Genzyme’s Alemtuzumab for Multiple Sclerosis Shows Durable Treatment Benefit in Review of Four-Year Phase 2 Trial Data

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Company’s CARE-MS II Phase 3 Trial Completes Enrollment

Additional Safety, Immunogenicity, and Disability Reduction Alemtuzumab Data Presented at ECTRIMS International Conference

CAMBRIDGE, Mass.--(BUSINESS WIRE)--) Genzyme Corporation (Nasdaq: GENZ) reported today that four-year follow-up data from its completed Phase 2 multiple sclerosis (MS) trial continued to show durable reductions in relapse rate and sustained accumulation of disability three years after the majority of patients received their last course of the investigational compound alemtuzumab. The CAMMS223 Phase 2 trial compared alemtuzumab to an approved MS therapy Rebif® (interferon beta-1a) in early, relapsing-remitting multiple sclerosis (RRMS) patients who had received no prior therapy. The accumulated four-year efficacy and safety data from the Phase 2 trial will be presented today in Germany at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) annual meeting, one of the largest annual international MS conferences. Three-year CAMMS223 trial data were reported in the New England Journal of Medicine (NEJM) last October.

"These longer-term Phase 2 data showed durable reductions in the occurrence of relapses and the accumulation of disability, extending for several years after patients’ last treatment,” said Alasdair Coles, MD, Senior Lecturer, Department of Clinical Neurosciences, University of Cambridge, a lead investigator of the Phase 2 clinical trial. “These findings confirm the extended duration of response observed in our pilot studies with alemtuzumab in patients with relapsing MS."

In the trial, alemtuzumab was given to patients in two or three annual cycles of not more than five days per cycle, while Rebif was given to patients three-times per week, every week for three years.

The four-year analysis of early RRMS patients from the CAMMS223 trial found that patients taking once-yearly cycles of alemtuzumab reduced their risk of relapse by 72 percent and the risk of sustained accumulation of disability by 73 percent compared to patients treated with the active comparator Rebif. These data closely mirror the three-year findings reported in the NEJM manuscript. Further, the annualized relapse rate and disability risk measured from year three to four remained at the same low level observed in prior years of the study.

The additional review data were obtained from patients participating in CAMMS223 beyond the initial three-year study period. The dataset analyzed consists of the originally-planned three years of patient follow-up, additional continuous post-three-year follow-up, and follow-up of patients who initially discontinued but returned to the study to participate in the risk management program. Approximately 15 percent of patients participating in the post-three-year follow-up used non-study MS disease modifying therapies. A sensitivity analysis that censored these patients found that the risk of relapse and sustained accumulation of disability similarly favored alemtuzumab.

(Three-year and updated four-year safety data can be found below.)

Pivotal Phase 3 MS Trials Enrolled

The company also announced that its CARE-MS II Phase 3 trial, one of two pivotal trials of alemtuzumab in the treatment of MS, has completed enrollment. The company's CARE-MS I Phase 3 trial completed enrollment earlier this year. CARE-MS I, a randomized trial comparing alemtuzumab to Rebif, is studying early, active RRMS patients who have received no prior therapy. CARE-MS II, which also compares alemtuzumab to Rebif, is studying RRMS patients who relapsed while on other MS therapies. Patients who enrolled at the start of both trials in 2007 will soon complete the protocol-specified two years of follow-up and begin to move into an extension trial. The extension trial allows patients previously treated with Rebif to receive alemtuzumab. Patients previously treated with alemtuzumab will be allowed to take another treatment cycle as needed.

“The enrollment of both pivotal trials is a significant accomplishment,” said Mark Enyedy, president of Genzyme Oncology and Multiple Sclerosis. “This achievement reflects strong interest from patients and significant support from our clinical investigators and patient organizations around the world.” Data from the trials are expected to be available in 2011 for regulatory filings, and approval is anticipated in 2012.

No Additive Infection Risk
Investigators also reported at ECTRIMS that repeated cycles of alemtuzumab did not lead to an additive increase in the risk of infection. “Alemtuzumab modulates the immune system, but this important analysis showed that there were a limited number of serious or severe infections and that infection rates did not increase with additional cycles of alemtuzumab,” said Sibyl Wray, MD, Director, Hope Neurology MS Center, Knoxville, Tennessee, an investigator in the alemtuzumab-MS program and lead author of the analysis of infectious adverse events abstract. In reviewing the CAMMS223 three-year data, researchers determined that infectious adverse events declined in incidence over time. In the Phase 2 trial, no life-threatening or fatal infections occurred in either the alemtuzumab or Rebif trial arms, and patients who did experience an infection responded to conventional therapies over a normal course of time.

Anti-Drug Antibody Impact Not Seen

Researchers reporting at ECTRIMS also found that anti-alemtuzumab antibodies did not affect alemtuzumab’s outcomes through three years of patient follow-up and up to three annual treatment cycles. “Anti-drug antibodies have been shown to negatively impact the efficacy and safety of some MS treatments, but this has not been seen with alemtuzumab through three years of follow-up,” said Krzysztof Selmaj, MD PhD, an investigator in the alemtuzumab-MS program, co-author of the NEJM publication, and lead author of the new report on anti-alemtuzumab antibodies. He explained that “the annual dosing regimen allowed the anti-drug antibody concentration to decline to a low level before the next treatment was administered.” Blood serum measurements taken one, three, and 12 months after treatment as part of the CAMMS223 study found that anti-alemtuzumab antibodies peaked after one month and thereafter declined until re-exposure.

Reduction In Disability Despite Relapse History, Patient Characteristics

As previously reported in the Phase 2 trial, the mean disability of patients improved from baseline when they were treated with alemtuzumab, reflecting the recovery of neurological functions previously impaired by MS. By contrast, the mean disability of patients on Rebif worsened. Researchers reported at ECTRIMS that patients who experienced a relapse just prior to alemtuzumab treatment had similar rates of improvement in disability compared to patients who did not suffer such a relapse. “This is a significant finding as it showed that relapse history had no correlation with the improvement in disability observed, and suggests that alemtuzumab reverses preexisting disability through other mechanisms,” said Dr. Coles, author of the abstract. Investigators also report at ECTRIMS that alemtuzumab patients who experienced sustained reduction in disability and a reversing of pre-existing disability did so regardless of patient sex, age, race, country, or disease duration or activity at initiation of treatment.

About CAMMS223 Phase 2 Study

In the Phase 2 trial, 334 patients with active RRMS were enrolled at 49 medical centers in Europe and the United States. Patients in the trial were randomized to treatment with alemtuzumab at one of two dose levels (12 or 24 mg per day intravenously) for five days during the first cycle and three days 12 months later during the second cycle of therapy, or Rebif (44 mcg administered by subcutaneous injection three times per week, as indicated in its product label). A third cycle of alemtuzumab therapy was received by 46 patients at month 24.

The trial compared the efficacy of alemtuzumab with Rebif using two primary outcome measures: the relapse rate and the time to sustained accumulation of disability as evidenced by an increase in the Expanded Disability Status Scale (EDSS) score for six consecutive months. Efficacy assessments were made by independent neurologists blinded to patients’ treatment assignments. The EDSS is a 10-point scale in which every 0.5-point step marks a notable deterioration in neurological capabilities.

The three-year analysis reported in the October 23, 2008 issue of NEJM showed that patients in the trial taking once-yearly cycles of alemtuzumab reduced their risk of relapse by 74 percent and the risk of sustained accumulation of disability by 71 percent compared to patients treated with Rebif.

The mean disability score of patients after alemtuzumab improved (by 0.39 EDSS points), indicating a recovery of neurologic functions. The median disability level improved to a similar extent after alemtuzumab. In contrast, mean disability worsened in the Rebif group (by 0.38 EDSS points) resulting in a difference of nearly a full EDSS point (0.77 difference, p<0.0001) at three years.

Common non-serious adverse events in the trial included infusion-associated reactions in the alemtuzumab patients and flu-like symptoms in patients using Rebif. Alemtuzumab-treated patients were more likely than Rebif patients to experience infections, particularly of the upper respiratory tract; infections were predominantly mild to moderate in severity and there were no life-threatening or fatal infections. Serious infections were limited in number in the alemtuzumab-treated patients.

Patients were strongly encouraged to continue for two additional years of follow-up after the original three years of the study. Of the original sample, 158 patients completed a month 48 study visit (alem 12 mg/day: n=58; alem 24 mg/day: n=64; SC IFNβ-1a: n=36). Alemtuzumab and Rebif were not provided by the study after the third year. Patients were allowed to receive other disease-modifying therapies during this follow-up period. The majority of patients last received alemtuzumab at Month 12.

The abstract reporting the CAMMS223 four-year analysis included updated safety data. The new safety data showed that approximately 28 percent of alemtuzumab-treated patients developed an autoimmune thyroid-related adverse event. These events either normalized spontaneously or were managed using conventional therapies. There have been no additional or recurrent events of immune thrombocytopenic purpura (ITP) reported in the trial. The alemtuzumab-treated patient who developed Goodpasture’s disease (anti-GBM disease) at month 51 continues to have stable renal function following medical treatment. Patient monitoring for ITP, thyroid disorders and anti-GBM disease is incorporated into all Genzyme-sponsored trials of alemtuzumab for the treatment of MS.

Alemtuzumab is an investigational drug for the treatment of MS and must not be used in MS patients outside of a formal, regulated clinical trial setting in which appropriate patient monitoring measures are in place.
Alemtuzumab Treatment Benefit is Durable: Primary Efficacy Outcomes of CAMMS223 at 4 Years, Alasdair J. Coles, MD, Senior Lecturer, Department of Clinical Neurosciences, University of Cambridge on behalf of CAMMS223 study group.

Immunogenicity of Alemtuzumab Treatment for Relapsing-Remitting Multiple Sclerosis: No Effect on Efficacy or Safety, Krzysztof Selmaj, MD, PhD, Chairman, Department of Neurology, Medical University of Lodz, Poland on behalf of CAMMS223 study group.

A Descriptive Analysis of Infectious Adverse Events in Alemtuzumab-treated Multiple Sclerosis Patients, Sibyl Wray, MD, Director, Hope Neurology MS Center, Knoxville, Tennessee on behalf of CAMMS223 study group.

Alemtuzumab Reverses Pre-Existing Disability in Relapsing-Remitting Multiple Sclerosis Patients Independent of Relapse History, Alasdair J. Coles, MD, Senior Lecturer, Department of Clinical Neurosciences, University of Cambridge on behalf of CAMMS223 study group.

Alemtuzumab Increases the Likelihood of Sustained Reduction in Disability, Independent of Baseline Demographic or Disease Characteristics. Daniel Wynn, MD, Director, Clinical Research Consultants in Neurology, Multiple Sclerosis Center, Northbrook, Illinois on behalf of CAMMS223 study group.

About Campath® (alemtuzumab)

Alemtuzumab is licensed in the United States as a single agent for the treatment of B-cell chronic lymphocytic leukemia (B-CLL), and outside of the U.S. for the treatment of B-CLL in patients who have been treated with alkylating agents and for whom fludarabine combination therapy is not appropriate. The product was launched in its oncology indication in 2001 in the US, where it is marketed as Campath®, and in Europe, where it is named MabCampath®.

Alemtuzumab is a humanized monoclonal antibody that binds to a specific target, CD52, on cell surfaces and directs the body’s immune system to destroy those cells. It is the first and only monoclonal antibody approved by the FDA for the treatment of patients with B-CLL.

Campath for B-CLL has a boxed warning that includes information on cytopenias, infusion reactions, and infections. The most commonly reported adverse reactions in patients with B-CLL were infusion reactions (fever, chills, hypotension, urticaria, nausea, rash, tachycardia, dyspnea), cytopenias (neutropenia, lymphopenia, thrombocytopenia, anemia), and infections (CMV viremia, CMV infection, other infections). Other commonly reported adverse reactions include vomiting, abdominal pain, insomnia and anxiety. The most commonly reported serious adverse reactions are cytopenias, infusion reactions, and immunosuppression/infections.

About Genzyme

One of the world's leading biotechnology companies, Genzyme is dedicated to making a major positive impact on the lives of people with serious diseases. Since 1981, the company has grown from a small start-up to a diversified enterprise with more than 11,000 employees in locations spanning the globe and 2008 revenues of $4.6 billion.

With many established products and services helping patients in nearly 100 countries, Genzyme is a leader in the effort to develop and apply the most advanced technologies in the life sciences. The company's products and services are focused on rare inherited disorders, kidney disease, orthopaedics, cancer, transplant and immune disease, and diagnostic testing. Genzyme's commitment to innovation continues today with a substantial development program focused on these fields, as well as cardiovascular disease, neurodegenerative diseases, and other areas of unmet medical need.

This press release contains forward-looking statements regarding Genzyme's future plans and business strategies, including: its expectations about when data will become available from the two phase 3 trials, the anticipated date of regulatory approval for alemtuzumab, and the success of alemtuzumab to treat MS. These statements are subject to risks and uncertainties that could cause actual results to differ materially from those projected in these forward-looking statements, including: that the phase 3 trials are not successful; the timing and outcome of discussions with the regulatory agencies regarding approval of alemtuzumab for MS; the actual safety and efficacy of alemtuzumab for MS; and the risks and uncertainties described in reports filed by Genzyme with the Securities and Exchange Commission under the Securities Exchange Act of 1934, as amended, including without limitation the information under the heading “Risk Factors” in Genzyme’s Quarterly Report on Form 10-Q for the quarter ending June 30, 2009. Genzyme cautions investors not to place substantial reliance on the forward-looking statements contained in this press release. These statements speak only as of the date of this press release, and Genzyme undertakes no obligation to update or revise these statements.

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