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Exploratory definition of a clinically meaningful change in intracranial EEG features: Analysis of data from a long-term treatment study of the RNS® System

Arnold R. Gammaitoni [a,*], Martha J. Morrell [b], Jacqueline A. French [c], Daniel Friedman [c], Kathryn A. Davis [d], Thomas K. Tcheng [b], Cairn G. Seale [b], Miganush Stepanians [e], Bradley S. Galer [f,1], William W. Motley [a]

[a] Rapport Therapeutics, Inc., Boston, MA, USA
[b] NeuroPace, Inc., Mountain View, CA, USA
[c] Comprehensive Epilepsy Center, Department of Neurology, NYU Grossman School of Medicine, New York, NY, USA
[d] Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA
[e] PROMETRIKA, LLC, Cambridge, MA, USA
[f] Mosaica Medicines, Boston, MA, USA

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ABSTRACT

Objective: Novel proof-of-concept designs utilizing biomarkers associated with an established clinically meaningful outcome are needed for antiseizure medication (ASM) efficacy assessment in patients with epilepsy, including drug-resistant focal epilepsy. Changes in long episode (LE) frequency, recorded by the responsive neurostimulator (RNS® System), are associated with changes in clinical seizure (CS) frequency following ASM initiation, suggesting that LEs may serve as a valid biomarker. Here, we aimed to establish the LE reduction magnitude associated with a clinically meaningful CS reduction.

Methods: Post hoc retrospective analyses of CS and LE frequencies, responder rate, and receiver operating characteristics from a long-term RNS open-label treatment study in patients who met predefined criteria were performed to evaluate the association between changes in LE and CS frequency and the LE reduction cutpoint associated with a $\geq$ 50% CS reduction.

Results: Patients (N=45) initiated clobazam (n=15), levetiracetam (n=4), or lacosamide (n=26). Patients achieved a median 30% LE and 50% CS reduction. Patients with <50% and ≥50% CS reductions had a median 5.9% LE increase and 52.4% LE reduction, respectively. A positive association between LE and CS frequency reduction across the entire range of responses (0–100%) was observed. A ≥30% LE reduction was associated with a ≥50% CS reduction; AUC=0.765, N=45.

Significance: If LE reductions may serve as a potential biomarker, a threshold associated with meaningful improvement in CSs is paramount. Results from this hypothesis-generating analysis support the use of a $\geq$ 30% LE reduction as a biomarker associated with clinically meaningful improvement in focal epilepsy.

1. Introduction

The timelines for developing new treatments for focal epilepsy are increasing due to challenges in recruiting patients into both Phase 2 (proof-of-concept [POC] study) and Phase 3 (pivotal efficacy and safety study) trials [1]. There is an urgent need to improve efficiency in making go/no-go decisions to progress new focal epilepsy antiseizure medication (ASM) treatment options to Phase 3 trials with confidence given the current size (>100 study centers across >15 countries), time (at least 2–3 years to recruit and enroll patients, years of trials), and cost required to conduct these registration studies [2,3].

While current Phase 2a POC study designs, such as measurement of photoparoxysmal response (PPR) in photosensitive epilepsy patients and transcranial magnetic stimulation (TMS) in healthy volunteers, do allow

* Corresponding author.
E-mail address: gammaitoni2013@verizon.net (A.R. Gammaitoni).
[1] Affiliated with Rapport Therapeutics, Inc., at the time of the study.

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assessment of some drug impact after a single dose, they do not directly measure drug activity and a clinically meaningful response in the intended focal epilepsy patient population [4]. Thus, they may not be predictive of a drug's ability to affect spontaneous seizures in the actual patient population with chronic dosing [5]. Furthermore, the PPR design is not well suited to assess drugs with a long half-life or those requiring titration (ie, those that cannot achieve an effective concentration following a single dose).

Lack of translatability in these POC models may lead some sponsors to additionally conduct Phase 2 trials in the intended patient population, utilizing the traditional efficacy outcome of clinical seizure (CS) frequency as assessed by patient seizure diaries. Measurement of change in CS frequency requires a high baseline CS frequency and often causes long lead times to study completion due to difficulties in recruiting a target population that meets the study's inclusion/exclusion criteria [6].

A challenge beyond lead times to study completion in Phase 2 focal epilepsy POC studies is the utilization of patient seizure diaries, which have been shown to both under- and over-report seizures [7]. These inaccuracies, due in part to lack of patient awareness of seizure occurrence (ie, nocturnal seizure occurrences, post-ictal amnesia) [8] and over-reporting of seizures, introduce subjectivity and variability, which create confounding factors to CS outcomes and necessitate larger placebo-controlled studies. Moreover, subclinical seizures, which may significantly impact clinical outcomes such as behavior and cognition, should ideally be included in assessments of ASM efficacy [9,10].

Novel POC designs for Phase 2 studies assessing the efficacy of an ASM on candidate objective biomarkers may reduce variability seen with patient seizure diaries, likely requiring lower enrollment numbers to predict the success of Phase 3 trials via models that represent CS activity [11,12]. According to the US Food and Drug Administration (FDA), an ideal biomarker should be specific for a particular disease, able to differentiate between different physiological states, safe and easy to measure, rapid, accurate, and consistent between ethnic groups and genders [13,14].

The responsive neurostimulator (RNS® System, NeuroPace, Mountain View, CA) continually monitors electrocorticographic (ECoG) intracranial EEG (iEEG) activity and responds to abnormal electrographic patterns and seizure-activity onset with bursts of electrical stimulation with the aim of suppressing the development of a CS [15]. Long episodes (LEs) are organized, detected epileptiform activity exceeding a specified duration set by the patient's epileptologist. For many patients, LEs most often represent electrographic seizures. Thus, LEs may provide an objective surrogate for CS counts [12,16]. To utilize LEs as a biomarker of CSs, the ability to define a clinically meaningful improvement is paramount for interpreting and predicting the clinical treatment response. Because LEs are device-specific outputs, their potential as a biomarker relies on the assumption that the RNS System was accurately implanted with optimal settings in order to increase generalizability to the greater focal epilepsy population. The association between LE frequency and CS frequency is strongest in patients with stable settings and high concordance between LEs and electrographic seizures [16]. A prior retrospective study of the RNS System suggested that without a ≥20%–25% LE reduction within the first 2 weeks following initiation of a new ASM, the ASM is unlikely to be clinically efficacious [17].

Using data from an open-label, long-term (up to 7 years) treatment study of the RNS System in patients with focal epilepsy resistant to ≥2 ASMs and an anchor-based approach on change in patient-reported CS frequency, we sought to:

- Examine the relationship between change in LE frequency and change in CS frequency;
- Building on previous observations that a ≥20% LE reduction was predictive of ASM response, define a clinically meaningful level of LE frequency reduction that is associated with a ≥50% reduction in CS frequency, a widely accepted benchmark for meaningful improvement in CS frequency; and
- Assess consistency in these findings among different ASMs.

2. Methods

2.1. Standard protocol approvals

The study protocols for the long-term treatment RNS System study (NCT00572195) [15,18,19] were approved by the institutional review boards of participating investigation sites. All trials were conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on the Harmonisation Good Clinical Practice guidelines. All patients provided informed consent.

2.2. Inclusion criteria and data used for this analysis

Patients in the long-term RNS treatment study [15,18,19] were included in the retrospective analysis if they:

- Initiated and maintained a new ASM for ≥3 months, had stable RNS System settings including LE detection criteria (eg, minimum duration thresholds) throughout the analysis windows, had RNS System settings with data available for both LE and CS frequency during an 8-week baseline period prior to and the 8-week period following the ASM initiation, and had a baseline 28-day (monthly) frequency of ≥8 LEs; and
- Had LE criteria (ie, required duration of epileptiform activity) predefined by their epileptologist within the RNS System.

Changes in RNS System settings, including detection and stimulation parameters, were allowed during the study to achieve optimal detection and response to therapy. Some patients in the original dataset initiated more than one ASM during the long-term treatment study. To provide context for the results of a Phase 2a focal epilepsy POC study for an ASM that aimed to use LEs as a supplemental endpoint to CSs (ongoing at the time of this analysis), we aligned the timeline of this post hoc analysis with the study design of the Phase 2a study in focal epilepsy [20]. The ASM with the greatest percent reduction in monthly CS frequency from the 8-week baseline pre-initiation period to the 8-week period following ASM initiation for each patient was assessed. LE frequency was derived from RNS System device data, which are continuously and automatically recorded. No LE data for included patients were missing during the analysis windows. CS frequency was derived from patient seizure diaries. ASMs initiated during the study were excluded if there were no diary data. For patients with partial diary incompleteness within an analysis window, monthly (28-day) CS frequency was calculated using available diary days only (total seizure count divided by the number of days with diary entries, multiplied by 28). No imputation was performed for missing diary days.

2.3. Study endpoints and statistical analyses

All analyses described were post hoc and exploratory, and no formal sample size calculation was performed. Categorical variables were summarized by frequency and percentages; continuous variables were summarized by mean ± SD and median (min–max). Study endpoints included the change in magnitude and percentage in monthly RNS System LE frequency and CS frequency from baseline for the entire post-baseline 8-week period.

LE frequency was continuously recorded by the RNS System, and CS frequency was recorded by patients in daily seizure diaries. Only focal with preserved consciousness with observable manifestations, focal with impaired consciousness, and focal to bilateral tonic-clonic seizures recorded in patient diaries were counted towards CS frequency. Monthly (28-day) frequency of LEs and CSs, calculated using normalization, prior

to and following ASM initiation and the corresponding frequency and percentage frequency changes were summarized. The null hypothesis of a median percent change from baseline of zero was assessed using a two-tailed Wilcoxon signed-rank test; the corresponding 95% confidence interval (CI) was presented.

Analyses included calculations of the proportion of LE responders overall and within each ASM treatment group, median change in LE frequency for each CS responder group, and receiver operating characteristics (ROCs) of the LE reduction threshold based on ≥50% and ≥75% reductions in CS frequency as the clinical response. ROC cutpoints were exploratory and not adjusted for multiplicity. LE responder rates were expressed as the percentage of patients who achieved LE frequency reduction that corresponded to ≥50% CS frequency reduction as assessed by ROC analyses. CS responder rates were pre-specified as the percentage of patients who achieved ≥25%, ≥50% (clinically meaningful), and ≥75% (profound) CS reduction. Pre-specified null hypotheses for LE and CS responder rates were tested using two-tailed one-sample tests of proportions.

Cumulative proportion of responders analysis (CPRA) was used to assess both LEs and CSs, such that the percentage of responders was examined across the range of 0% to 100% reduction in LEs and CSs. Graphical outputs of the cumulative distribution were produced to visualize the relationship between LE and CS responders across the range of response. The proportion of LE responders who also experienced a ≥50% monthly median CS reduction was summarized, overall and by ASM, for each responder group. The median monthly LE frequency change from baseline was also summarized by patients with <25%, 25 to <50%, 50% to <75%, and 75% to 100% reductions in CS frequency from baseline. CPRA outputs were exploratory and not adjusted for multiplicity. A Spearman's correlation was conducted to evaluate the relationship between LE and CS frequency reduction.

To determine the threshold of change in LE frequency associated with a clinically meaningful change in CS frequency, ROC analyses were conducted for each patient's 8-week post-initiation interval. Point estimates were based on a small sample without CIs. An anchor-based approach utilizing percent change in patient-reported CS frequency via patient diaries was used for this analysis. The independent variable was the percent change in monthly LE frequency; the dependent variable was CS responder status based on percent change in CS frequency. CS responder groups were categorized as patients with ≥25%, ≥50%, and ≥75% monthly CS frequency reduction in the 8 weeks following ASM initiation in comparison to the 8 weeks prior to ASM initiation. The clinically relevant threshold for percent change in monthly LE frequency from pre-initiation was characterized by the ROC cutpoints at which sensitivity was approximately equal to specificity for CS responder status of ≥50% CS reduction and ≥75% CS reduction. ROC analyses were summarized by percent change in LE frequency cutpoints, area under the curve (AUC), percent sensitivity, percent specificity, and percent correct for each post-initiation period.

3. Results

Among 45 patients included in the current analysis (Supplementary Fig. 1),15 (33%) initiated clobazam (CLB), 4 (11%) initiated levetiracetam (LEV), and 26 (57%) initiated lacosamide (LCM). Mean patient age at ASM initiation was 36.5 ± 11.8 y; 35.6% of patients were female (Table 1). RNS System lead placement foci were distributed evenly among the mesial temporal lobe (MTL), the neocortex, and both the MTL and neocortex. The median CS frequency per 28 days during the pre-initiation period was 7 (2–1045); the median LE frequency was 92 (8–4489).

3.1. CS and LE response

For the patients included in this analysis, the median reduction in LE frequency was 30% (interquartile range [IQR], 69), while the median reduction in CS frequency was 50% (IQR, 72; Fig. 1a). Overall, 23/45 (51.1%) of patients experienced a ≥50% reduction in CSs; 23/45 (51.1%) experienced a ≥30% reduction in LEs (Figs. 1b and 2). Of the ≥30% LE responders, 16/23 (69.6%) also experienced a ≥50% reduction in CSs. Of the ≥50% CS responders, 7/23 (30.4%) patients also experienced a <30% reduction in LEs. A ≥30% reduction in LEs following initiation of CLB, LEV, or LCM was reported at similar rates as a ≥50% reduction in CSs (Supplementary Table 3).

In total, 18/45 (40%) patients experienced a ≥50% reduction in LE frequency. Of the ≥50% LE responders, 7/18 (38.9%) also experienced a ≥75% reduction in CSs. An additional 4 patients experienced a ≥75% reduction in CSs with a <50% reduction in LEs.

Table 1
Baseline characteristics of enrolled patients.

	CLB n=15	LEV n=4	LCM n=26	Overall N=45
Female, n (%)	4 (26.7)	3 (75)	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
Baseline LE frequency, median[a] (min, max)	25 (10, 905)	360 (25, 1159)	100 (8, 4489)	92 (8, 4489)
Baseline CS frequency median[a] (min, max)	14.5 (2, 55)	10.3 (6, 19)	6.5 (2, 1045)	7 (2, 1045)
RNS® System lead placement[b] foci, n (%)				
Mesial temporal lobe (MTL)	4 (26.7)	1 (25)	9 (34.6)	17 (37.8)
Neocortical	5 (33.3)	2 (50)	10 (38.5)	14 (31.1)
MTL + Neocortical	6 (40)	1 (25)	7 (26.9)	14 (31.1)

ASM – antiseizure medication; CLB – clobazam; CS – clinical seizure; LCM – lacosamide; LE – long episode; LEV – levetiracetam; MTL – mesial temporal lobe; RNS – responsive neurostimulator.

[a] Frequency was calculated per 28 days.

[b] Placement based on seizure onset foci as mapped prior to implant of the RNS System. Reported foci include the frontal, temporal, occipital, and parietal lobes, hippocampus, amygdala, and insula. No electrodes were placed in the thalamus.

3.2. CS and LE relationship

A positive association between CS response (<50% versus ≥50% reduction in CS frequency from baseline) and percent reduction in LE frequency was observed, ρ(43)=0.47, 95% CI (0.20, 0.67) (Fig. 3 and Supplementary Fig. 2). Additionally, the CPRA showed the reduction in both LEs and CSs paralleled each other across the entire range of response (0–100%; Fig. 4). A ≥30% reduction in LE frequency was identified as the optimal cutpoint for a clinically meaningful (≥50%) reduction from baseline in CS frequency (AUC=0.765; Table 2, Supplementary Fig. 3A). An LE frequency reduction of ≥49.6% was identified as the cutpoint based on a profound (≥75%) reduction from baseline in CS frequency (AUC=0.735; Supplementary Fig. 3B).

4. Discussion

Due to the limitations of existing POC models utilized in epilepsy drug development and the challenges and well-known confounding factors in quantifying seizure outcomes via patient diaries, there is an urgent need for new Phase 2a focal epilepsy POC models that employ biomarkers with positive predictive ability that aid in making go/no-go decisions for later stages of novel ASM development. Phase 2a POC studies that measure treatment outcomes that are analogous to the clinical presentation in the intended patient population may provide a more accurate predictor of success in Phase 3 trials than those that are currently utilized, such as PPE and TMS. Patient diaries should continue to serve as an important complementary seizure frequency measure with the use of a validated biomarker to measure ASM effects on CS frequency. Patients with an implanted RNS System are clinically similar to patients who are typically enrolled in Phase 2 and Phase 3 drug-resistant

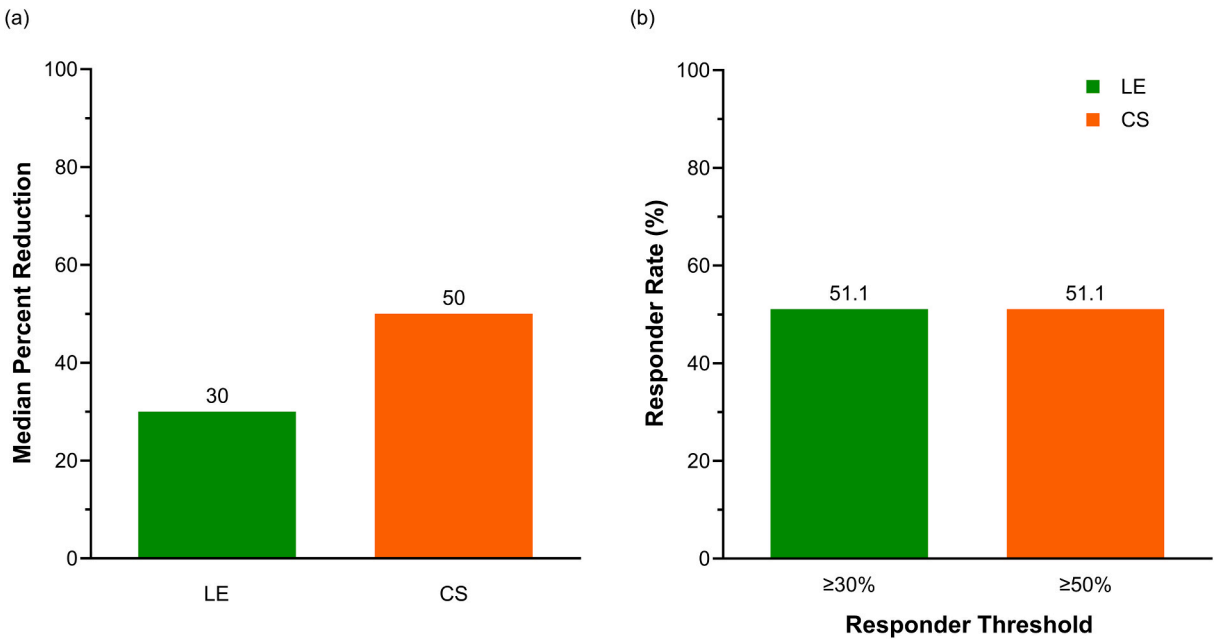

Fig. 1. LE and CS (a) Median Percent Reduction and (b) Responder Rates Following an ASM Initiation in Patients With an RNS® Device at Similar Rates Across ASMs and Overall. Clinically meaningful reduction in CS is defined as a ≥50% reduction in CSs. N=45; CLB (n=15), LEV (n=4), LCM (n=26). A ≥30% reduction in LEs is associated with a clinically meaningful (≥50%) reduction in CSs. A ≥50% reduction in LEs is associated with a profound (≥75%) reduction in CSs. ASM – antiseizure medication; CLB – clobazam; CS – clinical seizure; LCM – lacosamide; LE – long episode; LEV – levetiracetam; RNS – responsive neurostimulator.

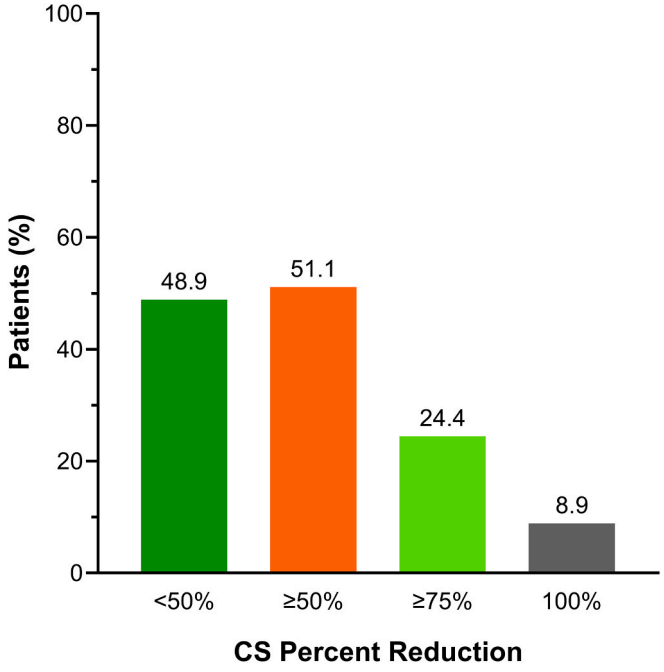

Fig. 2. Percentage of Patients with CS Reductions <50%, ≥50%, ≥75%, and 100% Following an ASM Initiation in Patients With an RNS® Device. N=45; CLB (n=15), LEV (n=4), LCM (n=26). Patients with a ≥50% reduction in CS include patients with ≥75% and 100% reductions in CS; patients with a ≥75% reduction in CSs include patients with a 100% reduction in CSs. ASM – antiseizure medication; CLB – clobazam; CS – clinical seizure; LCM – lacosamide; LEV – levetiracetam; RNS – responsive neurostimulator.

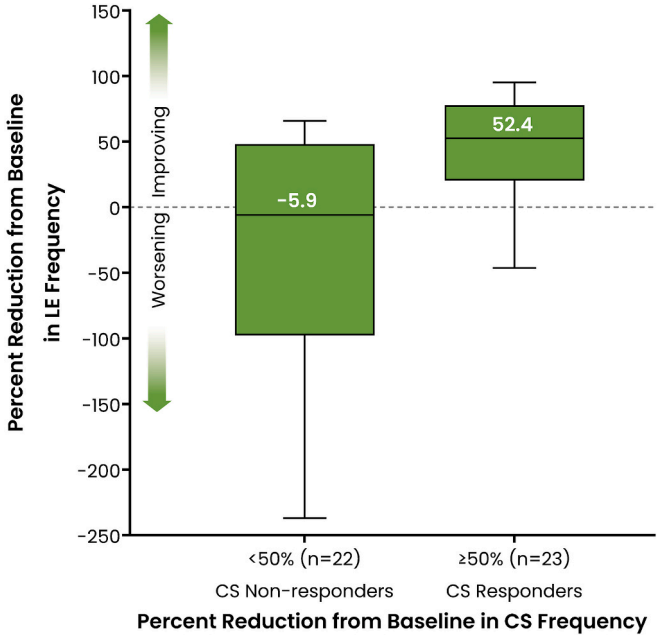

Fig. 3. Percent LE Frequency Reduction by CS Responder Group. The bottom and top edges of the box indicate IQR. The line inside the box indicates the median value (value in white text above median line). The vertical lines represent the most extreme point within 1.5 × IQR. In order to enhance readability, the y-axis ends at −250%, and the means and outliers are not included in the figure. Mean LE frequency reductions were −310.3% and 39.0% for CS non-responders and CS responders, respectively. Outliers were 6231.1% (CS non-responder) and −134.4% LE frequency reduction (CS responder). The <50% reduction category may include patients with no change or an increase in frequency of CSs. Clinically meaningful change: ≥50% reduction in CS frequency. CS – clinical seizure; IQR – interquartile range; LE – long episode.

focal epilepsy studies (Supplementary Table 1) and provide a population that mimics the standard study population recruited into registrational studies. Positive outcomes in a traditional Phase 3 study of an ASM corresponding to results from a Phase 2 study utilizing RNS System LE frequency as a biomarker would increase the generalizability of results from such a study. While utilizing RNS System LE frequency as a

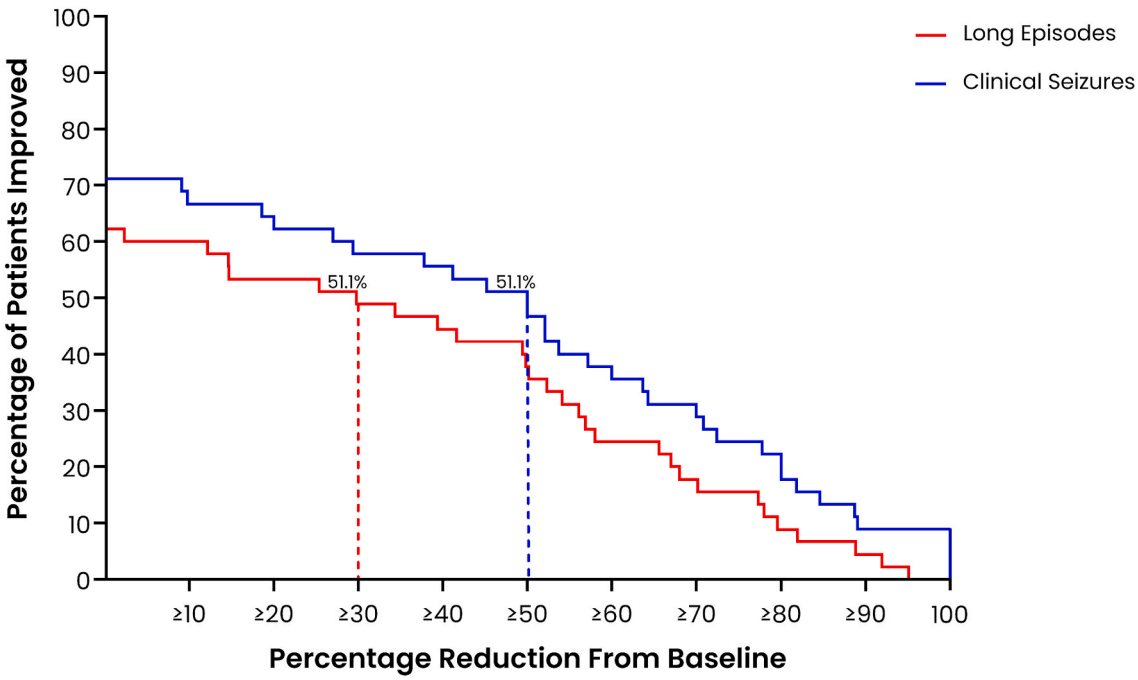

Fig. 4. Cumulative Proportion of Responder Curves for Percent Reduction in Monthly LEs and CSs Following an ASM Initiation in Patients with an RNS® Device. N=45. ASMs initiated: CLB (n=15), LEV (n=4), LCM (n=26). A ≥30% reduction in LEs (indicated by the red dashed line) is associated with a clinically meaningful (≥50%) reduction in CSs (blue dashed line). ASM – antiseizure medication; CLB – clobazam; CS – clinical seizure; LCM – lacosamide; LE – long episode; LEV – levetiracetam; RNS – responsive neurostimulator.

Table 2
Commonly used clinical seizure responder values and associated LE frequency reduction cutpoint, summarized by ROC (N=45).

CS Frequency Reduction	AUC	LE Frequency Reduction Cutpoint (%)	Sensitivity (%)	Specificity (%)	Percent Correct[a]
≥25%	0.725	25.6	64.3	64.7	64.4
≥50%[b]	0.765	30.0	69.6[d]	68.2[e]	68.9
≥75%[c]	0.735	49.6	63.6	64.7	64.4

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).
ASM – antiseizure medication; AUC – area under the curve; CS – clinical seizure; LE – long episode; ROC – receiver operating characteristic.
[a] Represents the percentage of time the cutpoint identified patients who had a ≥ 50% reduction in CSs.
[b] Clinically meaningful reduction in CS frequency.
[c] Profound reduction in CS frequency.
[d] 95% CI, (0.51, 0.88).
[e] 95% CI, (0.49, 0.88).

biomarker for Phase 2a POC studies of focal epilepsy would restrict trial sites to those with expertise in using the RNS System, this approach may be preferable to other established methods, such as the PPR and TMS designs (Supplementary Table 2), because it likely enables a more rapid progression into registrational trials via:

- Direct examination in the intended focal epilepsy patient population;
- Direct measurement of the ASM's effect on objective, spontaneous epileptiform activity;
- Chronic daily dosing (ie, not a single dose study); and
- Availability of detailed pharmacodynamic data to inform dose selection for registrational trials.

An examination of the CPRA demonstrates that, overall, the reductions in LEs and CSs remain parallel to one another across the spectrum of responses. This finding suggests that the LE response does not overpredict the CS response across the entire range of responses (0–100%). Results from the CPRA are important for anticipating the chance of success and making go/no-go decisions for Phase 3 studies. While the CPRA is a useful tool in determining the cutoff point where treatment effect is maximized, it is also important to note that there is a risk of sensitivity based on the selected threshold. Here, the selected thresholds for change in CS frequency were based on thresholds commonly used in focal epilepsy trials, while the conservatively selected threshold for LEs was based on a previous analysis.

The ROC analysis identified a ≥30% reduction in LE frequency as the optimal point associated with a clinically meaningful (≥50%) reduction in CS frequency. Similarly, a ≥49.6% reduction in LE frequency was identified as the optimal magnitude of change associated with a profound (≥75%) reduction in CS frequency. One possible explanation for the difference between LE and CS frequency reductions may be the efficacy of an ASM and its potential prevention of escalation from a subclinical to clinical seizure. Furthermore, ASMs may have reduced the severity of CSs: LEs may have been associated with seizures that were not recorded in patient diaries, such as non-motor focal onset seizures with preserved consciousness, following the addition of an ASM. Baseline LE frequency is higher than baseline CS frequency due to limitations in patient-reported seizures versus the ability of the RNS device to continually monitor electrographic events and is significantly correlated with clinical outcome [17]. Furthermore, not all LEs correspond with CSs; LEs may also include subclinical seizures and/or abnormal non-seizure electrographic activity. A limitation of the lower CS frequency at baseline is the constraint on frequency reduction that can be observed. The higher LE baseline frequency may also reduce the proportion of patients ineligible for a clinical trial, a major factor in low and/or slow patient recruitment [1].

A positive relationship between change in LE frequency and change in CS frequency was observed for all ASMs evaluated. This relationship was similar across all ASMs evaluated. The CPRA, in conjunction with the ROC analysis, provides further evidence of the relationship between the reduction in LEs and CSs [21,22]. In this retrospective analysis of a

long-term treatment RNS System efficacy study, we identified a cutpoint in LE frequency change that is associated with meaningful improvement in CS frequency, confirming results from previous studies regarding relationships between LE and CS frequency [12,17,23,24]. These results should be interpreted with caution due to the nature of this retrospective analysis, which utilized a small sample size without adjustments for multiplicity. Additionally, the 95% CI for AUC was not calculated; thus, statistical significance could not be evaluated.

In this post hoc analysis, we demonstrated that a change in RNS System LEs may fulfill several features of a useful biomarker for focal epilepsy: change in LEs was positively associated with change in CSs, was easy to measure in patients with an implanted RNS System device, and was associated with a clinically meaningful response in CS frequency. However, prospective validation and demonstration of clinical utility in controlled settings, including larger patient numbers per ASM, are still needed. A ROC-derived exploratory analysis confirmed the ≥30% LE reduction cutpoint was applicable overall and therefore may serve as a "measure of success" for a treatment being tested in a POC study. Previous literature showing that an early and rapid change in LE frequency predicts response to an initiated ASM, combined with these attributes, suggests that change above the specified magnitude in LE frequency measured by the RNS System is a feasible biomarker for clinically meaningful change in CSs per US FDA definition.

5. Limitations

The original data utilized for this retrospective analysis did not include comparable numbers of patients who initiated different ASMs, limiting the ability to analyze the ASM subsets with inferential statistics. In addition, the high variability in baseline LE and CS frequencies across the different ASM initiation subsets limits conclusions regarding drug-specific or patient-specific impacts. Results may be further affected by possible concomitant ASM adjustments, major clinical events, or non-ASM interventions that may have occurred during the pre- and post-initiation analysis periods. Additionally, selecting the ASM associated with the greatest frequency reduction in CSs per patient may exaggerate associations between LEs and CSs—alternative strategies such as the first ASM initiated following stable RNS System settings or the evaluation of all ASMs initiated following stable RNS System settings may be informative in future analyses. Future analyses stratified for additional variables in a larger dataset of patients may provide further insight into the treatment of patients with drug-resistant focal epilepsy. It is important to note that the population of patients with an implanted RNS System is small; a current post-approval study includes 324 patients. However, over 8,000 patients have an implanted RNS System. Open-label studies can introduce error due to the patient's knowledge of treatment and lack of placebo, leading to overestimation of treatment effects and underreporting of adverse events. This limitation is partially mitigated by objective measures such as changes in LE frequency.

While high concordance between the occurrence of LEs and of electrographic seizures is associated with a higher correlation between LEs and patient seizure diaries (ie, recorded CSs) [12], the concordance rate was unknown for this retrospective analysis. Concordance rates should be included in prospective studies of RNS System LEs as a biomarker for CSs in focal epilepsy studies. Flaws in patient seizure diaries, however, may impact the positive predictive ability of any electrographic biomarker [12]. Utilizing group change in LE frequency to predict CS response may overcome the limitations of individual patient-reported seizure occurrence, validating the utility of this measure as a biomarker. Additionally, patients were not excluded from this analysis based on the concordance between LEs and CSs; despite this, results from the ROC analyses were strong (72.5%–76.5% accuracy). Future studies should examine this concordance and its relationship with LE and CS frequencies in the context of a newly initiated ASM. Additional prospective biomarkers from the RNS System such as frequency of detections and episode starts should be assessed while continuing to consider sensitivity and specificity for CS frequency change. Another possible limitation on utilizing LEs to predict CSs is the LE specificity for electrographic seizures. While the correlation is high, some LEs are runs of interictal discharges, which ASMs may not impact at the same magnitude as they do electrographic seizures and CSs [12].

Evidence generation for LE frequency as a biomarker may be limited by the possibility of long-term changes in response to RNS stimulation itself; the natural history of variability and changes in LE frequency is currently uncertain. Efficacy of the RNS System increases significantly over the first 2 years and is sustained in the following years, suggesting that the potential long-term effect of RNS stimulation may have been mitigated by the 2-year studies required for invitation to the long-term treatment study [15]. Cyclical seizure risk states have been found to correspond to the activity of electrographic seizures, which can affect the parameters that clinicians set on the RNS System for their patients. Although exclusion of patients with any changes in RNS System settings during the 8-week period prior to and following ASM initiation controlled for this variable, the exclusion of these patients may have biased the dataset. For further confidence in ASM efficacy when utilizing RNS System LEs as a biomarker, a placebo-controlled study would be ideal.

6. Conclusion

In this exploratory post hoc analysis of long-term study data of the RNS System, reductions in LE frequency were associated with reductions in CS frequency. The results suggest that a ≥30% reduction in LEs represents a candidate threshold associated with a ≥50% CS reduction in this dataset. These results should be validated prospectively.

The potential use of LEs as a biomarker for clinically meaningful reduction in CSs may facilitate more rapid advancement of candidate focal epilepsy therapies to Phase 3 clinical trials than current POC models by including patients who mirror the intended population of patients to produce a reliable dose response. If confirmed in prospective, controlled studies, LEs serving as biomarkers could help streamline early-phase focal epilepsy trials. However, the practical and regulatory implications remain to be defined.

7. Prior presentation/publication

Data from this paper were presented at the American Epilepsy Society 2024 Annual Meeting (December 6–10, 2024; San Diego, CA) and encored at the American Association of Neurology 2025 Annual Meeting (April 5–9, 2025; San Diego, CA).

CRediT authorship contribution statement

Arnold R. Gammaitoni: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Martha J. Morrell:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Jacqueline A. French:** Writing – review & editing, Writing – original draft, Formal analysis. **Daniel Friedman:** Writing – review & editing, Writing – original draft, Formal analysis. **Kathryn A. Davis:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Thomas K. Tcheng:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Cairn G. Seale:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Miganush Stepanians:** Writing – review & editing, Writing – original draft, Formal analysis. **Bradley S. Galer:** Writing – review & editing, Writing – original draft, Formal analysis. **William W. Motley:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ARG, WWM: Rapport Therapeutics: employee; stock ownership. MJM, TKT, CGS: NeuroPace: employee; stock ownership. JAF: Epilepsy Foundation, Epilepsy Study Consortium: Salary support for consulting work and/or attending Scientific Advisory Boards for Acadia Pharmaceuticals, Acuta Capital Partners, AgriThera, Inc., Alterity Therapeutics Limited, Angelini Pharma S.p.A, Autifony Therapeutics Limited, Axonis Therapeutics, Baergic Bio, Beacon Biosignals, Inc., Biogen, Biohaven Pharmaceuticals, Bloom Science Inc., Bright Minds Biosciences, Inc., Camp4 Therapeutics Corporation, Cerebral Therapeutics, Cerecin Inc., Cerevel, Cognizance Biomarkers, Cowen and Company, LLC, Crossject, Eisai, Encoded Therapeutics, Engrail, Epalex, Epitel Inc, Équilibre BioPharmaceuticals, Genentech, Inc., Grin Therapeutics, IQVIA RDS Inc, iQure Pharma Inc., Janssen Pharmaceutica, Jazz Pharmaceuticals, Korro Bio Inc., Leal Therapeutics Inc, Lipocine, LivaNova, Longboard Pharmaceuticals, Marinus, Modulight.bio, Neumirna Therapeutics, Neurocrine, Neuronetics Inc., NeuroPace, Inc., NeuroPro Therapeutics, Neuroventis, Ono Pharmaceutical Co., Otsuka Pharmaceutical Development, Ovid Therapeutics Inc., Paladin Labs Inc., Praxis, PureTech LTY Inc., Rapport Therapeutics, Inc., Receptor Holdings Inc., Sage Therapeutics, Inc., SK Life Sciences, Stoke, Supernus, Takeda, Third Rock Ventures LLC, UCB, Ventus Therapeutics, Vida Ventures Management, and Xenon. Epilepsy Study Consortium: Research support funded by Eisai and UCB. President, Board of Directors. Epilepsy Foundation: Chief Medical/Innovation Officer. Epilepsy Study Consortium, the Epilepsy Foundation, Angelini Pharma S.p.A., Biohaven Pharmaceuticals, Cerebral Therapeutics, Cowen and Company, LLC, Longboard, Neurelis, Neurocrine, NeuroPace Inc., Praxis, Rapport, SK Life Science, Stoke, Takeda, and Xenon: Travel/meal reimbursement related to research, advisory meetings, or presentation of results at scientific meetings. GW/FACES/One8Foundation, NINDS, and UCB: Research support. Lancet Neurology, Neurology Today: Editorial board. DF: Epilepsy Study Consortium: salary support for clinical trial-related activities. Biogen, Biohaven, Cerebral Therapeutics, Cerevel, Encoded, Epalex, Équilibre, Jazz Pharmaceuticals, Jannsen, Longboard, Lundbeck, Marinus, Modulite, Neurocrine, Ono, Praxis, PureTech, Rapport Therapeutics, SK Life Science, Supernus, UCB, and Xenon: research services. Neurelis Pharmaceuticals and Meili Technologies: paid consultant. Epilepsy Foundation: travel support. NINDS, NeuroPace, Epitel, and the CDC: research support unrelated to this work. Neuroview Technology: equity interests. KAD: Rapport Therapeutics: consulting fees, travel/meeting support, advisory board participation. Epilepsy Foundation: travel support. NeuroPace: advisory board participation, travel/meeting support. NINDS: research support unrelated to this work. MS: PROMETRIKA, LLC: President, CEO, and chief statistical consultant. Rapport Therapeutics: contracted data management and statistical support. BSG: Rapport Therapeutics: employee during the time of the submitted work, including travel/meeting support and all IP during employment; stock ownership.

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Appendix A. Supplementary data

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