SAGE THERAPEUTICS

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Essential Tremor Exploratory Trial Results

September 3, 2015

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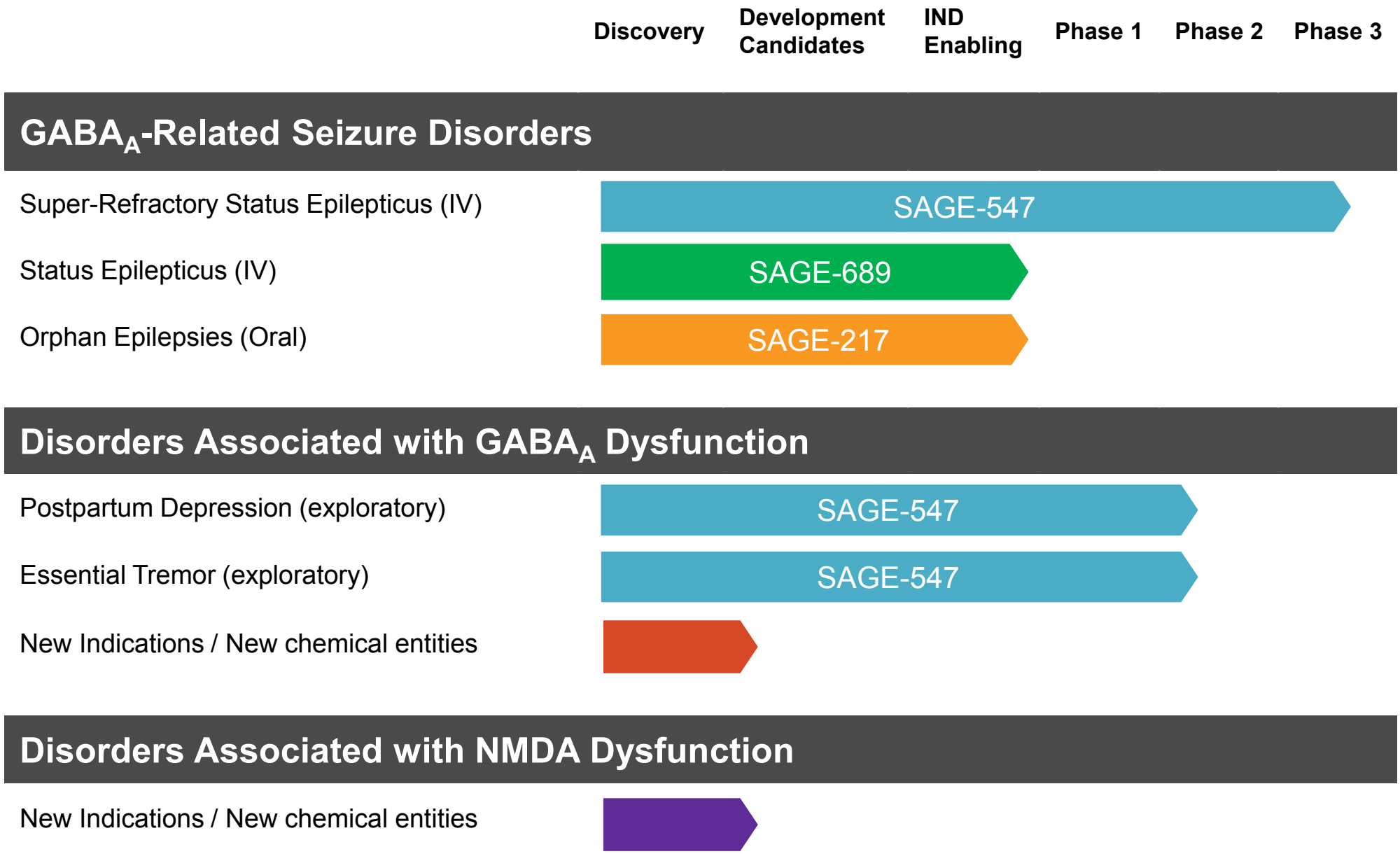
Building a Wholly-Owned Multi-Product Portfolio



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Using Human Data to Accelerate Development of Selected Candidate Molecules

- SAGE internal library has thousands of molecules with established mechanisms
- Well characterized IV agent enables quick readout if indications chosen wisely
- Signal-finding studies may be small, efficient and easily interpretable without major powering considerations (unlike conventional Phase 2 programs)
- Approach streamlines and accelerates development of NCEs; no NCE required for initial determination - data can guide NCE selection
- Positive data >>>→ develop; negative data >>>→ program elimination
- Signal-finding activity already accomplished in 2 proof-of-concept studies

SAGE strategy of leading with human data can accelerate and enhance development of NCEs for new indications

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Essential Tremor: Debilitating Neurological Disorder

- Involuntary, rhythmic shaking with no known cause[1]
- Affects ~10 million in U.S. and millions more worldwide[2]
  - Significant proportion are undiagnosed and untreated[3]
- Current treatments only moderately effective, reducing (not resolving) tremor amplitudes in ~50% of patients[4]
  - Common treatments include primidone, propranolol, gabapentin and benzodiazepines[5]
  - 1 out of 3 patients abandons treatment due to side effects or poor efficacy[6]
  - 1 out of 4 patients who seek treatment are forced to quit their profession[7]

Footnotes:

[1] NINDS Tremor fact sheet, http://www.ninds.nih.gov/disorders/tremor/detail_tremor.htm

[2, 3] International Essential Tremor Foundation website, http://www.essentialtremor.org/about-et/

[4] Thanvi et al., 2006, Gironell 2007

[5] Zesiewicz et al., 2002, 2005; Benito-Leon and Louis, 2006, 2007

[6] Louis et al, 2010

[7] Rautakorpi, 1978; Bain et al., 1994

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Study Design

- Exploratory study evaluating $GABA_A$ mechanism of action as treatment for essential tremor
- Designed for signal detection and to inform development methodology for second-generation oral SAGE molecule for chronic treatment
- Evaluate safety, tolerability, PK and efficacy of SAGE-547 mechanism

Stage 1

- 25 patients
- Randomized, double-blind, placebo-controlled crossover
- Dose-escalating step-up infusion to target steady state dose
- Tremor amplitude and frequency measured by TETRAS and accelerometer
- 30-day safety follow-up

Stage 2

- 17 patients returning from Stage 1
- Open-label, single-arm
- Dose-escalating step-up infusion to target steady state dose
- Tremor amplitude and frequency measured by TETRAS and accelerometer
- 30-day safety follow-up

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Inclusion Criteria

- Adults between 35-75 years of age
- Diagnosis of essential tremor, with symptoms clearly present in at least one upper limb confirmed by TETRAS
- Tremor present for at least two years prior to screening
- Off medication, or on a stable dose of medication, for at least 28 days prior to screening

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Trial Demographics

All Patients	Total (N=25)
Males / Females	10 / 15
Mean Age	64.2
Age Range	54-73
Race	
Caucasian	22 (88%)
Other	2 (8%)
African-American/African	1 (4%)

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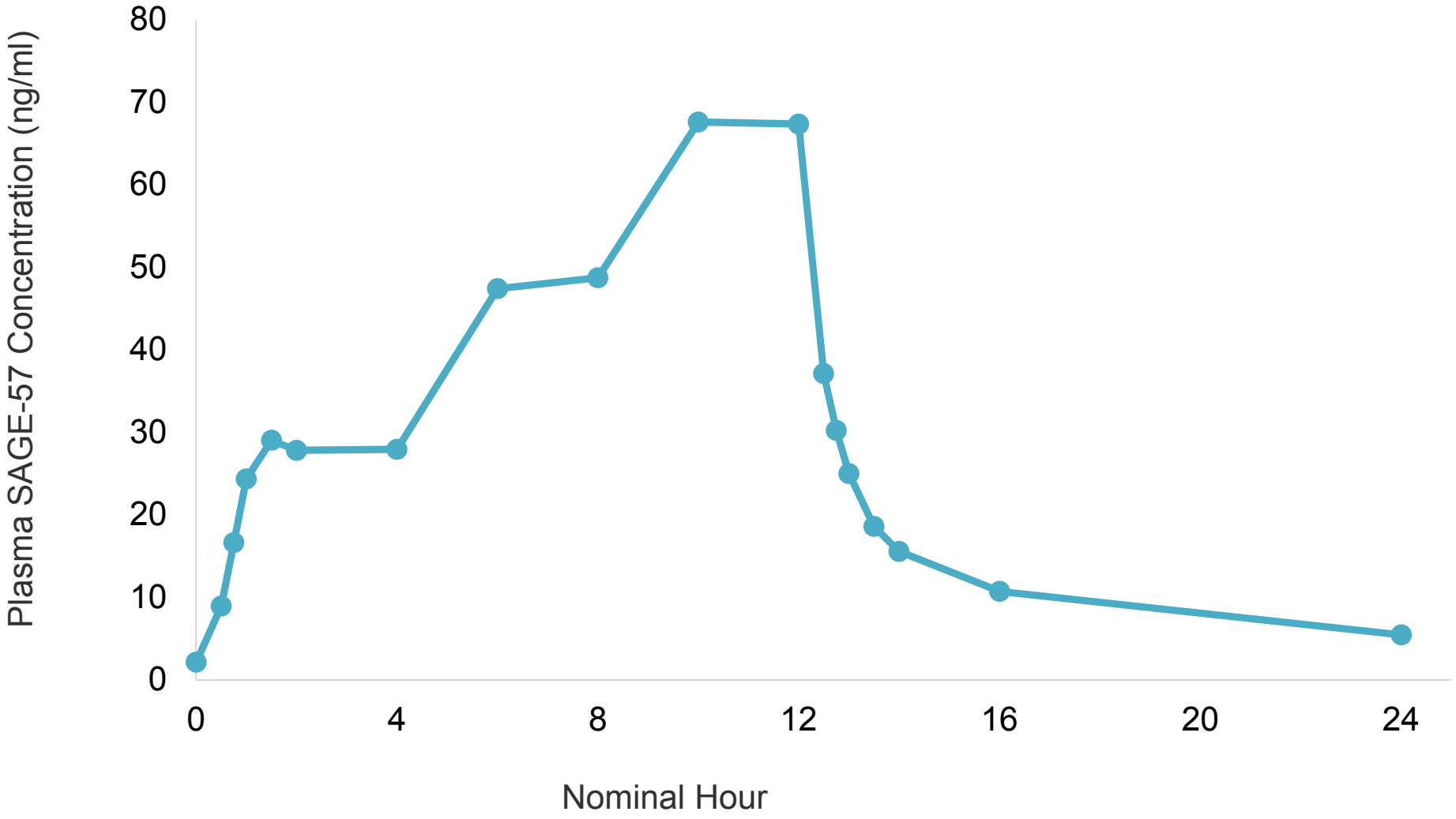
SAGE-547 Exposure in Placebo-Controlled Stage 1 Correlates to Peak Therapeutic Activity

Mean Concentration-Time Plot (All patients, n=25)



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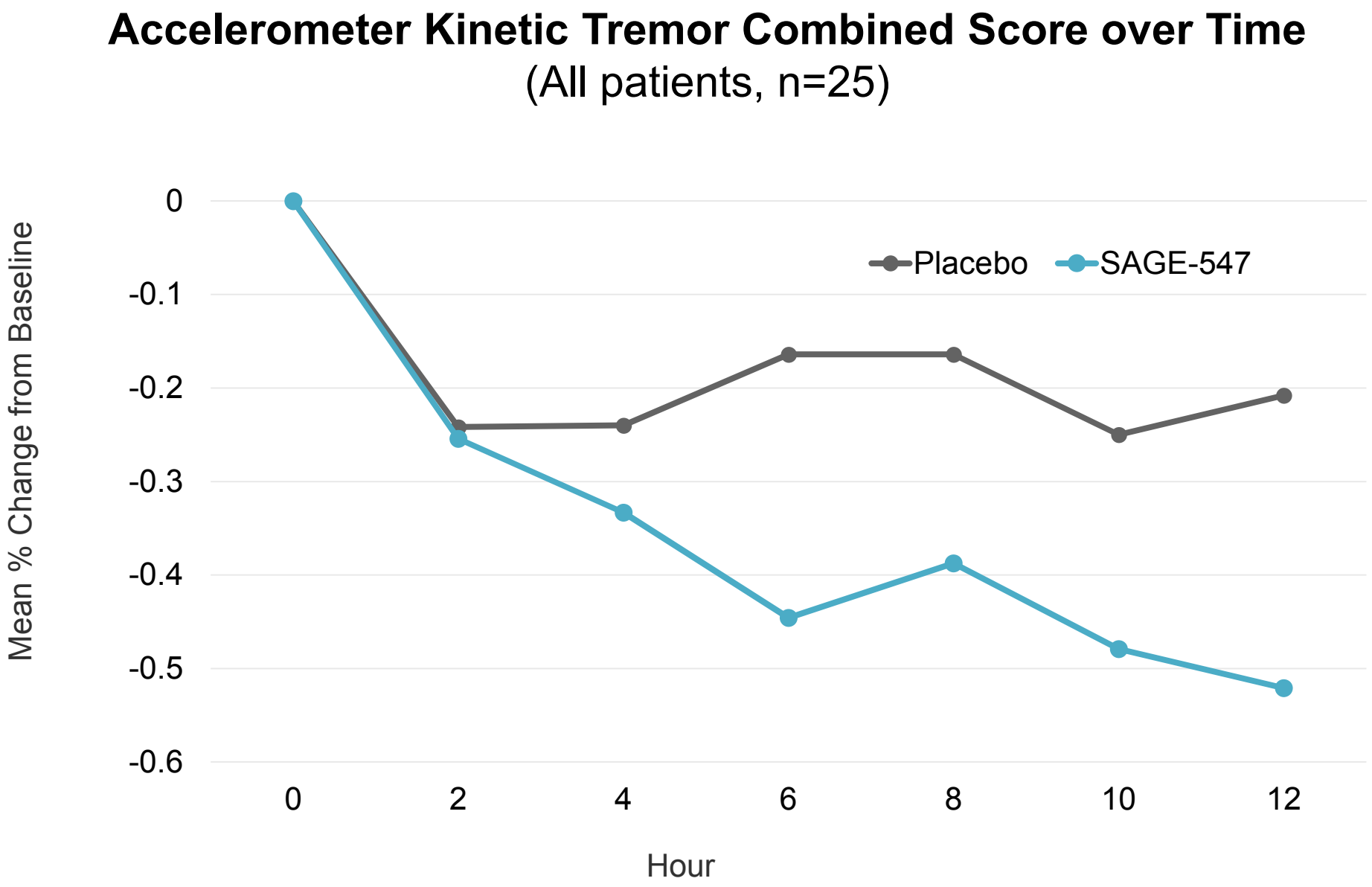
Upper Limb Response: Placebo-Controlled Stage (p=0.046 at 12 hours)



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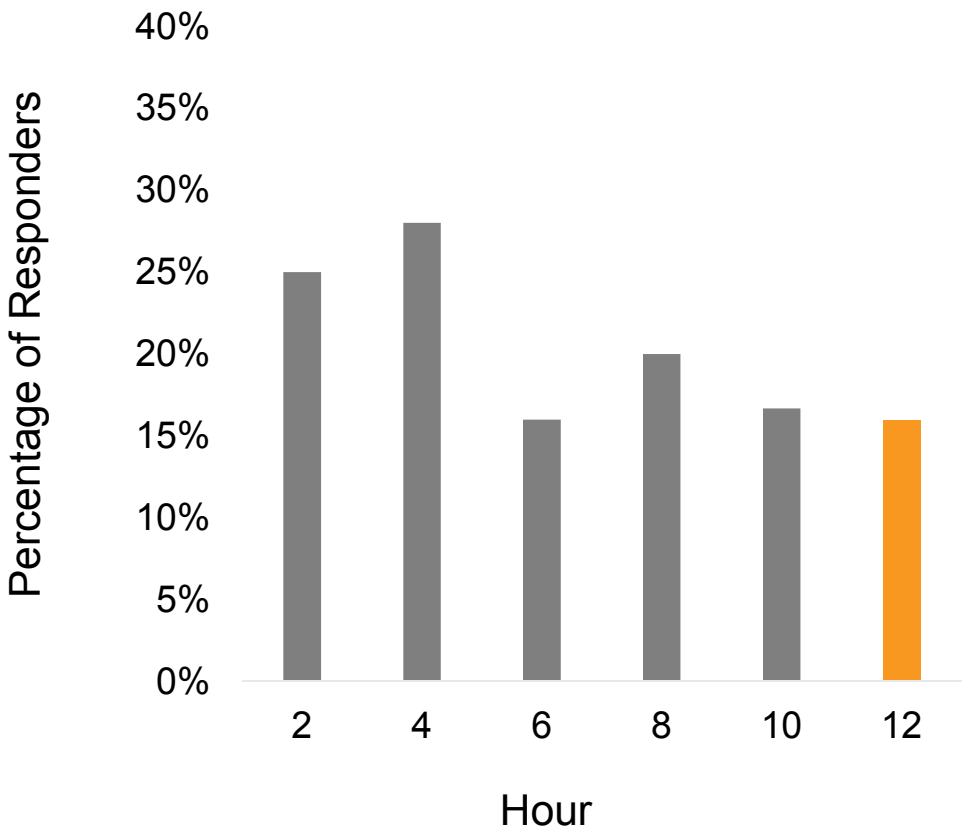
Strong Trend in Overall Response in Placebo-Controlled Stage

Accelerometer Response over Time

(At least 30% reduction from baseline; All patients, n=25)

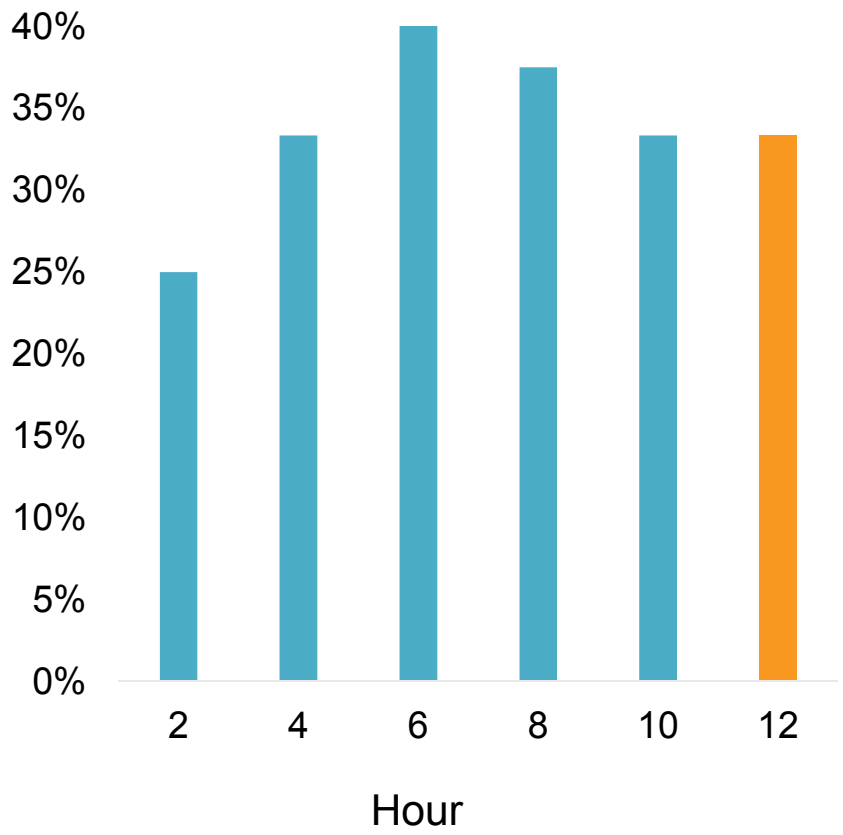
Placebo

16% response rate at 12 hours



SAGE-547

33% response rate at 12 hours (target steady state)



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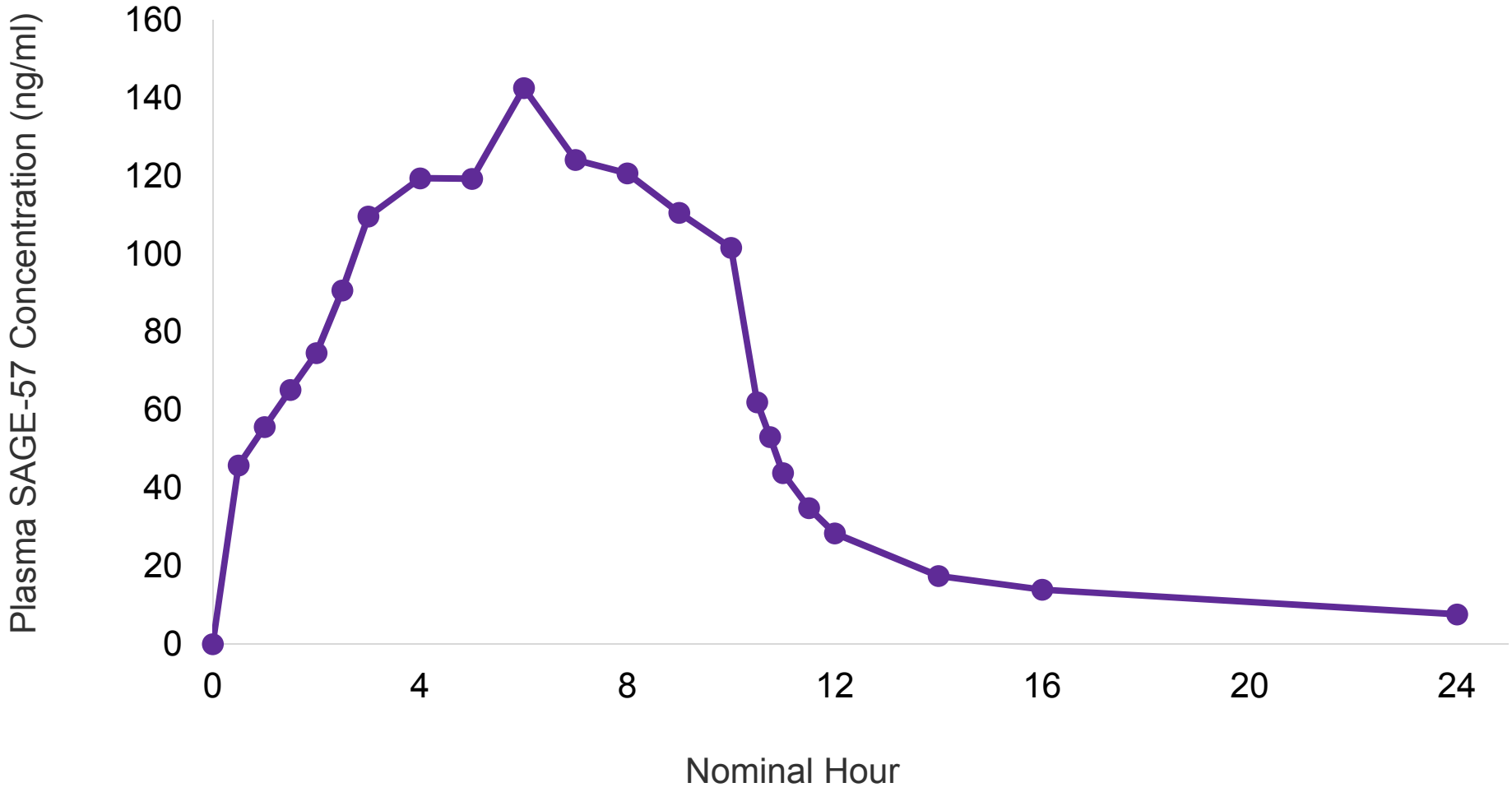
SAGE-547 Exposure in Open-Label Extension Correlates with Peak Therapeutic Activity

Mean Concentration-Time Plot (Stage 2 patients, n=17)



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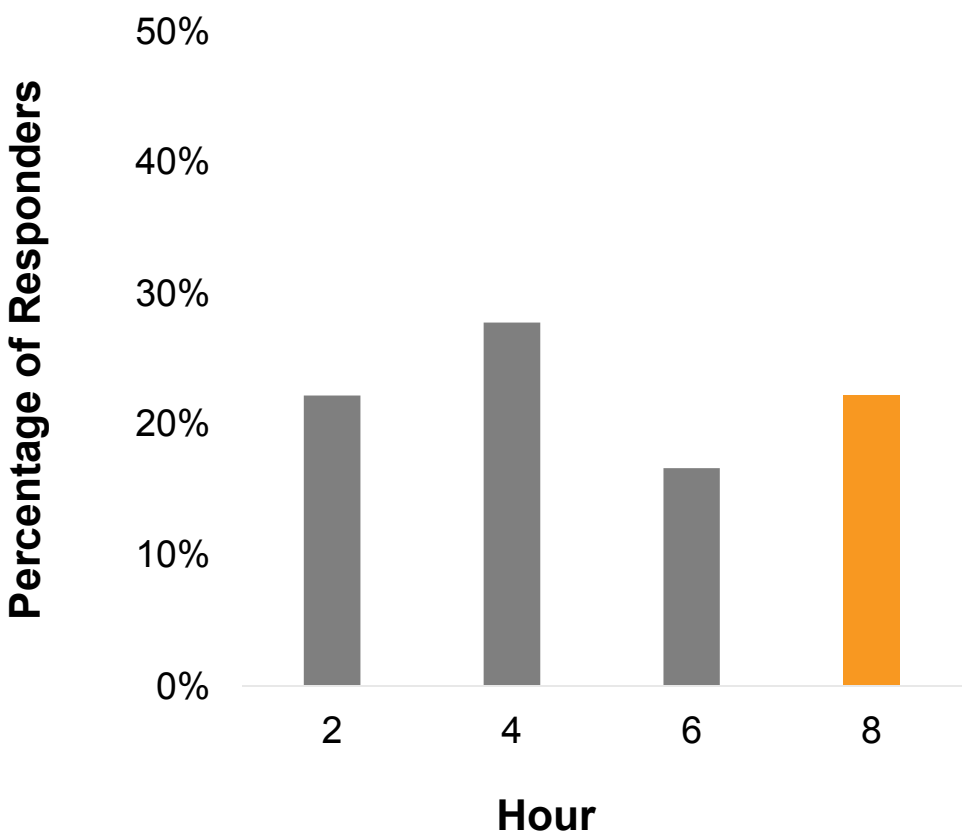
Overall Response Rate in Open-Label Extension vs. Matched Placebo

Accelerometer Response over Time

(At least 30% reduction from baseline; n=17)

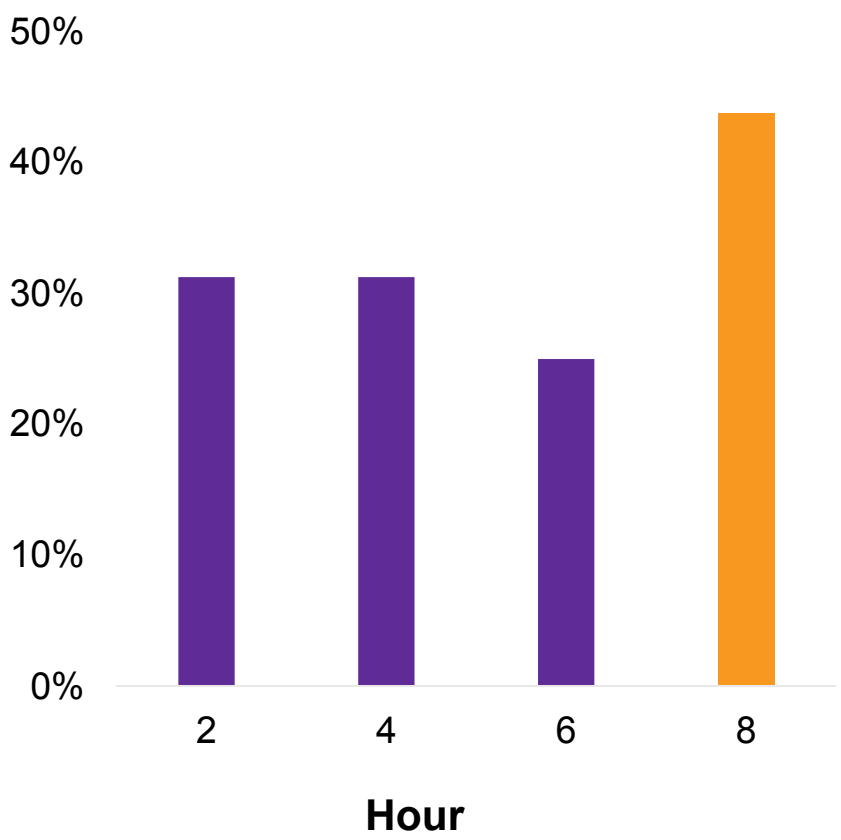
Placebo

22% response rate at 8 hours



SAGE-547

44% response rate at 8 hours



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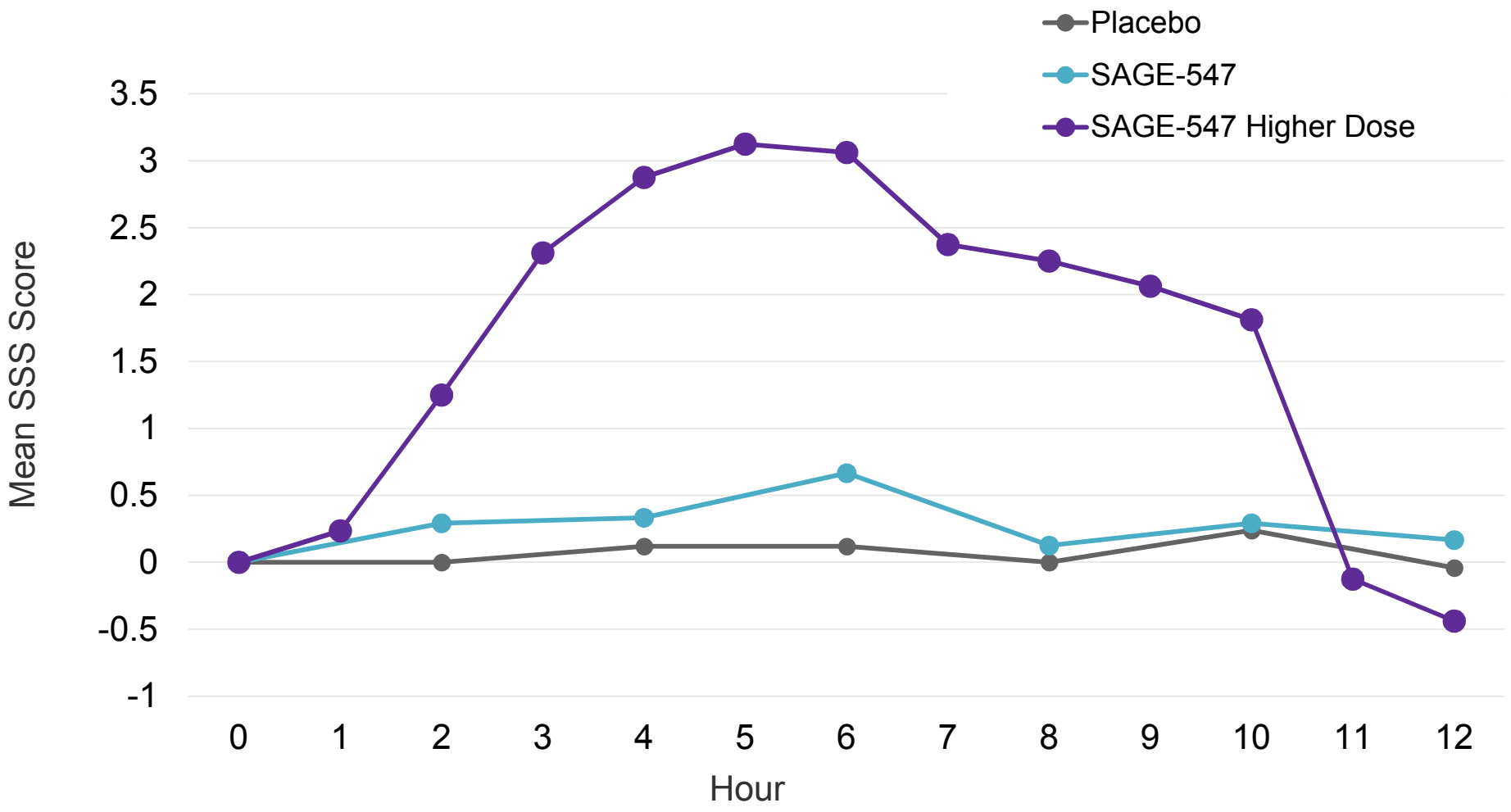
Sedation as Measured by Stanford Sleepiness Scale Placebo-Controlled vs. Open-Label Stages

Stanford Sleepiness Scale (SSS) Degree of Sleepiness Score over Time

(All patients, n=25)



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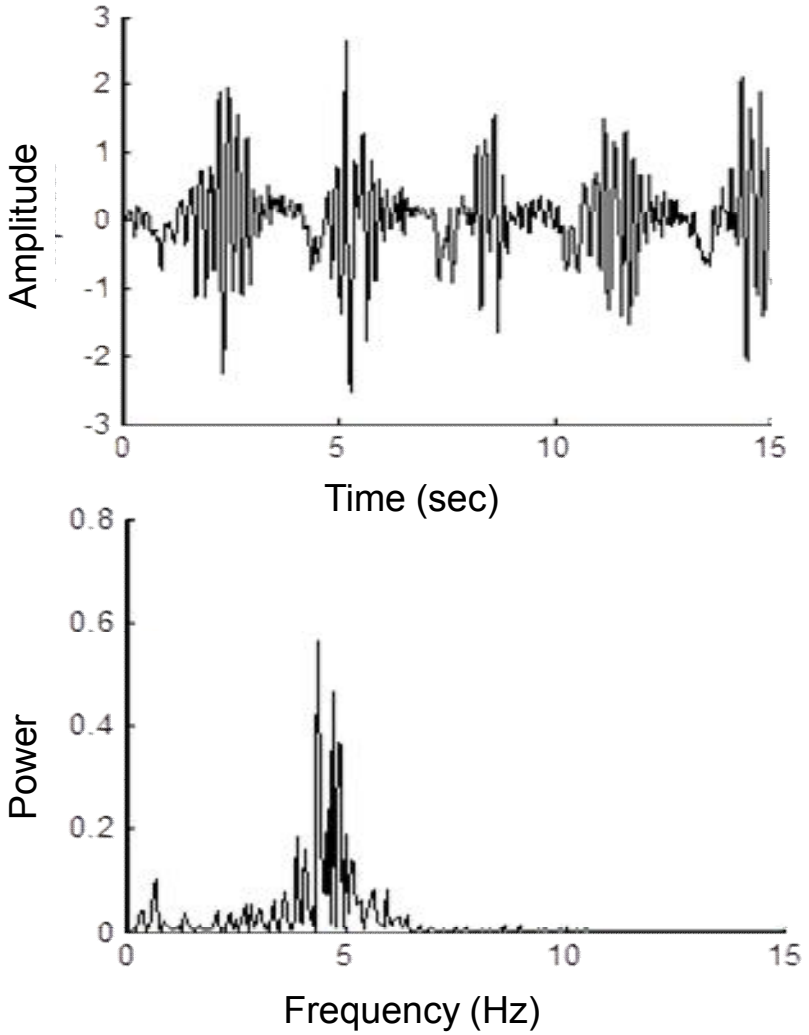
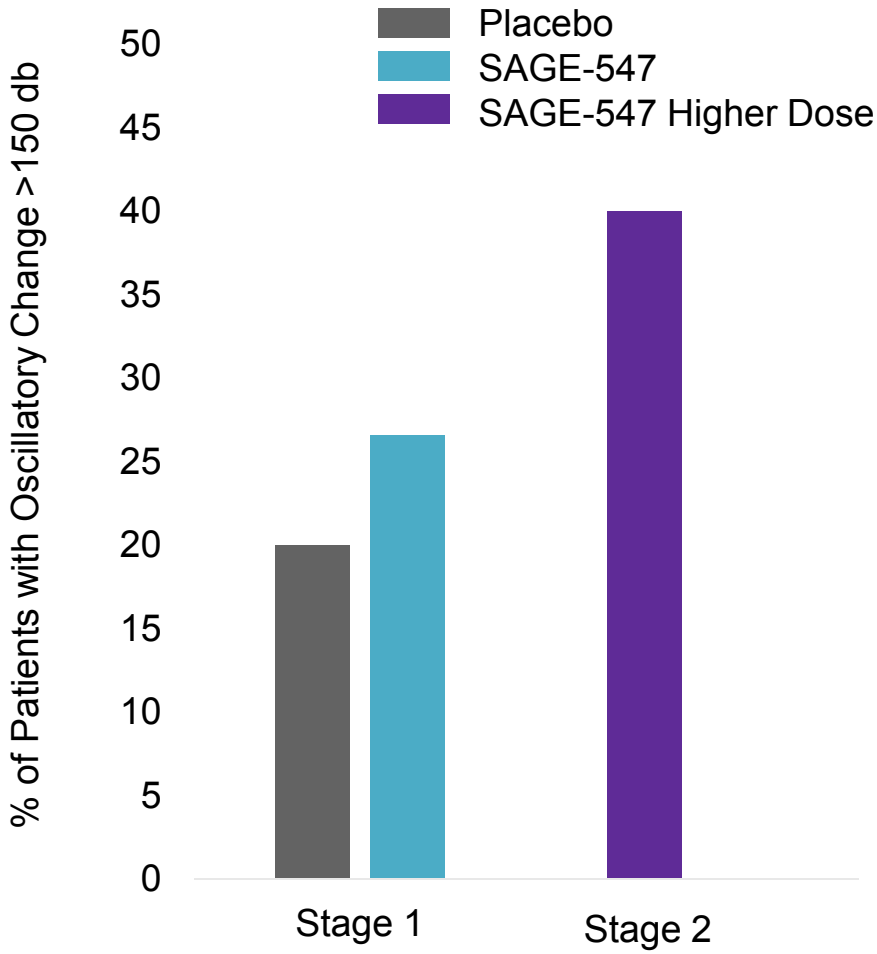
Objective Biomarker for Determining Treatment Effect

Tremor Oscillation as Assessed by Multi-dimensional Measurements





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Safety Profile

- No SAEs reported during treatment and follow-up periods
- Only AEs reported >1 time across all SAGE-547 treatment periods were fatigue and dizziness, predominantly in Stage 2
- Of 25 patients enrolled in Stage 1:
  - 3 patients reported at least one AE on blinded SAGE-547
  - 5 patients reported at least one AE on blinded placebo
- Of 17 patients enrolled in open-label, higher dose Stage 2:
  - 8 patients reported at least 1 AE
  - 1 patient discontinued due to hypotension with recovery following drug discontinuation

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Summary of Study Findings

- Clinically meaningful and significant reduction in tremor amplitude observed in patients exposed to target steady state dose for only 2 hours
- Anti-tremor effect may be uncoupled from sedation; tolerance to sedation may occur quickly
- SAGE-547 well-tolerated in conscious patients
- Results inform trial methodology for planned Phase 2 program using oral, second-generation $GABA_A$ modulator, such as SAGE-217
- Plan to submit detailed results, and further exploratory analyses, from trial for publication and presentations at future medical meetings

SAGE strategy of leading with human data can accelerate and enhance development of NCEs for new indications

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Questions & Answers

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