Media Release

Roche provides update on Alzheimer's Prevention Initiative study evaluating crenezumab in autosomal dominant Alzheimer's disease

- **Crenezumab did not slow or prevent cognitive decline in people with a specific genetic mutation which causes early-onset Alzheimer's disease**
- **For more than a decade Roche has been working in collaboration with Banner Alzheimer's Institute, the University of Antioquia in Colombia and the National Institute on Aging on this pioneering prevention study**
- **Initial data will be presented at the upcoming Alzheimer's Association International Conference**

Basel, 16 June 2022 - Roche (SIX: RO, ROG; OTCQX: RHHBY), together with Banner Alzheimer's Institute, today announced results from the Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease (ADAD) Colombia Trial. The study evaluated the potential of crenezumab, an investigational medicine, to slow or prevent Alzheimer's disease in cognitively unimpaired people who carry a specific genetic mutation which causes early-onset Alzheimer's disease. The trial did not demonstrate a statistically significant clinical benefit in either of its co-primary endpoints assessing the rate of change in cognitive abilities or episodic memory function, measured by the API ADAD composite cognitive score and the Free and Cued Selective Reminding Test (FCSRT) Cueing Index, respectively.

Small numerical differences favouring crenezumab were observed across the co-primary and multiple secondary and exploratory endpoints, but these were not statistically significant. No new safety issues were identified with crenezumab during the study. Further analyses of data are ongoing. Initial data will be presented at the Alzheimer's Association International Conference (AAIC) on August 2, 2022.

"We're disappointed that the treatment did not demonstrate a statistically significant clinical benefit," said Eric M. Reiman, M.D., Banner Alzheimer's Institute executive director and one of the study leaders. "At the same time, we're proud of the impact that this precedent-setting trial has had in shaping a new era in Alzheimer's prevention research and we're extremely grateful to our research participants and their families. This trial, the data, samples and findings that we'll share with the research community, and the related work that we and others are doing promise to further accelerate the evaluation and approval of future prevention therapies."

The trial enrolled 252 people who are members of the world's largest extended family with ADAD in Colombia, with 94% of participants completing the study. Two-thirds of participants carried the *Presenilin 1 E280A* mutation which typically causes cognitive impairment due to Alzheimer's disease around age 44. Participants were randomised to receive crenezumab, an

investigational treatment discovered by AC Immune SA, or placebo over five to eight years. During the trial, the dose of crenezumab was increased as knowledge about potential treatment approaches for Alzheimer's disease evolved.

"While this is a disappointing result, we would like to thank the participants and their families - they have made an enormous contribution to advancing both understanding and the search for new treatments for familial Alzheimer's disease," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "We remain committed to contributing further scientific evidence to advance how Alzheimer's disease is understood, diagnosed and treated."

The study, which was supported by the National Institute on Aging, generous philanthropic contributions to Banner Alzheimer's Foundation, and Roche, has generated a wealth of data that will advance the early detection, tracking and study of Alzheimer's disease and inform the design of future Alzheimer's prevention trials.

Within its Alzheimer's pipeline, Roche is also evaluating the potential of gantenerumab in autosomal dominant Alzheimer's disease, as well as for the prevention of sporadic Alzheimer's and treatment of early Alzheimer's in late stage clinical trials. Results from the phase III GRADUATE studies of gantenerumab in early Alzheimer's are expected in Q4, 2022.

About Banner Alzheimer's Institute

Since its inception in 2006, Banner Alzheimer's Institute (BAI) has sought to find effective Alzheimer's disease prevention therapies without losing another generation, establish a new model of dementia care for patients and family caregivers, and forge new models of collaboration in biomedical research. It has made groundbreaking contributions to the unusually early detection, tracking, diagnosis and study of Alzheimer's, and aims to find an effective prevention therapy by 2025. It includes the pioneering Alzheimer's Prevention Initiative (API), an extensive profile of research studies and clinical trials, comprehensive clinical, family and community service programs, a leading brain imaging research program, and strategic partnerships with numerous public and private research organisations around the world.

About the Alzheimer's Prevention Initiative (API) and the API ADAD (Colombia) Trial

The Alzheimer's Prevention Initiative (API) is an international collaborative formed in 2009 to launch a new era of Alzheimer's prevention research. Led by the Banner Alzheimer's Institute, the API conducts prevention trials in cognitively healthy people at increased risk for Alzheimer's disease. API continues to establish brain imaging, fluid biomarker and cognitive endpoints needed to rapidly test promising prevention therapies. It also leads participant recruitment registries to accelerate enrollment into Alzheimer's-focused studies. API is intended to provide the scientific means, accelerated approval pathway and enrollment

resources needed to evaluate the range of promising Alzheimer's prevention therapies and find ones that work without losing another generation.

First proposed by investigators from BAI, the API ADAD trial (NCT01998841) was a prospective, randomised, double-blind, placebo-controlled, parallel-group label enabling Phase II study of the efficacy of crenezumab versus placebo in cognitively unimpaired individuals who have no clinical symptoms of Alzheimer's disease and carry the *PSEN1 E280A* autosomal dominant mutation. Participants who are mutation carriers were randomised in a 1:1 ratio to receive either crenezumab or placebo for at least 260 weeks. Crenezumab was initially administered subcutaneously 300 mg every two weeks. Dosing was amended in 2015 to 720 mg subcutaneously every two weeks and in 2019 the option to increase the dose to 60 mg/kg, delivered intravenously every four weeks, was offered to participants. A cohort of participants (non-mutation carriers) were also enrolled and dosed solely on placebo.

The trial, which was supported by National Institute on Aging (NIA) generous philanthropic contributions to Banner Alzheimer's Foundation and Roche, was the first NIH-supported prevention trial of an experimental prevention therapy in cognitively unimpaired persons at known risk for the disease.

For more information, go to https://alzheimerspreventioninitiative.com/.

About Autosomal Dominant Alzheimer's Disease

Autosomal dominant Alzheimer's Disease (ADAD; also known as familial AD or dominantly-inherited AD [DIAD]) is a rare, inherited form of Alzheimer's disease caused by single gene mutations in the *APP*, *PSEN1* or *PSEN2* genes. Less than 1% of all Alzheimer's cases worldwide are thought to be caused by genetic mutations. It usually has a much earlier onset than the more common sporadic Alzheimer's disease, with symptoms developing in people in their 30s to 60s. If an individual has one of these mutations they are nearly certain to develop Alzheimer's and there is a 50% chance they will pass it on to each of their children.

About the *PSEN1 E280A* mutation and the Antioquia kindreds

The *PSEN1 E280A* or 'Paisa' mutation virtually guarantees that carriers will develop Alzheimer's at the average age of 44 and dementia at the average age of 49. The Colombian *PSEN1 E280A* kindred are the world's largest extended family with ADAD, with ~6,000 family members and ~1,200 with the mutation.

The API ADAD trial was conducted in collaboration with neurologist Francisco Lopera and his team, Grupo de Neurociencias de Antioquia (GNA), at the University of Antioquia in Medellín, Colombia. Dr Lopera followed the kindred for three decades prior to the start of the trial and has established a close relationship with many members.

About crenezumab

Crenezumab is an investigational, monoclonal antibody designed to neutralise neurotoxic oligomers, a form of beta-amyloid. Crenezumab has an antibody backbone (IgG4) designed to minimise the inflammatory response in the brain, which may result in a lower risk of certain MRI (magnetic resonance imaging) abnormalities known as ARIA (Amyloid-Related Imaging Abnormalities). The investigational medicine was discovered by Swiss biotechnology company AC Immune SA.

About Roche in Neuroscience

Neuroscience is a major focus of research and development at Roche. Our goal is to pursue groundbreaking science to develop new treatments that help improve the lives of people with chronic and potentially devastating diseases.

Roche is investigating more than a dozen medicines for neurological disorders, including multiple sclerosis, spinal muscular atrophy, neuromyelitis optica spectrum disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease and Duchenne muscular dystrophy. Together with our partners, we are committed to pushing the boundaries of scientific understanding to solve some of the most difficult challenges in neuroscience today.

About Roche

Founded in1896 in Basel, Switzerland, as one of the first industrial manufacturers of branded medicines, Roche has grown into the world's largest biotechnology company and the global leader in in-vitro diagnostics. The company pursues scientific excellence to discover and develop medicines and diagnostics for improving and saving the lives of people around the world. We are a pioneer in personalised healthcare and want to further transform how healthcare is delivered to have an even greater impact. To provide the best care for each person we partner with many stakeholders and combine our strengths in Diagnostics and Pharma with data insights from the clinical practice.

In recognising our endeavor to pursue a long-term perspective in all we do, Roche has been named one of the most sustainable companies in the pharmaceuticals industry by the Dow Jones Sustainability Indices for the thirteenth consecutive year. This distinction also reflects our efforts to improve access to healthcare together with local partners in every country we work.

Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan.

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