Modeling of daily seizure counts in focal epilepsy trials

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Objectives

- To compare different seizure count models for describing the change from baseline in individual seizure occurrences after treatment with brivaracetam or placebo in adjunctive treatment of focal epilepsy, and to establish an exposure-response relationship.

Methods

- **Data description**
  - Indication: Adjunctive treatment of focal seizures
  - Population: Adult patients (16-70 years) with partial onset seizures not fully controlled despite optimal treatment with 1 to 2 concomitant AED(s),
  - Recording: Daily partial onset seizure counts (diary).

  Five double-blind placebo-controlled efficacy studies with 1580 patients overall
  - Phase-II: Fixed dose, 4-week baseline + 7-10-week treatment
    - N01114 (Europe, 50 patients/arm): placebo, 50 mg/day, 150 mg/day with 3 weeks titration
    - N01193 (USA, LA, Asia, 50 patients/arm): placebo, 5 mg/day, 20 mg/day, 50 mg/day
  - Phase-III: Fixed dose, 8-week baseline + 12-week treatment
    - N01252 (Europe, Asia, 100 patients/arm): placebo, 20 mg/day, 50 mg/day, 100 mg/day
    - N01253 (NA, LA, Australia, 100 patients/arm): placebo, 5 mg/day, 20 mg/day, 50 mg/day
  - Phase-III: Flexible dose, 4-week baseline + 8-week dose finding + 8-week maintenance treatment
    - N01254 (Europe, Asia, 431 patients): non-forced titration 20 to 150 mg/day or matched placebo (3:1)

- **Basic features of the daily count model**
  - Previously, increases and decreases from baseline were described using different models with a mixture model to separate the two[1]
  - Now seizure frequency is modelled on log scale:

$$\lambda = 10^{Baseline+\eta_2+Q2\cdot\left(Plac+\eta_3+\frac{(E_{max}+\eta_4)\cdot Dose}{10^{LD50}+Dose}\right)}$$

  - where Q2 = 0 for baseline and 1 for post-baseline
  - For models with a Markovian aspect, Baseline+η2 is replaced by Baseline+η1+PDV1·(ΔBaseline+η2) where PDV1 is 0 if the preceding day had no seizures and 1 if the preceding day had 1 or more seizures
  - Inter-individual variability (IIV) on Emax which can be positive (deteriorators) and negative (improvers)
  - Initially without non-forced titration study data (N01254)

Results

- **Comparison of statistical models**
  - Different statistical models for count data were investigated
  - Delta objective function values (ΔOFV) for different statistical models with and without Markovian aspects, relative to Poisson without Markovian aspects:

Statistical model	ΔOFV without Markovian aspects	ΔOFV with Markovian aspects
Poisson	0	-4587
Zero-inflated Poisson	-9598	-12919
Negative binomial	-18766	-21495
Zero-inflated negative binomial	-18915	-21651
Zero-inflated Poisson+IIVP0*	-20589	-22538
Zero-inflated negative binomial+IIVP0*	-27182	-28917

*IIVP0: inter-individual variability on the zero-inflation parameter P0

  - The zero-inflated negative binomial model with inter-individual variability on the zero-inflation fraction (P0) and with Markovian aspects is the best model
  - Using AUC or Css_{trough} instead of dose did not result in improved data description

- **Goodness of fit graphs**
  - Population and individual residuals of mean daily seizure frequency per week by dose and week: no trends (Figure 1)
  - Observed vs Individual predictions of mean daily seizure frequency per week by dose on log-scale: no trends (Figure 1)

Figure 1: Goodness of fit graphs of residuals versus time (upper panel) and of observed mean daily seizure frequency per week versus individual predictions (lower panel)

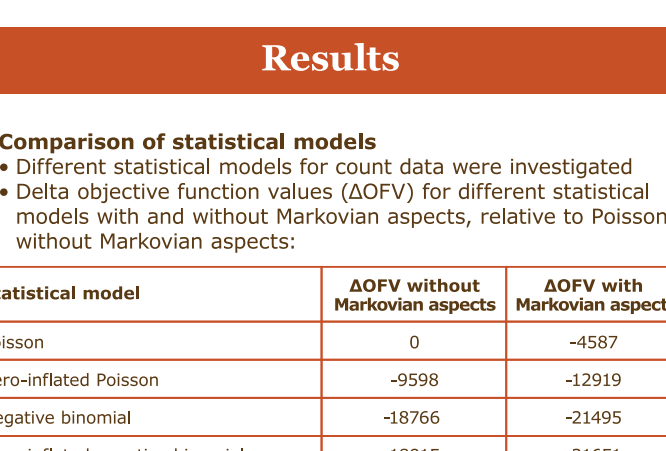
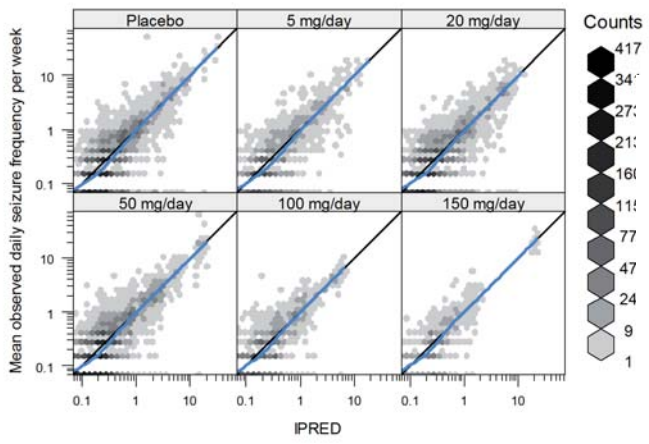


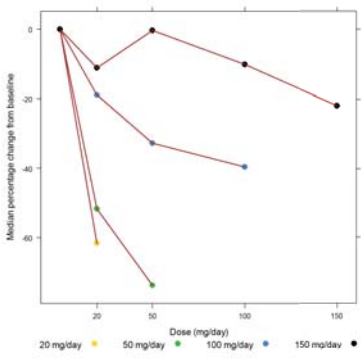
Figure 1 (continued)



- **Visual predictive checks (VPC)**
  - VPC of percentage deterioraters, responders and full responders illustrates nice overlap between simulated and observed response (not shown)

- **Special data set: non-forced titration study N01254**
  - 1:3 randomization to placebo or 20 mg/day, then optional titration by the investigator to 50, 100 or 150 mg/day over 8 weeks, then 8 weeks maintenance
  - Figure 2 gives median observed change from baseline for the 4 ultimate maintenance dose groups: selection of patients according to sensitivity
  - Can only be analyzed using a parametric model

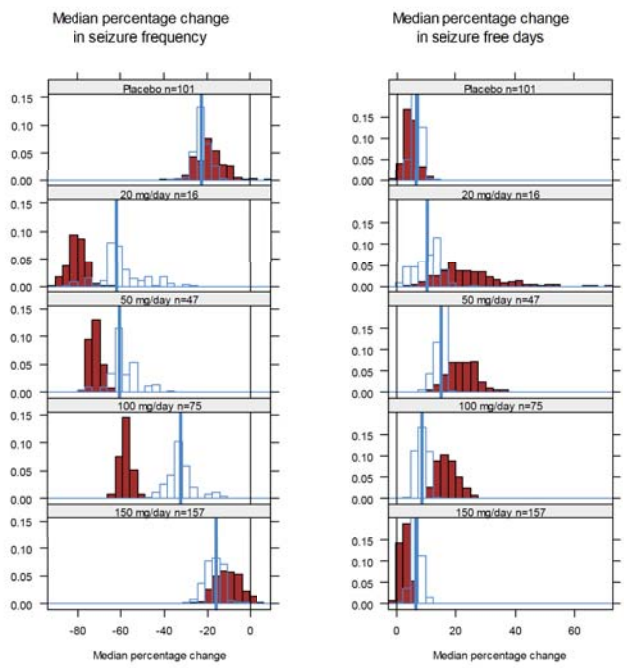
Figure 2: Observed median percentage change from baseline in seizure frequency versus final maintenance dose



How to simulate the 'clinical' decision to titrate to a higher dose level?

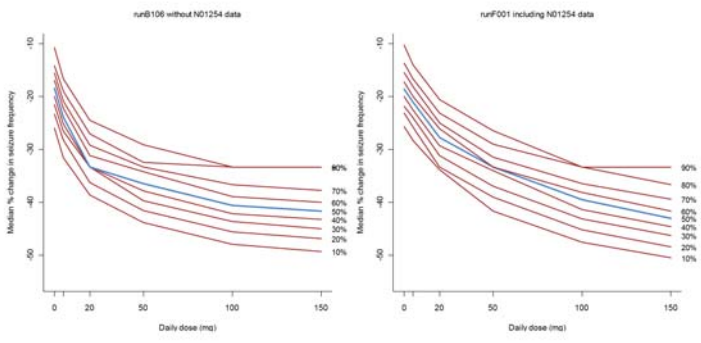
- Study N01254 was simulated using the base model
- Only (change in) seizure frequency is available as basis for decision
- Simulate two-week periods and calculate % change from baseline
- If decrease in seizure frequency for the preceding two weeks is less than a certain criterion, increase to the next available dose
- Criteria were selected to arrive at a distribution of patient numbers over the dose groups comparable to those observed in the N01254 trial
- Criteria for weeks 2, 4, 6 and 8: -80%, -70%, -60%, -50% change from baseline on the assumption that one wants to be conservative to keep a low dose to start with and be less so as the study progresses. Note: no decreases in dose.
- Simulate 400 trials of 400 patients each (100 patients on placebo) with 8 weeks maintenance at final obtained dose
- Predicted statistics (Figure 3) show good correspondence at placebo and 150mg (65% of the patients), but lower doses are predicted to be more extreme: apparently, the clinical decision is based on more than just decrease in seizure:

Figure 3: VPC (red histogram) of median percentage change in seizure frequency and median percentage change in fraction of seizure free days for the flexible dosing study by maintenance dose. Blue histogram: bootstrapped distribution for observed statistic, blue vertical line: observed statistic.



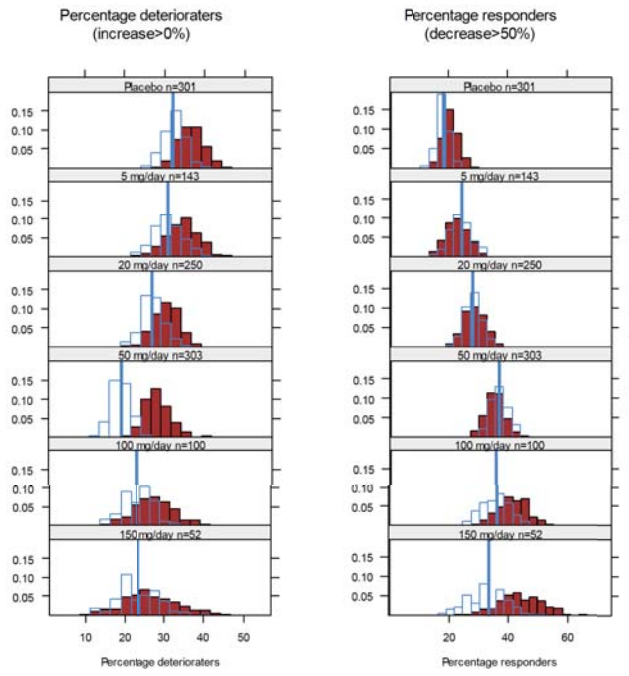
- The plots suggest that the median reduction in seizure frequency and the median increase in seizure-free days are similar for the top dose (150 mg/day) and placebo groups. This behavior is inherent to flexible dosing designs in the sense that non-responding patients tend to be pushed to the highest possible dose and still did not respond.
- Simulated trials for analyses without and with N01254 data indicate a similar maximum effect but a more gradual approach (Figure 4)

Figure 4: Quantiles of median percentage change in seizure frequency (left without N01254; right with N01254)



- VPCs of percentage deterioraters (>0% increase) and responders (>50% decrease) using the model with titration study data indicate excellent overlap (red bars: simulated, blue bars: observed with bootstrapped distribution):

Figure 5: VPC (red histogram) of percentage deterioraters (>0% increase) and responders (>50% decrease by dose. Blue histogram: bootstrapped distribution for observed statistic, blue vertical line: observed statistic.



- **Adding N01254 data:**
  - Simulating clinical decisions is not truly possible since these are based on more than just decrease in seizure frequency
  - One would for instance not expect so many deterioraters in the 20 mg group if the decision to administer 20 mg was based on efficacy alone. In real life some patients in the 20 mg group may be there because the physician did not consider it wise to increase the dose for reasons unrelated to efficacy
  - The qualitative behavior of the simulations is nevertheless judged sufficiently close to observed outcomes to allow inclusion of the N01254 data in the NONMEM analysis
  - Goodness of fit plots and VPCs are excellent and very similar to those shown for the base model

Conclusions

- Novel model approach (Emax model on log-scale allowing increases and decreases, zero-inflated Negative Binomial model including Markovian aspects) successful in describing daily count data
- Non-forced titration data add information and can be described using the same model
- The daily count model provided superior goodness of fit due to its more detailed statistical structure and provided enhanced flexibility due to its ability to incorporate day-to-day changes in dose and covariates even in non-forced titration designs.

References

1. Laveille C, Snoeck E, Lacroix B, Sargentini-Maier ML, Stockis A. Dose-response population modeling of the new antiepileptic drug brivaracetam in add-on treatment of partial onset seizures. PAGE 16 (2007) Abstr 1093 [www.page-meeting.org/?abstract=1093]

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