Press Release

Tolebrutinib designated Breakthrough Therapy by the FDA for non-relapsing secondary progressive multiple sclerosis

- Designation is based on positive results from the HERCULES study in adults with non-relapsing secondary progressive multiple sclerosis (nrSPMS)
- Tolebrutinib is the first and only brain-penetrant BTK inhibitor in MS to be designated Breakthrough Therapy by the FDA

Paris, December 13, 2024. The US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to tolebrutinib for the treatment of adults with non-relapsing secondary progressive multiple sclerosis (nrSPMS). This is based on positive results from the HERCULES phase 3 study, demonstrating that tolebrutinib delayed the time to onset of 6-month confirmed disability progression (CDP), by 31% compared to placebo (HR 0.69; 95% CI 0.55-0.88; p=0.0026), with further analysis of secondary endpoints demonstrating that the number of participants who experienced confirmed disability improvement was nearly double with tolebrutinib (10%) compared to those on placebo (5%) (HR 1.88; 95% CI 1.10 to 3.21; nominal p=0.021).

FDA Breakthrough Therapy designation is designed to expedite the development and review of medicines in the US that target serious or life-threatening conditions. Medicines qualifying for this designation must show preliminary clinical evidence that the drug may demonstrate substantial improvement on clinically significant endpoints over available medicines.

> ***Erik Wallström, MD, PhD***
> Global Head of Neurology Development, Sanofi
> *"This Breakthrough Therapy designation demonstrates the potential for tolebrutinib to delay disability progression, a critical unmet need for people living with multiple sclerosis. We look forward to working with the FDA during the regulatory review of this first of its kind medicine in non-relapsing secondary progressive multiple sclerosis where there are currently no approved treatments available."*

Liver enzyme elevations (>3xULN) were observed in 4.1% 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. The implementation of more frequent monitoring has helped mitigate serious liver sequelae.

Regulatory submissions of tolebrutinib are currently being finalized for the US and prepared for the EU. As with other medicines, Sanofi plans to confirm once a regulatory submission for tolebrutinib has been accepted. The PERSEUS phase 3 study in primary progressive MS is currently ongoing with study results anticipated in H2 2025.

Tolebrutinib is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority.

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 current medicines has been peripheral B and T cells, while innate immunity, which is believed to drive disability accumulation, remains largely unaddressed by current medicines. 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.

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 that achieves cerebrospinal fluid concentrations predicted to modulate B lymphocytes and disease-associated microglia. 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 participants with nrSPMS. nrSPMS was defined at baseline 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 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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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 pandemics or other 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, 2023. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.