R&D Day 1
Santen’s Contribution to Ophthalmology

Global R&D
Santen Pharmaceutical Co., Ltd.

July 12th, 2019
R&D Days

Day 1

Santen’s Contribution to Ophthalmology

Introduction of Ophthalmology and Santen’s Contribution
Santen’s Research and Development

Day 2

Santen’s Future R&D

Long-term Perspective of Ophthalmology
Santen’s R&D approach
Santen’s Values and Mission Statement

Values

天機に参与する

Tenki ni sanyo suru

1 “Exploring the secrets and mechanisms of nature in order to contribute to people’s health” Santen’s original interpretation of a passage from chapter 22 of Zhongyong (The Doctrine of the Mean) by Confucius.

We think carefully about what is essential, decide clearly what we should do, and act quickly.

Mission Statement

By focusing on ophthalmology, Santen develops unique scientific knowledge and organizational capabilities that contribute to the well-being of patients, their loved ones and consequently to society.
Genericized "Life of Vision" in the framework of "Global market"

Activities by General Pharmaceutical companies:
1. Supporting Congresses
2. Establishment of Guidelines in each country
3. Maximization & Penetration of Product value (Ph IV etc)
4. Raising disease awareness
5. PAP/ Program for continuation of treatment

Products:

- Congenital disorder
- Ocular Infection
- Refractive disorders (Myopia, Hyperopia, Astigmatism)
- Allergic conjunctivitis
- Dry Eye
- Age-related diseases (Retina, Glaucoma, Cataract, Presbyopia)

Doctors, Medical personnel
Patients and their families
Our original activities in Asia led Santen to No.1 in important markets -Up to and From today-

Huge economic area at the moment and in the future with over 3 billion population

Main treatment at the moment (low coverage in medical examine)

Mega shift

In some countries, the items below are progressing
-Acceleration of aging,
-Preventive treatment for children as important future (by decades)

Medical Infrastructure under way

- Ocular Infection: Blindness both parents and children
- Dry Eye: Rapid penetration of mobile phones and PCs
- Allergic conjunctivitis: Aggravation by pollutions
- Congenital disorder
- Refractive disorders (Myopia, Hyperopia, Astigmatism)
- Age-related (Glaucma, Retina, Cataract)

Samples of problems
- Low disease awareness in patients
- Low quality products
- Lack of Ophthalmologists
- Level-up of Ophthalmologist

Santen’s Strength
- Raising Disease awareness
- BFS/PF products/Dimple bottle
- Medical Caravan to remote areas in China
- EGC/ACS Santen Grant/…

Establishment of Treatment guideline

Efforts to Myopia

Samples of problems:
- Low disease awareness in patients
- Low quality products
- Lack of Ophthalmologists
- Level-up of Ophthalmologist

Age-related (Glaucma, Retina, Cataract)
- Refractive disorders (Myopia, Hyperopia, Astigmatism)
- Allergic conjunctivitis: Aggravation by pollutions
- Ocular Infection: Blindness both parents and children
- Congenital disorder

BFS; Blow Fill Seal, PF: Preservative Free, EGC: English Glaucoma Camp, ACS : Asia Cornea Society
Santen’s business activities aiming to protect “Life of Vision” of people around the world

Affected → Diagnosis → Treatment initiation → Treatment period → Continuation of treatment

Global
- Raising disease awareness
- Improvement of diagnosis rate
- Differentiated products
- Improvement of compliance
  - Improvement of usability
  - Minimally invasive
- Supports for stakeholders in ophthalmology
- Stable supply

Advanced Countries
- Prevention
- New technology for diagnosis and treatment
- Recurrence prevention
  - Initiatives to age-related chronic disease

Developing Countries
- Eco system
- Raising and Supporting of ophthalmologists
- Raising disease awareness
- High quality products

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Basic Policy on Santen R&D
Protect the Sight of People Around the World

Ophthalmic market (2018) and number of patients

- **Cataract**: Approx. 560M patients, 8B yen
- **Glaucoma**: Approx. 120M patients, 730B yen
- **Dry Eye**: Approx. 340M patients, 550B yen
- **Myopia**: Approx. 2600M patients
- **Retinal Diseases**: Approx. 270M patients, 860B yen
- **Ocular Infection**: 230B yen
- **Allergic Conjunctivitis**: 200B yen
- **Anti-Inflammatory**: 190B yen

Vision impairment estimated impacting 1 in 30 of world population

Source: WHO World Sight Day Poster

Source (Market): Copyright © 2019 IQVIA. IQVIA MIDAS 2018; Santen analysis based on IQVIA data. Reprinted with permission.
Problem of Eye Disease Becoming Larger as the World Population is Aging

Population Aged 65+


Number of Glaucoma patients

Data Source: Market Scope; Santen analysis

90.6M patients
80.4M patients
79.1M patients

(Data for 2015 and forecast for 2020)
MTP2020 Fundamental Policy and Strategic Goals

**FUNDAMENTAL POLICY**

• To become a “Specialized Pharmaceutical Company with a Global Presence”
• Construct a path for sustainable growth beyond FY2020

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**STRATEGIC GOALS**

- **1.** Grow faster than the market through progress in global business strategy
- **2.** Enhance the product pipeline and develop new treatment options
- **3.** Raise strength / efficiency of business framework; boost human resource and organizational capabilities

**Increase profitability**

**Increase customer satisfaction**

**Increase organizational strength**

**Responding to the needs of patients and medical professionals worldwide, Santen will achieve reliable growth while sustainably contributing to ophthalmic treatment worldwide**
Pursue development of much needed medical products, devices, information services by leveraging global R&D network

- **New Products**
  - Intraocular lens for cataract surgery
  - LENTIS® Comfort
  - Glaucoma and Ocular Hypertension Treatment
  - Eybelis
  - Assistive device for eye drop administration

- **Network**
  - Collaboration with SERI
    - Develop new therapies for eye disease that are prevalent in Asia
  - Gene therapy using iPS cell related technology
    - Aiming to develop Japan’s first gene therapy in collaboration with industry, academia and government
  - New drug discovery technology using macrocyclic/constrained peptides
    - New approach for drug discovery

- **Patient Support**
  - Assisting device for eye drop administration
  - Improved distinguishability
  - Drip prevention
  - Easy to squeeze bottle

- **Bring out joy “to be able to see” by fulfilling UMN’s**

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**Intraocular lens for cataract surgery**

**LENTIS® Comfort**

**Glaucoma and Ocular Hypertension Treatment**

**Eybelis**

**Devise for Glaucoma**

**US submission for DE-128 scheduled to be completed in 2019CY**
Bring Out Joy “to be Able to See” by Fulfilling UMN*

**Application of systemic drug**
- Eye infection
- Anti inflammatory
- Allergic Conjunctivitis

**Therapies specific to ophthalmology**
- Retinal disease
- Glaucoma
- Dry eye
- Refractive disorder

**New modality**
- Gene therapy
- Cell therapy
- Regenerative medicine
- etc.

**Formulation change**
- Low preservative
- Combination drug
- Dosage form change
- Container

**Administration**
- Intravitreal Injection

**New Dosage form**
- Long lasting formulation
- Drug Delivery System
- Medical device

**Treatment for vision impairment**
- QOL improvement

*Unmet Medical Needs
Proactively Introduce Products Approved in Japan & Europe to Asia

No. of approved products in recent 5 years: 147 Products / Total No. of products: 287 Products

Registration Status in China

September 2015
2015
2016
2017
October 2017

Only 27 new products have been approved by China FDA

4,400 pharmaceutical companies, including 200 foreign companies

Only Santen for ophthalmic agent
Overview of Eye Diseases
Conducting R&D Specific to Ophthalmology to Contribute to Improving QOL* in Patients Around the World

<table>
<thead>
<tr>
<th>Ocular Surface</th>
<th>Glaucoma / Optic Nerve Disorder</th>
<th>Back of the Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dry Eye</td>
<td>• Glaucoma</td>
<td>• Macular Diseases</td>
</tr>
<tr>
<td>• Allergic Conjunctivitis</td>
<td></td>
<td>• wetAMD</td>
</tr>
<tr>
<td>• Eye infection</td>
<td></td>
<td>• DME</td>
</tr>
<tr>
<td>• Cataract</td>
<td></td>
<td>• Diabetic retinopathy</td>
</tr>
<tr>
<td>• Myopia etc.</td>
<td></td>
<td>• Retinal vein occlusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Posterior Uveitis etc.</td>
</tr>
</tbody>
</table>

*Quality of Life

**Eye Diagram**
- Sclera
- Choroid
- Retina
- Fovea
- Optic disk
- Optic nerve
- Vitreous

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Glaucoma: Preserve Visual Field by Lowering Intraocular Pressure

The No.2*¹ cause of blindness in the world, No.1 in Japan*²

Optic nerve damage due to high intraocular pressure

Inhibiting progressive visual field loss
IOP lowering (Start/Continuation)

Inter Ocular Pressure

Optic nerve

Visual field loss

Initial stage
Late stage

Image (Right eye only)

Keep and recovery of visual field
Neuroprotection

*1: WHO Global Data on Visual Impairments 2010
Glaucoma: Respond to the Diverse Needs with Extensive Product Line

● IOP lowering agents (start)
  Instillation to lower intraocular pressure

● IOP lowering agents (Continuation)
  Continue treatment for a lifetime. Change or add the treatment depending on severity

● Laser
  The laser is applied to the part where the aqueous humor is discharged (trabecular meshwork) to promote the drainage.

● Surgery
  Removes a part of trabecular meshwork and creates the drainage route for aqueous humor. e.g. Trabeculectomy

Efficacy
- Stronger IOP lowering agents Supporting to non responders

Safety
- Reduction and avoidance of adverse reactions
- Reduction of invasiveness and complications of surgery

Usability
- Improve compliance
- Reduce Patients' burden (Easy to drop)

Timoptol XE 0.5%
Detantol 0.01%
Tapros 0.0015%
Eybelis 0.002%
Trusopt 1%
Tapcom
Dry-eye: Improve Condition by Targeting Causative Mechanism

A disease that can decrease productivity and worsen the QOL over time.

Normalization of tear film

Improvement of objective signs (by normalization of tear film)

Decreased tear volume
- Decreased tear secretion
- Increased evaporation of tears

Tear film instability
- Changed composition of tear fluid

Epithelial damage

Ocular surface inflammation

Improvement of subjective symptoms

Asthenopia, Dryness, Discomfort, Eye-pain, etc.
Abnormalities of visual function
# Dry-eye: Product line for Tear Film Oriented therapy

## TFOT (Tear Film Oriented Therapy)

<table>
<thead>
<tr>
<th>Target for Therapy</th>
<th>Topical eye therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid layer</td>
<td>Warm compress and lid hygiene</td>
</tr>
<tr>
<td></td>
<td>Low-dose ophthalmic ointment</td>
</tr>
<tr>
<td></td>
<td>Certain types of OTC</td>
</tr>
<tr>
<td></td>
<td>Diquafosol sodium</td>
</tr>
<tr>
<td>Aqueous/Mucous layer</td>
<td>Artificial tears</td>
</tr>
<tr>
<td></td>
<td>Sodium hyaluronate</td>
</tr>
<tr>
<td></td>
<td>Diquafosol sodium</td>
</tr>
<tr>
<td></td>
<td>Punctal plug</td>
</tr>
<tr>
<td>Secretory mucin</td>
<td>Diquafosol sodium</td>
</tr>
<tr>
<td></td>
<td>Rebamipide</td>
</tr>
<tr>
<td>Epithelium</td>
<td>Membrane associated mucins</td>
</tr>
<tr>
<td></td>
<td>Diquafosol sodium</td>
</tr>
<tr>
<td></td>
<td>Rebamipide</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>Autologous serum</td>
</tr>
<tr>
<td></td>
<td>EGF (Rebamipide)</td>
</tr>
<tr>
<td>Ocular surface inflammation</td>
<td>Cyclosporin</td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td><strong>Rebamipide</strong></td>
</tr>
</tbody>
</table>

*Diquafosol sodium may increase the function of the tear film lipid layer by promoting spreading of the lipid layer through lipid and tear fluid secretion. **Rebamipide may suppress the inflammation of the ocular surface in dry eye by its anti-inflammatory action.*

Supervision: Dry Eye Society
Allergic Conjunctivitis: Provide Treatment to All Patients from Mild to Severe

- **Improvement of main symptoms**
  - Anti-histamine ophthalmic solution
  - Chemical mediator release inhibitors

- **Improvement of main symptoms**
  - Anti-inflammatory ophthalmic solution

- **Improvement of safety and usability**
  - BAK free
  - Reduce dose frequency

**Itching Hyperemia / edema**

- Alegysal 0.1%
- Alesion 0.05%
- Lecrolyn® SD
- Verkazia®
- Papilock Mini 0.1%

*For vernal conjunctivitis

Reduce dose frequency
4 times/day → 2 times/day
Ocular Infection: Introduce Wide Range of Product Line to Emerging Countries

### Eye mucus, Hyperemia, Edema, Foreign body Mass (Sty, etc.)

### Glare, Tears, Eye pain Ulcer, Suppuration

#### Anti-inflammatory ophthalmic solution
- **Flumetholon 0.1%**
- **Proranon 0.1%**
- **Santeson ophthalmic ointment**

#### Antibacterial
- Basic treatment with antibacterial agent
- Depending on the type of bacteria, using ophthalmic ointment and oral medicine
- **Tarivid 0.3%**
- **Cravit 0.5%**
- **Cravit 1.5%**

#### Antiviral
- Antiviral ophthalmic solution
- Antiviral ophthalmic ointment
- **Ecolin ophthalmic ointment**
- **Tarivid ophthalmic ointment**
- **Zovirax ophthalmic ointment**
- **Tarivid ophthalmic ointment**
Cataract: New Concept Intraocular Lens

51% cause of blindness in the world*1. Affects all over 80 years old.*2

● Suppression of lens opacity
Ophthalmic agent to suppress lens opacity by stopping degeneration of lens protein

● Cataract surgery
The lens that has become cloudy is removed and replaced with an intraocular lens

*1: WHO Global Data on Visual Impairments 2010
*2: 科学的根拠 (evidence) に基づく白内障診療ガイドラインの策定に関する研究 2002
Myopia: Aim to Develop and Provide the World’s First Treatment

27% of the world population is estimated to have myopia*. Forecast to increase in the future.

- Suppression of the axial length elongation
  - Low dose atropine

- Vision Correction
  - Eye glasses, Contact lenses, LASIK

- Axial length growth

- Pathologic myopia

- Vision loss

- Treatment of the cause of vision loss
  - Regression of neovascularization (Anti-VEGF therapy)

*: IMPACT OF INCREASING PREVALENCE OF MYOPIA, Report of the Joint World Health Organization
### Retina/Uveal Diseases: Aim to Provide Better Treatment Option

<table>
<thead>
<tr>
<th>Wet Age-related Macular Degeneration (wetAMD)</th>
<th>Diabetic Retinopathy (DR)</th>
<th>Diabetic Macular Edema (DME)</th>
<th>Central Retinal Vein Occlusion (CRVO)</th>
<th>Branch Retinal Vein Occlusion (BRVO)</th>
<th>Posterior Uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal blood vessels begin to grow toward the macula. Then, the macula is impaired and can result in a severe loss of central vision.</td>
<td>The retina is damaged due to diabetes. If edema develops in macula (DME), it directly linked to vision loss.</td>
<td>Retinal hemorrhage and edema caused by the retinal vein occlusion. If this extends to the macula, vision loss occurs rapidly.</td>
<td>Inflammation occurs in the uvea (choroid) due to various causes, resulting blurred vision, ocular floater, photophobia and vision loss.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-VEGF therapy</strong>&lt;br&gt;Regression of the neovascular vessels and inhibition of neovascularization</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Photodynamic therapy (PDT)</strong>&lt;br&gt;Laser cauterize the lesion or related tissue.</td>
<td><strong>Laser photocoagulation</strong>&lt;br&gt;Laser cauterize the lesion or related tissue.</td>
<td><strong>Laser photocoagulation</strong>&lt;br&gt;Laser cauterize the lesion or related tissue.</td>
<td><strong>Laser photocoagulation</strong>&lt;br&gt;Laser cauterize the lesion or related tissue.</td>
<td></td>
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</tr>
<tr>
<td><strong>Steroid</strong></td>
<td><strong>Steroid</strong></td>
<td><strong>Steroid</strong></td>
<td><strong>Steroid</strong></td>
<td><strong>Steroid</strong></td>
<td><strong>Anticoagulant (Oral)</strong></td>
</tr>
</tbody>
</table>
Global R&D Network and Expedite Product Creation
Santen’s Global R&D Network
Addressing global unmet medical needs by networking around the world.
Expedite Product Creation by Leveraging Global R&D Network

Santen’s Product Development

- Improving Treatments
- Unmet Medical Needs
- Reducing Patient Burden

Glaucoma
Retinal and Uveal disorders
Keratoconjunctival disorders
Refractive disorders

Biomarker
Medical Devices
Diagnosis

Formulation/CMC
Drug Delivery System
Clinical Operation

Industry Partner
Santen’s Internal Expertise
Research Institute

Open Innovation
Digital
Academia

Santen's Product Development

Unmet Medical Needs

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Network Product Development

Expanding Partnerships globally

Academia
Research Institute

Industry Partner

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Improve PTS*

Building of Evidence for “Evidence Based Medicine” (Epidemiology)
- Enhancement of clinical evaluation technology
- Banking of clinical samples

Clinical Research (Individual)
- Translational research in the narrow sense
  - Validation of MOA in human
  - Analysis of pathology

Clinical Research (Cohort)
- Clinical epidemiology, Pharmacoepidemiology, Proteomics, Genomics
  - Clinical data analysis
  - Analysis of biospecimen

Higher PTS & Productivity

Basic research

*Probability of Technical Success
Clinical Development that are Fast and Have Higher Success Rates

- **Speed of clinical trials**
  - DE-117 clinical trials (Glaucoma)

<table>
<thead>
<tr>
<th>Phase 2a</th>
<th>Phase 2b</th>
<th>Phase 3 (AYAME study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development region: U.S.</td>
<td>Development region: U.S.</td>
<td>Development region: Japan</td>
</tr>
<tr>
<td>No. of patients: 91</td>
<td>No. of patients: 184</td>
<td>No. of patients: 253</td>
</tr>
</tbody>
</table>

  - Duration: 5 months, 8 months, 14 months

- **Phase 3 success rates in ophthalmology**
  - Santen: 92%
  - Industry Average: 58%

1. Internal analysis in 2006-2018
Pharmaceutical Development
Innovative Pharmaceutical Development to Meet Customer Needs

Less frequency
Reduce frequency of instillation
Reduce complexity by using many of combination

Improve usability
Continuous treatment by improving adherence and compliance

Ophthalmic Solution with High Safety
Reduce the effect on ocular surface by preservatives.

Easy-to-use bottle
Develop easy-to-use bottle for everyone including elderly
Less frequency: Reduce Patient Burden

Corneal Concentration
(AUC <0-72 hr>, ng/hr/g of tissue)

1.0 mg/mL Ciclosporin in cationic formulation
3.6 x HIGHER

0.5 mg/mL Ciclosporin in cationic emulsion
1.9 x HIGHER

0.5 mg/mL Ciclosporin in anionic

Rabbit corneal Corea, 2013;32:345-354

Corneal, 2013;32:345-354

Combination Drug

Tapros 0.0015%
Timoptol 0.5%

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Improve usability: Support Patients’ Adherence to Treatment

Kary Uni 0.005%

Cationorm® SD

Cationorm® PFMD

Lecrolyn® SD

Lecrolyn® PFMD

Source: Santen analysis
Ophthalmic Solution with High Safety: Prevent Treatment Withdrawal

Conventional preservative

Benzalkonium Chloride

Low BAK

Benzalkonium Chloride (Low Concentration)

BAK Free

Chlorhexidine gluconate solution

Preservative Free

N/A
Ophthalmic Solution with High Safety: Promote Continuous Business Grow

Sales Share Trend of Diquas in Japan

Sales Share Trend of Alesion in Japan

Launched BAK free formulation

Source: Copyright © 2019 IQVIA. IQVIA MIDAS 2014/1-2019/3; Santen analysis based on IQVIA data. Reprinted with permission.
“Dimple Bottle” was Developed by Bringing in Voice of Patients

1977~ Bottle pack
1992~ Chip & Cap
2002~ Dimple bottle
2019~

- Instillation success rate: 84%
- Assist tool for instillation
- Just In

Easy to drop
Easy-to-see display
Easy to see residual volume

- Concentration display on the top of the cap
- Product name labeling on top of the shrink label
- With the line of the same cap’s color
- Slits on both sides
- Sentence-enlarging labels
- With the design of holding position

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VISION EVERY DAY.
SANTEN R&D:
VANGUARDS OF VISION

Santen
R&D Leadership Members

Naveed Shams
Senior Corporate Officer & CSO, Head of R&D Division

Reza Haque
Senior Vice President, Head of Biomedical Strategy & Research

Kenji Morishima
Corporate Officer, Head of Pharmaceutics & Pharmacology Representative, Asia R&D

Peter Sallstig
Senior Vice President, Head of Product Development

Takeshi Matsugi
Head of R&D Strategic Operations