SPN-817 Phase 2a Study

Exploratory Open Label Study in Adult Patients with Treatment Resistant Epilepsy

Interim Results

May 23, 2024

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Introduction and Agenda

- Executive Summary
- SPN-817 Overview
- Phase 2a Study Design and Interim Results
- Conclusions

Executive Summary

- The preliminary and emerging clinical profile of SPN-817 suggests that it can be:

A highly differentiated anti-seizure product for focal seizures

- Overall strong efficacy
- High responder rates
- Higher efficacy in more severe patients
- Potential for cognitive improvement
- Safety with competitive tolerability profile
- Novel and unique MOA for epilepsy

SPN-817 Overview

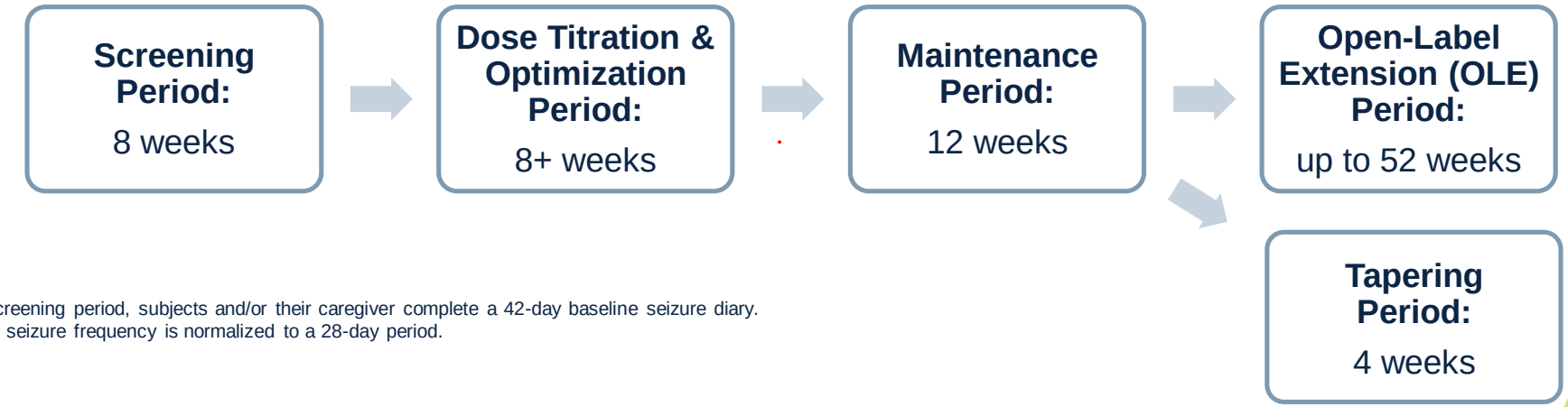
A New Class of Therapy
Only AChE Inhibitor in Development for Focal Seizures

- Huperzine A is a potent, selective and reversible acetylcholinesterase (AChE) inhibitor, an enzyme that metabolizes acetylcholine (ACh) after synaptic release[1,2]
- Inhibition of AChE increases extracellular levels of ACh
- ACh augmentation activates cholinergic pathways in different cellular types in the brain
  - Restores excitatory/inhibitory balance for seizure control
- Broad and potent anti-seizure effect in different seizure and genetic models of epilepsy[1-4]

[1] Supernus data on file
[2] Damar et al. (2016). *Expert Rev Neurother, 16*(6), 671-680
[3] Wong et al (2016). *Front Pharmacol, 7*, 357
[4] Wong et al (2021). *Neuropsychopharmacology, 46*(11), 2011-2020

SPN-817 Phase 2a Study Design

- **Design**: Phase 2a, open-label, flexible-dose, safety and tolerability exploratory study
- **Sample size**: 41 adult subjects with treatment resistant seizures
  - At least 4 motor seizures during screening - median baseline seizure frequency was 11.3
  - Took at least one concomitant anti-seizure medication (ASM), no upper limit - average number of concomitant ASMs was 3.4 (range 1-6)
- **Study sites**: 8 sites in Australia
- **SPN-817 administration**: Orally, twice daily, 0.25 mg – 4.0 mg



During the screening period, subjects and/or their caregiver complete a 42-day baseline seizure diary. The baseline seizure frequency is normalized to a 28-day period.

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SPN-817 Phase 2a Study Design

Primary Safety Endpoints

- Adverse events (AEs)
- AEs leading to discontinuation

Key Secondary/Exploratory Endpoints

- Percent change from baseline in quantifiable motor seizure frequency per 28 days throughout SPN-817 dosing during maintenance period/OLE
- Treatment response defined as ≥30%, ≥50%, and ≥75% reduction in quantifiable motor seizure frequency per 28 days relative to the baseline period
- Change from baseline in Clinical Global Impression-Severity (CGI-S) scores
- Change from baseline in cognitive profile as assessed by EpiTrack®

EpiTrack® is a cognitive screening tool designed for patients with epilepsy to evaluate cognitive effects of antiseizure medications

Subject Disposition

	All Screened Subjects n (%)
Screened	46
Safety Population	41
Discontinuation (Titration)	
Adverse event	9 (22.0)
Lack of efficacy	2 (4.9)
Withdrawal by subject	2 (4.9)
Discontinuation (Maintenance)	
Adverse event	1 (2.4)
Lack of efficacy	1 (2.4)

* Data cutoff – May 1, 2024

Safety and Tolerability Overall Summary

Category	Titration Period (n=41) n (%)	Maintenance Period (n=24) n (%)
Subjects with at least one treatment related TEAE	39 (95.1)	11 (45.8)
Subjects with any treatment related serious AE*	1 (2.4)	0
Maximum severity of treatment related TEAE**		
Mild	18 (43.9)	7 (29.2)
Moderate	21 (51.2)	4 (16.7)
Severe	0	0
Any AE leading to death	0	0

Safety Population (Main Study)

*One subject had a Serious AE of dizziness and nausea that led to hospitalization at 0.25mg BID of SPN-817. Subject recovered.
**Subjects are counted only once at the worst severity. If a severity designation is missing, it will be considered as severe.

The Main Study consists of relevant data from Screening, Titration/Optimization, and Maintenance.
Treatment Emergent Adverse Event (TEAE) is an adverse event (AE) with a start date on or after the first dose of study medication is taken, or that worsened following first administration of study medication.
Treatment Related AEs are those reported as Definitely Related, Possibly Related, and those with no relatedness reported.

Safety and Tolerability

Treatment related TEAEs (≥5% incidence)

Preferred Term	Titration (n=41) n (%)	Maintenance (n=24) n (%)
Subjects with at least one TEAE	39 (95.1)	11 (45.8)
Nausea*	20 (48.8)	3 (12.5)
Diarrhea	10 (24.4)	3 (12.5)
Headache	9 (22.0)	1 (4.2)
Dizziness	8 (19.5)	1 (4.2)
Decreased appetite	8 (19.5)	0
Fatigue	5 (12.2)	1 (4.2)
Insomnia	6 (14.6)	0
Vomiting*	5 (12.2)	1 (4.2)
Vision blurred	5 (12.2)	0
Somnolence	4 (9.8)	0
Irritability	3 (7.3)	0

*Anti-emetics only utilized in 7 subjects that experienced emetic events

Treatment Emergent Adverse Event (TEAE) is an adverse event (AE) with a start date on or after the first dose of study medication is taken, or that worsened following first administration of study medication.
AEs were coded using MedDRA version 25.0. Subjects are counted once for each preferred term.

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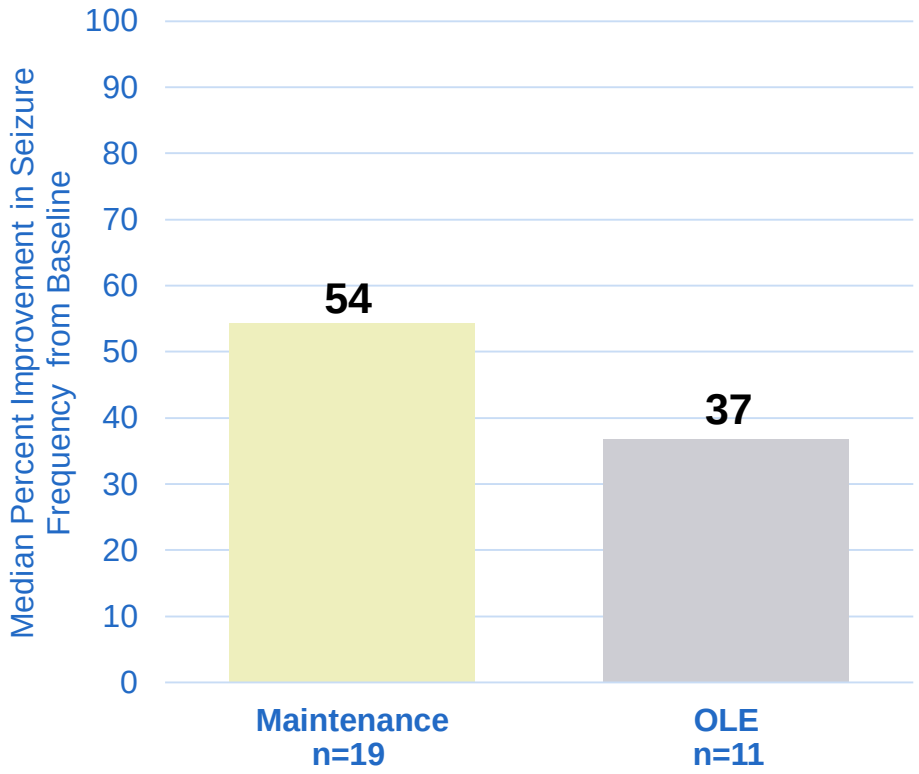
Efficacy in All Seizure Types Across All Doses

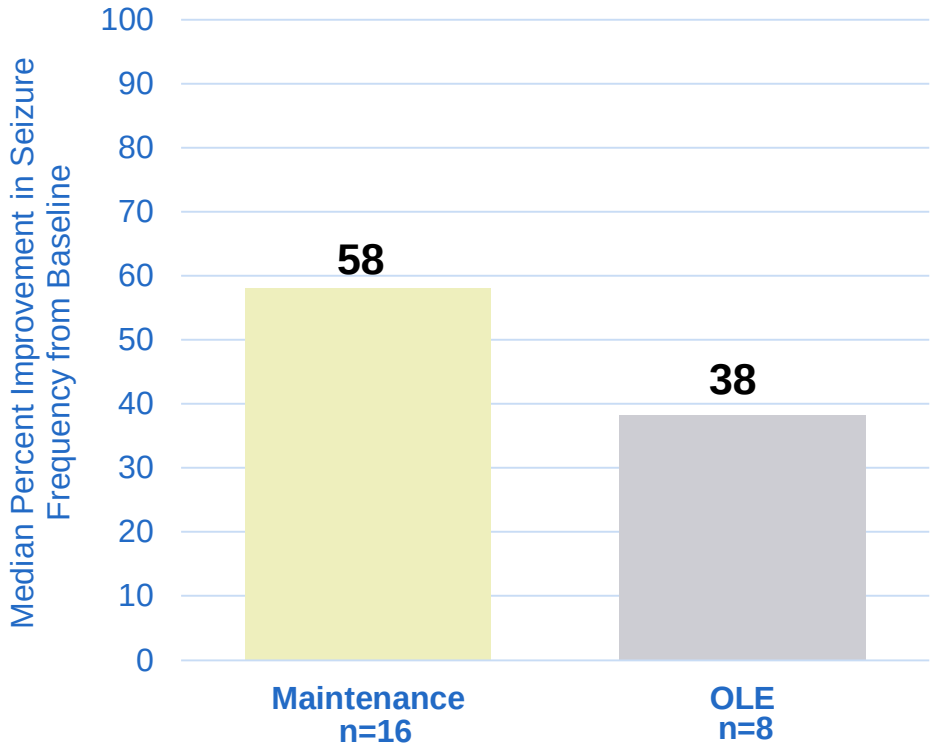
Percent Reduction from Baseline in Seizure Frequency



Baseline=42-day period prior to the initiation of study medication.
Graph includes only countable seizures (Types B, C, D, E, H, I, J, K, and L).
Subjects must have at least 14 days with seizure diary reported within the specified timeframe to be included in the timeframe.
Seizure Frequency is determined as the (number of seizures that occurred in the specified timeframe/number of days with seizure diary reported in the specified timeframe) * 28.

Efficacy in Focal Seizures Across All Doses

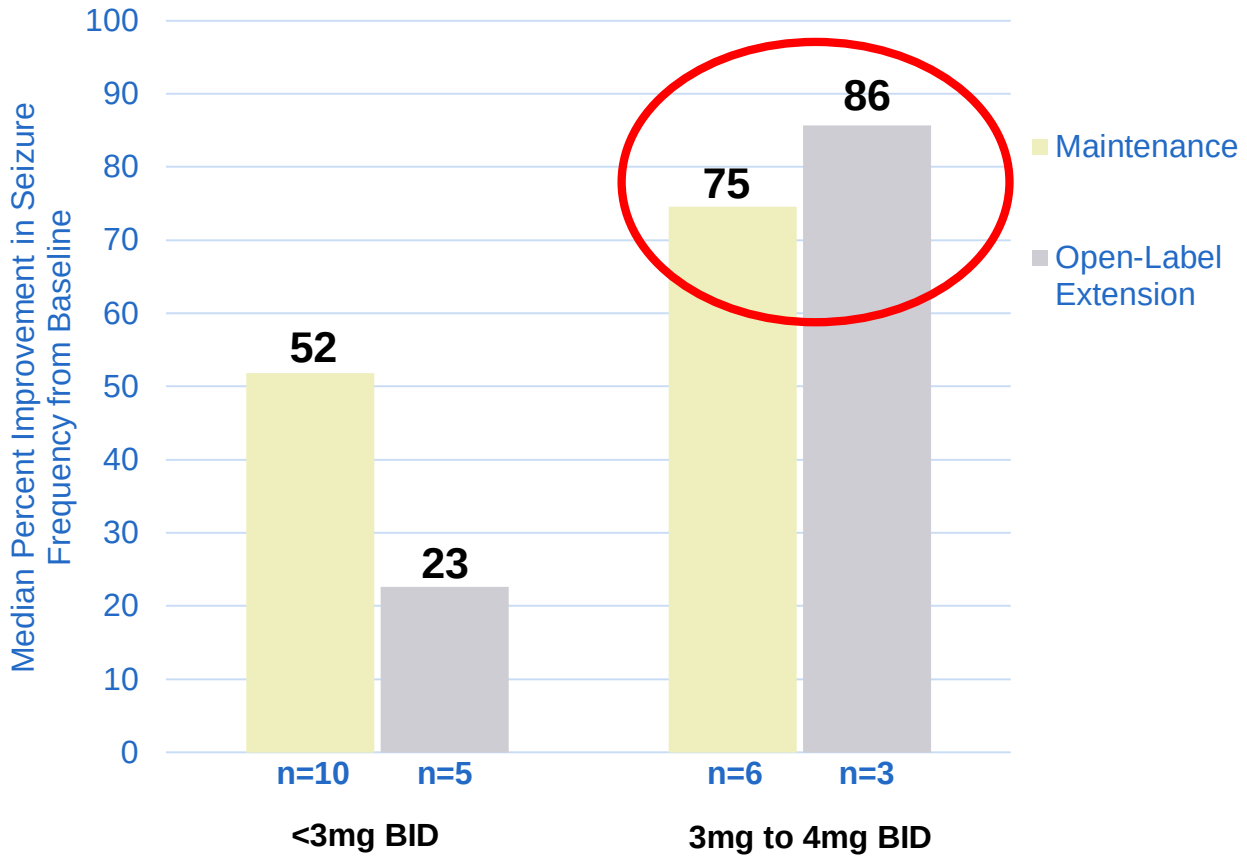
Percent Reduction from Baseline in Seizure Frequency



Subjects that had any Focal Type Seizures (A, B, C, or D) adjudicated at Baseline are included in the Focal Seizures group.

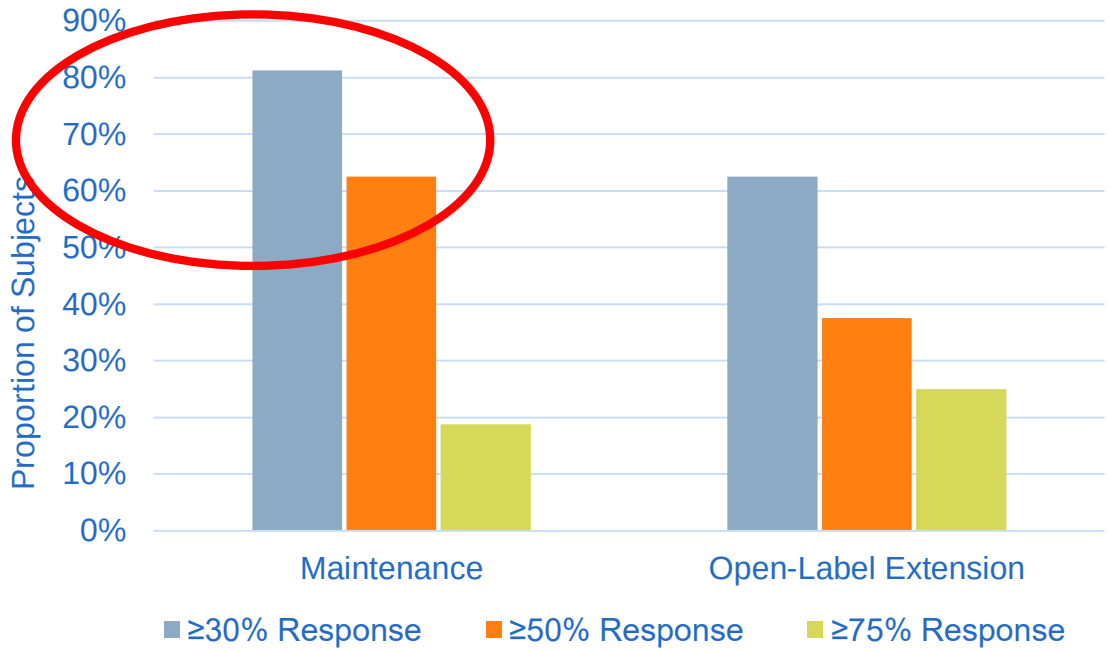
Efficacy in Focal Seizures by Maximum Dose

Percent Reduction from Baseline in Seizure Frequency



High Response Rate in Focal Seizures

Study Period	≥30% Response n/m (%)	≥50% Response n/m (%)	≥75% Response n/m (%)
Maintenance	13/16 (81%)	10/16 (63%)	3/16 (19%)
Open-Label Extension	5/8 (63%)	3/8 (38%)	2/8 (25%)*



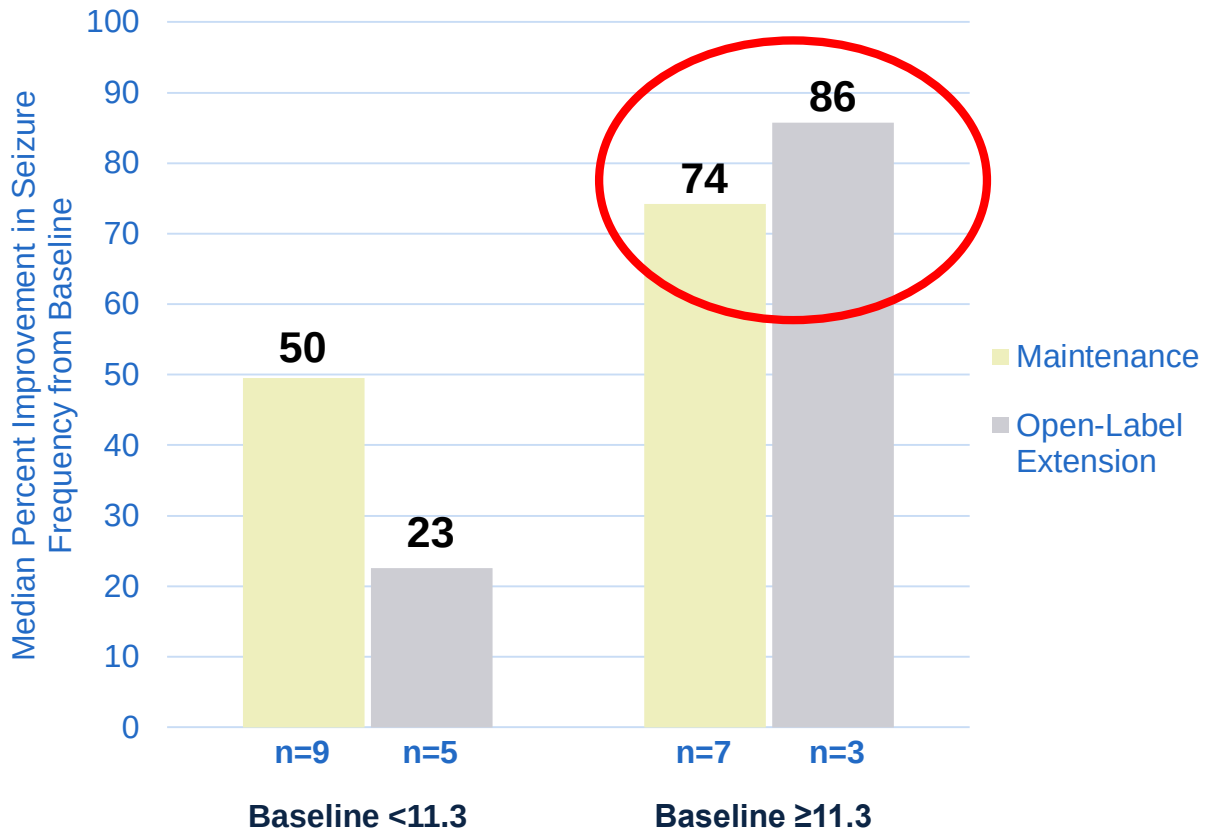
*One subject achieved **91%** seizure reduction during overall OLE and has been **seizure-free** for the most recent 7 weeks.*

*Another subject achieved **86%** reduction in the OLE.*

n is the count of subjects who have response in the category; m is the total count of subjects who have non-missing change from baseline data during the period.
Subjects that had any focal type seizures (A, B, C, or D) adjudicated at baseline are included in the focal seizures group.

Efficacy in Focal Seizures By Baseline Seizure Frequency

Percent Reduction from Baseline in Seizure Frequency



During the screening period, patients and/or their caregiver complete a 42-day baseline seizure diary. The baseline seizure frequency is normalized to a 28-day period.

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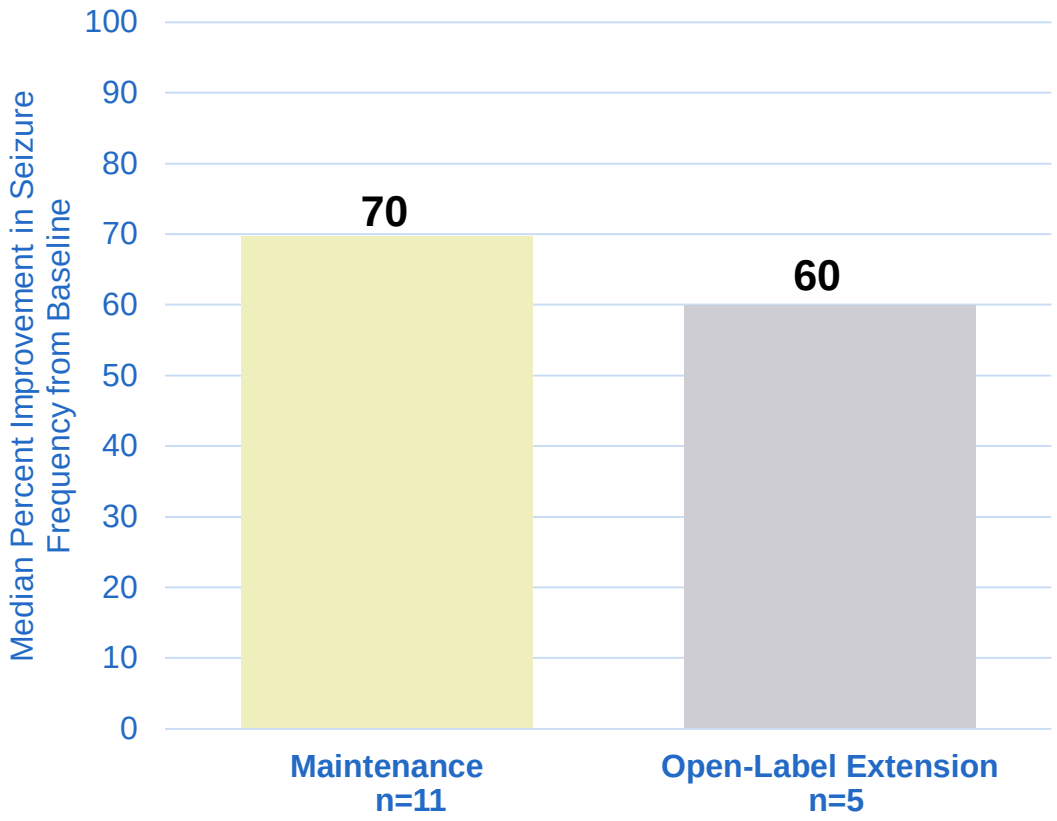
Efficacy in Focal Seizures
Subjects with ≥3 ASMs at Baseline

Percent Reduction from Baseline in Seizure Frequency



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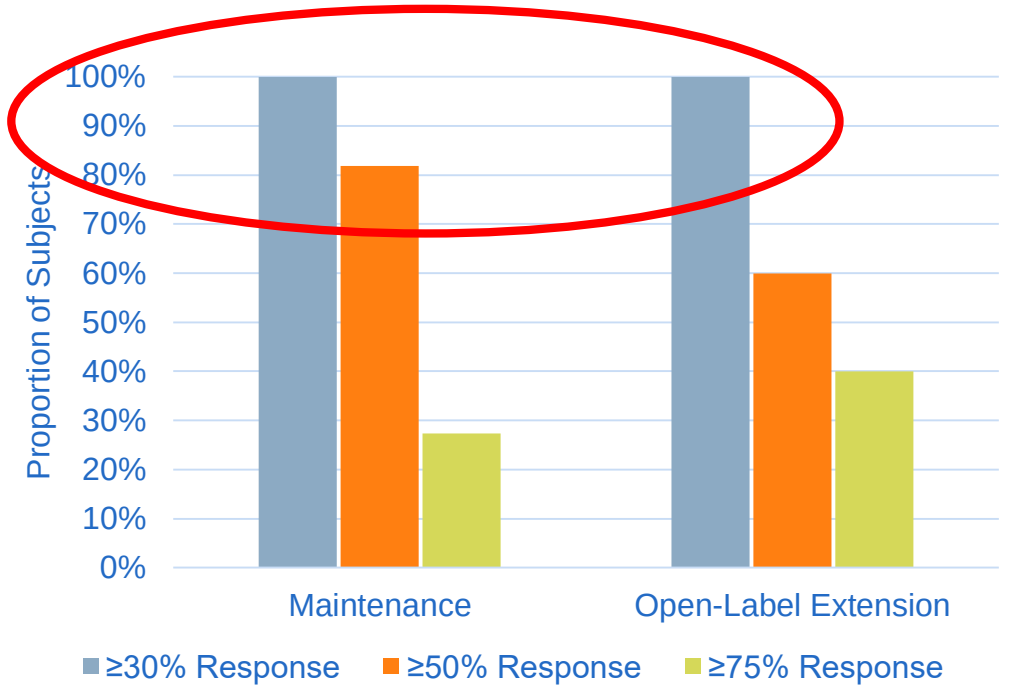
Response Rate (Focal Seizures)
Subjects with ≥3 ASMs at Baseline

Study Period	≥30% Response n/m (%)	≥50% Response n/m (%)	≥75% Response n/m (%)
Maintenance	11/11 (100)	9/11 (82)	3/11 (27)
Open-Label Extension	5/5 (100)	3/5 (60)	2/5 (40)



n is the count of subjects who have response in the category; m is the total count of subjects who have non-missing change from baseline data during the period.

CGI and EpiTrack Results

Secondary Outcome Measure	Baseline Mean (SD)	End of Maintenance Mean (SD)	End of Maintenance CFB Mean (SD)
CGI-S Score, n=16	3.4 (1.6)	2.7 (0.8)	-0.8 (1.4)
EpiTrack (Total Adjusted Score), n=12	**28.7 (8.1)**	**30.9 (6.4)**	**2.3 (5.7)**

- EpiTrack assessment of cognition
  - 10/12 (83%) improved or unchanged
  - 5/12 (42%) improved
    - 3 subjects improved from “significantly impaired” cognition (EpiTrack score ≤28) at baseline to “average” cognition (EpiTrack score of 32-38) at the end of maintenance period

Conclusions

- **Safety & Tolerability**
  - Most TEAEs occurred during titration
    - As expected, cholinergic side effects are the most common
  - In maintenance period, SPN-817 was well tolerated with 2.4% discontinuation rate due to AEs
  - Discontinuations during titration can be managed going forward with fixed short period of antiemetic use

- **Efficacy**
  - Strong efficacy in focal seizures at the 3mg to 4mg twice daily doses
    - 75% median seizure reduction in maintenance period
    - 86% median seizure reduction in OLE
  - High responder rates across all doses in maintenance period
    - 81% of subjects had 30% or more focal seizure reduction
    - 63% of subjects had 50% or more focal seizure reduction
    - 19% of subjects had 75% or more focal seizure reduction

Conclusions

- **Efficacy**
  - Median focal seizure reduction in subjects with 3 or more other ASMs:
    - 70% in maintenance period
    - 60% in OLE
  - High responder rates in subjects across all doses with 3 or more ASMs:
    - 100% of subjects had 30% or more focal seizure reduction
    - 82% of subjects had 50% or more focal seizure reduction
    - 27% of subjects had 75% or more focal seizure reduction
  - Median focal seizure reduction in more severe subjects with higher than 11.3 mean baseline number of seizures per 28-day period:
    - 74% in maintenance period
    - 86% in OLE
  - Median focal seizure reduction achieved by 16 subjects across all doses
  - 58% in maintenance period
  - 38% in OLE

Conclusions

- **Cognitive Improvement**
  - Assessment by the validated EpiTrack indicated:
    - 83% of subjects equally split between improved or unchanged at the end of maintenance period

- **Plan Forward**
  - Extending the open label study to assess approaches to mitigate typical cholinergic AEs
    - Full results of Phase 2a (excluding above extension) in 2H 2024
  - Initiation of Phase 2b by year-end 2024