Poster #1.494

Optimal Cut Point for Reduction in Long Episode Frequency to Predict Meaningful Change in Clinical Seizure Frequency

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Background

- Novel proof-of-concept (POC) designs utilizing validated biomarkers with positive predictive ability of antiseizure medication (ASM) treatment effects are needed that:
  - Provide smaller patient numbers with the ability to predict success of Phase 3 studies via models that closely represent clinical seizure (CS) activity[1]
  - Are not reliant on patient diaries, which have been shown to under- and over-report seizures[2]
- The responsive neurostimulator (RNS® System, NeuroPace)[3] continually senses electrocorticographic activity and responds to electrographic seizure onset with bursts of electrical stimulation
- The RNS® System also continuously detects long episodes (LEs): runs of ictal or interictal epileptiform activity (typically 30-60 sec) that represent electrographic seizures and provide an objective surrogate for CS counts[4]
- A change of at least 30% in LE frequency following a new ASM start has been reported to correlate with change in CS frequency[5,6]

Objectives

Using data from an open-label, long-term treatment study of the RNS® System and an anchor-based approach based on change in patient-reported CS frequency:

- Examine the relationship between change in LE frequency and change in CS frequency
- Define the cut point for LE frequency reduction that correlates with a clinically meaningful improvement in CS frequency (≥50% reduction)

Methods

- Retrospective data, including LE and CS frequency, were obtained from a long-term treatment study of the RNS® System[3,7,8]
  - Data inclusion criteria were based on inclusion criteria utilized for the POC Phase 2A study of RAP-219
  - Data from patients who met the following criteria were obtained for the 8 weeks prior to ("pre-start baseline") and 8 weeks following ("post-start period") ASM start:
    - Received ≥1 dose of a new ASM
    - No changes to the RNS® System settings during the pre-start baseline and post-start period
    - ≥8 LEs per 28 days during the pre-start baseline
    - Data available for both LE and CS frequency during the pre-start baseline and post-start period

Outcomes

- Relationship between the percentage change in LE frequency and percentage change in CS frequency
  - Median change (%) in LE frequency and in CS frequency per 28 days
    - Post-start period vs pre-start baseline
    - LE frequency: recorded by the RNS® System (LE criteria, individually predefined by epileptologist, held stable during assessment period)
    - CS frequency: recorded in daily seizure diaries
  - Change (%) in LE and CS frequency from baseline for each patient
  - Change (%) in LE frequency per 28 days from baseline was assessed by CS responder subgroup
    - Patients with <25%, 25 to <50%, 50% to <75%, and 75% to 100% reduction in frequency from baseline
  - Reduction (%) in CS and LE frequency in patients with ≥30% LE reduction
- Receiver operating characteristics (ROC) of the LE reduction threshold to predict clinically meaningful (≥50%) or profound reduction (≥75%) in CSs where sensitivity is approximately equal to specificity
  - CS responder status defined as <50% vs ≥50% reduction from baseline in CS frequency or <75% vs ≥75% reduction as the dependent variable

Results

- Data from 45 patients who initiated clobazam (CLB; n=15, 33%), levetiracetam (LEV; n=4, 11%), or lacosamide (LCM; n=26, 57%) were included in the analysis (**Table 1**)
- An RNS® System electrode was implanted in the mesial temporal lobe of ~70% of patients included in this analysis

Table 1. Demographics and Baseline Characteristics

	CLB n=15	LEV n=4	LCM n=26	Overall N=45
Female, n (%)	4 (26.7)	3 (75.0)	9 (34.6)	16 (35.6)
Age at ASM start, years, mean±SD	39.8±11.9	24.5±2.3	36.5±11.1	36.5±11.8
RNS® System lead placement[a] foci, n (%)				
Medial temporal lobe (MTL)	4 (26.7)	1 (25.0)	9 (34.6)	17 (37.8)
Neocortical	5 (33.3)	2 (50.0)	10 (38.5)	14 (31.1)
MTL + neocortical	6 (40.0)	1 (25.0)	7 (26.9)	14 (31.1)

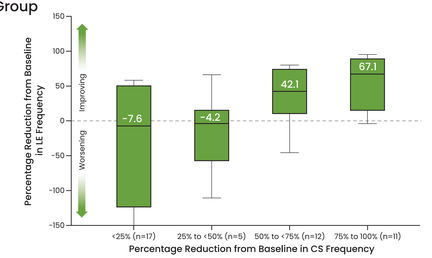
[a]Placement based on seizure onset foci as mapped prior to implant of RNS® System.
ASM – antiseizure medication; **CLB** – clobazam; **LEV** – levetiracetam; **LCM** – lacosamide; **MTL** – medial temporal lobe.

- Overall (N=45), patients experienced a median -27.8% change in LE frequency and median -47.6% change in CS frequency

Change in LE Frequency by CS Responder Group

- A linear correlation between change in LE frequency and CS responder group (patients with <25%, 25 to <50%, 50% to <75%, and 75% to 100% reduction in frequency from baseline) was observed (**Figure 1**)

Figure 1. Percentage LE Frequency Reduction by CS Responder Group

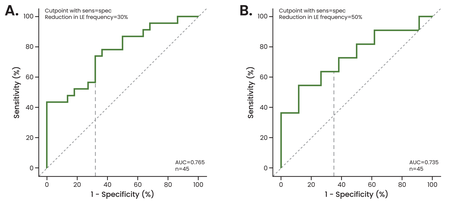


The bottom and top edges of the box indicate interquartile range (IQR). The line inside the box indicates the median value (value in white text above median line). The vertical lines represent the most extreme point within the 1.5*IQR. Any value more extreme than this is marked with a circle. The <25% reduction category may include patients with no change or an increase in frequency. Patients with greater than 150% worsening from baseline in LE frequency are included in the analysis but are not presented in the figure to enhance readability. Clinically meaningful change: ≥50% reduction in CS frequency; profound change: ≥75% reduction in CS frequency.
CS – clinical seizure; **LE** – long episode.

ROC Analysis

- A ≥30% reduction in LE frequency was identified as the optimal cut point that correlates with a clinically meaningful reduction (≥50% reduction from baseline) in CS (AUC=0.765; **Figure 2A, Table 2**)
- A ≥49.6% reduction in LE frequency was identified as the cut point for profound change (≥75% reduction from baseline) in CS (AUC=0.735; **Figure 2B**)

Figure 2. LE Frequency Percentage Reduction Cut Point for **A.** ≥50% and **B.** ≥75% CS Frequency Reduction



AUC – area under the curve; **CS** – clinical seizure; **LE** – long episode; **ROC** – receiver-operating characteristics; **sens** – sensitivity; **spec** – specificity.

Table 2. Clinical Seizure Reduction and Correlated LE Frequency Reduction

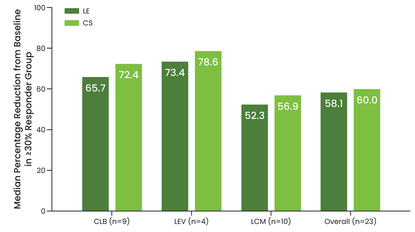
CS Frequency Reduction	AUC	Reduction Cut Point in LE Frequency (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Ability[a]
≥25%	0.725	25.6	64.3	64.7	64.4
≥50%[b]	0.765	30.0	69.6	68.2	68.9
≥75%[c]	0.735	49.6	63.6	64.7	64.4

[a]Represents the percentage of time the cutoff accurately identified patients who had a >25%, >50%, and >75% reduction in CS.
[b]Clinically meaningful reduction in CS frequency.
[c]Profound reduction in CS frequency.
Frequency was calculated per 28 days for each interval. Frequency reduction was compared between the baseline period (8-week interval prior to the ASM start) and Weeks 1-8 (8-week interval following ASM start). N=45.
AUC – area under the curve; **CS** – clinical seizure; **LE** – long episode; **ROC** – receiver-operating characteristics.

Outcomes in Patients with at Least a 30% LE Reduction

- The ≥30% LE responder group (n=23) experienced a median 60% reduction in CS frequency (**Figure 3**)
  - 16/23 (70%) patients with a ≥30% LE reduction experienced a ≥50% reduction in CS frequency (**Table 3**)

Figure 3. The ≥30% LE Responder Group (n=23) Median Percentage Reduction from Baseline in LE and CS Frequency



CLB – clobazam; **CS** – clinical seizure; **LCM** – lacosamide; **LE** – long episode; **LEV** – levetiracetam.

Table 3. Percentage of ≥30% LE Responders with ≥50% Reduction in CS was Similar Across ASMs

	CLB n=15	LEV n=4	LCM n=26	Overall N=45
≥30% LE responder rate, n (%)	9 (60.0)	4 (100.0)	10 (38.5)	23 (51.1)
≥30% LE responders with ≥50% CS reduction, n (%)	6 (66.7)	3 (75.0)	7 (70.0)	16 (69.6)

ASM – antiseizure medication; **CLB** – clobazam; **CS** – clinical seizure; **LCM** – lacosamide; **LE** – long episode; **LEV** – levetiracetam.

Conclusions

- A linear relationship was observed between change in LE frequency and change in CS frequency
- The ROC analysis identified that a ≥30% reduction in LE frequency was the optimal cut point associated with a clinically meaningful (≥50%) reduction in CS frequency, regardless of the ASM initiated
  - 70% of patients who achieved a ≥30% reduction in LE frequency following ASM initiation also experienced a clinically meaningful (≥50%) reduction in CS
  - Higher LE response thresholds were correlated with a profound (≥75%) reduction in CS
- LEs may serve as a viable biomarker for use in POC studies with positive predictive ability for clinical meaningful efficacy in reducing CS frequency in later stages of ASM development

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Disclosures

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