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

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Background

- Crenzumab (MABT102a, R05496245) is a humanized anti-Aβ monoclonal IgG antibody in development for the treatment of AD.
- Crenzumab binds to multiple forms of Aβ (monomers, oligomers, fibrils/plaques)—notably with high affinity for Aβ oligomers—and is hypothesized to reduce oligomer neurotoxicity and accumulation.1-3
- Crenzumab was tested in two Phase 2 trials (ABBY, NCT01343966; BLAZE, NCT01537547)3 in a mild-to-moderate AD population, evaluating a high 15 mg/kg IV Q4W dose and a low 30 mg QDW SC dose. In ABBY, there was no enrichment for Aβ pathology.
- The Phase 2 studies demonstrated a consistent treatment effect on cognition with the 15 mg/kg IV dose for the milder population (MME 2-22) in a post hoc analysis, while the low 30 mg QDW 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, crenzumab 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 IV Q4W are presented.4

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

Methods

- Using data from the ADNI study, 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.5,6 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 crenzumab on each clinical endpoint separately, as a Hyperbolic function (E model). No drug effect was seen on the volumetric MRI (Roche data on file). Therefore, no PK 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 crenzumab or placebo, factors for study and route were included for two parameters in the model: disease progression and maximum drug effect (E). 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.

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.

- 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 crenzumab treatment effect in the population of interest (mild 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 population PK model was developed using serum crenzumab concentration data from the Phase 1 (ABB0427H) and (ABB4612G) and Phase 2 studies (ABB461HG and ABB619HG). Total simulated serum concentrations for a 15 mg/kg IV Q4W (gray) and 30 mg SC Q2W (red) and 60 mg/kg IV Q4W is shown in Figure 5. An IV dose of 15 mg/kg Q4W predicted −1.5-, 2.5- and 5-fold higher exposure (Cmax, AUC, and C0) at steady state) compared with the 300 mg QDW SC dose. Using the model, a dose of 60 mg/kg IV Q4W is predicted to achieve 4-fold higher serum crenzumab concentrations compared with 15 mg/kg Q4W (Figure 6).

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

- A drug-disease progression model of both crenzumab and placebo cohorts adequately summarized the longitudinal decline in ADAS-Cog12 and CDR-SB in mild-to-moderate patients in the crenzumab 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.

Conclusions

- A drug-disease progression model of both crenzumab and placebo cohorts adequately summarized the longitudinal decline in ADAS-Cog12 and CDR-SB in mild-to-moderate patients in the crenzumab 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.

References


Abbreviations

Aβ: amyloid β; AD: Alzheimer’s disease; ADAS-Cog12: Alzheimer’s Disease Assessment Scale-Cognition subscale 12; ACR: Alzheimer’s Disease Neoradiology Initiative; APOE: apolipoprotein E; MRI: magnetic resonance imaging; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating-Sum of Box; Cmax: maximum concentration; Cmin: minimum concentration; Cmin, crenzumab; Cmax, maximum drug effect; IgG4: immunoglobulin G4; IV: intravenous; MMSE: Mini-Mental State Examination; MRI, magnetic resonance imaging; PK: pharmacokinetics; SC: subcutaneous; tmax: time to maximum concentration; Week: week; Cmax: maximum concentration; Cmin, crenzumab; tmax, maximum drug effect; IgG4: immunoglobulin G4; IV: intravenous; MMSE: Mini-Mental State Examination; MRI, magnetic resonance imaging; PK: pharmacokinetics; SC: subcutaneous; tmax: time to maximum concentration.

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