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Data Supporting Boceprevir Response Guided Therapy Presented at American Association for the Study of Liver Diseases (AASLD) Annual Meeting

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BOSTON, Nov. 1 /PRNewswire-FirstCall/ -- Schering-Plough Corporation (NYSE: SGP) today reported two data presentations supporting response guided therapy with boceprevir combination therapy in patients with chronic hepatitis C virus (HCV) genotype 1. These retrospective analyses were presented at the American Association for the Study of Liver Diseases (AASLD) Annual Meeting in Boston, Oct. 30-Nov. 3.

Boceprevir is an investigational HCV protease inhibitor. Phase III registration studies with boceprevir in treatment-naïve HCV patients and patients who failed prior treatment have been fully enrolled and are expected to be completed in mid-2010.

Boceprevir response guided therapy utilizes a unique 4-week lead-in of PEGINTRON(R) (peginterferon alfa-2b) and REBETOL(R) (ribavirin, USP) prior to the addition of boceprevir (800 mg TID) for an additional 24-44 weeks. Response guided therapy is intended to enable the physician to determine the duration of boceprevir combination therapy based on a patient's viral response during treatment. Although baseline characteristics cannot predict which patients may benefit from longer therapy, in-treatment virologic responses appear likely to do so. The lead-in strategy allows for an assessment to define a patient's response to peginterferon and ribavirin alone in this initial 4-week treatment period.

Boceprevir Response Guided Therapy in Null Responder Patients

The boceprevir Phase II HCV SPRINT-1 study in treatment-naïve patients with HCV genotype 1 had two treatment arms in which patients received a 4-week lead-in followed by the addition of boceprevir for an additional 24 or 44 weeks (n=206). In an oral presentation at AASLD,(1) researchers analyzed results from these two arms to determine SVR rates in patients who had a null response to peginterferon and ribavirin therapy (defined as <1 log decrease in HCV viral load) after the 4-week lead-in period. Overall, 38 percent of null responders achieved SVR (19/50), with 25 percent (7/28) of patients who received 28 weeks of therapy and 55 percent (12/22) of patients who received 48 weeks of therapy achieving SVR. Patients with null response to peginterferon and ribavirin are considered to be among the most difficult to treat successfully and historically achieve a low rate of SVR.

"Although the numbers are small, this analysis of the HCV SPRINT-1 study data showed that it was possible

to achieve SVR in a proportion of null responders to peginterferon and ribavirin when boceprevir was added to their backbone regimen," said Paul Kwo, M.D., associate professor of medicine and medical director, liver transplantation, Department of Medicine, Division of Gastroenterology/Hepatology, Indiana University School of Medicine, Indianapolis, and lead investigator of the study. "However, the risk of developing viral resistance to protease inhibitors in patients who do not achieve SVR must be carefully weighed against the potential benefits of treatment with this new class of direct antiviral agents. With the lead-in strategy, initial peginterferon and ribavirin responsiveness is determined prior to the addition of a protease inhibitor, thus allowing the physician to take into account the potential for the development of resistance."

The ongoing Phase III boceprevir registration studies employ the lead-in strategy for all patients and will provide greater insight into the relationship between peginterferon and ribavirin responsiveness and the likelihood of achieving SVR in a diverse patient population. These Phase III studies, in treatment-naïve patients (HCV SPRINT-2) and patients who failed prior treatment (HCV RESPOND-2), prospectively evaluate the use of rapid viral response (RVR) to determine which boceprevir patients can stop all treatment at 28 weeks or 36 weeks, respectively. Patients without RVR receive a 48-week boceprevir-based regimen. RVR in these studies is defined as undetectable virus (HCV RNA) in plasma at 4 weeks after the addition of boceprevir (treatment week 8).

Boceprevir Response Guided Therapy to Determine Treatment Duration

In a poster presentation at AASLD,(2) researchers reported that patients in the lead-in arms (4 weeks of PEGINTRON and REBETOL followed by the addition of boceprevir) of the Phase II HCV SPRINT-1 study who had RVR and were treated for 28 weeks achieved an 82 percent SVR (54/66). Patients in the lead-in arms who did not have RVR, but had undetectable virus by treatment week 16, and were treated for 48 weeks achieved a 79 percent SVR (15/19). These results doubled the 38 percent SVR (39/104) achieved by patients in the control group receiving 48 weeks of peginterferon and ribavirin alone. Overall, 64 percent of patients in the lead-in arms achieved RVR (132/206).

"These results are very exciting and provide important insights to help further define response guided therapy with boceprevir using a peginterferon and ribavirin lead-in strategy," Kwo said. "Building on the RVR rate seen in this Phase II study, the boceprevir Phase III study in treatment-naïve patients is designed to confirm whether the majority of patients can be treated with a 28-week boceprevir-based regimen."

SVR was the primary efficacy endpoint of the HCV SPRINT-1 study. Based on an intent-to-treat analysis (ITT), the 28-week and 48-week lead-in boceprevir arms had SVR rates of 56 percent (58/103) and 75 percent (77/103), respectively, and the no lead-in boceprevir arms had SVR rates of 54 percent (58/107) and 67 percent (69/103), respectively, compared to 38 percent SVR for the control group.(3-5)

In the HCV SPRINT-1 study, the most common adverse events reported in the boceprevir arms were fatigue, anemia, nausea and headache. The incidence of skin adverse events (rash or pruritus) observed in the boceprevir arms was similar to that seen in the PEGINTRON and REBETOL control arm. Anemia occurred in approximately half of the patients in the boceprevir arms and over a third of patients in the control arm. Erythropoietin (EPO) supplementation was allowed in the study at the discretion of the investigator with concomitant ribavirin dose reduction and was used for 26 percent of patients in the control arm and 39-51 percent of patients in the boceprevir arms with standard-dose REBETOL.

Treatment discontinuations due to adverse events were between 9 and 19 percent for patients in the boceprevir arms, compared to 8 percent for the control arm. Treatment discontinuations in the boceprevir arms due to viral breakthrough were fewer in the 28- and 48-week lead-in arms (4 and 5 percent, respectively) compared to the no lead-in arms (7 and 12 percent, respectively).

About the HCV SPRINT-1 Study

In the Phase II HCV SPRINT-1 (HCV Serine Protease Inhibitor Therapy-1) study, boceprevir (800 mg TID) was evaluated in three treatment regimens: 4 weeks of PEGINTRON (1.5 mcg/kg once weekly) and REBETOL (800-1400 mg daily based on patient weight) therapy followed by the addition of boceprevir to the combination for 24 or 44 weeks (totaling 28 or 48 weeks of treatment), boceprevir in combination with PEGINTRON and REBETOL at the doses described above for 28 or 48 weeks, and, in Part II of the study, boceprevir in combination with PEGINTRON and low-dose REBETOL (400-1000 mg daily based on patient weight) for 48 weeks. In Part I of the study, the boceprevir regimens were compared to a control of PEGINTRON (1.5 mcg/kg once weekly) and REBETOL (800-1400 mg daily based on patient weight) alone for 48 weeks (an approved treatment regimen). In Part II of the study, boceprevir in combination with PEGINTRON and low-dose REBETOL for 48 weeks was compared to a contemporaneous control of PEGINTRON, full-dose REBETOL and boceprevir for 48 weeks.

The HCV SPRINT-1 study was conducted at sites across the United States, Canada and Europe. Overall, 77 percent of the 595 patients in the study were enrolled in the United States. African-Americans represented 16 percent of the patients enrolled and 7 percent of the patients in the study were cirrhotic.

Rationale for Lead-In Regimen

The use of the peginterferon and ribavirin lead-in prior to the addition of boceprevir was shown in the HCV SPRINT-1 study to reduce the incidence of viral breakthrough regardless of treatment duration. The rationale for the lead-in treatment regimen is based on the fact that both PEGINTRON and REBETOL reach steady-state concentrations by week 4, therefore patients have the protease inhibitor added at a time when the backbone drug levels have been optimized and the patient's immune system will have been activated and primed by PEGINTRON. With the lead-in strategy, initial peginterferon and ribavirin responsiveness is determined prior to the addition of a protease inhibitor, thus allowing the physician to take into account the potential for the development of resistance.

For more information about ongoing boceprevir studies, please visit www.clinicaltrials.gov, search term boceprevir.

About Hepatitis C

Hepatitis C is a serious and potentially life-threatening disease. It is the most common blood-borne infection in America and Europe, and the most common form of liver disease, affecting nearly 5 million people in the United States, 5 million in Europe and some 200 million people worldwide. It is the leading cause of cirrhosis and liver cancer, and the number one reason for liver transplants in the United States and Europe.

About PEGINTRON

PEGINTRON is indicated for use in combination with REBETOL (ribavirin) for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease.

The following points should be considered when initiating therapy with PEGINTRON in combination with REBETOL: (1) These indications are based on achieving undetectable HCV RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose. (2) Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection. (3) No safety and efficacy data are available for treatment of longer than one year.

PEGINTRON is also indicated for use alone for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with interferon alpha and who are at least 18 years of age.

The following points should be considered when initiating therapy with PEGINTRON alone: Combination

therapy with REBETOL is preferred over PEGINTRON monotherapy unless there are contraindications to, or significant intolerance of, REBETOL. Combination therapy provides substantially better response rates than monotherapy.

Important Safety Information on PEGINTRON

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

Alpha interferons, including PEGINTRON, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping PEGINTRON therapy.

Use with Ribavirin: Ribavirin may cause birth defects and death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with REBETOL therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Contraindications

PEGINTRON is contraindicated in patients with known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis to interferon alpha or any other component of the product, autoimmune hepatitis, and hepatic decompensation (Child-Pugh score >6 [class B and C]) in cirrhotic CHC patients before or during treatment.

PEGINTRON/REBETOL combination therapy is additionally contraindicated in women who are pregnant or may become pregnant (see Boxed Warning and Pregnancy section), men whose female partners are pregnant, patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia), and patients with creatinine clearance <50 mL per min.

Pregnancy

REBETOL therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients during therapy and six months post-treatment. Patients should use at least two effective forms of contraception and have monthly pregnancy tests during therapy and for six months after completion of therapy. If this drug is used during pregnancy or if a patient becomes pregnant, the patient should be apprised of the potential hazard to a fetus. A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment, and for six months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

Incidence of Adverse Events

Most common adverse reactions (>40%) in adult patients receiving either PEGINTRON or PEGINTRON/REBETOL are injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and anxiety/emotional lability/irritability. Most common adverse reactions (>25%) in pediatric patients receiving PEGINTRON/REBETOL are pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.

In a study with PEGINTRON/REBETOL (weight-based) combination therapy in adult patients, anemia with weight-based dosing was 29%; however, the majority of these cases were mild and responded to dose reductions. The incidence of serious adverse reactions reported for the weight-based REBETOL group was

12%. In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some patients experienced ongoing or new serious adverse reactions during the 6-month follow-up period. Discontinuations for adverse events were 15% and were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions. Dose modifications due to adverse reactions occurred in 29% of patients.

Most common adverse reactions with PEGINTRON/REBETOL (weight-based) combination therapy were psychiatric, which occurred among 68-69% of patients. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up after treatment cessation. PEGINTRON induced fatigue or headache in approximately two-thirds of patients, with fever or rigors in approximately half of the patients. The severity of some of these systemic symptoms (e.g., fever and headache) tends to decrease as treatment continues. There was a 23-24% incidence overall for injection site reactions or inflammation.

Individual serious adverse reactions occurred at a frequency equal to or less than 1% and included suicide attempt, suicidal ideation, severe depression; psychosis, aggressive reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia, retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema, bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout, hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, sarcoidosis, aggravated psoriasis, urticaria, injection site necrosis, vasculitis, and phototoxicity.

Additional serious adverse events included suicide, homicidal ideation, aggressive behavior sometimes directed towards others, hallucinations, bipolar disorders, mania, encephalopathy (usually elderly treated with higher doses of PEGINTRON), hypotension, tachycardia, retinopathy including macular edema, retinal hemorrhage, cotton wool spots, papilledema, serous retinal detachment, ischemic and hemorrhagic cerebrovascular events, bone marrow toxicity (cytopenia and very rarely aplastic anemia), thyroiditis, dental and periodontal disorders, hemorrhagic/ischemic colitis, dyspnea, pulmonary infiltrates, pneumonia, interstitial pneumonitis, pulmonary hypertension, hepatic failure, increases in serum creatinine in patients with renal insufficiency, acute hypersensitivity (angioedema, bronchoconstriction, anaphylaxis and cutaneous eruptions), hypertriglyceridemia, and peripheral neuropathy.

During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years receiving PEGINTRON/REBETOL combination therapy, weight loss and growth inhibition were common.

Please see full prescribing information at <http://www.spfiles.com/pipeg-intron.pdf>.

About Schering-Plough

Schering-Plough is an innovation-driven, science-centered global health care company. Through its own biopharmaceutical research and collaborations with partners, Schering-Plough creates therapies that help save and improve lives around the world. The company applies its research-and-development platform to human prescription, animal health and consumer health care products. Schering-Plough's vision is to "Earn Trust, Every Day" with the doctors, patients, customers and other stakeholders served by its colleagues around the world. The company is based in Kenilworth, N.J., and its Web site is www.schering-plough.com.

SCHERING-PLOUGH DISCLOSURE NOTICE: The information in this press release includes certain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements relating to the potential market for boceprevir, PEGINTRON and REBETOL.

Forward-looking statements relate to expectations or forecasts of future events. Schering-Plough does not assume the obligation to update any forward-looking statement. Many factors could cause actual results to differ materially from Schering-Plough's forward-looking statements, including uncertainties in the regulatory process, among other uncertainties. For further details about these and other factors that may impact the forward-looking statements, see Schering-Plough's Securities and Exchange Commission filings, including Part II, Item 1A. "Risk Factors" in the Company's third quarter 2009 10-Q, filed October 29, 2009.

Endnotes

1. Kwo P, Lawitz E, McCone J, et al. High Sustained Virologic Response in Genotype 1 Null Responders to Peginterferon alfa-2b plus Ribavirin When Treated with Boceprevir Combination Therapy. American Association for the Study of Liver Diseases (AASLD) Annual Meeting; Oct. 30-Nov. 3, Boston, MA, USA; oral presentation, Abstract No. 62.
2. Kwo P, Lawitz E, McCone J, et al. Response-Guided Therapy for Boceprevir Combination Treatment? - Results from HCV SPRINT-1. American Association for the Study of Liver Diseases (AASLD) Annual Meeting; Oct. 30-Nov. 3, Boston, MA, USA; poster presentation, Abstract No. 1582.
3. Kwo P, Lawitz E, McCone J, et al. HCV SPRINT-1 Final Results: SVR 24 from a Phase 2 study of Boceprevir Plus PegIntron (Peginterferon alfa-2b)/Ribavirin in Treatment-Naive Subjects with Genotype 1 Chronic Hepatitis C. 44th European Association for the Study of the Liver (EASL) 2009 Annual Meeting; April 22-26, Copenhagen, Denmark; oral presentation, Abstract No. 4.
4. Intention-To-Treat (ITT) analysis includes any patient who took at least one dose of any study drug.
5. SVR, the protocol specified primary efficacy endpoint, is defined as achievement of undetectable HCV-RNA at 24 weeks after the end of treatment. Per protocol, if a patient did not have a 24-week post-treatment assessment, the patient's 12-week post-treatment assessment was utilized.

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