Safety, tolerability and pharmacokinetics of crenezumab in mild-to-moderate AD patients treated with escalating doses for up to 32 months

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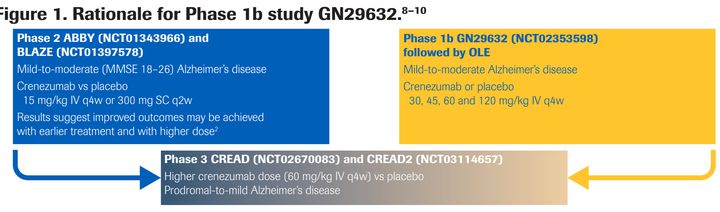
INTRODUCTION

- Crenezumab (RO5490245) is a humanized anti-amyloid β monoclonal immunoglobulin G4 (IgG4) antibody.[1]
- Clinical studies of crenezumab have been conducted in sporadic Alzheimer's disease (AD),[2,3] and further studies in sporadic and autosomal AD are ongoing (NCT02353598; NCT01998841; NCT02670083; NCT03114657).
- Proposed mechanism of action:
  - Crenezumab binds monomeric and aggregated forms of Aβ[1,4]
    - inhibits oligomer-induced neurotoxicity and promotes oligomer removal via microglial phagocytosis *in vitro*[1]
  - Following *in vivo* dosing in AD transgenic mice, crenezumab localizes to brain areas with putative high concentrations of Aβ oligomers (i.e. the periphery of amyloid plaques and hippocampal mossy fibres) but not to the dense core of plaques or vascular amyloid[5]
  - The low effector function of the IgG4 backbone and crenezumab's *in vivo* binding profile are hypothesized to reduce risk of amyloid-related imaging abnormalities (ARIA), allowing higher doses to be administered.[1,5]
- Although Phase 2 co-primary endpoints were not met,[2,3] exploratory analyses suggested that crenezumab should be tested for clinically meaningful efficacy at a higher dose and earlier disease stage.
- Two global, randomized, double-blind, placebo-controlled, parallel-group Phase 3 studies (CREAD [NCT02670083]; CREAD2 [NCT03114657])[6,7] are evaluating the efficacy and safety of crenezumab (60 mg/kg intravenously [IV] every 4 weeks [q4w]) in patients with prodromal to mild AD.
- The ongoing Phase 1b study, GN29632 (NCT02353598), was designed to provide information on the safety, tolerability and pharmacokinetics of crenezumab delivered at higher doses than those used in previous Phase 2 studies[2,3] (Figure 1) and to support the ongoing Phase 3 studies.[6,7]
- Early findings from GN29632 have been presented previously.[8–10] Here we present updated safety data from GN29632 for patients who have received crenezumab for up to 32 months, and pooled serum pharmacokinetics (PK) and plasma pharmacodynamics (PD) data from GN29632 plus the Phase 2 ABBY (NCT01343966) and BLAZE (NCT01397578) studies.[2,3]

Figure 1. Rationale for Phase 1b study GN29632.[8–10]



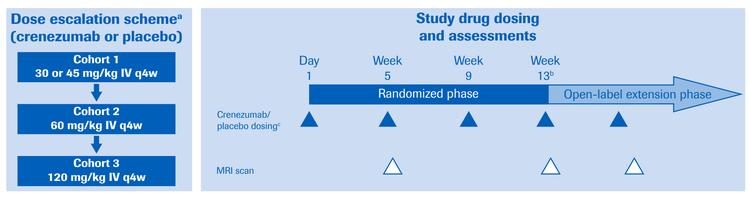
IV, intravenous; MMSE, Mini-Mental State Examination; OLE, open-label extension; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

METHODS

STUDY DESIGN

- In this multi-centre, Phase 1b study, enrolled patients were 5:1 double-blind randomized to receive an IV infusion of crenezumab at one of three dosing levels (Cohort 1: 30 or 45 mg/kg; Cohort 2: 60 mg/kg; Cohort 3: 120 mg/kg; all q4w) or placebo, up to Week 13 (Figure 2).
- After completing the placebo-controlled randomization phase at Week 13, patients could enter the open-label extension phase of the study. During this open-label extension phase:
  - Patients in Cohorts 1 and 2 could continue to receive crenezumab at the originally assigned dose (following a protocol amendment, patients in Cohort 1 could also increase to 60 mg/kg q4w dose after Week 133)
  - Patients in Cohort 3 switched to receive 60 mg/kg q4w
  - Patients who received placebo previously could cross over to receive crenezumab at the originally assigned dose for their cohort (or choose to receive 60 mg/kg q4w if assigned to Cohort 1).
- The primary objective for the study was to evaluate the safety and tolerability of multiple doses of crenezumab in patients with mild-to-moderate AD.
- A secondary objective for this study was to further characterize the pharmacokinetic (PK) characteristics of crenezumab in the serum of patients with mild-to-moderate AD.
- Exploratory objectives for this study included further characterization of the pharmacodynamic (PD) characteristics of crenezumab in the plasma of patients with mild-to-moderate AD.

Figure 2. Study design.[8–10]



[a] Dose regimens apply to double-blind randomized treatment phase; [b] Crossover to crenezumab at the dose originally assigned for patients on placebo, and switch to 60 mg/kg for patients in Cohort 3. Additionally, patients in Cohort 1 were given the option to increase to the 60 mg/kg dose after Week 133. IV, intravenous; MRI; magnetic resonance imaging; q4w, every 4 weeks.

STUDY POPULATION

- 50–90 years of age.
- Probable mild-to-moderate AD by National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria.
- Clinical Dementia Rating global score of 0.5 or 1.
- Mini-Mental State Examination score of 18–28.
- [^{18}F]-florbetapir positron emission tomography scan-positive for cerebral amyloid.
- At least 50% of the patients enrolled in each dosing level were apolipoprotein E (ApoE)4-positive (Table 1).

SAFETY ASSESSMENTS

- Brain MRI (central read).
- Incidence, nature and severity of AEs and serious AEs, graded according to Common Terminology Criteria for Adverse Events v4.0.
- Examinations: physical and neurological, vital signs.
- Laboratory tests (blood and urine).
- ECG assessments.

PHARMACOKINETIC AND PLASMA PHARMACODYNAMIC ASSESSMENTS

- Serum crenezumab concentrations were analyzed using a validated enzyme-linked immunosorbent assay with a lower limit of quantification of 0.05 µg/mL.
- Aβ40 and Aβ42 in human plasma were measured using a robust, non-commercial Elecsys® prototype assay on the cobas® e411 analyzer (Roche Diagnostics, Rotkreuz, Switzerland), with a lower limit of detection of <2 pg/mL (both assays).

STATISTICAL ANALYSIS

- Safety outcomes were assessed in all randomized patients who received ≥1 dose of study drug. Patients were grouped according to the treatment actually received.
- PK and plasma PD assessments were conducted in patients who were randomized to active treatment, received ≥1 dose of crenezumab and provided ≥1 evaluable post-dose PK sample and plasma PD sample, respectively.
- PK, PD and PK/PD analyses were based on pooled data from GN29632 and Phase 2 ABBY and BLAZE studies to assess the dose-proportionality and PK/PD relationship over a wider dose range.
- All statistical analyses presented are descriptive.

RESULTS

- In total, 75 patients were enrolled in the study and received at least 1 dose of study treatment; of these, 61 patients received crenezumab according to the assigned cohort dosing level and 14 patients received placebo during the 13-week randomized treatment period (Table 1). Seventy-one patients entered the open-label extension phase of the study. Seven patients in Cohort 1 (crenezumab group: 6; placebo group: 1) opted to increase crenezumab dose levels to 60 mg/kg q4w during the active extension phase of the study.
- Patient baseline characteristics and treatment exposure are presented in Table 1.
- The cut-off date for the safety data presented here is November 30, 2017. PK and plasma PD data included from GN29632 are for the randomized treatment phase of the study i.e. up to Week 13.

Table 1. Patient baseline characteristics and treatment exposure during the randomized treatment and open-label extension phases of the study.

	Cohort 1 30 mg/kg[a]		Cohort 1 45 mg/kg[a]		Cohort 2 60 mg/kg		Cohort 3 120 mg/kg → 60 mg/kg	
	Placebo (n = 2)	Crenezumab (n = 10)	Placebo (n = 3)	Crenezumab (n = 11)	Placebo (n = 5)	Crenezumab (n = 21)	Placebo (n = 4)	Crenezumab (n = 19)
Mean age, years (range)	72.0 (72–72)	73.4 (54–82)	75.3 (73–78)	73.3 (57–82)	71.8 (57–84)	72.9 (51–87)	67.8 (61–77)	69.4 (54–88)
Males, n (%)	2 (100)	6 (60)	2 (67)	4 (36)	2 (40)	13 (62)	0	10 (53)
Mean baseline MMSE (range)	22.0 (19–25)	23.3 (18–28)	20.7 (18–25)	22.2 (18–26)	20.2 (18–24)	23.2 (18–29)	21.3 (20–25)	22.9 (18–28)
ApoE status, n (%)								
E2/E3	0	0	1 (33)	0	0	0	0	1 (5)
E2/E4	0	0	0	0	0	0	0	1 (5)
E3/E3	0	4 (40)	0	1 (9)	1 (20)	4 (19)	2 (50)	5 (26)
E3/E4	2 (100)	6 (60)	2 (67)	7 (64)	4 (80)	14 (67)	0	7 (37)
E4/E4	0	0	0	3 (27)	0	3 (14)	2 (50)	5 (26)
Median duration of crenezumab exposure, weeks (range)[b]	116.6 (113–120)	130.0 (13–142)	71.0 (35–111)	108.3 (4–133)	57.0 (4–97)	108.4 (12–120)	57.1 (53–61)	72.1 (28–80)

Data cut-off: November 30, 2017. [a] Following a protocol amendment, patients in Cohort 1 were given the option to increase to the 60 mg/kg dose after Week 133. Where dose was increased, the duration of exposure on the 60 mg/kg dose was relatively short compared with the 30 mg/kg or 45 mg/kg doses, therefore these patients were grouped according to their prior dose for this analysis; [b] Exposure for placebo patients refers to crenezumab treatment exposure during the active extension-phase treatment. ApoE, apolipoprotein E; MMSE, Mini-Mental State Examination.

SAFETY

- Safety results for the randomized treatment phase of the study are presented in Table 2.
- Safety results for the combined randomized treatment and active extension phases of the study are presented in Tables 3 and 4:
  - No protocol-defined dose-limiting toxicities were reported.
  - No deaths occurred during the study.
  - There were no clear dose relationships or patterns in the types of AE reported.
  - No ARIA-E events were reported.
  - Of patients in Cohort 1 who increased to 60 mg/kg q4w crenezumab dose, no AEs were reported after the dose increase.

Table 2. Overview of safety during the 13-week double-blind, randomized treatment phase.

		Crenezumab			
Adverse events, n (%)	**Placebo (n = 14)**	30 mg/kg (n = 10)	45 mg/kg (n = 11)	60 mg/kg (n = 21)	120 mg/kg (n = 19)
Patients with ≥1 AE	6 (43)	8 (80)	7 (64)	14 (67)	6 (32)
AE related to study drug, per investigator[a]	1 (7)	1 (10)	4 (36)	3 (14)	1 (5)
AE grade ≥3 (severe, life-threatening or resulting in death)[b]	0	1 (10)	0	0	0
Serious AE[c]	0	1 (10)	0	2 (10)	0
Treatment withdrawal due to AE[d]	0	1 (10)	0	1 (5)	0

Data cut-off: November 30, 2017. [a] 30 mg/kg: dysgeusia, oral disorder (1 patient); 45 mg/kg: headache (1 patient), cerebral microhaemorrhage (2 patients), dizziness, headache (1 patient); 60 mg/kg: headache (1 patient), fatigue and hallucination (1 patient), agitation, confusional state, diarrhoea, fatigue, hallucination (1 patient); 120 mg/kg: blurred, narrowed vision (1 patient); [b] Common Terminology Criteria for Adverse Events v4.0. 30 mg/kg: malignant melanoma; [c] 30 mg/kg: malignant melanoma; 60 mg/kg: accidental overdose, pneumonia (1 patient); atypical chest pain; all events assessed as unrelated to study drug by investigator;[d] 30 mg/kg: malignant melanoma; 60 mg/kg; confusional state. AE, adverse events.

Table 3. Overview of safety during the randomized treatment and open-label extension phases.

	Cohort 1[a]		Cohort 2	Cohort 3		Total (n = 75)
Adverse events, n (%)	30 mg/kg (n = 12)	45 mg/kg (n = 14)	60 mg/kg (n = 26)	Placebo → 60 mg/kg (n = 4)	120 mg/kg → 60 mg/kg (n = 19)	
Patients with ≥1 AE	12 (100)	13 (93)	23 (89)	1 (25)	17 (90)	66 (88)
AE related to study drug, per investigator	2 (17)	5 (36)	4 (15)	0	3 (16)	14 (19)
AE grade ≥3 (severe, life-threatening or resulting in death)[b]	2 (17)	0	4 (15)	0	1 (5)	7 (9)
Serious AE[c]	3 (25)	0	5 (19)	0	2 (11)	10 (13)
Treatment withdrawal due to AE[d]	1 (8)	1 (7)	2 (8)	0	2 (11)	6 (8)

Data cut-off: November 30, 2017. [a] Seven patients in Cohort 1 switched to receive 60 mg/kg q4w; [b] Grade ≥3 AEs: all events assessed as unrelated to study drug by investigator; [c] Serious AEs: all events assessed as unrelated to study drug by investigator. Cohort 1: malignant melanoma, atypical chest pain, fall; Cohort 2: accidental overdose, pneumonia, subdural haematoma (1 patient), atypical chest pain, contusion (2 patients), nephrolithiasis; Cohort 3: non-cardiac chest pain, pulmonary emboli (1 patient), urinary bladder haemorrhage; [d] Treatment withdrawal due to AE: Cohort 1: malignant melanoma, cerebral microhaemorrhage; Cohort 2: confusional state, subdural haematoma; Cohort 3: pulmonary emboli, atrial fibrillation. AE, adverse events.

Table 4. Most common AEs and selected AEs during the randomized treatment and open-label extension phases.

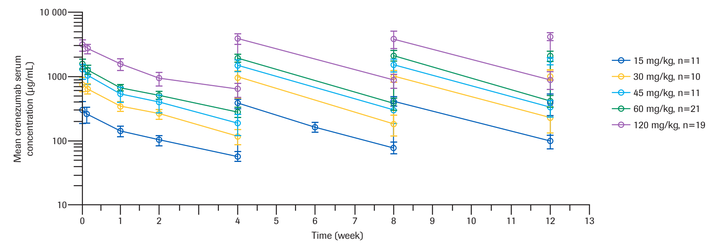
	Cohort 1		Cohort 2	Cohort 3		Total (n = 75)
	30 mg/kg (n = 12)	45 mg/kg (n = 14)	60 mg/kg (n = 26)	Placebo → 60 mg/kg (n = 4)	120 mg/kg → 60 mg/kg (n = 19)	
Common AEs, n (%)						
Fall[a]	2 (17)	1 (7)	5 (19)	0	4 (21)	12 (16)
Anxiety	3 (25)	2 (14)	3 (12)	0	2 (11)	10 (13)
Headache	1 (8)	3 (21)	3 (12)	0	1 (5)	8 (11)
Selected AEs, n (%)						
Cerebral haemorrhage[b]	2 (17)	2 (14)	2 (8)	0	1 (5)	7 (9)
Pneumonia[c]	0	0	1 (4)	0	2 (11)	3 (4)
Infusion-related reactions[d]	1 (8)	1 (7)	2 (8)	0	2 (11)	6 (8)

Data cut-off: November 30, 2017. [a] All events occurred during the active extension phase, and were assessed as not related to study drug by investigator; [b] Category includes ARIA events. Includes one event of cerebellar haemorrhage (30 mg/kg dose group); [c] One patient in 120 mg/kg → 60 mg/kg group reported an event of "pneumonia influenza"; [d] Per protocol, infusion-related reactions were defined as AEs that occurred during or within 24 hours after study drug administration and were judged to be related to study drug. AE, adverse events.

PHARMACOKINETICS AND PLASMA PHARMACODYNAMICS

- Crenezumab exhibited biphasic disposition over the 28-day period following the first administered dose.
- Steady-state concentrations were achieved within 13 weeks, with modest accumulation.
- Crenezumab serum concentrations increased proportionally between 15 mg/kg and 120 mg/kg q4w dose (Figure 3).

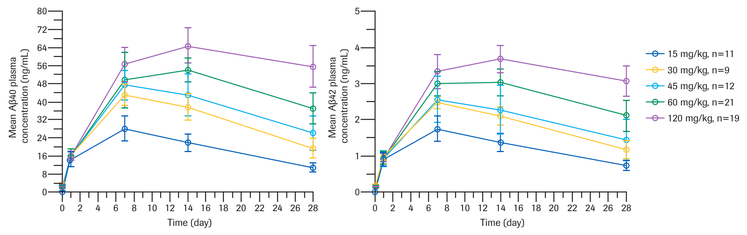
Figure 3. Mean (SD) serum crenezumab concentrations.



Data shown are from the Phase 2 ABBY study (SRI cohort) for 15 mg/kg dose and Phase 1b GN29632 for 30–120 mg/kg doses. PK and plasma PD data cut-off for GN29632: November 30, 2016. SD, standard deviation; SRI, safety run-in.

- Total plasma Aβ40 and Aβ42 significantly increased following administration of crenezumab, demonstrating peripheral target engagement (Figure 4), and total Aβ levels increased in a dose-dependent but not dose-proportional manner.
- PD response was delayed compared with crenezumab concentrations and reached maximum levels 7–14 days after initial dose (Figure 4).

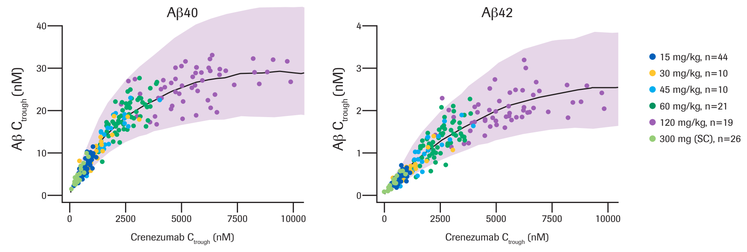
Figure 4. Mean (SD) total plasma Aβ40 and Aβ42 concentrations (Weeks 1–5).[11]



Total number of patients included = 72. Each line represents mean total Aβ40 or Aβ42 plasma concentration following IV administration; data shown are from the Phase 2 ABBY study (SRI cohort) for 15 mg/kg dose and Phase 1b GN29632 for 30–120 mg/kg doses; PK and plasma PD data cut-off for GN29632: November 30, 2016. Aβ, beta-amyloid; SD, standard deviation; SRI, safety run-in.

- Accumulation of total plasma Aβ reached a plateau following crenezumab 120 mg/kg q4w IV dosing (Figure 5).

Figure 5. Crenezumab and Aβ C_{trough} concentrations in Weeks 5, 9 and 13.[11]



Total number of patients included = 130. Data shown are from Phase 2 ABBY and BLAZE studies for all patients for 300 mg q2w SC and 15 mg/kg q4w IV, and from Phase 1b GN29632 for 30–120 mg/kg q4w IV. Solid lines and shaded areas represent the median and 5–95% prediction intervals, respectively, based on target-mediated drug deposition model predictions.[11] Aβ, beta-amyloid; IV, intravenous; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.

CONCLUSIONS

- Safety analyses of crenezumab in patients treated for up to 32 months in this Phase 1b study showed:
  - Majority of AEs were low-grade and non-serious
  - No protocol-defined dose-limiting toxicities
  - No investigator-assessed drug-related serious AEs
  - ARIA:
    - no ARIA-E (oedema/effusion) events were reported
    - few patients (7/75) experienced ARIA-H (haemosiderin deposition); all events were asymptomatic and no definite relationship with dose was noted.
- Crenezumab PK was dose-proportional between 15 to 120 mg/kg q4w and has a half-life of ~25 days, which is typical for IgG monoclonal antibodies.
- Serum crenezumab concentrations are in a huge excess compared with plasma Aβ levels, which suggests that the crenezumab in serum is predominantly free. This further suggests that crenezumab mainly enters into the brain and cerebrospinal fluid in its free form rather than being bound to Aβ.
- Peripheral target engagement was demonstrated by a significant increase in total plasma PD following each crenezumab administration and reaches a plateau with the 120 mg/kg q4w IV dose.
- These findings from the ongoing GN29632 study support the use of a crenezumab dose (60 mg/kg IV q4w) in the ongoing Phase 3 CREAD programme, which is four times higher than the IV dose evaluated in Phase 2 studies.
- Crenezumab is a monoclonal antibody that preferentially targets neurotoxic Aβ oligomers, and whose IgG4 backbone and binding profile are hypothesized to reduce the risk of ARIA.[1,5] This hypothesis is supported by the low number of ARIA events observed in this study.

REFERENCES

1. Adolfsson O, et al. J Neuroscience 2012;32:9677–9689.
2. Cummings J, et al. Neurology 2018 *[accepted for publication]*.
3. Salloway S, et al. Presented at CTAD 2014, Philadelphia, PA, USA.
4. Ultsch M, et al. Scientific Reports 2016;6:39374.
5. Atwal J, et al. Neurology 2017;88(Suppl):S7.005.
6. ClinicalTrials.gov ID: NCT02670083. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT02670083 on February 14, 2017.
7. ClinicalTrials.gov ID: NCT03114657. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03114657 on February 14, 2017.
8. Lin H, et al. Presented at CTAD 2016, San Diego, CA, USA.
9. Asnaghi V, et al. Poster presented at AAN 2017, Boston, MA, USA.
10. Asnaghi V, et al. Presented at AAIC 2017, London, UK.
11. Yoshida K, et al. Presented at CTAD 2017, Boston, MA, USA.

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DISCLOSURES

HL, AQ, NH, WC and SO are full-time employees at Genentech, Inc. AS, TB, and JS are full-time employees of F. Hoffmann-La Roche Ltd.

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