ORENCIA® (abatacept) Demonstrates Comparable Efficacy to Humira® (adalimumab) in Patients with Moderate to Severe Rheumatoid Arthritis in First Head-to-Head Study of These Agents

ORENCIA demonstrated comparable efficacy to Humira based on a non-inferiority endpoint for ACR20 response at 1 year

Kinetics of response for ACR20, 50 and 70, and inhibition of radiographic progression were generally comparable over 12 months

AMPLE is the first head-to-head study in adults with rheumatoid arthritis comparing two biologic drugs each on a background of methotrexate

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced the results of AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naïve rheumatoid arthritis (RA) Subjects With Background Methotrexate), a head-to-head clinical trial of 646 patients comparing the subcutaneous (SC) formulation of ORENCIA® (abatacept) vs. Humira® (adalimumab), each on a background of methotrexate (MTX), in biologic naïve patients with moderate to severe RA. AMPLE met its primary endpoint (as measured by non-inferiority) and demonstrated that ORENCIA plus MTX achieved comparable rates of efficacy for the American College of Rheumatology criteria of 20 percent (ACR20) response at 1 year of 64.8% vs. 63.4% Humira plus MTX.

ACR50, 70 and major clinical response (ACR70 for 6 consecutive months), considered to be more stringent measures of efficacy, as well as DAS-28-CRP, were also assessed at 1 year and found to be generally comparable for the two arms. Kinetics of response and inhibition of radiographic progression were generally comparable for the two groups over a 12-month period. Injection-site reactions (a key secondary endpoint) were statistically significantly fewer in the ORENCIA plus MTX group. Discontinuations due to adverse events were 3.5% for ORENCIA plus MTX compared to 6.1% for Humira plus MTX while discontinuations due to serious adverse events were 1.3% for ORENCIA plus MTX compared to 3% for Humira plus MTX. Autoimmune events (mild to moderate in severity) reported in the ORENCIA SC plus MTX group was 3.1% and 1.2% in the Humira plus MTX group. Other safety outcomes were similar at 12 months. The results of AMPLE were presented today at the European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology.

“Results from AMPLE provide important information comparing the efficacy of ORENCIA SC to Humira, including kinetics of response,” said Michael Schiff, M.D., M.A.C.R., University of Colorado, and principal AMPLE study investigator. “The results demonstrate comparability between two agents for the primary endpoint of ACR20 and provides relevant data on ACR50 and 70.”

“AMPLE is the first head-to-head study between two biologics which incorporates radiographic progression endpoints and provides important data on erosions and joint space narrowing in patients using ORENCIA SC and Humira, both on a background of methotrexate,” said Désirée van der Heijde, M.D. Ph.D., Professor of Rheumatology, Leiden University Medical Center.

About the Study

AMPLE is a phase IIIb randomized, investigator-blinded multinational study of 24 months duration with a 12 month efficacy primary endpoint (non-inferiority for ACR20). The study included 646 adult biologic-naive patients with active moderate to severe RA and inadequate response to MTX; 318 in the ORENCIA SC® (abatacept) plus MTX group and 328 in the Humira plus MTX group. Patients were stratified by disease activity and randomized to either 125 mg ORENCIA SC weekly (without an IV load) or 40 mg Humira every other week, both on background MTX. The primary endpoint was to determine non-inferiority of ORENCIA SC plus MTX to Humira plus MTX by a difference in ACR20 response at 12 months. Secondary endpoints included...
injection site reactions, radiographic non-progression as assessed using the van der Heijde modified total Sharp score (mTSS) method, safety and retention.

**Detailed Study Results**

Of 646 patients who were randomized and treated, 86.2% (274 of 318) ORENCIA SC plus MTX patients and 82% (269 of 328) Humira plus MTX patients completed 12 months.

Comparative ACR20 response rates at year 1 were 64.8% (95% confidence interval [CI]: 59.5, 70.0) for ORENCIA SC plus MTX and 63.4% (95% CI: 58.2, 68.6) for Humira plus MTX. The estimated difference between groups (95% CI) was 1.8 (-5.6, 9.2) supporting non-inferiority of ORENCIA SC plus MTX to Humira plus MTX.

Kinetics of response was generally comparable between the two groups for ACR20, 50 and 70 through the end of year 1. At 4 weeks, the ACR20 response rates were 42.5% ORENCIA SC plus MTX vs. 47.6% for Humira plus MTX, which remained comparable to the end of year 1 (64.8% ORENCIA SC plus MTX, 63.4% Humira plus MTX). Patients achieved generally comparable ACR50 and ACR70 responses between the ORENCIA SC plus MTX at year one (ACR50 and 70 were 46.2% and 29.2%, respectively) and Humira plus MTX groups (ACR50 and 70 were 46% and 26.2%, respectively).

ORENCIA SC plus MTX and Humira plus MTX treatment groups showed generally comparable inhibition of radiographic damage; at 12 months, mean change in radiographic non-progression rates as assessed using the mTSS method (0.58 and 0.38, respectively), erosion score (0.29 and -0.01, respectively) and joint narrowing (0.28 and 0.39, respectively) were observed.

Injection-site reactions occurred in significantly fewer patients in the ORENCIA SC® (abatacept) plus MTX group than the Humira plus MTX group (3.8% vs. 9.1%, 95% CI: [-9.13, -1.62]; p=0.006). Other safety outcomes were similar between ORENCIA SC plus MTX and Humira plus MTX treatment groups including rates of adverse events (34.9% and 39.9%), serious adverse events (10.1% and 9.1%), overall infections (63.2% and 61.3%), serious infections (2.2% and 2.7%) and malignancies (1.6% and 1.2%), respectively. Discontinuations due to adverse events were 3.5% in the ORENCIA SC plus MTX group and 6.1% in the Humira plus MTX group and discontinuations due to serious adverse events were 1.3% in the ORENCIA plus MTX group and 3% in the Humira plus MTX group. No serious infections in the ORENCIA SC plus MTX group led to discontinuation; 5 of the 9 in the Humira plus MTX group led to discontinuation. Autoimmune events (mild to moderate in severity) reported in the ORENCIA SC plus MTX group was 3.1% and 1.2% in the Humira plus MTX group.

**About ORENCIA**

ORENCIA SC and IV 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 rheumatoid arthritis. ORENCIA may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

ORENCIA IV is indicated for reducing signs and symptoms in pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA IV may be used as monotherapy or concomitantly with methotrexate (MTX). ORENCIA SC has not been studied in pediatric patients. ORENCIA should not be administered concomitantly with TNF antagonists.

ORENCIA is not recommended for use concomitantly with other biologic rheumatoid arthritis (RA) therapy, such as anakinra.

ORENCIA is intended for use under the guidance of a physician or healthcare practitioner.

**Important Safety Information**

**Concomitant Use with TNF antagonists:** Concurrent therapy with ORENCIA and a biologic DMARD is not recommended. In controlled clinical trials, adult 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:** Less than 1% of adult patients treated with ORENCIA experienced hypersensitivity reactions, including some cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of patients treated with ORENCIA® (abatacept) and generally occurred within 24 hours of infusion. There was 1 case of a hypersensitivity reaction with ORENCIA in JIA clinical trials (0.5%; n=190). Appropriate medical support measures for treating hypersensitivity reactions should be available for immediate use in the event of a reaction.

**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 immunsuppressive 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 as it 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 (97% vs. 88%, respectively). Respiratory disorders occurred more frequently in patients treated with ORENCIA compared to those on placebo (43% vs. 24%, respectively), including COPD exacerbations, cough, rhonchi, and dyspnea. A greater percentage of 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 pyrroloquinolinequinone (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 administration does not contain maltose; therefore, patients do not need to alter their glucose monitoring.

**Pregnant and Nursing Mothers:** ORENCIA® (abatacept) should be used during pregnancy only if clearly needed. The risk for development of autoimmune diseases in humans exposed in utero to abatacept has not been determined. Nursing mothers should be informed of the risk/benefit of continued breast-feeding or discontinuation of the drug. A pregnancy registry has been established to monitor fetal outcomes. Healthcare professionals are encouraged to register pregnant patients exposed to ORENCIA by calling 1-877-311-8972.

**Most Serious Adverse Reactions:** Serious infections (3% ORENCIA vs. 1.9% placebo) and malignancies (1.3% ORENCIA vs. 1.1% placebo). In general, adverse events in pediatric and adolescent patients were similar in frequency and type to those seen in adult patients.

**Malignancies:** The overall frequency of malignancies was similar between adult patients treated with ORENCIA or placebo. However, more cases of lung cancer were observed in 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.


**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 than in men, who account for 75% of patients diagnosed with RA.

**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](http://twitter.com/bmsnews).

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**Language:**
English

**Contact:**
Bristol-Myers Squibb Company
Media:
Ken Dominski, 609-252-5251
ken.dominski@bms.com
or
Celine Van Doosselaere, +33 1 58 83 60 27
celine.vandoosselaere@bms.com
or
Investors:
John Elicker, 609-252-4611
john.elicker@bms.com

**Ticker Slug:**
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Exchange: NYSE*

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