Mechanistic Pharmacokinetic/Pharmacodynamic Modeling of Neuroactive Steroids in Essential Tremor

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Disclaimers

Dr. Nguyen is an employee of Sage Therapeutics, Inc. with stock/stock options.

Zuranolone (SAGE-217) and SAGE-324 are investigational compounds and are not approved for any use.

Brexanolone injection is approved for the treatment of postpartum depression (PPD) in adults by the United States Food and Drug Administration. It is not approved for the treatment of essential tremor or any other use.
Essential Tremor: Epidemiology, Treatment, and Burden of Illness

- Essential Tremor (ET) is the most prevalent movement disorder; estimated to affect approximately 6.4 million (CI 4.6-7.6M) adults in the United States.¹

- The most common ET pharmacologic treatments consist of primidone (an anti-convulsant) and propranolol (a β-adrenergic blocker).²³
  - Propranolol was approved by the FDA for treatment of ET in 1967.³
  - No new medications have been approved specifically for ET since propranolol.³

- Approximately, 50% of treated patients do not respond or have sub-optimal response to standard of care treatments.⁴⁵
  - Approximately 33% of patients abandon pharmacologic treatments for ET.⁶

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Mild
Difficulty with fine motor tasks that require precision

Moderate
Difficulty with everyday tasks

Severe
Significant impairment in activities of daily living and independence

Decreasing ability to:
- Work
- Do chores/yardwork
- Use a phone
- Write
- Cook
- Use transportation
- Walk
- Take medication
- Get dressed
- Self-care
- Drink
- Eat

GABAergic Signaling is Implicated in the Etiology of Essential Tremor

- ET is associated with reduction in GABAergic tone in the cerebellum and thalamus, hypothesized to result from neurodegenerative changes.¹
- Reduced GABA levels have been measured in cerebrospinal fluid in ET patients.²
- Postmortem analysis of ET patients found a reduction of 35% in GABA₄ receptors (GABA₄Rs).³
- Drugs acting on GABA₄Rs, such as primidone, benzodiazepines, and ethanol, decrease tremor amplitude.¹,⁴

GABA_A Receptors Mediate both Phasic and Tonic Inhibition

Neuroactive Steroid $\text{GABA}_A$ Receptor Positive Allosteric Modulators are Pharmacologically Distinct From Benzodiazepines

- Neuroactive steroids can be positive allosteric modulators (PAMs) of synaptic and extrasynaptic $\text{GABA}_A$Rs.\(^1\)

- Neuroactive steroids bind at $\alpha$-$\beta$ subunit interfaces and are pharmacologically distinct from benzodiazepines, which bind the interface of $\gamma_2$ subunit and $\alpha_1$-$3$ and $\alpha_5$ (synaptic receptors only).\(^1\)-\(^4\)

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Sage Neuroactive Steroid GABA<sub>A</sub>R PAMs: Brexanolone and Zuranolone

- Brexanolone is chemically identical to endogenous allopregnanolone, and has low oral bioavailability.
  - An intravenous formulation of brexanolone, was approved for the treatment of adult women with PPD by the United States Food and Drug Administration.

- Zuranolone is an investigational, oral GABA<sub>A</sub> receptor PAM, with pharmacokinetics suitable for once daily dosing.
  - Zuranolone is in clinical development in PPD<sup>1</sup> and MDD.<sup>2</sup>

- Early clinical development trials also examined brexanolone and zuranolone in ET.

SAGE-324: An Investigational Orally Bioavailable Neuroactive Steroid GABA_A R PAM

- SAGE-324 is a structurally distinct, novel, proprietary, oral, next-generation GABA_A R PAM that is differentiated from brexanolone and zuranolone. In particular, SAGE-324:
  - has a long clinical half-life (90-120 hours), making it possible to achieve plasma concentrations with minimal daily fluctuations after multiple doses. This PK profile would support chronic dosing.
  - shows potential as a therapy for neurological conditions, such as epilepsy, and Parkinson’s disease, and is currently being examined for the treatment of movement disorders with GABA-related etiology, such as ET.
  - preclinical data suggest substantial therapeutic index between efficacy and sedation.
  - in early clinical studies SAGE-324 was generally well-tolerated; all treatment emergent adverse events were mild or moderate in severity.

**Pharmacology Model Describing Relative Ability to Modulate In-Vivo Endpoints in Rodents**

**Potentiation of synaptic and extrasynaptic GABA_A Rs by SAGE-324\(^1\)**

Mechanistic PK/PD Modeling Framework

- **A.** Representation of total functional activity at the receptor level
- **B.** Transform GABA-A receptor level activity to network level activity
- **C.** Fit/Prediction to observed clinical result downstream from brain

**Zuranolone Clinical Data Sets:**
1. PK
2. EEG Biomarker
3. Tremor

**Translational Component**

**Mechanistic Model**

**Oral Dose**
SAGE
GABA
PAM

**Absorption Process**

**SAGE-PAM TOTAL PLASMA (ng/mL)**

**Motor Circuitry**
Brain Compartment

**GABA-R’s Functional Activation**

**Observed Efficacy Or Biomarker**

**Train Model**

**Preclinical Comparison**

**Predict SAGE-324 Clinical Response**
1. Simulate PK
2. Predict PK/PD of EEG
3. Predict PK/PD of Tremor

**Relative ability to modulate in-vivo endpoints in rodents**

**Plot:**
- Zuranolone
- SAGE-324

**Functional Activity** vs. **Total Plasma Concentration (ng/mL)**
Essential Tremor and EEG Studies to Date: Testing the Mechanistic PK/PD modeling approach.

**Brexanolone**
Phase 2 ET Study
- Crossover study
- (n = 50 patients)
- Randomized 1:1
- IV Infusion

**Zuranolone ET Studies**
Phase 1 Signal Finding Study in ET Patients
- Zuranolone Oral Solution
  - (n = 6 patients)
Phase 2 Study in ET Patients
- Zuranolone Oral Solid
  - (n = 24 patients)

**Zuranolone EEG Studies**
- Single Dose EEG Study (SAD)
- Multiday EEG Study (MAD)

**Mechanistic PK/PD Modeling**
1) Train model using Zuranolone Data
2) Compute pharmacological relationship between SAGE-324 and Zuranolone
3) Predict EEG and Tremor Reduction for SAGE-324

**SAGE-324 Phase 1 Studies**
EEG Studies
- SAD (n = 16 HVs)
- MAD (n = 36 HVs)

SAD ET Study
- (n = 20 ET Patients total; n = 11 modeled)

Timeline

GABA PLATFORM DATA → PK/PD MODEL → DEVELOP SAGE-324 HYPOTHESIS → TEST SAGE-324 HYPOTHESIS
SAGE GABA_\text{A}R PAMs Exhibited Predictable Pharmacodynamic Effects and Activity in Essential Tremor

- Zuranolone linear PK/PD model of EEG is estimated from observed responses, and suggests marked increases in $\beta$-EEG.

- After a single dose, both brexanolone and zuranolone demonstrated a reduction in tremor in ET patients as a function of plasma concentration, as measured by TETRAS, Total Upper Limb Subscale.
Target Engagement by SAGE-324 was Hypothesized Using a PK/PD Model Prediction

- Zuranolone linear PK/PD model of EEG was estimated from observed PK/PD responses.
- Utilizing the relative pharmacological profiles of SAGE-324 and zuranolone, we used a mechanistic PK/PD model to infer the potential PK/PD EEG relationship for SAGE-324.
Reduction in Tremor by SAGE-324 was Hypothesized Using a PK/PD Model Prediction

- Zuranolone mechanistic PK/PD model of tremor reduction was estimated from observed patient responses.

- Utilizing the relative pharmacological profiles of SAGE-324 and zuranolone, we extrapolated the mechanistic PK/PD model to generate a SAGE-324 specific hypothesis.
The SAGE-324 Target Engagement Model was Tested in a Phase I Study

- The black data points are observed PK/PD EEG responses from healthy volunteers in a dedicated EEG study in Phase 1 (n=16, healthy volunteers).

- Linear PK/PD Model is fit to the EEG observed data.

- The blue-dashed line represents the prediction made from the existing zuranolone EEG response as well as the relative pharmacological profile of zuranolone vs. SAGE-324.
The SAGE-324 Reduction in Tremor Model was Tested in a Phase I Study

- The black data points are observed PK/PD responses from ET patients (n=11) in an open label Phase 1 trial.

- The blue-dashed line represents the prediction made from the existing zuranolone Tremor Reduction response model as well as the relative pharmacological profile of zuranolone vs. SAGE-324.
Conclusions

• The observed EEG biomarker response of the investigational compound SAGE-324 was consistent with predictions made using the clinical EEG response from zuranolone in healthy volunteers, the relative non-clinical pharmacology profile of zuranolone vs. SAGE-324, and our mechanistic PK/PD model.

• Similarly, the observed tremor reductions with SAGE-324 were consistent with mechanistic PK/PD modeling predictions.

• We generated model-based hypotheses and the observations from a Phase 1 study with SAGE-324 were highly consistent with our model-based predictions, suggesting that mechanistic PK/PD modeling provides a powerful tool for investigating PK/PD relationships.

• Such models can be used to accelerate the development for SAGE-324 as well as future assets in the SAGE GABA platform.

• Interpretation of these findings should consider that these preclinical and early clinical studies are relatively small, and further investigation of SAGE-324 in ET is warranted.
Thank You