Press Release

Tolebrutinib demonstrated a 31% delay in time to onset of confirmed disability progression in non-relapsing secondary progressive multiple sclerosis phase 3 study

- Data presented at ECTRIMS show that tolebrutinib, a brain-penetrant BTK inhibitor, addresses disability accumulation that occurs independently from relapse activity
- Global regulatory submissions will begin in H2 2024

Paris, September 20, 2024. Positive results from the HERCULES phase 3 study in people with non-relapsing secondary progressive multiple sclerosis (nrSPMS) demonstrated 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). Further analysis of secondary endpoints demonstrated that the number of participants who experienced confirmed disability improvement increased by nearly two-fold, 10% with tolebrutinib compared to 5% with placebo (HR 1.88; 95% CI 1.10 to 3.21; nominal p=0.021). These results were presented today as a late-breaking presentation at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2024 conference in Copenhagen, Denmark.

Robert Fox, MD
Vice Chair of Research at Cleveland Clinic's Neurological Institute, Cleveland, Ohio and Chair of the HERCULES Global Steering Committee
"Secondary progressive multiple sclerosis is characterized by insidious worsening of disability over time, independent of relapses, and represents a critical unmet need because we don't have effective treatments. The results of HERCULES show clearly that tolebrutinib delayed disability progression in people with nrSPMS – and some people even improved disability – by uniquely targeting the biological processes driving disease progression in the brain." Dr. Fox is a paid advisor to Sanofi for the HERCULES trial.

Based on preliminary analysis of the HERCULES study, there was a slight increase in tolebrutinib-treated patients of some adverse events. Liver enzyme elevations (>3xULN) were observed in 4.1% of participants receiving tolebrutinib compared with 1.6% in the placebo group, a side effect also reported with other BTK inhibitors in MS. 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 the revised study protocol with more stringent monitoring, one participant in the tolebrutinib arm received a liver transplant and died due to post-operative complications. To date, the implementation of more frequent monitoring has mitigated such serious liver sequelae. Other deaths in the trial were assessed as unrelated to treatment by investigator; deaths were even across the placebo and tolebrutinib arms at 0.3%.

Adverse events (≥10%*)	tolebrutinib N=752 (%)	placebo N=375 (%)
COVID-19 infections	192 (25.5%)	85 (22.7%)
Urinary tract infections	85 (11.3%)	49 (13.1%)

*For participants receiving tolebrutinib

Houman Ashrafian, MD, PhD
Head of Research & Development, Sanofi
"With no treatment options currently available for the broad population of patients with secondary progressive multiple sclerosis, tolebrutinib has demonstrated its ability to delay disability by targeting underlying drivers of the disease. We look forward to discussing these results with healthcare

authorities and are eager to see the results of tolebrutinib in primary progressive MS when they become available next year. We extend our deepest appreciation to the study participants, their families, and the healthcare professionals involved in these trials."

The GEMINI 1 and 2 phase 3 study results of tolebrutinib compared to Aubagio (teriflunomide), a standard-of-care treatment, in participants with relapsing multiple sclerosis (RMS) were also presented today as a late-breaking presentation at ECTRIMS. Both studies did not meet their primary endpoints of statistically significant improvement in annualized relapse rates (ARR) compared to Aubagio. However, in the key secondary endpoint, a pooled analysis of data from GEMINI 1 and 2, tolebrutinib delayed the time to onset of 6-month confirmed disability worsening (CDW) by 29% (HR 0.71; 95% CI: 0.53-0.95; nominal p=0.023). The results of the 29% delay in CDW endpoint in participants with RMS are in line with the 31% delay in CDP observed in participants with nrSPMS. The significant impact of tolebrutinib on disability accumulation versus Aubagio, in the absence of a statistically superior impact on relapses, suggests that tolebrutinib may address smoldering neuroinflammation, which manifests as progression independent of relapses.

Furthermore, results showed historically low ARR in the Aubagio arm in both GEMINI 1 and 2, and no difference was observed between Aubagio and tolebrutinib in a pooled analysis. These relapse rates amount to approximately 1 relapse every 8 years.

	tolebrutinib ARR	Aubagio ARR
GEMINI 1 (adjusted rate ratio 1.06; 95% CI: 0.80 to 1.39; p=0.67)	0.13	0.12
GEMINI 2 (adjusted rate ratio 1.00; 95% CI: 0.75 to 1.32; p=0.98)	0.11	0.11
Pooled analysis (adjusted rate ratio 1.03; 95% CI: 0.84 to 1.25; p=0.80)	0.12	0.12

In preliminary analysis of the GEMINI 1 and 2 pooled safety data, adverse events observed between the tolebrutinib and Aubagio arms were generally balanced. Liver enzyme elevations (>3x ULN) were observed in 5.6% of participants receiving tolebrutinib compared with 6.3% of participants receiving Aubagio, a side effect reported with other BTK inhibitors in MS and resolved without further medical intervention. 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 Aubagio and tolebrutinib arms, at 0.2% and 0.1% respectively, and were assessed as unrelated to treatment by investigator.

Adverse events (≥10%*)	Tolebrutinib N=933 (%)	Aubagio N=939 (%)
COVID-19 infections	225 (24.1%)	252 (26.8%)
Nasopharyngitis	119 (12.8%)	105 (11.2%)
Headache	117 (12.5%)	98 (10.4%)

*For participants receiving tolebrutinib

Study results will form the basis for future discussions with global regulatory authorities with submissions starting in H2 2024. Tolebrutinib is currently under clinical investigation, and its safety and efficacy have not been evaluated by any regulatory authority.

The PERSEUS phase 3 study in 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 results in accumulation of irreversible disabilities over time. The physical and cognitive disability impairments translate into gradual deterioration of health status and lower quality of life, impacting patients' care and life expectancy. Disability accumulation remains the significant unmet medical need in MS. To date, the primary target of current therapies has been peripheral B and T cells, while innate immunity, which is believed to drive disability accumulation, remains largely unaddressed by current therapies. Currently approved, or

medicines being tested for MS mainly target the adaptive immune system and/or do not act directly within the central nervous system (CNS) to drive clinical benefit.

RMS refers to people with MS who experience episodes of new or worsening symptoms (known as relapses) followed by periods of partial or complete recovery. nrSPMS refers to people with MS who have stopped experiencing confirmed relapses but continue to experience accumulation of disability, experienced as symptoms such as fatigue, cognition impairment, balance and gait impairment, loss of bowel and/or bladder function, sexual disfunction, amongst others.

About HERCULES

HERCULES (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 3-month change in 9 hole peg test and T25-FW test, 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, change in cognitive function at the EOS compared to baseline as assessed by the Symbol Digit Modalities Test and by the California Verbal Learning 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 Aubagio in participants with relapsing forms of MS. Participants were randomized in both studies (1:1) to receive either tolebrutinib and placebo daily or 14mg Aubagio 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 tolebrutinib

Tolebrutinib is an investigational, oral, brain-penetrant, and bioactive Bruton's tyrosine kinase (BTK) inhibitor that achieves CSF 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 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 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.