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Regeneron and Sanofi Announce Positive Phase 2 Study Results for Dupilumab in Patients With Active Moderate-to-Severe Eosinophilic Esophagitis

Late-breaking oral abstract presented at the the World Congress of Gastroenterology

TARRYTOWN, N.Y. and PARIS, Oct. 16, 2017 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Sanofi today announced positive results from a Phase 2 investigational study of dupilumab in adults with active moderate-to-severe eosinophilic esophagitis. The study showed that patients who received dupilumab weekly reported a significant improvement in the ability to swallow versus placebo. The results of this study [were presented](#) at the World Congress of Gastroenterology (WCOG) held in partnership with The American College of Gastroenterology Annual Scientific Meeting (ACG 2017) in Orlando, Florida.

Eosinophilic esophagitis is a chronic, allergic inflammatory disease that damages the esophagus and prevents it from working properly, leading to difficulties swallowing and food impaction.^[1] Food allergies are the main cause of eosinophilic esophagitis in a large number of patients. Corresponding with the increase in incidence of allergic diseases in the overall population, eosinophilic esophagitis is rapidly increasing in incidence.^[2]

The primary endpoint of the study was the change from baseline to week 10 in the Straumann Dysphagia Instrument (SDI) score, a patient-reported measure of swallowing difficulty on a 0-9 point scale, with 9 indicating more severe symptoms. A total of 47 patients were randomized into two treatment groups in this 12-week treatment study, and both groups had a mean baseline SDI score of 6.4. Patients received either dupilumab 300 mg weekly following a 600 mg loading dose or placebo. At week 10, patients who received dupilumab 300 mg weekly reported a significant improvement in the ability to swallow with a three point reduction in their SDI score (45 percent improvement) compared to 1.3 points (19 percent improvement) for those patients who received placebo (p=0.0304).

Secondary endpoints of the study included measures of the impact of dupilumab on endoscopic and histopathologic measures of disease severity, as well as symptoms. The results include:

- 1 The mean change in the Eosinophilic Esophagitis Endoscopic Reference Score (EoE-EREFS) was significantly reduced by 1.9 points from baseline (48 percent improvement) in patients who received dupilumab weekly compared to 0.3 points (7 percent improvement) for those who received placebo at 12 weeks (p=0.0006). EoE-EREFS is a visual measure of disease severity (inflammation and fibrosis in the esophagus) on a 0-8 point scale, with 8 indicating more severe disease. The mean baseline score for the dupilumab group was 3.9 and for the placebo group was 4.3.
- 1 The mean percent change in overall peak intraepithelial eosinophil count from baseline to 12 weeks was significantly reduced by 93 percent from baseline in patients who received dupilumab weekly compared to an increase of 14 percent in those who received placebo (p < 0.0001).
- 1 The mean percent change in a composite measure of symptoms and quality of life, as measured by Eosinophilic Esophagitis Symptom Activity Index (EEsAI), was numerically improved (although not statistically significant) by 35 percent in patients who received dupilumab weekly compared to an 11 percent improvement for those who received placebo at 10 weeks (p=0.085).

"Clinical manifestations of eosinophilic esophagitis in adults include difficulty swallowing and food impaction, which are consequences of pathological structural changes to the esophagus. Natural history studies have demonstrated an association between duration of untreated disease and the development of these esophageal changes," said Ikuo Hirano, M.D., Professor of Medicine, Northwestern University Feinberg School of Medicine. "Currently, there are no FDA-approved therapies for eosinophilic esophagitis. In this study, dupilumab, a monoclonal antibody targeting IL-4 and IL-13, significantly improved patients' ability to swallow, inflammation of the esophagus, and endoscopic signs of the disease. These positive Phase 2 results support further clinical development of dupilumab for patients with eosinophilic esophagitis."

There were no new significant safety concerns in this trial. Higher rates of injection site reactions were observed on dupilumab versus placebo.

Clinical and preclinical research indicates that the IL-4/IL-13 pathway may have an important role in allergic or Type 2 inflammation. Dupilumab, an antibody that inhibits IL-4/13 signaling, has been approved for moderate-to-severe atopic dermatitis in adults and has demonstrated clinical activity in other investigational areas under study (asthma and nasal polyps).

Eosinophilic esophagitis is a chronic disease characterized by high levels of eosinophils in the esophagus. The results of investigational IL-5 blocking studies in eosinophilic esophagitis suggest that eosinophils may act as a biomarker of broader allergic or Type 2 inflammation in the esophagus, but that eosinophils may not be solely responsible for disease activity. In the study presented today, the observed symptomatic and anatomic improvements associated with dupilumab, together with this reduction of eosinophils, suggest that dupilumab may have the potential to reverse multiple aspects of Type 2 inflammation in eosinophilic esophagitis.

Current treatment options for people with moderate-to-severe eosinophilic esophagitis are limited to diet modification, corticosteroids or surgery. The disease can affect patients' health-related quality of life, including altered eating behaviors and pain when swallowing. People with active, moderate-to-severe eosinophilic esophagitis live with the risk of complete blockage or injury to their esophagus because of food impaction, and emergency care is often required for severe obstructions.

Dupilumab recently received Orphan Drug Designation from the FDA for the potential treatment of eosinophilic esophagitis. This status is given to investigational medicines being developed for the treatment of rare diseases or conditions that affect fewer than 200,000 people in the United States.

The potential use of dupilumab in eosinophilic esophagitis is currently under clinical development and the safety and efficacy have not been fully evaluated by any regulatory authority.

About Dupilumab

Dupixent[®] (dupilumab) is the first and only biologic medicine FDA-approved for the treatment of adults with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies. Dupixent is also the first targeted biologic in the European Union to receive marketing authorization for use in adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

Dupilumab is a human monoclonal antibody that is designed to simultaneously inhibit overactive signaling of IL-4 and IL-13 cytokines, one of the root causes of Type 2 inflammation. Sanofi and Regeneron are studying dupilumab in a broad range of clinical development programs for diseases that are driven by Type 2 inflammation, including pediatric atopic dermatitis (Phase 3), uncontrolled persistent asthma (Phase 3), and nasal polyps (Phase 3). These potential uses are investigational and the safety and efficacy have not been evaluated by any regulatory authority. Dupilumab was discovered using Regeneron's proprietary *VelocImmune*[®] technology that yields optimized fully-human antibodies and is being jointly developed by Regeneron and Sanofi under a global collaboration agreement.

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

IMPORTANT SAFETY INFORMATION

Do not use if you are allergic to dupilumab or to any of the ingredients in DUPIXENT[®].

Before using DUPIXENT, tell your healthcare provider about all your medical conditions, including if you:

- | have eye problems
- | have a parasitic (helminth) infection
- | have asthma
- | are scheduled to receive any vaccinations. You should not receive a "live vaccine" if you are treated with DUPIXENT.
- | are pregnant or plan to become pregnant. It is not known whether DUPIXENT will harm your unborn baby.
- | are breastfeeding or plan to breastfeed. It is not known whether DUPIXENT passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. If you have asthma and are taking asthma medicines, do not change or stop your asthma medicine without talking to your healthcare provider.

DUPIXENT can cause serious side effects, including:

- | **Allergic reactions.** Stop using DUPIXENT and go to the nearest hospital emergency room if you get any of the following symptoms: fever, general ill feeling, swollen lymph nodes, hives, itching, joint pain, or skin rash.
- | **Eye problems.** Tell your healthcare provider if you have any new or worsening eye problems, including eye pain or changes in vision.

The most common side effects include injection site reactions, eye and eyelid inflammation, including redness, swelling and itching, and cold sores in your mouth or on your lips.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of DUPIXENT. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Use DUPIXENT exactly as prescribed. If your healthcare provider decides that you or a caregiver can give DUPIXENT injections, you or your caregiver should receive training on the right way to prepare and inject DUPIXENT. **Do not** try to inject DUPIXENT until you have been shown the right way by your healthcare provider.

Please click [here](#) for the full Prescribing Information. The patient information is available [here](#).

INDICATION

DUPIXENT is used to treat adult patients with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. DUPIXENT can be used with or without topical corticosteroids. It is not known if DUPIXENT is safe and effective in children. DUPIXENT is administered by subcutaneous injection every two weeks after an initial loading dose.

About Sanofi

Sanofi, a global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. Sanofi is organized into five global business units: Diabetes and Cardiovascular, General Medicines and Emerging Markets, Sanofi Genzyme, Sanofi Pasteur and Consumer Healthcare. Sanofi is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

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.

About Regeneron Pharmaceuticals, Inc.

Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for nearly 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to six FDA-approved treatments and over a dozen product candidates in development, all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye disease, heart disease, allergic and inflammatory diseases, pain, cancer, and infectious and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through its unique *VelociSuite*[®] technologies, including *VelociGene*[®] and *VelocImmune*[®], and ambitious initiatives such as The Regeneron Genetics Center, one of the largest genetics sequencing efforts in the world.

For additional information about the company, please visit www.regeneron.com or follow @Regeneron on Twitter.

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 regarding the marketing and other potential of the product, or regarding potential future revenues from the product. 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, unexpected regulatory actions or delays, or government regulation generally, that could affect the availability or commercial potential of the product, the absence of guarantee that the product will be commercially successful, the uncertainties inherent in research and development, including future clinical data and analysis of existing clinical data relating to the product, including post marketing, unexpected safety, quality or manufacturing issues, competition in general, risks associated with intellectual property and any related future litigation and the ultimate outcome of such litigation, and volatile economic conditions, as well as those risks 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, 2016. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

Regeneron Forward-Looking Statements and Use of Digital Media

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may

differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation Dupixent[®] (dupilumab) Injection; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products, such as Dupixent for the treatment of active moderate-to-severe eosinophilic esophagitis other potential indications; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators may be replicated in later studies and lead to therapeutic applications; unforeseen safety issues and possible liability resulting from the administration of products and product candidates in patients, including without limitation Dupixent; serious complications or side effects in connection with the use of Regeneron's products and product candidates (such as Dupixent) in clinical trials; coverage and reimbursement determinations by third-party payers, including Medicare, Medicaid, and pharmacy benefit management companies; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, research and clinical programs, and business, including those relating to the enrollment, completion, and meeting of the relevant endpoints of post-approval studies; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's products and product candidates, such as Dupixent; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; uncertainty of market acceptance and commercial success of Regeneron's products and product candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary) on the commercial success of Regeneron's products and product candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its sales or other financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as applicable), to be cancelled or terminated without any further product success; and risks associated with intellectual property of other parties and pending or future litigation relating thereto, including without limitation the patent litigation relating to Praluent[®] (alirocumab) Injection, the ultimate outcome of such litigation, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2016 and its Form 10-Q for the quarterly period ended June 30, 2017. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update publicly any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (<http://newsroom.regeneron.com>) and its Twitter feed (<http://twitter.com/regeneron>).

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[1] American Academy of Allergy Asthma & Immunology. Eosinophilic Esophagitis (EOE). <http://www.aaaai.org/conditions-and-treatments/related-conditions/eosinophilic-esophagitis>. Accessed Sept 2017.

[2] Wechsler, JB, Bryce, PJ. Allergic Mechanisms in Eosinophilic Esophagitis. *Gastroenterology Clinics of North America*. 2014; 43(2): 281-296.

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