# Safety, target engagement, and pharmacodynamic biomarker profile of single ascending doses of ENX-104, a potent $D_2/D_3$ receptor antagonist in development for the treatment of Major Depressive Disorder characterized by anhedonia

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## Introduction

- ENX-104 is a novel selective dopamine (DA) receptor antagonist with differential binding affinities for $D_2$ and $D_3$ receptors.
- ENX-104, at low doses, has been shown to increase striatal DA levels in preclinical studies through preferential blockade of presynaptic $D_2/D_3$ autoreceptors[1], representing a potential new therapeutic modality for the treatment of Major Depressive Disorder (MDD) associated with anhedonia.
- The objective of this First-in-Human study was to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending oral doses of ENX-104 in healthy participants.

[1]Vadodaria, K. C., Serrats, J., Brubaker, W., Kangas, B. D., Pizzagalli, D. A., Garvey, D. S., ... & Vanover, K. E. (2025). ENX-104: a selective and potent D2/D3 receptor antagonist enhances dopamine neurotransmission and reward responsiveness in translational rodent models. Neuropsychopharmacology, 1-9.

## Methods

- Randomized, double-blind, placebo-controlled, single ascending dose study in 46 healthy male and female participants.
- ENX-104:placebo (6:2) per cohort. Placebo (N=11) and ENX-104 orally at 5 different rising dose levels: dose 1 (N=6), dose 2 (N=11), dose 3 (N=6), dose 4 (N=6) and dose 5 (N=6).

- **Safety:** Treatment emergent adverse events (TEAEs), labs, electrocardiograms (ECGs), vital signs, physical and neurological examinations, and extrapyramidal symptom scales (EPS; Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, Modified Simpson-Angus Scale) up to 48h post-dose.
- **Pharmacokinetics (PK):** Pre-dose through 48h post-dose; PK parameters analyzed by non-compartmental analysis.
- **Pharmacodynamics (PD):**

  *Peripheral target engagement:* Serum prolactin.

  *Central target engagement:* NeuroCart test battery (Saccadic Peak Velocity, Visual Analogue Scales (VAS) [Bowdle, Bond and Lader], Adaptive Tracking, Body Sway, Alternate Side Tapping) analyzed by mixed model analyses of covariance.

## Results

### Safety

- No serious or severe TEAEs; all TEAEs mild except one (moderate gastroenteritis; deemed unrelated to ENX-104).
- TEAEs: lower incidence with ENX-104 vs placebo (62.9% vs 81.8%); no dose-response observed.
- Most common TEAEs in ENX-104 groups (>2 and more than placebo): tremor (N=6), and dizziness (N=3).
- No clinically significant changes in labs, vital signs, ECGs, physical exams or on EPS scales.

### Pharmacokinetics

- Linear, dose-dependent exposure.
- Short plasma half-life.

## Results (continued)

### Pharmacodynamics: Peripheral Target Engagement

Prolactin

- ENX-104 significantly increased serum prolactin compared with placebo.
- Dose-dependence was observed.
- Peak concentrations occurred between 1.5 – 4h post-dose; returned to baseline by 12h post-dose.

### Pharmacodynamics: Central Target Engagement

NeuroCart

- ENX-104 decreased adaptive tracking (representing sustained attention and/or fine motor skills) compared with placebo between dose 3 and dose 5; this effect was statistically significant and dose dependent ≥ dose 3. Decreases were evident for up to 24h (and up to 48h for dose 5).
- No systematic effects were observed on smooth pursuit (visuomotor coordination); body sway (postural balance); alternate side tapping (fine motor skills); VAS Bond and Lader (mood & calmness); VAS Bowdle (subjective drug effects).


## Conclusions

- Single oral doses of ENX-104:
  - were safe and well tolerated,
  - showed linear kinetics and a favorable PK profile with a relatively short plasma half-life,
  - transiently increased serum prolactin, confirming peripheral $D_2/D_3$ target engagement with a time course that followed plasma PK,
  - decreased adaptive tracking, consistent with long lasting central postsynaptic $D_2/D_3$ receptor antagonism, an effect outlasting plasma half-life.
  - demonstrated divergent time course trajectories of prolactin and adaptive tracking data, potentially illustrating the uncoupling of ENX 104's peripheral versus central PD effects, respectively.
- Together, these data support continued investigation of ENX-104 for the treatment of MDD characterized by anhedonia.