



Agreement Concerning Development of

Novel Anti-rheumatic Agent Anti-APO-1 Antibody in Japan

October 15, 2004 – Argenes, Inc. (headquartered in Tokyo, Japan) and Santen Pharmaceutical Co., Ltd. (headquartered in Osaka, Japan) announced that they entered into an agreement today concerning domestic development of the anti-APO-1 antibody,^{*1} which Santen had in-licensed from Centocor, Inc. (headquartered in Malvern, Pennsylvania, United States). Under this agreement, Argenes will conduct development of the agent, from pre-clinical and clinical studies, to filing of a new drug application with the Ministry of Health, Labour, and Welfare, aiming at a commercialization of the product. In addition to granting the domestic development rights of the anti-APO-1 antibody, Santen decided to invest in Argenes. Santen continues to hold the marketing rights in Japan, as well as the worldwide development and marketing rights.

The anti-APO-1 antibody is a potential drug candidate currently under preclinical development. Having obtained exclusive rights from Centocor to develop, manufacture and market the antibody in the U.S., Europe, Japan and the rest of Asia, Santen has demonstrated its therapeutic effect on rheumatoid arthritis through the collaboration of the Institute of Medical Science at the St. Marianna University School of Medicine. In joints affected by rheumatoid arthritis, apoptosis^{*2} (i.e. programmed cellular death) of the synovial cells^{*3} does not progress normally, resulting in synovial hyperplasia and the destruction of bone and cartilage.

The anti-APO-1 antibody has an action mechanism that induces apoptosis in synovial cells and thus inhibits their abnormal proliferation. When injected into the joint cavity, it would become a simple, safe and totally new treatment method for joint destruction, which cannot be cured with existing pharmaceuticals. The agent's efficacy in local administration is expected to satisfy the needs of patients with intractable diseased joints that are resistant to the latest treatments available, such as the anti-TNF antibody. In addition, the anti-APO-1 antibody is closer to a radical cure than any other existing treatment method, and would therefore generate a new market for the treatment of rheumatoid arthritis.

Argenes is one of the venture-capital organizations related with St. Marianna University School of Medicine, and it specializes³ in muscular and skeletal diseases such as rheumatoid arthritis, osteoarthritis, and osteoporosis. The company was founded in April 2004, funded by professors Dr. Kusuki Nishioka (Director) and Dr. Toshihiro Nakajima, both of the university's Institute of Medical Science. Argenes in-licenses novel biotechnology-based drug candidates and molecular-targeted drug candidates while in the developmental stage, in addition to conducting non-clinical and clinical studies, actively utilizing outside resources. The company develops pharmaceuticals with the goal of licensing out late-stage development rights and marketing rights, as well as obtaining manufacturing approval in Japan. Argenes has worked to reinforce its network with the Japanese research and development sector, including the Institute of Medical Science at St. Marianna University School of Medicine. Leveraging this network, the company succeeded in launching its business in the muscular and skeletal

disease area. The agreement with Santen will bring Argenes the development rights in Japan of a drug candidate in its specialty field, and will enable Argenes to begin full-scale business operations.

Santen positions the rheumatoid arthritis and osteoarthritis field as one of its specializations. Santen markets three anti-rheumatics: AZULFIDINE® EN Tablets, RIMATIL® and METOLATE® Tablets. Santen has potential projects in its development pipeline, such as DE-096 (TNF inhibitor; currently in Phase 1), in addition to the anti-APO-1 antibody. Santen expects to contribute to improve the quality of life of as many patients as possible, by accelerating the development of the anti-APO-1 antibody under the agreement with Argenes, and by focusing on its own development projects to offer more detailed therapeutic options tailored to each patient's condition.

For Reference

Technical terms

*1: anti-APO-1 antibody

Also called "anti-Fas antibody." By binding with the APO-1 antigen (receptor) on the surface of the cell, it introduces a signal into the cell and induces apoptosis.

*2: apoptosis

A process in higher organisms of beneficially killing their own cells for the sake of ontogeny and individual sustenance; a programmed cellular death. Abnormal apoptosis is known to occur in such hyperplastic diseases as cancers.

*3: synovial cells

The cells composing the synovium, the membrane that covers a joint. In rheumatoid arthritis, the synovium becomes hyperplastic, producing cytokine (a physiologically active protein secreted from cells) which causes inflammation and the destruction of the articular bone.

Company information

Argenes, Inc.

Location: 7F, Toranomon Pastoral Main Bldg.
4-1-1 Toranomon, Minato-ku, Tokyo, Japan

Head office: 15F, JT Bldg. 2-2-1 Toranomon, Minato-ku, Tokyo, Japan

Foundation: April 19, 2004

Paid-in capital: JPY27.5 million

Representative: Masaru Kamishohara

Business: Development of new drugs including biologics for the treatment of muscular and skeletal diseases (locomotors diseases) such as rheumatoid arthritis, osteoarthritis and osteoporosis

Santen Pharmaceutical Co., Ltd.

Head office: 3-9-19 Shimoshinjo, Higashiyodogawa-ku, Osaka, Japan

Foundation: 1890

Paid-in capital: JPY6,214 million

Representative: Takakazu Morita

Business: Research, development, manufacturing and marketing of prescription ophthalmic and anti-rheumatic pharmaceuticals, over-the-counter drugs and medical devices