**Background**

Variable and higher placebo response within and among clinical trials can substantially affect conclusions about the efficacy of new antipsychotic drugs. Developing a robust placebo model accounting for the factors like dropouts, patient characteristics, and trial design is crucial in order to facilitate better recognition of drug effect.

**Objectives:**

i) to develop a model for placebo response in schizophrenia as measured with the Positive and Negative Syndrome Scale (PANSS) under varying clinical trial conditions, accounting for dropout and relevant predictors of the placebo response

ii) to compare different Time to Event (TTE) modeling approaches used to describe the dropout patterns following placebo treatment in schizophrenia

**Modeling Approaches**

Pooled placebo PANSS total data (n=1338), 3 phase II & II phase III trials, which included acute and chronic, long-and short-term studies

**Placebo Response Modeling:**

- Structural Base Model Building
- Placebo-associated change in PANSS score was well described by the Weibull placebo model and the Indirect Response Model (IRM)\(^1\)

**Covariate Modeling:**

Systematic identification of covariates that contribute to high placebo response and dropouts were investigated. Final Weibull and IRM placebo base model using stepwise covariate model building approach, within PsN was used. Strict forward inclusion and backward exclusion criteria was set to identify clinically relevant covariates (ΔOFV of 10.83, P< 0.001). Both linear and non-linear covariate relationship were explored.

**Dropout Modeling:**

Previously, the exponential hazard model to predict the risk of dropout was attempted.\(^5\) In addition, predictors of dropout, and alternative TTE models like the Weibull and the Gompertz hazard models were examined together with different dropout patterns

- Missing Completely At Random (MCAR): independent of PANSS
- Missing At Random (MAR): depends on last observed PANSS
- Missing Not At Random (MNAR): dropout depends on predicted PANSS

**Results**

**Covariate Model:**

<table>
<thead>
<tr>
<th>Model</th>
<th>POP (95% CI)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weibull Placebo Model</td>
<td>91.1 (90.1-91.8)</td>
<td>-</td>
</tr>
<tr>
<td>TD (days)</td>
<td>12.7 (11.2 - 14.6)</td>
<td>-</td>
</tr>
<tr>
<td>PMAX (maximum placebo effect)</td>
<td>0.067 (0.072 - 0.102)</td>
<td>-</td>
</tr>
<tr>
<td>PDVW (shape Parameter)</td>
<td>1.24 (1.15 - 1.35)</td>
<td>-</td>
</tr>
<tr>
<td>(residual variability)</td>
<td>7.29 (6.7 - 7.9)</td>
<td>-</td>
</tr>
<tr>
<td>BASL-DIS (acute vs. chronic)</td>
<td>-0.038 (-0.06 - -0.014)</td>
<td>chronic patients had 3.8% lower PANSS BASL</td>
</tr>
<tr>
<td>PMAX-DUR (short vs. long-term)</td>
<td>-1.4 (-1.7 - -1.1)</td>
<td>long-term studies showed 140% lower placebo effect (meaning)</td>
</tr>
<tr>
<td>TD-US (USA vs. Non-USA)</td>
<td>0.36 (0.28-0.57)</td>
<td>time course of placebo effect lasted for longer duration (35%) for studies in Non-USA SL &amp; IL had 27% lower residual error compared to oral route</td>
</tr>
<tr>
<td>-ADIM (oral vs. IM/SL)</td>
<td>-0.274 (-0.33 - -0.19)</td>
<td>-</td>
</tr>
<tr>
<td>-DIS (acute vs. chronic)</td>
<td>0.50 (0.31-0.74)</td>
<td>50% higher residual error for chronic patients</td>
</tr>
<tr>
<td>-US (USA vs. Non-USA)</td>
<td>-0.28 (-0.38 - -0.25)</td>
<td>Non-USA studies showed 28% lower residual error</td>
</tr>
<tr>
<td>INV BASL (exponential) (CV%)</td>
<td>18 (14-16)</td>
<td>-</td>
</tr>
<tr>
<td>INV PMAX (additive)</td>
<td>19 (17-20)</td>
<td>-</td>
</tr>
<tr>
<td>INV (exponential) (CV%)</td>
<td>40 (34-44)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^*\) 95% CI from 2,000 bootstrap samples; IRM-covariate model also resulted in similar covariate-relationship (data not shown)

**Dropout Modeling:**

- Incorporation of the exponential dropout model improved the VPC of the PANSS score (Fig 4)
- Based on OFV, the Gompertz dropout model with MAR dropout pattern seems to describe the observed data best
- Further, simulations using predictors of dropout for all the TTE models are in progress

**Predictors of dropout:** Females, subjects in long-term studies and chronic patients had lower probability of dropping out from trials compared to males, subjects of short-term trials and acute schizophrenic patients

**Summary**

- Covariate analysis with the Weibull placebo model identified disease condition, study site, administration route and trial duration as contributing factors for the variable placebo response
- The exponential, Weibull and Gompertz hazard models performed equally well for short-term trials, while for long-term trials and for the entire pooled dataset, the Gompertz model was shown to be superior
- The probability of dropout from a trial depends on the change in PANSS score baseline, PANSS last score and the predicted PANSS score

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**Partners in this project include:**

- Johnson & Johnson Pharmaceutical Research and Development
- Merck Research Labs
- Pfizer Global Research and Development
- Leiden/Amsterdam Center for Drug Research

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**Full project title:** Mechanism-based PK-PD modeling platform

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