Filed Pursuant to Rule 433
Issuer Free Writing Prospectus dated October 3, 2023
Relating to Preliminary Prospectus dated September 29, 2023
Registration No. 333-274562

Disclaimers

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This presentation of Avenue Therapeutics, Inc. ("we," "us," "our," "Avenue," or the "Company") 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: the fact that we currently have no drug products for sale and that our success is dependent on our product candidates receiving regulatory approval and being successfully commercialized; the possibility that serious adverse or unacceptable side effects are identified during the development of our current or future product candidates, such that we would need to abandon or limit development of some of our product candidates; our ability to successfully integrate Baergic Bio, Inc. or develop BAER-101 or AJ201; the substantial doubt raised about our ability to continue as a going concern, which may hinder our ability to obtain future financing; the significant losses we have incurred since inception and our expectation that we will continue to incur losses for the foreseeable future; our need for substantial additional funding, which may not be available to us on acceptable terms, or at all, which unavailability could force us to delay, reduce or eliminate our product development programs or commercialization efforts; our reliance on third parties for several aspects of our operations; our reliance on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable; the possibility that we may not receive regulatory approval for any or all of our product candidates, or that such approval may be significantly delayed due to scientific or regulatory reasons; the fact that even if one or more of our product candidates receives regulatory approval, they will remain subject to substantial regulatory scrutiny; the effects of current and future laws and regulations relating to fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations; the effects of competition for our product candidates and the potential for new products to emerge that provide different or better therapeutic alternatives for our targeted indications; the possibility that the government or third-party payors fail to provide adequate coverage and payment rates for our product candidates or any future products; our ability to establish sales and marketing capabilities or to enter into agreements with third parties to market and sell our product candidates; our exposure to potential product liability claims; our ability to secure adequate protection of our intellectual property and our potential inability to maintain sufficient patent protection for our technology and products; our

Disclaimers

Cautionary Statement Regarding Forward-Looking Statements (cont'd)

ability to maintain compliance with the obligations under our intellectual property licenses and funding arrangements with third parties, without which licenses and arrangements we could lose rights that are important to our business; the fact that Fortress controls a voting majority of our Common Stock and has rights to receive significant share grants annually; our ability to comply with the applicable listing standards and maintain our current listing for our Common Stock on The Nasdaq Capital Market; and those risks discussed in our filings which we make with the Securities and Exchange Commission (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.

Important Information

The Company has filed a registration statement (including a prospectus) with the SEC for the offering to which this communication relates. Before you invest, you should read the prospectus in that registration statement and other documents the Issuer has filed with the SEC for more complete information about the Company and this offering. You may get these documents for free by visiting EDGAR on the SEC Web site at www.sec.gov. Alternatively, the Company, any placement agent or any dealer participating in the offering will arrange to send you the prospectus if you request it by emailing syndicate@maximgrp.com or calling (212) 895-3745.

Offering Summary

ISSUER:	Avenue Therapeutics, Inc. ("Avenue" or the "Company")
EXCHANGE/SYMBOL:	NasdaqCM: ATXI
OFFERING SIZE:	Up to $12.0 Million
OFFERING TYPE:	Best Efforts S-1 Follow-On Offering
SECURITIES OFFERED:	Units consisting of one share of Common Stock (or Pre-Funded Warrants in lieu thereof) and one Warrant to purchase one share of Common Stock
ANTICIPATED USE OF PROCEEDS:	• Advancement of clinical trials • Working capital and general corporate purposes
JOINT PLACEMENT AGENTS:	Maxim Group LLC & Lake Street Capital Markets
ANTICIPATED PRICING:	Week of October 9, 2023

Executive Summary

- Avenue Therapeutics is a company focused on developing therapies to treat neurologic diseases including acute hospital pain and a rare neuromuscular condition
- IV tramadol has completed two Phase 3 efficacy trials with one remaining safety trial
  - Phase 3 safety trial could be initiated in early 2024 and report data within 7-8 months to support a potential FDA approval in 2025
  - IV tramadol has been used globally ex-US for decades and addresses an unmet need in the U.S. postoperative pain market between stronger opioids and NSAIDs/Acetaminophen
- AJ201 is currently in an ongoing Phase 1b/2a and has a proof-of-concept data readout in 2024 for treatment of a rare neurologic disease for which there is nothing approved outside of Japan
  - Data readout in first half of 2024 for SBMA (spinal and bulbar muscular atrophy), also known as Kennedy's Disease

Two drugs are expected to deliver data in 2024 including the IV tramadol Phase 3 development program

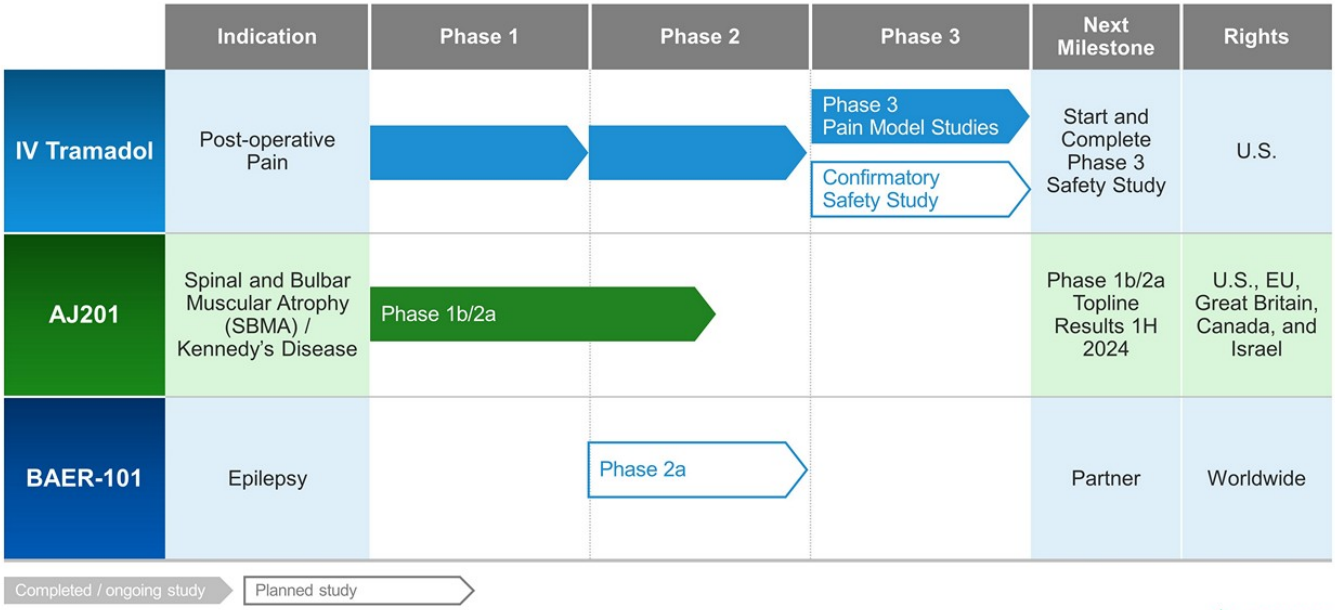
Note: Phase 3 tramadol trial initiation and data are subject to sufficient funding and/or partnering

Diverse portfolio including a first-in-class program in high-value neurologic landscape with significant unmet patient need

Pipeline Asset	IV Tramadol	AJ201	BAER-101
Indication	Post operative pain	Spinal and Bulbar Muscular Atrophy (SBMA/Kennedy's Disease)	Epilepsy and acute anxiety
Mechanism	Opioid agonist & inhibitor of norepinephrine & serotonin re-uptake	Activation of Nrf1 & Nrf2 and promotion of AR degradation	Selective GABA-A α2 and α3 receptor positive allosteric modulator
Key therapeutic value proposition	Schedule IV drug for acute care postoperative pain	No FDA approved therapies exist for SBMA patients	A safer and more tolerable benzodiazepine
Addressable population	~100M acute pain cases in U.S.[1]	Estimates vary widely, ranging from ~1:6887[2] to 1:30000[3]	~50M[4] patients with epilepsy & ~280M patients with anxiety worldwide[5]

Source: 1. Acute Pain Market to Observe Growth at a CAGR of 8.3% During the Study Period (2019-2032), Assesses DelveInsight, 2023.
2. M. Zanovello et al., Oxford University Press on behalf of the Guarantors of Brain. 2023 3. www.orpha.net, Kennedy's Disease..
4. www.who.int, epilepsy. 5. www.ourworldindata.org, anxiety

Multiple potential near-term catalysts in CNS-focused pipeline



Executing to plan with multiple value-driving milestones ahead

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; topline data expected within 7-8 months of trial initiation; results to form basis for resubmission of NDA to FDA

AJ201 in SBMA

- ☑ Compelling Phase 1 safety data in healthy volunteers
- ☑ Dosed eight patients in lead Phase 1b/2a study of AJ201 in SBMA since first patient in 3Q23
- ○ Final results for Phase 1b/2a study of AJ201 in SBMA expected in 2024

BAER-101 in Epilepsy & Acute Anxiety

- ☑ Compelling supportive clinical safety data across 10 clinical trials
- ☑ Ongoing presentation and publication of preclinical data for BAER-101 target selection
- ○ Phase 2a ready for epilepsy

Note: Milestones based on management's best estimates

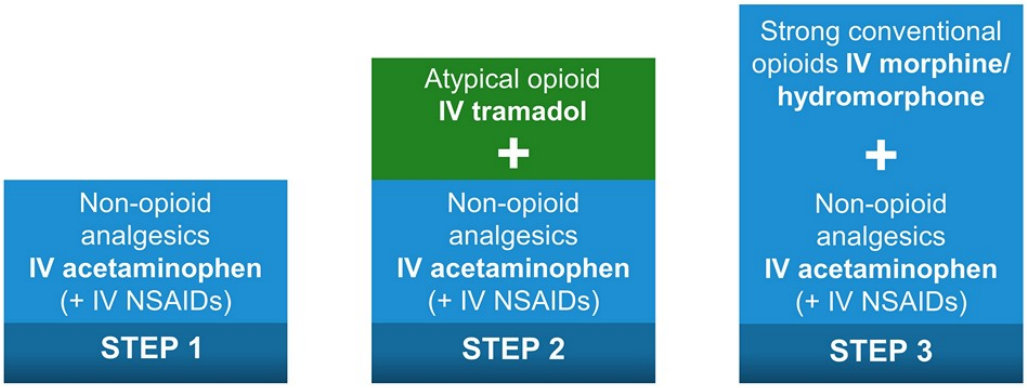
Tramadol has unique dual mechanism of action among IV analgesics designed to block patient's pain signal with reduced abuse potential

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

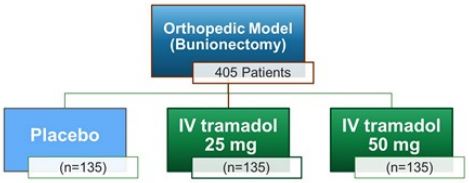
Note: Schedule IV substances are defined as drugs with a low potential for abuse and low risk of dependence. Schedule II substances are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence.
Source: https://www.dea.gov/drug-information/drug-scheduling

IV tramadol expected to be used before moving to stronger opioids

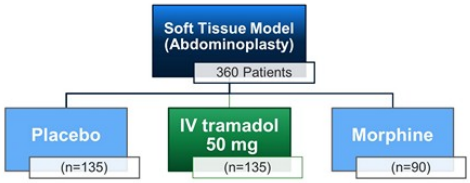


Source: Can Fam Physician. 2010 Jun; 56(6): 514–517; Avenue research

Phase 3 efficacy studies conducted in more than 700 patients



PRIMARY ENDPOINT
Sum of Pain Intensity Differences (SPID) through 48 hours post first dose

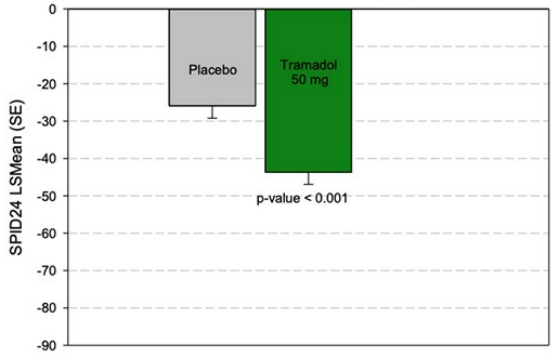


PRIMARY ENDPOINT
Sum of Pain Intensity Differences (SPID) through 24 hours post first dose

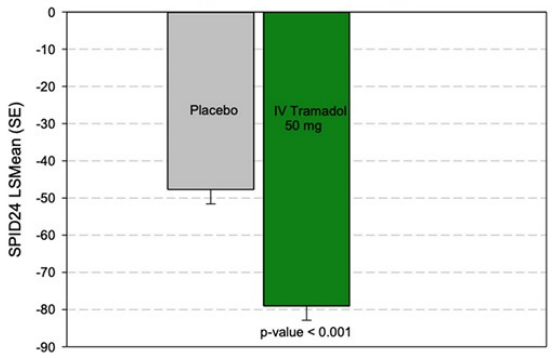
Note: IV tramadol is an investigational drug and remains subject to FDA approval

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

Study AVE-901-102 (Bunionectomy) SPID24



Study AVE-901-103 (Abdominoplasty) SPID24



p-value is comparing IV tramadol to placebo.

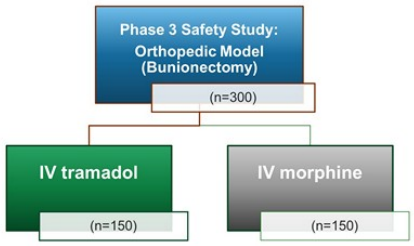
Both pain relief study models show benefit of tramadol over placebo

Regulatory history and now a path forward for IV tramadol NDA

2022	2023	2024+
Meeting held in August with FDA Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on potential path forward for a safety study design that could address FDA's concerns identified in previous Complete Response Letters (CRLs).	Discussed a clinical protocol with the FDA to assess the risk of respiratory depression related to opioid stacking on IV tramadol relative to IV morphine. Announced alignment with FDA on key elements of the Phase 3 safety study including primary endpoint and statistical analysis approach for a non-inferiority study. FDA agreement that a successful study will support submission to address the CRL and lead to potential approval of IV tramadol.	With financing, Avenue believes a trial could report Phase 3 safety data within 7-8 months of trial initiation and potentially support an approval of IV tramadol in 2025.

Note: more detailed disclosures regarding the regulatory history of IV tramadol are available on SEC EDGAR in Avenue's public filings

Phase 3 safety study to show non-inferiority of IV tramadol compared to IV morphine in opioid induced respiratory depression endpoint



- When patients require rescue medication for breakthrough pain for either arm (IV tramadol or IV morphine), they will receive IV hydromorphone, thereby creating opioid stacking
- Patients will be monitored for opioid-induced respiratory depression events throughout the 48-hour study, including somnolence, respiratory rate, and oxygen saturation level
- De-risked execution of safety study comparing IV tramadol to IV morphine for noninferiority given substantial clinical knowledge of:
  - EU experience with IV tramadol versus morphine
  - Published literature relating to tramadol

Note: trial sample size estimated based on current assumptions subject to final protocol review

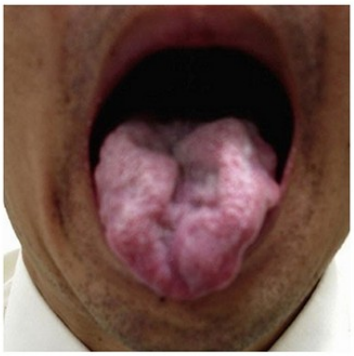
AJ201 in development as novel, first-in-class treatment for SBMA

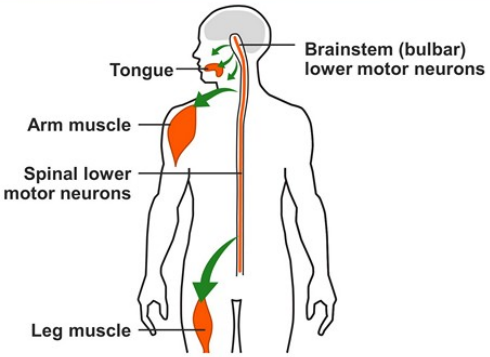
- First mover advantage in disease with no FDA approved treatments
- Novel protein degradation mechanism of action
- Promising preclinical efficacy and clinical safety data
- Results from Phase 1b/2a clinical trial expected in 2024
- Potential "Pipeline in a Product" for PolyQ diseases

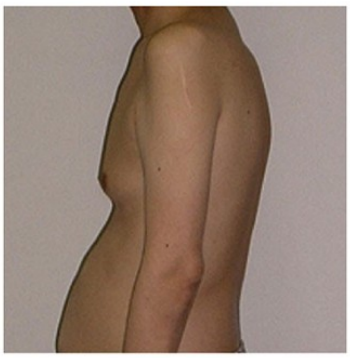
Awarded ODD* from U.S. FDA in multiple rare neuro indications and from EMA in SBMA

** Orphan Drug Designation*
SBMA is Spinal and Bulbar Muscular Atrophy, also known as Kennedy's Disease

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



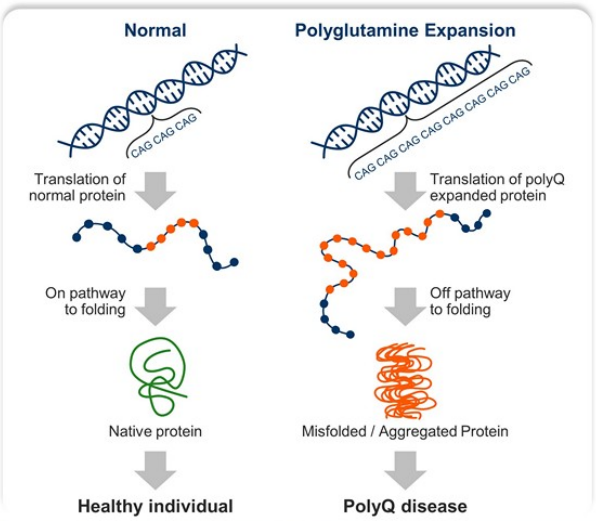




- Rare, X-linked PolyQ disease primarily affecting men
- Weakening of bulbar muscles affects chewing, speech and swallowing; SBMA also affects muscles in the limbs, leading to difficulty walking and often resulting in wheelchair usage
- Recent study used genetic analysis to estimate disease prevalence 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

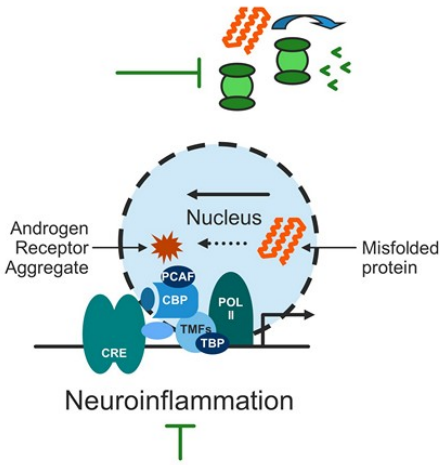
AJ201 awarded ODD* from U.S. FDA in SBMA, HD and select SCA indications

** Orphan Drug Designation*

Potential therapeutic activity of AJ201 includes enhancing mutant AR protein degradation and decreasing neuroinflammation

SBMA disease pathway

Dysfunctions of Ubiquitin–proteasome system (UPS)



AJ201 potential activity via three mechanisms

Mutant Androgen Receptor (AR) Degradation

Nrf1 Pathway Activation

Nrf2 Pathway Activation

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

Phase 1b/2a study of AJ201 in SBMA patients expected to report data in 1H 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

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

AJ201 is currently the lead clinical program targeting SBMA

Product	MoA	Preclinical	Phase I	Phase II	Phase III	Approved
Leuprorelin	Gonadotropin releasing hormone stimulant					Japan only & limited efficacy
AJ201	**Activation of Nrf1 / Nrf2 and promotion of AR degradation**					
NIDO361	AR BF3 modulator					
AAV-miRNA	Gene therapy to knockdown mutant AR					

AJ201 has multiple orphan disease designations that provide regulatory exclusivity upon approval

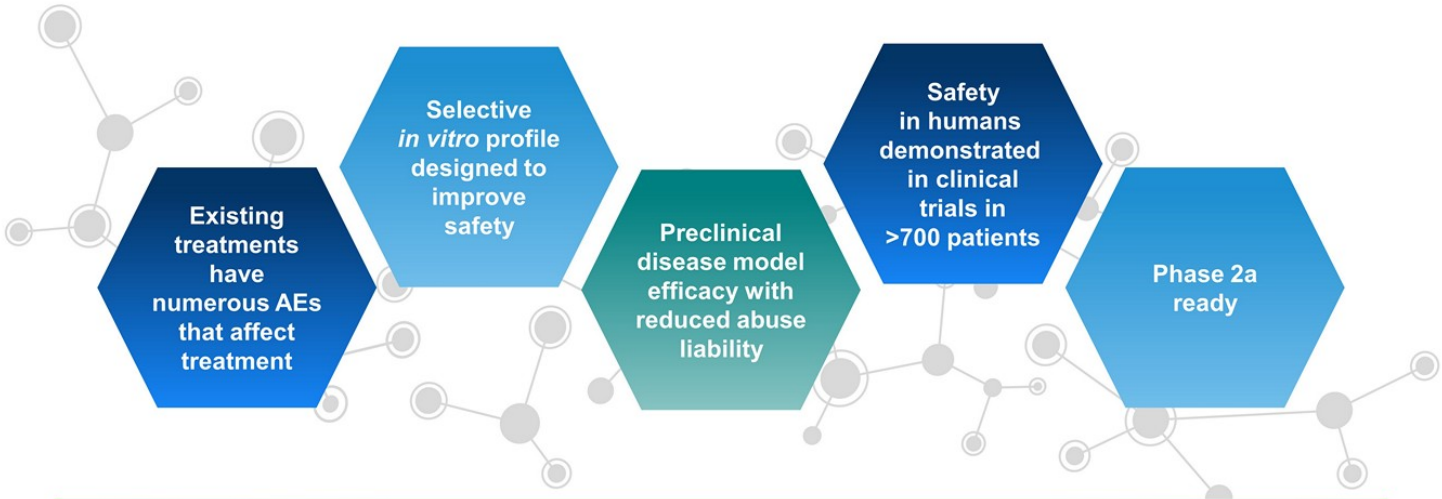
Orphan drug status granted

Indication	U.S. FDA	EMA
SBMA	✓	✓
Huntington's disease	✓	
Spinocerebellar ataxia	✓	

Intellectual property overview

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

BAER-101 in development as a differentiated targeted therapy for treatment of epilepsy



BAER-101 has alpha 2/3 subtype-preferring selectivity that may deliver improved tolerance and safety

BAER-101 targets GABA α2 and α3 subtypes more than α1 and α5, potentially improving side effect profile compared to nonselective benzodiazepines

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

- BAER-101 is designed to inhibit α2 and α3 subunits
- Goal of BAER-101 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

BAER-101 is differentiated from others in the class

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

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

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- ○ Phase 2a ready for epilepsy

Led by experienced management team and board of directors

Management

Alexandra MacLean MD
CEO

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David Jin
Interim CFO

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