Bristol-Myers Squibb Presents Promising Phase IIb Data for Novel, Investigational Attachment Inhibitor for HIV-1 Infected Treatment- Experienced Patients

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Terms:

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- **BMS-663068** has a unique mechanism of action in treating HIV. It is the first investigational antiretroviral to prevent initial viral attachment to the host CD4+ T cell and entry into the host immune cell by binding directly to the HIV virus.
- 24 week Phase IIb data showed similar response rates (HIV-1 RNA <50 c/mL) in treatment-experienced patients treated with BMS-663068 compared to a boosted protease inhibitor.
- Study data presented at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI) demonstrated that BMS-663068 was generally well-tolerated in these study patients, with no adverse events leading to discontinuation.

Globally, there are 34 million people who are infected with HIV. Due to significant scientific advances in management of HIV treatment over the last 20 years, patients are now living with HIV for a longer period of time and some patients have developed resistance to existing regimens or are unable to tolerate current available treatments. Additional treatment options, especially in new drug classes, are needed both today and into the future for these patients.

"By targeting the virus at an earlier step of the viral lifecycle, BMS-663068 disrupts the virus in a way unlike existing antiretroviral agents," said Jacob P. Lalezari, M.D., director of Quest Clinical Research and assistant clinical professor of medicine at UCSF/Mount Zion Hospital. "The data suggest that BMS-663068 is potentially as effective as one of the current standards of care and may provide another method of suppressing the virus in treatment-experienced patients who have failed a prior HIV regimen and need new treatment options."

Study Design and Results

In this active-controlled Phase IIb study, treatment-experienced HIV-1 infected adults (n=254) were randomized equally to one of four BMS-663068 treatment arms: (400 mg BID (twice daily); 800 mg BID; 600 mg QD (once daily); 1200 mg QD) and a control group of Reyataz® (atazanavir sulfate) and ritonavir (300/100 mg QD). Each treatment arm and the control group also included raltegravir (RAL) 400 mg BID and tenofovir disoproxil fumarate (TDF) 300 mg QD. The primary endpoints were the proportion of subjects with HIV-1 RNA <50 c/mL at week 24 and the frequency of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation through week 24.

Through week 24, BMS-663068 showed similar efficacy compared to Reyataz and ritonavir for treatment-experienced patients infected with HIV-1. Specifically, 69-80% of patients in the four treatment arms had HIV-1 RNA levels <50 c/mL, indicating virus replication was undetectable, compared to 75% of patients in the control group.

BMS-663068 was generally well-tolerated during the study, with no serious adverse events attributed to BMS-663068 nor any adverse events leading to discontinuation. The incidence of Grade 2-4 related AEs across BMS-663068 arms ranged from 3.9% to 12%, vs. 27.5% in the comparator arm (atazanavir sulfate and ritonavir) and no causal association was observed.
INDICATION and IMPORTANT SAFETY INFORMATION about

REYATAZ (atazanavir sulfate) 200mg/300mg Capsules:

INDICATION:

REYATAZ® (atazanavir sulfate) is indicated in combination with other antiretroviral agents for treatment of HIV-1 infection. This is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from controlled studies of 96 weeks (treatment-naive) and 48 weeks (treatment-experienced) duration in adult and pediatric patients at least 6 years of age. The following should be considered when initiating REYATAZ:

- In Study 045, REYATAZ/ritonavir and lopinavir/ritonavir were similar for the primary efficacy measure of time-averaged difference in change from baseline in HIV RNA. This study was not large enough to reach a definitive conclusion that REYATAZ/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy measure of proportions below the HIV RNA lower limit of detection.
- The number of baseline primary protease inhibitor mutations affects virologic response to REYATAZ/ritonavir.

IMPORTANT SAFETY INFORMATION:

- **Hypersensitivity:** REYATAZ is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the product components.
- **Contraindicated Drugs:** Coadministration with drugs highly dependent on CYP3A or UGT1A1 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These and other contraindicated drugs are alfuzosin, rifampin, irinotecan, orally administered midazolam, triazolam, dihydroergotamine, ergotamine, methylergogonovine, cisapride, St. John's wort (Hypericum perforatum)-containing products, lovastatin, simvastatin, pimozide, sildenafil, dosed as Revatio®, or indinavir.
- **Drug Interactions:** Coadministration with the following drugs is not recommended.
  - nevirapine, salmeterol
  - when REYATAZ is given with ritonavir: nevirapine, boceprevir, other HIV protease inhibitors, fluticasone propionate. Voriconazole should not be administered, unless assessment of benefit/risk justifies its use. Patients should be carefully monitored for adverse events and loss of efficacy.
  - when REYATAZ is given without ritonavir: buprenorphine, bosentan, carbamazepine, phenytoin, phenobarbital.
  - in treatment-experienced patients: proton-pump inhibitors or efavirenz
  - in patients with renal or hepatic impairment: colchicine

See Section 7 (including Table 13), of the Full Prescribing Information for additional established and other potentially significant drug interactions, and related dose modification recommendations.

- **Cardiac Conduction Abnormalities:** PR interval prolongation may occur in some patients. Atrioventricular (AV) conduction abnormalities were asymptomatic and generally limited to first-degree AV block. There have been rare reports of second-degree AV block and other conduction abnormalities. Use REYATAZ with caution in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval (including beta-blockers other than atenolol, diltiazem, verapamil, and digoxin), especially drugs metabolized by CYP3A. When used with REYATAZ, a 50% dose reduction of diltiazem should be considered, and ECG monitoring is recommended.
- **Rash** (all grades, generally mild-to-moderate maculopapular skin eruptions, regardless of causality) occurred in approximately 20% of patients treated with REYATAZ in controlled clinical trials. Cases of Stevens-Johnson syndrome, erythema multiforme, and toxic skin eruptions, including drug rash, eosinophilia and systemic symptoms (DRESS) syndrome, have been reported. Discontinue REYATAZ if severe rash develops.
- **Hyperbilirubinemia:** Reversible, asymptomatic elevations in indirect (unconjugated) bilirubin occurred in most patients treated with REYATAZ (atazanavir sulfate). There are no long-term safety data for patients with persistent
elevations in total bilirubin >5 times upper limit of normal. Alternative antiretroviral therapy may be considered if jaundice or scleral icterus present cosmetic concerns.

- **Hepatotoxicity**: Use REYATAZ with caution in patients with hepatic impairment because atazanavir concentrations may be increased. Patients with hepatitis B or C infection or marked elevations in transaminases are at risk of further transaminase elevations or hepatic decompensation. In these patients, hepatic laboratory testing should be performed before and during REYATAZ therapy.

- **Nephrolithiasis and cholelithiasis** have been reported during postmarketing surveillance in HIV-infected patients receiving REYATAZ. Some patients required hospitalization and some had complications. If signs or symptoms of nephrolithiasis and/or cholelithiasis occur, consider temporary interruption or discontinuation of therapy.

- New onset or exacerbation of **diabetes mellitus and hyperglycemia** have been reported in patients treated with protease inhibitor therapy. A causal relationship has not been established.

- **Immune reconstitution syndrome** has been reported in patients treated with combination antiretroviral therapy, including REYATAZ. Autoimmune disorders (such as Graves’ disease, polymyositis, and Guillain–Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

- **Redistribution and/or accumulation of body fat** have been seen in patients receiving antiretroviral therapy. A causal relationship has not been established.

- **Increased bleeding** has been reported in patients with hemophilia type A and B treated with protease inhibitors.

- Various degrees of **cross-resistance** among protease inhibitors have been observed.

- The **most common moderate or severe adverse reactions** were as follows, regardless of causality:
  - In **treatment-naive adult patients** (≥2%): nausea (4-14%), jaundice/scleral icterus (5-7%), rash (3-7%), headache (1-6%), abdominal pain (4%), vomiting (3-4%), peripheral neurologic symptoms (<1-4%), diarrhea (1-3%), insomnia (<1-3%), and dizziness (<1-2%).
  - In **treatment-experienced adult patients** (≥2%): jaundice/scleral icterus (9%), myalgia (4%), diarrhea (3%), nausea (3%), depression (2%), and fever (2%).
  - In **pediatric patients** (≥5%): cough (21%), fever (18%), jaundice/scleral icterus (15%), rash (14%), vomiting (12%), diarrhea (9%), headache (8%), peripheral edema (7%), extremity pain (6%), nasal congestion (6%), oropharyngeal pain (6%), wheezing (6%), and rhinorrhea (6%).

- REYATAZ should be used with caution in patients with mild to moderate hepatic impairment. REYATAZ should not be used in patients with **severe hepatic impairment** (Child-Pugh Class C). REYATAZ/ritonavir has not been studied in patients with hepatic impairment and is not recommended.

- REYATAZ should not be used in treatment-experienced patients with **end-stage renal disease managed with hemodialysis**.

Please see accompanying Full Prescribing Information 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](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 mentioned will receive regulatory approval or, if approved, that it will become a commercially successful product. 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, 2013 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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**Contact:**

Bristol-Myers Squibb

Media:

Julie Ferguson

Office: 609-252-5597

Cell: 312-385-0098

julie.ferguson@bms.com