



## Treatment Effects Maintained Over Five Years in Majority of Patients with Relapsing Remitting Multiple Sclerosis who Received Genzyme's Lemtrada<sup>®</sup> (alemtuzumab) in Clinical Trials

*- In the extension of two Phase III pivotal studies, 68 and 60 percent of Lemtrada-treated patients received no additional Lemtrada in the prior four years -*

*- Consistent effects seen across relapse, disability, brain atrophy and MRI lesion activity -*

**Paris, France - October 8, 2015** - [Sanofi](#) and its subsidiary [Genzyme](#) today announced positive new five-year investigational data from the extension study of Lemtrada<sup>®</sup> (alemtuzumab) for patients with relapsing remitting multiple sclerosis (RRMS). These results will be presented on October 9, 2015 at the 31<sup>st</sup> Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Barcelona, Spain.

In RRMS patients treated with Lemtrada in the Phase III pivotal studies, the effects described below observed in the two-year trials were maintained through three additional years in the extension study (years three, four and five). After the initial two courses of treatment in the pivotal studies, which were given at month zero and at month 12, 68 percent of Lemtrada patients from CARE-MS I and 60 percent from CARE-MS II did not receive additional Lemtrada treatment during the following four years, through month 60.

- The low annualized relapse rates observed in patients who received Lemtrada in CARE-MS I (0.18) and CARE-MS II (0.27) were maintained from year three (0.19 and 0.22) to year five (0.15 and 0.18).
- Through year five, 80 percent and 76 percent of patients who received Lemtrada in CARE-MS I and CARE-MS II, respectively, did not experience worsening of disability progression confirmed over six months as measured by the Expanded Disability Status Scale (EDSS).
- Through year five, 33 percent and 43 percent of patients who had some disability before receiving Lemtrada in CARE-MS I and CARE-MS II, respectively, had improvement in EDSS score confirmed over at least six months as compared with pre-treatment baseline.
- Through year five, patients who received Lemtrada in CARE-MS I and II experienced a slowing of brain volume loss as measured by brain parenchymal fraction on magnetic resonance imaging (MRI). In years three, four and five, the median yearly brain volume loss was -0.20 percent or less, which was lower than what was observed during the two-year pivotal studies.
- In each of years three, four and five, most patients had no evidence of MRI disease activity (70 – 72 percent, CARE-MS I; 68 – 70 percent, CARE-MS II).

Through year five, the incidence of most adverse events during the extension study was comparable or reduced compared with the pivotal studies. The frequency of thyroid adverse events was highest in year three and declined thereafter.



The Phase III trials of Lemtrada were randomized, rater-blinded, two-year pivotal studies comparing treatment with Lemtrada to high-dose subcutaneous interferon beta-1a (Rebif®) in patients with RRMS who had active disease and were either new to treatment (CARE-MS I) or who had an inadequate response to another therapy (CARE-MS II).

More than 90 percent of the patients who were treated with Lemtrada in the CARE-MS Phase III trials enrolled in the extension study. These patients were eligible to receive additional treatment with Lemtrada in the extension study if they experienced at least one relapse or at least two new or enlarging brain or spinal cord lesions.

*“These data illustrate that most Lemtrada patients experienced sustained effects of treatment, despite the absence of additional treatment courses,”* said Professor Eva Havrdová, MD, PhD, MS Center, Department of Neurology, First Medical Faculty, Charles University, Prague, Czech Republic. *“It is encouraging to see consistent effects maintained across multiple meaningful outcomes through five years.”*

In clinical trials, serious side effects associated with Lemtrada included infusion-associated reactions, autoimmune disorders (such as thyroid disease, autoimmune cytopenias, and nephropathies), infections and pneumonitis. Risk management programs incorporating education and monitoring help support early detection and management of key identified and potential risks. The most common side effects of Lemtrada are rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. (See Important Safety Information below.)

*“The five-year data announced today are exciting and important for people living with relapsing MS, because of Lemtrada’s potential to change the treatment approach for patients who continue to suffer from this debilitating disease, and for whom Lemtrada is an option,”* said Bill Sibold, Head of Genzyme’s Multiple Sclerosis business.

In CARE-MS I, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates; the difference observed in slowing disability progression did not reach statistical significance. In CARE-MS II, Lemtrada was significantly more effective than interferon beta-1a at reducing annualized relapse rates, and accumulation of disability was significantly slowed in patients given Lemtrada vs. interferon beta-1a.

### **Lemtrada® (alemtuzumab) U.S. Indication**

LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

### **CONTRAINDICATIONS**

LEMTRADA is contraindicated in patients who are infected with Human Immunodeficiency Virus (HIV) because LEMTRADA causes prolonged reductions of CD4+ lymphocyte counts.

### **Important Safety Information About Lemtrada**

#### **WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES**

**LEMTRADA causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease.**

**Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of LEMTRADA.**



**LEMTRADA causes serious and life-threatening infusion reactions. LEMTRADA must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period.**

**LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.**

**Because of the risk of autoimmunity, infusion reactions, and malignancies, LEMTRADA is available only through restricted distribution under a Risk Evaluation and Mitigation Strategy (REMS) Program. Call 1-855-676-6326 to enroll in the LEMTRADA REMS Program.**

## **WARNINGS AND PRECAUTIONS**

**Autoimmunity:** Treatment with LEMTRADA can result in the formation of autoantibodies and increase the risk of serious autoimmune mediated conditions, and may increase the risk of other autoimmune conditions because of the broad range of autoantibody formation.

Obtain complete blood counts (CBC) with differential, serum creatinine levels, and urinalysis with cell counts before starting treatment and then at monthly intervals for 48 months after the last dose of LEMTRADA, or longer, if clinically indicated.

**Infusion Reactions:** LEMTRADA causes cytokine release syndrome resulting in infusion reactions. In clinical studies, 92% of LEMTRADA-treated patients experienced infusion reactions. Serious reactions occurred in 3% of these patients and included anaphylaxis in 2 patients (including anaphylactic shock), angioedema, bronchospasm, hypotension, chest pain, bradycardia, tachycardia (including atrial fibrillation), transient neurologic symptoms, hypertension, headache, pyrexia, and rash. In some patients, infusion reactions were reported more than 24 hours after LEMTRADA infusion. Premedicate patients with corticosteroids immediately prior to LEMTRADA infusion for the first 3 days of each treatment course.

Consider pretreatment with antihistamines and/or antipyretics. Infusion reactions may occur despite pretreatment.

**Malignancies:** Monitor for symptoms of thyroid cancer. Because LEMTRADA is an immunomodulatory therapy, caution should be exercised in initiating LEMTRADA in patients with pre-existing or ongoing malignancies.

**LEMTRADA REMS Program:** Only prescribers, patients, pharmacies and healthcare facilities certified and enrolled in the REMS program can prescribe, receive, dispense or administer LEMTRADA. Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions (including anaphylaxis and cardiac and respiratory emergencies).

**Immune thrombocytopenia (ITP)** occurred in 2% of LEMTRADA-treated patients in clinical studies in MS. One LEMTRADA-treated patient developed ITP that went unrecognized prior to the implementation of monthly monitoring requirements, and died from an intracerebral hemorrhage. ITP has been diagnosed more than 3 years after the last LEMTRADA dose. If ITP is confirmed, promptly initiate medical intervention.

**Glomerular nephropathies** occurred in 0.3% of LEMTRADA-treated patients in MS clinical trials and have been diagnosed up to 40 months after the last dose of LEMTRADA. Anti-glomerular basement membrane (anti-GBM disease) can lead to renal failure requiring dialysis and transplantation and has in post-marketing cases of MS patients treated with alemtuzumab. Anti-GBM disease can be life-threatening if untreated; early detection and treatment may decrease the risk of poor outcomes.

**Autoimmune thyroid disorders** occurred in 34% of LEMTRADA-treated patients in clinical studies. Newly diagnosed thyroid disorders occurred throughout the uncontrolled clinical study follow-up period, more than 7 years after the first LEMTRADA dose. Serious thyroid events occurred in 2% of patients, including cardiac and psychiatric events. In LEMTRADA-treated



patients, 3% underwent thyroidectomy. In patients with an ongoing thyroid disorder, LEMTRADA should be administered only if the potential benefit justifies the potential risks. Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion, or longer, if clinically indicated. Thyroid disease poses special risks in women who are pregnant.

**Autoimmune cytopenias** occurred in LEMTRADA-treated MS patients in clinical trials.

One LEMTRADA-treated patient with autoimmune pancytopenia died from sepsis. Prompt medical intervention is indicated if a cytopenia is confirmed.

**Infections** occurred in 71% of LEMTRADA-treated patients compared to 53% of patients treated with interferon beta-1a. Serious infections occurred in 3% of patients treated with LEMTRADA and 1% of patients treated with interferon beta-1a and included: appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection. Consider delaying LEMTRADA administration in patients with active infection until the infection is fully controlled.

- Do not administer live viral vaccines following a course of LEMTRADA, as patients may be at increased risk of infection.
- Concomitant use of antineoplastic or immunosuppressive therapies could increase the risk of immunosuppression.
- Herpes viral infection developed in 16% of LEMTRADA-treated patients compared to 3% of interferon beta-1a patients. Administer antiviral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continue for a minimum of two months following treatment with LEMTRADA or until CD4+ lymphocyte count is  $\geq 200$  cells per microliter, whichever occurs later.
- Cervical human papilloma virus (HPV) infection occurred in 2% of LEMTRADA treated patients. Annual screening is recommended for female patients.
- Active and latent tuberculosis cases occurred in 0.3% of LEMTRADA-treated patients, most often in endemic regions.
- Fungal infections, especially oral and vaginal candidiasis, occurred in 12% of LEMTRADA-treated patients compared to 3% of interferon beta-1a patients.
- Cases of listeria meningitis occurred within 1 month of LEMTRADA dosing. Advise patients to avoid or adequately heat foods that are potential sources for *Listeria monocytogenes*.
- Before initiating LEMTRADA, consider screening patients at high risk of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infection. Carriers of HBV and/or HCV who receive LEMTRADA may be at risk of irreversible liver damage relative to a potential virus reactivation.

**Pneumonitis**, including hypersensitivity pneumonitis and pneumonitis with fibrosis, occurred in 6 of 1217 (0.5%) LEMTRADA-treated patients in clinical studies. Advise patients to report symptoms of pneumonitis (e.g., shortness of breath, cough, wheezing, chest pain or tightness, and hemoptysis).

**Drug Products with Same Active Ingredient:** LEMTRADA contains the same active ingredient (alemtuzumab) found in CAMPATH®. If LEMTRADA is considered for use in a patient who has previously received CAMPATH, exercise increased vigilance for additive and long-lasting effects on the immune system.

### **Adverse Reactions**

In clinical trials, the most common adverse reactions (incidence  $\geq 10\%$  and  $>$ interferon beta-1a) with LEMTRADA vs interferon beta-1a were: rash (53% vs 6%), headache (52% vs 23%), pyrexia (29% vs 9%), nasopharyngitis (25% vs 19%), nausea (21% vs 9%), urinary tract infection (19% vs 8%), fatigue (18% vs 13%), insomnia (16% vs 15%), upper respiratory tract infection (16% vs 13%), herpes viral infection (16% vs 3%), urticaria (16% vs 2%), pruritus (14% vs 2%), thyroid gland disorders (13% vs 3%), fungal infection (13% vs 4%), arthralgia (12% vs 9%), pain in extremity (12% vs 9%), back pain (12% vs 8%), diarrhea (12% vs 6%), sinusitis (11% vs 8%), oropharyngeal pain (11% vs 5%), paresthesia (10% vs 8%), dizziness (10% vs 5%), abdominal pain (10% vs 5%), flushing (10% vs 4%), and vomiting (10% vs 3%).



## Use in Specific Populations

LEMTRADA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Autoantibodies may be transferred from the mother to the fetus during pregnancy. Placental transfer of anti-thyroid antibodies resulted in a case of neonatal Graves' disease. Safety and effectiveness in pediatric patients less than 17 years of age have not been established. Use of LEMTRADA is not recommended in pediatric patients due to the risks of autoimmunity and infusion reactions, and because it may increase the risk of malignancies.

Please click [here](#) for full US Prescribing Information for Lemtrada, including Boxed **WARNING**.

## About Lemtrada<sup>®</sup> (alemtuzumab)

Lemtrada is approved in more than 40 countries, with additional marketing applications under review. Lemtrada is supported by a comprehensive and extensive clinical development program that involved nearly 1,500 patients worldwide and 5,400 patient-years of follow-up.

Alemtuzumab is a monoclonal antibody that targets CD52, a protein abundant on T and B cells. Circulating T and B cells are thought to be responsible for the damaging inflammatory process in MS. Although the exact mechanism of action for alemtuzumab is unknown, it is presumed to deplete circulating T and B lymphocytes after each treatment course. Lymphocyte counts then increase over time with a reconstitution of the lymphocyte population that varies for the different lymphocyte subtypes.

Genzyme holds the worldwide rights to alemtuzumab and has responsibility for its development and commercialization in multiple sclerosis. Bayer Healthcare receives contingent payments based on global sales revenue.

## About Genzyme, a Sanofi Company

Genzyme has pioneered the development and delivery of transformative therapies for patients affected by rare and debilitating diseases for over 30 years. We accomplish our goals through world-class research and with the compassion and commitment of our employees. With a focus on rare diseases and multiple sclerosis, we are dedicated to making a positive impact on the lives of the patients and families we serve. That goal guides and inspires us every day. Genzyme's portfolio of transformative therapies, which are marketed in countries around the world, represents groundbreaking and life-saving advances in medicine. As a Sanofi company, Genzyme benefits from the reach and resources of one of the world's largest pharmaceutical companies, with a shared commitment to improving the lives of patients. Learn more at [www.genzyme.com](http://www.genzyme.com).

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## About Sanofi

Sanofi, a global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. Sanofi has core strengths in the field of healthcare with seven growth platforms: diabetes solutions, human vaccines, innovative drugs, consumer healthcare, emerging markets, animal health and the new Genzyme. Sanofi is listed in Paris (EURONEXT: [SAN](#)) and in New York (NYSE: [SNY](#)).

## 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, the Group's ability to benefit from external growth opportunities, trends in exchange rates and prevailing interest rates, the impact of cost containment policies 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, 2014. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

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