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 antiepileptic 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

% Reduction

43%

-20%

83%

-75%
Endpoints in Epilepsy Clinical Trials
Time to Event Approach

Endpoints in Epilepsy Clinical Trials
Time to Baseline Monthly Seizure Count\textsuperscript{1}

**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


\(^2\)Janssen R&D, data on file
Time to Baseline Monthly Seizure Count
Re-analysis of perampanel Phase 3 clinical trials

Time to Baseline Monthly Seizure Count
Re-analysis of topiramate clinical trials

Double Blind Period

Maintenance Period

Placebo
Topiramate (200 mg - 1000 mg)
Time to Baseline Monthly Seizure Count
Re-analysis of carisbamate clinical trials

![Graph showing probability of baseline seizure frequency not achieved over time for Placebo and Carisbamate groups.

- Placebo
- Carisbamate (100 mg - 1600 mg)

Double Blind Period

Graphical representation of the data analysis with time in days on the x-axis and probability of baseline seizure frequency not achieved on the y-axis.
Relationship between Endpoints

Topiramate  Carisbamate  Perampanel

Strong relationship between endpoints.
Consistent across 3 different compounds.

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\(^5\)


- These models all share common features regarding \textit{patient variability} and \textit{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: \(\log \lambda_t = \theta_0\)

Treatment: \(\log \lambda_t = \theta_0 + \theta_1\)
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 ($\theta_1$): 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

- 4-week baseline period for determination of individual baseline seizure count
- Treatment $x$ mg (n=20)
- Placebo (n=20)
- Continue assigned double-blind treatment up to 12 weeks in subjects who did not reach their baseline seizure count in Period 1
**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

Medium Effect (30%)

Large Effect (50%)

Probability of baseline seizure frequency not achieved vs. Time, days
Simulated-based Power of the Design

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

*Cox proportional hazard model
Simulated-based Power ($\alpha=10\%$) 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