ZALTRAP® (ziv-aflibercept) Approved in the EU for Patients with Previously Treated Metastatic Colorectal Cancer

February 5, 2013

PARIS and TARRYTOWN, N.Y., Feb. 5, 2013 /PRNewswire/ -- Sanofi (EURONEXT: **SAN** and NYSE: **SNY**) and Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that the European Commission (EC) has granted marketing authorization in the European Union for ZALTRAP 25mg/ml concentrate for solution for infusion in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. This decision was based on the efficacy and safety results of the VELOUR Phase 3 trial.

"ZALTRAP is an important addition to the metastatic colorectal cancer treatment landscape and helps to fill a critical treatment gap," said Eric Van Cutsem, M.D., Ph.D., University Hospitals Leuven, Belgium and lead investigator of the VELOUR study. "ZALTRAP is the first and only agent to demonstrate a survival improvement in a Phase 3 trial in patients previously treated with an oxaliplatin-based regimen who are being treated with FOLFIRI for their metastatic disease."

"I would like to thank the physicians, patients, and their families for their support in moving ZALTRAP through the clinical trial process leading to approval in Europe," said Debasish Roychowdhury, M.D., Senior Vice President and Head, Sanofi Oncology. "We are thrilled to provide a new therapy that further extends the lives of patients with metastatic colorectal cancer and look forward to working with European health authorities to ensure patients have access to ZALTRAP."

In Europe, colorectal cancer is the most common cancer in both men and women and is the second leading cause of cancer death. In 2008, there were 436,000 new cases diagnosed and 212,000 deaths from colorectal cancer.[1]

Commenting on the marketing authorization, George D. Yancopoulos, M.D., Ph.D., Chief Scientific Officer of Regeneron and President of Regeneron Laboratories, added: "The European approval of ZALTRAP provides a new option to address the unmet medical need in this patient population. There continues to be a need to develop new cancer therapies and Regeneron and Sanofi are committed to finding novel investigational treatments and combinations."

ZALTRAP received approval from the U.S. Food and Drug Administration (FDA) in August 2012 after a Priority Review, and marketing authorization applications for ZALTRAP are under review with other regulatory agencies worldwide.

About the VELOUR Phase 3 Study
The ZALTRAP approval was based on data from the pivotal Phase 3 VELOUR trial, a multinational, randomized, double-blind trial comparing FOLFIRI in combination with either ZALTRAP or placebo in the treatment of patients with mCRC. The study randomized 1,226 patients with mCRC who previously had been treated with an oxaliplatin-containing regimen. Twenty-eight percent of patients in the study received prior bevacizumab therapy. The primary endpoint of the trial was overall survival. Secondary endpoints included progression-free survival, overall response rate, and safety.

The VELOUR trial showed that in patients previously treated with an oxaliplatin containing regimen, adding ZALTRAP to FOLFIRI significantly improved median survival from 12.06 months to 13.50 months (HR=0.817 (95% CI 0.714 to 0.935; p=0.0032), an 18 percent relative risk reduction. A significant improvement in progression-free survival from 4.67 months to 6.90 months (HR=0.758 95% CI 0.661 to 0.869; p=0.00007), a 24 percent relative risk reduction, was also observed. The overall response rate in the ZALTRAP plus FOLFIRI arm was 19.8% vs. 11.1% for FOLFIRI alone (p=0.0001).

The most common adverse reactions (all grades, greater than or equal to 20% incidence) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache. The most common Grade 3-4 adverse reactions (greater than or equal to 5%) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were neutropenia, diarrhea, hypertension, leukopenia, stomatitis, fatigue, proteinuria, and asthenia.

About ZALTRAP® (ziv-aflibercept)
ZALTRAP is a recombinant fusion protein which acts as a soluble receptor that binds to Vascular Endothelial Growth Factor-A (VEGF-A), VEGF-B, and placental growth factor (PlGF), as shown in preclinical studies. VEGF-A is one of the mediators contributing to angiogenesis. VEGF-B and PlGF, related growth factors in the VEGF family, may contribute to tumor angiogenesis as well. In the US, ZALTRAP is a registered trademark of Regeneron Pharmaceuticals, Inc.

In the US, ZALTRAP is approved with the US proper name ziv-aflibercept. The World Health Organization (WHO) recommended international non-proprietary name for ZALTRAP is aflibercept. Marketing authorization applications for ZALTRAP are also under review other regulatory agencies worldwide.

IMPORTANT SAFETY INFORMATION FOR
ZALTRAP® (ziv-aflibercept) INJECTION FOR INTRAVENOUS INFUSION

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, COMPROMISED WOUND HEALING

Severe and sometimes fatal hemorrhage, including gastrointestinal (GI) hemorrhage, has been reported in the patients who have received

ZALTRAP in combination with FOLFIRI. Monitor patients for signs and symptoms of GI bleeding and other severe bleeding. Do not administer ZALTRAP to patients with severe hemorrhage.

GI perforation including fatal GI perforation can occur in patients receiving ZALTRAP. Discontinue ZALTRAP therapy in patients who experience GI perforation.

Severe compromised wound healing can occur in patients receiving ZALTRAP/FOLFIRI. Discontinue ZALTRAP in patients with compromised wound healing. Suspend ZALTRAP for at least 4 weeks prior to elective surgery, and do not resume ZALTRAP for at least 4 weeks following major surgery and until the surgical wound is fully healed.

WARNINGS AND PRECAUTIONS

- Patients treated with ZALTRAP have an increased risk of hemorrhage, including severe and sometimes fatal hemorrhagic events.
    - Bleeding/hemorrhage (all grades) occurred in 38% of ZALTRAP® (ziv-aflibercept)/FOLFIRI patients vs. 19% of placebo/FOLFIRI patients. Grade 3-4 hemorrhagic events, including GI hemorrhage, hematuria, and post-procedural hemorrhage, occurred in 3% of ZALTRAP/FOLFIRI patients vs. 1% of placebo/FOLFIRI patients. Severe intracranial hemorrhage and pulmonary hemorrhage/hemoptysis including fatal events have occurred in patients receiving ZALTRAP.
    - Monitor patients for signs and symptoms of bleeding.
      Do not initiate ZALTRAP in patients with severe hemorrhage.
      Discontinue ZALTRAP in patients who develop severe hemorrhage.
- GI perforation including fatal GI perforation can occur in patients receiving ZALTRAP.
    - Across three clinical trials (colorectal, pancreatic, and lung cancer), GI perforation (all grades/Grade 3-4) occurred in 0.8% /0.8% of ZALTRAP patients and 0.3% /0.2% for placebo patients.
    - Monitor patients for signs and symptoms of GI perforation.
      Discontinue ZALTRAP in patients who experience GI perforation.
- ZALTRAP impairs wound healing in animal models. Grade 3 compromised wound healing occurred in 2 patients (0.3%) treated with ZALTRAP/FOLFIRI and none of the patients treated with placebo/FOLFIRI.
    - Discontinue ZALTRAP in patients with compromised wound healing.
    - Suspend ZALTRAP for at least 4 weeks prior to elective surgery and do not initiate/resume ZALTRAP® (ziv-aflibercept) until at least 4 weeks after major surgery and surgical wound is fully healed.
    - For minor surgery such as central venous access port placement, biopsy, and tooth extraction, ZALTRAP may be initiated/resumed once the surgical wound is fully healed.
- Fistula formation involving GI and non-GI sites occurs at a higher incidence in patients treated with ZALTRAP. Fistulas (anal, enterovesical, enterocutaneous, colovaginal, intestinal sites) were reported in 1.5% (9/611) of ZALTRAP/FOLFIRI treated patients and 0.5% (3/605) of placebo/FOLFIRI patients. Grade 3 GI fistula formation occurred in 2 patients treated with ZALTRAP (0.3%) and 1 placebo-treated patient (0.2%). Discontinue ZALTRAP therapy in patients who develop fistula.
- An increased risk of Grade 3-4 hypertension has been observed in patients receiving ZALTRAP.
    - There is no clinical trial experience administering ZALTRAP to patients with NYHA class III or IV heart failure. In patients with mCRC, Grade 3 hypertension (defined as requiring adjustment in existing anti-hypertensive therapy or treatment with more than one drug) was reported in 1.5% of patients treated with placebo/FOLFIRI and 19% treated with ZALTRAP/FOLFIRI. Grade 4 hypertension (hypertensive crisis) was reported in 1 patient (0.2%) treated with ZALTRAP/FOLFIRI. Of patients treated with ZALTRAP/FOLFIRI who developed Grade 3-4 hypertension, 54% had onset during the first two cycles of treatment.
    - Monitor blood pressure at least every two weeks, treat with appropriate anti-hypertensive therapy, and continue monitoring blood pressure regularly during ZALTRAP treatment.
      Temporarily suspend ZALTRAP until hypertension is controlled, and reduce ZALTRAP dose to 2 mg/kg for subsequent cycles.
      Discontinue ZALTRAP in patients with hypertensive crisis or hypertensive encephalopathy.
- Arterial thromboembolic events (ATE), including transient ischemic attack, cerebrovascular accident, and angina pectoris, occurred more frequently in patients who have received ZALTRAP® (ziv-aflibercept). ATE occurred in 2.6% of ZALTRAP/FOLFIRI patients and 1.7% of placebo/FOLFIRI patients. Grade 3-4 events occurred in 11 patients (1.8%) treated with ZALTRAP/FOLFIRI and 4 patients (0.7%) treated with placebo/FOLFIRI. Discontinue ZALTRAP in patients who experience an ATE.
- Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) occurred more frequently in patients treated with ZALTRAP.
    - Proteinuria was reported in 62% of ZALTRAP/FOLFIRI patients compared to 41% of placebo/FOLFIRI patients. Grade 3-4 proteinuria occurred in 8% of ZALTRAP/FOLFIRI patients compared to 1% of placebo/FOLFIRI patients. Nephrotic syndrome occurred in 2 patients (0.5%) treated with ZALTRAP/FOLFIRI compared to none of the patients treated with placebo/FOLFIRI. TMA was reported in 3 of 2258 patients with cancer enrolled across completed

studies.
    - Monitor proteinuria by urine dipstick analysis and urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria. Obtain a 24-hour urine collection in patients with a UPCR >1.
    - Suspend ZALTRAP® (ziv-aflibercept) when proteinuria greater than or equal to 2 grams/24 hours and resume ZALTRAP when proteinuria &< 2 grams/24 hours.
    - If recurrent, suspend until proteinuria &< 2 grams/24hours and then reduce ZALTRAP dose to 2 mg/kg.
    - Discontinue ZALTRAP if nephrotic syndrome or TMA develops.
- A higher incidence of neutropenic complications (febrile neutropenia and neutropenic infection) occurred in patients receiving ZALTRAP.
    - Grade 3-4 neutropenia occurred in 37% of ZALTRAP/FOLFIRI patients compared to 30% of placebo/FOLFIRI patients. Grade 3-4 febrile neutropenia occurred in 4% of ZALTRAP/FOLFIRI patients compared to 2% of placebo/FOLFIRI patients. Grade 3-4 neutropenic infection/sepsis occurred in 1.5% of ZALTRAP/FOLFIRI patients compared to 1.2% of placebo/FOLFIRI patients.
    - Monitor CBC with differential count at baseline and prior to initiation of each cycle of ZALTRAP. Delay administration of ZALTRAP/FOLFIRI until neutrophil count is greater than or equal to 1.5 x 10^9/L.
- Incidence of severe diarrhea and dehydration is increased in patients treated with ZALTRAP/FOLFIRI.
    - Grade 3-4 diarrhea was reported in 19% of ZALTRAP/FOLFIRI patients compared to 8% of placebo/FOLFIRI patients. Grade 3-4 dehydration was reported in 4% of ZALTRAP/FOLFIRI patients compared to 1% of placebo/FOLFIRI patients.
    - The incidence of diarrhea is increased in patients greater than or equal to 65 years of age compared to patients <65 years of age. Monitor closely.
- RPLS (also known as posterior reversible encephalopathy syndrome) was reported in 0.5% of 3795 patients treated with ZALTRAP monotherapy or in combination with chemotherapy. Confirm diagnosis of RPLS with MRI and discontinue ZALTRAP in patients who develop RPLS. Symptoms usually resolve or improve within days, although some patients have experiences ongoing neurologic sequelae or death.

ADVERSE REACTIONS

- The most common adverse reactions (all grades, greater than or equal to 20% incidence) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP® (ziv-aflibercept)/FOLFIRI arm, in order of decreasing frequency, were leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache.
- The most common Grade 3-4 adverse reactions (greater than or equal to 5%) reported at a higher incidence (2% or greater between-arm difference) in the ZALTRAP/FOLFIRI arm, in order of decreasing frequency, were neutropenia, diarrhea, hypertension, leukopenia, stomatitis, fatigue, proteinuria, and asthenia.
- Infections occurred at a higher frequency in patients receiving ZALTRAP® (ziv-aflibercept)/FOLFIRI (46%, all grades; 12%, Grade 3-4) than in patients receiving placebo/FOLFIRI (33%, all grades; 7%, Grade 3-4), including urinary tract infection, nasopharyngitis, upper respiratory tract infection, pneumonia, catheter site infection, and tooth infection.
- In patients with mCRC, venous thromboembolic events (VTE), consisting primarily of deep venous thrombosis and pulmonary embolism, occurred in 9% of patients treated with ZALTRAP/FOLFIRI and 7% of patients treated with placebo/FOLFIRI.

PREGNANCY AND NURSING MOTHERS

- ZALTRAP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females and males of reproductive potential should use highly effective contraception during and up to a minimum of 3 months after the last dose of treatment.
- It is not known whether ZALTRAP is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

About Colorectal Cancer

Worldwide, colorectal cancer is the third most commonly diagnosed cancer in males and the second most in females, with more than 1.2 million new cases diagnosed in 2008. One of the deadliest cancers, colorectal cancer was responsible for more than 600,000 deaths globally in 2008 alone. According to the American Cancer Society, approximately 60 percent of colorectal cancer cases are diagnosed at the locally advanced or metastatic stage. Although survival for early stage disease is relatively high, once colorectal cancer metastasizes to distant organs, five-year survival is estimated to be 12 percent.

About Sanofi Oncology

Based in Cambridge, Massachusetts, USA and Vitry, France, Sanofi Oncology is dedicated to translating science into effective therapeutics that address unmet medical needs for cancer and organ transplant patients. Starting with a deep understanding of the disease and the patient, Sanofi Oncology employs innovative approaches to drug discovery and clinical development, with the ultimate goal of bringing the right medicines to the right

patients to help them live healthier and longer lives. We believe in the value of partnerships that combine our internal scientific expertise with that of industry and academic experts. Our portfolio includes 11 marketed products and more than 15 investigational compounds in clinical development, including small molecules and biological agents.

About Sanofi
Sanofi, a global and diversified 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).

About Regeneron Pharmaceuticals, Inc.
Regeneron is a leading science-based biopharmaceutical company based in Tarrytown, New York that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron markets medicines for eye diseases, colorectal cancer, and a rare inflammatory condition and has product candidates in development in other areas of high unmet medical need, including hypercholesterolemia, rheumatoid arthritis, asthma, and atopic dermatitis. For additional information about the company, please visit www.regeneron.com.

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, 2011. 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
This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron, and actual events or results may differ materially from these forward-looking statements. 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 ZALTRAP® (ziv-aflibercept), unforeseen safety issues resulting from the administration of products and product candidates in patients, the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates, 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 drug candidates, competing drugs that may be superior to Regeneron's products and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with the Sanofi Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property and pending or future litigation relating thereto. 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, 2011 and its Form 10-Q for the quarter ended September 30, 2012. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

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[1] ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Annals of Oncol. 2012; 23: 2470-2516

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