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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Rec'd AUG 13 1999

OPHTHALMIC DRUGS SUB-COMMITTEE

OF THE

DERMATOLOGICAL AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

Wednesday, July 21, 1999

8:30 a.m.

Gaithersburg Hilton
Salons A and B
620 Perry Parkway
Gaithersburg, Maryland

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Jayne Peterson, Executive Secretary

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George A. Cioffi, M.D.
Leon W. Herndon, Jr., M.D.
Jacquelyn L. Goldberg, J.D., Consumer Representative

FDA CONSULTANTS (VOTING
Philip T. Lavin, Ph.D.
Alice Y. Matoba, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. FONG: Good morning. Welcome to the Ophthalmic Drug Advisory Subcommittee meeting. I am Dr. Donald Fong, and I am the chair of the subcommittee. I am with Kaiser Permanente and UCLA School of Medicine.

Before we begin, I would like everyone at the table to introduce themselves, starting with Johanna.

DR. SEDDON: Hello. I am Johanna Seddon, Associate Professor of Ophthalmology in Harvard Medical School Massachusetts Eye and Ear Infirmary, and director of the epidemiology unit at the Massachusetts Eye and Ear Infirmary, in Boston.

MS. PETERSON: I am Jane Peterson. I am acting as the executive secretary for the subcommittee meeting today.

DR. CIOFFI: I am Jack Cioffi. I am a glaucoma specialist and director of the glaucoma service at Devers Eye Institute in Portland, Oregon.

DR. HERNDON: I am Leon Herndon. Also, I am a glaucoma specialist, Assistant Professor at Duke University.

DR. LAVIN: I am Philip Lavin. I am a biostatistician with Harvard Medical School and also Boston Biostatistics.

DR. MATOBA: I am Alice Matoba. I am a cornea external disease specialist, and I am Associate Professor of

Ophthalmology at Baylor College of Medicine.

DR. DE LAP: I am Bob De Lap. I am Director of the Office of Drug Evaluation V at the FDA.

DR. CHAMBERS: I am Wiley Chambers. I am the Deputy Director for the Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products.

DR. BOYD: I am William Boyd. I am a medical officer in the same division.

DR. LU: Laura Lu, statistician, FDA.

DR. FONG: Now Jane Peterson will read the conflict of interest statement.

Conflict of Interest Statement

MS. PETERSON: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions. In accordance with 18 U.S.C. 208(b), full waivers have been granted to Drs. Philip Lavin and George Cioffi.

Copies of these waiver statements may be obtained

by submitting a written request to FDA's Freedom of Information Office, located in Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. George Cioffi has interests which do not constitute financial interests within the meaning of 18 U.S.C. 208(a), but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in his participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. FONG: Now Dr. Chambers will give us some introductory remarks.

Introductory Remarks

DR. CHAMBERS: Thank you. I would like to welcome

everybody to the Ophthalmic Drugs Subcommittee meeting. As you know, it is part of the Dermatological and Ophthalmic Drugs Advisory Committee.

Today we are going to discuss one particular drug product, and that is cyclosporine ophthalmic emulsion, and we will be discussing it for the treatment of keratoconjunctivitis sicca. The committee has all received background packages. Included in the background packages were both a medical officer's review and a statistical review. The statistical review was in final form. The medical office review was a draft at the point that the information had been reviewed at this point.

As everyone will notice, the conclusion at the end of that medical officer's review was that we will have discussion about the application. No final decisions, no real preliminary decisions on this application have been made.

There are also other parts to the application that include chemistry, manufacturing, preclinical, non-clinical animal studies that were not included as part of the package and that will be reviewed separately by the agency. You will also notice that the statistical review, which was in final form, recommended the application not be approved. The application, from a statistical perspective, did not show replication of the same parameters in multiple

different studies.

If the agency had come with the conclusion that the application is definitely not going to be approved we would not be having this meeting. That information was given to you because from a straight statistical perspective there is not a question that the application would not be approved. However, we are not here to discuss whether the application would be approved on a straight statistical merit. There are individual parameters which may be considered sufficient to show the safety and efficacy of the product even though they are not exactly replicating one another in each of the different trials. That is okay to still approve an application.

What we are interested in are particular comments by members of the committee on whether the parameters that have been studied are sufficient to ultimately show efficacy of the product even though they are not completely replicated with one another.

So I want to emphasize that just because the statistical review said it is not approvable, that does not mean this application is not approvable. It is one component, but we are interested in clinical comments about whether these parameters can be considered substantial evidence to show the safety and efficacy of the product.

There will be other discussions. There may be

statistical discussions; there may be other clinical discussions. That is fine. All that is fair game. We are interested in what your comments are.

I would also emphasize that there may be chemistry manufacturing issues that we will not discuss. So, even if the committee recommends approval we will not walk away today with the application either being approved or not approved. The agency will continue to work with the company to deal with any remaining issues, or any issues that the committee raises today.

With that, I want to thank you again for coming. We look forward to your comments as we go along. If there are any questions at any point, please feel free to raise them as we go along. Thank you.

DR. FONG: Jane will read a statement from the Sjogren's Syndrome Foundation.

Open Public Hearing

MS. PETERSON: Actually, now we are going to open the open public hearing session of the subcommittee meeting, and I will start out with a statement that we received, as Dr Fong said, from the Sjogren's Syndrome Foundation. After I complete reading the statement Dr. Fong will then ask for any other statements or anyone else. We have not actually received any notice that anyone else would like to speak at the meeting.

The Sjogren's Syndrome Foundation is the voice for more than four million Americans with Sjogren's syndrome. The Foundation is the clearinghouse for medical information and provides patients and their families practical information and coping strategies to manage the effects of this chronic multifaceted disease. As the national advocate for those with Sjogren's syndrome, we present this testimony as you review the new drug application, NDA 21-023, cyclosporine ophthalmic emulsion, 0.05 percent, for the treatment of moderate to severe keratoconjunctivitis sicca.

Sjogren's syndrome is the chronic autoimmune disorder that affects the moisture-producing glands of the body. The hallmark symptoms are dry eyes and dry mouth, however other major organ systems can be involved, including the kidneys, lungs, blood vessels, pancreas, liver and brain. Without proper treatment, serious complications, including vision impairment or loss may occur. One of the standards in diagnostic criteria for Sjogren's syndrome is the presence of keratoconjunctivitis sicca or dry eye syndrome.

Sjogren's syndrome affects an estimated four million Americans; 90 percent of them are women and the majority go undiagnosed. While Sjogren's, is most instances, is not life-threatening, it most certainly is life-altering and dramatically impacts on the quality of

life of those who have it. A recent quality of life survey conducted by the SSF in November, 1998 with our members -- 3400 returned responses -- indicates that 90 percent listed dry eyes as their most troubling symptom; 85 percent use artificial tears; 14 percent also suffer with blepharitis; 64 percent had been to an ophthalmologist within the past year for an eye problem; and 21 percent had been diagnosed with Sjogren's syndrome by their ophthalmologist. Although ocular problems represent a significant part of living with Sjogren's syndrome, few treatment modalities exist.

For those with Sjogren's syndrome, living with dry eyes ranges from inconvenient to excruciating and incapacitating. Imagine how it feels to wake in the morning, unable to open your eyes -- dryness so severe that the lid has attached itself to the eyeball. How it must feel to stumble to the bathroom to get a warm compress to place on your eyes to soothe the pain and provide enough moisture to open your eyes. Imagine having to put artificial tears in your eyes every 15 or 20 minutes all day long to alleviate the gritty, sandy sensation and pain in your eyes. Imagine wearing special wraparound sunglasses to avoid air currents that rob your eyes of moisture. And then at bedtime having to apply an ointment or place a shield or patch on your eyes to try to keep in some moisture so you can try to sleep comfortably. This is a typical day in the

life of someone with Sjogren's syndrome. And every day, quality of life is compromised.

Unfortunately, for the most part, the only relief for the dry eye complaints associated with Sjogren's syndrome is the instillation of over-the-counter artificial tear preparations. All too often, these products offer only temporary relief, and frequent use is required. The financial impact for the Sjogren's syndrome patient is staggering, with no reimbursement from insurance carriers, yet there is no recourse. And, artificial tears are only a palliative measure.

Drugs designed to treat the underlying causes of dry eye syndrome would be of significant benefit to Sjogren's syndrome patients, and would be added to the very limited list of drug treatments currently available for Sjogren's syndrome.

As you review the scientific data for cyclosporine ophthalmic emulsion, 0.05 percent, for efficacy and safety, please bear in mind the millions of Americans with Sjogren's syndrome who desperately seek relief from their dry eye symptoms, and hope to regain a quality of life they thought was forever lost to them.

There is one other thing I would like to note for the record, that I did not get any information regarding any financial interests from the Foundation in anything that is

going to be discussed at this meeting today. So, I did want to add that to the record.

DR. FONG: Is there anyone else who would like to make a statement? If so, please come to the microphone, introduce yourself, the organization you represent, identify any financial interests you have in the matter of which you speak. If none, please state so.

[No response]

There does not appear to be anyone making a statement. The next item is Allergan. Allergan will be making a presentation.

Allergan Presentation

Introduction

DR. GIBSON: Good morning. My name is John Gibson, and I am Senior Vice President for Pharmaceutical Development at Allergan.

First of all, I would like to thank the panel members and the FDA for this opportunity to present and to discuss our data.

We are here today to propose that Restasis be approved for the treatment of keratoconjunctivitis sicca. Restasis is cyclosporine ophthalmic emulsion 0.05 percent.

Cyclosporine is an important agent with substantial indications. In 1983, it was approved as a systemic agent for the prevention of solid organ graft

rejection. In 1997, also for systemic administration, it was approved for rheumatoid arthritis and severe psoriasis. In 1995, this time as a topical agent, it was approved for keratoconjunctivitis sicca in dogs. Earlier this year, the NDA for Restasis was submitted to the FDA and was granted a priority review.

Keratoconjunctivitis sicca is otherwise known as KCS or dry eye. KCS is a chronic, debilitating condition, and is a rational target for cyclosporine therapy. Evidence for this will be presented early in the agenda. Restasis itself is the only purpose-designed topical drug therapy for KCS.

In developing this agent, Allergan had to break significant new ground. New clinical research approaches and new clinical research tools had to be devised and developed. This was not a routine matter; this was challenging. But from this effort has come the largest database available today in the area of the treatment of keratoconjunctivitis sicca with drug therapy.

In the presentations which will follow, evidence will be provided showing that Restasis is effective, is safe for its intended use, is acceptable to patients from a tolerability point of view and, indeed, has a favorable risk to benefit ratio. It will also be clear that Restasis provides rational pharmacologically-based therapy where none

currently exists.

Dr. Stephen Pflugfelder will lead off the agenda. Dr. Pflugfelder is an internationally recognized expert in the field of ocular surface disease and of dry eye. He will present the medical review and discuss the impact of KCS on the patient.

Dr. Michael Stern will link the pathophysiology of KCS with the pharmacology of cyclosporine to provide a sound scientific rationale for the use of this agent in KCS.

Dr. Brenda Reis will present the evidence for clinical efficacy. Drs. Diana Tang-Liu and Reis will present the evidence for safety.

Dr. Peter Donshik, who is an expert ophthalmologist and a clinical investigator for Restasis, will present a clinician's viewpoint of the risks and benefits.

I will then return for some conclusions. Later in the day, Dr. Brenda Reis will facilitate our responses during the Q&A. Finally, this is a list, which is available in your package, of non-Allergan expert respondents who may be called upon during Q&A to answer questions.

Thank you for your attention. I will now call Dr. Stephen Pflugfelder to the podium. Thank you.

Medical Review

DR. PFLUGFELDER: Thank you, Dr. Gibson, and good

morning to the members of the panel. My name is Stephen Pflugfelder. I am a corneal external disease specialist at the Bascom Palmer Eye Institute of the University of Miami School of Medicine.

I have a long-standing clinical and research interest in dry eye and ocular surface disease, particularly the role of inflammation and causation of keratoconjunctivitis sicca. Many of the studies that I have participated in over the past 15 years have been funded by the National Eye Institute.

Today I would like to show you why dry eye is a common and a serious disease, and to review the diagnosis and clinical features of dry eye; the evolution of knowledge about dry eye and its treatment; and, finally, to show you that there is an unmet need for safe therapy for dry eye.

Dry eye is a common disease. It affects of millions of people worldwide, including 11 percent of the population between the ages of 30 and 60, with the prevalence increasing to about 15 percent of patients over the age of 65.

Dry eye is a costly disease and 15 percent of patients presenting to eye doctors complain of eye irritation, the second most common complaint to decreased or blurred vision. In 1998, approximately 20 million units of artificial tears were purchased in the United States, and it

has been estimated that artificial tears are routinely used by almost 11 percent of the population over the age of 65.

Based on this prevalence and its severity, dry eye was named one of the top funding priorities for the National Eye Institute over the next five years.

Many patients with dry eye and keratoconjunctivitis sicca often have to resort to extreme measures, such as the use of these moisture chamber goggles to control their symptoms.

In the worst case, dry eye can cause functional and occupational disability, such as this 30-year old patient of mine who has Sjogren's syndrome and such disabling keratoconjunctivitis sicca that she can no longer work and can barely take care of her family.

Dry eye can also lead to serious corneal disease, termed keratoconjunctivitis sicca, which results in an irregular and poorly lubricated corneal surface, as shown here, and in altered corneal barrier function.

These pathologic changes markedly increase the risk for developing bacterial keratitis, as well as sterile corneal ulceration that can go on to perforation of the cornea, decreased and sometimes loss of vision.

Dry eye is also a major risk factor for corneal transplant failure. In fact, we teach all of our residents and fellows that they need to identify keratoconjunctivitis

sicca before performing corneal transplantation in order to avoid poor healing, such as this patient with a chronic epithelial defect after a corneal transplant surgery.

About a decade ago a group of clinicians, researchers and members of industry met at the National Institute of Health campus to define dry eye as a disorder of the tear film due to tear deficiency or excessive evaporation which causes damage to the interpalpebral ocular surface, and is associated with symptoms of discomfort.

But clinicians like myself recognize that there are many facets of dry eye and keratoconjunctivitis sicca. It is more than just ocular irritation. Patients frequently present as unexplained corneal epithelial disease, as a factor complicating corneal surgery, such as corneal transplantation, and it is a major cause of decreased and blurred vision symptoms.

Dry eye is currently diagnosed by traditional tests that evaluate aqueous tear production, such as the Schirmer test, or evaluate the ocular surface disease either by clinical examination, usually with a slit lamp, or with use of special diagnostic dyes.

The Schirmer test is performed by placing a thin strip of filter paper into the tear film and then measuring the amount of strip wetting over a five-minute period. This can be performed without anesthesia, which has been reported

to measure reflex tear secretion, or following installation of topical anesthetics which can measure basal tear secretion. There really is no consensus among dry eye specialists as to which method is best.

Diagnostic dyes are used to assess severity of keratoconjunctivitis sicca and most experts agree that fluorescein is the best indicator for evaluating corneal disease, while either rose bengal or lissamine green are the best for evaluating conjunctival disease in KCS.

Now, at the time that the clinical trial that you are reviewing was initiated there was no commercially available rose bengal solution, and so Allergan resorted to using lissamine green which, most dry eye specialists agree, requires a longer learning curve in order to interpret the results.

As you can see here in this graph showing the correlation between aqueous tear production measured by the Schirmer test and the severity of keratoconjunctivitis sicca measured by rose bengal staining, the decreased aqueous tear production, shown here with the Schirmer test less than 10 mammography, is only part of the reason why keratoconjunctivitis sicca develops. We have identified that loss of the ability to reflex tear and response to sensory stimulation is another risk factor, and we are publishing a paper next month that shows that elevated

levels of inflammatory cytokines in the ocular surface is also strongly correlated with the severity of keratoconjunctivitis sicca.

Because of our evolving knowledge of how keratoconjunctivitis sicca develops, is probably the reason why Dr. Oliver Schein reported, just two years ago, in the discussion of one of his papers that the variable clinical presentation and poor correlation between diagnostic tests and irritation symptoms make dry eye a difficult disease to study. Now, given these constraints, I feel that the clinical trial which you are reviewing today really represents a major breakthrough in this area.

There has been a tremendous increase in our knowledge regarding the evolution of keratoconjunctivitis sicca in the last century. Between the decades of 1900 and 1970 we learned from Dr. Heinrich Sjogren that lacrimal gland inflammation leads to decrease aqueous tear production, with resulting ocular surface disease called keratoconjunctivitis sicca.

Then in the two decades between 1970 and 1990, we also learned that non-Sjogren's syndrome aqueous tear deficiency can be associated with lacrimal gland inflammation, albeit less in Sjogren's syndrome and, again, this leads to decreased aqueous tear production. We also learned that as tear production from the lacrimal gland

decreases there are compositional changes in the aqueous tear fluid, with decreased concentrations of protective factors for the ocular surface, such as lactoferrin or epidermal growth factor, and that these also contribute to the development of keratoconjunctivitis sicca.

Then, with advances in cellular and molecular techniques, over the past decade we have learned that as the eye becomes dry a chronic ocular surface inflammation develops, and investigators have measured increased levels of inflammatory cytokines, increased levels of immune adhesion molecules, increased concentrations of proteolytic enzymes which can digest the ocular surface tissue, and increase in infiltration of white blood cells onto the ocular surface in patients with keratoconjunctivitis sicca, and that these changes also seem to contribute significantly to development of keratoconjunctivitis sicca.

Unfortunately, our therapy has not kept up with knowledge about the pathogenesis of the disease. Artificial tear solutions, consisting of sodium chloride and boric acid, were first described in the early 1900s. And, perhaps the greatest advance in the treatment of dry eye to this day represents the introduction of unit dose non-preserved artificial tears in the mid-1980s.

Punctal occlusion to conserve aqueous fluid on the ocular surface was first described in 1936, and in the mid-

1970s punctal plugs were introduced which were reversible.

Then, over the past decade, because of increasing knowledge regarding the inflammatory etiology of dry eye, there have been reports of using anti-inflammatory therapies such as cyclosporine A or corticosteroids, to treat keratoconjunctivitis sicca. But you must remember that as of today there is no approved drug therapy for dry eye in the United States.

Well, artificial tears are the therapies that ophthalmologists currently have in their armamentarium to treat dry eye. They produce a transient improvement in irritation symptoms and mild improvement in ocular surface dye staining, but have not been shown to alter the underlying pathology called squamous metaplasia in keratoconjunctivitis sicca. As you already heard, patients with severe keratoconjunctivitis sicca may have to instill artificial tears up to every ten minutes.

About two months ago we reported in an article from our Institute, showing that perhaps a major reason why patients use artificial tears is to improve the smoothness of their cornea and the quality of their visual function, as can be seen here in this patient with severe corneal fluorescein staining, which has a markedly irregular cornea and a visual acuity of 20/60. Thirty seconds after installation of one drop of artificial tears there is marked

smoothing of the corneal surface and improvement in visual function.

The problem with artificial tears though is that this therapeutic effect is very short-lived, lasting maybe 10-20 minutes. What ophthalmologists really need are effective therapies that will heal and smooth the corneal surface and improve blurred vision and visual function. As you will hear a little bit later this morning in a presentation by Dr. Reis, cyclosporine demonstrates this therapeutic effect.

Well, you are here today to consider approval of anti-inflammatory therapy for treatment of keratoconjunctivitis sicca. Anti-inflammatory therapy makes sense based on the inflammatory etiology of the condition. It addresses the underlying mechanism of the disease, and these therapies have the potential to heal rather than just lubricate the cornea. And, the targeted therapy has a longer lasting effect than artificial tears, allowing a more convenient dosing schedule for patients.

Because of lack of other therapeutic options, I have resorted to use of topical corticosteroids to treat my patients with severe and debilitating keratoconjunctivitis sicca. As you can see here, these agents do result in improvement of keratoconjunctivitis sicca, shown here before topical steroids and after the use of topical steroids.

But as everyone recognizes, dry eye is a chronic disease that requires chronic therapy, and the toxicity of corticosteroids limits their potential for long-term use, including the risk of ocular hypertension and glaucoma, the development of posterior subcapsular cataracts and infection.

The principle that anti-inflammatory therapy can heal keratoconjunctivitis sicca indicates the real need for non-toxic therapies that can be used on a long-term basis.

Well, cyclosporine is an immunomodulatory agent that prevents T-cell activation and inflammatory cytokine production, the molecules that really modulate the inflammatory response on the ocular surface. Certain of its anti-inflammatory mechanisms, such as decrease in inflammatory cytokines, are shared with corticosteroids, and clinical studies indicate that cyclosporine is effective for treating keratoconjunctivitis sicca and its complications.

In this two-month trial, reported from Turkey, the investigators reported increase in tear breakup time and decrease in rose bengal staining on the ocular surface with cyclosporine.

In another six-week randomized, double-masked trial Dr. Laibovitz, in Austin, Texas, reported decrease in irritation symptoms and rose bengal staining with the use of topical cyclosporine.

Several years ago, our group in Miami reported that topical cyclosporine was efficacious in treatment of sterile corneal ulcerations, as I already showed you, that occur in patients with severe keratoconjunctivitis sicca.

Well, the efficacy and clinical experience of many corneal specialists has led to the use of pharmacy-formulated cyclosporine to treat keratoconjunctivitis sicca and its complications. I am very fortunate to be practicing in an institution where our pharmacy is willing to provide us with formulated cyclosporine, but I certainly hope that the panel will take the opportunity today to make a well-tolerated and safe formulation of cyclosporine available to ophthalmologists throughout the United States.

I would now like to turn the podium over to Dr. Michael Stern.

Pathophysiology and Pharmacology

DR. STERN: Thank you, Dr. Pflugfelder. I am Michael Stern, and I am here to discuss the pathophysiology of dry eye and the rationale for the use of cyclosporine.

As Dr. Pflugfelder has told you, dry eye is a serious clinical problem, with significant morbidity and long-term chronic suffering. Over the past ten years, in response to this situation, Allergan, scientists from academic institutions and the National Eye Institute have entered into a collaboration in an effort to understand the

pathophysiology of this disease and to determine appropriate therapeutic targets.

The goal of this collaboration was to elucidate the first mechanistic approach for the treatment of KCS. So, the message of my talk is really a simple one -- from a pathophysiologic and pharmacologic perspective topical cyclosporine makes sense in the treatment of KCS.

The agenda of my presentation is as follows: I will discuss the immune based inflammatory basis of dry eye as a rationale for the use of cyclosporine. I will also present a demonstration of some of our data using the spontaneously dry eye dog and data from human biopsies as part of our collaboration with the National Eye Institute.

Two components have been recognized in the initiation of ocular surface inflammation. They are, first, the hormonal link to the initiation of immunoreactivity and, secondly, the environment ocular surface irritation.

To illustrate this, this slide depicts the lacrimal reflex or functional unit. It is composed of the ocular surface, the main and accessory lacrimal glands and the interconnecting enervation. Tear film is engendered when stimulation of the ocular surface generates nerve impulses to the central nervous system, where they are integrated and yield efferent secretomotor impulses to the main and accessory lacrimal glands.

Immune based inflammation within the main and accessory lacrimal glands will interrupt this signaling. It is important to note that in normal individuals circulating hormones maintain the tissues of the ocular surface and lacrimal glands in an immunoquiescent state. So, the initiation of disease requires two components. First, the immunoreactivity -- the first component, is believed to be caused by a compromise of the anti-inflammatory umbrella provided by the presence of these circulating hormones. This occurs naturally at the time of menopause or with various pathologies. This facilitates the second component, and that is the irritated induction of inflammation.

These two components, as they relate to the spectrum of moderate to severe dry eye patients studied in our clinical trials are illustrated in this slide. We have the immunoreactivity and the irritated components. At the top of the circle would be represented primarily the non-Sjogren's KCS patients. These patients have moderate immunoreactivity with a large irritative component. As one moves to the bottom of the circle, we have the more immunoreactive states, such as the systemic autoimmunities or, used as an example here, Sjogren's syndrome. These patients have large amounts of immunoreactivity and require very little in the way of irritation to initiate ocular surface inflammation.

It should be noted that biopsies at baseline of any of the patients within this population would demonstrate inflammation, and the marker is shown here, at the bottom. Additionally, these patients have all presumably failed with the use of artificial tears because of insufficient lubrication. If sufficient lubrication were provided to the mainly irritative patients, significant clinical and symptomatic relief could be seen. However, this type of therapy would not address the underlying progressive nature of the immunoreactive state.

Our work in the dry eye dog, the spontaneously dry eye dog model, has indicated that there is an immune based inflammation of the ocular surface and lacrimal glands. This work has been confirmed in the human beings based on our collaboration with the National Eye Institute, and I will present that data later.

In addition, the dry eye dog is right now the best model of human KCS. We used two groups of dogs. The first group received topical cyclosporine ophthalmic emulsion b.i.d. for 12 weeks. The second group received only the vehicle. Biopsies of the accessory lacrimal glands and the conjunctiva were evaluated for the presence of immune cells, the status of these immune cells and the subpopulations of those, and of the apoptotic status or the status of programmed cell death within these tissues.

On the left you see a pretreated dog with canine KCS. What you can see is corneal translucency and a poor ocular reflex, indicating poor optical qualities of the ocular surface. After 12 weeks of treatment b.i.d. with topical cyclosporine, the same eye shows a lustrous ocular surface with a crisp ocular reflex indicating a clinical return to normalcy.

This clinical response has been confirmed using histology. On the left-hand side we see the conjunctiva and the accessory lacrimal glands in the pretreated animal. It can be noted here, under the epithelium of the conjunctiva, a large lymphocytic infiltration. In the lacrimal gland in the intralobular space, again, we see a large lymphocytic infiltration, a loss of cellular polarity within the secreting acinar cells and stasis material within the acinar lumens indicating a non-functional lacrimal gland.

After 12 weeks of treatment b.i.d., you see that the conjunctiva has returned to a very normal appearance. We see vascular tissue here, within the conjunctiva substantia propria, and some immunovigilant trafficking T-cells, as appears normally with the normal histology of the conjunctiva.

Within the lacrimal gland, no lymphocytic infiltration is seen, except for some trafficking lymphocytes within the intralobular space. One can notice

the open acinar lumen and lacrimal ducts, indicating a normal flowing return to function for this gland.

This is confirmed with the use immuno-histochemistry, the fact that this is an immune response. This is a CD3 antibody which demonstrates the presence of T-cells, the total T-cell population. You can see here in the conjunctiva under the epithelium a large T-cell infiltration. After treatment this T-cell infiltration has now resolved and there is just the presence of the normal trafficking immunovigilant T-cells within the tissue.

It should be noted that the fact that there is this accumulation of T-cells within the tissue demonstrates a deactivation or suppression of the normal apoptosis program, the normal cell death program that is in place to rid the body of extraneous immune cells and other cells that are no longer needed after having served their function.

Apoptosis, as I mentioned, is a normal physiological function. We have evaluated the pathological alterations of apoptosis, such as the suspension of apoptosis in the lymphocytes that I have just demonstrated. We have recently also got some startling data which showed that we have an inflammatory induced apoptosis within the normally stable, terminally differentiated epithelial cells of the lacrimal acinar and the conjunctiva.

These are sections from a dry eye dog, and the

brown cells -- the cells that appear brown are positive for apoptosis in the Tunel method. Now, we have used several methods to evaluate apoptosis in confirmation of this Tunel data. You can see large numbers of conjunctival epithelial cells here undergoing apoptosis. Yet, when you look at the lymphocytic infiltration, this is now negative. These cells are binding to integrins, are activated, secreting pro-inflammatory cytokines and causing the inflammation under the ocular surface. After treatment we see that the lymphocytic infiltrations in both instances here are gone. The T-cells within the substantial propria are now positive for apoptosis. They are undergoing their normal life span, their normal immunovigilance and then undergoing apoptosis, exiting the tissue en route to local lymph nodes, and the epithelium has now returned to a normal, non-apoptotic appearance.

This is confirmed by sections of the lacrimal gland. This is the accessory lacrimal gland of the dog. You can see numbers of apoptotic cells in the lacrimal acinar and the common duct and, yet, again we see lymphocytic infiltration that is negative for apoptosis. After treatment we have a normal lacrimal lobule here and, again, in the intralobular space we see positive lymphocytes that are now exiting the tissue and apoptosing on their way out.

So, our conclusions from the spontaneously dry eye dog is that this is, in fact, an immune based chronic inflammation. Cyclosporine b.i.d. over 12 weeks reduces histological markers of inflammation and restores the ocular surface to a more normal clinical appearance.

The KCS model has been confirmed by studies in the human being. We have had collaboration with the National Eye Institute where we were able to substantiate the presence of activated T-cells and inflammation in KCS patients. We are evaluating 30 patients and we have taken conjunctival biopsies from these individuals.

We have evaluated several markers of inflammation from these biopsies using immunohistochemistry. These markers evaluate immune cell upregulation, immune activation and upregulation of inflammation.

These biopsies are from the normal and from our KCS populations. This, again, is the CD3 antibody used to evaluate total T-cell populations. We have evaluated all the markers. We have histology for those, if required during the Q&A period later.

We can see here that in this normal individual, a 72-year old female, we have approximately 81 cells/mm^2. The mean population, the mean numbers from all of our KCS patients tested is 1307 cells/mm^2, a vast increase in the number of T-cells infiltrating this tissue.

If we look at the data from this study in graphic form, we can see here the difference between the KCS patients here, in blue, versus the normal control here, in pink. What you can see are large increases in the T-cell subpopulations, T-helper and suppressor cells, markers of activation, class 2 antigen HLA-DR and DQ, as well as the marker of inflammation or adhesion molecule, ICAM-1. These are vast increases over the normal population.

If we break this data down to comparison of Sjogren's versus non-Sjogren's individuals what you find is that in the vast majority of the markers we essentially have equivalence. You can see this in CD4, HLA-DR and DQ, the markers of activation, and ICAM-1, with a slight increase over the non-Sjogren's in the CD3 and the CD8 populations. This indicates an equivalence of pathophysiology between these two populations.

So, in conclusion, I have demonstrated the presence of the immune based inflammation in KCS, the presence of these activated T-cells and the induction of pathological apoptosis. In fact, in this disease the critical secreting tissues of these patients are actually dying, and that is quite a startling finding and, in fact, this can be reversed and prevented through the use of this topical cyclosporine.

We have provided a rationale, based on

pathophysiology and pharmacology, for the use of topical cyclosporine in the treatment of dry eye. It prevents T-cell activation and decreases inflammation, reversing abnormal apoptosis.

I would now like to ask Brenda Reis to come to the podium to present our clinical data. Thank you very much.

Program Design and Clinical Efficacy

DR. REIS: Thank you, Michael. Good morning. My name is Brenda Reis, and I am Allergan's representative for clinical research. I am going to share with you this morning Allergan's clinical program for the study of topical ophthalmic cyclosporine emulsion for the treatment of moderate to severe KCS.

Our clinical programs have consisted of 3 clinical trials, study 001, which was our Phase II dose-ranging trial which used a 12-week treatment period, and our 2 Phase III clinical trials, study 002 and study 003, which used a 6-month treatment period. All 3 trials used b.i.d. dosing, and I will be sharing the efficacy and safety data from all 3 studies.

Study 001, our Phase II dose-ranging trial was our first opportunity to evaluate our new emulsion formulation in humans. This was also the first of what we expected to be a series of the most comprehensive clinical trials of dry eye disease to date that have been conducted in a very

systematic way.

The design of our Phase II trial is shown here, and 162 enrolled patients were first put on a run-in period and all standardized to a common artificial tear, after which they were randomized to one of five of the treatment groups, four active cyclosporine treatment groups starting with the lowest concentration of 0.05, 0.1, 0.2 and 0.4 percent cyclosporine, and then also a vehicle control group. Following 12 weeks of treatment the patients were removed from treatment and put back on artificial tears only and observed for an additional 4-week post-treatment period.

Some of the important ocular inclusion criteria are summarized on this slide. Most importantly, we were looking for patients with aqueous deficiency, as demonstrated by Schirmer, with the presence of some ocular pathology, as indicated by corneal staining, and the patients needed to be symptomatic and at least have one symptom of discomfort associated with the disease. We were also enrolling patients who still had KCS despite conventional management with artificial tears.

The most important exclusion criteria are shown at the top. Patients who were considered to have very significant aqueous deficiency that we might even term end-stage were excluded, as demonstrated by a very low Schirmer score using the nasal stimulator Schirmer test.

Efficacy was assessed over two primary areas: objective endpoints and subjective endpoints, important objective endpoints being ocular surface staining, and we also included some experimental measures. We wanted to see if they could be developed and ultimately utilized effectively in our larger Phase III multicenter trials in the future. These included brush cytology for the harvesting of superficial epithelial cells and looking at various cellular markers, as well as the collection of tears to look at the various proteins that are secreted in tears.

The various subjective parameters are indicated here, including symptoms and an experimental questionnaire that Allergan developed, called the Ocular Surface Disease Index. This is a 12-item questionnaire that looks not only at symptoms but at vision-related function and the patient's sensitivity to environmental conditions and insults.

Adverse events were assessed in the typical way, with some important additions being included in Phase II such as an evaluation of formulation tolerability, the inclusion of standard chemistry and hematology, and the collection of conjunctival swabs to look for any changes in ocular microflora with treatment.

Disposition of patients from our Phase II trial shows that of the 162 enrolled 150 completed the 12-week treatment period, with a discontinuation rate that was quite

small, of only 7.4 percent. The reasons for discontinuation are shown below.

The demographic profile of the patients that we enrolled reflects the usual KCS patient being a postmenopausal female.

The data that I will review with you for Phase II will cover two populations, the intent-to-treat population or all 162 patients who were enrolled and then a subset of these patients that we refer to as the Phase III target population.

You have already heard from Dr. Pflugfelder's presentation that dry eye is a disease that is very heterogenous. In order to create a more homogeneous population and reduce some of the variability we went back to the data set and selected patients who had more severe staining at baseline, those who had a 1.5 instead of the 1 that we had enrolled, and a more severe Schirmer, a Schirmer of 5 instead of the 7 that had been required upon enrollment.

I am going to show you two graphs of the actual data, one for the objective sign of conjunctival staining, shown here. Let me take a moment to orient you to this slide. One parameter will be shown porcine endogenous retrovirus slide, in this case conjunctival staining. The grade for the staining is shown along the Y axis. In the

grey shaded area at the top you are looking at the raw conjunctival staining scores for the patients in the various treatment groups at baseline. In the black area you are looking at the movement or the decrease in staining at week 12 of treatment. The treatment groups are color coded and start, from your left, with the vehicle, in blue, and then followed by the active concentrations, starting in ascending order, from the 0.5 percent to the 0.1, 0.2, and 0.4. Off to your left, you are looking at the staining scores for the conjunctiva at the week 16 time point or following 4 weeks of being with artificial tears only and having stopped their treatment.

The important thing to note on this slide is that you have improvement for all of the treatment groups from baseline. You also do not have any incremental benefit beyond the 0.1 percent cyclosporine, with no additional benefit at 0.2 or at 0.4, and you are starting to see perhaps some slight migration of the staining back towards the baseline levels.

This is a graph of the subjective endpoint, the Ocular Surface Disease Index, which looked at the vision-related function and symptomatic component. The format is similar, with the score, shown here, going from 0-1. Again, you are seeing some improvement for the vehicle group but notable improvement with the cyclosporine groups,

particularly with the lower concentrations. This was an important finding and theme that we noticed in our Phase II study, that certainly on the subjective components the 0.5 appeared to do better, while for the objective components the 0.1 percent appeared to do better.

You can see that there is a very distinct difference between the vehicle response in these patients and active treatment, with some continuing symptomatic benefit in the post-treatment period.

To then summarize the efficacy results from our Phase II trial, statistical significance is shown in white. Variables that approached statistical significance are shown in yellow. For the Phase III target subpopulation statistical significance was approached for the conjunctival rose bengal staining and was achieved for the Ocular Surface Disease Index and for the symptom of sandy/gritty.

In the intent-to-treat population statistical significance was approached for the symptom of burning and stinging and for a reduction in the patient's need for artificial tear use.

There were no studies prior to this Phase II trial to provide a benchmark or guidance to us as to what we might expect for statistical significance. So our focus was to look for trends and evaluate clinical and statistical significant changes with cyclosporine treatment as a guide

in moving forward to Phase III. So, the clinical trends for the various signs and symptoms were very important.

In looking at the safety results from our Phase II study, it is important to note that the highest incidence of adverse events, regardless of how they are categorized, occurred in the vehicle group and then followed by the 0.4 percent cyclosporine group. In other words, cyclosporine itself was not contributing substantially to the adverse event profile, with perhaps the exception of some of the ocular findings which are shown here.

We do have an occurrence at the 0.4 percent for burning eye and SPK. It did also appear, however, in the vehicle. Additionally, for the 0.4 percent we have reports of photophobia.

So, the important conclusions that we drew from Phase II were that we had demonstrated an improvement in the signs and symptoms of the disease with cyclosporine treatment, and we had also noted that the new formulation was well tolerated in all of the groups.

Very importantly, and not surprising given some previous work that had been done by Sandoz, we had observed a threshold effect at the two lower concentrations, 0.05 and 0.1, with no additional benefit at the higher concentrations. We also learned that we had formulated a very good vehicle with important palliative effects because

the vehicle group also had important clinical improvement in signs and symptoms. We therefore chose the two lower concentrations, 0.05 and 0.1, to carry forward into our Phase III program.

The Phase II trials represent our large multicenter studies designed to confirm the safety and efficacy of cyclosporine ophthalmic emulsion. The 877 patients that were enrolled in both protocols were randomly allocated, again, after a two-week run-in period being standardized to artificial tears, to one of the two active cyclosporine treatment groups or to the vehicle group. Patients who had been randomly assigned to each of the active treatment groups have continued on this treatment for an entire 12-month period, while the patients who were randomized to vehicle at the end of the 6-month period were switched to the 0.1 percent concentration for the purpose of gathering additional safety data at the higher concentration.

The data that were submitted to the agency in support of our application, and which will be reviewed with you today, are the safety and efficacy for the 6-month treatment period.

Changes in the inclusion and exclusion criteria from the Phase II program are shown by the white and the strikeouts that you will see in the upcoming slides. We

made the Schirmer score more severe, from a 7 to a 5. We also required slightly more corneal staining, and we also moved to a different staining scale, using a system that had been validated by Prof. Tony Braun at Oxford that provided a pictorial representation to help standardize the investigator's ability to assess the staining.

Patients were still required to be symptomatic, and we required a minimum score on the Ocular Surface Disease index, as well as a minimal score on a facial expression subjective scale.

The exclusion criteria were the same as in Phase II, with the exception that patients who had dermatologic rosacea that involved the lids were excluded.

Efficacy was assessed over the two primary categories of objective and subjective endpoints. As had been mentioned previously by Dr. Pflugfelder, when we launched our Phase III programs a commercial solution of rose bengal stain was no longer available, and we had also learned in Phase II that this was a very uncomfortable stain and that patients would not tolerate it over repeated use in a long Phase III program. We, therefore, switched to lissamine green to evaluate the conjunctiva.

We added the Schirmer with anesthesia in addition to our Schirmer without, and we included a number of specialized laboratory tests which I will speak more to

later. A number of the experimental methods that had been put in Phase II were excluded because we had determined that there were too many technical complexities that made these tests impractical for use in a large multicenter setting. We also, in addition to the fluorescein and the lissamine, felt it important to look at the total staining or the sum of the entire ocular surface staining.

The subjective endpoints were exactly as we had included and assessed in our Phase II program. Because we had established the tolerability of the formulation in Phase II and had found no untoward or drug-related effects in the chemistry or hematology, nor did we find any remarkable changes in the conjunctival microflora in Phase II, these three measures were not carried forward into the Phase III program.

Study 002 was completed by 14 study centers who screened 641 patients to enroll 405, while study 003 was completed by almost twice as many centers, 24, who screened over 1400 patients in order to enroll 472.

The disposition of our patients indicates that at the end of the 6-month masked-treatment phase 76.5 percent, or 671 of the patients, had completed with a discontinuation rate of approximately 24 percent. This is higher than the discontinuation rate that we saw in Phase II but not unexpected since these patients were signing up for a much

longer clinical trial in Phase III, and this is not an unexpected attrition rate given the length of the program.

The reasons for discontinuation are shown below, with some of the more notable ones being personal reasons, for example adverse events at 7 percent, which was quite low and we will talk more about that in a moment.

The demographics of our Phase III patients enrolled, once again, reflect the typical dry eye patient, that being a postmenopausal female.

The key elements of our statistical methods applied to the Phase III data set included that the intent-to-treat population would be evaluated. Last observation carried forward was used to impute missing values. Our primary time point was month 6. We analyzed change from baseline for all of the measurements. Analysis included a 2-way ANOVA and CMH tests which were stratified by investigator. Multiplicity was accounted for, and the overall experiment-wise error rate was equivalent to 0.05.

The presentation of the efficacy data for Phase III is going to start with a summary of the statistical significance for the objective measures. Once again, those parameters that achieved statistical significance are shown in white and those that approached statistical significance are shown in yellow.

For study 002, statistical significance was

demonstrated for corneal staining, for our primary objective endpoint, as stated originally in the protocol, the sum of staining, and we approached statistical significance for the categorized Schirmer with anesthesia. In study 003, highly statistically significant difference was achieved for the categorized Schirmer with anesthesia. So statistical significance was demonstrated in at least one objective sign in each of the two studies.

This slide summarizes the subjective endpoints. For study 002 statistical significance was approached for our original prospective subjective endpoint, the Ocular Surface Disease Index, and was achieved for a number of the other subjective measures. In study 002 statistical significance was approached for the patients' reduced need to use artificial tears.

So, with respect to the subjective endpoints statistical significance was achieved in study 002 over a number of measures, and in study 003 it was approached for the artificial tear use reduction.

I am now going to take you through a series of graphs of the data. This is a graph of baseline and month 6 corneal staining scores shown in the format comparable to that shown for Phase II. Once again, you are looking at the raw baseline scores for these patients, the means porcine endogenous retrovirus group in the grey area, and in the

black area you are looking at the change that occurred for these scores following 6 months of treatment. Once again, we start with the vehicle on your left, shown in blue, and then followed by the active concentrations in ascending order, the 0.05 percent in yellow and the 0.1 in orange. Study 002 is shown on your left and study 003 is shown on your right.

You can see an improvement at the 6-month time point for all of the treatment groups, with more improvement for the active cyclosporine-treated groups, with statistical significance for the 0.05 percent being achieved at month 6 relative to vehicle. The asterisks reflect the pair-wise comparisons. Many of the changes from baseline for all of the groups were statistically significant within each group, but the asterisks are shown for only the pair-wise comparison to vehicle.

Now, one of the things that I want to point out on this slide is that you will see that the two active concentrations performed very similarly in the two studies. The difference occurs in the vehicle response. You have a much greater vehicle response in study 003. That is particularly evident on this slide which has now taken the two data sets that you saw previously and superimposed them. So, you can clearly see the similar response of the two active groups but the differing vehicle response.

[Slide]

Now for the sum of staining, the combined conjunctival and corneal staining, once again you are looking at improvement in all of the treatment groups in both studies, with statistical significance once again achieved in study 002 and, again, you will note the greater vehicle response in study 003.

For the categorized Schirmer with anesthesia an upward trend indicates improvement so baseline is now at the bottom instead of at the top, as you saw previously. What you are noting is an increase in Schirmer following 6 months of treatment for both of the active concentration groups relative to the vehicle. This also occurs in study 003, st statistical significance achieved in both of the active concentration groups relative to the vehicle.

For the Ocular Surface Disease Index, again, you see improvement in all of the treatment groups -- no statistical differences but again a strong vehicle response in study 003.

For the facial expression scale, again improvement; statistical significance achieved for the 0.1 in study 002 and again the rather strong vehicle response in study 003.

For the composite symptoms, which is basically the summation of all of the individual symptoms of discomfort --

for the individual symptom of sensitivity to light, and finally for the individual symptom of itching.

This table of data summarizes the global response to treatment, in other words, the percent of patients at month 6 who fell into the following categories for response to treatment, defined either as their disease being completely cleared, at one end of the spectrum, to their condition having worsened.

What you want to note is that in the active treatment groups in study 002 there are more patients who appear at this upper end of completely cleared or almost cleared than occurs for the vehicle group with statistical significance being achieved at the month 6 time point. In study 003 this was not statistically significant.

At this point, we want to review the clinical significance by looking specifically at the percent improvement by the month 6 time point from the change from baseline for the various parameters. There are a number of important points to be made with this slide.

The first one is that you can clearly see demonstrated the greater vehicle response of the patients in study 003, when you look here, relative to study 002, 18 and 25 percent versus in the mid-30 percent. That also occurs for the sum of the subjective endpoints, as you see here.

The other important point to note is that the

active concentrations performed similarly between the two trials if you look at the response for staining and, likewise, if you look at a number of the subjective measures.

Now, one might think that an 18, or a 20, or a 30 percent improvement in a corneal staining score or a subjective symptom may not be terribly clinically important, but what is critically important to these patients is that it is the sum total of the incremental improvement in all of the signs and symptoms of the disease that overall have resulted in these patients responding to treatment.

We will talk more about the vehicle response later. As Dr. Stern mentioned in his presentation, patients who have more of the irritative component can respond to palliative treatment and, given what was mentioned earlier about our vehicle, herein lies an important reason why we saw a strong vehicle response in study 003.

In 1993 and in 1994 the National Eye Institute, academic researchers in dry eye, representatives from industry working in this area and the FDA participated in a workshop to try to bring some uniformity and understanding to research in the area of dry eye disease. Now that we had a large database, Allergan felt it very important to take this large systematic database and to go back and see if we could confirm some of the important consensus statements

that came out of this working group.

One of the important statements that was made by this group is given here, and it demonstrates or points out that there is no gold standard for the evaluation of dry eye disease either in diagnosing the disease or in assessing treatment response. Additionally, this group made it clear that dry eye is a very multi-factorial disease and that relying solely on improvement in one endpoint may not be the most suitable approach.

We, therefore, took a retrospective look at our data, trying to apply the consensus statements from this working group and to see if, in fact, we could lend now some new learning to this area. We selected four endpoints, two objective and two subjective endpoints that we felt were clinically important in defining the disease, and we used these four components to construct an overall disease severity score.

The clinical rationale for the selection of these endpoints is shown here. We chose the Schirmer with anesthesia because there is less variability in this endpoint than there is in the Schirmer without. We chose blurred vision because it is least affected by changes in corneal sensitivity, which we knows waxes and wanes in change with dry eye disease, and also because of some of the more recent work by Dr. Pflugfelder showing that there might

be an association with blurred vision and the changes that we see in corneal pathology with the disease. We chose artificial tear use because this is a measure of the patient's need to intervene in their disease, and demonstrates their discomfort. Finally, we chose corneal staining because, given the newness of the lissamine green to a number of our investigators, we felt that the corneal fluorescein staining would be more reliable, and also that the corneal pathology is critically important to vision. Our selection of those four endpoints was supported by a statistical factor analysis that we conducted.

We then took the sum of these components and constructed an overall disease severity score for the patients at baseline and at month 6. We defined a responder as a patient who would improve in at least one disease category or more. In other words, they would move from a moderate to a mild.

I am going to take a moment to orient you to what will be a series of three slides coming up. You are looking at the distribution of the patients into the various disease categories, with the key shown at the bottom. The bar on the top shows day zero for the 0.05 percent treated patients in study 002. The bar at the bottom shows month 6.

What you will note is that the proportion of patients that were in the severe disease category moved from

23 percent to 9 percent by 6 months of treatment. On the opposite end of the spectrum, the number of patients in the mild category increased from 3 to 33 percent, and we also picked up some patients in the normal category.

We are now at the vehicle, and you will see that there is no change in the proportion of patients in the severe category that shift to a milder state. At the opposite end, we do pick up a few more mild patients, from 4 to 21 percent, and we do pick up some normals with the vehicle.

Now the data for the 0.05 percent for study 003 -- once again, a shift in the proportion of patients from the severe category from day zero to month 6, going from 31 to 13 percent. This time for the vehicle group you do see some shift for patients out of the severe category, from 17 percent to 9 percent, but we do not pick up any normals at the opposite end while we do pick up a few normals with active treatment.

Now, if we take the sum total of all of those changes for patients over the various disease categories and we look at the percent of patients that would be defined as responders, this graphical representation of the proportion of responders at month 3 and month 6 shows that there is a greater proportion of patients responding with active treatment relative to the vehicle group. Month 3 is shown

but month 6 is our important endpoint.

And, if we look at the summation of that information in a tabular format, you see that using this more comprehensive approach, as was suggested by this workshop and which we now had an opportunity to test, highly statistically significant differences for both studies were demonstrated for the two active concentrations relative to the vehicle.

Now I will ask you to reflect back to Dr. Stern's presentation on the conjunctival biopsy data that he showed you both in the spontaneously occurring dry eye dog and in the collaborative work with the National Eye Institute. Allergan knew launching into our clinical program that palliative treatment such as artificial tears could affect and improve things such as corneal staining and patient symptoms. This has been the mainstay of artificial tear treatment for these patients. We felt it was important to include some tests and endpoints that would very clearly demonstrate the therapeutic effect and benefit of cyclosporine that would likely not be achieved with vehicle or palliative treatment alone.

To do this, we collected conjunctival biopsies from a subset of patients. Now, because biopsy is an invasive test, these data are for a very small number of patients, but biopsy is considered the histological gold

standard and we very thoroughly evaluated these biopsy tissues for markers of immune reactivity, inflammation and infiltrating cells.

I will show just one histology slide that is representative of one of the patients in whom we evaluated the biopsy results. What you are seeing on your left is the biopsy prior to treatment with 0.05 percent cyclosporine emulsion. Following 6 months of treatment you can see a notable reduction in the number of infiltrating inflammatory cells.

The mean data for all of the patients for whom biopsy was taken and evaluated for CD3 is shown at the bottom of each of the slides, with over 2000 cells/mm^2 being evident prior to treatment and this was reduced to less than 800 following 6 months of treatment.

The data are summarized here graphically for CD3, CD4 and CD8 cells. Once again, the vehicle is shown in blue, and what you will note for most of the populations -- CD3, CD4 in the center and CD8 here, down at the end -- is a higher mean change or continuing increase, if you will, from baseline in the proportion of these cells at 6 months compared to the active-treated groups where you are seeing a reduction in the number of these cells.

Similarly, for CD11a, the marker of inflammation, you see a reduction by 6 months with active treatment. You

do not see this with vehicle. Similarly, for the marker of immune reactivity, HLA-DR, with statistical significance being achieved for the 0.05 percent group.

So, the biopsy data demonstrated some very specific effects of cyclosporine in reducing the immune activation and inflammation. So, while the vehicle provided lubricating palliation to these patients and could affect some of the standard measures, it did not affect the underlying immune reactivity and inflammation which characterizes this condition.

In summary of the efficacy, clinical and statistical significance favoring cyclosporine over vehicle was demonstrated in several ways. First, for one sign and one symptom in each of the Phase III studies for study 002 for corneal staining, for the sum of staining and for multiple symptoms, and in study 003 with high statistical significance for the Schirmer with anesthesia while we approached significance for the subjective of measure of a reduction in artificial tear use.

For the single standard measure across both studies, the statistical significance was very substantial in study 003 for the Schirmer with anesthesia and it approached significance at a 0.06 level in study 002.

Using a retrospective look at the data, given the guidance from the working group and the publication of 1995,

using the overall disease severity approach in both studies independently we saw statistically significant improvement for the active concentrations relative to the vehicle.

So, improvement in the multiple signs and the symptoms, as well as a reduction in the underlying cause of the disease resulted in clinically significant improvement for these dry eye patients.

At this point I would like to invite Dr. Diane Tang-Liu to the podium. She will present our preclinical safety data as well as our animal and human pharmacokinetic data.

Non-Clinical Safety and Human Pharmacokinetics

DR. TANG-LIU: Thank you, Brenda. Good morning. My name is Diane Tang-Liu and I represent Allergan to present the pharmacokinetic and safety profile of Restasis as evaluated in animals and man. I should mention that at the end of my presentation Dr. Reis will come back to the podium to continue presenting the human safety data collected in our Phase II and III trials.

My presentation will cover the following three areas as they relate to drug exposure and safety, first at a systemic level, then inside the eye and, lastly, at the ocular surface where our therapeutic targets are.

The first thing I want to tell you about Restasis is that the ophthalmic dose is extremely small. This slide

compares the total daily dose between Neoral and Restasis. Neoral is the trade name of systemic cyclosporine dosage forms by Sandoz. Neoral was recommended for approval by this committee four years ago for the treatment of psoriasis, and the total daily dose is about 190 mg, as compared to Restasis, one drop in both eyes twice daily. The total dose only adds up to 0.06 mg per day, 1/3000 of the approved systemic dose.

Knowing our dose will be so much smaller to start with, Allergan developed the state-of-art LC-MS/MS method which is much more sensitive than the conventional HPLC and radioimmunoassay. This assay is validated to detect blood concentrations as low as 0.1 ng/ml accurately and precisely.

Now, I would like to show you the blood concentrations monitored in our Phase III study using this extremely sensitive method. Again, the Neoral data is listed for comparison, and it was taken from the package insert. There are two components to our therapeutic drug monitoring in our Phase III. One is to identify the maximum systemic exposure. In a subset of patients serial blood samples were taken over one 12-hour dosing interval in order to map out the maximal possible blood concentration.

As you can see in our 0.1 percent arm, of the 144 samples collected only 3 contained detectable cyclosporine. The single highest observation is at our detection limit,

0.1 ng/ml. In our Restasis arm and our placebo arm, of all the samples collected none contained any detectable cyclosporine.

The second component of our therapeutic drug monitoring is to monitor C-trough. In a separate subgroup of patients every time they came back for a treatment visit a blood sample was taken. Again, in the 0.1 percent arm, out of 128 samples collected only 7 contained detectable cyclosporine. The highest is as low as 0.3 ng/ml. That is the single highest observation. Again, in our Restasis arm and the placebo none of the samples contained any detectable cyclosporine. In short, Restasis treatment up to one year produced no detectable systemic exposure.

Now I would like to compare the systemic exposure in our animal studies to Neoral. In our animal studies in rabbit and dog, they are subjected to an exaggerated dosing regimen, up to 0.4 percent 6 times daily for 6 months and 12 months respectively for rabbits and dogs. The mean maximal systemic exposure is only 1 ng/ml, 600 times lower than the therapeutic human blood concentration.

So, I would like to sum up the systemic aspect of Restasis. First, the systemic exposure from Restasis is several thousand times lower than from Neoral, and this is consistent with the large difference in dose. Upon chronic dosing up to one year in dogs and man there is no detectable

systemic accumulation. Since the systemic exposure is negligible, not surprisingly, we did not detect any treatment related adverse effects in animals and in man.

Now I would like to bring our attention back to the eye. Cyclosporine's bioavailability in intraocular structures is very limited. This is because cyclosporine is a large lipophilic molecule, meaning that it prefers to stay in oil and tissue but not in water.

This picture illustrates the ocular disposition of cyclosporine after it is put into the eye. The blue droplets are cyclosporine dispersed in tear film. Once it comes into contact with the ocular surface, cyclosporine will readily partition into the cornea epithelium, the conjunctiva and the accessory lacrimal glands, and cyclosporine will prefer to stay at the ocular surface, and cyclosporine will have difficulty further penetrating inside the eye.

This is because the corneal stroma is composed of mainly water, and the hydrophilic environment of corneal stroma is such that it presents itself as a very effective penetration barrier, thus preventing cyclosporine from migrating further into the intraocular structure. This leads to very low absorption inside the eye and, therefore, there are no intraocular adverse effects observed in animals and in man.

Restasis b.i.d. treatment provides a steady coverage over the ocular surface. This slide shows the tissue concentration over one 12-hour dosing interval, at steady state. Data are shown here for cornea, conjunctiva and the main lacrimal gland. At steady state cyclosporine has already achieved a trial steady state baseline, as evidenced here, and cornea happened to have the higher concentration than the conjunctiva and lacrimal gland. At steady state, after one drop, the tissue concentration will rise with time providing good coverage and will gradually come down to its original steady state trial baseline value at a 12-hour post-dose and be ready for the next dose to kick in.

Knowing the tissue concentrations in the rabbit, in the dog eye, and also knowing the literature reported corneal data in human, we are able to estimate that the ocular tissue concentration in cornea and conjunctiva, after Restasis treatment in human, is approximately 450-620 ng/g.

This slide compares the systemic tissue concentration from oral doses to ocular tissue concentration from the Restasis dose. Listed here are tissue concentrations in colon, ileum, kidney and liver from patients who have achieved successful systemic immunosuppression from oral cyclosporine doses. It is apparent that the ocular cornea and conjunctiva

concentrations from Restasis treatment, which is required to maintain immunomodulation effect, is much lower than systemic tissue concentrations that are required to produce successful systemic immunosuppression. Yet, it is this concentration that provides the basis of therapeutic benefit in KCS patients, as discussed by Drs. Stern and Reis earlier.

So, now I would like to tell you why ocular safety at this concentration is well supported for long-term human use. First, when dog eyes are exposed to high ocular surface concentration cyclosporine over one year there are no ocular adverse effects. This is a one-year oral toxicity study in dogs conducted by Sandoz. In this study the dogs are exposed to as high as 45 mg/kg daily for a year, reaching very high systemic exposure. This is at least 50,000-fold higher than what would be expected from the systemic exposure from Restasis. The corresponding ocular tissue concentrations in these dogs, again, are many multiples of human ocular tissue concentrations that one would expect from Restasis treatment. At this extremely high systemic exposure the dogs already achieve systemic immunosuppression, as evidenced by skin papillomatosis. Yet, there are no treatment-related ocular adverse effects seen in these dogs, supporting ocular safety.

Again, when rat eyes are exposed to high

cyclosporine levels over their lifetime there are no treatment-related ocular side effects and there are no pre-neoplastic findings in the eyes or in the structures surrounding the eyes.

This is an oral carcinogenicity study in rats conducted by Sandoz. The rats were exposed up to 8 mg/kg daily lifetime, achieving again extremely high systemic exposure and many multiples of ocular exposure as compared to the clinical use of Restasis. At the end of their lifetime there are no ocular findings microscopically or macroscopically related to the eye. There are no neoplastic or hyperplastic changes related to the treatment.

I should also mention that in a separate carcinogenicity study that Sandoz conducted in mice, treated up to 16 mg/kg per day over their lifetime the conclusions are the same. There are no microscopic or macroscopic findings in the eye and there are no neoplastic or hyperplastic changes that are treatment related.

As you all know, there are many cases of human use experience with cyclosporine, and from Sandoz there is an extensive cancer registry. There is no single instance report of ocular tumor related to human use.

So, at this point one can conclude that there is an extensive body of evidence out there supporting ocular safety of long-term and lifetime use of ophthalmic

cyclosporine based upon animal and human data from high systemic doses.

Independently, Allergan has conducted two ocular safety studies, in rabbit and in dog, up to 0.4 percent cyclosporine 6 times daily, and these animals are subjected to such an exaggerated dosing condition if you look at exposure levels as measured by dose that we put in the eye it is 34 times the human clinical dose. If one looks at the concentrations achieved in the cornea and conjunctiva in these animals, it is 30-70 times the human levels in the eye from ophthalmic dosing.

It is under these exaggerated dosing conditions that there are no clinical signs of conjunctivitis or keratitis. There are no opportunistic ocular infections. Again, there is no evidence of any local immunosuppression. There are no hematological, clinical chemistry or histomorphological findings in the body systems. Again, there is no evidence of any systemic immunosuppression.

So, I would like to conclude that the pharmacokinetic and safety profile of Restasis supports safe human use. Number one, the effective topical dose is extremely small, many thousand-fold lower than the approved systemic dose. There is negligible systemic exposure. Actually, the systemic exposure is not detectable using an extremely sensitive assay. The ocular pharmacokinetic

profile is favorable and supports twice daily dosing. Lastly, between Sandoz and Allergan there is a comprehensive and extensive safety package that supports long-term and lifetime safe use of Restasis in man.

At this point, I would like to ask Dr. Reis to come back to continue to present human safety data.

Clinical Safety

DR. REIS: Thank you, Diane. As you have just seen from Dr. Tang-Liu's presentation, the systemic exposure from topical use of the cyclosporine emulsion formulation is very minimal. Consequently, I am going to move rather quickly through the human systemic safety and on to the ocular safety.

With respect to the systemic and serious adverse events over our Phase II and our Phase III studies, we would say that the systemic adverse events were unremarkable. It is very important to note that none of the serious adverse events reported in any three of the clinical trials was considered to be related to study drug. And, the distribution of the adverse event severity was similar for the cyclosporine and the vehicle groups, with the exception of the ocular adverse events which I will get to momentarily.

Discontinuations due to adverse events are summarized in this slide, and you can see that they are, for

the most part, relatively low.

In both Phase III studies the adverse events are shown here and broken down as any adverse event, serious or ocular. Now, at first glance one might think that an adverse event rate in the 50 and 60 percentile would be unusual and particularly high, but I need to point out that this is a very conservative approach to adverse event reporting. We capture everything that happens to these patients during the course of the trial. So, this reflects things such as a headache, the flu, a cold or a broken hip.

If you look at the adverse events across the groups you see that the adverse events for the active treatment groups are really no higher than for the vehicle when you look at the "any adverse event" category or when you look at the serious adverse events.

Looking at ocular adverse events, we do note a greater incidence of ocular burning with the active treatment groups. In the vehicle, on the order of 7 percent of the patients experienced burning while with the active treatment groups it is on the order of 16-17 percent.

With respect to the duration of this burning and stinging, since these were captured as adverse events, we captured duration in the category of minutes, hours or lasting more than 24 hours. You can see that for the majority of the ocular burning the duration was in the order

of minutes.

Patients who actually had to discontinue treatment because of ocular burning are shown here, and you can see that the numbers were very small, from a low of two patients in study 003 to a high of five patients, and this is out of the total of 877 who were treated between the two studies.

Over all three of our trials, our Phase II and our two Phase III protocols, there were no ocular infections in any of the cyclosporine-treated patients. In Phase II there were no ocular infections reported at all, and in our Phase III trial, while there were two ocular infections, these were reported in the vehicle-treated patients only.

So, we would summarize the safety of topical ophthalmic cyclosporine that the adverse events that we saw were mostly mild or moderate. There was mild to moderate burning and stinging with active treatment that, for the most part, was transient.

Using the standard ophthalmic measures for safety, there were no treatment-related changes in intraocular pressure or visual acuity, or any of the parameters of biomicroscopy that we evaluated.

At this point, I would like to take the efficacy and the safety data that have been shown to you for Phase III thus far and try to summarize them into a benefit/risk assessment.

I am going to take a few moments to walk you through this slide. It is known as a shift table. What you are looking at is a shift for corneal staining for baseline and for month 6. We are asking a very simple question: At month 6 how many of the patients were better for staining than they were at baseline when they entered?

What you are looking at is the baseline corneal staining grade across top, 2, 3, 4, or 5. Recall that the patients were required to come in at entry with a minimum staining score of 2 for the cornea. At month 6 the patients could have ranged anywhere from complete clearance of staining, a zero, and down to a 5.

Now, if a patient came in at 2 and by month 6 they were at zero or they were at 1, they had improved. If they started at 2 and remained at 2 by month 6, they were unchanged. So, what you see in the blue bar represents those patients who would have been unchanged over the 6-month treatment period or by the 6-month time point. So, all the patients on the top represent the percent of patients who improved, while those below the blue diagonal represent the patients who got worse. So, the 67 percent improved and the 8 percent who got worse are shown right here.

For each of the four endpoints, for the corneal staining, for the Schirmer with anesthesia, for blurred

vision and artificial tear use, the percent of patients who improved or worsened for each of the three treatment groups is shown, with the vehicle shown at the bottom of each. A simple division was then done to convert these into a ratio and the numbers were rounded to whole numbers.

What is important to see on this slide is that the number for benefit, no matter where you look on this slide, is always greater than the number for risk. For the endpoints, such as corneal staining, the benefit outweighs the risk anywhere from 11-1 for the 0.1 percent group to a low of 6-1 for the 0.1 percent group in study 002.

If we take a similar approach and look at the risk side, the numbers that you are now looking at were generated from the total number of patients in each of the treatment groups and the number of patients who actually experienced an adverse event. Using the most conservative approach, again, for all adverse events, regardless of whether they had any relationship whatsoever to the drug and involved things such as colds and broken hips, you will see that the risk number is always lower than the benefit.

There were no serious adverse events that were related to treatment, but even if we take the total number of serious adverse events reported in the study you can see that the risk is always much lower compared to the benefit, even for the occurrence of ocular burning which was a very

specific treatment-associated event. So, the benefit/risk analysis is always in favor of the benefit.

At this time, I would like to turn the podium over to Dr. Peter Donshik who will present a clinical perspective on what the quantitative benefit/risk analysis that I just provided you means. Dr. Donshik was an investigator in both our Phase II and in our Phase III studies.

Risk/Benefit

DR. DONSHIK: Thank you, Brenda. My name is Peter Donshik. I was an investigator in both the Phase II and the Phase III studies. I am Chief of the Division of Ophthalmology at the University of Connecticut Health Center, and in that capacity worked closely with the rheumatologists and dentists in the diagnosis and management of patients with Sjogren's syndrome. In my private practice of over 3000 patients, I specialize in corneal and external disease and have a special interest in dry eye patients.

Over the last twenty years I have been involved in numerous studies, numerous dry eye studies. In addition, I have been involved in clinical studies with regard to blepharitis, conjunctivitis, corneal ulcers and contact lenses.

Let's look at the treatments available for our patients with keratoconjunctivitis sicca and their risk. Artificial tears is the mainstay of therapy. While it may

be effective in the mild cases, it is not very effective in the more moderate to severe cases. As the patients progress, their symptoms progress. They are no longer able to read, to sew, to go outside in bright light or to drive. Likewise, we see progression in the ocular surface disease, with increased staining both of the conjunctiva and the cornea; the potential for breakdown, ulceration and infection. This affects their quality of life. These patients are miserable; they are frustrated. They are constantly aware of their eyes with ocular discomfort and pain, and they are unable to function.

This often leads to more invasive therapies, such as punctal occlusion, which may or may not work; moist chamber goggles, which are uncomfortable -- the lenses themselves fog up, affecting vision and are cosmetically unacceptable. The need for topical steroids with their inherent complications of infection, corneal melting, glaucoma and cataracts and, in very severe cases, the tarsorrhaphy, where sewing of the eyelids together can have an effect on peripheral vision as well as having significant effects on the cosmetic presentation of that patient.

Let's look at the risks of cyclosporine. As we heard, the major risk was the burning and stinging, sort of similar to what one would expect of instilling medication into the eye, and for the most part this was very transient.

There were no reported cases of any significant side effects, and there is no systemic absorption.

What is the benefit of cyclosporine to the patient? They improve in symptoms. They had a decrease in awareness of their eyes; decrease in the sandy feeling and more comfort. They had improvement in the ocular surface, with less staining and improvement in vision. This improves their quality of life. These patients become more able to function, less aware of their eyes. In addition, the drug treats the underlying pathophysiology.

In my opinion, the benefits outweigh the risks. Keratoconjunctivitis sicca is a frustrating disease. It is frustrating for both the doctor and the patient. Presently, there is no good treatment available. Patients go from doctor to doctor looking for relief. Doctors often give patients a handful of tears and hope they go to another physician. Restasis is the first drug available to treat patients with keratoconjunctivitis sicca. As a clinician, it gives me a therapeutic agent to treat the signs and symptoms of my patients with keratoconjunctivitis sicca. It treats the underlying inflammation, eliminating the need for topical steroids. In most cases it stops the progression, eliminating the need for more invasive therapies such as tarsorrhaphy. It is a drug with an excellent safety profile.

Thank you. Now I would like to turn the podium back to Dr. Gibson.

Conclusions

DR. GIBSON: Thank you, Dr. Donshik. My conclusions will be brief and will focus on two areas, firstly, keratoconjunctivitis sicca. This is a serious condition. It is debilitating and it is associated with significant morbidity. In the worst cases it may be associated with a threat to vision itself. Furthermore, it represents a rational target for therapy with Restasis.

My second slide focuses on Restasis. This is the only purpose-designed topical therapy for KCS. The work that you have seen presented earlier shows the following: Restasis is effective in the target population. It is safe for its intended use. It is acceptable to patients from a tolerability point of view, and has a favorable risk/benefit profile. Finally, and very importantly, Restasis provides rational pharmacologically-based therapy where none currently exists.

I would like to thank you very much indeed for your attention.

Questions fm the Committee

DR. FONG: Are there any clarifying questions for Allergan? Dr. Matoba?

DR. MATOBA: Yes, I have a question regarding the

conjunctival biopsy data that was presented. For CD3, CD4 and CD8, you said that there was a decrease in the cells found in the conjunctiva at month 6 for cyclosporine 0.1 percent compared to vehicle. But the slide that you showed has quite a large standard error of either the mean or standard deviation, and at first glance it does not look like a statistically significant difference.

DR. REIS: You are correct that there is no statistical significance for any of those endpoints, with the exception of the HLA-DR, which is shown by the asterisk. There are no asterisks on the other bars so while there were decreases, they were not statistically significant.

DR. FONG: Are these clarifying questions? We can ask more extensive questions after we take a quick break. Would the panel like that? So, let's take a quick break for 15 minutes and return at 10:45. I want to remind the committee not to discuss the issues under discussion today outside of this room.

[Brief recess]

DR. FONG: Welcome back to the Ophthalmic Subcommittee meeting, and we would like to open up the flow of questions to Allergan. I believe Dr. Lavin had a question.

DR. LAVIN: Yes, Brenda, you made a comment in your presentation that the overall type-1 error was

controlled at 0.05. Can you respond to that, taking into account the fact that you had multiple time points, two active treatments, and you also had five subjective and five objective measures? Can you, just very briefly, go through what the rationale is; why you conclude the overall type-1 error is fixed at 0.05?

DR. REIS: Dr. Lavin, I will ask members of our statistical team to respond, Katherine Stern to respond to the month-6 time point, and then Dr. Strauss to respond to the multiple endpoint measures.

DR. K. STERN: Good morning. I am Katherine Stern, project biostatistician from Allergan. I believe you asked about multiplicity with respect to three different areas, and I will address each of those.

We did account for multiplicity with respect to pair-wise comparisons by using a protected test. So, pair-wise comparisons were only performed if the overall number of significance was different.

With respect to the time points, the differing time points, although patients were evaluated at multiple time points throughout the entire study, as we had stated in our statistical analysis plan, the primary endpoint was only the month 6 time point. Therefore, we did not do any further adjustments for multiplicity since none was necessary.

With respect to the different variables that were looked at, as stated a priori in our statistical analysis plan, we were going to be looking at one objective variable and one subjective variable. So, at that time no further adjustments for multiplicity were made. However, if you were to go and look now at multiple endpoints, you should adjust for multiplicity. You could do, for instance, a two-piece adjustment for multiplicity and quite a few of our among group differences that were presented remained significant. The highly significant ones would remain significant. For instance, in the 002 study the difference in corneal staining and sensitivity to light and itching would remain significant, and in the 003 study the difference among treatment groups would remain significant for the Schirmer with anesthesia.

DR. STRAUSS: Hello. I am David Strauss, Professor of Statistics at the University of California, and one of the external statisticians on the project.

Yes, the issue of multiplicity certainly is something you want to look at. I have had a chance to review some of the calculations done by Allergan, actually, on this and I thought I would mention a couple.

Firstly, in study 002 14/15 quantities looked at came out in the direction predicted, meaning that the effect of the drug was larger than that of the vehicle. Those 14

tests are dependent so an analysis was done taking account of the dependent structure and, not surprisingly, with 14/15 that came out highly significant all by itself.

Study 003 certainly wasn't so clear but one point I think worth mentioning from a purely formal point of view is that the Schirmer test was significant at the 0.001 level and in plain language, as you know, that means that there is less than one chance in a thousand of getting that result if, indeed, the drug was no better than the vehicle. So, that is pretty significant.

Now, you might say, "aha, but that's just 1 of 15 tests." But, as you know, you can do a Bonferroni adjustment on that, multiplying by 15, and so when you multiply 1 in 1000 by 15 you still get a probability of 1.5 percent, way less than 5 percent. So, from a formal point of view, study 003 is significant as well.

DR. LAVIN: I will have more comments on this later but that is fine.

DR. FONG: Dr. Seddon?

DR. SEDDON: Yes, I wonder if you could explain the reason for the improvement with vehicle in the 003 study? It seemed to be quite similar to effect of the drug on several measures, especially in the 003 study. Could you review that briefly, explain the reasons for that similarity?

DR. REIS: We have two responses to address that. One has to do with the actual mechanism of the disease and how palliation can affect things such as corneal staining, and Dr. Michael Stern will speak to that. Then Dr. Schiffman, who has looked at our Phase III independently with a specific look at the vehicle patients, will respond from a clinical perspective.

DR. STERN: This slide from my presentation shows that there are the two components of the disease, and it is known that the irritative component, that component that is caused by the environmental input, can be pushed around or modified through the use of sufficient lubrication. Now, we have done interferometry studies with our vehicle as compared to artificial tears which are known to remain on the ocular surface for approximately 2-5 minutes. This vehicle will remain on the surface between 2.5-3 hours. So the decrease in environmental intrusion into the surface is vastly decreased with this vehicle. Thus, the palliation is much greater here. However, the underlying immune response, the cellular infiltrates that are not impacted by the effect of this palliation -- that is what is progressing and can cause problems down the line, as Dr. Pflugfelder mentioned.

DR. SEDDON: Actually, that related to another question I had, given the clinical heterogeneity of the disease and the lack of correlation among the subjective

symptoms and objective signs and biomarkers, it seems that so far the most convincing evidence is related to the CD3, 4 and 8 results in that the vehicle did not affect the immunoreactivity as much as the drug. So, those results are very important. But I would like to have more information about those results too in terms of the number in each group and whether they were masked observations. So, that is another question.

DR. REIS: We will have Dr. Rhett Schiffman respond and finish up your question about the vehicle response in study 003, and then we will have Dr. Stern come back and address your follow-on question, if that is all right.

DR. SEDDON: Yes, thank you.

DR. SCHIFFMAN: Good morning. I am Rhett Schiffman. I am an internist and ophthalmologist at Henry Ford Health System. I have a masters degree in statistics from the University of Michigan, and the issue of discrepancies or differences in the findings of the two studies was what was most important to me to evaluate.

It actually appears on further analysis that there really is some consistency between the two studies, and I will describe that. In looking at the characteristics of the patients who enrolled in 003, you will see that twice the number of patients needed to be included in that study

to be enrolled. There was a fewer number of patients at more centers.

You will also see that there is a difference in the number of persons who did not see a doctor for their dry eye in the 003 study, compared with the 002 study, at the time of enrollment. Moreover, the mean number of visits to an eye doctor or a doctor for their dry eye was actually less in the 003 study than in the 002 study.

So, this suggests that there were some differences in the enrollment, and it is possible that some portion of the patients in the 003 study were perhaps less severe and less chronic, and it is possible that some of those patients, although they met entry criteria, could have undergone some degree of spontaneous improvement.

To be able to investigate whether or not that was a plausible hypothesis, I actually looked at the change in total staining from baseline to month one. The notion there was that at month one it was a little premature to see a full therapeutic effect from cyclosporine, and that at this time point one might see some degree of spontaneous improvement between both groups that related to this phenomenon that I described.

You will see that in the 003 study there was a substantially greater decrease from baseline in not only the vehicle but the 0.05 and 0.1, and a fairly similar magnitude

across the three groups but certainly much more than what we see here, suggesting that there might, in fact, have been a greater degree of spontaneous improvement going on in the 003 study than the 002 study.

Then my interest was to see what sort of conservative approach I might take to see how that influenced our further results. So, what I did was I removed those patients who had cleared their cornea entirely at month one and had no staining at month one. I removed those from both analyses, the 002 study and the 003 study, and looked at that subgroup which was really still a large sample.

This actually demonstrates the result for the Schirmer's test which demonstrates, in a pair-wise comparison actually, a statistically significant difference between the 0.05 and the vehicle group and, as we had seen previously, there are highly statistically significant differences in all pair-wise comparisons and among group comparisons here.

But I think the bigger point I want to make here as well as for the subsequent three or so slides is that the pattern now becomes somewhat more similar having addressed this issue of perhaps a slightly different population.

DR. CIOFFI: What were the Ns in that previous slide, number of patients?

DR. SCHIFFMAN: There were actually over 300 in both. There were actually some 50 or so patients removed from here and some 70 patients removed from here, perhaps 75 or so.

Here, again, we see an among group difference in corneal staining. We have seen this before, but this remains certainly statistically significant. What we do see here though is an apparent cyclosporine effect or drug effect in that both of these groups, although not statistically significant, did have greater reduction in corneal staining than the vehicle.

With respect to artificial tear use, once again looking just in terms of patterns between both studies, we see a statistically significant difference in a pair-wise comparison and a nearly statistically significant among group difference here -- but a very similar pattern between two studies with certainly a trend of therapeutic effect related to cyclosporine in comparison to vehicle.

Finally, with respect to blurred vision, we have a very borderline statistically significant difference here and borderline statistically significant differences here but, once again, these trends -- these comparisons really are much more comparable than sort of the overall analysis would have suggested.

So, in summary, I think one can conclude that if

you address what might be some reasonable differences in the study population and you do a post hoc analysis dealing with that, you actually do get fairly similar findings in terms of trends with respect to two clinically relevant objective findings and two subjective findings, and the same ones in both studies.

DR. STERN: Dr. Seddon, in response to your question -- it seems so long ago now, but you were asking about the cells that were present --

DR. SEDDON: Yes, I was saying that your presentations discuss the clinical heterogeneity of disease and the lack of correlation among all the different parameters, and one of the results you presented was the CD3, 4, and 8 results and the fact that the vehicle had no effect on immunoreactivity, which I think is very important. I would like additional information about that particular aspect of the study in terms of the number of people in each group and were these observations masked. We have already heard that apparently not too many of these differences were statistically significant but if you could elaborate on that component of the study, it would be helpful.

DR. STERN: Okay, I will start with the last one first. The reading center, which was Dr. Aileen Gibson's laboratory at Skateman's Eye Institute, was totally masked throughout the entire thing until the data was broken at the

end. So, they received frozen samples from a central center. They processed those samples. They counted them. We developed a procedure to do that, and then it was broken at the end of the study. So, they had no idea what they were looking at.

I think it is important when we look at these things -- the reason that we looked at the different types and markers we looked at is because numbers of cells and the T-cell subpopulations, CD3, CD4, and CD8 that you mentioned, are important. The fact that they are homing to this tissue is a critical piece of pathophysiology. But the other important point is what these cells are doing when they get there. Are they activated? Are they secreting cytokines? Are they upregulating inflammation? And, that is where the DR data really becomes critically important, even probably more important than just the absolute numbers of cells.

I will show a slide here. This is the HLA-DR pre- and post-vehicle. You can see here that we have a very large number of cells here, 1166 cells/mm^2 in the pretreated group. In fact, it even goes up to 1385.

So, this is the Sjogren's syndrome patients. This is pre- and post-0.05 percent. You can see here that we went from 2001 cells and you can see a mass of positive cells under the epithelium in the substantia propria, down to 819 cells/mm^2. So, this is a really significant decrease

in cells. It may not be down to normal yet, however, it is vastly improved over the pretreated biopsy.

Then, from a graphical perspective, what you can see here is that there is a decrease here and HLA-DR goes up over 150 percent in the vehicle during that time period, and down in both of the treated groups, and we see this routinely. There is not really enough power to show statistics in some of these things with the numbers of patients because, as Dr. Reis said, this is a very invasive procedure and not many patients are going to volunteer to do it.

DR. SEDDON: There were 32 total, so there are possibly 10 in each group here?

DR. STERN: I believe there were 13 in the 0.05 and vehicle group and there were 6 I believe in the 0.1 percent group. So, in all of the markers we saw I think there was a very startling difference numbers-wise. I think statistical power, and stuff, is really the only thing that prevented us -- and the fact that we showed statistical significance in any of them is really quite remarkable.

DR. SEDDON: Thank you very much.

DR. FONG: Dr. Matoba?

DR. MATOBA: Since topical cyclosporine does not significantly penetrate the lacrimal gland, what do you think is the basis for the improvement in Schirmer's test?

DR. REIS: Dr. Stern? Dr. Nelson has a response as well.

DR. NELSON: Dan Nelson, Professor of Ophthalmology at the University of Minnesota, and I work at a teaching hospital.

This is a perplexing question to answer breast cancer in the dog we know that the cyclosporine treatment increased Schirmer results, and when we studied the humans trying to figure out why Schirmer's with anesthesia would go up -- and, I think it is a real finding. If you look at this slide just showing Schirmer's with, and if we separate the main lacrimal gland from the accessory lacrimal gland, when we are doing it with anesthesia we are measuring the basal secretion of both. When we do it without anesthesia we are measuring the reflex tearing of the lacrimal gland, and it is unlikely that the accessory gland can generate significant reflex tearing so we are probably measuring continuing basal secretion.

So, pretreatment we measure decreased basal secretion with anesthesia and the reflex would again be decreased from the main lacrimal gland. In post-treatment, because the penetration of cyclosporine is low, we wouldn't expect to see an increase. However, in the accessory lacrimal glands where cyclosporine is reaching significant levels, we would see an increase in the basal secretion

which would result in a small but significant increase in Schirmer test with anesthesia.

DR. MATOBA: So, you are postulating that the increase is solely due to improvement in the status of an accessory gland?

DR. NELSON: Accessory gland, yes.

DR. STERN: I think one thing that we have been able to hypothesize is that it is known that inflammation -- the blue depicts the efferent pathways through the trigeminal nerve from the ocular surface. We have two pathways that come back, and those are the parasympathetic and sympathetic, and what we have is through the seventh nerve, the facial nerve, the parasympathetic and it synapses in the pterygopalatine ganglion and then goes on to enervate the accessory and main lacrimal glands.

What happens with chronic inflammation is that there is secretion of these pro-inflammatory cytokines, and it is known that IL-2, for example amongst several of them, will bind to opioid receptors on the neural membrane and shut these nerves down essentially, inhibit their activity. As Dr. Wilson mentioned, and other people have shown, there is a decrease in sensation on the ocular surface.

What happens after treatment with cyclosporine -- what we believe is going on is that there is a resolution of this inflammatory effect and a resurrection of the neural

pathway back towards normal. So, initially the gain is much greater at the beginning. We start to see a lot more tear flow. Then it starts to settle down slightly above baseline, and I believe that Dr. Nelson is exactly correct, what we are seeing is accessory glandular secretion and return to normal composition of the tears.

DR. FONG: Ms. Goldberg?

MS. GOLDBERG: Since your primary population for this, as I understand it, would be postmenopausal women, I was wondering what the impact of hormone replacement therapy is on the disease state and if there is anything to factor into these studies regarding HRT.

DR. REIS: I will give you first a response about the types of patients that were included in our Phase III program, then if you would like additional information on the hormone relationship to this disease Dr. Stern can elaborate further.

We did include patients in our Phase III program who were on hormone replacement therapy. Hormone replacement therapy, at least that which has been used to date, has not demonstrated an effect on the dry eye condition.

MR. GOLDBERG: Okay. That is kind of the first answer. I would like to hear what Dr. Stern has to say.

DR. REIS: Very well. Dr. Stern?

DR. STERN: I think that there are two things that we have to know about which hormones are having the effect here. In the initiation of the disease it is generally well accepted now that, in fact, it is androgens that are really causing the issue and, most hormonal replacement therapy is estrogen based except for some that have some mild androgens or progesterone added to them.

What is known from David Sullivan's work at Harvard, as well as Austin Mercheff at USC, is that androgens maintain the anti-inflammatory state. This is the hormonal link I was talking about in my talk. In fact, it is this loss of androgens that occurs at menopause and occurs in certain pathologies that really allows this or facilitates the inflammation to occur. In fact, it is known that systemic estrogens exacerbate autoimmune disease. So, it is really the androgen response that is immunoregulatory.

MS. GOLDBERG: Thanks.

DR. STERN: And we can see here that with age we get a decrease, and with disease we get a decrease and the normal androgen or testosterone levels in women from 74.5 ng/dl, and with dry eye, moderate or severe, it goes all the way down to about half. There is general agreement that there is a threshold below which this anti-inflammatory umbrella is compromised and then things start to occur.

DR. FONG: I would like to ask one question, and

if we don't finish we can ask questions after the FDA presentation and after lunch. I guess my question is, looking at the primary outcome variables from both studies, and specifically I am interested in the sum of corneal or conjunctival staining, and sort of the choice of test that was used at the statistical significance, has there been any work or do you know of information to show that the use of parametric testing is appropriate? Is the distribution of corneal and conjunctival staining normally distributed? If not, I would like for you to comment on whether the choice of parametric testing might overestimate the true significance, the true difference between the two groups..

DR. K. STERN: This is Katherine Stern again. The parametric tests were only used, as you said, for the corneal staining and for the Ocular Surface Disease Index because those have more of a continuous type of scale. So, it was anticipated that we could use a parametric test. We did check for normality, and also looked at non-parametric results, and though the non-parametric results were not as powerful we still did see significant difference for the staining.

DR. FONG: The statistical significance is 0.044 so that is just close to not being statistically significant. Do you have the results of the non-parametric testing?

DR. REIS: I do not have them with me, and I am doing it only from recollection, I know that the corneal staining was still significant and I can't recall what the p value is for the total staining. If you need that, I can have that done for you.

DR. FONG: I think it is important if we are doing statistical testing to have testing that is appropriate for the distribution of the variables.

DR. REIS: I can have that done for you after lunch.

DR. FONG: Dr. Lavin, is that a concern for you also?

DR. LAVIN: It actually was not a concern because of the large sample size, and I have had a lot of experience with data like that, analyzing it. I wasn't that concerned about that.

DR. FONG: Jack?

DR. CIOFFI: I have two questions. One, with a fairly large non-responder population, did you do any analysis after the fact to look back at who the responders are and who are not responding?

DR. REIS: I am presuming here that you are referring to our overall disease severity analysis, the responders were defined as having improved over a collection of two objective sings and two subjective symptoms. So, to

answer, the patients that were most likely to respond would be based upon their baseline criteria around corneal staining, blurred vision, their need for artificial tears, as well as their low Schirmer score.

DR. CIOFFI: So, did you pick those four factors based on your population, or did you pick those four factors based on the disease process?

DR. REIS: Those four factors were picked based upon the disease process.

DR. CIOFFI: Ahead of time, without looking at the population statistically?

DR. REIS: Let me clarify that the overall disease severity is a retrospective analysis. So, prior to having conducted that analysis we had the data for the individual endpoints. So, it was retrospective after having seen the response for individual variables. Blurred vision was, as a stand-alone, not statistically significant. Artificial tear use approached significance in one study only. Schirmer was significant in one study and approached significance in the other. Corneal staining was significant in one study. So, none of the four parameters were statistically significant across the studies independently, but they appear to be the most clinically important parameters given the moderate to severe dry eye patient population with aqueous deficiency.

DR. CIOFFI: An unrelated question, I am not sure

I understand the apoptotic lines of investigation for programmed cell death. I think you are simultaneously hypothesizing that this has the potential to downgrade apoptosis in one cell line and upgrade it in another.

DR. REIS: That is correct. Dr. Stern will address that.

DR. STERN: You are exactly right. We are seeing two opposite effects, however, I guess I wouldn't say that they are specifically downgrading in one and upgrading in the other. I think it is probably a resolution of the disease process that is allowing these things to happen. But what we know is that cyclosporine facilitates lymphocytic apoptosis primarily by decreasing complex formation, and it just inhibits T-cell growth and increases the apoptotic process there. It also prevents cross-linking of the T-cell receptor in the CD3, increasing calcium, decreasing PKC, and then we get an upregulation of T-cell apoptosis. Directly, it binds to the mitochondria PTP, or permeability transition pore, preventing its opening. I will show you a diagram of that, which prevents cytochrome C release in the epithelium. Indirectly, it upregulates PCL-2 which is an inhibitor of apoptosis; downregulates the pro-apoptotic factor P53, and then expression in epithelial cells would then, therefore, downregulate apoptosis.

This is the epithelial response. This is work

that was done by Dr. Bill Tadden, in New York. Essentially what happens is there is this opening of a permeability transition pore within the mitochondria. It allows the release of cytochrome C into the cytosol which allows the apoptosis processes to continue. What cyclosporine does, it binds to a cyclophilin binding site on the external leaflet of this permeability transition pore, thus keeping it shut and preventing cytochrome C release into the cytosol, thereby preventing epithelial apoptosis. So, the epithelial apoptosis phenomenon is a very direct one; the lymphocytic one is probably more indirect.

DR. FONG: At this point, we should probably go to the FDA presentation and then finish up with more questions after lunch.

FDA Presentation

Medical Review

DR. BOYD: My name is William Boyd, and I am a medical officer, an ophthalmologist, in the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

I would like to go over the three clinical trials submitted to the NDA. We have discussed most of this information. Cyclosporine ophthalmic emulsion is an immunomodulator. Its proposed indication is the treatment of moderate to severe keratoconjunctivitis sicca. The dosage form is an ophthalmic emulsion for topical

administration.

We have already discussed that there were two Phase III clinical trials, protocol 002 and protocol 003; one Phase II protocol that was a dose-ranging study, protocol 01.

We will review 002 first. This was a randomized, multicenter, parallel group, double-masked Phase III trial. It had three treatment arms with cyclosporine 0.05 percent, 0.1 percent, with a common vehicle. In the test drug schedule all the subjects received either a concentration of cyclosporine or vehicle bilaterally twice a day for six months. The total number of subjects was 405.

The objective signs, as put forth in the submitted study report, we have already discussed: corneal staining, conjunctival staining, the sum of corneal and interpalpebral conjunctival staining, the Schirmer tear test and tear breakup time.

The subjective symptoms we have actually already discussed, the symptoms of dry eye, the OSDI, the facial expression subjective rating scale, the investigator's global response, treatment and treatment success.

The criteria for effectiveness as put forth in the study report, the sponsor should show a statistically significant difference between the active treatment and the vehicle for one objective sign and one subjective symptom.

Safety criteria in this protocol were visual acuity, intraocular pressure, slit lamp examination, and pharmacokinetic parameters for subsets of subjects at selected centers.

Looking at significance in the objective signs in protocol 002, there is a statistically significant among group difference at month 6 that favors 0.05 percent cyclosporine over vehicle.

This is categorized Schirmer with anesthesia. A statistically significant among group difference is approached but not reached at month 6 that favors 0.05 percent cyclosporine over vehicle.

Blurred vision -- there are statistically significant among group differences at months 3 and 4 which favor 0.05 percent cyclosporine over vehicle.

Refresh use -- there is a statistically significant among group difference at month 3 that favors 0.05 percent cyclosporine over vehicle.

There are statistically significant among group differences at months 4 and 6 in sensitivity to light favoring 0.05 percent cyclosporine over vehicle.

In itching there are statistically significant among group differences at months 3, 4 and 6 which favor 0.1 percent cyclosporine over vehicle.

The composite score, which has already been

discussed, which is a total of patients' subjective symptoms, there are statistically significant among group differences at months 3 and 6 that favor both 0.05 percent and 0.1 percent cyclosporine over vehicle.

The Ocular Surface Disease Index -- there are statistically significant among group differences at months 3 and 4 in favor of 0.05 percent cyclosporine over vehicle.

In the facial expression subjective scale there are statistically significant among differences at months 3 and 6 that favor 0.1 percent cyclosporine over vehicle.

Moving on to safety of protocol 002, again the most common ocular adverse events were burning, eye pain, itching and stinging. There was no increase in ocular systemic infections.

Changes from baseline in visual acuity, slit lamp examinations and intraocular pressure were similar across all three treatment groups.

Summarizing protocol 002, the statistically significant objective sum was corneal staining, and the statistically significant subjective symptoms were blurred vision, refresh use, sensitivity to light, itching, the composite score, the OSDI, the facial expression subjective scale.

Moving on to protocol 003, protocol 003 is identical to protocol 002 with the exception that there are

no pharmacokinetic parameters drawn. This is also a randomized, multicenter, parallel group, double-masked trial with the same three treatment arms.

The test drug schedule is identical and all subjects received either cyclosporine or the vehicle bilaterally twice a day for six months. The total number of subjects was 472.

The objective signs we have already gone through and they are identical to protocol 002.

The subjective symptoms are identical to protocol 002.

Safety criteria are identical to protocol 002, with the exception that in the study pharmacokinetic parameters were not drawn.

This slide demonstrates corneal staining. Baseline mean corneal staining scores were significantly higher in the 0.05 percent and 0.1 percent cyclosporine groups than in the vehicle group, and there are no statistically significant among group differences here.

In the categorized Schirmer with anesthesia t here are statistically significant among group differences favoring both 0.05 percent and 0.1 percent cyclosporine over vehicle at month 6.

Blurred vision -- there are statistically significant improvements from baseline with both 0.05

percent and 0.1 percent cyclosporine at 6 months, but there are no statistically significant among group differences.

In refresh use, a statistically significant among group difference is approached but not reached at month 6 that would favor 0.05 percent cyclosporine over vehicle.

Moving on to subjective symptoms, this is the global response to treatment. It did show an among group difference that was statistically significant but only at month 3, with a p value of 0.031.

Again to summarize safety for this protocol, the most common ocular adverse events in protocol 003 were burning, conjunctival hyperemia, photophobia and stinging. and, again, there was no increase in ocular or systemic infections.

As seen in protocol 002, changes from baseline in visual acuity, intraocular pressure and slit lamp examination were similar across the three treatment groups.

Summarizing the statistically significant objective signs in protocol 003 were the categorized Schirmer with anesthesia.

The statistically significant subjective symptom of the global response to treatment was significant at month 3. Some investigators rated this global response based on their clinical evaluations of the subjects and other investigators asked subjects directly about their response

to treatment.

This chart just shows variables that approached significance favoring cyclosporine at 0.05 percent over vehicle. Objective signs at month 4, p value of 0.09. Subjective symptoms, and there are several -- dryness, sandy/gritty feeling, blurred vision and refresh use -- approach but do not reach statistical significance.

The last protocol, protocol 001 which was a dose-ranging protocol, was also randomized, multicenter, parallel group, double-masked. It had cyclosporine 0.05 percent, 0.1, 0.2 and 0.4 percent and the vehicle of cyclosporine 0.2 percent.

All subjects received either a concentration of cyclosporine or the vehicle bilaterally twice a day for 12 weeks, and the total number of subjects was 162.

The primary efficacy measures as set forth in the study were the Schirmer tear test without anesthesia, corneal staining and symptoms of dry eye which were collected both from diaries and case report form queries.

The secondary efficacy measures were tear film debris, rose bengal staining, tear breakup time and brush cytology, tear meniscus, meibomian gland health, tear proteins, the facial expression subjective rating scale, the OSDI, refresh use and the investigator's global evaluation response to treatment.

The safety criteria in this protocol were vital signs, visual acuity, intraocular pressure, biomicroscopy, conjunctival microbiology and selected blood work, CBC blood chemistry and whole blood cyclosporine concentration.

Looking at some of the primary efficacy measures, corneal staining, weeks 14 and 16 constitute the 4-week post-treatment phase. There are statistically significant improvements from baseline in each treatment group at each visit but there are no statistically significant among group differences.

The Schirmer values without anesthesia, there are no statistically significant among group differences. There are statistically significant improvements from baseline at weeks 4 and 8 for the 0.1 percent cyclosporine treatment group.

Here there is a statistically significant among group difference at week 12 that favors 0.2 percent cyclosporine over 0.05 percent cyclosporine, and at week 12 that favors vehicle over 0.05 percent and 0.4 percent cyclosporine.

Reviewing safety in protocol 001, there were no clinically significant changes in visual acuity, intraocular pressure or split lamp examination. There were comparable changes in microbial flora across all the treatment groups, including the vehicle, and there were no adverse events