Sustained Seizure Freedom with Perampanel 4 mg/day Monotherapy in Patients with Newly Diagnosed/Currently Untreated Recurrent Focal-Onset Seizures, With/Without Focal to Bilateral Tonic-Clonic Seizures: Post Hoc Analysis of Study 342 (FREEDOM)

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ABSTRACT DESCRIPTION

- **FREEDOM Study 342 evaluated perampanel monotherapy in patients with newly diagnosed or currently untreated focal-onset seizures, with or without focal to bilateral tonic-clonic seizures, in Japan and South Korea**
- **This interim analysis of the Study 342 Extension Phase assessed whether patients who achieved seizure freedom during the 26-week Core Study Maintenance Period sustained their seizure-free status through 52 weeks of continuous treatment with perampanel 4 mg/day monotherapy**
- **Overall, 62.5% (n=20/32) of patients who completed the Core Study while seizure free and then entered the Extension Phase remained seizure free during 52 weeks of treatment with perampanel 4 mg/day monotherapy**
- **Long-term (52 weeks) perampanel monotherapy was generally safe and well tolerated**

INTRODUCTION

- Perampanel is a once-daily oral anti-seizure medication (ASM) for focal-onset seizures (FOS) and generalized tonic-clonic seizures (GTCS)[1]
  - In the US and Japan, perampanel is approved as monotherapy and adjunctive therapy for FOS (with or without focal to bilateral tonic-clonic seizures [FBTCS]) in patients aged ⩾4 years, and adjunctive treatment of GTCS in patients aged ⩾12 years[1,2]
- FREEDOM Study 342 (NCT03201900) evaluated perampanel monotherapy in patients with newly diagnosed or currently untreated FOS, with or without FBTCS
  - Data from the Core Study Maintenance Period (26 weeks) indicate that perampanel 4 mg/day monotherapy is an effective and generally well tolerated treatment for FOS[3]
- This interim analysis of Study 342 aimed to assess whether seizure freedom with perampanel 4 mg/day achieved during the Core Study is maintained during 52 weeks of treatment

OBJECTIVES

- Study objectives included:
  - Establishing the long-term efficacy and safety of perampanel monotherapy in patients with newly diagnosed or currently untreated recurrent FOS
  - Determining the long-term outcomes of perampanel monotherapy in newly diagnosed patients with a history of different types of FOS

METHODS

Study design

- FREEDOM Study 342 was a multicenter, uncontrolled, open-label, single-arm, Phase III study of perampanel monotherapy in patients aged 12–74 years with FOS, with or without FBTCS, that was conducted in Japan and South Korea[3]
  - Patients had newly diagnosed epilepsy or recurrence of epilepsy after a period of remission (relapse ⩾2 years after the end of their most recent ASM treatment)
  - The Core Study consisted of 4-week Pretreatment and 32-week Treatment (6-week Titration; 26-week Maintenance) Phases
    - During the Titration Period, patients were titrated to perampanel 4 mg/day
    - Patients who tolerated perampanel 4 mg/day progressed to the 4 mg/day Maintenance Period; those who did not tolerate the titration schedule were discontinued from the study
    - Patients who could tolerate perampanel 4 mg/day but still experienced seizures during the 4 mg/day Maintenance Period could be transitioned to an 8 mg/day Treatment Phase (4-week Titration; 26-week Maintenance) based on the investigator's assessment of safety and tolerability
- After completion of the Core Study, patients who agreed could enter the optional Extension Phase and continue receiving perampanel monotherapy at the same dose as at the end of the Maintenance Period for an additional 26 weeks (total: 52 weeks of treatment)
- The 1981 International League Against Epilepsy seizure classification was referred to in the study protocol

Seizure-freedom rates

- This interim analysis of the Study 342 Extension Phase assessed sustained 52-week seizure-freedom rates for FOS in patients who achieved seizure freedom with perampanel 4 mg/day during the Core Study Maintenance Period (26 weeks) in the modified Intent-to-Treat (mITT) Analysis Set (the primary endpoint of the Core Study), and then sustained their seizure freedom through the Extension Phase (26 weeks) while continuing on perampanel 4 mg/day (Extension mITT Analysis Set)
  - The mITT Analysis Set included patients who provided informed consent, entered the Core Study 4 mg/day Maintenance Period, and had ⩾1 post-dose primary efficacy measurement in the Maintenance Period
  - The Extension mITT Analysis Set included all patients who received perampanel 4 mg/day from the mITT Analysis Set who entered the Extension Phase
- Sustained seizure freedom at 52 weeks was also analyzed based on medical history of seizure type
- Seizure freedom was recorded as the number and percentage of patients who were free from seizures and was based on entries from a patient's or caregiver's diary
- Data cut-off date for these analyses was February 28, 2019

Safety endpoints

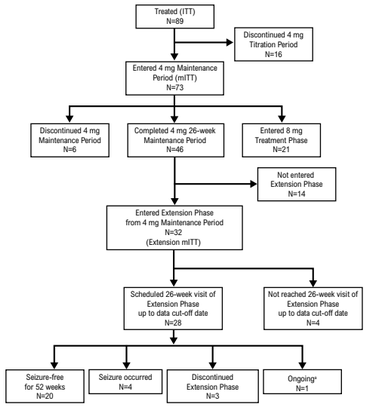
- Safety endpoints across the Core Study plus Extension Phase included monitoring of treatment-emergent adverse events (TEAEs)
  - TEAEs were defined as adverse events that emerged from the first perampanel dose to the last visit or 28 days after the patient's last dose, whichever came later, or adverse events that re-emerged during treatment, or worsened in severity during treatment relative to the pretreatment state
- Safety endpoints were assessed in the Safety Analysis Set (defined as all patients who provided informed consent, had received ⩾1 dose of perampanel, and had ⩾1 post-dose safety assessment), and were summarized using descriptive statistics

OUTCOMES

Patients

- Patient disposition is shown in Figure 1

Figure 1. Patient disposition



Data cut-off date: February 28, 2019
[a]Defined as patients remaining seizure free without reaching the Week 26 visit of the Extension Phase as of data cut-off
ITT, Intent-to-Treat; mITT, modified Intent-to-Treat

- In the Core Study, 89 patients with FOS received ⩾1 dose of perampanel and comprised the Safety Analysis Set
- Of these, 73 patients entered the 4 mg/day Maintenance Period and were included in the mITT Analysis Set
  - Six patients from the mITT Analysis Set discontinued, 46 patients completed the 4 mg/day Maintenance Period, and 21 patients experienced seizures and so entered the 8 mg/day Treatment Phase
- A total of 32/46 patients who completed the 4 mg/day Maintenance Period chose to enter the 26-week Extension Phase, giving a total of up to 52 weeks of treatment with perampanel 4 mg/day monotherapy; these patients were included in the Extension mITT Analysis Set
  - At data cut-off, 28/32 patients were scheduled to complete 52 weeks of treatment with perampanel 4 mg/day monotherapy (26-week Maintenance Period plus 26-week Extension Phase)

Seizure freedom at 52 weeks

- During the Core Study, 46/73 (63.0%) patients in the mITT Analysis Set achieved seizure freedom during the 26-week Maintenance Period with perampanel 4 mg/day monotherapy
- Of the 32 patients who then entered the 4 mg/day Extension Phase and were included in the Extension mITT Analysis Set, 20 (62.5%) patients achieved sustained seizure freedom at 52 weeks with perampanel 4 mg/day (27.4% of the Core Study mITT Analysis Set [n=20/73])
  - As noted above, there were four patients who entered the Extension Phase on 4 mg/day but had not completed 52 weeks of treatment at the time of data cut-off

Seizure freedom based on medical history of seizure type

- In patients with a history of FBTCS in the Core Study mITT Analysis Set, 31/48 (64.6%) patients achieved seizure freedom during the 26-week Maintenance Period
  - Analysis of the 17 patients with a history of FBTCS in the mITT Analysis Set who did not achieve 26-week seizure freedom showed that:
    - Four (23.5%) patients had no seizures but discontinued for other reasons
    - Thirteen (76.5%) patients experienced one or more seizures so entered the 8 mg/day Treatment Phase (FBTCS: n=6 [35.3%], focal impaired awareness seizures [FIAS]: n=5 [29.4%], focal aware seizures with motor signs: n=1 [5.9%], focal aware seizures without motor signs: n=1 [5.9%])
    - These data suggest that most patients with FBTCS who did not achieve 26 weeks of seizure freedom discontinued due to other reasons or experiencing other seizure types rather than a lack of control of FBTCS
- Based on patients in the Extension mITT Analysis Set who reported a history of FIAS (n=19), FIAS and/or FBTCS (n=31), or FBTCS (n=21), >55% of patients in each seizure group had sustained seizure freedom from 26 weeks through 52 weeks of perampanel 4 mg/day monotherapy treatment (Table 1)

Table 1. Seizure-freedom rates at 26 weeks (mITT Analysis Set) and 52 weeks (Extension mITT Analysis Set) based on medical history of seizure type

	Seizure-freedom rate, n (%)	
History of seizure type	26 weeks[a] n/N[b] (%)	52 weeks[c] n/N[d] (%)
FIAS	24/41 (58.5)	12/19 (63.2)
FIAS and/or FBTCS	43/70 (61.4)	19/31 (61.3)
FBTCS	31/48 (64.6)	12/21 (57.1)

Data cut-off date: February 28, 2019
[a]Includes the 26-week Core Study Maintenance Period
[b]Based on the mITT Analysis Set (patients who provided informed consent, entered the Core Study 4 mg/day Maintenance Period, and had ⩾1 post-dose primary efficacy measurement in the Maintenance Period)
[c]Includes the 26-week Core Study Maintenance Period plus the additional 26-week Extension Phase
[d]Based on the Extension mITT Analysis Set (all patients from the mITT Analysis Set who entered the Extension Phase on perampanel 4 mg/day)
FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; mITT, modified Intent-to-Treat

Safety outcomes

- TEAEs occurred in 72 (80.9%) patients in the Safety Analysis Set across the Core Study plus Extension Phase (Table 2)
- The most common TEAEs were dizziness, nasopharyngitis, and somnolence

Table 2. Overall incidence of TEAEs and most common TEAEs (⩾5% of patients) during the Core Study plus Extension Phase (Safety Analysis Set)

	Perampanel 4 mg/day (N=89)[a]	
	TEAEs	Treatment-related TEAEs
Any TEAE, n (%)	72 (80.9)	50 (56.2)
Most common TEAEs[b] (⩾5% of patients), n (%)		
Dizziness	32 (36.0)	29 (32.6)
Nasopharyngitis	17 (19.1)	0 (0.0)
Somnolence	12 (13.5)	10 (11.2)
Headache	11 (12.4)	2 (2.2)
Epilepsy	6 (6.7)	2 (2.2)

Data cut-off date: February 28, 2019
[a]Includes all treated patients
[b]Patients with >2 TEAEs with the same preferred term are counted only once for that preferred term
TEAE, treatment-emergent adverse event

CONCLUSION

- **Seizure freedom is sustained during long-term (52 weeks) treatment with perampanel 4 mg/day monotherapy in patients with newly diagnosed or currently untreated recurrent FOS, with or without FBTCS**
  - **52-week seizure freedom was achieved in 62.5% of patients who entered the Extension Phase on perampanel 4 mg/day having initially achieved seizure freedom in the Maintenance Period of the Core Study and then remained seizure free during the Extension Phase**
  - **Seizure freedom for 52 weeks was achieved irrespective of medical history of seizure type**
- **Perampanel 4 mg/day monotherapy was well tolerated during long-term treatment and the safety profile was consistent with the known safety profile of perampanel with no new TEAEs reported[1]**

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DISCLOSURES

Manoj Malhotra and Leock Y Ngo are employees of Eisai Inc.

Ji Hyun Kim and Sung Chul Lim have no real or apparent conflicts of interest to disclose in relation to this work.

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If you have any questions about this poster, please email or call Eisai Medical Information at ESI_Medinfo@eisai.com or 888-274-2378