DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Dermatologic and Ophthalmic Drugs Advisory Committee

Thursday, May 29, 2008

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5630 Fishers Lane
Rockville, MD

PAPER MILL REPORTING
(301) 495-5831

C O N T E N T S

PARTICIPANTS

Marijean M. Miller, Acting Chair
Yvette Waples, Pharm.D., Designated Federal Official

Dermatologic and Ophthalmic Drugs Advisory Committee

Ellen Strahlman, M.D., M.H.Sc., Industry Representative (Non-Voting)

Temporary Voting Members

Paula Cofer, Patient Representative
Joel Mindel, M.D., Ph.D.
Scott M. Steidl, M.D.

FDA CDER (Non-Voting)

Wiley Chambers, M.D.
Edward M. Cox, M.D., MPH
Sonal Wadhwa, M.D.

P R O C E E D I N G S

Call to Order

DR. MILLER: Good morning. This is the May 29, 2008 Meeting of the Dermatological and Ophthalmological Drugs Advisory Committee.

Introduction of Committee

DR. MILLER: Would each member of the Committee like to state their name.

DR. STRAHLMAN: Ellen Strahlman.

DR. MINDEL: Joel Mindel.

DR. STEIDL: Scott Steidl.

MS. COFER: Paula Cofer, Patient Representative.

DR. COX: Ed Cox from CDER/FDA.

DR. CHAMBERS: Wiley Chambers, CDER/FDA

DR. WADHWA: Sonal Wadhwa, CDER/FDA

DR. MILLER: The Conflict of Interest Statement, please.

Conflict of Interest Statement

DR. WAPLES: Again good morning. My name is Yvette Waples. I am a Designated Federal Official for this meeting.

The Food and Drug Administration, FDA, is

convening today's meeting of the Dermatologic and Ophthalmic Drug Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the Industry Representative, all members and consultants of the Committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, FD&C Act, are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special committee employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them including those of their spouses or minor children and for the purposes of 18 U.S.C. Section 208 their employers. These interests may include investment, consultant, expert witness testimony, contract grants, CRAVA, teaching, speaking, written patents and royalties, and primary employment.

Today's agenda involve discussions of New Drug Application NDA 22-212 difluprednate ophthalmic emulsion, ST-601, Sirion Therapeutics proposed for the treatment of inflammation and pain following ocular surgery.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers

have been issued in connection with this meeting.

Dr. Ellen Strahlman is serving as the Industry Representative acting on behalf of all regulated industry. Dr. Strahlman is an employee of Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue.

Thank you and again good morning.

DR. MILLER: Dr. Chambers.

FDA Introductory Remarks

DR. CHAMBERS: Thank you, Dr. Miller. I would like to personally and on behalf of the Agency welcome all of the Advisory Committee members and consultants. As I was reminded earlier this morning, this is the first meeting for an ophthalmic topic that the Dermatology and Ophthalmology

Advisory Committee has had in actually over a year.

Although we anticipate there will be more Advisory Committee meetings on ophthalmology topics as we continue to implement some of the changes that occurred with the FDAAA Act, which was passed and signed in September of last year, that requires, unless the Agency has good reason to have an advisory committee meeting for all new molecular entities, and the topic that we are discussing today is a new molecular entity that has been submitted requesting approval before our group.

I specifically want to thank you for both the time that you are spending today, your travel down here, and the time and preparation which we know is frequently at least as long as the discussions that go on during the meeting.

We welcome any comments at any time throughout the meeting. This is designed to be an open public forum for discussion of this topic, and we welcome ideas particularly those that we may not have thought of as we were reviewing the application. So, the fresh ideas are most certainly welcome.

If at any point there are questions, problems, or suggestions on ways to make these meetings better, I would

welcome those either now, during the meeting, or sometime afterward.

Thank you for coming.

DR. MILLER: Thank you, Dr. Chambers.

We will now proceed with the sponsor presentation. Before the presentation I would like to remind the public observer at this meeting that while this is meeting is open for the public observation, public attendees may not participate except at the specific request of the panel.

Thank you.

Yes, Dr. Mindel.

DR. MINDEL: Could the voting members of the Committee sitting around here be identified?

DR. MILLER: Yes, let's make a point to do that.

The voting members include myself, Dr. Marijean Miller, I am the Acting Chair today; Dr. Joel Mindel, who has just identified himself and asked the question; Dr. Scott Steidl, and also there is a Patient Representative here today, Paula Cofer, and that's it. Thank you.

I would like to recognize the sponsor and this is Dr. Roger Vogel, and he will be giving the sponsor presentation. Thank you.

Industry Presentation

Difluprednate: Efficacy and Safety Review

DR. VOGEL: Thank you, Dr. Miller.

[Slide.]

I am Roger Vogel, Chief Medical Officer of Sirion Therapeutics.

[Slide.]

The attendees from Sirion and our consultants are shown on this slide. They are sitting in this group here.

[Slide.]

Our presentation will cover the objectives of our development program, some background on difluprednate to show you what we feel is exciting about difluprednate, and I will then talk about the clinical studies and the efficacy and safety data, and our conclusions.

[Slide.]

Our objectives for the clinical program were to demonstrate the efficacy and safety of difluprednate in inflammation of pain following ocular surgery, and select a dose schedule based on the benefit to risk evaluation.

[Slide.]

A little background on difluprednate. It is a

prednisolone derivative created in 1970, but a new chemical entity in the USA as Dr. Chambers points out, but from a know class of drugs.

It is classified as a very strong steroid based largely on dermatological criteria, it is marketed in Japan for dermatology use, and has been so for 30 years.

Sirion licensed it from Senju based on the demonstrated efficacy in uveitis

[Slide.]

I will show you the results here from an open-label study in patients uveitis. Grade 4 is the highest grade on the scale. The group contained patients who had failed to respond to current therapy and were switched to difluprednate 4 times a day.

As you can see, there was a very good response and 72 percent of these subjects had a cell grade of 1 or less after just 14 days of 4 times a day therapy. The study group contained patients with Vogt-Koyanagi-Harada syndrome and sarcoidosis.

[Slide.]

To put the potency of difluprednate into perspective, Senju the widely accepted betamethasone as its

comparator in many of their studies and demonstrated that difluprednate was not inferior to betamethasone, which would make it at least 6 times as potent as prednisolone and with a longer half-life.

[Slide.]

Difluprednate is a modification of prednisolone molecule and was designed to penetrate epithelium and to have increased potency.

[Slide.]

It's fluorinated at two positions here. To increase penetration, this acetyl group added here to enhance inflammatory activity, a butyryl moiety added at the C21 position.

[Slide.]

Difluprednate is deacetylated at the epithelium and then forms the very active DFB molecule which is highly bound to glucocorticoid receptors. That is then metabolized to a number of other molecules of which diflupredniso lone is probably the most frequent. All of those have a lot less activity or no activity on the steroid receptors.

I want to highlight the potency of difluprednates and its unique chemistry which produces that potency whilst

reducing the potential for systemic side effects.

I would like you to feel that you are recommending approval of a valuable product here. This is not a soft steroid. The clinical studies that will be the main focus of the discussion here today are adequate to demonstrate the efficacy and safety of difluprednate, but may not represent the full potential of difluprednate to provide the first true innovation in ophthalmic steroid anti-inflammatory therapy in decades.

[Slide.]

Studies in rabbits on receptor binding showed that 0.05 percent concentration was more active than the lower concentrations that were tested, and betamethasone, and have also shown that higher concentrations of 0.05 percent were obtained in the anterior chamber and in the iris/ciliary body.

So, difluprednate has a penetration rate twice as fast as betamethasone and a half-life on the receptors that is about twice as long as betamethasone, and betamethasone is the most widely used, strong ophthalmic steroid in Japan and in several countries in Europe, but is not available in the USA.

So, in summary, high potency in receptor binding should equate to lower dose, longer half-life, supports less frequent dosing, and metabolism in the tissues results in lower systemic steroid exposure.

[Slide.]

A number of Phase 3 studies have been completed on difluprednate, two in the USA by Sirion, which you will see more of later, and three in Japan by Senju, two in postsurgical inflammation and one in uveitis.

[Slide.]

The safety data we submitted to the NDA were derived from all of the Phase 3 studies mentioned plus, in addition, two Phase 3 studies.

[Slide.]

Sirion conducted two identical studies in postsurgical inflammation in which difluprednate twice a day and 4 times a day was compared to the vehicle of difluprednate emulsion.

[Slide.]

I will now show you how the dose was selected and how we conducted the studies followed by the efficacy and safety results and our conclusions.

[Slide.`]

Our rationale for the selection of the 0.05 percent difluprednate for the Phase 3 studies was based on several pieces of data from Senju. The upper limit was set by the fact that the concentrations higher than 0.05 percent could not be formulated as an emulsion.

An emulsion was targeted because as everyone knows, prednisolone acetate suspension needs a lot of shaking and doesn't necessarily suspend. Suspension is not an ideal delivery system and work at Senju had shown quite clearly that penetration of difluprednate from an emulsion was 4 times better than from a suspension, so an emulsion was the ideal.

The receptor binding studies in rabbits, which I mentioned earlier, showed 0.05 percent to be superior and that it was superior in this assay also to betamethasone, and in a rabbit model of postsurgical inflammation, 0.05 percent was superior to the other concentrations, the lower concentrations of difluprednate tested and to betamethasone.

[Slide.]

In 3 clinical studies shown here difluprednate was 0.05 percent, was well tolerated in single and multiple dose

studies in volunteers and it was more efficacious the lower concentrations in postsurgical inflammation in a small Phase 2 study.

Based on these data, Sirion carried forward the 0.05 percent into our Phase 3 studies.

[Slide.]

Now, some discussion in our study design. First of all, I would point out the design we used for our studies was one that has been well tested by others before us. We received some recommendations on the design from our colleagues at CDER, two of which we adopted, and on the other we compromised.

[Slide.]

We proposed initially Day 15 to be the endpoint of drug treatment and endpoint for efficacy. FDA recommended Day 8 based on their experience, and we adopted Day 8 although maybe we should have stuck to our guns. As you will see later, results were more uniform at Day 15.

We proposed a cell grading system which defined Grade Zero as less than 5 cells. FDA recommended Grade Zero to equals no cells. We suggested a compromise which Grade Zero would equal no cell or 1 cell, a maximum of 1 cell

based on our review of the clinical literature, which I would like to discuss with you a little here.

[Slide.]

Substantial evidence exists for a normal eye to have a cell or 2 in the anterior chamber, and I show here 3 recent publications based on cell and flare meter data showing that 1 to 2 cells may be a normal finding in 10 percent of subjects.

One paper suggests that the cell count might be at its highest in subjects around the 60-year-old mark, the age at which people start turning up for cataract surgery.

[Slide.]

Furthermore, many published papers have used Grade Zero equals Zero or 1 cell, and so have used even Grade Zero to be less than 5 cells, and they are presented here.

Additionally, mydriatics are often used concomitantly in studies of ocular inflammation, and mydriatics may cause release of cells and pigment granules off the surface of the iris which may also appear as cells in the anterior chamber.

So we felt that a more realistic definition of clearing was to have patients who had 1 cell or no cells.

DR. MILLER: Just one second. A point of question. We are allowed to ask questions at the end of the presentation, correct? We have a member here who had one question at this moment. Is that possible? A point of protocol.

DR. CHAMBERS: Would you rather take questions now or to take questions at the end?

DR. VOGEL: I guess I could take a question now.

DR. MILLER: Okay.

DR. STEIDL: Just a quick one. Since the number of cells, determination of the number of cells is such a big issue, I am curious how that was carried through the different studies. Is it completely left to the discretion of the clinician evaluating it, to their interpretation of what was an inflammatory cell and what was a pigment cell, or was there a criteria for that?

DR. VOGEL: Well, yes, they were supposed to be looking for inflammatory cells, that's true. I mean they were supposed to not be counting red cells and bits of pigment, but a cell that has come off the iris might be counted as a cell. I mean we can't rule that out.

DR. MILLER: Thank you. I think we will keep most

questions until the end, but thank you for that.

DR. VOGEL: That's okay, because often you think of something as you are going by and can be clarified in the process.

[Slide.]

So, our studies, 2 multicenter, double-masked placebo-controlled studies using 26 centers in the US. They have divided into 2 studies. We refer to these as Study 1 and Study 2. I see that FDA's presentation refers to them as Study A and Study B. Study 1 is Study A. That is the way the protocol defined it. Study B is Study 2 .

Study 1 was population drawn from south of the 37th parallel. Study 2, Study B, was north of the 37th parallel.

Study drug was administered either twice or 4 times a day for 14 days and patients could have received difluprednate twice or 4 times a day or placebo twice or 4 times a day.

[Slide.]

So, the study design was this and I am going to go through it in a little detail. Subjects had a screening visit before surgery. Then, on Day Zero, they had their

surgery, and then, on Day 1, they were qualified to be randomized and receive their first dose.

They were seen on Days 3, 8, and 15, and I should emphasize that the protocol required physicians to withdraw any patient who was not responding satisfactorily at any visit because this was a placebo-controlled study.

At the Day 15 visit, if a subject was progressing well, which might not mean that inflammation was totally cleared at that time, the physician made the decision to have the patient continue into the tapering period of a further 14 days. The tapering regimes are shown in the box below.

If all was well on Day 29, the subject would stop study drug and be seen a week later on Day 36 for a follow-up visit. If the physician felt the subject needed further treatment, the subject was withdrawn from the study and given alternative medication.

Anyone that was withdrawn from the study at any stage still had a follow-up visit one week after they stopped study drug.

[Slide.]

Our inclusion and exclusion criteria.

[Slide.]

Key inclusion criteria was patients having uni-ocular surgery on the day prior to study enrollment. They also had to have an anterior chamber cell grade of 2 or more on the day after surgery, Day 1.

[Slide.]

Some exclusions were made at screening, prior to surgical procedure, and those are listed here. I won't read them out, but they are fairly common exclusions for steroid therapy.

[Slide.]

On Day 1, the day following surgery, there were some additional exclusion criteria. An intraocular pressure of 24 mm or greater was an exclusion, a cell grade of less than 2 was an exclusion, and any intraoperative complication which would have made it inappropriate for the subject to enter a placebo-controlled study was also an exclusion.

[Slide.]

Now, the demographics and baseline characteristics.

[Slide.]

I am going to show here the 4 times a day treated

subjects from both Study 1 and Study 2. The only remarkable observation is the difference in baseline intraocular pressure at Day 1 between the two studies and also the proportion of dark irides, bearing in mind Study 1 was in the south.

[Slide.]

Now, the twice a day treatment group, and there is a lesser difference between the studies for intraocular pressure and proportion with dark irides, but the tendency is still there.

[Slide.]

Now, the race and ethnicity for the 4 times a day groups, you see there were more Hispanics in Study 1 than Study 2, and a similar situation in the BID-treated groups.

[Slide.]

Now, the efficacy, and in the next few slides I will address the analysis of the proportion of subjects with an anterior chamber cell grade of Zero, those with an Visual Analog Scale pain of Zero, and all the efficacy data you will see from the intention-to-treat last observation carried forward analysis, and address the period up to the Day 15, end of treatment visit.

I draw your attention in advance to the similarity between the twice a day and 4 times a day treatments.

[Slide.]

Here we have the proportion of subjects with an anterior chamber cell Grade Zero as measured using a slit lamp.

[Slide.]

The clear superiority for 4 times a day difluprednate compared to placebo at Day 8 and Day 14 is seen in both studies.

[Slide.]

In the twice a day group in both studies, the twice a day treatment group was superior to placebo at Day 8 and 15 for the proportion of subjects with anterior chamber cell grade of Zero.

[Slide.]

Here now graphically, you see the twice a day and 4 times a day groups and how similar they are and how both are nicely separated from placebo. That is Study 1.

[Slide.]

A similar picture for Study 2, good correspondence between the twice a day and 4 times a day groups.

[Slide.]

Looking at the twice a day and 4 times a day results for Day 8 on the same slide, numerically, there was good agreement between the two studies and between the treatment groups. There was some variability in the response in the placebo-treated group which clearly affected p-values for twice a day and 4 times a day at this time point. You can see almost twice as many placebo responders here, but that did not affect the Day 15, which is the next slide.

[Slide.]

Here we see the Day 15 results with clear superiority over placebo for both 4 times a day and twice a day at Day 15.

[Slide.]

Now, the analysis of the proportion of subjects with a pain score of Zero, the days that were derived using the Visual Analog Scale. We asked all subjects to look at the 100-mm long line, zero to the left, no pain at all, and 100 was the worst pain that they could imagine.

They were asked to indicate their pain level by marking the line. We then measured the distance between the

zero and the subject's mark, and that was their score.

Now, this slide and those that follow shows the proportion who scored zero, no pain. Now, I have to pause and say this is truly remarkable, any of you that treat patients, that any patient that comes into your office and is happy to report that they have no pain. But anyway that is what we are recording here.

[Slide.]

Firstly, the 4 times a day group showing clear superiority over placebo at all time points.

[Slide.]

For those treated twice a day, the difference between placebo was clear in Study 2 at both Day 8 and 15, but less marked in Study 1 at Day 8, although the proportions of patients were really very similar, 40 percent.

[Slide.]

Here, I present graphically the mean pain scores on the Visual Analog Scale, and we see how similar the twice a day and 4 times a day groups were and the separation from placebo. That is Study 1.

[Slide.]

In Study 2, an even tidier picture, if you like.

[Slide.]

We conducted three analyses which may give you some added clinical perspective on difluprednate twice a day and 4 times a day. The first was the change from baseline, the day after surgery, in cell grade.

The second was an analysis used in recently published papers in which we combined a cell count of 5 or less, which will be a trace of cells, with an anterior chamber flare grade of zero. This is regarded in peer-reviewed journals as a clinically acceptable definition of control of inflammation, and we also looked at the analysis of the proportion of subjects withdrawn for lack of efficacy.

[Slide.]

On this slide, we have both studies in both BID and QID dose groups. Both treatment groups were superior to--and we are now looking at the change from baseline in cell grade. By Day 8, both twice a day and 4 times a day groups in both studies had over a cell grade change, and by Day 15, almost 2 cell grade steps.

[Slide.]

Those days were shown graphically here. This is the main mean change from baseline in anterior chamber cell grade for Study 1.

[Slide.]

And for Study 2.

[Slide.]

Looking at the proportion of subjects with clearing of inflammation using the definition I gave you, both the 4 times a day and twice a day treatment groups were successful in clearing inflammation in over 70 percent of subjects. That is at Day 15 and over half the subjects at Day 8.

[Slide.]

You will remember that because this was a placebo-controlled study, the protocol advised investigators to remove subjects who were not responding adequately.

This slide shows the results of that with dramatically more subjects on placebo being withdrawn for lack of efficacy.

[Slide.]

If we look at that another way around, here, the proportion of subjects not removed or not leaving the study

for any reason, and therefore, those successfully completing the study. You see around 90 percent or up of all subjects were satisfactorily managed regardless of whether they were on twice a day or 4 times a day.

[Slide.]

So, based on the data that you have seen, we have shown two Phase 3 placebo-controlled trials, statistically significant improvement in pain and inflammation, as well as other endpoints.

Twice a day or 4 times a day subjects achieved cleared anterior chamber inflammation at Day 8 and Day 15.

Subjects who received placebo were much more likely to withdraw from the study due to a lack of treatment effect.

The twice a day dosing regime provided the lowest effective dose, and clinical evidence supports both twice a day and 4 times a day dosing.

[Slide.]

Now, I am going to give a brief overview of the safety. The data analysis here is largely from the Sirion studies, but with reference to the Senju studies where necessary for completeness particularly in the serious

adverse events and intraocular pressure.

Firstly, the adverse events and then we will spend a little more time on one of the side effects, which is the more pressing concern with a strong steroid, and that is the effect on intraocular pressure.

[Slide.]

Very few serious adverse events were seen, and I will expand on those in a minute. Only one death that was due to a stroke in a man who discontinued his anticoagulants before surgery, and he was in the placebo group.

Adverse events leading to discontinuation here quite clearly more frequent in the placebo control group than in either of the treatment groups.

[Slide.]

There were no ocular serious adverse events in our Phase 3 studies, in the Sirion Phase 3 studies. These systemic adverse events which are listed here were all not related to study drug and were all conditions that were expected in an elderly population undergoing intraocular surgery.

[Slide.]

In the Senju studies, there were some ocular

serious adverse events reported, and I have put them all together here, but you can see the first three were in the postoperative inflammation studies, the last two were in uveitis studies.

Only one of these was regarded as treatment related, and that was posterior synechia requiring surgery. The corneal perforation you see down here in the uveitis study was actually the contralateral eye that was not receiving treatment, but had herpes.

The other adverse event was a viral necrotizing retinitis in a patient with uveitis, and this was not diagnosed by the physician prior to initiating study therapy.

[Slide.]

I am representing here the adverse events from our studies using the MedDRA classification and showing first those in which there were more in one of the difluprednate groups than in the placebo group.

Most events were the result of surgery, and not directly related to steroids, numerically, not very different between the active and placebo groups except in the iritis twice a day group, slightly higher, and these

were mainly patients with an increase in anterior chamber cells after discontinuation of study therapy, and one in whom that happened on Day 8 during the study.

[Slide.]

Here are those adverse events which are more frequent in the placebo group. Most, if not all, of these adverse events were the outcome of surgery. Bear in mind that patients had surgery before they went into this study, so any of these could well be the outcome of the surgery rather than anything to do with the drug.

However, the placebo group suffered substantially more of these and one would really imagine that that was due to the fact that the placebo group was not receiving an anti-inflammatory agent at all, whereas, the other groups were, and I think that accounts for the difference in the adverse events.

[Slide.]

Now, a rise in intraocular pressure is a common side effect of steroid treatment in the eye. Generally speaking, this is proportional to the strength of the steroid or to the level of duration of the dosing.

In this slide, you see the mean intraocular

pressure and standard deviations for all the groups in both Studies 1 and 2 combined. The means and the standard deviations lie between the limits of a normal intraocular pressure for all groups at all times.

[Slide.]

In case the means were hiding some individual patients with severe intraocular pressure rises, we took an accepted definition of a clinically significant increase in intraocular pressure, that is, an increase of 10 mm of mercury or more from baseline, which also achieved a level of at least 21 mm of mercury.

This would be an intraocular pressure increase which might be viewed as needing treatment. I am showing here the number and percentages for the Sirion studies and for all the Senju studies.

In the Sirion studies, less than 3 percent in the treatment groups, slightly higher in the Senju studies, but with an overall mean of around 4 percent. This is lower than the range published in various places for prednisolone acetate Pred Forte, which starts around 6 percent and may be as high as 15 percent.

[Slide.]

So, to summarize our safety analysis, we found in our studies no ocular serious adverse events. Fewer ocular adverse events were reported for subjects in the twice a day and 4 times a day groups compared with placebo.

The vast majority of the adverse events reported in the study were related to the outcome of surgery.

A higher proportion of subjects in the placebo group withdrew from the study due to an adverse event.

Less than 3 percent of subjects in our studies had a clinically significant intraocular pressure rise.

[Slide.]

In conclusion, difluprednate is a further addition to the available topical ocular steroids with some advantages and possibly less risk than available products.

I believe that you will probably conclude that this product can be recommended for approval.

However, there might be some differences between our presentation and that of the FDA with regard to interpretation of the data particularly as it affects the twice a day regime in one of the two studies.

Nevertheless, the evidence is that over the 14-day treatment period, twice a day and 4 times a day

difluprednate was similarly effective for the treatment of pain and inflammation.

Analysis of treatment success shows no clinical important difference between the twice a day and 4 times a day dose regimes with around 90 percent or more on either twice a day and 4 times a day being satisfactorily managed.

The difference between the doses in adverse event frequency was also not clinically important or dose consistent. Currently available steroids are indicated for twice or 4 times a day dosing, and the data we have presented leave me to feel very comfortable suggesting to you that it might be reasonable to conclude that, in the clinical practice situation, doctors should have the option to prescribe difluprednate either twice or 4 times a day for the management of inflammation and pain following ocular surgery.

Thank you for your attention.

DR. MILLER: Thank you, Dr. Vogel, for your extensive presentation. It was very informative.

Questions/Clarifications

I would like to start questions from the Committee first. Dr. Steidl had already had one question. Would you

like the opportunity to start first or other questions at this moment?

DR. STEIDL: I have no questions at this moment.

DR. MILLER: Other members?

DR. MINDEL: I have a lot of questions. I don't know whether to save some of them for after the FDA presentation. Most of them are aimed at the sponsor.

DR. MILLER: I would welcome some questions now if you feel they are appropriate. If you feel they will be answered possibly by the FDA discussion, we can wait. But, if you feel there are specific issues, let's get to them now.

DR. MINDEL: The major issue I had was it is possible to have 50 percent of your patients be inflammatory-free in terms of cells, and 50 percent of the patients be pain-free, and none of the patients be both pain and inflammation-free.

You haven't shown a correlation of both pain and inflammation, and I was wondering why that data was not shown.

DR. VOGEL: I think we will have that shortly, because I agree.

DR. MILLER: Would you like a moment to find that?

DR. VOGEL: No. Bingo! I think we can go. Thank you. There we go.

[Slide.]

Yes, it's a very good question and we did this analysis. These are patients with an anterior-chamber cell grade of zero plus pain-free on Day 8, and 4 times a day, twice a day in Study 1 and Study 2.

I think the patent really is very similar to that which you see for pain and there is slightly less significance attached to the twice-a-day-group in Study 1. It is very similar proportion of subjects involved here, but different P values because of the comparison with the placebo. That was Day 8.

When you look at Day 15, which gives you the more complete picture, that is being shown there.

DR. MINDEL: I have some difficulty with your use of Grade zero. I would like the FDA use of zero cells. Have you had the same analysis using zero cells in the AC?

DR. VOGEL: This one we didn't do, no.

DR. MINDEL: Which leads me to another question I read. The FDA presented how cells were counted and it was

very precise as to the width of the-slit lamp beam and the height of the slit-lamp beam. But there was nothing said about the duration of treatment, the duration of the examination, and whether the beam was maintained stationary or swept back and forth.

It is possible if you have one cell in the anterior chamber with the circulation of fluid, that, if you count for two minutes, that one cell may be counted as three or four, and if you sweep back and forth, a 1-mm beam, you see the whole anterior chamber as opposed to a very narrow cross-section if you don't.

DR. VOGEL: The instruction was that they should focus this beam across the anterior chamber and they should count the cells that were in the beam. We did not tell them only sit there for five minutes. We said count until you are sure that you have a number and then stop.

DR. MINDEL: You did not sweep. You kept it stationary.

DR. VOGEL: No, no, it was stationary.

DR. MINDEL: It stayed stationary.

DR. VOGEL: We tried to make that as standard as possible. It was belabored at the investigators' meetings

which we held.

Our discussion as to whether Grade zero should be no cells or 1 cell is a bit academic, but I think it's important. However, we did do our analysis using a cell count of zero. In fact, I think that is going to be presented anyway later.

The conclusions were not that different, really and truly.

DR. MINDEL: But for the cell count of zero and pain, you don't have that data to present.

DR. VOGEL: No, no, no. After all, we didn't think that a cell count should be absolutely zero, so we didn't do that.

DR. MINDEL: But just to comment on that, Grade zero to most of us sitting here just reading the data would initially make me think zero was zero, so I found it troubling to find that zero could also mean some inflammation was still present.

DR. VOGEL: Well, I think we tried from our search of the literature to point out--can we go back to that slide--that in studies of lots of healthy normal eyes, it was possible to find one or two cells in 10 percent of them,

and on the mean, the mean was 1 or 2 cells. If we can get that up again.

[Slide.]

Here you see, I mean this is not a small study. These were using cell and flare counter, so this was fairly objective data. The mean cell count was 1.1 in normal healthy volunteers, here 2.2, a range of zero to 2 with a mean of 0.9.

So, I don't know. I mean it just means that would you start treatment on somebody who had one cell floating in their anterior chamber, and the question is in a clinical one.

DR. MINDEL: I don't consider seeing any cells in the anterior chamber as not needing an explanation in the normal patient. Let me put it that way.

Could you identify the journals that those publications appeared in?

DR. VOGEL: We have that. I doubt whether we can put that up, but we can certainly get it. Do we have it? We can provide that as a follow-on. We don't have it here.

DR. MINDEL: All right. I will move on to another area. It is not clear to me why you divided two identical

studies that were probably performed simultaneously into one north of the 37th parallel.

It sees like if you wanted four studies, you could have had a longitudinal division, as well. Can you give an explanation for why you did that?

DR. VOGEL: FDA likes us to provide two geographically distinct studies, and that's what we did.

DR. MINDEL: It was at the FDA's request

DR. VOGEL: Right.

DR. MILLER: Dr. Chambers.

DR. CHAMBERS: The Food, Drug, and Cosmetic Act says that, to establish safety and efficacy, it should be with adequate and well-controlled trials with an "s" at the end of that trials within the law, so we have normally assumed that unless there are some particular outstanding circumstances, that we expect there to be more than one trial.

That does not mean the trials have to be identical, but identical trials are perfectly acceptable. So, we generally encourage replication of the particular study results that can be done either sequentially or it can be simultaneously.

Obviously, simultaneously speeds up the overall drug development. So, if you run two trials, even though they are constructed identically, at the same time, and analyze them separately, that gives a greater reassurance that there was not something unusual, funny, some systematic bias with in a trial that would potentially confound the results. So it's a stronger result.

DR. MILLER: Dr. Mindel.

DR. MINDEL: I had trouble with the use of the term "clinically significant" that has been used. First, the clinically significant drug-induced elevation of intraocular pressure, it was defined as an intraocular pressure of more than or equal to 21. That was also more than 10 mm of mercury higher than the baseline taken the day after surgery.

However, I learned from the FDA information that was sent that excluded from the study were not only patients with a history of ocular hypertension, glaucoma, and a history of steroid-induced hypertension, but also the presence of an intraocular pressure of more than or equal to 24 mm of mercury on the day after surgery was a cause for exclusion.

With such a convoluted definition of an intraocular pressure elevation being significant, it is surprising that almost any patients had elevated intraocular pressure.

DR. VOGEL: Well, some did. I take your point. Clearly, because we were doing a study with what we believe is a strong steroid, we did not want to specifically expose patients to the likelihood that their pressure would go up.

In fact, although we excluded patients who had a history of steroid-responsive glaucoma, we actually excluded very, very few patients on that basis. Most patients coming to cataract surgery don't know, have never had a steroid before, and don't have that information.

We actually checked that with the investigators afterwards. But I agree. I mean we did, if you like, bias this away from having patients with high intraocular pressure, I absolutely agree, and the definition we chose was one that within this context would have been likely to result in the doctor initiating pressure lowering therapy.

I mean I think an elevation less than that, most physicians would just wait until the inflammation was gone, wait until the patient was off drug, and then if the

pressure was still up, they might then initiate therapy.

So, we tried to pick that definition, but I mean we could have chosen another one. We could have just chosen an elevation of 10 mm of mercury and we can show you those data, as well.

DR. MINDEL: And how many patients were excluded with a pressure of 24 or more on the day after surgery?

DR. VOGEL: We don't recall, no. It certainly wasn't a major source of patients not being enrolled.

DR. MINDEL: The statement is made that there is no clinically meaningful difference in efficacy for difluprednate whether dosed twice a day or 4 times a day. And I am referring to your sponsor's presentation of information that was given to us on pages 25 and 27, and then also concluding with--this is Section 9-1--no clinically meaningful difference in inflammation and pain referring again to twice a day versus 4 times a day.

But in two of the slides, and in your page 27, on Day 3 there was 40 percent pain-free from twice a day and 50 percent free 4 times a day in Study 1, and by Day 8, the difference was even greater. It was 40 percent and 67 percent. The 40 percent stayed the same, but the BID and

the QID was then 67 percent. To me, those are clinically significant differences.

In Study 2, the differences were not as great, but in Study 1, they were.

DR. VOGEL: I don't totally disagree. I mean I think the message is that really those differences would be unlikely to make a lot of difference in the clinic situation.

The fact is that by the time you get to Day 15, and all of those analyses, and these are last observation carried forward analyses, that the two frequencies of dosing are really virtually the same. So yes, twice a day might not be as good. The earlier time point is 4 times a day. I am not arguing about that, but I think if you had the opportunity, patient-by-patient, to prescribe either twice a day or 4 times a day, you could make the clinical decision.

Clearly, that would be how we would expect people would do it.

DR. MINDEL: But you are requesting this drug for twice a day, approval for twice a day, and for the purposes of pain and inflammation.

DR. VOGEL: As I said in my conclusions, I think

the data really support two or four times a day dosing. I would agree that twice a day only would not be sufficient. I would think you would need to be able to say twice or 4 times a day, so the physician has the flexibility.

DR. MINDEL: You are going to change the request for twice, 4 times a day?

DR. VOGEL: Sure, I think that's a more reasonable --

DR. STRAHLMAN: I think the original request was for 2 or 4 times a day, is that correct?

DR. MILLER: And speaking now? I am sorry, just identify yourself.

DR. STRAHLMAN: I apologize.

DR. MILLER: That's okay.

DR. STRAHLMAN: Ellen Strahlman.

DR. MILLER: Just in case the record needs that.

DR. STRAHLMAN: Yes, I apologize also for not asking to be recognized.

I just wondered, it was my understanding from reading that, the request was 2 or 4 times a day as opposed to only 2 times a day; is that correct?

DR. CHAMBERS: Labeling is still something that is

under negotiation. We welcome both comments from the Advisory Committee, as well as we will have further discussions with the company after taking all of what you say as well as our analysis into account, but we would welcome recommendations from this group.

DR. MILLER: Dr. Mindel, does that answer your question?

DR. MINDEL: I didn't have a question. I was pretty certain that the request was for twice a day.

DR. MILLER: So, we will have more thoughts on that as we proceed.

I had some questions, too, if I could take a moment now. I am concerned in any topical steroid medication about those unsuspecting patients that have the potential for steroid response.

There are some figures on some of the topical steroids on rate of response in known steroid responders. You have mentioned that this new drug is non-inferior to betamethasone, but we don't know on these characteristics, which are known complications of steroids, where this particular drug is going to fall.

Your rate of glaucoma rate was low in this very

defined group where you have excluded all glaucoma smell, but the real world isn't like that, and we don't want to have subsets suffer having the medicine.

I wondered if you have any thoughts relative to the other, more similar topical steroids where this might fall or any indication you have in your data.

DR. VOGEL: Yes, we probably have from the Senju data the frequency of intraocular pressure rises. No, not that, comparing betamethasone to difluprednate in the Senju studies with regard to pressure rises.

DR. MILLER: Because we aren't as familiar with the betamethasone in this country.

DR. VOGEL: I understand.

DR. MILLER: We have an impression that certain topical steroids are much less risky to use, so it would be important to have some feel for this drug.

DR. VOGEL: Well, I will show this slide, but do we also have the frequency of high pressures in the two studies? What we have got here just shows you the betamethasone-treated group 4 times a day and the difluprednate-treated group, the mean intraocular pressures and the standard deviations in both of these studies was

really very similar.

What would be more interesting, if we could find it, would be the frequency of high pressures in the betamethasone group using the criterion.

DR. MINDEL: Dr. Vogel, I am assuming that in this particular study, the inclusion criteria were similar, these aren't a glaucoma risk group that's known, right?

DR. VOGEL: These are patients with known risk of glaucoma were not included certainly in this group.

DR. MILLER: Right.

DR. VOGEL: Do we have that? Okay. One minute, please.

[Slide.]

That is what we have already seen. I was looking for the frequency of significant pressure rises on betamethasone as well as difluprednate. We don't have that for betamethasone.

DR. MILLER: Another area, this was a postsurgical group and as an ophthalmologic surgeon, wound healing comes up as a question. It was not an area that was look at, at all. You weren't really looking at surgical results, more inflammation results, but that is an area we expect steroids

will vary in terms of problems.

Did you have any wound healing problems, wound leaks, resuturing? Were these clear cornea incisions, what kind of surgery was done, do you know?

DR. VOGEL: We had a variety of different incisions in the study. I don't have a breakdown by exactly what, but we had no wound leaks or wound problems of the sort that you are asking about.

We have got the sort of surgery, we can break that down, but that's really not what you are talking about.

DR. MILLER: If it were predominantly one type of another, perhaps clear cornea without a suture, you might be more likely to get a leak versus limbal where you are going to have inflammation that self-seals, so it is interesting although if it is a big mix, it probably wouldn't tell us.

I am interested also in that adverse event that had the iris adhesions, and what was happening to the inflammation in that case. Was it responding at all to the medicine or how do we explain that case, was there something else going on, or did the drug just fail?

DR. VOGEL: Can we pull that up? This was a case in one of the Senju studies, the Senju study with

postoperative inflammation.

The important thing, perhaps put this slide up, so that we have something in front of us.

[Slide.]

It rather suggests since iris adhesions were present on Day 2, that this was a patient that really had a very inflamed eye after surgery, and I think by Day 2, clearly, the patient had not responded as well as either they were very inflamed to start with or they didn't respond as well as expected, but they did continue all the way through to Day 12, but had surgical posterior synechia ultimately at Day 5.

So, it occurred very early. I think it's a postoperative inflammatory situation.

DR. MILLER: There might be something in the operative report about how they put the lens in or something else, but it's an interesting adverse event.

DR. VOGEL: It's a 69-year-old male, iris adhesions manifested Day 2 of the study, administration of difluprednate. Thereafter the iris adhesions progressed and the subject went posterior synechia ultimately at 5 days after termination of treatment with a prolonged

hospitalization period, which is why it became--well, both of those reasons would make it a serious adverse event.

The iris adhesions were resolved by surgery.

DR. MILLER: Were there lots of cells that didn't go away, or was it just the iris?

DR. VOGEL: That's all we have on that patient I am afraid.

DR. MILLER: Those are my questions for now. Any other? Yes. Please identify yourself. Thank you.

MS. COFER: Paula Cofer. Remember my questions are from a patient perspective. I am not a medical doctor.

But the question I have came up when we were looking at Slide 61, and my question--it is two parts--is the main concern of 4 times a day dosing versus 2 times a day dosing just the increase in intraocular pressure, or are there other concerns with the increase in dosing? That is the first part of my question.

DR. VOGEL: I think from a safety point of view, it was interesting to note the 4 times a day did not cause any higher increase in pressure than twice a day.

MS. COFER: And that is where I was going with that. Are there other concerns with the 4 times a day

dosing over 2 times a day dosing? I realize intraocular pressure increases is the main concern, is that correct?

DR. VOGEL: Yes.

MS. COFER: And are there secondary concerns, as well?

DR. VOGEL: Well, we have mentioned wound healing, we didn't see any problem there. Those are really the two.

MS. COFER: Thank you.

DR. MILLER: We can't forget to mention infection rate, but I do think that all of your adverse situations you could explain in terms of a missed diagnosis, in terms of the retinitis, the retinal necrosis, and the other patient had herpes in the other eye, and we wouldn't want any patient on any steroid with those situations.

So, I think you explained those, but certainly those will be standard labeling issues if I had any say in that. Thank you.

DR. VOGEL: Thank you.

DR. MILLER: Dr. Chambers, are there any other questions, any other committee members?

Perhaps it would be an appropriate time to take a break now. We will reconvene according to the schedule at

9:35 for the FDA presentation.

Thank you very much, Dr. Vogel.

DR. VOGEL: Thank you. Thanks for your attention.

[Break.]

DR. MILLER: We will now proceed to the FDA presentation section. Dr. Sonal Wadhwa from the FDA.

FDA Presentation

NDA 21-212 Difluprednate

DR. WADHWA: Good morning.

[Slide.]

My name is Sonal Wadhwa. I am a medical officer at the FDA. I will be giving the FDA presentation on difluprednate.

[Slide.]

As you know, the applicant is Sirion Therapeutics.

[Slide.]

The drug we are talking about today is difluprednate, also referred to as ST-601 in the application, which is a topical ophthalmic emulsion formulation of difluprednate for ocular instillation.

Difluprednate is a synthetic glucocorticoid receptor agonist, and it is a derivative of prednisolone.

[Slide.]

The proposed indication for this product is for the treatment of inflammation and pain with ocular surgery.

[Slide.]

Some more information about the drug product, is the proposed proprietary name is Durezol. The established name is difluprednate ophthalmic emulsion.

The classification of this new drug application or NDA, it was designated as a priority. Applications, when received at the FDA, can be designated as either a priority or standard application. A priority application means upon receipt at the FDA, there is a 6-month clock at which a decision has to be made versus a standard application, which is a 10-month clock.

This product was given priority designation because this is the first steroid with the proposed indication of the treatment of pain with ocular surgery.

The pharmacologic category, as we know, is a steroid, and the dosage form is a topical ophthalmic emulsion.

[Slide.]

In terms of supporting efficacy of this drug, two

Phase 3 clinical trials were reviewed which are referred to as Study 2a and 2b, or Study 1 and 2, as was in Dr. Vogel's presentation.

Studies 2a and 2b were both double-masked, randomized, placebo-controlled clinical trials evaluating difluprednate in the treatment of inflammation and pain following ocular surgery.

Each study was a completely identical protocol, but separate, separated based just on geography, north and south of the latitude of 37 degrees.

[Slide.]

In each study, the efficacy and safety of difluprednate was dosed with BID or QID for 14 days, and was compared to vehicle in subjects who had undergone unilateral ocular surgery.

On Day 15, after completion of the planned treatment course, subjects who had an AC grade of quote, unquote "zero," which was defined as less than or equal to 1 cell, or who had responded satisfactorily judged by the investigator, then began a taper.

[Slide.]

Patients in the QID dosing group at this point of

taper were then tapered to BID for the subsequent 7 days and then once a day for the next 7 days. Patients in the BID dosing group were tapered to once a day dosing for the next two weeks.

At Day 28, the study drug was discontinued and if further tapering was thought by the investigator to be needed, then, a suitable alternative was started at this point, but the study drug was stopped at Day 28.

[Slide.]

In terms of inclusion criteria for Studies 2a and 2b, the patient had to have unilateral ocular surgery on the day prior to enrollment.

Patients had to have an AC cell grade of greater than or equal to 2, which was defined as 11 to 20 cells per high power field on post-op Day 1.

Patients had to be older than 2 years. They had to have a negative urine pregnancy test, and they had to provide written consent.

[Slide.]

In terms of defining the analysis populations, the Safety or Intent to Treat population was defined as all randomized subjects that received at least 1 dose of the

study drug.

The Per Protocol population was defined as all randomized subjects who had no protocol violations, and protocol violations included things such as a violation of entry criteria, lack of compliance, and the use of prohibited medications.

[Slide.]

In Studies 2a and 2b the total number of subjects in the ITT population was 438 of which 111 were in the BID group, 107 were in the QID group, and 220 patients were in the Vehicle group.

[Slide.]

If we look at the disposition of patients in Study 2a in the ITT population, 91 percent completed in the BID group, 92 percent of patients completed in the QID group, and 63 percent of patients completed the study in the Vehicle group.

As you can see from this table, the majority of patients who didn't finish, who were withdrawn early in the Vehicle group, was largely in part due to lack of efficacy.

[Slide.]

Similarly, in Study 2b, 88 percent completed in

the BID group, 92 percent completed the study in the QID group, and 49 percent completed the study in the Vehicle group. Here, as well, the majority of patients that did not complete the study was due to lack of efficacy.

[Slide.]

In Study 2a, 58 patients were randomized in total to the BID group, 55 were randomized in the QID group, and 107 were randomized in the Vehicle group. Then, you can see the ITT and the Per Protocol population numbers.

[Slide.]

In Study 2b, 54 patients were randomized to the BID group, 52 in the QID group, and 114 in the Vehicle group.

[Slide.]

What we have touched upon already, but I will go over again, the proposed primary efficacy endpoint for Studies 2a and 2b was the proportion of subjects with an AC cell grade of, quote, unquote, "zero," which was defined as less than or equal to 1 cell, as compared between the difluprednate QID group and the placebo groups.

However, since the Agency considers that a clinically meaningful endpoint would be a complete clearing

of AC cells where a grade of zero equals zero cells in the anterior chamber, the Agency utilized complete clearing of AC cells in our efficacy determinations.

[Slide.]

So, if we look at a grade of zero, which equals zero cells in the ITT population in Study 2a, if we look at Day 8 and Day 15, we see a statistically significant difference between the QID dosing group and vehicle.

[Slide.]

If we look at Study 2b with the same Grade zero equals zero cells in the ITT population, again there a statistically significant difference between the QID dosing group and vehicle.

[Slide.]

The second part of the proposed indication, which is the treatment of pain associated with ocular surgery, this was based on the Visual Analog Scale where pain and discomfort was rated by the subjects at each visit where zero equaled absent pain and 100 equaled maximal pain or discomfort.

The study looked at the proportion of subjects who had a pain/discomfort score of zero.

[Slide.]

When we look at the ITT population in Study 2a, and we are looking at proportion of patients with a pain/discomfort score of zero, when looking at the QID dosing group at Day 8 and Day 15, there was a statistically significant difference compared to vehicle.

[Slide.]

Looking at the same endpoint in Study 2b, again there was a difference between the QID dosing compared to vehicle at Days 8 and 15.

[Slide.]

Moving on from evaluating efficacy to evaluating safety, there were 7 studies that were used to evaluate the safety of this drug product.

Two of the studies which we have already talked about, Studies 2a and 2b, which were the Sirion postsurgical studies that were performed in the US, there were an additional two Senju postsurgical studies performed in Japan, and then there were three Senju uveitis studies performed in Japan, as well.

If we combine all these studies, there was 314 patients treated with difluprednate 4 times a day for

approximately 14 days.

[Slide.]

In Studies 3, 4, 6, and 7, the comparator drug was betamethasone, which is used for the treatment of ocular inflammation in countries outside the US.

In Studies 2a and 2b, as we have discussed, vehicle was the control.

[Slide.]

The safety assessments performed in these various 7 studies included examinations of things, such as palpebral injection, corneal endothelial cell density, intraocular pressure, visual acuity, slip lamp examination, ophthalmoscopy, and the collection of adverse events.

All of these trials were randomized, multicenter, double-masked, parallel-group, and comparative, except for Study 11, which was an open-label trial.

[Slide.]

If we look at the mean duration of exposure to study drug, in Study 2a and 2b, in the QID dosing group, it was approximately, the mean duration was approximately 26 days in both studies.

[Slide.]

In Study 2a, you can see that the majority of patients had an exposure time between 19 and 33 days, and in Study 2b, as well, the majority of patients had an exposure lasting between 19 and 33 days.

[Slide.]

If we look at all 7 studies, in the Sirion postsurgical US studies, the mean exposure was 26.9 days. In the Senju postsurgical Japanese studies, which were Studies 3 and 4, the mean exposure was 13.2 days, and in the Senju uveitis Japanese studies, which were Studies 6, 7, and 11, the mean exposure was 14 days.

[Slide.]

The overall incidence of SAEs in the 7 clinical studies was 11 of 425 patients or 2.6 percent exposed to difluprednate. The 425 patients includes patient on both BID and QID dosing.

Of the patients in the combined postsurgical studies, the Sirion and Senju studies, 8 subjects or 2 percent had an SAE.

[Slide.]

I know we have gone over these SAEs already, but we will review them again here briefly.

In postsurgical studies, Studies 2a and 2b, in the BID group, 1 of the 111 patients had an SAE of syncope, 4 of the 107 in the QID group had 1 SAE each. These were syncope, UTI, headache, and pneumonia.

Two patients in the vehicle group had 1 SAE each of respiratory distress and a CVA.

[Slide.]

In the Senju postsurgical studies, Studies 3 and 4, 3 of the 110 subjects in the QID group had 1 SAE each. These were maculopathy, retinal detachment, and iris adhesions.

In the Senju uveitis studies, Studies 6, 7, and 11, three of the 96 patients in the QID group had 1 SAE each, which were monoarthritis, corneal perforation in the non-study eye secondary to reactivation of known HSF keratitis, and necrotizing retinitis.

[Slide.]

I know this is a busy slide, but what I wanted you to take away from the slide was just the most common AEs that were observed between all the studies, and the stop 3 were posterior capsular opacification, which was 6.8 percent, conjunctival hyperemia, which was 6.6 percent, and

punctate keratitis, which was 5.9 percent.

[Slide.]

Other safety studies that were performed were--intraocular pressure, and as we know--IOP elevations is a common treatment-related AE with topical corticosteroid use. However, it is important to note that many of the patients were postoperative patients, so in the immediate postoperative period there are other factors that can lead to either elevations, increases or decreases in IOP, so there are other confounding factors.

[Slide.]

If we look at a definition of just looking at proportion of subjects with an increase of just 10 mm of mercury or more, which is what we looked at, there was no significant difference between the QID group and the vehicle group.

[Slide.]

In Study 2b again, looking at the proportion of subjects with the increase of IOP of 10 mm of mercury or more, there is no significant difference between the QID or Vehicle group.

[Slide.]

Even though we did not observe a significant increase in intraocular pressure with the use of this product--since it is a steroid it will have the same labeling precautions as other products in this pharmacologic group. These would include precautions, such as the elevation in IOP, formation of cataract, and inhibition of wound healing.

[Slide.]

Another safety study performed was corneal endothelial cell counts at baseline and Visit 6, and Visit 6 occurred approximately between 5 and 6 weeks postoperatively.

This measurement was only done in Studies 2a and 2b.

The Agency recommends performing corneal endothelial cell counts at baseline and at 3 months because if performed sooner there may not be sufficient time to observe changes.

[Slide.]

Therefore, to look at the baseline compared to the Visit 6, it is difficult to make a conclusive decision, but the results comparing Visit 1 or baseline to Visit 6 did not

show any significant difference in mean corneal endothelial cell count in either of the groups compared to vehicle.

[Slide.]

We have no postmarketing experience because difluprednate is not marketed in any country.

[Slide.]

I leave you with the last slide of the questions we pose for the Advisory Committee, the first question being: Do you think difluprednate ophthalmic emulsion should be approved for the treatment of ocular inflammation and pain following cataract surgery?

If no, what additional studies should be performed?

If yes, should any additional Phase 4 studies be performed?

Do you have any suggestions concerning the labeling of the product?

I thank you for your time.

DR. MILLER: Thank you, Dr. Wadhwa.

Questions/Clarifications

This would be the time for questions from Committee members.

Would anyone have a question? Yes, please.

MS. COFER: Will I be addressing the question to you or who?

DR. MILLER: Yes. The questions now would be for Dr. Wadhwa, but I imagine if there are additional questions for Dr. Vogel, we could also speak to him.

MS. COFER: My question is about the FDA's recommendation to count endothelial cells. I believe that was at 3 months. The question is if there were a difference in endothelial cell density, that would be attributable to the surgery, and not to the drug, is that correct?

DR. WADHWA: Well, surgery itself can cause a decrease in corneal endothelial cell count, so there would be a confounding factor, but we are hoping that we would see that difference if we carried it out to 3 months and if it was from the drug product as well.

MS. COFER: I also have a question about the punctate keratitis. Would that be related to the drug or to the surgery, or is that another gray area?

DR. WADHWA: It could be both, either.

MS. COFER: Thank you.

DR. MILLER: Other questions?

DR. MINDEL: Does the FDA have concerns about the intraocular pressure exclusion criteria that were used being so limited?

DR. CHAMBERS: Each of the different safety factors for any particular product were evaluated on an individual product basis. This product, being a corticosteroid, we automatically assumed a number of potential adverse events that you saw. Dr. Wadhwa put up on here, those being for a corticosteroid, that it was going to raise intraocular pressure in people that are steroid responders, that it was going to delay wound healing and that it is going to cause cataracts.

Some of those are readily studyable, some of them are studyable in this particular indication, some of them are not. In the case of wound healing, there are not enough patients studied here to expect to see wound healing differences. So the fact that we don't see them in the trials here is a good thing but not enough to keep us from putting those kind of statements in the labeling when it ultimately is approved.

Intraocular pressure is not best studies in a postcataract population for a number of reasons, some of

which were mentioned by Dr. Wadhwa, the most likely increase in intraocular pressure immediately post-op is due to the visco elastic, so immediate increases, you tend to get are generally not due to things like a corticosteroid or a dilating agent.

They are due to the visco elastic, again well known, but it would be difficult to sort out whether the drug product was doing it in that particular setting.

Later rises in intraocular pressure, there is one you would not expect it from a topical corticosteroid for at least 5 to 10 days, so you wouldn't see it in the early postoperative period.

We would not expect to see elevations in ocular pressure that were due to steroid responses until at least later on, meaning at least the Day 8, if not Day 15 or Day 29 visit.

There are not a whole lot of cases along here to go and see, but again there are these confoundings. In addition, uveitis is known to lower intraocular pressure, so if the steroid is not working particularly well, and you have a lot of inflammation, that will lower the intraocular pressure, so you may see some elevations just because you

are clearing the inflammation.

If you really want to study steroid response, you do it in normal volunteers, and you need to go for at least six weeks, and you evaluate elevations in intraocular pressure.

The companies that do those studies are ones that are generally looking for particular claims that they have less IOP elevations for their corticosteroid. Those particular claims are not being proposed by this company. They are not being currently entertained by the Agency for this product.

If at some future time the company wanted to try and state that it had less IOP elevations, those would be distinct replicated trials that specifically addressed that question, and so in the absence of that type of information, the Agency intends to label it as it is going to raise intraocular pressure and all the warnings, precautions that go along with that and all the rest of the corticosteroids are intended to be placed on this product.

The third issue that was not studied would be the cataract formation, again well known with corticosteroids, obviously difficult to study in a population where you are

taking the cataracts out.

So, we don't expect to evaluate it. You could argue you should have looked for posterior capsule opacification. That is not as well associated as straight cataract posterior subcapsular formation, so it just wasn't the right population to study.

Again, we would include it in the label of this particular product until such studies were done to show it wasn't going to occur with this product. I personally believe that is unlikely to be the case, but if we were shown data that showed it to be true, we would entertain that as a potential labeling statement.

Did I address your question?

DR. MINDEL: Yes.

DR. MILLER: I have a question, Wiley. Define Phase 4 studies.

DR. CHAMBERS: Phase 1 studies are generally the initial trials that are done often in normal healthy volunteers. Phase 2 are the dose-ranging studies. Phase 3 are the studies that are usually done to establish definitive efficacy. So, those were the two that you were seeing along here that we talked about the most.

There were also a couple of Phase 3 trials, one in uveitis done by Senju and one postoperative inflammation done by Senju. We don't think they are quite as complete as what we provided with you, but we do have those study results.

Phase 4 is what is done after approval, so if we believe that there is sufficient information to warrant approval at this time, there may still be nice to know pieces of information that we think are important to be studied, and we would ask the company to commit to doing those studies after approval and provide a time sequence which does get posted on the web as far as what the status of those particular Phase 4 studies are.

We already have in mind a Phase 4 trial which we will be suggesting to the company and expecting them to complete, and that is in the area of pediatrics.

Again, with the passage of FDAAA last year, there is a requirement to account for all age groups for any product that is approved. As you will note, the studies that have been done here have all been in people above the age of 16. Cataract surgery is done in patients below the age of 16, and we therefore think it needs to be accounted

for as far as the development of the product.

Included within the provisions of FDAAA is the ability to defer pediatric studies, and one of the recognized reasons for deferring pediatric studies is that the application is otherwise ready for approval in adults.

So, that would potentially be the case here where the application would otherwise be ready for approval in adults. We would not want to deny adults the opportunity to take a safe and efficacious product. But, by the same token, we would want it ultimately studied in pediatric patients, so we would ask the company to commit to doing a Phase 4 study in pediatric patients and we would work out a timeline for when those studies would be done.

The question that you see up here, are there any other studies that you think are more on a nice--it is not just nice to know, there are always plenty of things that would be nice to know, but that would significantly help the use and understanding of the particular product, and are really relevant for a particular population that just wasn't --you know, again you don't want to hold up the product from being approved, but it still would significantly aid in a physician's ability to use the product later on.

So, if you end up having recommendations, those are the things that we will consider as we are working through the final stages of the approval process.

DR. MILLER: Thank you.

I think it is appropriate to ask this question. In looking at existing labeling for some of the other topical steroids, there are sections where people have looked at steroid response rate in steroid responding populations, and those have been done specifically because those particular drugs wanted to say they were safer for people with glaucoma, not because they were required to do that?

DR. CHAMBERS: That is correct. Each of the companies that have done trials to show what the steroid response rate is have been in products trying to demonstrate that they were less likely to raise intraocular pressure.

So, FML--

DR. MILLER: Vexol.

DR. CHAMBERS: Vexol and loteprednol all did studies to try and demonstrate that they had less tendency to raise intraocular pressure. And they usually ask for two different claims, only one of which has ever been

purposefully granted, that being we have yet to see any corticosteroid that, if you don't give it long enough, won't ultimately raise intraocular pressure. But there have been differences in the length of time it takes before you get an elevation, which is why we would not even entertain studies that were less than 6 weeks in duration because we have seen plenty of products that don't raise it in two week but do raise it six weeks, and we think that is useful information to know.

DR. MILLER: The reason this comes up in my mind is we are looking at a product that is a strong steroid compared to be non-inferior to betamethasone, which is a drug we are not as familiar with.

I wanted to know what our requirements were in terms of safety for understanding this drug before we could give approval, so that is helpful information. Thank you.

DR. CHAMBERS: The other thing to remember is this indication is different than many of the other corticosteroids. Most of the corticosteroids meaning ophthalmic corticosteroids were approved under what is called the DESI process. It was a review process that was done for products that were on the market because they were

safe, but hadn't shown efficacy and initially introduced between 1938 and 1962.

Those products--the literature was then reviewed and an indication of steroid responsive disease was given for that whole class of products. That includes Pred Forte. That includes dexamethasone. It includes a number of different products.

That indication did not include postoperative surgery. So the steroid response was uveitis, allergic conjunctivitis, a whole bunch of conductivities, but did not include post-op. Post-op has always been a separate indication, not considered this steroid responsive indication, and so companies wanting that indication have had to do separate studies. So you will see that distinction.

The duration of treatment is also a shorter period of time. As you see, these studies go for 2 to 4 weeks. The issues with raising intraocular pressure--even if you raise intraocular pressure, the amount of harm that you are likely to do in a 2-week period of time of having raised the pressure is not the same as raising it for months to years.

These elevations go away once you stop the

corticosteroids. So, because we are not talking about treating uveitis, we are not expecting this treatment to be 6 weeks, 10 weeks, 12-week kind of period of time.

We are expecting people to use it as labeled. Do we know everybody uses products as labeled? No, we know that they don't. That is why we would put additional warnings on there, but there is also not an expectation that they are going to be using it for months.

DR. MILLER: Thank you.

Additional questions?

DR. STEIDL: I am just trying to figure out how I feel about this. But I am curious what the FDA position is on the zero reading of cells being no inflammation. This is inclusive of cells being present.

I would have to agree with Dr. Mindel that if I am seeing inflammatory cells, I don't consider the person to be inflammation-free. A lot of these people have pain and photophobia even just with a cell or two, so just curious what your feelings are.

DR. CHAMBERS: I do occasionally joke around that there are certain lessons that I expect people to learn in kindergarten, some of those being that zero equals zero, and

zero doesn't equal 1.

Yes, that is brought home to me because I have an 8-year-old, but there are certain levels of inflammation or certain scores that we think really mean that particular number.

I am by no means questioning that there are people that have an inflammatory cell potentially within the room that we are sitting in here. The particular studies that were presented are not particularly strong evidence to me because they are using the cell flare meter, and the cell flare meter does not distinguish between pigmentary cells and inflammatory cells.

But even if it was true that there are inflammatory cells, 1 or 2 in everybody in the room, that doesn't mean that's the goal that should be achieved if you were trying to rid yourself of inflammation.

If the goal is to get rid of inflammation, from our perspective, it has been to get rid of inflammation, and our marker of inflammation is inflammatory cells, so the fact that you see them, and it is a sampling of aqueous, it is not the whole aqueous. We don't empty the aqueous and go and screen to see if there are any inflammatory cells along

there. We take a sampling, and so it's a representative amount.

You have got to set a goal someplace and this is essentially the point that we have gone and set that. It doesn't mean that they are not scales that are perfectly valid that include that.

One of the other ways to potentially approve a product such as this is to look at mean scores and look for mean differences. Many of the other corticosteroids have been approved because they had a mean 1 unit change along here, and if you use a mean 1 unit change it doesn't really matter what the bottom is because everybody is being treated the same way and the relative differences between the scales are the same.

So, if you have a 1, 2, 3, and 4, and at Day 8 the average in placebo is a 3, and the average in your drug group is a 2, that is a mean 1-unit change, and it doesn't matter that you didn't define zero as being exactly zero.

If, on the other hand, the goal is to get to zero, and that was the case in these particular trials, then, we believe if you were going to try and get to zero, you should be at zero.

DR. MILLER: Yes, Dr. Mindel.

DR. MINDEL: Sorry to come back with a question, but yours raises a question that I would ask the sponsor. Since you are so rigid, and I agree about the definition of zero, did FDA do an analysis of the correlation of pain-free and zero cells? The sponsor can't present that information.

DR. CHAMBERS: We have not at this point done that analysis. As you know, from me, if I hear a comment like that at a meeting like this, you can be sure we will do it when we go back and look at the information.

I can guess at what the result is going to be, but there is not a whole lot of point of me guessing what it is going to be when I can have an analysis done. So, if that raises something strange within the overall package, we will investigate it further, but I can assure you we will do that particular analysis.

The history of having combined different endpoints is that it usually does not show a significant--it usually make the drug look better, not look worse.

Usually, the analysis of two separate events bring out particular problems more than merging the two information, but we will do that analysis.

DR. MILLER: Additional questions?

I think at this point it will be time to take a break, but I have a script that I am supposed to say before break, which I failed to say before the last break, so I am going to say it now.

We will now take a short 15-minute break. Panel members, please remember there should be no discussion during the break amongst yourselves regarding the issue at hand or with any member of the audience.

We will resume at 10:30.

[Break.]

Open Public Hearing

DR. MILLER: We are going to move on to the open public hearing section. It is my understanding that there are no registered people for this, but we will still have an open public hearing if anyone in the audience would like to participate.

I have a script to read before that section.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee

meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement, to advise the committee if you do not have any financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their considerations of the issues before them.

That said, in many instances and for many topics,

there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the Chair. Thank you for cooperation.

At this time, is there anyone who would like to speak?

[No response.]

DR. MILLER: It appears that there is not.

At the conclusion of the open public hearing, I have another script to read, which I will read for formality.

The open public hearing portion of this meeting has now concluded and we will no longer take comments.

The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee as well as the public comments.

Panel Discussion/Questions

We will now proceed to have the discussion. One point I would like to bring up right at the beginning of this discussion that has come to my attention is that on the

agenda, difluprednate is proposed for the treatment of inflammation and pain following ocular surgery.

On the questions that were written and given to us, No. 1, should it be approved for treatment of ocular inflammation and pain following cataract surgery, so we might want to discuss first the scope of what we would like to recommend as a group.

Does anyone have any comments?

DR. MINDEL: The studies, Study 1 was 98.2 percent of the patients had cataract surgery, and Study 2 was 96.8 percent. So, it is reasonable to limit the request to cataract surgery, postcataract surgery inflammation and pain.

DR. MILLER: Do you anticipate a difference with another sort of surgery that would be likewise a short course? I am trying to think of the rationale there. We certainly have only studied cataracts in this setting, there is no question about that. I am trying to think of what would make it different, what other surgeries. I guess corneal transplant surgery, anything where you are expecting this to be a longer course, we are in unchartered territory here.

DR. STRAHLMAN: I guess the clarification I was seeking was that other steroids I think are labeled for ocular surgery even though most of those studies, as Dr. Chambers had pointed out had been done in cataract surgery, so I was just not certain about what the scope of the question was meant.

Maybe I will ask FDA for clarification in phrasing it that way.

DR. CHAMBERS: I think the heart of the matter is, as Dr. Miller was pointing out, what do you do as a--you obviously don't study all ocular surgery, so what do you do as a model for if you want the indication for ocular surgery.

By and large, we have generally thought of cataract surgery as being a reasonably good model for relatively short courses of postoperative inflammation.

I think the question will remain if you decide that it's not a good model for ocular surgery for an indication of ocular surgery, what else you would do to provide convincing evidence to get to the condition of ocular surgery, or are you suggesting that we have studies in every ocular surgical procedure, which seems to me

relatively extensive.

That doesn't mean we couldn't do it, and you could label it just for there, but are you promoting then more off-label use if you limit it only to those things. It seems to me at some point you might expect some extrapolation.

DR. STRAHLMAN: I guess in reading the question, were you asked the Committee just to comment on these particular studies? That is not necessarily the intention of the ultimate label, because I guess what I was confused about was again other steroids are labeled for ocular surgery, and this is a steroid.

So, I am still not certain about where the question is and they you have also asked us for labeling suggestions, so what the thought was there.

DR. CHAMBERS: Yes, we directly asked the question for the studies that were done, figuring that was the most concrete example of what you had already seen. We asked the question about labeling because we are looking at whether you think we should then expand from what was exactly done and just to how far we should expand that to cover.

So, in effect, we are asking both in the two

different questions.

DR. MILLER: Dr. Steidl.

DR. STEIDL: Well, particularly if there is a precedent of labeling it for general surgical use, if it has been studied in cataracts, I don't see how this would be significantly different.

If you are talking about surgeries that have a similar duration of treatment, retinal surgery, glaucoma surgery, I am not really sure why this surgical implications would be particularly different.

I would, just from what I have heard, recommend that it be for general ocular surgery. How has it been labeled, you say, for just other steroids, how they can actually--

DR. CHAMBERS: Again, most of the corticosteroids are not labeled for surgery at all, they are labeled for steroid responsive disease and doesn't include the surgery.

I hesitate in a public forum like this to, off the top of my memory, quote the indication for the others without actually pulling it out and reading it. Whether somebody can do that or not, I don't know, but I am not going to state it because I would probably get it wrong.

Vexol, which does have the indication it is a steroid, is indicated for the treatment of postoperative information following ocular surgery. The others I have in this review are nonsteroidals, some or which are cataract surgery and some of which I will say refractive surgery, but the only other steroid says ocular surgery.

DR. MILLER: Dr. Cox and Dr. Vogel have passed information to Dr. Chambers with indication data, right? Yes, thank you.

DR. CHAMBERS: Lotemax, which is the other steroid, among its other indications it is also indicated for the treatment of postoperative inflammation following ocular surgery, so it looks like we have been consistent.

DR. MILLER: Were there any cases where you had a steroid that was excluded for a specific surgery with a surgery indication? I can't think of--is there a time course written into the surgical care there, does it say for two weeks?

DR. CHAMBERS: I read you the entire indication.

DR. MILLER: Thank you.

Dr. Mindel.

DR. MINDEL: I am cantankerous about the drug, and

I will explain why in a minute, but this is to me a me-too drug that is looking for a niche, and other anti-inflammatory drugs are probably just as good at reducing pain and inflammation, they just haven't asked for the indication.

So, I think if they are going to look for a niche, we should define that niche. What bothers me and why I am cantankerous is, in reading the sponsor's material, it seems that the definitions were designed more for the marketing in the future and publications rather than for the approval.

I don't like the terms low incidence of clinically significant IOP rise, which I have had several times when it has been defined and limited in such a way that it really excludes most IOP rises. This is in the sponsor's statement low incidence of clinically significant IOP rise.

We didn't talk about their definition of clearing of inflammation. They use the term clearing of inflammation as clinically significant clearing of inflammation. Clearing of inflammation is defined as less than or equal to 5 cells per view of the anterior chamber and a flare of zero. To me, that is still inflammation.

I mean I can just see the paper saying clinically

significant clearing of inflammation. It is being asked for both pain and inflammation, which we are still waiting to hear the proof of that, because we have to have the FDA look at that.

Also, there is the statement in the inflammation we received, the sponsor says there is no clinically significant difference between twice a day and 4 times a day use, and yet there is at times what I consider clinically difference.

Then, there is the difference between--getting back again the Grade zero, how it would look in a publication and zero cells. As someone who is disturbed by how often the publications and comments of the salesmen don't quite jibe with what the FDA expects. It makes me sensitive.

So, I am coming down on encouraging a very specific use for a very specific drug or a very specific indication. So, I am in favor of saying cataract.

DR. MILLER: To get information for you, I would be interested in knowing these other drugs, the ones that actually did get approval for surgery were based on the model of cataract surgery, were they not?

I am trying to think of what exceptions of surgery where you could potentially--I mean you are right, the data is for cataract surgery here--there is no question about that--but where could you envision causing harm in another application?

I mean for a short course, are you saying if we say ocular surgery, it is going to apply to posttraumatic or --I am trying to figure out the difference and what is means in my own mind.

DR. MINDEL: I think you can argue that you want the study to prove the indication. We don't have to extrapolate if we don't want to, or the FDA doesn't have to extrapolate if it doesn't want to, and, as I said, I am cantankerous because of the way I see the definitions and it sensitized me to this drug and this presentation.

DR. STRAHLMAN: I had a question about one of the things that you said just for clarification.

You said something about proof for pain and inflammation. Now, I guess in reading how the studies were designed with individual endpoints, the statistical analyses certainly showed a difference to my reading between the individual endpoints and placebo, so could you clarify what

you mean by that? I think you have something else somewhat in mind, that you are also expecting from the FDA as well.

DR. MINDEL: You could get the indication right now for pain or ocular inflammation. They haven't shown that in the same patient, there is a statistically significant reduction of pain and inflammation.

DR. MILLER: Was it shown, however, though, that for both of those items, by the end of the treatment course, significantly were improved, so you might say the curve is different during the time period of treatment, but I seem to be under the understanding from the FDA presentation that both were improved by the end of the treatment course, is that not the case?

DR. MINDEL: I don't want to speak for the FDA, but my reading of the information is that both were improved, but the word "and" means to me that in the same individual, both were improved, and that is what hasn't been shown. That is why the word "or" might be just as appropriate at this time as the word "and."

DR. MILLER: I see what you are speaking about. That can be clarified or it could be with an "or" potentially.

DR. CHAMBERS: We will do the analysis to make sure that those results are consistent with what you have already seen. If they are not, then, we will look into why or potentially consider other labeling.

DR. MILLER: Thank you.

Does that answer?

DR. MINDEL: Yes.

DR. MILLER: We still have not fully resolved the cataract versus ocular surgery issue to everybody's satisfaction, but we have brought this up and discussed it as an issue and that. among other drugs in this class, that cataract surgery has been the accepted model for this test.

We certainly acknowledge that there is a difference and that maybe such a difference that it is a problem for some members.

Are there other areas we should discuss right now?

I am sorry, you have been waiting so patiently, I apologize.

MS. COFER: My question or concern is really about the indication for ocular surgery versus cataract surgery, as well, and one question I have, Dr. Chambers, as you were talking about some of the other ocular topical steroids, and

they were indicated for ocular surgery, I know the sponsor said that this is considered a strong steroi. So my question is about the induction of cataracts in other types of ocular surgery, and can this become a problem with a strong ocular steroid.

If it is not indicated specifically for cataract surgery, my concern obviously is the induction of cataracts.

DR. CHAMBERS: As I stated earlier, there are three things that we intend to include in the label even though we didn't see them, and those are that there is a potential for delay in wound healing, there is the potential for rises in intraocular pressure, and there is the potential for development of cataracts, because we know corticosteroids do these things.

So, we intend to put the same precautionary warning statements that we have on other corticosteroids in the labeling for this product, so that people would know to be concerned, monitor and such for those with this product, particularly so that if they end using it for another ocular surgery, where it may be relevant, that people are informed.

MS. COFER: My question, though, is if this a stronger steroid and does that mean there is more of a risk

of induction of cataracts.

DR. CHAMBERS: The question of what it takes to cause a cataract has been studied for at least 50 years, and to the best of my knowledge, there is not a straight strength relationship or dose relationship beyond if you use them, you increase your risk.

Obviously, there must be some formula that using it more increases your chances, but I have never seen any data that points to a direct relationship to the quote, unquote, strength of the corticosteroid. And, if you remember in the sponsor's presentation, the strength that they determined is based on a dermatological skin test scale, and that is considered the best of the scales that we have, but it is how basically, there is blanching within--it is a straight skin test.

I am not going to go into all the details of how you do that skin test, but I don't know that is necessarily is relevant to all the same factors that we are talking about here.

MS. COFER: When we talk about twice a day dosing versus 4 times a day dosing, and then we are talking about a strong steroid indicated for ocular surgery versus strictly

cataract surgery, that is my concern. I just don't know if the data supports that as far as the safety data and adverse events.

DR. CHAMBERS: I guess from my perspective I think you have to always have in the back of your mind if you don't have a cataract, and you are given a steroid, you are increasing your chances of having a cataract, and that always has to be part of the equation in evaluating whether this patient should receive this medication, and if you are not prepared to deal with the consequences of a cataract, maybe you should be given something else.

MS. COFER: Thank you.

DR. MILLER: It is interesting, though, in the discussion, it is a real important interest as the person getting the drug or the person giving the drug, prescribing it, that we talk about a strong steroid, but we don't know relatively where things fall into place in terms of wound healing, secondary glaucoma, and the other issues for a specific steroid until we have some longer term experience with a drug.

My understanding is that with making it clear these are a risk, that we have done our due diligence in

terms of the safety issue, because it is that class of drug--but if we had any indication that these were a higher risk for a particular category, then, we should be asking for more studies.

We don't have any indication from anything so far that this is an outlier, is that true, Dr. Chambers?

DR. CHAMBERS: That's correct, we don't have anything that says this is an outlier. I guess one of the aspects is you have to think about what studies you would run, and while--let's take the example of intraocular pressure.

If the purpose is to demonstrate that you have less IOP elevations, it is probably worth running the particular trial because you are attempting to show that it happens less frequently.

If, on the other hand, you don't believe that you have less frequency and potentially you have more of a frequency, then, you are talking about running a trial where you are proposing to intentionally harm patients, and that is the goal of the trial.

We generally don't encourage trials where the purpose is to show that more people are going to get a bad

outcome, particularly since we are now talking about not doing it in patients. We are talking about doing it in normal individuals, because that is the only way they get rid of the confounding factors.

So, I think we would think twice of suggesting somebody run this trial where you purposely harm patients for no gain. The same thing can be said for cataracts, giving people a corticosteroid without expressed gain to see if you can get more cataracts I don't think is necessarily in everybody's best interest.

And I am not sure that we are going to label it any--the labeling we are putting in says it is going to cause cataracts or it is going to cause intraocular pressure. It doesn't say, you know, maybe in a couple of people it will, it says it is going to do this.

I don't know that we could do the labeling any stronger than saying it is going to do this.

DR. MILLER: Relevant to her question about the twice a day versus 4 times a day, we don't have information to suggest that one or the other would be worse for any of these adverse effects.

Perhaps our best route is to go by what we believe

the data shows efficacy. That is my opinion.

DR. CHAMBERS: I think the other way to look at the studies that were done is, at least my view, that efficacy was increased with 4 times a day versus twice a day.

That potentially is showing a drug effect, the fact that you give it more often, you get more inflammation is as positive pharmacological effect.

To the extent that I believe formation of cataracts, intraocular pressure, wound healing are pharmacological effects, yes, I expect to see them more frequently with 4 times a day than I do with twice a day. It all goes along with having the pharmacological effect.

But again the intention is to label it as yes, this has the possibility of occurring, and that you should, for intraocular pressure, monitor it for wound healing. You monitor what is going on amd, in cataract, you are prepared to take the cataract out if that is what develops.

I think if you go in with that understanding, you have the potential safe use of the product. But you can't assume that it is going to happen in somebody else, not happen in my patient that I am giving this to.

DR. MILLER: Does that satisfy your concerns at this point?

MS. COFER: That answers my question, thank you.

DR. MILLER: Are there other areas of question?

DR. STEIDL: Just a quick clarification. So, what is the protocol then for changing a label? I assume that if this turned out to be an outlier, caused much more than expected cataract progression, that would be monitored as the natural course, and then eventually a label would be changed. But how does that work?

DR. CHAMBERS: We routinely monitor adverse events that occur with all drug products. There are reports that are submitted to the Agency that the company receives on a quarterly basis initially, then semiannual, and then annual following that.

We have obviously encouraged direct reporting to the FDA from consumers, professionals in addition.

Each time those adverse event reports come in, the company is required to evaluate the total database that they have and make a determination about whether these were significant enough to warrant a change in the label.

Not only do they review it, the Agency reviews

those same reports and if we agree with the particular statement that it doesn't warrant a change, we let that go on. If there is a disagreement in favor of we think the labeling changes done, we would suggest at that time either in writing or some kind of conversations that a labeling change be done.

If the company believes a labeling change done without the prodding of the FDA, they are free to submit a proposed labeling change. If there is a disagreement in whether a change needs to be made, there are now provisions within the Food, Drug, and Cosmetic Act which will allow the Agency to effectively force a change if it comes to that.

I have yet to have a situation where we have not been able to get a label that we were satisfied with. At least it was in the ophthalmology area.

DR. MILLER: Additional questions, concerns?

[No response.]

DR. MILLER: We will now be moving on to the voting section.

These are the questions for the Advisory Committee, and the question is going to stand as written. This is what we are voting on, however, there has been

discussion that this definition perhaps when adopted by the FDA, or reviewed by the FDA, will consider wider application, but we will be voting on the data presented. Is that fair according to the FDA intention?

DR. CHAMBERS: Yes, that is correct. Again, you have the opportunity in the last question to make comments about as far as whether that should get expanded, should get not expanded, whatever you believe you should feel free to express.

DR. MILLER: For the first item, my understanding is that we will be doing simultaneous voting. So that I am going to read the question. But what you need to do first, if you are a voting person, is to press the Attend button, which is on the left of your microphone, not the base. That is only the voting members that we have identified previously.

I will now read the question.

Do you think difluprednate ophthalmic emulsion should be approved for the treatment of ocular inflammation and pain following cataract surgery?

The Committee is now asked to cast their vote.

Yvette is now asked to read the results into the

record.

DR. WAPLES: For the record, for Question No. 1: 3 Yes, zero No, and there is one Abstain.

DR. MILLER: Now, I would like to ask all members voting Yes to raise their hands and we know from there who did that, and to say your name starting on my left.

MS. COFER: Paula Cofer.

DR. MILLER: Marijean Miller.

DR. STEIDL: Scott Steidl.

DR. MILLER: Then, I would like those members who abstained to state their name.

DR. MINDEL: Joel Mindel.

DR. MILLER: I believe at this juncture we should move on to the next item on the list.

We have no Noes, so we will skip that item unless Dr. Mindel would like to make any comments at this point.

Moving on to: If yes, should any additional Phase 4 studies be performed?

I would like to go first on this item if that is possible. I guess it is, I have got the microphone.

I have seen really devastating problems with glaucoma in children, and I am interested in relative

steroid response rate with a stronger steroid. This may not be something that the FDA wants to require, and I guess Dr. Chambers' logic is that if you actually think it is a significant concern, then, in doing the study, you may be placing some people at harm.

But before I heard that logic, I did look at the labeling of some of the other topical steroid on the market, and they have looked at a subgroup of steroid responders and looked at rates of glaucoma in that group, which might give the clinician some indication of how closely to follow people that were at risk although I would say we had the advantage, in this setting when we are doing postoperative cataract care, that most patients are going to be seen frequently and are going to have their pressure checked frequently.

So, that would be my comment. That would be my area of at least interest.

Regarding the pediatric studies, as being a pediatric ophthalmologist, we are very used to using drugs off label when we need to because few are approved in children. But it's appreciated the emphasis to try to correct that.

Next, anybody else here?

[No response.]

DR. MILLER: Let's go on to the last item.

Do you have any suggestions concerning the labeling of the product? Dr. Mindel, perhaps.

DR. MINDEL: All right. I am holding the sponsor to its studies and it used the exclusionary criteria that it wished, and it chose the subjects that it wished, so I would say one drop twice or 4 times a day for 14 days beginning post-op Day 1 if the intraocular pressure is less than 24 mm of mercury for the treatment of postcataract inflammation postcataract pain, in patients with no prior history of ocular hypertension, glaucoma, or corticosteroid induced hypertension, period.

DR. MILLER: Your attention to detail is appreciated. That is discussion of the very strong specifics here.

Did you have a comment, Wiley?

DR. CHAMBERS: I guess I would be particularly interested in comments from the panel about BID versus QID since there has been some discussion about that as we were going along. If it doesn't otherwise come up, I guess I

would encourage it.

DR. STEIDL: That was going to be my main comment, that I don't think that the dosing seems to have similar efficacy and it should be clarified simply because people who haven't gone to the level of evaluation that we have see a drug rep.

They say this is a TID drug. They get that in their mind, and they use it that way, and I think it is really critical that people understand that there might be a difference between the two dosings. So I think that is important to make clear. I don't know how you do that.

DR. MILLER: Dr. Mindel.

DR. MINDEL: If I can defend the sponsor on this one, I think, if it's pain or inflammation, the sponsor has shown efficacy. In my opinion, the data does support that for both BID and QID.

Whether, when you correlate both pain and inflammation in the same patients, the "or" will disappear and other problems surface, that remains to be seen. But, for what has been presented at this meeting, I think both BID and QID were shown to be effective for one or the other.

DR. MILLER: I am actually in agreement with that.

There was one section where it was less positive at the BID dosing. The second study, it was positive both in the FDA and although Dr. Wadhwa was emphasizing the QID, because that was the presentation in the FDA data, as well, at the BID dosing, it was predominantly, very efficacious.

So, I would agree with that, BID or QID. What I was going to add if we were to do the very detailed approach to the labeling, family history of steroid response would be something that would make you more at risk of a steroid response.

MS. COFER: I am comfortable with BID or QID in the Indication provided it is indicated for cataract surgery. I still have that concern about induction of cataracts, but we voted on the indication for cataract surgery, so I am comfortable with the twice a day or 4 times a day dosing.

DR. MILLER: You know, potentially, you start at QID and cut back quickly if it's working. What is the group where the BID didn't work? It seems like if you waited long enough, both were fine.

I recommend in general that it could be either the BID or QID, but I defer to the FDA on that.

Any other comments? Questions?

[No response.]

DR. MILLER: Dr. Chambers, did we address the issues of concern?

DR. CHAMBERS: I thank you very much. I don't believe that we have any additional questions or clarifications that we need. We do certainly thank you very much for your time and effort.

DR. MILLER: Thank you to all the members, the sponsor, the everyone in attendance.

The meeting is now adjourned.

[Meeting adjourned at 11:17 a.m.]