New Mechanistic Study Explores the Relationship Between a Key Genetic Marker and Clinical Efficacy of ORENCIA® (abatacept) or adalimumab in Moderate-to-Severe Early Rheumatoid Arthritis Patients

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- Findings from head-to-head Early AMPLE study are consistent with earlier studies, adding to body of research showing differences between mechanisms of biologic therapies
- Results suggest that a genetic marker linked to autoantibody production and a more severe RA disease course - “Shared Epitope” - can help identify patients who may receive enhanced benefit from treatment with ORENCIA
- Late-breaking oral presentation is one of 27 Bristol-Myers Squibb sponsored abstracts featured at the Annual European Congress of Rheumatology (EULAR 2019)

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced data from a Phase IV mechanistic study exploring differences in the cellular and molecular mechanisms by which ORENCIA® (abatacept) and another treatment, adalimumab, interfere with disease progression in moderate-to-severe early rheumatoid arthritis (RA) patients seropositive for certain autoantibodies. These results, which are from a prospective analysis of the Early AMPLE head-to-head trial, are featured in a late-breaking oral presentation at the Annual European Congress of Rheumatology (EULAR 2019), June 12-15 in Madrid.

Among 80 adult patients with early (≤ 12 months from symptom onset) moderate-to-severe RA who had never been treated with a biologic medication and tested positive for autoantibodies called anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF), numerically higher efficacy responses were seen with ORENCIA at week 24. ACR 20/50/70 responses with ORENCIA were 83, 70 and 48 respectively; ACR 20/50/70 scores for adalimumab were 63, 45 and 30, respectively. Higher responses were observed in patients with a well-known genetic marker of RA prognosis called the “Shared Epitope” (SE). In SE+ patients, numerically greater efficacy was observed with ORENCIA [estimate of difference in the SE+ group for ACR 20 was 28.6 (95% CI 4.6, 51.7); for ACR 50 was 31.5 (95% CI 6.8, 54.5); for ACR 70, 27.6 (95% CI 1.4, 50.5); for DAS28-CRP remission (<2.6), 27.4 (95% CI 1.2, 49.8)]. Patients in both arms of the study were also treated with stable, oral methotrexate (MTX) weekly.

Rheumatoid factor and ACPA are biomarkers associated with a more severe disease course in RA. The HLA-DRB1 allele, which codes for SE, provides instructions for making a protein that plays a key role in helping the immune system distinguish one’s own proteins from those of harmful invaders, such as bacteria and viruses. Shared Epitope has been shown to be strongly associated with RA, and is thought to be involved with the continuous activation of immune cells, called T cells, that characterizes RA. Shared Epitope is present in 70-80 percent of RA patients positive for ACPA.

“The Early AMPLE results are consistent with previous abatacept research in patients who test positive for anti-citrullinated protein antibody, and offer important insights into the underlying genetic mechanisms at work in these patients,” said Vivian P. Bykerk, BSc, MD, FRCP, rheumatologist at Hospital for Special Surgery. “This research advances our understanding of these mechanisms and the value of the applicability of precision medicine for patients with highly active, progressive rheumatoid arthritis.”

Similar numbers of related adverse events (ORENCIA: 12 [30%]; adalimumab: 11 [27.5%]) and related serious adverse events (ORENCIA: 0; adalimumab: 1 [2.5%]) were observed in the two treatment arms. The overall safety profile of ORENCIA was consistent with prior studies, with no new safety signals identified.

“Investigating the impact of biomarkers is central to our goal of informing better, more personalized approaches in
immune-mediated diseases where treatment options are limited or improvements are needed,” said Dr. Brian Gavin, development lead, ORENCIA, Bristol-Myers Squibb. “The results from Early AMPLE are exciting because they support the clinical profile of ORENCIA as a first-line treatment option for patients with moderate-to-severe RA, and further our understanding of which patients may benefit most from ORENCIA therapy.”

At the Annual European Congress of Rheumatology (EULAR 2019), Bristol-Myers Squibb sponsored a total of 27 abstracts. These include clinical and real-world results on ORENCIA that support our focus on furthering precision medicine in RA and addressing unmet patient needs in moderate-to-severe juvenile idiopathic arthritis. Findings on new modes of action being explored as part of Bristol-Myers Squibb’s early Immunoscience program also will be shared. A full list of abstract titles and authors can be accessed online here.

About the Early AMPLE Study

Early AMPLE, a phase IV randomized, head-to-head, single-blinded study of 24 weeks duration with multiple exploratory endpoints (changes to autoantibody levels, changes to cytokines, changes to percentages of immune cell subsets, and changes to activation states of immune cell subsets), compared the efficacy of the subcutaneous (SC) formulation of ORENCIA versus adalimumab on a background of MTX in adult, biologic-naïve patients with moderate-to-severe RA.

In this prospective analysis, adults with early (≤ 12 months from symptom onset), moderate-to-severe RA (ACR/EULAR 2010 criteria) seropositive for ACPA and RF, were randomized 1:1 to SC ORENCIA 125 mg weekly or SC adalimumab 40 mg every 2 weeks (both with stable, oral MTX weekly) for 24 weeks. Patients were grouped by SE status (+/−) based on HLA-DRB1 genotype (−: no SE allele; +: ≥ 1 SE allele). Safety was analyzed throughout the trial and up to 8 weeks post last study drug dose. Clinical efficacy was assessed at week 24 to determine the proportion of ACR20/50/70 responders in the ORENCIA versus adalimumab arms, and the adjusted mean changes from baseline in DAS28 (CRP), SDAI and CDAI. Treatment differences between ORENCIA and adalimumab in SE+ and SE- pts were assessed for ACR20/50/70 responders and DAS28 (CRP) remission at week 24.

Eighty patients were treated: 40 ORENCIA (9 SE−, 30 SE+, 1 SE unknown) and 40 adalimumab (9 SE−, 31 SE+). Baseline characteristics were balanced. Mean (SD) age, disease duration and DAS28 (CRP) were 46.0 (14.4) years, 5.5 (2.6) months and 5.2 (1.1), respectively; 75% were female.

About Rheumatoid Arthritis

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

About ORENCIA

ORENCIA® is an immunomodulator that disrupts the continuous cycle of T-cell activation that characterizes RA.

U.S. Indications/Usage and Important Safety Information for ORENCIA® (abatacept)

Indication and Usage

Adult Rheumatoid Arthritis (RA): ORENCIA® (abatacept) is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. ORENCIA may be used as monotherapy or concomitantly with disease-modifying, anti-rheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

Juvenile Idiopathic Arthritis (JIA): ORENCIA® (abatacept) is indicated for reducing signs and symptoms in patients 2 years of age and older with moderately to severely active polyarticular JIA. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).

Adult Psoriatic Arthritis (PsA): ORENCIA® (abatacept) is indicated for the treatment of adult patients with active PsA.

Important Limitations of Use: ORENCIA should not be administered concomitantly with TNF antagonists, and is not recommended for use concomitantly with other biologic RA therapy, such as anakinra.

Important Safety Information for ORENCIA® (abatacept)

Concomitant Use with TNF Antagonists: Concurrent therapy with ORENCIA and a TNF antagonist is not recommended. In controlled clinical trials, adult RA patients receiving concomitant intravenous ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively), without an important enhancement of efficacy.

Hypersensitivity: Anaphylaxis or anaphylactoid reactions can occur during or after an infusion and can be life-threatening. There were 2 cases (<0.1%; n=2688) of anaphylaxis or anaphylactoid reactions in clinical trials with adult RA patients treated with intravenous ORENCIA. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in <0.9% of patients. There was one case of a hypersensitivity reaction with ORENCIA in JIA clinical trials (0.5%; n=190). In postmarketing experience, a case of fatal anaphylaxis following the first infusion of ORENCIA was reported. Appropriate medical support measures for treating hypersensitivity reactions should be available for immediate use. If an anaphylactic or other serious allergic reaction occurs, administration of ORENCIA should be stopped immediately and permanently discontinued, with appropriate therapy instituted.

Infections: Serious infections, including sepsis and pneumonia, have been reported in patients receiving ORENCIA. Some of these infections have been fatal. Many of the serious infections have occurred in patients on concomitant therapy. If there is any increase in infection rates or signs of infection require treatment, ORENCIA should be discontinued immediately.
immunosuppressive therapy which, in addition to their underlying disease, could further predispose them to infection. Caution should be exercised in patients with a history of infection or underlying conditions which may predispose them to infections. Treatment with ORENCIA should be discontinued if a patient develops a serious infection. Patients should be screened for tuberculosis and viral hepatitis in accordance with published guidelines, and if positive, treated according to standard medical practice prior to therapy with ORENCIA.

**Immunizations:** Live vaccines should not be given concurrently with ORENCIA or within 3 months of its discontinuation. The efficacy of vaccination in patients receiving ORENCIA is not known. ORENCIA may blunt the effectiveness of some immunizations. It is recommended that JIA patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating therapy with ORENCIA.

**Use in Patients with Chronic Obstructive Pulmonary Disease (COPD):** Adult COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea. In adult RA studies, 97% of COPD patients treated with ORENCIA developed adverse reactions versus 88% treated with placebo and respiratory disorders occurred more frequently in patients treated with ORENCIA compared to those on placebo (43% vs 24%, respectively), including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of adult RA patients treated with ORENCIA developed a serious adverse event compared to those on placebo (27% vs 6%), including COPD exacerbation (3 of 37 patients (8%) and pneumonia (1 of 37 patients (3%). Use of ORENCIA in patients with RA and COPD should be undertaken with caution, and such patients monitored for worsening of their respiratory status.

**Blood Glucose Testing:** ORENCIA for intravenous administration contains maltose, which may result in falsely elevated blood glucose readings on the day of infusion when using blood glucose monitors with test strips utilizing glucose dehydrogenase pyroloquinoline quinone (GDH-PQQ). Consider using monitors and advising patients to use monitors that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase or glucose hexokinase test methods. ORENCIA for subcutaneous (SC) administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

**Pregnancy:** There are no adequate and well-controlled studies of ORENCIA use in pregnant women and the data with ORENCIA use in pregnant women is insufficient to inform on drug-associated risk. A pregnancy registry has been established to monitor pregnancy outcomes in women exposed to ORENCIA during pregnancy. Healthcare professionals are encouraged to register patients by calling 1-877-311-8972.

**Lactation:** There is no information regarding the presence of abatacept in human milk, the effects on the breastfed infant, or the effects on milk production. However, abatacept was present in the milk of lactating rats dosed with abatacept.

**Most Serious Adverse Reactions:** Serious infections (3% ORENCIA vs 1.9% placebo) and malignancies (1.3% ORENCIA vs 1.1% placebo).

**Malignancies:** The overall frequency of malignancies was similar between adult RA patients treated with ORENCIA or placebo. However, more cases of lung cancer were observed in RA patients treated with ORENCIA (0.2%) than those on placebo (0%). A higher rate of lymphoma was seen compared to the general population; however, patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of ORENCIA in the development of malignancies in humans is unknown.

**Most Frequent Adverse Events (≥10%):** Headache, upper respiratory tract infection, nasopharyngitis, and nausea were the most commonly reported adverse events in the adult RA clinical studies. Other events reported in ≥5% of JIA patients were diarrhea, cough, pyrexia, and abdominal pain. In general, the adverse events in JIA and adult PsA patients were similar in frequency and type to those seen in adult RA patients.

**Note concerning ORENCIA administration options:** Intravenous dosing has not been studied in patients younger than 6 years of age. The safety and efficacy of ORENCIA Clickject™ Autoinjector for subcutaneous injection has not been studied in patients under 18 years of age.

Please see Full Prescribing Information at [http://packageinserts.bms.com/pi/pi_orencia.pdf](http://packageinserts.bms.com/pi/pi_orencia.pdf). ORENCIA® (abatacept) is a registered trademark of Bristol-Myers Squibb Company.

**About Bristol-Myers Squibb Immunoscience**

With a robust pipeline of immunomodulatory therapies, Bristol-Myers Squibb is committed to the discovery and development of transformational medicines that could lead to long-term remission in patients with immune-mediated diseases. As we discover more about the immune system in such diseases with substantial unmet medical needs, the potential for developing novel therapies that target specific pathways in the immune system continues to drive our research efforts.

**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 us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

**Bristol-Myers Squibb Forward-Looking Statement**

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be
beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that future study results will be consistent with the results to date, that ORENCIA may not receive regulatory approval for the additional indication described in this release and, if approved, whether ORENCIA for such additional indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol-Myers Squibb’s business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2018, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol-Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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