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 (RO5-3899) is a humanized monoclonal immunoglobulin G4 (IgG4) antibody
• Clinical studies of crenezumab have been conducted in symptomatic Alzheimer’s disease (AD) and preclinical Alzheimer’s disease (PreAD) using the rodent 5xFAD model (St George-Hyslop, Rochester, Sweden) with a lower limit of detection of 2 µg/µL (both sexes).

RESULTS

• In total, 255 patients were enrolled in the study and received at least 1 dose of study treatment. Of these, 41 patients received crenezumab according to the assigned cohort dosing level and 16 patients received placebo in the 12-week randomized treatment period (Table 1). Overall, patients enrolled in the open-label extension phase of the study. Seven patients in Cohort 1 (crenezumab group) 5 patients in Cohort 2 (crenezumab group) 1 patient in Cohort 3 (placebo group) were increased to levels below those used in previous in vivo studies (Figure 2).
• Early finding from GN29632 has been presented previously. Here we present updated safety data from GN29632 for an additional 90 patients enrolled in 3 different dosing levels, all on placebo or up to Week 133 (Figure 2).
• 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 crenezumab treatment exposure during the active extension-phase treatment. ApoE, apolipoprotein E; MMSE, Mini-Mental State Examination.

STUDY DESIGN

• In the study phases Phase 1a/b Phase 1b patients received a double-blind randomised to receive an IV infusion of crenezumab at one of three dosing cohorts Cohort 1 30 mg/kg Cohort 2 60 mg/kg Cohort 3 120 mg/kg (all safety patients) or placebo on Weeks 1 (Figure 2).
• After completing the placebo-controlled randomisation phase in Week 15 patients could enter the open-label extension phase of the study. During this open-label extension phase:

  - Patients in Cohort 1 and 2 continued to receive crenezumab at the originally assigned dose Following a protocol amendment, patients in Cohort 1 could also increase to 40 mg/kg prior to dose Week 133.
  - Patients in Cohort 3 switched to receive 60 mg/kg q4w.

• The primary objective of the study was to evaluate the safety and tolerability of multiple doses of crenezumab in patients with mild-to-moderate AD.
• A secondary objective of the study was to further characterize the pharmacokinetics (PK) and pharmacodynamics (PD) characteristics of crenezumab in the plasma of patients with mild-to-moderate AD.

EXPLORATORY OBJECTIVES FOR THIS STUDY INCLUDED FURTHER CHARACTERIZATION OF THE PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) CHARACTERISTICS OF CRENEZUMAB IN THE PLASMA OF PATIENTS WITH MILD-TO-MODERATE AD.

METHODS

STUDY POPULATION

- 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 ≥20.
- \( (T) \) freedom of position extension testing symmetric score for any extended arm.
- At least 50% of the patients enrolled in each dosing level were apolipoprotein E4-positive (Table 1).

SAFETY ASSESSMENTS

- Brain MRI (control study).
- Incidence, nature and severity of AEs and serious AEs graded according to Common Terminology Criteria for Adverse Events (CTCAE v4.03).
- ECGs.
- Laboratory tests (hematology and blood chemistry).
- ECG assessments.

PHARMACOKINETIC AND PLASMA PHARMACODYNAMIC ASSESSMENTS

• Serum concentrations were analyzed using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification of 0.85 µg/mL.
• Aβ1-42 and Aβ1-40 in human plasma were measured using a robust, non-commercial Elecsys® (Roche Diagnostics, Germany) platform for the ELISA 5F3D antibodies (St George-Hyslop, Rochester, Sweden) with a lower limit of detection of 2 µg/µL (both sexes).

STATISTICAL ANALYSIS

• Safety analyses were based on all patients enrolled in the randomized treatment and open-label extension phases who received at least 1 dose of study drug.
• Efficacy analyses were based on all patients enrolled in the randomized treatment and open-label extension phases who received at least 1 dose of study drug.

PHARMACOKINETICS AND PLASMA PHARMACODYNAMICS

• Crenezumab inhibited Aβ1-42 deposition over the 35-day period following the first administered dose.
• Dose-related decreases were noted with 10 mg/kg, with higher modulation.
• Serum concentrations increased proportionally between 15 mg/kg and 120 mg/kg (Figure 3).

CONCLUSIONS

• Safety analyses of crenezumab in patients treated up to 32 months in this Phase 3a study showed:
- Majority of AEs were low-grade or non-serious.
- No protocol-defined serious treatment-related AEs were reported.
- No observation of drug-related serious AEs.
- No AEs were reported that were not observed in the placebo group.
- At least 50% of the patients enrolled in each dosing level were apolipoprotein E4-positive (Table 1).

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REFERENCES

5. F Hoffmann-La Roche Ltd. Presented at CTAD 2017, Tokyo, Japan.