Roche’s fenebrutinib shows unprecedented positive phase III results as the potential first and only BTK inhibitor in both relapsing and primary progressive multiple sclerosis

Roche announced that the first phase III (FENhance 2) of two pivotal, similarly-designed phase III studies (FENhance 1 and 2) in patients with relapsing multiple sclerosis (RMS) met its primary endpoint. Fenebrutinib, an investigational Bruton’s tyrosine kinase (BTK) inhibitor, significantly reduced the annualised relapse rate (ARR) compared to teriflunomide over a period of at least 96 weeks of treatment.

Additionally, the phase III FENtrepid pivotal study evaluating fenebrutinib, compared with Ocrevus (ocrelizumab) in patients with primary progressive multiple sclerosis (PPMS), met its primary endpoint. The results showed that fenebrutinib was non-inferior compared to ocrelizumab, the only approved therapy in PPMS, as measured by a delay in the onset of composite confirmed disability progression over a period of at least 120 weeks of treatment. A numerical benefit for fenebrutinib compared to ocrelizumab was seen as early as week 24, and lasted throughout the observation period.

“Fenebrutinib substantially reduced the number of relapses in RMS and slowed disability progression in PPMS. These unprecedented results suggest that fenebrutinib could potentially become a best-in-disease medicine as the first high-efficacy, oral treatment for people with RMS or PPMS,” said Levi Garraway, M.D., Ph.D., Roche’s chief medical officer and head of global product development. "Therefore, these pivotal results for fenebrutinib may offer new hope for people living with MS, and they reaffirm our enduring commitment to the MS community.”

Liver safety was consistent with previous fenebrutinib studies. Additional safety data is being further evaluated. The results of the second RMS phase III trial (FENhance 1) are expected by the first half of 2026.

Fenebrutinib targets cells in the immune system known as B cells and microglia. Targeting B cells helps control the acute inflammation that causes relapses, while targeting microglia inside the brain addresses the chronic damage that is thought to drive long-term disability progression. Fenebrutinib, a non-covalent BTKi, is designed to have high potency, selectivity and reversibility. This design allows it to act throughout the body, and also to cross the blood-brain barrier into the central nervous system (CNS) targeting chronic inflammation.

FENhance 1 and 2 are similarly designed phase III multicentre, randomised, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of investigational fenebrutinib compared with teriflunomide in a total of 1,497 adult patients with RMS. Eligible participants were randomised 1:1 to receive treatment with either oral fenebrutinib twice a day (and placebo matched to oral teriflunomide once a day) or oral teriflunomide once a day (and placebo matched to oral fenebrutinib twice a day) for at least 96 weeks.

The primary endpoint is annualised relapse rate (ARR). Key secondary endpoints include the time to onset of composite 24-week confirmed disability progression (cCDP24), 12-week confirmed disability progression (CDP12) and 24-week confirmed disability progression (CDP24).

Following the double-blind treatment period, patients have the option to enter an open-label extension (OLE) phase, in which all patients receive treatment with fenebrutinib.

FENtrepid is a phase III multicentre, randomised, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of fenebrutinib compared with Ocrevus in 985 adult patients with PPMS. Eligible participants were randomised 1:1 to receive treatment with either daily oral fenebrutinib (and placebo matched to intravenous [IV] Ocrevus) or IV Ocrevus (and placebo matched to oral fenebrutinib) for at least 120 weeks.

The primary endpoint is the time to onset of 12-week composite confirmed disability progression (cCDP12). The cCDP incorporates three measures of disability – total functional disability measured by the Expanded Disability Status Scale (EDSS), walking speed measured by the timed 25-foot walk (T25FW), and upper limb function measured by the nine-hole peg test (9HPT). This comprehensive composite endpoint offers greater sensitivity than the EDSS alone, capturing additional aspects of disability and often earlier. Key secondary endpoints include the time to onset of 24-week composite confirmed disability progression (cCDP24), 12-week confirmed disability progression (CDP12) and 24-week confirmed disability progression (CDP24).

Following the double-blind treatment period, patients have the option to enter an open-label extension (OLE) phase, in which all patients receive treatment with fenebrutinib.

Fenebrutinib is an investigational oral, central nervous system (CNS)-penetrant, reversible and non-covalent Bruton's tyrosine kinase (BTK) inhibitor with an optimised pharmacokinetics (PK) profile. Fenebrutinib has been shown to be 130 times more selective for BTK vs. other kinases. Fenebrutinib is an 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 of disability progression in people living with multiple sclerosis and providing comprehensive multiple sclerosis care. The fenebrutinib phase III programme includes two similarly-designed trials in relapsing multiple sclerosis (RMS) (FENhance 1 and 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.

Ocrevus is a humanised monoclonal antibody designed to target CD20-positive B cells, a specific type of immune cell thought to be a key contributor to myelin (nerve cell insulation and support) and axonal (nerve cell) damage. Ocrevus IV and Ocrevus subcutaneous (SC; marketed as Ocrevus Zunovo [ocrelizumab hyaluronidase-ocsq] in the US) are the only therapies approved for both RMS (including relapsing-remitting multiple sclerosis [RRMS] and active, secondary progressive multiple sclerosis [SPMS], as well as clinically isolated syndrome [CIS] in the US) and primary

progressive multiple sclerosis (PPMS). Both Ocrevus IV and SC are administered every six months. The initial IV dose is given as two 300 mg infusions two weeks apart with subsequent doses given as single 600 mg infusions. Ocrevus SC is given as a single 920 mg subcutaneous injection every six months.

Multiple sclerosis is a chronic disease that affects more than 2.9 million people worldwide. People with all forms of multiple sclerosis experience disease progression from the beginning of their disease. Therefore, an important goal of treating multiple sclerosis is to slow, stop and ideally prevent progression as early as possible.

Approximately 85% of people with multiple sclerosis have a relapsing form of the disease (RMS) characterised by relapses and also worsening disability over time. 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.

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.

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.

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