Sanofi Genzyme highlights rare disease data at WORLDSymposium 2018

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• Results from 31 presentations provide new insights on multiple lysosomal storage disorders and related diseases

New investigational data on Sanofi Genzyme’s marketed treatments for a number of lysosomal storage disorders, Sanofi’s rare disease development pipeline and studies advancing knowledge in certain rare diseases will be presented at the 14th Annual WORLDSymposium. These data include findings related to acid sphingomyelinase deficiency (ASMD), Fabry disease, Gaucher disease, mucopolysaccharidosis type I (MPS I), Parkinson’s disease with an associated GBA mutation, Pompe disease, Tay-Sachs disease and Sandhoff disease as well as the genetic diagnosis of lysosomal storage disorders (LSDs) across multiple diseases.

“Sanofi Genzyme has been a pioneer in rare diseases and lysosomal storage disorders for more than 35 years. That leadership continues with our support for the wide range of important new findings that will be presented at the WORLDSymposium,” said Sébastien Martel, Global Head of Rare Diseases, Sanofi Genzyme. “Our experience bringing many of the first therapies to treat a number of lysosomal storage disorders to patients has continually demonstrated the critical importance of new research in advancing patient care.”

The WORLDSymposium is taking place February 5-9, 2018 at the Manchester Grand Hyatt in San Diego, California. Following are the 31 Sanofi Genzyme-sponsored and grant-funded, investigator-sponsored studies to be presented. Grant-funded, investigator-sponsored studies are noted with an asterisk (*). All others are Sanofi Genzyme-sponsored presentations.

ASMD (also known as Niemann-Pick disease types A and B)
• Disease severity scoring system for acid sphingomyelinase deficiency: severity score domains and components (P42; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
• Integrated quantitative systems pharmacology (QSP) model of lysosomal diseases provides an innovative computational platform to support research and therapeutic development for the sphingolipidoses (P174; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)

Cross-LSD
• Fast genetic diagnosis of lysosomal disorders by means of a novel NGS-based resequencing gene panel* (P70; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
• Factors influencing patient preferences for oral versus intravenous (IV) enzyme replacement medication* (Poster; P176; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)

Fabry Disease
• A survivor analysis for major clinical events in heterozygous female patients with Fabry disease using group consensus phenotype classifications from hemizygous male patients (P151; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
• Proposal of a rating scale to recognize Fabry disease in patients with nonspecific gastrointestinal symptoms (P146; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
• Do we understand the pathophysiology of gastrointestinal symptoms in patients with Fabry disease? (P145; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
• Therapeutic goals in Fabry disease: European expert consensus recommendations based on current clinical evidence (P393; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
• Fabry disease symptoms and impacts on daily life -- a conceptual model (P128; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
• Integrated approaches for Fabry disease biomarker discovery and qualification (P283; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
• Kidney information network for disease research and education (KINDRED) abstract: screening for Fabry disease among United States hemodialysis patients* (P371; Poster Session I; February 7; 4:30 – 6:30 p.m. PT)

KINDRED abstract: screening for Fabry disease among United States hemodialysis patients* (P371; Poster Session I; February 7; 4:30 – 6:30 p.m. PT)
Gaucher Disease

- Long-term stability in randomized and non-randomized patients in the phase 3 randomized, double-blind EDGE trial of once- versus twice-daily dosing of eliglustat in patients with Gaucher disease type 1 (Clinical Trials II; Platform Presentation; February 8; 3:45 p.m. PT)
- Long-term treatment response based on severity of Gaucher disease type 1 at baseline after 8 years of treatment with oral eliglustat: final efficacy and safety results from a phase 2 clinical trial in treatment-naive adult patients (Clinical Trials II; Platform Presentation; February 8; 4:00 p.m. PT)
- Long-term adverse event profile from four completed trials of oral eliglustat in adults with Gaucher disease type 1 (P303; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
- Impact of hepatic and renal impairment on the pharmacokinetics and tolerability of eliglustat (P209; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
- Disease epidemiology and prevalence of neurological manifestations in neuronopathic Gaucher disease: comprehensive review of the literature (P265; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
- Blood and brain biomarkers of oxidative stress and inflammation in type 1 Gaucher disease: effect of antioxidant therapy* (P177; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
- Effect of two different therapeutic interventions: SRT in comparison to ERT on immune aspects and bone involvement in Gaucher disease* (P214; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)

Parkinson’s Disease with an associated GBA mutation

- Evaluation of glucosylceramide synthase (GCS) inhibition for GBA-associated Parkinson’s disease (Clinical Trials II; Platform Presentation; February 8; 4:15 p.m. PT)

MPS I

- Open-label, single arm, pilot study of intravenous laronidase following allogeneic transplantation for Hurler syndrome* (Clinical Trials I; Platform Presentation; February 8; 8:45 a.m. PT)
- North American experience with laronidase enzyme replacement therapy for mucopolysaccharidosis type I in a home infusion setting (P113; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
- Natural history of cardiac findings in mucopolysaccharidosis type I: report from an international registry (P32; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
- Neurocognitive outcomes of intrathecal enzyme replacement therapy and transplant in Hurler syndrome* (P80; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
- Post-transplant iduronidase attenuates skeletal disease in MPS IH* (P226; Poster Session I; February 6; 4:30 – 6:30 p.m. PT)
- Defining clinical measures of skeletal disease severity in MPS I* (P310; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
- Awareness of MPS I among cardiologists (P258; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)

Pompe Disease

- NEO1 and NEO-EXT: long-term safety of repeat neoGAA (avalglucosidase alfa) dosing in late-onset Pompe disease patients for 3.5 years (LB-45; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
- Comprehensive exploratory study to identify novel biomarkers of Pompe disease (Translational Research II; Platform Presentation; February 7; 4:00 p.m. PT)
- Long-term study of growth and development outcomes in patients with infantile-onset Pompe disease receiving alglucosidase alfa: safety data update (P364; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)
- Transcriptome analysis in muscle biopsies of late-onset Pompe patients treated with alglucosidase alfa or neoGAA (P416; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)

Avalglucosidase alfa is an investigational agent and has not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency worldwide for the use under investigation.

Tay-Sachs and Sandhoff Disease

- Functional performance in late-onset GM2 gangliosidosis (Tay-Sachs and Sandhoff diseases), longitudinal data over 3 consecutive years (P321; Poster Session II; February 7; 4:30 – 6:30 p.m. PT)

About Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are a group of more than 40 diseases. Each is caused by a genetic mutation that results in the deficiency or malfunction of a particular enzyme needed to remove unnecessary material from cells. These waste molecules then accumulate, or build up, in cell lysosomes (smaller compartments within cells), disrupting cell function and causing a variety of symptoms. LSDs can be progressive, life-threatening and severely debilitating. Because these disorders are extremely rare, it can be difficult to find information about them. In the case of the most common of these disorders, Gaucher disease, it is estimated that only 10,000 people have been diagnosed worldwide. It is thought that many more people are affected by rare diseases than have been diagnosed. This is why access to information about LSDs is so important.

About CERDELGA ® (eliglustat)

CERDELGA ( eliglustat ) capsules are indicated for the long-term treatment of adults with Gaucher disease type 1 (GD1) who
are CYP2D extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect. A specific dose cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers)

**Important Safety Information for CERDELGA® (eliglustat)**

CERDELGA is contraindicated in the following patients due to the risk of significantly increased eliglustat plasma concentrations, which may result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias: EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor and IMs or PMs taking a strong CYP3A inhibitor.

Drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat; CERDELGA dose adjustment may be needed, depending on metabolizer status. See section 7 of the full Prescribing Information for more details and other potentially significant drug interactions.

Because CERDELGA is predicted to cause increases in ECG intervals at substantially elevated plasma concentrations, use is not recommended in patients with pre-existing cardiac disease, long QT syndrome, or in combination with Class IA and Class III antiarrhythmic medications.

The most common adverse reactions (≥10%) for CERDELGA are: fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain.

Only administer CERDELGA during pregnancy if the potential benefit justifies the potential risk; based on animal data, CERDELGA may cause fetal harm. Discontinue drug or nursing based on importance of drug to mother. CERDELGA is not recommended in patients with moderate to severe renal impairment, end-stage renal disease or in patients with hepatic impairment or cirrhosis.

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Genzyme Corporation at (1-800-745-4447) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including patient Medication Guide, for additional important safety information.

**About ALDURAZYME® (laronidase)**

ALDURAZYME® (laronidase) is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established.

ALDURAZYME has been shown to improve pulmonary function and walking capacity. ALDURAZYME has not been evaluated for effects on the central nervous system manifestations of the disorder.

**Important Safety Information for ALDURAZYME® (laronidase)**

**WARNING: Risk of anaphylaxis.** Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME® infusions. Therefore, appropriate medical support should be readily available when ALDURAZYME is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.

Anaphylaxis and severe allergic reactions have been observed in patients during or up to 3 hours after ALDURAZYME infusions. Some of these reactions were life-threatening and included respiratory failure, respiratory distress, stridor, tachypnea, bronchospasm, obstructive airways disorder, hypoxia, hypotension, bradycardia, and uti.caria. If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of ALDURAZYME and initiate appropriate treatment. Caution should be exercised if epinephrine is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients. Interventions have included resuscitation, mechanical ventilatory support, emergency tracheotomy, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.

In clinical studies and postmarketing safety experience with ALDURAZYME, approximately 1% of patients experienced severe or serious allergic reactions. In patients with MPS I, pre-existing upper airway obstruction may have contributed to the severity of some reactions. Due to the potential for severe allergic reactions, appropriate medical support should be readily available when ALDURAZYME is administered. Because of the potential for recurrent reactions, some patients who experience initial severe reactions may require prolonged observation.

The risks and benefits of re-administering ALDURAZYME following an anaphylactic or severe allergic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

Patients with an acute febrile or respiratory illness at the time of ALDURAZYME infusion may be at greater risk for infusion reactions. Careful consideration should be given to the patient’s clinical status prior to administration of ALDURAZYME and consider delaying ALDURAZYME infusion.

Sleep apnea is common in MPS I patients. Evaluation of airway patency should be considered prior to initiation of treatment with ALDURAZYME. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments readily available during infusion in the event of an infusion reaction or extreme drowsiness/sleep induced by antihistamine use.

Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload or patients with an acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated.
These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusions. Appropriate medical support and monitoring measures should be readily available during ALDURAZYME infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient.

Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusion. If an infusion-related reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

The most serious adverse reactions reported with ALDURAZYME treatment during clinical trials were anaphylactic and allergic reactions.

In a 26-week, placebo-controlled clinical trial in patients 6 years and older, the most commonly reported infusion reactions regardless of treatment group were flushing, pyrexia, headache, and rash. Flushing occurred in 5 patients (23%) receiving ALDURAZYME; the other reactions were less frequent. Less common infusion reactions included angioedema (including face edema), hypotension, paresthesia, feeling hot, hyperhidrosis, tachycardia, vomiting, back pain, and cough. Other reported adverse reactions included bronchospasm, dyspnea, urticaria, and pruritus. In the open-label, uncontrolled extension phase of this clinical trial, the infusion reactions were similar, but also included abdominal pain or discomfort and injection site reaction. Less commonly reported infusion reactions included nausea, diarrhea, feeling hot or cold, vomiting, pruritus, arthralgia and urticaria. Additional common adverse reactions included, back pain and musculoskeletal pain.

In an open-label, uncontrolled clinical trial in patients 6 years and younger who received ALDURAZYME treatment for up to 52 weeks, the most commonly reported serious adverse events (regardless of relationship) in patients 6 years and younger, were otitis media (20%), and central venous catheterization required for ALDURAZYME infusion (15%). The most commonly reported adverse reactions in patients 6 years and younger were infusion reactions reported in 35% (7 of 20) of patients and included pyrexia (30%), chills (20%), blood pressure increased (10%), tachycardia (10%), and oxygen saturation decreased (10%). Other commonly reported infusion reactions occurring in ≥5% of patients were pallor, tremor, respiratory distress, wheezing, crepitations (pulmonary), pruritus, and rash.

In postmarketing experience with ALDURAZYME, severe and serious infusion reactions have been reported, some of which were life-threatening, including anaphylactic shock. Adverse reactions resulting in death reported in the postmarketing setting with ALDURAZYME treatment included cardio-respiratory arrest, respiratory failure, cardiac failure, and pneumonia. These events have been reported in MPS I patients with significant underlying disease. Additional common adverse reactions included erythema and cyanosis. There have been a small number of reports of extravasation in patients treated with ALDURAZYME. There have been no reports of tissue necrosis associated with extravasation. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In clinical trials, 99 of 102 patients (97%) treated with ALDURAZYME were positive for IgG antibodies to ALDURAZYME. In the 2 trials of patients 6 years and older, 9 patients who experienced severe infusion reactions were tested for ALDURAZYME-specific IgE antibodies and complement activation. One of the nine patients had an anaphylactic reaction consisting of urticaria and airway obstruction and tested positive for both ALDURAZYME-specific IgE binding antibodies and complement activation. In the postmarketing setting, approximately 1% of patients experienced severe or serious infusion-allergic reactions and tested positive for IgE. Of these IgE-positive patients, some have discontinued treatment, but some have been successfully re-challenged. The clinical significance of antibodies to ALDURAZYME, including the potential for product neutralization, is not known.

Please click here for full U.S. Prescribing Information for Aldurazyme including Boxed WARNING.

About LUMIZYME ® (alglucosidase alfa)

**INDICATION**

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency).

**IMPORTANT SAFETY INFORMATION**

**WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, and RISK OF CARDIORESPIRATORY FAILURE**

- Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, peri orbital edema, and face edema), and urticaria, have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated-reactions and have them seek immediate medical care should signs and symptoms occur. Infantsile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring.

**WARNINGS AND PRECAUTIONS**

Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. If anaphylaxis or severe hypersensitivity
reactions occur, immediately discontinue infusion and institute appropriate medical treatment. Appropriate medical support and monitoring measures should be available during infusion.

**Immune-Mediated Reactions:** Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs.

**Risk of Acute Cardiorespiratory Failure:** Patients with acute underlying respiratory illness and compromised cardiac and/or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion and some patients may require longer observation times.

**Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement:** Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.

**Risk of Antibody Development:** As with all therapeutic proteins, there is potential for immunogenicity. There is some evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy. Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter.

**ADVERSE REACTIONS**

The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

**USE IN SPECIFIC POPULATIONS**

Pregnancy: Based on animal data, alglucosidase alfa may cause fetal harm.

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see the [Full Prescribing Information](https://news.genzyme.com/press-release/sanofi-genzyme-highlights-rare-disease-data-worldsymposium-2018) for complete details, including boxed WARNING.

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 Genzyme focuses on developing specialty treatments for debilitating diseases that are often difficult to diagnose and treat, providing hope to patients and their families. Learn more at [www.sanogenzyme.com](http://www.sanogenzyme.com).

Sanofi, Empowering Life

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