PRECISION NEUROSCIENCE.
TRANSFORMATIONAL THERAPIES.

CORPORATE SUMMARY | 3Q 2023

Engrail THERAPEUTICS

Engrail is a clinical-stage, neuropsychiatry-focused pharmaceutical company

Rapidly advancing programs create
near-term milestones and value creation

Phase 1 and Phase 2 data readouts
Multiple INDs
Class clinical validation

Deep and differentiated pipeline

Psychiatry
Rare Disease
Neurology

Unique approach
improving probability of success

Scientific / mechanistic validation
Best-in-class profiles
Understood diseases and high-potential indications

Experienced leadership with
a track record of success in neuropsychiatry

>100 years of neuropsych drug development
>30 product launches

Portfolio is deep and diverse, with discovery to clinical stage compounds across MOAs and potential indications

Program	MoA	Lead Indication	Discovery	Preclinical	Phase 1	Phase 2
Psychiatry						
ENX-102	$GABA_A$ $\alpha_{2,3,5}$ PAM, α_1 antagonist	Generalized anxiety disorder				
ENX-104	D2/D3 antagonist	Depression / Anhedonia				
ENX-105	D2/D3 antagonist, 5-HT_{1A} and 5-HT_{2A} agonist	PTSD / Mood disorders				
Rare Disease						
ENX-103	Copper transport	Menkes disease				
Neurology						
ENX-101	$GABA_A$ $\alpha_{2,3,5}$ PAM, α_1 antagonist	Epilepsy				
ENX-106	$GABA_A$ $\alpha_{2,3,5}$ PAM, α_1 antagonist	Spasticity / Pain				
ENG-002	$GABA_A$ $\alpha_{2,3,5}$ PAM, α_1 sparing	Spasticity / Pain				

MoA, mechanism of action; $GABA_A$, gamma-aminobutyric acid A receptor; PAM, positive allosteric modulator; D2/D3, dopamine receptor 2/3; P, phase; IND, investigational new drug.

SUBTYPE SELECTIVE $GABA_A$ MODULATION

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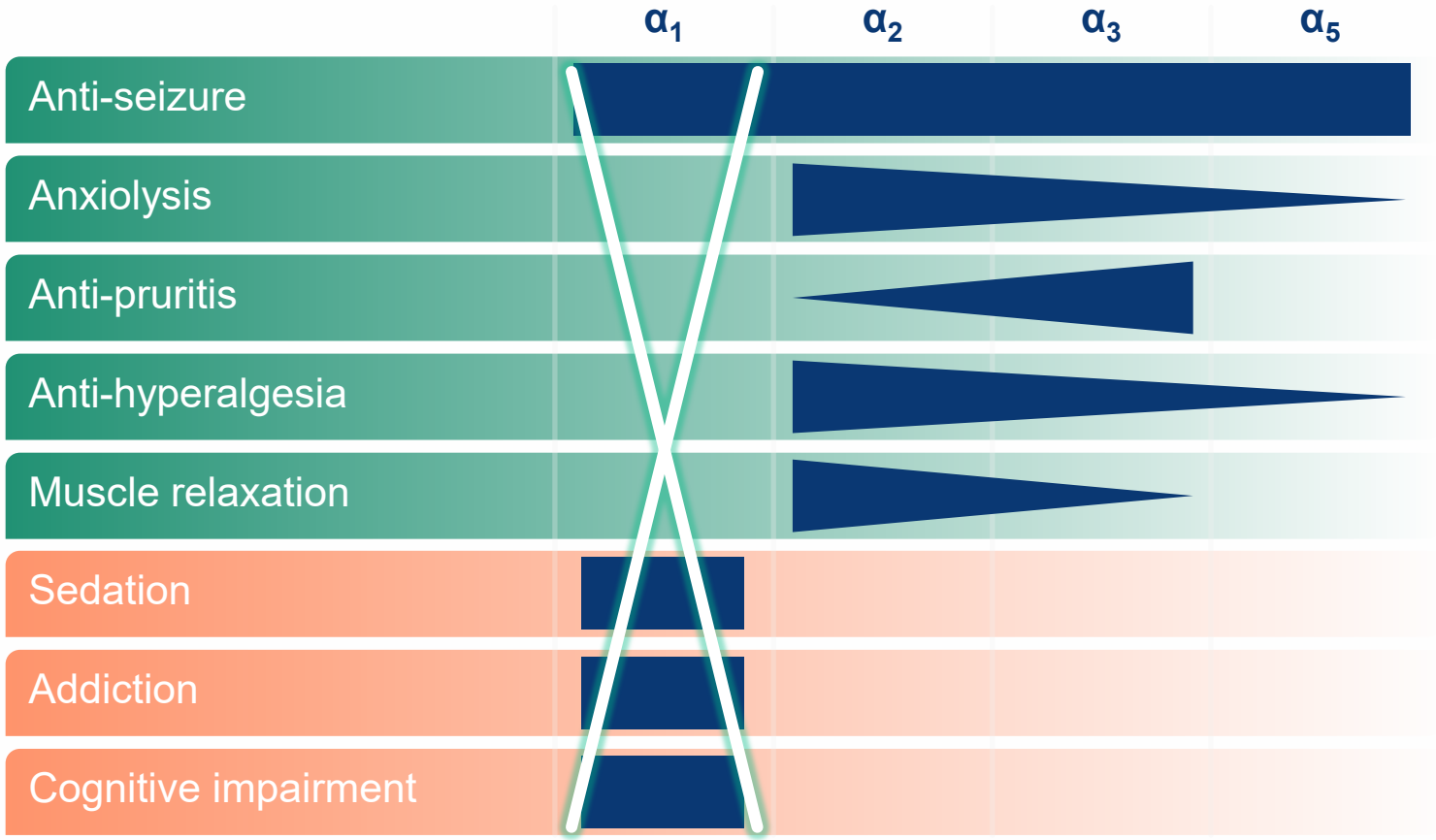
Selective $GABA_A$ $\alpha_{2,3,5}$ PAMs designed to maximize clinical benefits and minimize liabilities

Precision targeting: positive allosteric modulation of $GABA_A$ $\alpha_{2,3,5}$ and antagonism of α_1



Selective $GABA_A$ $\alpha_{2,3,5}$ PAMs designed to:

- ≥ Efficacy
- ↓ Sedation
- ↓ Addiction potential
- ↓ Tachyphylaxis
- ↑ Ability for chronic dosing

$GABA_A$, gamma-aminobutyric acid A receptor; PAM, positive allosteric modulator.

Cheng T, et al. Neuropsychiatr Dis Treat. 2018;14:1351–1361. Olsen RW. Neuropharmacology. 2018;136:10–12.
Adapted from Zeilhofer HU, et al. Br J Anaesth. 2019;123:e176–e179.

Our optimized profiles, while distinct, are superior to other $GABA_A$ $\alpha_{2,3,5}$ PAMs in development

Compound	Phase	Functional Activity				Half-life	Indication
		α_1	α_2	α_3	α_5		
Darigabat (CVL-865, PF-06372865)	2	+	++	++	++	~11 hours	Epilepsy Panic disorder
ENX-101	2	-- antagonist	+++	+++	+++	~20 hours	Epilepsy
ENX-102 (TPA023B)	2	-- antagonist	+++	+++	+++	~50 hours	Generalized anxiety disorder
BAER-101 (AZD7325)	1	--	+	+	--	~9 hours	Unspecified

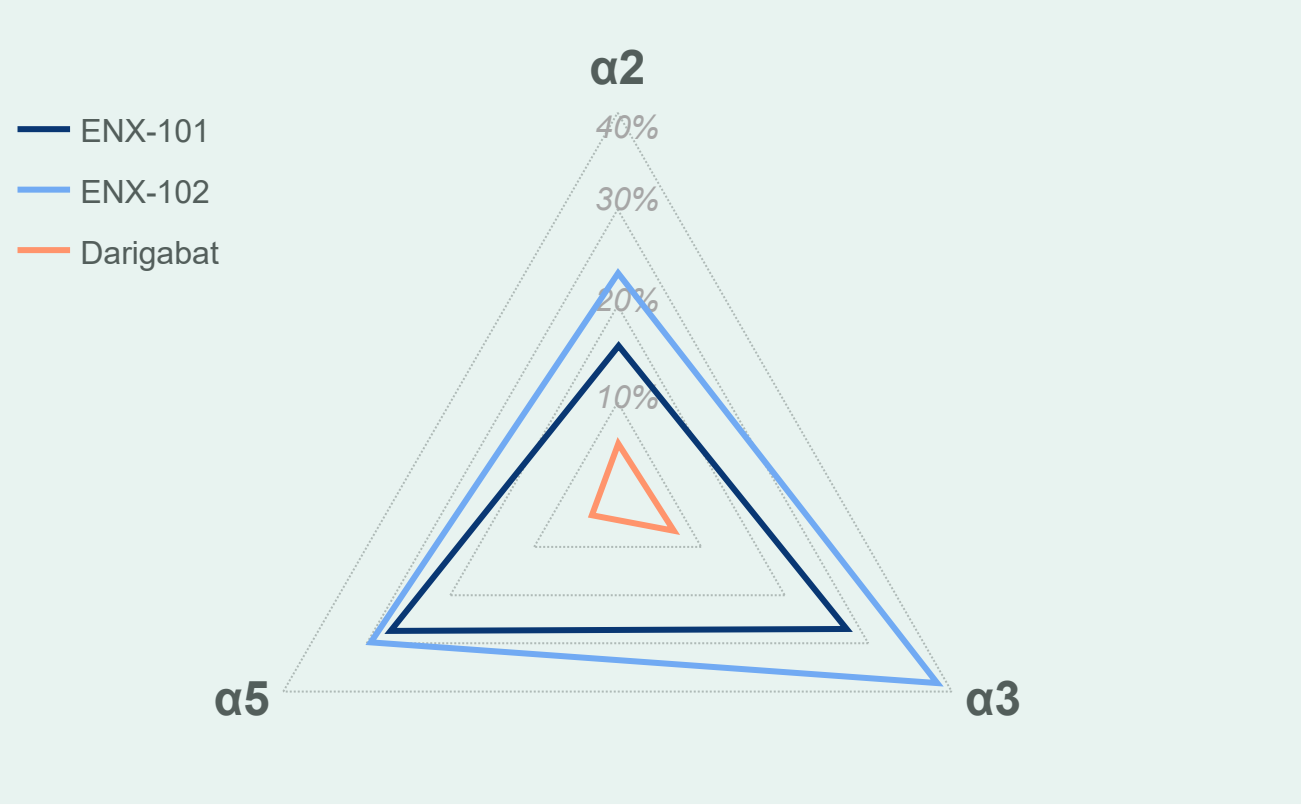
Tolerability / Safety **Efficacy** **Ease of dosing**

$GABA_A$, gamma-aminobutyric acid A receptor; PAM, positive allosteric modulator.
ENX-101 and ENX-102 have completed Phase 1b and are ready to enter phase 2.
Data on File; Gurrell R, et al. Clin Pharmacol Drug Dev. 2021;10:756–764. Chen X, et al. Br J Pharmacol. 2014;78:1298–1314.

Our optimized profiles, while distinct, are superior to other $GABA_A$ $\alpha_{2,3,5}$ PAMs in development

Receptor Function

Matched to 65% receptor occupancy (RO) at steady-state



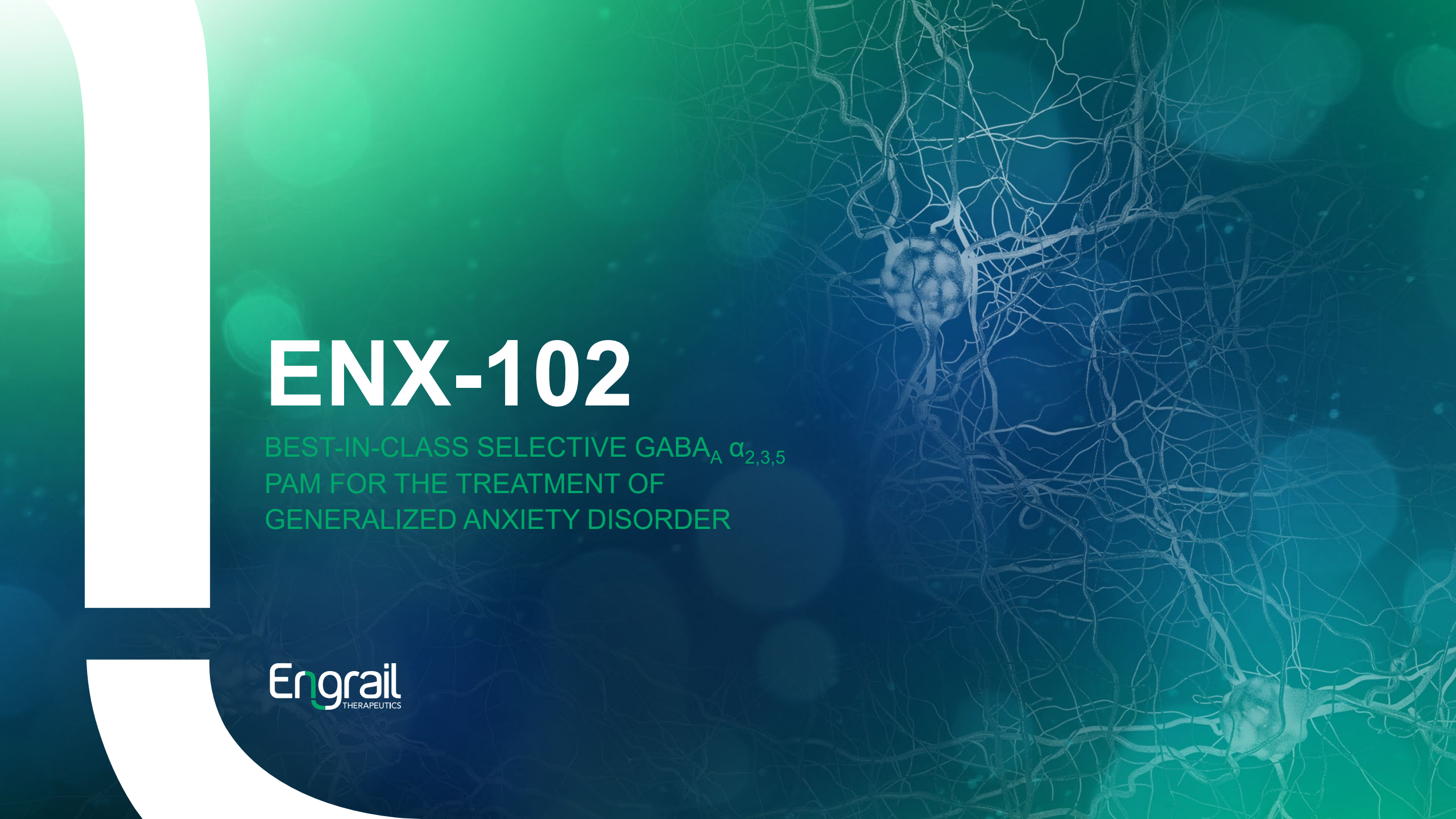
- ENX-101 and ENX-102 have **distinct profiles**
- Both compounds **drive more intrinsic activity** on $GABA_A$ $\alpha_{2,3,5}$ than darigabat
- ENX-101 and ENX-102 each exhibit **longer half lives** (~20 and ~50-60 hrs) than darigabat (~11 hrs)

Optimized and distinct profiles drive different preclinical and clinical outcomes

"predicted observed" RO using 50% alpha1+ (25% alpha2 +25% alpha3) formula from Nickolls et al.
Data on file.

ENX-102

BEST-IN-CLASS SELECTIVE $GABA_A$ $\alpha_{2,3,5}$ PAM FOR THE TREATMENT OF GENERALIZED ANXIETY DISORDER



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Anxiety is an epidemic

Standard screening is recommended for all adults <64 years old

USPSTF Clinician Summary of USPSTF Recommendation

Screening For Anxiety Disorders in Adults

June 2023

What does the USPSTF recommend?

B Grade

Adults 64 years or younger, including pregnant and postpartum persons:
Screen for anxiety.

I Statement

Older adults 65 years or older:
The evidence is insufficient to assess the balance of benefits and harms of screening for anxiety disorders.

To whom does this recommendation apply?

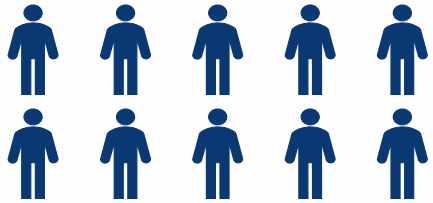
This recommendation applies to adults (19 years or older), including pregnant and postpartum persons, and older adults (65 years or older) who do not have a diagnosed mental health disorder and are not showing recognized signs or symptoms of anxiety disorders.

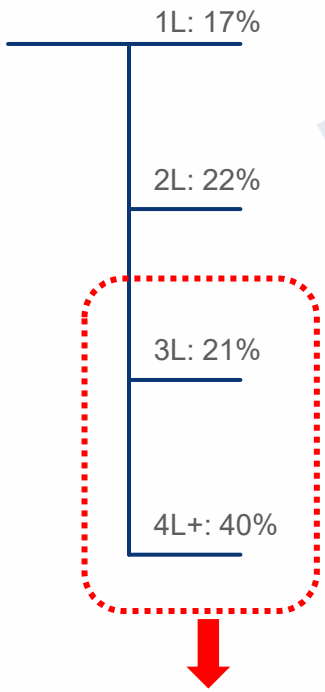
What's new?

This is a new USPSTF recommendation.

There is substantial need for new options to treat GAD

>5.4 M US patients
currently being treated for GAD





Additional patients

+ 1.4 M patients on treatment for depression with GAD as a secondary indication

+ 9.2 M patients on treatment for anxiety (unspecified)

>60% of GAD patients **fail** first and second lines of therapy

Two primary therapeutic strategies

SSRI / SNRI / Buspirone

Benzodiazepines

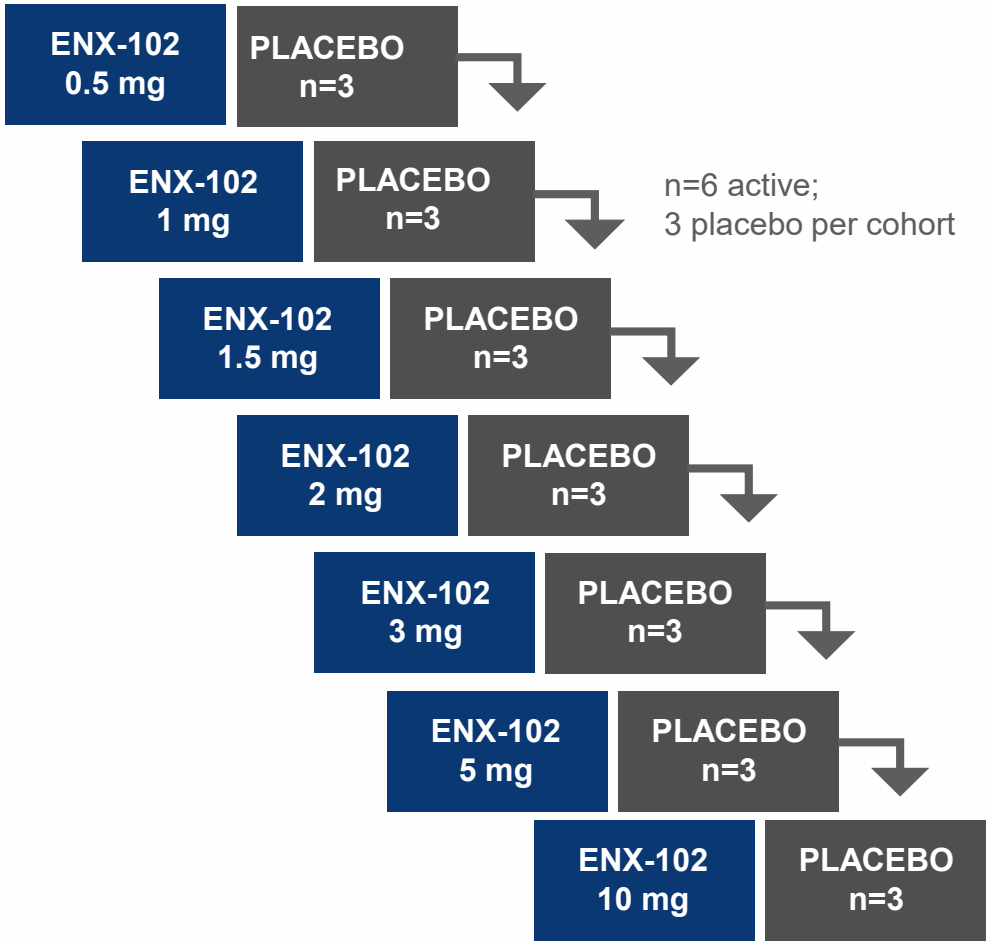
1L, first line; 2L, second line; 3L, third line; 4L, fourth line; GAD, generalized anxiety disorder; BZP, benzodiazepine.
IQVIA LRx and Dx Data Analysis; index period: Nov 2020 to Oct 2021, lookback period Nov 2014 to Nov 2020; data analysis completed Feb 2022.

ENX-102 has demonstrated efficacy in multiple preclinical disease models

Indication / application	Model	(+) Activity
Translational biomarker	Quantitative EEG	✓
Anxiety – Rodents	Elevated plus maze	✓
Anxiety – Rodents	Conditioned suppressed drinking	✓
Anxiety – Rodents	Fear-potentiated startle	✓
Anxiety – Non-Human Primates	Emotional Response Assay	✓
Acute focal seizure	6Hz	✓
Chronic focal seizure	Amygdala kindling	✓
Chronic generalized absence seizure	GAERS rats	✓
Dravet Syndrome	Hyperthermic Seizure Priming in mice	✓
Pain	Fibromyalgia	✓
Itch	Multiple – Chloroquine, Histamine, BNP, Dermatitis, Dry skin and Allergic itch	✓

Phase 1a SAD: ENX-102 is safe and well-tolerated

Randomized, double-blind, placebo-controlled single ascending dose study in healthy volunteers



Key findings

Safe and well tolerated

- Mild transient AEs
- Dose-related increases in CNS AEs ≥ 3 mg
- No SAEs reported

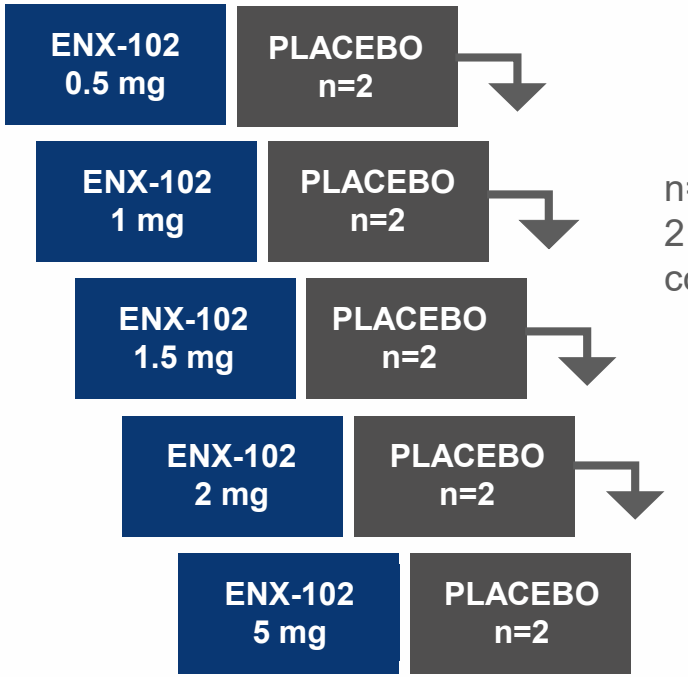
Dose proportional pharmacokinetics support once-daily dosing

– $t_{½}$ ~50-60 hours

AE, adverse event; CNS, central nervous system; SAD, single ascending dose; SAE, severe adverse event; $t_{½}$, half life.
Data on File.

Phase 1b MAD: safe and well-tolerated with confirmed target engagement

Randomized, double-blind, placebo-controlled multiple ascending dose in healthy volunteers



n=6 active;
2 placebo per cohort

Key findings

Safe and well tolerated

- AEs were predominantly mild and transient
- Most frequent AEs: somnolence and fatigue
- No SAEs reported

PK data continue to support QD dosing – $t_{½}$ ~50-60 hours

Pharmacodynamic biomarkers confirm target engagement

AE, adverse event; MAD, multiple ascending dose; PK, pharmacokinetics; QD, once daily; SAE, serious adverse event
Moderate AEs included 2 subjects with somnolence (one each at 2 mg and 5 mg), one subject with balance disorder (5 mg), and one subject with myalgia (5 mg), and two AEs considered not related: headache (2 mg), gastroenteritis (0.5 mg)

ENX-102 exhibits target engagement with a differentiated profile

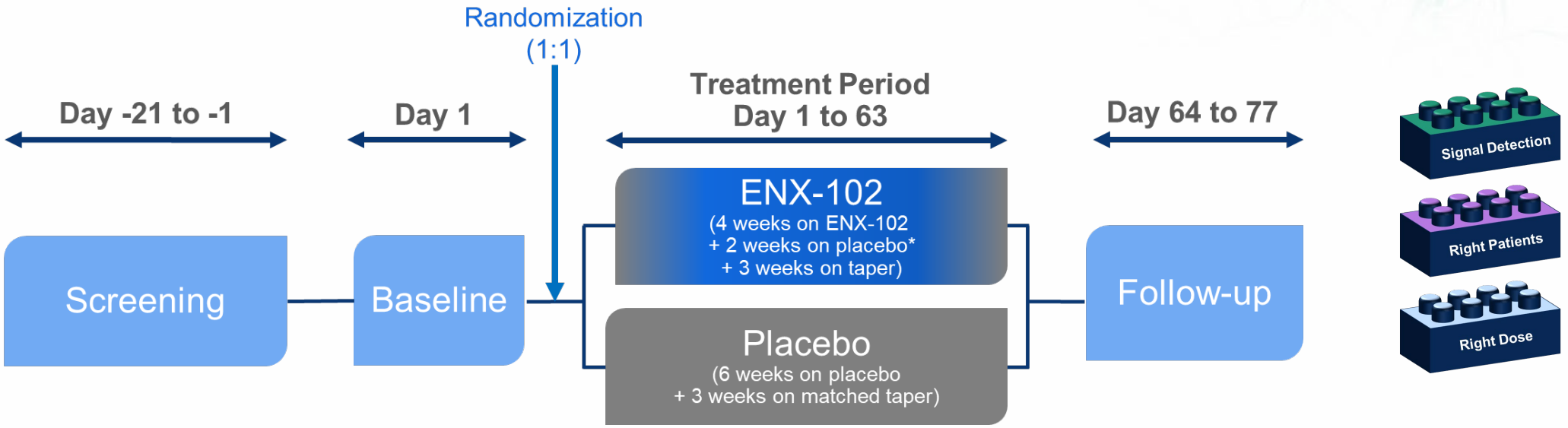
Treatment effect distinct from benzodiazepine signature pattern

Biomarker	Rationale	ENX-102 Treatment Effect	BZP Signature Pattern
Saccadic peak velocity	**Decrease** indicates $GABA_A$ $\alpha_{2,3}$ **target engagement**	↓	↓
VAS alertness	**Decrease** indicates **impaired subjective alertness**	–	↓
Adaptive tracking	**Decrease** indicates **impaired sustained attention**	–	↓
Body sway	**Increase** indicates **impaired psychomotor function**	–	↑
VAS feeling high	**Increase** indicates **subjective euphoric effects**	–	↑
VVLT Delayed recall	**Decrease** indicates **impaired memory**	–	↓

– *No main effect of treatment*

BZP, benzodiazepine; qEEG, quantitative electroencephalography; VAS, visual analog scale; VVLT, Visual Verbal Learning Test
Phase 1b multiple ascending dose study, data on file

We have designed our registrational-quality phase 2 ENCALM trial to maximize probability of success



1° endpoint:

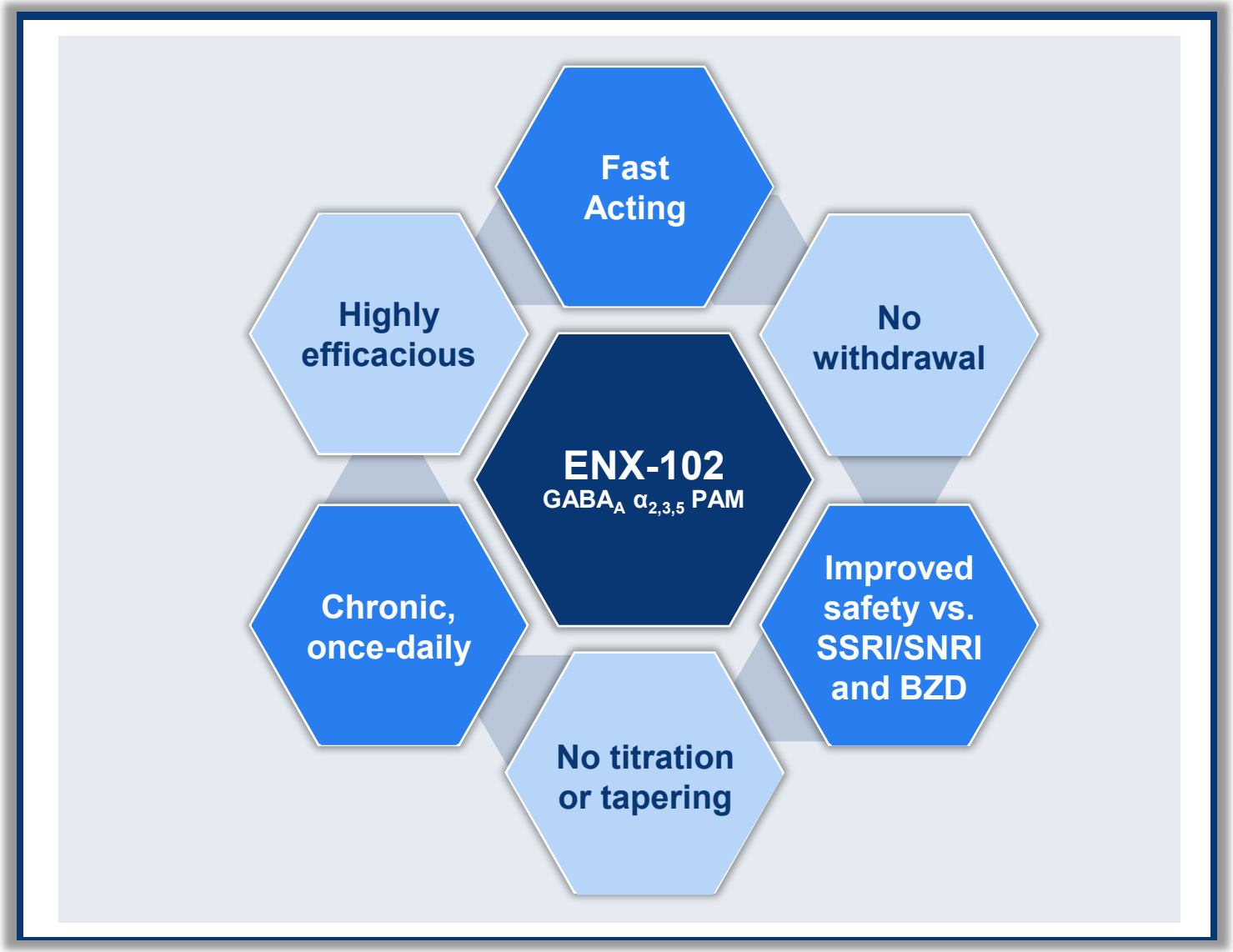
- HAM-A

Exploratory 2° endpoints:

- CGI
- Responder/Remission Rates
- Psychic and Somatic Anxiety
- Daily GAD-7
- HAM-D-6 (depression)
- Functioning Survey
- PSWQ-10 (worry)
- Insomnia Severity Index
- Treatment Satisfaction
- Saccadic Peak Velocity
- Physician Withdrawal Checklist-20

GAD, generalized anxiety disorder; HAM-A, Hamilton anxiety rating scale; CGI, clinical global impression-improvement and -severity scales; GAD-7, 7-item Generalized Anxiety Disorder questionnaire; HAM-D-6, 6-item; Hamilton Depression rating scale; PSWQ-10.

ENX-102 has the potential to be first-in-class and the best anxiolytic for GAD



ENX-104
ENX-105

PRECISION TARGETING OF DOPAMINE RECEPTORS FOR THE TREATMENT OF DEPRESSION CHARACTERIZED BY ANHEDONIA AND PTSD / MOOD DISORDERS

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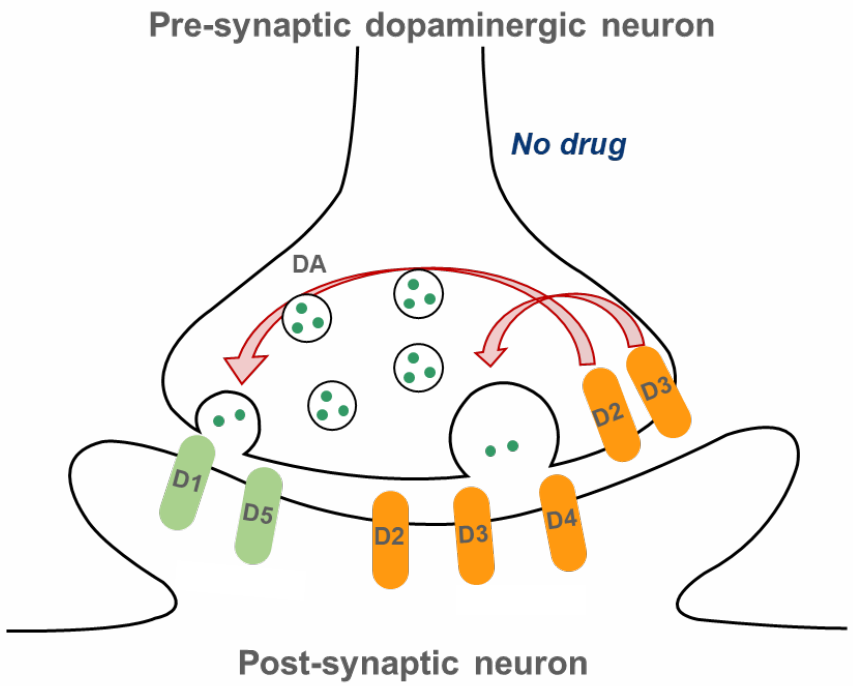
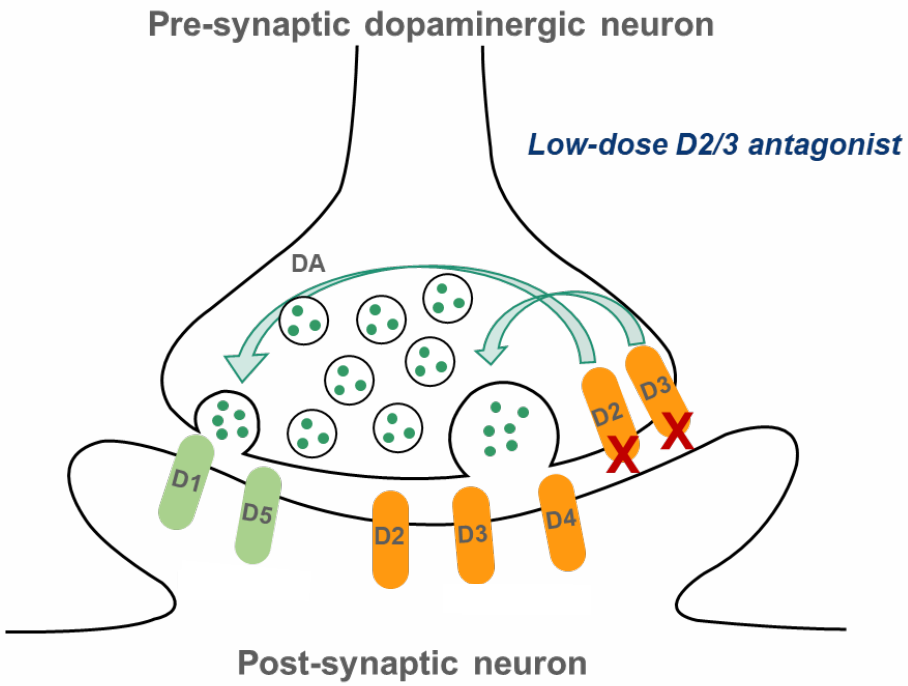
Dopamine D2/3 antagonism is a clinically-validated approach for the treatment of depressive disorders

Low-dose D2/3 antagonism blocks pre-synaptic autoreceptors, increasing dopamine release





Amisulpride, D2/D3 antagonist, is approved for the treatment of dysthymia in select EU countries

D2/3, dopamine receptor 2/3.

We undertook a targeted approach to identify and develop a best-in-class treatment for MDD characterized by anhedonia

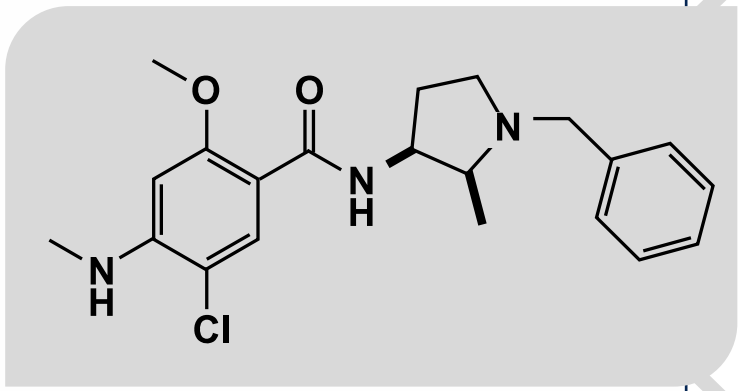
~500 drugs reviewed

Categorized for evaluation

Low-dose D2/D3 antagonist

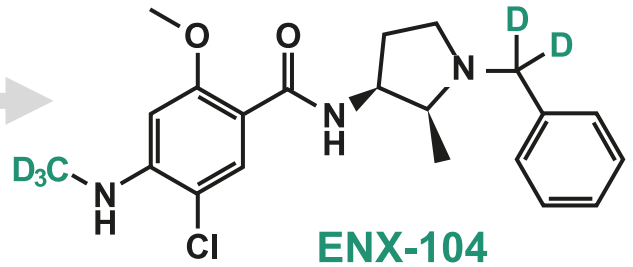
Nemonapride (racemic)

- Most potent D2/3 antagonist approved for human use
- Leverage established safety (20+ years)
  - Commercially available (JPN & SK) for treatment of schizophrenia
  - Low-dose pharmacology for treating mood disorders previously unexplored



Deuterated enantiomers provided new discoveries:

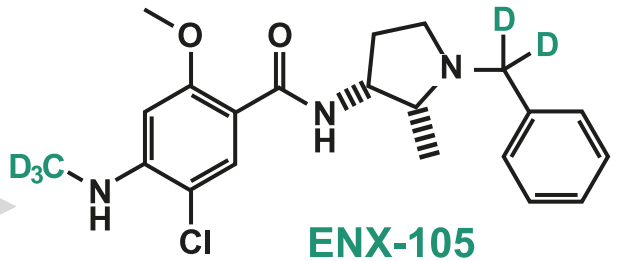
- Dramatically improved brain pharmacokinetics
- Differentiated pharmacology



ENX-104

D2/3/4 antagonist

Exactly what we were looking for



ENX-105

D2/3/4 antagonist; 5-HT$_{1A}$ and 5-HT$_{2A}$ agonist

Unprecedented pharmacology

D2/3, dopamine receptor 2/3; MDD, major depressive disorder.
Data on File.

Anhedonia is a core symptom of MDD and represents a significant unmet need

Anhedonia is diminished interest or loss of pleasure in almost all activities

Anhedonia is 1 of 2 hallmark symptoms of MDD

- No treatments for MDD specifically target this core symptom
- Anhedonia is associated with poor response to antidepressant treatment

Dysregulated dopaminergic neurotransmission, particularly in reward systems, is thought to underlie anhedonia

>16 M U.S. adults with MDD, of which only ~8 M are treated

3.8 M patients suffer with moderate-to-severe anhedonia

2.3 M have **inadequate response** to at least one antidepressant

High unmet need to treat MDD with anhedonia with more targeted approaches

MDD, major depressive disorder.
Belujon P, Grace AA. Int J Neuropsychopharmacol. 2017;20:1036–1046. Reckner Associates Research 2021.

ENX-104 is an oral, once-daily dopamine D2/3/4 antagonist in IND-enabling studies

Engineered to directly increase dopamine neurotransmission

- ✓ Novel deuterated form of nemonapride (approved in Asia)
- ✓ Highly potent and selective D2/D3 receptor antagonist with minimal off-target effects
- ✓ Anti-anhedonic effects at low dose
- ✓ Wide therapeutic index vs. catalepsy
- ✓ Prolonged half-life in the brain

Significant commercial opportunity

- ✓ >$1B in US peak sales

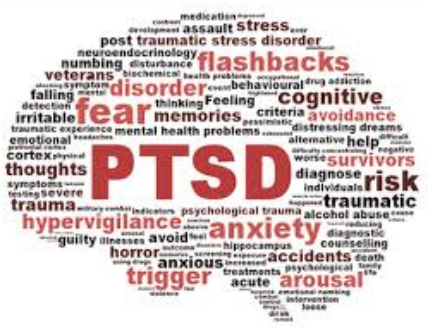
Posttraumatic stress disorder (PTSD) is a common psychiatric condition with few available treatments

PTSD is a disorder in which a person has difficulty recovering after a traumatic event

>8M US adults with PTSD, <20% diagnosed

>80%

comorbidity overlap including depression, social phobia, psychosis, anxiety, etc.



Lack of approved therapies aside from select SSRIs

Zoloft® (sertraline HCl)

PAXIL Paroxetine

Need for novel approaches that address PTSD and common comorbidities

ENX-105 is an oral, once-daily dopamine D2/3/4 antagonist serotonin 5-HT_{1A} and 5-HT_{2A} agonism in IND-enabling studies

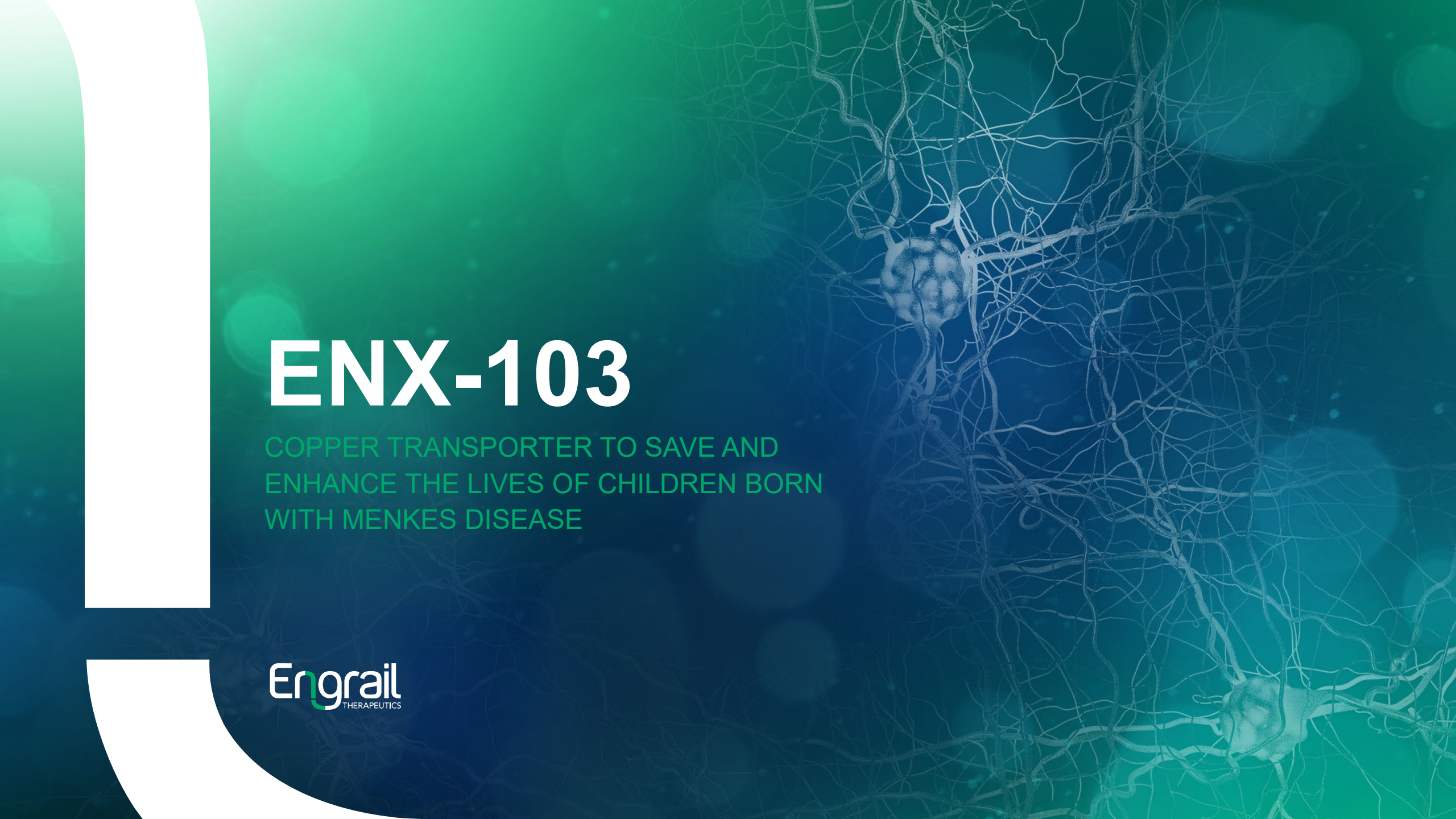
Novel profile anticipated to provide psychedelic-like antidepressant and anxiolytic activity without hallucinations

- ✓ Anti-anhedonic effects at low dose
- ✓ Negative head-twitch response indicates no hallucinogenic effect
- ✓ Wide therapeutic index vs. catalepsy
- ✓ Prolonged half-life in the brain

Unmet needs, sizeable patient population, and pricing dynamics in PTSD and mood disorders drives significant commercial opportunity

ENX-103

COPPER TRANSPORTER TO SAVE AND ENHANCE THE LIVES OF CHILDREN BORN WITH MENKES DISEASE



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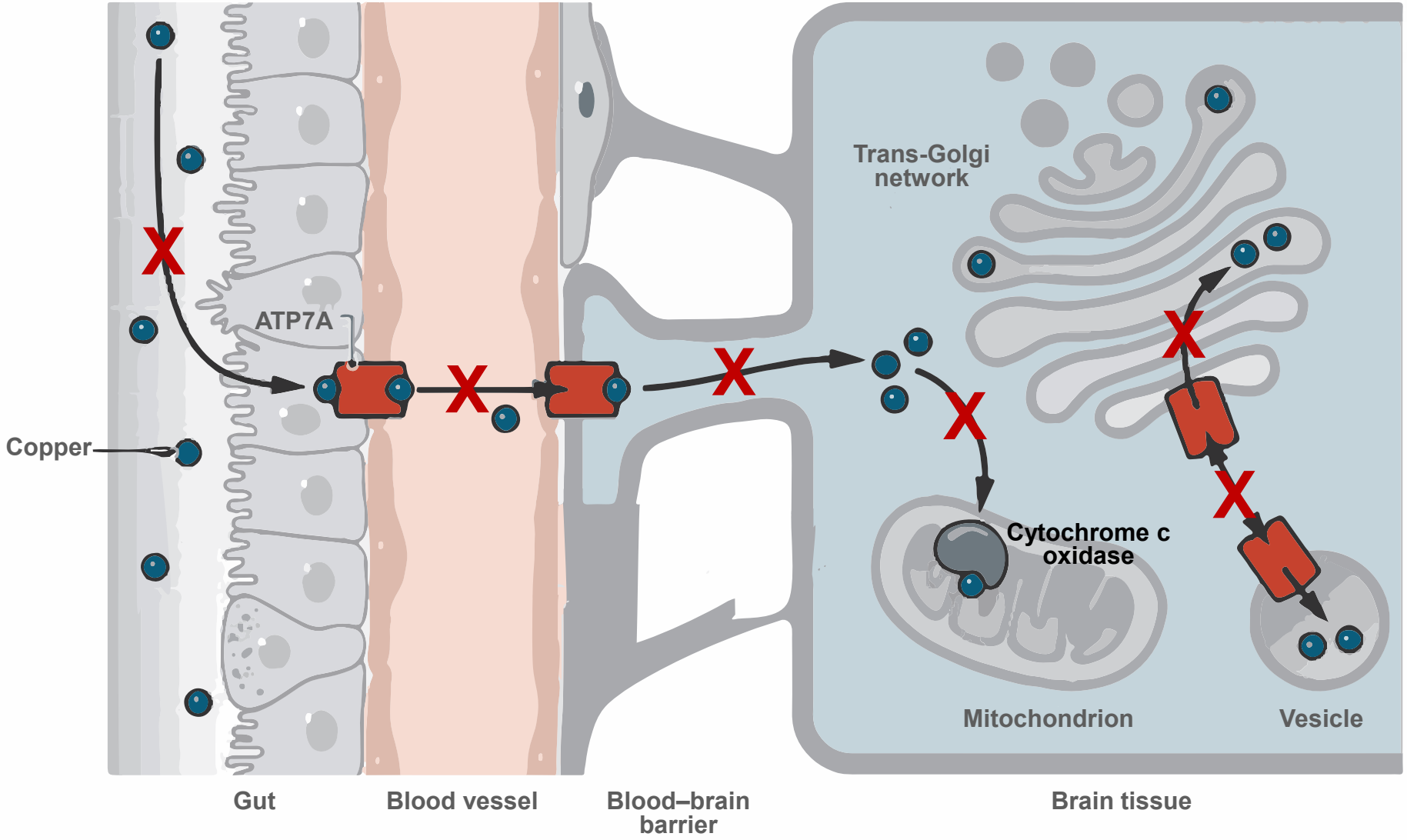
Copper transport defect leads to a severe deficiency of brain copper



Lack of mitochondrial transport and secondary cytochrome c oxidase dysfunction causes progressive neurologic injury and death

ATP7A, ATPase copper transporting alpha.
Lutsenko S. Science. 2020;368:584–585.

Menkes disease is a fatal ultra-orphan disease resulting from a copper transport defect

Menkes disease is ultra-orphan

- Incidence of 1/35,000 male births

ATP7A mutation leads to a copper transport defect that causes poor distribution of copper throughout the body

- Severe lack of copper, especially in the brain
- Excess copper in other tissues, including kidneys

Prognosis is fatal

- Early death, often before 3 years of age

ATP7A, ATPase copper transporting alpha.

Genetic Home References, NIH (https://ghr.nlm.nih.gov/condition/menkes-syndrome#statistics). Lutsenko S. Science. 2020;368:584–585.
NORD – Menkes Disease (https://rarediseases.org/rare-diseases/menkes-disease/). Horn N, Wittung-Stafshede P. Biomedicines. 2021;9:391.
Bhattacharjee A, et al. J Biol Chem. 2016;291:16644–16658. Cox DW. Br Med Bull. 1999;55:544–555.

ENX-103 is a copper transporter with life-saving and life-enhancing potential for Menkes disease

Addresses underlying copper deficiency to promote healthy neurodevelopment and survival

- ✓ Elesclomol was previously studied in oncology, up to phase 3; demonstrated safety, failed for efficacy
- ✓ Elesclomol (copper transporter) pre-charged with copper
- ✓ Enhances copper delivery to the brain
- ✓ Significant survival increase and neurodevelopment improvements in ‘Menkes mice’
- ✓ In exceptional named patient treatment – demonstrating promising safety and efficacy results

Attractive commercial opportunity

- ✓ >$250M in US peak sales
- ✓ Eligible for priority review voucher (value ~$100-$200M)

CONCLUSIONS

Engrail THERAPEUTICS

We are well on our way to building a leading neuroscience company

Deep and differentiated pipeline

Experienced leadership with
a track record of success in neuropsychiatry

Rapidly advancing programs create
near-term milestones and value creation

"Neuro-comps"

KARUNA THERAPEUTICS
$8.4B
market cap

Intra-Cellular THERAPIES
$6.1B
market cap

cerevel
$5.1B
market cap

AXSOME THERAPEUTICS
$3.7B
market cap

Note: Market caps are as of 6/26/2023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