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The New England Journal of Medicine Publishes Pivotal Studies Showing Potential of New Investigational Treatment for Chronic Infection with Hepatitis C Virus Genotype 1

Addition of boceprevir significantly increased treatment success in more patients and in a significantly shorter time period compared to standard treatment

MONTREAL, QUEBEC, March 30, 2011 – Two Phase III studies (HCV RESPOND-2 and HCV SPRINT-2) are published in the March 31 edition of the *New England Journal of Medicine (NEJM)* demonstrating that addition of the investigational oral medication boceprevir to standard treatment significantly improved sustained virologic response (SVR) – the goal of treatment – in a significantly greater number of adult patients who failed previous treatment (treatment-failure) and in those who were new to treatment (treatment-naïve) for chronic hepatitis C virus (HCV) genotype 1, compared to standard therapy alone. Also, both studies investigated a new treatment strategy resulting in many patients being able to shorten the duration of therapy from the standard 48 weeks.¹

“These results signal a truly important change in the treatment of hepatitis C genotype 1 infection, one of the most prevalent genotypes in Canada,” said Dr. Marc Bilodeau, a Canadian investigator in the SPRINT-2 study and Associate Professor of Medicine at Université de Montréal. “The addition of boceprevir not only substantially increased the success rates, but also by using response-guided therapy – which indicates how individuals are responding to treatment – many patients taking the drugs for the first time saw their treatment times cut almost in half.”

“Being able to shorten the length of treatment is extremely important given that one of the most challenging aspects of treating HCV is managing the debilitating side effects. Because the side effects are so hard to take, unfortunately some patients stop their course of therapy,” said Dr. Mark Levstik, an investigator in the SPRINT-2 NEJM-published study and Assistant Professor, Department of Medicine, Division of Gastroenterology, University of Western Ontario.

Boceprevir, an investigational agent not currently available in Canada, belongs to a novel class of direct-acting antiviral agents – called HCV protease inhibitors – that reduce the amount of virus in the blood through inhibition of the function of a viral protein called ‘protease’ that HCV needs to replicate.²

An estimated 250,000 individuals in Canada are infected with HCV and there are 3,200 to 5,000 newly infected individuals each year.³ HCV damages the liver and may lead to serious complications, including death, when left untreated.⁴ It is the leading cause of liver transplants in Canada.⁵

“The use of a protease inhibitor to treat hepatitis C infection is an important advance in the management of the disease,” said Dr. Alnoor Ramji, an investigator in both the SPRINT-2 and the RESPOND-2 published studies and a Clinical Assistant Professor at the University of British Columbia. “As a Canadian investigator, I am encouraged that the studies have been published in this prestigious medical journal. It reinforces the importance of our results.”

Treatments Improve, Stigma Persists

Karen Stacey lived with the virus for many years before experiencing any symptoms. Her diagnosis came slowly, and only after many tests and visits to multiple physicians.

“I remember constantly feeling dizzy and nauseous, and having a hard time with my memory,” said Ms. Stacey. “When I was finally diagnosed with hepatitis C, I had this sinking feeling that people felt I deserved to get this disease. In the minds of many people, only drug addicts or alcoholics get this virus.”

Past or current drug use accounts for more than 56 per cent of all hepatitis C infection in Canada.⁶ In addition, the virus may be contracted via use of unscreened blood or blood products in medical procedures, body piercing, mother-child transmission and accidental needle-sticking in medical settings. In Karen’s case, she contracted the virus following a blood transfusion, which she required during a failed pregnancy in the 1970s.

“To help eliminate the terrible stigma I suffered following my diagnosis, I’m dedicated to educating Canadians about the disease,” said Ms. Stacey. “The most frightening thing about the stigma is that it creates an enormous barrier for people infected with hepatitis C to get diagnosed and receive treatment that could cure their disease.”

About HCV: A Silent Disease

Approximately one-in-three of those infected with HCV are not aware of their infection and it often goes undetected for many years until symptoms appear.⁷ Symptoms can include fever, fatigue, reduced appetite, stomach pain, dark urine, jaundice (yellowing of skin or eyes), nausea and vomiting, aching muscles and joints, and poor concentration.⁸ If left untreated, HCV may lead, in some patients, to liver fibrosis, cirrhosis, liver cancer and liver failure.⁹

About the Studies

The two studies (HCV RESPOND-2 and HCV SPRINT-2) each evaluated two new treatment strategies with boceprevir administered in combination with peginterferon alfa-2b and ribavirin (PR) to assess the ability of boceprevir to improve SVR rates – the goal of treatment – and potentially shorten overall treatment duration compared to the use of PR alone for 48 weeks, which is the current standard duration of therapy.

The HCV RESPOND-2 study examined the use of boceprevir in adult patients who previously failed to eradicate the virus with current standard therapy, including patients who had either relapsed after initially clearing the virus or were non-responders to prior treatment with PR. The HCV SPRINT-2 study examined the use of boceprevir in adult patients who were treatment-naïve (no prior treatment).

A total of 1,500 patients participated in the two studies, with nearly 10 per cent of patients (146) recruited at 15 Canadian investigation sites. In each study, patients were randomized to one of three treatment arms:

- **Response-guided therapy (RGT)**, in which total treatment duration was based on certain early response criteria. Treatment-failure patients with undetectable virus (HCV-RNA) at week eight were eligible to stop all treatment at 36 weeks. Treatment-naïve patients who had undetectable virus (HCV-RNA) during weeks eight through 24 were eligible to stop all treatment at 28 weeks.
- **48 weeks of treatment**, in which patients received a four-week lead-in with PR followed by the addition of boceprevir for 44 weeks.
- **Control**, in which patients received PR for 48 weeks.

In the HCV RESPOND-2 study (treatment-failure patients), the addition of boceprevir in the RGT arm resulted in 59 per cent of patients eliminating the virus and 66 per cent in the 48-week treatment arm, compared to 21 per cent in the control group ($p < 0.0001$).

In the HCV SPRINT-2 study (treatment-naïve patients), the addition of boceprevir in the RGT arm resulted in 63 per cent of patients eliminating the virus and 66 per cent for the 48 week treatment arm, compared to 38 per cent in the control group ($p < 0.0001$).

Study authors reported that nearly half of all patients in the RGT arms of both studies met the early response criteria, meaning that they received a shorter total duration of therapy. In the HCV RESPOND-2 study, 46 per cent of patients met the early response criteria, and were able to stop all treatment at 36 weeks (12 weeks shorter than current standard therapy). In the HCV SPRINT-2 study, 44 per cent of patients met the early response criteria and were able to stop all treatment at 28 weeks (20 weeks shorter than current standard therapy).

In the HCV RESPOND-2 study, the most commonly reported side effects were fatigue, headache, nausea, chills and influenza-like illness. Serious adverse events were reported in 10 per cent of patients in the RGT arm of the study, 14 per cent of patients in the 48-week treatment arm and in five per cent of patients in the control group. Discontinuation of treatment due to adverse events over the total course of the study was eight per cent in the RGT arm, 12 per cent for the 48-week treatment arm and three per cent for control.

Tolerability profile in treatment-failure patients

The five most common treatment-related adverse events in the HCV RESPOND-2 study reported for patients receiving boceprevir in RGT, boceprevir in a 48-week treatment regimen and control, respectively, were: fatigue, headache, nausea, anemia and chills. Serious adverse events were reported in 10, 14 and five per cent of patients in the study arms, respectively. There was one death in the study, a suicide in the group receiving boceprevir in RGT, which occurred 18 weeks after the end of the study treatment and was considered to be unrelated to the study treatment.

Treatment discontinuations due to adverse events over the total course of all treatment were eight per cent and 12 per cent for patients receiving boceprevir in RGT and boceprevir in a 48-week treatment regimen, respectively, compared to two per cent for control. Treatment discontinuations due to anemia were 0 per cent and three per cent for the treatment groups receiving boceprevir, respectively, compared to 0 per cent for control.

Tolerability profile in treatment-naïve patients

The five most common treatment-related adverse events in the HCV SPRINT-2 study reported for patients receiving boceprevir in RGT, boceprevir in a 48-week treatment regimen and control, respectively, were: fatigue, headache, nausea, anemia and dysgeusia (bad taste). Serious adverse events were reported in 11, 12 and nine per cent of patients in the study arms, respectively. There were six deaths during the study: four patients in the control group died, as did two patients in the boceprevir groups. Two suicides (one patient in the control group and one patient receiving boceprevir in RGT) were judged to have possibly been related to peginterferon. No other deaths were considered to be drug-related.

Treatment discontinuations due to adverse events over the total course of all treatment were 12 per cent and 16 per cent for patients receiving boceprevir in RGT and boceprevir in a 48-week treatment regimen, respectively, compared to 16 per cent for control. Treatment discontinuations due to anemia were two per cent for each of the treatment groups receiving boceprevir compared to one per cent for control.

The HCV RESPOND-2 and HCV SPRINT-2 studies each employed futility or “stopping” rules, whereby patients in any treatment arm who had detectable virus at week 12 in the HCV RESPOND-2 study or at week 24 in the HCV SPRINT-2 study were considered treatment failures and discontinued all treatment. The stopping rules allowed study patients who did not respond to treatment to have therapy stopped early, thereby avoiding unnecessary treatment.

Boceprevir is an investigational medication and not currently available in Canada.

Merck’s global commitment to advancing hepatitis therapy

Merck is committed to building on its strong legacy in the field of viral hepatitis by continuing to discover, develop and deliver vaccines and medicines to help prevent and treat viral hepatitis. Extensive research efforts are underway to develop differentiated oral therapies that bring innovation to viral hepatitis care.

About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.ca.

Forward-Looking Statement

This news release includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. Such statements may include, but are not limited to, statements about the benefits of the merger between Merck and Schering-Plough, including future financial and operating results, the combined company's plans, objectives, expectations and intentions and other statements that are not historical facts. Such statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. Actual results may differ from those set forth in the forward-looking statements.

The following factors, among others, could cause actual results to differ from those set forth in the forward-looking statements: the possibility that the expected synergies from the merger of Merck and Schering-Plough will not be realized, or will not be realized within the expected time period; the impact of pharmaceutical industry regulation and health care legislation; the risk that the businesses will not be integrated successfully; disruption from the merger making it more difficult to maintain business and operational relationships; Merck's ability to accurately predict future market conditions; dependence on the effectiveness of Merck's patents and other protections for innovative products; the risk of new and changing regulation and health policies in the United States and internationally and the exposure to litigation and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2009 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

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- ¹ Merck news release: In Pivotal Phase III Studies, Merck's Investigational Medicine Boceprevir Helped Majority of Patients with Chronic Hepatitis C Genotype 1 Infection Achieve Sustained Virologic Response, the Primary Endpoint of the Studies. Available at: http://www.merck.com/newsroom/news-release-archive/research-and-development/2010_0804.html. March 15, 2011.
 - ² *Ibid* .
 - ³ Canadian Institutes of Health Research. About the Hep C Research Initiative. <http://www.cihr-irsc.gc.ca/e/38855.html>. Accessed March 23, 2011.
 - ⁴ Public Health Agency of Canada. <http://www.phac-aspc.gc.ca/hepc/pubs/multiling-hepc/index-eng.php>. Accessed March 23, 2011.
 - ⁵ Canadian Liver Foundation. http://www.liver.ca/Liver_Disease/. Accessed March 23, 2011.
 - ⁶ Sherman M, Shafran S, Burak K, et al. Management of Chronic Hepatitis C: Consensus Guidelines. *Can J Gastroenterol* (2007).
 - ⁷ Public Health Agency of Canada. <http://www.phac-aspc.gc.ca/hepc/pubs/ihp-ips/index-eng.php>. Accessed March 21, 2011.
 - ⁸ Health Canada. <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/diseases-maladies/hepc-eng.php>. Accessed March 23, 2011.
 - ⁹ Public Health Agency of Canada. <http://www.phac-aspc.gc.ca/hepc/pubs/multiling-hepc/index-eng.php>. Accessed March 18, 2011.