PRECISION NEUROSCIENCE.
TRANSFORMATIONAL THERAPIES.

CORPORATE OVERVIEW | Q3 2022

Engrail THERAPEUTICS

Engrail has embarked on the journey to build a leading neuroscience company with transformational therapies

Rapidly advancing programs create **near- and long-term value**

Deep and differentiated precision neuroscience pipeline

Unique approach **improving probability of success**

Experienced leadership with a track record of success in neuroscience

Our experienced leadership team has rapidly built and advanced the pipeline

Vikram Sudarsan, PhD
President and
Chief Executive Officer
Board Member

Stephen Cunningham, MD
EVP, Development and
Chief Development Officer
Board Member

Kimberly Vanover, PhD
Chief Scientific Officer

Eve Taylor, PhD
VP, Clinical Development

Esti Arce, PhD
VP, Translational Science
& Clinical Development

Bill Brubaker, PhD
VP, Drug Metabolism &
Pharmacokinetics

Jordi Serrats, PhD
VP, Preclinical
Development &
Neurobiology

Camilla Gomiero
VP, Commercial Strategy
& Business Development

Neil Mhaskar, PhD
VP, Drug Development &
Manufacturing

Rex Bosen, CPA
Acting Chief Financial
Officer

Anil Vootkur, PharmD
VP, Corporate Development

22
full-time employees
and consultants

>100
years of neuroscience
experience

>30
product approvals
and launches

Diverse and accomplished employee base

50:50 female to male ratio

>70% advanced degree

Learning and development emphasis

Allergan · AstraZeneca · Acadia · Biogen · Cipla · cytori · EMD Serono · Gilead · ICON · imshealth · Intra-Cellular Therapies · Janssen · Johnson & Johnson · Lundbeck · Novartis · Pfizer · ORIC · Takeda

Our approach will enable us to rapidly bring transformational neuroscience therapies to patients

SCIENTIFICALLY VALIDATED

- KNOWN CHEMISTRY
- PROOF OF CONCEPT
- ESTABLISHED TARGETS

BEST-IN-CLASS MEDICINES

- NEW CHEMICAL ENTITIES
- DIFFERENTIATED

HIGH PROBABILITY OF SUCCESS

CLEAR PATH TO APPROVAL

- DEFINED REGULATORY PATHWAYS
- WELL-CHARACTERIZED DISEASES

HIGH-VALUE INDICATIONS

- FAVORABLE COMMERCIAL DYNAMICS
- SIGNIFICANT UNMET NEEDS

Deep, differentiated pipeline uses precision neuroscience to address significant unmet needs

Compound	MoA	Lead Indication	Preclinical	Phase 1	Phase 2	Phase 3
GABA modulation portfolio						
ENX-101	$GABA_A$ α2,3,5 PAM, blocks α1	Focal epilepsy				
ENX-102	$GABA_A$ α2,3,5 PAM, blocks α1	Generalized anxiety disorder				
ENX-106	$GABA_A$ α2,3,5 PAM, blocks α1	Undisclosed				
Dopamine modulation portfolio						
ENX-104	D_2/D_3 antagonism	Depression / Anhedonia				
ENX-105	Selective dopamine / serotonin modulation	Mood disorders				
Rare disease portfolio						
ENX-103	Copper transport	Menkes disease				

MoA, mechanism of action; $GABA_A$, gamma-aminobutyric acid A receptor; PAM, positive allosteric modulator; D_2, dopamine receptor 2; D_3, dopamine receptor 3.

$GABA_A$ MODULATOR PORTFOLIO

ENX-101 AND ENX-102
PRECISION TARGETING OF THE $GABA_A$ α SUBUNIT

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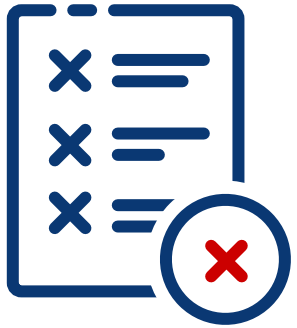
Nonselective $GABA_A$ modulators are efficacious treatments, but have significant side effects and risks

Nonselective $GABA_A$ modulators, such as benzodiazepines, are **highly efficacious** and widely used for multiple diseases

- Acute epilepsy
- Anxiety
- Agitation
- Insomnia
- Spasticity

Liabilities limit chronic use of nonselective $GABA_A$ modulators



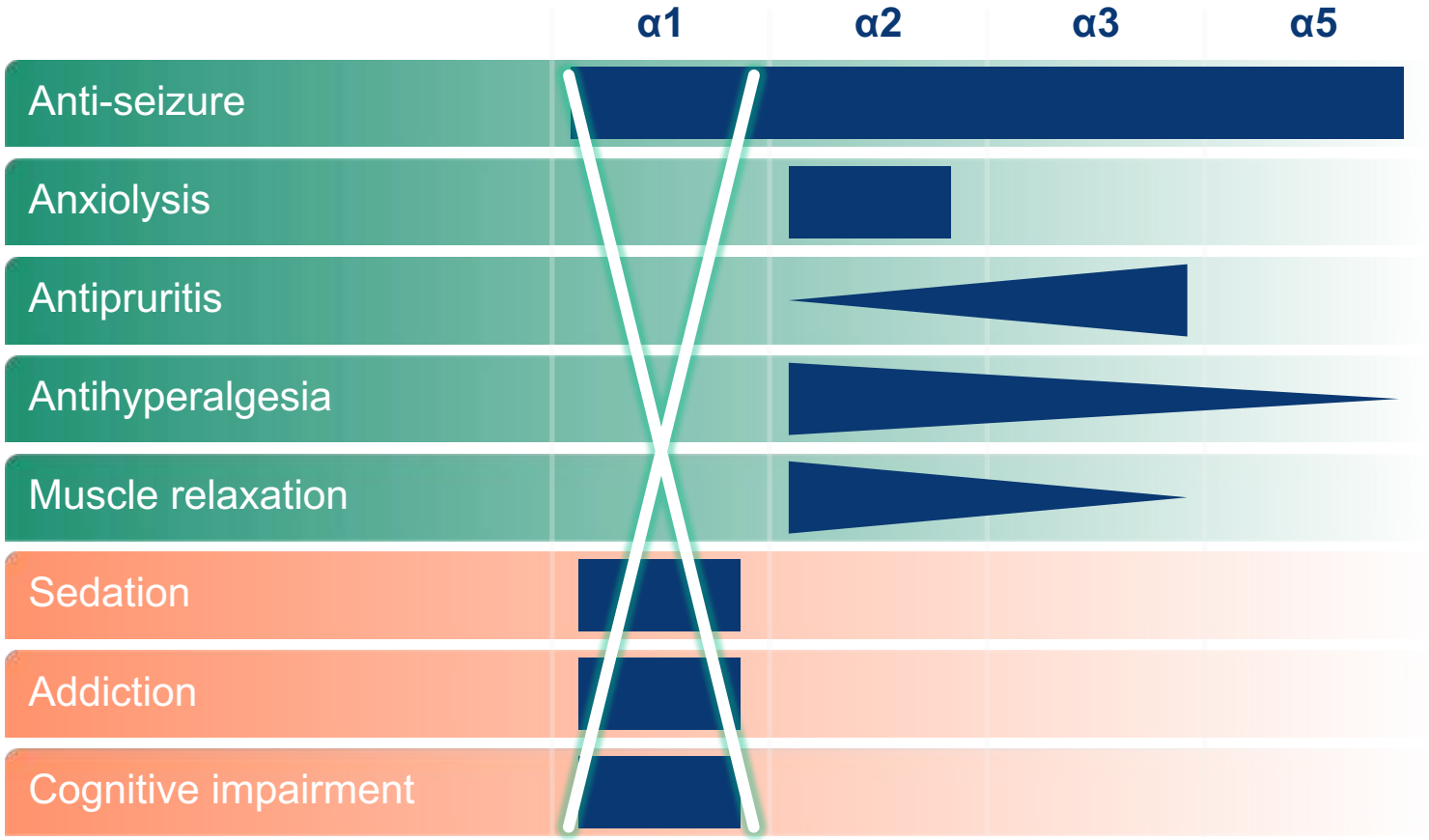
- Sedation
- Cognitive impairment
- Ataxia
- Tachyphylaxis
- Addiction potential

$GABA_A$, gamma-aminobutyric acid A receptor.

Cheng T, et al. Neuropsychiatr Dis Treat. 2018;14:1351–1361. Olsen RW. Neuropharmacology 2018;136:10–12.

Selective $GABA_A$ α2,3,5 PAMs designed to maximize clinical benefits while reducing side effects and risks

Precision targeting: positive allosteric modulation of $GABA_A$ α2,3,5 and blocks α1



Selective $GABA_A$ α2,3,5 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. Zeilhofer HU, et al. Br J Anaesth. 2019;123:e176–e179.

ENX-101 FOR FOCAL EPILEPSY

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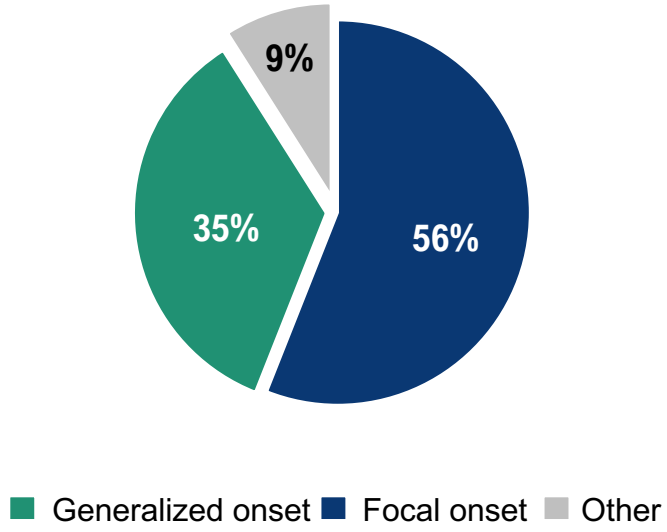
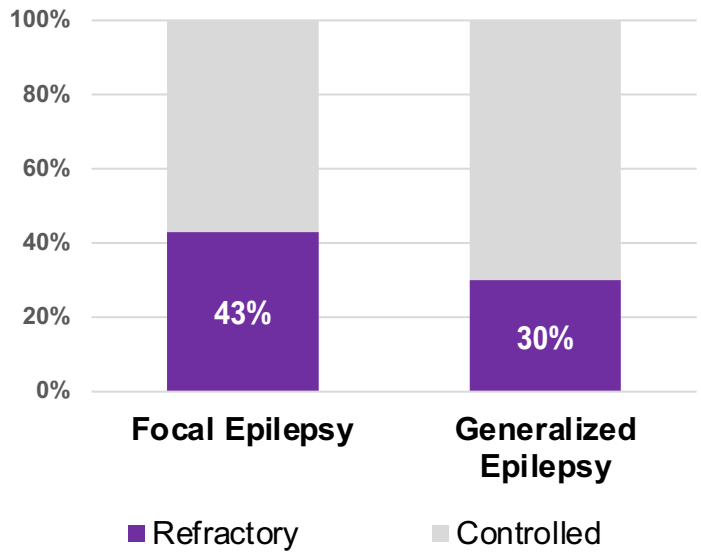
Epilepsy is an area of high unmet need with a substantial refractory population

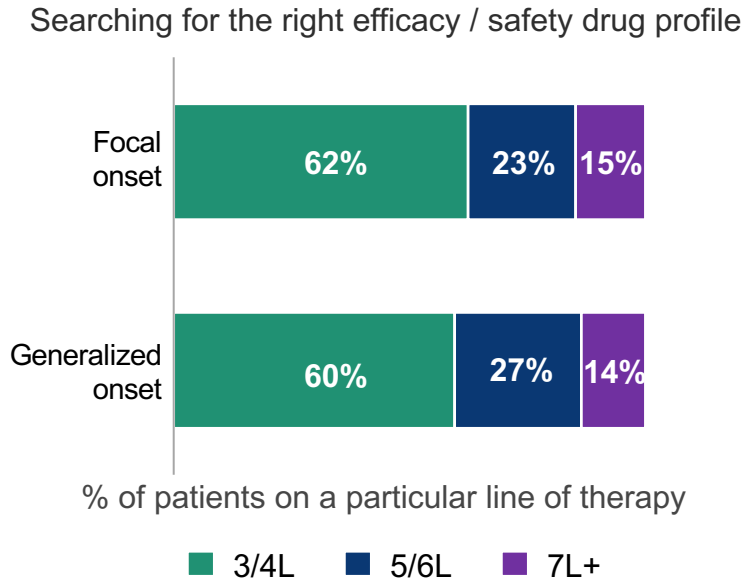
>4M US patients with epilepsy



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 offers strong value proposition for the treatment of focal epilepsy

Anticipated profile based on preclinical and early clinical findings

Novel MoA

- **Complementary MoA** to standard of care and most antiseizure medications

Ease of administration

- Oral
- With or without food
- **No titration**
- **Minimal drug–drug interactions**

Favorable safety and tolerability profile

- **Mild, transient AEs**
- Sedation, ataxia and cognitive impairment rates similar to placebo

Sustained efficacy

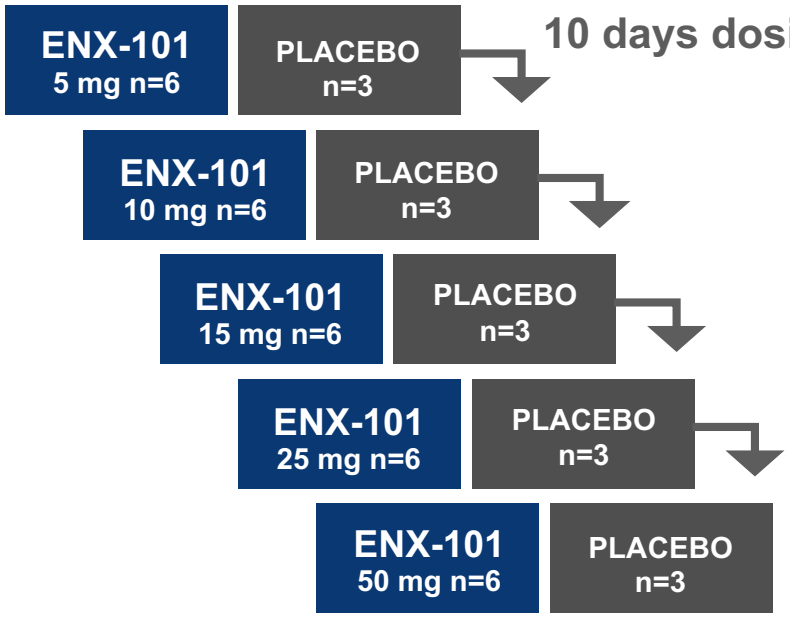
- Unlike BZDs, can be **used chronically**
- No tachyphylaxis
- Potential ancillary benefits (anxiolytic)

Supporting Evidence:			
	✓ Phase 1 data ✓ CYP studies	✓ Phase 1 data	✓ Phase 1 data ✓ Extensive preclinical studies ✓ Clinical data for class

MoA, mechanism of action; AE, adverse event; BZD, benzodiazepine.
Data on File.

Phase 1b clinical data demonstrates favorable tolerability profile, target engagement and lack of tachyphylaxis

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



Primary endpoint:
- Safety and tolerability

Secondary endpoints:
- ECG/QTc
- Pharmacokinetics
- Biomarker analysis

Phase 1b results

Safe and well tolerated
- Mild transient adverse events

Predictable dose-related exposure

Biomarker analysis:
- Confirms target engagement
- Predicts anti-seizure efficacy
- Indicates minimal to no effect on alertness, cognition, and motor function with repeated administration

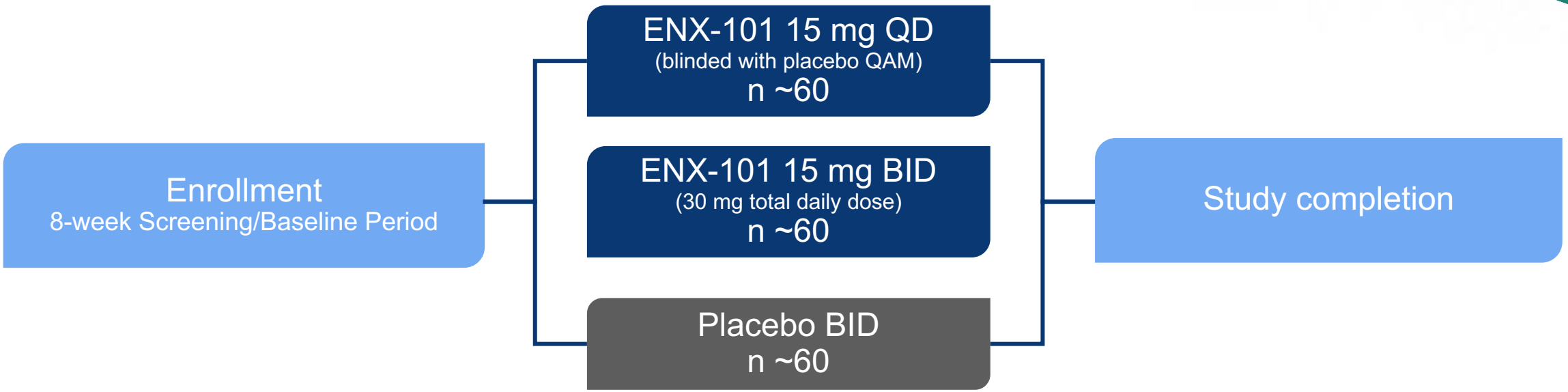
Clinical data support progression into phase 2

ECG, electrocardiogram; QTc, QT corrected for heart rate; MoA, mechanism of action.
Data on File.

Registrational-quality phase 2b trial in focal epilepsy planned to initiate in 2H 2022

Study design informed by key epilepsy advisors, pre-IND advice from FDA, and Phase 1b data

Randomized, double-blind, placebo-controlled adaptive adjunctive treatment study



8-week treatment period and 4-week taper

Administered as an adjunct to 1 to 4 antiseizure medications

Primary endpoint

- Median percent change from baseline in focal seizure frequency compared to placebo

Key secondary endpoints

- Responder rate (≥50% reduction)
- Seizure freedom rates

Other exploratory endpoints

- CGI-S and CGI-I
- Quality of life measures

BID, twice daily; CGI-I, clinical global impressions scale – improvement; CGI-S, clinical global impressions scale – severity; IND, investigational new drug; QAM, once every morning; QD, once daily.

ENX-102 FOR GENERALIZED ANXIETY DISORDER

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Substantial need for new options to treat generalized anxiety disorder

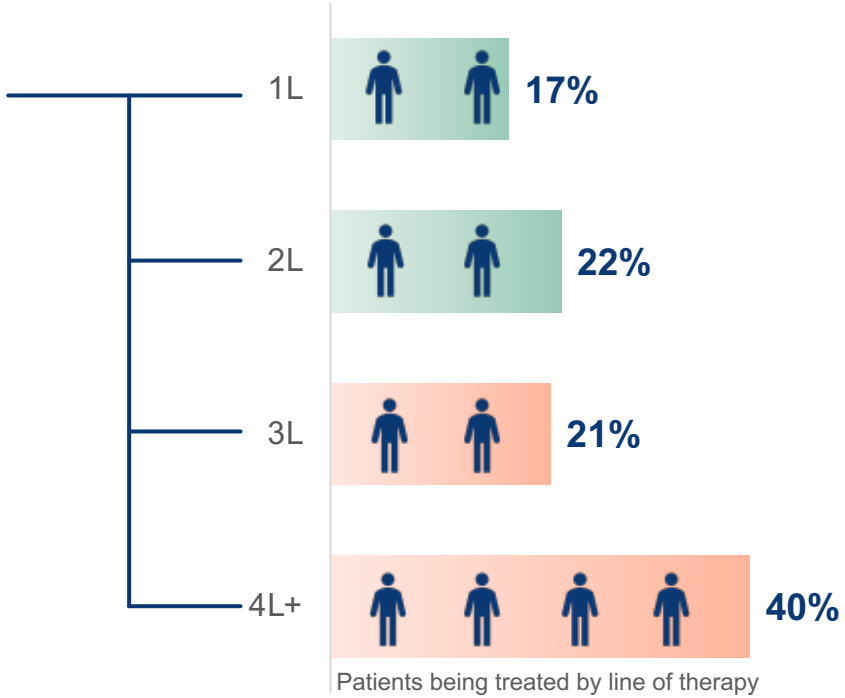
>5.4 M US patients currently being treated for GAD

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

BZDs 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; BZD, 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 offers strong value proposition for the treatment of GAD

Anticipated profile based on preclinical and early clinical findings

Fast onset of action

- **No titration required**; efficacious dose on day 1
- Similar onset of action and efficacy as BZDs

Clean safety and tolerability profile

- **Mild, transient AEs**
- Sedation, ataxia and cognitive impairment rates similar to placebo

Chronic treatment

- Unlike BZDs, can be **used chronically**
- Minimized abuse liabilities

Supporting Evidence:

- ✓ **Phase 1 data**
- ✓ **Preclinical studies**
- ✓ **Clinical data for the class**

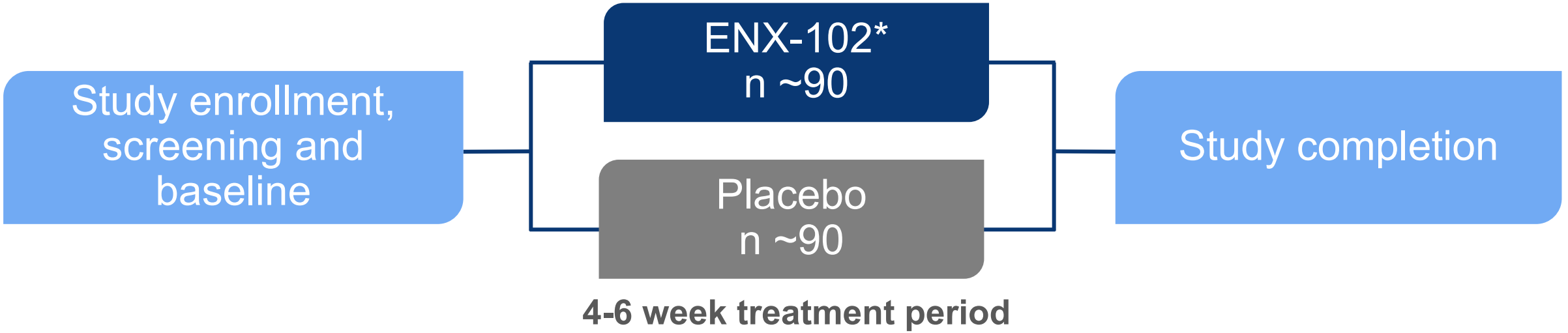
- ✓ **Phase 1 data**

- ✓ **Preclinical abuse liabilities studies for $GABA_A$ α2,3,5 PAMs vs BZDs**
- ✓ **Preclinical chronic studies**
- ✓ **Phase 1 data**

MoA, mechanism of action; AE, adverse event; BZD, benzodiazepine.
Data on File.

Registrational-quality phase 2b trial in GAD planned to initiate in 2H 2022

Randomized, double-blind, placebo-controlled adaptive monotherapy study



Primary endpoint:
- HAM-A

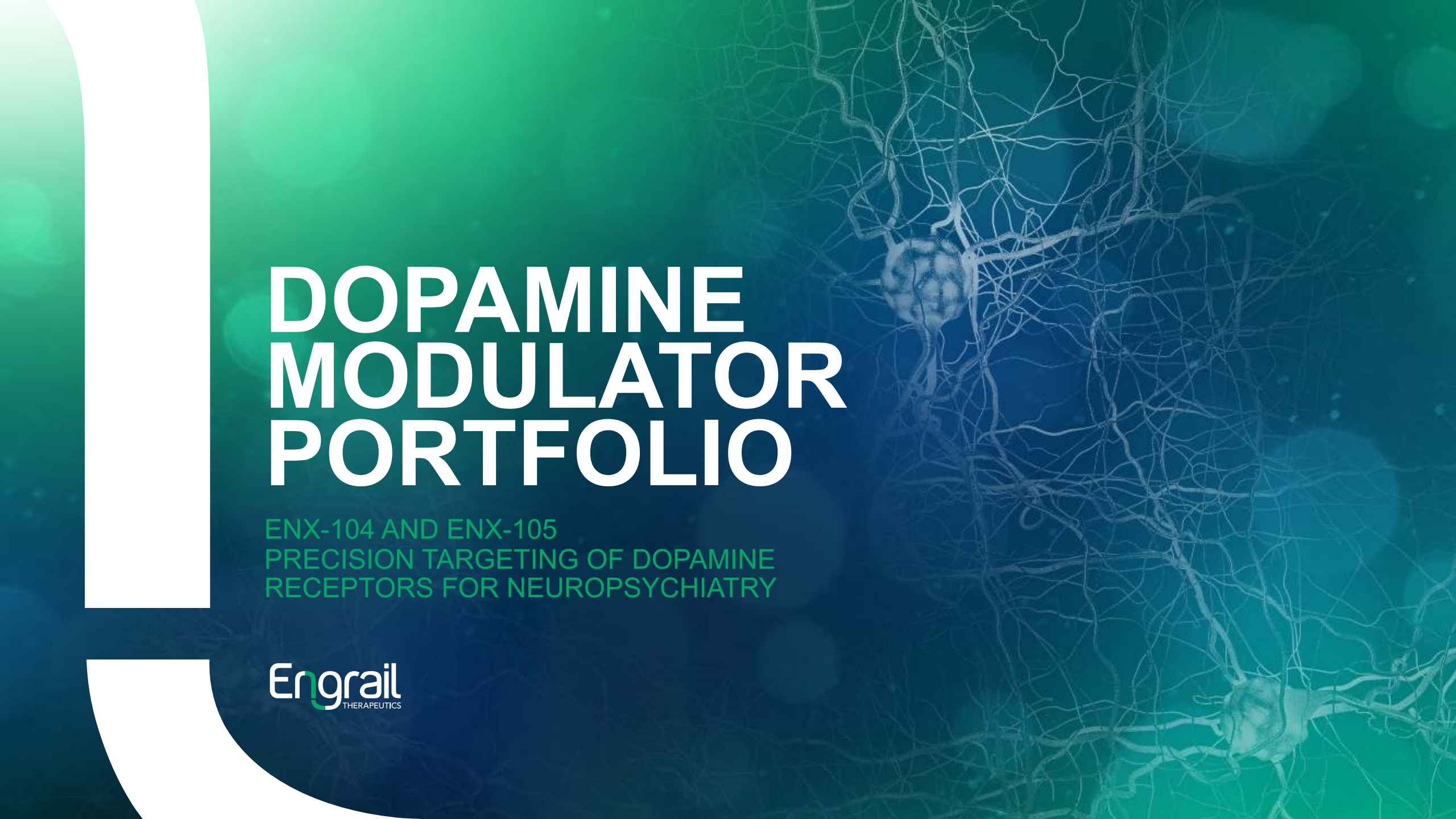
Key secondary endpoint:
- CGI

*Dose selection will be informed by the ongoing Phase 1b study to confirm target engagement

GAD, generalized anxiety disorder; HAM-A, Hamilton anxiety rating scale; CGI, clinical global impression-improvement scale.
Data on File.

DOPAMINE MODULATOR PORTFOLIO

ENX-104 AND ENX-105
PRECISION TARGETING OF DOPAMINE RECEPTORS FOR NEUROPSYCHIATRY



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Anhedonia is a core symptom of major depressive disorder (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

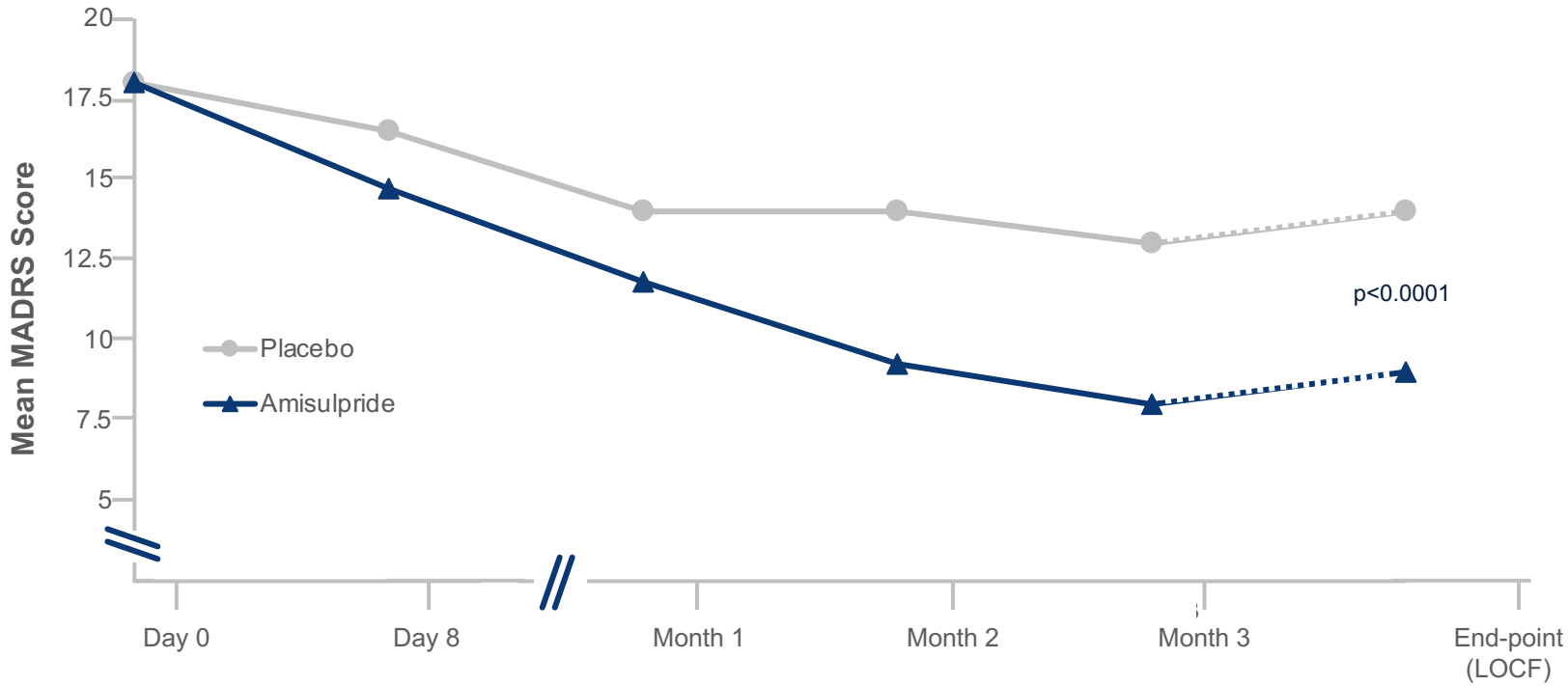
2.3 M have **inadequate response** to at least one antidepressant

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

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

Clinical proof-of-concept has been established with D_2/D_3 modulation for the reduction of anhedonia and depression

Effective low-dose dopamine D_2/D_3 antagonism



Adapted from Boyer P, et al. *Neuropsychobiology.*1999;39:25–32. Copyright © 1999 Karger Publishers, Basel, Switzerland.

Clinical proof-of-concept

- ✓ Low-dose amisulpride preferentially blocks presynaptic autoreceptors, causing dopamine release
- ✓ Increasing dopamine neurotransmission can alleviate symptoms of depression and anhedonia
- ✓ Amisulpride is approved for the treatment of dysthymia in select EU countries

D_2, dopamine receptor 2; D_3, dopamine receptor 3; LOCF, last observation carried forward; MADRS, Montgomery–Äsberg Depression Rating Scale.
Boyer P, et al. Neuropsychobiology.1999;39:25–32. Zagani C, et al. Hum Psychopharmacol Clin Exp. 2021;36:e2801.

Engrail's dopamine modulation portfolio leverages exciting pharmacology for an array of neuropsychiatric conditions

ENX-104:
a potent D_2/D_3 antagonist in development for MDD with anhedonia

At low doses designed to preferentially block presynaptic autoreceptors to **increase dopamine release**

- Highly potent and selective D_2/D_3 antagonist
- Excellent brain:plasma exposure supports QD dosing
- Proof-of-concept demonstrated in preclinical models

ENX-105:
a unique D_2/D_3 antagonist in development for mood disorders

- Potential for psychedelic-like antidepressant efficacy without the hallucinations or fear/anxiety
- Excellent brain:plasma exposure supports QD dosing
- Proof-of-concept demonstrated in preclinical models

D_2, dopamine receptor 2; D_3, dopamine receptor 3; MDD, major depressive disorder; QD, once daily.
Data on File.

ENX-103 FOR MENKES DISEASE

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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

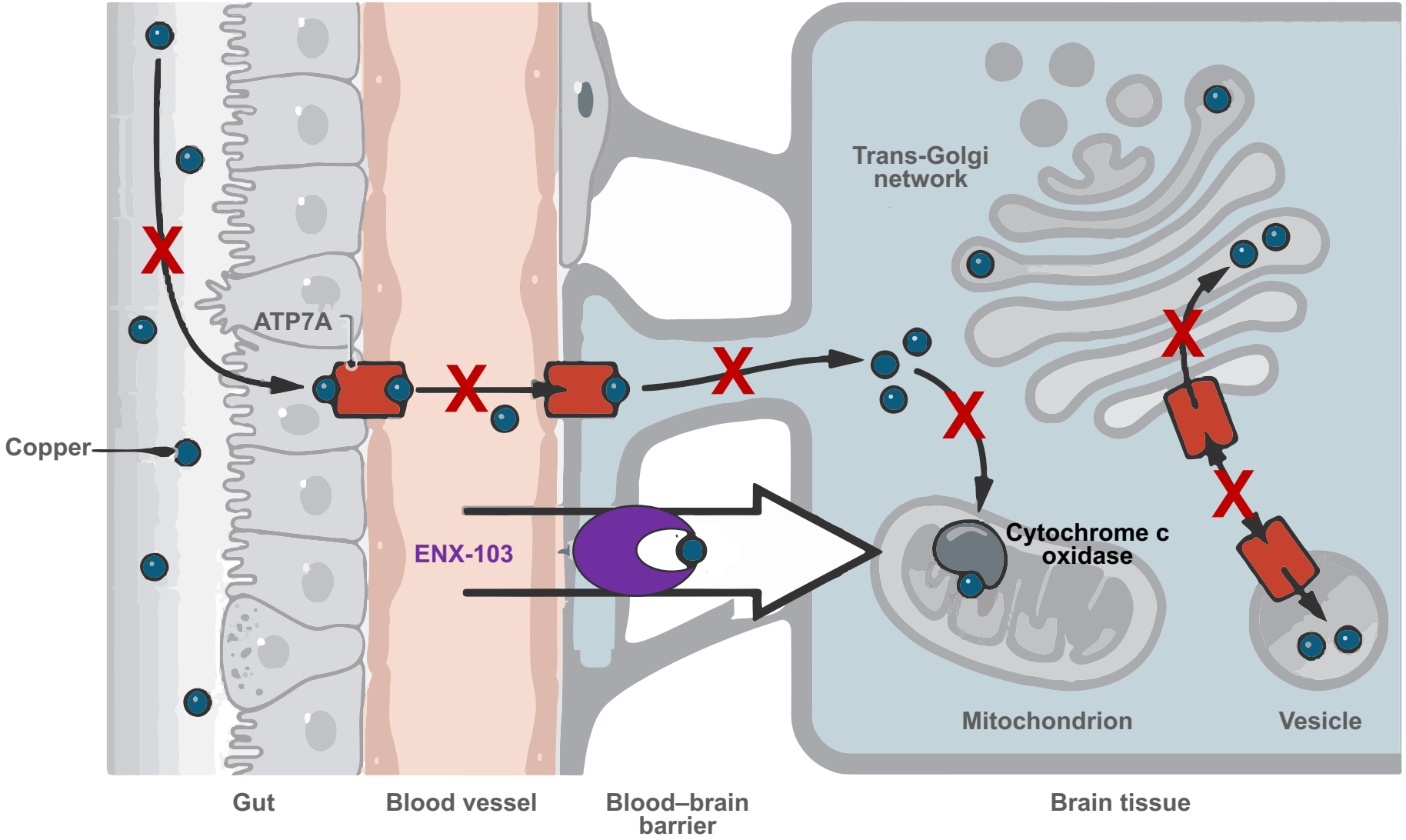
Prognosis is fatal

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



ATP7A, ATPase copper transporting alpha.
From Lutsenko S. Science. 2020;368:584–585. Reprinted with permission from AAAS.

ENX-103 has the potential to increase survival and improve quality of life for patients with Menkes disease

Median survival in Menkes disease mouse model improved from 14 days to 203 days with ENX-103 treatment

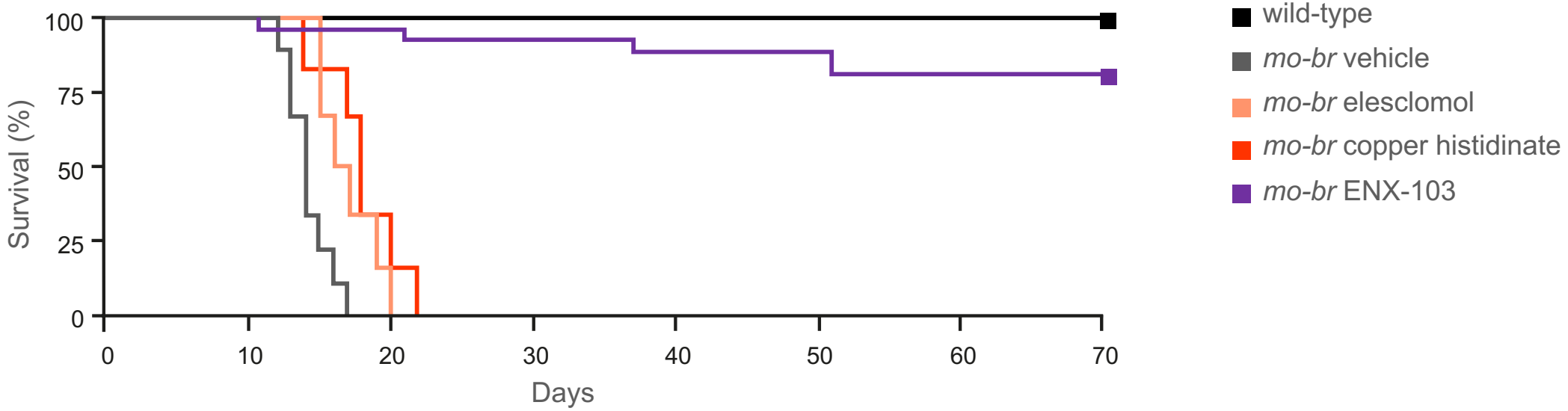
ENX-103 treatment resulted in the survival of 82% of Menkes model (*mo-br*) mice at 10 weeks

Treated with
ENX-103
8 weeks (thriving)

Image courtesy of Vishal Gohil, PhD

Untreated
14 days (death)

Image from Guthrie LM, et al. Science. 2020;368:620–625. Reprinted with permission from AAAS.



mo-br, mottled-brindled.
Guthrie LM, et al. Science. 2020;368:620–625.

THANK YOU

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