# PRECISION NEUROSCIENCE.
## TRANSFORMATIONAL THERAPIES.

CORPORATE SUMMARY | 1Q 2023

Engrail THERAPEUTICS

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

Rapidly advancing programs create
**near-term milestones and value creation**

**Deep and differentiated** pipeline

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

Unique approach
**improving probability of success**

*Psychiatry*
*Rare Disease*
*Neurology*

**Experienced leadership** with
a track record of success in neuropsychiatry

*Scientific / mechanistic validation*
*Best-in-class profiles*

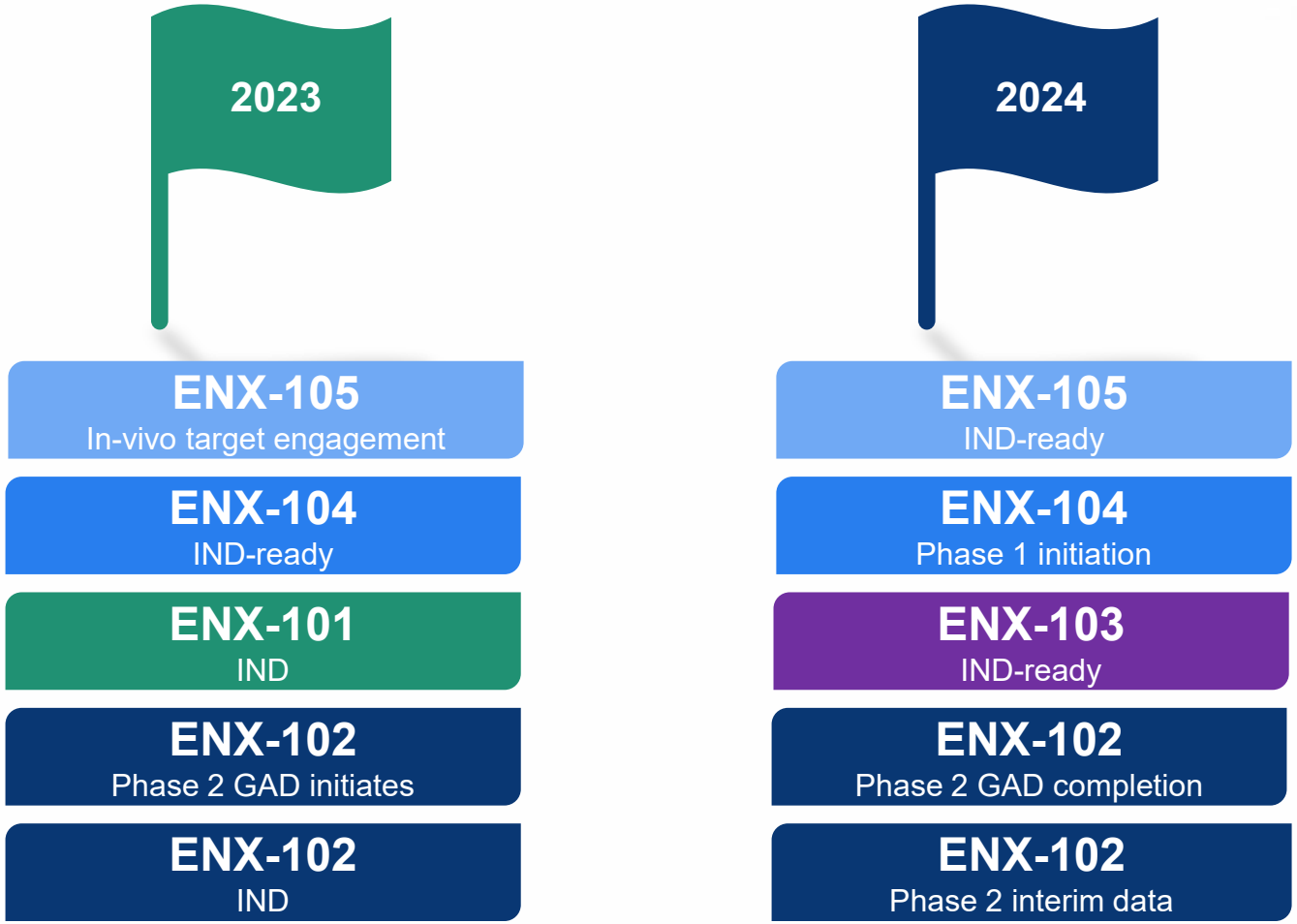
*>30 product launches*

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

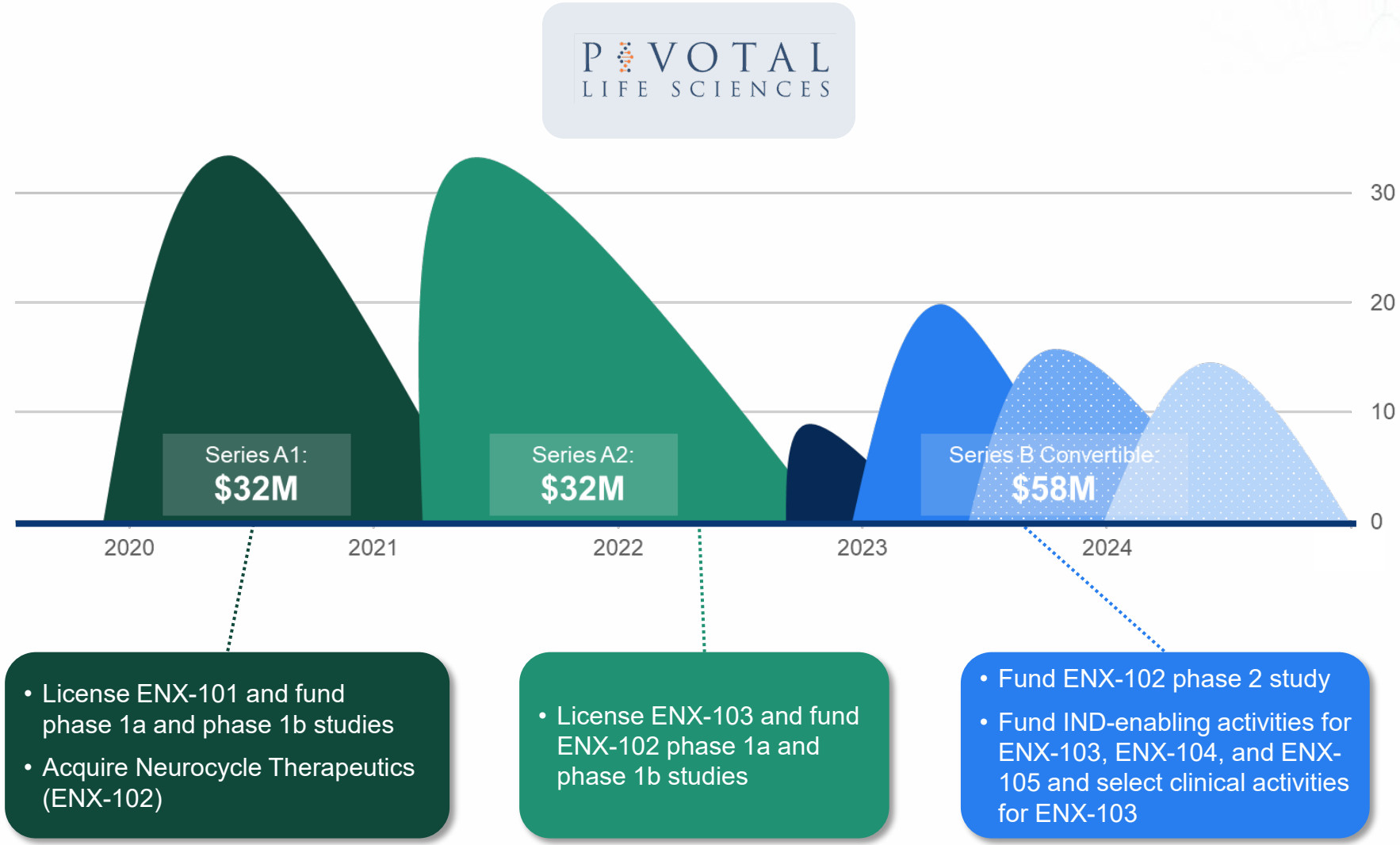
| Program | MoA | Lead Indication | Discovery | Preclinical | Phase 1 | Phase 2 |
|---|---|---|---|---|---|---|
| ***Psychiatry*** | | | | | | |
| **ENX-102** | $GABA_A$ $\alpha_{2,3,5}$ PAM, $\alpha_1$ antagonist | Generalized anxiety disorder | | | | |
| **ENX-104** | D2/D3 antagonist | Depression / 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, $\alpha_1$ antagonist | Epilepsy | | | | |
| **ENX-106** | $GABA_A$ $\alpha_{2,3,5}$ PAM, $\alpha_1$ antagonist | Spasticity / Pain | | | | |
| **ENG-002** | $GABA_A$ $\alpha_{2,3,5}$ PAM, $\alpha_1$ 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.

# Pipeline is set to deliver significant news flow and value inflection points over next two years



# Since inception, Engrail has raised $122M



# SUBTYPE SELECTIVE $GABA_A$ MODULATION

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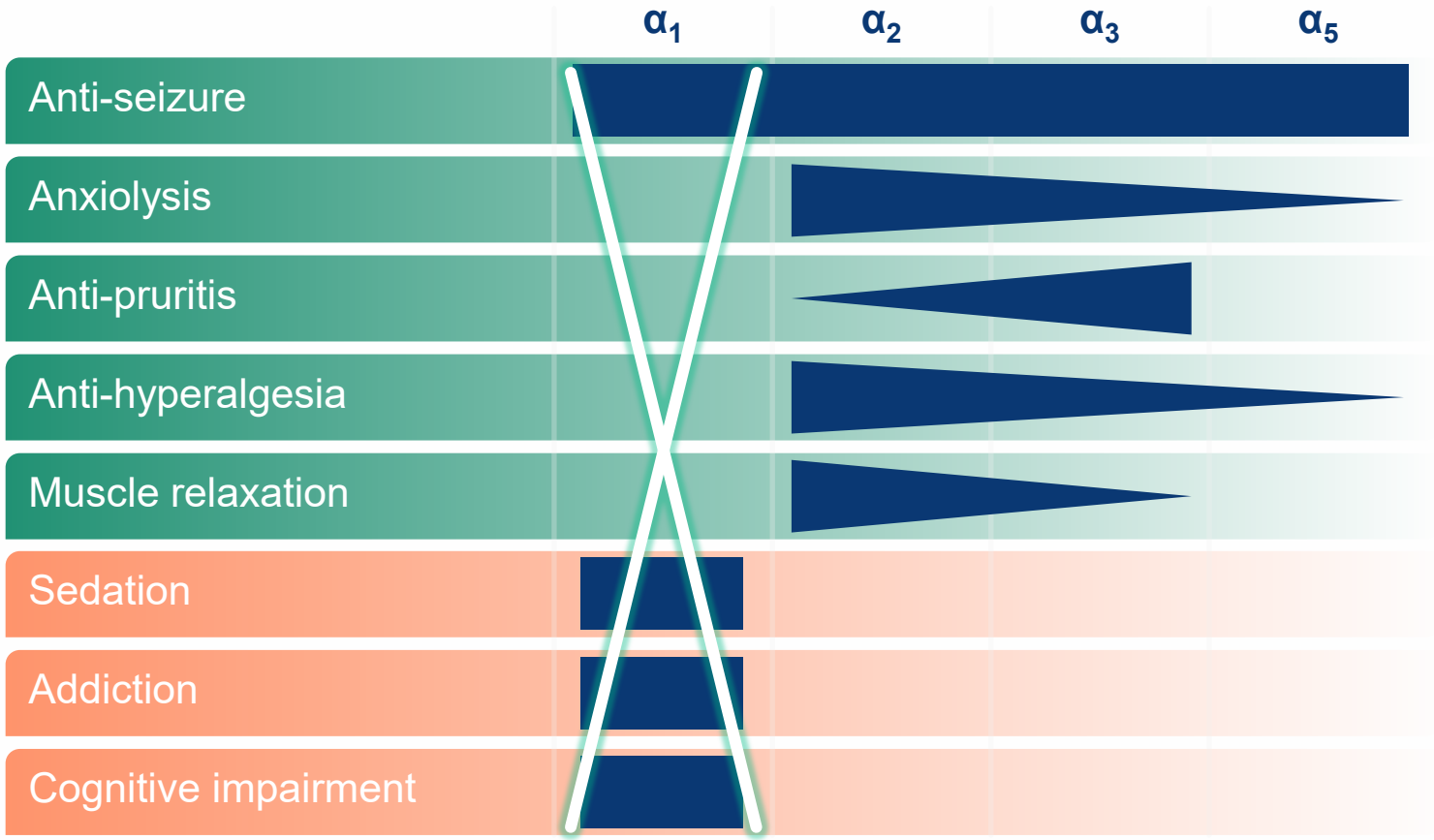
# Selective $GABA_A$ $\alpha_{2,3,5}$ PAMs designed to maximize clinical benefits and minimize liabilities

## Precision targeting: positive allosteric modulation of $GABA_A$ $\alpha_{2,3,5}$ and antagonism of $\alpha_1$




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

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

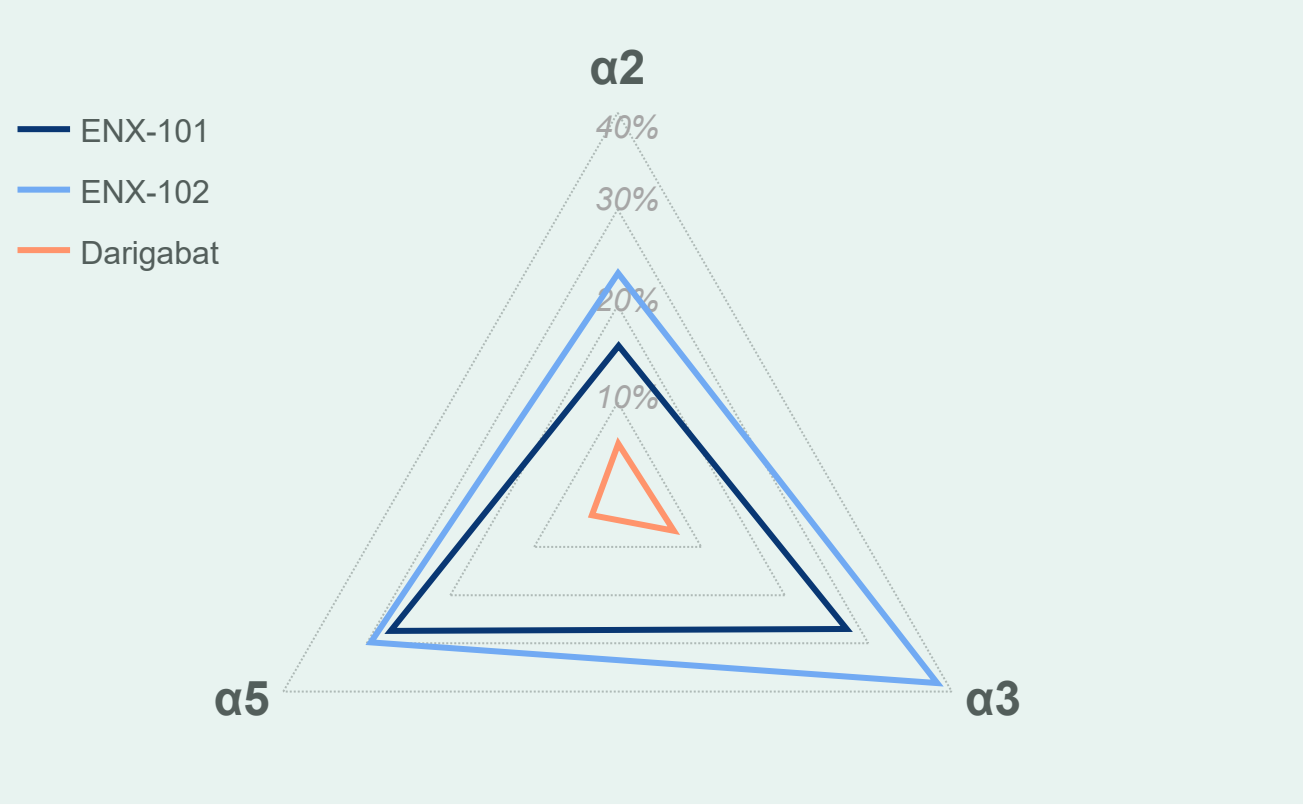
$GABA_A$, gamma-aminobutyric acid A receptor; PAM, positive allosteric modulator.


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.

# ENX-101 and ENX-102 have distinct and optimized profiles

## Receptor Function

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



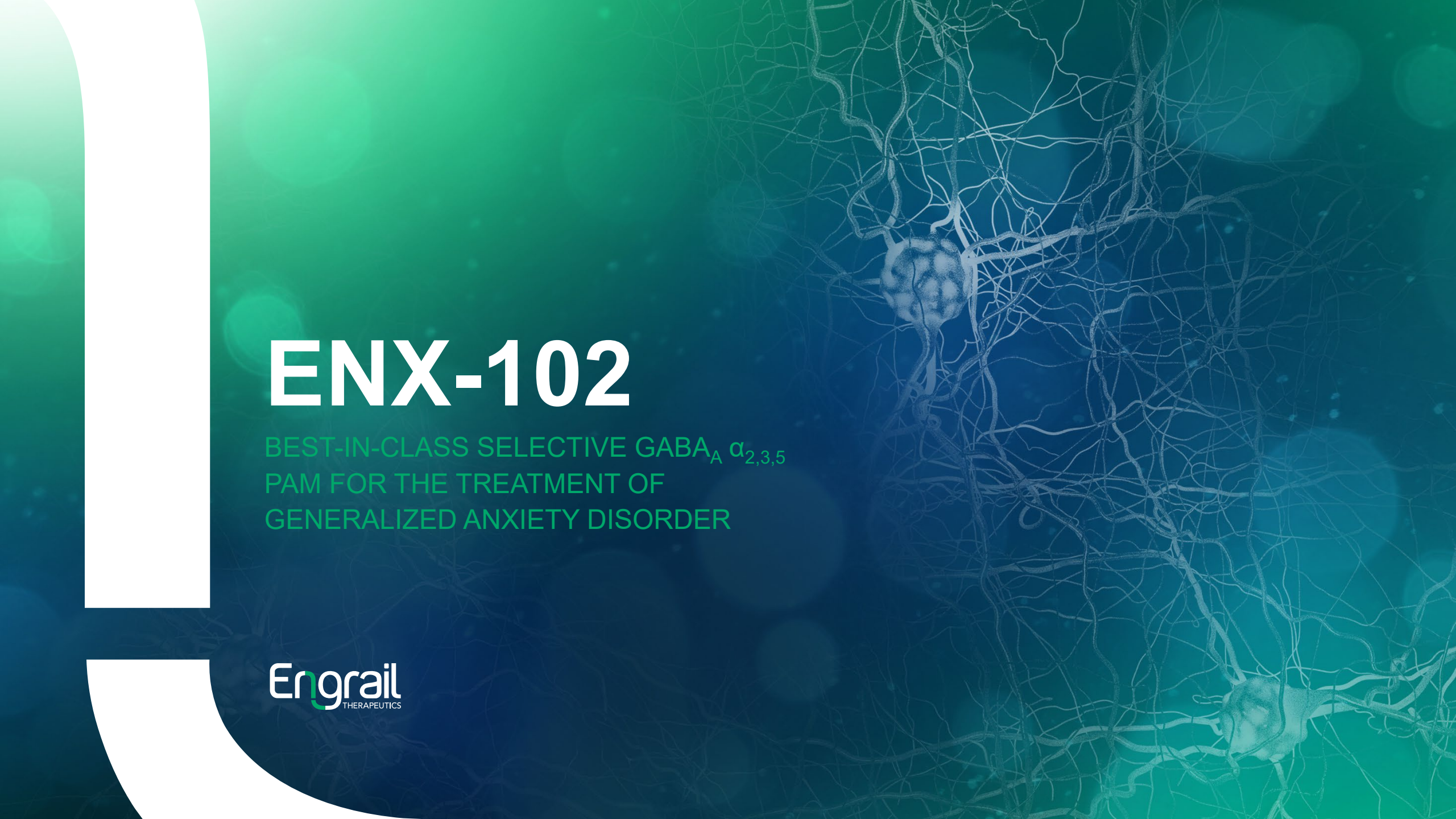

- ENX-101 and ENX-102 have **distinct profiles**
- Both compounds **drive more intrinsic activity** on $GABA_A$ $\alpha_{2,3,5}$ than darigabat
- ENX-101 and ENX-102 each exhibit **longer half lives** (~20 and ~50-60 hrs) than darigabat (~11 hrs)

**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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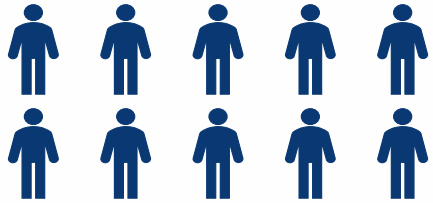
# Substantial need for new options to treat generalized anxiety disorder

**>5.4 M** US patients currently being treated for GAD

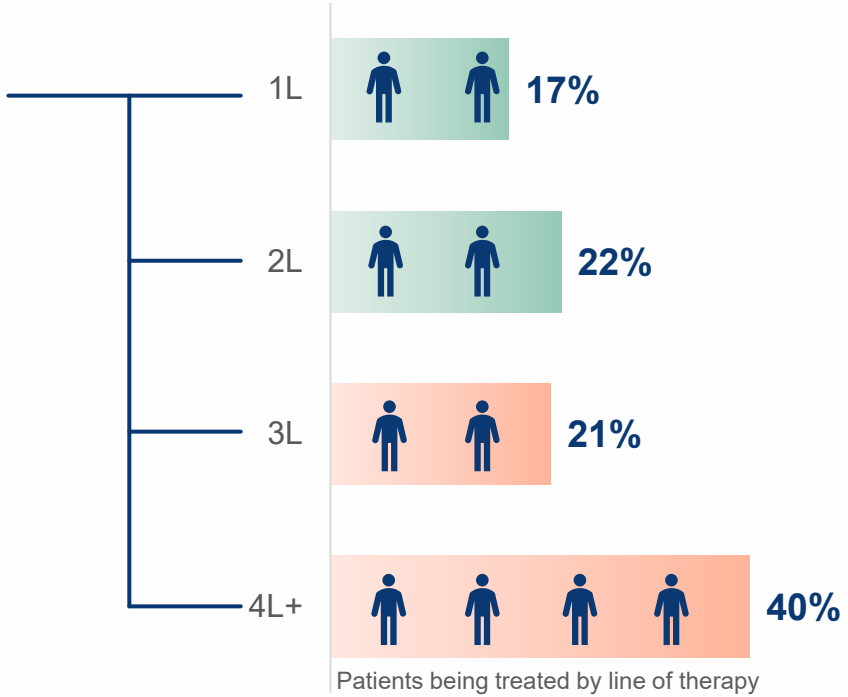


Additional patients

+ 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 patients fail** initial lines of therapy




**Existing therapies have limitations**

**BZPs are** remarkably effective but **limited to short-term use**


**Later-line therapies have unfavorable tolerability** and generally **less robust efficacy**

Need for **new efficacious and safe** treatment options **that can be used chronically**

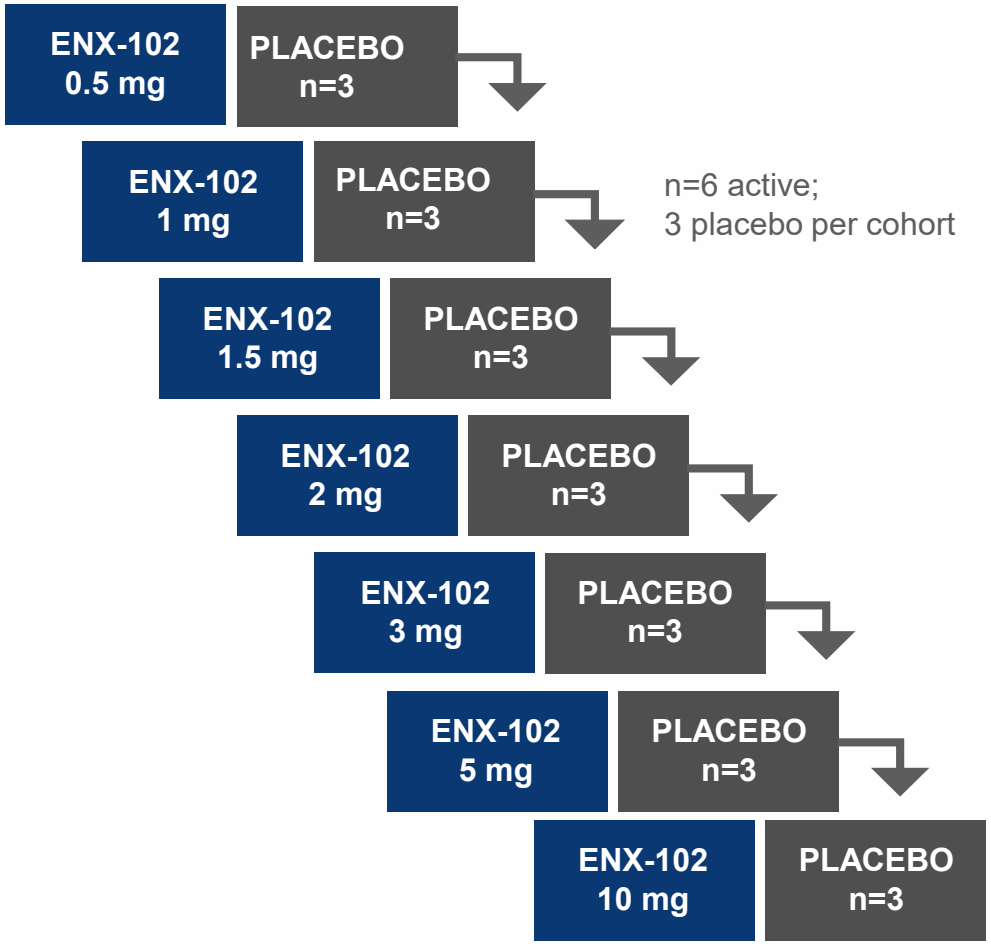
1L, first line; 2L, second line; 3L, third line; 4L, fourth line; GAD, generalized anxiety disorder; BZP, benzodiazepine.
IQVIA LRx and Dx Data Analysis; index period: Nov 2020 to Oct 2021, lookback period Nov 2014 to Nov 2020; data analysis completed Feb 2022.

# 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

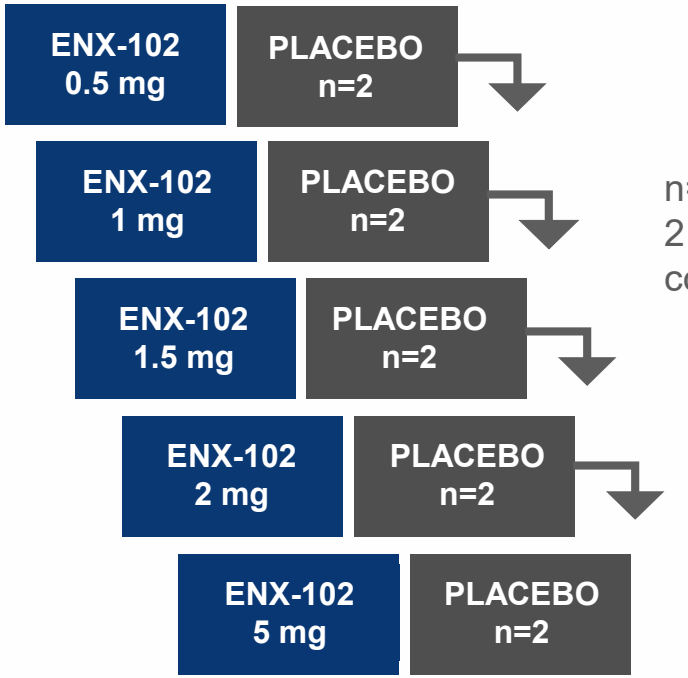
### Dose proportional pharmacokinetics support once-daily dosing

– $t_{½}$ ~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-104
# ENX-105

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

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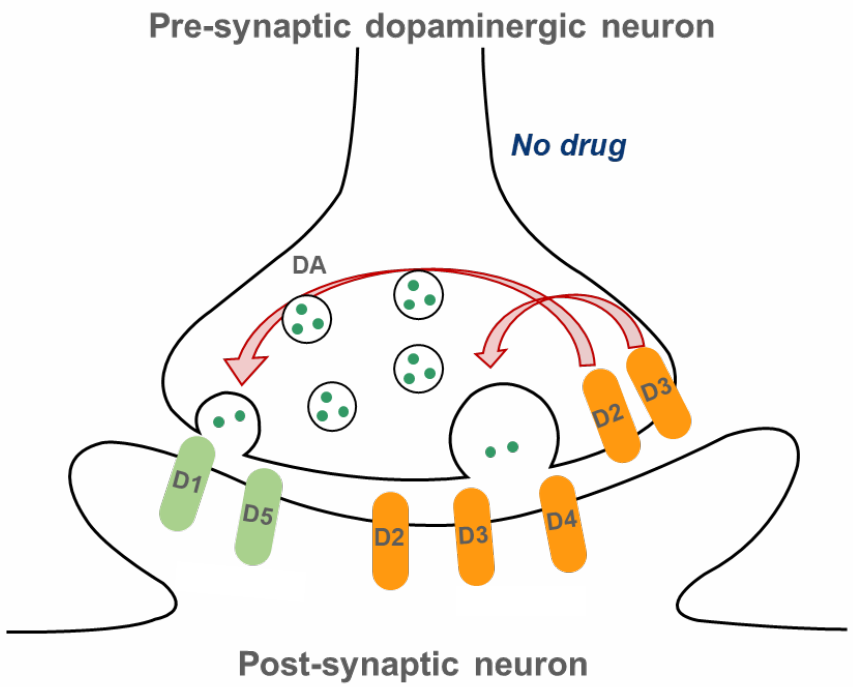
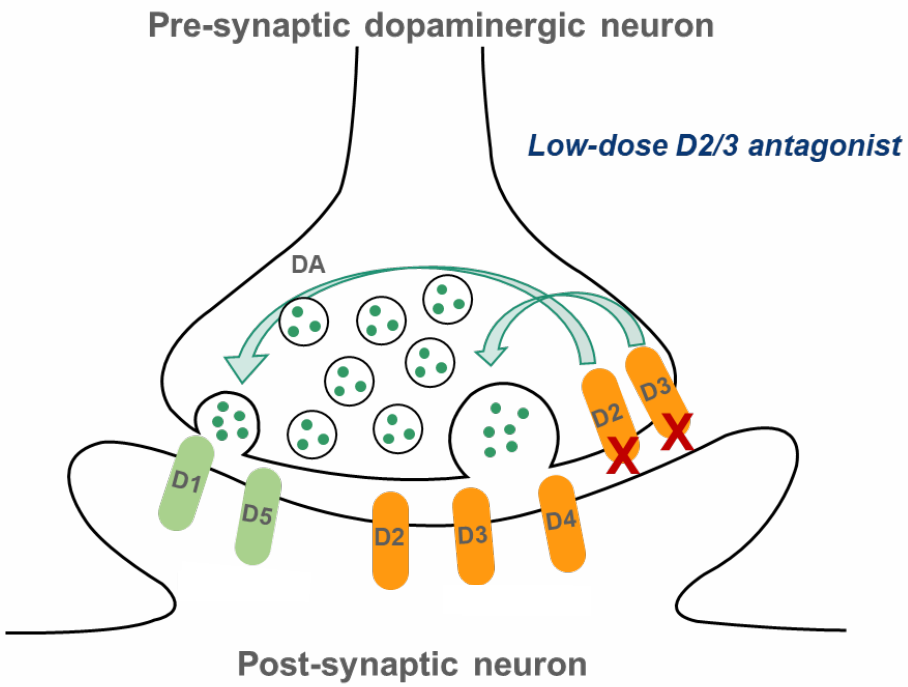
# Dopamine D2/3 antagonism is a clinically-validated approach for the treatment of depressive disorders

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

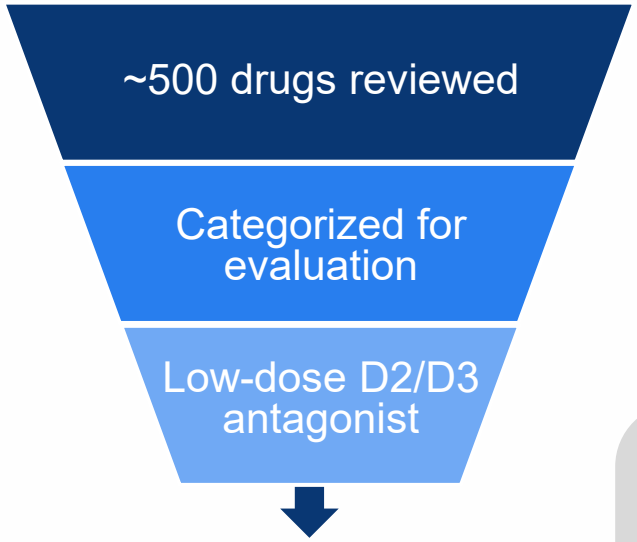



Amisulpride, D2/D3 antagonist, is approved for the treatment of dysthymia in select EU countries

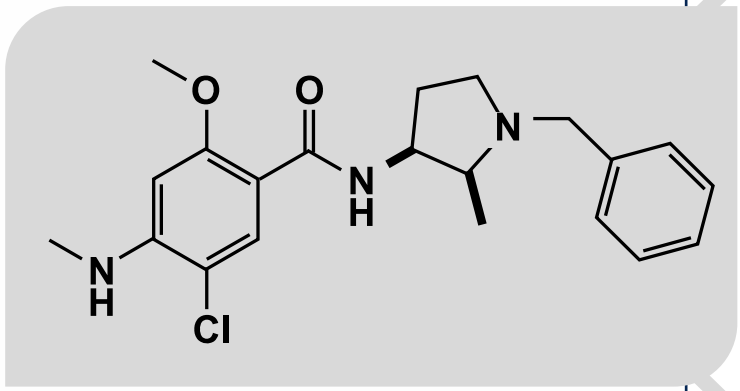
D2/3, dopamine receptor 2/3.

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



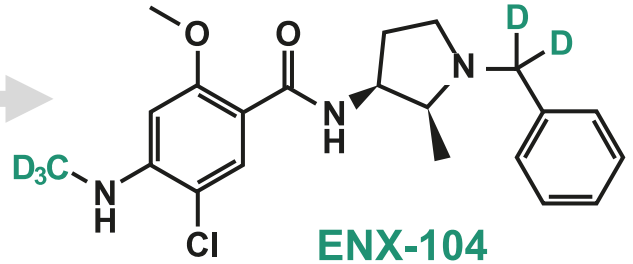

**Nemonapride** (racemic)

- 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:**

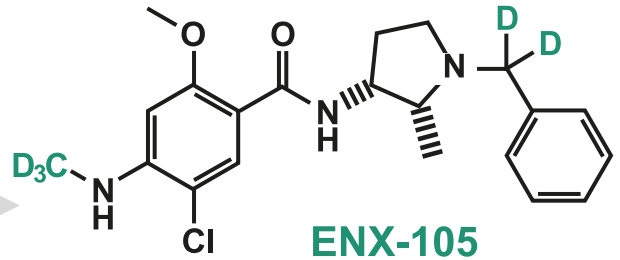
- Dramatically improved brain pharmacokinetics
- Differentiated pharmacology



**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 development for anhedonia in major depressive disorder

## 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

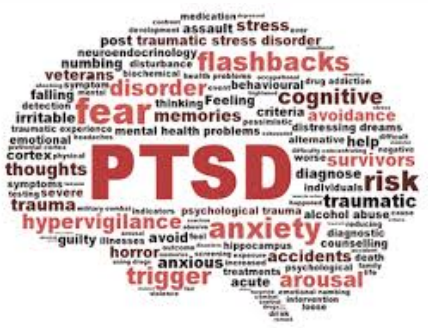
# Post-traumatic stress disorder (PTSD) is a common psychiatric condition with few available treatments

## 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.



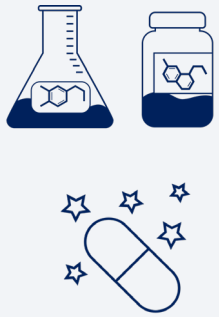

Lack of approved therapies aside from select SSRIs

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 development for PTSD



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

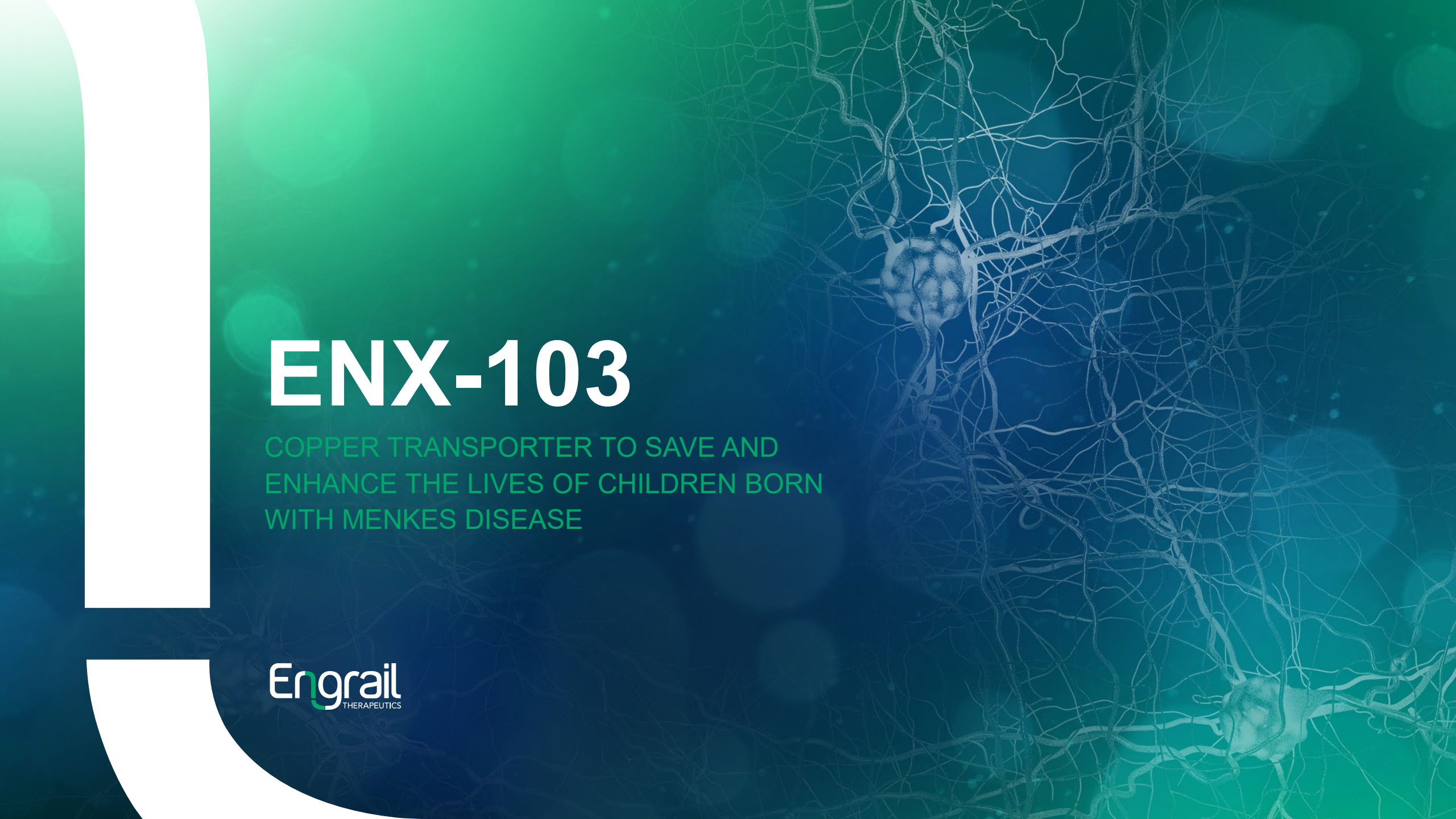
- ✓ Anti-anhedonic effects at low dose
- ✓ Negative head-twitch response indicates no hallucinogenic effect
- ✓ Wide therapeutic index vs. catalepsy
- ✓ Prolonged half-life in the brain

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

PTSD, post-traumatic stress disorder.

# ENX-103

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



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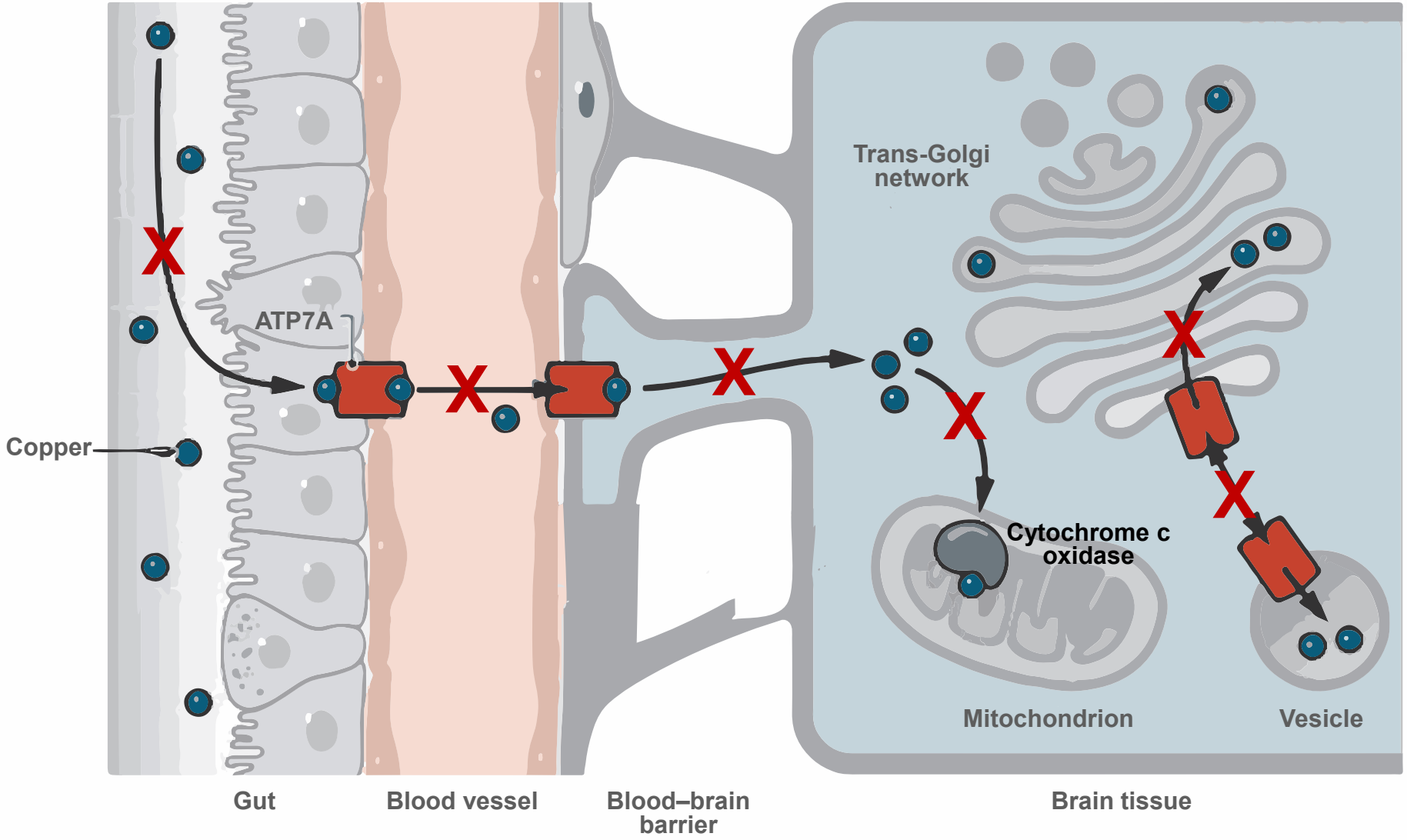
# Copper transport defect leads to a severe deficiency of brain copper




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)

# ENX-101

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

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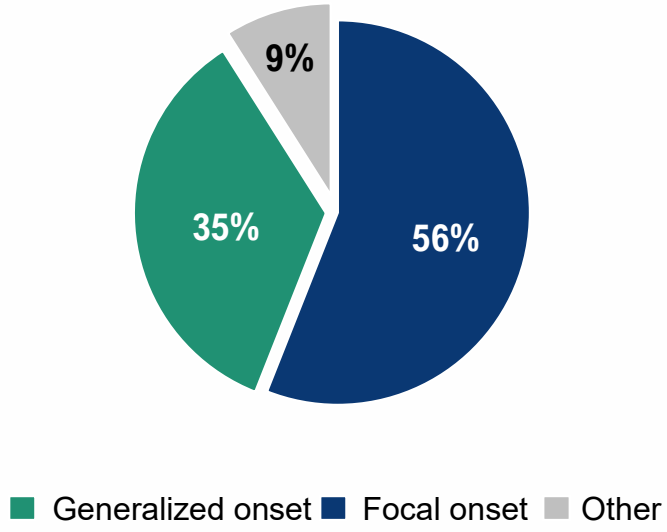
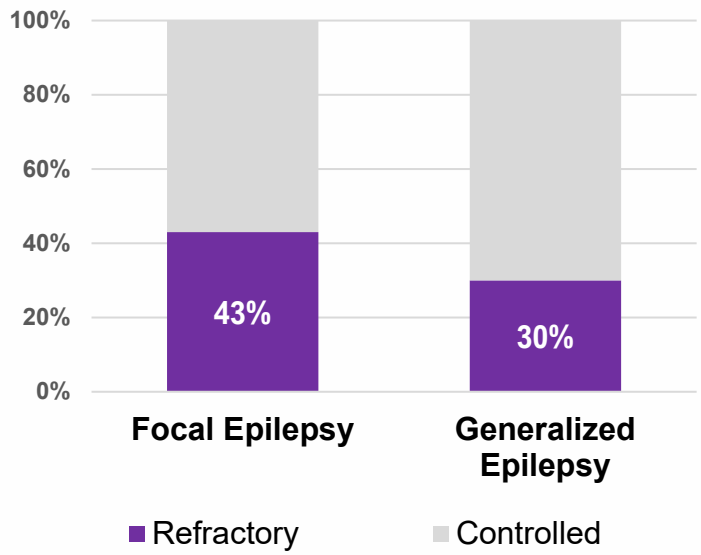
# Epilepsy is an area of high unmet need with a substantial refractory population

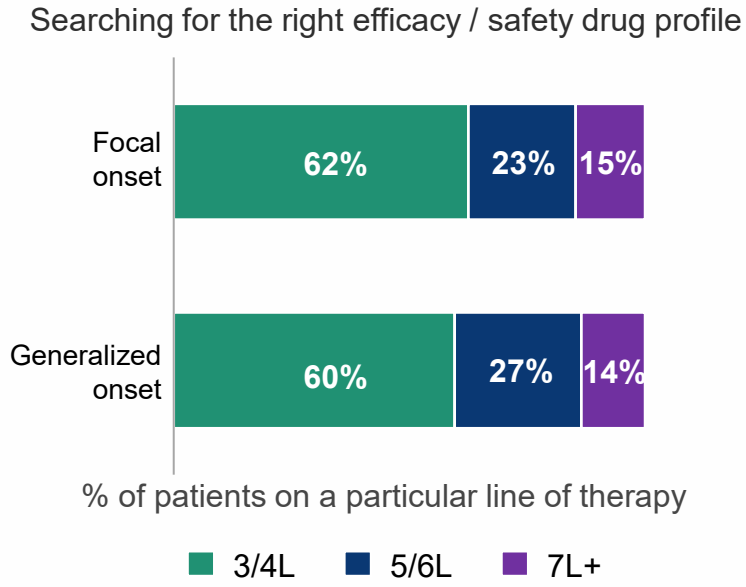
## >4M US patients with epilepsy




## Significant refractory population



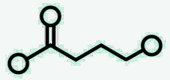

## Refractory despite many lines of therapy




Need for medications with new mechanisms of action to **better control disease and improve quality of life for patients**

IQVIA Research 2021 (Quantitative surveys, N=30, average patients/month=124).
Based on 1.2% prevalence figures, total number of patients estimated for 2020.

# ENX-101 is a novel and best-in-class selective $GABA_A$ PAM for the treatment of epilepsy



## Oral, once-daily $GABA_A$ $\alpha_{2,3,5}$ PAM, $\alpha_1$ antagonist; phase 1 trials completed

- ✓ Under FDA clinical hold due to prior animal tox finding
- ✓ Approved to proceed to phase 2 ex-US

## Data supports best-in-class profile

- ✓ Safe and well tolerated
- ✓ Target engagement confirmed
- ✓ Highly efficacious across preclinical epilepsy models
- ✓ Significantly differentiated profile from BZPs and other AEDs
- ✓ Rapid onset without need for titration
- ✓ Minimal drug-drug interactions
- ✓ Half-life supports once-daily dosing


## Significant commercial opportunity

- ✓ >$850 M in peak US sales (focal epilepsy)

# THANK YOU