Press Release

Tolebrutinib phase 3 data published in NEJM demonstrate benefit on disability progression in multiple sclerosis

- Results from the HERCULES phase 3 study showed delay in disability progression in people living with non-relapsing secondary progressive multiple sclerosis
- Tolebrutinib has the potential to be the first therapy to modulate immunologic drivers of chronic inflammation behind the blood–brain barrier, a key driver of disability accumulation in MS
- Tolebrutinib is being evaluated under priority review in the US with a target action date of 28 September 2025; regulatory submission dossier is under review in the EU with a decision expected in Q1 2026

Paris, April 8, 2025. *The New England Journal of Medicine* (NEJM) published positive results from the HERCULES phase 3 study demonstrating that tolebrutinib delayed disability progression in people with non-relapsing secondary progressive multiple sclerosis (nrSPMS), where there are currently no treatment options approved. These findings further support the differentiated mechanism of oral, brain-penetrant tolebrutinib, targeting disability progression independent of relapse activity. These results were first presented at the ECTRIMS conference on September 20, 2024 in Copenhagen, Denmark and further analyses were also presented today during the Clinical Trials Plenary Session at the 2025 Annual Meeting for the American Academy of Neurology (AAN) in San Diego, California.

> ***Robert Fox, MD***
> Vice Chair of Research at Cleveland Clinic's Neurological Institute, Cleveland, Ohio, US, and chair of the HERCULES global steering committee
> *"Tolebrutinib represents a new class of therapy for the treatment of multiple sclerosis. In this large phase 3 study, tolebrutinib was found to slow the progression of disability in a subset of multiple sclerosis for which we have no approved therapies – non-relapsing secondary progressive disease. The results of this study signal a new chapter in multiple sclerosis because we finally found a potential way to treat non-relapsing secondary progressive forms."*
> Dr Fox is a paid advisor to Sanofi for the HERCULES study.

> ***Erik Wallström, MD, PhD***
> Global Head of Neurology Development
> *"By targeting disability progression mechanisms behind the blood-brain barrier, tolebrutinib has the potential to be a practice-changing therapeutic option for people living with multiple sclerosis. The data published in NEJM support our larger commitment to the multiple sclerosis patient community, transforming the treatment paradigm to defy disability across the disease spectrum."*

The HERCULES data demonstrated that tolebrutinib delayed the time to onset of 6-month confirmed disability progression (CDP) by 31% compared to placebo (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.55-0.88; p=0.003). Additionally, results from the GEMINI 1 and 2 phase 3 studies, evaluating tolebrutinib in people with relapsing multiple sclerosis (RMS) were also published in *NEJM* and presented today during the Clinical Trials Plenary Session at the AAN 2025 Annual Meeting.

The GEMINI 1 and 2 results did not show superiority on the primary endpoint of reducing annualized relapse rate (ARR) over teriflunomide. The ARR during the study period was 0.13 in the tolebrutinib group and 0.12 in the teriflunomide group in GEMINI 1 (adjusted rate ratio, 1.06; 95% CI 0.81-1.39; p=0.67) and was 0.11 in both groups in GEMINI 2 (adjusted rate ratio, 1.00; 95% CI 0.75-1.32; p=0.98). A pooled analysis for a key secondary endpoint, not controlled for multiplicity, showed that tolebrutinib delayed the time to onset of 6-month confirmed disability worsening by 29% versus teriflunomide (HR 0.71; 95% CI 0.53 to 0.95).

Tolebrutinib was generally well-tolerated across all arms of the studies for all participants. In HERCULES, liver enzyme elevations (>3xULN) were observed in 4.0% of participants receiving tolebrutinib compared with 1.6% in the placebo group. A small (0.5%) proportion of participants in the tolebrutinib group experienced peak ALT increases of >20xULN, all occurring within the first 90 days of treatment. All but one case of liver enzyme elevations resolved without further medical intervention. Prior to the implementation of more frequent liver enzyme monitoring following treatment initiation, one participant in the tolebrutinib arm received a liver transplant and died due to post-operative complications. The implementation of more frequent liver monitoring may help to mitigate serious liver sequelae. Other deaths in the study were assessed as unrelated to treatment by investigators; deaths were even across the placebo and tolebrutinib arms at 0.3%.

In an analysis of the GEMINI 1 and 2 pooled safety data, adverse events observed between the tolebrutinib and teriflunomide arms were generally balanced. Liver enzyme elevations (>3xULN) were observed in 5.6% of participants receiving tolebrutinib compared to 6.3% in the teriflunomide arms. A small (0.5%) proportion of participants in the tolebrutinib group experienced peak ALT increases of >20xULN, all occurring within the first 90 days of treatment. Deaths were balanced across the teriflunomide and tolebrutinib arms, at 0.2% and 0.1% respectively, and were assessed as unrelated to treatment by the investigators.

The safety and efficacy of tolebrutinib have not been determined by any regulatory authority. The regulatory submission for tolebrutinib to treat nrSPMS and to slow disability accumulation independent of relapse activity in adult patients is being evaluated under priority review by the US Food and Drug Administration with a target action date of September 28, 2025. A regulatory submission is also under review in the EU.

About multiple sclerosis

Multiple sclerosis is a chronic, immune-mediated disease of the central nervous system 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' 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 multiple sclerosis. Unlike conventional MS therapies that primarily address peripheral inflammation, tolebrutinib crosses the blood-brain barrier to achieve therapeutic cerebrospinal fluid concentrations, allowing it to modulate both B-lymphocytes and disease-associated microglia within the central nervous system. This mechanism is thought to directly address the underlying pathology of progressive MS by targeting the inflammatory processes that contribute to neurodegeneration and disability accumulation.

Tolebrutinib was previously 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. Tolebrutinib is being evaluated in a phase 3 clinical study for the treatment of primary progressive multiple sclerosis and its safety and efficacy have not been determined by

any regulatory authority worldwide. For more information on tolebrutinib clinical studies, please visit www.clinicaltrials.gov.

Tolebrutinib represents Sanofi's commitment to developing innovative treatments that address the underlying causes of neurological diseases and potentially transform the treatment landscape. Standing at the intersection of neurology and immunoscience, Sanofi is focused on improving the lives of those living with serious neuro-inflammatory and neuro-degenerative conditions including MS, chronic inflammatory demyelinating polyneuropathy, Alzheimer's disease, Parkinson's disease, age-related macular degeneration, and other neurological diseases. The neurology pipeline currently has several projects in phase 3 studies across 7 indications.

About HERCULES

HERCULES (clinical study identifier: NCT04411641) was a double-blind randomized phase 3 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 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 14 mg 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.

About Sanofi

We are an innovative global healthcare company, driven by one purpose: we chase the miracles of science to improve people's lives. Our team, across the world, is dedicated to transforming the practice of medicine by working to turn the impossible into the possible. We provide potentially life-changing treatment options and life-saving vaccine protection to millions of people globally, while putting sustainability and social responsibility at the center of our ambitions.

Sanofi is listed on EURONEXT: SAN and NASDAQ: SNY

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Sanofi forward-looking statements
This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions, and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects", "anticipates", "believes", "intends", "estimates", "plans" and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the fact that product candidates if approved may not be commercially successful, the future approval and commercial success of therapeutic alternatives, Sanofi's ability to benefit from external growth opportunities, to complete related transactions and/or obtain regulatory clearances, risks associated with intellectual property and any related pending or future litigation and the ultimate outcome of such litigation, trends in exchange rates and prevailing interest rates, volatile economic and market conditions, cost containment initiatives and subsequent changes thereto, and the impact that global crises may have on us, our customers, suppliers, vendors, and other business partners, and the financial condition of any one of them, as well as on our employees and on the global economy as a whole. The risks and uncertainties also include the uncertainties discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2024. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.