Investigational Hepatitis C Quad Therapy Regimen of Daclatasvir and Asunaprevir Plus Interferon Alfa and Ribavirin Achieved SVR24 in 93% of Difficult-to-Treat Genotype 1a/b Prior Null Responders in Expanded Phase II Study

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- Quad therapy treatment groups included predominantly genotype 1a patients, a patient population with limited treatment options
- Findings support the ongoing development of multiple daclatasvir-based treatment regimens to help meet the needs of diverse HCV patient population

BOSTON--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced new Phase II data demonstrating that an investigational quad therapy regimen combining the NS5A replication complex inhibitor daclatasvir (DCV), the NS3 protease inhibitor asunaprevir (ASV), and a backbone of alfa interferon and ribavirin (alfa/RBV) achieved sustained virologic response rates 12- and 24-weeks post-treatment (SVR12 and SVR24) of 95% (39/41) and 93% (38/41), respectively, in patients with genotype 1 (GT1) hepatitis C virus (HCV) who were prior null responders to alfa/RBV. The DCV ASV Quad treatment groups included predominantly GT1a patients (36/41), a patient population with limited effective treatment options.

These data were presented today at the American Association for the Study of Liver Diseases congress in Boston, along with safety and efficacy data on DCV/ASV Dual therapy in GT1b prior null responders enrolled in this same study.

There were no serious adverse events related to study drug or discontinuations due to adverse events in the DCV ASV Quad therapy treatment groups of this study. Overall, headache was the most common adverse event in the DCV ASV Quad treatment groups (60%, 43%).

“In this study, we are encouraged to see that patients who are among the most difficult to treat – those with genotype 1a who did not respond to previous treatment with alfa interferon and ribavirin – demonstrated high SVR rates of 93 percent,” said Brian Daniels, MD, senior vice president, Global Development and Medical Affairs, Research and Development, Bristol-Myers Squibb. “The results seen with this daclatasvir-based quadruple regimen are important as we continue to evaluate treatment approaches that improve response rates in this challenging patient population.”

Daclatasvir is the first NS5A replication complex inhibitor to be investigated in HCV clinical trials and is currently in Phase III development. Asunaprevir is an oral, NS3 protease inhibitor in Phase III development with daclatasvir.

Study Design and Results

The expansion of this randomized, open-label, phase IIa study evaluated the antiviral activity and safety of the combination of DCV and ASV with and without alfa/RBV in 101 HCV genotype 1 prior null responders to alfa/RBV. The primary endpoint of the study was the proportion of patients achieving undetectable viral load (HCV RNA < LLOQ_TND) 12 weeks post-treatment (SVR12).

Patients received one of five treatment regimens for 24 weeks. Genotype 1b infected patients were randomized to receive one of four treatment regimens for 24 weeks (two DCV/ASV Dual treatment groups, two DCV/ASV/Alfa/RBV Quad treatment groups). Genotype 1a infected patients were randomized to receive one of two treatment regimens for 24 weeks (two DCV/ASV/Alfa/RBV Quad treatment groups). A fifth group (DCV/ASV/RBV Triple therapy) included both GT1a and GT1b infected patients and enrolled separately. The DCV/ASV Quad treatment groups received DCV 60 mg once daily and ASV 200 mg either twice daily (Group B1) or once daily (Group B2). Both groups received a backbone of PEG-interferon alfa-2a 180 µg once weekly and ribavirin 1000-1200 mg daily (according to body weight) in two divided doses.

Virologic Response

DCV ASV Quad therapy resulted in high rates of sustained virologic response in this predominantly genotype 1a prior null
responder patient population. Of patients in Groups B1 and B2, 85% (17/20) and 91% (19/21) had HCV genotype 1a.

- Group B1 patients (ASV dosed BID), achieved SVR12 and SVR24 rates of 95% (19/20) and 90% (18/20), respectively. One patient did not receive a viral load measurement at 24 weeks post-treatment.
- Group B2 patients (ASV dosed QD) achieved SVR12 and SVR24 rates of 95% (20/21).
- There was no virologic breakthrough in either Group B1 or B2. Two patients relapsed post-treatment, one Group B1 patient at week 4 and one Group B2 patient at week 12.

The study also found that in a GT1a prior null responder population, an interferon-free regimen of DCV, ASV 200 mg BID and ribavirin resulted in a high rate of viral breakthrough and did not warrant further investigation.

**Safety**

In the patients treated with DCV ASV Quad therapy, there were no serious adverse events due to study drug, no deaths, and no treatment discontinuations due to adverse events (AEs). Most AEs were mild to moderate in severity. The most common AEs (≥40% in any group) were:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Group B1 DCV + ASV 200 mg BID + alfa/RBV</th>
<th>Group B2 DCV + ASV 200 mg QD + alfa/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>60% (12/20)</td>
<td>43% (9/21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45% (9/20)</td>
<td>33% (7/21)</td>
</tr>
<tr>
<td>Weakness</td>
<td>30% (6/20)</td>
<td>57% (12/21)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40% (8/20)</td>
<td>24% (5/21)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>45% (9/20)</td>
<td>14% (3/21)</td>
</tr>
</tbody>
</table>

Eleven patients experienced Grade 3 or 4 neutropenia. Eight patients experienced Grade 3-4 lymphopenia (absolute). Four patients experienced Grade 3-4 leukopenia. Grade 3-4 ALT/AST elevations were infrequent. None were accompanied by elevated total or direct bilirubin and all AST/ALT elevations improved without intervention.

**About Bristol-Myers Squibb’s Commitment to Liver Disease**

Bristol-Myers Squibb is studying a portfolio of compounds that aims to address unmet medical needs across the liver disease continuum, including hepatitis C, hepatitis B and liver cancer. The Company’s hepatitis C pipeline includes compounds with different mechanisms of action, pursuing both biologics as well as small molecule DAAs. These compounds are being studied as part of multiple treatment regimens with the goal of increasing SVR rates across diverse patient types and geographies.

Daclatasvir is an NS5A replication complex inhibitor that is being extensively studied as a key component of potential DAA-based hepatitis C treatment regimens. Studied in more than 3,000 patients to date, daclatasvir is in Phase III development. Asunaprevir is an NS3 protease inhibitor in Phase III development for hepatitis C as a component of daclatasvir-based treatment regimens, and has been studied in more than 1,200 patients to date.

**About Hepatitis C**

Hepatitis C is a virus that infects the liver and is transmitted through direct contact with infected blood and blood products. An estimated 170 million people worldwide are infected with hepatitis C, with genotype 1 being the most prevalent genotype. Up to 90 percent of those infected with hepatitis C will not clear the virus and will become chronically infected. Twenty percent of people with chronic hepatitis C will develop cirrhosis and, of those, up to 25 percent may progress to liver cancer.

**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.bms.com](http://www.bms.com) or follow us on Twitter at [http://twitter.com/bmsnews](http://twitter.com/bmsnews).

**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 compounds described in this release will support regulatory filings, or that the compounds will receive regulatory approvals or, if approved, 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, 2011, 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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