New Data Suggest Long-Term Treatment with BARAACLE(R) (entecavir) May Reduce Liver Damage Caused by Chronic Hepatitis B

Release Date:
Sunday, November 2, 2008 11:00 am EST

Terms:
Corporate/Financial News

Dateline City:
SAN FRANCISCO

Long-term cohorts evaluated for liver histology, including fibrosis, and viral load reduction

SAN FRANCISCO--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced data from two separate cohort evaluations, in which long-term treatment with BARAACLE® (entecavir) was associated with improved liver histology, including improvement in fibrosis, in chronic hepatitis B patients. The histology data were presented today at the 59th Annual Meeting of the American Association for the Study of Liver Diseases.

New long-term histology results were presented from a cohort of 57 nucleoside-naive patients from rollover study ETV-901. ETV-901 provided long-term treatment with BARAACLE 1 mg for patients who completed phase 2-3 studies. Patients followed in this cohort received BARAACLE for a median of six years across the studies (ETV-022, -027 and -901) and had evaluable baseline and long-term liver biopsies. Of the 57 patients, 96 percent (55/57) experienced improvement in liver histology (improvement in how the liver tissue looks under a microscope). Improvement in liver histology was defined as greater than or equal to a two-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score. Additionally, 88 percent of patients (50/57) experienced a reduction in liver fibrosis, defined as improvement in Ishak fibrosis score (greater than or equal to a one-point decrease). Fibrosis occurs when excessive fibrous connective tissue builds up in the liver in response to chronic inflammation, which can be caused by chronic hepatitis B infection.

Control of viral replication is an important goal of chronic hepatitis B treatment. At the time of the ETV-901 long-term biopsy, 100 percent of subjects with evaluable liver biopsies (57/57) had undetectable viral load [HBV DNA less than 300 copies/mL by polymerase chain reaction (PCR)].

Histology results were also presented from the open-label rollover study ETV-060, which evaluated Japanese patients with chronic hepatitis B. This cohort included 37 treatment-naive patients and 27 patients resistant to treatment with lamivudine from two Phase 2 studies (ETV-053, ETV-052) who had liver biopsies after receiving at least three years of treatment with BARAACLE®. Of these 64 patients, 100 percent (37/37) of treatment-naive patients and 89 percent (23/26†) of lamivudine-refractory patients experienced improvement in liver histology (measured by a greater than or equal to a two-point decrease in Knodell necroinflammatory score), and 47 percent (17/36†) of treatment-naive and 32 percent (8/25‡) of lamivudine-refractory patients experienced an improvement in liver fibrosis (greater than or equal to a one-point decrease in Knodell fibrosis score).

"These data suggest that long-term treatment with BARAACLE has the potential to stop liver damage and may even improve liver fibrosis caused by chronic hepatitis B infection," said Professor Yun-Fan Liaw, lead investigator for the Long-term Histology Cohort (subset of ETV-901), from Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan. "The ability to provide effective long-term treatment with a potent antiviral with minimal resistance represents a positive step forward."

About the ETV-901 Analysis

ETV-901 is a long-term rollover study for patients who previously completed phase 2-3 entecavir studies. The long-term histology cohort included 57 nucleoside-naive patients who received a minimum of 3 years of cumulative therapy with BARAACLE from the start of studies ETV-022 or -027,1,2 (BARAACLE 0.5 mg) to the time of their last observed biopsy in ETV-901 (BARAACLE 1 mg), and had adequate baseline and long-term liver biopsies. These patients were treated with BARAACLE for a median of six years. The co-primary long term histology endpoints were the proportion of patients with histologic improvement (defined as greater than or equal to a two-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score) and the proportion of patients with improvement in Ishak fibrosis score (greater than or equal to a one-point decrease), both compared to baseline.

Results of patients in ETV-901 who agreed to undergo long-term liver biopsies (median of 6 years of treatment)

- 96% of patients had improvement in liver histology at long-term liver biopsy – an increase from 73% at week 48.
• The proportion of patients with improvement in Ishak fibrosis score increased from 32% at 48 weeks to 88% at long-term liver biopsy.

• Of the 43 patients with a baseline fibrosis score of ≥2, 58% had a 2-point or more decrease in Ishak fibrosis score.

• 100% of patients achieved undetectable viral load (HBV DNA < 300 copies/mL by PCR).

• Grade 3-4 adverse event(s) were reported in 20% of patients, and serious adverse event(s) were reported in 25%. The most common adverse events were upper respiratory tract infection (23%); headache (16%); nasopharyngitis, an inflammation of the nose and throat (16%); ALT increase, an increase in the production of the liver enzyme ALT, which may indicate inflammation of the liver or liver damage (14%); abdominal pain (13%); influenza (13%); back pain (12%); pyrexia-fever (12%); arthralgia-joint pain (10%); cough (10%); hypertension (10%); insomnia (10%); and pharyngolaryngeal pain - throat pain (10%).

About the ETV-060 Analysis

ETV-060 was an open-label rollover study of Japanese chronic hepatitis B patients, including 66 treatment-naive patients who completed 52 weeks of treatment with BARACLUDE® 0.1 mg or 0.5 mg in study ETV-053, and 82 lamivudine-refractory patients who completed 52 weeks of treatment with BARACLUDE 0.5 mg or 1 mg in study ETV-052. In the ETV-060 rollover study, patients continued treatment with BARACLUDE at 0.5 mg (treatment-naive patients) or 1 mg (lamivudine-refractory patients). The current analysis evaluated the long-term histologic results for patients who had liver biopsies after receiving at least three years of continuous treatment with BARACLUDE (37 patients from ETV-053 and 27 patients from ETV-052). Histologic improvement (greater than or equal to a one-point decrease in Knodell necroinflammatory score) and improvement in Knodell fibrosis score (greater than or equal to a one-point decrease) were evaluated for patients with biomarkers at baseline, Week 48 and Week 148.

Results of patients in ETV-060 who agreed to undergo long-term liver biopsies (at least 3 years of treatment)

• Among both treatment-naive and lamivudine-refractory CHB patients, liver histology improved after three years of continuous BARACLUDE® treatment. At week 148, 100% (37/37) of treatment-naive patients and 89% (23/26) of lamivudine-refractory patients experienced improvement in Knodell necroinflammatory score, and 47% (17/36) of treatment-naive and 32% (8/25) of lamivudine-refractory patients experienced an improvement in liver fibrosis as measured by the Knodell fibrosis score.

• At week 148, 95% (35/37) of treatment-naive patients and 56% (15/27) of lamivudine-refractory patients had HBV DNA < 400 copies/mL.

• Safety results for this cohort analysis were not reported at this conference. Please see the following Important Safety Information for BARACLUDE, including boxed WARNINGS in bold.

About Chronic Hepatitis B

Chronic hepatitis B is a serious global health issue. Worldwide, more than two billion people (one out of every three people) have been infected with the hepatitis B virus and approximately 350 million people are chronically infected. An estimated 1.25 million Americans are chronically infected with hepatitis B, and over half are of Asian descent.

About BARACLUDE

Discovered at Bristol-Myers Squibb, BARACLUDE is a nucleoside analogue indicated for use in adults with chronic hepatitis B infection with compensated liver disease, evidence of active viral replication, and either evidence of persistent elevations of the blood levels of aminotransferases – a marker for liver disease – or active liver disease as determined by biopsy. BARACLUDE® has been approved in more than 86 countries and regions around the world.

Indication and Important Safety Information About BARACLUDE-0.5 mg and 1 mg Tablets

BARACLUDE is a prescription medicine used for chronic infection with hepatitis B virus (HBV) in adults where the virus is multiplying and damaging the liver. BARACLUDE does not cure HBV or stop the spread of HBV to others.

Patients taking BARACLUDE should tell their healthcare provider right away if they have any side effects or conditions, including the following:

• Worsening of HBV infection if patients stop taking BARACLUDE: Hepatitis B symptoms may get worse or become very serious if they stop taking BARACLUDE. Healthcare providers will need to follow their patients and do blood tests to check the liver if BARACLUDE is stopped. Patients should not stop taking BARACLUDE without talking to their healthcare provider.

• Patients who have or get HIV infection (the virus that can cause AIDS): For patients taking BARACLUDE to treat chronic hepatitis B and not taking medicines for HIV at the same time, some HIV treatments that they take in the future may be less likely to work. Patients are advised to get an HIV test before starting to take BARACLUDE and anytime after that when there is a chance they were exposed to HIV. BARACLUDE will not help HIV infection.

• Feeling very weak or tired, unusual muscle pain, trouble breathing, stomach pain with nausea and vomiting, feeling cold (especially in the arms and legs), feeling dizzy or lightheaded, or a fast or irregular heartbeat may be signs of a serious condition called lactic acidosis (buildup of an acid in the blood). Lactic acidosis is a medical emergency and must be treated in the hospital. This has happened in some patients who have taken medicines like BARACLUDE.

• Yellowing (jaundice) of the skin or the white part of the eyes, darkening of the urine, lightening in the color of bowel movements (stools), not feeling like eating food for several days or longer,
**feeling sick to the stomach (nausea), or having lower stomach pain,** may be signs of serious liver problems called hepatotoxicity. This may occur with liver enlargement (hepatomegaly) and fat in the liver (steatosis). This has happened in some patients taking medicines like BARACLUDE®.

Patients should not take BARACLUDE if they are allergic to any of its ingredients. BARACLUDE has not been studied in children and is not recommended for anyone less than 16 years old.

Patients should tell their healthcare provider right away if they have any conditions, including the following:

- Kidney problems: Because BARACLUDE is removed from the body through the kidneys, a lower dose or a different dose schedule may be needed. Healthcare providers may want to do tests to see if a lower dose is needed or if BARACLUDE should be taken less often than once a day.
- Pregnant or planning to become pregnant: it is not known if BARACLUDE is safe to use during pregnancy. It is not known if BARACLUDE helps to prevent a pregnant mother from passing HBV to her baby. A pregnant woman and her healthcare provider will need to decide if BARACLUDE is right for her. A woman should not breastfeed if she is taking BARACLUDE.

Patients should discuss with their healthcare provider all prescription and non-prescription medicines, vitamins, herbal supplements, and other health preparations they are taking or plan to take. BARACLUDE may interact with medicines that leave the body through the kidneys.

The safety and effectiveness of BARACLUDE in liver transplant recipients are unknown. These patients must be carefully monitored before and during treatment with BARACLUDE, and they should discuss treatment with their doctor.

The most common side effects of BARACLUDE® in clinical studies were headache, tiredness, dizziness, and nausea. This list of side effects is not complete at this time because BARACLUDE is still under study. Patients should report any new or continuing symptom to their healthcare provider.

BARACLUDE® should be taken exactly as prescribed and on an empty stomach (at least two hours after a meal and at least two hours before the next meal).

Please see accompanying Full Prescribing Information, including boxed WARNINGS, or visit [http://www.baraclude.com](http://www.baraclude.com) or [http://www.bms.com/](http://www.bms.com/).

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to extend and enhance human life. Visit Bristol-Myers Squibb at [www.bms.com](http://www.bms.com).

BARACLUDE® (entecavir) is a registered trademark of Bristol-Myers Squibb Company.

**Endnotes**

*One patient had a baseline biopsy not evaluable for necroinflammation

†One patient had a baseline biopsy not evaluable for fibrosis

‡Two patients had baseline biopsies not evaluable for fibrosis

**References**


**Language:**

English

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**Ticker Slug:**

*Ticker: BMY
Exchange: NYSE*