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NEWS RELEASE

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New data from Janssen presented at the Annual European Congress of Rheumatology (EULAR 2019) shows sustained clinical benefit and reduction in severe flares with Stelara® (ustekinumab) in patients with systemic lupus erythematosus (SLE)

MADRID, SPAIN, 13 June, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson presented this week results of two analyses from a Phase 2 study of Stelara®* (ustekinumab) in systemic lupus erythematosus (SLE). The studies highlight not only the sustained clinical benefit of ustekinumab - an anti-interleukin (IL) IL-12/23 p40 neutralising monoclonal antibody - on SLE disease activity at one-year, but also show a reduction in the rate of severe flares. They also provide new insights into the possible pathway through which ustekinumab is acting in SLE patients who respond to IL-12/23 p40 blockade.[1,2]

The Phase 2 study, presented by lead study investigator Ronald van Vollenhoven MD PhD and colleagues, is a global randomized, placebo-controlled trial in 102 adults with seropositive SLE by Systemic Lupus International Collaborating Clinics (SLICC) criteria and active disease despite ongoing standard of care therapy (steroid, antimalarial and/or immunosuppressive therapies).[1] Patients were randomized (3:2) to receive intravenous (IV) ustekinumab or placebo, both in addition to standard of care therapy for 24 weeks. At week 24, patients in the placebo arm crossed over to active study agent.[1]

Results reported previously at week 24 showed the considerable efficacy of ustekinumab vs placebo on both global and organ-specific disease measures.[1] The new long-term results (48 weeks) confirmed the sustained clinical efficacy of ustekinumab, with all measures maintained over a one-year period.[1] Importantly, ustekinumab reduced the occurrence of severe British Isles Lupus Assessment Group (BILAG) flares.[1,3] Results showed a 4-fold decrease in the rate of severe flares with ustekinumab vs placebo in weeks 0–24.[1] The flare rate was also lower in week 24-48 compared to placebo or ustekinumab rates in weeks 0-24.[1] In addition, the safety profile of ustekinumab through one year in SLE was consistent with that observed in other immune-mediated conditions.[1]

Commenting on the results, van Vollenhoven, who is also Professor and Chief of Rheumatology at the Amsterdam University Medical Center explained, "*SLE flares are very unpredictable and have a major impact on patients' quality of life. As such, these results present an impactful and clinically relevant finding, and suggest ustekinumab could in the future offer patients a valuable new treatment option*."

The ustekinumab group had a severe BILAG flares rate of 2.1/10,000 patient-days in weeks 0–24, compared to 8.4/10,000 patient-days in the placebo group.[1] In weeks 24–48, the rate of severe BILAG flares for patients in the ustekinumab group was 1.1/10,000 patient-days. Patients in the placebo group who crossed over to ustekinumab at week 24 had severe BILAG flare rate of 4.6/10,000 patient-days.[1]

The second study, presented by Dr George Tsokos, the study steering committee lead and Chief of the Division of Rheumatology and Clinical Immunology, Beth Israel Deaconess Medical Center, Boston, was an additional analysis of the ustekinumab Phase 2 study using biomarker data that could help to explain the mechanism through which ustekinumab may be effective in SLE. Biomarker data was collected over 24 weeks from ustekinumab responders, ustekinumab non-responders and patients on placebo.[2] The analysis specifically showed an association of clinical response with novel biomarker responses that were independent of IFN-I.[2] The analysis measured the cytokines interferon gamma (IFN-γ), IL-17 A/F and IL-22 which are downstream mediators of the IL-12/IL-23 pathways, as well as type I interferons (IFN-I), believed to be a major contributor to SLE pathogenesis.[2]

The results showed that people who responded to ustekinumab had durable reductions in IFN-γ protein levels relative to baseline – a finding which was not observed in patients who did not respond to ustekinumab or who received placebo. Other biomarkers measured including IFN-I, IL-17 A/F and IL-22 remained largely unchanged. These findings implicate the involvement of

the IL-12 pathway linked to IFN-γ production and not the IFN-I pathway in SLE responders to ustekinumab, but this will require confirmation in an ongoing Phase 3 study.[2]

The common (≥1/100) adverse reactions reported in controlled periods of the adult psoriasis, psoriatic arthritis and Crohn's disease clinical studies with ustekinumab as well as post-marketing experience were: upper respiratory tract infection, arthralgia, back pain, diarrhoea, dizziness, fatigue, headache, infection site pain, injection site erythema, myalgia, nasopharyngitis, nausea, oropharyngeal pain, pruritus and vomiting.[11]

The IL-12 pathway is important in T-helper-1 and T-follicular-helper cell differentiation in autoimmune diseases, production of IFN-γ, and activation and function of cytotoxic cells.[4] Helping to put these observations into context, study investigator, Dr George Tsokos, commented, "*This is an important finding because SLE drivers have, until recently, been considered to be led by IFN-I. These results suggest that the classical model suspected to be functioning in SLE may be supported by an alternative mechanism of disease via IL-12/-23-dependent T-helper-1 cell differentiation and IFN-γ. It might be this pathway helping to improve clinical disease activity and reduce severe flares, which are currently challenging to manage with lupus*."

"Lupus is a complex disease, it can produce many symptoms and in some cases, can take years to be diagnosed. If left untreated, this disease can be fatal," commented Dr Jaime Oliver, Therapeutic Area Lead, Immunology and CVT, Europe Middle East & Africa, Janssen Cilag GmbH International. "*We are committed to advancing our understanding of lupus in order to develop therapies that have the potential to change the lives of people in need.*"

SLE most often affects women and disproportionately affects women of African American, Hispanic, Asian and Native American descent compared to Caucasian women.[5] Incidence rates vary across European countries, ranging from 2.2 cases/100,000 in Spain to 5 cases/100,000 in France.[6]

The findings from both analyses will be confirmed in the ongoing Phase 3 LOTUS study (NCT no. NCT03517722 / EudraCT no. 2017-001489-53).

END

About the Phase 2 ustekinumab SLE Trial

The efficacy and safety of ustekinumab was evaluated in a global Phase 2, randomised, placebo-controlled trial in 102 adults with seropositive SLE by Systemic Lupus International

Collaborating Clinics (SLICC) criteria and active disease despite ongoing standard of care therapy (steroid, antimalarial and/or immunosuppressive therapies) (NCT no. NCT02349061 / EudraCT no. 2014-005000-19).[1] Patients were randomised (3:2) to receive intravenous (IV) ustekinumab 6 mg/kg or placebo (PBO) at week 0, followed by subcutaneous (SC) injections of ustekinumab 90 mg or placebo every eight weeks, both in addition to standard of care therapy for 24 weeks. At week 24, patients in the placebo arm crossed over to active study agent.[1]
The primary endpoint was the proportion of patients achieving SLE Responder Index-4 (SRI-4) response at week 24. The SRI combines scores from three different validated lupus disease indexes to define responders versus non-responders, and has previously been accepted by health authorities in SLE registration trials.[1] To achieve SRI-4 response, an individual with lupus must have at least a four-point improvement on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, less than 10% increase in Physician's Global Assessment (PGA) of disease activity and no worsening of moderate/severe organ disease on the BILAG disease activity index.[1] Major secondary endpoints included change from baseline in SLEDAI-2K score, change from baseline in PGA of disease activity, and proportion of patients with BILAG-based Combined Lupus Assessment (BICLA) response, all at week 24. Joint and cutaneous disease activity were also assessed with joint counts and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), respectively.[1] Ustekinumab response rates were sustained through one year in organ-specific disease measures (≥50% improvement in active joint counts: week 24: 87% vs week 48: 87%; ≥50% improvement in CLASI activity score: week 24: 53% vs week 48: 69%).[1]

Endpoint analyses included all patients who received at least one dose of study agent, had at least one measurement prior to administration, and had at least one post-baseline measurement. Patients with missing data and treatment failures were imputed as non-responders. Long-term safety and efficacy data are currently being collected through 104 weeks.

About systemic lupus erythematosus (SLE)

Lupus is a chronic, inflammatory autoimmune disease that can affect many different body systems, including joints, skin, heart, lungs, kidneys and brain. Most people with lupus have mild disease characterised by episodes of disease worsening called flares. When a flare occurs, many people will either notice a return of symptoms, an increase in symptom severity or may develop new symptoms. Common symptoms that indicate a flare include ongoing fever not due to an infection or other cause, painful or swollen joints, fatigue, rashes or sores or ulcers in the mouth or nose.[7] During a flare signs and symptoms get worse for a while, then improve or even disappear completely for a time.[8] SLE can range from mild to severe and is characterised by

inflammation of any organ system including the kidneys, nervous system and brain.[9] Lupus is estimated to affect at least 5 million people worldwide.[10]

About ustekinumab[11]

In the European Union, ustekinumab is approved for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or psoralen plus ultraviolet A (PUVA), and is also indicated for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older who are inadequately controlled by or are intolerant to other systemic therapies or phototherapies. In addition, ustekinumab is approved alone or in combination with MTX for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying antirheumatic drug (DMARD) therapy has been inadequate. Ustekinumab is approved by the European Commission for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha antagonist or have medical contraindications to such therapies.

*Ustekinumab is currently under investigation and is not approved for SLE. A Phase 3 programme evaluating ustekinumab in the treatment of adults with active SLE is ongoing.

The common (≥1/100) adverse reactions reported in controlled periods of the adult psoriasis, psoriatic arthritis and Crohn's disease clinical studies with ustekinumab as well as post-marketing experience were: upper respiratory tract infection, arthralgia, back pain, diarrhoea, dizziness, fatigue, headache, infection site pain, injection site erythema, myalgia, nasopharyngitis, nausea, oropharyngeal pain, pruritus and vomiting.

The Janssen Pharmaceutical Companies of Johnson & Johnson maintain exclusive worldwide marketing rights to ustekinumab, which is currently approved for the treatment of moderate to severe plaque psoriasis in 89 countries, paediatric psoriasis in 44 countries, psoriatic arthritis in 83 countries and Crohn’s disease in 70 countries.

Stelara® (ustekinumab) is a registered trademark of Johnson & Johnson.

Important Safety Information

For complete European Union (EU) prescribing information, please visit: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf.

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About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com/EMEA. Follow us at www.twitter.com/JanssenEMEA. Janssen-Cilag International NV and Cilag GmbH International are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding development of ustekinumab in systemic lupus erythematosus. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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