# ADAS-Cog Placebo Response Modelling in Alzheimer's Disease

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## Background

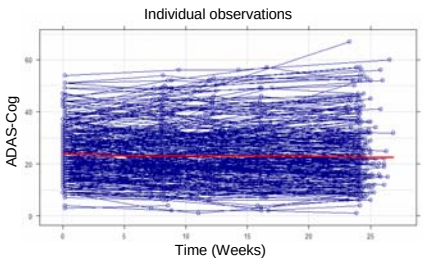
Alzheimer Disease Assessment Scale (ADAS-Cog) is the standard clinical score used to assess cognition in Alzheimer's Disease (AD). It is scored by number of errors ranging from 0 to 70 [1]. An increase in ADAS-Cog score implies worsening cognition. Several recent 6 month clinical trials of investigative medications for AD have failed to detect cognitive decline in placebo groups by ADAS-Cog, potentially obscuring true treatment effects. The lack of cognitive decline in the placebo groups has renewed interest in a better understanding of the time course of placebo response.

## Objective

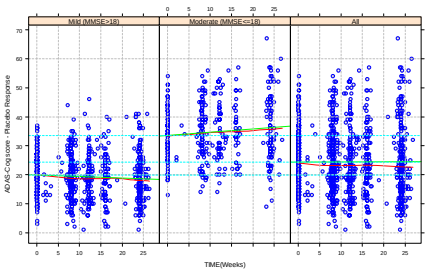
The aim of this work is to investigate the ADAS-Cog placebo response model in Alzheimer's Disease to aid the design of future clinical trials by taking into account the information about which patients are more likely to be placebo responders.

## Methods

Data from the placebo arms of 3 recent clinical trials (n=307) were pooled to investigate the placebo response as a function of time and disease severity given by Mini Mental Status Exam (MMSE). Mild AD severity was associated with MMSE > 18 and moderate AD severity was associated with MMSE ≤ 18.




### Placebo ADAS-Cog Individual Longitudinal Scores




### ADAS-Cog Placebo Response vs. Time for Mild, Moderate and Overall Subjects

Nonlinear Mixed Effects Modelling Approach was applied to this data using NONMEM V6. The following models were explored:

Model A [2]:

$$ADAS_{ij} = ADAS0_j + K_j t_{ij} - A_j\left[\exp\left(-koff_j t_{ij}\right) - \exp\left(k_j t_{ij}\right)\right] + \varepsilon_{ij}$$

where *ADAS0*= ADAS-Cog at baseline, *K*=disease progression slope, *A*= magnitude of placebo contribution, *koff*= offset rate of placebo response and *k*= onset rate of placebo response.

Model B [3]:

$$ADAS_{ij} = ADAS0_j \cdot \exp\left(-\frac{t_{ij}}{k_j}\right) + K_j t_{ij} + \varepsilon_{ij}$$

## *Structural Identifiability Analysis*

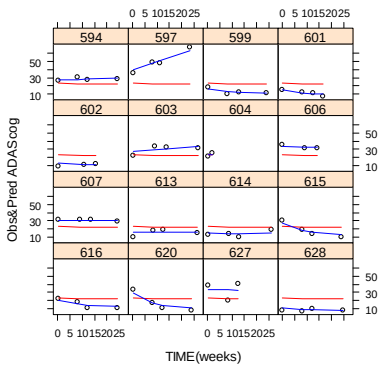
Identifiability Analysis was used to test whether the proposed model was structurally correct and appropriate for deriving clinically meaningful conclusions.

Structural Identifiability analysis based upon Taylor's series approach [4] showed that in presence of flat placebo response, Model A parameters are not uniquely identifiable. Hence, to alleviate this problem, Model B was proposed.

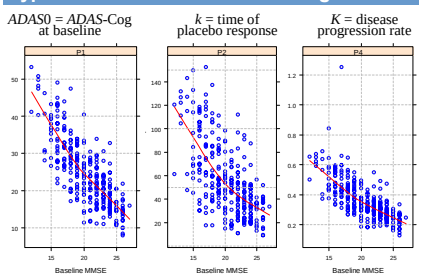
Model B not only takes into account flat placebo response, but is generic and also applicable for modelling other diseases.

## Results

The following figure shows the typical individual (blue line), population (red line) ADAS-Cog model predictions and observed data (circles). For each parameter, between-subject variability was tested and covariate analysis was investigated.

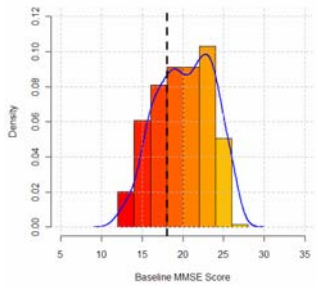



### Typical Individual Fit of ADAS-Cog vs. Time




### Correlation between Model Parameters and Disease Severity

The above plots show that the model parameters are correlated with disease severity (MMSE). The covariate analysis showed that the addition of baseline MMSE as a covariate, on ADAS-Cog at baseline and disease progression rate, further improved the data fitting.




### Baseline MMSE Score Distribution

## Model Validation

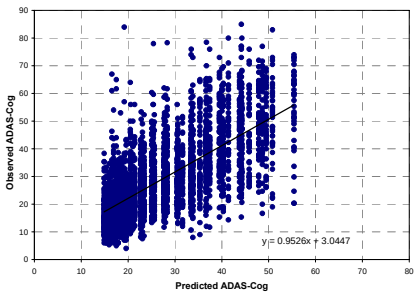
External model validation was carried out using data from internal GSK studies (n=733).

Summary of the placebo groups from the 6 validation trials

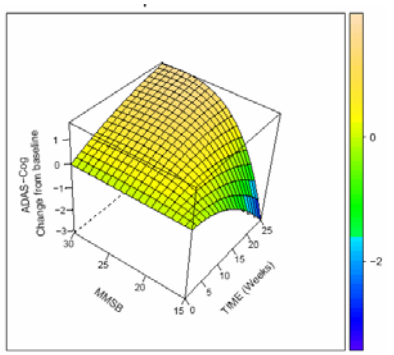
| Study | Countries | Centers | Randomized to Placebo | Completers | Placebo 24 week ΔADAS-cog completers (SD) |
|---|---|---|---|---|---|
| 023 | 2 | 31 | 133 | 100 | **2.4 (6.1)** |
| 044 | 4 | 54 | 155 | 141 | **1.0 (5.3)** |
| 045 | 1 | 39 | 138 | 112 | **2.1 (6.2)** |
| 046 | 7 | 43 | 136 | 121 | **2.3 (6.1)** |
| 047 | 3 | 44 | 142 | 126 | **1.4 (7.5)** |
| 048 | 1 | 37 | 152 | 133 | **2.0 (7.2)** |

ADAS-cog: Alzheimer's Disease Assessment Scale – cognitive subscale.
SD: Standard deviation

### Validation Datasets




### Observed and Model Predicted ADAS-Cog Scores




### Placebo Surface Response of the Model

The placebo response model is described as a function of time and disease severity at inclusion. In the above surface response plot, negative values of ADAS-Cog change from baseline denote cognitive decline and positive values denote cognitive improvement. This plot demonstrates that at 24 weeks, for moderate AD severity cognitive decline is observed, and for mild AD severity cognitive decline is not observed.

## Conclusions

- Structural Identifiability is important for obtaining reliable predictions
- Model B adequately describes flat placebo response
- Including baseline MMSE score can improve predictions of ADAS-Cog response
  - Maximize the possibility of detecting clinical response

## References

1. R.F. Zec *et. al.*, *Alzheimer Dis. Assoc. Disord.* **6** (1992) 89-102.
2. N.H.G. Holford and K.E. Peace, *Proc. Natl. Acad. Sci.* **89** (1992) 11466-11470.
3. R. Gomeni and E. Merlo-Pich, *Br. J. Clin. Pharmacol.* **63** (2007) 595-613.
4. M.J. Chappell *et. al.*, *Mathematical Biosciences*. **102** (1990) 41-73.