A Phase 2b, Randomized, Dose-Response Study of SAGE-324/BIIB124 for the Treatment of Essential Tremor: KINETIC 2 Trial in Progress

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Introduction

- Essential tremor (ET) is one of the most common movement disorders and is estimated to affect 6.4 million adults in the US.[1,2]
- Approximately 50% of individuals with ET have a suboptimal response to pharmacologic oral treatments.[3-5]
- As altered γ-aminobutyric acid (GABA) neurotransmission has been implicated in the pathophysiology of ET, positive allosteric modulators (PAMs) of $GABA_A$ receptors may have therapeutic utility for ET.[6]
- Early-phase clinical trials demonstrated target engagement and tremor reduction, supporting further development of $GABA_A$ receptor PAMs for the treatment of ET.[7,8]
- SAGE-324/BIIB124 is an investigational $GABA_A$ receptor PAM that was evaluated in the proof-of-concept Phase 2 KINETIC trial.[9]
  - KINETIC met its primary endpoint; SAGE-324/BIIB124 (60-mg tablets orally for 28 days) significantly reduced tremor severity in participants with ET, as measured by The Essential Tremor Rating Assessment Scale-Performance Subscale (TETRAS-PS) Item 4 upper limb tremor score at Day 29.
  - 33 of 34 participants (97.1%) who received SAGE-324/BIIB124 had ≥ 1 treatment-emergent adverse event (TEAE) of any grade; 9 of 34 participants (26.5%) discontinued SAGE-324/BIIB124 due to a TEAE.
- The clinical profile of SAGE-324/BIIB124 observed in KINETIC supported the further development of SAGE-324/BIIB124 as a potential therapeutic option for individuals with ET.
- The Phase 2b KINETIC 2 trial (NCT05173012; kinetic2trial.com) was designed to evaluate different doses of SAGE-324/BIIB124 in participants with ET and is ongoing.

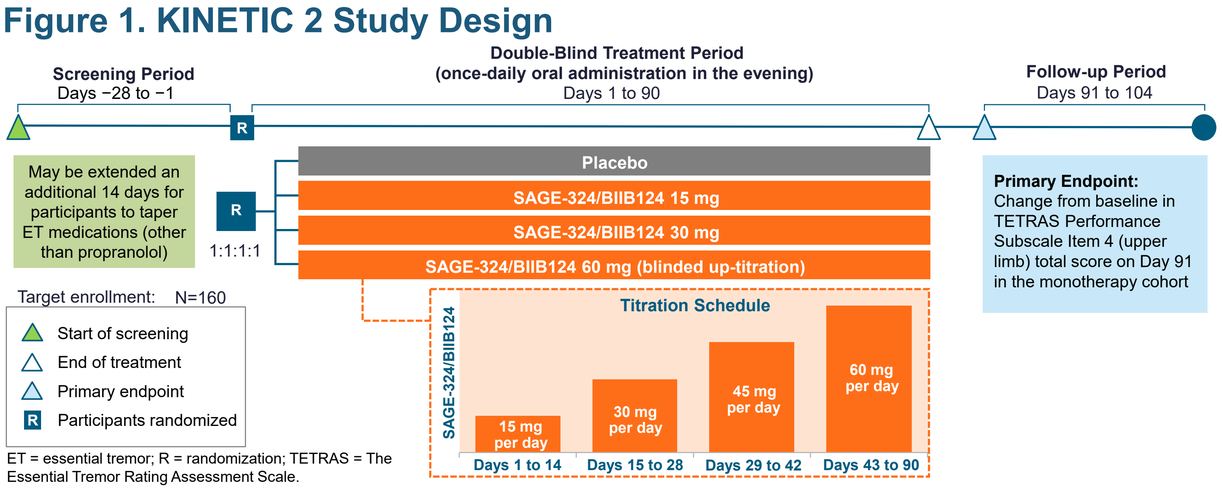
Study Objectives

- To evaluate the dose-response relationship of different doses of SAGE-324/BIIB124 on upper extremity tremor in the monotherapy cohort (primary objective) and specified activities of daily living (ADL) in the monotherapy cohort (secondary objective).

Study Design

- The Phase 2b KINETIC 2 trial is a double-blind, randomized, placebo-controlled, dose-response study of SAGE-324/BIIB124 for the treatment of ET (**Figure 1**).
- The study aims to enroll 160 participants from up to 60 sites worldwide, with ≥ 104 participants receiving monotherapy and ≤ 56 receiving adjunct therapy.
- Participants are randomized 1:1:1:1 to receive once-daily (evening) oral administration of 15-mg, 30-mg, or 60-mg SAGE-324/BIIB124 tablets, or placebo, respectively, stratified by baseline propranolol use (adjunct therapy) for 90 days; a 60-mg dose of SAGE-324/BIIB124 will be reached after blinded up-titration from 15 mg over 42 days.

Figure 1. KINETIC 2 Study Design



ET = essential tremor; R = randomization; TETRAS = The Essential Tremor Rating Assessment Scale.

Study Eligibility Criteria

- Key study eligibility criteria are described in **Table 1**.

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age of 18 to 80 years • Diagnosis of ET[1] • Combined TETRAS-PS Item 4 score of ≥ 12 for upper limb tremor at Screening and predose on Day 1 with a total score of ≥ 6 for the dominant upper limb • Baseline TETRAS-ADL Subscale score of ≥ 20 at Screening • Absence of other relevant neurological signs • Willingness to discontinue medications taken for the treatment of ET except propranolol, limit use of alcohol, and maintain prestudy consumption of nicotine ≥ 1 week prior to receiving SAGE-324/BIIB124 and through Day 97 • Adjunct therapy cohort receives a stable dose of propranolol for the treatment of ET (maximum daily propranolol dose of ≤ 320 mg) from 3 months prior to Screening through Day 97	• Known causes of enhanced physiological tremor • Recent exposure to tremorgenic drugs[2] • Presence of an alcohol withdrawal state • Previous surgical procedure for the treatment of ET • Use of Cala Trio bracelet for the treatment of ET from 2 weeks prior to Day 1 through Day 97 • Receipt of botulinum toxin for treatment of ET within 6 months of Screening • Body weight of > 140 kg or BMI of ≥ 50 at Screening

BMI = body mass index; ET = essential tremor; TETRAS-ADL = The Essential Tremor Rating Assessment Scale Activities of Daily Living; TETRAS-PS = TETRAS-Performance Subscale.

[1] ET defined as isolated tremor syndrome having bilateral upper limb action tremor for ≥ 3 years with or without tremor in other locations.

[2] Fourteen days or 5 half-lives, whichever is longer, prior to Day 1.

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Endpoints and Assessments

- Primary endpoint: change from baseline (CFB) in TETRAS-PS Item 4 (upper limb) total score on Day 91 in the monotherapy cohort.
  - TETRAS-PS is a validated, comprehensive clinical assessment of ET.[10]
  - Using TETRAS-PS Item 4, upper limb tremor will be assessed in both arms, first in the right arm and then the left, during 3 maneuvers.
  - TETRAS-PS Item 4 rates postural tremor (limbs extended forward maneuver, and wing-beating [elbows flexed] maneuver), and kinetic tremor (finger-nose-finger maneuver) on a scale of 0 (no tremor) to 4 (severe tremor) in 0.5 increments.
  - TETRAS-PS Item 4 score for each upper limb ranges from 0 to 12; the score for both upper limbs ranges from 0 to 24.
- Secondary endpoint: CFB in TETRAS-ADL subscale composite score in the monotherapy cohort.
  - TETRAS-ADL subscale assesses how ET affects ADL, such as drinking from a cup and eating with a spoon.
  - The TETRAS-ADL subscale consists of 12 items that are each rated on a scale from 0 (normal) to 4 (severe abnormality).
  - The TETRAS-ADL composite score comprises items 1 to 11 of the ADL subscale and item 6 of the performance subscale; each item is rated on a scale from 0 (normal/slight abnormality) to 3 (severe abnormality), and the overall range is 0 to 36. A negative CFB indicates improvement.
- Safety and tolerability of SAGE-324/BIIB124 will be evaluated by stratum (monotherapy cohort and adjunct therapy cohort) and overall using incidence of TEAEs and serious adverse events (SAEs).

Statistical Methods

- Primary and secondary endpoint analyses
  - Mixed-effects model for repeated measures (MMRM) analyses will be used to evaluate the primary and secondary endpoints, with fixed effects of treatment, baseline TETRAS-PS Item 4 score, assessment timepoint, timepoint-by-baseline TETRAS-PS Item 4 score, and timepoint-by-treatment.
  - After the MMRM analyses, the estimated mean and covariance matrix will be passed to the Multiple Comparisons and Modeling analysis to test the dose-response relationship.
- Safety analyses
  - Safety and tolerability of SAGE-324/BIIB124 will be evaluated by stratum (monotherapy cohort an adjunct therapy cohort) and overall using incidence of TEAEs and SAEs and CFB in vital signs, clinical laboratory parameters, 12-lead electrocardiogram findings, Epworth Sleepiness Scale scores, and 20-item Physician Withdrawal Checklist scores. Suicidality will be analyzed by propranolol use based on Columbia-Suicide Severity Rating Scale scores.

Results

- The KINETIC 2 trial is estimated to be completed in 2024.

Clinical trial contact information

Study website: kinetic2trial.com
Call: +1-857-384-8308
ClinicalTrials.gov identifier: NCT05173012

Conclusions

- The Phase 2b KINETIC 2 trial is designed to evaluate SAGE-324/BIIB124 dose response in participants with ET based on clinically relevant endpoints and safety.
- Enrollment is ongoing, and the results will inform future SAGE-324/BIIB124 clinical development.

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