ENX-102 Demonstrates Central Target Engagement as a Gamma-aminobutyric Acid Type A Alpha-2,3,5 Positive Allosteric Modulator in a Phase 1b Multiple Ascending Dose Clinical Study in Healthy Volunteers

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Background

ENX-102 is a gamma-aminobutyric acid type A receptor (GABA-AR) positive allosteric modulator (PAM) that enhances inhibitory neurotransmission. By agonizing GABA-AR containing alpha-2,3,5 subunits and blocking alpha-1 subunits, ENX-102 may demonstrate anxiolysis clinically, while avoiding untoward sedative, psychomotor, and cognitive effects associated with non-selective GABA-A-PAMs such as benzodiazepines (BZDs).

Methods

- Randomized, double-blind, placebo-controlled, multiple ascending dose
- ENX-102: 0.5 – 5.0 mg (or placebo) administered orally once daily for 12 days
- Healthy female and male volunteers (N=40)

Primary objective: safety and tolerability of ENX-102
Secondary objective: PK and PD characterization
(Mixed model analyses of covariance)

Results

Safety: no clinically meaningful changes.
85% of adverse events (AEs) were mild; all were transient.
No difference from placebo in clinician-observed sedation.

ENX-102 Most Frequent AEs

Adverse Event n (%)	Placebo (N=10)	0.5 mg (N=6)	1.0 mg (N=6)	1.5 mg (N=6)	2.0 mg (N=6)	5.0 mg (N=6)
Somnolence	5 (50.5%)	6 (100%)	5 (83.3%)	5 (83.3%)	6 (100%)	5 (83.3%)
Fatigue	4 (40.0%)	5 (83.3%)	5 (83.3%)	6 (100%)	5 (83.3%)	5 (83.3%)

Pharmacokinetics (PK): dose proportional exposure.

Summary of Steady State PK Parameters

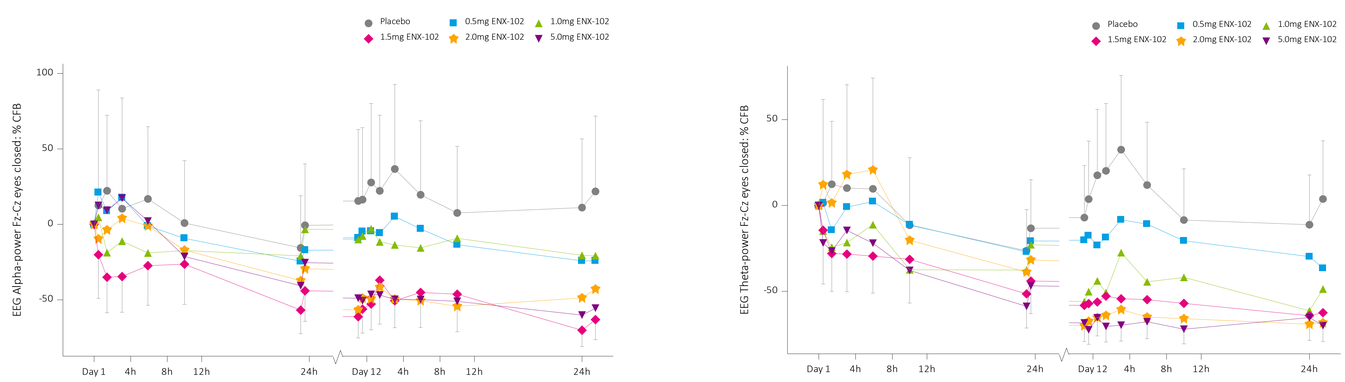
Parameter	0.5 mg	1.0 mg	1.5 mg	2.0 mg	5.0 mg
C_{max} (ng/mL)	11.66	23.33	41.70	49.82	99.12
AUC_{tau} (ng*h/mL)	197.54	410.07	705.65	873.17	1803.45
T_{max} (h)	3	3	3	3	3
$t_{1/2}$ (h)	66	61	51	61	39

Pharmacodynamics (PD): target engagement.
No untoward effects with repeated administration.

Result	Putative interpretation	ENX-102 Treatment Effect*
↓ SPV	Decrease indicates reduced arousal $GABA_A$ $a_{2,3}$ target engagement	P< 0.05
- VAS alertness	Decrease indicates impaired subjective alertness	p=0.342
- Adaptive tracking	Decrease indicates impaired sustained attention	p=0.394
- Body sway	Increase indicates impaired postural balance	p=0.192
- VVLT Immediate recall	Decrease indicates impaired encoding	p=0.307
- VVLT Delayed recall	Decrease indicates impaired retrieval	p=0.345
- VVLT Delayed recognition	Decrease indicates impaired consolidation	P=0.206

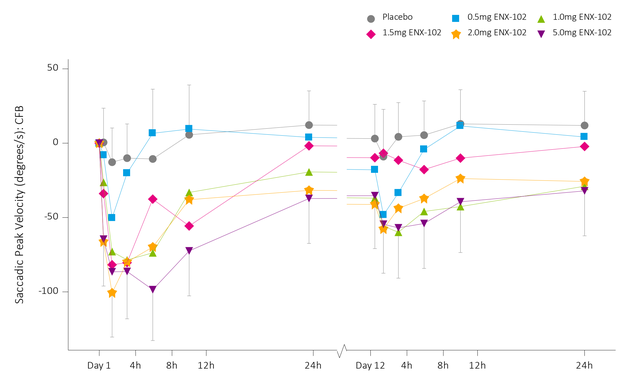
SPV=saccadic peak velocity; VAS= visual analog scale; VVLT=Visual Verbal Learning Task
*p-value refers to the entire dosing period of 12 days

Pharmacodynamic results
Figure 1: ENX-102 significantly decreased qEEG alpha-power (p<0.05*) and theta-power (p<0.05*), indicating sustained reduced arousal.



Percent change from baseline (CFB) in qEEG alpha-power and theta-power (Fz-Cz; eyes closed)

Figure 2: ENX-102 significantly decreased SPV (p=<0.05*), consistent with an anxiolytic-like profile.



Change from baseline (CFB) in SPV(degrees/s)

Conclusions

- ENX-102 was safe and well-tolerated following repeated dosing in healthy subjects.
- Its PD profile demonstrated central target engagement indicative of sustained reduced arousal, consistent with an anxiolytic-like pharmacodynamic profile.
- ENX-102 lacked untoward effects on alertness, psychomotor function, or memory, a pattern distinct from GABA-AR non-selective BZDs in humans.

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Disclosures: KEV, SP, and ET are full-time employees of Engrail Therapeutics and may hold stock or stock