



## FOR IMMEDIATE RELEASE

### **Promising Phase IIb Data On Clazakizumab In Patients With Moderate-To-Severe Rheumatoid Arthritis To Be Presented At The 2013 Annual Meeting Of The American College Of Rheumatology**

- *All clazakizumab treatment arms, both as monotherapy as well as in combination with methotrexate (MTX), met the primary endpoint of ACR20 response at 12 weeks, compared to MTX alone.*
- *Clazakizumab demonstrated promising rates of low disease activity and remission based on DAS28, CDAI and SDAI criteria in the study which included MTX and anti-TNF comparator arms.*
- *Overall the safety profile was consistent with the known pharmacology of IL6 blockade. The most frequent AE for clazakizumab was dose-related injection site reactions and these were mostly mild with few leading to discontinuation.*
- *Clazakizumab is a humanized anti-IL-6 monoclonal antibody directed against the IL-6 cytokine rather than the receptor.*

Monday, October 28, 2013 7:30 am EDT

SAN DIEGO—([BUSINESS WIRE](#))—[Bristol-Myers Squibb Company](#) (NYSE:BMY) and [Alder Biopharmaceuticals](#) today announced the presentation of efficacy and safety data from a Phase IIb dose-ranging study of subcutaneous (SC) clazakizumab in adults with moderate-to-severe rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX). Clazakizumab is a humanized anti-IL-6 monoclonal antibody that is directed against the IL-6 cytokine rather than its receptor.

In the Phase IIb study clazakizumab doses ranging from 25-200 mg monotherapy and in combination with MTX were studied vs. MTX alone. Adalimumab in combination with MTX was included as an active reference arm. All clazakizumab treatment arms, alone or in combination with MTX, demonstrated efficacy in controlling the signs and symptoms of RA, and met the predefined primary endpoint of a higher ACR20 response rate vs. MTX alone after 12 weeks of treatment. All clazakizumab treatment groups were also associated with improved ACR 20/50/70 response rates and HAQ-DI scores vs. MTX at week 24. Rates of low disease activity and remission with clazakizumab plus MTX, as measured by DAS28 CRP, CDAI and SDAI criteria were numerically greater for clazakizumab at 12 and 24 weeks than the active comparator.

The adverse event (AE) rates were similar across all clazakizumab arms. The most frequent AE for clazakizumab was dose-related injection site reactions. The most frequent reason for discontinuation due to AE in clazakizumab treated patients was laboratory abnormality, predominantly transaminase elevations, more frequent in MTX-containing arms. The most

frequent serious adverse events (SAEs) were serious infections. Rates of serious infections were generally comparable for clazakizumab and adalimumab combination arms and were numerically greater than MTX alone.

“There is a great need for additional disease-modifying therapies that can provide more patients with deep and sustainable remission, helping preserve function and limit further joint damage,” said Paul Emery, M.D., director of MSK Biomedical Unit at the Leeds Teaching Hospitals Trust in the United Kingdom. “Currently, less than 30% of RA patients experience sustained remission as defined by ACR criteria. Clazakizumab is an investigational therapy that neutralizes IL-6 signaling by blocking the IL-6 cytokine, and provides promising remission data that will need to be further investigated.”

“Bristol-Myers Squibb has a long-standing commitment to immunoscience research and the development of innovative medicines for patients living with chronic immune-mediated diseases, such as RA,” said [Brian Daniels](#), MD, senior vice president, Global Development and Medical Affairs, Research and Development, Bristol-Myers Squibb. “Despite the recent advances in the treatment of RA, more efficacious therapies are needed. The results of this study support the potential for clazakizumab to fulfill the need for new medicines that can help patients with RA achieve disease control and remission.”

Bristol-Myers Squibb has exclusive worldwide rights to develop and commercialize clazakizumab for all indications outside of cancer under a collaboration agreement with its discoverer, Alder Biopharmaceuticals.

“We are excited about the Phase IIb data and its confirmation of the earlier promise seen in Phase IIa,” added Randall Schatzman, PhD, president and CEO of Alder Biopharmaceuticals. “We look forward to the clinical advancement of clazakizumab and the potential it has to bring a new treatment to patients suffering with RA.”

In a separate pre-clinical study of in-vitro assays, also being presented at the ACR annual meeting, clazakizumab was shown to bind to the IL-6 cytokine with high affinity and block various IL-6-induced functions more potently than tocilizumab, an RA treatment currently on the market that targets the IL-6 pathway.

### **About the Phase IIb Study**

This was a randomized, dose-ranging, Phase IIb study which evaluated the efficacy and safety of clazakizumab subcutaneous injection alone or in combination with methotrexate (MTX). The study included 418 adults with moderate-to-severe active rheumatoid arthritis (RA) who experienced an inadequate response to MTX. Participants were enrolled and treated in 115 sites throughout North and South America, Europe and Asia.

Participants were randomized to one of seven treatment arms: once monthly clazakizumab 25mg, 100mg or 200mg, all on MTX background; once monthly clazakizumab 100mg or 200mg without MTX; MTX alone; or twice monthly adalimumab 40mg + MTX.

At week 12, ACR20 response rates (the primary endpoint) were: 78%, clazakizumab 25mg + MTX ( $p < 0.001$ ); 71.7%, clazakizumab 100mg + MTX ( $p < 0.001$ ); 60%, clazakizumab 200mg + MTX ( $p = 0.015$ ); 55.0%, clazakizumab 100mg alone ( $p = 0.042$ ); 61%, clazakizumab 200mg alone ( $p = 0.015$ ); versus 39.3%, MTX. The ACR20 response rate for adalimumab 40mg + MTX was 76.3%.

Key secondary endpoints included ACR70 at week 12 and 24, as well as measures of low disease activity and remission. At week 24 ACR70 rates ranged from 27.1% to 38.3% in the clazakizumab combination arms vs. 6.6% for MTX. The ACR70 rate was 18.6% for adalimumab + MTX. Low disease activity, as measured by DAS28-CRP<2.6, ranged from 41.7% to 49.2% for the clazakizumab + MTX arms vs. 13.1% for MTX. The DAS28-CRP<2.6 rate for adalimumab +MTX was 23.7%. Remission rates by CDAI and SDAI criteria (CDAI<2.8 and SDAI<3.3) were numerically greater for clazakizumab combination arms (15.3% to 20% for CDAI remission and 18.6% to 23.3% for SDAI remission) as compared to the MTX arm (1.6% for CDAI and 4.9% for SDAI remission). Rates of CDAI and SDAI remission for the adalimumab + MTX arm were both 8.5%.

The safety profile of clazakizumab was similar at 12 and 24 weeks. At 24 weeks, rates of adverse events were similar across all clazakizumab arms (ranging from 83.1% to 96.7%), compared to 59% and 74.6% for the MTX and adalimumab arms respectively. The most frequent AE for clazakizumab was dose-related injection site reactions ranging from 32.2% to 63.3%. 83.7% of these were rated as mild and none were considered serious adverse events. Across all clazakizumab arms the most frequent reasons for discontinuation due to AE were laboratory abnormalities (predominantly transaminase elevations), infections and ISRs. Discontinuations for laboratory abnormality ranging from 0% to 5% across the clazakizumab arms, and 3 patients (1%) discontinued for ISRs. There were no discontinuations for AEs in the 25mg + MTX arm. 0% and 1.7% discontinued due to AEs in the MTX and adalimumab arms, respectively. The rates of serious adverse events (SAEs) ranged from 8.3% to 13.6% in the clazakizumab arms versus 3.3% for MTX and 5.1% for adalimumab + MTX. The most frequent SAEs were serious infections. Rates of serious infections ranged from 1.7% to 5.1% in the clazakizumab arms versus 0% for MTX and 3.4% for adalimumab + MTX. Additionally, the clazakizumab arms showed increases in mean total cholesterol without changes in HDL/LDL ratio, increases in hemoglobin, and decreases in polymorphonuclear neutrophils and platelets, which are expected from IL-6 antagonism.

### **About the Pre-Clinical Study**

In a separate preclinical study, multiple in vitro assays for IL-6-induced functions and IL-6/sIL-6R-mediated functions were used to compare the potencies of clazakizumab and tocilizumab, the only currently marketed antibody targeting the IL-6 pathway. The study looked at inhibiting signaling, proliferation, activation, antibody production and secretion of acute phase protein. Clazakizumab was between 3 and 120 times more potent than tocilizumab in blocking these IL-6-induced cell functions based on the results of this study.

### **About Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune disease characterized by inflammation in the lining of joints (or synovium), causing joint damage with chronic pain, stiffness, swelling and fatigue. RA causes limited range of motion and decreased joint function. The condition is more common in women, who account for 75% of patients diagnosed with RA, than men.

### **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 about Bristol-Myers Squibb, visit [www.bms.com](http://www.bms.com) or follow us on Twitter at <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 product development. 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 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.*

## **About Alder Biopharmaceuticals**

Alder Biopharmaceuticals Inc. uniquely identifies, develops and manufactures novel antibody therapeutics to alleviate human suffering in cancer, pain, cardiovascular and autoimmune and inflammatory disease areas. Clazakizumab, BMS-945429, previously known as ALD518, is Alder's investigational monoclonal antibody to the pro-inflammatory cytokine IL-6. Clazakizumab has been licensed to Bristol-Myers Squibb for development in all indications outside of cancer (including rheumatoid arthritis and other autoimmune indications) based on a 2009 agreement. Alder's management team combines decades of industry experience with a proven track record for identifying and developing novel antibody therapeutics and enabling partners through the out-licensing of its technologies. For more information, visit [www.alderbio.com](http://www.alderbio.com).

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