AstraZeneca

PHASE III RESULTS LESINURAD COMBINATION THERAPY

ASTRAZENECA ANNOUNCES TOP-LINE RESULTS FROM THE PHASE III PROGRAMME OF LESINURAD IN COMBINATION WITH XANTHINE OXIDASE INHIBITORS IN GOUT PATIENTS

AstraZeneca today announced positive top-line results from CLEAR1, CLEAR2 and CRYSTAL, the pivotal Phase III clinical trials investigating the potential of lesinurad, a selective uric acid re-absorption inhibitor (SURI), as a combination therapy for the treatment of patients with symptomatic gout. Lesinurad is an investigational agent that inhibits the URAT1 transporter, increasing uric acid excretion and thereby lowering serum uric acid (sUA).

CLEAR1 and CLEAR2 studied lesinurad (200mg and 400mg once daily) in combination with the xanthine oxidase (XO) inhibitor allopurinol, in symptomatic gout patients not achieving target sUA levels on their current allopurinol dose. CRYSTAL studied lesinurad (200mg and 400mg once daily) in combination with the XO inhibitor febuxostat (80mg once daily) in gout patients with tophi (visible nodules of uric acid crystals that are deposited in joints and skin).

In the CLEAR1 and CLEAR2 trials, both lesinurad 200mg and 400mg in combination with allopurinol met the primary endpoint, with a statistically significant higher proportion of patients reaching the target sUA goal of <6.0mg/dL at month 6 compared to allopurinol alone ($p<0.0001$).

In the CRYSTAL trial, lesinurad 400mg in combination with febuxostat met the primary endpoint, with a statistically significant higher proportion of patients reaching the target sUA goal of <5.0mg/dL at month 6 compared to febuxostat alone ($p<0.0001$). Although lesinurad 200mg did not achieve statistical significance at month 6 ($p=0.13$), this dose in combination with febuxostat, was superior to placebo plus febuxostat at all other time points (measured at months 1 to 5, 8, 10 and 12; nominal $p<0.05$).

The three most commonly reported adverse events across the CLEAR1 and CLEAR2 trials for patients receiving lesinurad in combination with allopurinol were upper respiratory tract infection, nasopharyngitis and back pain. In CRYSTAL, the three most commonly reported adverse events for patients receiving lesinurad in combination with febuxostat were nasopharyngitis, arthralgia and upper respiratory tract infection.

The incidence of renal-related adverse events (including serious events) and incidence of kidney stones with lesinurad 200mg plus XO inhibitor was comparable to placebo plus XO inhibitor. The incidence of renal-related adverse events and kidney stones was higher with lesinurad 400mg plus XO inhibitor. A full assessment of the safety and tolerability findings of all three studies is ongoing.

“Gout is a serious, chronic and debilitating inflammatory disease. There is a significant unmet need, with 40 to 70 percent of gout patients not reaching target levels of serum uric acid with the current standard of care,” said Briggs Morrison, Executive Vice President, Global Medicines Development and Chief Medical Officer. “We are encouraged by our initial review of the top-line results from the CLEAR1, CLEAR2 and CRYSTAL studies which provide important new information on the efficacy and safety of lesinurad in combination with febuxostat and allopurinol. These data indicate that combination therapy with lesinurad may be a potential treatment option for gout patients.”

CLEAR1, CLEAR2 and CRYSTAL were conducted by Ardea Biosciences, a wholly-owned subsidiary of AstraZeneca. Results from these Phase III clinical trials will be submitted to a scientific meeting later in 2014. The company is proceeding with preparation of regulatory submissions for lesinurad (200mg) combination therapy.

About the Design of the Studies

CLEAR1 and CLEAR2 (Combining Lesinurad with Allopurinol in Inadequate Responders) were 12-month (US and global, respectively) multicenter, randomised, placebo-controlled studies (n=603 and n=610, respectively) comparing the efficacy and safety of lesinurad (200mg and 400mg once daily) when added to the patient’s current stable medically-appropriate dose of allopurinol (at least 300mg daily, and at least 200mg daily for those with moderate renal impairment) compared to placebo plus allopurinol. Patients entering CLEAR1 and CLEAR2 had multiple sUA levels above target and had also reported at least two gout flares in the 12 months prior to randomisation.

CRYSTAL (Combination Treatment Study in Subjects with Tophaceous Gout with Lesinurad and Febuxostat) was a 12-month global multicenter, randomised, placebo-controlled study (n=324) comparing the efficacy and safety of lesinurad (200mg and 400mg once daily) in combination with febuxostat (80mg) compared to febuxostat (80mg) plus placebo in gout patients with tophi and sUA levels above target. In the CRYSTAL study all patients were started on febuxostat three weeks prior to the initiation of the randomised study medication (with either placebo or lesinurad).

Patients who completed the randomised pivotal Phase III clinical studies had the option to enroll in two on-going open-label, uncontrolled extension studies to continue to evaluate the safety and efficacy of combination therapy with lesinurad 200mg and 400mg with XO inhibitors.

About Gout

Gout is a serious, chronic and debilitating inflammatory arthritis. There were 15.3 million diagnosed cases of chronic gout in major markets in 2013 and this is forecast to grow to 17.7 million by 2021. Gout is caused by a metabolic disorder, hyperuricemia (elevated sUA) which leads to the deposition of crystals in musculoskeletal structures including joints, in the kidneys, and in other tissues.

The goal of all urate lowering treatments is to reduce sUA levels to the recommended targets. International treatment guidelines from the American College of Rheumatology, European League Against Rheumatism and the British Society for Rheumatology recommend achieving an sUA target at a minimum of < 6 mg/dL in all gout patients and often to < 5 mg/dL in gout patients with greater disease severity and urate burden, such as those with tophi.

About Ardea Biosciences

Ardea Biosciences, Inc. was acquired by AstraZeneca in June 2012. It is located in San Diego, California and is a wholly owned subsidiary of AstraZeneca PLC. Ardea is developing a portfolio of molecules for the treatment of gout, including lesinurad and RDEA3170.

About AstraZeneca

AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: www.astrazeneca.com

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