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

Rajesh Pahwa, MD[1]; Aaron L. Ellenbogen, DO[2,3]; Dimitrios Arkilo, MD[4]; Tien Dam, MD[5]; TinaMarie Lieu, PhD[4]; Bonnie Hersh, MD[5]; Min Qin, PhD[4]; Svetlana Garafola, MD[4]; Margaret E. Gerbasi, PhD[4]; Helen Colquhoun, MBChB[4]

Presented by Rosalind Chuang, MD[5]

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[1]University of Kansas Medical Center, Kansas City, KS; [2]Michigan Institute for Neurological Disorders, Farmington Hills, MI; [3]Quest Research Institute, Farmington Hills, MI; [4]Sage Therapeutics, Inc, Cambridge, MA; [5]Biogen Inc., Cambridge, MA.

Disclosures

- **Dimitrios Arkilo, MD, TinaMarie Lieu, PhD, Min Qin, PhD, Svetlana Garafola, MD, Margaret E. Gerbasi, PhD, and Helen Colquhoun, MBChB** are employees of Sage Therapeutics, Inc and may hold stock or stock options.
- **Tien Dam, MD, Bonnie Hersh, MD, and Rosalind Chuang, MD** are employees of Biogen Inc. and may hold stock.
- **Rajesh Pahwa, MD** is a consultant for Abbott, AbbVie, ACADIA, Acorda, Amneal, Artemida, Britannia, Cala Health, Global Kinetics, Impel, Insightec, Jazz, Neuropharma, Kyowa, Neurocrine, PhotoPharmics, Sage Therapeutics, Scineuro, Sunovion, Supernus and XWPharma and receives research support from Abbott, AbbVie, Addex, Biogen Inc., Biohaven, Boston Scientific, Bukwang, Cerevance, Cerevel, Global Kinetics, Impax, Jazz, the Michael J Fox Foundation, Neuroderm, Neuraly, Neurocrine, the Parkinson's Foundation, Praxis, Roche, Sage Therapeutics, Scion, SIS, Sun Pharma, Sunovion, and Voyager.
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Background

- 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]
- Altered GABA neurotransmission has been implicated in the pathophysiology of ET, and 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]

ET = essential tremor; GABA = γ-aminobutyric acid; PAM = positive allosteric modulator.

1. Crawford S, et al. 3rd Pan American Parkinson's Disease and Movement Disorders Congress. February 14-16, 2020; Miami, FL. Poster 192. 2. Haubenberger D, Hallett M. *N Engl J Med*. 2018;378(19):1802-1810. 3. Louis ED. *Front Neurol*. 2012;2:91. 4. Deuschl G, et al. *Lancet Neurol*. 2011;10(2):148-161. 5. Zesiewicz TA, et al. *Neurology*. 2011;77(19):1752-1755. 6. Paris-Robidas S, et al. *Brain*. 2012;135(pt 1):105-116. 7. Kaul I, et al. 2nd Pan American Parkinson's Disease and Movement Disorders Congress; June 22-24, 2018; Miami, FL. Poster 135. 8. Ellenbogen AE, et al. AAN 2016 Annual Meeting; April 15-21, 2016; Vancouver, BC, Canada. Poster P4.297.

Early-Phase Study of SAGE-324/BIIB124

- SAGE-324/BIIB124 is an investigational $GABA_A$ receptor PAM that was evaluated in the proof-of-concept Phase 2 KINETIC clinical trial (NCT04305275).[1]
  - 69 individuals aged 18 to 80 years with moderate to severe ET[a] were randomized 1:1 to receive SAGE-324/BIIB124 (60-mg orally once daily) or placebo for 28 days.
  - Primary endpoint was change from baseline compared with placebo in upper limb tremor score as measured by TETRAS-PS Item 4 at Day 29.
- The clinical profile of SAGE-324/BIIB124 observed in KINETIC supported the further development of SAGE-324/BIIB124 as a potential therapeutic option for patients with ET.

ET = essential tremor; GABA = γ-aminobutyric acid; PAM = positive allosteric modulator; TEAE = treatment-emergent adverse event; TETRAS-PS = The Essential Tremor Rating Assessment Scale-Performance Subscale.

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04305275. Accessed May 2023.

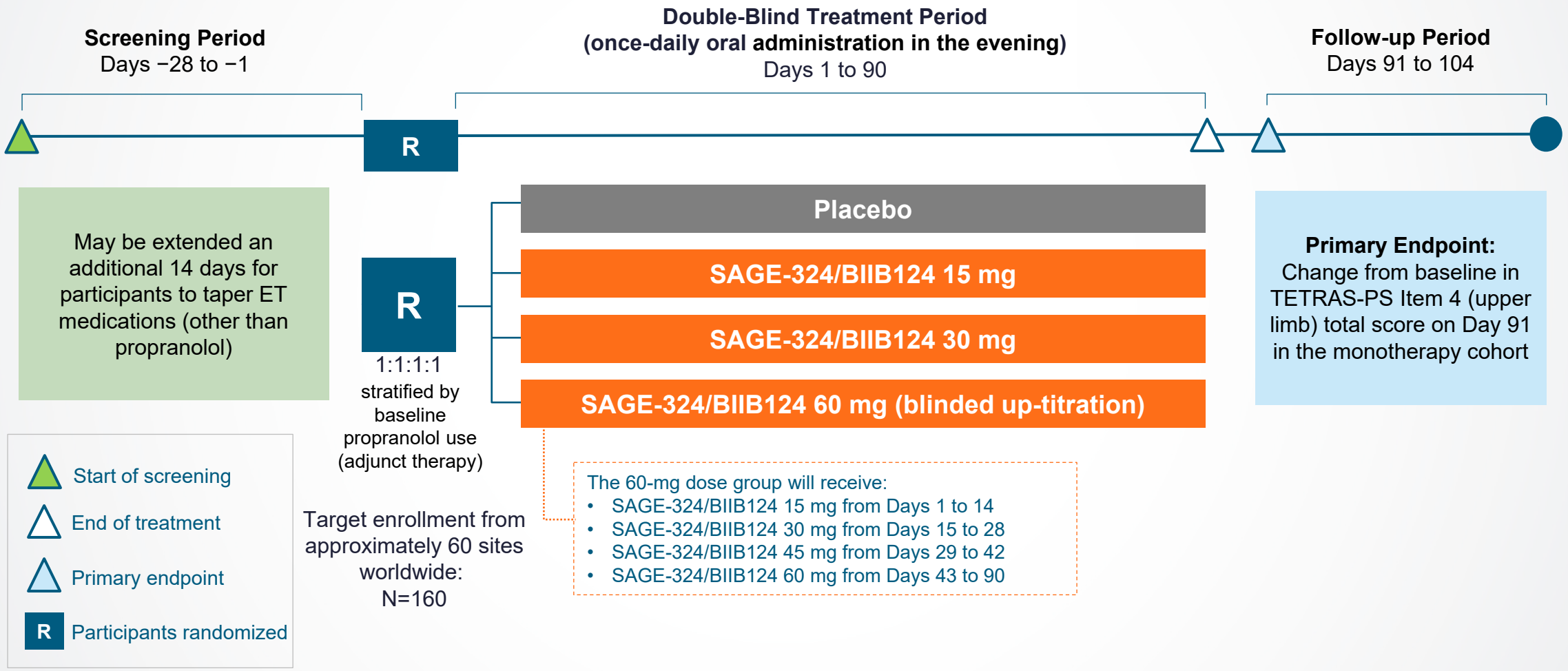
1. Bankole K, et al. MDS Virtual Congress 2021; September 17-22, 2021. Abstract LBA 10.

[a] Determined by a TETRAS-PS Item 4 score of ≥ 10 [scale of 0 to 24]) at both Screening and prior to dosing on Day 1.

KINETIC 2 Study Objectives

- The objectives of the KINETIC 2 study are to evaluate the dose-response relationship of different doses of SAGE-324/BIIB124 in the monotherapy cohort on:
  - Upper extremity tremor (primary objective)
  - Specified activities of daily living (secondary objective)

KINETIC 2 Study Design (NCT05173012)



ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT05173012. Accessed April 2023.
ET = essential tremor; R = randomization; TETRAS-PS = The Essential Tremor Rating Assessment Scale-Performance Subscale.

KINETIC 2 Study Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Aged 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-containing products ≥ 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 allowed) from 3 months prior to Screening through Day 97	• Presence of known causes of enhanced physiological tremor • Recent exposure[2] to tremorgenic drugs • 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 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.

KINETIC 2 Study Endpoints and Assessments

Endpoint	Assessment
 **Primary endpoint** **CFB in TETRAS-PS Item 4 (upper limb) total score on Day 91 in the monotherapy cohort**	**TETRAS-PS Item 4** • A validated, comprehensive clinical assessment of ET[1] • Upper limb tremor will be assessed in both arms, first in the right arm and then the left, during 3 maneuvers • 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 • Score for each upper limb ranges from 0 to 12 and for both upper limbs from 0 to 24
 **Secondary endpoint** **CFB in TETRAS-ADL subscale composite score on Day 91 in the monotherapy cohort**	**TETRAS-ADL** • Assesses how ET affects ADL, such as drinking from a cup and eating with a spoon • Consists of 12 items that are each rated on a scale from 0 (normal) to 4 (severe abnormality). • 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 change from baseline indicates improvement
 **Safety and tolerability**	**Evaluated by stratum (monotherapy cohort and adjunct therapy cohort) and overall using incidence of TEAEs and SAEs**

ADL = activities of daily living; CFB = change from baseline; ET = essential tremor; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TETRAS-ADL = The Essential Tremor Rating Assessment Scale-Activities of Daily Living; TETRAS-PS = The Essential Tremor Rating Assessment Scale-Performance Subscale.

1. Elble R, et al. *Mov Disord*. 2013;28(13):1793-1800.

KINETIC 2 Study Statistical Methods

Primary and secondary endpoints will be evaluated by:

- MMRM analyses, 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 and tolerability will be evaluated by:

- Incidence of TEAEs and SAEs
- Changes from baseline in vital signs
- Clinical laboratory parameters
- 12-lead electrocardiogram findings
- ESS scores
- PWC scores
- C-SSRS scores

C-SSRS = Columbia-Suicide Severity Rating Scale; ESS = Epworth Sleepiness Scale; MMRM = Mixed-effects model for repeated measures; PWC = Physician Withdrawal Checklist; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TETRAS-PS = The Essential Tremor Rating Assessment Scale-Performance Subscale.

KINETIC 2 Study Results and Conclusions

Results

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

Conclusions

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

ET = essential tremor.

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