Crenezumab exposure–response across AD endpoints supports a higher dose for Phase 3

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Background

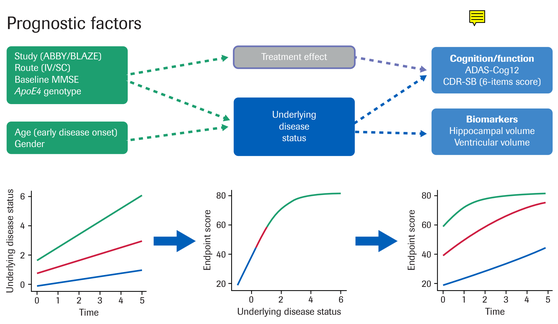
- Crenezumab (MABT5102A, RO5490245) is a humanized anti-Aβ monoclonal IgG4 antibody in development for the treatment of AD.
- Crenezumab binds to multiple forms of Aβ (monomers, oligomers, fibers/plaques)—notably with high affinity for Aβ oligomers—and is hypothesized to reduce oligomer neurotoxicity and accumulation.[1, 2]
- Crenezumab was tested in two Phase 2 trials (ABBY, NCT01343966; BLAZE, NCT01397578)[3, 4] conducted in a mild-to-moderate AD population, evaluating a high 15 mg/kg IV Q4W dose and a low 300 mg Q2W SC dose. In ABBY, there was no enrichment for presence of Aβ pathology.
- The Phase 2 studies demonstrated a consistent treatment effect on cognition with the 15 mg/kg IV dose for the milder population (MMSE ≥ 22) in a post hoc analysis, while the low 300 mg Q2W SC dose level lacked a consistent treatment effect, suggesting that higher doses in more mildly affected patients may be associated with greater efficacy signals. In both Phase 2 studies, crenezumab was generally well tolerated, with only one case of ARIA-E across both studies, indicating that higher doses could be investigated further.
- Safety, tolerability and PK of higher IV doses in mild-to-moderate AD is currently being investigated in a Phase 1b study (NCT02353598). Blinded safety and PK data from 30, 45 and 60 mg/kg IV Q4W are presented.[5]

Here we present the exposure–response analysis supporting a higher dose of 60 mg/kg IV Q4W in the ongoing Phase 3 study CREAD (NCT02670083).[6]

Methods

- Using data from the ADNI study,[7] a disease progression model for mild-to-moderate AD was developed. The model adequately described the longitudinal changes of the clinical endpoints (ADAS-Cog12 and CDR-SB) and the biomarkers (hippocampal and ventricular volumetric MRI) simultaneously for subjects in the ADNI study.[8-11] The model included analysis of key baseline characteristics that are thought to influence disease progression (Figure 1).
- The disease progression model was extended to describe the drug effect of crenezumab on each clinical endpoint separately, as a hyperbolic function (E_{max} model). No drug effect was seen on the volumetric MRI (Roche data on file). Therefore, no MRI data are shown here.
- The model was used to analyze the Phase 2 studies (ABBY and BLAZE) simultaneously. However, to account for the staggered enrollment and within-cohort randomization to crenezumab or placebo, factors for study and route were included for two parameters in the model: disease progression and maximum drug effect (E_{max}). This allows for a separate estimation of the placebo response and drug effect for each cohort.

Figure 1. Schematic of the AD disease progression model.[8,9]



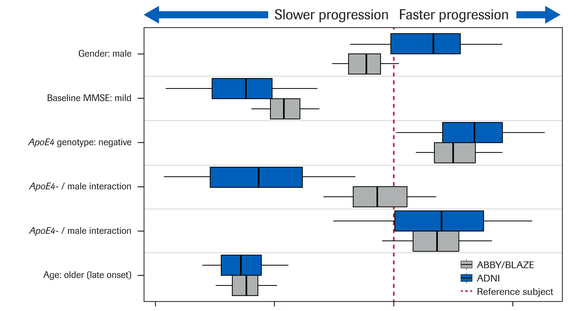
Line graphs indicate longitudinal relationships between endpoint score and a latent underlying disease status that evolves linearly over time according to patient-specific rates, influenced by baseline MMSE, *ApoE4* genotype, age (disease onset time) and gender.

- Clinical trial simulations representing 1000 replications of the Phase 3 study design were conducted across a range of doses, assessing the likelihood of achieving a relative reduction in disease progression in treated patients compared with placebo as measured by ADAS-Cog12 and CDR-SB.

Results

- Key baseline characteristics that influence disease progression were consistent between the ADNI population and the ABBY/BLAZE population (Figure 2). The analysis showed faster disease progression in:
  - moderate AD (lower baseline MMSE)
  - *ApoE4*-positive genotype
  - female gender
  - early onset (age).

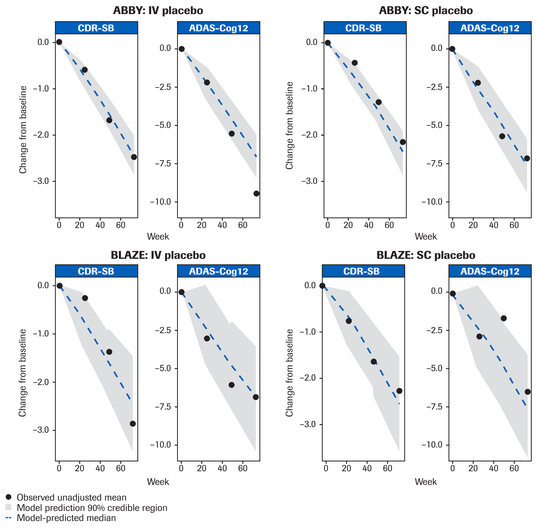
Figure 2. Analysis of influence of key baseline patient characteristic on rate of disease progression.



Posterior estimated effect of normalized prognostic factors relative to reference subject (with uncertainty).
Reference subject: *ApoE4*-positive genotype, baseline MMSE 22, age 70, female, placebo.

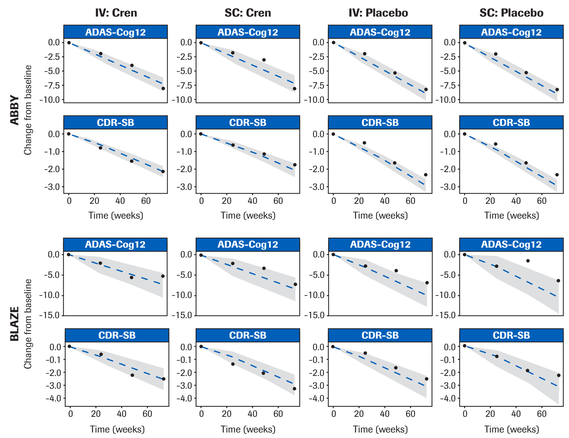
- Simulations using the disease model developed on ADNI data alone demonstrated that the observed placebo decline in both cohorts of ABBY and BLAZE is largely consistent with expectations (Figure 3).

Figure 3. Observed cognitive decline as measured by CDR-SB and ADAS-Cog12 compared with disease progression model simulations for ABBY and BLAZE placebo cohorts.



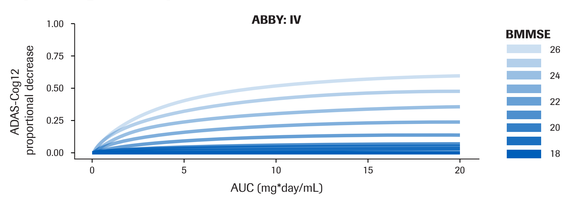
- Validation of the extended disease progression model fitted to Phase 2 data demonstrated that the model replicated the Phase 2 longitudinal data accurately. The model is therefore fit for purpose for simulation of the disease progression and crenezumab treatment effect in the population of interest (milder AD population, baseline MMSE 22–26; Figure 4).

Figure 4. Comparison of observed cognitive decline as measured by CDR-SB and ADAS-Cog12 and extended disease progression model simulations for ABBY and BLAZE Phase 2 studies.



- A correlation was observed between crenezumab exposure (AUC at steady state) and treatment effect (ADAS-Cog12 and CDR-SB), which appeared to reach an asymptote at the projected exposures of the dose of 60 mg/kg Q4W. The treatment effect of crenezumab was associated with high baseline MMSE, suggesting better treatment effect earlier in AD (Figure 5). In addition, *ApoE4* genotype had a minor influence on the treatment effect (Roche data on file).

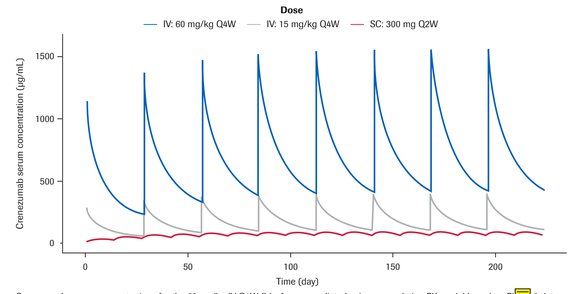
Figure 5. Association between ADAS-Cog12 and crenezumab exposure given the patient baseline MMSE.



* Assumes ABBY IV parameters. Steady-state AUC over 28 days interval.

- A population PK model was developed using serum crenezumab concentration data from the Phase 1 (ABE4427g and ABE4662g) and Phase 2 studies (ABE4869g and ABE4955g). Model-simulated serum concentrations for a 15 mg/kg IV Q4W (gray) and 300 mg SC Q2W (red) and 60 mg/kg IV Q4W is shown in Figure 6. An IV dose of 15 mg/kg Q4W provided ~1.5-, 2.5- and 5-fold higher exposure (C_{min}, AUC and C_{max} at steady state) compared with the 300 mg Q2W SC dose. Using the model, a dose of 60 mg/kg IV Q4W is predicted to achieve 4-fold higher serum crenezumab concentrations compared with 15 mg/kg Q4W (Figure 6).

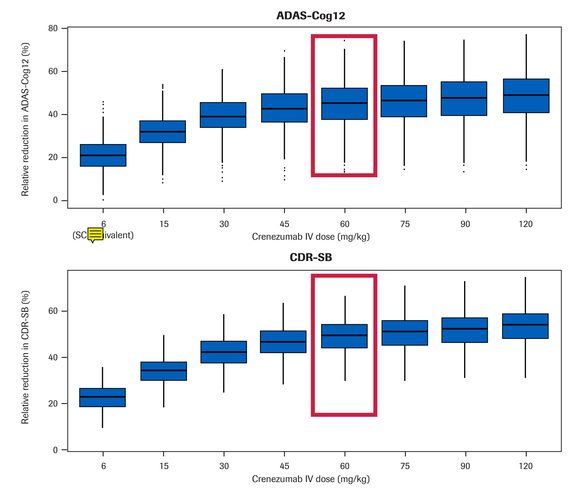
Figure 6. Simulated crenezumab serum concentrations.



Crenezumab serum concentrations for the 60 mg/kg IV Q4W (blue) were predicted using a population PK model based on Phase 2 data using doses of 15 mg/kg (gray) and 300 mg SC Q2W (red).

- Clinical trial simulations of the Phase 3 study design using the drug-disease model showed that a 4-fold increase in dose to 60 mg/kg Q4W is predicted to achieve a 41% greater relative reduction on ADAS-Cog12, and 44% on the CDR-SB in the milder AD population (baseline MMSE 22–26) (Figure 7). However, since Phase 2 data were used as the training set for the model, uncertainty in estimated efficacy is greater where exposure is outside the levels observed in Phase 2.

Figure 7. Dose–response of crenezumab dose IV Q4W on cognitive endpoints (ADAS-Cog12 and CDR-SB) in patients with mild AD (baseline MMSE 22–26) based on clinical trial simulations using the drug-disease model.



Conclusions

- A drug-disease progression model of both crenezumab and placebo cohorts adequately summarized the longitudinal decline in ADAS-Cog12 and CDR-SB in mild-to-moderate patients in the crenezumab Phase 2 studies (ABBY/BLAZE).
- A 60 mg/kg IV Q4W dose was selected for Phase 3, supported by clinical trial simulations using the drug-disease model, which predicts greater treatment effect at higher exposures in patients with mild AD.

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Abbreviations

Aβ, amyloid-beta; AD, Alzheimer's disease; ADAS-Cog12, Alzheimer's Disease Assessment Scale Cognition subscale 12; ADNI, Alzheimer's Disease Neuroimaging Initiative; ApoE4, apolipoprotein E4; ARIA-E, amyloid-related imaging abnormalities edema; AUC, area under the curve; BMMSE, baseline Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; C_{max}, maximum concentration; C_{min}, minimum concentration; Cren, crenezumab; E_{max}, maximum drug effect; IgG4, immunoglobulin G4; IV, intravenous; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PK, pharmacokinetics; Q2W, dose every 2 weeks; Q4W, dose every 4 weeks; SC, subcutaneous.

Acknowledgments

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