Press Release

Tolebrutinib regulatory submission accepted for priority review in the US for patients with multiple sclerosis

- If approved, tolebrutinib would be the first and only brain-penetrant BTK inhibitor to both treat non-relapsing secondary progressive multiple sclerosis (MS) and slow disability accumulation independent of relapse activity
- Tolebrutinib has the potential to be the first therapy to target smoldering neuroinflammation, a key driver of disability accumulation in MS
- Tolebrutinib was granted breakthrough therapy designation by the FDA based on positive results from the HERCULES phase 3 study in adults with non-relapsing secondary progressive MS

Paris, March 25, 2025. The US Food and Drug Administration (FDA) is evaluating under priority review the regulatory submission of tolebrutinib to treat non-relapsing secondary progressive multiple sclerosis (nrSPMS) and to slow disability accumulation independent of relapse activity in adult patients. The target action date for the FDA decision is September 28, 2025. A regulatory submission is also under review in the EU.

The regulatory submissions in the US and the EU are supported by the results from the phase 3 studies HERCULES in nrSPMS and GEMINI 1 and 2 in relapsing MS (RMS). The findings from these studies, as well as additional clinical and preclinical studies, support the differentiated mechanism of tolebrutinib to target disability progression independent of relapse activity, and the scientific hypothesis that smoldering neuroinflammation represents a key inflammatory process in MS and is a critical driver of disability accumulation.

> ***Erik Wallström, MD, PhD***
> Global Head of Neurology Development
> *"The totality of data across our clinical program validates our scientific understanding of smoldering neuroinflammation as a distinct inflammatory process in MS. People living with non-relapsing secondary progressive multiple sclerosis or who experience disability independent of relapse activity suffer from disability that worsens over time due to persistent inflammation in the brain, known as smoldering neuroinflammation, which is the primary driver of disability. The demonstrated ability of tolebrutinib to delay disability by targeting underlying drivers of the disease represents a potential paradigm shift in treating these patients."*

Tolebrutinib is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority. The PERSEUS phase 3 study of tolebrutinib in patients with primary progressive MS is currently ongoing with study results anticipated in H2 2025.

About multiple sclerosis

Multiple sclerosis is a chronic, immune-mediated, neurodegenerative disease that may result in accumulation of irreversible disabilities over time. The physical and cognitive disability impairments translate into gradual deterioration of health status, impacting patients' care and quality of life. Disability accumulation remains the significant unmet medical need in MS. To date, the primary target of currently approved medicines has been peripheral B and T cells, while innate immunity within the CNS, which is believed to drive disability accumulation, remains largely unaddressed. Currently approved or late-stage medicines being tested for MS mainly target the adaptive immune system and/or do not act directly within the central nervous system to drive clinical benefit.

Living with nrSPMS refers to people with MS who have stopped experiencing relapses but continue to accumulate disability, experienced as symptoms such as fatigue, cognitive impairment, balance and gait impairment, loss of bowel and/or bladder function, sexual disfunction, amongst others.

About tolebrutinib

Tolebrutinib is an investigational, oral, brain-penetrant, and bioactive Bruton's tyrosine kinase (BTK) inhibitor specifically designed to target smoldering neuroinflammation, a key driver of disability progression in MS. Unlike currently approved MS therapies that primarily address peripheral inflammation, tolebrutinib uniquely crosses the blood-brain barrier to achieve therapeutic cerebrospinal fluid concentrations, allowing it to modulate B-lymphocytes and disease-associated microglia within the CNS. This mechanism is believed to address the underlying pathology of progressive MS by targeting the inflammatory processes that contribute to neurodegeneration and disability accumulation.

Tolebrutinib is being evaluated in phase 3 clinical studies for the treatment of various forms of multiple sclerosis and its safety and efficacy have not been evaluated by any regulatory authority worldwide. For more information on tolebrutinib clinical studies, please visit www.clinicaltrials.gov.

About HERCULES

HERCULES (clinical study identifier: NCT04411641) was a double-blind randomized phase 3 clinical study evaluating the efficacy and safety of tolebrutinib in patients with nrSPMS. At baseline, nrSPMS was defined as having a SPMS diagnosis with an expanded disability status scale (EDSS) between 3.0 and 6.5, no clinical relapses for the previous 24 months and documented evidence of disability accumulation in the previous 12 months. Participants were randomized (2:1) to receive either an oral daily dose of tolebrutinib or matching placebo for up to approximately 48 months.

The primary endpoint was 6-month CDP defined as the increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.0, or the increase of ≥0.5 point when the baseline EDSS score was >5.0. Secondary endpoints included time to onset of 3-month CDP as assessed by EDSS score, total number of new or enlarging T2 hyperintense lesions as detected by MRI, time to onset of confirmed disability improvement, 3-month change in 9-hole peg test and T25-FW test as well as the safety and tolerability of tolebrutinib.

About GEMINI 1 and 2

GEMINI 1 (clinical study identifier: NCT04410978) and GEMINI 2 (clinical study identifier: NCT04410991) were double-blind randomized phase 3 clinical studies evaluating the efficacy and safety of tolebrutinib compared to teriflunomide in patients with RMS. Participants were randomized in both studies (1:1) to receive either tolebrutinib and placebo daily or 14mg teriflunomide and placebo.

The primary endpoint for both studies was the annualized relapse rate for up to approximately 36 months defined as the number of confirmed adjudicated protocol defined relapses. Secondary endpoints included time to onset of CDW, confirmed over at least 6 months, defined as an increase of ≥1.5 points from the baseline EDSS score when the baseline score is 0, an increase of ≥1.0 point from the baseline EDSS score when the baseline score is 0.5 to ≤5.5 or an increase of ≥0.5 point from the baseline EDSS score when the baseline score was >5.5 in addition to the total number of new and/or enlarging T2 hyperintense lesions as detected by MRI from baseline through the end of study, the total number of Gd-enhancing T1 hyperintense lesions as detected by MRI from baseline through the end of study and the safety and tolerability of tolebrutinib.

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millions of people globally, while putting sustainability and social responsibility at the center of our ambitions.

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