A Time-To-Event Model for Early Efficacy Signal Dose-Finding in Epilepsy Clinical Trials

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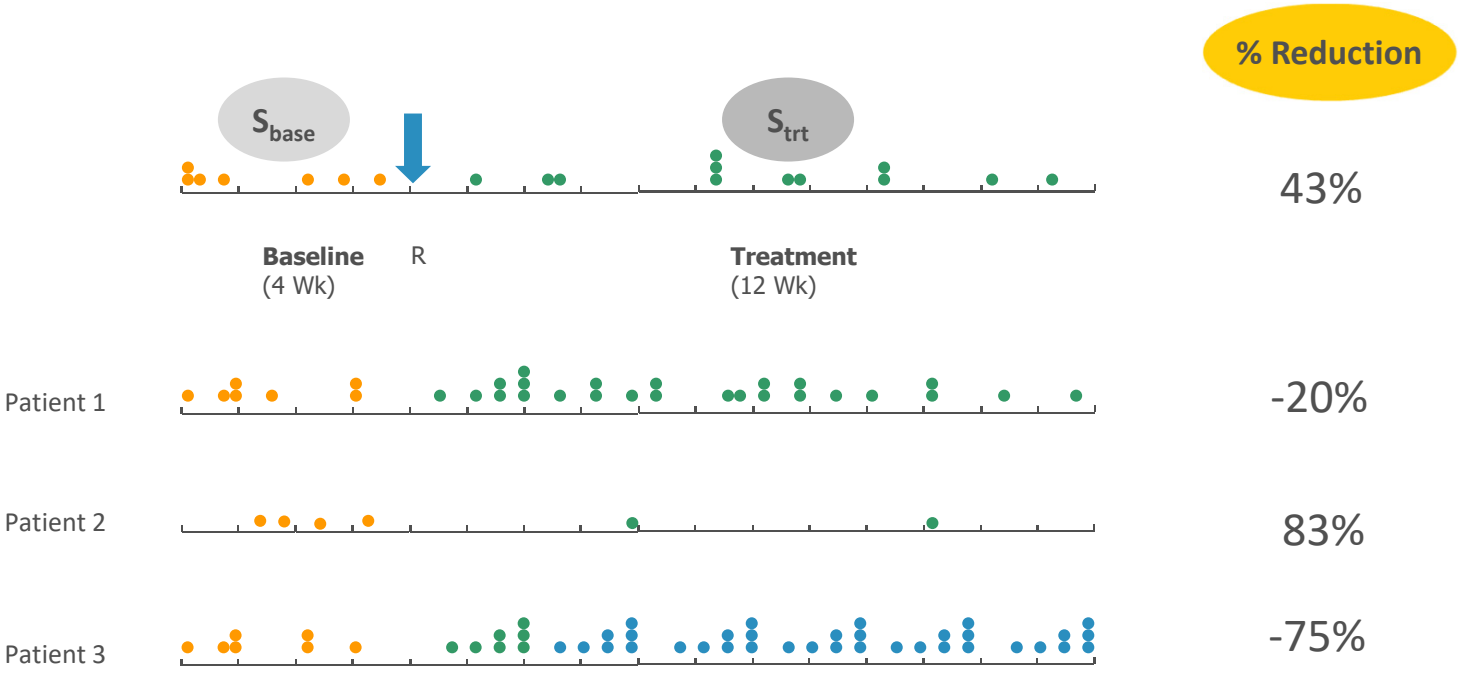
Introduction

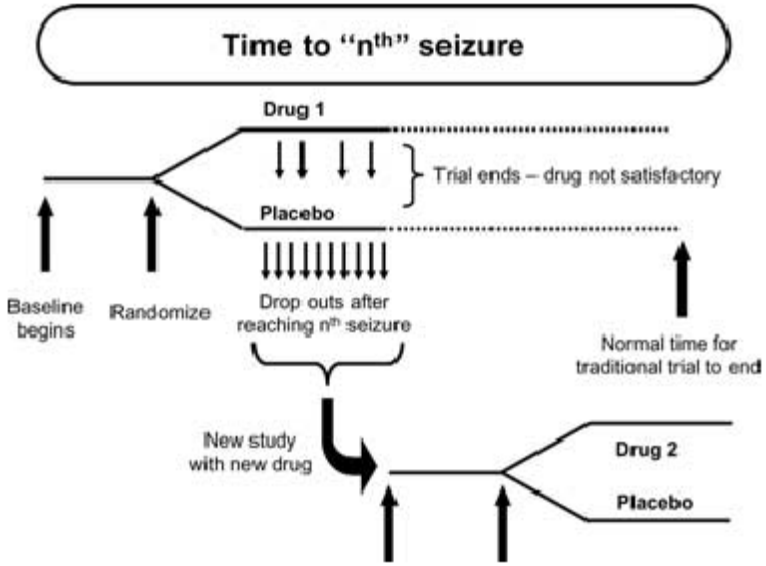
- Epilepsy is a neurological disorder characterized by transient but recurrent disturbances of brain function, usually associated with impairment or loss of consciousness and abnormal movements or behavior.
- A seizure is a sudden, excessive discharge of nervous-system electrical activity that usually causes a change in behavior for a short time (0.5 - 2 minutes).
- Clinical trials for the development of new treatments for *refractory* epilepsy require a baseline period and treatment period (up to 24 weeks)
- Time-to-event endpoints have been proposed to establish the effect of anti-epileptic drugs in clinical trials to reduce trial duration and thus the exposure of patients to placebo or a possible ineffective treatment

Endpoints in Epilepsy Clinical Trials

% Monthly Seizure Rate Reduction



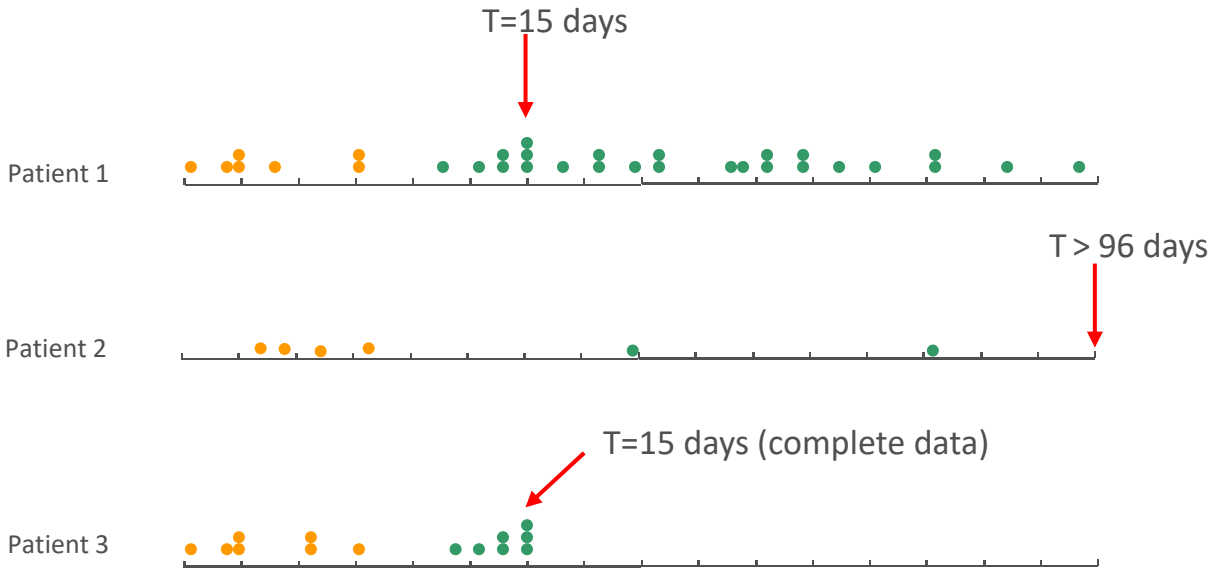
Endpoints in Epilepsy Clinical Trials
Time to Event Approach



[1]Dichter M.A. (2007). Epilepsia 48 (Suppl1): 26-30. Special Issue: Pharmacoresistance: From Clinic to Mechanism

Endpoints in Epilepsy Clinical Trials

Time to Baseline Monthly Seizure Count[1]



[1]French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. (2015) Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint. Neurology 84(20):2014-2020

Time to Baseline Monthly Seizure Count
Evaluation

Re-analysis of clinical trial data of 3 anti-epileptics

- Add-on therapy in refractory partial onset epilepsy
- Perampanel[1], Topiramate[2], Carisbamate[2]
- Placebo-controlled, double blind Phase 2/3 trials
  - 12 placebo arms (3-5)
  - 26 AED arms (7-10)
  - 4-7 doses
  - N=40-200/arm

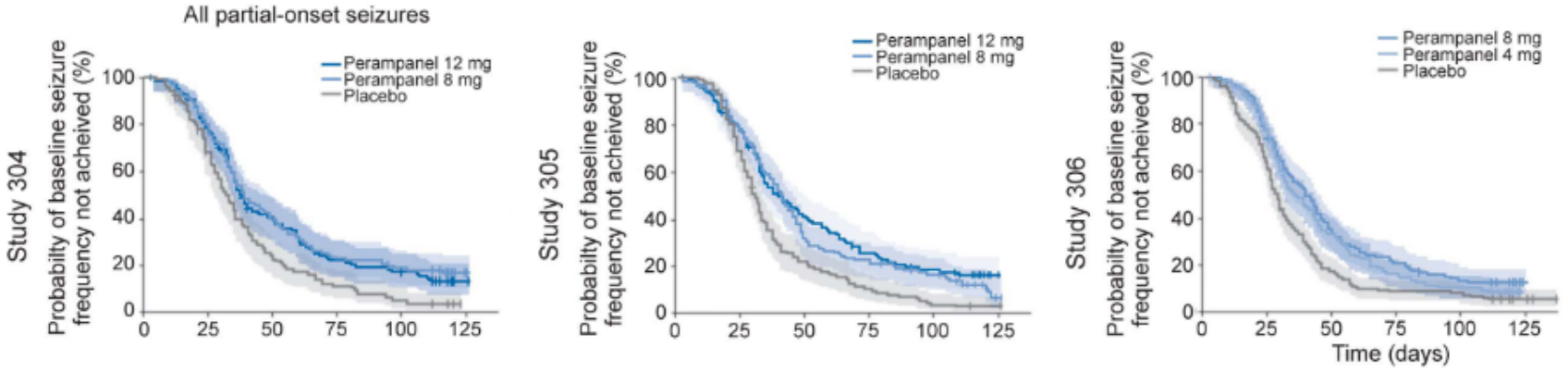
Simulation

- Longitudinal model for daily seizure counts
- Relation of endpoints
- Clinical Trial Simulation
  - Power and sample size
  - Impact of length of baseline period
  - Impact of minimum number of baseline seizures

[1]French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. (2015) Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint. Neurology 84(20):2014-2020
[2]Janssen R&D, data on file

Time to Baseline Monthly Seizure Count

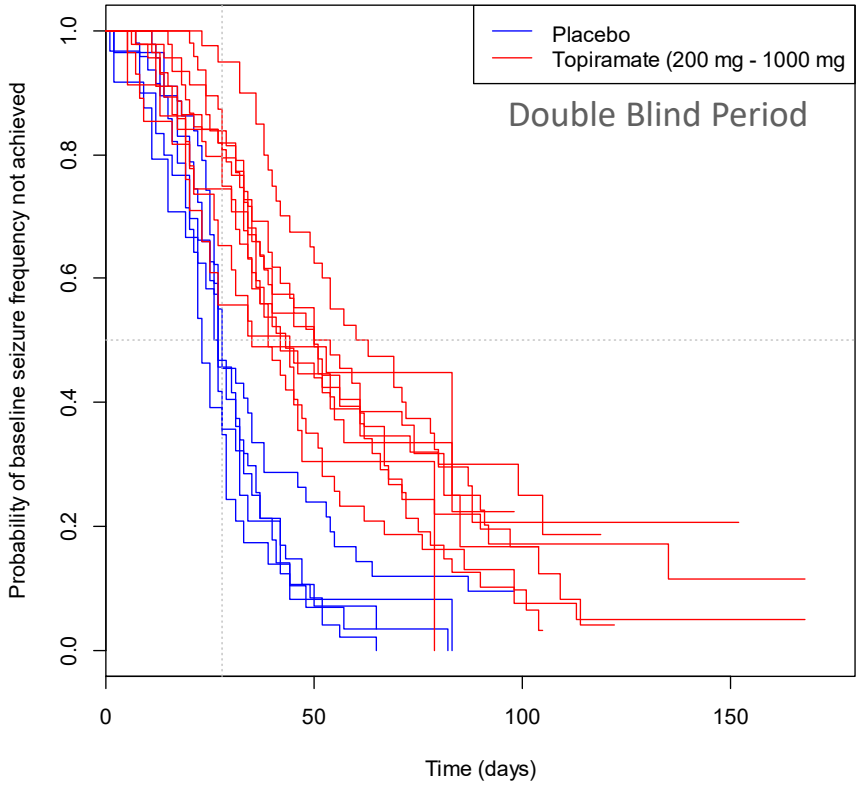
Re-analysis of perampanel Phase 3 clinical trials[1]

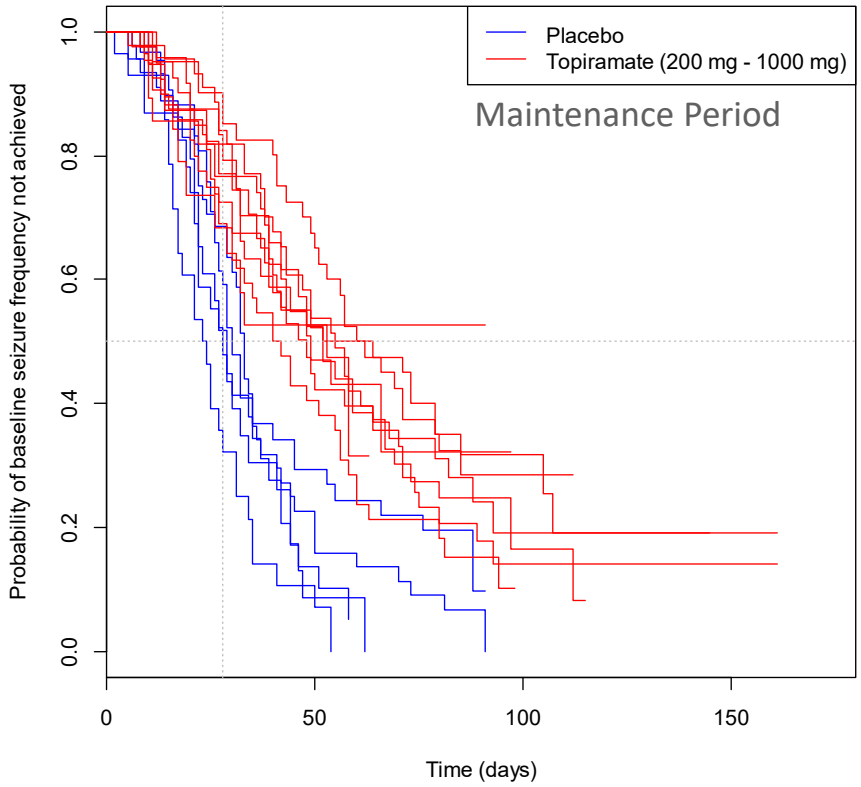


[1]French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. (2015) Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint. Neurology 84(20):2014-2020

Time to Baseline Monthly Seizure Count

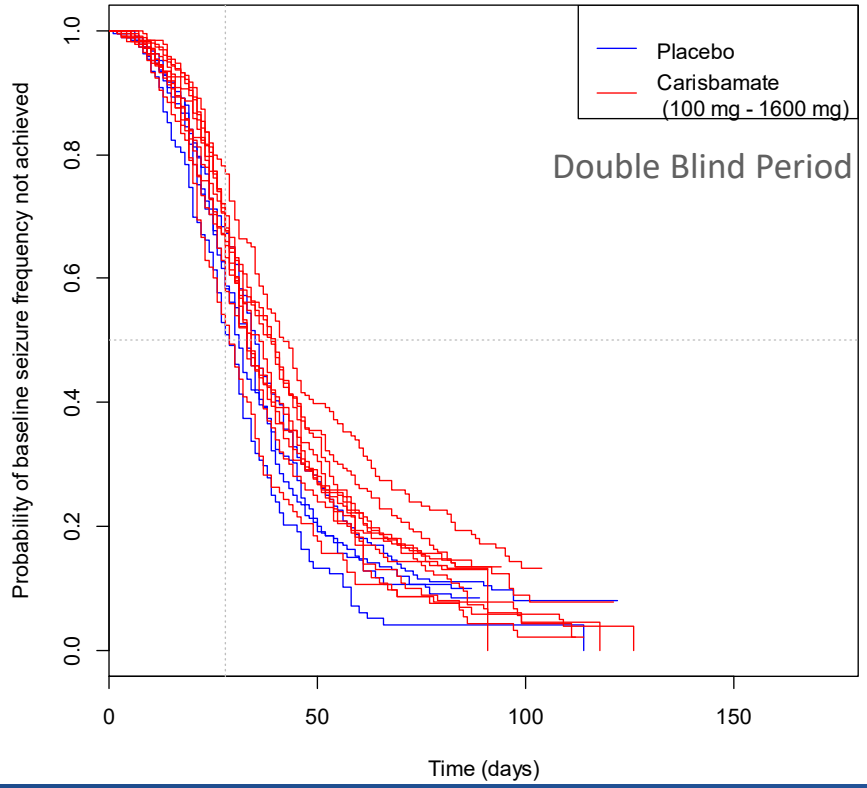
Re-analysis of topiramate clinical trials



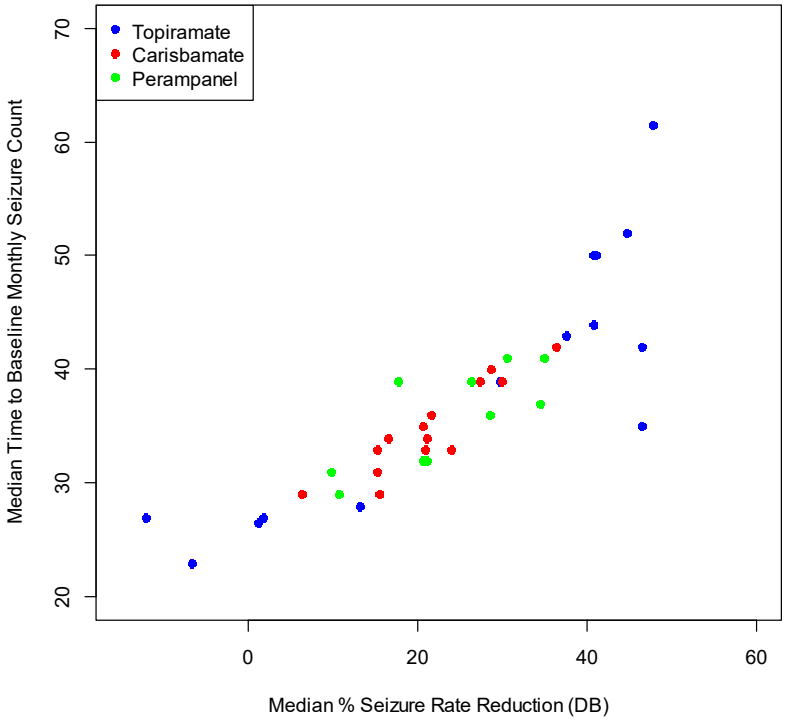


Time to Baseline Monthly Seizure Count

Re-analysis of carisbamate clinical trials



Relationship between Endpoints
Topiramate Carisbamate Perampanel[1]



Strong relationship between endpoints.

Consistent across 3 different compounds.

[1]French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. (2015) Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint. Neurology 84(20):2014-2020

Simulation-based Evaluation of the Endpoint and Design

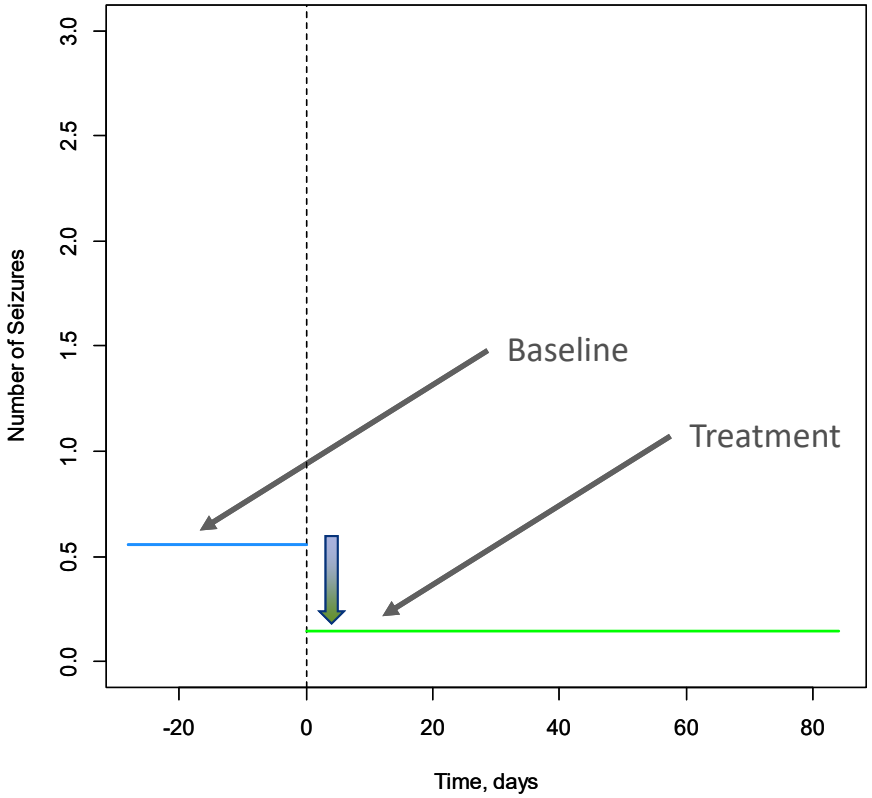
- Several longitudinal models for daily seizure counts in subjects with refractory epilepsy have been published
  - Clinical trial data of different AEDs: levetiracetam[3], pregabalin[1], gabapentin[4], vigabatrin[2]
  - Real World Data[5]

[1]JE Ahn, EL Plan, MO Karlsson and R Miller (2012) J Clin Pharmacol 52:880-92
[2]Nielsen, J. C., Hutmacher, M. M., Wesche, D. L., Tolbert, D., Patel, M. and Kowalski, K. G. (2015) J Clin Pharmacol 55: 81–92
[3]Snoeck E and Stockis A. (2007) Epilepsy Research 73: 284-291
[4]Trocóniz, I.F., Plan, E.L., Miller, R. et al. (2009) J Pharmacokinet Pharmacodyn 36: 461-477
[5]Tharayil, J. J., Chiang, S., Moss, R., Stern, J. M., Theodore, W. H. and Goldenholz, D. M. (2017) Epilepsia 58:835-844

- These models all share common features regarding *patient variability* and *stochastic models* for seizure counts
- A generic model with key features of the published models without drug specific parameters was derived

Longitudinal Model for Daily Seizure Counts

Mean Daily Seizure Count for 1 Virtual Subject

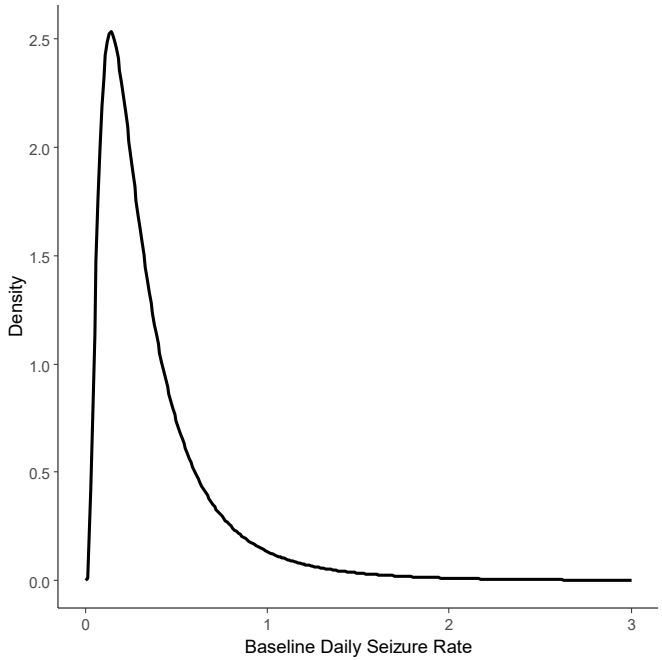


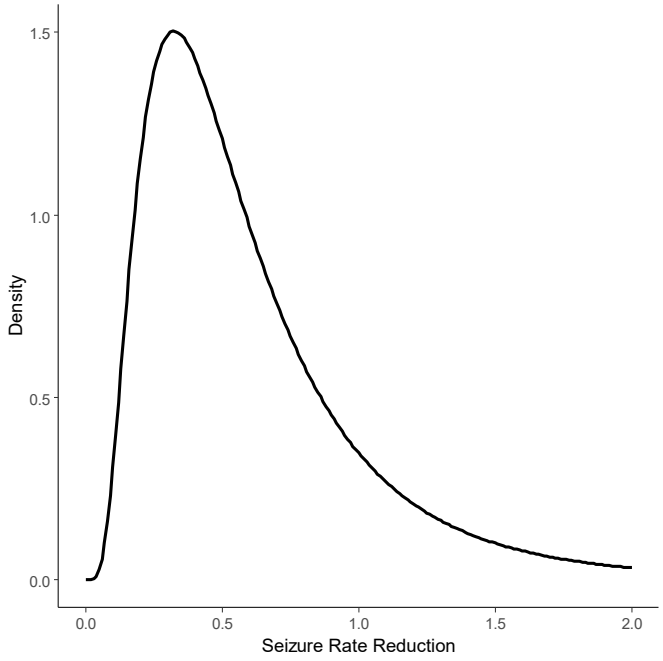
Baseline $\quad log\,\lambda_t = \theta_0$

Treatment $\quad log\,\lambda_t = \theta_0 + \theta_1$

Longitudinal Model for Daily Seizure Counts

Population of Subjects

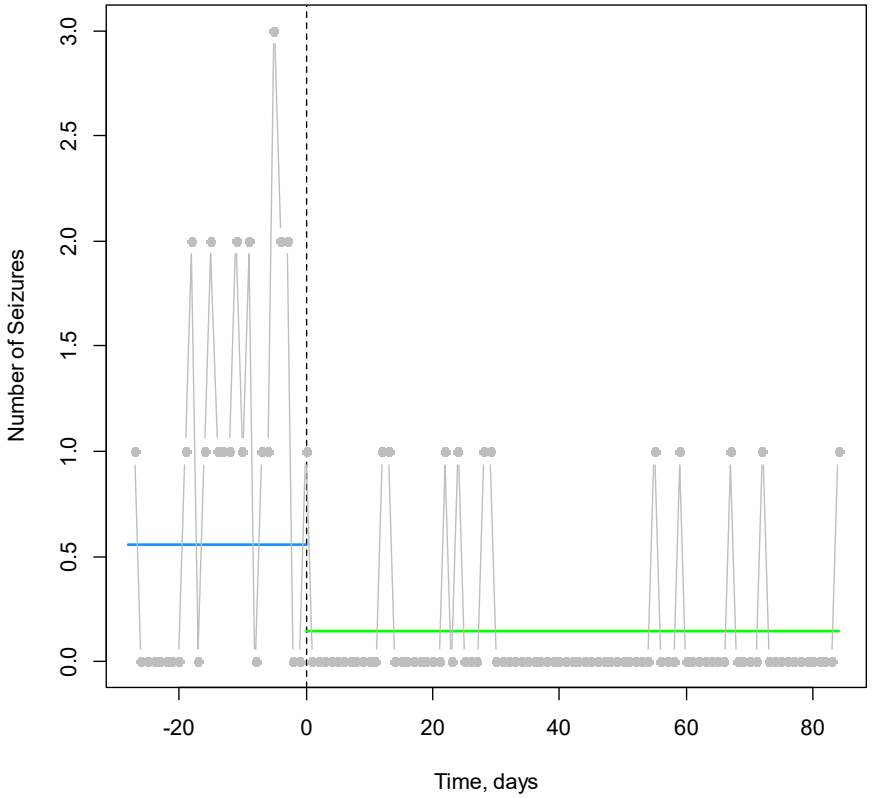




$$log\ \lambda_{i,t} = (\theta_0 + \eta_{i,0}) + (\theta_1 + \eta_{i,1})$$

Longitudinal Model for Daily Seizure Counts

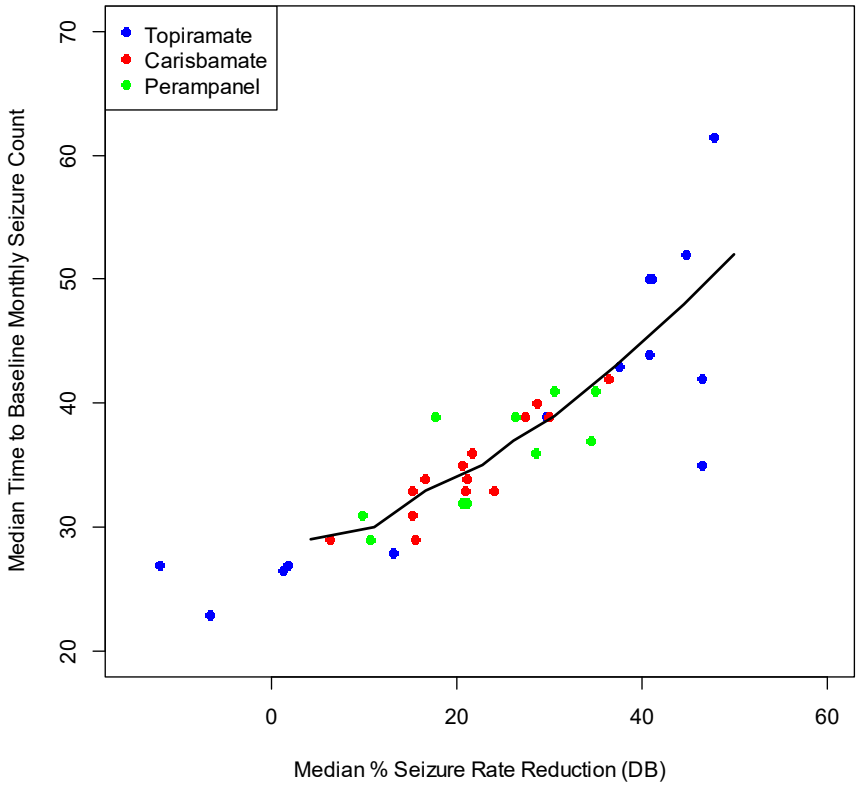
Observed Daily Seizure Count for 1 Virtual Subject



Stochastic component of the model (negative binomial with serial dependence) allows for

- Large day-to-day variability
- Clustering of seizures
- Series of seizure free days
- Consecutive days with seizures

Model-Based Prediction of the Relationship between Endpoints



Simulation:

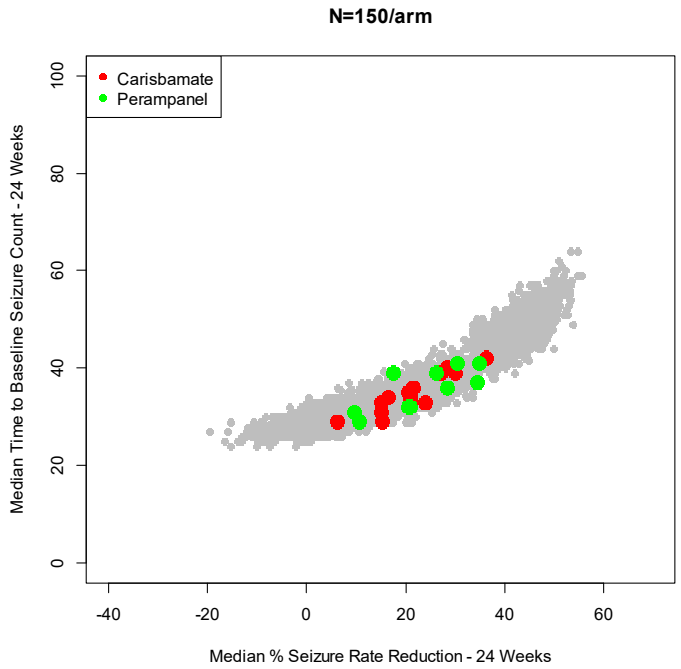
- 4-week baseline, 24-week treatment
- Mean Treatment Effect (θ_1): 0.05-0.60
- N=10000

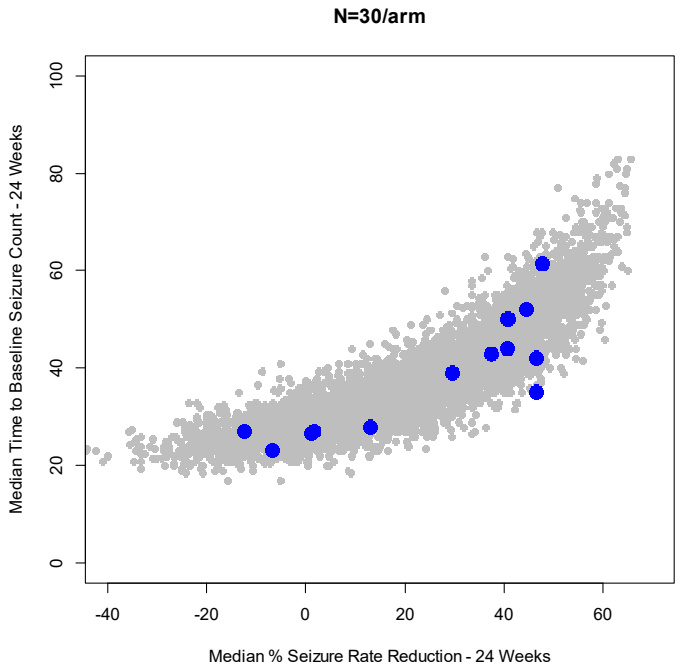
Analysis of daily seizure count:

- Median % monthly seizure rate reduction
- Median time to baseline seizure count

Model-based prediction of the relationship between endpoints agrees well with data of 3 AEDs

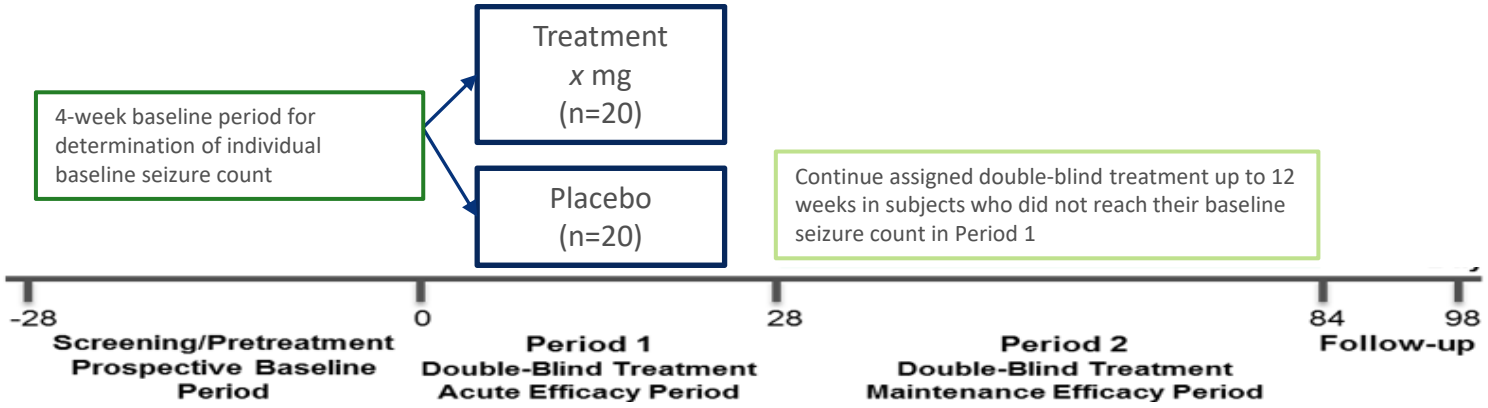
Model-Based Prediction of the Relationship between Endpoints in (small) clinical trials





Design of a Phase 2a POC Study

Adaptive Design
Interim Analysis when all patients have completed Period 1 to decide the dose for a next cohort of 40 subjects

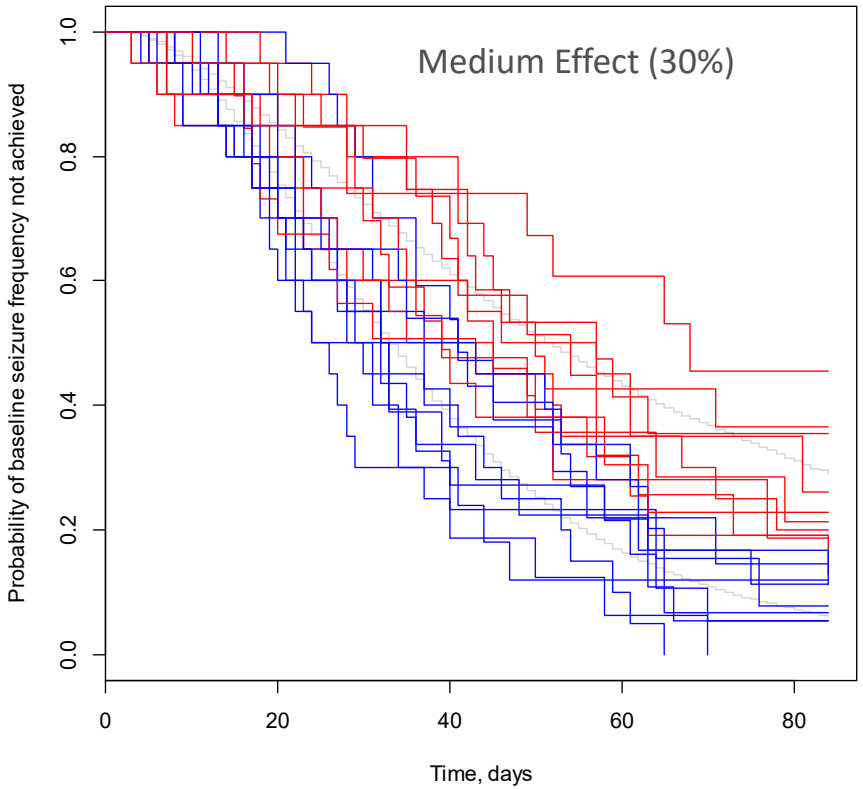


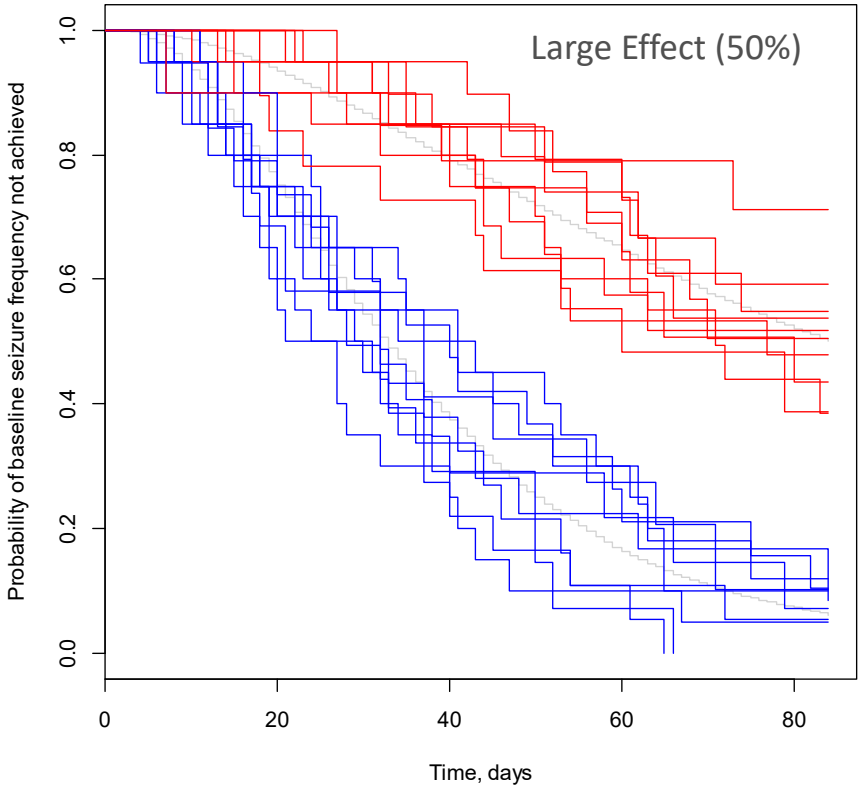
Clinical Trial Simulation

- Daily seizure counts simulated taking into account the following trial characteristics
  - Length of the baseline period
  - Length of the double-blind period
  - Number of patients per arm
  - Minimal number of baseline seizures for inclusion
  - Interim analysis when all subjects have completed Period 1
- Additional assumptions
  - No titration period
  - Immediate onset of drug action
  - Placebo-effect: 15% seizure rate reduction
  - A drop out rate of 5%
- Simulated daily seizure count data are analyzed
  - Baseline monthly seizure count
  - Time to baseline monthly seizure count during treatment period
  - Kaplan-Meier plot
  - Cox proportional hazard analysis comparing two arms (power)

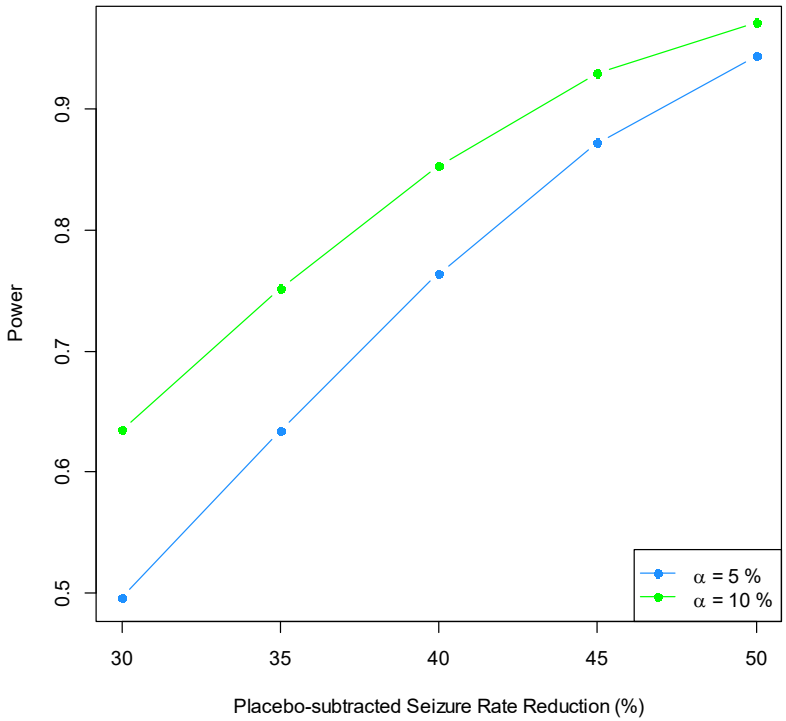
Clinical Trial Simulation

10 random replicates





Simulated-based Power of the Design

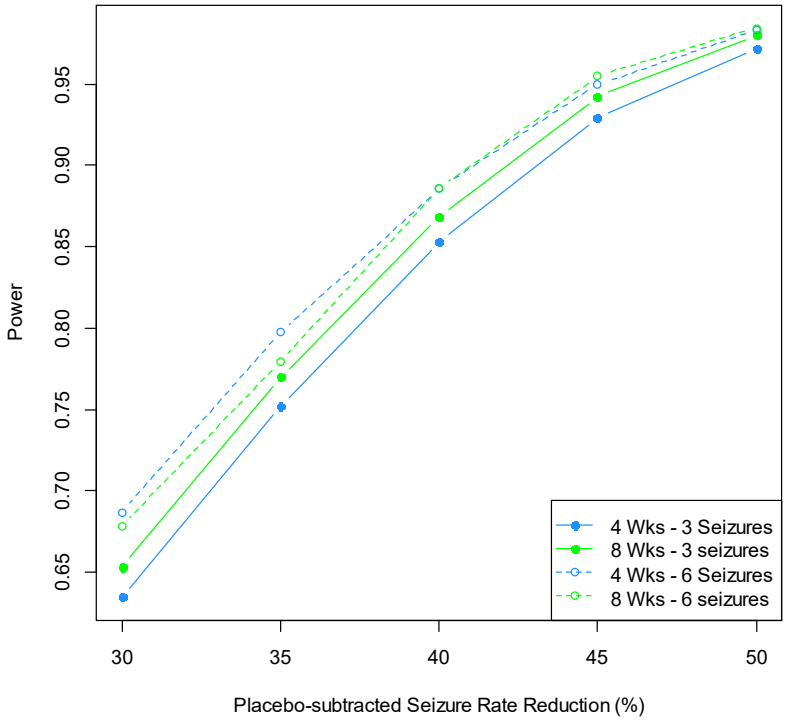


Proposed trial (N=20/arm, 4-week baseline) using the TBS endpoint has adequate power (α=10%) to establish* an efficacy signal if the experimental treatment has a placebo-subtracted effect larger than 35%

*Cox proportional hazard model

Simulated-based Power (α=10%) of the Design

Baseline Duration and # of Seizures



Length of Baseline Period

A 8 Wk baseline period increases power only minimally compared to a 4 Wk baseline.

Minimum of Seizures

Including subjects with at least 6 seizures during the baseline period increases the power, especially at lower effect sizes

Conclusion

- The relationship between the *median time to baseline monthly seizure count (*TBS*)* and the classical endpoint of *median % seizure rate reduction* in topiramate and carisbamate clinical trails was similar to the one previously described for perampanel.
- The relationship was confirmed by simulation using a model for longitudinal daily seizure counts
- Simulation-based evaluation of Phase 2a study design using the TBS endpoint support the use of the TBS endpoint seizure count in early dose finding studies in refractory epilepsy
  - Interim Analysis after 4 weeks of treatment after 4 weeks treatment allows early signal detection and rapid decision making
  - Reduced prolonged exposure of subjects to placebo and/or a ineffective treatment
  - Continuation of treatment up to 12 weeks in subjects who do not meet the exit criteria allows an assessment of responder rate and seizure freedom rate