Pharmacokinetics and pharmacodynamic effect of crenezumab on plasma and cerebrospinal fluid beta-amyloid in patients with mild-to-moderate Alzheimer’s disease

Kenta Yoshida¹, Anita Moein¹, Tobias Bittner², Susanne Ostrowitzki¹, Helen Lin¹, Lee Honigberg¹, Jin Y. Jin¹ and Angelica Quartino¹*

Abstract

Background: Crenezumab, a fully humanized anti-beta-amyloid (Aβ) immunoglobulin G4 (IgG4) monoclonal antibody, binds to both monomeric and aggregated forms of Aβ. We assessed the pharmacokinetics (PK)/pharmacodynamics (PD) of crenezumab and its interaction with monomeric Aβ(1–40) and Aβ(1–42) peptides in serum/plasma and cerebrospinal fluid (CSF) samples from the phase II ABBY and BLAZE studies and the phase Ib GN29632 study.

Methods: In ABBY, BLAZE, and GN29632 studies, patients with mild-to-moderate AD were treated with either placebo or crenezumab (300 mg subcutaneously every 2 weeks [q2w], or 15 mg/kg, 30 mg/kg, 45 mg/kg, 60 mg/kg, or 120 mg/kg intravenously q4w). Serum/plasma PK/PD analyses included samples from 131 patients who received crenezumab in all three studies. CSF PK/PD analyses included samples from 76 patients who received crenezumab in ABBY or BLAZE. The impact of baseline patient factors on Aβ profiles was also evaluated.

Results: The serum concentration of crenezumab increased in a dose-proportional manner between 15 and 120 mg/kg q4w. Total monomeric plasma Aβ(1–40) and Aβ(1–42) levels significantly increased after crenezumab administration. The mean crenezumab CSF to serum ratio was ~ 0.3% and was similar across dosing cohorts/routes of administration. No clear correlation was observed between crenezumab concentration and Aβ(1–42) increase in CSF at week 69. The target-mediated drug disposition (TMDD) model described the observed plasma concentration–time profiles of crenezumab and Aβ well. Elimination clearance (Clₑₚ) and central volume of distribution (Vₑₚ) of crenezumab were estimated at 0.159 L/day and 2.89 L, respectively, corresponding to a half-life of ~ 20 days. Subcutaneous bioavailability was estimated at 66.2%.

Conclusions: Crenezumab PK was dose proportional up to 120 mg/kg, with a half-life consistent with IgG monoclonal antibodies. Our findings provide evidence for peripheral target engagement in patients with mild-to-moderate AD. The study also showed that a model-based approach is useful in making inference on PK/PD relationship with unmeasured species such as free plasma Aβ levels.

Trial registrations: ABBY: ClinicalTrials.gov, NCT01343966. Registered April 28, 2011. BLAZE: ClinicalTrials.gov, NCT01397578. Registered July 19, 2011. GN29632: ClinicalTrials.gov, NCT02353598. Registered February 3, 2015.

Keywords: Pharmacokinetics, PK/PD, Plasma beta-amyloid, Nonlinear mixed-effects modeling, Target-mediated drug disposition model

* Correspondence: quartino.angelica@gene.com
¹Genentech, Inc., South San Francisco, CA 94080, USA
Full list of author information is available at the end of the article

© The Author(s). 2020 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
Alzheimer's disease (AD) is the most common cause of dementia, thought to affect 47 million people worldwide [1]. Accumulations of beta-amyloid (Aβ) peptides and amyloid plaque deposition in the brain are characteristic of AD [2]. Aβ peptides can exist as monomers or aggregated forms (soluble oligomers, fibers, and plaque), and although the extent to which different Aβ species contribute to the pathophysiology of AD remains uncertain, in vitro and ex vivo evidence suggests that soluble oligomers may be major drivers of neurotoxicity [3–5].

Crenzumab is a fully humanized anti-Aβ immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to monomeric as well as aggregated forms of Aβ [6, 7]. In vitro, crenzumab has been shown to block Aβ aggregation, promote disaggregation, and protect neurons from oligomer-induced cytotoxicity [6]. Completed clinical trials of crenzumab in patients with mild-to-moderate AD include the phase II ABBY (NCT01343966) and BLAZE (NCT01397578) studies [8, 9]. Despite these studies not meeting their primary endpoints, exploratory post hoc analyses of the effects of crenzumab in a subset of patients with very mild AD in the high-dose 15 mg/kg intravenous (IV) cohort suggested the utility of testing earlier treatment of AD with higher doses of crenzumab [8]. Interim data from a phase Ib GN29632 study (NCT02353598) [10–12] supported further testing of higher doses of crenzumab. Two phase III studies (CREAD, NCT02670083; CREAD2, NCT03114657) investigated the efficacy and safety of crenzumab at a dose of 60 mg/kg IV every 4 weeks (q4w), i.e., fourfold higher than the high dose in phase II, compared with placebo in patients with early (prodromal-to-mild) AD [13, 14]. These studies were recently discontinued following a pre-planned interim analysis of CREAD, which indicated the study was unlikely to meet its primary endpoint; no safety signals were observed in this analysis and the overall safety profile was similar to that seen in previous trials [15]. A study of the efficacy and safety of crenzumab in individuals who carry the PSEN1 E280A autosomal-dominant mutation and do not meet the criteria for mild cognitive impairment due to AD or dementia due to AD are, thus, in a preclinical phase of AD (autosomal-dominant AD) is ongoing [16].

Here we report the PK of crenzumab and its interaction with monomeric Aβ(1–40) and Aβ(1–42) peptides (peripheral target engagement pharmacodynamic (PD) biomarkers) as assessed in serum/plasma and cerebrospinal fluid (CSF) in samples from phase II ABBY and BLAZE studies and the phase Ib GN29632 study. Monomeric Aβ(1–40) and Aβ(1–42) peptides were evaluated in this analysis, as they can be measured reliably in plasma and CSF using automated high-precision immunoassays. While Aβ oligomers have also been measured successfully in CSF from the ABBY and BLAZE studies [17], it is technically challenging to measure those forms of Aβ in plasma. PK/PD characteristics of mAbs such as crenzumab, and their interactions with target molecules, can be described by target-mediated drug disposition (TMDD) models, which take into account the binding affinity of the antibody for its target molecule and the resulting degradation/clearance of the antibody–target complex and as such can provide insights to unmeasured species such as free target concentrations. This is of high value as development of assays for free targets are often technically challenging. We constructed a TMDD model to describe crenzumab serum concentrations and plasma Aβ(1–40) and Aβ(1–42) peptide levels in patients treated with crenzumab to help quantitatively interpret observed interactions and simulate the concentration of unmeasured species, such as free plasma Aβ. In addition, plasma Aβ levels have been reported to be influenced by baseline patient characteristics, e.g., age and renal function [18]; therefore, we also used this model to assess the impact of baseline patient characteristics on the Aβ profiles.

Methods

Study design and subjects
In this analysis, crenzumab PK and PD data, i.e., serum total crenzumab concentrations and plasma total monomeric Aβ(1–40) and Aβ(1–42) levels, collected from patients enrolled in the phase II ABBY and BLAZE studies and the phase Ib GN29632 study were used. The detailed methodology, study randomization, and sample size determination for the studies have been described previously (Table 1) [8, 9, 12].

ABBY was a phase II, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of crenzumab in patients with mild-to-moderate AD [8]. Patients received low-dose 300 mg SC crenzumab or placebo q2w, or high-dose 15 mg/kg IV crenzumab or placebo q4w. To assess the potential for using a higher dose of crenzumab compared with phase I, part 2 of ABBY was preceded by a safety run-in (SRI) period (for SRI dosing schemes, see Table 1) [8].

BLAZE was a phase II, randomized, double-blind, placebo-controlled study designed to evaluate the effects of crenzumab on brain amyloid plaque load as assessed by florbetapir positron emission tomography (PET) and other biomarkers in patients with mild-to-moderate AD [9]. Patients were required to have evidence of elevated amyloid burden consistent with a diagnosis of AD. The study was conducted in two parts as described above for the ABBY study without the SRI period/cohort. Dosing
regimens and patient numbers for both ABBY and BLAZE are described in Table 1.

In both ABBY (including the SRI period) and BLAZE, blood samples were collected for PK measurement of serum crenezumab concentrations at week 1 (on day 1, including a pre-dose baseline sample), at specified times throughout the treatment period (through week 69), during the efficacy and safety follow-up visits (weeks 73, 81, and 85), and at end-of-treatment/discontinuation visits. For patients in the SC cohort, samples were collected prior to study drug administration on dosing days; for those in the IV cohort, samples were collected prior to study drug administration and 60 min after the end of infusion, unless otherwise specified. Blood samples for PD analysis were collected during the screening period and at the week 1 (day 1) visit, at specified times during the treatment period (through week 69), weeks 73, 81, and 85 of the safety follow-up visits, and at end-of-treatment/treatment discontinuation visits. On dosing days, blood samples for PD analysis were collected prior to study drug administration. In ABBY, CSF samples were collected as an optional procedure at week 1 (day 1/baseline) and before study drug administration at week 69 (steady state). In BLAZE, CSF samples were collected from all patients at screening and prior to dosing at week 69 or at early termination/discontinuation, if necessary.

GN29632 was a phase Ib, multicenter, randomized, double-blind, placebo-controlled, parallel-group ascending dose study followed by an open-label extension (OLE) study. This study was designed to assess the safety, tolerability, and PK of crenezumab delivered at higher doses than those used in the phase II program. Patients were randomly assigned to one of the three cohorts and received between 30 and 120 mg/kg IV q4w of crenezumab or placebo. Dosing regimens and patient numbers per cohort are detailed in Table 1. Blood samples for serum PK and plasma PD analyses were collected at baseline (week 1/day 1; pre-dose, 1 min, and 60–90 min post-administration), week 1/day 2, week 1/day 8 (± 2 days), week 2/day 15 (± 2 days), week 5 (± 2 days), week 9 (± 2 days), week 13 (± 2 days), week 21 (± 2 days), at end of treatment, and at the start of the OLE study. Per protocol, all scheduled serum PK and plasma PD samples were obtained just prior to study drug administration and 60–90 min after the end of infusion.

All studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and complied with Good Clinical Practice. A central investigational review board and individual site institutional review boards reviewed and provided approval for the protocols as well as informed consent forms. All subjects provided informed consent and consent for publication.

Table 1 Overview of characteristics of included crenezumab studies

| Study | Phase | Design | Treatments | Subjects |
|-------|-------|--------|------------|----------|
| ABBY [8] II | Double-blind, placebo-controlled, randomized, parallel-group study | Part 1: Low-dose 300 mg SC crenezumab q4w | 431 patients with mild-to-moderate AD aged 50–80 years were randomized 2:1 (crenezumab:placebo) |
| | | Part 2: High-dose 15 mg/kg IV crenezumab q4w | - Part 1: 184 patients |
| | | Placebo q4w | - Part 2: 241 patients |
| | | SRI: At least 2 monthly administrations of 15 mg/kg IV crenezumab or placebo | - SRI: 13 patients |
| BLAZE [9] II | Double-blind, placebo-controlled, randomized study | Part 1: Low-dose 300 mg SC crenezumab q4w | 91 Aβ-positive patients with mild-to-moderate AD aged 50–80 years were randomized 2:1 (crenezumab:placebo) |
| | | Part 2: High-dose 15 mg/kg IV crenezumab q4w | - Part 1: 39 patients |
| | | Placebo q4w | - Part 2: 52 patients |
| GN29632 [10–12] | Double-blind, placebo-controlled, randomized study followed by open-label extension | Double-blind phase: Cohort 1: 30 or 45 mg/kg IV crenezumab q4w | 75 patients with mild-to-moderate AD aged 50–90 years were randomized 5:1 at each of the crenezumab dosing levels, or placebo up to week 13: |
| | | Cohort 2: 60 mg/kg IV crenezumab q4w | - Cohort 1: 30 mg/kg: 10 patients |
| | | Cohort 3: 120 mg/kg IV crenezumab q4w | - 45 mg/kg: 11 patients |
| | | Placebo q4w | - Cohort 2: 21 patients |
| | | Open-label extension: Cohort 1 and 2 could continue to receive crenezumab at the originally assigned dose | - Cohort 3: 19 patients |
| | | Cohort 3 switched to 60 mg/kg q4w | 71 patients entered the open-label extension |
| | | Placebo could cross over to crenezumab at the originally assigned dose and 60 mg/kg if assigned to cohort 1 or 3 | |

*Following a protocol amendment, patients in cohort 1 could increase to 60 mg/kg q4w dose after week 133.
PK/PD assessments
Total serum crenezumab concentrations were analyzed using a validated enzyme-linked immunosorbent assay with a lower limit of quantification of 0.05 μg/mL for serum. Total monomeric plasma Aβ(1–40) and Aβ(1–42) levels (which correspond to free and crenezumab-bound Aβ levels) were measured using a robust, non-commercial Elecsys® drug-tolerant prototype assay on the cobas® e411 analyzer (Roche Diagnostics, Rotkreuz, Switzerland), with a lower limit of detection of < 2 pg/mL (both assays). For the ABBY study, we measured Aβ levels only for the SRI cohort with the current assay system due to method availability, and only the data from that cohort (in addition to data from BLAZE and phase Ib studies) are included in subsequent analyses. Total CSF crenezumab concentrations were analyzed using a validated enzyme-linked immunosorbent assay (limit of detection 12.5 ng/mL) as described previously [9]. Total Aβ(1–42) in CSF was measured using the Elecsys® β-Amyloid (1–42) immunoassay commercially available from Roche Diagnostics (Penzberg, Germany), which was confirmed to be tolerant to the presence of crenezumab in the sample [19].

PK/PD analysis
Crenezumab PK and Aβ kinetics from all randomized subjects who received at least one dose of study treatment (placebo or active) and had at least one post-dose assessment of both PK and Aβ levels during the three studies were analyzed using nonlinear mixed-effects modeling with NONMEM (version 7.3., ICON Development Solutions, Ellicott City, MD, USA). In total, 1332 serum PK and 2203 plasma PD samples from 131 patients were used for the analysis.

A TMDD model with Michaelis–Menten approximation [20] was used to describe the observed serum concentrations of crenezumab, plasma concentrations of Aβ(1–40) and Aβ(1–42), and the PK/PD relationship (Fig. 1). Michaelis–Menten approximation was selected because crenezumab concentration is in excess of the Aβ concentration at clinical doses and Aβ concentration increases upon crenezumab administration [20].

A stepwise covariate model (SCM) building tool developed in Perl-speaks-NONMEM (PsN), version 4.7.0 [21] was used to assess the impact of baseline patient factors, including age at enrollment, sex, body weight, and glomerular filtration rate (GFR) on Aβ profiles, with p values of 0.01 and 0.005 as criteria for the forward selection and backward elimination, respectively.

For evaluating PK/PD relationships in CSF, 76 PK and 74 PD samples from 76 patients enrolled in ABBY and BLAZE studies and receiving active treatment were analyzed using descriptive statistics.

Results
Serum crenezumab concentration and plasma Aβ(1–40) and Aβ(1–42) levels after the first dose of crenezumab
The serum PK profile of crenezumab showed a biphasic disposition over the 28-day period following the first dose (Fig. 2). The serum concentration of crenezumab increased in a dose-proportional manner between 15 and 120 mg/kg q4w doses.
Total monomeric plasma Aβ(1–40) and Aβ(1–42) levels significantly increased after administration of crenezumab, demonstrating peripheral target engagement (Fig. 3). PD response was delayed compared with the time to peak crenezumab concentration and reached its maximum level 7–14 days after the initial dose (Fig. 3).

Total plasma Aβ levels increased in a dose-dependent, but not dose-proportional manner. Analyses of pre-dose serum crenezumab (C<sub>trough</sub>) and plasma Aβ suggest that the accumulation of total plasma Aβ reached a plateau following crenezumab 120 mg/kg q4w dosing (Fig. 4).

### CSF crenezumab concentrations and CSF Aβ(1–42) levels

The ratio of crenezumab detected in the CSF vs serum was consistent across dosing cohorts/routes of administration with a mean crenezumab CSF to serum ratio of ~ 0.3%. The mean (standard deviation) steady-state pre-dose crenezumab concentrations in CSF were low (0.19 [0.14] μg/mL in the 300 mg SC cohort; 0.25 [0.12] μg/mL in the 15 mg/kg IV cohorts). As described previously for the BLAZE study [9], there was a significant increase in CSF total Aβ(1–42) concentrations in patients treated with
crenezumab. In the low-dose SC cohort, CSF A\(\beta\) mean change from baseline was −52.11 pg/mL in the placebo arm, while in the crenezumab arm mean change from baseline was +74.90 pg/mL (crenezumab vs placebo difference of 127.01 pg/mL, \(p = 0.001\)). In the high-dose IV cohort, CSF A\(\beta\) mean change from baseline was −86.65 pg/mL in the placebo arm, whereas in the crenezumab arm mean change from baseline was +7.86 pg/mL (crenezumab vs placebo difference of 94.51 pg/mL, \(p = 0.022\)).

There was no clear PK/PD correlation between steady-state pre-dose CSF crenezumab levels and CSF A\(\beta\) changes at week 69 (Fig. 5). The crenezumab serum and CSF concentrations in BLAZE were similar to those in ABBY \([8, 9]\).

Model-based analysis of serum crenezumab and plasma A\(\beta\) concentrations

The final TMDD model with Michaelis–Menten approximation (Fig. 1) described the observed profiles of crenezumab and A\(\beta\) well (Fig. 6). Overall, the PK/PD parameter values obtained through the nonlinear mixed-effects modeling were reasonable, with relative standard error of less than 10% for most fixed effects (Table 2). Estimated baseline plasma A\(\beta\) (1–40) and A\(\beta\) (1–42) were 12 nM and 9.37 nM, respectively.

Crenezumab exhibited dose-proportional PK with the estimated elimination clearance (CL\(_{el}\)) and central volume of distribution (\(V_{cent}\)) of 0.159 L/day and 2.89 L, respectively, which are consistent with typical values for IgG mAbs \([22]\) and correspond to a half-life (\(t_{1/2}\)) of ~20 days. SC bioavailability (\(F_{sc}\)) was estimated at 66.2%. Estimated intrinsic clearance of the crenezumab–A\(\beta\) complex (CL\(_{int}\)) was 1.01 L/day, sixfold faster than that of crenezumab alone (Table 2).

Analysis of impact of patient baseline characteristics on crenezumab and A\(\beta\) kinetics in plasma and serum

We evaluated the effects of selected patient characteristics (subsequently referred to as covariates) on crenezumab and plasma A\(\beta\) kinetics. Body weight was a statistically significant covariate for crenezumab PK (CL\(_{el}\), CL\(_{int}\), and \(V_{cent}\)), age and GFR were statistically significant covariates for baseline plasma A\(\beta\) levels, and sex was a statistically significant covariate for degradation rate constant of plasma A\(\beta\) (K\(_{deg}\)). Estimated BSV of CL\(_{el}\) and \(V_{cent}\) decreased from 25 to 19% and 23 to 18%, respectively, after incorporating the effect of body weight, although it did not appear to be a major source of the observed BSV; between 90% of the observed range (52.4–95.9 kg), differences in area under the curve (AUC) and peak concentration (\(C_{max}\)) were 1.1-fold higher (higher exposure with smaller body weight) (Fig. 7). After incorporating the effect of age and GFR,
estimated BSV for baseline levels of Aβ(1–40) and Aβ(1–42) decreased from 11 to 8.3% and 16 to 14%, respectively. Differences in baseline levels of Aβ(1–40) and Aβ(1–42) in 90% of the observed range of GFR (94.0 to 46.5 mL/min/1.73 m²) were 1.2- and 1.25-fold higher in patients with smaller GFR. Differences in baseline levels of Aβ(1–40) in 90% of the observed range of age (54–82 years) were 1.1-fold higher in patients with higher age (Fig. 7). Incorporating the effect of sex on $K_{\text{deg}}$ decreased BSV from 19 to 18%.
Simulations of the effect of varying crenezumab doses on free and bound Aβ kinetics based on the developed PK/PD model

Crenezumab was detected in a large excess compared with plasma Aβ levels (approximately 150-fold difference at steady-state C_{trough} for 60 mg/kg dose); therefore, the crenezumab in serum was predominantly free. As may therefore be expected, the modeling data suggested that plasma Aβ was predominantly bound (Fig. 8). The reduction in free plasma Aβ levels associated with crenezumab treatment was better maintained at higher doses, even after the increase in total Aβ level had plateaued.

### Table 2 Estimated PK/PD parameters determined using nonlinear mixed-effects modeling

| Parameter                      | Estimate | RSE (%) | BSV (CV%) | RSE (%) |
|-------------------------------|----------|---------|-----------|---------|
| Crenezumab                    |          |         |           |         |
| CL_{el} (L/day)                | 0.159    | 3.0     | 19.1      | 8.4     |
| CL_{int} (L/day)               | 1.01     | 5.8     | 15.3      | 25      |
| V_{cent} (L)                   | 2.89     | 3.4     | 18.3      | 8.8     |
| V_{periph} (L)                 | 1.84     | 10      | 75.2      | 9.7     |
| Q (L/day)                      | 0.142    | 4.8     | –         | –       |
| F_{sc} (%)                    | 66.2     | 3.9     | –         | –       |
| k_{s} (L/day)                  | 0.161    | 64      | –         | –       |
| k_{s} Aβ(1–40) (nM)            | 12.0     | 3.0     | 13.6^a    | 12      |
| k_{s} Aβ(1–42) (nM)            | 9.37     | 2.5     | 13.6a     | 12      |
| BWT (kg) on CL_{el}            | 0.835    | 12      | –         | –       |
| BWT (kg) on CL_{int}           | 0.474    | 42      | –         | –       |
| BWT (kg) on V_{cent}           | 0.725    | 17      | –         | –       |
| Aβ(1–40)                       |          |         |           |         |
| Baseline (pM)                  | 142      | 1.3     | 8.3       | 10      |
| k_{deg} (1/day)                | 114      | 5.7     | 17.9^a    | 12      |
| Q (L/day)                      | 8.72     | 31      | –         | –       |
| V_{periph} (L)                 | 3.77     | 11      | –         | –       |
| Age (year) on baseline         | 0.0037   | 27      | –         | –       |
| GFR (mL/min/1.73 m^2) on baseline | – 0.0035 | 20     | –         | –       |
| Sex (male) on k_{deg}^-1      | – 0.16   | 36      | –         | –       |
| Aβ(1–42)                       |          |         |           |         |
| Baseline (pM)                  | 5.98     | 1.7     | 13.8      | 9.9     |
| k_{deg} (1/day)                | 287      | 6.5     | 17.9^a    | 12      |
| Q (L/day)                      | 229      | 15      | –         | –       |
| V_{periph} (L)                 | 8.19     | 7.8     | –         | –       |
| GFR (mL/min/1.73 m^2) on baseline | – 0.0048 | 22     | –         | –       |
| Sex (male) on k_{deg}^-1      | – 0.16   | 36      | –         | –       |

Patient factors are incorporated as the exponential and linear form on the parameters for crenezumab and Aβ, respectively. *Same BSV was used on Aβ(1–40) and Aβ(1–42) for k_{s} and k_{deg}.*

### Discussion

In this pooled analysis of data from the phase II ABBY and BLAZE studies and the phase Ib GN29632 study, we showed that the PK of crenezumab in patients with mild-to-moderate AD was dose proportional across the dose range tested (15–120 mg/kg q4w IV and 300 mg q2w SC) and was characterized by clearance and t_{1/2} values expected of IgG mAbs (0.159 L/day and t_{1/2} ~ 20 days, respectively) (Table 2) [22]. Body weight was shown to influence the elimination clearance of crenezumab (CL_{el}), intrinsic clearance of crenezumab–Aβ complex (CL_{int}), and central distribution volume (V_{cent}), all of which increased with increasing body weight (Fig. 7). These
findings are consistent with the results observed for other therapeutic IgG molecules that exhibit linear kinetics in humans [22].

Total plasma $\beta(1–40)$ and $\beta(1–42)$ levels increased significantly following each administration of crenezumab demonstrating peripheral target engagement of monomeric $\beta(1–40)$ and $\beta(1–42)$. The increase in total $\beta(1–40)$ and $\beta(1–42)$ levels can be attributed to slower elimination of crenezumab–$\beta$ complex than free $\beta(1–40)$ and $\beta(1–42)$: 0.36 vs 114 [A$\beta$(1–40)] or 287 [A$\beta$(1–42)] on day 1. The observed increase in total plasma $\beta$ levels was dose dependent but not dose proportional and reached a plateau with the 120 mg/kg q4w IV dose. A TMDD model developed to characterize the observed serum crenezumab concentrations, plasma $\beta(1–40)$ and $\beta(1–42)$ levels, and the PK/PD relationship between them, successfully described the observed data, including the non-dose-proportional increase in plasma $\beta$ levels. This model suggested that reductions in free $\beta$ levels associated with crenezumab dosing are better maintained at higher doses, even after the total plasma $\beta$ levels had plateaued (Fig. 8).

Our analysis suggested that age and GFR explain some of the BSV in baseline $\beta$ levels. This is consistent with a previous study by Toledo and colleagues [18] who analyzed baseline $\beta$ measures in 715 subjects from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (http://www.adni-info.org/index) and reported that age, platelet count, total protein, and creatinine concentration were independent predictors of baseline $\beta(1–40)$ and $\beta(1–42)$ levels, explaining 12.1% and 12.9% of the observed variability in the respective parameters [18]. The model estimated $K_d$ of crenezumab against $\beta(1–40)$ and $\beta(1–42)$ were similar to each other. This is consistent with in vitro observation that crenezumab has similar binding affinity to these two $\beta$ species (~10 nM) [F. Hoffmann-La Roche Ltd.; data on file]. Patient factors, such as age or sex, were not identified as significant covariates for $K_d$, suggesting that the binding of crenezumab to $\beta$ is independent of currently evaluated patient factors.

The PK/PD data from this study provide evidence of peripheral target engagement by crenezumab at evaluated dose levels. This complements the target...
engagement in the central nervous system previously suggested in the phase II ABBY and BLAZE studies through the increase of total monomeric Aβ(1–42) in CSF of patients with mild-to-moderate AD treated with crenezumab [8]. The increase in total monomeric Aβ(1–42) is likely due to slower elimination of crenezumab–Aβ complex. We further evaluated relationships between crenezumab concentration and Aβ(1–42) increase in CSF, but no clear correlation was observed (Fig. 5), which could be due to limited ranges of evaluable doses and high variability between patients for demonstrating exposure–response relationships in CSF. The concentration of crenezumab in CSF was much higher than the concentration of Aβ, yet still much lower than in serum (approximately 0.3% of serum). This suggests that a wider dose range is needed to be able to quantify the exposure–response relationship in the central nervous system.

The PK/PD simulation provided several important insights. Firstly, the simulation showed that circulating crenezumab is predominantly unbound. This indicates that the transfer of crenezumab to peripheral organs and
the central nervous system is likely not influenced by its binding to Aβ. The low concentration of crenezumab–Aβ complex, compared with total crenezumab, also suggests that the transfer of the binding complex is unlikely to serve as a new source of Aβ for peripheral organs including the central nervous system.

Another interesting observation is that predicted free Aβ levels continued to decrease with increasing dose, even after the accumulation of total Aβ reached a plateau (Fig. 8), suggesting that total Aβ change may not be fully reflective of actual drug effect. The reason for this apparent discrepancy between total and free Aβ profiles is that accumulation of total Aβ is due to slower elimination of crenezumab–Aβ complex than free Aβ. Therefore, once the crenezumab–Aβ complex becomes the predominant species of total Aβ, there will be no further increase in total Aβ with increased crenezumab dose. In contrast, binding of crenezumab to residual free Aβ can still occur with a higher free crenezumab concentration. Additionally, since analytical quantification of free Aβ is technically challenging due to changing levels of bound vs free Aβ in vitro after CSF collection that might differ from the levels in vivo, the model proposed in the current study could be a promising tool to integrate available information, such as total Aβ levels, and provide further insights on the kinetics of unmeasured species such as free Aβ.

Conclusion

In this study, we showed that crenezumab PK was dose proportional at doses between 15 and 120 mg/kg with a $t_{1/2}$ consistent with IgG mAbs, and provided evidence of peripheral target engagement in patients with mild-to-moderate AD, based on data pooled from three clinical trials of crenezumab (two phase II studies; one phase Ib study). We also observed dose-dependent increases in total monomeric Aβ(1–42) levels in CSF; however, exposure–response relationships need to be further evaluated at higher doses and in larger studies. We demonstrated how a TMDD model can be used to integrate available information, such as the serum PK characteristics of crenezumab and the plasma total Aβ levels, and to make inferences to unmeasured species such as free Aβ levels.

Abbreviations

$A_{\beta}$: Amount of beta-amyloid; AD: Alzheimer’s disease; ADNI: Alzheimer’s Disease Neuroimaging Initiative; AUC: Area under the curve; Aβ: Betaamyloid; BSV: Between-subject variability; BWT: Body weight; $C_{[\text{con}]min}$: Concentration of crenezumab; $CL_{[\text{el}]min}$: Elimination clearance; $CL_{[\text{int}]min}$: Intrinsic clearance; $C_{\text{pmax}}$: Peak concentration; CSF: Cerebrospinal fluid; $C_{\text{through}}$: Pre-dose serum crenezumab; CV: Coefficient of variation; $F_{\text{cmax}}$: SC bioavailability; GFR: Glomerular filtration rate; IgG: Immunoglobulin G; IV: Intravenous; $K_{\text{a}}$: Absorption rate constant; $K_{\text{int}}$: Estimated equilibrium constant governing antibody-ligand binding; $K_{\text{deg}}$: Degradation rate constant; $K_{\text{el}}$: Zero-order input rate constant for ligand; mAb: Monoclonal antibody; OLE: Open-label extension; PD: Pharmacodynamics; PET: Positron emission tomography; PK: Pharmacokinetics; Q: Inter-compartment clearance; $q_{\text{lw}}$: Every 2 weeks; $q_{\text{kw}}$: Every 4 weeks; RSE: Relative standard error; SC: Subcutaneous; SCM: Stepwise covariate model; SD: Standard deviation; SRI: Safety run-in; $t_{1/2}$: Half-life; TMDD: Target-mediated drug disposition; $V_{\text{CSF}}$: Central volume of distribution; $V_{\text{periph}}$: Peripheral distribution volume

Acknowledgements

Crenzumab was discovered and is being developed, in collaboration with AC Immune SA, Lausanne, Switzerland. Medical writing support for the development of this manuscript was provided by Jonathan Plumb, PhD, of Bioscript Medical, Macclesfield, UK, and Rachel Johnson, PhD, of Health Interactions, funded by F. Hoffmann-La Roche Ltd. COBAS and Elecsys are trademarks of Roche.

Authors’ contributions

All authors were involved in drafting the work or revising it critically for important intellectual content. All authors have read and approved the final version of the manuscript and agree both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. KY contributed to the conception and design of the work, analysis and interpretation of the data, drafting of the work, and substantial revisions of the work. AM contributed to the analysis of the data and drafting part of the work. TB contributed to the design of the work and acquisition and interpretation of data. SO contributed to the acquisition and interpretation of the data and revisions of the manuscript. HL contributed to the acquisition and interpretation of the data. LH contributed to the conception and design of the work. AQ contributed to the conception and design of the work, acquisition, analysis and interpretation of the data, reviewing and editing of the work.

Funding

This study was funded by F. Hoffmann-La Roche Ltd. The study sponsor was responsible for the overall study management, drug supply, data management, statistical analysis, PK and PD analysis, and the drug safety process. The study sponsor was involved in the design of the study, data analysis and interpretation, and in writing the manuscript.

Availability of data and materials

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche’s criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are/how_we_work/clinical_trials/our_commitment_to_data_sharing.htm. Further details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are/how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Ethics approval and consent to participate

All studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and complied with Good Clinical Practice. A central investigational review board and individual site institutional review boards reviewed and provided approval for the protocols as well as informed consent forms. No modifications were made to the protocol after receipt of the independent Ethics Committee approval. All subjects provided informed consent and consent for publication.

Consent for publication

Not applicable.

Competing interests

KY, AM, TB, SO, HL, JYJ, and AQ are full-time employees of F. Hoffmann-La Roche Ltd/Genentech, Inc. Authors who are not employees of F. Hoffmann-La Roche Ltd/Genentech, Inc., have no conflict of interest to declare.

Author details

1Genentech, Inc., South San Francisco, CA 94080, USA. 2F. Hoffmann-La Roche Ltd, Basel, Switzerland.
References

1. Alzheimer's Disease International. World Alzheimer Report 2016 – Summary sheet: improving healthcare for people living with dementia. Coverage, quality and costs now and in the future. https://www.alz.co.uk/research/worldalzreport2016sheet.pdf. Accessed 8 July 2019.

2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297:353–6.

3. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol. 2007;8:101–12.

4. Benilova I, Karran E, De Strooper B. The toxic Aβ oligomer and Alzheimer's disease: an emperor in need of clothes. Nat Neurosci. 2012;15:549–57.

5. Wang ZX, Tan L, Liu J, Yu JT. The essential role of soluble Aβ oligomers in Alzheimer's disease. Mol Neurobiol. 2016;53:1905–24.

6. Adolfsson O, Pihlgren M, Toni N, Varisco Y, Buccarello AL, Antoniello K, et al. An effector-reduced anti-amyloid (Aβ) antibody with unique Aβ binding properties promotes neuroprotection and glial engulfment of Aβ. J Neurosci. 2012;32:9677–89.

7. Liltsch M, Li B, Maurer T, Mathieu M, Adolfsson O, Muhs A, et al. Structure of crenezumab complex with Aβ shows loss of β-hairpin. Sci Rep. 2016;6:39374.

8. Cummings JL, Cohen S, Van Dyck CH, Brody M, Curtis C, Cho W, et al. ABBY: a phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease. Neurology. 2018;90:e1889–97.

9. Salloway S, Honigberg LA, Cho W, Ward M, Friesenhahn M, Brunstein F, et al. Amyloid positron emission tomography and cerebrospinal fluid results of crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE). Alzheimers Res Ther. 2018;10:96.

10. Asnaghi V, Lin H, Rabbia M, Ostrowitzki S, Smith J, Cho W, et al. Safety and tolerability of escalating doses for up to 25 months. Alzheimers Dement. 2017;13:P602.

11. Asnaghi V, Lin H, Hu N, Smith J, Cho W, Ostrowitzki S. Safety and tolerability of crenezumab in mild-to-moderate AD patients treated with escalating doses for up to 25 months. Alzheimers Dement. 2017;13:P602.

12. Kerchner GA, Asnaghi V, Rabbia M, Ward M, Quartino A, Honigberg L, et al. A phase Ib, randomized, double-blind, placebo-controlled, multiple dose study to assess the safety, tolerability and pharmacokinetics of escalating doses of crenezumab in patients with mild-to-moderate Alzheimer's disease (AD). Neurology. 2017;88(Suppl 16):6.083.

13. ClinicalTrials.gov. CREAD study: a study of crenezumab versus placebo to evaluate the efficacy and safety in participants with prodromal to mild Alzheimer's disease (AD). ClinicalTrials.gov Identifier: NCT02670083. https://clinicaltrials.gov/ct2/show/NCT02670083. Accessed 8 July 2019.

14. ClinicalTrials.gov. A study of crenezumab versus placebo to evaluate the efficacy and safety in participants with prodromal to mild Alzheimer's disease (AD) (CREAD 2). ClinicalTrials.gov Identifier: NCT03114657. https://clinicaltrials.gov/ct2/show/NCT03114657. Accessed 8 July 2019.

15. F. Hoffmann-La Roche Ltd. Roche to discontinue phase III CREAD 1 and 2 clinical studies of crenezumab in early Alzheimer's disease (AD) – other company programmes in AD continue [media release]. 30 January 2019. https://www.roche.com/media/releases/med-cor-2019-01-30.htm. Accessed 8 July 2019.

16. ClinicalTrials.gov. A study of crenezumab versus placebo in preclinical presenilin1 (PSEN1) E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease (AD), including a placebo-treated non-carrier cohort. https://clinicaltrials.gov/ct2/show/NCT01998841. Accessed 6 Aug 2019.

17. Yang T, Dang Y, Ostaszewska B, Mengel D, Steffen V, Rabe C, et al. Target engagement in an Alzheimer trial: crenezumab lowers amyloid β oligomers in cerebrospinal fluid. Ann Neurol. 2019;86:215–24.

18. Toledo JB, Vanderstichele H, Figurksi M, Asen PS, Petersen RC, Weiner MW, et al. Factors affecting Aβ plasma levels and their utility as biomarkers in ADNI. Acta Neuropathol. 2011;122:401–13.

19. Bittner T, Zetterberg H, Teunissen CE, Ostlund RE Jr, Miletto M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1–42) in human cerebrospinal fluid. Alzheimers Dement. 2016;12:2517–26.

20. Dua P, Hawkins E, van der Graaf PH. A tutorial on target-mediated drug disposition (TMDD) models. CPT Pharmacometrics Syst Pharmacol. 2015;4:324–37.

21. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Prog Biomed. 2005;79:241–57.

22. Deng R, Iyer S, Theil FP, Mortensen PJ, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? MAbs. 2011;3:61–6.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.