

# Research and Development



## Focusing Management Resources on the Core Therapeutic Segments

Santen's fundamental R&D strategy is to focus resources on growth areas where its strengths can be fully utilized and where there is significant growth potential. As part of this strategy, we have strengthened our R&D capabilities, especially at the Nara Research and Development Center, which specializes in the fields of ophthalmology and rheumatology. Within these fields, we narrowed our thematic focus even further to target the core therapeutic fields of glaucoma, corneal disorders and retinal disorders to enable us to pursue effective and faster new drug development.

The markets for glaucoma and corneal disorder treatments are expanding as the global population ages and the number of patients in these segments grows. Although the number of patients with retinal disorders is also rising, there are few treatments available in this area, resulting in a considerable need to develop effective products. By developing new drugs in these important fields, Santen contributes to fulfilling unmet medical needs and to enhancing patients' quality of life (QOL). It is through these contributions that the Company will continue to grow.

## Implementing Efficient Research Activities that Make the Most of External Resources

While working to discover new drug candidates using our own research capabilities, we are proceeding in parallel with a unique method called "network-based drug discovery," which utilizes external resources. This method of drug design takes simultaneous advantage of Santen's considerable accumulated knowledge and technologies as well as leading-edge technologies from other pharmaceutical companies and research institutions, primarily based in



Nara Research and Development Center

Japan. For example, by accessing the chemical library of a collaborating pharmaceutical company and applying our own abundant resources in an ophthalmic disease-model, we can select and strategically introduce highly effective compounds in our target market segments. We also successfully engage in joint research efforts to develop powerful new candidate compounds based on in-house ideas, including DE-085 (Tafluprost) and DE-104.

By applying these highly efficient development methods, we have created a development pipeline that will generate a steady flow of marketable new products. For each development candidate, Santen prepares backup compounds to reduce the inherent risk of additional R&D activities and expenses.

## Promoting Speed and Globalization in Research and Development

Competition among pharmaceutical companies is becoming fiercer on the global stage. To stay ahead of competitors, it is essential to quickly develop and launch globally innovative and competitive new drugs. To achieve this, we place a strong emphasis on "accelerating" and "globalizing" our R&D efforts.

On the "accelerating" front, Santen has worked solidly to achieve the specific time-reduction targets set out in its 2003–2005 Medium-term Management Plan to shorten preclinical testing to one and a half years (from a previous timeframe of approximately three years) and clinical testing to five years (from approximately seven to eight years). The 2006–2010 Medium-term Management Plan also highlights acceleration through ongoing reviews of in-house R&D processes.

For "globalizing," we now have a clinical development network spanning three centers—Japan, the U.S. and Europe—and are currently carrying out clinical trials for several products in Europe and the U.S. Also, by categorizing new drug candidates for overseas marketing as either global strategic products<sup>1</sup> or global products<sup>2</sup>, Santen is able to pursue priority

development efforts of global strategic products. In addition to Japan, the U.S. and Europe, Santen is looking to integrate Asia into its clinical development network, thus shortening the time used in clinical work and rationalizing costs by standardizing clinical trial protocols and sharing data among regions.



Santen Oy (Finland)

## Development Advances

Santen maintains its active R&D focus on the core therapeutic fields of glaucoma, corneal disorders and retinal disorders.

### ● Glaucoma Segment

In July 2006, we filed a new drug application (NDA) for the prostaglandin derivative DE-085 (Tafluprost) in Japan, and in April 2007 filed for marketing approval in major European countries. Approval was granted first in Denmark in April 2008 and subsequently in Germany and several other countries. The European approvals process is progressing smoothly and we are now assessing the commercial viability of filing in the U.S. Phase II clinical trials of the angiotensin II receptor antagonist DE-092 (Olmesartan) were temporarily suspended as it did not demonstrate clear dose–response. We have now commenced a Phase II pilot study using a modified formulation. The ROCK inhibitor DE-104, for glaucoma and ocular hypertension, is in concurrent Phase II clinical trials in Japan and the U.S.

### ● Corneal and Conjunctival Epithelial Disorder Segment

In May 2008, we filed an NDA in Japan for DE-089 (Diquafosol sodium), a treatment for corneal and conjunctival epithelial disorders associated with dry eye. Santen suspended clinical studies of DE-099 (Gefarnate) based on Phase II trial results in Japan. DE-101 (Rivoglitazone) is in Phase II clinical trials in Japan and about to enter Phase II clinical trials in the U.S. The phosphodiesterase type 4 inhibitor for allergic conjunctivitis, DE-103, is in Phase II clinical trials in Japan.

### ● Retinal Disorder Segment

DE-102 is in Phase I/II clinical trials in Japan to determine safety and efficacy in patients. Santen entered into an R&D collaboration and licensing agreement for the development of DE-109 (Sirolimus) with MacuSight, Inc. (U.S.), in May 2008, and is now in the process of formulating a development plan for patients with wet age-related macular degeneration (wet AMD) and with diabetic macular edema (DME).

### ● Other Areas

DE-098 is an anti-rheumatoid arthritis agent licensed to Argenes, Inc., for development in Japan. It is now in Phase I/II clinical trials in Europe and Japan to determine safety and efficacy. Santen owns the domestic marketing rights and overseas development and marketing rights of DE-098.

In October 2006, we received approval in Japan for *Eternity* foldable intraocular lenses made of a new high-refractive optical material, and will begin marketing it in fiscal 2008 after making adjustments to the design of the injector to better suit doctors' needs.

## 1. Global Strategic Products

New drug candidates with a new mechanism of action that have potential to generate higher sales than existing products in Japan, the U.S. and Europe.

## 2. Global Products

Drug candidates that improve on existing mechanisms of action for which the anticipated sales are on par with existing products in Japan and certain overseas regions.

## About Research and Development

After passing preclinical tests for safety and efficacy, new drug candidates are put through the clinical trial phases outlined below. Once Phase III is completed, an NDA is filed with the appropriate regulatory agency in each of our global regions. If it passes evaluation, the drug receives approval for manufacture and marketing.

### Phase I Clinical Trials

Estimate initial safety and tolerability of drug on a small number of healthy volunteers

### Phase II Clinical Trials

Investigate and determine the appropriate dose and regimen for a specific treatment purpose on a small number of patients

### Phase III Clinical Trials

Confirm safety and efficacy relative to existing drugs and placebos on a large number of patients

# Pipeline of Prescription Pharmaceuticals (Clinical Development)

As of July 31, 2008

● Global strategic product ● Global product ● Domestic (Japan) product

Category	Generic Name	Dev. Code	Indication	Region	Phase			NDA Filed	Approved	Characteristics
					I	II	III			
<b>Glaucoma</b>										
●	Tafluprost	DE-085	Glaucoma Ocular hypertension	Japan				July 2006		Prostaglandin derivative treatment for glaucoma and ocular hypertension. DE-085, which facilitates the outflow of the aqueous humor from the uveal and scleral channels, exhibits a powerful and stable effect for alleviating ocular hypertension. In April 2008, the first national approval was granted in Denmark and subsequently in Germany and several other countries.
				Europe				April 2008		
				U.S.						
●	Olmesartan	DE-092	Glaucoma Ocular hypertension	Japan					Angiotensin II receptor antagonist. The Phase II studies did not demonstrate clear dose-response, and therefore we decided to suspend clinical studies. We are now conducting the Phase II pilot study with different formulation.	
				U.S./ Europe						
●	Lomerizine HCl	DE-090	Glaucoma	Japan					Calcium antagonist. A new type of oral glaucoma treatment studied for inhibiting the progression of visual field defects. Compared with NMDA receptor antagonists, fewer systemic side effects are expected, thus having excellent safety. Marketed by Schering-Plough Corporation as a migraine treatment.	
●	Undetermined	DE-104	Glaucoma Ocular hypertension	U.S.					ROCK inhibitor co-developed with Ube Industries for treatment of glaucoma and ocular hypertension that has a different action mechanism from other existing drugs. It is expected to show a strong intraocular pressure reduction by promoting aqueous humor outflow by acting directly on trabecular meshwork cells.	
				Japan						
<b>Corneal and conjunctival epithelial disorders</b>										
●	Diquafosol sodium	DE-089	Corneal and conjunctival epithelial disorder associated with dry eye, etc.	Japan				May 2008		A treatment for corneal and conjunctival epithelial disorder mostly associated with dry eye, etc., that stimulates the ocular surface to secrete tear fluid and components. Expected to be used in combination with existing treatments.
●	Rivoglitazone	DE-101	Corneal and conjunctival epithelial disorder associated with dry eye, etc.	U.S.					Expected to show a potent effect on corneal and conjunctival epithelial disorder mostly associated with dry eye, etc., 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. The compound is currently under development by Daiichi Sankyo as an oral anti-diabetic drug in the U.S.	
				Japan						
●	Undetermined	DE-103	Allergic conjunctivitis	Japan					PDE4 (Phosphodiesterase type 4) inhibitor for allergic conjunctivitis that has a different action mechanism from the existing drugs. Expected to be effective for allergic conjunctivitis through its inhibitory effect against PDE4.	
<b>Retinal disorders</b>										
●	Undetermined	DE-102	Diabetic macular edema (DME)	Japan				Phase I/II		Steroid microsphere product for a sustained release injection. Animal studies demonstrated sustained efficacy by local injection. In order to produce sterile microsphere in commercial scale, we collaborate with Oakwood Laboratories (U.S.).
●	Sirolimus	DE-109	Wet age-related macular degeneration (wet AMD) Diabetic macular edema (DME)	Japan				Preparing for Phase I/II		Subconjunctival or intravitreal injection having immunosuppressive effect, anti-angiogenic effect, etc. Phase I clinical trials in patients with wet AMD and DME have shown patients who participated in these studies exhibited improvements in visual acuity that were consistent with morphological changes following a single administration of Sirolimus. In May 2008, Santen made an R&D collaboration and license agreement with MacuSight, Inc. (U.S.), for the Japanese and Asian development and commercialization of Sirolimus for the treatment of ocular diseases and conditions, including wet AMD and DME.
<b>Rheumatoid arthritis</b>										
●	Undetermined (license out)	DE-098	Rheumatoid arthritis	Japan				Phase I/II		Joint injection that induces apoptosis in diseased joints of rheumatoid arthritis patients. Bulk pharmaceutical manufacturing process for actual production scale has been established. Santen granted the domestic development rights to Argene, Inc. The compound had been in-licensed from Centocor Inc. (U.S.). In Japan and Europe, the clinical study has been started. Santen continues to hold the marketing rights in Japan and the overseas marketing and development rights.
				Europe					Phase I/II	