

Research and Development

Santen's R&D vision is to provide a continuous flow of products that satisfy unmet medical needs and contribute to improved patients' quality of life (QOL). To realize this vision, we focus our resources in ophthalmology and other specific fields where we can play a leading role, and work to expand the number of new drug candidates, to manage clinical development in an effective manner, and to bring products to market as quickly as possible. To the same end, we are both strengthening our R&D systems and utilizing external resources for product development, including joint research with other firms and technology partnerships.

Development Update and Outlook

In R&D, we have defined glaucoma, retinal conditions, and corneal and conjunctival disorders as our three priority therapeutic fields. We are striving to boost new drug development by improving the quality and efficiency of our ophthalmology research—an area where we have extensive experience.

In the glaucoma field, we filed for manufacturing and marketing approval for DE-085 (generic name: tafluprost), a treatment for glaucoma and ocular hypertension, in Japan in July 2006. We are preparing to file for approval in Europe during the year ended March 31, 2007 and we will decide whether to file in the U.S. on the basis of an analysis of future business potential. In addition, we have signed an agreement with Ube Industries, Ltd. on the joint development of DE-104, which has a novel mechanism of action compared with existing drugs. We are moving ahead with preparations for clinical studies. In other news, we have temporarily suspended clinical studies on DE-092 (olmesartan) and will decide whether to restart clinical development once we have repeated dose-finding studies based on an improved formulation.

In the field of retinal conditions, we have started Phase II clinical trials in Japan on DE-096 for diabetic macular edema. DE-096 is also undergoing Phase II trials as a treatment for rheumatoid arthritis. In March 2006, we signed an agreement with U.S. firm Oakwood Laboratories L.L.C. on the development and licensing of manufacturing technologies for DE-102, a steroid microsphere-based product (note 1) that is also being developed to treat diabetic macular edema. Under the agreement, Santen will work with Oakwood on the development of manufacturing technologies, utilizing Oakwood's technical and developmental expertise in the area of microsphere products.

In the field of corneal and conjunctival disorders, we have begun Phase III clinical trials in Japan on DE-089 (diqafosol tetrasodium), a treatment for corneal and conjunctival epithelial disorders including dry eye. We are also conducting Phase I trials in the U.S. on DE-101 (rivoglitazone) as a treatment for corneal and conjunctival epithelial disorders including dry eye. Santen has acquired exclusive development, manufacturing and marketing rights worldwide for this compound from Sankyo Co., Ltd.

In the field of inflammation and allergies, in January 2006, we launched the vernal keratoconjunctivitis treatment *PAPILOCK* Mini ophthalmic solution 0.1%, which had been developed as an orphan drug (note 2). In March 2006, we signed an agreement with Ono Pharmaceutical Co., Ltd. on the exclusive development, manufacturing and marketing rights in Japan to DE-103 for allergic conjunctivitis.

We are also actively engaged in discovery research on next-generation ophthalmic drugs. As part of this work, in March 2006, we signed a three-year joint research contract with CytoPathfinder, Inc. on the application of its cubic liquid crystal technology to ophthalmic drug development. This technology is expected to have a wide range of applications, including in drug delivery and the search for drug discovery targets for the treatment of ophthalmic disorders using genetics-related assessment techniques. We will be conducting research to identify drug targets and therapeutic nucleotide derivatives and small molecules.

Notes 1: Steroid microsphere-based product: A product comprising a steroid encapsulated within a microsphere.

2: Orphan drug: A drug for which there is a high degree of medical need but small patient numbers mean that the drug is unlikely to be profitable. Orphan drug R&D is eligible for government subsidies in Japan.

Pipeline of prescription pharmaceuticals (Clinical studies)

As of September 2006

Generic name	Brand name/ Dev. Code	Indication	Region	Phase I	Phase II	Phase III	NDA Filed	Characteristics
Pemirolast potassium	Alamast	Allergic conjunctivitis	Europe				○	A mast cell stabilizer with superior efficacy on allergic conjunctivitis and vernal keratoconjunctivitis.
Tafluprost	DE-085	Glaucoma/ Ocular hypertension	Japan Europe USA				○ ○ (In preparation)	Prostaglandin glaucoma treatment for ocular hypertension. Has demonstrated a potent and stable inter ocular pressure-lowering effect by promoting uveoscleral outflow. It can be stored at room temperature.
Diquafosol tetrasodium	DE-089	Corneal and conjunctival epithelial disorder associated with dry eye, etc.	Japan				○	A treatment for corneal and conjunctival epithelial disorder associated with dry eye, etc. that stimulates the ocular surface to secrete tear fluid and moisture. Expected to be used in combination with existing dry eye treatments.
Levofloxacin + prednisolone A	DE-094	Infectious keratitis	USA		○			Fluoroquinolone antibacterial agent. A combination treatment with steroids.
Oltmesartan	DE-092	Glaucoma/ Ocular hypertension	Japan USA/ Europe		○ (Suspended) ○ (Suspended)			The angiotensin II receptor antagonist. Currently, the clinical studies are suspended. We will decide whether we resume the clinical studies after conducting another pilot study with different doses and different formulation.
Lomerizine HCL	DE-090	Glaucoma	Japan		○			A new type of oral glaucoma treatment studied for inhibiting the progression of visual field defects. The only calcium antagonist in full-fledged development as a glaucoma treatment. Compared with NMDA receptor antagonists, fewer generalized side effects are expected, thus having excellent safety. Marketed by Nippon Organon as a migraine drug.
(Undetermined)	DE-096	Rheumatoid arthritis Diabetes Macular Edema	Japan Japan		○ ○			An oral TNF inhibitor. Anti-rheumatic effect comparable to injectable biological agents. In addition to RA, the effect on DME was also observed in basic research, and the phase II studies are being conducted with both diseases.
Gefarnate	DE-099	Corneal and conjunctival epithelial disorder associated with dry eye, etc.	Japan	○				Treats corneal and conjunctival epithelial disorder mostly associated with dry eye, by stimulating the secretion of mucin and promoting the corneal epithelial migration. Preservative-free eye ointment that can be used in combination with existing drugs.
Rivoglitazone	DE-101	Corneal and conjunctival epithelial disorder associated with dry eye, etc.	USA	○				It is expected to show a potent effect on corneal and conjunctival epithelial disorders by directly acting on the corneal and conjunctival epithelial cells. It has an action mechanism which differs from any other existing treatment or drug candidate in development.

When safety and efficacy of candidate compounds are determined in preclinical studies, they undergo the following clinical trials. After completing the Phase III clinical trials, a new drug application (NDA) is filed for marketing approval.

Phase I: Tests to check drug safety with a small number of healthy volunteers.

Phase II: Tests to determine dosage and administration method with a small number of patients.

Phase III: Tests to confirm safety and efficacy by comparing to existing drugs and placebo with a large number of patients.