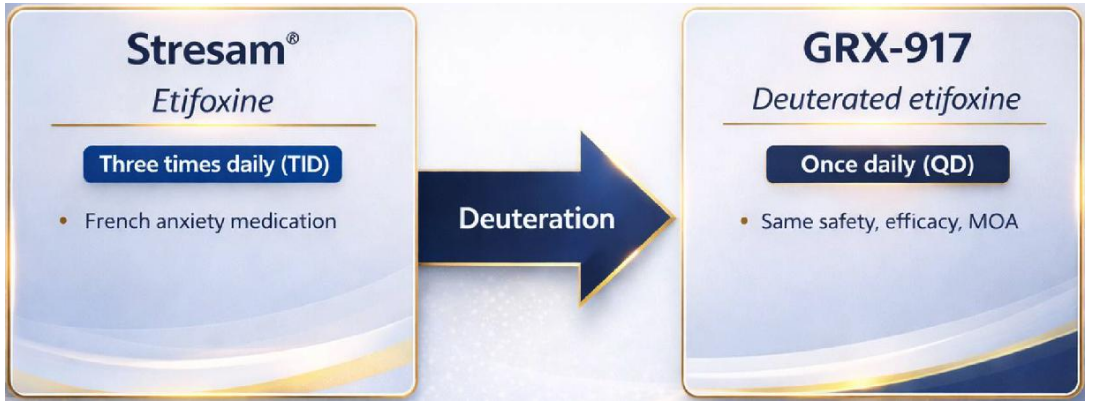
GABA Therapeutics, Inc. – June 2026

GRX-917 – Safe, Fast & Effective Anxiolytic for Chronic Use

gaba THERAPEUTICS

GRX-917 Potential First-Line Anxiolytic

- GRX-917 is deuterated etifoxine – with the same MOA and pharmacology, but improved PK (from TID to QD).
  - Etifoxine is an approved anxiolytic (ex-US) with over 100M Rx and +100 published studies on its MOA, safety and efficacy.
- GRX-917 produces endogenous neurosteroids with rapid efficacy comparable to benzodiazepines, but non-addictive with placebo like side effects.
- SAD/MAD dose escalation completed, oral drug product Phase 3 ready
- Phase 3 readout (2-yrs), NDA in GAD (2030), $2.5B peak revs (US)
- Additional blockbuster indications in PPD, pain, epilepsy, obesity
- Strong IP with composition of matter patents underpinned by unexpected (non-obvious) properties through 2042 (US) and potentially 2046.



De-Risked Program

✓	**Target Engagement**
✓	**Pharmacokinetics (PK)**
✓	**Efficacy**
✓	**Commercial Differentiation**

Deuteration is a Multi $Billion Pharma Strategy

- Deuteration minimizes risk in product development
- Pharmacology of deuterated drugs is the same or superior to non-deuterated precursors, due to reduced toxic or reactive metabolites or improved PK
- No approved deuterated drug has unique adverse effects vs precursor

SUN PHARMA
LEQSELVI™ (deuruxolitinib) tablets 8mg
$1B Revs
Peak Estimate

teva
Austedo® (deutetrabenazine) 6 mg, 9 mg, and 12 mg tablets
$2.5B Revs
2026

Bristol Myers Squibb™
SOTYKTU™ (deucravacitinib) 6 mg tablets
+$300M Revs
2026

VERTEX
alyftrek
(Vanzacaftor/Tezacaftor/Deutivacaftor)
+1B Revs
2026

teva
AUSPEX PHARMACEUTICALS
$3.2B
2015

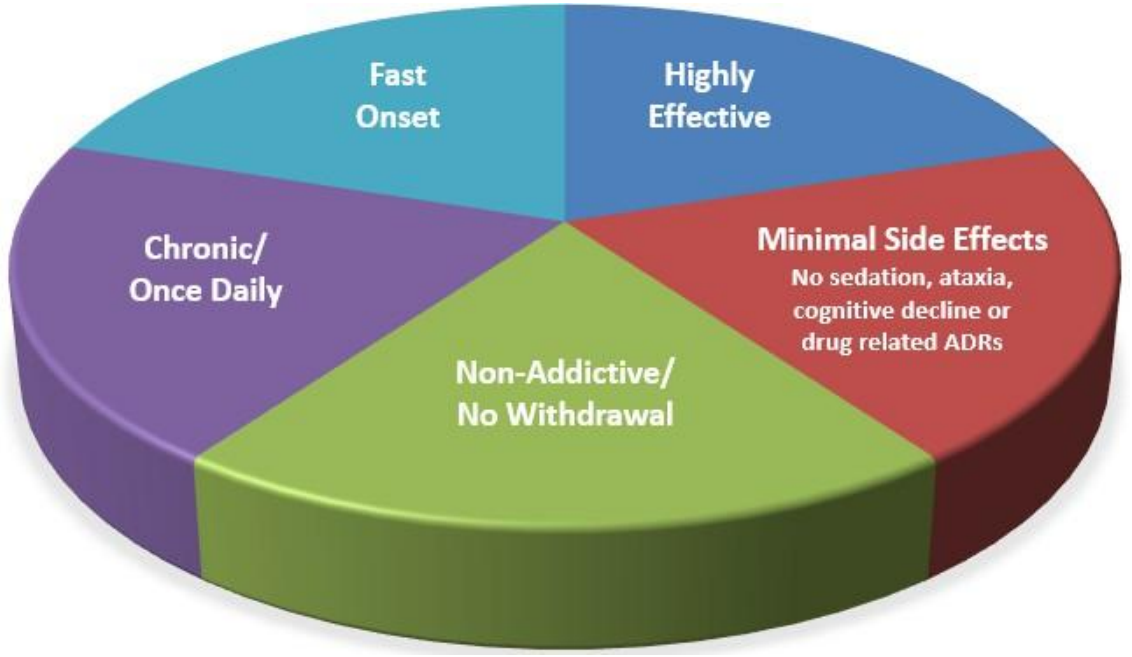
Otsuka
AVANIR pharmaceuticals
$3.5B
2014

GSK
CoNCERT Pharmaceuticals Inc.®
D-atazanavir
$1B
2009

GRX-917 Target Product Profile in Anxiety

- **Optimal Efficacy**
  - Rapid-onset and efficacy superior/comparable to Xanax®, Ativan®, Klonopin®
- **No Addiction Liability**
- **Minimal Adverse Events**
  (at 10x Phase 1 therapeutics doses)
  - No sedation
  - No cognitive impairment
  - No ataxia
- **Once Daily, Chronic Dosing**

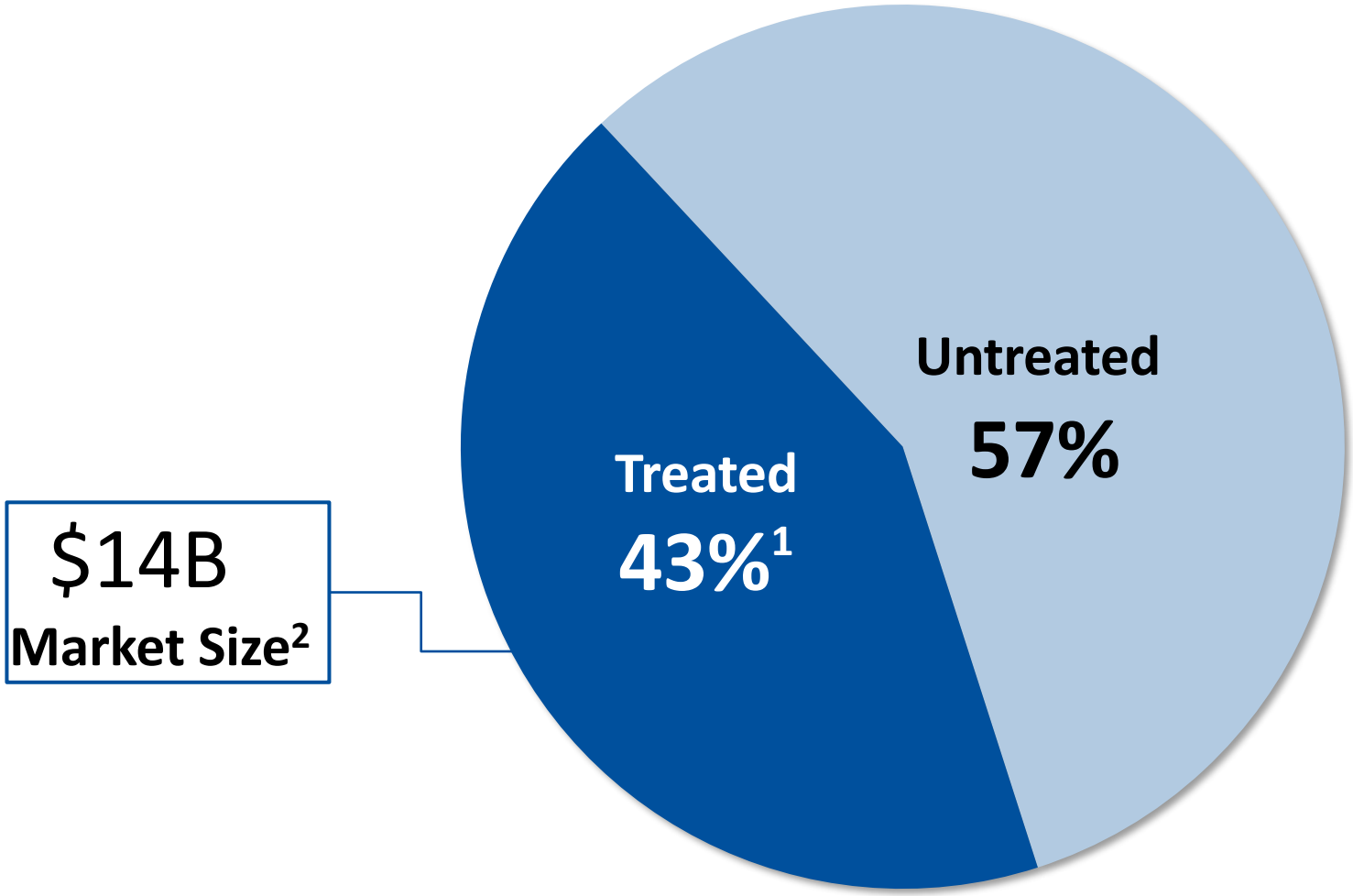
"A Fast and Effective Anxiolytic for Chronic Use"



GRX-917 vs. Current Available Treatments

Key Attributes	GRX-917	Benzodiazepines	SSRIs/SNRIs
Rapid Onset	✓	✓	4-8-week delay
Efficacy	✓	✓	Inferior
Side Effects	✓	Sedation, ataxia, impaired cognition	GI, sexual dysfunction, insomnia, weight gain
Addiction Liability	✓	x	✓
Chronic Usage	✓	x	✓

Most GAD Patients Do Not Use Available Anxiolytics



[1]Anxiety and Depression Association of America (2024)
[2]Global Anxiety Market: IMS, per Foster Rosenblatt Market Research

Etifoxine: Comparable Efficacy to Xanax®, Ativan®, Klonopin®

Maurizio Fava, MD, Psychiatrist-In-Chief at MGH/Harvard, estimates an **80% probability of success** for GRX-917 in GAD, based on below studies. Maurizio is on our SAB and can discuss his rationale.

Etifoxine Study Result	Etifoxine Clinical Study	N	Reference	Date
Comparable onset and efficacy to Alprazolam (Xanax®)	(P3) ETX vs Alprazolam (Xanax®) Marketing Authorization in India 2024	260	Prabhakar et al (2024)[1]	2024
Superior efficacy to Clonazepam (Klonopin®)	(P4) ETX vs Clonazepam (Klonopin®)	179	Vicente[2]	2020
Comparable onset and efficacy to Alprazolam (Xanax®)	(P4) ETX vs Alprazolam (Xanax®)	202	ETIZAL S.650/EN	2015
Superior efficacy to Phenazepam	(P4) ETX vs Phenazepam	90	Aleksandrovsky[3]	2010
Comparable onset and efficacy to Lorazepam (Ativan®)	(P4) ETX vs Lorazepam (Ativan®)	191	ETILOR S.392/EN	2006
Superior efficacy to Buspirone	(P4) ETX vs Buspirone	170	STRETI S.226/GB	1998

Etifoxine is prescribed to over 50% of new anxiety patients by high prescribers in France. Interviews are in the VDR.

1. Prabhakar et al. Role of Etifoxine in Generalized Anxiety Disorder: a phase III randomized, double-blind, double-dummy, active-controlled study in India. Neuroscience Applied, Vol 3, Supplement 2, 104122 (2024).
2. Vicente et al., Psychopharmacology 237, 3357–3367 (2020)
3. Aleksandrovsky et al., Russian Psychiatric Journal;Therapy of the mentally ill; No. 1; 74-78 (2010)

Etifoxine: Non-Addictive

“No cases of abuse, misuse or pharmacodependence.”[1]

15.7 million prescriptions of etifoxine (Stresam®) were reviewed and analyzed by the French National Agency for the Safety of Medicines and Health Products, between 2000 and 2012 (“**ANSM Report**”), for marketing reauthorization.

1) Cottin et al., Fundamental & Clinical Pharmacology 30 (2016) 147–152.

GRX-917/Etifoxine: Placebo Like Side Effects

Phase 1 – GRX-917

Placebo like side effects

up to 10x therapeutic doses

Nervous System Disorders	GRX-917 (n=75)	Placebo (n=25)
Dizziness	4%	4%
Headache	17%	12%
Paresthesia	1%	4%
Somnolence	0%	8%
Ataxia	0%	0%
Lethargy	3%	0%
Cognitive Deficit	0%	0%

GRX-917 Phase 1: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Ascending Doses of GRX-917 in Healthy Adult Subjects

EMA Etifoxine SAE Assessment

Across All Controlled Clinical Trials +40 Years

System Organ Class (SOC) MedDRA PT	Etifoxine hydrochloride	Blinded	Active comparator	Placebo
Ear and labyrinth disorders	**0**	**0**	**1**	**0**
Vertigo	0	0	1	0
Eye disorders	**0**	**0**	**1**	**0**
Retinal artery thrombosis	0	0	1	0
Hepatobiliary disorders	**1**	**0**	**0**	**0**
Jaundice	1	0	0	0
Injury, poisoning and procedural complications	**1**	**4**	**1**	**1**
Contusion	0	1	0	0
Ligament injury	1	0	0	0
Ligament sprain	0	1	0	0
Overdose	0	0	1	0
Road traffic accident	0	1	0	0
Wound	0	1	0	0
Injury	0	0	0	1
Musculoskeletal and connective tissue disorders	**0**	**0**	**1**	**0**
Back pain	0	0	1	0
Neoplasms, benign malignant and unspecified (incl cyst)	**1**	**0**	**0**	**0**
Fibroma	1	0	0	0
Nervous system disorders	**0**	**0**	**1**	**0**
Somnolence	0	0	1	0
Psychiatric disorders	**0**	**0**	**1**	**0**
Suicidal ideation	0	0	1	0
Surgical and medical procedures	**1**	**0**	**0**	**0**
Cervical conisation	1	0	0	0
TOTAL	**4**	**4**	**6**	**1**

Source: EMA/CHMP Etifoxine Assessment Report, Jan 2022

Phase 1 PK Modeling and Dose Prediction

GRX-917 Predicted Dose: 60 mg QD

- GRX-917 demonstrated improved PK and once-daily dosing vs. etifoxine.
- Certara (world leader) will conduct advanced GRX-917 PK bridging dose selection to ensure optimal safety and efficacy.

	Etifoxine[1]	GRX-917[2]
Half-life	4 hours	>12 hours
Daily dose	150 mg - 200 mg	60 mg
Dosing regimen	BID - TID	QD

1) Stresam® Summary of Product Characteristics, dated 11th April 2022.
2) Phase 1 PK comparisons of etifoxine and GRX-917.

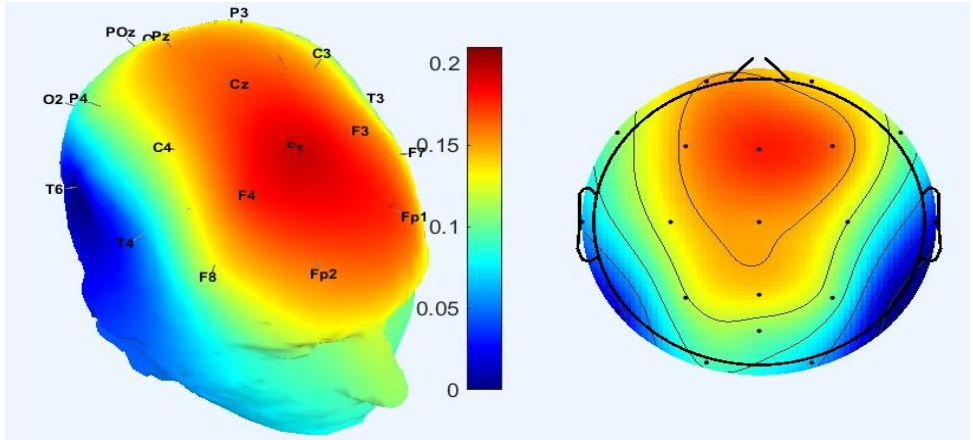
GRX-917 qEEG Beta Power Increase Supports Anxiolytic Efficacy

Phase 1 Study

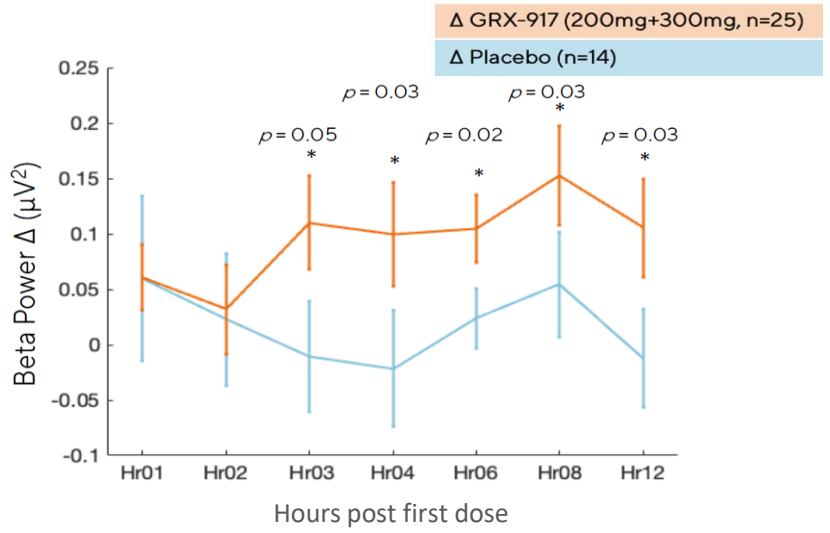
Increased Beta Power:

- Confirms $GABA_A$ target engagement
- Dose- and time-dependent for 12 hours ($p<0.05$)
- Demonstrates GRX-917 exposure response ($p<0.0001$)
- Rapid onset, sustained, significant

GRX-917 Exposure Response Heat Map (p<0.0001)



GRX-917 Increases qEEG Beta Power



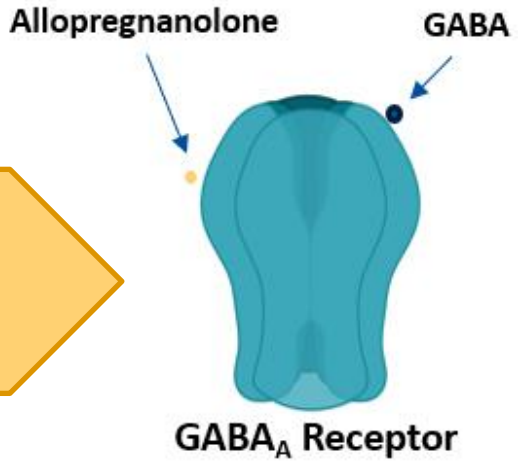
GRX-917 Phase 1: (Study GRX-917-01) - A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Ascending Doses of GRX-917 in Healthy Adult Subjects

GRX-917 – Induction of Endogenous Neurosteroids

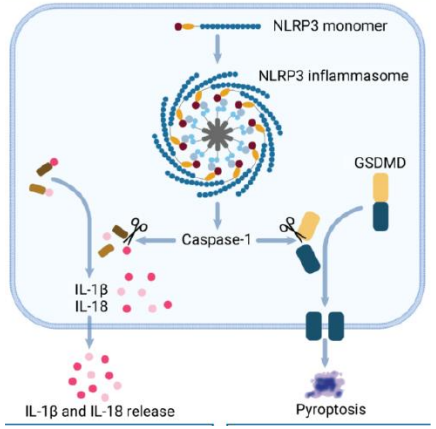
Potent neuromodulatory and anti-inflammatory activity

GRX-917/etifoxine increase neurosteroid synthesis[1]

Neurosteroids modulate receptors[2]
(anxiety, depression, epilepsy)



Neurosteroids inhibit NLRP3 inflammation[3]
(epilepsy, MS, pain, obesity)



NLRP3/IL-1beta Pathway

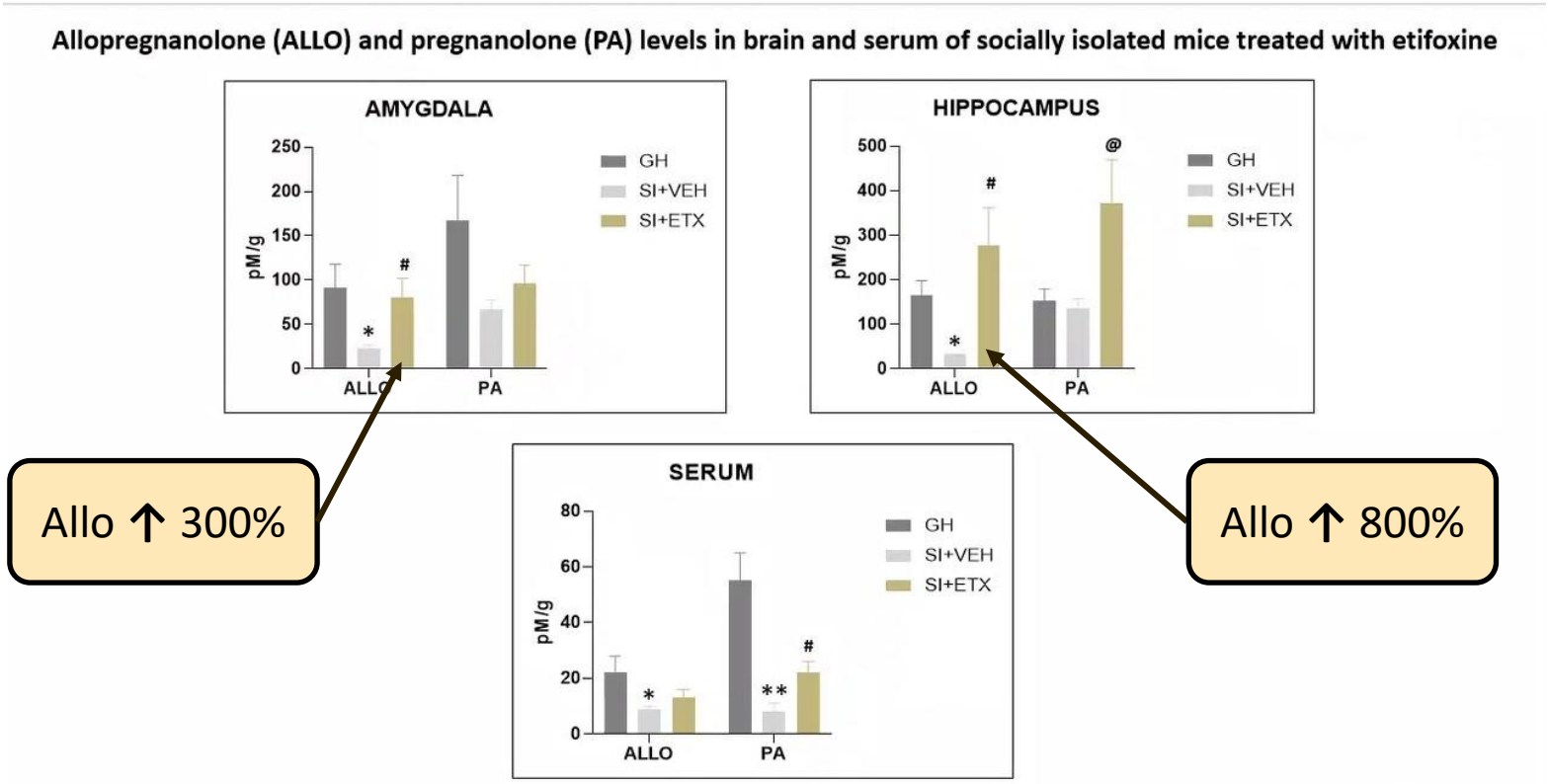
[1]do Rego JL et al (2015) PLoS ONE 10(3): E0120473 ; internal data

[2]Lambert et al (2003) Prog Neurobiol 71(1); 67-80.

[3]Osmond et al (2023)

Etifoxine – Rapid, significant increases in brain neurosteroid levels

Highly selective regional distribution 60 minutes following etifoxine administration.



Etifoxine was administered at the dose of 50mg/kg IP and mice were killed 60 min after drug injections. Results are Mean ± SEM of 5-10 mice. *P<0.05 and **P<0.001 compared with group-housed (GH) mice; #P<0.05 compared with socially isolated (SI) mice plus vehicle (VEH); @P=0.06 compare with SI + VEH

Source: Graziano Pinna PhD, Univ IL Chicago

GRX-917 Oral Drug Product (ODP) - Phase 3 Ready

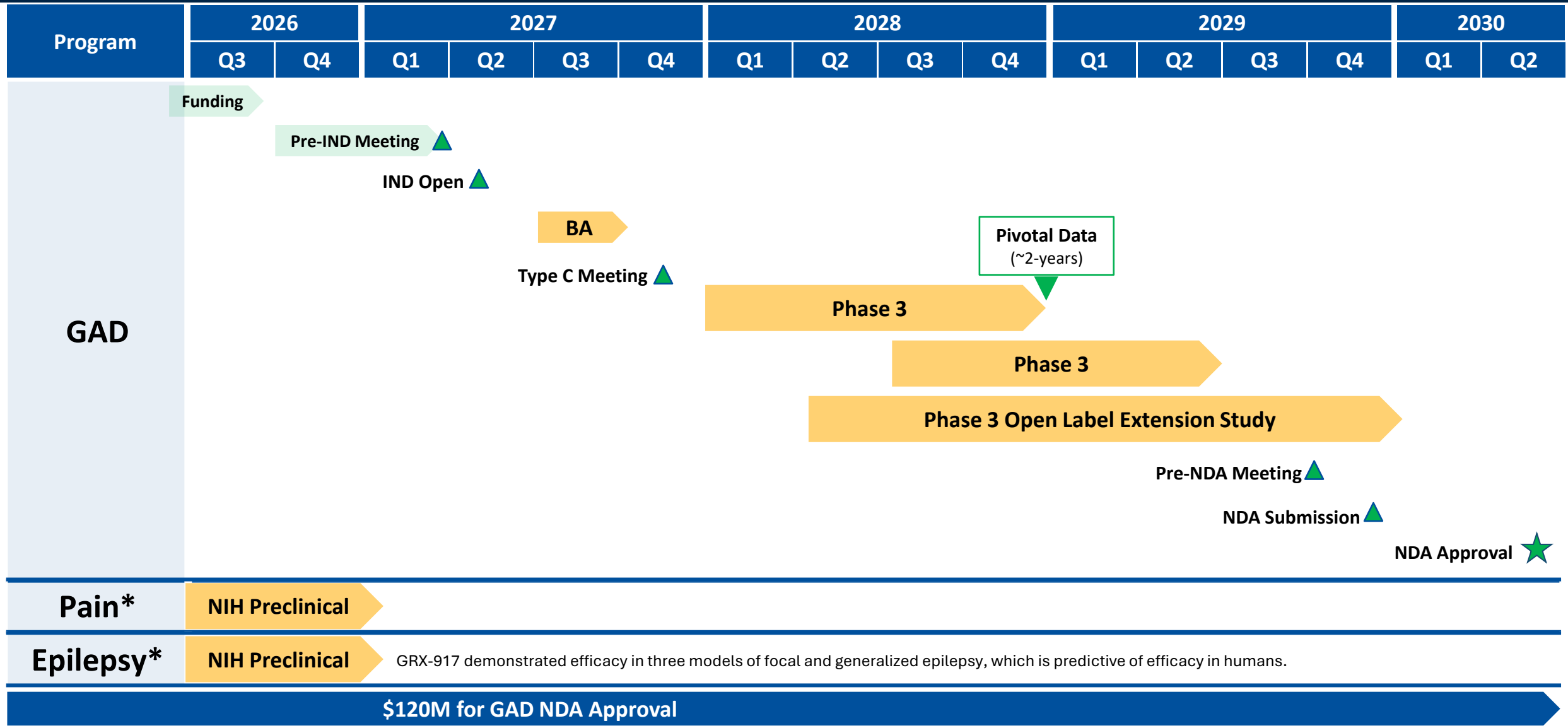
GRX-917 ODP suitable for conducting phase 2 and phase 3 clinical trials globally, potentially commercializable.

1) 50% improvement in oral bioavailability (vs. API in capsule) – monkey PK
2) +3-year shelf stable at room temperature
3) New composition of matter patents expected to extend global IP through 2046

Intellectual Property Overview: Global CoM IP Strategy through 2046

Patents	Non-Obvious/ Inventive Factors	Countries	Priority	Int'l Filing	Expiry
PCT/US16/23231 (WO 2016/154039) DEUTERATED ANALOGS OF ETIFOXINE, THEIR DERIVATIVES AND USES THEREOF - 10,080,755 claims compounds including GRX-917; methods of treatment - 10,736,901 claims GRX-917 compounds; methods including treating anxiety - 11,672,805 claims methods of treating anxiety with GRX-917 - 12,433,896 claims methods of treating convulsive disorder	Specific deuteration at a location differing from expected metabolic "hot spot" led to novel deuterated molecule (GRX-917) with optimal metabolic stability (see EU prosecution)	US, AU, BR, CA, CN, EP, IL, IN, JP, KR, MX	62/135,979 filed 2015 Mar 20	2016 Mar 18	**2036** Mar 18 **PTE** TBD
PCT/US23/77643 (WO 2024/091943) METHODS OF TREATMENT ANXIETY AND OTHER DISORDERS USING DEUTERATED ANALOGS OF ETIFOXINE - 18/493,488 - US 20240189316 A1 - PTA current est. 2 months	Claims directed to specific dosing regimen with GRX-917 that unexpectedly avoids autoinduction	US, AU, BR, CA, CN, EP, IN, JP, KR, MX, NZ	63/380,737 filed 2022 Oct 24	2023 Oct 24	**2043** Oct 24
100016_00055 - US - 63/793,999 - Stable Oral Solid Formulation of Deuterated Etifoxine HCl, THEIR DERIVATIVES, AND USES THEREOF	Oral composition for GRX-917 that provides significant and unexpected stability and bioavailability		US & PCT to be filed 2026 Mar 24		**2046** Mar 24

GRX-917 Core GAD Clinical Program



*NIH programs are entirely funded and executed by NIH.

Key Advisors

Decades of successful leadership in pharma development, psychiatry, and regulatory

Robert Berman, M.D.
Scientific Advisory Board Chairman
Co-Founder, Biohaven

biohaven pharmaceuticals

Bristol Myers Squibb

Pfizer

Yale SCHOOL OF MEDICINE

Maurizio Fava, M.D.
Clinical & Regulatory Advisor
Psychiatrist-in-Chief
Mass General/ Harvard Med

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY

Thomas Laughren, M.D.
Clinical & Regulatory Advisor
Former Director, Div. Psych Products, FDA/CDER

FDA

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY

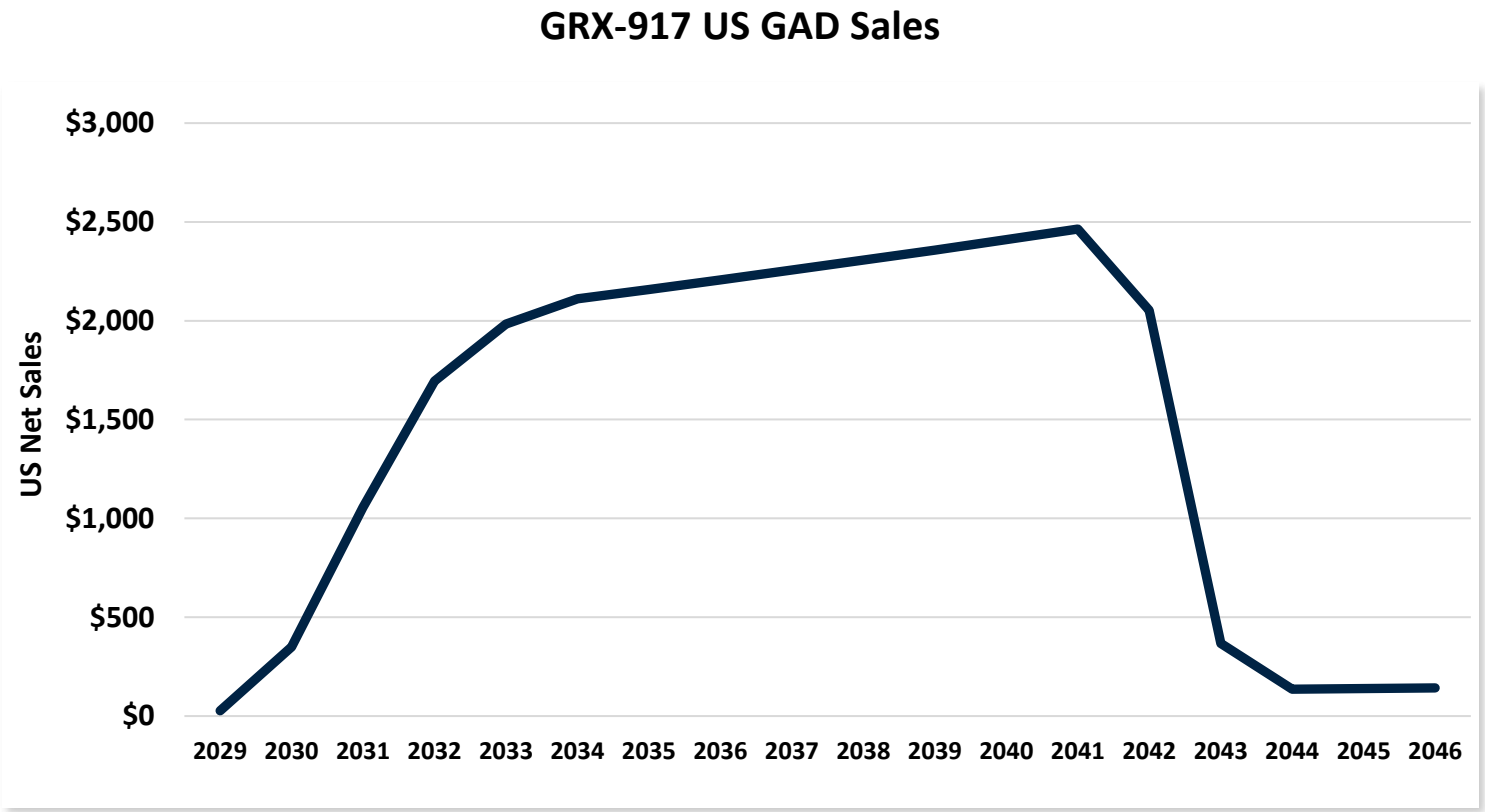
Capital Requirements and Use of Funds

$ in millions

Use of Funds	First Phase 3 GAD	Total to NDA
IND Opening Studies	$4.5	$4.5
Clinical Trials	$19.0	$58.0
Tox & Research	$4.3	$10.6
CMC	$0.6	$18.2
Regulatory	$0.5	$2.5
G&A	$13.5	$27.7
Total	**$42.0**	**$121.0**

All costs supported by vendor quotes.

GRX-917 US GAD Sales Forecast: $2.5B Peak Revs ($3.5B Global)



Key Forecast Assumptions

- US GAD prevalence (2029): 10.8m
- US GAD treated patients (2029): 4.9m
- GRX-917 peak penetration:
  - First line treatment: 10%
  - Uncontrolled patients: 20%
- GRX-917 peak patients on drug: 653k
- Average Rx per year: 4.7
- GRX-917 gross price per Rx: $623 at launch increasing 1.5% per year
- Gross to net discount: 30%
- US peak revenue: $2.5B
- Gross margin: 90%

Source: Rosenblatt Life Science

Key Executives

Decades of successful leadership, clinical development, and commercialization in pharma and biotech

Mario Saltarelli, M.D., Ph.D.
Chief Executive Officer,
Director

Richard Farrell
Chief Financial Officer,
Director, & Founder

Kathryn King, Ph.D.
Chief Operating Officer

Mary Szela
Commercial Consultant

David Putnam, Ph.D.
Chief Scientific Officer

Olivier Dasse, Ph.D.
Senior VP of Chemistry

Pfizer
Abbott
Shire
Johns Hopkins School of Medicine

EY
Deloitte.

Abbott
abbvie
Takeda
APTINYX

Abbott
abbvie
TriSalus Life Sciences
melinta therapeutics

Roche
ucb

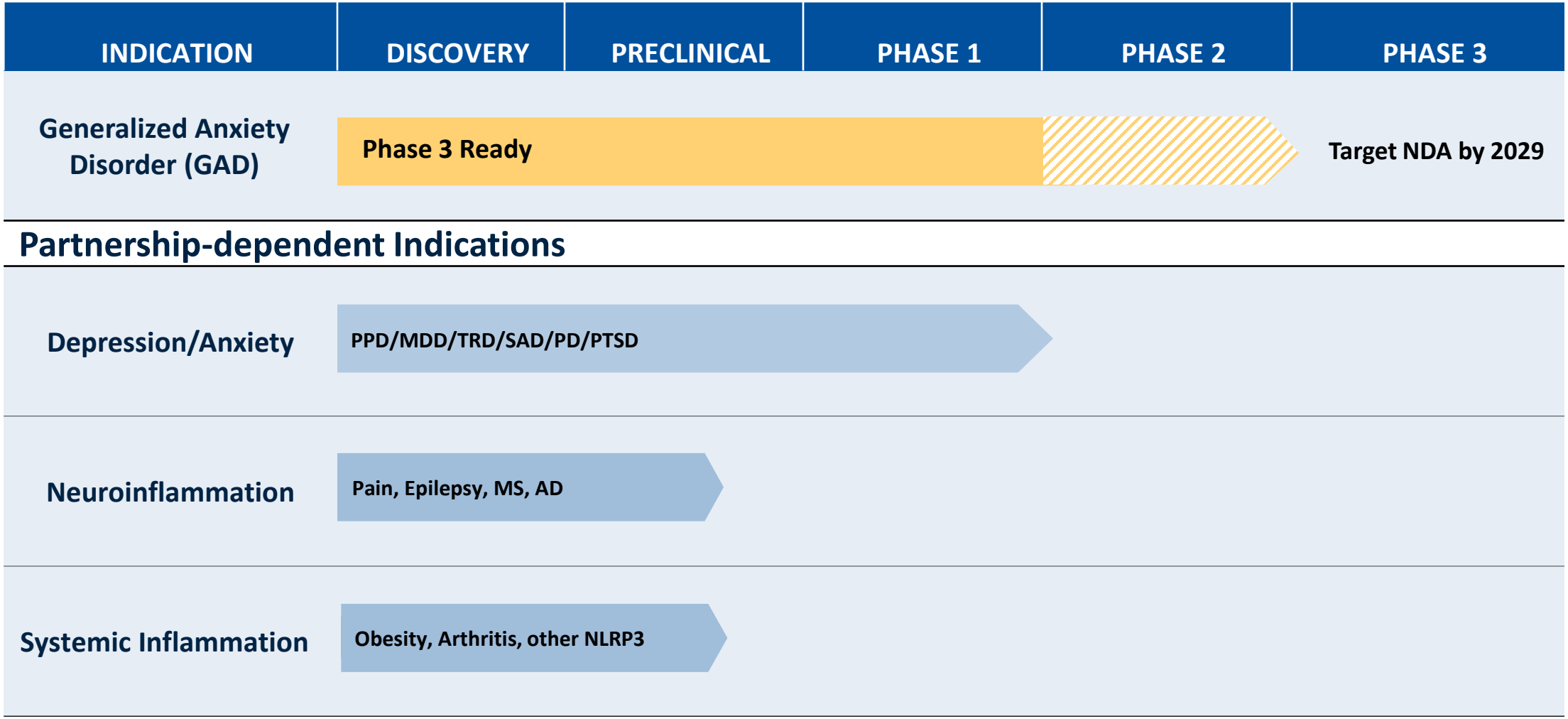
ucb

Appendix

- Additional Indications
- ETX and GRX have Identical Pharmacology / Metabolite Profile

GRX-917: Pipeline-in-a-Drug

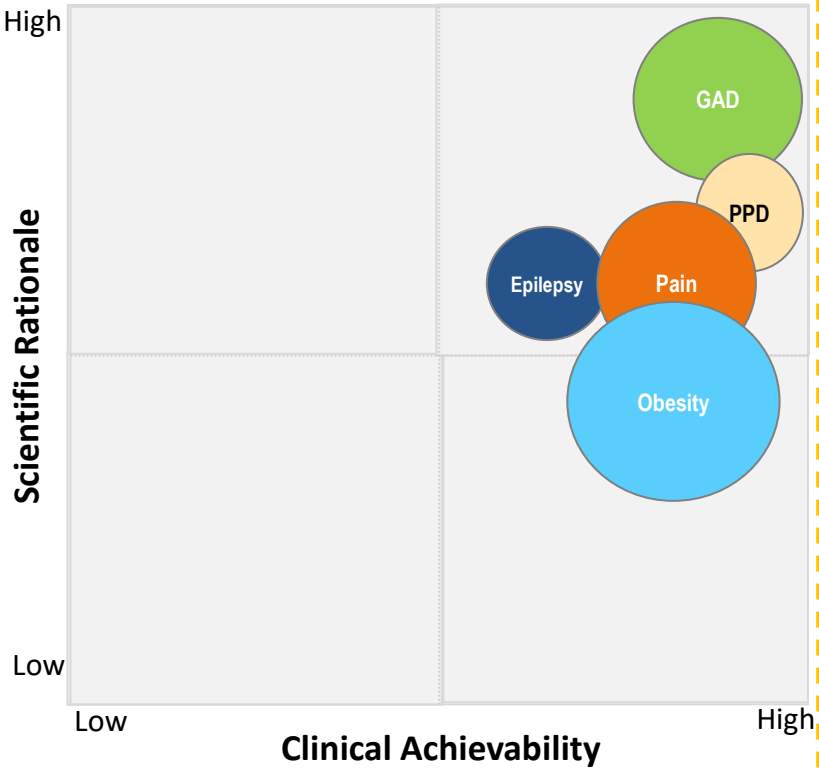
De-risked indications ready to begin clinical trials



Derisked by MOA, preclinical, and/or clinical efficacy

GRX-917 Additional Indications Strategy

Phase 2 ready for multiple blockbuster indications beyond GAD



Market size.

PPD/MDD/TRD	• Validated by neurosteroid MOA and zuranolone efficacy in PPD/MDD/TRD • Improved safety/tolerability and suitable for chronic use (vs. zuranolone) • Established development and regulatory pathways
Pain	• Broad-spectrum analgesic efficacy demonstrated in multiple animal models • Non-addictive, non-opioid oral analgesic with minimal side effects • Potential "Pipeline in a product" similar to gabapentin - efficacy in pain, anxiety, and epilepsy – with improved side effect profile.
Epilepsy	• GRX-917 and ETX exhibit potent antiepileptic activity in acute seizure models • Similar efficacy profile to neurosteroid analogs (ganaxolone) and GABA modulators, yet with improved safety/tolerability index • Potential use in temporal lobe, Dravet, and other inflammatory epilepsies • NIH/NINDS collaboration will confirm specific indications
Obesity	• ETX produced semaglutide-like weight loss in a mouse obesity model • Normalized inflammatory cytokines and dyslipidemia in animal models • MOA – Inhibition of brain NLRP3 inflammation pathway • Potential for monotherapy or combo therapy with GLP-1R agonists, without AEs

GRX-917 Effects in Acute & Chronic Seizure Models

Broad-spectrum anti-epileptic efficacy confirmed at tolerated doses

ETSP GRX-917 Data

March/April 2026

	Maximal Electroshock (acute generalized seizure model)	**6 Hz Test** (acute focal seizure model)	**Corneal Kindled Mouse** (chronic focal seizure model)
Antiseizure Activity	75, 100, 150 mg/kg	85, 100, 200 mg/kg	25, 50, 100, 150 mg/kg
ED_{50}	86.6 mg/kg	104 mg/kg	81.5 mg/kg
TD_{50} (Rotarod)	183.9 mg/kg	138.3 mg/kg	Not reported
Protective Index	2.1	1.3	Not reported

GRX-917 Rationale in PPD & MDD

Zuranolone Approved in PPD (14-days only)

GRX-917 Rationale in PPD & MDD

- Mechanism of action – allopregnanolone $GABA_A$ PAM activity
- Efficacy and approval of both brexanolone and zuranolone for PPD
- Efficacy of zuranolone in MDD (see next slide)

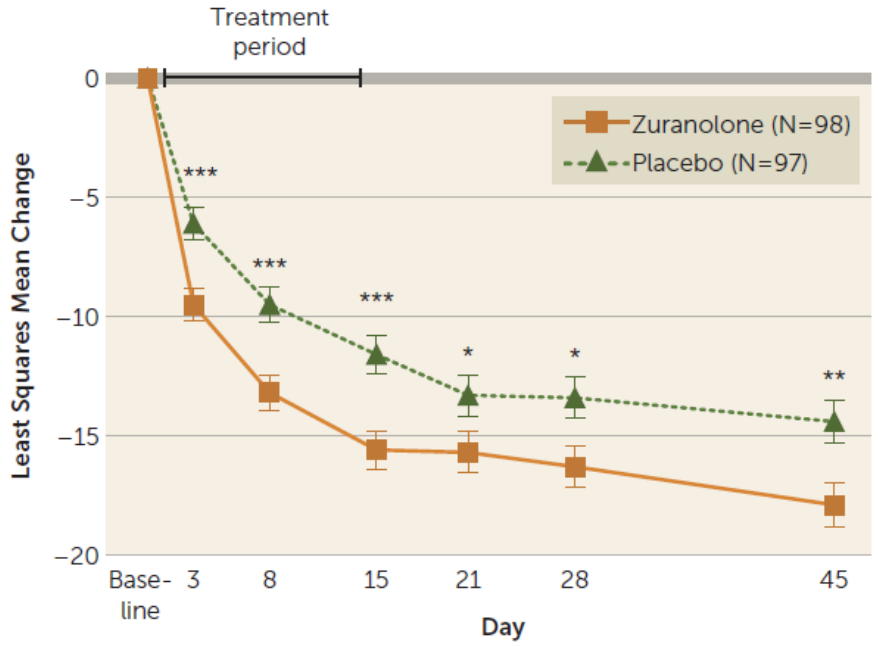
Depression Rationale	Zuranolone (ZURZUVAE®)	GRX-917/ETX
Administration	Exogenous Allo analog	Endogenously produced Allo
Regional Selectivity	None (all brain regions)	Regionally specific (hippocampus, amygdala, cortex)
Max Dose	50mg due to safety concerns	No MTD (Phase 1)
Duration	14 days due to safety concerns	Chronic

GRX-917 Superior Profile in PPD & MDD

- No dose limitations due to wide therapeutic index
- Ability to dose chronically vs. 14-days
- Minimal adverse events vs. blackbox
- Lack of abuse potential and scheduling
- Potential for enhanced efficacy due to above

Zuranolone for the Treatment of Postpartum Depression (Phase 3)

FIGURE 2. Change from baseline in HAM-D score in a placebo-controlled trial of zuranolone 50 mg/day for postpartum depression (full analysis set)[a]



[a] The primary endpoint was change from baseline in score on the 17-item Hamilton Depression Rating Scale (HAM-D) at day 15, and the key secondary endpoints included change from baseline in HAM-D score at days 3, 28, and 45. Multiplicity was accounted for when analyzing primary and key secondary endpoints. All other secondary endpoints were not adjusted for multiplicity and are to be interpreted with nominal p values. Error bars indicate standard error. *p<0.05. **p<0.01. ***p<0.001.

https://psychiatryonline.org/doi/10.1176/appi.ajp.20220785

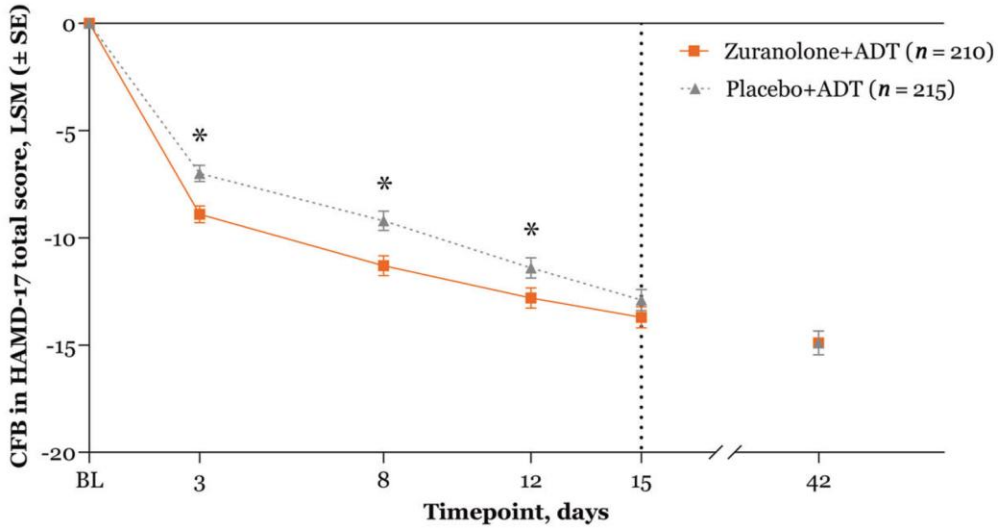
GRX-917 MDD/TRD Rationale

Zuranolone demonstrates efficacy in MDD

Phase 3 CORAL Zuranolone MDD[1]

Outcome

Rapid, statistically significant reductions in HAMD-17 observed by day 3
Efficacy not sustained following cessation of dosing on Day 14

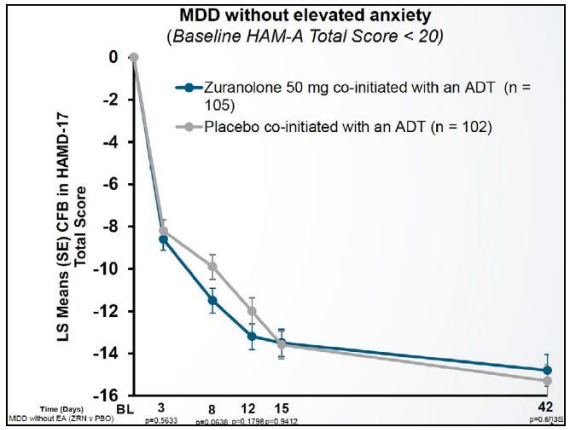


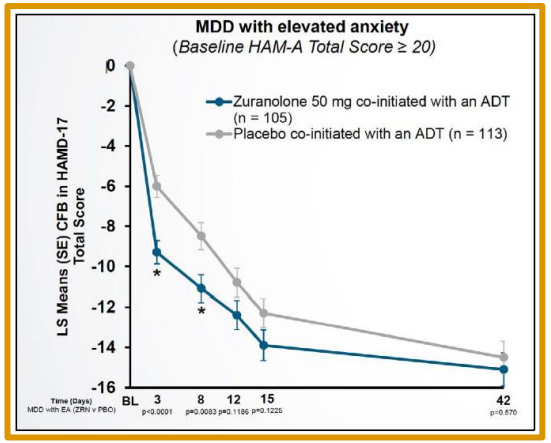
Phase 3 CORAL Study Design

- Ph3, randomized, double-blind, parallel-group, placebo-controlled
- Baseline HAMD-17 Total Score ≥ 24 (potentially TRD)
- Zuranolone 50 mg vs. placebo (plus open label ADT) x 14 days

CORAL Post-hoc Analysis

Presence of comorbid anxiety symptoms (HAM-A total score ≥ 20) confers rapid (3 days), enhanced treatment response





Opportunities for GRX-917 in MDD/TRD

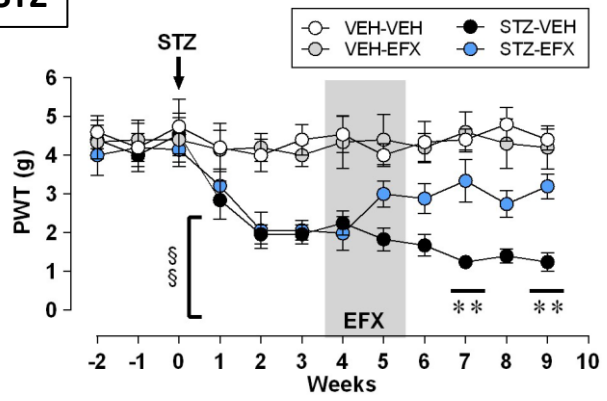
- Treatment of co-morbid anxiety and depression
- Dose escalation
- Chronic dosing
- Monotherapy

1) Sage Therapeutics CORAL study (NCT04476030) of adjunctive use of Zuranolone (SAGE -217) in MDD
https://doi.org/10.1038/s41386-023-01751-9

Etifoxine Demonstrates Broad Spectrum Efficacy in Rodent Pain Models

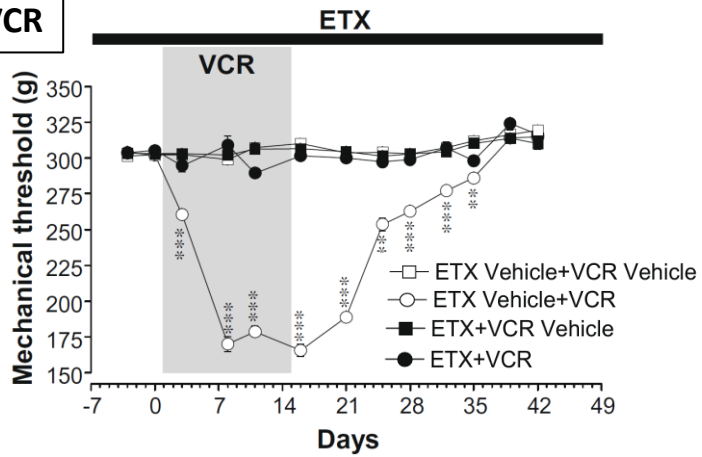
Supports human efficacy in neuropathic, diabetic, and inflammatory pain

STZ



The non-benzodiazepine anxiolytic etifoxine limits mechanical allodynia and anxiety-like symptoms in a mouse model of streptozotocin-induced diabetic neuropathy
Gazzo et al., PLOS ONE 2021
https://doi.org/10.1371/journal.pone.0248092

VCR



Reduction and prevention of vincristine-induced neuropathic pain symptoms by the non-benzodiazepine anxiolytic etifoxine are mediated by 3α-reduced neurosteroids
Aouad et al, Pain 2009
DOI: 10.1016/j.pain.2009.08.001

Profound analgesic efficacy across all pain models

- Rapid onset, complete in sciatic cuff
- Sustained following dosing cessation
- Pretreatment blocks development of pain (VCR)

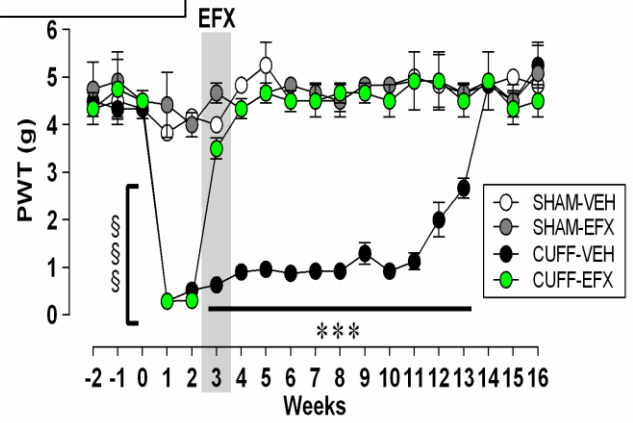
Etifoxine reduces mechanical allodynia in rodent pain models

- mononeuropathy model (Sciatic Cuff)
- inflammatory pain model (CFA)
- streptozotocin diabetic neuropathy (STZ)
- vincristine toxic neuropathy (VCR)

Etifoxine's analgesic efficacy is associated with

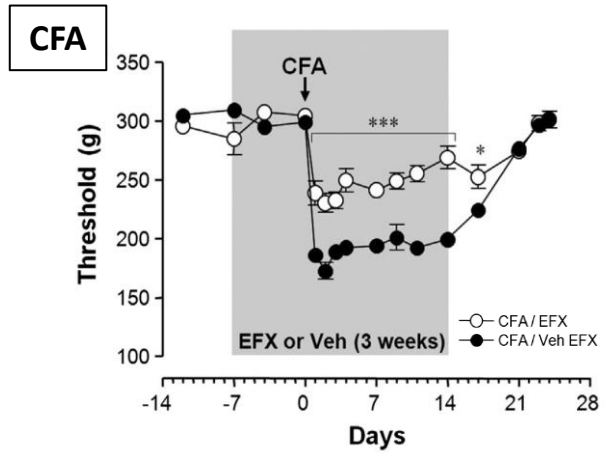
- Increased spinal cord ALLO levels
- Reversal by neurosteroid synthesis inhibitors (e.g. finasteride)
- Marked reductions in NLRP3 inflammatory cytokines, including IL-1B
- Reduced anxiety in animals

Sciatic Cuff



Long-lasting analgesic and neuroprotective action of the non-benzodiazepine anxiolytic etifoxine in a mouse model of neuropathic pain
Kamoun et al. Neuropharmacology 2021.
https://www.sciencedirect.com/science/article/abs/pii/S0028390820304755

CFA



Etifoxine analgesia in experimental monoarthritis: A combined action that protects spinal inhibition and limits central inflammatory processes Aouad et al 2014
http://dx.doi.org/10.1016/j.pain.2013.11.003

Etifoxine Weight Loss Comparable to Semaglutide

Phase 2 Ready in Obesity

Obese High Fat Diet Model

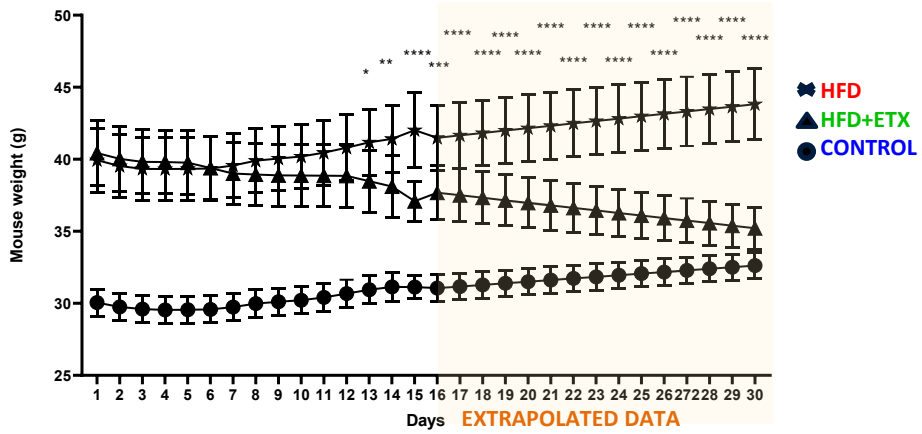
Mechanism of Action in Obesity:

- Obesity is an NLRP3-driven neuroinflammatory disease
- Etifoxine is a brain-penetrant inhibitor of TLR/NF-kB/NLRP3/IL-1β pathway

1

Etifoxine induced 11% weight loss in 15 days, comparable to:

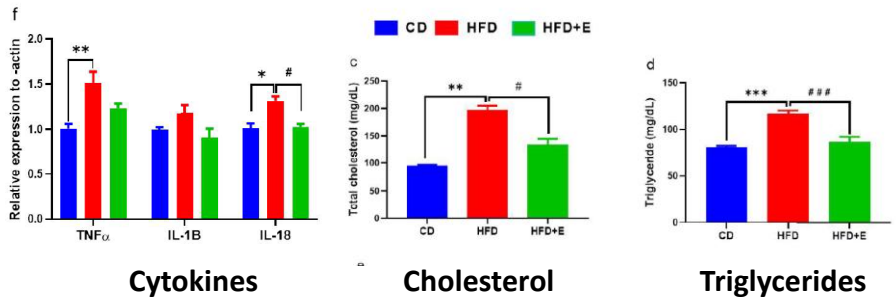
- Semaglutide
- Brain-penetrant NLRP3 inhibitors (e.g. NT-0796)



2

Etifoxine normalized:

- Proinflammatory markers (IL-18, IL-1β, TNFα)
- Serum lipids (cholesterol, triglycerides)



1) Ibrahim, K. S., Craft, J. A., Biswas, L., Spencer, J., & Shu, X. (2020). Etifoxine reverses weight gain and alters the colonic bacterial community in a mouse model of obesity. *Biochemical Pharmacology*, *180*, Article 114151. https://doi.org/10.1016/j.bcp.2020.114151

Potential Additional Therapeutic Indications

NLRP3/IL-1Beta Inflammatory Diseases

Neuroinflammatory Diseases	Systemic Inflammatory Diseases	Cardiometabolic Diseases
Anxiety	Rheumatoid arthritis	Obesity
Depression	IBD	MASH
Epilepsy Seizures	OA	NAFLD
Pain	Gout	Atherosclerosis
Neuropathy	Asthma	Diabetes
Multiple sclerosis	Systemic juvenile idiopathic arthritis	
Alzheimer's disease	Still's disease	
Parkinson's disease	Psoriasis	
Traumatic brain injury	SLE	
ALS	Endometriosis	
	Cystic fibrosis	
	Hidradenitis suppurativa	
	Lupus nephritis	

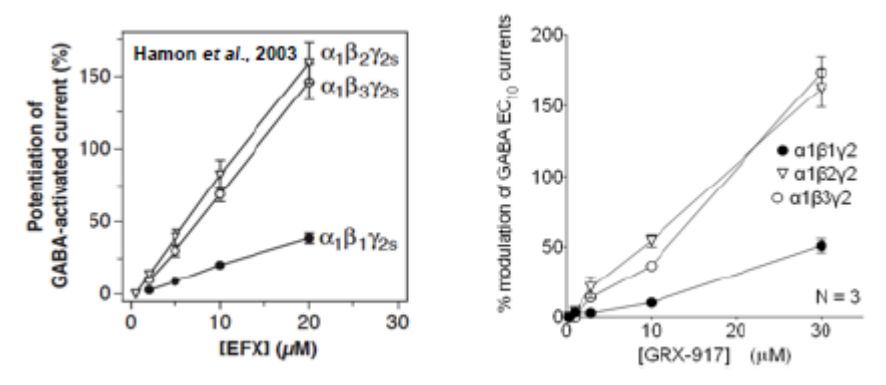
Efficacy Supported by Etifoxine Preclinical Data

Deuterated Etifoxine (GRX-917) & Etifoxine

Identical Anxiolytic Activity, MOA and Pharmacology

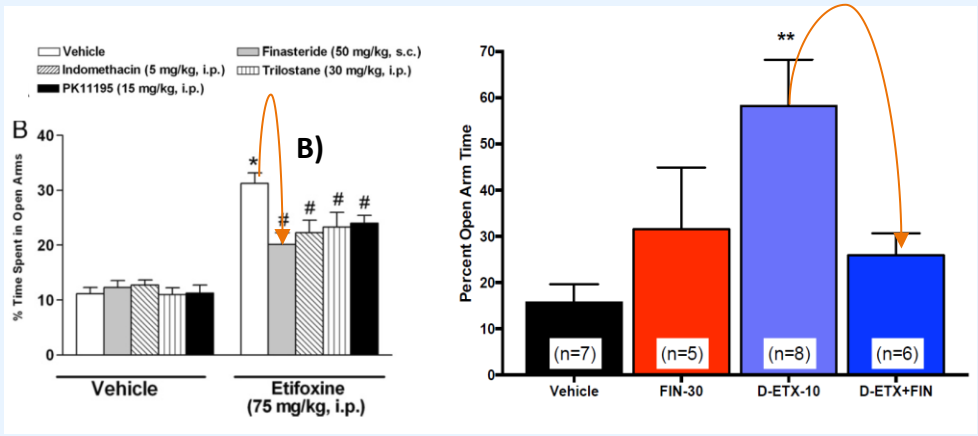
Identical GABA-A Channel Activity

ETX and GRX-917 show the same profile for β2/3-subunit-containing $GABA_A$ receptors.



Identical Induction of Neurosteroid MOA

ETX and GRX both increase % time in open arm in EPM which is reversed by 5-alpha reductase inhibitor (finasteride)



Ugale, R. *et al.* Brain research 1184 (2007), 193-201

Finasteride 30 mg/Kg i.p., GRX-917 10 mg/Kg i.p.

Comparative Data Shows GRX = ETX Across Multiple Preclinical and Clinical Data Sets

Clinical Evidence

- Superior human safety and tolerability (lack of GABA AEs)
- Wide therapeutic index
- qEEG Beta power increase – PD marker for GABA-A target engagement
- Absence of qEEG Alpha power decrease
- Same metabolite profile –M4 only major metabolite (inactive)

Preclinical Pharmacology and MOA Evidence

- Equivalent in vitro receptor binding profile (CEREP screen)
- Equivalent EPM activity
- Same neurosteroid MOA (as confirmed by finasteride reversal)
- Maximal electroshock seizure model activity
- Identical GABA-A channel profile in vitro

Chemical Structure Evidence

- Identical chemical structures (except for deuterated hydrogens)

Deuterated Etifoxine (GRX-917) & Etifoxine

Identical Metabolite Profiles

The same metabolites were produced in the same ratios by both molecules but in lower overall amounts for deuterated etifoxine.

Major metabolites (Mass shift only) of Etifoxine and GRX-917 incubated with human liver microsomes in the presence of NADPH (0 min or 60 min)

Etifoxine					
Peak ID	Mass Shift	Found m/z	R.T. (min)	UV absorption*	MS peak area
				HLM (60 min)	
Parent (0min)	0	301	4.98	100.00%	3.45E+05
Parent (60 min)	0	301	4.98	13.55%	9.86E+04
M1	-18	283	4.37	+	2.03E+03
M2	-12	289	4.66	+	5.37E+03
M3	+16	317	4.72	+	3.08E+04
M4	-28	273	4.74	50.81%	2.42E+05
M5	+16	317	4.99	+	2.09E+03

GRX-917					
Peak ID	Mass Shift	Found m/z	R.T. (min)	UV absorption*	MS peak area
				HLM (60 min)	
Parent (0min)	0	306	4.98	100.00%	3.12E+05
Parent (60 min)	0	306	4.98	31.31%	1.41E+05
M1	-18	288	4.37	+	4.47E+03
M2	-17	289	4.66	+	2.33E+03
M3	+15	321	4.72	+	1.15E+04
M4	-33	273	4.74	35.69%	1.60E+05
M5	+16	322	4.99	+	7.34E+03

*All percentages were calculated based on the detected UV absorption relative to that of parent in T_{0min} samples (normalized as 100%)
+: only detected in MS