Media & Investor Release

Roche's BTK inhibitor fenebrutinib significantly reduced brain lesions in people with relapsing forms of multiple sclerosis

- **Fenebrutinib is an investigational, potent and highly selective oral Bruton's tyrosine kinase (BTK) inhibitor, the only reversible BTK inhibitor currently in Phase III multiple sclerosis (MS) trials**
- **Phase II study met its primary and secondary endpoints by reducing the total number of new gadolinium-enhancing T1 brain lesions and significantly reducing the total number of new or enlarging T2 brain lesions compared to placebo**
- **The safety profile of fenebrutinib was consistent with previous and ongoing clinical trials across more than 2,400 people to date**

Basel, 17 May 2023 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today positive results from the Phase II FENopta study evaluating investigational oral fenebrutinib in adults with relapsing forms of multiple sclerosis (RMS). The study met its primary and secondary endpoints, showing oral fenebrutinib significantly reduced magnetic resonance imaging (MRI) markers of MS disease activity in the brain compared to placebo. Additionally, pre-clinical data have shown fenebrutinib to be potent and highly selective, and it is the only reversible inhibitor currently in Phase III trials for MS.

"I am encouraged by this clinical data for fenebrutinib, which is important news for people living with MS," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "Fenebrutinib's mechanism of action which can inhibit both B cells and microglia, has the potential to both reduce MS disease activity, such as relapses, and also impact disease progression."

Fenebrutinib significantly reduced the total number of new gadolinium-enhancing T1 brain lesions compared to placebo, the primary endpoint of the trial (p=0.0022). Additionally, fenebrutinib significantly reduced the total number of new or enlarging T2 brain lesions compared to placebo, a secondary endpoint. Furthermore, a higher proportion of patients treated with fenebrutinib were free from any new gadolinium-enhancing T1 brain lesions and new or enlarging T2-weighted brain lesions compared to placebo. T1 lesions, as measured by MRI, are a marker of active inflammation and T2 lesions represent the amount of disease burden or lesion load.

The safety profile of fenebrutinib was consistent with previous and ongoing fenebrutinib clinical trials across more than 2,400 people to date. There were no new safety concerns identified in the FENopta study.

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Detailed results will be shared at an upcoming medical meeting. The Phase III fenebrutinib clinical trial programme in RMS and primary progressive MS (PPMS) is ongoing.

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. Pre-clinical 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 and contribute to long-term safety outcomes.

Fenebrutinib is a dual inhibitor of both B-cell and microglia activation. This dual inhibition has the potential to reduce both MS disease activity and progression, thereby 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 primary progressive MS (PPMS) (FENtrepid) in which fenebrutinib is being evaluated against OCREVUS® (ocrelizumab). To date, more than 2,400 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 Neurosciences

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. Our MS franchise also includes OCREVUS, which has been approved in more than 100 countries globally with 300,000 people treated to date. 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 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.

For more information, please visit www.roche.com.

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