BRIGHT MINDS

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BMB-101 in Absence Seizures and Developmental and Epileptic Encephalopathy (DEE): An Open-Label Phase 2 Study

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Background

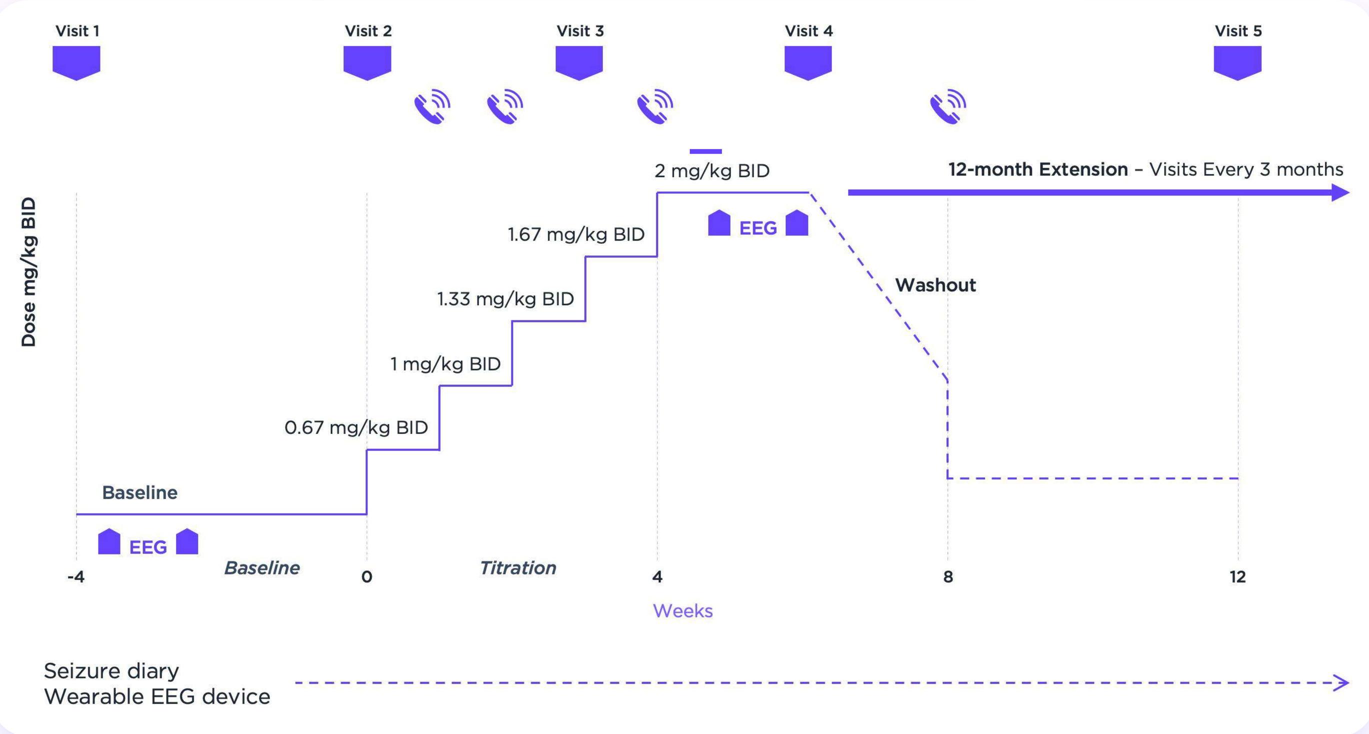
- **Absence seizures have high unmet need**
  - Current drugs fail to treat all patients effectively and have tolerability and potentially severe safety issues
  - The unmet need is in both people solely with typical Absence seizures and those with absence seizures as a part of a mixed seizure disorders, including Developmental and Epileptic Encephalopathy (DEE) epilepsies
  - These patients need an effective, wide-spectrum, safe, and well-tolerated therapy
- **DEEs represent the most severe form of epilepsy, marked by treatment-resistant seizures and developmental slowing or regression**
  - These patients face elevated risks of status epilepticus and sudden unexpected death in epilepsy (SUDEP)
  - Achieving better seizure control for patients with DEE remains a significant challenge, especially for the patients outside of Dravet Syndrome, Lennox–Gastaut syndrome, CDKL5 deficiency disorder (CDD), tuberous sclerosis complex
- **BMB-101 is uniquely positioned to address major unmet needs in epilepsy**
  - Highly selective 5-HT_{2C} agonist
  - The only G protein-biased 5-HT_{2C} agonist
  - BMB-101 has demonstrated efficacy in the preclinical models of Dravet Syndrome, Absence seizures, a model of SUDEP, and others indicating the potential to address multiple seizure types in patients with DEE
  - Highly "druggable", as seen in a Phase 1 study of 64 participants
  - Safety, pharmacokinetic (PK), and pharmacodynamic properties were also demonstrated
  - Proof of mechanism was also confirmed in Phase 1 (increased gamma-power on quantitative electroencephalography [qEEG])
- **An open-label Phase 2 study of BMB-101 in patients with Absence seizures and DEE is ongoing (BREAKTHROUGH, NCT06401538)**

Study Design

- Open-label, Phase 2 study for Absence seizures and DEE
- An open-label extension trial is offered as an option for those responding to BMB-101, if agreed to by their physician

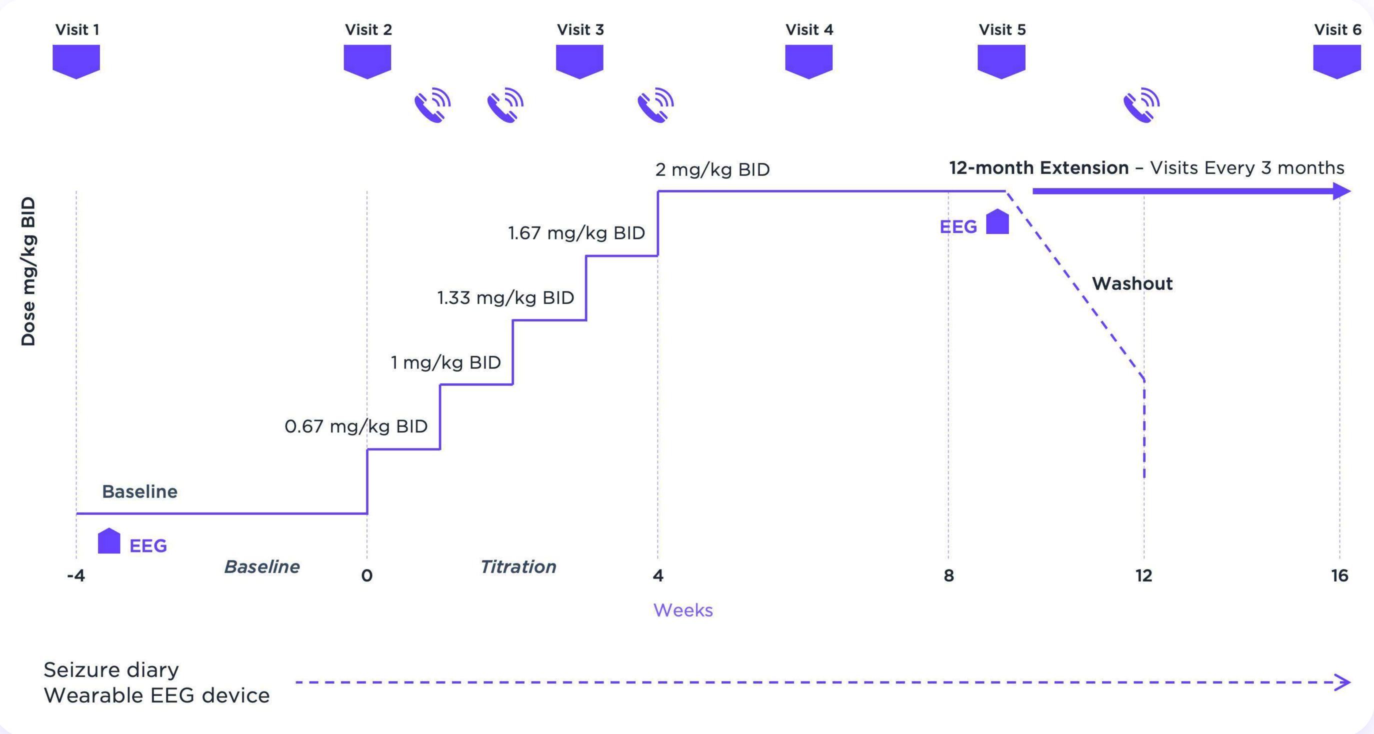
Absence cohort:

- A 4-week baseline period is followed by weekly dose escalation of BMB-101 beginning at 0.67 mg/kg and ascending weekly by 0.33 mg/kg to a maximum of 2.0 mg/kg then a maintenance period of 3 weeks.
- Two 24-hour ambulatory EEGs are obtained in baseline and at the end of the maintenance phase



DEE cohort:

- A 4-week baseline period is followed by weekly dose escalation of BMB-101 beginning at 0.67 mg/kg and ascending weekly by 0.33 mg/kg to a maximum of 2.0 mg/kg then a maintenance period of 5 weeks
- Seizure calendars are kept throughout the study
- One 24-hour ambulatory EEG is obtained at baseline and at the end of the maintenance phase



Dosing

- BMB-101 oral liquid (10 mg/mL) is administered by the participant or caregiver in the morning and evening using an oral dosing syringe
- The dose is adjusted for weight, with a starting dose of 0.67 mg/kg twice a day (BID)
- The dose may be titrated to a maximum of 2 mg/kg BID in 0.33 mg/kg increments based on tolerability

Objectives

There are separate primary objectives for Absence seizures and DEE:

Absence cohort

Primary	To decrease the number of generalized spike-wave discharges (GSWD) by 30% on a 24-hour EEG
Secondary	To decrease the number of seizures by 30% as recorded on the participant/caregiver diary
Tertiary	To assess the effect of BMB-101 on the Clinical Global Impression of Change scale (CGI-C), Clinical Global Impression of Severity scale (CGI-S), patient-reported Clinical Global Impression of Change scale, and the Quality of Life in Epilepsy Inventory (QOLIE-31) in those with Absence with or without Epilepsy with Eyelid Myoclonia (EEM)
Safety	To evaluate the safety, tolerability, and PK of BMB-101 in those with Absence seizures with or without EEM

DEE cohort

Primary	To decrease the number of seizures by 30% as recorded on the participant/caregiver diary
Secondary	To decrease the number of electrographic seizure discharges by 30% on the 24-hour EEG
Tertiary	To assess the effect of BMB-101 on the CGI-C, CGI-S, patient-reported Clinical Global Impression of Change scale, and the QOLIE-31 in those with DEE
Safety	To evaluate the safety, tolerability, and PK of BMB-101 in those with DEE

Number of participants

Initial planned enrollment includes at least 10 evaluable participants with Absence and at least 10 evaluable participants with DEE

Eligibility criteria

Inclusion criteria

- Diagnosis of Absence Epilepsy with or without eyelid myoclonia (Jeavons Syndrome) or a diagnosis of DEE such as Dravet syndrome or Lennox-Gastaut syndrome or other DEE
- Participants with Absence must experience at least 4 occurrences of 3-4/second SWD lasting at least 3 seconds each in a 24-hour EEG during the baseline period.
  Those with DEE must have a typical EEG pattern for DEE on a routine 24-hour EEG and experience at least 4 seizures during the 4-week baseline period prior to BMB-101 administration.
- Male or female age 18-65 inclusive at baseline
- Participant must have tried at least one anti-seizure medication at a recommended dose and duration and must be on a stable dose on their current anti-seizure medications for at least 4 weeks prior to baseline and remain stable throughout the study
- Participant and/or their caregiver (if applicable), is willing and able to comply with diary completion, visit schedule, and study drug accountability
- Women of childbearing potential must have a negative urine pregnancy test at baseline. Individuals of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control (including abstinence) during the study and for 90 days after the last dose of study drug.

Exclusion criteria

- Individuals with slow SWDs are not eligible for the Absence portion of this study but may qualify for the DEE portion
- Current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, pulmonary hypertension, myocardial infarction or stroke, or clinically significant structural cardiac abnormality
- Moderate or severe hepatic impairment. Asymptomatic participants with mild hepatic impairment (elevated liver enzymes < 3x upper limit of normal [ULN] and/or elevated bilirubin <2x ULN) may enter the study after review and approval by the Medical Monitor in conjunction with the sponsor, in consideration of comorbidities and concomitant medications.
- Severe renal impairment (estimated glomerular filtration rate <30mL/min/1.73m2)
- Clinically significant electrocardiogram (ECG) abnormality such as QTcF >450 msec (men) or >470 msec (women)
- Concomitant therapy with: fenfluramine, lorcaserin, monoamineoxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants or other serotonergic agonists or antagonists (antipsychotics)
- Currently receiving an investigational medicinal product
- Participation in another clinical trial within the past 30 days (calculated from that study's last scheduled visit). Participation in non-treatment trials will be reviewed by the medical monitor.
- History of drug or alcohol abuse within the last 12 months or a positive urine drug screen (except for cannabinoids)
- A current Columbia-Suicide Severity Rating Scale (C-SSRS) score of 4 or 5 at baseline or history of suicide attempt at any time during the past year
- A clinically significant condition or clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the baseline visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the participant
- Any condition that is thought to be a degenerative neurological disease
- Participant has been taking felbamate <1 year prior to baseline and/or does not have stable liver function and hematology laboratory tests, and/or the dose has not been stable for at least 60 days prior to the baseline visit
- Participant is institutionalized in a general nursing home (i.e., in a facility that does not provide skilled epilepsy care)

Endpoints

Absence cohort

Primary	The change in frequency of seizures on the 24-hours EEGs during the baseline period (Visit 1 to Visit 2) compared to the EEGs while on the maintenance dose of BMB-101 during Weeks 4 to 6
Secondary	The change in frequency of seizures recorded on the paper seizure diary during the baseline period (Visit 1 to Visit 2) compared to the paper seizure diary while on the maintenance dose of BMB-101 during Weeks 4 to 6

DEE cohort

Primary	The change in mean (or median) daily frequency of seizures between the initial baseline period (Visit 1 to Visit 2) and while on the maintenance dose of BMB-101 during Weeks 4-10 as assessed by the participant on the paper seizure diary
Secondary	The change in frequency of seizures on the EEGs during the baseline period (Visit 1 to Visit 2) compared to while on the maintenance dose of BMB-101 during Weeks 4-10

Other endpoints (all participants)

- The change from baseline in CGI-C, CGI-S, patient-reported Clinical Global Impression of Change scale, and the QOLIE-31
- Safety, tolerability, and PK endpoints, which may include adverse events, vital signs, clinical laboratory assessments, physical examinations, ECGs, and the C-SSRS