



Lilly Oncology Reveals Findings From Study of JAK2 Inhibitor for Blood Cancers at ASH Meeting

SAN DIEGO, Dec. 12, 2011 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced data from an oncology pipeline molecule today at the 53rd Annual Meeting of the American Society of Hematology (ASH). At the meeting, Lilly Oncology presented Phase I data from the investigational therapy LY2784544, a small-molecule Janus kinase 2 (JAK2) inhibitor, in development for the treatment of certain types of myeloproliferative neoplasms (MPNs), a group of blood cancers[1] characterized by abnormal production of red blood cells or myeloid cells (non-lymphocyte white blood cells).[2]

"Research into myeloproliferative neoplasms demonstrated the importance of the JAK2 genetic mutation as a target for potential treatment options," said Richard Gaynor, M.D., vice president of product development and medical affairs at Lilly Oncology. "These data show that our compound has the potential to inhibit the JAK2 mutation and should be studied further. We hope that this study is the first in Lilly's ongoing research and development of LY2784544 and that our findings signal a potential new treatment for patients fighting myeloproliferative neoplasms."

The Role of JAK2 in MPN

In 2005, researchers reported that a point mutation in the JAK2 gene occurs in more than 95 percent of patients with the MPN subtype polycythemia vera (PV) and the majority of patients with the subtypes myelofibrosis (MF) and essential thrombocythemia (ET).[2,3] The JAK2 point mutation observed in MPNs substitutes the amino acid phenylalanine for valine (at position 617 [V617F]) of the JAK2 protein.[2] The mutation makes JAK2 constantly active, triggering several signaling pathways that cause blood-forming cells to proliferate and resist apoptosis (programmed cell death).[4]

Phase I Study Sought to Ascertain Safety, Tolerability

In pre-clinical study, LY2784544 selectively targeted JAK2 V617F while minimally inhibiting wild-type JAK2 so that normal marrow function wasn't impeded.

The primary objectives of this ongoing study were to determine the safety and tolerability of LY2784544 and to define a recommended oral daily dose for further study in patients with JAK2 V617F-positive MF, ET or PV. At the time of the interim analysis, 19 patients (1 PV, 1 post-ET MF and 17 MF) were evaluated.

Secondary objectives of the trial included determining pharmacokinetics, evaluating patient response to therapy using criteria developed by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), and evaluating symptoms using the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).

An effective MPN treatment will ideally reverse splenomegaly (spleen enlargement)—a painful complication caused by an overabundance of blood cells infiltrating the organ. In this study, a palpable reduction in spleen length of at least 35 percent was seen in 13 of 17 evaluable patients (76%, including 16 MF and 1 PV). After five cycles of therapy, a reduction in severity of bone-marrow fibrosis was observed in three of five MF patients for whom follow-up biopsies are available.

When laboratory results were analyzed, one case of laboratory tumor lysis syndrome (LTLS) and three cases of grade 2 clinical tumor lysis syndrome (CTLS) were detected. TLS is a consequence of cancer treatment that encompasses metabolic complications caused when dying cancer cells release breakdown products. Specifically, the TLS occurrences involved one case of hyperuricemia at the 240 mg dose and three cases of creatinine increase at the 200 mg dose, resulting in 200 mg and 240 mg doses of LY2784544 being reported as dose-limiting toxicities.

Based on analysis of pharmacokinetics, doses of LY2784544 associated with TLS appear to overlap the lower boundary of the biologically efficacious dose (BED) range predicted from pre-clinical evaluations. To permit testing of doses within the BED, the dosing regimen has been amended to include a lower-dose lead-in period for the purpose of reducing tumor burden, and the likelihood of TLS, prior to further testing of dose escalation.

Assessing symptoms using the MPN-SAF questionnaire showed that most patients reported alleviation of symptoms within the first two therapy cycles. Fifty-nine percent of patients reported symptom improvement of greater than or equal to 50% in key MPN-SAF symptoms, and 47 percent reported a greater than or equal to 50% improvement in fatigue-associated parameters. At the doses tested, no reduction has been observed in the mutant allele burden (i.e., the percentage of blood cells carrying

the JAK2 V617F mutation).[5]

Four patients discontinued therapy, one for each of the following reasons: adverse event, progressive disease, investigator decision and subject's decision. Serious drug-related adverse effects were seen in four patients (4 saw grade 2 creatinine increase, 2 saw grade 4 hyperuricemia and 1 saw grade 1 hyperkalemia). Temporarily interrupting treatment allowed all adverse events to resolve within 14 days. The most frequently reported drug-related adverse events were diarrhea (3 patients with grade 2, 5 with grade 1); nausea (2 patients with grade 2, 4 with grade 1); transient increased creatinine (4 patients with grade 2); anemia (3 patients with grade 2, 1 with grade 1); and hyperuricemia (2 patients with grade 4).

About Myeloproliferative Neoplasia

Over 200,000 people in the U.S. have some form of myeloproliferative neoplasm (MPN), a category of diseases in which genetic mutations in bone marrow stem cells cause the bone marrow to have abnormal production of red blood cells, white blood cells or platelets.[6] Symptoms for patients can be many or few[7] and not all patients will experience symptoms.[8] Treatment of MPNs depends on the presence and type of symptoms, and typically aims to correct the abnormal blood counts.[7]

About Lilly Oncology

For more than four decades, Lilly Oncology, a division of Eli Lilly and Company, has been dedicated to delivering innovative solutions that improve the care of people living with cancer. Because no two cancer patients are alike, Lilly Oncology is committed to developing novel treatment approaches. To learn more about Lilly's commitment to cancer, please visit www.LillyOncology.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers — through medicines and information — for some of the world's most urgent medical needs.

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This press release contains forward-looking statements about the potential of LY2784544 for the treatment of myeloproliferative neoplasms and reflects Lilly's current beliefs. However, as with any pharmaceutical compound, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that this compound will be approved by the relevant regulatory authorities or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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[1] National Cancer Institute. What Are Myeloproliferative Disorders?, www.cancer.gov/cancertopics/types/what-are-myeloproliferative-disorders (Accessed: November 8, 2011).

[2] Garber, Ken. JAK2 Inhibitors: Not the Next Imatinib But Researchers See Other Possibilities." *J of the National Cancer Institute*, vol. 101, pgs. 980-982 (Issue 14, July 15, 2009).

[3] A. Tefferi and A. Pardanani. JAK inhibitors in myeloproliferative neoplasms: Rationale, current data and perspective. *Blood Reviews* vol. 25, pgs. 229-237 (2011).

[4] F.P.S. Santos and S. Verstovsek. JAK2 inhibitors: What's the true therapeutic potential? *Blood Reviews* vol. 25, pgs. 53-63 (2011).

[5] Passamonti and E. Rumi. Clinical relevance of JAK2 (V617F) mutant allele burden. *Haematologica*. Vol. 94, No. 1, pgs. 7-10 (2009).

[6] The National Cancer Institute, "General Information About Chronic Myeloproliferative Disorders," Updated: September 27, 2011. <http://www.cancer.gov/cancertopics/pdq/treatment/myeloproliferative/Patient#Keypoint1>, (Accessed: November 7, 2011).

[7] The University of California San Francisco Medical Center, "Myeloproliferative Disorders," Updated: September 15, 2011. http://www.ucsfhealth.org/conditions/myeloproliferative_disorders/, (Accessed: November 7, 2011).

[8] University of Maryland Medical Center, "Myeloproliferative Disorders." <http://www.umm.edu/altmed/articles/myeloproliferative-disorders-000114.htm>, (Accessed: November 7, 2011).

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