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CENTER FOR DRUG EVALUATION AND RESEARCH

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Constance E. West, M.D.

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R. Todd Plott, M.D.

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Jonca Bull, M.D., Director Office of Drug Evaluation V
Wiley A. Chambers, M.D., Deputy Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

C O N T E N T S

Call to Order and Introductions,
William Gene Gates, M.D. 4

Conflict of Interest Statement,
Kimberly Littleton Topper, M.S.,
Executive Secretary 6

Introduction and FDA Presentation,
Wiley Chambers, M.D. 8

Novartis Presentation:

Introduction, Ken Green, Ph.D. 19

Definition, Prevalence, Natural History and
Risk Factors of Myopia in the U.S.,
Jane Gwiazda, Ph.D.,
New England College of Optometry 21

Consequences of Myopia,
Joseph Miller, M.D., MPH,
University of Arizona 27

Proposed Clinical Study Design,
Karla Zadnik, O.D., Ph.D. 52

Overall Summary, Ken Green, Ph.D. 65

Committee Discussion 67

Committee Discussion of Questions from the FDA 136

P R O C E E D I N G S

Call to Order and Introductions

DR. GATES: Good morning. I would like to welcome you to the meeting of the Dermatologic and Ophthalmic Drug Advisory Committee. I am William Gates, Nashville, Tennessee, and I will be the acting chair today.

First, I would like to start off with having each of us introduce ourselves, and we will begin from my left and go to the right. So, I will have you start, Dr. West.

MS. LITTLETON TOPPER: When everyone speaks, please make sure you press the button; release it; the red light will come on; speak into the microphone and then turn it off when you are finished. Thank you.

DR. WEST: I am Constance West. I am Director of Pediatric Ophthalmology at Cincinnati Children's Hospital in Cincinnati, Ohio.

DR. GORDONSON: I am Lewis Gordonson. I am originally an optometrist from Iowa State and am now Professor of Ophthalmology at New York University in New York.

DR. BULLIMORE: My name is Mark Bullimore. I don't normally speak like this; I have a cold. I am Associate Professor of Optometry and Vision Science, from Ohio State University.

DR. CHEW: I am Emily Chew. I am from the National Eye Institute. I am an ophthalmologist and epidemiologist.

DR. FEMAN: I am Stephen Feman. I am an ophthalmologist. I am a professor of ophthalmology at St. Louis University.

DR. MILLER: I am Marijean Miller. I am a faculty member at Children's National Medical Center here, in Washington, D.C.

DR. STEIDL: I am Scott Steidl. I am a retina specialist at the University of Maryland, in Baltimore.

DR. BOYD: I am William Boyd. I am an ophthalmologist, clinical team leader with the FDA in the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

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

DR. GATES: Thank you. Next I will have Kimberly begin by reading the conflict of interest statement.

Conflict of Interest Statement

MS. LITTLETON TOPPER: The following announcement addresses the issue of conflict of interest with respect to

this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike other issues before the committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees and federal guests have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the following SGEs which permits them to participate in today's discussions: Dr. William Gates, Dr. Richard Gorman, Dr. Stephen Feman and Dr. Mark Bullimore.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant and guest.

Dr. Todd R. Plott, who will be down in just a moment, has been invited to participate as a non-voting

industry representative acting on behalf of regulated industry.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee these potential conflicts are mitigated.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's involvement and their exclusion will be noted for the record.

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

I would also like to state that some of you might notice we have one committee member from the full Dermatologic and Ophthalmic Advisory Committee and we are required to have two. Our second one, at the last minute, had a problem and was unable to come and we made the determination that the meeting was more important than canceling it because of the inability to have two members. Thank you.

DR. GATES: Thank you, Kimberly. Next I will call on Dr. Chambers for the FDA presentation.

Introduction and FDA Presentation

DR. CHAMBERS: Thank you, Dr. Gates and good morning, everyone.

The purpose of today's meeting is to try and discuss, on a preliminary basis, the information that the FDA needs to try and develop guidance documents for the development of drug products or therapies to prevent the slow progression of myopia. The FDA has a number of different guidance documents in different levels of development. One of the first processes is to try and collect information. The purpose of this meeting is to try and do just that as a first step.

We recognize that myopia is a very common disease, if you want to call it disease; condition if that is what you want to call it. There are lots of different terms that are used for it but the prevalence estimate for myopia is somewhere on the order of 20-50 percent in the United States so it affects a lot of people.

The potential use of any product, we believe, that would try and slow or prevent myopia is likely to occur in children whose parents are myopic, or where there are parents that believe their children will become myopic

because we believe that the most likely case for any drug products will be in the early stages, basically developing pediatric development. Unlike the other treatments for myopia, such as glasses, such as contact lenses, such as different refractive procedures, we think drug products are much more likely to be used early on as opposed to later in life. But that does not preclude that there may be products developed later on and, to the extent that that comes up, we welcome any discussion.

As I mentioned earlier, our goal is to try and develop guidance for evaluating drug products to either slow or prevent myopia. Ultimately, any approvals that the Food and Drug Administration makes will be based on data. But in order to collect good data we need to have good trials.

To date, as we have looked through, we believe the natural history has not been particularly well studied. Yes, there are some studies that go on for a couple of years but, since we believe this phenomenon goes on for a much longer period of time, we are not aware of good long-term follow-up, taking individuals and following them throughout the course of their life as opposed to cross-sectional data which we think there is lots of. There are also a great number of myths and anecdotal associations, some of which

are bound to be completely valid and some of which are probably just myths.

We note that refractive changes come from a variety of different sources. Some may be non-lens related and, as I say, we generally tend to think of them as occurring between birth through at least 30 years of age; accommodation related, which also occur starting at birth and go on generally up to about 65 years of age; lens related changes, which generally occur a little bit later in life, generally 40--this is an arbitrary number--but continue on until people either get a cataract removed or no longer have the need.

We believe there are a number of potential influences of myopia. Listed on this chart are the two big categories that people tend to think of, genetics and environmental factors. Within environmental factors there are a number of subgroups. This is certainly not an all-inclusive list and part of the purpose of discussion today is to try and go through what people believe are the causes.

When we are thinking about therapies, we expect that therapies may not necessarily be limited to directly affecting the disease process. By that, I mean we may know what the cause is and the therapy may be directed directly at what caused the myopia. There may be cases where we

don't know what the cause is and therapies may or may not be directed because we don't know.

We do not limit ourselves though to just therapies affecting the direct cause of myopia. For example, if the cause is that the eye is getting too long and we have a drug product that changes the shape of the cornea to compensate, that is acceptable. So, we are trying not to limit ourselves in the potential therapies but recognize we may either affect the direct cause or we may affect something that compensates.

We recognize that as we try and develop protocols the issues will be complicated. They are complicated by things like genetics. They are complicated by the environmental factors; things that people believe are likely to affect myopia, either progression and/or things that may imbalance a particular trial. We expect those types of phenomena to be things like genetics, environmental factors like education, light exposure, refractive correction, work or play habits. These may or may not be factors and there may be additional things that we are not currently aware of.

To start out with, I am going to try and start with the basics. The basics, from our perspective right now, are what is myopia? Who has it? Is all myopia necessarily bad? If not, is some worse than others? How

long do we need to study it? How frequently do we need to look? And, how are we going to know when we have had a successful outcome?

We have tried to translate these questions into more workable questions that we can deal with and, consequently, you have a whole long list of questions with many sub-parts. We expect that to occupy the majority of the day.

But our goal is two things. Our goal is to have a discussion of the topic. That is equally important to answering the questions. So, the extent to which you can identify what we both know and what we don't know is important to the agency. As we go through the questions we would like to hear a consensus if one exists, but we don't believe that that is the end-all to answering any of the questions. If there is a range of answers, that is perfectly acceptable to us. We would like to know what that range and variety of different answers is; why you believe those particular answers; or if they are just hunches or if you would like to see that developed. Those are also things we would like to know.

If we have not asked the right questions or if there are additional questions that we should have asked, please tell us. As I said, this is a beginning process. We

think it will go on for some time. So, if there are other areas that you think we should be exploring, please let us know.

Everybody has the questions in their handouts. I will go through them very quickly right now and then later on in the day we will specifically go through them point by point. These are the same questions that were in the background package although we have changed the order to them just a little bit to group things a little bit more appropriately.

The first question is what is the minimum rate--when we say rate we want both amount and time--of a refractive change that determines whether myopia is classified as progressive, stable or regressing? These are probably the main categories of what myopia does. It either changes, stays the same or gets worse but we are not sure exactly how to define that.

The term is sometimes used of high risk myopia, or people who are at high risk. To the extent that we can try and define what that group is, we are interested.

Which population should be studied prior to approving a drug treatment for the prevention or retarding of myopia? We recognize that we can never study everything that we need to know about a drug product before we approve

it. If we took the time to study every aspect of a product we probably wouldn't have these products in our lifetime. So, we think there is some kind of balance with benefits and risk. So, what we are trying to ask is what things do we think need to be studied prior to approving a product. For example, we have listed ages, education levels, ethnic groups, family history of myopia or other defining characteristics.

If there is a minimum amount, what is that minimum baseline level of myopia for a multicenter set of associated factors that might justify a pharmacological intervention to arrest progression? Again, things like minimum axial length, minimum refractive error, minimum corneal curvature, and what period of time that needs to be observed over.

What is the minimum amount of change that would justify a pharmacological intervention to arrest progression? If we decide that we don't want to look just at a baseline characteristic but if we want to look at people that are changing, what is the minimum amount of change that you would feel is necessary to answer those same aspects?

Then looking at goals, what do we think the ideal refractive error is? Is there some ideal range? It may be emmetropia, it may be something else.

How much of a refractive change is considered an important change for a particular individual? We have given a list of starting ranges of refractive error. This is tied to the earlier question, what should we be trying to get to if you start either at low ends of myopia or start at high ends of myopia? We have broken it down to a bunch of different categories. The answers may be the same for some of these categories or they may be different for every one of these but we are interested in your opinion.

What is the minimum amount of change that would be considered a success if you are just trying to slow it as opposed to stopping it?

Which are the clinically relevant, acceptable endpoints for myopia-induced ocular disease? These are diseases that we believe are potentially associated with myopia so if we were going to try and have a decrease in retinal tears because you believe that myopia is causing an increased risk in retinal tears, or decrease in retinal detachments because we believe there is an increased risk. Again, these are possible associations. We are looking at whether you think they are things that should be pursued.

Then we go on to the different methods. How should the particular parameters be studied and measured? Do we think there are currently reliable, reproducible

measures for assessing this in children? If so, what are they? We are looking for things potentially for refraction, both automated and cycloplegic; axial length measurements and the rest.

Because we have heard a lot about high myopia being bad and how it affects someone's quality of life we would like to start addressing that early on. So, if there are particular ways of measuring quality of life, we are interested in hearing how you think that should be measured.

Obviously, once we start doing these measurements we need to know how frequently to do the measurements. We don't want to do things that are overly burdensome but we want to do things that capture the information we need.

The counterpart to how frequently do we need to do it, we need to know how long we need to do it for, both in testing durations of treatment and the follow-up that occurs afterwards.

Obviously, a concern to us is having an effect, knowing what that effect is, looking to see if there is some kind of rebound associated with that effect and how long does it take to do all those things.

There are a couple of safety questions that we have put at the end not because they are less important but just because we needed some place to fit them. One of the

concerns has been in studying children that potentially have the risk for developing amblyopia. There have been concerns raised from time to time about whether it is appropriate to study children that are at risk of amblyopia and potentially altering their refractive error. So, we are putting that question just out on the table, is it acceptable to study children in that potential range or not?

As we know, most drug products, in fact all drug products that I am aware or have some risks associated to them if they have any benefits. Those risks are frequently evaluated by looking at adverse events that occur. The frequency of adverse events is primarily dependent on the number of patients you study. If you study very few patients you are not likely to see relatively rare adverse events. So, we are looking at what is the frequency of adverse events you want to pick up in studying a particular drug product, recognizing that this is going to be directly correlated to the number of patients that need to be studied.

Because we recognize that there may be some conditions that are probably considered more serious than others, retinal detachments probably being a more serious condition than general myopia, if those risks change because

the condition gets more serious, we would like to know how that affects your answer too.

Last but not least, if there are areas we have missed--as I said in the beginning, we are most interested in the discussion that goes on so if there are additional comments, additional questions, anything else, we would like to hear that.

Again, I want to thank you for your time and effort today in advance. Thank you.

DR. GATES: Thank you, Wiley. Next we have a presentation by Dr. Ken Green, from Novartis.

Novartis Presentation

Introduction

DR. GREEN: Good morning. I am Ken Green, with Novartis Ophthalmic. On behalf of Novartis Ophthalmic, I would like to thank the agency and I would like to thank this panel for organizing this meeting and for allowing us to be part of it.

In the time allotted to us this morning we would like to cover the following agenda: After my introduction we will present three experts in the field of myopia research and they will cover a variety of topics, ranging from a discussion of natural history and prevalence of myopia, a discussion of the consequences of myopia to the

patient and to the physician, and then a proposal of a clinical study design and an endpoint. Then I will finish with an overall summary.

As part of the introduction, Novartis believes that the development of pharmacological treatments for myopia is important. We believe that patients and physicians continue to desire new ways to treat myopia and we would note, as an example, the significant rise in LASIK procedures in the past two years.

There are two main impacts to a person who develops abnormal axial elongation, myopia and the refractive error associated with myopia, which is the immediate impact, and there are potential pathologic changes that Dr. Chambers referred to, which are long term.

We specifically propose an indication for the treatment of myopia based on assessing the change in refractive error. It is not our intention to seek an indication for reduction in potential pathologic changes.

Last year we were part of various discussions with the agency regarding study designs and endpoints for a pharmacological treatment for myopia. Those discussions culminated in a request to the agency to have this panel meeting so that we could get some clarification on some of these questions.

Our primary objectives in our presentation are the following: We want to provide some background information on myopia, and we would like the opportunity to propose the rationale and study design for pharmacologic treatment for juvenile-onset myopia.

With that, I would like to introduce the first presenter, Dr. Jane Gwiazda, from New England College of Optometry. Dr. Gwiazda?

Definition, Prevalence, Natural History and Risk Factors of Myopia in the U.S.

DR. GWIAZDA: I am Jane Gwiazda, from the New England College of Optometry. I am a Professor of Vision Science and I also am the Chair of the recently completed COMET study, which was an NEI-funded clinical trial investigating a spectacle lens intervention for slowing the progression of myopia in children.

I am going to give a brief overview of myopia, definition and risk factors. I am sure most of you are aware of the condition that we are here to discuss today. Myopia is a refractive error where rays of light come to focus in front of the retina, mainly due to the eye growing too long. What this means for the patient is that he or she has blurry distant vision but can see clearly at near, hence the term near-sightedness that is commonly used for myopia.

Juvenile-onset myopia occurs during the period from 6-16 years of age. What happens over this period is that the myopia progression is faster closer to onset and then, by the end of this period at about 15 or 16 years, the progression is considerably slowed and in most children has stabilized.

You should note that this definition does not include any mention of potential pathologic complications of myopia. This figure just demonstrates that the myopic eye is longer, oval shaped, and a point source of light comes to focus in front of the retina, whereas in the normal emmetropic eye the point source comes to focus on the retina.

Levels of myopia are often defined in this way, low, 0.5 to less than 3 diopters; moderate, between 3 and 6 diopters; and then high or severe myopia would be anything over 6 diopters. You should note that in this presentation these definitions may change because they are not always used by all studies.

The most commonly cited figure for the prevalence of myopia in the United States, even though these data are now--well, they were published 20 years ago and they were collected 30 years ago but they are still being cited. These are from Sperduto et al., the NHANES study. The

prevalence between 12-54 is 25 percent. You can see that there is more myopia in women than in men. There is also more myopia in whites than in blacks.

If you look more closely at these data, you can see that the lower levels of myopia, either less than 2 diopters or between 2 diopters and 8 diopters, are much more prevalent than the high myopia where we only have a prevalence in this study of 0.2 percent.

Turning to the progression of myopia, a number of studies have shown that in Caucasian children, during the period when myopia is progressing most rapidly, the annual progression rate is approximately 0.5 diopter per year. For children in Asia, many studies have shown that the annual rate of progression may be up to twice as great.

These are data on progression of myopia in the COMET children. COMET, as I mentioned, was a study to investigate a spectacle lens treatment, that is, progressive addition lenses as compared to single vision lenses, which is the standard treatment for myopia in slowing the progression of myopia in children.

We enrolled 469 children. They were randomized to one of these two lens types. Their mean age at the start of the study was about 9.5 years, and their mean myopia was close to 2.5 diopters at the start of the study. So, what I

am showing here are data from the children who wore the single vision lenses, starting at baseline when their myopia was around 2.5 diopters. On average, in the first year their myopia progressed 0.6 diopter; in the second year, 0.5 diopter; and in the third year, 0.4 diopter. So, this is how we get the average of 0.5 diopters per year from the COMET data.

We are continuing to follow COMET children so we will, in five years, actually have data showing what happens to progression beyond the first three years. Right now, we have extrapolated out three additional years, conservatively estimating that the progression will slow by 0.1 diopter per additional year. So, when you get out six years, the progression of myopia is slowing down considerably, if not stabilizing, in most children.

We also know, and this may seem obvious, that if a child has myopia starting at a younger age, by the time the myopia progression is stopping that child is going to have more myopia. These are data from Mantyjarvi, et al., in Finland. What they show is that if the onset of myopia is at about 7-8 years of age, those children at 15-16 years of age have five times as much myopia as those children whose onset is at 15 years of age.

Turning to risk factors for developing myopia, Dr. Chambers has mentioned both genetic and environmental factors, and I certainly believe both are involved and there is a complex interplay between the two. What we show first is that there is a strong association between myopia and parents with myopia and their children. These are data from Mutti et al. in a recent study. I have similar data from my own laboratory. What they show is that if a child has two myopic parents--these are children who are 13-14 years of age, the prevalence of myopia is 33 percent. With one myopic parent, it is reduced to 18 percent. If neither parent is myopic, it is only 6 percent. You can see that the odds increase with increasing numbers of myopia parents.

We also know from a study in Singapore, and I also have some data in my own laboratory showing that number of myopic parents is not only a risk factor for developing myopia, it also is a risk factor for progression of myopia. So, there is greater progression in children with one or two myopic parents compared to zero.

I really don't have time to get into the environmental factors today. The one that is most commonly cited is near work activities in children, but there are many others that are out there in the literature.

To summarize, the key points are that myopia is found in at least 25 percent of individuals in the United States; that the lower levels of myopia are much more prevalent than the higher levels. The mean progression in Caucasian children is approximately 0.5 diopter per year. Earlier onset of myopia in children results in higher levels by the age of 16 when myopia progression is slowing. And, the risk of developing myopia is related to both genetic and environmental factors.

Now I would like to introduce Dr. Joe Miller.

Consequences of Myopia

DR. JOSEPH MILLER: Thank you. My name is Joseph Miller. I am a pediatric ophthalmologist at the University of Arizona, and a professor in the Departments of Ophthalmology at the Optical Sciences Center and in our College of Public Health.

As far as my research background, I am a practicing pediatric ophthalmologist and I carry with me the perspective of a practitioner who takes care of children and consults with the parents of those children. I am an NIH-funded investigator, researching the effect of astigmatism on visual development of native American children. With regard to myopia, I am an investigator in the CLEAR study and, finally, I serve on a data monitoring and oversight

committee for early treatment of retinopathy of prematurity, a disease which has a very strong association with myopia. So, I have some research experience with myopia.

Pertinent to this study, however, I was also an investigator in the pirenzepine 205 study, PRI 205, and I was on the planning board for that and, additionally, served on the planning board for the amblyopia treatment study number 1, which was the atropine study that demonstrated the use of atropine as an effective and safe alternative to eye patching. So, I am not a myopia maven in the sense of people who do animal research, but I am a clinician who works in the area and a scientist who works in the field.

What I would like to do is to try and break this into two different categories, the implications if you have myopia as far as the risk of other eye diseases and then from the perspective of the patient or the child who has myopia, what are the effects of that myopia in terms of the induced refractive error and the eye changes in terms of how they see.

Well, first off, in order to get to what the effects of myopia are on the eye, it is worthwhile remembering that when we are talking about myopia we are talking about light not falling in focus on the retina. That can occur from one or two reasons. Either the optical

power of the anterior segment of the eye is too great, causing the light to fall into focus prematurely in front of a normal eye in terms of axial length, or you can have an eye which has a "normal" optical power in its anterior segment but there is too long an eyeball and axial elongation present, resulting in the light falling into focus an appropriate position for a normal eye but in the case of a myopic individual the eye is too long and the light falls into focus ahead of the retina, or it can be a combination of the two, resulting in some sort of mismatch between the two.

We talk about myopia in units of diopters. There are lens equations that describe what a diopter is but, for the purposes of this discussion, the basic rule of thumb is that about 2.67 diopters is the difference of 1 millimeter in axial length. In measurement of axial length there are ways that this can precisely be measured either with light refraction measurements, ocular coherence tomography, or partial coherence. There are also ultrasound measurements so we can measure the length of the eye. We can measure the power of the anterior segment of the eye, particularly the cornea. We know the shape of the cornea quite precisely. But clinically the defining characteristic of myopia is a procedure called refraction where various lenses are placed

in front of the eye and adjusted until the light for that individual patient falls in focus on the retina.

So, the types of data that we are able to collect from people who have myopia are related to the length of the eye, the optical power of the eye and where the light needs to be adjusted in front of the eye in order to fall into focus on the retina.

As this eye grows things can get out of balance and the disease which we call juvenile-onset up seems to be characterized by an abnormal rate of growth of the eye itself. Axial elongation seems to be the defining characteristic of juvenile-onset myopia, the predominant form of myopia that we are discussing today.

If you have an eye which was originally intended to be this size and it grows to be bigger because the sclera, the white part of the eye, is growing and the inside lining of the eye, the retina, does not grow to keep up, then what happens is that the eye becomes stressed in a fragile tissue. The retina itself has the strength and consistency of about wet tissue paper, whereas the sclera is much more expansible and can grow. So, as the eye grows one of the consequences of myopia is that changes occur in the retina. Initially stress results in stretches, in tugs and pulls leading to myopic degenerations. Finally, if those

stresses are exceeded, catastrophic failures can occur such as retinal detachment.

Frequently also cited in the literature in textbooks, besides these retinal associations, is that glaucoma is associated with progressive levels of myopia.

Let's first talk about myopic retinopathy. Myopic retinopathy is the condition, as I mentioned, where the retina has been tugged and pulled and there are various changes that occur. Typical names are lacquer cracking that you see referred to as a characteristic. What happens is that the retina is stressed and little tears develop or where the retina is attached, it becomes stressed in those locations. This is a very common condition among people with advanced levels of myopia, for sure. If you have 9 diopters of myopia or about 3 millimeters of axial elongation, over half of those people show these degenerative changes in the retina.

But what surprised me when I reviewed this literature is just how common it is in moderate levels of myopia. In the 3-5 diopter range we find that just slightly less than 5 percent of the people show these changes. So, this is a very prominent and very common finding among people with myopia.

Fortunately, much less common is the event of retinal detachment. In the general population about 1 person in 20,000 will experience a lifetime risk of retinal detachment developing. These papers are cited, the Eye Disease Case-Control Study Group and a paper from Japan by Ogawa, et al. that reviewed the risk of retinal detachment developing as compared to levels of myopia, case-control studies, if you will.

These have been reevaluated as univariate odds so that we can compare them. What is striking to me is across continents how similar these numbers are in terms of what happens to people who have progressive levels of myopia.

This number of 3.87, 3.81 or about 4, please don't interpret that as meaning that one person in four develops retinal detachment. That is not what these numbers mean. Retinal detachment is a rare event, but what it does mean is that if you are a practicing ophthalmologist and someone comes into your office with a retinal detachment, that person is four times as likely to have that retinal detachment if they exhibit low myopia compared to the condition called emmetropia where the optical power of the eye is in balance with its axial length.

At moderate levels of myopia the risk of being associated with myopia increases to about 10-fold. In the

Ogawa paper, where they further stratified people into having 6 diopters or more of myopia the odds ratio increases to 26-fold elevation of risk for 6 diopters or more.

The perception of many of us in the practicing ophthalmologic field is that myopia is associated with disease. But from the perspective of the patient, myopia is associated with a problem of seeing things far away, and if you can get closer to things you can see them more clearly. People also associate it with the need for wearing eyeglasses or some other correction. They often associate it as well with a certain point in their life. They can remember when they started having trouble seeing things, or the experience in the classroom that led them to say something about it that led to them ultimately receiving eyeglasses. So, there is a definite relationship as well between the amount of the myopia that is present and visual impairment.

A standard textbook, Bennett and Rabbetts "Clinical Visual Optics," has a nice table in it that I have adapted here that relates the amount of myopia present with the expected level of uncorrected visual acuity and the number that we use in analysis of data, the logMAR, in terms of how much myopia is present and how well we see. So, these numbers are the Snellen fractions that we normally

think of when you go to get a driver's license, and 20/40 vision is what we use as a cut-off for being able to see in most states for getting a driver's license. That number is associated with 0.75 diopter of myopia.

If you have ever had your eyes checked and you have sat behind that machine called a foropter and the doctor is flipping back and forth with those knobs, each click of that knob is 0.25 diopter on the sphere dial. One of the things that we learn very early as clinicians is that when you are refracting someone and you are trying to refine their refraction and intentionally make their vision blurry by giving them too much plus power, effectively making them a mope, for each click of the knob they should give you back one more line of visual acuity and improvement.

So, this is a clinical rule of thumb that I think clinicians learn very early in their practice but as far as what the literature is to support this, actually there is really quite a bit that has been studied. One of the best papers I think to look at this was by Maj. Pincus, given a task to evaluate the relationship between refractive error and unaided visual acuity. The reason for this study was quite simply that people were trying to get into the service and claiming that they had better vision than they actually

had. So there was this condition called positive malingering that was an issue.

Over 7,000 cycloplegic refractions went into this data set in which the individuals had a cycloplegic refraction; they had an unaided visual acuity and everybody that was in the study had a best corrected visual acuity of 20/20 or better. Each of the data points that you see here is an average of a large number of individuals. So, at a given level of refractive error, sphere and cylinder, the average acuity was calculated from that 7,000 value.

What I have done is taken that data set and extracted from it the individuals who had 5 diopters or less spherical equivalent myopia and 1 diopter or less cylinder, and plotted them against the more modern scale, which is logMAR acuity. Across the bottom is spherical equivalent refractive error. There is a very striking linear relationship that you can see here. If you have 0.75 diopter of myopia you are in a cluster over here that is 0.3 logMAR units, or 20/40. If you double the amount of myopia from 0.75 diopter to 1.5 diopters, you are sitting at 0.6 logMAR, or 20/80. As this linear scale continues it starts to flatten out at higher levels of myopia.

That is a bit of data about numbers but as far as how people see with myopia, to try and give you an idea of

what that actually looks like I turned to my colleague, Jim Schweigerling at the University of Arizona. Dr. Schweigerling is an optical scientist in our department and our department has developed an eye model, a computerized eye model that includes such factors as pupil size, axial length, the pupil function and is an exact rate trace model that is based on the standard eye.

So, what these computer simulations are trying to demonstrate is to give you an idea of what an uncorrected myope would see without wearing their glasses. As they take their glasses off, this is as best we can build a model of what the vision looks like in terms of both blur, in terms of contrast sensitivity and, finally, this is a single average pupil size but it is important to remember that in real life our pupils get bigger and smaller. So, our actual vision is sometimes worse or sometimes better depending upon whether the light is very bright and our pupil is small or our pupils are large. But this is the best that I think we are able to do under the current state-of-the-art in actually estimating what it is people see and perceive.

I think the first thing that you will see is that for uncorrected myopia of 5 diopters you have a hard time seeing what those things hanging up on those trees are. They are called leaves. I had a resident that I was with

that kicked them around until first grade and didn't know they are associated with trees because he had 9 diopters of myopia and didn't know it until he got to first grade.

The second thing that I think you will see is that if you are comparing the pictures in the center column to those on the right, this picture looks more like this picture than it does like this picture. I mentioned that at higher levels of myopia the visual degradation starts to flatten out. We become less and less sensitive to blur in our brain with higher levels of myopia than with lesser levels of myopia.

One of the things that I think is pretty clear is that at these very high levels, if you don't have an optical correction on, you are severely disadvantaged and you wouldn't be able to do much beyond act in a Mr. Magoo cartoon. The people that are walking with 7.5 diopters of uncorrected myopia, they may be able to find where the open door is to get out of a room but they are severely disabled in terms of their vision and these are people that tend to wear their correction all the time.

On the other hand, as you move to lesser amounts of myopia, lesser magnitudes, at 2.5 diopters of myopia you can recognize that the tree has leaves and you might be tempted to go skiing without wearing your correction.

But it is important also to remember that myopia is characterized not by fixed poor vision at all distances, but people who are myopic see things up close better than they see things further away. So, the child's visual environment, as the child develops myopia, is something that they can manipulate. If they are able to get up and move closer to the object of regard, the thing they are trying to look at, they will do so.

So, let's think of this in terms of the perception of a child who is perhaps starting to develop myopia and is now starting to experience what is going on in terms of not being able to see clearly in the distance but perhaps better at near.

Here is a simulation of a child trying to find a friend in a crowd. The child is modeled as having 3 diopters of myopia. These children are assumed to be 20 ft away for the purposes of this simulation, and our task as observers is to try and identify our buddy, Waldo, across the field. So, this is sort of a "Where's Waldo" game. At 3 diopters of uncorrected myopia you are going to have a hard time spotting your buddy. It is actually, I think, kind of hard to know who is a girl and who is a boy in this crowd. Unless you know what it is your friend is wearing you would probably run into problems. Three diopters of

myopia is associated with an expected visual acuity of 20/320. The best corrected vision of 20/200 is legal blindness so if you are not wearing your glasses you would be in the range of visual acuities that are called legally blind.

As we decreased this by 0.75 diopter to 2.25, you can see a dramatic improvement in terms of what the child is able to see. You are starting to recognize who is a boy, who is a girl and it starts to pop out at you that this is probably Waldo over here. But, certainly, no details about these children are clear. You don't know whether the child is smiling at you. You certainly can't make eye contact.

At 20/80 vision you start to see things that I would consider to be details. You can see that some of these children are smiling. You see the body language that is going on here. One guy is leaning on another guy. The second thing that becomes apparent at this level of myopia, if you are clinician, is that there are an awful lot of kids that come in and get their first pair of glasses at this level of myopia. A pretty common first prescription for glasses is in the minus 1.5 to minus 1 diopter range. That is when a child finally shows up in your office. So, there are an awful lot of kids who develop myopia and have it for a while that are running around like this. It leads me to

think that many kids then tolerate this level of myopia because they haven't started complaining yet or it hasn't become so apparent yet to their parents that they know something is wrong.

Let's decrease this by another 0.75 diopter, down to 0.75 diopter. We are now at a 20/40 level of vision. This is the level of vision that you are expected to have to drive a car uncorrected. Really quite a bit of detail is now apparent. You can see the buttons on the children's shirts. You can see the smiles. You are going to get the social clues that are going on.

But what I do want you to look at right now is the overall image quality that we are seeing here and compare it to this image, which is no refractive error. For me, the biggest thing that I see different is the loss of contrast that someone with a small amount of uncorrected refractive error experiences. We hear this message taught to us over and over again by patients who are refractive surgery patients when they learn that visual acuity is only one component of how well we see. How far you read down on the eye chart is just one point in our visual function and contrast sensitivity is an important measure.

So, the overall image quality when you have myopia is not just impacting how far down the eye chart you can

read, but also how well you perceive other things, how bright the bright colors appear to be. You hear this from people when they get a new pair of glasses, that things look crisper, brighter.

The other thing that I would mention is that very often the difference between here and here is what brings people back to the office to get a new pair of glasses. The 0.75 diopter change is a typical number that you see being used when clinicians decide whether to give a new prescription that is slightly stronger.

That is the perception from a distance task. You could argue that the child, if they really wanted to know what was going on, could walk the 20 ft and see what is going on. But if you are a kid in the classroom and you have already been moved to the front of the class and you are sitting in the first row, it is a little different.

This is a simulation of a child at the blackboard. This child is now 6 ft away from the blackboard. What we are trying to do is look at what happens here to various levels of visual acuity and associated levels of myopia. In terms of how well the child reads the eye charts, this is the eye chart at 20 ft, a logMAR chart, and this is the child in a classroom looking at a friend at the blackboard and trying to read the blackboard.

If you are sitting up close, I think the first thing is that even at 20/160 vision you can see the blackboard and if the teacher has written large and clearly and you have a blackboard that is using white chalk against a dark background you can make out these numbers even with 2.25 diopters of uncorrected myopia. Unfortunately, I think nowadays the more typical complaint I hear from students is that the teacher is using an overhead projector with a dried out fuchsia colored marker, and the contrast is terrible and they can't see in the classroom even with relatively low levels of uncorrected refractive error.

So, despite the fact that we are in this range of 2.25 diopters of myopia and at 20/160 vision, you can understand how some children sit in the front of the class or get moved to the front of the class and still function. Is this ideal or desirable? I would submit not.

We now have moved by 0.75 diopter to 1.5 diopters and it is a three-line jump on the visual acuity chart. We are now looking at a line and able to resolve a line that is half the size it was before. You can see a big improvement in how well the blackboard is seen. Again, 1.5 diopters of myopia is a level of myopia with which a lot of kids participate in sports without correction. A lot of kids will be advised to take their eyeglasses off for playing

soccer. So, you are a kid, you are out on the playground a lot of times, running around without your glasses on and this is sort of the expected level of vision if you have 1.5 diopters of myopia.

We now jump to 0.75 diopter of myopia which, again, sounds like a very small amount but it is in that range of 20/40 vision. The details really are quite apparent. You can start to make eye contact if you are sitting in the front row. The numbers are legible if the teacher is writing big. If you move into the upper grades, however, the material in classroom work becomes smaller and more difficult. If you are holding it up close you are going to be able to see it but if it is far away and you can't change where you have been seated, you are going to have problems.

Lastly, let's look at the fully corrected child or the child who has no refractive error. They see all the way down to the 20/20 line on the eye chart. Things are sharp and in focus. But now let's think about this as a slightly different thing, what if you are a child who is, say, 3 diopters myopic and you have worn those glasses for a while and the glasses are only correcting 2.25 diopters of your myopia? So, you are under-corrected by 0.75 diopter. If you had your full strength glasses on, this is what it would

look like. But if you have those glasses which are not strong enough by 0.75 diopter, this is what the world would look like.

So, these simulations can also be scaled back for wearing lesser amounts than the full correction to give you an idea of what the child is perceiving if they are not wearing their glasses and they are not fully correcting the problem at hand. So, as best we can tell, with the exception of a small effect in terms of making the overall world seem smaller, one of the effects of wearing a high optical correction, if you have ever looked at someone who is wearing a myopia pair of glasses, their eyes look small when you look at their face through the glasses. The same thing happens in reverse. As they look at the world, the world becomes minified. With the exception of this minification effect, these same numbers can be applied to trying to estimate what the effect of under-correction is in a child's vision.

So, I tried to give you an idea of what the visual perception is of these children who are having a level of myopia. What I hope I have demonstrated to you is that there is a real, appreciable difference that is associated with this doubling of the visual angle. A doubling of the visual angle means that each time that we jump up by three

lines the line becomes twice as large in terms of the eye chart. But not just how well a child can read an eye chart, it translates into real and significant effects in terms of how they perceive the world, not just in terms of how fine a detail can be resolved, but in how sharp and crisp and clear the image is.

This 0.75 diopter progression is a value that is supported in the literature. It is a value that has been drilled into us from the first day of refracting. And, it is a number that seems to have both clinical and statistical significance.

This is an idea, I hope, as to how the children with myopia see but now let's turn it into the perception of the parent who is bringing a child in who can't see because they have been moved to the front of the class and they are already sitting in the front row, and finally the message gets across that the child needs a pair of glasses. So, I am moving back to the position of being an eye doctor and I have a child sitting in front of me. What are the options that I have to offer a child who has myopia?

Well, these options are listed in I think roughly increasing levels of risk for that child, and probably in terms of convenience or desire of 13-year old kids to have the reverse list. But single-vision glasses are the

cheapest, the easiest way to correct somebody's myopia. They are safe if you are not hit by a soccer ball. They are very effective. Single-vision lenses are inexpensive and they are widely used as the primary treatment for refractive error.

Contact lenses--I think really the first three in this category are different than ortho-keratology, which is a procedure where the cornea is being remodeled to a shape that changes the front power, the optical power of the eye in order to bring the light into focus at the appropriate place. So, this is a contact lens procedure but its goal is to reshape the cornea.

Finally, are refractive surgery options for when the children are older, and in some places in the world are actually being offered to younger children now.

This list gets old after about the second or third time the parent has brought the child in to see me for a stronger pair of glasses, and it doesn't take long before I get asked the question, "Doctor, isn't there anything else you can do to keep this from getting worse?" Then I bring up my little spiel about, "well, we have some options. Some have been investigated." When I talk about what those options are I start with you can save the old pair of glasses and you can wear those glasses in the evening to

read with, intentionally under-correcting the child at near. I talk about the COMET study and the addition lenses that have been used, and relate the fact that I put both of my kids in progressive addition lenses when they were younger and that their myopia stabilized, but then I point out you look to me like you are really quite myopic and neither my wife nor I are. So, I don't know whether they didn't progress because they weren't genetically predetermined to or because the PAL lenses worked. But the kids like the lenses. Because they didn't have a line they were acceptable to the kids and they wore them, or at least they told me they did.

Rigid gas permeable lenses, the thinking here is, rather than ortho-K to reshape the cornea, this is to stabilize the cornea to its present shape. As I said earlier, however, juvenile-onset myopia is characterized by axial lengthening more than changes in the optical power of the eye. So, I am not sure how that is going to play out. Certainly, in terms of studies the amount of data in good studies, talking about RGP lenses to control the progress of myopia, is lesser.

That leads me to pharmacologic treatments. I talk about the fact that in various parts of the world, various things have been used to various extents. The one thing

that we know is that atropine is very effective at slowing or stopping the progression of myopia. But the problem with atropine is its side effects. The very same side effects that make atropine so undesirable to put in both eyes to use for the treatment of amblyopia are those side effects that we went after to use atropine as a penalizing method in the treatment of amblyopia. Its effect is to paralyze accommodation and widely dilate the pupil. You can give that child a pair of bifocal glasses to wear and the child is able to see at all distances, in theory, well but it is instantly making that child as presbyopic as you would be if you were 55 years old. Just as happy as you were to get your first pair of bifocals, these children are when they become dependent upon bifocals with atropine.

That is the first effect. The second effect is the huge pupil that you get from atropine. The larger the pupil size, the more aberrations enter the eye and the image quality degrades to some extent even if it is fully corrected with spectacle.

The last issue about atropine is that, because the pupil is so large and unresponsive, the light seems to be very bright and the child is often faced with glare problems when they are outside playing. In the amblyopic treatment study we advise children to wear hats and sunglasses as

appropriate and we always place the child in ultraviolet blocking lenses in order to try and protect the child against these side effects.

But one of the things that I strongly believe is that if we are going to have an effective pharmacologic treatment it has to be a medicine that does not carry with it the side effects of atropine. Because even though atropine has been available off-label as an effective use for slowing the progression of myopia, it is very seldom used because the side effects are so profound.

That leads me to where I am today, which is requesting that we find a way to develop a safe, effective and approved medicine that can be used in slowing the progression of myopia. I would like to have an option to offer these parents who come to me and say I don't want my child to be as myopic as I am. I don't want my child to need to have stronger glasses each time.

So, in order to discuss issues around such a design of a trial, I would like to introduce my colleague, Dr. Karla Zadnik.

Proposed Clinical Study Design

DR. ZADNIK: I am Karla Zadnik, from the College of Optometry at Ohio State University. I have chaired first

a single-center and then a multicenter study of the development of refractive error in children since 1989.

In the spirit of jump-starting or giving a beginning place for the discussions as Dr. Chambers outlined--that is a pretty lofty agenda--what we would like to do is present a proposed study design. It hits on many of the issues that Dr. Chambers introduced. It probably also introduces a couple of other issues. So, that is really the purpose of my presentation.

The proposed indication that, in representing Novartis, I am proposing is that a pharmacological agent be looked at to reduce myopia progression in children diagnosed with juvenile-onset myopia. So, those are the children already with myopia of a certain degree, as you will see.

This is perhaps analogous to the approved indication on the devices side of the house for refractive lasers, which reads, "for the reduction or elimination of myopia," but it is not an indication that would claim or promise to have any demonstrated effect on whether a child would develop retinal findings in their 20s or retinal detachment in their 40s, nor would it claim to reduce the risk of those things happening to that person in the future.

So, a study design to put on the table is a prospective one. The children would be randomized to the

study treatment or to placebo. It would be double-masked and conducted in an appropriate fashion.

The time period is a huge issue. It was raised early this morning, and we would propose 30 months on drug to establish the safety and efficacy of that agent. That is a time period that we arrived at because it resonated with clinicians that we spoke to. It also exceeds international regulatory guidelines and would be longer than the usual in terms of assessing the safety of something that would be used in children specifically.

There would be also a 6-month off drug period to address the potential for what has been termed a rebound effect. I am sure there are lots of ways we could think about rebound for an agent like this that would retard the progression of myopia in some way. I think rebound would not be that the child went off drug and the myopia progression resumed as would have happened to the child at the age he is at that time. So, that would not be a rebound; it would just be he is off drug so the drug isn't working anymore. Rebound would be if the eye growth accelerated to make up for the period of time that a child had been on treatment. That sounds like a rebound effect for a drug like this.

Lastly, the number of subjects, the sample size, would be determined to detect adverse events at the one percent level. I think one of your discussion points is whether that would be sufficient for a study of any agent that might be used in children.

So, for proposed study entrance criteria the children would be 6-12 years old at the time that they entered the study and they would have myopic refractive error ranging from 1-4 diopters as measured by cycloplegic auto refraction and specified by the spherical equivalent component of their refraction.

They could have 1.25 diopters of astigmatism in either eye, and they could not have anisometropia as much as a diopter that is a difference between the eyes. They could not have strabismus or eye turn, and they would have to be able to see well with their spectacles on. So, their best corrected visual acuity would need to be at least 20/32 in each eye. It would seem obvious that you would rule out any children who had any ocular or systemic or neurological conditions that would be known to affect growth of the eye or refractive development.

One issue is what would be the outcome of a study like this. What would be the things that you would want to measure, and what would be the measurement that you would

hang your hat on? Well, it seems fairly obvious that if the indication were to slow the progression of myopia the primary outcome would be the progression of myopia. One of the issues is how to measure that in children. I think we could all argue that cycloplegia and paralyzing the ability of a child to accommodate during the measurement would be important to stabilize that measure. Many studies have investigated whether subjective refraction or auto refraction or other methods that one might use are appropriate.

I think auto refraction has sort of come out the winner out of previous studies. All the child has to do, even a 6-year old, is just to sit there, face in a chin rest. They wiggle a little but they can do that pretty well. It also allows you to get multiple measures. With an auto refractor each click of a button is equivalent to the whole refraction procedure that you go through when you answer which is better, one or two, over and over and over. So, you can take 10 measurements on a child very quickly which gives you the ability to improve your repeatability with multiple measures. So, I think auto refraction under cycloplegic conditions is probably the most repeatable, most reliable and valid way to measure refractive error. Then, that progression of myopia would be specified as the change

from the baseline refractive error that the child had when he or she entered the study.

For any pharmaceutical agent that purported to slow the growth of the eye, that is, one that affects the underlying cause, you would want to measure the axial length. That seems fairly obvious. But I can imagine that secondary outcomes might be different for pharmaceutical agents that proposed to have a different method of action. If you were proposing to somehow change the shape of the cornea in a way that would be acceptable in children then, obviously, corneal curvature would be an important thing to measure. But for the purposes of one that really did slow this abnormal growth of the eye, axial length would be an appropriate and logical secondary outcome measure, measured in a repeatable fashion.

Now, one thing that we have really wrestled with is what would constitute for any agent a clinically important, meaningful change to children, to parents to clinicians. So, we have sought feedback and tried to put that story together from a variety of ways, one of which is direct feedback from eye doctors--what do you think is a significant reduction in the myopia progression? Dr. Miller presented the idea that there can be some logical correlation to change in uncorrected visual acuity.

Lastly, there is just a hint of beginning data on quality of life in patients who are myopic as it relates to the magnitude to their refractive error.

So, when we have convened some advisory panels of clinicians, both internationally and in the U.S., what they tell us is that a change in refractive error for them of 0.5 diopter to 0.75 diopter is clinically meaningful to them. So, we can talk about that when they change glasses on a child, but that seems to be a number that we keep hearing from clinicians.

Dr. Miller presented that doubling of the visual angle correlates well with a 0.75 diopter change in refractive error and gave you a very visual idea of what it would be like to double your visual angle over and over and over as your myopia worsened. That change in visual acuity that corresponds to that doubling of the visual angle has been accepted in ophthalmic drug trials in the form of best corrected visual acuity and in device trials in the form of uncorrected visual acuity.

I think one thing we perhaps have come to realize with the advent of and popularity of refractive surgery is that maybe uncorrected visual acuity is a lot more important to our patients than we ever though. As eye care practitioners, we are in the business of putting something

on people and making them see well, but what we find is that patients tell us I care quite a bit about whether or not I can see the alarm clock, or when I stay in a hotel I have to know where my glasses are on the nightstand in case there is a fire so I can make it out the door. So, based on these criteria, this sort of brought us to this 0.75 diopter change as being clinically significant.

On the topic of quality of life, there are a variety of groups that are now working in the development of quality of life instruments that are specific to refractive error. They attempt to measure whether a patient reports a better quality of life on this questionnaire if they wear contact lenses instead of glasses or if they have refractive surgery instead of wearing spectacles or contact lenses. One of those is the Refractive Status and Vision Profile, out of John Hopkins University. It has been validated and it is the only group whose device and testing of that device has matured enough that there is actually published data.

So, this particular paper by Susan Vitale reports on a cohort of 550 people who have mostly myopia and no previous refractive surgery, most of the sample, and then a small portion of the sample at least three months past their refractive surgery.

What they found was that for each additional diopter of myopia that the person had, they were significantly more likely to say they were dissatisfied with their vision. So, there was a relationship between higher, increasing myopia and saying, "I'm not really very happy with the way I see," on this particular questionnaire.

Now, an issue that I don't think was raised at the beginning of the morning that I am going to put on the table for discussion is that in studies like this there is an issue of how to analyze the data. I don't promise to be a biostatistician but let's see if I can outline this for you.

One is to simply analyze the difference in the mean progression of myopia in the treatment group compared to the placebo group, and statistical significance would tell us that the mean change from baseline was significantly less in the treatment group. That is one way to do it.

In addition, this clinically meaningful difference comes into play because it would be important that the observed difference between those two means of the two groups would be clinically meaningful. So, that is where this 0.75 diopter idea comes along.

An alternative way to analyze data like this, whether it is in a myopia trial or in any clinical trial, would be to say what we are really interested in, or one way

to analyze the data would be to say we are going to take that clinically meaningful amount and we are going to look at the proportion of children whose myopia progresses by that amount or more and compare those proportions between the treatment group and the placebo group. A statistically significant result would be if the treatment group had fewer children, a smaller proportion, who had progressed by that prespecified clinically meaningful amount--the same data set but two different ways of approaching it statistically.

As think about all of these things put together, what we would like to do is recommend a primary efficacy variable as follows: Number one, we have told you from different approaches and by some visual displays that we believe a change of 0.75 diopter would be clinically significant. But from some previous discussions over the last couple of years with FDA, our impression is that a change of something on the order of 2 diopters would be viewed by FDA as clinically significant. So, 0.75 diopter and 2 diopters are a fair amount apart. So, we took that suggestion or that impression very seriously as advice and sought to model data based on myopia progression to see where that would take us.

This is the slide that Dr. Gwiazda showed you. Let me just refresh your memory. These are the control

children wearing single-vision glasses, from the COMET study of progressive addition lenses. These are the real data that have been collected to date. As. Dr. Gwiazda mentioned, those may be collected but these are imputed data as follows: In the first year the single-vision group progressed 0.6 diopter, in the second year 0.5 diopter, in the third, 0.4 diopter.

So, each of these subsequent years where we have extrapolated the data, we have just decreased the progression rate by 0.1 diopter. You can do the calculations. If the children are 9.5 when they entered the study on average, they would be on average, 15.5 at the end of this curve.

Now, if we then assume a pharmaceutical agent that would have a 50 percent treatment effect, here is what we see. So, each year the progression of myopia is reduced by 50 percent and out at six years what we find, if we were comparing the means of these two groups--the first analysis method that I mentioned--what we would see is that we could only see a difference between the means of the two groups of a diopter, not the 2 diopters that I presented before as perhaps being required for clinical significance. So, given the underlying distribution of the progression of myopia in the target population, it means that at most, if you started

with average age 9.5 year olds, you would find a diopter difference between the two, not 2 diopters.

In the spirit of taking that advice seriously and in the spirit of compromise we might propose a primary efficacy variable based on that comparison of proportions between the two treatment groups where the cut point, the clinically meaningful cut point that we would use would be 2 diopters or more of myopia progression. So, that would bring into play the 2 diopters clinically meaningful endpoint but it would be based on a proportions analysis.

To summarize, the proposed population to study might be 6-12 year old children who have myopia of 1-4 diopters at the time the study begins.

The primary outcome would be spherical equivalent refractive error measured by cycloplegic auto refraction, and specified as a change from baseline.

The study would be 30 months long. The children would be on treatment for 30 months. There would also be a six-month period off drug, and both of those periods would address the safety, efficacy, rebound effect, those sorts of things.

Lastly, what we have sort of proposed in light of this 0.75 diopter overlay is a primary efficacy variable that is based on a comparison of the proportions between

treatment and placebo groups who progress at least 2 diopters in their myopia.

So, that is an overview to begin your discussion. With that, I would like to turn it back over to Dr. Green.

Overall Summary

DR. GREEN: Thank you. Dr. Zadnik, Dr. Miller and Dr. Gwiazda, I would like to thank each of you for your presentations.

In terms of an overall summary, the blurry vision from progressing myopia is important to children, to parents and to eye care practitioners. Dr. Miller I think very effectively presented a simulation of what that is like.

We have proposed an indication for reduction of myopia progression in children diagnosed with juvenile-onset myopia. As you just heard from Dr. Zadnik, we recognize that for a development program there is a requirement to define a primary efficacy variable, and what we have attempted to do is to take into consideration all the feedback that we have gotten, but to try to do it in a way that we think would allow for a feasible development of a pharmacologic agent.

We do, however, believe that a change in refractive error of 0.75 diopter is a clinically significant

change. We have proposed a study design to assess any pharmacologic treatment of juvenile-onset myopia.

That concludes our presentation. On behalf of Novartis Ophthalmic, I would like to thank the FDA. I would like to thank the panel members for organizing this and allowing us to participate. Thank you for your attention.

DR. GATES: The committee would like to thank the FDA for their presentation and also Novartis. We will adjourn for a 20-minute break and convene at 9:45.

[Brier recess]

DR. GATES: At this time we will reconvene the meeting. If you came in after the initial introductions, I am going to ask you to introduce yourselves and we will again go from my right to left.

DR. PLOTT: My name is Todd Plott. I am serving on the committee as an industry representative, non-voting member by the way. I am a dermatologist and have spent all my career at various pharmaceutical companies developing a variety of different pharmaceutical products.

DR. GORMAN: I am Richard Gorman. I am a pediatrician in private practice. I stand on the FDA's Pediatric Advisory Subcommittee and I represent on that committee, but not here, the American Academy of Pediatrics,

and I chair the National American Academy of Pediatric's Committee on Drugs.

DR. BULL: Good morning. I am Jonca Bull, the Director of the Office of Drug Evaluation V.

Committee Discussion

DR. GATES: Thank you. Now we will begin our first segment for discussion. With the first segment of discussion I would like to start by asking are there any questions for Novartis from the committee or the FDA. So, we will open the floor.

DR. BULLIMORE: Do I need to announce my name every time I speak? A couple of questions for Novartis. Obviously, we are embarking on a new phase here, a new group of drugs and new potential indications. One of the things that we are being asked to assess later today is complications of adverse event rates. Based on experiences at home and abroad to date, are there any specific kind of events or complications that the panel should be discussing today that relate to this particular product, be it pirenzepine or whatever other drugs are under development?

DR. GREEN: Dr. Bullimore, I will take that question. In terms of pirenzepine specifically are there specific events, as you know, we are working on pirenzepine. We specifically have not tailored this presentation about

pirenzepine. Pirenzepine is one example candidate that we are looking at. There are other candidates that other companies may be looking at. So, we would prefer not to talk about pirenzepine specifically.

We chose the one percent level. It is consistent with typical guidelines for chronically administered drugs, but we acknowledge that it is a topic open for discussion.

DR. BULLIMORE: I have a second question. You threw out in the course of the presentations two criteria for effectiveness. One was 0.75 diopter and the other, which you inferred came out of discussion with the FDA, was 2 diopters. I am looking at your progression graphs that you presented. Am I right in assuming that, based on the COMET baseline and entry criteria, in order to get a 2 diopter effect you pretty much have to stop myopia in its tracks in a group of 9-year olds followed for 6 years? Is that a correct interpretation?

DR. GREEN: That is a correct interpretation.

DR. GORMAN: I have three questions for Novartis. Being a pediatrician, I get to ask all the questions the ophthalmologists might be more worried to ask. The mechanism of action of this class of agents, if it is not your particular agent, is it a growth inhibitor? If it is a

growth inhibitor, is it planned to be administered orally or systemically or topically?

DR. GREEN: We have a particular agent which we are looking at which is a muscarinic antagonist, but we are not proposing that that is the only mechanism of action. We are also not proposing that the route of administration would only be topical. It could be oral; there could be other ways. I think, depending on the route of administration, those sorts of details would probably have to be a point of further discussions in terms of the details of the clinical development program. They might affect the level of adverse event rate. They might affect certain details.

For us, the primary open question was just simply the endpoint, the primary efficacy variable, how we assess the effectiveness and sort of the generalities of the study design.

DR. GORMAN: How did you decide, or would you be willing to share your decision--you call this a treatment of myopia which is, not to mince words, not exactly correct; you are preventing progression. How did you choose to treat myopic children rather than prevent myopia by using this in an at risk population?

DR. GREEN: I will ask Dr. Zadnik to address that.

DR. ZADNIK: That has been the choice of Novartis, but we have done quite a bit of work actually in our studies on what child is at risk for the development of myopia, and what we find is the best predictor is their refractive error at age 8. That is what we have looked at in our data set.

It is an interesting game to try to predict either the onset of myopia or the progression of myopia. For example, the prediction at age 8, you might argue, gosh, that is already after some children have become myopic. We do that with about 87 percent sensitivity and about 75 percent specificity.

Let's see, let's think about that. We would accurately treat lots of kids, and treat kids who didn't need to be treated, about 25 percent of those. I think I have it right. So, depending upon what the drug was, its safety profile and its efficacy profile, you could decide I suppose down the line whether that kind of prediction ability was good enough. It kind of depends on the nature of the drug; how expensive it is; how safe it is; how well it works. Would you want to put those 25 percent of children at risk? Would you want to miss the 13 percent that you wouldn't treat? So, the prediction game is an interesting one, and one we have been working on in my lab.

DR. GORMAN: And a third question, and I promise this will be my last for a while, you introduced the concept of rebound, which is a concept that pediatricians are very comfortable with. When you speak of rebound, however, do you mean that you will resume the rate of myopic progression that you would have predicted at the start of therapy? Would that be an acceptable rebound, or would you hope that progression that continued would be at the rate predicted at the new age when therapy was ceased?

DR. ZADNIK: I think it would be the latter. I think you would hope that the eye wouldn't just have stopped growing or showed the treatment effect over the period of time and then sped up in that period. Let's say, for example, a child was on a drug from age 6 to age 9 and then they were off it, you would hope they would grow like a 9-year old's, not like a 6-year old's eye.

DR. GORMAN: Thank you.

DR. GATES: Dr. Chew?

DR. CHEW: This may be too much detail at this point, but following along the aspects of the details of the trial and thinking about whether this is going to be a safety issue and, obviously, efficacy, and the efficacy that you are proposing is perhaps 30 months or 36 months after being off the drug, you know, looking at the natural history

and how children are progressing, is that sufficient? Would you need to treat even longer than that and how would you address that issue?

DR. GREEN: That is a good question. We have spent a lot of time thinking about it. Dr. Zadnik made reference at one point to an international advisory panel. We have tried to get the best people possible to advise us on all the different aspects of this development.

As you heard from Dr. Gwiazda, progression essentially stops by around age 16. So, we would anticipate that most likely you would have to treat until around 16. What we have found from the discussions that we have had though is that an exposure of 30 months in general would be adequate. They would feel comfortable with that much information if the drug were on the market. That is how the balance of all that played out.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: Just a point of clarification, I am not used to dealing with drugs, but in order to demonstrate effectiveness you proposed a 30-, 36-month trial but the indications for use would exceed that period?

DR. GREEN: That is correct. I think we understand that part of our responsibility would be that the patients that were part of a clinical study, we would

continue to follow those patients. We wouldn't just stop and no longer follow those patients once we had filed for registration.

DR. GATES: Dr. Feman?

DR. FEMAN: With the information that was presented so far in terms of the work that I think Dr. Zadnik was presenting, you have a way of measuring the efficacy or one that is being given to us as a potential. With the data that is already available and knowing what the natural history is, one should be able to calculate something like a sample size. What size population you would have to study to detect this. Do you have any estimates? Have your statisticians had a chance to review this?

DR. GREEN: The sample size is going to be a function of the method of analysis certainly, is it a comparison of proportions; is it a comparison of means. It is also going to be driven by the sample size necessary to detect a certain level of adverse events. What we anticipate is that that is probably going to be the largest driving factor.

DR. FEMAN: So, what would the number be approximately? Are you talking about 1,000 children or are you talking about 5,000 children?

DR. GREEN: In terms of the number of children exposed, we have a requirement to do two Phase III, two pivotal clinical trials. So, each one of those trials would probably have approximately 500 children on drug. That is an approximate number.

DR. GATES: Dr. West?

DR. WEST: To review again, the children at entry would be between 6 and 9 years of age. Is that correct?

DR. GREEN: Six and 12 is what we proposed.

DR. WEST: And how will you deal with girls who may be approaching menarche and may be at risk for pregnancy?

DR. GREEN: Certainly, we would have to monitor that with pregnancy testing on a regular basis.

DR. WEST: And logistically, how would that be accomplished?

DR. GREEN: In terms of the visit schedule, do you mean?

DR. WEST: Yes.

DR. GREEN: I don't think we have finalized a specific visit schedule, but probably what we would anticipate is at least quarterly visits, something like that. But, I mean, specific logistic details--we know it is an issue; we know that it has to be monitored; we know that

it is important. We are not ignoring that but we don't have a specific plan right now.

DR. WEST: Then, my second question is more urgent to me, and that is the choice of spherical equivalent as the outcome, which mathematically is inaccurate although that is what clinicians are the most comfortable with. The rank and file clinicians are more comfortable with the spherical equivalent but as the major outcome it is mathematically quite flawed.

DR. GREEN: Okay, but I didn't understand the question.

DR. WEST: I would hope that data other than spherical equivalent alone would be reported. For instance, a child who enters with a refractive error of minus 2, plus 1 and comes out as a minus 2.5, plus 1 would have a spherical equivalent change of 0.5 diopter.

DR. GREEN: Okay.

DR. WEST: If the treatment caused the refractive error to change to minus 3, plus 3, you would have thought that that child was successfully treated because you had no progression of spherical equivalent but, in fat, that child would be far worse off than if they had progressed according to a normal curve. So, using spherical equivalent as the outcome is not potentially a good choice, although I

understand that as a choice since many practicing ophthalmologists and optometrists are very comfortable with spherical equivalent. Mathematically it is really inaccurate, and it has been shown to be inaccurate in the refractive surgery literature as well.

DR. GREEN: If any of our experts want to comment, I will certainly ask you to do that, but it is also the outcome measure that is commonly reported and used in most clinical studies. Most of the experts that we talked to, that is the recommendation that we received. Would we, as a company, collect the details of spherical myopia and astigmatism, would we have that information? We would. But right now, based on what we know, the primary outcome measure would be spherical equivalent refractive error.

DR. JOSEPH MILLER: It may have been somewhat myopic for us to have used spherical equivalent in the sense that there are three components to refractive error that are statistically independent of each other. Astigmatism comprises two of those components. Spherical equivalent is the third. Of the three numbers, spherical equivalent is the number which is directly varying with axial length and that is why it was selected.

However, your charge was also to consider other modalities of treatment which include the cornea. So, if

cornea is on the table, if treatments are being considered which theoretically could affect corneal curvature or lens growth, then I agree certainly that all three components of refractive error--traditionally, spherical equivalent was the only one that was thought of as a way of conveniently combining the astigmatism component with the spherical component of refractive error. But certainly in the last two decades statistics have caught up with clinicians and Vision Science now routinely uses a three-dimensional vector to describe and track refractive error, and we would certainly do our analyses on those bases.

But if the primary endpoint is being considered a treatment for slowing axial elongation of the eye, my suspicion is that of the three components the one which will be most sensitive to those changes will be spherical equivalent.

DR. GWIAZDA: I would like to add that in the COMET trial we enrolled children with similar inclusion criteria that we have presented here, limited amounts of astigmatism, less than a diopter, and after three years we found very little change in either the J0 or the J45 components. So at least in our trial, if you start with a limited amount of astigmatism there is not going to be a whole lot of change over the course of the three years.

Obviously, the action of a drug might be different, could affect the cornea and the J0 and J45 have to be carefully monitored.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: I think Dr. West is thinking very broadly and raises a good issue. One way to deal with this but perhaps still have spherical equivalent as the primary outcome measure, may be myopia in the most myopic meridian and the least myopic meridian, and astigmatism the secondary measures that the sponsor be asked to contribute and present for analysis.

DR. GATES: One question for myself, is there any dilatory effect of this medication on the pupil?

DR. GREEN: Of the specific medication that we are studying right now with respect to pupil dilation? Do you consider that dilatory?

DR. GATES: Yes.

DR. GREEN: The particular medication that we are studying does appear to have a mild dilatory effect. It doesn't mean that every medication studied for slowing progression of myopia would. This particular one, as we have reported, does have a mild effect.

DR. GATES: And, as far as the cycloplegic effect compared with atropine?

DR. GREEN: Ours does have a mild--much, much less.

DR. GATES: Any quantitation of that?

DR. GREEN: None that I can report right now.

DR. GORMAN: I would like to follow-up on that question and ask it from the opposite direction. Do people who take this new class of agents that you are hopefully developing need more ophthalmologic intervention during treatment? Do they need different glasses, or more glasses, more frequent exams? This is outside the clinical study that you are proposing, if this goes into widespread use, would they need more ophthalmologic intervention during the time they were on the medicine?

DR. ZADNIK: That is an interesting question. Certainly, if it slowed the progression, the child, you would hypothesize, would not need the spectacle or prescription changes. I am sure as the drug were begun in usage--you know, when a child first went on it there would be appropriate follow-up visits to make sure he was tolerating it well and the usual things you might anticipate. But, as I think about it, the idea would be that if their myopia slowed in its progression, they would not be coming in, in August or when school starts and saying, "you know, I can't see the blackboard again, mom. I

don't think these glasses are working anymore," because their progression would have been slowed.

DR. GORMAN: Let me ask that question more specifically, will there be an acute visual change when you use the medicine?

DR. ZADNIK: I mean, I guess I would ask Dr. Green to speak to that for this specific medicine but, as you might imagine from a whole variety of things, I think it would depend on the individual agent and what it did to the child's vision initially. I hadn't thought about that one before. That is a good question.

DR. GREEN: I don't know if that answered your question but, unfortunately, I can't add a whole lot more to that.

DR. GORMAN: Well, it didn't answer my question but it gives me pause in terms of study design and in terms of if there is an acute visual effect of any agent when you come on and off the medicine, if I can draw an equivalent from adult medicine, it would be like diabetics who get out of control and their visual acuity changes as their lenses swell or shrink from the glucose in their lens. It would potentially make the quality of life measures and visits to healthcare more frequent.

DR. ZADNIK: Yes, I think only if there were something that happened apart from the visits where you would already be seeing the child for tolerability of the medicine to begin with. So, only if it were a little bit longer-term change than that would that add a visit than you would otherwise have incorporated in the child's follow-up.

DR. GATES: Dr. Plott?

DR. PLOTT: A question for Dr. Miller. In your presentation you mentioned using a pharmacological agent, and what would be the criteria for initiating a pharmacological agent in the course of therapy relative to the refractive error? Would it be, for example, more rapid progression? What would be the criteria for using that, and how would that be reflected in a clinical trial?

DR. JOSEPH MILLER: The story that I was telling was relating to my experience with parents who are asking for alternatives to treatment. What I was relating was the fact that the one medication that has been shown to be effective, I did not use it and I did not give it as an option because the side effects were so severe.

To answer your question, however, I think the question becomes why would patients or their parents want to be placed on this medicine? Why would they ask for it if it was someone requesting this, or when would it be recommended

by a practitioner? I believe that what would happen is, as in the same event that I described, the child would come in, having gone from normal, good distance vision, at first impairment of distance vision where the child comes in and receives a pair of glasses for a very low level of myopia. Many people stabilize and don't become more myopic. But the next time that they show up and request a pair of glasses, I suspect that is when the questions would be raised.

The only thing I can really speak to in terms of study design, however, would be our entry criteria. We believe that children who are listed in the entry criteria would be the children that would be the most likely to benefit from such a treatment initially or at least in the evaluation stage.

DR. PLOTT: Just as a follow-up, what would be the change in refractive error that would typically cause a clinician to say that there has been a clinically significant change and I need to provide more glasses or go to another agent?

DR. JOSEPH MILLER: That is as precisely defined as what my favorite color is on a given day and I have to find a shirt to match that tie. But the problem is that everybody has a different threshold depending on how much the child is whining; how much the parents are able to

afford a new pair of glasses. If they just bought a new pair of glasses oftentimes there is a reluctance to replace them. But a value that I frequently hear from colleagues is that 0.75 diopter, 0.5 diopter change is significant; 0.25 diopter change is not significant in people's minds. When you get to larger values of change, the changes are so dramatic that it is not a question whether a new pair of glasses are appropriate.

Many insurance companies will replace glasses if there is any change in the prescription. One of the criteria that I hear frequently from practice surgery colleagues is that a laser enhancement procedure is offered to a postoperative patient if they are outside of a 0.75 diopter window. So, that 0.75 diopter among adults seems to be a threshold of requesting a change.

But in terms of how people actually act, it is largely determined by how fussy they are about their vision. Some people are acutely aware of the slightest change. We had one patient who actually owned their own trial lens set when I was a fellow and would refract himself. There are all sorts of people out there and they all have different demands. Was that specific enough?

DR. PLOTT: Yes.

DR. JOSEPH MILLER: Thank you.

DR. GATES: Dr. Chew?

DR. CHEW: This goes back to the adverse events and what would be tolerated by the patient. I guess one concern I have, without speaking specifically about any drugs, it is going to be hard to mask the patients and the examiners as to who is being treated and not treated. The masking may be an issue. Even if it was not masked, it would be important to mask the people who were obtaining the refractive errors in the study.

DR. GREEN: We would agree. At minimum, the people obtaining refractive error data must be masked.

DR. ZADNIK: However, that is one of the arguments for using an auto refractor under cycloplegic conditions. If, for example, you were worried that the children on treatment pupils would be a little bigger, if everybody were cyclopleged before they headed to see the auto refractor I think you could say that the refraction examiner would be pretty well masked, and using an objective measure that neither he or she nor the child could really affect in a substantive way. So, I think the cycloplegic part of the endpoint is key to doing that if there is a pupil dilation effect of an agent under study.

DR. GORDONSON: I agree and you are not really prescribing this. All you are really looking for is a change. So, I think that paradigm would be good.

DR. GATES: Dr. Steidl?

DR. STEIDL: This is something someone might want to make a brief comment about, the proposed mechanism by which these drugs affect myopia, cycloplegics or muscarinic, are they affecting axial length?

DR. GREEN: The muscarinic antagonists appear to affect axial length, slow the growth of the sclera.

DR. STEIDL: Do you have any idea by what mechanism?

DR. GREEN: Not definitive, sorry.

DR. STEIDL: I guess a second, follow-up question, perhaps if I had extreme myopia myself I would be more sympathetic but I understand that people would prefer not to have to wear glasses and that sort of thing but, just a very broad, wide question, would this be better than making glasses available with more frequent exams? In other words, trying to give people what they need, and I understand the argument about being in a hotel room and be worrying about fires, and all that, but I am just curious, in general, why the chronic drug use in a child versus just more frequent exams?

DR. GREEN: I think one of the things that Dr. Miller reflected when he made his presentation is that people continue to look for alternatives. The array of alternatives obviously aren't satisfactory. Last year there were approximately 1.5 million LASIK procedures even if people could wear contact lenses or glasses. So, we find that people continue to look for alternatives. The things that are available, glasses, they aren't affecting the structural changes and the potential impact of the structural changes is obviously very long-term but they are not impacting that.

DR. GATES: Dr. Miller?

DR. MILLER: In my clinical practice it seems as though it is the younger onset kids, who are going a diopter a year in terms of change, where the parents come in with extreme alarm and they want to know about trials across the country to look at this. So, I am not really worried about those kids that are changing 0.5 diopter a year if they have come in especially after age 9 or 10. I am more interested in capturing and looking at helping the kids that come in at the younger age with the faster rates of progression. So, capturing that group and showing a change in that higher, faster changing group would be much more convincing to me.

DR. ZADNIK: Well, I think that resonates with the evaluation of the proportion of children who progress some pretty high amount over the three years. I mean, I think 2 diopters over 30 months would perhaps be the younger children and the faster progressors and that analysis would really, in some sense, focus on them, I think, because the hard part is predicting who they are going to be. You get back into that prediction game. It is easy for a 6-year old. In our data the only good predictor is age but it is not perfect. So, I think that comparison of proportions analysis starts to get at that.

DR. MILLER: We will end up studying a lot of kids that won't have anything bad happen to them to get that information because the older kids will not be changing that much, but yes.

DR. ZADNIK: And yet we get an estimate by including them for what any agent would be able to do for them as well in a trial.

DR. MILLER: Right.

DR. GATES: If there is a cycloplegic effect to the medication, how do we address that particular child's, in the treatment groups, near vision needs?

DR. GREEN: It depends on the degree of the cycloplegic effect. If it was a very significant cycloplegic effect you would probably have to use bifocals.

DR. ZADNIK: Or take their glasses off to read if it would be profound enough that they would need to do that.

DR. JOSEPH MILLER: Measuring accommodation disorder is very tricky in young children and I think that to try to get an actual number that measures how well a child, and how rapidly a child, and how precisely a child accommodates is a difficult question. So, in terms of generating a protocol that could give a secondary outcome measure that precisely measures how much accommodation disorder is a challenge for us, and one that we would attempt to rise to--I can tell you that many children, if you encourage them appropriately, can read very, very fine print even if they do have an accommodation disorder. So, simply asking them to read an eye chart or a near card and ask how far down they can go may not get to the answer that we are looking for, and we may need to have more robust measures of accommodation in order to answer your question.

DR. GORDONSON: Children go to school. That is the most important thing in their lives. There are so many things that have to be brought together and they have to learn. If you penalize their accommodation you also affect

the accommodation conversions ratio. Although they may do well in your office, if they spend any length of time reading it may affect their ability and their motivation.

DR. GATES: Dr. Bullimore?

DR. GWIAZDA: I just wanted to mention--excuse me, Mark, that in the COMET study in children, 6-12 years of age, we did objectively measure accommodation using a Canon R-1 auto refractor and concomitant measures and were able to calculate ACA ratios. So, I do believe that in this age group we could obtain objective measures of accommodation and convergence, such that we can monitor accommodation convergence and ACA ratios.

DR. GORDONSON: Would that exclude certain children?

DR. GWIAZDA: At the outset, I mean, if we measured accommodation initially and they had accommodative insufficiency, that is a possibility.

DR. BULLIMORE: I think the panel here is starting to identify some of the safety issues and explore the way in which we might measure them. Clearly, for a drug that has some fundamental anti-muscarinic properties, presumably specific and not broad, accommodation is a reasonable concern and it may be worthwhile in a group of children, say, 10-12 diopters of accommodation, to think about how

much reduction in accommodation we would find alarming or significant or would classify as unacceptable. I mean, certainly reducing a child's amplitude of accommodation to 6 D or 8 D--speaking to somebody who is in their 40s, that seems an awful lot of accommodation even if it is reduced by 30 percent.

Likewise, with pupil size, if there are concerns there we need to better document that, and likewise with their visual acuity. There are some issues that we could certainly put some parameters on today that might help in the develop of a guideline document. Dr. Gwiazda mentioned objective measures of accommodation. I think that would be a reasonable thing to include in a trial and some measurement of their visual acuity to ensure that the child is able to function on a day-to-day basis without too much penalization due to the therapy.

DR. GATES: Dr. West?

DR. WEST: I think it is dangerous to extrapolate what our accommodative needs are to that of children. They may be less tolerant and be willing to extend less effort. Furthermore, an accommodative amplitude of 6-8 diopters for somebody who is of normal size and grown up size may be quite sufficient. Children are smaller. They have shorter

working distances and they may have greater accommodative needs than we do.

The second point that I thought was important to bring up is that although many lay people are having refractive surgery and this seems to be an indication of people's dissatisfaction with myopia and its treatment, I think it is extraordinarily important that the panel, the public and Novartis realize that almost no eye care practitioners have refractive surgery done on themselves.

DR. BULLIMORE: I will disagree with that. I was at a meeting this weekend with a very-well respected refractive surgeon who, himself, has done 400 procedures on ophthalmologists. Now, he might have exaggerated a little bit but that was what he told me and I trust him in that regard.

DR. WEST: I think that if you asked how many of us are myopic and how many of us have had it done, you would find--I think that you have a bias, a selection bias in that population and some swaggering but, you know, of all the ophthalmologists in Cincinnati only one has had it done. I don't know about the optometrists. But I think it is very important that myopia may not be such a bad disease, especially as one approaches presbyopic years, especially since 50 percent of the myopes have refractive errors of

less than 3 diopters and, in fact, that may be beneficial in the workplace.

DR. GORDONSON: I was president of the Long Island Ophthalmological Society and we have the largest geographic ophthalmological society in the country. We have 225 members just in one county, and I don't know of any ophthalmologist that has had refractive surgery.

DR. GATES: Dr. Miller, I believe you had a question.

DR. MILLER: I do feel we have to really focus on the accommodative effects of a new medicine very carefully. I find that in some cases I get a sense that the child is not performing well in school because although they can accommodate temporarily in my office, they can't continue that accommodation long enough in a school setting to do well. I will make a decision to correct hyperopia that I might not always correct in a child with some delays or school problems.

So, it is definitely a fear of mine that we could get adequate accommodative numbers for a ten-minute setting in a child who is very motivated in the office and still have some effect on their behavior, and perhaps we want to get some behavioral measurements as well or some sort of more prolonged reading accommodative measure. I am not

familiar with all the measures you are speaking about with the COMET study, but it would be important to look very carefully at those in applicability to a school setting.

DR. GWIAZDA: I agree that that is very important. In the COMET study we take measurements just at one point in time using a near target and taking a few readings using an auto refractor that has an open field of view so we could put targets both at near and far and measure the children's accommodation while, at the same time, we had an attached motorized Risley prism so that we could measure their fore areas. That is at one point in time.

In my laboratory we are now taking measurements of accommodation and convergence while children are reading. So we are getting more naturalistic data. This is apart from the COMET study. But you are absolutely right that those are extremely important data, and the myopia research community is very aware of that.

DR. MILLER: Just to follow-up, not all refractions are alike in the sense that, depending on how strong a cycloplegic agent you do for your auto refraction, you will get less reserve for accommodation with your glasses if you fully cycloplege with an atropine level of refraction. So, it also depends on how much effect your

medicine has and what cycloplegic agent you choose for your refraction which will give a little more or less reserve.

If you had a very, very good functional measure, then you don't have to tease all those things out. If the kid succeeds in school you know your answer. But otherwise you have to dissect out so that they are covered for that period when they are in school.

DR. GWIAZDA: Yes, I agree.

DR. GATES: Dr. Steidl?

DR. STEIDL: This is another general question. If someone wants to comment on this from Novartis, fine; if not, it is okay. But I am just getting confused in a sense as I look through these questions trying to determine what we are trying to accomplish. I would just like your thoughts on this. Are we trying to make people happier or are we trying to avoid the pathologic side effects of myopia? You know, there have been a lot of comments about how the need for this drug is mirrored in the desire to have refractive surgery which, to me, is a completely different issue.

DR. GREEN: One of the reasons that we specifically presented that we weren't looking for an indication based on pathologic changes is because they are so long-term and we think it would be very difficult to

develop an agent if that is an endpoint. So, that is why the endpoint we are focusing on to assess the efficacy is the refractive error endpoint. Long-term, would that agent result in having a positive impact on those things? I don't think we will know until we have long-term exposure.

DR. GATES: Dr. Miller?

DR. MILLER: For instance, in your entry criteria if you had children with some myopia and then at that second visit they were already starting to be off the curve by some criteria, then you would be looking at a group where the risks involved or the potential issues become more reasonable to me. Half a diopter a year if they are on the curve, including them in the study, if they started at age 6, well, yes. When you get to 3-5 diopters later on, that is a problem but you are going to include so many kids that I don't consider it a problem, and maybe that is my bias.

So, I am wondering if in your inclusion criteria it can be weighted, those 500 kids that you do, towards the kids that are more likely to have the alarmed parent. You will get them in your study, first of all, but that is the group of interest to me if we can't study retinal breaks ten years later.

DR. GREEN: So, that group of children who are already demonstrating a fairly significant rate of

progression at a young age is the primary criterion you are talking about.

DR. MILLER: That is my personal interest for the first year, but I am not designing.

DR. STEIDL: Just a follow-up, I understand that it is hard to determine drug efficacy with the endpoint of decreasing retinal damage but, to me, nonetheless, if that is ultimately what we are after I am going to answer these questions differently than if we are just trying to give people the satisfaction of lower power lenses.

DR. GREEN: Ultimately what we are after is an indication for reducing the progression of myopia. That is what we are after.

DR. GORDONSON: I think that comes down to these children, when they are adults will they thank you or not, and that is something you can't get at.

DR. GATES: Dr. Gorman?

DR. GORMAN: Again back to the general issue, do you have an animal model that shows this agent or class of agents is successful?

DR. GREEN: We have animal data that shows that it has an effect on axial elongation.

DR. GORMAN: Thank you.

DR. GATES: Dr. Miller?

DR. MILLER: Getting back a little bit to what Dr. West was saying, these mild myopes--you know, sometimes we reassure the parent by saying your child is a little bit worse now but the payoff is when they hit 40 and they don't need bifocals and they can function to read. So, we should also think about if we are adding risk, if we are actually taking away something that has some benefit later on if they are in the minus 1.75 or less group or minus 2 or less group.

DR. GATES: Dr. Plott

DR. PLOTT: I just wanted to respond, as an industry representative here on the committee, to the question about long-term benefit because there might be risk as well as benefit. It is just very difficult for us in industry to develop a product that has a very, very long-term endpoint because at some point you have to make a decision about does this work and get the product to the market, otherwise it is not an attractive product to develop; it is not worthwhile. Sometimes we focus on those earlier endpoints. It is also very important to look at those long-term endpoints as well because, while there may or may not be benefit of a product long-term, it is important to know what those are simply for instructions. For many of our products that we develop it could be a very

long time before we know all the things that we have done, and that is part of possibly recommending Phase IV clinical studies after an approval. It might be that a company can continue to observe those patients and measure the long-term outcomes.

DR. JOSEPH MILLER: Could I respond to Dr. Miller's question or comment? I wish that I reasonably foresaw a medication that was 100 percent effective in stopping myopia in its tracks. If that were the case, we could make a rational decision to stop myopia at 1.5 diopters, 1.75 diopters. You could probably get some kind of informed consent signed by the parent that said, "I will guarantee not to sue you for stopping at 1.5 instead of 2." I am just projecting if this were a medication that was so designer in origin that you could specify what the myopia would end at when the person was an adult. But that is not the case. We are talking about a trial with entry criteria of a diopter of myopia, and if your personal suspicion is that your child would be happiest if as an adult they were minus 1.5 and they were 45 and could sort of struggle along without glasses either up close or far away, and that is the desired endpoint for your child, you have to know with absolute certainty that your child is the child that is

going to stop at 1.5 either on this medicine or off this medicine.

But with our entry criteria, many of these children that would be entered may stop on their own naturally at 1.5, or they may have been the child that would have gone on to be a minus 3 or minus 4 but, if on treatment, they would stop at minus 1.5. So, some of these kids would end up at 1.5 because of treatment, others would end up at 1.5 in the placebo group.

DR. GATES: Have there been any other trials of this medication outside the United States, human trials?

DR. GREEN: Of our particular medication? Yes, in Asia.

DR. GATES: Dr. Gorman?

DR. GORMAN: Again as a non-expert, are any of the mechanical procedures necessary to the outcome measures fairly variably at different ages? Are there lower age limits for automated refraction or cycloplegic refraction or ultrasonic axial measurement length? Is there an age at which that becomes unreliable at the younger end?

DR. ZADNIK: I can answer that. Our longitudinal study has started with children in the first grade, average age 6, 6.5. We have done ultrasound contact axial length measures in those children from the very beginning of the

study, as well as auto refraction, as well as the kind of detailed accommodative measures that Dr. Gwiazda described and even a video system where we videotape the shape of the surfaces of the crystalline lens while the child holds his or her eye still and looks at a light. In my experience, children as young as 6, the youngest age for these entry criteria--the kinds of measurements you need to take are really pretty easy to do actually and we don't see a huge variability in the performance of those measures as a function of age within this range.

DR. GORMAN: Do they vary between practitioners? If age is not a factor, would there be reproducibility if you measured child A and then researcher B measured child A?

DR. GWIAZDA: I can answer that from the COMET study. When we designed our protocol we had optometrists who had never taken axial length measures before, and some of them wondered how variable the data might be, especially in the young children, the 6, 7, 8 year olds. So, we had training and certification. After the three years of data collection, we are about to publish a paper reporting that the axial length measurements, using slit lamp mounted probe, are remarkably repeatable across examiners and across children.

DR. GORMAN: Thank you.

DR. GATES: Dr. Miller?

DR. MILLER: In your study design it will be important--I understand the idea of the cycloplegic auto refraction for the glasses aspect, as a pediatric ophthalmologist, I understand that. But it will be important to do a very good screening evaluation at the beginning to make sure you are not missing someone with a family history of juvenile retinoschisis, something hidden that might be seen at the periphery, or a clinical history with a family that might be vague, because that would really skew your progression of myopia. So, we will need to be sure that we don't have those hidden factors.

DR. ZADNIK: I would agree. The implementation of that last entry criterion, no ocular, systemic, no neurological conditions that would develop refractive development, it would be very important to make sure you could find those.

DR. GATES: Dr. West?

DR. WEST: Knowing that a pharmaceutical in this class of drugs was tested in Asia where the progression of myopia is higher, how is it proposed or how can it be designed so that we get adequate representation among different racial and ethnic groups which may have different predispositions to progress in their myopia?

DR. GREEN: In terms of the United States, ensuring that we have a representative sample in the United States?

DR. WEST: Yes. For instance, as Dr. Miller brought out, if children whose myopia is progressing at a greater rate have more concerned parents, would there be an enrollment? I don't think you can have all white kids, all black kids or all Asian kids. Even among subgroups of those there may be different predispositions for refractive progression.

DR. GREEN: I mean, there could be and I think that is one of the purposes of multicenter, randomized clinical studies across many, many centers of the United States. As you know, some studies require some sort of stratification. At this point we wouldn't propose that but we are certainly open to discussion.

DR. GWIAZDA: I should say that in the COMET study we worked very hard to choose our centers in parts of the country where we would make sure that we had an adequate number of Hispanics and African American and white children. We tried to get a number of Asian children but our numbers fell a bit short in that ethnic group.

DR. GATES: Dr. Miller?

DR. MILLER: I don't know how to do this but in your randomization you almost want to have some sort of balancing for degree of parental myopia and a degree in the family history, or a cap on the number of, you know, minus 6 or above below age 8 in the different groups, or your two groups will be very different because there is no good way to balance for genetic loading. I don't know--you are going to have parents wanting to participate if they have the problem.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: If I can add sort of a second part to that question, what really is the state of our knowledge regarding progression as a function of race, as a function of parental history? If you enrolled patients based the proposed entry criteria, is there strong evidence that you would see variations in progression by race and family history, or is it so moot that stratification is not necessary?

DR. ZADNIK: I am going to tell you we have looked at the prediction of fast progression in our data set of 5,000 children and of all ethnicities, save native Americans on which we don't have the data yet, and we find the only statistically significant predictor of rapid progression of myopia is age of onset, not number of myopia parents, not

race. One of the things we are finding in these different ethnic groups is that myopia is myopia, is myopia and, to our surprise, we have not even found in Asian Americans that being Asian is a predictor of them being a fast progressor, although that seems counter-intuitive. Most of the data we have about rapid progression in Asians is from Asia and I think much of our information to date, or clinical impressions are that the Asian children are in more often and progressing more rapidly. But in our big data set we have so far found the only significant predictor of rapid progression to be age of onset. However, in our data set we enroll everybody at age 6 and follow them to age 14 so we are waiting for the myopes to ripen in that data set so that we can learn more about them and how to predict both their onset and their progression.

DR. GATES: Dr. Gordonson?

DR. GORDONSON: Every time I have a myopic child in the chair, I always turn to the mother--usually the mother, and if she is not wearing glasses I ask her if she is wearing contact lenses and I am surprised how often she says, oh, this is not my child; this is an adopted child. So, I think maternity can be in question and certainly it is a wise man who knows his father--

[Laughter]

--so it is very hard to know exactly what you are dealing with, and the only thing to do this is with a DNA study and I think that the whole area is a bag of worms and you shouldn't go there.

DR. BULLIMORE: So, what I am hearing, if we were in the process of putting down some guidance here, is if there is no compelling reason to stratify based on parental history and race, then it shouldn't be a requirement or, you know, we could place the burden on the sponsor to justify whatever strategy they chose to pursue.

Since I have the microphone on, I have a question for Dr. Gorman. We have talked about loss of accommodation, school achievement and difficulties. Are there any standardized tests that you are aware of that would be appropriate to include in a protocol as a measure of safety to make sure that the children aren't being impaired by the use of the drug? Maybe that is something we can come back to later.

DR. GORMAN: There is an analog classroom that is used repetitively in ADD work where children are put in a classroom situation for an 8-12 hour period, which even by my children's school day is long. Then they are observed for their performance during the course of those 12 hours by trained observers every 15 minutes. They are looking at

activity levels but I am sure it would not take a large modification to see if they were able to perform for accommodative issues over those particular periods of time. So, there is a model out there. I am not aware if it has ever been used for visual issues.

DR. BULLIMORE: I think you probably made the sponsor very nervous with that 8-12 hour requirement, but I think it is something we should discuss further in terms of ensuring that any drug that is being evaluated is safe.

DR. GORMAN: Having only been cyclopleged twice in my career, that 8-12 hours will come as no surprise to them because they will have other difficulties when they cycloplege them at the beginning. I also think that the report card is an excellent measure of school performance.

DR. GATES: Any other comments pertaining to this line of questioning?

DR. MILLER: Related, not exactly the same. If we had some data on this particular medication in terms of how long there is a cycloplegic effect in a child and the degree, some quantification, then we might not ask so many questions about this. But it would be nice to know just a little bit more in a subset of kids in helping the design because it is very cumbersome to do this testing, checking accommodative function for days on end. I mean, we have to

be practical because these are healthy kids. So, it would be interesting to know more about that when it is available, or to suggest perhaps a subset, a small subset of information on that to help with the design of the full trial.

DR. GREEN: Just considering generalities, is it possible to consider with respect to in general what effect on accommodative reserve would heighten more concern in terms of thinking about a general guidance? There is this particular medication but there are other medications that may or may not have any effect at all, or may have more effect or less effect.

DR. GATES: Dr. Steidl?

DR. STEIDL: Maybe I misunderstood you but my understanding is that there is no real good hypothesis as to how this medication affects myopia. So, number one, I am concerned about its implications in the eye but also for systemic involvement since drops go beyond the eye. Did you say that you have a dog model? Did I understand that?

DR. GREEN: I didn't say a dog model. We have a preclinical model.

DR. STEIDL: Preclinical? I am just curious if you have any information on any of these medicines as to structurally what is happening, as to size or interweaving

of collagen changing. Is it altering structurally the tissue from what you would typically find in myopia? Do you have any information on that?

DR. GREEN: For our particular medication, nothing that I could present right now but, certainly, those type of things would be things that we would have to present to talk about for a specific example.

DR. STEIDL: Because depending upon its mechanism in a growing child, it could have implications that are concerning.

DR. GATES: Dr. Plott?

DR. PLOTT: You mentioned that for these patients their mean progression is 0.5 diopters per year, and criteria have been proposed for a 2 diopter change. That would imply that you would need to follow the average patient for four years, which would be a pretty formidable study and a lot of drug exposure before you had any results. What is the rationale for that level of change, that mean level of change of 2 diopters?

DR. GREEN: In terms of a comparison of proportions?

DR. PLOTT: For a primary efficacy variable because, you know, that level really is going to drive the design of your trial, and as a mean change either your trial

is too short or 2 diopters is a huge change to try to capture there. Looking at it as a proportion of patients is an interesting idea. In dermatology we do that but with a PASI score of 75, the number of people that reach that kind of clearance. But I wonder if you would just address the rationale for that level.

DR. GREEN: Sure. The rationale for that level of change was driven to a large extent by a lot of the discussions that we had, our impressions from a lot of the discussions that we have had with the agency. In looking at the data that we have, our own data, and sort of projecting what would be feasible, what we thought might be achievable, that is where that arose from.

DR. PLOTT: The 2 diopters is achievable? Is that what you are saying?

DR. GREEN: We believe that it would be achievable in that period of time in terms of a comparison of proportions showing a statistically significant difference.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: I am confused. You are saying that a 2 diopter reduction is achievable in terms of a comparison of means?

DR. GREEN: No, not in terms of a comparison of means, in terms of comparing the proportion of patients that

progress by 2 diopters or greater. That comparison over a 30-month period we think is achievable. We do not think that that level of threshold is necessary. We think that it goes beyond the level of clinical significance. As we have made the argument, we think a change of 0.75 diopter in refractive error is a clinically significant change and that is the hurdle that we would ideally propose to use whether it is a comparison of means or even if it was a comparison of proportions. Even if we had a primary variable based on a comparison of proportions of 2 diopters, we would still look at many of the cuts in the data. But we have to define a primary variable.

DR. BULLIMORE: So, the 2 diopters came from the agency?

DR. ZADNIK: Yes.

DR. BULLIMORE: Was it presented with the same level of justification that you made for the 0.75 criteria or was it just a sort of arbitrary number that somebody pulled out of thin air?

DR. GREEN: It was the result of a lot of discussions.

DR. GATES: Dr. Chew?

DR. CHEW: Well, it would seem to me that this is going to be a very big treatment effect here that you are

talking about and we may need a longer trial to get that sort of effect, I would think.

DR. GREEN: We are not claiming that the proportion progressing by 2 diopters or greater in this data set over a 30-month period would be a huge amount, but from the data that we have, when we look at the numbers that could progress and we think about potential treatment effect, if we were forced to use this hurdle, we could show a statistically significant difference. Again, our preference would be to use a hurdle of 0.75 diopters. We think that is a clinically significant hurdle.

DR. CHEW: Well, judging from the COMET trial, unless you have a larger treatment effect you are going to need much larger numbers or a longer trial, and perhaps you may even need a three-arm trial. You are proposing to stop it at 30 months for one group. You may need longer treatment for some of these others to see that.

DR. GREEN: But the COMET data you are looking at is the difference of means.

DR. CHEW: Sure.

DR. GREEN: So, we haven't seen that data broken down dichotomously.

DR. CHEW: Sure.

DR. GATES: Dr. Miller?

DR. MILLER: Perhaps a different strategy would be to study just the younger age group, the ones that are really the ones you want to catch early because they are going to hit the bigger numbers so to test 500 of the 6-9 year olds or 6-10 year olds you have a higher proportion of the hit rate of the ones that are going to have the rapid progression. Or, perhaps we could reconsider a lower target or if we were looking more at the ones that will become pathologic based on some more of your data.

DR. ZADNIK: Yes, you could certainly manipulate the orange curve I showed by changing the entry criteria. Right? I mean, younger; if Asian bore out to be true; girls as opposed to boys. There are ways you could manipulate that to change that COMET curve that I showed in terms of patients. What you would have to consider is where you would end up in terms of would you have an indication then that was only for this drug in 6-year old Asian girls who happen to be 1.75 diopters.

DR. MILLER: And that gets back to my own interest in the more pathologic group. But if you are going to say you are going to apply it to the ones that end up ultimately with very mild myopia, then perhaps 2 diopters proportion is a reasonable number.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: To pick up on something I heard earlier, it seems that your sample size of 500 is going to be driven by the adverse event rates rather than the progression rates. It seems to me that with that many subjects you are going to be able to answer both Dr. Miller's questions and assess it in a more generalizable population quite comfortably. Obviously, the panel, the public, the community is going to take great interest in not only the primary outcomes but also the subgroup analyses to see which groups benefit most. Intuitively, one would expect your hypothesis to be borne out by the data.

The other thing I want to put on the table is that all of us, as clinicians, have been confronted by the parent of the myopic child who asks us, you know, what can be done to slow the progression but, in light of what has been said about family history we have probably also been confronted by a pair of myopic breeders who are worried about their offspring and saying, you know, what can be done to prevent it.

I don't want to be making strategic or business decisions for the sponsor or anybody else, but how does the panel feel about trials of drugs, of any drugs, on pre-myopic individuals, high risk individuals? If you look at the data, if you have two myopic parents and if you throw in

a myopic sibling as well you probably have a high risk of that child becoming myopic. How would we feel about administering a drug to a as yet non-myopic kid to see whether the myopia could be prevented or, when it develops, to modulate its severity?

DR. GATES: Dr. Gorman?

DR. GORMAN: Having dealt with this issue in pediatric drug development for a lot of years, it wouldn't be the group you would choose first, but, not speaking for the sponsor but trying to think like a sponsor, if it is effective in preventing the progression of myopia and if it has a very lovely side effect or adverse event profile the temptation to use it by practitioners in groups that are not myopic but at high risk would be irresistible.

DR. BULLIMORE: Do you see with other drugs a drug being developed for a group of children with a given condition and then it being used on an off-label basis on other children?

DR. GORMAN: I can use good examples of that and bad examples. I can start with Acutane, a drug developed for nodular cystic acne under basically an orphan indication, projected to be used in less than 50,000 children. I think it had six million new prescriptions written last year. So, acne being an issue of adolescence,

it was designed for severe acne; it is incredibly effective but it was rapidly generalized for all acne. So, there was a case of a drug that was designed for a very specific indication and was rapidly generalized.

For the group of parents who wish their children never to wear glasses, if this drug turns out to be safe and effective to prevent progression, I think it would be irresistible for them not to try it. They would try it.

DR. BULLIMORE: And from a regulatory point of view, how palatable is that to the agency?

DR. CHAMBERS: The agency believes that if there is a high likelihood that a product would be used in that particular indication, we generally believe it should be studied prior to approving it.

DR. GATES: Dr. West?

DR. WEST: Can somebody go back to telling me how the period of six months off drug was chosen to assess potential for progression or how was that window chosen, and what is the scientific basis for six months versus three months versus a year or two years?

DR. GREEN: I can't give you honestly a strong scientific basis. It was really the result of discussions among a lot of people. If you look at other drugs and other therapies where you might have seen some sort of rebound

phenomenon, how quickly does it occur? You cease drug therapy; you have an up-regulation of a receptor, how quickly does that phenomenon usually happen? That is where that time frame came from.

Does that address longer-term, over years what might happen? It obviously doesn't. That is where we recognize that we will have to commit to follow people long-term after the registration of the drug. How would that follow-up affect this particular group of off-drug people once the drug is approved, if they want to go back on the drug? Those sort of logistic details we would have to think about.

DR. WEST: The problem is if a drug were proven to benefit the progression of myopia but the study were not powered to detect if people changed over to what their natural history was going to be, you would have people going on a medicine for no end purpose. So, I think it is very important that at the end you know not only what happens while they are on the drug, but what happens when they are off the drug because then you have all the expense and headache of doing a medicine which has an effect while you are on it but nothing really at the end, anyway.

DR. GREEN: Yes, I certainly understand your point, but I guess for the development of lots of

chronically administered drugs where potentially people are going to go off or change to some different type of therapy with a different pharmacologic action--I guess that potential is there and I don't know that that requirement of understanding the incidence of that rebound effect that might or might not happen is typically required.

DR. WEST: But as a parent, giving a medicine potentially twice a day for three years, and the headache of doing that and the expense, the cost to the insurers and parents, is going to be large and if it works while I am on it but in the end it doesn't make any difference anyway, what is the use of the three years of treating? I think it is very important what happens at the end.

DR. GREEN: I think it is important to know what happens and I think that is the basis for the commitment to follow people for that extended period of time. I guess, you know, it is always hard to project what sample of people you would have. People drop out; people move; people's lives change. You run a clinical study and you do the best you can. You have some number at that point. Would that be reflective of answering the question that you are asking? We think that it would be because it is difficult to project all of those different variables. We think it would be reflective; it would be indicative of what you could expect.

DR. WEST: But you have just told me that you really don't have any modeling or that you don't have any way to predict, to know that six months will be sufficient power-wise, sample size-wise. This is a medication that has such huge potential for use both on-label and off-label afterwards that it is a huge cost to society and I think it really behooves a potential sponsor to know what is going to happen after the medication. If the indication is only to retard or stop the progression of myopia, which is something that people would like but, as Dr. Steidl said, really where is the true morbidity medically? It is in the complications of the myopia later, not of the refractive error.

DR. GREEN: Maybe I don't understand. Are you recommending a sample size in which at later ages we would be able to pick up differences in retinal complications?

DR. WEST: No, no, no. I think everybody here has agreed that the issue of the complications, the medical complications of the myopia, meaning potentially retinal complications, glaucoma, cataract, that it is probably not feasible to study those. But I am trying to understand why it is not feasible to know what the rate of recidivism is for the myopia after the drug is discontinued. Because if there is significant recidivism, then it negates the benefit of using the medication, which was to retard the

progression. So, I am just trying to make sure that the study is constructed in such a way and powered in such a way that you would be able to tell what the recidivism is.

DR. GREEN: Meaning both the short-term, let's say within that six-month window, and then the long-term at the age of 16?

DR. WEST: Yes.

DR. GREEN: You are trying to address both?

DR. WEST: If, once you stop the medication you go back to what you were going to be anyway, then the long-term benefit of not being myopic is far smaller. Then you only have the school age benefit of not wearing glasses.

DR. GREEN: In terms of the short-term benefit, let's say a six-month period off drug, I think most likely the sample size we are talking about and the retention of patients would answer that question. In terms of the long-term, at the age of 16, I think that is something that requires some additional discussion.

DR. GATES: Any other comments along the line of this?

DR. CHEW: I would agree with Dr. West. I think it is very important to really look at what happens. Six months if really too short for, you know, a long period for quite a cost and perhaps you may need as long as two years

to check that out, and perhaps have another arm in which you are extending the treatment even further. Because what I heard earlier was that you are going to treat them for 30 months and, if it works maybe they will do it off-label for a longer period of time. So, why not study it now and see what happens with longer term. So, what I am suggesting is I think your follow-up needs to be longer than six months. I think you need to have a longer period of time to see what happens with those patients as time goes on.

DR. GREEN: I think one of our questions though is the amount of follow-up that we would and should commit to as a sponsor to understand that long term.

DR. GATES: Other comments on this line? Dr. Miller?

DR. MILLER: Isn't this somewhat of a statistical question? If we know the curve change per year, when would you suddenly be alarmed that there was a recurrence? At what time period? If you saw twice as much as the average curve? To what time point statistically do you have to follow them to answer this question? Six months sounds a little short to me if the mean is 0.5 diopter a year and there are errors in our measurement, which might be 0.25 diopter or 0.5 diopter right there. So, there must be a

statistical way to say this is the statistical answer and then we can make a clinical judgment too.

Clinically, my best answer would be, you know, where are they at age 16? That is the ultimate gold standard answer but that is not practical. If you do include the older age kids in your study, then you will have a group that stops and you will know they should have got to their historical endpoint. So, that is an advantage of including the older age group.

Do you see what I am saying? Is there a statistical answer and then what is the reasonable clinical answer that we can come to?

DR. GATES: Dr. Steidl?

DR. STEIDL: Along those lines, it seems like the real question is what is the rate after cessation of the drug? Is it zero? In other words, have you fixed the myopia? Does it continue at the previous rate? Or, does it accelerate to the point to where the effect is lost? I have to agree with Dr. Chew that my gut feeling is that you need a couple of years to do that, and then you would probably want a small group to follow for long-term effects, ideally. I don't see how you could do that in six months.

DR. GREEN: I would agree. The question is what amount of that follow-up would be adequate to support an

application to register the drug. That doesn't mean that that would be the end of the follow-up period. It doesn't mean that would be the end of the observation period.

DR. GATES: Dr. Gorman?

DR. GORMAN: I have a question for the agency on this. Recently a precedent--maybe it is not a precedent but it was a precedent to me--was set with a drug, IRESSA, that was approved while it was still in clinical trials for an agent for cancer that was shown to have some effectiveness but still hadn't been studied for side effects--partial approval; accelerated approval. Is that now a recognized class of approvals in the FDA or was that a once in a lifetime event?

DR. BULL: I think that setting, particularly when you get into diseases where the outcome is basically death, cancer therapies, is in a class by itself. In terms of citing the example of IRESSA, that is not a broad standard. It is a standard that is very specific to specific settings where you are basically looking at outcomes that are attached to mortality rather than the kinds of settings that we are discussing here today. That is not a broadly applied standard. That is something that really is on a case-by-case basis and specific to a specific type of setting for the kind of disease that the drug is attempting to impact.

DR. GORMAN: Under the 1998 Pediatric Rule, which has now been suspended, you would have a regulatory mechanism to require pharmaceutical companies to conduct trials after approval. Is there any mechanism in place today that requires studies after approval?

DR. BULL: Those are generally called Phase IV commitments and those can be conditions of approval. Certainly, in instances, say, in a setting such as IRESSA where basically a surrogate is used and then you try to attach that to a longer-term outcome but there is a credible case made that the drug demonstrates sufficient benefit that you can attach to a more clinically meaningful outcome at a later time based on further study of the drug. that is a mechanism.

I think what you are saying here in terms of this particular setting, and whether or not there are long-term outcomes that one would look at post-approval, those are certainly areas that could be part of the conditions of approval for a specific product even in this setting.

DR. GORMAN: One of the impetuses for the 1998 Pediatric Rule was the fact that less than 20 percent of Phase IV commitments for pediatric studies were ever implemented and no adult indication was ever pulled for the lack of those studies. Has there ever been a case where a

Phase IV commitment has not been met and a drug has been approved for an adult indication?

DR. CHAMBERS: We are currently not aware of any that you are talking about. But if I come back to the area of ophthalmology, that your percentage that you are talking about is not true. In fact, virtually all of the Phase IV requirements were tracked and were followed and were carried out. We are not anticipating that that would be an issue.

DR. BULL: I would also add that for historical data that you cited the agency is definitely undertaking a much more vigilant process for tracking Phase IV commitments, and we don't see having these commitments in an approval and not following through on it. We are definitely being much more vigilant in that regard.

DR. GORMAN: If I sounded harsh, it is because I am particularly prone to hearing those commitments for pediatric studies that were not followed through on. I guess the question still remains if a Phase IV commitment was not met, have you ever pulled approval for a drug after they committed for a Phase IV study and then did not provide it?

DR. BULL: I am not familiar with any. We could certainly look into that and get back to you.

DR. GORMAN: Thank you.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: Just to agree with Dr. West and some of the other folks who have been talking about this, I think six months even in a pre-approval process may be a little too short. I would like to see something closer to a year of washout to see if there is any profound rebound.

But what I am hearing also from the comments from the agency and from the panel is that it is reasonable to expect that six months or a year be available when the drug was considered for approval. There seems to be a clear commitment on the part of this sponsor and an interest from the panel to follow those patients in Phase IV. Is that the same as post-market surveillance? That seems to be where we are heading on this particular issue.

DR. GATES: Dr. Chambers?

DR. CHAMBERS: Post-market surveillance and Phase IV are not the same on the drug side. Phase IV would be specific commitments that would be attached to the approval letter and would be outlined and would be expected to be completed. Post-marketing is something that continues virtually indefinitely following the approval of the drug.

DR. BULLIMORE: Then strike everything I said about post-market and replace it with Phase IV, please.

DR. GATES: Dr. West?

DR. WEST: Regarding the follow-up, I am not necessarily saying that I think six months is too short. I don't think that we mathematically and model-wise know what the right answer is and I think it is foolish to say that six months is the right length or one year is the right length. What I am looking for from the sponsor is that they will be able to demonstrate to me that the follow-up time is sufficient to demonstrate a sustained benefit from treatment which will be given to children. Children will be asked to participate as subjects, and I think we owe it to the potential beneficiaries of treatment and certainly the subjects and their families who would participate that the treatment benefit for this disorder is sustained, not just that it works but, more importantly, that the effect is sustained. I am looking for somebody to tell me how long can we reasonably think that we could do this. I am not asking to follow children to their grave, just for a mathematically long enough period to have a reasonably degree of certainty that the treatment benefit would be sustained and of such a magnitude that it would be clinically important.

DR. GREEN: Your question though seems to be--maybe what I am not understanding is do you want this answer prior to an application for registration? Or, do you

ultimately want this answer at the age of 16 when, presumably, myopia progression stops? Or, if we have an understanding of a mean rate of progression over a year and we have a cohort that we have taken off for a year and we look at what their progression is so we can make some statements about the continued benefit of the drug? What specific issue is your concern?

DR. WEST: I would imagine since there were overseas trials of this medication in human subjects that there has been--I would hope there has been some follow-up of that cohort and that you would know, now that they are off drug, what a range of recurrence or non-recurrence was, and that you could take that time course of recurrence or stability and match that against what the typical progression would be over a period of time for that age group of children and that we would have sufficient follow-up. I am not saying that it needs to be a certain length but that it would be of sufficient time that, certainly, you could statistically draw conclusions about whether there was recurrence of the myopia; whether you get back to your old curve or stay on a good curve. What is the hope? Because you are asking patients to commit for a long time to treatment eventually with a medication like this.

DR. GATES: Are there any more questions or comments for Novartis?

DR. FEMAN: I was just wondering if somebody could repeat--I think we mentioned it earlier but I forget who was the one that raised the question, the drug that they are looking at now as a proposal or as a concept is being done in what manner? It is used as a drop once a day? Twice a day? Once a week? Once a month? How is this done?

DR. GREEN: The particular compound that we are looking at right now is a gel that is applied twice a day.

DR. FEMAN: And when this gel is applied, what does it do to vision at the moment it is applied? It blurs the vision obviously because it is a gel, at the minute that you put it in. How long does the gel itself blur the vision? Are we saying you are taking a 6-year old and you are going to blur the vision for two hours after you put it in, and blur it again in the evening? At breakfast time before they go to school, if they go to school, and again at lunchtime or again in the evening so they can't watch television? Again, just with this hypothetical drug because this may not be the one that you want to study, but tell us about the mechanism of what you are doing here.

DR. GREEN: Well, I think it is hard to answer the mechanism of what we are doing because right now I am not in

a position to talk about the details of if there is a mild cycloplegic effect how long it may affect vision, which probably is very, very minimal. But there could be other drugs that have other side effects separate from vision that would have to be considered and would have to be part of the plan. I don't think that adequately answers your question but I am trying not to specifically talk about this one drug because it is just this one drug.

Committee Discussion of Questions from the FDA

DR. GATES: Any other comments? Once we start with our discussion of the questions we won't be able to go back and ask any more questions of the company. If not, why don't we start with an open discussion of question number one in your handout?

Excuse me, there is a correction. We are going to have the open public hearing now. Does anybody have a comment from the gallery?

[No response]

It appears no one has a comment so now we can start off with our questions and this discussion is confined to the committee. Let's start with an open discussion of question one. We will come back later and vote after lunch. We can have more time for discussion at that time. We may all disagree; we may have a consensus but this will be a

time where we will just go around and discuss what we think about each individual question. We will start off on my left, if you would. Dr. Plott, if you would begin?

DR. PLOTT: Ms. Topper, am I allowed to participate in this part?

MS. TOPPER: Because you are industry rep, you are allowed to participate in discussion but when we take a vote you may not participate in the vote.

DR. PLOTT: Thank you for that clarification. I think it is important for this question to answer it relative to the way that the protocol would be designed because that is our task today. I think it is important for this particular agent that the patient population be characterized as being one of a certain type, whether it be progressive or stable. But if the indication that is being sought is for a progressive indication, I think the population has to be reflected. You, know, what is the minimum rate? I think that is something that just has to be defined in the protocol and probably be better answered by other experts.

DR. GATES: Dr. West?

DR. WEST: I think the question about minimum rate over amount and time of refractive change really depends upon the accuracy and reliability of the measures that are

being used to assess it. So, if the tool has very good reliability, has small error, then one can detect a small change. So, I don't know that it is possible to be able to answer that question without knowing what the measure is.

DR. GATES: Dr. Chambers?

DR. CHAMBERS: For the purposes of this question what we were thinking of defining is basically in diopters. How much of a change in diopters would you consider someone as not changing or as progressing? For example, 0.5 diopter over a year, would you consider that as being stable, or if somebody didn't change within 0.25 diopter over six months? How would you know somebody was changing versus not changing in terms of diopters?

DR. WEST: Do you mean if I know they are changing or if I consider it significant? For instance, if the way to assess the refractive error of the eye is only accurate to within 0.25 diopter, then I am not going to feel comfortable saying that something is progressive until it is 0.75 diopter. So, it really depends upon how accurate the measure is. I mean, if I can only measure it to within a 0.25 diopter or 0.5 diopter, then you couldn't statistically say that it was progressive unless it was a larger amount. I am not meaning to be evasive.

DR. CHAMBERS: I think as we start talking about auto refractors, in some cases you get numbers that are in tenths of a diopter. The question is whether you, as a clinician, necessarily believe that there is a difference. Just because the auto refractor told you it was 0.1 and at the next visit it was 0.2, do you necessarily believe that that is the same or whether that is a difference? What we are literally looking for is when do you think somebody is staying the same? How much error do you think there is around somebody who is staying the same versus how much there is--

DR. BULLIMORE: We are talking about an individual patient--

DR. CHAMBERS: We are talking about an individual, correct.

DR. BULLIMORE: --rather than a group.

DR. CHAMBERS: Correct. The group can be done mathematically; it is the individual.

DR. BULLIMORE: For a point of information and at the risk of upsetting people sitting in the back over there, from the Office of Device Evaluation, it is kind of ironic that in a lot of the refractive surgery labeling myopia is defined as less than or equal to 0.5 diopter per year as being stable from the point of view of being eligible to

have LASIK or a similar refractive procedure. In fact, I have seen more recently labeling that defines stable myopia as up to a diopter of change.

So, with that in mind, I think I would agree with Dr. West. If you have extreme confidence in your method of measurement, and certainly we have evaluated auto refractors where not only the standard deviation but the 95 percent limits of agreement are on the order of 0.25 diopter, then you could say, well, 0.5 diopter is progressing or anything beyond a statistically obtained confidence interval, or we should probably call it limits of agreement--anything beyond that you would call progressing and the other side regressing.

So, I think it does depend on how you measure it. If you are talking about subjective refraction, that is going to be more variable. As clinicians we might not like to admit that but it is more variable than cyclopleged auto refraction. It may not be any less valid. In fact, it may be more valid from the point of view of prescribing spectacles but, certainly, one would have difficulty saying that 0.25 diopter represents a progressor on any method, and probably 0.5 diopter would be a line in the sand. It would be my line in the sand.

DR. GATES: Dr. Gordonson?

DR. GORDONSON: I was thinking about it and if a child came to me at 8 and was a minus 2 myope, and came back to me when he was 10 and he was still a minus 2 myope, I would say stable. If he comes back to me with 0.5 diopter increase in myopia he is progressing. Question (c) is interesting. Do myopia children regress or is it just a mistake in your refractive day? I think some do very, very rarely but only at the lower levels, low ones, minus 0.75, and that is my answer.

DR. GATES: Dr. Chew?

DR. CHEW: I would agree that it is difficult, depending on how you are going to obtain that. I am used to doing clinical trials and doing subjective refractions. In fact, we had a trial where we found one clinic had no change in refraction for the whole, entire follow-up of the last three years of study --

[Laughter]

--and we got worried because that just didn't seem right. When we looked at the rest of our clinic, we varied between 0.5 diopter to 0.75 diopter for our patients at each visit. So, that is how much we are talking about, just measurement error with a subjective refraction. So, I think it is very hard to pin down exactly what you mean by stable and progressive. I have the disadvantage of not seeing

children; I see adults, and adults with problems that often wax and wane. So, for me, a diopter is not much of a change so it depends where you are coming from and what you are measuring with. Perhaps there are machines like auto refractors that are fairly precise so that you may be able to get a better measurement in that sense, but that can be all over the map. Do you want me to say a specific number?

DR. CHAMBERS: Before you go too far down the line, we are looking for both amount and time. The issue is how often to bring people back. So, if you are going to say, you know, if it doesn't change over a diopter in a week versus a diopter in a year, those are very different types of things.

DR. CHEW: Sure. I would say 0.5 diopter in a year, to me, would be a change.

DR. BULLIMORE: Is this from the point of view of an outcome measure or eligibility criteria or both?

DR. CHAMBERS: We are assuming we are going to try and be consistent. So, if it is stable in eligibility criteria, later on in follow-up, if we are going to say this person has now reached this plateau and is stable, we will use that same criteria.

DR. WEST: This is sort of an unfair question. I think the question you really want to get at is how

clinically meaningful is a change. That is what you really want, isn't it? How meaningful is a change over time? That is what you really want for a trial.

DR. CHAMBERS: I guess the reason I think it is not an unfair question is because it is a question we get asked all the time. People will try to put in the label, you know, we have decreased how much they are changing and they are now stable at this particular point of time, and we need definitions for those. So, these terms get used a lot and we would like to have relatively common use of those terms at least for the clinical trials. So, we are asking for help in defining these terms at least for the purposes of clinical trials.

DR. BULLIMORE: But stable is one of those things that is very difficult to define. I mean, somebody once told me that a normal patient is just one that hasn't been tested enough--

[Laughter]

--and a stable patient may be one that you haven't measured enough times, or you haven't measured with sophisticated enough equipment. We have looked at some very nice data from Dr. Gwiazda that shows, you know, following what looks like a half-life curve, things are slowing down. When does it stop progressing? I don't know. I mean, we

have people progressing into their late teens. Have you established in that patient that they are stable? I think 0.5 diopter per year is reasonable but what if you then have data at two years and they have progressed by 0.5 at years years? Are they progressing or are they stable? We have a National Institute-funded study of adult progression and our criteria for progression is 0.75 diopter over five years. So, it is a difficult one.

DR. GATES: Dr. Feman?

DR. FEMAN: I agree with all that has been discussed so far, but looking in terms of what this study might be, I think it is going to be balanced out to some degree since there will be some people on placebo and some people on drug and they are going to have masked examiners. So, I think 0.5 diopter per year is something that should be a feasible goal for them to work for in terms of whether or not something is progressive. By using the same type of information where we are going to have some on placebo and some not and having masked examiners, stable would be less than 0.5 diopter a year and regressing would be, I guess, no change at all. I guess it is someone who was myopic and was no longer myopic. Does that mean they become less myopic at 0.5 diopter a year? In spite of what Dr. Gordonson

described, I don't think I have seen very many people doing that.

DR. GATES: I am also leading myself toward progressive being 0.5 diopter a year. It seems to be something we commonly see in the literature, with stable from zero to less than 0.25.

DR. GORMAN: Sometimes it is good to be the simple country pediatrician. For me, I have heard both in this room and when I talk to my ophthalmologic friends that they prescribe new glasses at 0.5 diopter and the patients say, "God, that's better." So, that is progression because if you put a new pair of glasses on them and they say that is better, that is a progression that you have then corrected. So, if 0.5 diopter is the number where you get new glasses and it makes a difference, then 0.5 diopter is progression. Stable would be no new glasses. I guess that would vary from clinician to clinician whether it is 0.25 diopter or 0.5 diopter but it seems that 0.5 diopter is becoming a fairly consensus type of position.

There could be an argument, and I am not going to make it here, that progressive and stable might be defined as relative to the slope that is being developed in the COMET study.

DR. GATES: Dr. Miller?

DR. MILLER: Yes, I think that the slope in the COMET study is very convincing. As I was looking at this before our discussion, I was thinking in my own mind what would be that alarming rate of progression that causes the parents to be very concerned, and that would be a diopter or more a year. Those parents call you. They call you three times the first week after the visit. So, that would be the alarming level. But for a cut-off to consider for this study and find out what is going on, I would say 0.5 diopter or more per year and stable would be less than that.

Regressing--it is interesting, I would say in children at 10 years I have probably had three or four kids where, seeing them biannually perhaps, they have gone down 1 diopter, 1.5 diopters, 2 diopters, and I have done the refractions. We are talking cycloplegic. There are definitely kids that regress but it is a handful. So, if you wanted a definition of that for that odd-ball group, which you probably won't even see in your study, over a two-year course reduction of at least 0.75 diopter or more.

DR. GATES: Dr. Steidl?

DR. STEIDL: With the term stable I have a personal bias I guess. I have never liked studies that have patients getting worse and they call them stable. To me, stable means things are okay, not changing. I might even

request a different word use if you want to track people along an acceptably worsening line as being non-progressive. But it seems like there is a consensus. I kind of agree with the 0.5 just because I think with less than that it might be hard to measure reliably. If you have somebody starting at age 6 with 0.5 diopter a year, they are probably going to be a high myope by age 16 anyway. So, it seems reasonable to consider 0.5 diopter as the progression point. I don't have a comment really on regression.

DR. GATES: Any other comments on question one? Dr. Bullimore?

DR. BULLIMORE: I like Dr. Miller's addition of, if you like, the rapid progressor. If the agency wanted to add that to its classification, I think that is reasonable criteria.

DR. GATES: Any other comment on number one? If not, we will move on to number two, is there an accepted evidence-based baseline characterization of patients who are at high risk of developing progressive myopia? First off, do we need Wiley to say what he is looking for in this question or to expand it before we get started? Would you like to do that, Wiley?

DR. CHAMBERS: Again, this is more a definition type thing. People will say, you know, we want to enroll

people that are high risk and we don't have common definitions for what high risk is. So, if there currently is a consensus, we would like to know what that is or if you think there is a current range of what that is. If not, we can ultimately leave it to individual protocols. But, again, to the extent that we can use common terms and people have ideas of what those mean, we would like to know about them.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: So, since you have used the phrase progressive myopia, should we use the criteria for progressive that we have just defined, or are you looking at some other type of myopia here? Are you looking at people who are going to have rapidly progressing myopia or just common or garden 0.5 diopter per year myopia?

DR. CHAMBERS: We will take whatever you give us.

DR. BULLIMORE: Splendid!

DR. GATES: All right, let's go around the table again. Dr. Plott?

DR. PLOTT: I think that there would be probably a check list in other conditions I am familiar with. For example, in atopic dermatitis there is a check list of things that define people who are at high risk and sometimes it is getting, you know, two out of three or a minimum

number. But the things that we have heard seem to be convincing, positive family history and age of onset being important factors, maybe not the only factors but elements that are important to view in a clinical trial.

DR. GATES: Dr. West?

DR. WEST: I would agree with Dr. Plott that there is nothing from the American Academy of Ophthalmology that says who is going to develop myopia but we know from the data that is there that if the child already has myopia, they are at much higher risk of developing progressive myopia than a child who doesn't. Likewise, a child who has at least a mother and maybe a father--with 90 percent certainty--that has myopia they are at higher risk than a child who doesn't. So, the high risk characteristics would then be already having myopia and having a positive family history.

DR. GATES: Dr. Gordonson?

DR. GORDONSON: Because myopia is a failure of the emmetropic gene, as we all know, if you stop 100 people in the street who are perfectly visioned, 20/20, you would expect that all the optical elements would be the same and the arrangement would be the same and, to your astonishment, they are all over the lot. So, there is a gene responding to the blur circle being presented to the retina. At birth,

with the early plasticity of the organism, that starts to rearrange the optical elements and this is what is wrong in myopia. This gene is somehow asleep or somehow impaired. A child is born with the normal amount of hyperopia. I think we all agree to that. I think that if you see a rapid loss of normal hyperopia in the very, very young child with a parental history of myopia, that would be someone who is at high risk of developing progressive myopia.

DR. BULLIMORE: At the risk of being repetitive, somebody who is already myopic, they are going to progress. I think that is one of the few certainties in eye care that we can rely on. Certainly younger age and parental history are in there. As far as the people who aren't yet myopic, Dr. Zadnik and her colleagues, as mentioned today, have shown that the people who have less than 0.5 diopter of hyperopia at the age of 8 are more likely to become myopic than those who have more of a hyperopic buffer. So, that is it.

DR. CHEW: I don't have much more to add, other than what was said already, younger individuals who are already myopic and perhaps with the genetic factors of the family being involved. I am not sure in terms of any lifestyle in terms of close reading. It seems that all the children are playing Game Boys and doing other things. So,

I don't think we can differentiate them that much at this point--perhaps in other cultures. I think those are the key features that we have identified.

DR. FEMAN: Well, I have to agree with everyone so far, but I need to point out some things that have already been included in the discussion. I don't recall whether Dr. Gwiazda or Dr. Zadnik pointed out that the key thing in their studies was whether or not the child was myopic at the beginning. It didn't matter what the genetic status was or the family history. I think Dr. Gordonson highlighted that also. So, I think the child actually defines what is going on, the child that you are looking at. So, a child that is myopic, well, how much is myopic? Dr. Bullimore mentioned perhaps 0.5 diopter, and earlier people said at a very low level and it is very difficult to measure it. So, I would define what you are asking in question number two as a child already having one full diopter. That way there is no uncertainty in your mind that the child has myopia and progresses at 0.5 diopter a year so that child was already 1 diopter myopic and has gone on in a year to another 0.5 diopter more myopic. By all means, that should be a child that is at high risk for developing progressive myopia.

DR. BULLIMORE: So, what you are saying is that they need to be 1.5 diopters--

DR. FEMAN: Before they enter the study.

DR. BULLIMORE: Yes. I think by the time they get to a diopter we have probably eliminated any possibility that it is a measurement error and, particularly if they are young, there is a high probability that they will progress. I don't want for us to be unnecessarily burdensome and say you have to follow people for a year or two years before they can be enrolled trial. So, while I agree with your 1 diopter criteria, I don't necessarily agree with the need to document progression prior to enrollment and randomization in a randomized clinical trial.

DR. FEMAN: I agree with you. Thank you.

DR. GATES: Myself, I believe those that are high risk are especially ones with presentation at the younger end of the spectrum. From the data, those seem to be most likely to be at very high risk in the higher amounts of myopia.

DR. GORMAN: I have nothing to add.

DR. MILLER: I agree with the minus 1 diopter criteria. Perhaps, though, looking at the COMET data there would be an even lower level inclusion criteria for the older kids. I don't know. As you were just mentioning that, I was thinking in a 12 year old that is minus 0.5 that previously was somewhat hyperopic that would also be a

progressing kid, I would predict. But the minus 1 diopter is a clear endpoint to go with.

DR. STEIDL: First of all, there are a lot of conditions--Dr. Miller was alluding to this earlier--a lot of conditions that predispose to myopia that you probably want to exclude. The list is pretty long although it is not maybe highly prevalent. It involves connective tissue disorders and kids with ROP and many metabolic abnormalities. In general, I think people with any kind of RPE disease have a predilection to developing myopia. You might want to exclude that.

I agree with the minus 1 diopter. One of the papers has a plot of four typical children with myopia and one kid with about 1.25 and never went worse. I just bring up that I think there are kids that do that. But it seems to me that this has to be derived from the data that we are looking at. It may alter at a different age but it sounds pretty reliable that a specific refraction at a specific age is highly predictive. You add to that if you have siblings and parents involved. But in general I think the minus 1 diopter sounds good to me.

DR. GATES: Any more comments about question number two? If not, we will adjourn for lunch. We will meet back promptly at one o'clock. For the members of the

committee, there is a table reserved in the back of the restaurant for lunch. Thank you for your comments, questions and debate this morning.

[Whereupon, at 11:52 a.m., the proceedings were recessed for lunch, to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. GATES: At this time I would like to reconvene the drug advisory committee for Dermatologic and Ophthalmic Drugs. First off, we are going to have the open public hearing time again. It was initially announced at one o'clock, so earlier when we had the open mike time there might have been some folks who were planning on coming exactly at one o'clock. So, if there is anyone who would like to make a comment, would they proceed to the microphone?

[No response]

Thank you very much. We will proceed with our discussions of the questions. So, question number three, which populations should be studied prior to approval of a drug treatment for prevention or retarding myopia?

Since this is a different session we will start over to the right, if you would, Dr. Steidl.

DR. STEIDL: Well, addressing what we have here, going (a), (b), (c), (d), I am just referring to some graphs that are in the handout and it seems that the active time is in 6-7 years to 16. It seems to me that the most active time period is probably around age 9 or so. So, I would be inclined, just looking at this, and this is a fairly

arbitrary comment, to shoot for something in the 9-12 range. But I would be very open to other people's comments.

As far as the other issues, in general it seems to me that we would like a cross-section unless, as we discussed before about the ethnic groups, there is some data to suggest that it is not needed. So, as far as educational levels, you might want both less educated as well as more educated. I would be inclined to have a cross-section of Hispanics, African Americans, Caucasians and others unless there is data to suggest that that is not needed. Of course, you would want to study those with a family history of myopia as well as those without, it would seem to me. The other defining characteristics are things we have mentioned before, such as various diseases, ocular diseases, systemic diseases and other things that could impact on myopia. I would want to exclude them.

DR. GATES: Thank you. Dr. Miller?

DR. MILLER: It seems as though you want to try to know whether you can apply this drug broadly to healthy kids. It sounds as though really the defining issue is degree of myopia and the younger age group when they start progressing the fastest.

They should make an effort to study a variety of-- to mimic the U.S. population but I don't think we have to

target specific groups to answer that question. If they want to have a group that has progressive myopia, then they should make sure they include some Asian groups. But myopia is found in Hispanics and Caucasians and blacks but I don't think they have to target the ethnic groups because we are looking at similar outcomes when it does occur, except for the Asian group which may tend to have a more alarming rate.

This perception that we have that family history makes a difference, it sounds like there are some other studies disputing that and if they just start out with significant myopia, we may just be able to make it simple and go with that.

DR. GATES: Dr. Gorman?

DR. GORMAN: I am going to echo some of Dr. Miller's comments in the sense that I think this study should be age front-loaded, and 6-12 in my opinion is perhaps a little broad in terms of the group that is most likely to gain the most benefit from this. So, I would probably wish to start recruitment in the first graders. If the incidence is 25 percent in the United States population, that would give you 250,000 potential subjects per year. No matter how large a clinical study needs to be, that should give you enough to recruit an adequate number in a rapid period of time.

Educational levels and ethnic groups are going to be represented by your study sites. The family history of myopia, I think they will be over-represented in any study because I think there will be a motivated subpopulation who will be seeking treatment. So, I don't think you will need to recruit for them. In fact, it may be difficult to statistically correct for them.

Other defining characteristics, I can understand for the clarity of the data and interpretation why you would want to have a population with no other ocular disease but, just to play the devil's advocate, you might want to see whether it prevents progression in other diseases as well that also are confounded with myopia.

DR. GATES: Thank you. Myself, I am very interested in the 6-10 year old population from reading the background information, probably more than from 9-12--the younger folks.

Education levels and ethnic groups and family history I think just need to echo the U.S. population. Family history I believe will bear out as the numbers are looked at.

DR. FEMAN: Well, I sound like I am just echoing what you have already said but, again, somewhat front-loaded. Although this disorder continues to progress until

the children are 16 or so, I think you really want to look at a younger age range when this is just starting out. We have already talked earlier this morning about having children initially getting into the study when they are almost a diopter myopic. So, I think that will define the population quite well.

Whether or not there is an education level or particular ethnic group or family history, those are all interesting asides but I don't think those will really affect what the results are with this.

Other defining characteristics--earlier this morning people talked about ruling out other retinal disorders and things like that, but that is a standard part of any type of drug trial. Providing other disorders are ruled out, there should be no problem. So, 6-9, 6-10, in that range.

DR. GATES: Thank you. Dr. Chew?

DR. CHEW: I would agree with what has been said already. I think the earlier the better in terms of event rates. It sounds like these people may actually progress a lot more rapidly and you may get more events with that. On the other hand, you want to be generalizable so that you would be able to see if people who already have myopia of 1 diopter by the time they are 12 years old, would they still

benefit from it. So, from that point of view, you may want to extend it from 6 to 12 for that reason.

What has been said already, I agree with the educational level, ethnic groups and family history having no bearing. We don't need to stratify at least by those issues.

Again, I think systemic diseases and other optic diseases--as Steve said, these are just natural for clinical trials and we would try to exclude those patients. It may be too small a number to do any subset analysis on so it is best to go with that general group.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: I am in violent agreement with most things. I think 6-12 is reasonable but I think any sponsor should be cognizant of the fact that David Gossen and his colleagues have indicated that in girls myopia tends to stabilize around the age of 13 and a little later in boys, for obvious reasons. So, I would certainly be nervous about recruiting too many 12-year old girls into a study given the fact we wouldn't expect them to progress much beyond that age.

A couple of other things, the group from Novartis proposed that astigmatism be a consideration. I have no strong views on that but I think avoiding anisometropia of

more than a diopter, strabismus and enrolling people with 20/30 in each eye are perfectly sensible things to do.

DR. GORDONSON: I think I would separate to get different groups. Also, the starting out group, the first graders and the ones that are very active, 9, 10, 11 and those there are slowing down, or other groups. And, the family history is important and I have no other additions to the defining characteristics.

DR. WEST: I agree with what has been said so far, but I would point out that in Table III in the blue handout, as well as the top slide on page 8 of the Novartis material, although patients who present with myopia at a younger age end up with a higher degree, in fact, if you just assume a straight line progression, the rate of progression for the younger children is only 0.6 diopters per year while that of the 13, 14 and 15 year olds actually ends up being 0.85 to 1.15 diopters per year. So, in fact, assuming that the younger children have a steeper progression is not borne out by the Mantyjarvi data.

So, I think that one of the nice things about including the younger group is that it gets around some of the differences in consent issues per site, for the practicalities, and it also obviates the potential issues for surveillance for pregnancy in menstruating females which

could be difficult socially for girls who would need to undergo pregnancy testing perhaps as frequently as every month. That could be a significant barrier for enrollment.

DR. GATES: Dr. Plott?

DR. PLOTT: I think the important thing to think about is the disease that is being considered for the indication and that the population should reflect that disease. So, whether it is in a subpopulation of patients found only in a small number of individuals or can be cast by a variety of different ages, it should reflect those people.

I think Dr. West has made an important point that in addition to age of onset, it is maybe the duration with the disease that may be important with regard to the progression of the disease. So, the age is certainly important and younger sounds, to me, better.

I am not sure what educational level would impart but ethnic population, again, ought to reflect the disease population. Of course, the family history is important. One of the other characteristics I might add that could be important, thinking about the long-term, is a family history of myopia with an associated pathology that comes later that has been mentioned--retinal detachment, retinal degenerative changes and glaucoma. If there is that combination of

association in the family history, it could be instructive in long-term studies of these patients whether by the course of treatment they have they avoided some of these longer-term associated conditions.

DR. GATES: Dr. Chambers?

DR. CHAMBERS: I would like to go back and clarify two particular age groups just so I know we haven't skipped over them. There has been a lot of discussion about earlier is better and if it works in one age group it is likely to be used in another age group. I want to make sure that the committee is not suggesting that we not initially studying 3-6 year olds. Obviously, it is possible to determine where they are in refractive stage and if they are not at the hyperopic level you might expect that people may infer that they are headed down that path. But if that is a group that you think is better to study later and not to study early, before approval, specifically I would like you to comment on that.

The second is an age group that we haven't talked about much today, and that is the 20 to 27, 30 year olds who are typically post high school but in college who develop a low end of myopia. They tend to act differently than what we have mostly been talking about this morning. Is that a

group that you would think should be studied prior to approving a product for this?

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: Just from a practical point of view, as far as the very young subjects, there are likely to be very few under the age of 6. One might say, well, these are a different group altogether. I guess it also depends on what the sponsor is seeking in terms of an indication. If they were seeking some claim of prevention or delay of onset, then obviously it would behoove them to recruit children before they were myopic, maybe those considered to be at high risk based on family and sibling history. But if we are just talking about slowing down the progression myopia, then it seems pretty fruitless to go below the age of 6 just in terms of the age of incidence.

DR. GATES: Dr. Miller?

DR. MILLER: I would agree with that. My general impression in this loss of hyperopia group that I follow, because I see a lot of former premies and I keep a good eye on them because they are supposed to develop myopia in a large amount, is it seems just kind of variable. I will have kids where it is a little bit less and then when I look at the family history I don't feel as though it tells me--I don't think we would have as neat and clean defining ways to

find a group and this should be studied secondarily. It is a very interesting question, can you prevent it from occurring or can you slow the beginning? I mean, a diopter is a lot for that first diagnosis, but not as a first pass, in my opinion.

The other question about the older people who are stable and then suddenly develop myopia, as a resident I always thought that it would be great to study a group of people going to law school and test them at the beginning and end of law school. You know, they have been stable for a while and you get a constant statement about sudden progression during law school of myopia and they have been stable. So, I wish we had a way to quantify percent of the day you spend doing near activities and have that in some sort of clinical trial that we are doing, but I don't see any way to do that. So right now, no, I would stick with 6 to 10, 12 year olds.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: I actually study adults and adult myopia progression but I do think, from the point of view of pharmacological intervention, it would be a very difficult group to study because the progression rate is so low. You could try and enroll a group of law students who, as Dr. Miller suggests, do progress quite a bit but, you know,

college age students seem to have different things on their mind and I would be worried about compliance and things like that. Again, it is up to the sponsor I guess what indication they want.

DR. GORDONSON: If you are going to study law students, if they are minus 3 they are exerting no accommodative effort at all and if they progress that is an interesting group. So, I would look at that with--I don't know, a jaundiced eye, something like going to law school and not going to the ophthalmologist and finally going at the end of three years--I don't know. But, certainly, if you get to minus 3 you are not exerting any accommodative effort.

DR. GATES: Dr. West?

DR. WEST: For clarification, you mean you wouldn't exert any accommodative effort if you were reading without correction?

DR. GORDONSON: Well, we are assuming they are going to read without their correction. If they spend 12, 15 hours reading, I assume many of them will read without their correction.

DR. WEST: Many do, a lot don't though I think.

DR. GATES: Wiley, is that enough discussion on number three?

DR. CHAMBERS: Yes, thank you.

DR. GATES: Right, we will go to number four, what is the minimum baseline level of myopia and/or a baseline set of associated factors that might justify a pharmacological intervention to arrest its progression? Wiley, would you like to preface number four with any remarks?

DR. CHAMBERS: I think you started down this path earlier in some of the discussion but I think I would just like to see that fleshed out. Thank you.

DR. STEIDL: I am not sure I have much to say. I think the minimum refractive error rate--if I am understanding the question correctly, a lot of us are thinking that minus 1 would be appropriate. I think if you pick that a lot of the other things will just fall into place and it is not a big enough study to separate out a lot of these other issues probably.

As a retinal specialist, I am extremely interested in axial length with regard to progression, but in terms of how that affects the baseline level selection, I am not sure that it is that relevant to me. You wouldn't want someone with corneal disease. I don't know how many 6-year olds have significant corneal disease but, again, I would exclude

anyone with that but, that being said, the cornea isn't a big issue for me personally either.

The period of time for changes to be observed, I am not sure I understand that. Is that the period of time before enrollment? Was that the issue?

DR. CHAMBERS: It comes back to the issue of stability and if you measure somebody do you want to measure them again a month later, or do you want to measure them again a week later and make sure they really are at that particular point? This is all entry criteria. Again, we get a little more into question five, it is truly looking at rates. Obviously, in writing the questions ahead of time we weren't sure which way the discussion was going to go. We didn't know whether the committee would ultimately think it was better to pick particular entry criteria based on a single observation or based on a rate. So, we wrote both questions. You tell me what you think.

DR. STEIDL: Yes, I think it would be just simpler to pick a refractive level of, say, minus 1 and just stick with that and not expect a lot of prior evaluation. I am curious what other people think.

DR. GATES: Dr. Miller?

DR. MILLER: I think we have discussed this before and the minus 1 criteria is something that we have settled

on. I would say that if I saw someone with 0.5 diopter of myopia and at the last visit they had been plus 1, I would also say they fit the sense of the inclusion criteria but that would have to be flushed out differently and the sponsor will not have trouble finding patients for this study so there is probably no reason to go to that level of extra work.

DR. GATES: Dr. Gorman?

DR. GORMAN: I would agree with the 1 diopter. Going back to the glasses analogy, if you put on glasses and they make a dramatic change for someone, then that would be somebody whom I would consider enrolling in a study.

The concern about progression though, I am not clear in my mind yet, from the data that has been presented this morning or the data that I read beforehand, what fraction of children will be needlessly treated if they are in the stable group. So, if you are 1 diopter at age 6, your chances of progression are 90 percent or 80 percent or 70 percent, and since I don't have a good handle on that it would give me pause until I had a better handle on that for what number of patients or human subjects would be treated for no benefit. So, I have this desire for either knowing the progression rate so I know that number or having a

progression rate put into the entrance or eligibility criteria.

DR. GATES: For myself, I am very interested in axial length, although I would have to defer to my pediatric colleagues to know where to set the number. I am more interested in the change of axial length from entrance into the study and its conclusion. I am very interested in that. As far as where to set it, I would have to defer. The minus 1 refractive error point I am very comfortable with. Corneal curvature--I think it should be looked at but I don't feel like it is going to tell us as much as the other variables.

DR. FEMAN: I seem to be repeating everyone again but let me make some points on this. First of all, someone, and I think it was Dr. Chambers, talked about the section (d) period of time for changes to be observed. I think that becomes a key issue in many ways in that you don't want a child perhaps coming in and being examined and being a 1 diopter myope first and then 30 days later being something else, perhaps less, and maybe it is a testing phenomenon. So, I would think that for enrollment in a study such as this any child would have to have two exams confirming these features before they embarked on three years or so of being on an investigational drug. So, I would think that as part

of the beginning of the study it might be best to have a child have an exam and then come back within 30 days or 60 days, or whatever we would all agree upon, for a repeated test confirming that that is what the findings truly were. That is the first thing.

The second one is that I don't know what the real data is, normative data for axial length for children in the 6-9 age range. I know what it is for adults, for people 20-30 years of age. And, I don't think there are really good criteria and this would be a great way to find it, using this and looking at the data for all of these children. I am sure we can get ultrasonic measurements of the axial length but that wouldn't be what brings a child into the study. What would bring a child into the study is the minimum refractive error, and I think we have all agreed so far, I think, as minus 1 being a standard to start with.

Corneal curvature--wouldn't this be an interesting phenomenon to study? Again, it is not part of the study. It is not really directly related to the question but I don't know what this investigational drug does to corneal curvature over a two- or three-year period, and I don't know if the manufacturer representatives know that either. It would be interesting to find out if there is any change.

DR. GATES: It could bear out, Steve, to be a factor like corneal thickness in the ocular hypertensive trial. It would be very interesting to follow. Dr. Chew?

DR. CHEW: I think I am just echoing what everyone said as well. You have to look at the practicality of doing a trial and you have to decide whether the patient is going to come and have all these things done. It takes time. These are working parents usually so you have to be careful you are not making it so heavy that it is not very practical.

On the other hand, axial length is I think very interesting, particularly in terms of what happens with the corneal/retinal changes in the end. So, that should at least be in a subset of patients. I think the same is true of curvature. You may not do it on all patients but I think you should have some data on this subset. Again, I think the minimum refractive error would be one that brings the patient in and 1 diopter seems to be very reasonable to do.

I guess I am concerned about Steve's comments on the reproducibility of this. We have been refracting patients for a long time. So, I just wonder how much reproducibility data do we have and is there enough from other trials to really know do we need to have almost a qualifying visit and then a randomization visit again that

adds to the burden to the study. So, I think it will have to be, again, the sponsor's prerogative to look at this more carefully.

DR. FEMAN: I wasn't questioning reproducing the data as much as questioning whether or not the child was adequately cyclopleged at the time of doing the refraction. So, if you can do two tests to show that your cycloplegic refraction was identical, that would confirm it.

DR. BULLIMORE: Minimum axial length, unnecessary. Minimum corneal curvature, unnecessary. Minimum refractive error, minus 1. Repeat visit, we don't do that for our study and we enroll people based on the cycloplegic refractive error. It is adults but I don't think we should do it for kids.

I am worried, like Dr. Chew, about respondent burden. Period of time for changes to be observed, I think the data are out there so if you were to talk to Dr. Gwiazda, Dr. Zadnik and other people who have natural history studies in myopia and say, okay, if you had subjects at a given time point who were minus 1 or more how many of them are likely to progress, they would be able to provide that data. I think that, given these fine scientists who work with this particular sponsor, they would be able to come up with a rationale for probably not doing a two-time

point eligibility criteria. If they are minus 1, they are in. If they are not going to progress, then that is going to limit the power of the study so I think it is in their interests to ensure that my impression is borne out by the data that exists in their vaults.

DR. GORDONSON: Being that you could find practically any axial length in the normal eye, the issue is that the emmetropization, again, which is failing--I don't think axial length is important. Minus 1 is good. I think the cornea is minimal in this. Time to be observed, I would say a year.

DR. WEST: Minimum axial length, I would say probably not needed unless you were worried that somebody had refractive emmetropia and I think that that would help to actually weed some oddballs out, for instance, children who have significant ROP and develop myopia. It is not an axial myopia, it is a refractive myopia so it would be a safeguard to keep the population more clear by having a minimal axial length, that you had to have an axial length above a certain length.

I was thinking about corneal curvature not in terms of minimum but in terms of maximum, and that would also help to give you a more purely axial myopic group rather than a combination of axial and/or refractive. The

minus 1 refractive error seems fine with me. The period of time for changes really depends on what you hypothesize the drug's effect would be compared to the natural history, and the data so far seem to suggest that a two- to three-year time period is necessary.

The other idea that I had about the two enrollment visits that would be needed is that you could assess accommodative amplitude prior to cycloplegia and then after cycloplegia and make sure that there was accommodative paresis from the cycloplegic agent.

DR. PLOTT: For enrollment at baseline for a protocol, I would think you would need some level of disease present in combination with the age. There seems to be association there, particularly given the time frame. I would leave most of these questions to the experts but depend on the data regarding the period of time that we need to look at, although I think it could be a short amount of time that you need prior to baseline.

DR. GATES: Any other discussion or comments on question four? If not, we will proceed to question five, what is the minimum amount of change that would justify a pharmacological intervention to arrest its progression? Dr. Bull?

DR. BULL: I just wanted to ask people here for comments on the period of time of changes for changes to be observed. Wiley, was that intended as an interval?

DR. CHAMBERS: Basically, I heard most people saying they just wanted a single visit; a couple of people saying they wanted some kind of repeated, whatever.

DR. BULL: My concern was if we are looking at progressive myopia and how long the diagnosis had been established, what I am not clear on is whether or not if a child presented to an office first visit with myopia of 1 diopter, is that a sufficient criterion for entry in the study or would there need to have been a past history of having established a diagnosis and moving up to 1 diopter.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: My impression, without having hard numbers, is that if somebody shows up at the age of 6, 8, 9 or whatever with minus 1 in recent history they were probably less than that and in the future will be more than that. I think you may be able to glean from the patient's symptoms that there has been an onset of myopia by some--you know, not having difficulty seeing the blackboard and all of a sudden having difficulty. But, again, in terms of respondent burden, I think I lean toward if they are minus 1 in your chair, then they are in.

DR. BULL: I guess I am still not entirely clear on the response from the committee as to where you are on number one with progressive myopia and the increase of, you know, 0.5 or greater for classifying the myopia. I guess in terms of entry criteria, are you establishing that it is sufficient? You just want a diagnosis of myopia without a qualifier on it as to whether or not--

DR. BULLIMORE: That is why I asked the question when the issue was raised. Are we defining these from the point of view of entry criteria?

DR. BULL: Entry criteria, yes.

DR. BULLIMORE: So, I can say progressive is at least 0.5 diopter over a year, but I can then turn around and say but I don't think that is necessary as an entry criterion. That is kind of where I stand on that.

DR. WEST: And I think perhaps the confusion arises from comparing adults to children, and it is apples to oranges because in adults myopia is typically stable and if there is progression you need to define it. But, by its very nature, myopia in a 6-year old is progressive, or almost always is. So, the idea of needing to observe progression before making the diagnosis--we assume that myopia in children will be progressive.

DR. GATES: Dr. Miller?

DR. MILLER: I definitely agree with that, and I would say that the ones that don't progress are almost shocking. You follow someone who stayed at 1.25 for four years and you will discuss it with the family you are so surprised it happened. You might say, conversely, that if you had someone who was minus 1 and you knew a year ago they were minus 1 you might exclude them because they are so unusual. But just to have them show up as minus 1 on a new diagnosis, the chances are it is going to progress.

DR. GATES: Any other opinions on that to the contrary? We are all in fair agreement there. All right, let's proceed to number five.

DR. STEIDL: If this is a question that is, again, for entry criteria, I don't think that the axial length is ultimately an issue. Again, if this is entry criteria I am not sure that we need to calculate a rate prior to entry. So, I guess it is not relevant then. The same with corneal curvature, I guess (d) also.

DR. GATES: Wiley, do you need us to go around the table on number five?

DR. CHAMBERS: Only if there is anybody that disagrees.

DR. BULLIMORE: Are we talking about progression now and we are no longer on entry criteria?

DR. CHAMBERS: We are saying progression as an entry criterion, whether progression is necessary as an entry criterion.

DR. BULLIMORE: Ah!

DR. CHAMBERS: If you change your mind now--

DR. BULLIMORE: Immovable!

DR. GATES: All right, let's proceed to number six, what is the an ideal refractive error or range of refractive errors?

DR. BULLIMORE: Well, I am a minus 6.25 and I think that is pretty ideal.

[Laughter]

DR. CHAMBERS: This is meant as a final goal, what should we be trying to get people to?

DR. STEIDL: Just going by the tables in here, there is a big jump in that minus 5 to minus 7 range. It went from--I don't know what it was, something like 3 or 4 to something like 11. So, I think when you are getting around to that 6 diopter range the pathologic changes do start to kick in, it seems to me. So, again, at this point although I am very interested in changes in axial length, I don't know how to quantify that at the moment. So, I would say minus 6 diopters probably. Actually (b) is a rate of

change. So, rate per year, is that what we are talking about?

DR. CHAMBERS: No, we are on question six. From the original background package there were a couple of questions that were switched in order. The questions are the same but we just switched the order to group some of the baseline questions and put them together and some of the other endpoints to make it easier to flow for this discussion.

DR. BULLIMORE: This is really one for the philosophers. I mean, we could say I kind of like my 1.5 but would I like more? Maybe.

DR. CHAMBERS: Okay, if you get to recreate yourself, what would you like to be?

DR. BULLIMORE: A little hairier.

[Laughter]

DR. CHAMBERS: With respect to refractive criteria?

DR. GATES: Go ahead, Dr. Miller.

DR. MILLER: I will tell you what I would say for the answer, minus 1, plus 0.5 at 90 because I guess you get a little depth of field too. Right, if you could pick it? But this is a real question though. The question is what is considered bad? You know, what do we consider bad enough so

that you would let your child be in a protocol? So, what do we want to stop? Is it the cosmetic issue of the glasses or is it that at a certain point we consider it is unacceptable to be beyond a certain amount myopic? So, it is getting at a real question.

But my problem is defining when I would let my child be in a trial. So, if I had a child who came in with minus 1 and I had a history of progression of minus 1 over one year, there is no question I would put them in a trial. But that is what we are considering the rapid progression group so I guess that is an easy one. Then the question is, you know, in the progression group what would be reasonable. The sponsor wants to present it in a fashion so that their medicine will be widely applicable but, on the other hand, is it reasonable? I, personally, don't know enough about the medicine and the potential side effects. We are getting ahead of ourselves a little bit in trying to define what is a risk versus benefit sort of thought process here because if you are talking about rapid progression I feel comfortable giving you a number on that, but I don't feel like I know enough to do the lower level.

DR. CHAMBERS: Let me try rephrasing it another way. Say we could give you a single drop and it would change your refractive error to some number, and two drops

get you this, three drops get you this, one drop gets you this and that would get you a number. What number should we be trying to get people to?

DR. GORDONSON: Plano in one eye and minus 0.75 in the other.

DR. MILLER: That is brilliant.

DR. BULLIMORE: let me take another stab at this. I think really this is kind of a little foreplay for question seven. I think when you look at the risk of some of the nasties that happen in all eyes, you have more risk if you got more myopia. I think, you know, less is clearly better. I think if you got somebody who, based on their age of onset, is destined to be a minus 5, then with many, many years of treatment of you could hold them down to a minus 2 or minus 3, then that would be worthwhile. I think there is a difference between being a minus, say, 1.5, which is what I am normally, and I wouldn't want to be anymore myopic because 1.5 is kind of perfect for my computer. As a presbyope who has yet to come out of the closet--

[Laughter]

--I am quite happy at that distance but wouldn't want to be 2.5 because I probably wouldn't be able to see my computer comfortably without correction. So, I could think about how we function in the distance, how we function at

intermediate but I think if we can minimize the amount of myopia then we are minimizing the disability that people experience without their correction. We minimize the risk of detachment and other stuff and, I will throw it on the table now, if you talk to a friendly refractive surgeon, you know, a minus 3 is easier to deal with than a minus 6. So, there are a range of benefits but drawing a line in the sand and saying this is the best one is tough.

DR. CHAMBERS: If you take it to the full extreme though, less myopic means you end up being hyperopic. Would you rather be minus 0.5 or would you rather be plus 1?

DR. BULLIMORE: Looking at my future years, I am minus 1.5 now but if I believe the literature I will be ametropic by the time I am 65 or 70. So, I am quite happy being a minus 1.5 myope because that is my future. If I was ametropic at this age, which people of my age who have had LASIK are, they are going to be hyperopic and relatively miserable when they get into their 60s and 70s because they will be 1, maybe 2 diopters hyperopic. So, again, I think a little bit of myopia is okay but keeping it under control I think is a worthy goal. So, I would rather be myopic than hyperopic, in answer to your question.

DR. GATES: Dr. Gorman?

DR. GORMAN: I think this is the argument that all conditions rather than diseases faces, how much of a condition is a bad thing? If you are an obsessive-compulsive but functionally become a physician--

[Laughter]

So, I think that one of the criteria that the sponsor and company seem to measure is issues about quality of life, and I think we have all danced around that without being willing to say it. That is, if you are 6 years old and can function in school okay without your glasses but better with your glasses, so they were helpful but not essential, I think we would all be pretty happy with that definition. I don't know how to put that into a regulatory guidance or a protocol statement or an outcome variable, but I think it is the same thing that I feel right now with my progressive farsightedness. I can carry glasses around as a crutch so I can use them, but in a pinch I can read a page without them. So, I am happy to have them to help but I don't need them yet. In five more years I will need them. So, where are the drops for me is what I really want to say, as opposed to this.

The other issue is the trade-off for what are you looking to give up in your life for this change of refractive error? I think we have the answer if it is a

one-time intervention such as surgery. I have think we have a dollar value that people are willing to pay. It is hard for me to decide if the increase in LASIK surgery is because the price has plummeted, therefore, it is on sale, or if it because more people want it. Or, did all those people really want it and now they can just afford it. So, there will be a pharmacoeconomic discussion that will go inside the company, inside the country and, you know, at the family kitchen table as to whether this is worth fewer years in glasses or fewer changes in glasses. So, I think there are a couple of ways to say the ideal refractive error.

DR. GATES: Dr. Bull?

DR. BULL: I was just going to ask the question, in the context of question six about an ideal refractive error, how would you define that for a clinical trial with an entry criterion of minus 1? Would success be that you kept that patient at the minus 1, or that when they are 40 years old is the goal to have then at minus 1.5 so they can comfortably read? What does this mean in terms of trial design for what we have under discussion?

DR. GATES: Who wants to take that?

DR. WEST: I just don't think that there is any blanket statement that can be made for what is the ideal refractive error for all people. What is my ideal may not

be what my best friend's might be if she is a mountain climber and never reads. So, it is very different and will depend upon what that child is destined to be as to what their refractive correction should end up being. I am very happy as a minus 1.5 and a minus 3. I do a lot of needlepoint so I would prefer to have my near eye a little bit nearer than my taller colleague.

DR. BULL: I can't resist the urge to follow-up because I guess this gets to something that Dr. Gorman is aware of with pediatric interventions and things that say if you had been a child and your parents elected to have your myopia arrested so you never got to your minus 1.5 and your 3 that you are happy to have--we are looking at an intervention that has long-term implications for a child and asking parents to make decisions for that child based on their concerns at a particular age. I guess, as you alluded to, we could end up with the situation where the child's ideal may not have been what the parent's ideal was. I feel a little bit compelled to make that point.

DR. GORMAN: The comment that you make, I think most of us eventually become happy with who are, no matter what that is. But I think if you were going to ask--I can't redesign the study and I can't redesign the agency, but I think if you wanted an outcome that I think everyone around

the table would agree with as a parent of their child, if you could prevent them from having to put on glasses the first time, they would take that. But we are dealing with a group that, to identify them well, already have to have glasses on. So, I think if you are looking for the intervention that would be the ideal it would prevent them from having to wear glasses during their childhood. Then, when you get to be--how old?--65 when you are going to need your glasses--

DR. BULLIMORE: Forty-seven--

DR. GORMAN: Forty-seven when he needs his glasses, as the closet presbyope, then you can deal with them as adults deal with putting on glasses. I think that would be ideal but that is not the world we are presently living in. We are living in a world where I think you are going to have to define ideal as slowing the progression of their myopia and not have a number. It is going to be a slope issue.

DR. GATES: Any other comments on number six? We will proceed to number seven, how much of a refractive change is considered an important change for an individual who would otherwise have the following refraction? We can just go down the list as such.

DR. STEIDL: Well, I think you need a global concept, so the idea for example of doubling of the visual angle, to me, is a reasonable one. I think it was a 0.75 change that we said. I wouldn't come up with a different one for each of these, personally, but I am curious what other people think.

DR. MILLER: I agree with that because I don't think it is something we can reasonably control. We are talking about a study where we are including kids where they just go along with their natural history versus, if they follow the tables, we shouldn't be getting very minus 7 or minus 12 in the whole study.

DR. CHAMBERS: Can I try and rephrase this question? The idea of this question is you enroll whatever population you enroll and half your group, say, gets one intervention and the other half gets the other, and your control group ends up, say for (d) with minus 4. What would you want the treatment group to be to consider that a success? So, if the treatment is minus 3.75, or minus 3.25 and the control group was 4, if the matched control patient would have been 4 and you have now made them 3.25, did you help them?

DR. BULLIMORE: What did you enroll them as?

DR. CHAMBERS: The issue is not how they were enrolled--

DR. BULLIMORE: Well, it is--

DR. CHAMBERS: --the control group is going to go through its natural history. Maybe it is a ten-year trial, maybe it is a one-year trial, this is looking at the endpoint. How much of a change? I guess in my mind I would have thought if you were going to be a minus 1, and we are trying to change you from being a minus 1, you might put up with something a little bit less than if you were going to be a minus 7. You probably wouldn't be as happy if you only changed 0.75 diopter. That was the way I was thinking of the question but, you know, the question is for you to answer.

DR. BULLIMORE: I will take a stab at your question in a minute but if you enter the study as a minus 1 and you were destined to be a minus 4, then the expectations are very different than if you entered the study as a minus 3 destined to be a minus 4. So, you know, we could have all sorts of 6 X 6 tables and mark what the number would be in each, but I think from a practical point of view I am still coming down to, you know, 0.75 being the minimal effect that is meaningful. Clearly, what you are leading us towards is that for people with high degrees with myopia, you know,

should we consider a larger number to be a meaningful change? Certainly, if you go down to the 7-12 diopter range, a minus 0.75 difference when you are a minus 10 isn't going to mean beans to your quality of life or anything.

In that regard, for the high myopes, the rapidly progressive myopes, if you like, you might want to set the bar a little higher. But I think, given the entry criterion of a diopter, your control group is going to end up probably in the 3-5 range. What is meaningful? I don't know, a halving? What does that give us? I can't do the math.

DR. CHAMBERS: The other part of the question, and the reason there are these different ranges is because, say, in the (a) group if you were destined to become a minus 1 you might argue you don't want to be moving from that. Based on what some of the people were saying earlier on, that is what you would like to continue to be on.

DR. BULLIMORE: And based on our entry criteria of one diopter, you are not; you are not going to get any better. It is kind of moot for that group. I think we should concentrate our efforts, in terms of what we know about progression of myopia and the age range we are thinking about for these kids. Thinking about (c) and (d) here, people are going to end up in the 2 and 5 range is going to be the most fruitful. Really the ones at either

end are either outside the purview of the kind of trials we have been discussing today, unless we go back and start to think about predicting myopia and treating it before it becomes manifest and if we want to consider the high myopes separately but, you know, the common or garden type of myopia that we have been discussing today is contained in the 2-5 diopter destination range. That is where most of these kids seem to end up. We got the percentages from the Framingham study which suggest that that is the bulk of the myopia, and of course I can't find it in my handout now. So, I think ultimately that is where it is easiest for us to come out with a number.

DR. CHAMBERS: If you want to start there, but we are trying to think of a guidance that covers all the different ranges of different things that will include people where we will attempt to treat high myopia as well as those people where we will try to arrest progression very early on. Even if it is not the first thing that is studied, we are just trying to get as much information as we can from you at this point in time.

DR. GATES: Dr. Gorman?

DR. GORMAN: I think when I was reading the briefing packet I missed why there were two potential different outcome analyses presented by the sponsor. I

think I now understand. Because I think there is an actual objective criteria that makes some sense of a different prescription, 0.75 or 0.5 diopters, but there is also another progression category of how many people progress to severe impairment of their life. I don't think they are independent. I thought they were independent before I got here this morning, but now I am convinced they are not independent. I don't think they should, therefore, be independent outcome variables. So, there needs to be some criteria linking that for people who don't progress very far, smaller numbers are okay; it shows an effect, but for people progressing a long distance, they can't progress as far as they would have. So, there needs to be a study of proportions of whether or not the same number of people get into the life-interfering level of myopia.

DR. CHAMBERS: Right, and that is why this question was written for the individual.

DR. GORMAN: Right, so for the individual there has to be a minimum criteria that their particular eyes have to do no less than 0.75 diopters or less than 1 diopter for their eyes. Then, as you take them into their group of people, whatever group they fall into, not very fast progressors, progressors or rapid progressors, they need to be not progressing as a group as far as they would have been

predicted to. So, for the individual at least a diopter or 0.75 diopter and then, as a group, not going as far as they would have been predicted to.

DR. GATES: Dr. Steidl?

DR. STEIDL: Just as a clarification, are you trying to separate these into groups of people who progress at different rates? Because I think what we have been hearing from Novartis is that their data at this point says that there is a certain average progression, 0.5 per year and maybe Asians might be faster and that you can predict, based on where they start, roughly where they are going to be in a few years. Because we don't know who they are going to be necessarily unless we are following them for a period of time ahead of the study, at what rate they are.

DR. CHAMBERS: We don't know exactly--I mean, the idea was to try and say we will have a control group for all these particular things and look where the control group tends to put people, and then look and see where the treatment intervention has taken that group. The idea is have we made a difference in that group? You can judge that either by means or you can judge it by percentages that have reached some particular criteria but we were trying to get a sense for an individual how much of a difference do we think we would want to have accomplished to have made a difference

to them. Maybe that answer is 0.75 diopter; maybe it is 1 diopters, maybe it is 10 diopters. We are asking the question.

DR. GATES: Dr. West?

DR. WEST: I think that although Novartis has proposed to study, and I think it is reasonable to study just the refractive change, all of us, as ophthalmologists and optometrists, would hope that if this drug did have an effect on refractive change there would also be a change in the proportion of people that then development complications of myopia, including myopic retinopathy and all those things.

So, I think that you need to think about the person who is a 5 diopter myope versus a 9 diopter myope in two ways, one, in terms of their refraction and the practical implications of going with or without their refractive correction, in addition to considering the possible complications. So, an 8 diopter myope and a 12 diopter myope, neither would functionally read without their glasses because their working distance would be too short, but you would be better off as an 8 diopter myope than a 12 diopter myope in terms of your chances of developing a Fuchs' spot or a chordal neurovascular membrane. So, you are asking both questions, I guess.

DR. CHAMBERS: Correct.

DR. WEST For me, I think I can answer explicitly that it appears to be, if you look at the data from Vongphanet, in Ophthalmology, 2002, that a 1.5 to 2 diopter change in the final level of ametropia is clinically significant in terms of what you end up with for correction of complications from high myopia when you are above a 5 diopter myope. But, practically speaking, for any of those you are not going to go around without your glasses. Then, I think that for people who are less than 5 diopters myopic, probably 05. to 0.75 is clinically significant for going without refractive correction because the risks of complications from myopia, sight-threatening complications, become far less.

DR. BULLIMORE: Those are the numbers I have written down. I think if you look at the data both for retinal detachment and myopic retinopathy, if you are destined to be in the 5-7 bin there is a real benefit in being in the 3-5 bin. So, you might have to treat somebody for a long time and start early to keep them that way, but 2 diopters seems to be a tangible benefit in that group. But in the lower groups, 0.75 plus/minus 0.25 seems to make good sense. Keeping them out of the high range is the goal. If you want to go to the very high range, even 7-12 diopters, I

think to make a meaningful difference you have to knock 4 diopters off it but those are an exceptional group of patients rather than particularly common.

DR. GATES: Dr. Plott?

DR. PLOTT: There was an important point about a co-primary endpoint made. Just to be clear, a co-primary endpoint makes a study very complicated. I think what the sponsor, in their slide 49, has proposed is an endpoint based on means. So, for a population treated versus a placebo group, having some change from baseline as a mean versus another possible endpoint, having a proportion of subjects achieving a certain amount of change in the placebo group and probably having a smaller proportion of patients change. Putting those two things together can be important. It can be relevant. It is done. It should be known by the committee that saying that these two things are linked and you have to win on both of these can be a daunting task.

DR. GATES: Dr. Gorman?

DR. GORMAN: You are dealing with the schizophrenia of pediatricians. We have the desire to treat the individual, which was one part of the question, but we also have a public health role. If I couldn't guarantee that you would be able to walk around without your glasses but I could predict that your chances of retinal hemorrhage,

tears or eventual blindness would go down by this treatment, both of those I would consider wins. I didn't mean to tie them together, except, as my colleague who spoke later, if you are in the low myopic group 0.75 makes sense. If you are in the high myopic group moving down a couple of buckets makes sense. I think they presented it much more clearly than I did. But I am not sure if the drug has no effect at the lower diopters but has a great effect at the high diopters it wouldn't be a drug that wouldn't be pursued, you know, in terms of having a public health benefit rather than an individual person benefit.

DR. GATES: Wiley?

DR. CHAMBERS: I don't know if we have heard from everybody.

DR. MILLER: No, I think that the primary outcome, the way it has been described by the sponsor, looking at the 2 diopters, the proportions in the two groups is reasonable, and that the data will be there to look at what happens in the higher group. It sure would be nice if it just plain cut off the higher end, but I don't think that that is necessary to prove. By having this discussion we have already decided that it is reasonable to do this in the groups that are not rapidly progressing. So, we should accept a difference between the groups with the lower

myopias. So, I don't think we have to get into this discussion of the higher group and we will find out over time whether there is some benefit with retinal disease.

DR. GATES: Would anyone else like to comment?

DR. CHEW: I would agree with that. I think it would be very hard for us to think that we could demand an outcome that is sort of proportional, like a 25 percent change depending on where you are coming from. I think that is a very difficult endpoint to work from. I think it keeps it much cleaner, and we are starting with probably not quite as high myopes anyway to begin with and if you are going to demand more of that, I think that is very tough to do for a sponsor, for anyone to do. I think it would be unfair to give that sort of outcome. I think what is clinically significant, as we have discussed, is 0.75 diopter is meaningful. So, I think it is important to stick with that regardless where you came from.

DR. CHAMBERS: I couldn't keep track because you were skipping around. Is that everybody?

DR. FEMAN: I don't know if I officially commented during that session but I agree with what Dr. Chew just described. I think someone earlier talked about the practicality from an individual's perspective, that at a 0.75 diopter change you are going to go get yourself a new

pair of glasses, no matter what. So, if you are stabilizing someone so that they don't have a 0.75 change, no matter where they are in the range between minus 1 and minus 7, you are going to prevent them from having to buy a new pair of glasses. So I think, just like Dr. Chew had indicated, it is appropriate.

DR. GATES: Yes, Dr. Miller?

DR. MILLER: I have one question. We have talked about our stable group definition, less than 0.5 a year and that progression is 0.5 diopter a year or 0.75 diopter a year. When we discussed it we talked about 0.5 diopter a year but often we have gone into Dr. Joseph Miller's discussion of 0.75. I just wondered what we have decided as a group.

DR. BULLIMORE: I have been working on the assumption that question seven refers to the duration of the study. So, I have been working on the assumption of at the end of the study or at the end of the intervention period, what is a meaningful difference, whether that is two years, three years, four years, but what would make a difference at the end of the study; how much difference between the treatment and the control groups would be meaningful to you as a patient and/or a clinician.

DR. MILLER: Right, as 0.5 diopter or 0.75 diopter per year or the 2 diopters proportion--I am confused now. Wiley?

DR. GATES: Wiley, would you clarify? Dr. Miller has a question over the time span.

DR. CHAMBERS: The assumption in question seven was at the end of the trial, how much of a change you were basically going to effect from the beginning of the trial to the end of the trial, not per year; total amount of change.

DR. GATES: Everybody had time to express their opinion on question seven. We will move on to number eight.

DR. CHAMBERS: What I have heard has been ranges between 0.75 diopter and 2 diopters. That is what I heard as people went through.

DR. BULLIMORE: Are we going to go back and vote on these one by one?

DR. CHAMBERS: No.

DR. BULLIMORE: Okay, well, let me see if I can get some consensus then. For (a) through (f), I have written down 0.5 diopter, 0.75, 0.75, 0.75, 2 and 4, 4 being for the 7-12 group.

DR. GATES: Any other comments, or would anyone like to propose any other criteria for the categories?

DR. CHAMBERS: As I said, we are not looking for definitive votes or answers. We are looking for ranges. This is a starting point to try to develop a guidance.

DR. GATES: So, we will move on to number eight, what is the minimum amount of change that would be considered a pharmacological success in slowing progression? Why don't we start over on the left-hand side of the room? Dr. Plott?

DR. PLOTT: Just listening to what I have heard here--I am not the expert, but what I hear is that 0.75 of a change is important and that is what I would stay with during the course of a study.

DR. CHAMBERS: This particular question is rate. Whereas the last question was the total amount, this question is rate.

DR. GATES: Rate.

DR. WEST: Can you go on to the next and then come back to me?

DR. CHAMBERS: That is the chairman's prerogative and he is welcome to do it whichever way, as well as if you think this is not the way to be studying things. I mean, remember we wrote these questions ahead of time, trying to make sure we covered different bases. If you think particular questions are not relevant, tell us so.

DR. WEST: No, what I was just trying to figure out was the rate because we have really been thinking about the endpoint over time. If someone is looking at the data, that there is a different rate for different ages and you would need to cut your rate by a different amount at different ages to end up having a clinically significant outcome. I was just trying to figure out what that was.

DR. GATES: Dr. Gorman?

DR. GORMAN: I think this question is unanswerable in our present understanding of the agent. If the agent works by stopping the progression for 18 months and then it goes back to its previous rate, no matter what you do, is one answer. If it is equally effective, no matter what the progression rate--I mean, this agent may be very effective in the 3-6 year old range, 6-9 year old range, or it may have a fixed rate reduction so it always reduces it by 10 percent of whatever its growth rate is. Since we don't know how the agent works, I am not sure that the rate becomes a meaningful question as much as the outcome. If it is a steady state effect over the course of therapy, then this is a meaningful question but if it is not a steady state effect over the progression of the disease, then this question has little meaning except in terms of the endpoint of how much does it slow down the progression.

Because we don't know how this agent or other agents that may come down the pike are going to affect the progression, I want to use the analogy of when HMOs came alon there was a huge cost savings for one year and then the rate of increase progressed from then equally. So, for one year we saved all that money and from then it just progressed at the regular rate. If a drug works like this, then there will be one year where there will be zero growth. And, it may be growth dependent. If the eye is growing in axial length it may only slow that rate of growth by a certain amount. I am not sure we know enough about the agent to answer this question.

DR. BULLIMORE: Dr. Gorman is speaking as if he has read the myopia clinical trial literature very carefully because there is an emerging body of evidence that suggests that for certain therapies you get a lot of effect in the first year and then the two groups basically follow a parallel course beyond that. So, I would share Dr. Gorman's hesitation about defining what is a successful rate when that slowing may vary at different times of the study. Of course, at the risk of misquoting Dr. Gwiazda's COMET trial, I think they observed a relatively large effect in the first year of the study and smaller effects in years two and three. I think we see that in the atropine data as well and

maybe in some other trials too. So, you know, if the FDA wants a number, then, I don't know--an average of 0.25 diopter over the duration of the trial.

Certainly in light of what has been discussed here, I think it is important to have a period of time greater than a year. It would be ignoring recent studies to do a one-year trial and feel that was sufficient. But two to three years seems to be the minimum, and a rate of change, if you want a number, 0.25 diopter per year but I would be cautious about holding someone to that number when the effect may vary from year to year.

Corneal curvature, we are not expecting to change given the current ranges of agents that have been tried and tested. So, I don't regard that answer relevant. So, 0.25 diopter, 0.1 millimeter axial length but with a caveat that this might vary over the course of the trial, the effectiveness of the agent may vary over the course of the trial.

DR. GATES: Any other proposed baselines? Dr. Steidl?

DR. STEIDL: You could look at this from the point of view of what does the patient want, patient satisfaction, quality of life. That would be very difficult to assess but, from my point of view, I am still quite concerned about

pathologic changes. So, you arrive at a number. Like you said, when you hit minus 5 your likelihood of developing problematic retinopathy increases. Then to come up with an answer for this, I would do calculations based on that. If you are minus 4, small increases to that number would be significant. If you are minus 1, you know, your rate might change depending upon the time when you are looking and all of that, but I would use that as the endpoint and calculate everything from that since that is the one absolute concern that could lead to severe vision loss.

DR. MILLER: That is very interesting to me but my concern with that is you might decide that the drug was a failure but there might have been a role if you had started the treatment earlier. So, it might make sense to look, as has been suggested, over a longer period--because we don't know much about the rate of this, to look at it over a longer period of time and have a manageable number like 2 because we know in the normal changes it is 0.5 diopter a year. So, if over 30 months we are looking at some people who have come up by a 2 diopter change, then for people who have followed the normal curve we have gone long enough to know that something different has happened.

I am very interested in axial length measurements getting measured, to know that information as a pediatric

ophthalmologist, but it is really refractive error as the endpoint that is important because with kids you can get some error and you get more of a numerical change with refractive error for the millimeter change. So, I would stick mostly to refractive error and secondarily measure axial length in these things. That is why I haven't talked about it that much.

DR. GATES: I concur. I am very interested in the refractive error as opposed to the axial length. I am interested in that data retrospectively to see where it goes, but I am more interested prospectively in looking at refractive error.

DR. FEMAN: I agree with what you have just discussed. Essentially, the study is designed to be measuring the change in refractive error and we have already discussed these levels. These other features, axial length, cornea etc., are just things to be measured while we are doing it.

DR. GATES: Dr. Chew?

DR. CHEW: I don't have anything more to add.

DR. GATES: Any other comment on number eight? Dr. Miller?

DR. MILLER: You could say that the study drug is a roaring success if you don't get any minus 5 or worse

myopes and it is a failure if you do, in a sort of simplistic way, if you want to look at the pathologic myopia. Anyway, I think we have covered this.

DR. GATES: All right, we will change cues here and go to number nine and start off with Dr. Steidl. What are clinically relevant, acceptable endpoints of myopia-induced ocular disease? We have talked a little bit about the refractive error and now we will talk a little bit about the disease.

DR. STEIDL: Relevant and acceptable I guess are different. We wouldn't accept retinal detachment. All of these things are relevant and I guess there are many ways of looking at this question but the most important thing I think to follow for is development of retinal tears, glaucoma that couldn't be otherwise explained and development of retinopathy. Lattice degeneration is common and that is not I think a particular issue although you want to know that it is there. Retinal holes generally, depending upon who you read, can be followed but, again, you would want to know they are there. Retinal detachment is quite a catastrophic event so, again, you would want to know about that but that wouldn't be an acceptable endpoint. So, I guess it depends on how you define it.

DR. CHAMBERS: Yes, say in a trial we were not going to follow for the refractive change. Say we were just going to look at the two groups and say, okey, the endpoint is going to be retinal detachments. If we get less retinal detachments in the treatment group than in the control group, is that something we should approve a product based on?

DR. FEMAN: I have a problem with the discussion going on because the literature at the present time does not show that these are cause and effect relationships to myopia. They are coincidental to the disorder but just because a person is a myopic is not what causes them to develop the retinal tear. Retinal tears develop in people that are myopic. These are associations but not causally related. So, that is a different approach than saying this is a treatment done to prevent a retinal disorder of some sort. Unless someone else is aware of literature that I am not aware of. Emily?

DR. CHEW: Well, my concern is that, you know, if we are looking at these as endpoints you are going to have a long, long-term study. These things don't happen in children. Retinal detachments are in much older people so you are not going to be able to look at this until years, and years, and years, decades down the road. We already

have very good data that suggests that retinal detachment is associated with increasing myopia. The risk more than doubles if you are even 1-3. So, I think it is going to be very hard to incorporate this in a clinical trial that you are going to demand of a myopia study. That is my personal view. These obviously are very important clinical features that we are hoping to prevent, but there is no way you are going to be able to design a trial that is only that long to look at it.

I think Steve is right, there are some associations, like lattice degeneration, that may not be just myopia. It is fairly common and people don't treat lattice degeneration or asymptomatic holes. Those are not important unless they become symptomatic with retinal tears. So, these are difficult endpoints that I would not put in a trial for myopia treatment.

DR. CHAMBERS: We are basically looking for different options. We are trying to give sponsors different choices and ways to do the trials. Whether you agree that is the most efficient or the best way is one story, but if you were to design a clinical trial that said I am going to treat one group with one particular agent and have a control group there and you found less retinal detachments in your group, would you say that was a legitimate endpoint to use

to approve the product? Clearly, we have put in a number of different things.

Yes, we recognize that lattice is far less serious than having a retinal detachment. If I had to guess about how you would answer the question before we started, I would have said retinal detachment was fairly straightforward, you are all going to say if we prevent retinal detachment, that is a good thing. I am not so clear about a bunch of the other things that are on here. So, that is why they were put into this question. The assumption is not whether the trial can be done or not. It is, if we were to try and use anatomical endpoints, which ones do you think would be appropriate and which ones would not be appropriate to use as an endpoint, assuming the trial is 20 years long.

DR. BULLIMORE: So, you want us to enter into your fantasy world right now?

[Laughter]

With all respect, it just seems, you know, a waste of everybody's time to be discussing even the concept. I mean, just thinking about the duration of the study and the sample size, retinal detachments even in a myopic population, have something like 0.6 percent per year event rate. I don't have enough life expectancy to do this study.

DR. BULL: Just as a point of clarification, I think the intent was not just to think in the box of the example provided by Novartis, but if you were hypothetically, as Wiley pointed out, to conceive of a study design that would look at an anatomic type of endpoint, does that have any relevancy here? From what I am hearing, I think it is certainly reasonable that these kinds of endpoints would not be ones that you would reasonably see in the pediatric age group for a study that would have the kind of duration that one would look at to try to get a drug on the market in our lifetime; that to try to see whether or not the children enrolled would develop these is conceivably so long that it would not occur within what would be a two to three-year study frame, if that is deemed to be an acceptable time frame for the study. But I think it is raising the question, trying to look at potential models of looking at endpoints for the study and to get your comments on that.

DR. GATES: Dr. Steidl?

DR. STEIDL: Briefly, you said we could say if we didn't think it was a relevant question and, in a sense, I would say that that is the case here just in the case, as you were saying, of a reasonable study of appropriate duration. I would say (a) through (e)--I agree with what

Dr. Feman says, that, in fact, it is pretty hard to connect those to myopia from the start. What is relevant is development of myopia-related retinopathy and you would have an enormously long study for that. So, I don't think it is really relevant as a question.

DR. GATES: Dr. Gorman?

DR. GORMAN: I was reacquainted with the word earlier when someone used it, recidivism. If some of these rare events occur in pediatrics and they have a repeatability that is predictable, such as retinal tears, and if you have one, will you have another? If this drug was shown to prevent the repeating or the recidivism rate, reduce the recidivism rate, I could see that as being a useful piece of information but certainly not for the indication presently sought by the sponsor.

DR. GATES: I would love to know this information but I think, you know, the time over which it would be attainable would be insurmountable. Has everybody had a chance to make a comment that would like to on number nine?

Let's go on to number ten. Which method or combination of methods do you consider the most reliable and reproducible for the assessment for measuring myopia in children? Dr. Steidl, do you want to begin again?

DR. STEIDL: I see the argument for the automated refraction and perhaps, just in practical terms, that is the best way to go. If you could have certified examiners who could fly to locations for difficult cases, for example, if you did serial axial length measures and got really erratic readings because of child compliance or other reasons, that might be a nice backup. When I was reading this, I didn't initially think that auto refraction would be reasonable but I think that it might possibly be now. I don't have anything to add with regard to axial length measurements in kids because I have never tried it and I don't know anything about it.

DR. GATES: Dr. Miller?

DR. MILLER: Clinically the gold standard that we use all the time is a physician cycloplegic refraction but I think for the purposes of the study automated refraction will be the most practical. My question is which cycloplegic agent will be used. It should by Mydriacyl; it should be Cyclogyl one percent, in my opinion. In this age group even consideration should be given for an atropine refraction, but that is something that should be talked about because those numbers can be very different.

I don't see axial length on there--yes, I do axial lengths in children this age before cataract surgery without

much difficulty. So, I think you will have an occasional child you can't do it with but it is doable.

DR. GATES: Dr. Gorman?

DR. GORMAN: I defer to my colleagues who do this on a daily basis.

DR. GATES: I am agreeable to cycloplegic auto refraction if the other colleagues that work with children on a regular basis feel that is valid. I would concur with that.

DR. FEMAN: My only question is that I don't see cycloplegic auto refraction on that list. Is that what you mean by number (a)?

DR. GATES: On our papers it is (d).

DR. FEMAN: Okay, cycloplegic auto refracted spherical equivalent--somebody had debated whether or not a spherical equivalent is an appropriate term. I think (a) as a cycloplegic automated refraction ought to be the option. I think that (a) should not be just automated refraction but cycloplegic automated refraction.

DR. CHAMBERS: That is why we have (e) there.

DR. FEMAN: Well, that is (e).

DR. MILLER: I agree with Dr. Feman. I agree.

DR. CHEW: I think the cycloplegic is important also in terms of asking if there are going to be adverse

effects you are going to see, and I think important to mask for the investigator, the examiner, to really try and cut down on bias as much as possible.

DR. BULLIMORE: Yes, cycloplegic auto refraction. I think atropine is a little cruel and unusual even for this kind of study. Personally, I am a big Mydriacyl fan but I can live with Cyclogyl. I defer to Dr. Miller.

As far as axial length measurement, ultrasound is good and doable. I don't have an interest in the company but the Zeiss IOL Master is excellent in myopia studies. It is objective; it is quick; it is non-contact and its repeatability is exquisite. It is really very, very repeatable. But, obviously, requiring a sponsor to use a specific instrument is probably inappropriate but just to draw people's awareness to the fact that there are alternatives to ultrasound out there that may fit the bill very well.

DR. GORDONSON: Cycloplegic auto refraction is the best if you are only looking for change. As long as you don't prescribe it, it is fine.

DR. WEST: Automated refraction without cycloplegia is worthless. Cycloplegic refraction by an observer is not reproducible. Axial length is a measure only of axial length and not of myopia without information

about the contribution of the refracting elements of the eye. So, that is unacceptable as a primary outcome. Cycloplegic automated refraction is the most reproducible but it has to have a sufficient cycloplegic agent for all colors of eyes, realizing that blue eyes in general will have a larger effect from tropicamide or cyclopentolate than dark irises will. So, I would vote (e), other, cycloplegic automated refraction, not spherical equivalent because of previously stated loss of information.

DR. PLOTT: I defer to the experts.

DR. GATES: Any discussion? We will go on to number 11, starting on the left-hand side. "High" myopia has been attributed to a diminution in an individual's quality of life. How is quality of life most appropriately assessed in these clinical trials? Dr. Plott, do you want to begin?

DR. PLOTT: I have just a little bit of experience with quality of life trials, enough to know that they are very highly variable instruments and they need to be validated. This particular population presents an unusual challenge because of the age. So, to use a validated instrument would seem to be very difficult without validation. There is something to be said, just for the

common sense quality of life and being able to see better. That is about all.

DR. WEST: I don't know of a way to assess quality of life in an 8 year old with myopia.

DR. GORDONSON: High myopia is going to be found later. These kids may be projected to have high myopia but at the ages at which they are going to be studied--and kids always say everything is okay--"How are you doing in school?" "Things are okay"--even though a report card says otherwise.

[Laughter]

So, I don't know how this question applies. Even adults, if you have to ask them do you want to go through this business or accept the way you are, I don't know what answer you would get.

DR. BULLIMORE: As Novartis and the experts suggested, there are things like the RSVP and the RECQ that have been developed to assess quality of life as a function of refractive error and refractive correction, but I am not aware of those being used in kids. I guess there could be an instrument developed. I think issues of dependency on the refractive correction, quality of vision without their correction, all those kind of things are the issues that I think should be on there, but I am not about to go develop

an instrument to do it. I think that is up to the sponsor to do, but one would like to see the appropriate validation done before it is used in a trial of this nature.

DR. CHEW: I would agree with Mark. I think the other issue you have to address is the adverse effect of treatment. That has to be in the quality of life questionnaire as well, what sort of tolls does it take, and it would have to be addressed to the family, you know, parents as well rather than just the child.

DR. FEMAN: Well, quality of life is something that is very important for all of us. The National Eye Institute has already established--correct me if I am wrong; Dr. Chew works there once in a while so she would know in more detail--

[Laughter]

--but they have already established a superb quality of life technique for evaluating such changes in adults, particularly when you are studying macular diseases and things like that. There is a group I guess in Philadelphia that does econometric planning based on these quality of life statements so one can really use this to talk about dollars and things like that. But I don't know that anyone has extrapolated this to the pediatric population. Wouldn't this be a lovely population for

someone at the Eye Institute or elsewhere to try to develop a quality of life system?

DR. CHEW: That takes a lot of resources and a lot of time. So, it is not so simple. I think that the NEI FQ took several years of just field testing and focus groups. It took almost five years before it was developed. So, unless the sponsor is willing to wait for five years, I don't think you want to do that. But that is a challenge.

DR. GATES: I would concur that delves very deeply into social sciences beyond my scope. Dr. Gorman, I will pass to you.

DR. GORMAN: I defer to my colleague on the right. I wrestled with this question more than almost any of the other questions on the list, especially since the reality is that assuming the drug or other drugs are effective and they don't arrest progression, they just slow progression, the quality of life for both of these groups is going to deteriorate. Pharmaceutical companies and myself are always looking for things that improve quality of life, but in this particular case, if it is a sensitive measure and it actually works, the quality of life will be deteriorating but just not as much as in the other group. So, it is going to be a very difficult thing for the marketing force to go

out with to say, "oh, if you use this you'll only be half as unhappy as if you don't use this."

[Laughter]

So, it posed some difficulties for me. I think there are global indexes of the quality of your life that are available in pediatrics that are not very sight sensitive, but they are there and they have been validated, but they are global and I am not sure how many of the questions are going to be specific enough that the visual acuity is going to factor into it. But I would continue to look at participation in sports, cessation of activities that people used to do. Adults generally find that they need glasses when they stop reading and start watching television at night and then they realize that perhaps something is wrong with their eyes; they can't read anymore in the dark or maybe they go to restaurants and they can't read the menu. But I think one of the things I would be looking for, for my personal thing, is activities that were ceased and see if the treatment group ceases fewer activities than the non-treatment group.

DR. GATES: Dr. Miller?

DR. MILLER: I would be particularly interested in reading and near activities. I don't know of any scale for that but, you know, how long they spend doing the Game Boy

or something. I am afraid it is going to affect some level of near work, from what I have heard. I do know some generalized scales on quality of life in kids in the diabetic population. I have seen some scales used even for children who don't write yet, looking at pictures--"are you more like the child on this side or that side" in the book. So, there are measures out there but it is not something we have used in ophthalmology at all. It might be adaptable.

DR. STEIDL: I think that quality of life is probably the most important issue, as is true of virtually everything that we do, but it is commonly not measured or measured well. This would be no exception, although I am not sure that it is measurable. So, I would be skeptical. Validating something that would be a reliable instrument might be out of the scope of what is possible, as Dr. Chew said. So, I don't know, I think it is important but I am not sure that it could be done, but you might run some pilot studies looking into the possibility of seeing how certain instruments or at least modified instruments could work.

I am kind of concerned though about other things, and I think that they have to be followed. I know we are just generalizing here, but would medication affect growth? Would it affect psychology? Would it affect irritability? There are many other things that I think would need to be

assessed that could come into the purview of quality of life but I don't think they are the kind of things you are going to ask a child. They may have to be objectively measured in some way.

DR. GATES: Dr. Miller, do you have another comment?

DR. MILLER: There probably are attention span indices that are pretty objective, if you were talking about reading scores and attention span--I had a psychology background in college but it was a long time ago.

DR. GATES: Dr. Feman?

DR. FEMAN: Yes, just another comment because someone commented and I don't know if it was picked up at the microphone earlier, if we are talking about quality of life evaluations in children in this type of a study, we have to incorporate quality of life evaluations in the family because this child is not going to be putting the ointment or drops in their own eyes. So, one needs to extend this to not just the child but the family involved.

DR. GATES: Dr. West?

DR. WEST: I am sorry, I thought the question was quality of life of high myopia which was the outcome, and I think the conversation is getting on to quality of life

during treatment and I was looking for direction on which one we are being asked to discuss.

DR. CHAMBERS: As you have probably figured out, we are interested in both aspects.

DR. GATES: Well, thank you, all. We are going to take a ten-minute break now and we are going to convene promptly and finish the questions after that. Thank you.

[Brief recess]

DR. GATES: Thank you, we will begin, now that we are back in session, with question 12. How frequently should assessments be made? We will start with Dr. Miller, on my right, and we will go down toward my left and end with Dr. Steidl.

DR. MILLER: I would suggest that assessments be made every six months. Then, I like the idea of the 30-month endpoint for the study, but I do think that for the rebound effect I would favor a year out. But I also think that right after the start of treatment an assessment within the first month, and then you could also check the vision with that new pair of glasses as kind of a double check on things too, but also check compliance and all the other basic study things. You want to make sure they are doing the study and you have connected them. But in terms of measurement of change, I would probably recommend

cyclopleging them every six months and doing an auto refraction.

DR. GATES: Dr. Gorman?

DR. GORMAN: I think efficacy measures every six months is very reasonable. I think safety measures, every month for the first year, to be combined with dispensing of the medication and, therefore, measuring compliance because I think compliance in a twice a day drug over three years, with no--how shall I put this?--no hope of getting rid of glasses that you already have may become a major issue for the completion of the study. So, efficacy every six months; safety every month for the first year, combined with dispensing the drug and compliance measures.

DR. GATES: I am comfortable with the assessments being made every six months. Dr. Feman?

DR. FEMAN: I agree with what you have already discussed. I think Dr. Gorman raised a very important point though about having the family and the child return every month for safety measures and also to verify compliance during the introduction to the study. Whether that is for the six months of the first year I don't know but it needs to be done like that to be sure it is being done.

DR. GATES: Dr. Chew?

DR. CHEW: I would agree that the six-month visits for endpoint measurement is good but I question the monthly. As a clinical trialist, that is not easy, to have someone come back on a monthly basis. There could be telephone calls. It also depends on what adverse effects you are talking about as well. That also leads into the issue of rebound as well and how often would you do that afterwards. I think that has to depend. Some of the data they already have perhaps can help with that. I think it is hard to come up with hard and fast rules, but every six months at least for the endpoint and then, depending on what adverse effects you have, you can tailor that.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: I think outcome measures every six months is more than enough. I could even be persuaded to go annually since we are cyclopleging and looking at something that seems to be progressing relatively slowly. As far as safety measures, obviously you might want to front-load your schedule a little bit and have a one-month visit but maybe six-monthly visits thereafter for safety issues. Obviously, compliance is going to be so important that I expect any self-respecting sponsor would work pretty hard at that and do whatever it takes, with people calling up and diaries and

give them a video, showing them putting a drop in every morning--I don't know.

DR. GATES: Dr. Gordonson?

DR. GORDONSON: I think six months is a good idea, but certainly for compliance it probably will depend on experience--judge how much fluid is left or ointment is left and being on the phone, and all that, but I think six months is very long to go unless you do something about compliance, whether it is one month or two months, or if you learn how compliant they will be as time goes by.

DR. GATES: Dr. West?

DR. WEST: I too am comfortable with the every six months assessment. As a mother of two, I think that compliance is going to be a big issue. Even for something that hurts my child, like an earache or sore throat, it is difficult to comply with ten days of twice a day treatment, let alone three years or years and years in the very end. So, I think if there is a dose meter or if the sponsor's medication were to be in a liquid gel that could be sensitive to a tilt meter, that might be good, or perhaps weighing the residuals that come back to see how much, in fact, was used. It wouldn't negate against dumping of the medication to feign compliance. One could also survey not only the care giver but also the child separately. For

instance with patching, when parents come back and say that they have been patching but when I put the patch on and the child asks, "what's that?" I know the compliance has not been--

[Laughter]

DR. GATES: Dr. Plott?

DR. PLOTT: Probably the visit schedules are going to be driven by the need to get a new tube of medication and, you know, look at compliance from a practical standpoint and the evaluations only to the experts.

DR. BULLIMORE: I am perfectly comfortable with just measuring one eye and cyclopleging that every outcome measure visit. How do other people feel about that, or do you want measures on both eyes?

DR. FEMAN: Are you planning to test the drug in one eye of the child or both eyes of the child?

DR. BULLIMORE: Well, there is a rule of diminishing return when, you know, you try and analyze data from two eyes. Certainly, if you are worried about respondent burden, dilating one eye in a patient to get an outcome measure is less of a burden from the point of view of the rest of their day than dilating both of their eyes. So, assuming the effect is going to be correlated in the two eyes, personally, I would seriously consider just doing the

outcome measures on one eye and doing the cycloplegic auto refractions on one eye, whatever we thought the schedule was appropriate.

DR. GATES: Dr. Miller?

DR. MILLER: I disagree because one of the things in children that is very important is keeping the balance set between the two eyes so that you don't have a preference for one eye over the other. So, if one eye is changing--you want the eyes to be the best balance possible. It mostly applies to the younger kids. In most kids you don't notice any change in their behavior with Cyclogyl in terms of going back to school. I just say you can't take a test today. But within three hours they are fine. The pupil is big for a long time. So, I would advocate checking both to keep the glasses with the same level of currency if you are going to change them.

DR. BULLIMORE: Yes, I am assuming, and this might be wrong, that one might be prescribing glasses for the child independent of the outcome measure. For example, in the COMET trial there was a patient care team, I believe, that took care of the glasses and then there was a master examiner who did the cycloplegic auto refraction. Again, Dr. Gwiazda, I apologize if I got that a bit wrong. But that is not uncommon in trials of this kind. Obviously,

there is a concern for the ongoing care of the child and they are going to get the usual standard of care in terms of their refractive needs, but in terms of cyclopleging an eye every six months to get an outcome measure, if there is no, or limited, statistical benefit of taking those measures on both eyes, then it can minimize the respondent burden by just doing one eye.

DR. GATES: Dr. West?

DR. WEST: I think that there would need to be very strict guidelines as to spectacle prescription and on what one was basing it because that would be a potential confounding variable. If you were under-minusing that may accentuate any treatment effect of the proposed medication. So, if you decided that you would only do one eye each six months, you would have to have times when you changed spectacles either for loss, breakage or something like that. So, you would need the data from both eyes in order to give a balanced refraction.

DR. GATES: Dr. Steidl?

DR. STEIDL: I think that is an extremely interesting issue, the idea of doing one eye. I would defer to someone who knows more about statistics of clinical trials, but it is intriguing. I would suspect the epidemiologists that I work with would want both eyes.

I think the every six-month exam would be okay. You would have to have separate safety and compliance exams or phone calls. The alternative would be front-loading it so that you do it all in exams, maybe one month, six months, 12, like that.

DR. GATES: Any other discussion? Well, let's go on to number 13. Trials should be of adequate duration to determine whether a therapy slows myopic progression, whether the effect is permanent as opposed to shifting the curve to the right, and whether there is a rebound effect after discontinuation. Assuming a best-case scenario where the drug product halts the progression of myopia, what would be the minimum? I would like to start with Dr. Miller again, if I may.

DR. MILLER: I think that the 30-month duration proposed by the sponsor is really quite reasonable. My preference though would be for doubling the follow-up interval after treatment and then having some sort of monitoring for a longer period, but to have data presented on up to a year after treatment to understand the drug.

DR. GATES: Dr. Gorman?

DR. GORMAN: I also like the 30-month duration. If the treatment effect changes the slope by half it will

give an outcome measure that we, I think, agreed would be both clinically and statistically significant.

The follow-up after treatment in the active part of the study, I think six months to a year is reasonable because of the concern about rebound and, more than rebound, determining what the new slope of the line would be in terms of the progression of the myopia.

I understand the difficulty of this and I certainly wouldn't make this a condition of approval of the drug, but I think there needs to be an endpoint that is somewhere further down the line to see what the final number is, whether it is what they predicted. If the lines diverge during the treatment and don't converge during the one-year follow-up, is the outcome different at 16 years of age? In other words, did you do anything at the final endpoint, if 16 is the point at which juvenile myopia stops progressing?

DR. GATES: I would like to echo that the 30-month period is very doable and I think that is valid; also, with the 12-month follow-up rather than the six-month. Dr. Feman?

DR. FEMAN: I agree with what Dr. Gates just said.

DR. GATES: Dr. Chew?

DR. CHEW: I think 30 months is reasonable. I don't know how ethical it is, I have been told it is not

ethical to re-randomize these patients and have half of them stay on the drug and see what happens if you continue for another year-plus, compared to those who don't have the drug and see what happens with the rebound effect; whether the slope is different. If you kept them on, is there more suppression of the myopia? I think that 30 months seems reasonable but you may need longer than that and I think that may be something you might consider doing.

DR. BULLIMORE: I will echo those sentiments. You know, we saw one study design presented and for the effect size 30 months seems reasonable, but I am sure a different sponsor or the same sponsor may come back with a different design, different sample size, different criteria. Six months or 12 months for the washout follow-up.

I like the idea that Dr. Chew proposed for randomizing the treatment group to continuation or cessation of the treatment. Again, using the parameters presented by the sponsor today, I think that we should have a bucket-load of subjects available. The sample size can be driven by the safety aspects. If we are looking at long-term effectiveness of the drug we should be able to randomize the subjects once again and get some meaningful information. Now, whether that is handled in a pre-approval situation or

as part of a Phase IV study, I don't know, but there is certainly some wriggle room around here.

DR. GORDONSON: I think the 30 months is fine, and follow-up treatment, six months, and if there is an abrupt change we would probably hear from the patient anyway, so I think those are two good numbers.

DR. GATES: Dr. West?

DR. WEST: I agree with Dr. Gordonson.

DR. GATES: Dr. Plott?

DR. PLOTT: I will take a different point of view. Speaking generally maybe not just for this drug but other drugs that are studied in this indication, the duration of the trial should reflect the type of outcome that is expected.

On sponsor's slide number 51, they anticipated a 50 percent effect. Let's say that that effect was, you know, a 75 percent effect, I think a clinical trial could be done of a shorter duration than 30 months, or whatever the duration should be would be driven by the expected difference in the power of the clinical study to detect differences between active and controls. So, if there was a significant benefit, or let's say that we came across a product that simply halted the progression of the condition, then that might be something that we want to take to the

market more quickly because the risk/benefit favored the product so strongly. So, thinking broadly, I think it has to be driven by the anticipated differences and could be shorter depending on what is anticipated.

Where that comes from though is from good Phase II clinical trials, dose-finding trials where there are statistical trends that are developed on different doses and there are observations about what might be expected over a certain period of time or in a certain population with a certain concentration. So, I think it can be calculated not blindly but with the help of those Phase II clinical trials.

DR. GATES: Dr. Steidl?

DR. STEIDL: I am equally interested I think in what happens when you stop the drug as to what is happening when you are giving the drug. So, I might differ from a few of the folks here. I understand the issues of cost and time. If you had six-month follow-up it might be one data point and it is hard to know exactly what that means unless it was dramatic. I might even be willing to hedge on the 30 months just to get a little bit more time on the other side. So, I would think you would probably want to follow for at least a year, preferably for me maybe longer, but I don't know what is feasible. But, you know, the 30 months would

be adequate, as far as I am concerned, for the primary trial.

DR. GATES: Any more discussion? For question 14 I would like to begin with Dr. West. I will read the question and we will come back toward my right. Refractive errors prior to age 7-9 years old may cause or correct amblyopia. Individuals ultimately developing high degrees of myopia frequently demonstrate refractive errors prior to ages 7-9 years. Should children who are still at risk for developing amblyopia be studied, or should studies be limited to older children?

DR. WEST: I think it is fine to include children who may be visually immature still, and those may be children that are less than 6 or 7 or it may even be children who are less than 10-15. We don't know when children become visually mature yet. The old dogma is that it is at 6 years of age but, in fact, it is probably older than that and it probably varies from individual to individual. So, I think as long as the child receives the treatment in both eyes it is fine to treat children who are not yet visually mature. But I would be against a study that was designed where each child acted as their internal control for, if there was a treatment effect, it would have the potential to cause emmetropia, although the amount of

effect that has been anticipated would not be likely to cause anisometropia that would cause amblyopia. I think it is pretty remote, but still I would not want to see children receive one eye control and one eye drug.

DR. GATES: Dr. Gordonson?

DR. GORDONSON: I have never seen a myopic child get amblyopic from the myopia, that is, if their eyes are perfectly aligned, of course. You do see in older individuals who have high degree of myopia something which appears to be amblyopia to a mild degree, which probably has to do with the fineness or coarseness of the retinal mosaic because of the stretching of the retina. I don't know what myopia has to do with amblyopia if the eyes are perfectly aligned because I have never seen it.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: I don't really believe there is too much of a risk here so I don't think this is something we should worry about. But I do agree with Dr. West that doing treatment in one eye and not the other is probably not the way to go for a number of reasons that I won't go into.

DR. GATES: Dr. Chew?

DR. CHEW: I don't have anything more to add.

DR. GATES: Dr. Feman?

DR. FEMAN: I agree with my colleagues, but let me just add one other aspect. This is the reason why I thought we would need to be evaluating both eyes in the children whenever they came back for the repeat part of the study, rather than just doing one eye evaluation because of the fear that there may be something developing that you are not picking up.

DR. BULLIMORE: Just to clarify my one eye comment earlier, I wasn't advocating treating one eye; I was just, from a statistical and practical point of view, assessing the outcome in one eye only. I apologize for any confusion.

DR FEMAN: I understand, but what I am getting at is that we need to assess the outcome in both eye because of the slight risk. Even though you are treating both eyes, you are treating a child that potentially has a chance to develop amblyopia. We don't know what is happening in their home and I think you need to be assessing both eyes every time the child comes in.

DR. GATES: Dr. West, do you have a comment?

DR. WEST: I think that Dr. Feman is correct and that it may be easier for the parent to get it in the first eye or the second eye. There may be more of an effect in one eye due to differences in the way the medication is administered.

DR. GATES: Any other comments? I am most comfortable with both eyes being treated and followed. I know that amblyopia would be an extremely low risk but that is not acceptable to my thinking. Dr. Gorman?

DR. GORMAN: Disagreeing with my learned colleagues, I am still intrigued by the one eye study in older children once they have become at least partially visually mature. With this rate of follow-up that we have suggested with six months of refractive exam, I think the chance of developing such a difference in refractive error as to develop amblyopia would be minimized, and it would be the most rapid way of showing a treatment effect because you would see divergence between the progression in two eyes with each person acting as their own control.

On the issue of examining both eyes, I think that there is an absolute need to examine both eyes. If 85 percent of the American population is right-handed there is a chance that just that one factor alone will influence which eye you are more effective in getting the medicine in. If you are preferentially always putting it in one eye prior to the other, there is a chance of having a different treatment effect.

DR. MILLER: I have changed my thinking listening to the people here. I don't think there is really any

chance of getting amblyopia on a refractive basis because we are excluding anisometropia from the beginning. So, they are going to be in the same ball park whatever happens with the medicine. But if there is a cycloplegic effect from the medicine that is significant, we do know that if we treat kids with atropine there is the potential of inducing amblyopia in the treated eye. So, we should be following both eye and just making sure that the best corrected vision remains good throughout the study, mostly because we are treating healthy kids.

DR. GATES: Dr. Steidl?

DR. STEIDL: Well, strictly answering the question, I don't know what "prior"--how early that means. But it seems that in general, as the others have said, the risk of amblyopia in the parameters that we have discussed is very low. So, I don't think that it is a big risk and I don't think it should be limited to older children.

DR. GATES: Dr. Plott?

DR. PLOTT: I will pass.

DR. GATES: Any other comments on question 14? Then we will move on. Question 15, given the potential for wide use in a pediatric population, what level of adverse events should clinical trials in this area be designed to detect, 1 percent, 0.5 percent, 0.1 percent, 0.05 percent,

0.01 percent, 0.001 percent, 0.0001 percent? We will begin the discussion again with Dr. West.

DR. WEST: What type of adverse event are we discussing? Are we discussing burning on installation or are we talking about something that is sight- or life-threatening? Are we talking about an SAE or not?

DR. CHAMBERS: Just the ability to pick up any adverse event; in fact, to study enough patients to even note low frequency adverse events.

DR. BULLIMORE: From the point of view of the agency, could you define adverse event and differentiate it from a complication?

DR. CHAMBERS: They are the same as far as the agency is concerned.

DR. GATES: Dr. Miller?

DR. MILLER: I haven't done this before, what levels do you usually use as your standard in similar trials? Because I think we should be a little bit on the strict side because we are doing healthy children.

DR. CHAMBERS: The ICH guidance documents say in general that we should be treating, in the overall drug development, at least 1,500 patients and should be treating 300-600 patients at least for the initial duration, and 100 patients for six months for long-term therapies. From an

ophthalmology perspective, we generally have had an absolute lower limit of 300 patients studied during the duration that you expect to go on in order to be able to determine a one percent adverse event rate. If you study 300 patients you have a 95 percent chance of detecting one event at a one percent rate. So, if you study 300 patients the odds are you will see at least one patient with an event. Whether you will recognize that that was really attributable to the drug or not because of one event is questionable but the odds are that will come up. If you wanted to look for events that are lower than that, you have correspondingly higher numbers of people you need to study.

DR. GATES: Dr. Steidl?

DR. STEIDL: Just for clarification, if you have a condition that might occur, like a retinal detachment, in 1/1,000 or 1/500, how does that relate to this? Would that 1/1,000 be 0.1 or is it more complicated than that?

DR. CHAMBERS: No, that is correct, 1/1,000 would be 0.1 percent. If you wanted to make sure that you were going to at least see one of those cases you would need to study 3,000 patients. There is a direct relationship between these percentages and the number of patients you would need to study in the overall program.

DR. GATES: Dr. West?

DR. WEST: So, then now I can answer? So, I would say that it depends upon the event that you are looking for, especially since you are treating healthy children. If an adverse event is as meager as burning on installation, I would like to know about that, but if this is a muscarinic antagonist and if it caused bowel obstruction that was severe enough to kill the child, I would want to know at a frequency of, you know, 1/10,000 or 1/100,000. I mean, suppose you gave eye drops to prevent myopia and you killed kids with bowel obstructions?

DR. CHAMBERS: The difficulty is we won't know before the trial runs--

DR. WEST: Right.

DR. CHAMBERS: --what events we are looking for. I mean, we tell people to look for everything but we don't know ahead of time what events or at what frequency they are likely to occur.

DR. GATES: Dr. Gorman?

DR. GORMAN: I think there is another layer of complexity that we haven't begun to address. If I had to guess, the most common adverse event from this agent will be eye burning or eye irritation. It will be followed by conjunctivitis, a disease I see in my population every day without taking drops. Then there will be some number of

corneal lacerations from getting the applicator too close to the eye in a struggling 6 year old. Then there will be some small but probably real global punctures from this particular administration, especially in year 6 when I just don't want to do this anymore. All those things--because the eyes are so emotionally charged for most parents, you know, it is one of those organ systems that is very emotionally charged--are going to get reported with very high frequencies, both conjunctivitis and corneal irritations, lid swelling, eye redness so that there is going to be a difference between adverse events and differences between the rate in the treatment group versus the placebo group that is going to make this a lot more difficult. That didn't answer your question at all, I know.

DR. GATES: Dr. Plott?

DR. PLOTT: One other thing that is important for the committee to remember is that while it is very important to understand why adverse events might occur and to observe that during the clinical trial, after any product is approved there is a safety surveillance. Now, it is not as rigorous as what is in the clinical trial but now sponsors typically collect all adverse events regardless of how minor. Those adverse events are collected, put into a database. Whether or not they are related is immaterial.

For the first couple of years anyway those adverse events are reported on a quarterly basis or very frequent basis and then they are reported annually for the duration of the life of that product. So, it is not as though when we stop clinical trials we stop learning. There is also an ongoing learning process that does have an impact in labeling as appropriate. But it is important also to realize that that is not done with the same kind of rigor that is done in a clinical study.

DR. GATES: Dr. Chambers, if we were looking at an antibiotic in this patient population what would be a typical target number?

DR. CHAMBERS: As most things in life, it depends. In the case of anti-infectives or antibiotics, it depends on how much we know about the compound ahead of time. If it is a product that has already been systemically administered at concentrations that are much higher than what is going to be given topically, we have not looked for as many patients to be treated. That is where we get the more typical 300-500 number of patients because we have systemic information at a much higher concentration. The same is true of some of our beta blockers. We have a number of medications that have been studied systemically before they ever come to the eye.

For things that are new to the eye, we tend to raise those numbers and it depends on what we think the overall potential pharmacological activities are and what the population is. Yes, there is a tendency to study more patients as we go down in age because we are more risk averse.

DR. GATES: Dr. Miller?

DR. MILLER: In the studies that were done overseas was there any preliminary information that would be helpful to us? I haven't heard anything about that.

DR. CHAMBERS: Except that we are looking for guidance for all products, not necessarily this product.

DR. MILLER: Right. So, the answer is there is a range of answers depending on how much we know. We don't know anything now so we have to pick one percent.

DR. GATES: But I still think, even though we are not doing this in terms of this one pharmacological agent that has been evaluated overseas, that could give us some guidance as to drugs of this variety that are being used for this purpose. Do we have any data regarding anything like that?

DR. CHAMBERS: Well, any of the compounds we have very rarely start just at a Phase III trial. We have some initial information from earlier trials but they also tend

to be in smaller numbers of patients. The issue with rare adverse events is if you don't study enough people you don't really have a chance of seeing them. So, you don't know what it is you are missing.

DR. BULLIMORE: Basically, study enough patients till you see something. I am being facetious, I apologize. If I give you a number can I go home? I mean, I think one percent seems reasonable but we are being asked to give a number. We have in our mind the protocol given by Novartis this morning. I mean, clearly, if this company or another company were to come along with something with perhaps a higher risk profile than a selective anti-muscarinic, then we might be a little bit more concerned. But for the kind of things that are being talked about in the context of the data presented today, then one percent seems reasonable. If it is stuff with growth factors in there, then maybe higher. I don't know. Am I going in the right direction, Dr. Gorman?

DR. GORMAN: I like the one percent number for a lot of reasons, but also realize that for a product that we may be talking about today in the sense that it is a "maybe" product, you are talking about one percent over ten years, which is a really high burden to bear because if the product is going to be used for the ten years of developing myopia

that is going to be a long burden. But I still like that number.

I like that number for eye toxicities. I don't like that number for systemic toxicities. So, the bowel obstructions that were talked about, or growth interruption, or intellectual functional loss, or school failure, or increased juvenile delinquency, hair loss--

[Laughter]

--if there are those, I think those numbers have to be less common. The benefit is in the eye so I will accept a little more risk in the eye but I will not accept as much risk to the rest of the body.

DR. GATES: Yes, Dr. Bull

DR. BULL: I just wanted to revisit a point that Wiley had made earlier, and also just to make the distinction between the kinds of numbers you would look at if, say, there was a large treatment effect you won't need a lot of numbers, potentially not need a lot of numbers in the studies. There is still a number that you need of exposure. I have certainly had applications that have been in for review by our divisions that have raised issues just because there were not enough people exposed to the product. Even though the study design was able to evidence an effect,

there was still an issue of numerically having enough patients exposed to the product.

You know, just to revisit, we also operate on what are called the ICH, International Conference on Harmonization, guidelines which, for chronic therapy, advise to have in the ball park for safety purposes between 300-600 at six months and a minimum of 100 at 12 months. That would be a bit different given that, you know, we are probably looking at several years of the trial being under way for these products. So, in terms of how long you would need and how many patients you would anticipate you would need to enroll because you are probably going to have a significant number of dropouts in these kinds of studies as well.

DR. GATES: Dr. Gorman?

DR. GORMAN: The search for rare events is one of those "Holy Grails." Having been involved in the rotovirus study as an investigator, there were 5,000 people in the study and we still missed the rare events. We were talking about he signal to noise before. The signal was there in the clinical data when we went back and looked at it the second time with the irritability after the dosing of the rotovirus vaccine but we missed it until over a million doses were given.

So, I appreciate the agency's quest for safety data, but has there ever been a study powered, looking at safety of rare events, and the answer is no. The International Conference for Harmonization gives you guidelines for numbers to look for to make you feel better.

DR. BULL: I would cite as an example that we have had some large outcome studies that have been done that have enrolled in excess of 10,000. There is one ongoing that has enrolled about 18,000. There are studies that are designed to look for rare events.

DR. GORMAN: It is a "Holy Grail" that you are not going to reach because, no matter how large the study is, when it goes out to a million people the next level of rare events is going to rear its ugly head. So, I am not sure how rare you want to get. I think a one percent number is reasonable to look for in a clinical trial, knowing that there is surveillance, both active and passive, after a new drug comes out. Your own numbers through the reporting system indicate that when a new drug gets released the number of reports of adverse events is pretty high. Then, as the drug goes out into use for many years, those numbers drop off. People are looking for adverse events--I am not going to say they look for them but they are more aware of adverse events when they start using a new drug.

DR. GATES: Dr. West?

DR. WEST: As a parent and a physician, I would be unwilling to accept adverse events for a disease that does not kill or maim you. Whereas I would be willing to accept serious adverse events for something that might save my child's life, like a treatment for cancer, if we are talking about not needing glasses as much it had better be really safe. So, I wouldn't necessarily be comfortable with a one percent detection. I mean, with the potential widespread use of this, even if you didn't detect it in your clinical trials, when it was released there would be such a large number of doses of this taken that you might find some very serious adverse events. So, I think for something that is such a benign condition as myopia, our tolerance should be less.

DR. GATES: Dr. Gordonson?

DR. GORDONSON: I think one percent is right, as others have said.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: One percent.

DR. GATES: Dr. Chew?

DR. CHEW: I think one percent is reasonable but I think it would be good if we had other data in other drugs that give you any sort of inkling before you prejudge one

percent as being the only one--if there is some inkling of anything that may be possible, then I think you have to go to a larger sample size to make sure you are not missing that rare event.

DR. GATES: Dr. Feman?

DR. FEMAN: I think one percent is reasonable. We are talking about a drug that is going to be applied twice a day to however many hundreds of children for a three-year interval approximately and I think one percent is going to pick up certainly what we are looking for.

DR. GATES: One percent. Dr. Gorman?

DR. GORMAN: One percent, again realizing it is one percent over ten years of therapy. So, over a three-year trial maybe it is a third of a percent.

DR. GATES: Dr. Miller?

DR. MILLER: I agree with the one percent. I would love to take under advisement any information from overseas trials for whatever drug was brought to be investigated, but one percent is what I go with now.

DR. GATES: Dr. Steidl?

DR. STEIDL: I am very concerned about what Dr. West brought up because we are basically taking, from my point of view, a relatively healthy eye and we are doing something to it in a chronic method. I think we really have

to be very cautious to be convinced that this is a safe product.

Just for a point of clarification, when you say 300, are you talking about a total of 600, 300 in each arm, or 3,000 would be a total of 6,000? How does that work?

DR. CHAMBERS: We are talking about 300 on drug.

DR. STEIDL: Okay, so it is really double that for the trial.

DR. CHAMBERS: Assuming you have a 1:1 randomization, yes.

DR. STEIDL: I would be tempted to possibly go to 0.5.

DR. GATES: Dr. Plott?

DR. PLOTT: I don't have anything else to add.

DR. GATES: Any more discussion on question 15A? We will go on to question 15B in the same order. Would this answer change for a product which demonstrated a reduction in the frequency of retinal detachments? Dr. West?

DR. CHAMBERS: I will just remind you, you threw out those endpoints as a potential endpoint. You can continue to answer the question if you want, but since you said there wasn't an acceptable use of those as an endpoint I am not sure that that question has relevance anymore.

DR. WEST: Because that is not our endpoint.

DR. GATES: That is fine. Are there any more comments from the FDA, any more questions that we could help with?

DR. CHAMBERS: I just want to make sure there is the opportunity for people--I mean, these are the questions that we came up with prior to starting this. If there are comments or if there are other questions or other things that you believe we should have talked about or asked, we would like to hear that before you leave.

DR. GATES: Dr. Bullimore?

DR. BULLIMORE: We have talked about safety issues without really saying what we might do to ensure safety. I threw some things out earlier like measuring accommodative function, some tests of near vision, monitoring things like school achievement. I mean, if we are trying to retard the growth of the eye, is it unreasonable to measure the height and weight of the child? I don't know. I leave that to the pediatricians.

I think measuring visual acuity is important, using an age appropriate test; probably measuring uncorrected acuity at least potentially as a surrogate measure. We were talking about refractive error and we have seen some data on how closely that is related to uncorrected visual acuity, but I guess the sponsor should have the

option of collecting some data to make that point more compelling.

Other things, I mean, I am not suggesting retinal photographs but tests of retinal function other than visual acuity that we should be doing. Should we be doing tests every year on these kids to make sure there are no early retinal changes? I am just thinking aloud, which is probably a mistake.

DR. GATES: Dr. Gorman?

DR. GORMAN: With this new class of agents in what is described as a healthy population, other than their one disease, I think that the performance of this trial without a truly independent data safety management committee would be a mistake.

I have talked before about front-loading the safety collection data at once a month, and I think that would put to rest a fair number of my anxieties about embarking on this new era. I do think myopia is a condition that parents will choose to treat, and I do think that there is a place for this drug assuming it is effective and has few side effects. But until I get to that place I would like to make sure that the data for the safety is collected early and often and independently reviewed.

DR. GATES: Any other comments? Well, I want to thank you, all, for attending today, and I want to thank Novartis for their presentation. I want to thank the FDA for their guidance with the questions, and we hope that our time was helpful to you, all.

DR. CHAMBERS: Again, I just want to thank everybody for taking the time to come and give us your comments, and for all the thought you have given before coming, and wish everybody safe travel home. Thank you.

DR. GATES: Now we will adjourn.

[Whereupon, at 4:00 p.m., the proceedings were adjourned.]

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