Media & Investor Release

Late-breaking data for Roche's BTK inhibitor fenebrutinib show brain penetration and significant reduction in lesions in patients with relapsing multiple sclerosis

- **New data from Phase II FENopta study in relapsing multiple sclerosis (RMS) show fenebrutinib crosses the blood-brain barrier with the potential to act directly on the chronic inflammation related to multiple sclerosis (MS)**
- **More than 90% relative reduction in new/enlarging T2 lesions and new T1 gadolinium-enhancing (Gd+) lesions with fenebrutinib beginning at 8 weeks**
- **The safety profile of fenebrutinib was consistent with previous and ongoing clinical trials across more than 2,500 people to date**

Basel, 13 October 2023 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced new data from the Phase II FENopta study showing that investigational, oral fenebrutinib is brain penetrant and reduces brain lesions in people with relapsing multiple sclerosis (RMS) with a consistent safety profile to other fenebrutinib trials. The late-breaking data were featured in an oral presentation at the 9th Joint ECTRIMS-ACTRIMS Meeting (European and Americas Committees for Treatment and Research in Multiple Sclerosis).

"These interesting results raise the possibility that fenebrutinib slows MS disease progression in part by acting directly within the brain," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "These data, which we are currently confirming in pivotal trials of both relapsing and progressive MS, suggest that fenebrutinib may have the potential to counteract acute and chronic inflammation within the brain to reduce disease activity in people with MS."

Brain penetrance was measured by the level of fenebrutinib in the cerebrospinal fluid (CSF) of a subgroup of 11 patients with RMS. After 12 weeks of continuous treatment, the mean fenebrutinib concentration was 43.1 ng/mL. Similar fenebrutinib concentrations can produce near-maximal inhibition (IC90) in preclinical studies. Thus, the level of fenebrutinib in the brain and central nervous system may conceivably become high enough to reduce MS disease activity and progression in patients.

Fenebrutinib significantly reduced the total number of new T1 gadolinium-enhancing (T1 Gd+) brain lesions which are markers of active inflammation, and the total number of new or enlarging T2-weighted (T2) brain lesions, which represent the amount of disease burden or chronic lesion load. A rapid onset of lesion reduction was observed by 4 weeks, with relative reductions of 92% and 90% in T1 Gd+ lesions and relative reductions of 90% and 95% in T2 lesions observed at 8 and 12 weeks, respectively.

Furthermore, patients treated with fenebrutinib were four times more likely to be free from any new T1 Gd+ brain lesions and new or enlarging T2 brain lesions at weeks 4, 8, and 12 combined, compared to patients who received placebo (odds ratio 4.005, p=0.0117).

The safety profile of fenebrutinib was consistent with previous and ongoing fenebrutinib clinical trials across more than 2,500 people to date. There were no new safety concerns identified in the FENopta study. Overall rates of adverse events were 38% for fenebrutinib and 33% for placebo. The most common adverse events that were higher with fenebrutinib than placebo were abnormal liver enzyme levels (5.5% fenebrutinib, 0% placebo), headache (4.1% fenebrutinib, 2.8% placebo), nasopharyngitis (2.7% fenebrutinib, 0% placebo) and upper abdominal pain (2.7% fenebrutinib, 0% placebo).

Fenebrutinib is the only non-covalent and reversible BTK inhibitor in Phase III trials for MS and was designed to be highly selective, which may be important in reducing off-target effects of a molecule and potentially contribute to long-term safety outcomes. An open-label extension of FENopta is ongoing, with Phase III studies FENhance 1 and 2 currently enrolling patients with RMS and FENtrepid fully enrolled for patients with primary progressive MS (PPMS). Roche is committed to advancing innovative clinical research programmes to broaden the scientific understanding of MS, further reduce disability worsening in RMS and PPMS and improve the treatment experiences for those living with the disease.

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 MS. 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 can potentially reduce off-target effects of a molecule.

Fenebrutinib is a dual inhibitor of both B-cell and microglia activation. This dual inhibition may be able to reduce both MS disease activity and disability progression, thereby potentially addressing the key unmet medical need in people living with MS. The Phase III programme includes two identical trials in RMS (FENhance 1 & 2) with an active teriflunomide comparator and one trial in PPMS (FENtrepid) in which fenebrutinib is being evaluated against OCREVUS®

(ocrelizumab). To date, more than 2,500 patients and healthy volunteers have been treated with fenebrutinib in Phase I, II and III clinical programmes across multiple diseases, including MS and other autoimmune disorders.

About the FENopta study

The FENopta study is 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 RMS. The primary endpoint is the total number of new gadolinium-enhancing T1 lesions as measured by MRI scans of the brain at 4, 8 and 12 weeks. Secondary endpoints include 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 gadolinium-enhancing T1 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 is to characterise the effect of fenebrutinib on MRI and soluble biomarkers of disease activity and progression, and it includes an optional substudy to measure cerebrospinal fluid biomarkers of neuronal injury. Patients who complete the double-blind period are eligible for an open-label extension study.

About multiple sclerosis

Multiple sclerosis (MS) is a chronic disease that affects more than 2.8 million people worldwide. MS 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 muscle weakness, fatigue and difficulty seeing, and may eventually lead to disability. Most people with MS 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 MS experience disease progression – permanent loss of nerve cells in the central nervous system – from the beginning of their disease even if their clinical symptoms aren't apparent or don't appear to be getting worse. Delays in diagnosis and treatment can negatively impact people with MS, 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 MS is to slow, stop and ideally prevent disease activity and progression as early as possible.

Relapsing-remitting MS (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 MS are initially diagnosed with RRMS. The majority of people who are diagnosed with RRMS will eventually transition to secondary progressive MS (SPMS), in which they experience steadily worsening disability over time. Relapsing forms of MS (RMS) include people with RRMS and people with SPMS who continue to experience relapses. Primary progressive MS (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 MS 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.

About Roche in Neuroscience

Neuroscience is a major focus of research and development at Roche. Our goal is to pursue ground-breaking science to develop new treatments that help improve the lives of people with chronic and potentially devastating diseases. Roche and Genentech are investigating more than a dozen medicines for neurological disorders, including MS, spinal muscular atrophy, neuromyelitis optica spectrum disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease, acute ischemic stroke, Duchenne muscular dystrophy and Angelman syndrome. 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 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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