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Study of SPRYCEL(TM) (Dasatinib) or 800 MG of Imatinib-Mesylate Shows Patients Treated With SPRYCEL Achieved High Cytogenetic Responses and Prolonged Progression-Free Survival

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- New Data Presented at the 48th Annual Meeting and Exposition of the American Society of Hematology (ASH)

For Non-US Journalists Only

New data presented today showed that a substantial number of patients with chronic-phase chronic myelogenous leukaemia (CML) resistant to imatinib mesylate achieved cytogenetic and haematologic responses within three months and maintained these responses through one year when treated with SPRYCEL(TM) (dasatinib, formerly known as BMS-354825). The randomised Phase II open-label, multi-centre international trial was designed to examine the efficacy and safety of SPRYCEL at 70mg twice daily or an increased dose of imatinib mesylate to 800mg/day (patients enrolled in the trial had been previously treated with imatinib mesylate less than or equal to 600mg/day).(1)

"This study may help answer important questions about treating resistant chronic-phase CML patients and suggests that physicians should consider treatment with SPRYCEL in patients resistant to lower doses of imatinib mesylate," said Neil Shah, MD, PhD, Assistant Professor, Division of Hematology/Oncology, University of California, San Francisco.

Analysis of the data at three months and 15 months follow-up show that the number of patients who achieved and maintained a major cytogenetic response increased from 36 percent to 53 percent with SPRYCEL, and from 29 percent to 33 percent with escalated doses of imatinib mesylate.

While the study was not powered to compare SPRYCEL to high-dose imatinib mesylate, analysis of the data after a median follow-up of 15 months show a statistically significant difference between SPRYCEL and high-dose imatinib mesylate in major and complete cytogenetic responses ($p=0.023$ and $p=0.004$, respectively), major molecular response ($p=0.038$) and progression-free survival (length of time during which the leukaemia does not progress) ($p<0.0001$).

Study Design and Results

This international, open-label, randomized Phase II study (START R, 017) was conducted in 23 countries. The study evaluated adult patients with chronic-phase CML who had primary or acquired resistance to 400-600mg doses of imatinib mesylate. Patients were randomized in a 2:1 ratio to start treatment with SPRYCEL 70mg twice a day (bid) (n=101) or imatinib mesylate 400mg bid (n=49). The primary endpoint of the study was major cytogenetic response rate at 12 weeks. Secondary efficacy endpoints included duration of, and time to achieve, major cytogenetic response as well as complete haematologic response. Major cytogenetic response is defined as complete (no signs of Philadelphia chromosome positive [Ph+] cells in the bone marrow) plus partial (less than 35 percent of Ph+ cells in

the bone marrow) cytogenetic responses. Complete haematologic response is a measure of how effective a treatment is in returning blood counts to normal and occurs when blood counts appear normal and patients have no signs or symptoms of disease.

Important non-haematologic adverse events of any severity in the SPRYCEL arm included diarrhoea (35%), nausea (24%), pleural effusion (17%), superficial oedema (15%), vomiting (9%), pulmonary oedema (3%), and muscle spasm (2%). Important non-haematologic adverse events in the imatinib mesylate arm included superficial oedema (39%), nausea (33%), diarrhoea (29%), vomiting (25%), and muscle spasm (12%). Grade 3 or 4 cytopenias observed in the SPRYCEL arm included low absolute neutrophil blood count (59%), platelets (55%), leukocytes (20%), and haemoglobin (18%). Grade 3 or 4 cytopenias observed in the imatinib mesylate arm included low absolute neutrophil white blood cells (39%), leukocytes (16%), platelets (14%), and haemoglobin (8%).

About SPRYCEL

SPRYCEL, which has been granted orphan drug status, received rapid approval from regulatory authorities in Europe for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy, including imatinib mesylate in November 2006. SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

Resistance to therapy is thought to involve the following mechanisms:(2)
- mutations of Bcr-Abl, the key protein responsible for CML and Ph+ ALL
- overexpression of Bcr-Abl
- other proteins involved in cancer pathways, such as the Src pathway, which is thought to play a role in CML and Ph+ ALL as well as other cancers.

Mutations can change the shape of the Bcr-Abl protein. When this happens, imatinib mesylate, the current standard treatment, may be unable to block its activity. SPRYCEL is an oral, multi-targeted therapy that can inhibit the action of Bcr-Abl in the presence of all but one known mutation.(3,4)

The European Medicines Agency reviewed the efficacy and safety of SPRYCEL based on the analysis of five Phase II multi-centre studies in patients with resistance or intolerance to imatinib mesylate in all phases of CML or Ph+ ALL.(2) The studies were conducted on five continents (33 countries) and SPRYCEL was shown to have a predictable and manageable side-effect profile.

In the 911 patients receiving SPRYCEL in clinical trials, the most common side effects were fluid retention (including pleural effusion and peripheral oedema), gastrointestinal (diarrhoea, nausea and vomiting), skin rash, headache, haemorrhage, fatigue, and dyspnoea (difficulty in breathing).

Myelosuppression (a reduction in blood-cell production by the bone marrow) was reported in all studies and was generally reversible. The frequency was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML.(2)

Full SPRYCEL Product Information and the European Public Assessment Report (EPAR) will be available at www.emea.europa.eu

About Bristol-Myers Squibb

Bristol-Myers Squibb is dedicated to the discovery, development and exhaustive exploration of innovative cancer-fighting therapies that extend and enhance the lives of patients living with cancer. More than 40 years ago, Bristol-Myers Squibb built a unified vision for the future of cancer treatment. With expertise, dedication and resolve, that vision led to the development of a diverse global portfolio of anti-cancer therapies that are an important cornerstone of care today. Hundreds of scientists at Bristol-Myers Squibb's Pharmaceutical Research Institute are studying ways to improve current cancer treatments and identify better, more effective medicines for the future.

Bristol-Myers Squibb is a global pharmaceutical and related health care products company whose mission is to extend and enhance human life.

References

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Contact:

Media contact: Yvette Venable, Bristol-Myers Squibb, Tel: +33-1-58-83-81-89, Mobile: +33-6-31-43-76-26, Email: yvette.venable@bms.com

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