

June 5, 2014  
Seikagaku Corporation  
(Securities Code: TSE 4548)

## **Seikagaku Announces Results of Phase III Clinical Trial in Japan for SI-6603, Indicated for Treatment of Lumbar Disc Herniation**

Seikagaku Corporation (Tokyo) today announced the results of a Phase III clinical trial in Japan for SI-6603 (generic name: condoliase), indicated for the treatment of lumbar disc herniation were presented at the 41st Annual Meeting of The International Society for the Study of the Lumbar Spine, being held in Seoul, Korea, on June 4, 2014.

The trial was a multicenter, double-blind, randomized, placebo-controlled study in 163 patients with lumbar disc herniation. The primary endpoint was the change from baseline at 13 weeks after administration in the mean visual analog scale (VAS) score of worst leg pain over the past 24 hours.

The change from baseline in the VAS score of worst leg pain at 13 weeks after administration was significantly greater in the SI-6603 group ( $p=0.001$ ), indicating marked improvement in the leg pain. The percentage of subjects whose VAS scores of the leg pain had improved by 50% or more from baseline values (response rate) was 72.0% in the SI-6603 group compared with 50.6% in the placebo group ( $p=0.008$ ). In addition, the SI-6603 group demonstrated significantly greater change in physical functional disability and quality of life (QOL) evaluation scores, thus improvements in functional disability and QOL were also confirmed. As for safety up to 52 weeks after administration, although the frequency of adverse events, such as back pain and disc height decrease, was higher in the SI-6603 group, SI-6603 was well tolerated.

Kazuhiro Chiba, M.D., Ph.D., Chairman, Department of Orthopaedic Surgery, and Associate Director, Kitasato University Kitasato Institute Hospital, a lead investigator of this clinical trial, said, "The effect of condoliase to improve leg pain is comparable to that of lumbar disectomy. It was well tolerated and did not cause clinically important adverse events. Because treatment by condoliase was much less invasive than lumbar disectomy, it would enhance earlier return of patients to work and normal life and contribute to reduction of medical expenses and economical burden to the society. Condoliase can be a novel and potent treatment for patients with lumbar disc herniation unresponsive to conservative treatment."

Since currently there is no fundamental pharmacological therapy for lumbar disc herniation, the launch of SI-6603, of which a single injection treatment expected to be as effective as lumbar disectomy in improving symptoms, would contribute to the alleviation of physical burden and improvement of QOL of the patients. Seikagaku submitted a new drug application to the Ministry of Health, Labor and Welfare of Japan in January 2014 and it is now under review. The company is also focusing on the progress of the Phase III clinical trials underway in the U.S.

«Appendix»

**【Reference 1: Overview of the Phase III Clinical Trial of SI-6603 in Japan】**

Purpose	Examine the efficacy and safety of SI-6603 for the treatment of lumbar disc herniation compared with the placebo group
Study design	Phase III, multicenter, double-blind, randomized, placebo-controlled study
Observation period	For 52 weeks. After evaluation of efficacy and safety at 13 weeks after administration, a follow-up study related to efficacy and safety was conducted up to 52 after administration
Subjects	Patients 20 to 70 years of age with L4/L5 or L5/S1 contained-lumbar disc herniation for which no improvement is found from conservative treatment for 6 weeks or longer Patients with sciatica in a single leg, mean VAS* score of 50 mm or more, and positive in the straight leg raising (SLR) test
Number of patients and group allocation	163 patients (SI-6603 group: 82 patients /placebo group: 81 patients)
Sex	Male and female
Number of centers	35
Trial period	March 2012 to February 2014
Primary endpoint	Change in the score of worst leg pain over the past 24 hours at 13 weeks after administration from baseline
Main secondary endpoints	Worst back pain over the past 24 hours, neurological examination, change in disc height and hernia volume in image analysis
Method of administration	Single dose intradiscal administration of 1.25 U of condoliase or a placebo (1 mL)

\* VAS: A psychometric response scale which can be used in questionnaires.

Patients record his/her current pain level between 100 mm at maximum and 0 mm at minimum.

**【Reference 2: SI-6603 for the treatment of lumbar disc herniation】**

Lumbar disc herniation is the partial protrusion of the nucleus pulposus at the core of each intervertebral disc or the anulus fibrosus, the disc's outer layer. The resulting pressure on the spinal nerve root causes pain and numbness. SI-6603 is an injectable drug using an enzyme named condoliase that specifically degrades glycosaminoglycans (GAG) \*, which are the main components of the nucleus pulposus. A direct injection of SI-6603 into the intervertebral disc would cause reduction of the pressure on the nerves by shrinking the nucleus pulposus through degrading GAG. Because SI-6603 does not break down proteins, it is thought to have no effect on surrounding tissues such as blood vessels and nerves.

\*Glycosaminoglycans (GAG): one of the constituents of complex carbohydrates such as chondroitin sulfate and hyaluronic acid.

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