Media & Investor Release

Roche's fenebrutinib demonstrated near-complete suppression of disease activity and disability progression for up to 48 weeks in patients with relapsing multiple sclerosis

- **New Phase II data show vast majority of patients experiencing no relapses or disability progression**
- **Fenebrutinib suppressed acute and chronic MRI lesions**
- **Fenebrutinib's safety profile was consistent with previous and ongoing clinical trials across multiple diseases including more than 2,700 people to date**

Basel, 04 September 2024 - Roche (SIX: RO, ROG; OTCQX: RHHBY) will present new 48-week data for the investigational Bruton's tyrosine kinase (BTK) inhibitor fenebrutinib from the Phase II FENopta open-label extension (OLE) study at the 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Copenhagen, Denmark on 18 September 2024. Results demonstrate that patients with relapsing multiple sclerosis (RMS) treated with fenebrutinib for up to one year maintained very low levels of disease activity and no disability progression.

"After a year of treatment, our BTK inhibitor fenebrutinib was able to suppress nearly all disease activity and disability progression in people with multiple sclerosis," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "If these results are validated in the ongoing Phase III trials, fenebrutinib could further advance the treatment landscape for people living with multiple sclerosis."

During the OLE period, 96% of patients treated with fenebrutinib were free of relapses at one year, with an annualised relapse rate (ARR) of 0.04, and no change in disability over 48 weeks as measured by the Expanded Disability Status Scale (EDSS).

Fenebrutinib treatment suppressed disease activity in the brain as measured by MRI scans. At 48 weeks, 99% of patients were free of T1 gadolinium-enhancing (T1-Gd+) lesions, markers of active inflammation. Over the 48 weeks of OLE with continued fenebrutinib treatment, there was three times more reduction in the volume of T2 lesions, which represent chronic disease burden, compared to the end of the double-blind period (-0.33 cm^3 vs. -0.11 cm^3, respectively).

The safety profile of fenebrutinib in the OLE was consistent with previously reported data. The most common adverse events (AEs) in >5% of patients were urinary tract infection (8%), COVID-19 (7%) and pharyngitis (5%). Serious AEs occurred in one patient (1%). In the OLE, an asymptomatic alanine aminotransferase elevation occurred newly in one patient (1%) and resolved with treatment discontinuation.

Three Phase III clinical trials are ongoing, including the FENhance 1 and 2 trials in RMS and the FENtrepid trial in primary progressive multiple sclerosis (PPMS). Data from these studies, which will characterise the effects of fenebrutinib on disease progression across the multiple sclerosis spectrum, are expected at the end of 2025.

About fenebrutinib

Fenebrutinib is an investigational oral, reversible and non-covalent Bruton's tyrosine kinase (BTK) inhibitor that blocks the function of BTK. BTK, also known as tyrosine-protein kinase BTK, is an enzyme that regulates B-cell development and activation and is also involved in the activation of innate immune system myeloid lineage cells, such as macrophages and microglia. Preclinical data have shown fenebrutinib to be potent and highly selective, and it is the only reversible inhibitor currently in Phase III trials for multiple sclerosis. Fenebrutinib has been shown to be 130 times more selective for BTK vs. other kinases. These design features may be important as the high selectivity and reversibility may limit off-target effects of a molecule and potentially contribute to better long-term safety.

Fenebrutinib is a dual inhibitor of both B-cell and microglia activation. This dual inhibition may be able to reduce both multiple sclerosis disease activity and disability progression, thereby potentially addressing the key unmet medical need in people living with multiple sclerosis. The fenebrutinib Phase III programme includes two identical trials in relapsing multiple sclerosis (RMS) (FENhance 1 & 2) with active comparator teriflunomide and the only trial in primary progressive multiple sclerosis (PPMS) (FENtrepid) in which a BTK inhibitor is being evaluated against OCREVUS. To date, more than 2,700 patients and healthy volunteers have been treated with fenebrutinib in Phase I, II and III clinical programmes across multiple diseases, including multiple sclerosis and other autoimmune disorders.

About the FENopta study

The FENopta study was a global Phase II, randomised, double-blind, placebo-controlled 12-week study to investigate the efficacy, safety and pharmacokinetics of fenebrutinib in 109 adults aged 18-55 years with relapsing multiple sclerosis (RMS). The primary endpoint was the total number of new T1 gadolinium-enhancing (T1-Gd+) lesions as measured by MRI scans of the brain at 4, 8 and 12 weeks. Secondary endpoints included the number of new or enlarging T2-weighted lesions as measured by MRI scans of the brain at 4, 8 and 12 weeks, and the proportion of patients free from any new T1-Gd+ lesions and new or enlarging T2-weighted lesions as measured by MRI scans of the brain at 4, 8 and 12 weeks. The goal of the FENopta study was to characterise the effect of fenebrutinib on MRI and soluble biomarkers of disease activity and progression, and it included an optional substudy to measure cerebrospinal fluid fenebrutinib levels and biomarkers of neuronal injury.

Data from the 12-week study showed that fenebrutinib is central nervous system (CNS) penetrant (crosses the blood-brain barrier) and has the potential to impact mechanisms underlying chronic progressive disease biology in multiple sclerosis patients. Fenebrutinib

significantly reduced new T1-Gd+ lesions and new/enlarging T2 lesions compared to placebo. The safety profile of fenebrutinib was consistent with previous and ongoing fenebrutinib clinical trials and there were no new safety concerns identified.

Patients who completed the FENopta study were given the option to take part in an open-label extension (OLE) study, in which all patients receive fenebrutinib up to 192 weeks. Ninety-nine patients entered the OLE and 96 remained in the OLE after one year.

About multiple sclerosis

Multiple sclerosis is a chronic disease that affects more than 2.9 million people worldwide. Multiple sclerosis occurs when the immune system abnormally attacks the insulation and support around nerve cells (myelin sheath) in the central nervous system (brain, spinal cord and optic nerves), causing inflammation and consequent damage. This damage can cause a wide range of symptoms, including weakness, fatigue and difficulty seeing, and may eventually lead to disability. Most people with multiple sclerosis experience their first symptom between 20 and 40 years of age, making the disease the leading cause of non-traumatic disability in younger adults.

People with all forms of multiple sclerosis experience disease progression – permanent loss of nerve cells in the central nervous system – from the beginning of their disease even if their symptoms aren't apparent or don't appear to be getting worse. Delays in diagnosis and treatment can negatively impact people with multiple sclerosis, in terms of their physical and mental health, and contribute to the negative financial impact on the individual and society. An important goal of treating multiple sclerosis is to slow, stop and ideally prevent progression as early as possible.

Relapsing-remitting multiple sclerosis (RRMS) is the most common form of the disease and is characterised by episodes of new or worsening signs or symptoms (relapses) followed by periods of recovery. Approximately 85% of people with multiple sclerosis are initially diagnosed with RRMS. The majority of people who are diagnosed with RRMS will eventually transition to secondary progressive multiple sclerosis (SPMS), in which they experience steadily worsening disability over time. Relapsing forms of multiple sclerosis (RMS) include people with RRMS and people with SPMS who continue to experience relapses. Primary progressive multiple sclerosis (PPMS) is a debilitating form of the disease marked by steadily worsening symptoms but typically without distinct relapses or periods of remission. Approximately 15% of people with multiple sclerosis are diagnosed with the primary progressive form of the disease. Until the FDA approval of OCREVUS, there had been no FDA-approved treatments for PPMS and OCREVUS is still the only approved treatment for PPMS.

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 neuromuscular diseases: Duchenne muscular dystrophy, facioscapulohumeral muscular dystrophy and spinal muscular atrophy; neuro immune diseases: multiple sclerosis and neuromyelitis optica spectrum disorder; and neurodegenerative diseases: Alzheimer's disease, Huntington's disease and Parkinson's disease. 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 in 1896 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 endeavour 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 fifteenth 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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