BMS Submits First All-Oral, Interferon-Free and Ribavirin-Free Treatment Regimen for Regulatory Review in Japan for Patients with Chronic Hepatitis C Infection

- An overall SVR24 rate of 84.7 percent was achieved in Phase III study of daclatasvir (DCV) and asunaprevir (ASV) in high unmet need genotype 1b patient population1

- DCV+ASV achieved 87.4% SVR24 rates in interferon-ineligible/intolerant patients and 91.9% SVR24 among this population aged 65+, providing potential treatment alternative for many people who currently have no options1

- In this study, the DCV+ASV regimen had low rates of discontinuation (5%) due to adverse events, and low rates of serious adverse events (5.9%)1

- Data presentation led AASLD Viral Hepatitis Presidential Plenary session on Tuesday, November 5

UXBRIDGE, UK, NOVEMBER 6, 2013 – Bristol-Myers Squibb (BMS) has announced the submission of a New Drug Application (NDA) for what would become the World’s first interferon-free and ribavirin-free treatment regimen for patients with chronic hepatitis C (HCV). BMS has filed the NDA with Japan’s Pharmaceutical and Medical Devices Agency, with a view to making additional, similar submissions to other global health authorities in the future. The submission is based on results from a Phase III study demonstrating that the 24-week, all-oral, interferon-free and ribavirin-free regimen of daclatasvir (DCV) and asunaprevir (ASV) achieved an overall sustained virologic response 24 weeks after the end of treatment (SVR24) of 84.7% in Japanese patients with chronic hepatitis C genotype 1b who were either interferon-ineligible/intolerant (87.4% SVR24) or nonresponders (null and partial) to interferon-based therapies (80.5% SVR24).1

These Phase III data led the Presidential Plenary at the Viral Hepatitis Session on November 5 during the 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Washington D.C.

Globally, there are up to 170 million people who are infected with HCV.2 There are approximately 1.2 million people living with HCV in Japan3,4 and around 70 percent of these patients have genotype 1b5, which has one of the lowest response rates to current treatments.6 In 2010 there were an estimated 64,000 patients with genotype 1b in the UK.7 The prevalence of genotype 1b in the UK is around 43% of cases7 and HCV-related end stage liver disease hospital
admissions have continued to rise. Data estimates hospital admissions have increased from 612 in 1998 to 1,979 in 2010. Many patients with HCV are over the age of 60, and this group is commonly associated with more disease-related complications and a decreased likelihood of tolerating interferon-based therapies, the standard for treating HCV.

“With our submission in Japan, we are pleased to be one step closer to bringing a potential new treatment option to the many people living with HCV in that country,” said Brian Daniels, MD, senior vice president, Global Development and Medical Affairs, Research and Development, Bristol-Myers Squibb. “The all-oral regimen of DCV plus ASV in this study represents the potential for a significant advance in the treatment of HCV infection in Japan, particularly when considering that Japanese patients chronically infected with HCV are often older than in other countries and predominantly infected with genotype 1b, both factors which impact response to therapy.”

The regimen used in the Phase III study resulted in low rates of discontinuation (5%) due to adverse events (AEs). In addition, the rate of serious adverse events (SAEs) was low (5.9%) and varied among patients. Nasopharyngitis was the most common adverse event in the study (30.2%, 67/222).

“The Phase III study results of daclatasvir plus asunaprevir are exciting to see, especially in this difficult-to-treat patient population. If approved, this regimen has the potential to offer HCV patients in Japan, who are unable to achieve SVR with the current interferon-based standard of care, a new treatment option,” said lead study investigator Kazuaki Chayama of Hiroshima University, Japan.

- ENDS -
NOTES TO EDITORS

Study Design and Results

In this open-label, parallel group, Phase III study, interferon ineligible/intolerant (IN/I) patients (n=135) and interferon/ribavirin nonresponder (NR) patients (n=87) received DCV 60 mg once daily plus ASV 100 mg twice daily for 24 weeks. The primary endpoint was the percentage of patients with a sustained virologic response at 24 weeks after the end of treatment (SVR24).

Virologic Response
- High rates of SVR24 were achieved in the two studied patient populations – those IN/I patients with limited therapeutic options (87.4%, 118/135) and those NR patients typically associated with low responses to interferon-based therapies (80.5%, 70/87).
- Patients ≥ 65 years of age had SVR24 rates similar to those in patients < 65 years and age did not appear to impact response rates. SVR24 rates for those ≥ 65 years of age were 91.9% (57/62) in the IN/I elderly patient population and 85.2% (23/27) in the NR elderly population.
- There was no clinically significant difference in SVR24 by traditionally important baseline factors including gender, age, baseline HCV RNA, cirrhosis, and IL28B genotype.
- There were low rates of virologic breakthrough and EOT (end of treatment) detectable HCV RNA (17/222 patients (7.7%)), and low rates of relapse (17/213 patients (8.0%)).

On-Treatment Safety

No deaths were reported and the study discontinuation rate was low (12.6%, 28/222). There were low rates of serious adverse events (5.9%, 13/222) and few adverse events were reported in greater than 10% of patients. The most common adverse events reported were nasopharyngitis (30.2%, 67/222), increased ALT (15.8%), increased AST (12.6%), headache (15.8%), diarrhea (9.9%) and pyrexia (12.2%). A limited number of Grade 3-4 laboratory abnormalities were observed in greater than 3 percent of patients.
The most common AE leading to discontinuation was ALT/AST elevation, a measure of liver inflammation. Of the 11 patients who discontinued due to an AE, 10 discontinued due to ALT/AST elevation. Despite early discontinuation, 80% of these patients achieved SVR\textsubscript{24} and all ALT/AST values returned to normal.

**About Bristol-Myers Squibb’s HCV Portfolio**

Bristol-Myers Squibb’s hepatitis C pipeline includes compounds with different mechanisms of action, pursuing both biologics as well as small molecule direct-acting antivirals. These compounds are being studied as part of multiple treatment regimens with the goal of increasing SVR rates across diverse patient types and geographies.

- Our investigational NS5A replication complex inhibitor daclatasvir (DCV) has been extensively studied in thousands of patients to date as a foundational agent for multiple DAA-based combination therapies and is currently in Phase III development. DCV has shown antiviral potency and pan-genotypic activity across HCV genotypes *in vitro*. DCV has a drug-drug interaction profile that supports its continued study in a variety of HCV combination regimens
- Asunaprevir (ASV) is an NS3 protease inhibitor in Phase III development for hepatitis C as a component of DCV-based treatment regimens
- BMS-791325 is a non-nucleoside inhibitor of the NS5B polymerase, currently in Phase II development for hepatitis C as a component of DCV-based treatment regimens
- Lambda is an investigational type III interferon that has the potential to offer an alternative to alfa-interferon in patients for whom an interferon-based regimen is required or preferred

**About Hepatitis C**

Hepatitis C is a virus that infects the liver and is transmitted through direct contact with infected blood and blood products.\textsuperscript{10} Up to 170 million people worldwide are infected with hepatitis C, with genotype 1 being the most prevalent genotype.\textsuperscript{2} Up to 90 percent of those infected with hepatitis C will not clear the virus and will become chronically infected.\textsuperscript{11} According to the World Health Organization, 20 percent of people with chronic hepatitis C will develop cirrhosis and, of those, up to 25 percent may progress to liver cancer.\textsuperscript{12,13} In Japan, the
hepatitis C virus is the most common cause of chronic hepatitis and cirrhosis, and approximately 1.2 million people there are living with the hepatitis C virus.\textsuperscript{3,4}

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [http://www.b-ms.co.uk](http://www.b-ms.co.uk).

**Bristol-Myers Squibb Forward Looking Statement**

*This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that the clinical trials of these compounds will support regulatory filings, or that the compounds described in this release will receive regulatory approvals or, if approved, that they will become commercially successful products. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2012, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.*

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