Adjunctive Perampanel for Generalized Tonic-Clonic Seizures: Time to Seizure Onset in Phase III Study 332

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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, perampanel is approved as monotherapy and adjunctive therapy for FOS (with or without focal to bilateral tonic-clonic seizures) in patients aged ⩾4 years, and for adjunctive treatment of GTCS in patients aged ⩾12 years[1]
- Adjunctive perampanel 8 mg/day has previously been shown to be well tolerated and effective at improving control of GTCS in the randomized, double-blind, placebo-controlled, Phase III Study 332 (NCT01393743) in patients aged ⩾12 years[2]
- This post hoc analysis further evaluates the efficacy of adjunctive perampanel for GTCS by assessing the time to first seizure following perampanel administration using data from Study 332

OBJECTIVES

- Study objectives included:
  - Determining whether the use of perampanel 8 mg/day leads to the prolonged time to first seizure onset in patients with GTCS and in patients with any seizure type when compared with placebo
  - Further establishing the safety of adjunctive perampanel 8 mg/day in patients with GTCS

METHODS

Study design and endpoints

- The design of Study 332 has been previously published[2]
  - Briefly, patients aged ⩾12 years with idiopathic generalized epilepsy and uncontrolled GTCS, despite treatment with 1–3 ASMs, were randomized to receive once-daily placebo or adjunctive perampanel (target dose: 8 mg/day) across a 17-week Double-blind Treatment Period (4-week Titration; 13-week Maintenance)
- Primary efficacy endpoints in the Full Analysis Set (all randomized patients who received ⩾1 dose of study drug and had any post-baseline seizure frequency data) were median percent change in GTCS frequency per 28 days from baseline and 50% responder rates (proportion of patients with a ⩾50% reduction in seizure frequency during Maintenance compared with baseline; primary endpoint in the EU)
  - Efficacy outcomes for all seizure types were also assessed
- Safety was assessed in the Safety Analysis Set (all patients who received ⩾1 dose of study drug and had any post-baseline safety data), and included monitoring of treatment-emergent adverse events (TEAEs)

Time to first seizure analysis

- For this post hoc analysis, time to first seizure onset from Day 1 of placebo or perampanel administration (initial dose of 2 mg/day, up-titrated in weekly 2-mg increments to the targeted dose of 8 mg/day) was assessed in the Full Analysis Set using the Kaplan–Meier method
- Summary statistics were determined without taking into account any censoring

OUTCOMES

Patients

- Overall, 163 patients were included in the Safety Analysis Set (placebo, n=82; perampanel, n=81) and 162 in the Full Analysis Set (placebo, n=81; perampanel, n=81)

Table 1. Baseline patient demographics and disease characteristics (Full Analysis Set)[2]

	Placebo (n=81)	Perampanel 8 mg/day (n=81)	Total (N=162)
Mean (SD) age, years	29.5 (12.2)	27.3 (10.5)	28.4 (11.4)
Female, n (%)	45 (55.6)	46 (56.8)	91 (56.2)
Mean (SD) time since epilepsy diagnosis,[a] years	18.6 (12.6)	15.7 (10.8)	17.2 (11.8)
Seizure type[a,b]			
Tonic-clonic	82 (100.0)	81 (100.0)	163 (100.0)
Myclonic	33 (40.2)	32 (39.5)	65 (39.9)
Absence	41 (50.0)	42 (51.9)	83 (50.9)
Clonic	1 (1.2)	0 (0.0)	1 (0.6)
Tonic	2 (2.4)	0 (0.0)	2 (1.2)
Atonic	1 (1.2)	0 (0.0)	1 (0.6)
Number of concomitant ASMs at baseline,[a] n (%)			
1	29 (35.4)	26 (32.1)	55 (33.7)
2	36 (43.9)	39 (48.1)	75 (46.0)
3	16 (19.5)	16 (19.8)	32 (19.6)
4	1 (1.2)	0 (0.0)	1 (0.6)

[a]Based on the Safety Analysis Set (n=82 for placebo and N=163 for total column)
[b]Patients may have more than one seizure type
ASM, anti-seizure medication; SD, standard deviation

- Patient demographics and clinical characteristics were similar across treatment groups (Table 1)[2]
- The most common concomitant ASMs received during baseline were lamotrigine (n=64 [39.3%]), valproic acid (n=55 [33.7%]), levetiracetam (n=51 [31.3%]), and topiramate (n=25 [15.3%])
- Median (minimum, maximum) GTCS frequency per 28 days during baseline was 2.6 (1.4, 18.5) for patients in the perampanel group and 2.5 (1.0, 11.7) for patients in the placebo group

ABSTRACT DESCRIPTION

- **This poster presents a post hoc analysis of time to first seizure onset following administration of placebo or adjunctive perampanel 8 mg/day in patients (aged ⩾12 years) with generalized tonic-clonic seizures (GTCS) who participated in Study 332**
- **Time to first GTCS was prolonged by once-daily adjunctive perampanel 8 mg/day administration (45.3 days) compared with placebo (27.0 days)**
- **Time to first seizure of any type was also prolonged with perampanel 8 mg/day (31.2 days) compared with placebo (12.5 days)**
- **These data further support the efficacy of adjunctive perampanel 8 mg/day for the treatment of GTCS**

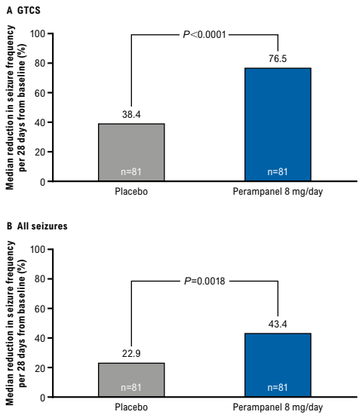
Primary efficacy endpoints

- As previously reported, adjunctive perampanel 8 mg/day conferred significantly greater median percent reductions in GTCS frequency per 28 days from baseline compared with placebo ($P<0.0001$; Figure 1A)[2]
- For all seizure types, median percent reductions in seizure frequency were also significantly greater with adjunctive perampanel 8 mg/day vs placebo ($P=0.0018$; Figure 1B)
- Fifty-percent responder rates were significantly greater with perampanel 8 mg/day compared with placebo for GTCS (64.2% [n=52/81] vs 39.5% [n=32/81], respectively; $P=0.0019$)[2]
- For all seizures, 50% responder rates were numerically higher with perampanel 8 mg/day compared with placebo (45.7% [n=37/81] vs 34.6% [n=28/81], respectively), but the difference was not statistically significant ($P=0.1826$)

Time to first seizure

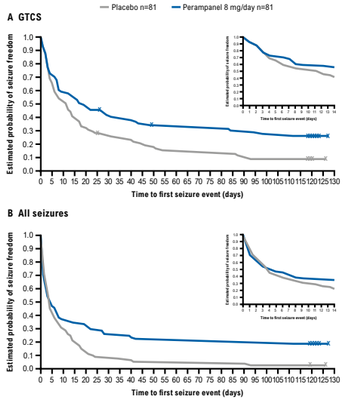
- Treatment with adjunctive perampanel 8 mg/day prolonged the time to first GTCS compared with placebo ($P=0.0076$; Figure 2A)
- Adjunctive perampanel 8 mg/day was also associated with a longer time to first seizure of any type compared with placebo ($P=0.0086$; Figure 2B)

Figure 1. Median percent reductions in seizure frequency per 28 days with placebo and adjunctive perampanel 8 mg/day in Study 332 for (A) GTCS[2] and (B) all seizures (Full Analysis Set)



GTCS, generalized tonic-clonic seizures

Figure 2. Kaplan–Meier plots of time to first seizure in patients who received placebo vs once-daily adjunctive perampanel 8 mg/day in Study 332 for (A) GTCS and (B) all seizures (Full Analysis Set)



Estimated survival probability is based on the number of days to first seizure
+ represents a censored observation
GTCS, generalized tonic-clonic seizures

- Summary statistics for time to first seizure are shown in Table 2
  - Mean time to first GTCS was 45.3 days for perampanel 8 mg/day and 27.0 days for placebo
  - Mean time to first seizure of any type was 31.2 days for perampanel 8 mg/day and 12.5 days for placebo

Table 2. Summary statistics for time to first seizure (Full Analysis Set)

	Placebo (n=81)	Perampanel 8 mg/day (n=81)
Time to first GTCS, days		
Mean	27.0	45.3
Median (min, max)	12 (1, 126)	19 (1, 127)
Time to first seizure (any type), days		
Mean	12.5	31.2
Median (min, max)	4 (1, 126)	5 (1, 127)

GTCS, generalized tonic-clonic seizures; max, maximum; min, minimum

Safety outcomes

- Safety data have been published previously for Study 332[2]; however, briefly, TEAEs were reported by 82.7% of patients receiving perampanel 8 mg/day and 72.0% of patients receiving placebo (Table 3)
  - The most common TEAEs were dizziness, fatigue, and headache (Table 3)
  - Serious TEAEs were reported in similar proportions of perampanel- and placebo-treated patients (7.4% and 8.5%, respectively)
  - TEAEs leading to discontinuation were reported in nine (11.1%) perampanel-treated patients and five (6.1%) placebo-treated patients
    - Those that led to discontinuation of more than one patient in the perampanel group included dizziness (n=2) and vomiting (n=2)

Table 3. Overview of TEAEs and the most common TEAEs (occurring in ⩾5% of patients in either group) in Study 332 (Safety Analysis Set)[2]

	Placebo (n=82)	Perampanel 8 mg/day (n=81)
Any TEAE, n (%)	59 (72.0)	67 (82.7)
Serious TEAEs, n (%)	7 (8.5)	6 (7.4)
TEAEs leading to discontinuation, n (%)	5 (6.1)	9 (11.1)
Most common TEAEs, n (%)		
Dizziness	5 (6.1)	26 (32.1)
Fatigue	5 (6.1)	12 (14.8)
Headache	8 (9.8)	10 (12.3)
Somnolence	3 (3.7)	9 (11.1)
Irritability	2 (2.4)	9 (11.1)
Nasopharyngitis	7 (8.5)	7 (8.6)
Vertigo	2 (2.4)	7 (8.6)
Vomiting	2 (2.4)	7 (8.6)
Weight increased	3 (3.7)	6 (7.4)
Contusion	3 (3.7)	5 (6.2)
Nausea	4 (4.9)	5 (6.2)

TEAE, treatment-emergent adverse event

CONCLUSION

- **Adjunctive treatment with once-daily perampanel 8 mg/day prolonged the time to first GTCS (45.3 days) or any type of seizure (31.2 days) in patients aged ⩾12 years with GTCS compared with placebo (27.0 and 12.5 days, respectively)**
- **Adjunctive perampanel doses of 8 mg/day have previously been shown to be generally well tolerated in patients with GTCS[2]**
- **These data are consistent with the primary efficacy endpoints of Study 332 and further support the efficacy of perampanel 8 mg/day for the treatment of GTCS**

BIBLIOGRAPHY

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DISCLOSURES

Manoj Malhotra is an employee of Eisai Inc.

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Poster presented at the Neuroscience Nursing Annual Conference, Phoenix, AZ, USA, March 12–15, 2022*

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