INTRODUCTION

• Pregabalin offers a new approach in the treatment of Generalized Anxiety Disorder (GAD).
• Adverse events (AEs) are the predominant component of study withdrawal (dropout) contributing with at least 60% to total dropout incidence for this indication, considerably more than other dropout components/categories2,4 (Figure 1).

METHODS

Discrete Survival and Conditional (Hazard) Probabilities

• Time to subject dropout (T) is modeled as discrete survival variable. S(tj) is the probability that an individual survives in the study (does not drop out) beyond time tj, where j indexes study day.

\[ S(tj) = Pr(T > tj) \]

• Survival probability is related to hazard h(tj), the probability of the event (dropout) occurring in the time interval tj provided it has not occurred prior to j, among those “at-risk” in study, during interval jj. S(tj) is also the product of conditional survival probabilities, i.e., sequential survival across each individual period tj.

\[ h(tj) = \frac{Pr(T = tj | T > tj)}{Pr(T > tj)} \]

• Assuming that the probability of dropout (likelihood) is only dependent on the covariate (AE score) in a particular time interval, it is:

\[ Pr(T = tj) = h(tj) \left[ 1 - h(tj) \right] \]

Conditional Probabilistic Cumulative Hazard Model

• A discrete-time survival model was fit to GAD dropout time, assuming that the hazard depends on the current self-reported AE score and time since first study day.

\[ h(tj) = \exp \left( \alpha + \beta_1 \text{AE}_1(tj) + \beta_2 \text{AE}_2(tj) \right) \]

• Hazard was highest with high severity of either dizziness and somnolence decreasing with time for individuals with Gompertz model (exponentially decreasing hazard with time). 

\[ \lambda = \gamma e^{-\mu t} \]

RESULTS

Fig 1. Generalized Anxiety Disorder (GAD) Dropout Incidence (ITT)

Adverse Events Incidence Self-Reporting

Placebo 150 mg/day 600 mg/day

Dizziness (%) 6-8 10-23 29-39

Somnolence (%) 11 15-29 36-50

Others (%) <20 <20

Fig 2. Titrated Doses Across Study Arms (Randomized Doses)

Adverse Events Across Dose at 10 weeks

Table:

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>% Dizziness</th>
<th>% Somnolence</th>
<th>% Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>5</td>
<td>2</td>
<td>10</td>
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<tr>
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<td>7</td>
<td>4</td>
<td>25</td>
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</table>

Fig 3. Fitted Hazard Probability Distribution Models to the Observed Conditional Probabilities

REFERENCES