

AgingEye Times

Affiliated with University of Illinois at Chicago



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FDA
Dermatologic and Ophthalmic Drugs
Advisory Committee

September 25, 2003

Study Designs of Trials in the
Treatment of Myopia

Briefing Document

For Public Disclosure Without Redaction

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List of abbreviations

AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
BSVA	Best-spectacle corrected visual acuity
CDRH	Center for Devices and Radiologic Health
CNV	Choroidal neovascularization
COMET	Correction of Myopia Evaluation Trial
D	Diopters
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HANES	National Health and Nutrition Examination Survey
ICH	International Committee on Harmonization
IOP	Intraocular pressure
LASIK	LAser in Situ Keratomileusis
NEI	National Eye Institute
PAL	Progressive Addition Lenses
RSVP	Refractive Status and Vision Profile
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SER	Spherical equivalent refractive error
UCVA	Uncorrected visual acuity
UK	United Kingdom
US	United States
VA	Visual acuity
WHO	World Health Organization

1 Purpose

The main purpose of this document is twofold. It is to:

- Provide background information on myopia
- Provide a rationale and study design for a pharmacological treatment for juvenile onset myopia.

Novartis has been studying myopia for many years and considers it a serious ocular condition that warrants the development of new therapies. Based upon discussions with various experts around the world, as well as with Health Authorities including the Food and Drug Administration (FDA), we are proposing a clinical trial design that we believe is adequate to assess the safety and efficacy of a pharmacological treatment of myopia.

2 Background

2.1 Introduction to myopia

Juvenile onset myopia, or shortsightedness, is defined as refractive error where parallel rays of light come to focus in front of the retina due to axial elongation of the eyeball, resulting in blurred vision. This does not include myopia secondary to other ocular, systemic, or neurodevelopmental conditions which are outside the scope of Novartis' research. Juvenile onset myopia usually occurs during the ages of 6 to 16 years (school-age myopia) with mean cessation ages ranging from 14.44 to 15.28 years for females and 15.01 to 16.66 years for males ([Goss and Winkler 1983](#)).

The axial elongation results from uncontrolled growth of the sclera and leads not only to the refractive error in the optical system of the eye but also to stress on the tissues of the eye due to the resulting anatomical defect ([Figure 1](#)). Depending on the degree, this stress can lead to serious ocular complications later in life. While refractive error is most significant to the myopic patient, this defect is merely a symptom of the underlying pathophysiologic changes. These changes have the potential to lead to long-term complications such as retinal detachment, retinal degenerative changes, glaucoma, and cataracts. The stages of myopia have commonly been categorized as low (-0.50 to less than -3.00 diopters (D)), moderate (-3.00 to less than -6.00 D), and severe (more than -6.00 D).

Myopia is highly prevalent, increasing with age until maturity ([Negrel, et al 2000](#)). Refractive errors are one of the most common causes of impaired vision in the United States (US), affecting approximately 25% of persons aged 12 to 54 years old ([Sperduto, et al 1983](#), [Wang, Klein, and Moss 1994](#)). Myopia is a significant problem, not only because of its high prevalence, but also because it can contribute to visual morbidity and increase the risk of vision-threatening conditions. Although many researchers agree that children's refractive status is in part genetically determined, evidence shows that visual experiences early in life (i.e., amount of near work) may affect ocular growth and eventual refractive status ([Mutti, et al 2002](#)).

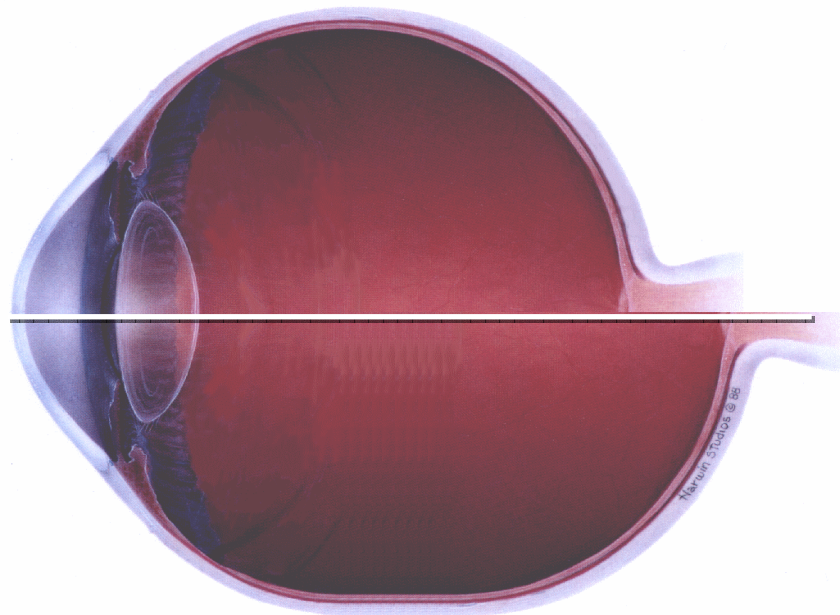
As the fifth most frequent cause of registrable blindness in developed countries ([Curtin 1985](#)), myopia is recognized as an important health concern by many public health organizations.

The World Health Organization (WHO) has selected five conditions to study with the goal of eliminating avoidable blindness. Refractive error is one of these conditions. Indeed, patients with myopic retinopathy are legally blind for an average of 17 lifetime years, compared to 5 lifetime years of blindness due to diabetes and age-related maculopathy, and 10 lifetime years from blindness in glaucoma (Green, Bear, and Johnson 1986).

The National Eye Institute (NEI) has included support for myopia-related research in its 5-year strategic program. The NEI plans to “identify human risk factors of myopia and abnormal eye growth and evaluate promising treatments for preventing the onset of or slowing the progression of myopia, such as special spectacles or contact lenses or pharmacological treatments” (National Advisory Eye Council 1998). The annual cost of myopia in the US is approximately \$4.8 billion” (PolyTech University-Hong Kong 2003).

Figure 1 **Normal versus myopic eye**

Shorter / Rounder Emmetropic Eye



Longer / Oval Shaped Myopic Eye

2.2 Prevalence of myopia

As part of HANES (National Health and Nutrition Examination Survey) conducted by the National Center for Health Statistics in the US from 1971 to 1972, eye exams were performed on 9,882 of the 14,147 person sample. From this dataset, the prevalence of myopia in the US, in persons aged 12 to 54 years old, was estimated to be 25% (Table 1). Whites had substantially higher rates than blacks, and women had significantly higher rates than men up

to the age of 35. Interestingly, the prevalence of myopia increased as family income rose and also increased markedly for all age groups as the number of years of school completed rose. With respect to geography, the prevalence of myopia seems to vary by country (Table 2; [Wilson et al 1989](#)).

Table 1 Prevalence of myopia in the US

Race and Sex	All ages	Age 12-17	Age 18-24	Age 25-34	Age 35-44	Age 45-54
All Races						
Both sexes	25.0%	24.0%	27.7%	24.2%	24.5%	24.8%
Men	22.8%	21.7%	22.5%	20.2%	26.1%	24.4%
Women	27.1%	26.4%	32.5%	27.8%	23.2%	25.1%
Whites						
Both sexes	26.3%	25.8%	29.7%	25.6%	24.9%	25.5%
Blacks						
Both sexes	13.0%	12.0%	10.4%	12.3%	14.8%	17.3%

Source: [Sperduto, et al 1983](#)

Table 2 Prevalence of myopia by country

Country	Myopia %
China	70%
US	25%
UK	27%
Sweden	33%
India	22%
Israel	18.4%
Germany	13.8%

Source: [Wilson and Woo 1989](#)

2.3 Natural history of myopia

Progression of myopia is highly variable among individuals. Once myopia appears in a child, it almost always increases in severity ([Bücklers 1953](#)). Generally, a progression rate of -0.45 D per year is observed in juvenile Caucasians (8 to 12-year-old) ([Goss and Cox 1985](#)). For juvenile onset myopia in Asians, the rate of progression typically observed is twice that in Caucasians ([Saw, et al 2002](#)).

A correlation has been observed between the age of onset and final refractive status, where earlier onset seems to lead to a higher final amount of myopia ([Goss and Cox 1985](#), [Mäntyjärvi 1985](#), Table 3). An important aspect of this trend may be the consideration of puberty, where onset of myopia prior to puberty may result in greater final myopia.

Table 3 Earlier onset leads to higher levels of myopia

Age of the onset of myopia (years)	Mean diopters at age 15 to 16
7 to 8	5.00
9	4.43
10	4.16
11	3.16
12	2.75
13	2.54
14	2.11
15	1.15

Source: [Mäntyjärvi 1985](#)

2.4 Risk factors for developing myopia

Generally, the causes of myopia are classified in terms of either genetic or environmental. ([Mutti and Zadnik1995](#), [Zadnik 2002](#), [Mutti, et al 2002](#)). Studies have shown that the prevalence of myopia in children with 2 myopic parents is 32.9%, decreasing to 18.2% in children with 1 myopic parent, and to less than 6.3% in children with no myopic parents (Table 4). The most common environmental factor cited is near work, where a statistical association between myopia, increasing education and higher amounts of near work has been observed.

Table 4 Association between myopia in parents and children

Parental Myopia	Prevalence of children with myopia	Univariate odds ratios (95% CI)
None	6.3 %	---
1 myopic parent	18.2 %	3.31 (1.32-8.30)
2 myopic parents	32.9 %	7.29 (2.84-18.7)

Source: [Mutti, et al 2002](#)

2.5 Quality of life issues associated with myopia

In trying to better understand the impact of myopia from the perspective of the patient on daily life, it is useful to consider 2 concepts, namely, the far point and the effect that myopia has on loss of visual acuity (VA). The far point is the furthest point at which a person can see clearly. For myopes, this point moves closer and closer to the eye, as the degree of myopia increases. For example, the far point of -1.00 D myope = 40 inches; for a -2.00 D myope, the far point = 20 inches. Objects beyond the far point are recognizable, however, they become progressively more “blurred” with increasing distance. This change in the far point is what gives rise to the phenomenon of high myopes (-6.00 D or more of myopia) holding books very close to their face to read when they are not wearing their spectacle correction.

To appreciate the magnitude of the impact of myopia with respect to loss of uncorrected visual acuity (UCVA), we can consider a “rule of thumb” relationship that is used by many

clinicians when they refract patients (Table 5; [Bennett and Rabbetts 1989](#)). This provides an approximate relationship between unaided vision and spherical myopia.

Table 5 Relationship between acuity and refractive error

Visual Acuity*	Spherical Error (D)
20/20	-0.25
20/30	-0.50
20/40	-0.75
20/60	-1.00
20/80	-1.50
20/120	-2.00
20/200	-2.00 to -3.00

*Uncorrected

Based on this relationship, a -2.00 D myope would have an unaided VA of approximately 20/120. To better understand the significance of this decay in unaided VA, consider the following subjective clinical overview of vision requirements for various activities and professions (Table 6). This list was compiled based on Novartis' discussions with clinicians working in the field of myopia research.

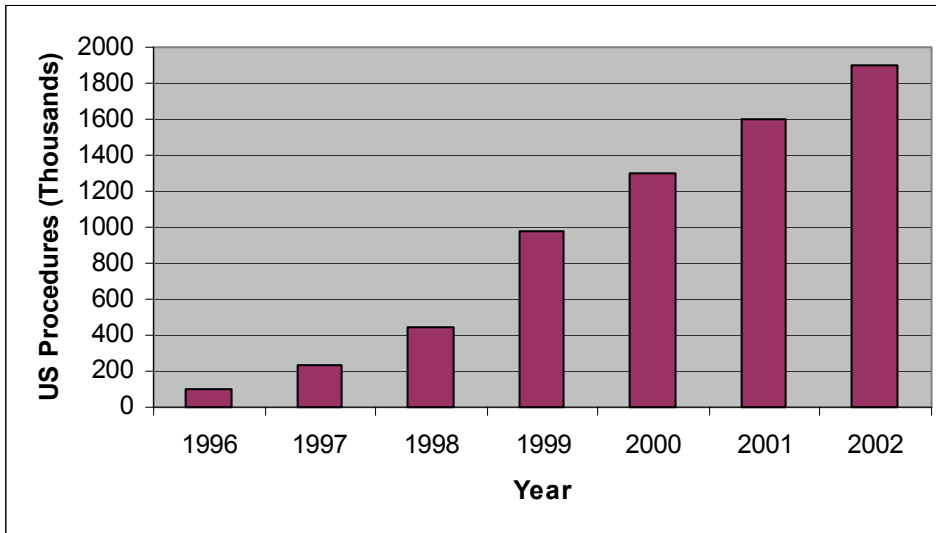
Table 6 Visual requirements for certain activities and professions

Activity	Minimum Vision Required					
	20/20	20/25	20/30	20/40	20/50	20/60
Hit an overhand baseball	X					
Obtain a pilot license	X					
See chalk board from back of class room		X				
Interpret coach/director instructions from field or stage			X			
Obtain an unrestricted drivers license in most states				X		
See necessary distances for diving and swimming				X		
Scan full distance of soccer or football field				X		
Perform near work at comfortable distance					X	
Recognize faces across a crowded room						X

In light of the effect of myopia on the far point as well as unaided VA, it is noteworthy to consider the significant number of people with myopia who have opted to undergo laser refractive surgery (Figure 2). The fact that so many myopic patients choose this alternative when non-invasive treatment options exist appears to be reflective of the significance of

myopia on their daily quality of life and their dissatisfaction with these treatment options (Market Scope Research, 2003).

Figure 2 US LASIK procedures by year

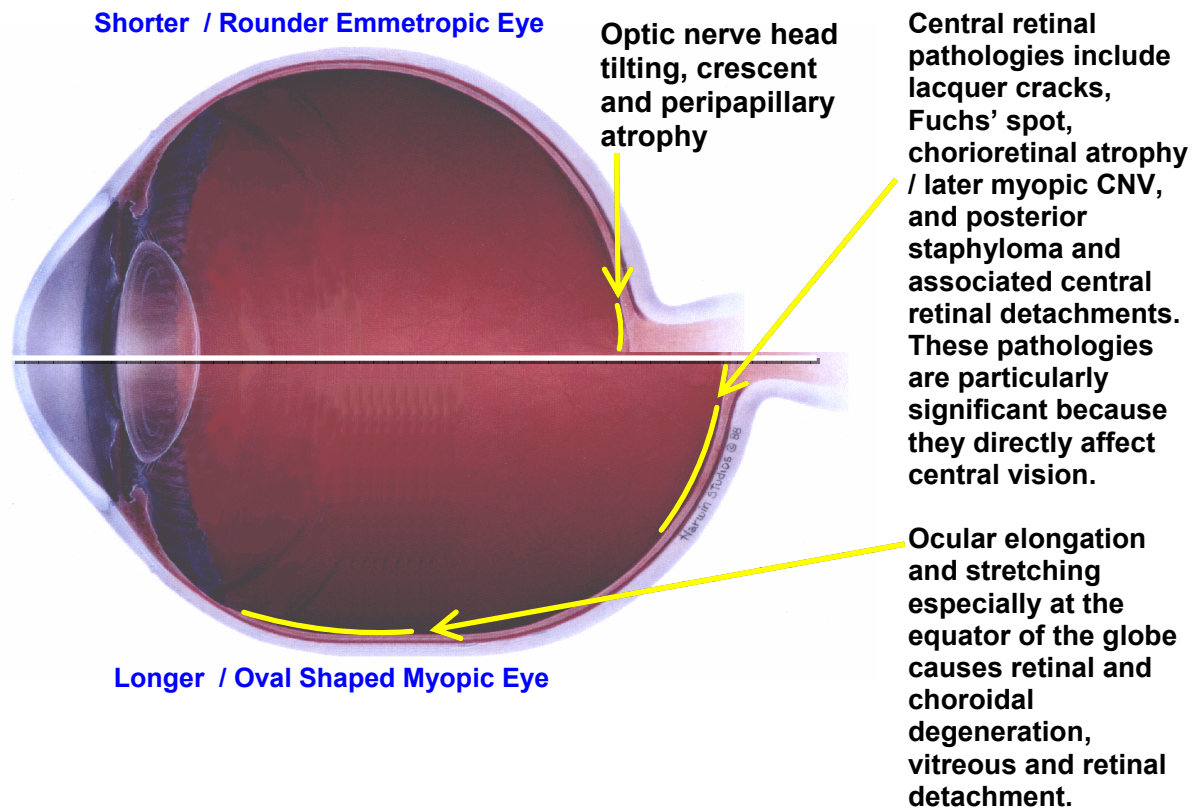


Quality of life measures are often difficult to quantify, and indeed, it is very difficult to find published studies in this regard with respect to myopia. However, in the United Kingdom (UK), a study was performed to assess the effect of degree of myopia on quality of life. The control group for this study was a group of keratoconus patients who were being treated with optical correction. Quality of life was assessed using the VF-14 questionnaire as well as data from interviews. It was determined that high myopes (more than -10.00 D) experienced an impaired quality of life similar to patients with keratoconus (Rose, et al 2000).

2.6 Complications associated with myopia

This section summarizes the main medical complications associated with myopia. As seen in Figure 3, the effect of significant axial elongation on the structure of the eye can result in various complications which typically manifest later in life.

Figure 3 Potential complications of myopia



2.6.1 Retinal disease and myopia

2.6.1.1 Myopic retinopathy

Myopic retinopathy has long been recognized as a serious cause of blindness. Myopic retinopathy is characterized by a variety of degenerative retinal changes. Progressive and excessive elongation of the eye associated with high myopia results in various fundus changes within the peripheral and central retina (Rabb and LaFranco Garoon 1981, Noble and Carr 1982, Curtin 1985, Steidl and Pruett 1997). These changes include chorioretinal atrophy, lacquer cracks, subretinal hemorrhage, choroidal neovascularization (CNV), Fuchs' spot (Levy, Pollock, and Curtain 1977, Hotchkiss and Fine 1981, Jalkh, et al 1987, Hayasaka, Uchida, and Setogawa 1990), and posterior staphyloma (Curtin and Karlin 1971, Curtin 1985). Among the various myopic fundus lesions, macular CNV is the most common vision-threatening complication of high myopia (Fried, Siebert, and Meyer-Schwickerath 1981, Hampton, Kohen, and Bird 1983, Avila, et al 1984).

Myopic retinopathy has been surveyed infrequently in population-based studies. However, the population-based Blue Mountains Eye Study determined prevalence rates of myopic retinopathy in a population aged 49 years or older (Table 7; Vongphanit, Mitchell, and Wang 2002). In this population, the prevalence of myopic retinopathy increased markedly with increasing levels of myopia. This observation is consistent with other studies showing a

higher prevalence of pathologic signs at greater axial lengths ([Curtin and Karlin 1971](#) and [Gozum, et al 1997](#)).

Table 7 **Prevalence of myopic retinopathy**

Spherical equivalent refraction (D)	Myopia n (%)	Myopic retinopathy n (%)
> -1.00	3179 (87.0)	10 (0.3)
-1.00 to -2.99	295 (8.1)	2 (0.7)
-3.00 to -4.99	101 (2.8)	3 (3.0)
-5.00 to -6.99	44 (1.2)	5 (11.4)
-7.00 to -8.99	14 (0.4)	4 (28.6)
< -9.00	21 (0.6)	11 (52.4)

Source: [Vongphanit, Mitchell, and Wang 2002](#)

2.6.1.2 Lattice degeneration and myopia

Estimates of the prevalence of lattice degeneration due to myopia range from 6% to 8% ([Byer 1979](#), [Straatsma, et al 1974](#)). In eyes with retinal detachment due to myopia, ([Straatsma and Allen 1962](#)) previously found that 30% of eyes had lattice degeneration. Törnquist had similar findings and noted patients experiencing retinal detachment with lattice degeneration were more likely to be younger and myopic ([Törnquist, Törnquist, and Stenkula 1987](#)).

2.6.1.3 Retinal detachment

Myopic eyes are at an increased risk for retinal detachment ([Perkins 1979](#), [Ogawa and Tanaka 1988](#), [The Eye Disease Case-Control Study Group 1993](#)). This increased risk occurs even at low degrees of myopia and increases in patients with higher myopia. As one example, The Eye Disease Case-Control Study found that the risk for retinal detachment in eyes with -1.00 D to -3.00 D of myopia is more than 4 times that compared to no myopia, whereas this risk for an eye with more than -3.00 D of myopia is nearly 10 times that of an eye with no myopia. In another case-controlled study, similar risks were found for mild and moderate levels of myopia compared to no myopia. For eyes with severe myopia, the risk of retinal detachment is 26 times that of an eye with no myopia ([Ogawa and Tanaka 1988](#)).

While the incidence of retinal detachment is relatively low, the cost of treatment and impact on vision are high. ([Burton 1982](#)) observed that only 40% of treated eyes recover to 20/50 or better acuity when the detachment involved the macula.

2.6.2 Glaucoma and myopia

An association between myopia and glaucoma has been recognized for decades. Larger recent studies support a relationship between the two, even for low degrees of myopia. In the Blue Mountains Eye study ([Mitchell, et al 1999](#)), an association was observed between degree of myopia and prevalence of glaucoma. In this population-based study, persons with low myopia (-1.00 to -3.00 D) were twice as likely to have glaucoma (OR, 2.3; 95% CI 1.3 to 4.1) whereas those with moderate myopia (-3.00 D and greater) were 3 times as likely to have glaucoma (OR, 3.3; 95% CI 1.7 to 6.4). Other studies have shown a correlation between

myopic refraction and increasing intraocular pressure (IOP) and an increased odds of having glaucoma in persons with myopia (Wong, et al 2003).

2.6.3 Cataract and myopia

An association between cataract and myopia has been reported in cross-sectional population based studies (Wong, et al 2001, Younan, et al 2002). In the Blue Mountains Eye study, the strongest association was reported between high myopia and nuclear cataract, moderate to high myopia and posterior subcapsular cataract, and any myopia and cataract surgery. In the Beaver Dam Eye Study, an association between any myopia and cataract surgery was reported, however, an association between nuclear, cortical and subcapsular cataracts was not observed.

2.7 Current treatments for myopia

The current treatments for myopia include spectacles with single-vision lenses, contact lenses, and refractive surgery. These treatments only correct the refractive error due to myopia. They do not address the underlying pathophysiologic changes associated with excessive axial elongation of the eye. A recently published article reinforces this point:

“Popular (refractive) procedures seem almost irrelevant to the discussion of high myopia. These procedures improve cosmesis, but provide no relief for the pathological process of high myopia” (Bell 1993).

Reports of interventions attempting to retard the progression of myopia have included progressive addition and bifocal spectacles, contact lenses and eyedrops including atropine and the topical beta-blocker, timolol maleate (Saw, et al 2002, Gwiazda, et al 2003). Studies involving bifocal spectacle lenses with various additions, progressive addition lenses (PAL), topical tropicamide and topical timolol have not demonstrated clinically significant effects with respect to slowing either the progression of refractive error or the increase in axial length growth. Reports involving topical atropine in concentrations of 0.5% and 1.0% have demonstrated statistically significant effects. However, the side-effects associated with topical atropine are generally considered unacceptable for long-term therapy, and therefore, topical atropine has not been accepted as a treatment for slowing progression of myopia. In a recent review of all published interventions for slowing the progression of myopia, it was noted that “the latest evidence from randomized clinical trials does not provide sufficient information to support interventions to prevent the progression of myopia” (Saw, et al 2002).

3 Proposal and rationale of a study design for a pharmacologic treatment of myopia

3.1 Indication

Novartis is proposing the following indication based on the population and primary variable being proposed for study: Reduction of progression of myopia in patients diagnosed with juvenile onset myopia.

3.2 Population

Eligible patients will be diagnosed with juvenile onset myopia, aged 6 to 12 years, and meet the following criteria:

- Refractive status as determined by cycloplegic autorefraction: -1.00 to - 4.00 D
- Astigmatism: ≤ 1.25 D in either eye
- Anisometropia: ≤ 1.00 D (spherical equivalent between eyes)
- No known ocular, systemic, or neurodevelopmental condition that might affect refractive development.

3.3 Study design

Prospective, randomized, double-masked, placebo controlled study. For the purposes of registration, Novartis proposes a period of 30 months on-drug as being an adequate period of time to establish efficacy and safety.

Given the patient population being studied, it is appropriate to have additional safety data resulting from an extended exposure period. The length of exposure being proposed is consistent with feedback from experts in the myopia treatment community and exceeds the ICH guideline regarding the exposure period required for drugs intended for long-term treatment of non-life-threatening conditions (i.e., this guideline stipulates that 300 to 600 patients should have exposure data for 6 months and a minimum of 100 patients should have exposure data for 12 months).

An “off drug” period of 6 months is also being proposed to address the potential concern regarding rebound associated with discontinuation of therapy. It is important to understand that cessation of therapy during the period of life where myopia is naturally progressing, will result in a resumption of progression of myopia. This phenomenon is not a rebound effect. The concern regarding rebound centers around the potential for an acceleration of progression of myopia to occur upon cessation of therapy. A period of 6 months is considered adequate for the manifestation of any rebound effect.

3.4 Primary outcome measure

The primary outcome measure is progression of myopia as expressed by the change from baseline in spherical equivalent refractive error (SER) assessed using cycloplegic autorefraction.

3.5 Efficacy variables

3.5.1 Primary

Novartis proposes a primary efficacy variable based on a comparison of the proportion of patients in the treated versus placebo groups whose myopia progresses by -2.00 D or greater at a predetermined time point.

3.5.2 Secondary

The proposed secondary efficacy variable is a comparison of change in axial length between treated and untreated groups.

3.6 Rationale for the primary efficacy variable and treatment period

3.6.1 Rationale for outcome measure

The progression of myopia can be characterized as having 2 primary outcomes that are significant to the patient. These are the change in refractive error that reduces unaided VA and the development of ocular complications. The development of ocular complications results from the stress on the ocular system arising from axial elongation of the ocular globe due to increased vitreous chamber length. The increased axial length of the ocular system leads to the change in refractive status of the system and results in the most immediate impact to the patient, a reduction in the ability to see clearly. Using refractive error as assessed by cycloplegic autorefraction is the best method for assessing the refractive status of the ocular system. It is an objective measure with minimal variability and is the approach generally accepted by experts in the field as being most relevant for clinical research. Thus, change in refractive status as assessed by change in refractive error is a clinically significant outcome measure for a treatment of juvenile onset myopia.

3.6.2 Rationale for magnitude of change

To use change in SER as a primary measure of efficacy, we must define the magnitude of change that is clinically meaningful. We will address this by defining:

- The change in refractive error considered to be clinically significant based on objective criteria. This change = 0.75 D.
- The change in refractive error considered to be clinically significant based on subjective criteria. This change = 1.00 D to 2.00 D.

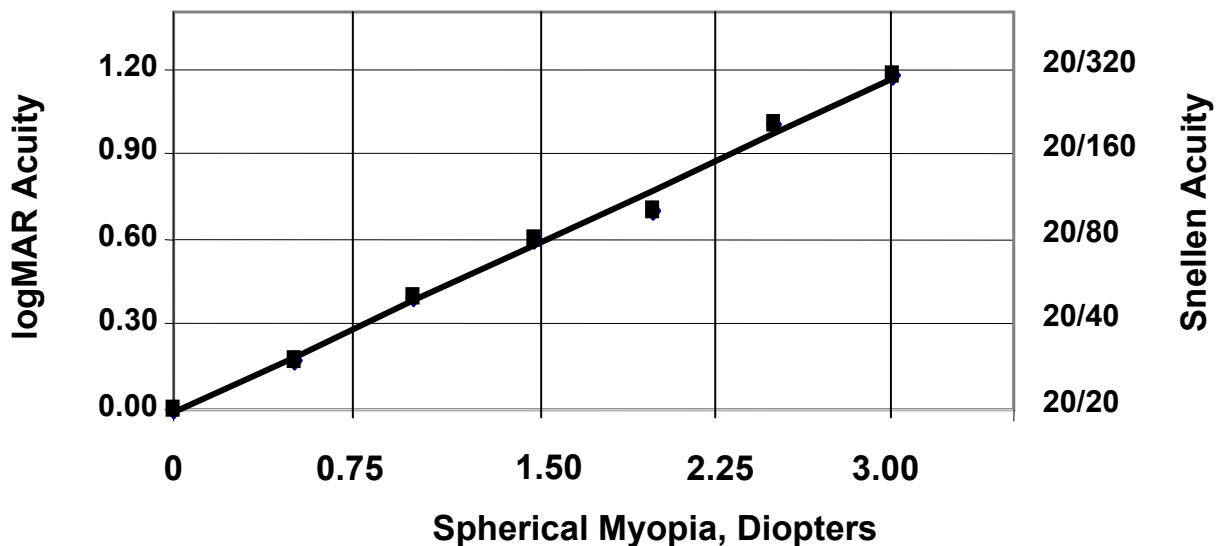
3.6.2.1 Change in refractive error considered to be clinically significant based on objective criteria

When either best-corrected visual acuity (BCVA) or UCVA have been used as endpoints to approve new treatments in ophthalmology, a change that corresponds to a doubling of the visual angle has been considered clinically significant.

- For Drugs—a 3-line loss in BCVA on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart has been accepted by the FDA as clinically significant for the purpose of approving new drugs for age-related macular degeneration (AMD); this change corresponds to a doubling of the visual angle.
- For Devices—lasers approved for laser refractive surgery, the effectiveness endpoint based on VA defined in the FDA guidance document is “percentage of eyes with UCVA 20/40 or better ([best-spectacle corrected visual acuity (BSVA)] 20/20 or better preoperatively).” Thus, for eyes in which it is possible to correct to 20/20, a primary endpoint is based on the percentage of eyes whose UCVA does not decay beyond a doubling of the visual angle.

The change in refractive error that corresponds to a doubling of the visual angle can be calculated to be 0.75 D. This number arises from evaluating VA decay with refractive error changes. For this evaluation, we used a dataset of 45,206 physical examination records where 7,482 refraction records were reviewed (Pincus 1946). Figure 4 presents the UCVA data prior to dilation in the subset of patients that exhibited spherical myopia on cycloplegic refraction.

Figure 4 Relationship between uncorrected visual acuity and refractive error



Source: [Pincus 1946](#)

In addition to criteria that have been defined for VA changes that can be considered as clinically significant, the following criteria have been defined in the Center for Device and Radiologic Health's (CDRH) guidance document for Refractive Surgery Lasers with respect to refractive error changes that are part of the definitions of effectiveness. Based on the inclusion of these criteria, changes of these magnitudes are considered to be clinically significant:

Percentage of eyes that achieve predictability (attempted versus achieved) of manifest refraction spherical equivalent of ± 2.00 D, ± 1.00 D, and ± 0.50 D.

3.6.2.2 Change in refractive error considered to be clinically significant based on subjective criteria

Two subjective criteria have been chosen to support a determination of clinical significance, a patient-driven treatment decision option and a measure of quality of life associated with change in refractive status. Based on these criteria, a change in refractive error of 1.00 to 2.00 D can be considered clinically significant.

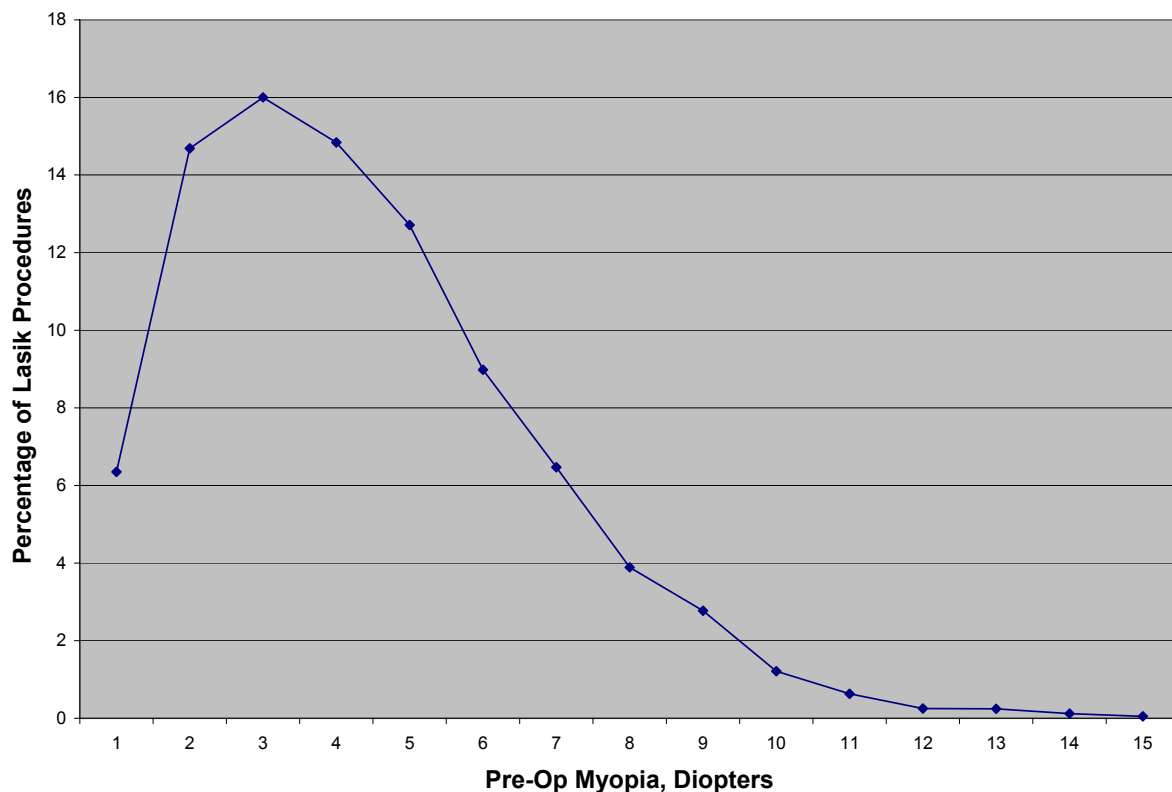
3.6.2.2.1 Patient-driven treatment option

When considering options to pursue for correction of the optical defect associated with myopia, patients have a variety of non-invasive and invasive treatments from which to

choose. We considered the choice of a patient to pursue an invasive treatment option such as laser refractive surgery to be a significant indication of their dissatisfaction with their refractive status.

We used the most prevalent form of laser refractive surgery (i.e., LAser in-Situ Keratomileusis (LASIK)) and a sample of over 6,000 LASIK patients undergoing this procedure during the years 1996 to 2002. In considering the distribution of the percent of patients undergoing LASIK as a function of pre-operative myopia, a significant rise in the incidence occurs as the pre-operative refractive status approaches -2.00 D. This rise does not occur as the pre-operative refractive status approaches -3.00 D or -4.00 D. It is important to note that the prevalence of myopia in the population is highest at lower levels and is similar in the 2.00 to 5.00 D range. Using this subjective criteria, a 2.00 D change in refractive error can be considered clinically significant.

Figure 5 Percent of LASIK refractive procedures compared to pre-operative refractive status



Source: Market Scope Research, 2003

3.6.2.2.2 Quality of Life Measure Associated with Change In Refractive Error

The Refractive Status and Vision Profile (RSVP) is a validated questionnaire designed specifically to measure self-reported vision-related health status via evaluation of symptoms, functioning, expectations and concern in persons with refractive error.

The RSVP includes 8 subscales, and an overall score which assess physical-social functioning, driving, psychological functioning, symptoms, optical problems, glare, problems with corrective lenses, and expectations (specifically, expectations related to post-surgical outcome associated with refractive surgery).

When the effect of changes in SER were considered in terms of reported patient satisfaction in patients who have not undergone laser refractive surgery, it was found that for every additional diopter of SER (i.e., with increasing severity of myopia), people are significantly more likely to report being dissatisfied with their vision, even after adjustments for age, gender, lens type (spectacles or contact lenses), and RSVP subscale quality of life measures. As expected, for every additional 2.00 D of change in SER, the reduction in satisfaction is even more pronounced (Vitale, et al 2000).

3.6.3 Rationale for a dichotomous versus continuous variable

Novartis is proposing a dichotomous variable as the primary variable because we believe it better reflects the treatment effect of a therapy for juvenile onset myopia.

Given the population we are proposing to study, a dichotomous variable of 2.00 D reflects the treatment effect in preventing the progression of the population through significant steps of myopic progression (Table 8). It reflects the difference between the treated and untreated groups in the percent of patients who progress from mild to moderate and from moderate to severe myopia.

Table 8 Change in stage of myopia with –2.00 D progression

Baseline myopia (SER) (D)	Progression of 2.00 D and greater	Stages reflected
-1.00 to less than -3.00 D	-3.00 to less than -6.00 D	Mild to moderate
-4.00 D	-6.00 D and greater	Moderate to severe

Definitions of Stages of Myopia:

- 1.00 D to less than -3.00 D = Mild myopia
- 3.00 D to less than -6.00 D = Moderate myopia
- 6.00 D and greater = Severe myopia

If a continuous variable were to be required, it would not be reasonable to impose a requirement of demonstrating a 2.00 D difference between groups at 30 months. Novartis does not believe a continuous measure is a clinically meaningful as a dichotomous measure, but if it were to be required a different threshold for clinical significance should be applied. To better understand what this threshold should be, we undertook a statistical modeling experiment.

We used as the basis for our modeling the recently published data (Gwiazda, et al 2003) from the Correction of Myopia Evaluation Trial (COMET). This study enrolled a population that is very similar to the population we are proposing to study. These data were collected from a double-masked, randomized sample based in the US.

When the sample size was determined for the COMET study, a potential treatment effect of 33% was assumed as part of the calculation. This magnitude of treatment effect was

considered clinically significant by the COMET study group. We used this same assumption to model the theoretical difference in mean refractive error that could be achieved if a treatment exhibited a 33% treatment effect each year for a period of 3 years. Additionally, we considered the potential treatment effect in the model if a 50% treatment effect were achieved (Tables 9 and 10).

Table 9 Estimated changes from baseline (slopes) in mean refraction assuming active reduces myopic progression by 33%

Interval	Active	Control	Annual Treatment Effect	Cumulative Treatment Effect
0-1 Year	-0.40	-0.60*	0.20	0.20
1-2 Year	-0.33	-0.49*	0.16	0.36
2-3 Year	-0.26	-0.39*	0.13	0.49
Total	-0.99	-1.48	0.49	--

*Estimated values from COMET SVL group (N=234; Mean age = 9.4 yrs; Mean refraction = -2.37 D).

Table 10 Estimated changes from baseline (slopes) in mean refraction assuming active reduces myopic progression by 50%

Interval	Active	Control	Annual Treatment Effect	Cumulative Treatment Effect
0-1 Year	-0.30	-0.60*	0.30	0.30
1-2 Year	-0.25	-0.49*	0.24	0.54
2-3 Year	-0.20	-0.39*	0.19	0.73
Total	-0.75	-1.48	0.73	--

*Estimated values from COMET SVL group (N=234; Mean age = 9.4 yrs; Mean refraction = -2.37 D).

As can be seen from Table 9, a treatment of myopia that can maintain a 33% year-over-year improvement versus the control group will result in a treatment difference of - 0.49 D after 3 years of treatment. As seen in Table 10, a treatment of myopia that can maintain a 50% year-over-year improvement versus the control group will result in a treatment difference of - 0.73 D after 3 years of treatment. Based on an assumption of a reasonable treatment effect, namely 33% and 50%, it would not be possible to achieve a treatment effect difference (i.e., difference in mean refractive error between groups) of 2.00 D, even if the clinical study were to involve 3 years of treatment. It may be possible, however, to achieve a treatment effect of 0.75 D, which is consistent with the clinically significant effect we defined based on objective criteria.

4 Conclusion

The condition of myopia continues to be a problem in society. The issues surrounding myopia can be characterized by the following:

- Myopia has been recognized by governmental health agencies as a significant public health condition requiring research and new treatments.

- Patients diagnosed with myopia continue to search for treatments to alleviate this condition. This is reflected by the significant growth in laser refractive surgery over the last decade, even when many non-invasive treatment options exist.
- Current available treatments address only the optical defect associated with myopia, they do not affect the underlying pathophysiologic changes that lead to long-term complications.
- An association between myopia and significant long-term complications has been reported by many investigators. These complications include retinal detachment, myopic retinopathy and glaucoma.
- Evidence also suggest an increasing risk for developing certain of these complications with higher degrees of myopia.
- Patients diagnosed with myopia continue to search for treatments to alleviate this condition. This is reflected by the significant growth in laser refractive surgery over the last decade, even when many non-invasive treatment options exist.

A pharmacological approach to treatment represents the only avenue for addressing both the optical defect associated with myopia as well as the underlying pathophysiologic changes resulting from excessive axial elongation.

Because the significant complications associated with myopia do not generally manifest until later in life, but the physiologic defect leading to these complications occurs early in life, a clinical development program based on the development of a complication associated with myopia is not feasible. Therefore, another outcome measure is needed if new therapies are to be developed.

Refractive error associated with myopia is the optimal alternative. It represents the aspect of myopia that is most relevant to patients, has the greatest immediate impact on their life and is reflective of the underlying pathophysiologic changes that are occurring.

Novartis has presented a proposal for an endpoint based on using change in refractive error as an outcome measure. We have defined a clinically significant change in this parameter which can be used to measure a treatment effect based on various criteria and have proposed a treatment period that addresses the safety concerns reflective of the population being studied.

We believe this approach represents the best balance between measuring a treatment effect using a parameter which is clearly important to the patient but also allows for the reasonable development of new treatments in a safe manner.

5 References

NOTE: Selected references are provided in Appendix 1.

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