

R&D Day 2

**The Future of
Santen R&D**



Global R&D
Santen Pharmaceutical Co., Ltd.
September 6th, 2019

Agenda

 R&D Day2

 Q&A session for DE-128 (MicroShunt)

We have prepared two opportunities namely Santen R&D Day to help you deepen your understanding on Santen's R&D activities, which is one of our strengths. The first R&D Day was held in July, and today is the second of the R&D Days titled "The Future of Santen R&D". We will show you how Santen will drive R&D going forward and how it will contribute to ophthalmology.

We are planning to have a Q&A session about DE-128 *MicroShunt*, as press release on August 30th was issued. Today, we will have two sessions. First, R&D Day 2 followed by Q&A session and a separate Q&A session specifically on the press release of DE-128 *MicroShunt*.

Opening Remarks

Shigeo Taniuchi

President and Chief Operating Officer



Hello, good afternoon, my name is Taniuchi. I am participating over the phone today. Unfortunately, I'm


not able to be there in person but very happy to see many people participating in this event. I am in Suzhou, CCOS (Congress of Chinese Ophthalmological Society) is being held. I am sure you can see the picture on the screen– around 14,000 people are attending altogether. It's full of energy. Santen's Asia, China presence and activities are introduced and I do see the energy here, it's a very powerful atmosphere, and in this large-scale event, everybody is learning. Today, R&D activities are introduced and all the members on the front line, including Naveed will be explaining our R&D activities. Later, there will be individual presentations. I hope you will understand that Santen is quite unique. It has its unique idea in R&D activities. Santen's value, philosophy is "*Tenki ni sanyo suru*". We aim to make contribution to people's health. We have a history of 130 years with patient-centric mindset. We need to understand the needs of the market, needs of the patient, and to fill the unmet needs, we want to develop technologies in-house or together with partners. Santen has grown by repeating this over the past years. Today, R&D members will explain the strength and uniqueness of Santen as a company specialized in ophthalmology, and I hope that this event will deepen your understanding.


The other day we had the press release of DE-128 *PRESERFLO MicroShunt*. We will spend some time today to provide further explanation.

Glaucoma is a serious disease and there are many unmet needs. We are very happy that we are able to confirm the data of DE-128 *PRESERFLO MicroShunt* in the clinical trial. Having said that, we may not have given you full explanation on the study design and procedures, and what trabeculectomy surgery, the comparator is all about. I'm sure you have questions, so today is a good opportunity as Naveed will give you detailed explanation. We hope that will deepen your understanding on the potential and the value of this product. Now I am going to pass the microphone to Naveed. I hope today is a meaningful day for all of you. Thank you.

Bringing the Joy of Sight

Naveed Shams, MD, Ph.D.
Senior Corporate Officer & Chief Scientific Officer,
Head of Global R&D

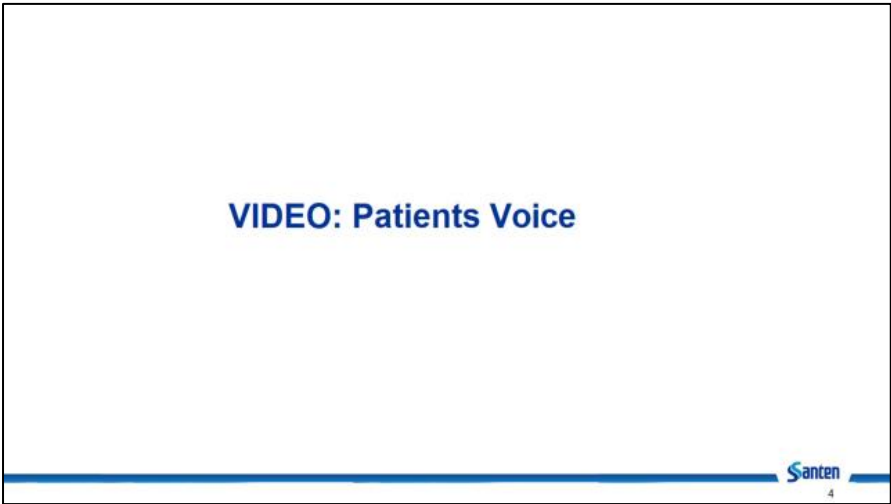


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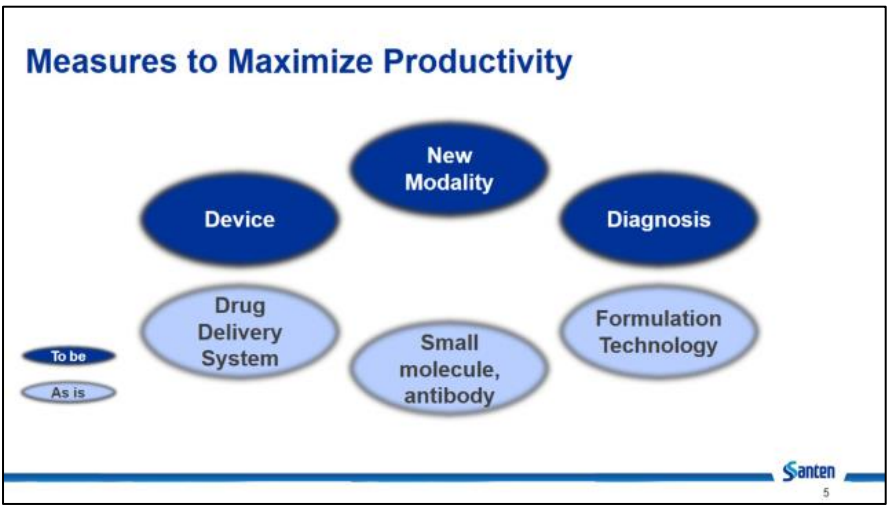
Before I start, I'd like to thank you for joining us today on behalf of all employees at Santen, the President and Chief Operating Officer, Mr. Kurokawa, CEO, and my management team that is sitting here. I know everybody is busy and we would like to take the next hour or so to explain how R&D is going to support the business. And then I am quite sure a lot of you are interested in getting some more understanding of the DE-128 *PRESERFLO* data. So, I'll do my best to help you with that.

As some of you know, maybe most of you know, my name is Naveed Shams and I am a Senior Corporate Officer & Chief Scientific Officer and the Global Head of R&D for Santen. So, which means I really have

three jobs. However, my number one job today is to give you the formula for how R&D is going to help patients in need around the world. Specifically, I will outline how we will solve unmet needs in all regions, become more than a prescription for patients, build disease area strategies that have the capability and the partnerships to succeed, and infuse a concept of patient centricity as the guiding force behind everything we do and what I mean by this will be reflected in the following video. So please take a look.



For R&D people at Santen and Santen all by itself, we would like, based on our work to have this kind of an impact on our patients. If you think oncology is the only place where there is pain, wait until you see our eye patients. So, we are committed to doing this for our patients and that will drive Santen's growth. Because at Santen, we recognize that our patients are also people; they are grandfathers and they are grandmothers, people who want to behold their loved ones, they want to see the sight of a sunrise, the thrill of a football match - like this patient. By fulfilling unmet needs around the world, we can restore the joy of these sights to those who suffer from ophthalmic diseases. In order to achieve this consistently, we must have the most productive R&D organization anywhere.



Some of the measures we will take to address our mission will include a strong focus on developing devices and diagnostics to treat diseases to improve outcomes.



Perhaps you are wondering how we are going to do it. Well, I can't give away all the secrets but I can tell you that we will enhance our internal capacity and capabilities and partner with key stakeholders including patients, caregivers, academics, regulators and industry colleagues as we may not be able to do this all by ourselves.



Our three major R&D functions must operate in sync in order to deliver products to patients globally and on time. Our strategic planning team, in partnership with the discovery and development teams, provides achievable plans in line with the disease area strategy. Our discovery engine provides validated targets for intervention. And finally, our development team registers our products quickly and efficiently. We will see a measurable reduction in development times, that's the objective, that's the goal.



There will be renewed focus on patients in the next five to ten years. What does this mean? We currently have focus too. Well, we will seek their advice and counsel, as we develop our strategies and product development plans. You have my personal commitment and the President’s commitment that no project will be funded without patient input.

R&D Leadership Team

 <p>Naveed Shams Senior Corporate Officer & Chief Scientific Officer, Head of Global R&D</p>			
 <p>Reza Haque Senior Vice President, Head of Biomedical Strategy & Research</p>	 <p>Kenji Morishima Corporate Officer, Head of Pharmaceuticals & Pharmacology Representative, Asia R&D</p>	 <p>Peter Sallstig Senior Vice President, Head of Product Development Representative, US R&D</p>	 <p>Takeshi Matsugi Head of R&D Strategic Operations</p>

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In order to achieve these aggressive goals, we have recently restructured the R&D organization under new leadership. And now it’s my pleasure to introduce to you one of my leadership team members, Reza Haque, who’s strategic planning team is developing strategies to help solve unmet needs.

Disease Area Strategy

Reza Haque, MD, Ph.D.

Senior Vice President,
Head of Biomedical Strategy & Research



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Hello, my name is Reza Haque. I am the Senior Vice President, Head of Biomedical Strategy & Research. Based on the fact that Santen is the global ophthalmology player, we understand the science behind eye care. That leadership enables us to deploy a disease area strategy comprehensive enough to satisfy needs in every region of the globe. We have enough knowledge and experience in ophthalmology to create disease strategies and operate non-clinical and clinical development. We know when to make a strategic investment. Our goal is to provide the best strategy leads to best treatment options for patients and caregivers to tackle the unmet needs. Today, I will update you on front of the eye diseases, glaucoma, retina and myopia.

We Can Enhance QoL for Patients

Suffering from Various Eye Diseases



Addressing the needs of a changing world

Asia

Increasing Myopia Patients

Myopia progression
Pathologic myopia

Developing world

Reaching More Patients to Eye Care

Infectious disease

Developed world

Aging Society

Age related diseases (AMD, Glaucoma etc.)
Chronic illness (Dry Eye, DR/DME, etc.)

Genetic diseases

Improving Therapeutic Tech.

Rare Diseases




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Ultimately, it is Santen's goal to enhance a patient's quality of life. Treatments need to be effective in the most unobtrusive way possible. But meeting the needs of the patients is a rapidly changing target. Patient needs are not the same as 10 or even 15 years ago. For example, if you asked a cataract patient in 2003 about their expectations following surgery, the common answer was, "I want to read the newspaper and walk around freely". But now, they want to do everything, from playing golf, playing piano and driving. And these expectations are pretty similar from developed to developing countries. We also are addressing different diseases in different parts of the world. Example, if you think about Asia, myopia is an epidemic. Parents are very concerned about the high progression of the disease in children. The developing world, they need more attention in infectious diseases like bacterial and fungal keratitis. On the other hand,

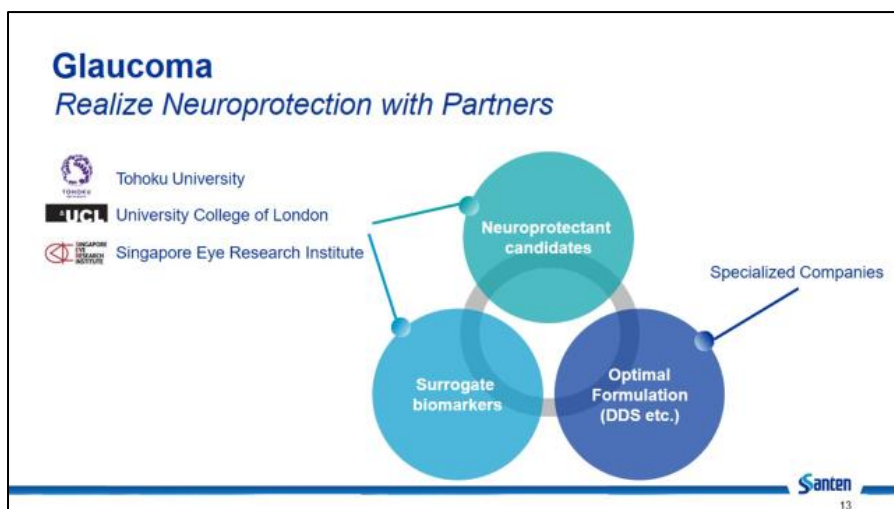
developed countries have different issues because of their aging population, like macular degeneration, glaucoma, diabetic retinopathy, diabetic macular edema, and these kinds of diseases. On the top of everything, as we have better diagnostic tools to diagnose rare genetic disease, we need to address those discoveries as well.

Strategies to Address Future the Unmet Need

Disease Area	Strategy
Glaucoma	<ul style="list-style-type: none"> • <i>DDS Rx Delivery</i> • <i>Improved Eye Drop Delivery</i> • <i>Continuous IOP-Monitoring Devices and Earlier Disease Progression Detection</i> • <i>Surrogate Biomarkers</i> • <i>Neuroprotection</i>
Retinal and Uveal Disorders	<ul style="list-style-type: none"> • <i>Anti-VEGF (Adjunctive, Long-Duration, Low Cost)</i> • <i>Therapy for Rare Disease</i> • <i>Cell Therapy</i> • <i>Gene Therapy</i> • <i>Stem Cell Therapy</i>
Myopia	<ul style="list-style-type: none"> • <i>Prevention (Superior)</i> • <i>Treatment for Pathologic Myopia</i>
Others	<ul style="list-style-type: none"> • <i>New MOA</i> • <i>New molecules</i>

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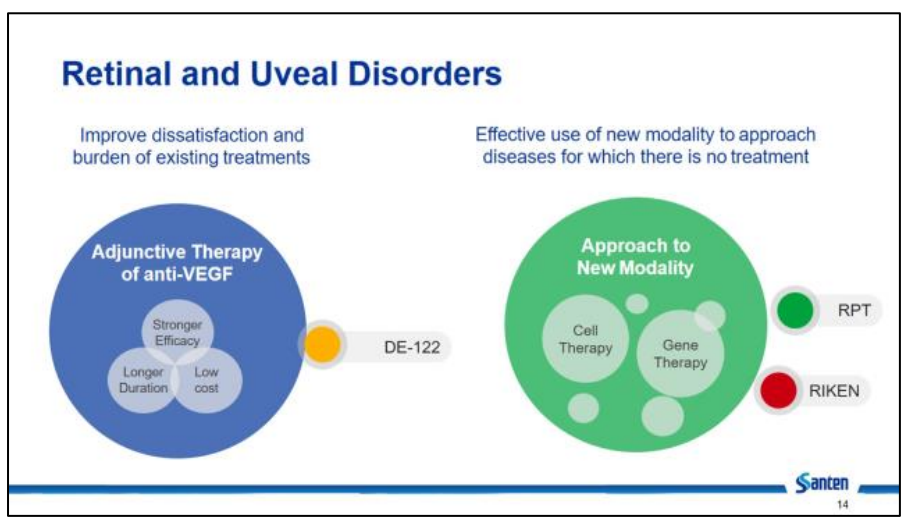
For future strategies, we are working on different disease areas. First, glaucoma. We are not focusing on another IOP lowering drugs but, developing sustained-release formulations of IOP-lowering drugs, creating devices to improve eye drop delivery as well as monitor eye drop compliance and developing continuous IOP-monitoring devices as well as surrogate biomarkers, thereby allowing earlier detections of disease progression. And also developing neuroprotective therapies to change the course of glaucoma progression. Let's talk about retina. Again, we don't want to create number 5 or number 6 anti-VEGF drug in the market but instead our focus is to address the anti-VEGF treatment burden and how to address the patients who are becoming refractory to their effect. Regarding dry eye products, Santen is working on several MoA to address different unmet needs in dry eye therapies. On infectious front, Santen is working with academia to explore new molecules to address unmet needs in both bacterial and fungal keratitis.



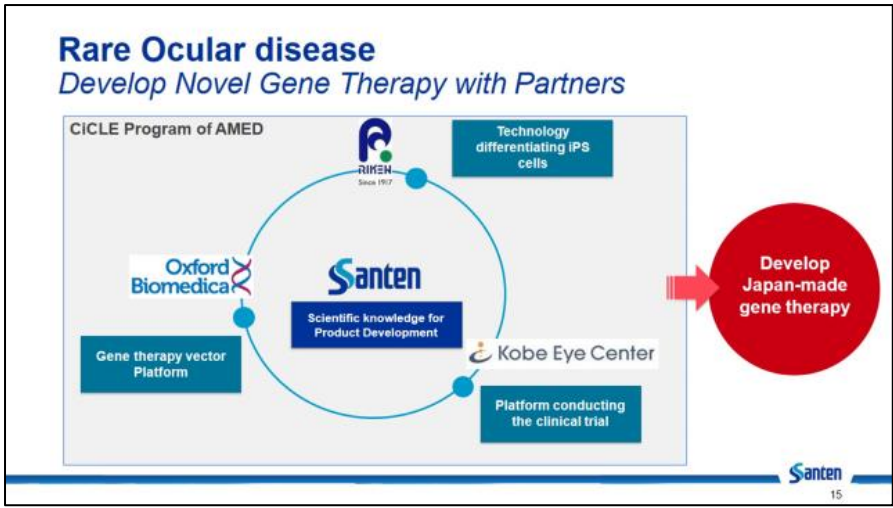
Glaucoma is becoming an increasingly important cause of blindness. As the world's population ages, new statistics gathered by World Health Organization shows that glaucoma is now the second leading cause of

blindness globally, after cataract. However, glaucoma presents perhaps an even greater public health challenge than cataract, because the blindness it causes is irreversible. It is estimated that by the year 2020, 11.2 million people will be blind due to glaucoma. Neuroprotection in glaucoma refers to any intervention independent of IOP reduction that can prevent or delay retinal ganglion cell and axonal death. As we all know that no major health issues can be tackled without strong partnerships between research institutes, universities, and public sector. It is known that in some glaucoma patients, death of retinal ganglion cell continues despite intraocular pressure reduction.

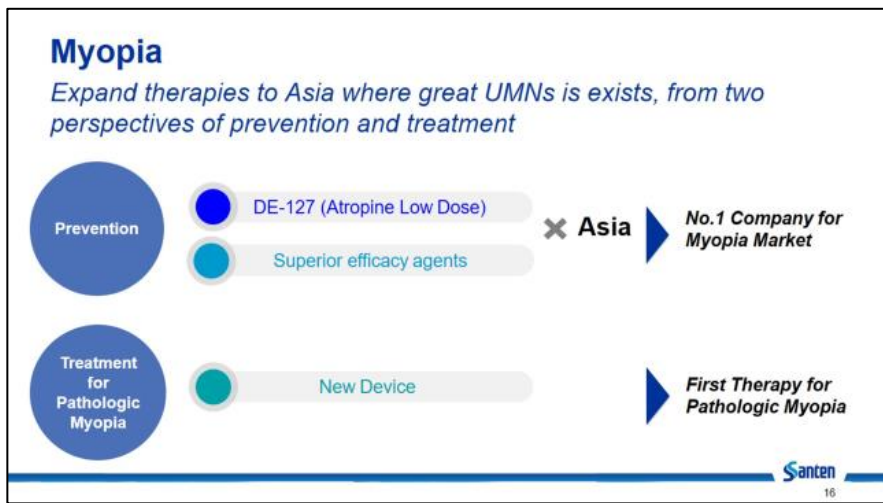
To achieve neuroprotective treatment, we are working with the best research institutes around the world like Tohoku University of Japan, University College of London in England and Singapore Eye Research Institute. In cooperation with the partners, Santen is investigating surrogate biomarkers in order to enable better clinical development program design and evaluating the potentials of numerous neuroprotection candidates as well as their compatibility with various drug delivery platforms.



Now, let's talk about retina and uveal disorders. There are two main strategies for the use of retinal diseases - to resolve unmet need of current treatment by increasing the efficacy for longer duration, lower cost and relieve treatment burden. And also in new modality, we are working in diseases where there is no cure. New modality is used to create new treatments. Introduced more than a decade ago, anti-VEGF therapy has radically changed the treatment of retinal diseases such as wet macular degeneration and diabetic macular edema. However, there is a still, an unmet medical need, in this area as these therapies come with the burden of requiring monthly injections and growing percent of patients have become refractory to their effect. Santen continues to invest and partner with companies and institutions that specialize in next generation modalities, like cell and gene therapies, to address previously untreatable retinal diseases like genetic diseases, dryAMD and so on.



With the FDA approval of the first gene therapy in 2017, Santen has recognized the importance of this modality to treat what were once thought to be untreatable diseases. Santen is proud to have initiated its first gene therapy program for inherited ocular disease in March of 2019. And this program is a collaboration between Santen, Oxford BioMedica, Riken, Kobe Eye Center, and is supported by the grant from the government of Japan Medical Research and Development Organization, called AMED. We are working with the best partners to achieve the gene therapy firstly in Japan.



As I mentioned earlier, myopia is epidemic in Asian countries due to genetic and environmental reasons. Santen is taking myopia very seriously and tackle the issue in two ways – to prevent the progression in mild and moderate myopia, and treatment for severe pathological myopia. Our goal is to launch atropine in Asia in the fastest possible way and we will create products that are easier for children to use and also targeting the Asian countries. Santen is also working on the second generation of anti-myopia drug to achieve superior efficacy over low-dose atropine. And Santen is also working on extensively to find a cure for pathological myopia.

Keratoconjunctival Disorders

Handling the global/regional UMNs of each disease carefully utilizing new technologies



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We also intend to use our assets to grow the business. Corneal blindness is the third leading cause of preventable blindness. This is a complex problem. It plagues more than 12 million people around the world, 98% of whom live in low- and middle-income countries. We are working diligently to address the issues. Thank you for your attention. It is my pleasure to introduce Kenji Morishima who is heading our Pharmaceuticals and Pharmacology Group.

Pharmaceutical Development

Kenji Morishima

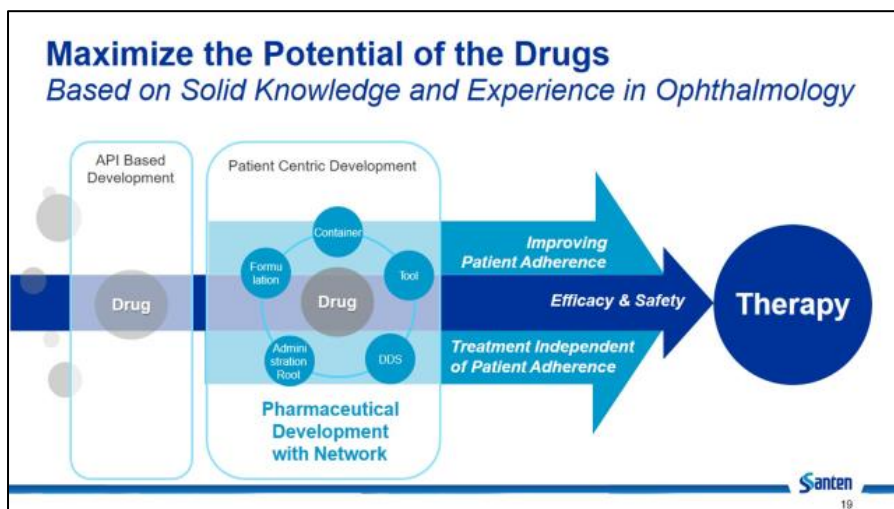
Corporate Officer,
Head of Pharmaceuticals & Pharmacology
Representative, Asia R&D



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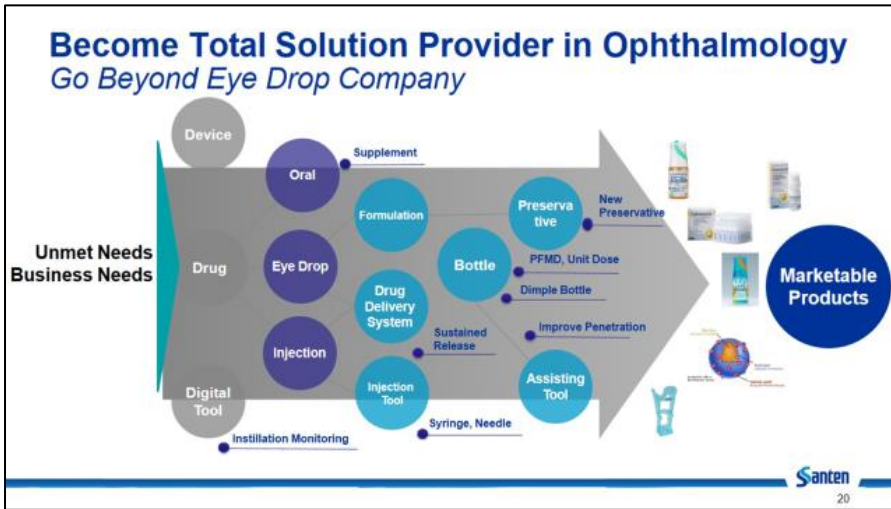
My name is Kenji Morishima. I am Corporate Officer, Head of Pharmaceuticals & Pharmacology, Representative of Asia R&D. Today, I will brief you on our pharmaceutical development, how we maximize the potential of the drugs and how we will become the total solution provider in ophthalmology.



In the previous R&D Day, we provided examples of Santen’s product development. Our mission, maximizing the potential of drugs remains unchanged. In the drug development, the strength of pharmacological and adverse effect of the drug itself is very important. However, formulation technology is necessary to make drug available for treatment. In a real clinical setting that is the best way to connect patients and treatment, and we have the ability to do it.

Eye drop development is very different from other dosage forms such as oral drugs. Oral drugs are absorbed by the same mechanism that takes nutrients from food. In case of eye drops, a big challenge is the defense function of the body which prevents entering foreign bodies into the eyes. Therefore, it is necessary to fully understand the structure and function of the eye and make a formulation of the drug to reach the target tissue going through an evading defense mechanism. To make it realize, our experience and knowledge as the specialty ophthalmology company dealing with many ophthalmic drugs in 100 years is essential. Even with the same drug, the efficacy and incidence of side effects can change drastically with a slight change in formulation, pH and excipients.

Also, even if a great formulation is developed, efficacy cannot be expected unless it can be instilled. An easy-to-use bottle is an essential treatment tool to enhance treatment effects. The Dimple Bottle introduced at the previous R&D Day is so popular that the patients ask for it and we are confident that this will prevent the switch to generic products. Additionally, in order to improve adherence, an assisting tool for instillation is provided to improve the accuracy of instillation. In future, we aim to realize treatment that does not rely on patients’ adherence by developing DDS. This will further improve the quality of treatment. Having solid knowledge and experience in the ophthalmic area and understanding potential needs of patients, Santen can develop excellent formulation technology with competitive advantage.



As explained in the previous slide, we will evolve compounds into products by selecting different formulation technologies. Up until now, eye drops have been the main ophthalmic treatment, but now we are exploring all ophthalmic treatment options possible. Santen may have made a strong impression as an eye drop company but it is not limited to that. In addition to the eye drops, vitreous injections are being developed like DE-109 and supplements are also sold as oral agents. We have options for the optimal route of administration based on unmet needs, business needs and scientific feasibility.

As Reza explained earlier, new modality such as antibody, cell therapy, and gene therapy will be coming up in the future and formulation technology to meet them will be required. We are not particular about technology development in-house. We are planning to achieve commercialization using the latest technologies in-house and outside the company. In addition, we believe that treatment devices which replace drugs and digital tool for diagnosis, etc. will be needed in the future as well. Of course, for eye drops, we will continue to develop PFMD containers and improve formulations by understanding the need in each region. Santen aims to become the total solution provider in ophthalmology by incorporating new modality and treatment technologies in addition to conventional eye drops.

Providing joy to patients by creating new product value. 100% focusing on ophthalmology, that's exactly why we can do it.

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We work hard to understand patients' unmet needs and conduct our research and development based on this information. However, not only that, we want to dig into potential needs that patients are not aware of and create better products. That's what we can do as a specialized company, and we think it is our mission

to do so. In such efforts and activities, the voice of joy from patients is very happy and is the driving force for the next activity. Here are comments from the actual patients who used *Kary Uni*, when the Dimple Bottle was released. They said “The bottle is brilliant”, “Instillation has become much easier”, “Expect other product’s bottles to change as well”. We received a lot of appreciative words for the Dimple Bottle. With this, we realized that the approach, that not only provides our products, but also improves the quality of treatment, is really required for patients.

In this way, we think we can compete with generic products as fans of Santen products are choosing our products even in the environment of promotion of generic use. And we believe this can contribute to our business success. There are many things we need to work on, and it is necessary to do it in an efficient manner. We will continue to provide the joy of sight to patients by creating new value. Thank you for your attention. I now present to you, Peter Sallstig. Peter is heading up our Product Development function. Thank you.

Product Development

Peter Sallstig, MD, MBA
Senior Vice President,
Head of Product Development
Representative, US R&D



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Good afternoon, my name is Peter Sallstig. I am the Senior Vice President, Head of Product Development, U.S. Representative of R&D.

A New Approach to Product Development

- Increased predictability** through accurate, science- and evidence-based study designs, plans, and budgets
- Shortened timelines** through faster study start-up and timely patient enrollment and trial completion
- Optimized clinical operations** and data collection

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In order to meet the vision of the company, the organization has recognized a need to change and is

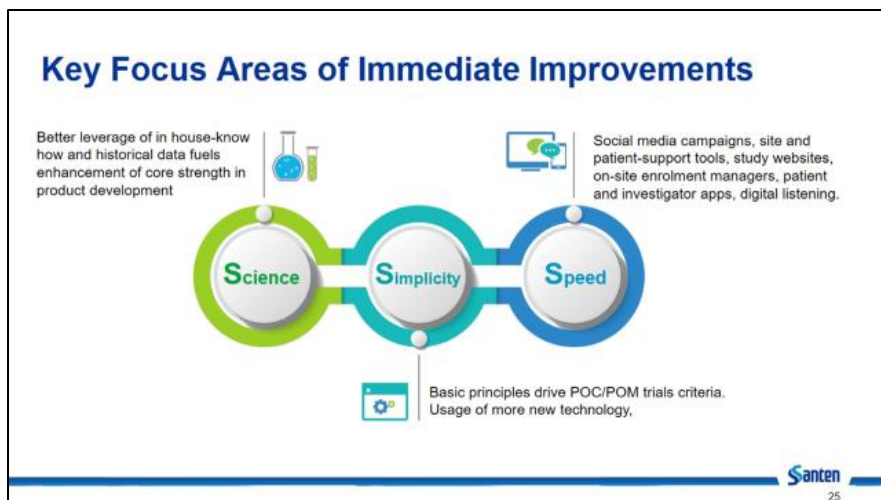
transforming itself. We are at an inflection point. After listening to my colleagues, I do hope you have the impression that at Santen, not only do we see things differently now, but even more so, are we doing things differently. In fact, we have adopted a whole new approach to product development.

As evidence of this new approach, here are some examples of how we conduct our programs now. This includes a better understanding of and a clearer focus on science with integration of the evidence needed in study designs to help fulfill patients, physicians and payers' needs; clinical development plans that are well thought through utilizing proof of concept will help us establish early benefits for the patient. One of the aspects that differentiates us is our vigorous use of proof of concept or proof of mechanism studies. We believe that this will help us have a more predictable product course, so that we can make at risk investments early on, before late stage development. We will also have the introduction of new technology to significantly enhance speed, efficiency and quality, all this while staying within budget. We also have a medical affairs team that is passionate about delivering treatments to more and more patients. Many of them have family members affected by vision deterioration and know the preciousness of eyesight. We aim to reach 5% more patients each year. In addition, we are offering solutions through our new external collaborations.

So, we are building a robust R&D organization designed to shorten timelines through faster study start-up, accelerated patient enrollment, all of this leading to a faster trial completion. How? Our unique patient-centricity. We have a long history in ophthalmology and we know the patients and the physicians the best. We believe this will take us to the forefront of data collection. In fact, in the next three years, we will aim to shorten study times by 10%. In addition, the data we gather, both from of our real-world evidence and our clinical trials, will be looped back when designing our new clinical trials, all this in order to benefit the next patient. So, we try really hard to envision the most optimized product development aimed at urgently helping patients fulfill their potential in life by maintaining their vision.



Now product development is one area where we, quite frankly, have had our share of difficulties in the past, and we recognize that. We believe however that through the changes we are making now, we will obtain a competitive advantage. We will be delivering launches on time and with a higher value generation. Insights from all regions will be incorporated to ensure a truly global approach, first in our understanding, and then of course in meeting all the patient needs. In addition, the teams we will have, will be the right people, right numbers, right regions - all to expedite this transformation. To be able to deliver on our promise to patients, we will act with a sense of urgency, a core value of each Santen employee.



Now, meeting unmet needs sooner is at the forefront of every step of our product development. And we are committed to change. So therefore, immediately we will focus on the following areas – science, simplicity and speed. In practice, this means a better leverage of our 130-year-old history and understanding of unmet needs. It also means we won't get bogged down by internal 'red tape'. So, the sense of urgency will be present at all levels. Building also up on our Japanese heritage, we will also utilize smart clinical trial logistics, both for patients as well as for physicians. We believe that utilizing this will improve compliance, efficiency, to name a few, and thus enhance study start-up and more importantly completion. We are also immediately investing heavily in our outreach to patients - younger patients, patients that live remotely. This is all in the quest to fulfill patients and their potential to see.

We are Addressing Changing Ophthalmic Treatment

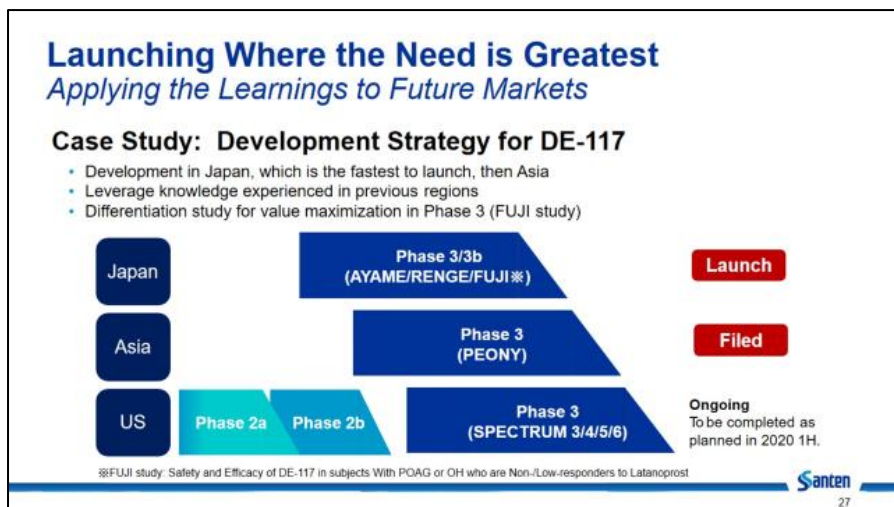
Disease Area	Pipeline
Glaucoma	IOP Lowering
	• New agent
	• Compliance (MIGS)
Retinal and Uveal Disorders	Anti-VEGF (Adjunctive)
	Therapy for Rare Disease
	Prevention
Myopia	Improve Usability (Line Extension)
Keratoconjunctival Disorders	Territory Expansion

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Now let's turn our attention from talking about processes to the products that lay ahead of us. Not only are we focused on innovating products that helps treat patients today, but even so, tomorrow. So, in the glaucoma neuroprotection therapeutic area, Santen is bringing a novel *MicroShunt* device to patients. *PRESERFLO* is already approved in some markets and is in pre-market approval in the US. Santen is also bringing new pharmaceutical glaucoma agents. DE-117 or *Eybelis* is already approved in Japan, is being filed across Asia as we speak, and is in phase 3 trials in the US. DE-126 phase 2 study is complete and we are assessing now the next steps.

In the retina and uveal disorder therapeutic area, we have DE-122, carotuximab, DE-109, intravitreal sirolimus, LUMINA trial ongoing. Both of these two agents are going well. In the field of myopia, we have

DE-127 for the prevention of myopia, to start later this year. We are also optimizing the potential of other current assets, focusing on territory expansions.



Now, I would like to give you two examples of our strategy when launching products. Let me start with DE-117 or *Eybelis*. We launched *Eybelis* where discussions indicated it to be the greatest. So, when we discussed with patients, physicians, health authorities, giving us an indication that bringing this novel agent with a novel mechanism of action served the greatest unmet need. So therefore, the support from the above-mentioned groups was very helpful and all this helped us to serve the next future markets each time, utilizing the learnings, serving our next patients better. This is why for DE-117 or *Eybelis*, we developed it in Japan first, because Japan fulfilled all those criteria mentioned before. DE-117 or *Eybelis* is currently being expanded to Asia, and shortly after that to the US, each time building upon our knowledge, experience in each region.



Looking at the next case example of DE-128, *PRESERFLO*. Well here at first we received the CE marking in Europe. This helped us to learn and experience from the commercialization activities. This again, we believe will help us in our plans to utilize this learning in our biggest market to come – the US. Once launched in the US, we will then utilize again the knowledge, the data, for submission in Japan, Asia, China, and other countries moving forward.



As we have seen so far, Santen's research and development aims to protect the patient's vision and quality of all the patients around the world. The way Santen stands out are – number one, we are the only major pharma company 100% focused on ophthalmology; number two, we cover all disease areas in the eye; and number three, we capitalize all kinds of technology and innovation to cover all kinds of treatment options, ranging from essential diagnosis to innovative surgical treatments. So, throughout our 130 years of history and dedication to ophthalmology, we have indeed established a close relationship with our patients across the globe. Our clear focus on the patient's well-being, combined now with excelling in product development, globalization of opportunities, only adds to our unique competitive advantage. Santen is committed to contributing to ophthalmology like no one else. Santen is committed to enable each patient to see ahead of them a fulfilling life, fulfilling their dreams. Thank you.

Q&A

Q1:

First question is about the basic policy. I think you mentioned that in 2017, Santen has changed its stance, shifting from applied development and now more focusing on pursuing new technologies. This led to reorganization, is that the correct understanding? Second question is about myopia project. You talked about highly efficacious product and a new device for myopia. If you have any additional information on that I would appreciate it. And third, about the gene therapy. You talked about Oxford and other institutions. When are you going to start trials? If you could share the timeframe with us, we would appreciate it. Thank you.

A1:

(Naveed)

Let me give you a high-level response to your first question which is, we in 2017, made some adjustments, strategic adjustments. It was 2018 actually, we did a review as you may recall we met like this about four

years ago and we had some metrics. It was time to check how we were doing, and based on that we made some changes. And part of the leadership team that you see here today is a result of that evaluation that was conducted in 2018. Overall the strategy, both from the R&D development strategy and the disease area strategy has not changed much. However, what we need to focus on is delivery, is execution. We need to focus on execution. We need to deliver products on time, on budget and reliably. And that is what I think Peter was talking about. And so there is going to be a renewed focus on that. As far as myopia, I will have Reza-san here maybe comment on the future of the myopia program and the gene therapy program. But I can say this much is that as you know DE-127 is already recruiting and then we have undisclosed program that I can tell you is moving quite well through our research pipeline. And the goal is to, of course, bring one of those products that are in the research pipeline. I can tell you there are two and I'm hoping that one of them is going to be the successor to atropine. On the other hand, we would need a device to address the complications of high myopia, which becomes pathologic in some cases. And so currently we are evaluating a device to treat and manage that complication. Reza, if you want to say something, please.

(Reza)

As Naveed mentioned that we have one program started, we have another one that we cannot talk right now. And our main focus in Asia right now, Japan, then China and other Asian countries.

(Morishima)

As for gene therapy, the development has just started. Oxford BioMedica is working on creating the new vectors at the moment. We will see expression of genes and we will see proteins and it will start to function. These are done at Riken using iPS cells. We have patient cells and healthy cells to confirm expression. We hope that time can be shortened for such development. As for the process after going into a trial, of course that is something that we need to discuss and consult with government. Once it is ready, we would like to file in Japan and aim for obtaining a conditional and time-limited approval. Of course there is no guarantee, but we hope we be able to come up with a treatment with a value. We have already identified the gene and there are many patients at Kobe Eye Center. We hope to accelerate the development. At this moment we cannot really say clearly when the launch will be, but we would like to say that we will achieve that as soon as possible. Thank you.

Q2:

I have two questions. First question is about global development. Till now, you start with one region based on regional specific situation and then roll out in other regions or area. But considering the speed, global simultaneous research and development may be better in the future. Have you considered this option? And regarding the position of China, the situation has changed very much. In the past, China came last. But nowadays maybe priority of China has changed?

Second question is Santen's strength. Today you introduced gene therapy and devices. How your strength and experience of developing eye drops will be leveraged in development of devices and other areas? If you have any specific examples, can you explain? For instance, development of *MicroShunt* made use of your strength, if you have such story, please share with us.

A2:

(Peter)

I think the approach that we have realized is obviously we will have to have a more of a global approach upfront. I think the examples that are indicated for you is, of course, processes development that has happened in the past. I think in order to expedite as much as possible, we will try to globalize as much as possible. However, again in the sense of patient, patient-centricity, obviously there are certain diseases which are very specific to certain regions where its more prominent, so in those circumstances we will still obviously be focusing more regionally first and then of course expanding as needed to be. As part of this globalization that we are trying to achieve, of course China is extremely important. So China will be part of our globalization effort. This will be at the forefront. So as and when we start developing the programs in the future as you will be seeing it, China will always be at the forefront.

(Naveed)

The head of China is right here. So, as you mentioned correctly, we could not make China part of our global plans because it was so slow. However now, we are thinking of launching products in China first. That's how different it is. So, China first launch, is now possible, especially if you consider products like myopia. Clearly, Asia is the place for that product and that class. So, as a strategy company wide, Asia and China is extremely important in that area. So that is a major change for us moving forward. You had one more question about devices, I think so. Let me also highlight it by saying that our new President and COO, and the CEO and the board really want Santen to be a truly end to end provider of ophthalmic care, focusing on the quality of life of the patient. It's a renewed focus. And so whether it is a device or whether it is a diagnostic or whether it is a therapeutic, we would be interested in exploring all those possibilities. However, we have to keep in mind we are a business and we have to deliver our value to you guys and to our shareholders and to our patients. So there may be some up and down, but that is the mission for R&D, to support the business. Therefore, devices are in the next. We have *MicroShunt*. We got very, very smart people who developed the *MicroShunt*. At least one of them is right here, Dr. Raymund, who is going to help me answer your questions on DE-128, and so we are getting more comfortable with the device side. On the diagnostic side, we need diagnostics to properly position our products and improve the probability of technical success. As you know my statement was, "We want to be productive". To be productive I feel we need diagnostics. And so Nakamura-san, who is sitting in the back, and his team, is looking for diagnostic. He has one more year to deliver one diagnostic to Santen. We are serious, and I think Nakamura-san is going to fulfill this promise.

(Suzuki)

Just to add comment regarding China. There are needs and diseases in China that fits our global priorities and strategies. Meanwhile, there are something that are specific to China apart from global trend. As Peter explained earlier, myopia may fit global strategy as the government is keen to tackle the issue of high myopia among children. On the other hand, glaucoma in China is low in priority. We have global asset at Santen but Chinese authority and the patient and the patients' family, how much are they willing to pay or urgency is felt, it may not be the same. So simply put, we will take a hybrid approach. Morishima-san will explain about our strength being adapted to some of the devices other than eye drops.

(Morishima)

Santen is doing both, that's our strength. We have devices, the *MicroShunt*, and also we have the ability to develop additional drug to maximize the potential of *MicroShunt*. Device plus drugs in combination can give enhanced drug efficacy. We want to have that type of solution. So, within the same organization we can cover device and drugs. And we hope in near future we are able to realize that. We are now in early stage to explore that possibility. Including *MicroShunt*, we hope to provide total solution that can enhance the potential of devices. That's what we pursue.

Q3:

I have two questions. First, page 13. You talk about glaucoma neuroprotection. Is this concept solidified, by how much? And at what kind of development stage is it? And what is the timeline for the future.

As for partnering, it's been a while since you have partnered with the partners you mentioned here, so can you talk about the progress in partnership please. And the second question, at the R&D briefing four years ago, you talked about DDS for quite some time. Morishima-san, I believe gave us a detailed presentation on DDS but he didn't touch on it today. So, is positioning of DDS changed since four years ago? Has it been progressed or not progressed? Thank you.

A3:

(Naveed)

Thank you for your question. I think let's do that neuroprotection and status of that.

(Reza)

For neuroprotection, it is a long-term therapy and it's very important to have surrogate endpoints for neuroprotection, otherwise you cannot do a study for six-seven years long. We are working diligently with the other institute to find a surrogate endpoint and also looking for the platform - how to deliver the drug. And once we have these two things, we can move forward. We have some compounds that we are working on right now.

(Naveed)

You asked a very important question because you were here four years ago. What has happened to the partnership is that the myopia program and the neuroprotection program are the direct result of our partnership with Singapore Eye Research Institute and Santen. Our next generation myopia products are also in partnership with Singapore Eye Research Institute. So our partnership with Singapore has been extremely productive. We have moved products through our early pipeline into development. And the neuroprotection side, at least one target has been identified in partnership with the Singapore Eye Research Institute. We are at the point where we need to identify molecules or drugs that will be good enough to manage or hit this target. That's where we are. And as Reza mentioned, there are other challenges of keeping the trial short - because it's very expensive, very time consuming, so we are moving slowly in that direction. But we are also looking for opportunities out there. I believe if I can give you a hint, is that, if you follow the Alzheimer space closely, there may be modalities in the Alzheimer space that could apply to glaucoma. So that's a hint. So, we are looking very, very carefully. But we are making slow progress, but

we are making progress.

(Morishima)

As for DDS, as you know, our competitor in the U.S. had a filing. We are targeting best in class DDS. Therefore, not only in-house technology, but external collaboration is something that we are exploring. Several companies have already started the trials so we are trying to select the best choice there is. It may take time. However what Santen is aiming for is best in class DDS. After the launch of the competitors, we hope that we will be able to come up with a DDS that can win against our competitors. So we would target best in class DDS globally. Thank you.



(Naveed) I'm sure you guys are waiting for discussion on *MicroShunt PRESERFLO*. And we are here to answer any questions you have. I have nothing else to do, so ask me any number of questions. I'll do my best to answer them. If I don't have them, I will get back to you. I would like to introduce to you Dr. Raymund Angeles. If you don't like *MicroShunt*, you can blame me. But all the success of the *MicroShunt* goes to this guy and his team. He is a brilliant surgeon works for Santen, was around when we licensed the product and so he knows everything about *MicroShunt*. And if needed, he can help me answer some of your questions. I think as we were getting ready for this meeting and we made the press release, we were kind of wondering as to how to address this issue in today's meeting. We thought the best way to do this would be to clarify the value proposition with the *MicroShunt*. Why are we so excited at Santen about the *MicroShunt*? Why are our investigators and key opinion leaders in Europe and the U.S. are looking forward to this approval? Of course, there is no guarantee of approval, so, I would like to keep this academic. There are no commitments on whether the FDA will approve this device or not, however, we are going to work as hard as we possibly can, to bring this on schedule, to the market next year. Everything is moving according to plan and we will be trying our best to file as quickly as possible and bring the product to market next year.

The value proposition. I'm sure you're wondering why are we so excited. I will take this opportunity to show you some data and I will take this opportunity to let you make your own decision based on two videos. The first one is *MicroShunt*, its animation. The second one is a video from one of our patients, and you can compare the two procedures. I can answer any questions, Raymund can help you answer some questions

and then we'll take it from there. And then I'll answer any questions you have. These are not very long videos, three minutes each, to give you a flavor for what is involved. And I will maybe intervene and say something.



(Video) Carefully examine the package containing the *MicroShunt* for signs of damage that could compromise sterility. If damaged, discard the device. Wet the *MicroShunt* using a solution of balanced salt solution. Standard ophthalmic surgery techniques according to institution protocol should be used to prepare the patients and the eye for surgery. Dissect a fornix-based subconjunctiva and subtenon's flap at the supranasal or supratemporal quadrant over a circumference of 90-120 degrees, at least 8-10-millimeters posterior to the limbus. Bipolar diathermy or cauterization can be used at the surgeons' discretion. Apply 0.2-0.4 milligram per milliliter Mitomycin-C for two to three minutes of exposure. Placement, time and concentration of Mitomycin-C is at the surgeons' discretion. Remove the sponges from the eye and irrigate with a sterile balanced salt solution. Using the 3-millimeter scleral marker provided, mark a point 3 millimeters from the posterior border of the surgical limbus in the blue grey zone.

(Naveed)

I just wanted to make a comment here. This is the only dissection we do before inserting the *MicroShunt*. It's important to note because that is part of the value proposition. Okay thank you very much, start again.

(Video)

At the distal marked point on the sclera, use the provided 1-millimeter wide double step knife to create a transscleral tract into the anterior chamber and a shallow scleral pocket. With a pair of non-tooth forceps, hold the proximal end of the...

(Naveed)

Before we insert the device, we create a 25-gauge tract. 25 gauge is tiny, another point to remember.

(Video)

Thread the *MicroShunt* gently into the transscleral track to approximately 1-millimeter increment to prevent kinking until the proximal tip is in the anterior chamber. After successful insertion of the *MicroShunt* into the

anterior chamber, wedge the fin into the scleral pocket. Ensure that the *MicroShunt* is not in contact with the iris and the posterior part of the cornea. Confirm consistent percolation of aqueous humor at the distal end of the *MicroShunt*. Slight pressure on the cornea will help initiate flow. If needed, conduct paracentesis or use a 23-gauge thin walled cannula to prime the *MicroShunt* at the distal end. Once flow is established, tuck the distal end of the *MicroShunt* underneath the tenon's capsule and conjunctiva, making sure that it is straight and free of tissue. Reposition the tenon's and conjunctiva to the limbus and perform closure using sutures with a well-established history of successful using glaucoma surgery. Use a moistened fluorescent strip to check for leakage from the wound or from conjunctival tears. Verify that the proximal end of the *MicroShunt* is in the anterior chamber and that the distal end is straight.

(Naveed)

Depending on the surgeon and how many times you have used or done this procedure, it still requires a little bit of training. We estimate about ten procedures before we let them go...

We think you should practice this ten times before do whatever you like with it. At that point we can't control you. So, it takes time to get used to a new device, a new system, a new technique. That's also a very surgical device issue. It's not like putting eye drops in the eye, there's training involved. The next is going to be an actual video of a surgery with trabeculectomy and I have to tell you that there is blood and if you cannot see it, my apologies. But to make the value proposition crystal clear, I think it is important to see it. If you can't see it, I can explain it later. Please close your eyes, turn around, however you want to deal with stress.



(Naveed) We have shortened the video. It's only three minutes okay, not the whole thing.

[Video]

(Naveed) This is the part where you will see the value of *MicroShunt*. A key differentiator. Trabeculectomy is very effective. It lowers IOP really well. It has been developed over the last 50 years by surgeons. And even today surgeons make adjustments and changes and somebody does a square flap and somebody does a triangular flap and everybody has their tricks. So, now I want you to pay attention to the hole that we are going to create in the eye.

[Video]

(Naveed) That's called a flap. We have just created a flap. Please pay attention to the complexity of the procedure. Now we are going to make a hole, actual hole in the eye.

[Video]

(Naveed) That's called a flap. We have just created a flap. Please pay attention to the complexity of the procedure. Now we are going to make a hole, actual hole in the eye.

[Video]

(Naveed) That is the hole. Now we are going to pull the iris inside the eye, and cut it. It's called iridectomy. The reason to do that is because the iris will come outside if we don't do it. When the pressure goes up, the iris will come through the hole and it's going to block it and will cause other problems. Now we have cut everything out. Now we are ready and even after this, I'm not going to go all through. There are many, many things that can cause issues. And then you put sutures. You can put three sutures, four sutures, five sutures, it depends on the surgeon. And these sutures have to be removed. And these sutures are used to control and manage IOP and complications of too low of IOP. So, this tool is available to the surgeon to manage IOP. That's why it's so hard to be superior to a trabeculectomy procedure in terms of lowering IOP. Because of such a big hole, one of the biggest problem with this procedure is too low of IOP. Unpredictable. And you don't know who is going to be with too low, who is going to be with too high, and the first three months are spent trying to figure that out.

So now let me show you why we licensed this product and also show you some data to support the contention that we are more predictable, that we have less complications and while I can't share with you some other new data but only the data that's in the press release, you will get the idea on why somebody should be using a *MicroShunt* before going to this very complex procedure. You always have the option of doing this, but before you do this, you now have another option. That is the value proposition.

Value Proposition & Our Objective

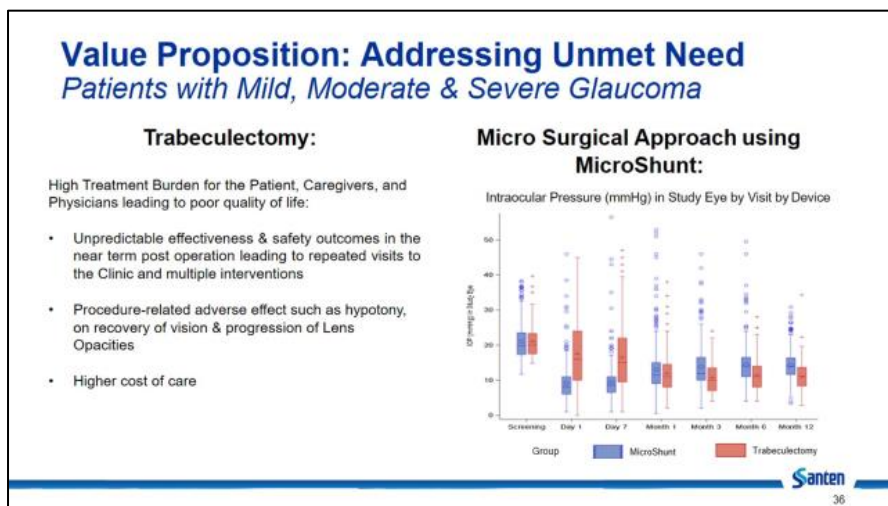
First FDA approved minimally invasive stand alone procedure for mild, moderate, and severe stage open angle Glaucoma, that lowers and sustains IOP under 15 mmHg, and completely eliminates eye drop medications in most patients.

Santen
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When we acquired this device, our objective was this, stated on this slide. This is why Santen acquired the device. We wanted to be the first FDA approved, minimally invasive, standalone - not in combination with cataract or anything else – standalone, procedure for mild, moderate and severe open angle glaucoma, that

lowers and sustains the IOP under 15 mmHg. You may have a question about why 15, why not 12, why not 13, why not 16, why not 15.5. This was the goal. And completely eliminate the use of medication in most patients', and I have not changed this sentence at all. This is what was there four years ago when we licensed the product. And clearly, from our data, topline data, we have achieved this objective. If approved of course, no guarantees, I think we will be somebody that can sustain IOP below 15. Our average at month 12 is around 14, which is pretty good, and 70% of the patients do not require medications. Without going into too much detail, I would say, when you do the *MicroShunt* surgery, there are no sutures that I can manipulate to lower my IOP, if it's high. But, if you were a trabeculectomy patient, the surgeon can manipulate the IOP by going in and cutting the sutures. IOP will drop. The trabeculectomy is effective in lowering the IOP around 12 or so, on average.

Then of course there's going to be variability from study to study, plus or minus, however you wish to call it. That's where we are.



So, what happened in our trial? Exactly what I just explained to you happened in our trial and let me show you a plot of data. What is this? If you look on the right side, this is IOP. This is a box in whiskers plot and on the x-axis, there is time. And I'd like you to notice that Day 1 post-op, Day 7 post-op, month 1 post-op, on average, the length of the whisker is twice as wide as the length of the whisker on the *MicroShunt* patient. What is the importance of this whisker? This shows you the variability in the IOP. There are patients with very high IOP one day after, and there are patients with very, very low IOP on Day 1. This is coming from the complexity of the procedure, the size of the hole, the sutures and everything else. And it keeps the patient and the doctor very, very busy. They cannot sleep, because you will have complications if you don't manage your IOP. That is the unmet need. That is the unmet need we are trying to address. We want good IOP lowering and we want to get rid of the burden on the patient and the physician, and ultimately the payer.

If you notice, it takes about 1 to 3 months before the red whisker here becomes as competitive as the *MicroShunt*. The variability settles, and we expect this will continue for a long time – one year, two years, probably, right. And, because we don't have any capability, at least in this study, to manipulate this IOP, you couldn't add drugs for example were prohibited, you couldn't do any other procedure because that would be failure, so you had to manage it within the limits of the protocol. Therefore, you can call it an apple to orange

comparison, but doesn't matter. Our IOP lowering was very effective. 6 to 7 mmHg at month 12 when they were already on, at least three medications. We were able to reduce it even further, by 7 millimeters. So, what we have achieved is or what we think we have achieved is or what we think we will convince the agency to look at is, we have removed the unpredictable nature of the procedure. You can sleep well, you don't have to rush to the clinic back every day or two or three or for the first three months. You know what you are going to get. We have removed that. There is no need for further intervention, no suture lysis, no multiple interventions, no poking the eye, rubbing the eye, whatever, to keep the IOP low. And because we are doing that, procedure related adverse effects, such as, very low IOP and recovery of vision and cataract progression is under control. When the IOP is too low, you can imagine, it takes time for the vision to come back after surgery. That's a problem with a trabeculectomy patient. They can't see very well for months. We think that the use of a micro device will help in the recovery of their vision faster, as far as time is concerned. No guarantees about the quality but at least it should recover faster. So, you can then also imagine that to manage all of these complexities, the patient is consuming the time of the clinician. And therefore, the cost of keeping the IOP down is relatively high. So, by reducing the number of visits to the clinic, we would imagine that we will reduce the burden on the MHLW. Less frequent visits reduce cost. I thought I would walk you through this as slowly as I possibly can and then I can open it up for questions. So, any questions?

Q&A

Q1-1:

I have one question please. I was able to understand what you explained to us. I want to ask you, the primary endpoint you shared with FDA beforehand, according to clinical.com, it says IOP reduction of more than 20%. Did you meet the endpoint? Did FDA require differentiation from trabeculectomy? I couldn't understand that bit, the press release.

A1-1:

(Naveed)

The very simple answer to your question about meeting 20% reduction from baseline or screening, was met. The way this works is that a substantial number of patients, more than half the patients should meet that criteria. Based on FDA's guidance* we met the criteria. Approximately 54% of the patients saw a reduction of 20% or more. In the trabeculectomy arm, the number was approximately 70% of the patients. So, there was a difference of about 18%. But, completely expected. No surprise there. But we met the guidance from the agency.

* <https://www.fda.gov/media/115672/download>

Q1-2:

So, comparing the two, comparison is not required. But *MicroShunt*, 54% of the patient met the criteria.

The requirement is more than 50, so you are able to meet that criteria, now you can file?

A1-2:

(Naveed)

You didn't ask me this question but I would recommend reading the most recent guideline. I think it was published just this month or maybe August, the FDA guidance on benefit-risk for devices. I would highly recommend that. You can google it. How does FDA evaluate benefit-risk for a device. It is very different than a drug. I hope that would help you even more in understanding the whole program.

Q2:

I have just one simple question related to the first question. In this trial, *MicroShunt* versus trabeculectomy, non-inferiority was the objective in my understanding. But statistically this was not met. When you look at the result of the trial, FDA may impose some kind of exercise, assignment or some condition, that was our impression. But according to what you said today, value propositions can overcome those issues. That is your idea, am I right?

A2:

(Naveed)

That is absolutely correct. Because at the end of the day, it has to be a benefit and a risk. If my benefit is a little lower, my risk is way lower. That needs to be taken into account for benefit-risk and that's how the device side makes the assessment. And also, I would recommend, if you have time, to read the FDA's guidance. It is in two stages. The main outcome has to be 20% or less from screening or baseline. What you do after that, what comparisons you run after that, depend on your controls. What kind of a control arm are you going to use - is it a placebo, is it a standard of care, whatever it is. So, if it's a placebo, you have to show superiority. If the standard of care, you have to go for non-inferiority. Things like that. They are two stages. But your understanding is correct.

Q3:

Then why, did you choose non-inferiority as a primary endpoint? Why did you plan such a study? With trabeculectomy, in order to show non-inferiority, it became a very large study for that reason. If the objective at first was lower, maybe you could have conducted a very small trial and maybe have approval earlier. And also, when we think about the potential of sales, it is not a comparison against trabeculectomy, but, with other devices that are already penetrated in the market you didn't comment on that today. So, may I have your comment please. And the last question. On page 36, you talked about the variability. "Of course, at first the variability is quite small, however, as time goes by the variability has reversed, it seems". For glaucoma patients suffer from this disease for a long term, if you see it from a longer-term perspective, I feel a bit of a concern against the efficacy of this *MicroShunt*. Maybe it will not stabilize well. So, what do you think about that please?

A3:

(Naveed)

Your first question had to do with, why did you even bother to do a study head to head with trabeculectomy. Well, when we licensed the product, we had the same question. If you recall, the study was already running when we acquired it, and we decided to stick with the plan that was approved and that was running. It would have cost us a lot of time and money to start from scratch. And the calculation was always what I just mentioned, its risk-benefit. We never ever intended to be like 10% or 20% better than trabeculectomy. That would be even a much larger trial to show that. It was unrealistic. So, the best option was to stay the course, finish the study as soon as possible.

The second issue has to do with reimbursement. And because we were going to be positioned as an alternative to the trabeculectomy, the payer as you can imagine would ask, "How do you look versus...", and then I would have no data. Right now, I have excellent data to say if you want to reduce your cost, you need to get rid of the variability and the non-predictability of it, and that's how you are going to reduce your cost. Good for the patient, good for the physician, good for the payer.

The second question you asked was variability. I don't know if you can see this very clearly but there is no data up to month 12 and we have 12...24-month data coming. We will have 24-month data available to us during the review of this product and that would be key to our approval. Please remember this is not an adjunctive mixed device. This is not. So, comparison with other devices that are on the market is probably not the right thing to do. They are positioned way upstream when you don't even have glaucoma. For example, their vision loss is less than half a decibel. Basically, you are not quite blind or nothing. In our case, our mild cases have to be three decibels or higher. That's the difference. So, you can't compare the two. However, our safety and our efficacy in our segment of the patients who are we going to target, is as good. They cannot compete in our space. That's the differentiation and control of our space. For your question about variability, up to 12... this is 12 months... but there is the variability of the trabeculectomy gets better over time. But there is no place, there is no impact on our variability. We are the same approximately as you were here in the beginning all the way to the end. So, if I can get you your IOP down to 14, I am reasonably sure I can keep you at 14, at least for 12 months. When we have 24-month data, that will be very important to answer your question. But I don't want to make any claims or anything, but our data suggests a very stable IOP and we will be showing that data, all of the data that we have, even the topline data, will be at a scientific meeting, hopefully at the American Academy or other meetings. So, that will be available to you soon.

We have more than this data that we showed you in the press release of course, because otherwise I run into the trouble, because I cannot publish that data because I've shown it to you. So I don't want to do that. I need the publication. I hope that answers your question.

Q4:

Thank you for the explanation. 24 months data, its soon to come and then that will be the key to discussion for the review and for approval. What kind of data do you expect would help you as positive input for approval or what kind of down side risk are there?

A4:

(Naveed)

I don't know what the outcome would be but, what we have to show is stability. We don't want to show instability of our response. And at least for whatever it means if you can trust me or Raymund, we think, that should not be a problem. We will be very, very stable. We have ex-U.S. data, long term data, that clearly shows that we can keep the IOP stable for many, many years, not just one, two, or three, or four, but five. So, based on that small data set, based on what we have right now, over time, it will be quite stable. So, I don't expect, frankly, any major ups and downs or anything like that. The critical portion, because it's a surgery, I hope you can understand that all of the... what needs to happen, or what happens is early, not late. So I feel comfortable that we are going to be okay.

Q5-1:

Patients who had gone through cataract surgery, can they use *MicroShunt*? The other question is about trabeculectomy. Some physicians may choose electric scalpel while other use laser. They will be doing incision. Does that make likelihood of IOP lowering higher? Which is better, laser or electric scalpel?

A5-1:

(Naveed)

Second question is tough. The first question was about people who have been getting cataract surgery or other procedures, what happens to them? They can certainly use the *MicroShunt*, when and if needed.

(Raymund)

Yes. In this current study, the PMA study with the FDA, it wasn't combined with cataract surgery. However, we have a history of the device being implanted together with cataract surgery in our site in Europe.

(Naveed)

Yes. I guess the answer is not only these patients can receive it, they can also receive it in combination or an adjunctive to cataract surgery, if that is what the physician wants.

Q5-2:

In the real world, some patients have gone through the IOL surgery first, and then five years, six years later they are diagnosed glaucoma. Does your product provide solutions to patients like that?

A5-2:

(Raymund)

Yes. Because the standard of care for cataract surgery now is clear cornea. Meaning, unlike in the old days we used to cut the incision through the tissues that were seen being dissected here. So, to answer your question, yes. Even if a patient had a cataract surgery previously, we can implant *MicroShunt*, a few years after it.

(Naveed)

Second question is tough question. Because it does depend on the patient's condition, it does depend on where you practice, it does depend on what kind of glaucoma you have, and such. I think we can leave it to the physician to make the decision. However, there is no reason why a patient who is going to go for a laser trabeculoplasty cannot receive a *MicroShunt*. I would just say I'd leave it at that, but the rest will depend whether the physician wants to use it, whether the patient wants to use it. But technically speaking, the efficacy of the product and the safety of the product would be reasonable choice for the patient. It's just they have to make the choice. I can't recommend it as a company.

Q5-3:

In Europe, how many surgeons have already received ten procedures or more?

A5-3:

(Naveed)

Our requirement, is that you must be trained before we can ship the device for commercial purposes. And that training is ten sessions under supervision. Of course, the surgeon operates, and we coach them, we train them. After the tenth surgery they can do whatever they like. That is also a little important because as a company, we cannot promote or witness, an off-label use of a product. And surgeons by habit do everything off-label. And so, after the first ten, we don't want our people to participate in off-label use of the product. Then they can do whatever they like. But we know that we have trained them, they are capable, they can get the outcome that they need.

End