

Sanofi brain-penetrant BTK inhibitor significantly reduced disease activity in Phase 2 trial in relapsing multiple sclerosis

- Primary and secondary objectives were met with 85% or greater relative reduction achieved in the number of new gadolinium-enhancing T1 and new or enlarging T2 hyperintense lesions
- No new safety signals identified
- Sanofi's BTK inhibitor will potentially be first disease-modifying therapy to address sources of multiple sclerosis (MS) damage in the brain
- Sanofi to initiate four Phase 3 clinical trials in relapsing and progressive forms of MS

PARIS – April 23, 2020 – Sanofi's investigational BTK (Bruton's tyrosine kinase) inhibitor, an oral, brain-penetrant, selective small molecule achieved both the primary and secondary endpoints in a Phase 2b trial evaluating efficacy and safety in participants with relapsing forms of multiple sclerosis. The BTK inhibitor (SAR442168) significantly reduced disease activity associated with multiple sclerosis (MS) as measured by magnetic resonance imaging (MRI).

The Phase 2 study was designed to assess the dose-response relationship after 12 weeks of treatment with SAR442168, by measuring the number of new brain lesions on MRI. The study evaluated four doses ranging from 5mg – 60mg after 12 weeks and used placebo data obtained at four weeks. In the primary objective measuring the number of new Gd-enhancing T1 hyperintense lesions, a multiple comparison procedure with modeling was applied to the dose-response data, revealing the exponential model provided the best fit ($p=0.03$). The treatment effect of SAR442168 at the 60mg dose was 85% relative reduction of new Gd-enhancing T1 hyperintense lesions. For the secondary objective measuring the number of new or enlarging T2 hyperintense lesions, the linear model was the best fit ($p<0.0001$), and compared to placebo, treatment with SAR442168 60mg resulted in an 89% relative reduction.

The BTK inhibitor modulates both adaptive (B-cell activation) and innate (CNS microglial cells) immune cells thought to be linked to neuroinflammation and neurodegeneration in the brain and spinal cord, the clinical significance of which is under investigation.

“The results of this study give hope that SAR442168 may become an important treatment for relapsing MS,” said Daniel Reich, MD, PhD, Senior Investigator at the National Institutes of Health, Chief of the Translational Neuroradiology Section in the National Institute of Neurological Disorders and Stroke, and the academic principal investigator of the Phase 2b study. *“In the context of compelling, emerging data about the role of the brain's innate immune system in smoldering MS lesions,*

there is also good reason to believe that SAR442168 — due to its molecular mechanism of action and ability to cross the blood-brain barrier — may have additional effects that we need to study more deeply. In my view, it's important to move forward with broad and innovative testing of this BTK inhibitor in phase 3 studies in MS.”

In the US and Europe, approximately 1.2 million people have been diagnosed with MS, an unpredictable, chronic disease that attacks the central nervous system. Despite current treatments, many MS patients continue to accumulate disability, and one in four MS patients suffers from progressive forms of the disease with limited or no treatments available.

“We believe that our brain-penetrant BTK inhibitor shows promise for reducing both neuroinflammation and neurodegeneration, markers of disability progression in people living with MS,” said John Reed, MD, PhD, Sanofi’s Global Head of Research & Development. *“The effect on brain lesions seen in our Phase 2b study is encouraging. As we go forward, we will explore whether our brain-penetrant BTK inhibitor offers strong efficacy and exceptional safety for a broad spectrum of MS patients with either relapsing or progressive forms of disease. Our phase 3 program is moving rapidly to initiate four pivotal clinical trials.”*

In the Phase 2b trial, no new safety signals were identified, with only a single serious adverse event (MS relapse) reported, in a patient treated with SAR442168, over 12 weeks. The most frequent adverse events (AEs) were headache (3 to 13%), upper respiratory tract infection (3 to 6%) and nasopharyngitis (3 to 9%).

The BTK inhibitor SAR442168 is currently under clinical development, and its safety and efficacy have not been confirmed by any regulatory authority.

About the Phase 2b Trial

The Phase 2b trial was a randomized, double-blind, placebo-controlled, cross-over, 12-week dose-ranging trial evaluating SAR442168 in patients with recurring MS.

In one group, patients (n=64) received one of four doses of SAR442168 for the first 12 weeks, then crossed over to placebo for four weeks. The other group of patients (n=66) received 4 weeks of placebo before crossing over to SAR442168, providing data that were used to estimate a dose-response curve while minimizing exposure to placebo.

In the study, SAR442168 demonstrated a dose-response relationship in reducing the number of new gadolinium-enhancing T1-hyperintense brain lesions after 12 weeks of treatment.

The prespecified model that provided the best-fit to the dose-response relationship will be used for selection of the Phase 3 dose. 123 of 129 participants who completed the trial have enrolled into a long-term safety follow-up study to assess safety and tolerability of SAR442168.

About SAR442168

SAR442168 is an investigational, oral, brain-penetrant, selective small-molecule inhibitor of BTK. SAR442168 has shown BTK binding as well as cerebrospinal fluid exposure in Phase 1 studies. Sanofi obtained global rights to develop and commercialize SAR442168 under a license agreement with Principia Biopharma, Inc.

For more information on SAR442168 clinical trials, please visit www.clinicaltrials.gov.

About Sanofi

Sanofi is dedicated to supporting people through their health challenges. We are a global biopharmaceutical company focused on human health. We prevent illness with vaccines, provide innovative treatments to fight pain and ease suffering. We stand by the few who suffer from rare diseases and the millions with long-term chronic conditions.

With more than 100,000 people in 100 countries, Sanofi is transforming scientific innovation into healthcare solutions around the globe.

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Sanofi Forward-Looking Statements

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