Aducanumab is a human monoclonal antibody that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils.1

1. Sevigny J, et al. Aducanumab was granted accelerated approval by the US Food and Drug Administration for the treatment of Alzheimer’s disease. According to the US Food and Drug Administration, treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.1,2

A robust dose-dependent reduction in brain Aβ plaque levels, as measured by amyloid positron emission tomography, was demonstrated across aducanumab clinical studies (PRIME, EMERGE, and ENGAGE).1,2

An exposure-response model characterizing the relationship between aducanumab exposure and reduction in Aβ levels in the brain has been characterized previously.3

Here, we describe an exposure-response model to characterize the changes in Aβ plaque levels and CDR-SB (primary endpoint) following treatment with aducanumab in the ENGAGE and EMERGE phase 3 studies.

Methods
Because there are standard uptake value ratio (SUVR) observations for only about one-third of the sample set, the exposure–SUVR model (an indirect response model with no assumption of plaque elimination) was used to generate ad hoc model imputed typical individual predicted SUVR profiles for all individuals within the placebo group. Therefore, baseline covariates and the final covariate model.

The CDR-SB is a bounded scale (0-18), so scaled CDR-SB (SB) was modeled on the logit scale. This analysis was performed on the logit scale to ensure that predictions of the model were constrained within the bounds of the original scale.

CDR-SB was modeled sequentially using individual pharmacokinetic-pharmacodynamic parameters incorporated in the data set. SUVR change from baseline calculated as (SUVRBL-SUVRt)/SUVRBL was used as a predictor of the CDR-SB response.

Base models were developed, evaluating disease progression and drug effect components. Internal visual predictive check was used to assess predictive performance of the final model on data used in model development.

The analyses were performed using NONMEM® software, version 7.4.3. Postprocessing of model output, including graphical analyses, was performed using R software, version 3.6.0.

Results
A linear model in the logit-transformed CDR-SB best described the changes over time in the placebo group.

To account for the considerable variation in disease progression rates, a mixture model was used that assigned subjects into 2 or 3 latent classes: (1) slow progressors (individuals with no progression over the 78-week period); (2) typical progressors; and (3) fast progressors.

The disease progression model developed based on the placebo data was augmented to include the therapeutic activity of aducanumab as an additive effect and subsequently evaluated based on the randomized subjects without any dose interruption over a period of 18 months (Figure 1).

Because there are standard uptake value ratio (SUVR) observations for only about one-third of the sample set, the rate parameters are transformed from logit to linear scale for baseline and proportion parameters; the rate parameters are invariant in Typical and Rapid Progressors With Censored Data.

Table 2: Runs to Investigate the Influence of Study on Drug Effect Using SUVR With Drug Effect Invariant and Rapid Progressors With Censored Data

Figure 1: Model-Predicted Treatment Effect Over 18 Months in Subjects Treated With a Titration to 10 mg/kg Aducanumab Regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
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<th>Exposure-response model</th>
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<td>NONMEM estimates</td>
<td>Bootstrap estimate median (95% CI)</td>
<td>Bootstrap estimate median (95% CI)</td>
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