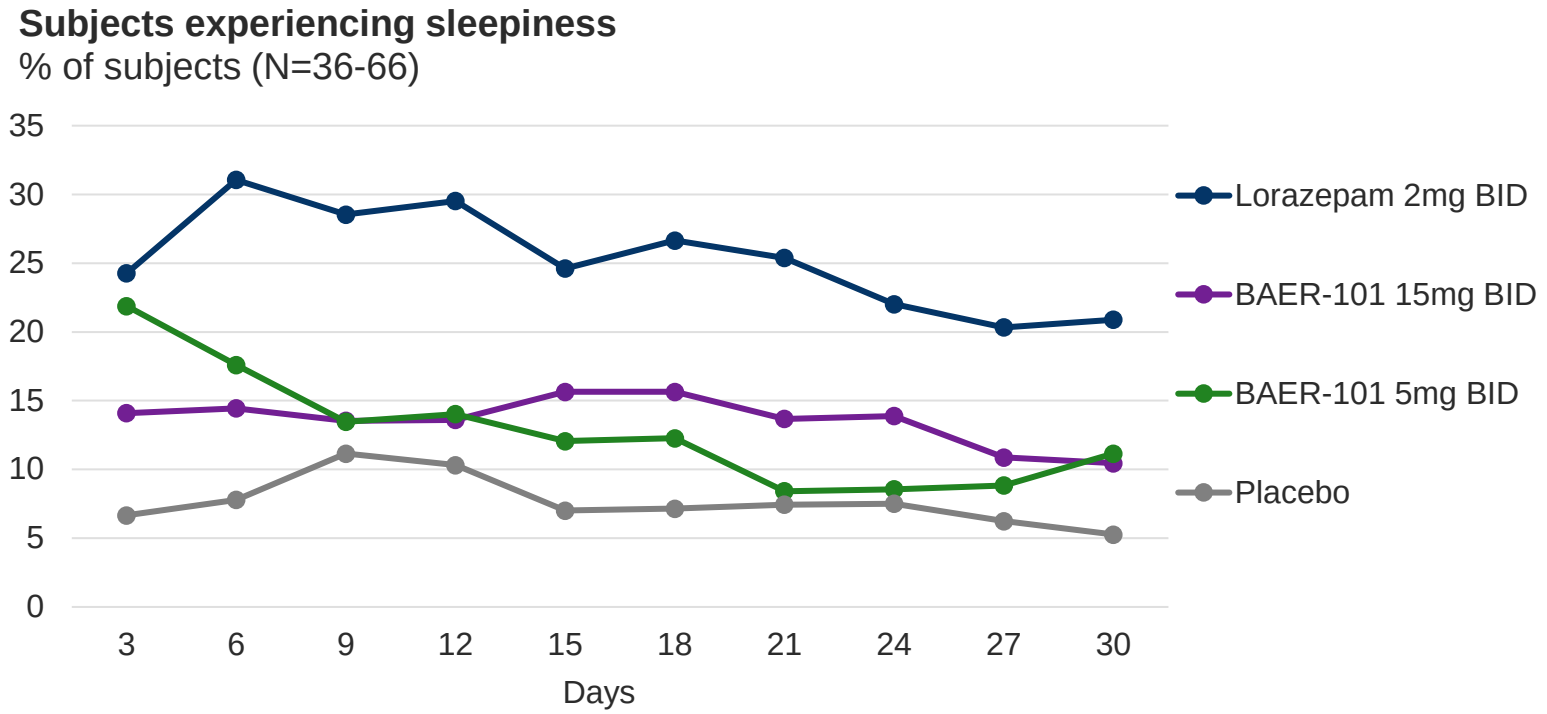
- BAER-101/AZD7325 was tested in over 700 subjects (healthy volunteers and patients)
- Side effects were mild or moderate with the most common side effects being dizziness and somnolence
- In two Phase 2 studies, BAER-101 was tested in patients with generalized anxiety disorder (GAD), but missed the 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)

AVENUE THERAPEUTICS

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

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

AVENUE THERAPEUTICS

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

AVENUE THERAPEUTICS

Company Overview

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

Imaging and Biomarker Driven Endpoints

Feasible Clinical Development Programs with Reasonable Costs

Clinical Stage with Human Data

AVENUE THERAPEUTICS

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

AVENUE THERAPEUTICS

Executive Summary

- Avenue Therapeutics is a specialty pharmaceutical company focused on the development and commercialization of therapies for the treatment of rare and neurologic diseases

- In February 2023, we executed a license with AnnJi Pharmaceutical for AJ201; this business development effort brings a cutting-edge asset into Avenue's pipeline that is the lead molecule in the clinic to treat Spinal and Bulbar Muscular Atrophy (Kennedy's Disease), a debilitating rare neuromuscular disorder

- We expect that our diversified portfolio of three assets, with AJ201 leading the way, will deliver for investors in the near term, and patients in the longer term:
  - **AJ201** (Phase 1b/2a) for Spinal and Bulbar Muscular Atrophy (SBMA)
  - **IV Tramadol** (Phase 3) for acute postoperative surgical pain
  - **BAER-101** (Phase 1b) for epilepsy and acute anxiety