Positive topline results demonstrated by olipudase alfa, first and only investigational therapy in late-stage development for acid sphingomyelinase deficiency

Paris--(BUSINESS WIRE)--Olipudase alfa, an investigational recombinant human acid sphingomyelinase, demonstrated positive results in two separate clinical trials evaluating olipudase alfa for the treatment of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients. Olipudase alfa is the first and only investigational enzyme replacement therapy in late-stage development for the treatment of ASMD. No treatments are currently approved for ASMD.

“These significant results for olipudase alfa mark a major scientific advancement for ASMD and an important step toward providing a potential therapy for adult and pediatric patients who currently have no approved treatment options for this devastating disease,” said John Reed, M.D., Ph.D., Global Head of Research and Development at Sanofi. “We look forward to engaging with regulatory authorities to bring this potential new treatment to patients.”

Trial in Adult Patients with ASMD (ASCEND)

The randomized Phase 2/3 trial enrolled 36 adult patients with ASMD across 24 centers in 16 countries. Patients received either placebo or olipudase alfa intravenous infusion every two weeks at a dose of up to 3mg/kg administered every two weeks over 52 weeks.

The trial contained two independent primary efficacy endpoints to address separate critical manifestations of ASMD, progressive lung disease and enlarged spleen, which are prominent clinical features in patients with ASMD. The study protocol defines the trial outcome as positive if one of the independent primary endpoints was met.

The first independent primary endpoint measuring improvement in lung function, using the percent predicted diffusing capacity of carbon monoxide (DLco), was met; therefore, ASCEND is declared positive. The relative improvement from baseline to week 52 was 22% for the olipudase alfa arm compared with 3% for the placebo arm. The difference between the two treatment arms (19%) was statistically significant (p=0.0004).

The other independent primary endpoint measuring the effect of olipudase alfa on spleen size, assessed as percent change from baseline in multiples of normal (MN) of spleen volume, was met per the study protocol. In the olipudase alfa arm, spleen volume was reduced by 39.5%, compared with a 0.5% increase in the placebo arm. The difference between the two treatment arms (40%) was statistically significant (p<0.0001).

For the U.S., the spleen volume endpoint was further combined with a patient-reported outcome (PRO) measurement of symptoms associated with enlarged spleen called Splenomegaly Related Score (SRS). Compared to baseline, the SRS was reduced by 8.0 points in the olipudase alfa arm and 9.3 points in the placebo arm (p=0.70); therefore, this combination endpoint was not met.
“These are important data in a disease with no approved treatments available currently,” said Melissa Wasserstein, MD, Chief, Division of Pediatric Genetic Medicine, Children's Hospital at Montefiore; Professor of Pediatrics and Genetics, Albert Einstein College of Medicine; and an investigator in the ASCEND trial. “Treatment with olipudase alfa showed clinically meaningful improvement in pulmonary function and reduction in spleen size, critical manifestations of this progressive disease. Both of these findings are consistent across the clinical studies with olipudase alfa. The absence of an effect on SRS in this trial requires exploration, in light of the significant reduction in spleen size.”

Over the 52-week period, all patients in both the placebo and olipudase alfa arms experienced at least one adverse event. The number of events was lower in the olipudase alfa arm (242 events) compared with the placebo arm (267 events). Severe adverse events were less frequent in the olipudase alfa arm (3 events) compared with the placebo arm (13 events). There were five serious adverse events in the olipudase alfa arm and 11 in the placebo arm, none of which were treatment related. There were no adverse events that led to treatment discontinuation or study withdrawal. The most common adverse events (as defined by percentages of events greater than or equal to 2% and number of patients greater than or equal to two in all olipudase alfa treated patients; occurring with higher percentages in olipudase alfa patients compared to placebo patients) seen in this trial were headache, nasopharyngitis, upper respiratory tract infection, cough, and arthralgia.

**Trial in Pediatric Patients with ASMD (ASCEND-Peds)**

The single arm, open label Phase 2 trial enrolled 20 pediatric patients (birth to <18 years) with ASMD in six countries. Children with rapidly progressive neurological disease were excluded. The primary objective of the trial was to evaluate the safety and tolerability of olipudase alfa at a dose of up to 3mg/kg administered intravenously every two weeks for 64 weeks.ii

Over the 64-week treatment period, all patients experienced at least one adverse event. These events were mostly mild and moderate, with one patient experiencing a severe and serious (see below) anaphylactic reaction that was considered related to olipudase alfa. Five treatment-related serious adverse events were observed in three patients: two cases of transient, asymptomatic alanine aminotransferase (ALT) increase in one patient, one case each of urticaria and rash in one patient, and one anaphylactic reaction in one patient. No patients had to permanently discontinue treatment due to an adverse event. The most common adverse events (as defined by percentages of events greater than or equal to 2% and number of patients greater than or equal to two in all olipudase alfa treated patients) seen in this trial were pyrexia, cough, vomiting, nasopharyngitis, diarrhea, headache, upper respiratory tract infection, contusion, abdominal pain, nasal congestion, rash, urticaria, scratch, and epistaxis.

The study also explored secondary endpoints of progressive lung disease and enlarged spleen. After one year of treatment (52 weeks), the percent predicted DLco increased by a mean of 33% in nine patients who were able to perform the test at baseline (children over the age of five were assessed if they were able to perform the test). Additionally, at 52 weeks, the spleen volumes decreased by 49% as assessed by mean MN (individual patient decreases ranged from 23% to 61%).

Results from these trials will be submitted to future medical meetings and will form the basis of global regulatory submissions expected to begin the second half of 2021.

**About ASMD**

Traditionally referred to as Niemann-Pick Disease (NPD) Type A and Type B, ASMD is a rare, progressive and potentially life-threatening lysosomal storage disorder that results from a deficient activity of the enzyme acid sphingomyelinase (ASM), which is found in special compartments within cells called
lysosomes and is required to breakdown lipids called sphingomyelin. If ASM is absent or not functioning as it should, sphingomyelin cannot be metabolized properly and accumulates within cells, eventually causing cell death and the malfunction of major organ systems. The deficiency of the lysosomal enzyme ASM is due to mutations in the sphingomyelin phosphodiesterase 1 gene (SMPD1). The estimated prevalence of ASMD is approximately 2,000 patients in the U.S., Europe and Japan.

ASMD represents a spectrum of disease caused by the same enzymatic deficiency, with two types that may represent opposite ends of a continuum sometimes referred to as NPD Type A and Type B. NPD Type A is a rapidly progressive neurological form of the disease resulting in death in early childhood due to central nervous system complications. NPD Type B is a serious and potentially life-threatening disease that predominantly, but not only, impacts the lungs, liver, spleen and heart. NPD Type A/B represents an intermediate form that includes varying degrees of neurologic involvement. Another type of NPD is NPD Type C, which is unrelated to ASMD.

**About Oliupudase alfa**

Oliupudase alfa is an investigational enzyme replacement therapy designed to replace deficient or defective ASM, allowing for the breakdown of sphingomyelin. Oliupudase alfa is currently being investigated to treat ASMD Type A/B and B. Oliupudase alfa has not been studied in NPD Type A patients. Oliupudase alfa is an investigational agent and the safety and efficacy have not been evaluated by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), or any other regulatory authority.

The FDA has granted *Breakthrough Therapy* designation to oliupudase alfa. This designation is intended to expedite the development and review of drugs intended to treat serious or life-threatening diseases and conditions. The criteria for granting *Breakthrough Therapy* designation include preliminary clinical evidence indicating that the molecule may demonstrate substantial improvement over available therapies on a clinically significant endpoint.

The EMA has awarded PRIority MEdicines, also known as PRIME, designation to oliupudase alfa. This designation is designed to aid and expedite the regulatory process for investigational medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options.

Oliupudase alfa was awarded the SAKIGAKE designation in Japan. SAKIGAKE is intended to promote research and development in Japan for innovative new medical products that satisfy certain criteria, such as the severity of the intended indication.

**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.

Sanofi, Empowering Life

*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 absence of guarantee that the product candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, Sanofi's ability to benefit from external growth opportunities 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 conditions, the impact of cost containment initiatives and subsequent changes thereto, the average number of shares outstanding as well as those 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, 2018. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

i www.clinicaltrials.gov; ClinicalTrials.gov Identifier: NCT02004691

ii www.clinicaltrials.gov; ClinicalTrials.gov Identifier: NCT02292654