

# *Olipudase alfa shown to provide sustained improvement across multiple clinical manifestations of ASMD*

- \* Investigational data from long-term, follow-up studies showed that olipudase alfa provided sustained improvement in lung function (as measured by DLco) and reduction of spleen and liver volumes over time in patients with ASMD
- \* If approved, olipudase alfa will become the first-and-only therapy for the treatment of ASMD

**Paris, February 9, 2022.** Positive results from long-term, open-label extension studies demonstrated that olipudase alfa provided sustained improvement in lung function (as measured by diffusing capacity of the lung for carbon monoxide, or DLco) and reduction of spleen and liver volumes in adult and pediatric patients with non-central nervous system (non-CNS) manifestations of acid sphingomyelinase deficiency (ASMD), a rare, progressive, and potentially life-threatening disease with no approved treatments. The data consist of 6.5-year outcomes for five adult patients with ASMD and 2-year outcomes in 20 pediatric patients, as well as the open-label extension from the Phase 3 ASCEND trial in adults. These data were presented at the 18th annual *WORLDSymposium*<sup>™</sup> held this week in San Diego, California.

### ***Alaa Hamed, MD, MPH, MBA***

Global Head of Medical Affairs, Rare Diseases, Sanofi

*“ASMD can lead to progressive damage across multiple organ systems, and the risk of premature death often increases as symptoms become worse. Currently, patients living with this extremely rare disease have no treatment options. These collective findings demonstrate the promise of olipudase alfa to positively impact the progressive nature of ASMD, providing improvement that was observed early and did not diminish over an extended follow-up period up to 6.5 years.”*

## *Long-term Data in Adult and Pediatric Patients with ASMD*

A single-arm, open-label, long-term trial (NCT02004704) enrolled five adult patients and 20 pediatric patients, all with ASMD, from two different parent clinical trials (NCT01722526 and NCT02292654, respectively). The primary objective of this long-term study was to assess the safety of olipudase alfa in patients exposed to long-term treatment with the investigational enzyme replacement therapy.

### **Data from Five Adult Patients over 6.5 Years**

Five adult patients with non-CNS manifestations of ASMD, aged 22 to 47 years, received olipudase alfa in an open-label Phase 1b trial. After six months, all five patients transitioned to the long-term study, in which they received olipudase alfa for a total of 6.5 years. Efficacy and safety outcomes from these five adults were reported.

Improvements were demonstrated in all patients; at 6.5 years of follow-up (all values are reported from the baseline of the original study):

- The percent predicted DLco mean increase was 55.3%
- Spleen volume mean decrease was 59.5%
- Liver volume mean decrease was 43.7%

Nearly all adverse events (99%) were mild, with no serious treatment-related adverse events, and all five patients currently remain in the long-term study. Four of the five patients had protocol-defined infusion-associated reactions; 78% of these occurred during the first year of treatment. The most common treatment-related adverse events were: abdominal pain, arthralgia, and nausea (all were considered related in four patients), and headache (which was considered related in three patients).

### **Data from 20 Pediatric Patients over 2 Years**

20 pediatric patients with ASMD, aged 1 to 17 years, were enrolled in a single-arm, open-label, Phase 2 trial in seven countries (ASCEND-Peds). 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-escalation regimen up to 3 mg/kg administered intravenously every two weeks for 64 weeks. Following the open-label ASCEND-Peds trial, all patients continued treatment in the long-term safety study of olipudase alfa.

This study showed that olipudase alfa was generally well tolerated over the two years, with the majority of adverse events (99%) during Weeks 65 to 104 being mild and moderate. Seven serious adverse events were observed in four patients (three in Year 1 and one in Year 2): one patient had an anaphylactic reaction but restarted treatment after tailored desensitization and reached the target dose; one patient had two events of transient alanine aminotransferase elevation; one patient had urticaria and rash; and one patient had two hypersensitivity reactions.

The study also explored efficacy endpoints of progressive lung disease and of spleen and liver enlargement. Among the nine patients able to perform baseline pulmonary function tests (primarily age-dependent), the percent predicted DLco showed a mean increase of 46.6% from baseline (of the original study) to Year 2. During the second year, spleen and liver volumes showed a mean decrease of 60.9% and 49% from baseline (of the original study), respectively, at Month 24 for both.

### ***Data in Adult Patients with ASMD (ASCEND Extension Period)***

In the double-blind ASCEND clinical trial (NCT02004691), 36 patients were randomized to receive either olipudase alfa or placebo. In the primary analysis period (52 weeks), the first independent primary endpoint, DLco, was met; therefore, ASCEND was declared positive. The other independent primary endpoint measuring the effect of olipudase alfa on spleen volume was met per the study protocol. 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 improved to a similar extent in both the olipudase alfa and placebo arms; therefore, this combination endpoint was not met. Findings from the primary analysis were previously presented at the [American Society of Human Genetics \(ASHG\) 2020 Virtual Meeting](#).

Following the one-year primary analysis, 33 adult ASMD patients completed a second year in the open-label, single-arm extension evaluating the long-term efficacy and safety of olipudase alfa. Patients randomized to olipudase alfa at study entry (n=18) and continuing to receive olipudase alfa maintained the benefits throughout Year 2 (all values reported from baseline):

- The percent predicted DLco mean increase was 28.5%, n=10 (Year 1 increase: 22.2%, n=17)
- Spleen volume mean decrease was 47%, n=14 (Year 1 decrease: 39.5%, n=17)
- Liver volume mean decrease was 33.4%, n=14 (Year 1 decrease: 27.8%, n=17)

#### ***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

*“These latest clinical findings show olipudase alfa continued to provide improvements in key markers of disease progression, over an extended period of time.”*

Patients previously treated with placebo (n=18) crossed over to olipudase alfa, with gradual dose escalation to 3 mg/kg. These patients achieved improvements in Year 2 similar to those observed in the olipudase alfa group from the primary analysis period (all values reported from baseline):

- The percent predicted DLco mean increase was 28%, n=10
- Spleen volume mean decrease was 36%, n=11
- Liver volume mean decrease was 30.7%, n=11

Overall, nearly all treatment-related adverse events (99%) were mild or moderate, with one serious treatment-related adverse event. The most frequently reported adverse events were headache and transient transaminase elevations (i.e., increased levels of liver enzymes). No patient discontinued treatment due to adverse events.

Across all of the open-label, extension studies, olipudase alfa was administered via a dose-escalation regimen up to 3 mg/kg (target maintenance dose), every two weeks via intravenous infusion.

### *About ASMD*

Historically referred to as Niemann-Pick disease (NPD) type A and type B, ASMD is a rare, progressive, and potentially life-threatening disease for which no treatments are currently approved. ASMD 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 disease-causing variants in the sphingomyelin phosphodiesterase 1 gene (SMPD1). The estimated prevalence of ASMD is approximately 2,000 patients in the United States, Europe (EU5 countries), 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 ASMD type A and ASMD type B. ASMD type A is a rapidly progressive neurological form of the disease resulting in death in early childhood. ASMD type B is a serious and potentially life-threatening disease that predominantly, but not only, impacts the lungs, liver, and spleen, as well as other organs. ASMD 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 olipudase alfa*

Olipudase alfa is an investigational enzyme replacement therapy designed to replace deficient or defective ASM, allowing for the breakdown of sphingomyelin. Olipudase alfa is currently being investigated in pediatric and adult patients to treat non-CNS manifestations of ASMD. Olipudase alfa has not been studied in ASMD type A patients.

The U.S. Food and Drug Administration (FDA) has granted to olipudase alfa the Breakthrough Therapy designation, which is intended to expedite the development and review of drugs intended to treat serious or life-threatening diseases and conditions. A Biologics License Application (BLA) for olipudase alfa was submitted to the FDA, and the FDA designated the BLA for Priority Review.

The European Medicines Agency (EMA) awarded olipudase alfa the PRIority MEdicines (PRIME) designation, intended to aid and expedite the regulatory process for investigational medicines that may offer a major therapeutic advantage over existing treatments or that may benefit patients without treatment options. The EMA accepted for review under an accelerated assessment procedure the Marketing Authorization Application (MAA) for olipudase alfa.

In Japan, olipudase alfa was awarded the SAKIGAKE designation, which 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. Sanofi filed the J-NDA submission for olipudase alfa.

Olipudase alfa has not been approved by any regulatory authority, and its safety and efficacy are currently being evaluated.

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### *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.

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### **Sanofi Forward-Looking Statements**

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