Mirikizumab Up-Regulates Genes Associated with Mucosal Healing in Ulcerative Colitis for Up to One Year in Phase 2 Study

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INDIANAPOLIS, July 9, 2021 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced new Phase 2 data showing that gene expression changes induced by mirikizumab in patients with ulcerative colitis (UC) over a 12-week induction treatment were maintained for up to one year. These gene transcript changes, which were unique among those who responded to mirikizumab compared to placebo, were associated with mucosal healing, indicating that mirikizumab affects a distinct molecular healing pathway, compared to the spontaneous healing that occurred among those who responded to placebo.

Mirikizumab is being studied in Phase 3 trials for UC and Crohn's disease (CD), two forms of inflammatory bowel disease that can cause serious and debilitating symptoms, and disruptions in daily life.

A separate analysis of patients with moderate to severe UC evaluated meaningful improvement of bowel urgency, a common symptom of UC that is associated with higher levels of disease activity, decreased work productivity and worse quality of life. These results are being presented virtually at the Congress of the European Crohn's and Colitis Organisation (ECCO), July 8-10, 2021.

Mirikizumab Showed Early and Sustained Gene Expression Changes Associated with Mucosal Healing in UC for Up to One Year

In a previously-published Phase 2 study evaluating patients with UC, mirikizumab down-regulated several gene transcripts associated with inflamed mucosa and up-regulated gene transcripts correlated with healthy mucosa and markers of functional healing after 12 weeks, as defined by clinical disease indices of endoscopy and histology.

In this analysis, a set of differentially-expressed gene transcripts were identified in patients who responded to mirikizumab that were not found in those who responded to placebo at 12 weeks. Of the modulated genes, 71% (n=63) were present only in patients who responded to mirikizumab, 5.6% (n=5) were present only in those who responded to placebo, and 23.6% (n=21) were present in both groups. Effect size estimates were also examined to account for differences in sample size and associated power between treatment groups. The set of gene transcripts regulated by mirikizumab correlated with UC disease activity indices, demonstrating consistency of these molecular changes across symptomatic, clinical, endoscopic and histologic indices of UC disease activity.

The results observed at 12 weeks were maintained for up to one year in patients receiving mirikizumab. For methodology, see the "About the Studies" section below.

"In the first clinical study of an anti-IL-23p19 therapy in ulcerative colitis to evaluate gene expression on this large scale, mirikizumab demonstrated an ability to down-regulate the gene transcripts associated with inflammation and up-regulate transcripts associated with mucosal healing in ulcerative colitis, with changes maintained for up to one year," said Walter Reinisch, Director of the Clinical IBD Study Group, Department of Gastroenterology and Hepatology, Medical University of Vienna. "These results support the continued development of mirikizumab as a potential treatment option for ulcerative colitis, given the importance of mucosal healing and functional healing as key treatment goals for this difficult-to-treat disease."

Patients with UC Reported on Definition of Meaningful Change in Bowel Urgency

Bowel urgency, the sudden or immediate need for a bowel movement, is one of the most distressing symptoms experienced by patients with UC. In this qualitative study of patients with moderate to severe UC, patients defined both bowel urgency severity and what would be a meaningful improvement in bowel urgency based on an 11-point numeric rating scale (NRS).

In this study, half of patients with UC (50%, n=10) reported that a 1-point change on the urgency NRS would be a meaningful change, indicating improved emotional well-being and greater confidence to leave the home or do their work.

A quarter of respondents (25%, n=5) indicated that a 2-point improvement in the urgency NRS was required to be considered meaningful, and another 25% of respondents (n=5) noted that a 3-point change or more was needed to achieve improvements in quality of life.

Importantly, among the 75% of patients who endorsed a 1 to 2-point change in urgency NRS, initial scores on the urgency NRS ranged from 2 to 9, indicating that this amount of change was meaningful regardless of the severity of an individual's bowel urgency. For methodology, see the "About the Studies" section below.

"We are very excited to present these findings at ECCO, which provide one of the first analyses from the patient perspective on the impact of bowel urgency and what would constitute a meaningful change," said Prentice Stovall, Jr., Global Development Leader, Immunology at Lilly. "Given the impact that bowel urgency has on an individual's ability to work and overall quality of life, this analysis will help us further understand the experience of people with UC and the potential impact of our treatments on this burdensome and debilitating symptom."

About The Studies

- **Mirikizumab-Induced Transcriptome Changes in Patient Biopsies at Week 12 Are Maintained Through Week 52 in Patients with Ulcerative Colitis**
  Patients who achieved clinical response at 12 weeks, as measured by a decrease in 9-point Mayo subscore (rectal bleeding, stool frequency, endoscopy) of ≥2 points and ≥35% from baseline, with either a decrease of rectal bleeding

subscore of ≥1 or an RB subscore of 0 or 1) continued onto maintenance mirikizumab treatment. Patients given placebo in induction who achieved clinical response continued on placebo in the maintenance period. In this study, colonic biopsies from 52 patients were obtained at Weeks 0, 12 and 52 from the most affected area ≥30 cm from the anal verge (mirikizumab, n=31, placebo, n=7). Of those patients, 31 were 200 mg mirikizumab responders and seven responded to placebo. Transcript changes at Week 12 from baseline in the placebo and mirikizumab arms were clustered into differentially expressed genes using the Bayesian Limma R-package. Differentially expressed genes which maintained their Week 12 expression level through Week 52 in both the placebo and mirikizumab arms were identified and designated as similarly expressed genes. Overall, the safety profile at 52 weeks was consistent with that of mirikizumab in studies of UC and with the class.

- **A Qualitative Study Exploring Meaningful Improvement in Bowel Urgency among Adults with Moderate to Severe Ulcerative Colitis**
  In this qualitative study assessing meaningful improvement in bowel urgency based on a NRS, in-depth interviews were conducted in the United States with 20 adults with clinician-confirmed moderate to severe UC. Using an 11-point NRS developed specifically to assess bowel urgency severity, participants were asked to define levels of bowel urgency (where 0=no urgency and 10=worst possible urgency). Participants were also asked to describe what would be a meaningful improvement based on how this change would impact their daily life.

About Mirikizumab
Mirikizumab is a humanized IgG4 monoclonal antibody that binds to the p19 subunit of interleukin 23. Mirikizumab is being studied for the treatment of immune diseases, including ulcerative colitis and Crohn's disease.

About Ulcerative Colitis
Ulcerative colitis is a chronic inflammatory bowel disease that affects the colon. UC occurs when the immune system sends white blood cells into the lining of the intestines, where they produce chronic inflammation and ulcerations. There is an unmet need for additional treatment options for UC that provide meaningful symptom relief, including bowel urgency, and deliver sustained clinical remission.

About Eli Lilly and Company
Lilly is a global health care leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. P-LLY

Lilly Forward-Looking Statement
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about mirikizumab as a potential treatment for patients with ulcerative colitis and/or Crohn's disease and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there can be no guarantee that future study results will be consistent with study results to date, that mirikizumab will prove to be a safe and effective treatment or that mirikizumab will receive regulatory approvals or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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