Supplementary Materials

Efficacy and Safety of Adjunctive Cenobamate in Chinese Participants with Focal Seizure

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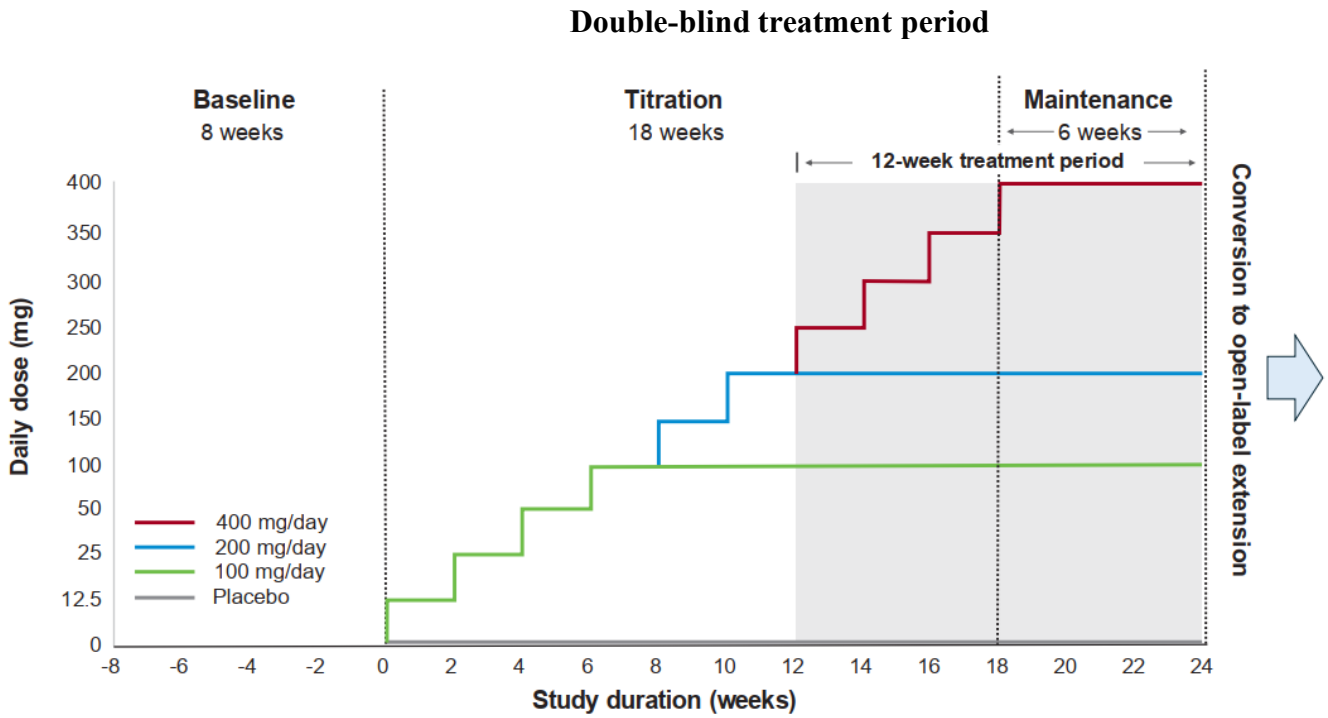
Supplementary Table S1. Detailed inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Eligible subjects with the following criteria were enrolled in the study: 1. Male or female patients aged 18 to 70 years inclusive at the time of signing the informed consent and assent (if applicable) 2. Weight at least 35 kg 3. Written informed consent signed by the subject prior to entering the study in accordance with the ICH GCP guidelines. For all underage subjects, according to the specific laws of the country, consent will be obtained from the parent/legal guardian. If the written informed consent is provided by the parent/legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. 4. A diagnosis of partial-onset seizures as per the International League Against Epilepsy's Classification of Epileptic Seizures (1981). Diagnoses were established by clinical history and an electroencephalogram (EEG) 5. EEG performed within 5 years prior to Visit 1 that is consistent with localization-related epilepsy; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (i.e., clinical history). 6. Need additional antiepileptic drug (AED) treatment despite having been treated with at least one AED for the last 2 years. 7. During the 8-week screening/baseline period, subjects must have at least 8 partial seizures, including only simple partial seizures with motor component, complex partial seizures, or secondarily generalized seizures without a seizure-	Subjects with any of the following criteria were excluded: 1. Female subjects who are pregnant (or planning to become pregnant during the study), lactating or breast-feeding 2. History of non-epileptic or psychogenic seizures 3. Presence of only non-motor simple partial seizures or primary generalized epilepsies 4. History or presence of seizures occurring only in clusters (too frequently or indistinctly separated to be reliably counted) 5. Presence or previous history of Lennox-Gastaut syndrome 6. Scheduled epilepsy surgery within 8 months of Visit 1 7. Evidence of any clinically significant laboratory abnormalities or disease (e.g., psychiatric, behavioral problems, cardiac, respiratory, gastrointestinal, hepatic [liver transaminases, ALT or AST, more than twice the upper limit of normal (ULN) or total or direct bilirubin not within normal limits], or renal disease) that, in the opinion of the Investigator, could affect subject's safety or the conduct of the study 8. Any clinically significant active central nervous system (CNS) infection, demyelinating disease, degenerative neurologic disease, or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results 9. Presence of psychotic disorders and/or unstable recurrent affective disorders evident by use of antipsychotics; presence or recent

free interval of greater than 25 days, any time during the 8-week period. Subjects must have at least 3 of these partial seizures during each of the two consecutive 4-week segments of the Screening/Baseline Periods, respectively. 8. Currently on stable antiepileptic treatment regimen: a. Subject must have been receiving stable doses of 1 to 3 AEDs for at least 4 weeks before Visit 1, to be continued unchanged throughout the Double-blind Treatment Period. b. Vagal nerve stimulator (VNS) or deep brain stimulator (DBS) will not be counted as an AED; however, the parameters must remain stable for at least 4 weeks prior to Visit 1 and during the study. VNS or DBS must have been implanted at least 5 months prior to Visit 1. c. The daily use of benzodiazepines (except for diazepam) for epilepsy, or for anxiety or sleep disorder, will be counted as 1 AED and must be continued unchanged throughout the study. additional approved AEDs will be allowed. d. Subjects receiving felbamate as a concomitant AED must meet the following criteria: i. Two-year history of felbamate use and a history of a fixed dosing regimen for a minimum of 60 days prior to Visit 1 ii. No prior or known history of hepatotoxicity or hematologic disorder due to felbamate 9. Computed tomography (CT) or magnetic resonance imaging (MRI) scan performed within the past 10 years ruled out a progressive cause of epilepsy. If a CT or MRI has not been performed within the past 10 years, one must be performed prior to	history (within 6 months) of major depressive episode 10. Use of intermittent rescue benzodiazepines more than once per month (1 to 2 doses in a 24-hour period is considered as 1 rescue) in the 1-month period prior to Visit 1 11. Current or recent use (within 30 days prior to Visit 1) of any of the following medications: diazepam/phenytoin/phenobarbital (or metabolites of these drugs), clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, efavirenz, natural progesterone or traditional Chinese/herbal medicines 12. Current or recent (within 5 months prior to Visit 1) use of vigabatrin or ezogabine. Subjects with a prior history of treatment with vigabatrin must have documentation showing no evidence of a vigabatrin associated clinically significant abnormality in a visual perimetry test. Subjects with a prior history of treatment with ezogabine should have no evidence of retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies. 13. Previous exposure to cenobamate 14. Participation in any other trials involving an investigational product or device within 30 days prior to Visit 1 15. History of alcoholism, drug abuse, or drug addiction within the past 2 years prior to Visit 1 16. History of status epilepticus within 3 months of Visit 1 17. History of any serious drug-induced hypersensitivity reaction (including but not limited to Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms [DRESS]) or any drug-related rash requiring

randomization. 10. Ability to reach the subject by telephone 11. Use of an acceptable form of birth control by female subjects of childbearing potential 12. Subject taking a ketogenic diet will be allowed as long as the diet has been stable for at least 3 months prior to Visit 1 and will remain stable for the duration of the study.	hospitalization 18. History of AED-associated rash that involved the conjunctiva or mucosae 19. History of any drug-related hypersensitivity reaction that required discontinuation of the medication 20. Presence of Familial short QT syndrome or relevant replicated QTc interval (QTcF less than 340 msec or greater than 450 msec in males and greater than 470 msec in females) on electrocardiogram (ECG) 21. Absolute neutrophil count less than 1,500/μL 22. Platelet counts lower than 80,000/μL in subjects treated with VPA 23. Creatinine clearance less than 60 mL/min, as calculated by Cockcroft-Gault equation 24. History of positive antibody/antigen test for hepatitis B, hepatitis C, or HIV 25. More than 1 lifetime suicide attempt 26. Any suicidal ideation (with intent with or without a plan) at Visit 1 (Screening) or Visit 3 (Randomization) (i.e., answering YES to Question 4 and/or Question 5 on the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale [C-SSRS]) 27. Subject is a staff member or immediate family member of study staff Any potential exception to the inclusion as well as exclusion criteria allowing de minimis (clinically minimal or trivial with no impact on the protocol objectives) variations must be approved by the Medical Monitor.

Supplementary Figure 1: Study Design



The current study analyzed the 24-week double-blind period data.

Supplementary Table S2A: Percentage Change from Baseline Seizure Frequency Reduction and Responder Rates During the Double-Blind Period (MITT population).

	Placebo (N=57)	Cenobamate 100 mg (N=55)	Cenobamate 200 mg (N=56)	Cenobamate 400 mg (N=57)
Percentage Change from Baseline in Seizure Frequency Reduction				
Median (Q1, Q3)	-17.0 (-36.9, 7.9)	-37.1 (-54.0, -11.0)	-60.8 (-78.7, -45.6)	-65.8(-78.5, -45.3)
P value (vs. placebo)		0.004	<0.001	<0.001
Responder Rates, n (%)				
≥50% Reduction from Baseline				
Yes	8 (14.0)	17 (30.9)	40 (71.4)	40 (70.2)
No	49 (86.0)	38 (69.1)	16 (28.6)	17 (29.8)
P value (vs. placebo)		0.033	<0.001	<0.001
≥75% Reduction from Baseline				
Yes	2 (3.5)	3 (5.5)	16 (28.6)	20 (35.1)
No	55 (96.5)	52 (94.5)	40 (71.4)	37 (64.9)
P value (vs. placebo)		0.620	<0.001	<0.001
≥90% Reduction from Baseline				
Yes	1 (1.8)	2 (3.6)	4 (7.1)	4 (7.0)
No	56 (98.2)	53 (96.4)	52 (92.9)	53 (93.0)
P value (vs. placebo)		0.539	0.166	0.172
≥100% Reduction from Baseline				
Yes	0	1 (1.8)	0	1 (1.8)
No	57 (100)	54 (98.2)	56 (100)	56 (98.2)
P value (vs. placebo)		0.309	NE	0.317

MITT, modified intent-to-treat. NE, not evaluable.

Supplementary Table S2B: Percentage Change from Baseline Seizure Frequency Reduction and Responder Rates During

12-week Treatment Period (12-Week MITT population)

	Placebo (N=53)	Cenobamate 100 mg (N=49)	Cenobamate 200 mg (N=50)	Cenobamate 400 mg (N=52)
Percentage Change from Baseline in Seizure Frequency Reduction, %				
Median (Q1, Q3)	-18.1 (-43.4, 10.0)	-41.0 (-62.8, -24.1)	-83.9 (-100.0, -55.8)	-95.3 (-100.0, -76.7)
P value (vs. placebo)		0.002	<0.001	<0.001
Responder rates, n (%)				
≥50% Reduction from Baseline				
Yes	11 (20.8)	21 (42.9)	41 (82.0)	46 (88.5)
No	42 (79.2)	28 (57.1)	9 (18.0)	6 (11.5)
P value (vs. placebo)		0.017	<0.001	<0.001
≥75% Reduction from Baseline				
Yes	3 (5.7)	10 (20.4)	31 (62.0)	40 (76.9)
No	50 (94.3)	39 (79.6)	19 (38.0)	12 (23.1)
P value (vs. placebo)		0.026	<0.001	<0.001
≥90% Reduction from Baseline				
Yes	2 (3.8)	4 (8.2)	19 (38.0)	33 (63.5)
No	51 (96.2)	45 (91.8)	31 (62.0)	19 (36.5)
P value (vs. placebo)		0.349	<0.001	<0.001
≥100% Reduction from Baseline				
Yes	-	3 (6.1)	13 (26.0)	21 (40.4)
No	53 (100)	46 (93.9)	37 (74.0)	31 (59.6)
P value (vs. placebo)		0.069	<0.001	<0.001

12-week MITT, 12-week modified intent-to-treat. The 12-week treatment period combined the last 6 weeks of the titration phase and the 6-week maintenance phase.

Supplementary Table S3: Summary of Adverse Event for those Receiving Cenobamate Combined with SCBs in the Safety Population

MedDRA Preferred Term, n (%)	Placebo (N=52)	Cenobamate 100 mg (N=48)	Cenobamate 200 mg (N=52)	Cenobamate 400 mg (N=52)
Subjects with TEAEs	39 (75.0)	39 (81.3)	43 (82.7)	48 (92.3)
Number of TEAEs	146	126	219	375
TEAEs with Maximum Severity				
Mild	22 (42.3)	26 (54.2)	23 (44.2)	13 (25.0)
Moderate	17 (32.7)	13 (27.1)	20 (38.5)	32 (61.5)
Severe	0	0	0	3 (5.8)
TRAEs	29 (55.8)	28 (58.3)	39 (75.0)	48 (92.3)
Serious TEAEs	0	0	1 (1.9)	3 (5.8)
Serious TRAEs	0	0	0	1 (1.9)
TEAEs Leading to Study Drug Withdrawal	1 (1.9)	1 (2.1)	1 (1.9)	9 (17.3)
TEAEs Leading to Study Drug Interruption	0	0	2 (3.8)	0
TEAEs leading to Dose Reduction	0	3 (6.3)	2 (3.8)	12 (23.1)
TEAEs Leading to Death	0	0	0	0

SCB, sodium channel blocker; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
MedDRA, medical dictionary for regulatory activities

Supplementary Table S4: Summary of Adverse Event for those Receiving Cenobamate Combined with Non-SCBs in the Safety Population

MedDRA Preferred Term, n (%)	Placebo (N=4)	Cenobamate 100 mg (N=7)	Cenobamate 200 mg (N=4)	Cenobamate 400 mg (N=5)
Subjects with TEAEs	3 (75.0)	4 (57.1)	4 (100)	5 (100)
Number of TEAEs	5	13	24	30
TEAEs with Maximum Severity				
Mild	2 (50.0)	3 (42.9)	2 (50.0)	3 (60.0)
Moderate	1 (25.0)	0	2 (50.0)	1 (20.0)
Severe	0	1 (14.3)	0	1 (20.0)
TRAEs	1 (25.0)	4 (57.1)	3 (75.0)	3 (60.0)
Serious TEAEs	0	1 (14.3)	0	1 (20.0)
Serious TRAEs	0	0	0	0
TEAEs Leading to Study Drug Withdrawal	0	0	0	0
TEAEs Leading to Study Drug Interruption	0	0	0	1 (20.0)
TEAEs leading to Dose Reduction	0	0	0	0
TEAEs Leading to Death	0	0	0	0

Non-SCB, non-sodium channel blocker; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event. MedDRA, medical dictionary for regulatory activities

Supplementary Table S5: Summary of Adverse Events Among Patients Who Received Cenobamate with 1 Baseline ASM (Safety Population)

MedDRA Preferred Term, n (%)	Placebo (N=7)	Cenobamate 100 mg (N=9)	Cenobamate 200 mg (N=5)	Cenobamate 400 mg (N=7)
Subjects with TEAEs	4 (57.1)	5 (55.6)	5 (100)	6 (85.7)
Number of TEAEs	8	20	24	56
TEAEs with Maximum Severity				
Mild	4 (57.1)	3 (33.3)	4 (80.0)	1 (14.3)
Moderate	0	1 (11.1)	1 (20.0)	3 (42.9)
Severe	0	1 (11.1)	0	2 (28.6)
TRAEs	2 (28.6)	5 (55.6)	4 (80.0)	5 (71.4)
Serious TEAE	0	1 (11.1)	0	2 (28.6)
Serious TRAE	0	0	0	0
TEAEs Leading to Study Drug Withdrawal	0	0	0	0
TEAEs Leading to Study Drug Interruption	0	0	0	0
TEAEs leading to Dose Reduction	0	0	1 (20.0)	2 (28.6)
TEAEs Leading to Death	0	0	0	0

ASM, antiseizure medication; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event
MedDRA, medical dictionary for regulatory activities

Supplementary Table S6: Summary of Adverse Events Among Patients Who Received Cenobamate with 2 Baseline ASMs (Safety Population)

MedDRA Preferred Term, n (%)	Placebo (N=25)	Cenobamate 100 mg (N=16)	Cenobamate 200 mg (N=24)	Cenobamate 400 mg (N=21)
Subjects with TEAEs	16 (64.0)	12 (75.0)	20 (83.3)	19 (90.5)
Number of TEAEs	47	27	100	131
TEAEs with Maximum Severity				
Mild	10 (40.0)	9 (56.3)	12 (50.0)	6 (28.6)
Moderate	6 (24.0)	3 (18.8)	8 (33.3)	12 (57.1)
Severe	0	0	0	1 (4.8)
TRAEs	11 (44.0)	8 (50.0)	18 (75.0)	18 (85.7)
Serious TEAEs	0	0	1 (4.2)	2 (9.5)
Serious TRAEs	0	0	0	1 (4.8)
TEAEs Leading to Study Drug Withdrawal	1 (4.0)	0	1 (4.2)	4 (19.0)
TEAEs Leading to Study Drug Interruption	0	0	0	1 (4.8)
TEAEs leading to Dose Reduction	0	0	1 (4.2)	2 (9.5)
TEAEs Leading to Death	0	0	0	0

ASM, antiseizure medication; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event
MedDRA, medical dictionary for regulatory activities

Supplementary Table S7: Summary of Adverse Events Among Patients Who Received Cenobamate with >2 Baseline ASMs (Safety Population)

MedDRA Preferred Term, n (%)	Placebo (N=24)	Cenobamate 100 mg (N=30)	Cenobamate 200 mg (N=27)	Cenobamate 400 mg (N=29)
Subjects with TEAEs	22 (91.7)	26 (86.7)	22 (81.5)	28 (96.6)
Number of TEAEs	96	92	119	218
TEAEs with Maximum Severity				
Mild	10 (41.7)	17 (56.7)	9 (33.3)	9 (31.0)
Moderate	12 (50.0)	9 (30.0)	13 (48.1)	18 (62.1)
Severe	0	0	0	1 (3.4)
TRAEs	17 (70.8)	19 (63.3)	20 (74.1)	28 (96.6)
Serious TEAEs	0	0	0	0
Serious TRAEs	0	0	0	0
TEAEs Leading to Study Drug Withdrawal	0	1 (3.3)	0	5 (17.2)
TEAEs Leading to Study Drug Interruption	0	0	2 (7.4)	0
TEAEs leading to Dose Reduction	0	3 (10.0)	0	8 (27.6)
TEAEs Leading to Death	0	0	0	0

ASM, antiseizure medication; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event
MedDRA, medical dictionary for regulatory activities