PRECISION NEUROSCIENCE.
TRANSFORMATIONAL THERAPIES.

CORPORATE SUMMARY | 1Q 2024

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

Our talented team has extensive experience in neuroscience drug discovery, development, and commercialization

Vikram Sudarsan, PhD
Founder
President and Chief Executive Officer
Board Member

Kimberly Vanover, PhD
Chief Scientific Officer
Board Member

Quentin McCubbin, PhD
Chief Technical Officer

Eve Taylor, PhD
Sr. VP, Clinical Development

Bill Brubaker, PhD
Sr. VP, Nonclinical Development
and Head of DMPK

Estibaliz Arce, PhD
VP, Translational Science
& Clinical Development

Shawn Hossain, DO
Executive Medical Director

Natalia Serrano, MD
Medical Director

Camilla Gomiero
VP, Commercial Strategy
& Business Development

Anil Vootkur, PharmD
VP, Corporate Development

Internal capabilities + external expertise

- Nonclinical Development
- Drug Metab. / Pharmacokinetics
- Technical Operations / CMC
- Clinical Development
- Clinical Operations
- Project Management
- Commercial Strategy
- Business Development
- Corporate Development
- Financial Planning and Analysis

Diverse and accomplished employee base

20 full-time employees and contractors | **~70% advanced degree** | **~50:50 female to male ratio**

ACADIA · Allergan · AstraZeneca · Biogen · Cipla · cytori · EMD Serono · GILEAD · ICON · imshealth · Intra-Cellular Therapies · janssen · Johnson & Johnson · Lundbeck · NOVARTIS · ORIC · Pfizer · Takeda

We are focused on advancing our deep and diverse neuropsychiatry portfolio

Program	MoA	Lead Indication	Discovery	Preclinical	Phase 1	Phase 2
ENX-102	$GABA_A$ $\alpha_{2,3,5}$ PAM	Generalized anxiety disorder				
ENX-104	D2/D3 autoreceptor inhibitor	Depression / Anhedonia				
ENX-105	D2/D3 antagonist, $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ agonist	PTSD / Mood disorders				
ENX-103	Copper transporter	Menkes disease	**In named patient studies***			

MoA, mechanism of action; $GABA_A$, gamma-aminobutyric acid A receptor; PAM, positive allosteric modulator; D2/D3, dopamine receptor 2/3 antagonist.
*Not sponsored by Engrail Therapeutics

We are targeting indications characterized by high unmet needs and significant commercial opportunity

ENX-102

Generalized Anxiety Disorder

>6 million
Diagnosed patients

~60% fail initial lines of therapy

Unfavorable and unapproved later-line options

Attractive pricing and access expectations

ENX-104

Anhedonia in Major Depressive Disorder

>3 million
Mod-to-severe patients

~50% fail 1st line

Targeted approaches for anhedonia needed

Attractive pricing references

ENX-105

Post-Traumatic Stress Disorder

>2 million
Diagnosed patients

Only 30% achieve remission on approved SSRIs

New therapeutics targeting multiple symptoms needed

ENX-103

Menkes Disease

Rare
~50 newborns/year

Fatal disease – no approved therapies

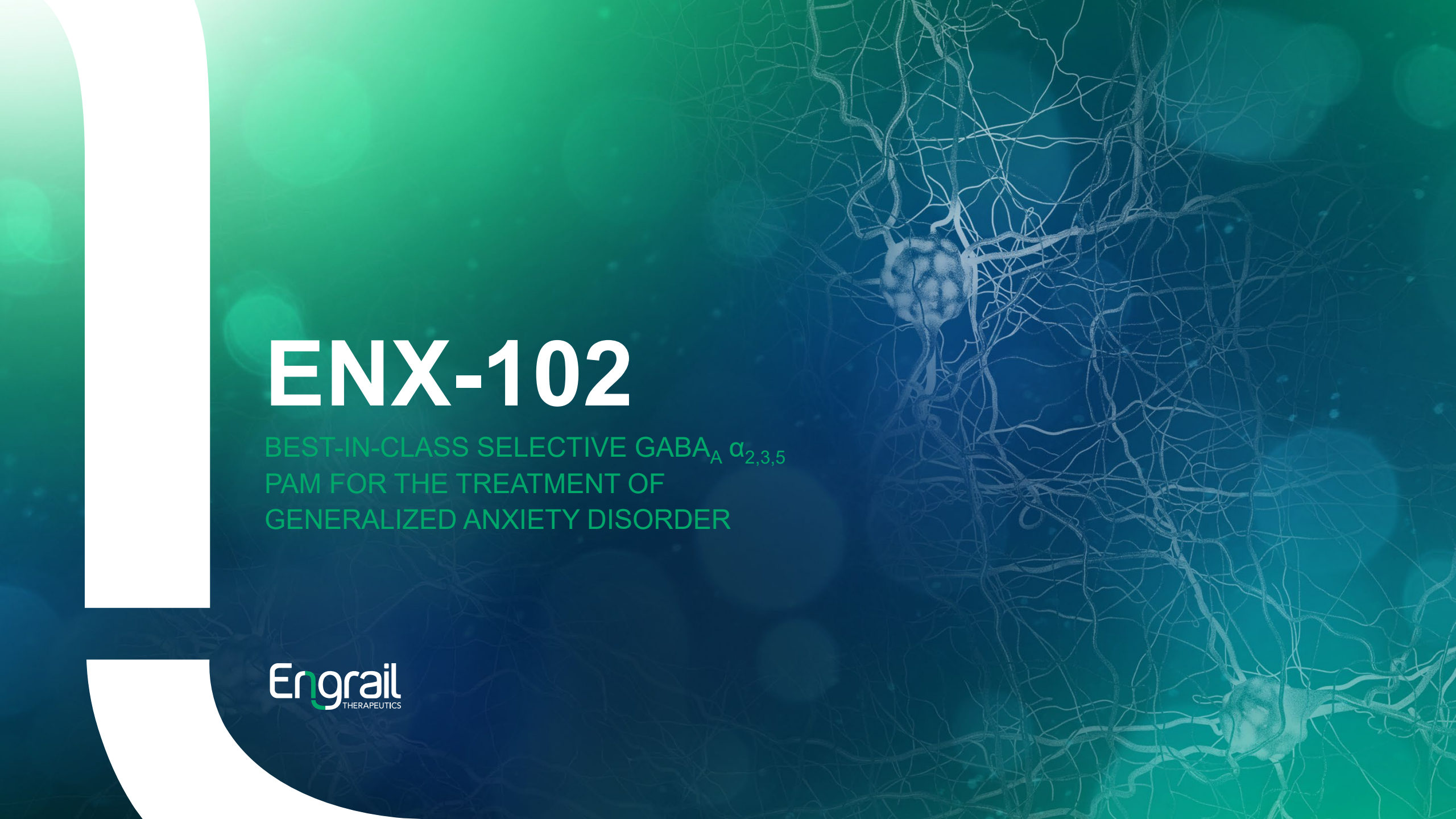
Life-saving opportunity

Favorable commercial dynamics

IQVIA Research 2021 (Quantitative surveys, N=30, average patients/month=124). Prevalence and incidence estimates are for US only.

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 <65 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?

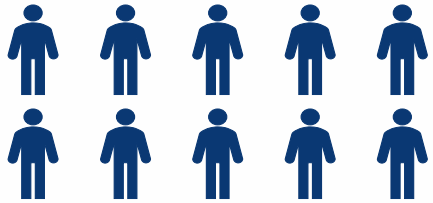
This recommendation applies to adults (19 years or older), including pregnant and postpartum persons, and older adults (65 years or older) who do not have a diagnosed mental health disorder and are not showing recognized signs or symptoms of anxiety disorders.

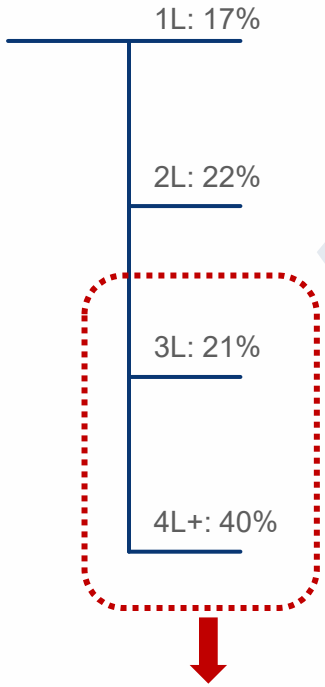
What's new?

This is a new USPSTF recommendation.

Substantial need for new options to treat generalized anxiety disorder (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

1

Wellbutrin XL bupropion HCl
Zoloft (sertraline HCl)
VENLAFAXINE HCl EFFEXOR XR
Lexapro escitalopram oxalate
PROZAC fluoxetine hydrochloride
BuSpar (buspirone HCl, USP)

Various antidepressants and anxiolytics

2

Ativan (lorazepam)
VALIUM (diazepam)
Xanax alprazolam tablets
KLONOPIN clonazepam

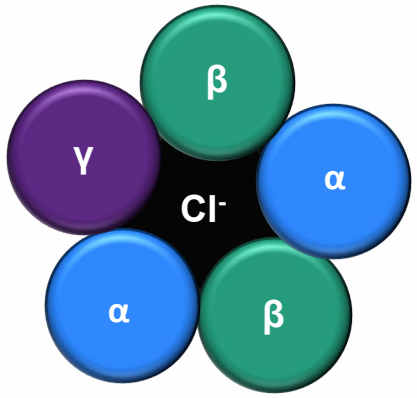
Benzodiazepines

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.

Side effects of benzodiazepines are largely related to their non-selective $GABA_A$ activation

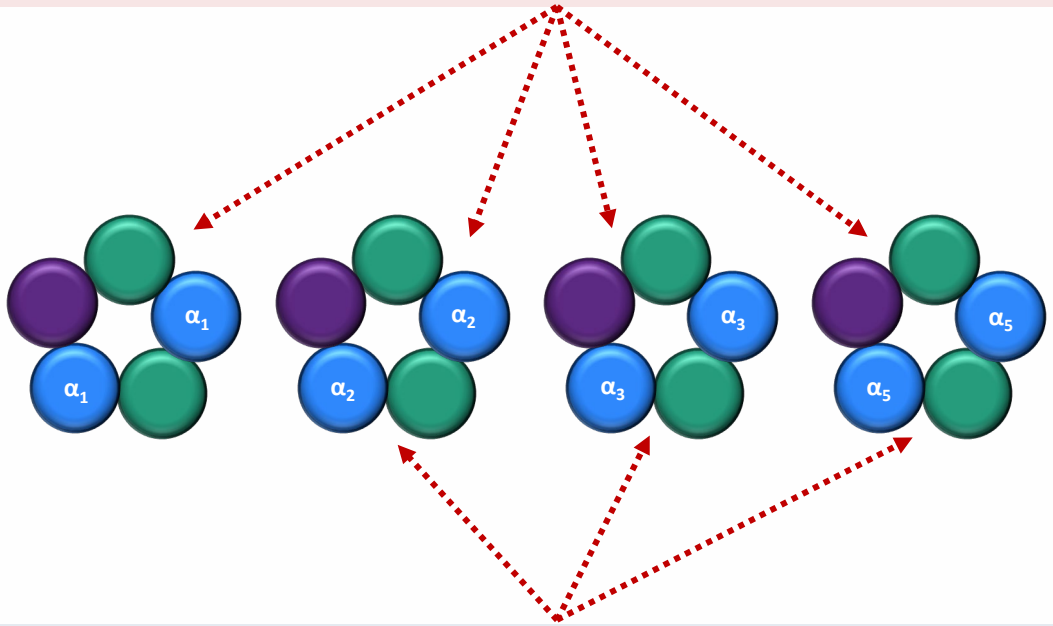
GABA is the major inhibitory neurotransmitter in the brain

$GABA_A$ receptors have 5 subunits



Benzodiazepines specifically activate $GABA_A$ channels to reduce anxiety

Benzodiazepines non-selectively activate the major $GABA_A$ channels **leading to undesirable side effects**



ENX-102 selectively activates α_2, α_3 and α_5 containing channels while **avoiding** α_1 channels, leading to a safer profile

Adapted from Olsen and DeLorey (1999) GABA Receptor Physiology and Pharmacology in Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th edition.
GABA, gamma-aminobutyric acid.

ENX-102 has a favorable profile over the significant limitations of current therapies

Clear potential to address key unmet needs in GAD

	GAD approval (chronic)	Efficacy	Rapid onset	No titration requirement	No withdrawal symptoms	No sexual dysfunction	No significant cognitive impairment	No significant DDI/alcohol interactions	Minimal abuse potential
SSRIs	✓	✓	X	X	X	X	✓	✓	✓✓
BZDs	X	✓✓	✓	X	X	✓	X	X	X
ENX-102	✓	✓✓	✓	✓	✓	✓	✓	✓	✓

An ideal product would harness the efficacy of benzodiazepines without the limitations

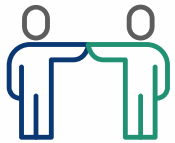
The ENX-102 Phase 1b study predicts efficacy with a well tolerated, sedation-free profile

Randomized, double-blind placebo-controlled trial in healthy volunteers

- Five doses of ENX-102 tested; 40 subjects included
- Twelve day dosing duration

Pharmacodynamic biomarkers confirm target engagement

- ENX-102 enters the brain and exhibits effects consistent with its mechanism



ENX-102 was safe and well tolerated

- Side effects were predominantly mild and transient with no sedation observed
  - Most frequent were somnolence and fatigue, which can be mitigated with repeated administration and once-evening dosing

Pharmacokinetic data support once-daily dosing (~50-60 hour half-life)

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Data on file.

ENX-102 exhibits an anxiolytic profile without the negative effects seen with benzodiazepines

	Biomarker	Rationale	Benzodiazepine Signature Pattern	ENX-102 Treatment Effect
Efficacy	SPV	**Decrease** indicates $GABA_A$ $\alpha_{2,3}$ **target engagement**	↓	↓
Sedation and Cognitive Impairment	VAS alertness	**Decrease** indicates **impaired subjective alertness**	↓	–
Sedation and Cognitive Impairment	Adaptive tracking	**Decrease** indicates **impaired sustained attention**	↓	–
Sedation and Cognitive Impairment	Body sway	**Increase** indicates **impaired psychomotor function**	↑	–
Sedation and Cognitive Impairment	VAS feeling high	**Increase** indicates **subjective euphoric effects**	↑	–
Sedation and Cognitive Impairment	VVLT delayed recall	**Decrease** indicates **impaired memory**	↓	–

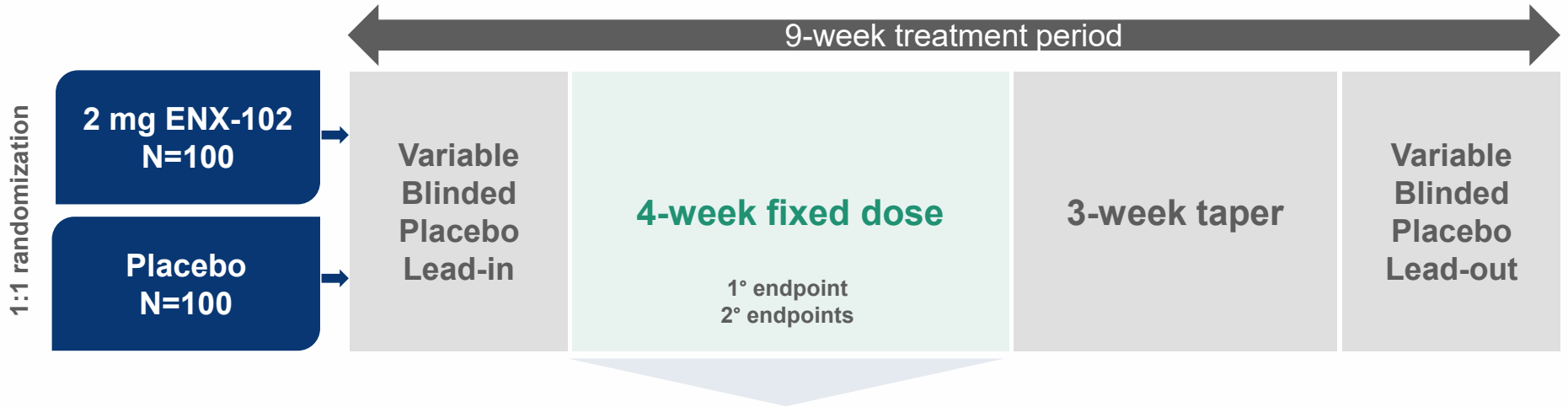
– *No main effect of treatment*

SPV, saccadic peak velocity; VAS, visual analog scale; VVLT, Visual Verbal Learning Test
Data on file.

ENX-102 phase 2 study initiated in mid-2023

Study designed to maximize probability of success

Confirmed GAD diagnosis
- At least moderately severe
- Independently adjudicated



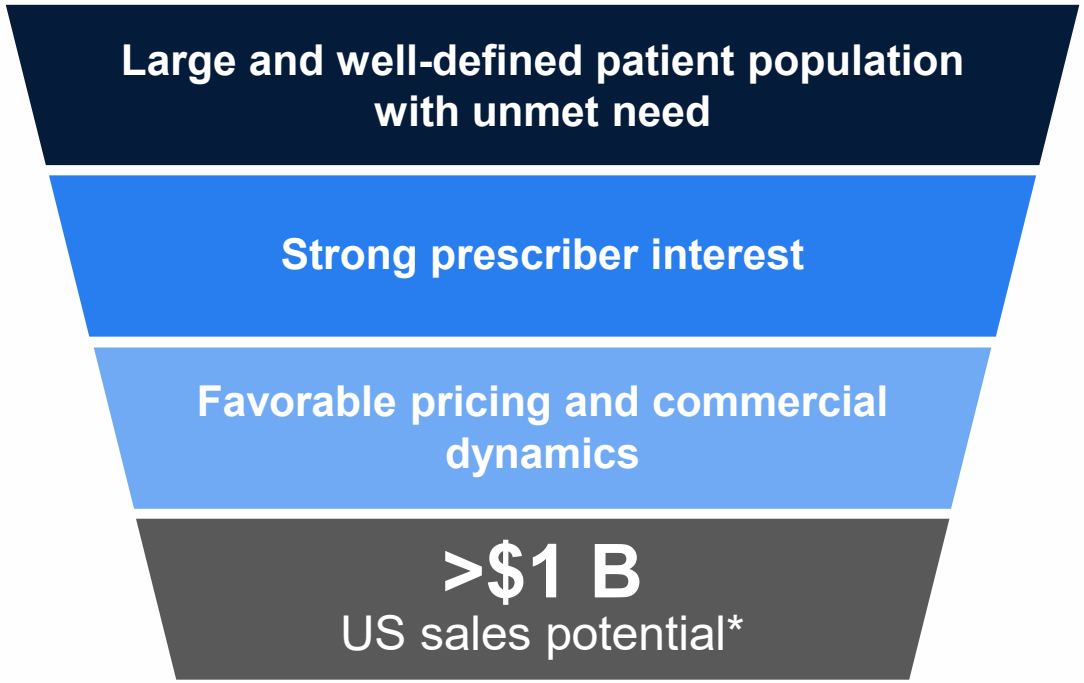
1° endpoint: HAM-A
- Severity of anxiety symptoms

2° endpoints will explore:
- Rapidity of onset
- Impact on depression
- Impact on insomnia
- Satisfaction, worry, other markers of efficacy

GAD, generalized anxiety disorder; HAM-A, Hamilton anxiety rating scale

ENX-102 has blockbuster commercial potential

IQVIA Thorough external commercial evaluation commissioned by Engrail



Engrail THERAPEUTICS *year 6 post-launch

IQVIA

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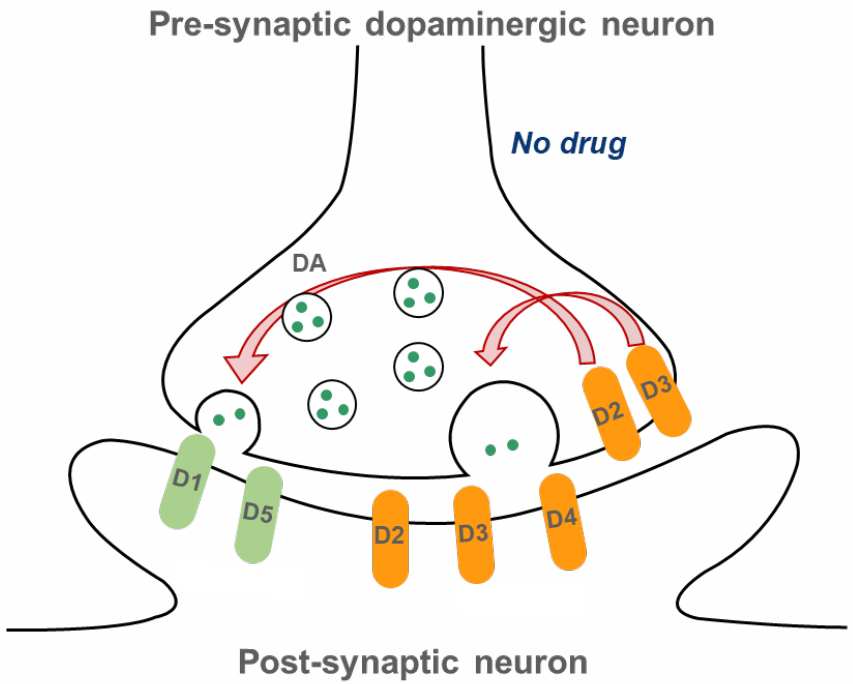
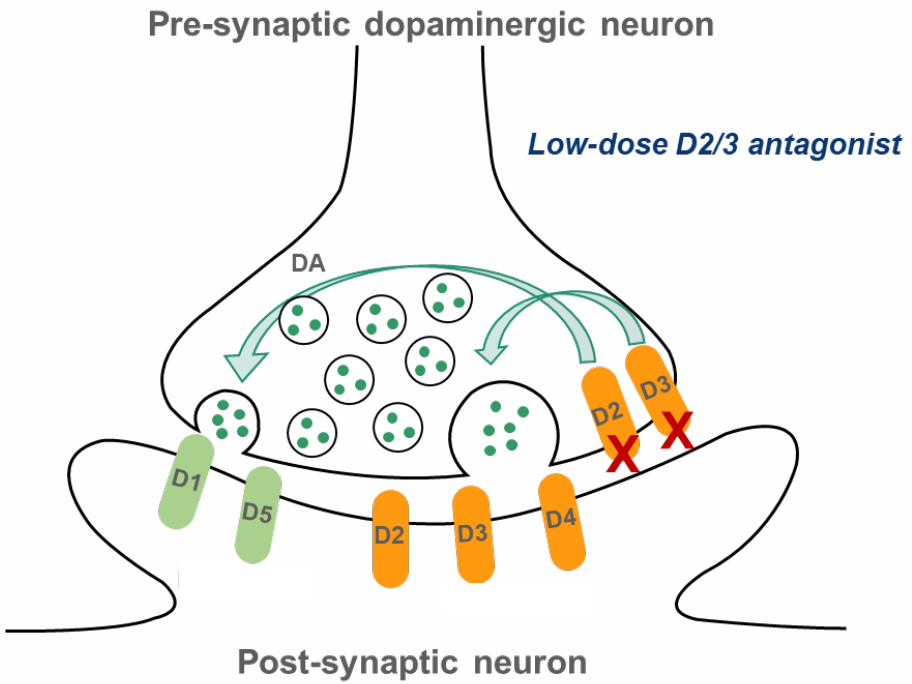
Dopamine D2/3 antagonism is a clinically-validated approach for the treatment of depressive disorders

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





D2/3, dopamine receptor 2/3.

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

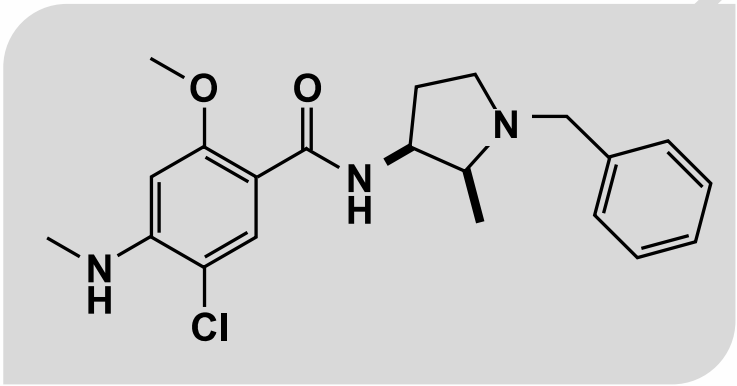
2.3 M have **inadequate response** to at least one antidepressant

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

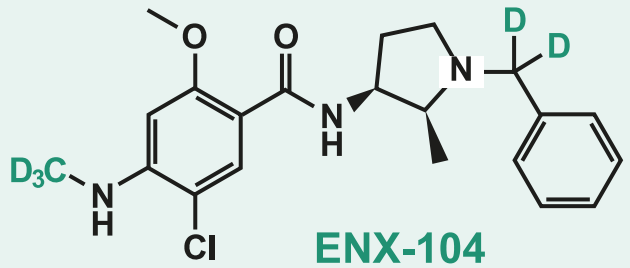
MDD, major depressive disorder.
Belujon P, Grace AA. Int J Neuropsychopharmacol. 2017;20:1036–1046. Reckner Associates Research 2021.

We created a potent D2/3 autoreceptor antagonist to boost dopamine levels

Nemonapride enantiomer + deuteration provides improved brain PK and differentiated pharmacology



Nemonapride



ENX-104

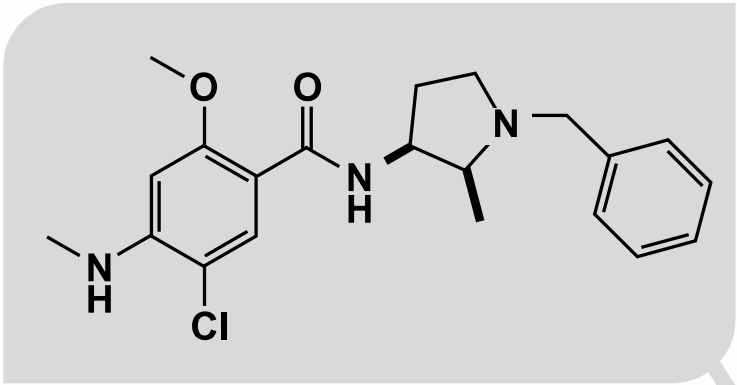
D2/3/4 antagonist

Exactly what we were looking for and de-risked

- ✓ PK profile of an ideal CNS therapeutic
- ✓ Sustained release of dopamine in the reward circuit
- ✓ Preclinical POC achieved
- ✓ Clinical validation via amisulpride

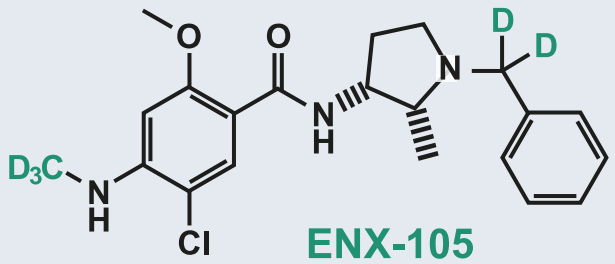
Serendipitous discovery provides novel pharmacology

Nemonapride enantiomer + deuteration yields a unique combination of dopamine and serotonin modulation



Nemonapride

- ✓ Pharmacology holds promise for psychedelic-like anxiolytic and antidepressant activity without hallucinations
  - Sustained release of dopamine in the reward circuit
  - Preclinical confirmation of antidepressant effect
  - No observed headshakes / hallucinogen-like activity



ENX-105

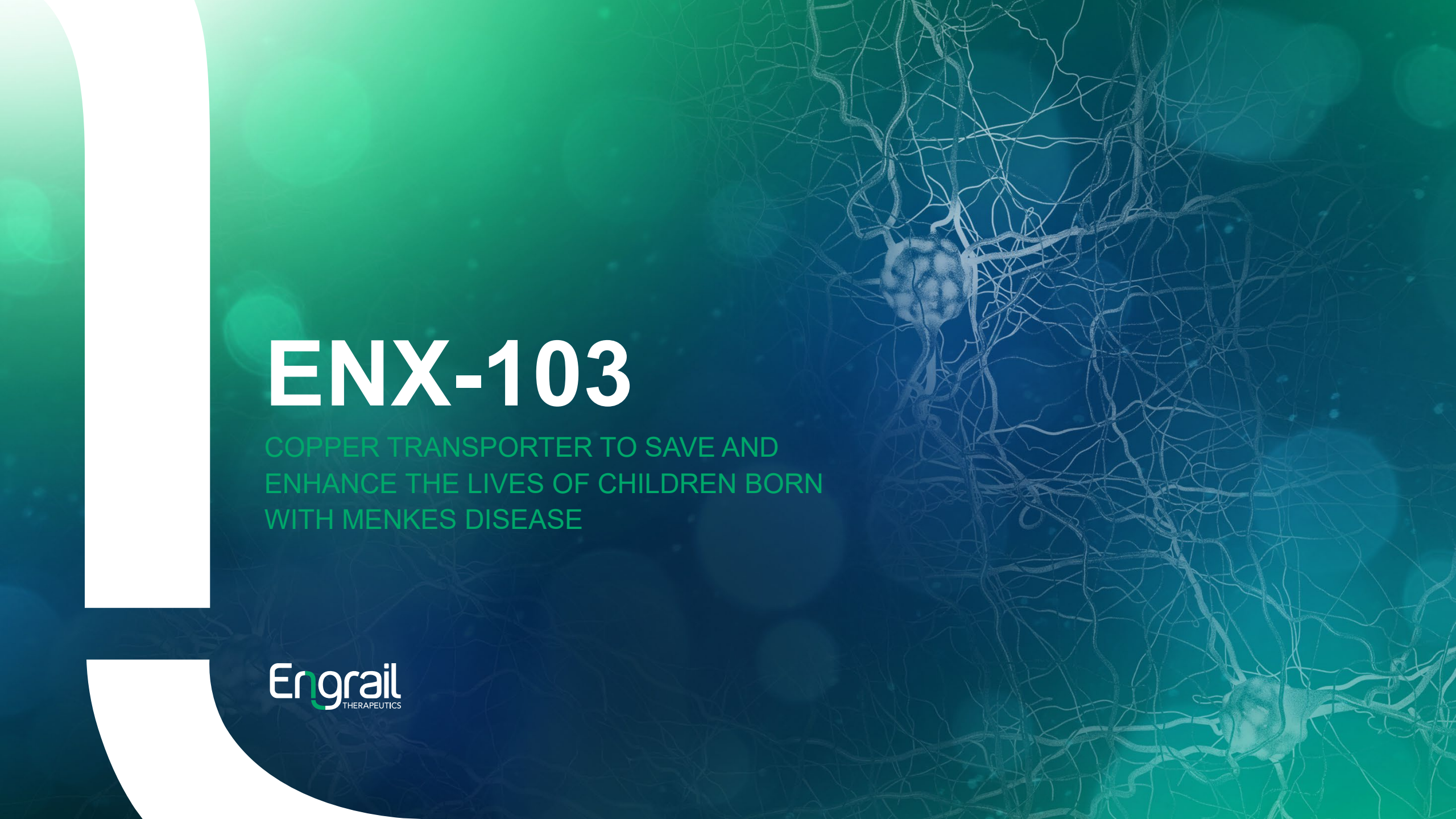
D2/3/4 antagonist
5-HT$_{1A}$ and 5-HT$_{2A}$ agonist

Unprecedented and novel pharmacology

Discovered additional NCEs to optimize 5-HT function

ENX-103

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



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

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

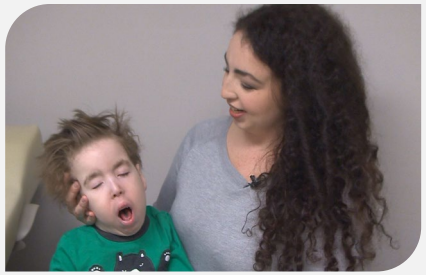
- Severe lack of copper, especially in the brain
- Excess copper in other tissues, including kidneys

Menkes disease is ultra-orphan

- US incidence = 1/35,000 male births (~56 births /year)
- US estimated prevalence: 1/8,664 live male births (~225 patients/year)

Prognosis is fatal

- Early death, often before 3 years of age

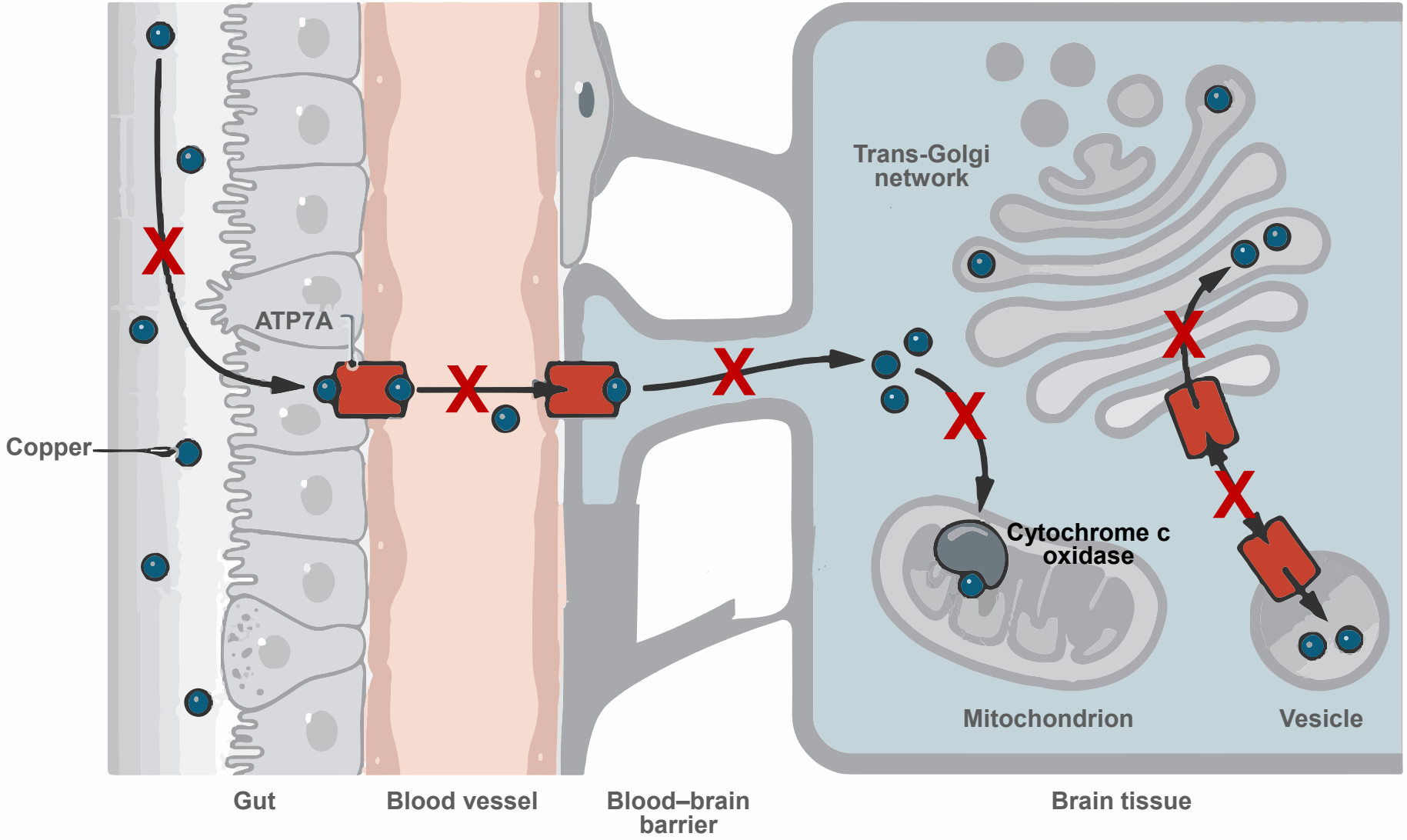


- Hypopigmentation
- Silvery and abnormal hair
- Neurological impairment
- Particular facies

- Abnormal hair
- Neurological impairment
- Bombed forehead
- Hypopigmentation

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. Image courtesy of Creative Commons Attribution-NonCommercial 4.0 International; https://www.wctv.tv/content/news/Local-4-year-old-living-with-Menkes-Disease-414413573.html; https://www.dailymail.co.uk/health/article-4859452/Film-children-rare-disease-unites-families.htm

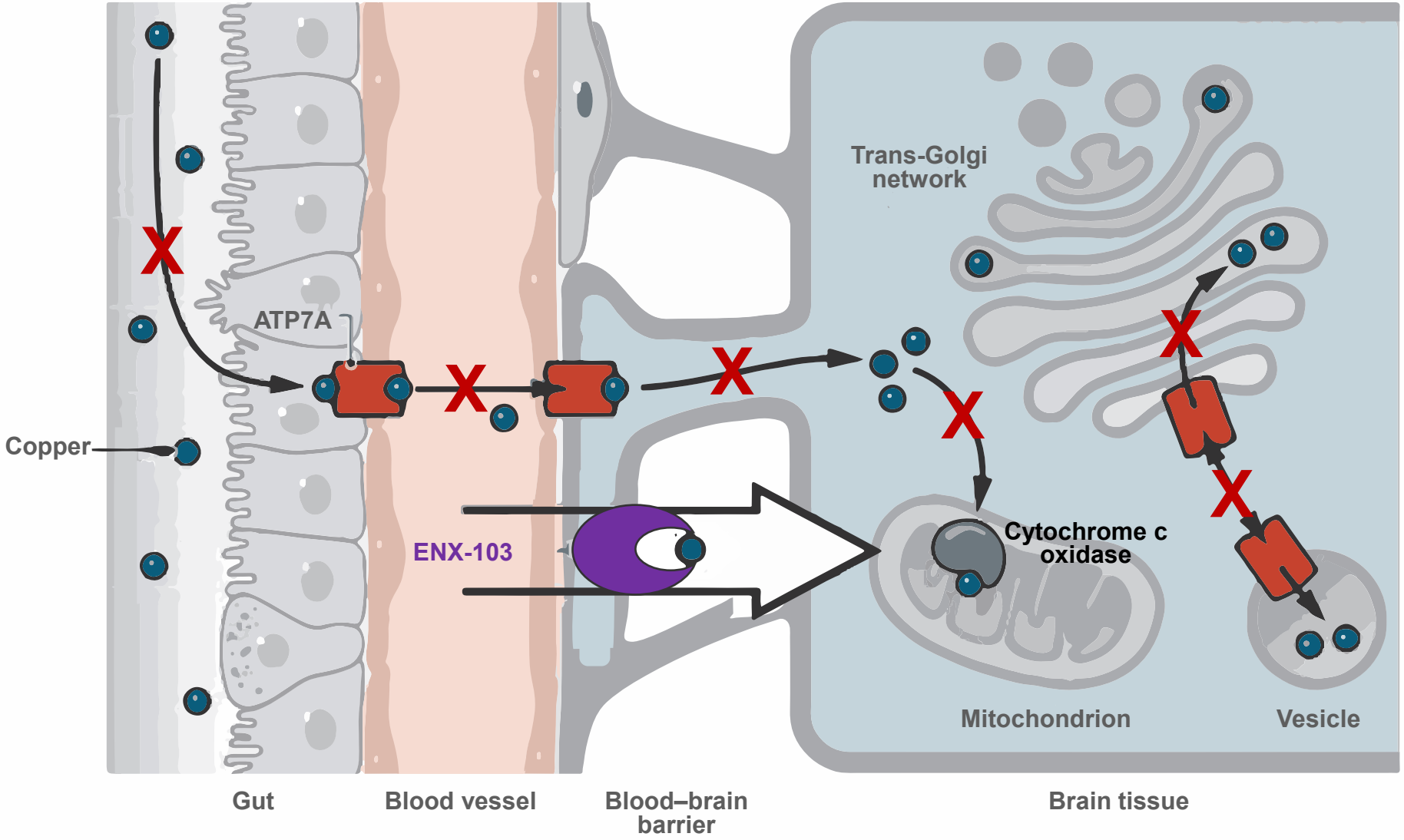
ATP7A mutations lead to a severe deficiency of plasma and brain copper



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.

ENX-103 effectively delivers copper to the brain, especially to mitochondria, improving cellular respiration



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

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

- ✓ Enhances copper delivery to the brain
- ✓ Significant survival increase and neurodevelopment improvements in ‘Menkes mice’
- ✓ Promising profile in multiple named patients with >1 year of treatment

Benefits from ultra-orphan disease market dynamics

- ✓ Creative paths to approval
- ✓ Eligible for priority review voucher

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

Neumora
$2.3B
market cap

AXSOME THERAPEUTICS
$3.4B
market cap

Intra-Cellular THERAPIES
$6.3B
market cap

cerevel
$7.7B
market cap

KARUNA THERAPEUTICS
$12B
market cap

Bristol Myers Squibb
$14B acquisition
closed 03/18/24

abbvie
$8.7B acquisition
announced 12/6/23

"Neuro-comps"

Note: Market caps are as of 03/18/2024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