Phase IIIb Comparison of BARACLUDE® (entecavir) Monotherapy Versus BARACLUDE Plus Tenofovir Combination Shows No Statistical Difference Between Study Arms

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- 96-week study in a population of nucleos(t)ide-naïve patients with chronic hepatitis B (CHB) infection
- Data presented at the American Association for the Study of Liver Diseases congress in San Francisco

SAN FRANCISCO--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced 96-week results from the BE-LOW™ study, a Phase IIIb clinical trial comparing BARACLUDE monotherapy (0.5mg once daily) with BARACLUDE (0.5mg once daily) plus tenofovir (300mg once daily) in treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB) with compensated liver disease. In this study, no statistically significant difference was observed between the two treatment arms in the primary efficacy endpoint of HBV DNA <50 IU/mL (approximately 300 copies per mL)1 at 96 weeks: 76.4% in the BARACLUDE monotherapy arm and 83.2% in the BARACLUDE plus tenofovir arm (p=0.0882).

Overall, both study arms had similar safety profiles. Serious adverse events (SAEs) in this study were reported in 6.6% (12/182) of patients in the BARACLUDE monotherapy arm and in 7.1% (14/197) of patients in the BARACLUDE plus tenofovir arm. These data were reported today at the 62nd annual meeting of the American Association for the Study of Liver Diseases (AASLD) in San Francisco, California (Abstract #223, presented orally during the Presidential Plenary Session on Viral Hepatitis).

“In these 96-week data comparing entecavir monotherapy to combination of entecavir plus tenofovir, we found that combination therapy did not result in statistically significant difference in virologic response compared to entecavir monotherapy. The BE-LOW study data confirmed the results of previous studies showing limited or no benefit of combination therapy compared to monotherapy for treatment-naïve patients with chronic hepatitis B,” said principal investigator Anna Lok, MD, FRCP, director of clinical hepatology and professor in the department of internal medicine at the University of Michigan Medical School in Ann Arbor.

Study Results
In this study, 379 nucleos(t)ide-naïve patients with CHB were randomized to receive either BARACLUDE (entecavir) 0.5 mg once daily (n=182) or BARACLUDE 0.5 mg plus tenofovir 300 mg once daily (n=197). Key findings at week 96 are:

- A comparable proportion of patients in both treatment arms achieved the primary efficacy endpoint of HBV DNA <50 IU/mL at 96 weeks: 76.4% (139/182) in the BARACLUDE monotherapy arm and 83.2% (164/197) in the BARACLUDE plus tenofovir arm (p=0.0882).

- Among HBeAg-positive patients, the proportion achieving HBV DNA <50 IU/mL was 69.8% (88/126) in the BARACLUDE monotherapy arm versus 80.4% (111/138) in the BARACLUDE plus tenofovir arm (p=0.0460). Further analysis suggested that this difference could be accounted for by the subset of patients with a high baseline viral load. Among those HBeAg-positive patients with a baseline viral load ≥10^8 IU/mL, 83% achieved HBV DNA <50 IU/mL in both treatment arms (BARACLUDE monotherapy 39/47; BARACLUDE plus tenofovir 44/53; p=ns). However, for those with a baseline viral load ≥10^8 IU/mL, 62% (49/79) of the patients in the BARACLUDE monotherapy arm and 78.8% (67/85) of the patients in the BARACLUDE plus tenofovir arm achieved HBV DNA <50 IU/mL.

- Among HBeAg-negative patients, the proportion achieving HBV DNA <50 IU/mL was 91.1% (51/56) in the BARACLUDE monotherapy arm versus 89.8% (53/59) in the BARACLUDE plus tenofovir arm.

Secondary efficacy endpoints measured in the study included alanine aminotransferase (ALT) normalization, HBeAg seroconversion, and HBeAg loss. ALT normalization was observed in 81.9% (149/182) of patients in this study in the BARACLUDE (entecavir) monotherapy arm versus 69% (136/197) in the BARACLUDE plus tenofovir arm. HBeAg seroconversion was observed in 32.5% (41/126) of patients in the BARACLUDE (entecavir) monotherapy arm versus 21.7% (30/138) in the BARACLUDE plus tenofovir arm in this study.
Two patients (1.1%) in the BARACLUDE monotherapy arm compared to five patients (2.5%) in the BARACLUDE plus tenofovir arm discontinued treatment prior to week 96. Patients who discontinued therapy prior to week 96 were considered treatment failures.

The overall adverse event profiles were similar across study arms. A total of three deaths occurred among treated patients, all on the BARACLUDE plus tenofovir arm: one due to bile duct tumor; one due to a late-onset exacerbation of hepatitis which was associated with breakthrough viremia while on continued treatment; and one due to cardiac arrest. One patient (0.5%) in the BARACLUDE monotherapy arm and two patients (1.0%) in the BARACLUDE plus tenofovir arm experienced on treatment ALT flares, defined as >2x baseline ALT and >10x ULN. No patients (0.0%) in either arm experienced off-treatment ALT flares. Six patients (3.3%) in the BARACLUDE monotherapy arm and four (2.0%) patients in the BARACLUDE plus tenofovir arm experienced serum creatinine increase ≥0.3 mg/dL. A total of five malignancies occurred among patients in the study: four (2.2%) patients in the BARACLUDE monotherapy arm and one (0.5%) patient in the BARACLUDE plus tenofovir arm. In the BARACLUDE monotherapy arm, there were three diagnoses of hepatocellular carcinoma (two on-treatment and one off-treatment) and one case of gastric cancer. In the BARACLUDE plus tenofovir arm there was one case of breast cancer.

Two patients (1.0%) in the BARACLUDE monotherapy arm and seven patients (3.6%) in the BARACLUDE plus tenofovir arm experienced virologic breakthrough. No recognized genotypic resistance mutations were observed in either treatment arm.

About The Study
The BE-LOW study is an open-label, multicenter, Phase IIIb study of 379 nucleos(t)ide-naïve patients with CHB. The patients were randomized 1:1 and treated with either BARACLUDE 0.5 mg once daily (n=182) or BARACLUDE 0.5 mg plus tenofovir 300 mg once daily (n=197). Nucleos(t)ide-naïve, HBeAg-negative CHB patient enrollment was capped at 30%. The primary efficacy endpoint was the proportion of patients with HBV DNA <50 IU/mL at week 96.

About Chronic Hepatitis B
Approximately 350 million people worldwide are chronically infected with hepatitis B (approximately 5% of the world’s population) and 75% of these cases occur in the Asia-Pacific region. Most people with chronic hepatitis B show no signs or symptoms, so many of those chronically infected are unaware of their status. A blood test can diagnose chronic hepatitis B. Patients should speak with their doctor about options available for this condition.

About BARACLUDE (entecavir)
BARACLUDE, a nucleoside analogue discovered at Bristol-Myers Squibb, was first approved by the U.S. Food and Drug Administration in March 2005 for use in adult chronic hepatitis B patients with compensated liver disease. The initial approval was based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative CHB infection and compensated liver disease. BARACLUDE is also indicated for use for the treatment of chronic hepatitis B in adult patients with decompensated liver disease based on virologic, biochemical, serologic, and safety data.

INDICATION and IMPORTANT SAFETY INFORMATION about BARACLUDE (entecavir) Tablets:

INDICATION
BARACLUDE is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

The following points should be considered when initiating BARACLUDE (entecavir):

- This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection and compensated liver disease.
- Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease.
- Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy.

IMPORTANT SAFETY INFORMATION
WARNINGS: SEVERE ACUTE EXACERBATONS OF HEPATITIS B, PATIENTS CO-INFECTED WITH HIV AND HBV, and LACTIC ACIDOSIS AND HEPATOMEGALY

- Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.
- Limited clinical experience suggests there is a potential for the development of resistance to HIV (human immunodeficiency virus) nucleoside reverse transcriptase inhibitors if BARACLUDE (entecavir) is used to treat chronic HBV infection in patients with HIV infection that is not being treated. Therapy with BARACLUDE is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART).
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, alone or in combination with antiretrovirals.
**Warnings and Precautions**

- Before initiating BARACLUDE (entecavir) therapy, HIV antibody testing should be offered to all patients. BARACLUDE has not been studied as a treatment for HIV infection and is not recommended for this use.
- Lactic acidosis with BARACLUDE use has been reported, often in association with hepatic decompensation, other serious medical conditions, or drug exposures. Patients with decompensated liver disease may be at higher risk for lactic acidosis. BARACLUDE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

**Adverse Reactions**

- In clinical trials in patients with compensated liver disease, the most common (≥3%) adverse reactions of any severity with at least a possible relation to study drug for BARACLUDE-treated subjects were headache, fatigue, dizziness, and nausea. In these trials, the most common adverse reactions of moderate to severe intensity (grades 2-4) were diarrhea, dyspepsia, nausea, vomiting, fatigue, headache, dizziness, somnolence, and insomnia.
- In the decompensated liver disease trial, the most common adverse reactions of any severity among patients treated with BARACLUDE, regardless of causality, included: peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). In this trial, 18% (18/102) of BARACLUDE patients and 20% (18/89) of adefovir patients died during the first 48 weeks of therapy. The majority of those deaths were due to liver related causes.

**Drug Interactions**

BARACLUDE is primarily eliminated by the kidneys, therefore coadministration of BARACLUDE with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Patients should be monitored closely when receiving BARACLUDE with other renally-eliminated drugs.

**Pregnancy and Nursing Mothers**

- There are no adequate and well-controlled studies of BARACLUDE (entecavir) in pregnant women. BARACLUDE should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.
- There are no studies on the effect of BARACLUDE on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.
- It is not known whether BARACLUDE is excreted into human milk; however, many drugs are excreted into breast milk. Due to the potential for serious adverse reactions in nursing infants from BARACLUDE, risks and benefits should be considered when deciding whether to discontinue breast-feeding or discontinue BARACLUDE in nursing women.

**Pediatric Use**

- Safety and effectiveness of BARACLUDE in pediatric patients below the age of 16 years have not been established.

**Renal Impairment**

- Dosage adjustment of BARACLUDE is recommended for patients with a creatinine clearance <50 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis.
- The safety and efficacy of BARACLUDE in liver transplant recipients are unknown. Renal function must be carefully monitored both before and during treatment with BARACLUDE in a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus.

**Dosage and Administration**

BARACLUDE should be administered on an empty stomach (at least 2 hours after a meal and at least 2 hours before the next meal).

The recommended dose of BARACLUDE (entecavir):

- in nucleoside-naive adults and adolescents (16+ yrs) with compensated liver disease is 0.5 mg once daily
- in adults and adolescents (16+ yrs) with compensated liver disease, and refractory to lamivudine or with known lamivudine or telbivudine resistance mutations (rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L) is 1 mg once daily
- in adults with decompensated liver disease is 1 mg once daily

The optimal duration of treatment with BARACLUDE for patients with chronic HBV infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

**Additional Information**

BARACLUDE (entecavir) is not a cure for HBV. Patients should be advised that treatment with BARACLUDE has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination.

Please see accompanying Full Prescribing Information, including Boxed WARNINGS, or click here.

**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 or follow
HBV DNA carries the genetic blueprint of the hepatitis B virus. The number of HBV DNA “copies” found in a person’s blood, or “viral load,” indicates how rapidly the virus is reproducing in their liver. Low levels of HBV DNA, recognized as 300 copies per milliliter or less, indicate an “inactive” hepatitis B infection.

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**Ticker Slug:**

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