June 11, 2020

Ono and Seikagaku Announce the Results from a Phase III Clinical Study in Japan of ONO-5704/SI-613 in Patients with Knee Osteoarthritis Presented at an Academic Conference

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; "Ono") and Seikagaku Corporation (Tokyo, Japan; "Seikagaku") announced today that the results from a Phase III clinical study of ONO-5704/SI-613 in Japan in patients with knee osteoarthritis ("the Study") were presented at the 93rd Annual Meeting of the Japanese Orthopaedic Association, an on-line annual meeting being held from Thursday June 11 to Monday August 31, 2020. ONO-5704/SI-613 is being jointly developed in Japan by the companies for the treatment of osteoarthritis.

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The phase III study of Diclofenac etalhyaluronate (ONO-5704/SI-613) in osteoarthritis of the knee

The Study was a randomized, double-blind, placebo-controlled, parallel-group comparative study, to evaluate the efficacy and safety of ONO-5704/SI-613 in 440 patients with knee osteoarthritis who received either ONO-5704/SI-613 or a placebo (6 injections into the knee joint cavity every 4 weeks).

ONO-5704/SI-613 group demonstrated a statistically significant difference in the primary endpoint of the Study, the mean change in WOMAC pain score (a knee pain evaluation index, 100 mm VAS scale) versus placebo group, from baseline to 12 weeks after the initial administration (3 injections every 4 weeks) with the difference of -6.1 mm ($p<0.001$). ONO-5704/SI-613 group also demonstrated a statistically significant difference (-5.6 mm) compared to placebo group in mean change from baseline to 24 weeks after the initial administration ($p=0.001$). Furthermore, ONO-5704/SI-613 group demonstrated a statistically significant difference compared to placebo group in WOMAC stiffness score and physical function score from baseline to 12 weeks after the initial administration, secondary endpoints of the Study. In the results of safety evaluation, no difference in frequency of adverse events and no clinically evident problems were found.

Outline of the Phase III Clinical Study in Patients with Knee Osteoarthritis in Japan (the Study):

Purpose	Examine superiority of efficacy of ONO-5704/SI-613 over a placebo, when repeatedly administered every four weeks into the knee joint cavity of patients with knee osteoarthritis.
Study design	Multicenter, randomized, placebo-controlled, double-blind, parallel-group comparative study
Observation period	24 weeks after the initial administration
Subjects	Males and females aged 40 to 75 Diagnosed with knee osteoarthritis according to the criteria of the American College of Rheumatology Kellgren-Lawrence radiographic scores of Grade 2 or 3 Pain from knee osteoarthritis continuing one year or longer Pain from knee osteoarthritis that meets the criteria at the time of participation in the Study

Number of patients and randomization	440 patients (ONO-5704/SI-613 group: 220 patients / placebo group: 220 patients)
Number of study sites	50 sites
Study period	April 2017 to January 2019
Primary endpoint	WOMAC A (pain) score (100 mm VAS) Primary analysis: mean change from baseline to 12 weeks after the initial administration
Main secondary endpoints	WOMAC B (stiffness) score, WOMAC C (physical function) score, etc.
Method of administration	Administration of ONO-5704/SI-613 (30 mg/ 3 ml) or a placebo (3 ml) into the knee joint cavity 6 times every 4 weeks

In January 2020, Seikagaku submitted an application for manufacturing and marketing approval of ONO-5704/SI-613 in Japan for the treatment of osteoarthritis (knee joint, hip joint and ankle joint) based on the results of the Study and the other two Phase III clinical studies.*1

Ono and Seikagaku aim to contribute to improvement of QOL in patients by providing a new treatment option for osteoarthritis (of the knee joint, hip joint and ankle joint) and will work together to obtain an approval of ONO-5704/SI-613 as soon as possible.

*1: 1) Phase III confirmatory study in patients with knee osteoarthritis (the Study)
2) Phase III study in patients with osteoarthritis (four joint sites: shoulder, elbow, hip and ankle)
3) Phase III long-term study in patients with osteoarthritis, primarily for safety evaluation (five joint sites: knee, shoulder, elbow, hip and ankle)

About ONO-5704/SI-613

ONO-5704/SI-613 is a formulation in which hyaluronic acid and diclofenac (an anti-inflammatory drug) are chemically bound using Seikagaku's own proprietary technology. The product combines the pain relief and anti-inflammatory effect of diclofenac designed for sustained release*2 using a drug delivery system*3 with the joint function improving effect of hyaluronic acid. It is expected to provide prompt and long-lasting relief of the pain and inflammation associated with osteoarthritis (of the knee joint, hip joint, and ankle joint). Further, since the product is administered directly into the joint cavity as an injectable treatment, systemic exposure to diclofenac is low, and the risk of systemic adverse drug reaction is thought to be low.

*2: Sustained release is the gradual release of the active pharmaceutical ingredients of a drug to achieve a sustained therapeutic effect.
*3: Drug delivery system (DDS) is a technology for the controlled release, targeting, and absorption improvement of drugs.

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