Media Update

New preclinical tolebrutinib data demonstrated superior brain penetration and potency

Preclinical findings showed that tolebrutinib, among the investigational BTK inhibitors tested, had the best combination of brain penetration and potency that reinforces its potential to impact neuroinflammation

Paris, February 24, 2022. New preclinical data demonstrated that tolebrutinib, Sanofi's investigational oral Bruton's tyrosine kinase (BTK) inhibitor for the treatment of multiple sclerosis (MS), was the only BTK inhibitor with sufficient central nervous system (CNS) exposure and potency to modulate BTK signaling pathways within the CNS, as compared with evobrutinib and fenebrutinib. These results are being presented in a live poster presentation at the 7th annual Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum.

Disability accumulation, or worsening of neurologic function, remains a reality for many people living with MS. Inhibition of BTK, an important intracellular signaling pathway within the CNS, is being investigated as an MS treatment strategy. However, to effectively inhibit BTK within the CNS, investigational therapies must cross the blood-brain barrier with sufficient exposure to engage targets and modulate signaling.

In experiments using well-established preclinical methods, tolebrutinib was shown to be more potent than evobrutinib (50x) and fenebrutinib (9.3x), resulting in durable BTK inhibition. The analyses comprised *in vitro* kinase and cellular assays and *in vivo* pharmacokinetic (PK) sampling of cerebrospinal fluid (CSF) in non-human primates cynomolgus macaque (Macaca fascicularis). These data reinforce that targeting BTK has the potential to target inflammation both in the periphery and directly in the CNS. Further research is needed to determine the potential clinical efficacy and safety of tolebrutinib in treating MS.

> ***Tim Turner, PhD***
> Global Project Head for Tolebrutinib, Sanofi
> *"Based on this preclinical analysis comparing late-stage BTK inhibitors, tolebrutinib demonstrated a superior combination of CSF exposure and potency that exceeded the IC90, a measure of substantial target engagement in the brain. These data make us optimistic about the potential for tolebrutinib to address the drivers of disability in the CNS, and we look forward to seeing the first Phase 3 readouts next year."*

Sanofi will host a virtual investor session to review data presented at ACTRIMS and provide an update on the company's broader neurology portfolio. The audio webcast and conference call for investors will include presentations followed by a Q&A session. The session will be held on February 25 from 10:00-11:00 EST/ 16:00-17:00 CET; to register, click here.

About the Study

The study characterized the relative potency and CNS exposure of tolebrutinib, evobrutinib, and fenebrutinib in a preclinical model of MS. Analyses of *in vitro* kinase profiling assays determined that tolebrutinib inhibited BTK 64 times faster than evobrutinib (K_{inact}/K_i value of 4.37 x 10^{-3} versus 6.82 x 10^{-5} $nM^{-1}*s^{-1}$), and ~1,780 times faster than fenebrutinib. Assays measuring antigen-stimulated B cell activation were consistent with *in vitro* kinase assays and showed potent BTK inhibition with tolebrutinib (estimated IC_{50} value of 3.2nM, compared to 80.9nM for evobrutinib and 19.8nM for fenebrutinib).

Researchers translated the *in vitro* results to determine each drug candidate's potential *in vivo* pharmacokinetics. All three agents, administered as a single oral dose of 10 mg/kg daily,

achieved similar CSF concentrations in cynomolgus monkeys. Tolebrutinib CSF concentrations (4.8 ng/mL) (kp,uu CSF=0.40) exceeded the estimated IC90 (3.1 ng/mL), while both evobrutinib (3.2 ng/mL) (kp,uu CSF=0.13) and fenebrutinib (12.9 ng/mL) (kp,uu CSF=0.15) failed to reach exposure levels approaching their IC90 values (144 and 40.6 ng/mL, respectively).

The analyses of *in vitro* kinase and cellular assays were conducted by a third-party vendor and test articles were provided in a blinded fashion, identified by a code generated by Sanofi. In the non-human primate pharmacokinetic studies, three healthy male animals were used in a crossover study conducted by a third-party vendor. All test articles were provided in a blinded fashion.

About tolebrutinib

Tolebrutinib is an investigational brain-penetrant Bruton's tyrosine kinase inhibitor that achieves CSF concentrations needed for targeting B lymphocytes and microglial cells. Tolebrutinib is being evaluated in Phase 3 clinical trials for the treatment of relapsing forms of MS (RMS), non-relapsing secondary progressive MS (nrSPMS), and primary progressive MS (PPMS), and its safety and efficacy have not been evaluated by any regulatory authority worldwide. For more information on tolebrutinib clinical trials, 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 some 100 countries, 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

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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, 2020. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.