ATXI – Corporate Presentation

AVENUE THERAPEUTICS, INC. | NASDAQ: ATXI | AUGUST 2023

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Overview

Our Mission:
Deliver impactful therapies to patients suffering from neurologic diseases

Diverse portfolio including first-in-class and best-in-class assets utilizing novel approaches to overcome limitations of existing CNS treatments

Multiple near-term catalysts for all three assets, with AJ201 as a potential “pipeline in a product” in PolyQ diseases

Compelling clinical and preclinical profiles demonstrate promising safety and efficacy signals

Diverse portfolio including first-in-class and best-in-class programs in high-value neurologic landscape with significant unmet patient need

Pipeline Asset	AJ201	BAER101	IV Tramadol
Indication	Spinal and Bulbar Muscular Atrophy (SBMA/Kennedy's Disease)	Epilepsy	Post-operative pain
Mechanism	Activation of Nrf1 & Nrf2 and promotion of AR degradation	Selective $GABA_A$ α2 and α3 receptor positive allosteric modulator	Opioid agonist & inhibitor of norepinephrine & serotonin re-uptake
Key therapeutic value proposition	No FDA approved therapies exist for SBMA patients	A safer and more tolerable benzodiazepine	Schedule IV drug for acute care post-operative pain
Addressable population	Estimates vary widely, ranging from ~4,060[1] to 23,580[2] men in U.S.	~65M patients with epilepsy worldwide[3]	~100M acute pain cases in U.S.[4]

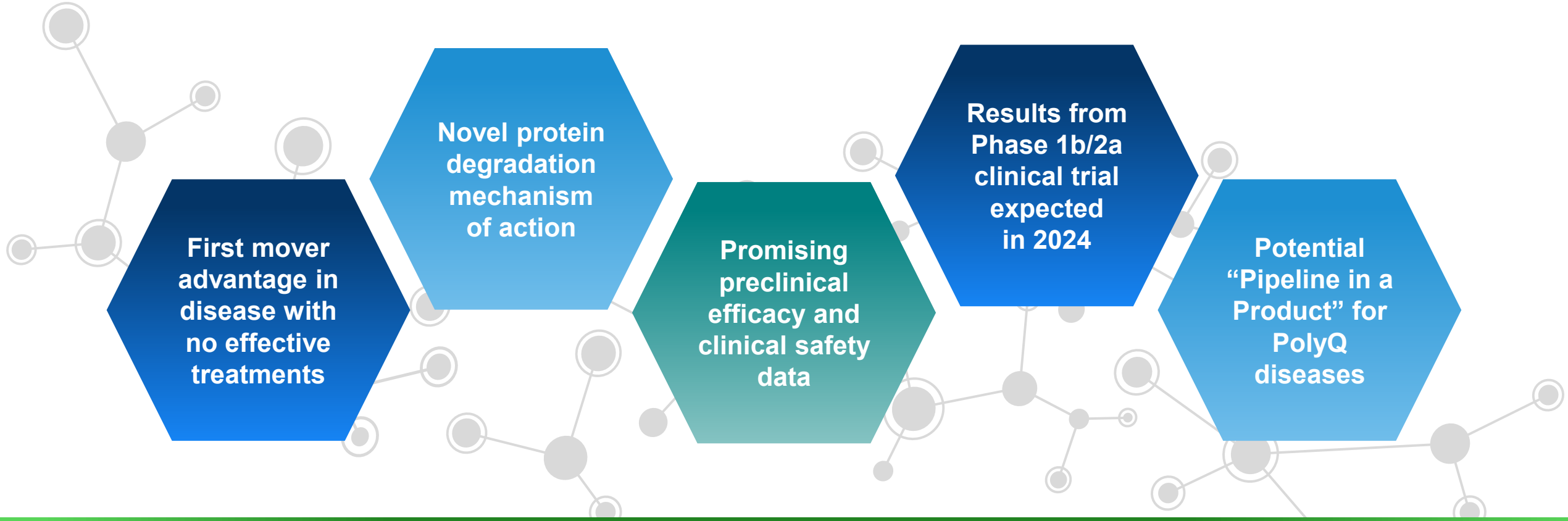
Source: 1. National Organization of Rare Disease, "Kennedy's Disease," 2022.
Source 2: M. Zanovello et al., Oxford University Press on behalf of the Guarantors of Brain. 2023. Based on U.S. male population of ~162M.
Source: 3. Bott et al., Hum Mol Genet. 2016.
Source 4. Acute Pain Market to Observe Growth at a CAGR of 8.3% During the Study Period (2019-2032), Assesses DelveInsight, 2023.

Multiple potential near-term catalysts in CNS-focused pipeline

	Indication	Phase 1	Phase 2	Phase 3	Next Milestone	Rights
AJ201	Spinal and Bulbar Muscular Atrophy (SBMA) / Kennedy's Disease	Phase 1b/2a			Phase 1b/2a Results Expected in 2024	U.S., EU, Great Britain, Canada, and Israel
BAER101	Epilepsy		Phase 2a		Initiate Phase 2a Trial 2024	Worldwide
IV Tramadol	Post-operative Pain			Phase 3 Pain Model Studies Confirmatory Safety Study	Initiate Final Phase 3 Safety Study	U.S.

Completed / ongoing study | Planned study

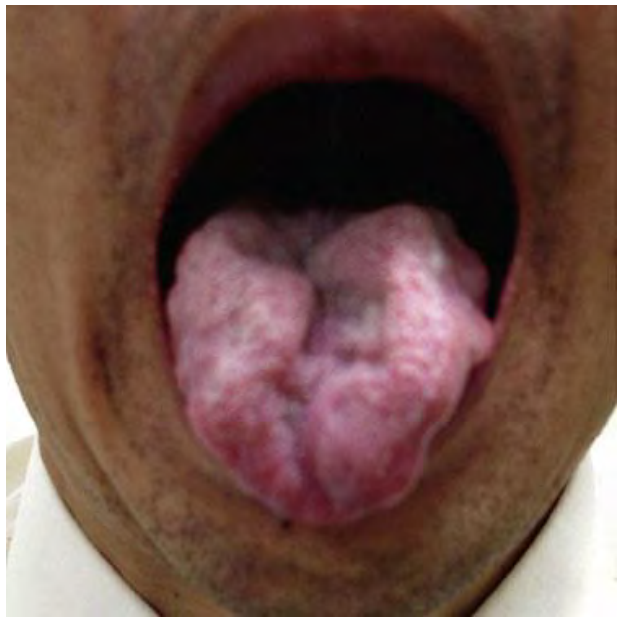
AJ201 in development as novel, first-in-class treatment for SBMA

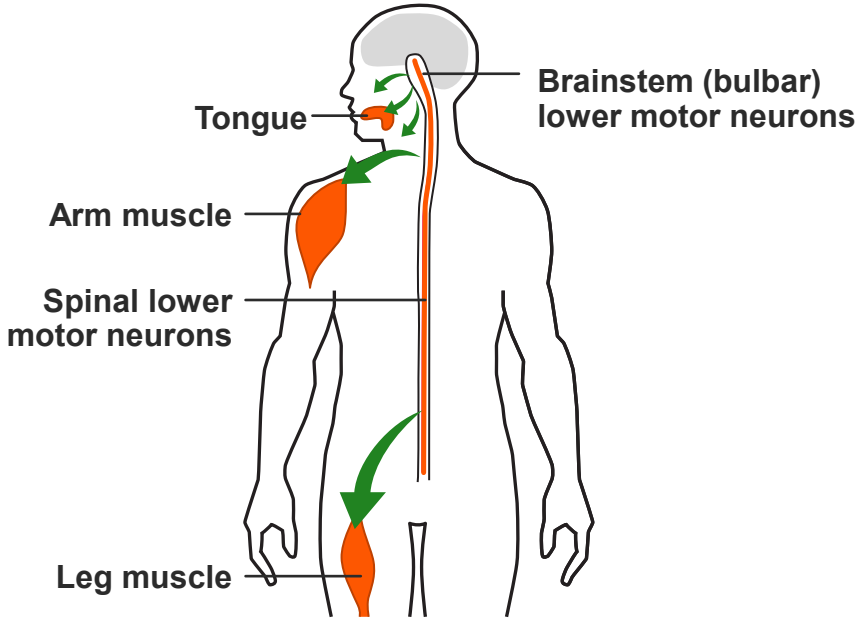


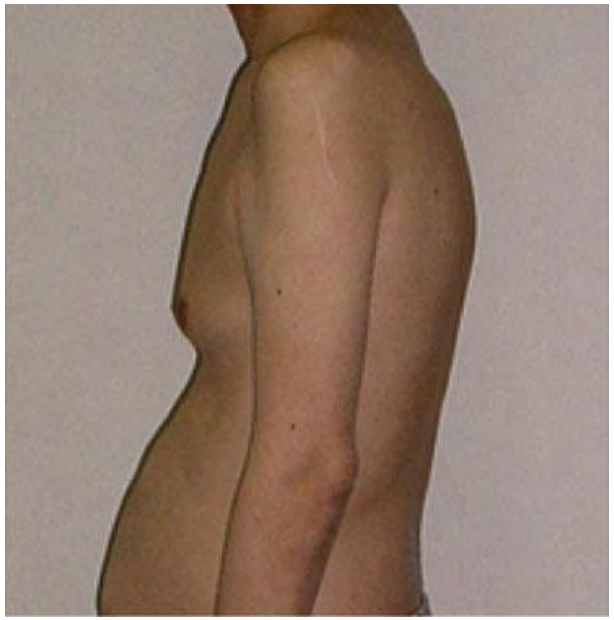
Most advanced investigational treatment for SBMA in U.S.
Awarded ODD* from U.S. FDA in multiple rare neuro indications and from EMA in SBMA

* "Orphan Drug Designation"

SBMA: Devastating, rare neurodegenerative disease with no FDA approved treatments for patients



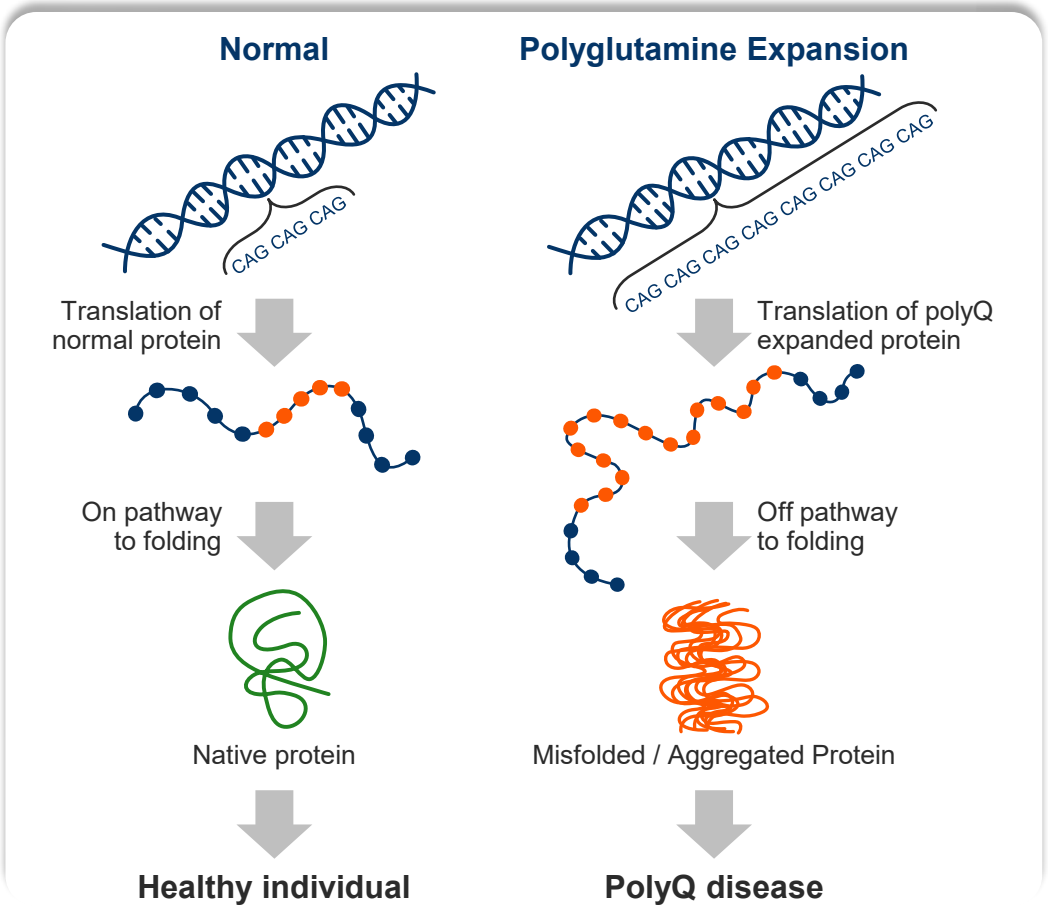




- Rare, X-linked PolyQ disease primarily affecting men
- Weakening of bulbar muscles affects chewing, speech and swallowing; SBMA also affects muscles in the limbs, leading to difficulty walking and often resulting in wheelchair usage
- Recent study used genetic analysis to estimate disease prevalence of 1:6,887 males[1]
- Age of onset ranges from 18-64
- Patients are currently and often poorly 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.

Polyglutamine (PolyQ) diseases are characterized by mutant protein aggregation and progressive neurodegeneration



- **9+** neurodegenerative diseases (NDD) caused by expansion of CAG repeats encoding polyQ tracts in affected genes, resulting in aggregation of mutant proteins in brain and other tissues
- Misfolded / aggregated protein causes toxicity as well as nerve and muscle death
- AJ201's innovative mechanism of action has potential therapeutic affect across multiple polyQ diseases driven by similar pathway:
  - Huntington's Disease
  - Six types of Spinocerebellar Ataxias
  - Spinal and Bulbar Muscular Atrophy
  - Dentatorubral Pallidoluysian Atrophy

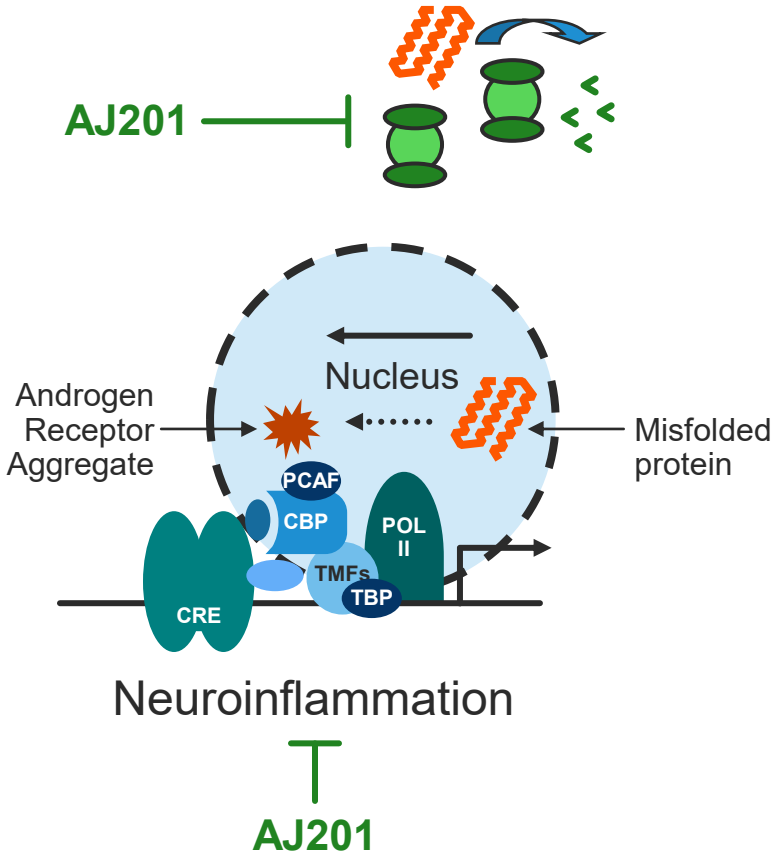
AJ201 awarded ODD* from U.S. FDA in SBMA, HD and select SCA indications

* "Orphan Drug Designation"

AJ201 enhances mutant AR protein degradation and decreases neuroinflammation through unique, three-fold mechanism of action

SBMA disease pathway

Dysfunctions of Ubiquitin–proteasome system (UPS)



AJ201 potential therapeutic activity

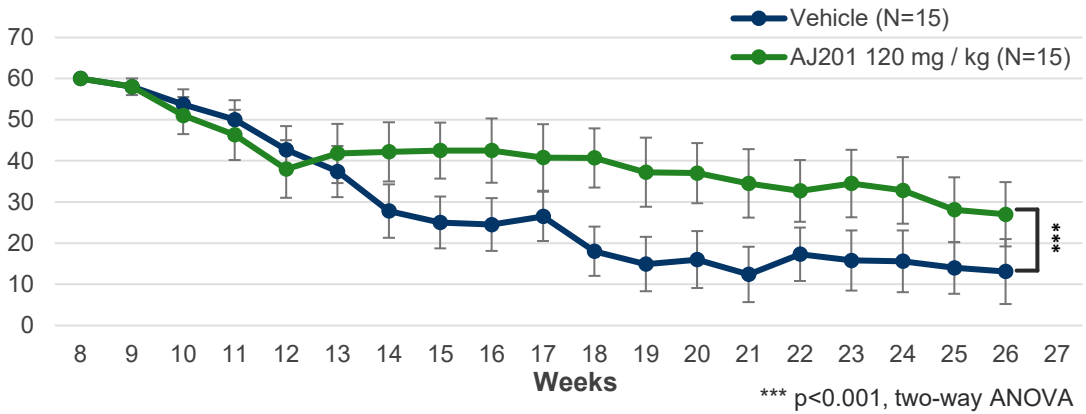
- **Mutant Androgen Receptor (AR) Degradation**
- **Nrf1 Pathway Activation**
- **Nrf2 Pathway Activation**

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

Preclinical data demonstrate promising efficacy signals in grip test and dose-dependent mutant AR degradation in SBMA models

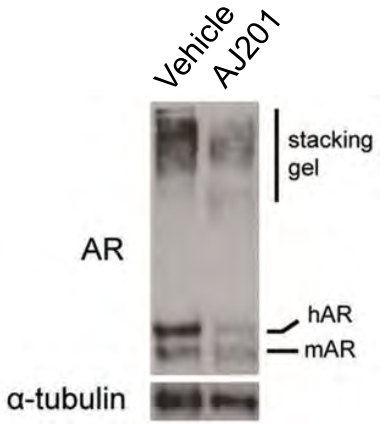
AJ201 led to improved motor function in symptomatic animals compared with vehicle control

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

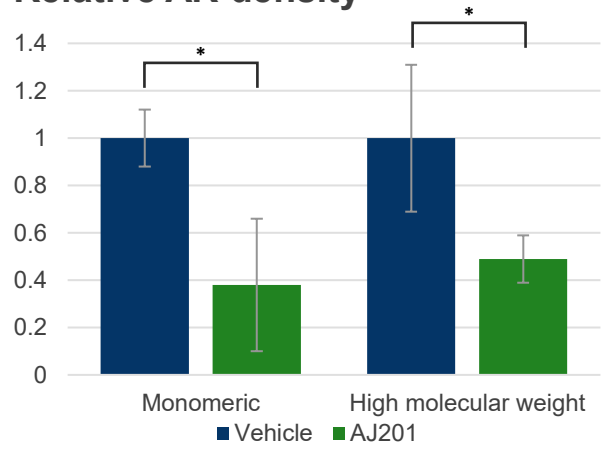


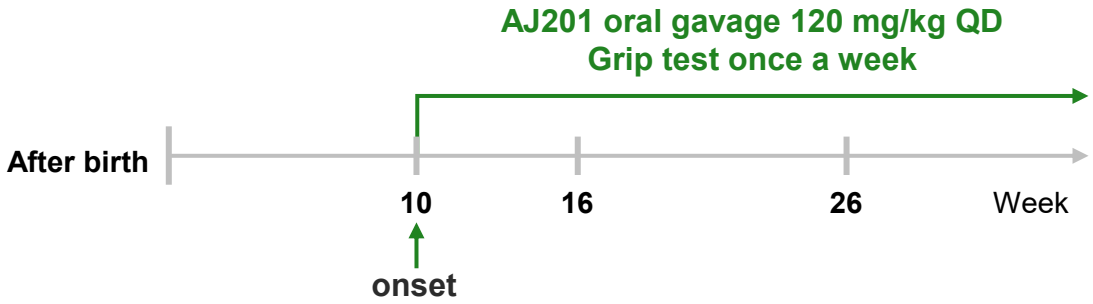
*** p<0.001, two-way ANOVA

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

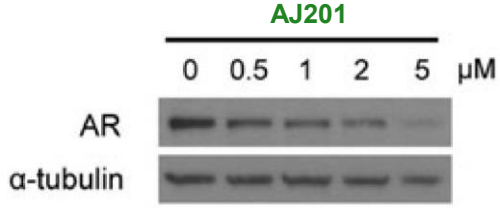


Relative AR density





AJ201 enhanced degradation of mutant AR in SBMA patient fibroblasts



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

Ongoing Phase 1b/2a study of AJ201 in SBMA patients expected to deliver final results in 2024

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

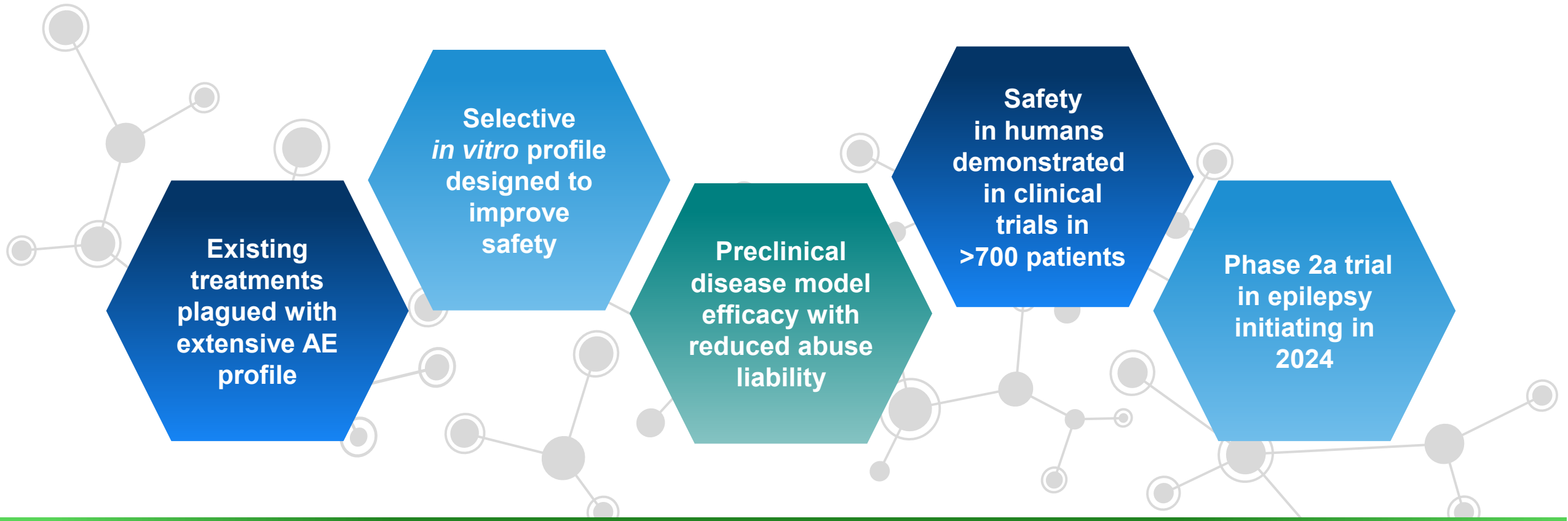
Primary Objective	Assessing safety, tolerability of AJ201 in subjects with clinically and genetically defined SBMA
Secondary Objective	Assessing pharmacokinetics (PK), and pharmacodynamics (PD) biomarkers of AJ201 in skeletal muscles
Exploratory Objective	Evaluate the proposed clinical assessments in subjects with SBMA as potential clinical outcome measures for future efficacy studies
Six Sites	Stanford University; UCI University of California, Irvine; NIH National Institutes of Health; MAYO CLINIC Jacksonville; MAYO CLINIC Rochester; Washington University in St. Louis

Phase 1b/2a study design

4 weeks Screening	**AJ201, 600mg, QD, 12 weeks Treatment (n=15)** **Placebo, QD, 12 weeks Treatment (n=5)**	**4 weeks Follow-up**

Hypothesis: AJ201 degrades mutant AR proteins and activates antioxidant response in muscles, therefore a future efficacy study may show clinical benefit in SBMA patients

BAER101 in development as potential best-in-class targeted therapy for treatment of epilepsy



Advanced development candidate with alpha 2/3 subtype-preferring selectivity, an important differentiating factor in improving tolerance and safety

BAER-101 may address large unmet need in the epilepsy market

Epilepsy

U.S. Prevalence	**3–4M patients** (~65M patients worldwide) • ~1M US patients are resistant to available drugs (known as drug resistant epilepsy) • Above categories include some orphan (including pediatric) populations
Disease	**Chronic disease** that manifests as recurrent seizures from abnormal electrical discharge in brain
Treatment	Use of one or more anti-seizure medications, such as benzodiazepines
Unmet Need	Benzodiazepines are effective, but **not well-tolerated due to significant side effects** including sedation, cognitive impairment, ataxia and addiction

Source: CDC.gov; Kalilani L et al. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018 Dec; ADAA.org

BAER101 targets $GABA_A$ α2 and α3 subtypes more than α1 and α5, potentially improving side effect profile compared to nonselective BZDs

Predicted effect of targeting $GABA_A$ subtypes

	Therapeutic Effect	$GABA_A$ subtypes			
		α1	α2	α3	α5
Positive	Anti-convulsant	✚✚	✚✚	✚✚	
Positive	Anxiolysis		✚✚	✚✚	
Positive	Analgesia		✚✚	✚	✚✚
Positive	Muscle Relaxation		✚✚	✚✚	
Negative	Sedation	✖✖			
Negative	Cognitive Impairment	✖✖			✖✖
Negative	Tolerance	✖✖			✖
Negative	Addiction	✖✖	✖		

BAER101

- **Most advanced therapy** in development designed to solely inhibit α2 and α3 subunits
- Goal of BAER101 is to provide anticonvulsant and anxiolytic activity by **minimizing adverse events** and risk of tolerance and abuse

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

BAER101 demonstrated a compelling safety profile at selected doses in 10 trials, as well as non-sedating tendencies

Safety profile

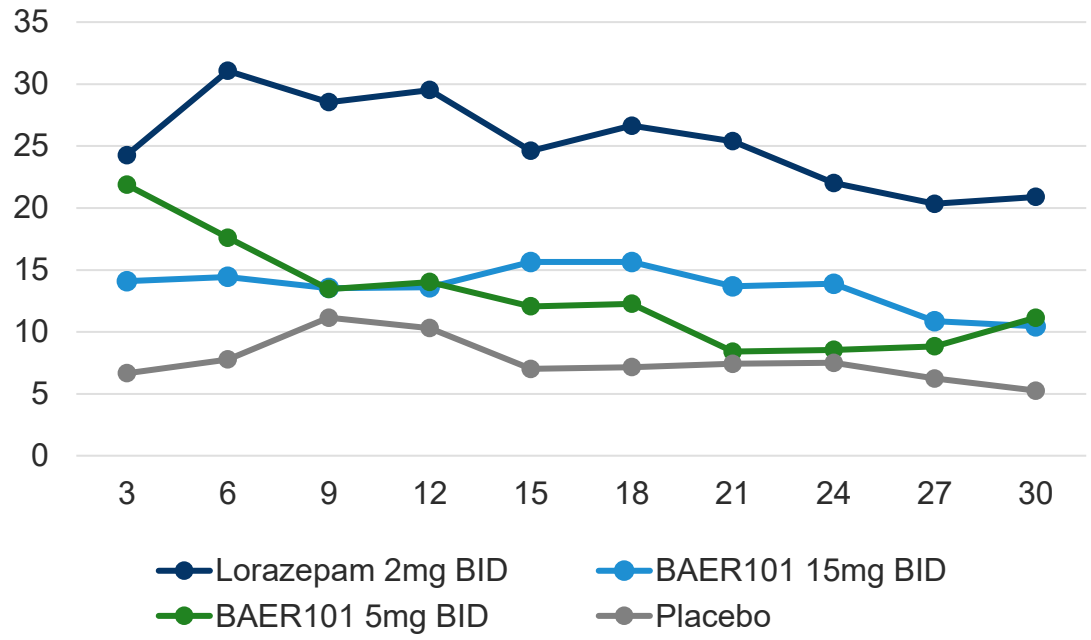
- BAER101 tested in over 700 subjects (healthy volunteers and patients)
- Side effects were mild or moderate with most common side effects being dizziness and somnolence
- BAER101 was also tested in human abuse liability study where risk abuse with BAER101 appeared lower than lorazepam (a BZD)

Efficacy profile

- Clinical data sub-analysis 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

Example: subset analysis from Phase 2 generalized anxiety study

Subjects experiencing sleepiness
% of subjects (N=36-66)



BAER101 shows full suppression of seizure activity with minimal effective dose in GAERS[1] model of absence epilepsy by Synapcell

Evaluation of BAER101 in GAERS Model

Background:

- GAERS model mimics behavioral, electrophysiological and pharmacological features of human absence seizures
- Proven and informative indicator of safety and efficacy in anti-seizure drug development for 20+ years
- Collecting spike-and-wave discharges (SWDs) recorded using EEG

BAER101 Reduces SWD Incidence and Duration Dose-Dependently

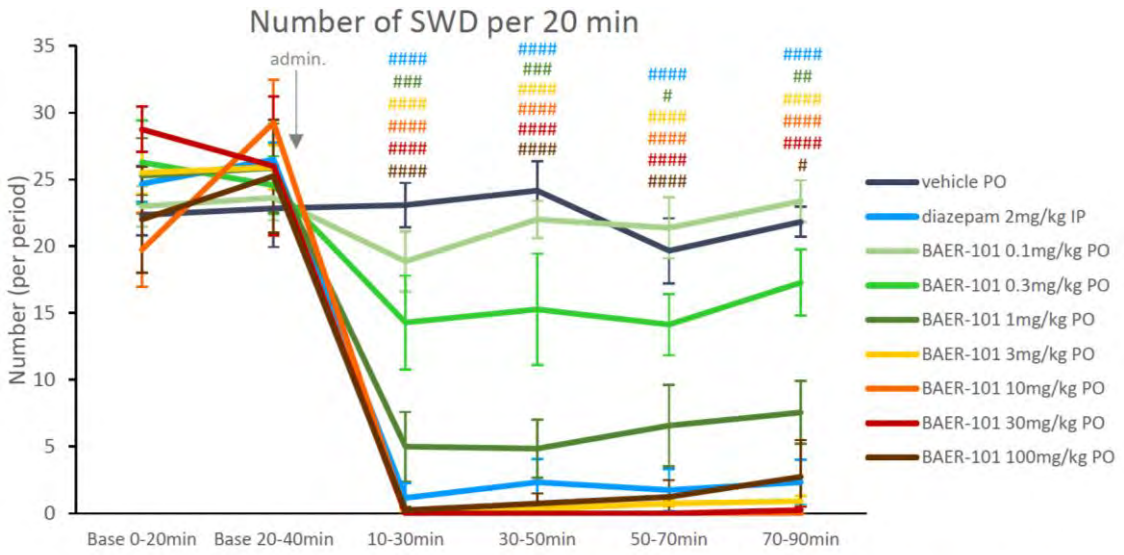


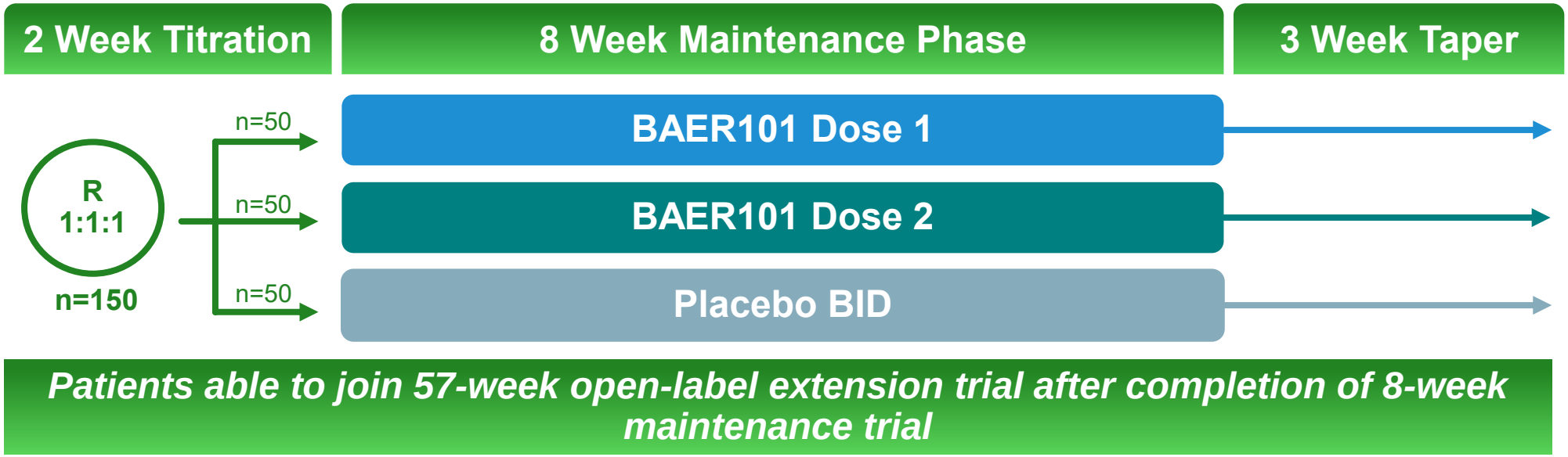
Figure 2 : Number of SWD per 20 min, in the vehicle condition (dark blue), diazepam at 2 mg/kg IP (light blue), and BAER-101 at 0.1 to 100 mg/kg PO (other colours). The grey arrow indicates the administration. #, ##, ###, ####: $p < 0.05$, 0.01, 0.001 and 0.0001 as compared to vehicle (n = 4 to 12).

Promising preclinical results support further clinical development of BAER101 in Phase 2a study in absence epilepsy

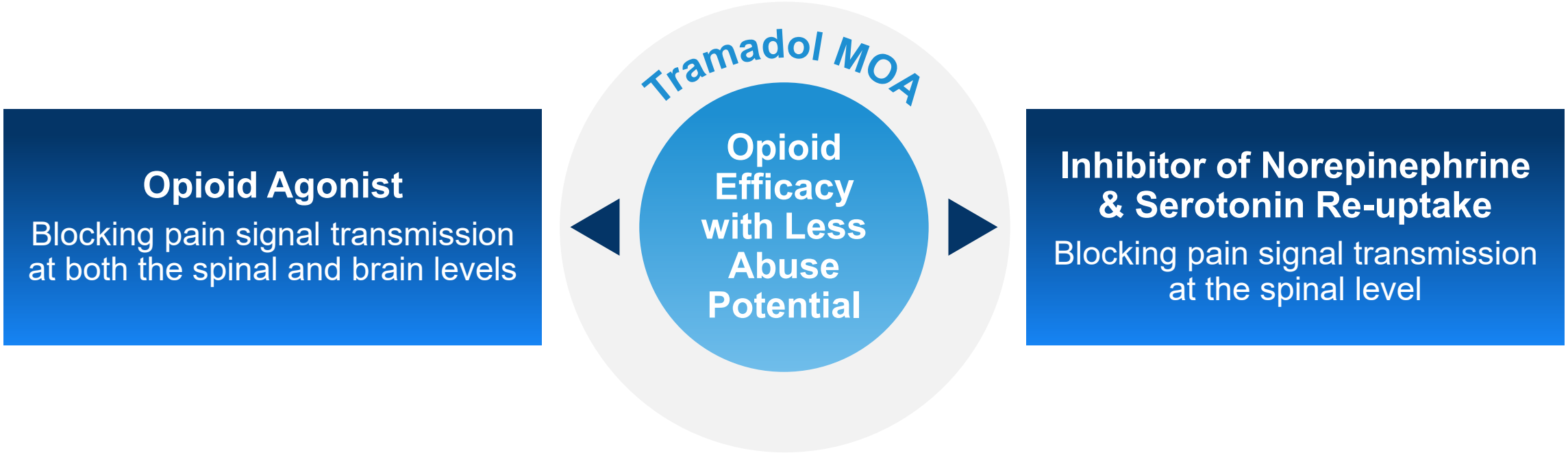
1 - Genetic Absence Epilepsy Rat from Strasbourg (GAERS)

BAER101 is Phase 2a study ready

- Opportunity to design a Phase 2a program for a strong POC signal in focal epilepsy and/or orphan indications (for example, Development and Epileptic Encephalopathies (DEEs), Lennox Gastaut Syndrome, Dravet)
- For focal epilepsy:



Tramadol has unique dual mechanism of action among IV analgesics designed to block patient's pain signal with reduced abuse potential



Schedule IV versus Conventional Narcotics (Schedule II)

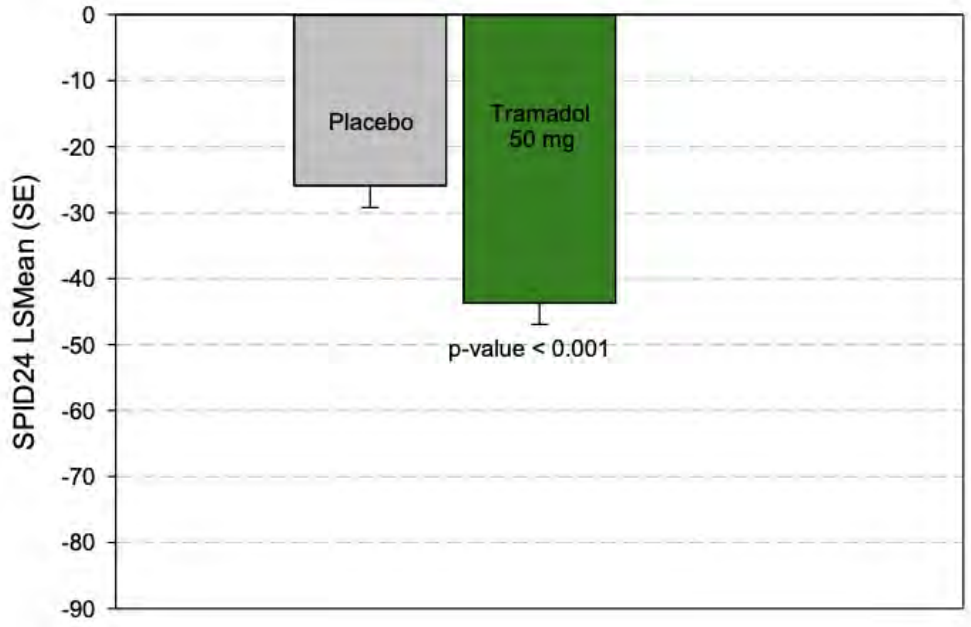
IV Tramadol safely used in Europe for 30 years –
Approximately 370 million doses were administered in Europe from 2010 to 2019

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

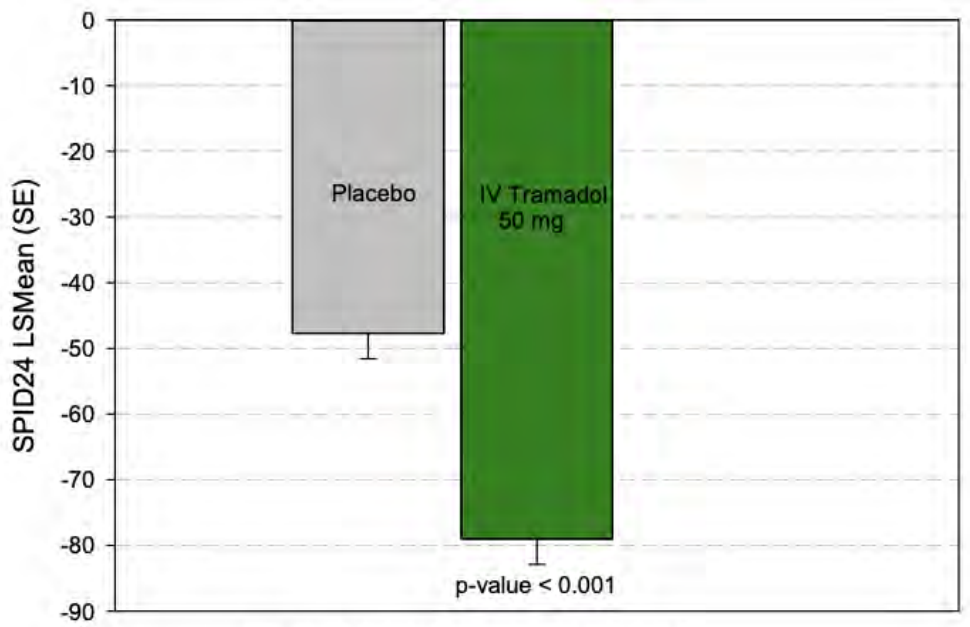
Proven safety and efficacy profile demonstrated in two Phase 3 trials in over 700 patients

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

Reached Agreement with FDA on the Phase 3 Safety Study Design

- Met with FDA to discuss study design to address agency's concern regarding opioid stacking
- Reached agreement with the FDA on the noninferiority study design including primary endpoint and analysis approach
- IV Tramadol should prove to be safer than IV Morphine in this noninferiority study
  - EU experience with IV tramadol versus morphine highlights this
  - Published literature also is supportive
- Will enroll patients in this acute pain study using the bunionectomy model
- Study appears feasible
- FDA feedback and protocol is available for review under CDA

Goal to initiate Phase 3 Safety Study in 2024

Executing to plan with multiple value-driving milestones ahead

AJ201 in SBMA

- ✓ Compelling Phase 1 safety data in healthy volunteers
- ✓ Activated six clinical trial sites across the U.S. and actively screening patients for Phase 1b/2a study of AJ201 in SMBA
- ✓ Dosed first patient in lead Phase 1b/2a study of AJ201 in SBMA in 2Q23
- ○ Final results for Phase 1b/2a study of AJ201 in SBMA expected in 2024

BAER101 in Epilepsy

- ✓ Compelling Phase 1 safety data across 10 clinical trials
- ✓ Announced topline preclinical data demonstrating high-potency and full efficacy of BAER101
- ○ Initiate Phase 2a trial of BAER101 in epilepsy in 2024

IV Tramadol for Pain

- ✓ Strong safety and efficacy profile across multiple late-stage clinical trials
- ✓ Met with FDA to discuss study design to address agency's concern regarding opioid stacking
- ✓ Finalized trial design with FDA for final Phase 3 safety study
- ○ Initiate Phase 3 safety study; results to potentially form basis for resubmission of NDA to FDA

Led by experienced management team and board of directors

Management

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