PROTOCOL CONCEPT SHEET 2 – PROTOCOL

Compound No. E2007

Name of Active Ingredient: Perampanel

Study Protocol Title

An Open-label, Observational, Prospective, Multicenter Study to Evaluate the Long-term Efficacy and Safety of Perampanel as Monotherapy in Subjects Age 4 Years and Older with Focal Onset Seizures

Investigators

Dr. Naoki Akamatsu (Principal)

Sites

Approximately 10-15 sites in Japan

Study Period and Phase of Development

From April 2021 to December 2024 (from first patient in to last patient out), including a 12-month enrollment period for 30 months of monotherapy treatment or until perampanel is discontinued, whichever comes sooner

Phase 4

Objectives

Primary Objective

The primary objective of the study is to evaluate 24-month seizure freedom in response to perampanel monotherapy in subjects age 4 years and older with focal onset seizures (FOS) (with or without focal-to-bilateral tonic clonic seizures [FBTCS])

Secondary Objectives

1. To evaluate the treatment effectiveness as measured by pragmatic seizure-free rate in response to perampanel monotherapy at 6, 12, 18 and 30 months
2. To evaluate the treatment effectiveness as measured by sustained seizure freedom in response to perampanel monotherapy at 12 and 24 months
3. To evaluate 6, 12, 18, 24 and 30 months retention on perampanel monotherapy in subjects with FOS
4. To evaluate safety and tolerability of perampanel monotherapy in subjects with FOS over the entire study and the specific time points (month 0-3, 4-12 and 13-30)
5. To evaluate the impact of perampanel monotherapy on the subject's quality of life (QOL) from the baseline to the specific time points (month 1, 3, 6, 12, 18, 24, 30)

Exploratory Objectives

1. To explore the effect of perampanel monotherapy on sleep quality using the HARU-1 wearable device
2. To evaluate the treatment adherence of perampanel
3. To explore clinical factors that influence seizure freedom rate in subjects receiving perampanel monotherapy

Study Design

This is an observational, prospective study in subjects with a diagnosis of FOS (with or without FBTCS), for whom the treating physician has made the decision to initiate perampanel as

monotherapy.

Subjects will be identified by sites from the electronic/paper medical and pharmacy records of patients attending their usual epilepsy clinic. The clinical decision to initiate perampanel as monotherapy will already have been made before the subject is identified for the study – ie, the decision to add perampanel is independent of the decision to enroll the subject in the study.

Before any study procedures, signed informed consent/assent form must be first obtained (informed assent [verbal only] will be taken from age 7 until 12 years, and informed assent [verbal + sign] will be taken from age 13 to 19 years. In addition, legal representatives should signed informed consent on behalf of subjects who are less than 20 years). Subjects will then enter into Screening Period for eligibility determination. Demography and medical history (including epilepsy history and baseline seizure frequency based on retrospective collection from 3 months before Day 0 [day of first dose of perampanel]) will be collected. Subjects, age 20 years or older who have provided informed consent and who report a tendency to a poor night's sleep, defined as a subjective sleep onset latency [sSOL] of 30 minutes or more, or subjective wake after sleep onset [sWASO] of 60 minutesat least 3 times a week over the previous month will be participate in the sleep substudy. They will be provided with a HARU-1 wearable device and instructed in its use for recording of baseline sleep parameters.

Subjects who are eligible will then enter the Treatment Period and perampanel monotherapy will be initiated. During the Treatment Period, data will be collected prospectively via 2 types of assessments: on-site and off-site.

- For on-site assessments, site visits and visit frequency during the treatment period are based on clinical practice. When subjects visit the site, concomitant medication use and treatment-emergent adverse events (TEAEs) will be recorded using electronic data capture (EDC) system.
- For off-site assessments, subjects will be provided with an electronic patient report outcome (ePRO) device and instructed in its use for recording seizure diaries, study drug adherence, and QOL (EQ-5D-5L, VAS and PedsQL). The seizure diaries input can be recorded at anytime when a seizure occurs and the presence or absence of a seizure is confirmed once a month via ePRO device reminder. Study drug adherence and QOL assessments will be performed at 1, 3, 6, 12, 18, 24 and 30 months. For subjects less than 18 years old, family members/caregivers should enter on behalf of the subjects.
  For sleep substudy, subjectswho have received perampanel monotherapy for at least 3 months after treatment initiation and remain stable at target dose of 4-8 mg/day for at least 4 weeks will have post-baseline sleep measurements taken onceusing the HARU-1 wearable device at any time until Months 12. The data on the time that subjects start trying to sleep and the time they get up in the morning will be recorded using the device by pressing the button on the device.

Subjects who discontinue perampanel because of adverse events or other reasons will be followed up approximately 1 month (+ 2 weeks) after last dose for TEAE/serious adverse event (SAE) follow up and subjects will need to completed ePRO assessment at perampanel discontinuation and 1 month (+ 2 weeks) after.

Number of Subjects

Approximately 60 subjects

Inclusion Criteria

1. Male or female, age 4 years or older at the time of informed consent (in the case of minors, consent from a legal representative [eg, one parent] is required)

2. Diagnosed with FOS (with or without FBTCS) according to International League Against Epilepy (ILAE) 2017 classification

3. Newly diagnosed or recurrent epilepsy. For subjects with recurrent epilepsy, they must have relapsed at least 2 years after the end of the last antiepileptic drug (AED) treatment.

4. Subjects for whom the decision to initiate perampanel has been made, according to the judgment of the investigator

Specific criteria for participating in the sleep substudy

5.1 Subjects age 20 years or older who agree to participate in sleep assessments.

5.2 Subjects who self report a tendency to a poor night's sleep defined as a sSOL of 30 minutes or more, or sWASO of 60 minutes, for at least 3 times a week over the previous month

Exclusion Criteria

1. A history of receiving any AED (including AED used as rescue treatment) for more than 2 weeks in total within 2 years before Day 0

2. Previously treated with perampanel at any time

3. A history of hypersensitivity to any of the excipients of perampanel

4. Severe hepatic impairment

5. Subjects who have participated in a study involving administration of an investigational drug/biologics or device within 4 weeks or within approximately 5 half-lives of the investigational drug/biologics,whichever is longer, before screening.

6. Not appropriate for the study according to the judgment of the investigator

Study Treatment

Not applicable, this is an observational study. Perampanel will be administered as per the judgment of the treating clinician.

Duration of Treatment

Subjects will be observed for up to 30 months (2.5 years) after initiation of perampanel monotherapy.

Concomitant Drug/Therapy

Not applicable.

Assessments

Demography data will be collected and recorded during screening period. It will consist of gender, age, hospitalization/outpatient, pregnancy, height, weight, history of drug allergies, comorbidities, complications, concomitant medications. Data from the treatment period will be obtained and recorded using EDC and the ePRO device. Concomitant medication and TEAEs will be recorded using EDC at each subject visit. Seizure diaries, study drug adherence, and QOL assessments will be recorded using an ePRO device provided to each subject.

Efficacy Assessments

1. Retention on perampanel will be assessed by treatment status (ongoing on perampanel or not) at each visit. Reasons for discontinuation will be recorded.

2. Number of seizures will be collected from the ePRO device. Subjects or their family members/ caregivers will be instructed in its use for recording seizure diaries. The seizure diaries input can be recorded at anytime when a seizure occurs and the presence or absence of a seizure is confirmed once a month via ePRO device reminder. This information will be recorded, sent to the data server, and used to calculate the seizure freedom. Seizure frequency data will be collected

retrospectively during the 3 months up to the day before Day 0 to ensure adequate data to calculate baseline seizure frequency per 28 days.

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

Safety Assessments

Safety assessments will consist of monitoring and recording all TEAEs. Information on TEAEs will be collected by open/general questions to subjects at each visit. Any spontaneously reported TEAEs between visits will also be captured. Exposure to perampanel will be assessed by recording perampanel dose at each visit.

Other Assessments

1. Overall QOL will be assessed using the EQ-5D-5L (with VAS) questionnaires with ePRO device for adult (16 years and older). For children from 12 to less than 16, it can be self-completed on a case-by-case basis. For children less than 12 years of age, it should be completed by parent/proxy.

The EQ-5D is the most widely used multi-attribute utility (MAU) instrument for measuring health-related quality of life in cost-effectiveness analysis. Questionnaires should be self-read and self-completed unless the subject has a physical disability that prevents him or her from doing so, or for children who are unable to do so. In these cases, a caregiver or study coordinator should read and/or record the subject's answers.

2. Psychosocial quality of life will be assessed using the PedsQL-Generic core scale questionnaires (emotional functioning, social functioning, and work/studies functioning domains) with ePRO device for adult (26 years and older), young adult (18-25 years old), adolescent (13-17 years old, children (8-12 years old), and young children (5-7 years old). PedsQL will not be administered for subjects 4 years of age as of date of informed consent.

The PedsQL Measurement Model is a 23-item modular approach for measuring health related quality of life in individuals in all age rangeswith acute and chronic health conditions. It is responsive to clinical changes over time. Questionnaires should be self-read and self-completed unless the subject has a physical disability that prevents him or her from doing so, or is unable to do so (e.g illiterate; pre-school). In these cases, a caregiver or study coordinator should read and/or record the subject's answers using the subject age-specific proxy versions of the PedsQL. For adult (26 years and older) and young adult (18-25 years old) there will be self administered only, and for adolescent (13-17 years old), children (8-12 years old), and young children (5-7 years old), there will be both self administered and proxy administered.

3. Brain wave activity during sleep will be assessed using the HARU-1 device.

HARU-1 is a palm-sized wearable device with a highly accurate patch-type EEG sensor to measure brain wave activities using multi-channel, stretchable, and user safety electrode sheet. The sensor makes continouous brain wave measurement possible for up to 10 hours. The data are sent automatically via bluetooth to the data center. Total sleep time (minutes of sleep from sleep onset until lights on), sleep efficiency (proportion of total sleep time per time spent in bed), sleep latency (estimated minutes from the time that the subjects attempts to sleep until sleep onset), WASO (minutes of wake from the onset of persistent sleep until lights on) and duration of sleep stage will be recorded.

4. Clinical factors to predict efficacy

Data for clinical factors to predict efficacy will be taken and recorded as medical history at the screening period, which are baseline seizure frequency, age at diagnosis, time since diagnosis, etiology (idiopathic, structural), and epileptic focus. Additionally, seizure freedom status at 3 months will also be considered as clinical factors.

5. Study drug adherence

Adherence on perampanel will be input by subjects using the ePRO device.

Bioanalytical Methods

Not applicable.

Statistical Methods

Data will be analyzed according to the Statistical Analysis Plan (SAP) using SAS or other validated statistical software, as necessary. The data will be fully tabulated with summary statistics for continuous variables and frequency and percent for categorical variables. Graphs, using summary values and individual line plots as appropriate, will be used to describe the data.

Study Endpoints

Primary Endpoint

1. Pragmatic seizure free rate at 24 months

Secondary Endpoints

1. The pragmatic seizure-free rate at 6, 12, 18 and 30 months

2. The sustained seizure-free rate at 12 and 24 months

3. Retention rate at 6, 12, 18, 24 and 30 months

4. Incidence of TEAEs over the entire study and the specific time points (month 0-3, 4-12 and 13-30)

5. Change from baseline in EQ-5D-5L and PedsQL to the specific time points (month 1, 3, 6, 12, 18, 24, 30)

Exploratory Endpoints

1. Change from baseline in total sleep time, sleep efficiency, sleep latency, WASO, and duration of sleep stage at the post-baseline measurement (at least 3 months after treatment initiation and remain stable at target dose of 4-8 mg/day for at least 4 weeks) until Months 12

2. Study drug adherence rate at month 1, 3, 6, 12, 18, 24 and 30

3. Clinical factors to predict seizure freedom at 3, 12 and 24 months

Analysis Sets

1. The Safety Analysis Set is the group of subjects who received at least 1 dose of perampanel and had at least 1 postdose safety assessment.

2. The Full Analysis Set (FAS) - All subjects who received at least 1 dose of perampanel will be included in the FAS.

Efficacy Analyses

1. For sustained seizure freedom rate: the number (percentage) of subjects with FOS who achieved seizure-freedom throughout the entire specified time period (numerator) as assessed in the FAS (denominator). Kaplan-Meier will be performed for survival analysis.

2. For pragmatic seizure-free rate: the pragmatic seizure-free rate at 6, 12, 18, 24 and 30 months in the FAS (the number of subjects free of all seizures at 6 months [and for the previous 3 months], and free of all seizures at 12, 18, 24 and 30 months [and for the previous 6 months][numerator], as a proportion of the FAS[denominator]). There will be no imputation for missing data – subjects

with missing data or not ongoing on perampanel at 6, 12, 18, 24 and 30 months will be assumed not to be seizure free.

3. For retention rate: the number (percentage) of subjects remaining on perampanel during the specified time period as assessed in the FAS.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Pharmacokinetic Analyses

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses

All safety analyses will be performed based on the Safety Analysis Set. Safety will be assessed over the entire study and also at specific timepoints (month 0-3, 4-12 and 13-30).
The TEAE verbatim descriptions (investigator terms from the case report form [CRF]) will be coded to system organ class (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number (percentage) of subjects with TEAEs and serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. The incidence of TEAEs will be summarized by severity (mild, moderate, or severe). Categorical variables (age range) will be summarized as number (percentage) of subjects by visit. Exposure to perampanel will be assessed by recording perampanel dose at each visit. Discontinuations because of adverse events will be analysed.

Other Analyses

1. QOL:
   - Overall QOL will be reported as the change in EQ-5D-5L score from the baseline at each designated time.
   - QOL will be reported as the change in the PedsQL-Generic core scales from the baseline at each designated time. Paired t-test will be performed for significance. To obtain the total scale score, scoring will be done following the PedsQL^{TM} algorithm.
2. Total sleep time, sleep efficiency, sleep latency, WASO, and duration of sleep stage
   - The changes from baseline in sleep variables (total sleep time, sleep efficiency, sleep latency, WASO, duration of sleep stage) collected in the HARU-1 device at the post-baseline measurement at any time until Months 12 will be determined. Each variable recorded in the device will be calculated using the data from 1 day or mean of the last 3 days before the visit.
3. Clinical Factor to predict efficacy
   - Logistic analysis will be performed. The dependent variable will be seizure free or not seizure free. Baseline seizure frequency, age at diagnosis, time since diagnosis, etiology (idiopathic, structural), and epileptic focus will be assessed individually in univariate analyses; however, all variables will be evaluated using multivariate analyses with forward, backward, or no selection. This analysis is aimed to identify potential predictive clinical factors for achieving seizure freedom or not in subjects with FOS at 3, 12 and 24 months. Additionally, seizure freedom status at 3 months will be used to explore predictiveness of long-term seizure freedom at 12 and 24 months
4. Study drug adherence rate

- The number (percentage) of subjects with more than 80%, 50 to 80%, and less than 50% perampanel taken will be summarized. Calculations of adherence are a snapshot of each designated time point (month 1, 3, 6, 12, 18, 24 and 30).

Interim Analyses

Since there is still lack of real world data of perampanel monotherapy, the length of the study, and perampanel LOE approaching soon, we want to make earlier publication. Thus, a total of 2 interim analyses are planned to be conducted. The first interim analyses will be conducted when all subjects have provided 6 months of data and the second one will be conducted when 12 months of data have been provided.

Sample Size Rationale

This study aims to collect data from approximately 60 subjects. No formal sample size calculation has been made, but this sample size is considered appropriate for an observational, open-label study. Assuming that the frequency of perampanel use is about 1.2 cases per month at epilepsy-specialized facilities that are actively prescribing perampanel monotherapy, it is estimated there would be approximately 120 cases annually at 10 facilities. Although this study is an observational study, the target number of subjects was set at 60, assuming that the consent acquisition rate will be 50% because the subjects required a certain degree of information and communications technologies (ICT) literacy. If additional facilities are considered necessary to proceed with the study, it will be limited to a maximum of 15 facilities. In addition, it is estimated that about 30% of wearable devices will be implemented, thus it will secure around 20 cases for the analysis.

Schedule of Procedures/Assessments in E2007-M081-515

Study Period	**Screening Period**	**Treatment Period**								**FU Period**
Timing	**Month -1 to Day 0**	**Day 0**	**Month 1[a]**	**Month 3[a]**	**Month 6[a]**	**Month 12[a]**	**Month 18[a]**	**Month 24[a]**	**Month 30[a] /DC**	**FU after DC[b]**
On-site assessments (during site visit)[a]										
Informed Consent[c]	X									
Demography	X									
Medical history (including epilepsy history)	X									
Inclusion/exclusion criteria	X									
Perampanel prescription[d]		X[d]								
Prior/Concomitant medication[d]	X	X[d]								X
Adverse event[d]		X[d]								X
Off-site assessments (using ePRO device) [e]										

Seizure diaries[e]		→								X
EQ-5D-5L and PedsQL[e]		X	X	X	X	X	X	X	X	X
Study drug adherence[e]			X	X	X	X	X	X	X	X
Sleep assessment	(X)[f]			(X)[g]						

DC = discontinuation, ePRO = electronic patient reported outcome, FU = follow-up, QOL = quality of life, LPS = latency to persistent sleep, TEAE = treatment emergent adverse event, SAE = serious adverse event

a. Each evaluation date is specified based on the date of Day 0, and each evaluation date should be implemented within ±7 days of the specified date.

b. For discontinued cases, follow-up evaluation will be conducted 4 weeks (+ 2 weeks) after last dose for TEAE/SAE follow up.

c. Obtain consent by electronic or paper based application. Informed consent/assent must be obtained before any study related procedure.

d. Site visit schedule during treatment period is based on the clinical practice. When subjects visiting the site, perampanel will be prescribed and concomitant medication and TEAEs will be recorded.

e. Subjects will enter data for seizure diaries, QOL, and study drug adherence using the ePRO device. For subjects less than 18 years old, family members/caregivers should enter on behalf of the subjects. The seizure diary input can be recorded at anytime when a seizure occurs, but the presence or absence of a seizure is confirmed once a month via ePRO reminder. For study drug adherence, subject will answer a question to review their adherence in the past one-month period at each designated time points.

f. At screening, the wearable device will be provided only for the subjects who have provided consent to sleep assessment and who report a tendency to a poor night's sleep (defined as a subjective sleep onset latency [sSOL] of 30 minutes or more, or subjective wake after sleep onset [sWASO] of 60 minutes), which are self-reported in the medical interview for at least 3 times a week over the previous month. Subject will be asked to take sleep measurements use the device for 1 day or mean of the last 3 days.

g. Only for subjects who have been on perampanel monotherapy for at least 3 months after treatment initiation and remain stable at target dose of 4-8 mg/day for at least 4 weeks will have post-baseline sleep measurements taken once using the HARU-1 wearable device at any time until Months 12.