Violet Light for the Treatment of Myopia

Version 6.0

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1. Background and Summary

1.1 Epidemiology and Disease Burden

Myopia (shortsightedness) is the most common eye condition in the world and is only increasing in prevalence, with studies predicting 4.7 billion afflicted by 2050.[1] This increase in prevalence is particularly notable in East Asia, but myopia is increasing in the US as well: a study done with a contemporary American cohort in Southern California found that 41.9% of the cohort, aged 5-19 years old, were myopic.[2,3] Although visual impairment caused by myopia is generally correctable (via glasses, contact lenses, etc.), uncorrected refractive error costs $202 billion annually in global GDP.[2,3] High myopia is associated with increased risks of glaucoma, cataracts, and retinal detachment.[4–6]

1.2 Current Treatments

Slowing the progression of myopia has been attempted through a range of treatments with varying degrees of success. Among the most promising have been soft bifocal contact lenses, orthokeratology, and antimuscarinic agents (pirenzepine, atropine, etc.).[7,8] However, these treatments are not without side effects: atropine can cause side effects such as photophobia, and orthokeratology carries the risk of microbial keratosis.[9] In addition, compliance with contact lens wear can be poor.[10]

1.3 Myopia and Violet Light

An abundance of studies have shown that outdoors exposure is protective against myopia onset.[11–16] Meta-analysis indicates that one additional hour spent outdoors per week translated to a 2% reduced odds of developing myopia.[14] Some studies have also shown that outdoor exposure can reduce myopic progression.[14,16] The mechanism for this is yet unclear, but it has been theorized that violet light may be key to this protective effect.[17] Due to overzealous UV protection, violet wavelengths have been rendered nearly absent from modern life despite being part of the visible spectrum: windows have very low transmittance for wavelengths below 400 nm, indoor lighting does not incorporate violet, and UV blocking glasses and contact lenses are abundant.[17]

Previous studies by Torii et al. indicated that violet light is protective against myopia progression in humans. A retrospective study compared patients wearing non-violet transmitting eyeglasses, partially violet-blocking contact lenses, and violet light transmitting contact lenses, and found that patients wearing violet light transmitting contact lenses had a significantly decreased amount of myopia progression as measured by axial length elongation.[17] Additionally, violet light was shown to influence high adult myopia: patients who received non violet light transmitting phakic intraocular lens implantations were significantly more myopic than patients who received violet light transmitting implantations.[18]

Animal studies indicate that the light-sensitive protein OPN5 may be key in violet-light mediated suppression of myopia. OPN5 has previously been shown to regulate light-dependent vascular development in the murine eye via suppression of vitreal dopamine, which simultaneously increased retinal dopamine.[19] This is significant because retinal dopamine has been widely hypothesized to antagonize myopia development.[20,21] Violet light has been shown to reduce axial length elongation in chicks as well as stimulate a higher long-term retinal dopamine level than blue, red, or white light.[17,21]

Most recently, OPN5 has been shown to be necessary for violet-light mediated suppression of lens defocus-induced myopia in mice. Violet light delivered for 3 hours in the evening (pre-dusk) protected mice from lens defocus-induced myopia, an effect that was shown to be both time and wavelength dependent – but did not protect OPN5 conditional null mice.[22]

1.4 Role of Genetics in Myopia

Large-scale genetic studies have been performed in myopia and have implicated the important role of genetic factors. Through molecular techniques, such as linkage analysis, association studies, and sequencing analysis, many of the genes associated with myopia have been identified.[23] Furthermore, the prevalence of myopia increases significantly with the number of myopic parents; the associated development risk rates are 7.6% for no myopic parents, 14.9% for one myopic parent, and 43.6% for two myopic parents.[24] The evidence is conclusive of a genetic contribution to myopia beyond environmental factors, and exploring the genetic component of patients with myopia is critical in better understanding the disease.

1.5 Bios SkyView Lamps

In order to effectively deliver violet light, the BIOS SkyView lamp will be used. BIOS lighting uses patented circadian lighting technology to produce the highest melanopic to photopic lux ratio for a given color temperature, translating to better equivalent melanopic lux for a lower correlated color temperature than other LEDs.[25] The BIOS SkyView lamps are equipped with wavelength-specific LEDs, able to provide a full profile of violet light (385 nm) for the purpose of this study.[26] The SkyView lamps have been approved by CCHMC for research use (assessment ID: 109744). The Aooshine bedside lamps, which will act as the control light source, have also been approved by CCHMC for research use (assessment ID: 133975).

1.6 Impact of UV Blocking Lenses

UV blocking glasses are ubiquitous in modern society. Pediatric patients are commonly prescribed polycarbonate eyeglasses due to their innate UV-blocking capabilities and shatter resistance.[25] However, polycarbonate also attenuates the violet wavelengths that could potentially be crucial to myopia control.[17,18,22] UV-blocking glasses, which typically seek to block wavelengths below 400 nm in an overabundance of caution, result in the elimination of much of the violet spectrum (380 nm to 450 nm), and could potentially be a contributing factor to the myopia epidemic.

4.9 Study Design

A) Study Groups:

To assess the effects of violet light and potential contribution from UV-blocking glasses, three study groups will be established:

1. A group (n = 24) will use the BIOS SkyView lamp with violet LEDs enabled for at least one hour during dawn and at least one hour during dusk. The group will wear CR-39 (UV-transmitting).

2. A group (n = 24) will use the BIOS SkyView lamp with violet LEDs enabled for at least one hour during dawn and at least one hour during dusk. The group will wear polycarbonate (UV-blocking) glasses for the duration of the study.

3. A group (n = 24) will use the Aooshine lamp without any violet LEDs enabled for at least one hour during dawn and at least one hour during dusk. The group will wear CR-39 (UV-transmitting).

The study lamp (BIOS or Aooshine) should be the sole source of artificial illumination in participant rooms for the duration of lamp exposure, and throughout the study, exposure to natural light during designated dawn and dusk times should be minimized. Light is a noninvasive source of therapy, and as such, tracking the actual exposure to the lamps and compliance to the study design can be difficult. Therefore, the HOBO Occupancy Sensor (UX90-005), which measures movements of heat emitted by people in motion via passive infrared technology, will be paired with each BIOS lamp.

B) Designating Dawn and Dusk

The best times for the SkyView and Aooshine lamps to undergo the dawn and dusk transition will be chosen individually per participant based on their anticipated daily schedule to maximize effectiveness. Each participant will be given a survey prior to enrollment so that research staff can determine the optimal times on an individual basis.

The one-hour timeframe is chosen to be consistent with known biological responses and the length of the natural dawn/dusk transition. The SkyView/Aooshine lamp will automatically turn on at dawn and automatically turn off after dusk. Both dawn and dusk are chosen because while dusk exposure was protective in the murine myopia model, this effect may be present at dawn in diurnal mammals.[22]

C) Onset HOBO Occupancy Sensor (UX90-005M)

As light is a noninvasive form of treatment, assessing the amount of 'light' received is difficult to quantify in measuring the efficacy of violet light in slowing the progression of myopia. The Onset HOBO Occupancy Sensor uses infrared technology to measure fluctuations of temperature within a 5-meter radius. The temperature fluctuation readings are logged as numerical data which can then be retrospectively collected to then measure exposure to light during the duration of the study.

D) DNA Storage via Saliva

In addition to exploring the efficacy of violet light exposure in treating myopia, the effects of genetic factors will be assessed from DNA extraction for research purposes only. In recent years, alongside the advent of more sophisticated molecular techniques such as linkage analysis, association studies, and sequencing analysis, many of the genes associated with myopia have been identified.[23] Prevalence of myopia has proven to be significantly linked to genetics[24], and if conclusive findings are made from this study, further analysis of DNA collected from saliva could provide valuable information for posterity. Participants will be asked to spit 2-3 mL of saliva into a self-collection container provided by the study. A slight dryness in the mouth may occur; this will be a one-time collection. Collected saliva samples are for DNA extraction for the DNA to be banked for future, unspecified use. All future research accessing the samples or genetic datasets would be IRB approved and reviewed by the study team on a case-by-case basis.

Participants will be informed that they are donating genetic material, and the most likely outcome is that they will receive no further information regarding those samples.

1.8 Study Objective

The purpose of this short-term, pilot, randomized trial is to investigate the efficacy of violet light exposure through the BIOS SkyView Lamps at dawn and dusk versus non-violet light exposure through Aooshine Bedside Lamps in slowing the progression of myopia in school aged children as an alternative to current clinical treatments to determine whether to proceed to a full-scale longer-term randomized trial. This decision will be based primarily on assessing responses to light exposure by comparing treatment groups on the following outcomes:

- Axial length elongation
- Spherical refractive error
- Quality of life
- The proportion of participants reporting adverse effects
- The proportion of participants reporting >75% light exposure compliance

1.9 Timing of Intervention and Outcome for Proposed Study

To evaluate the response to violet light exposure for at least one hour at dawn and at least one hour at dusk compared to non-violet light exposure for at least one hour at dawn and at least one hour at dusk, this pilot randomized clinical trial (RCT) is proposed. If a reasonable initial response without significant adverse effects is found, a subsequent full-scale RCT would further evaluate the effectiveness of violet light exposure via the SkyView lamp for myopia treatment. We will define success as violet light exposure intervention demonstrating at least 80% non-inferiority compared to the control group.

2. Considerations

2.1 Risks

Safety testing of both the BIOS SkyView lamp and the Aooshine Bedside Lamp was completed via Underwriter Laboratories. (Document: QOVZ.E516890). Both the SkyView lamp (assessment ID: 109744) and the Aooshine Bedisde Lamp (assessment ID: 133975) have both been approved for IRB study use by CCHMC.

There is a risk associated with wearing CR-39 lenses, as they are not as impact resistant as polycarbonate (mechanical strength class S vs F, respectively). Parents and participants will be educated on the risk via the consent form and encouraged to either remove eyeglasses or wear different eyeglasses for activities where there is a strong risk of impact to eyeglass lenses (i.e. sports). If participants are assigned to study group 2 (CR-39 lenses throughout the day), parents and participants will be reminded verbally of this risk using the language present in the consent form.

2.2 Risk of Examination Procedures

The procedures in this study are part of daily eye care practice in the United States and pose no known risks.

2.3 Risk Assessment

It is the investigator's opinion that the protocol's level of risk falls under DHHS 46.404, which is research not involving greater than minimal risk.

2.4 Reporting of Adverse Events

There are no expected long-term adverse events associated with violet light exposure. The investigator will abide by CCHMC IRB reporting requirements.

2.5 Study Costs

This study will be funded internally through CCHMC RIP grant. The department of ophthalmology will be the final dispenser of funds.

The subject or his/her insurance provider will be responsible for the costs that are considered standard of care. Because the treatment used in the study is not standard of care, the Enrollment/Randomization, Equipment Pickupand 2 Follow-Up visits will be paid for by the study. The cost of the SkyView/Aooshine lamp will also be paid for by the study. For subjects who wear prescription lenses and are assigned to a group that requires CR-39 or polycarbonate lenses to be worn, the study will provide spectacles and lenses from Zenni Optical not to exceed $80 subject to the following:

- If the patient/parent desires more expensive frames, they will be responsible for costs that exceed $80.
- Lens add-ons and upgrades are at study participant's own expense (e.g., transition lenses, premium polycarbonate lenses).

3. Study Outline

	Enrollment/Randomization	Visit 2: Equipment Recieval	6-Month Visit	12- Month Visit
	Day ≤0	Week 4 ± 2 weeks	6 Months ± 2 weeks	12 Months ± 2 weeks
Informed Consent	X			
Demographics	X			
Medical History	X		X	X
Standard Refraction	X		X	X
Cycloplegic Autorefraction	X		X	X
Distance Visual Acuity Testing	X		X	X
Binocular Near Visual Acuity	X		X	X
Monocular Amplitude of Accomodation	X		X	X
Axial Length Measurement	X*	X*		X**
OCTA	X*	X*		X**
Prescribe Refractive Correction If Needed	X		X	
Randomization	X			
Receive Lamp		X		
Receive Glasses		X		
Receive HOBO Sensor		X		
Receive Automated Wall Plug-In		X		
HOBO Sensor Data Collection			X	X

*Only required if not able to complete at Enrollment/Randomization Visit.

** Testing may occur at a separate testing visit if testing equipment is unavailable at the 12-Month Visit. This must occur ± 2 weeks of the 12- Month Visit.

4. Enrollment

4.1 Eligibility Assessment

A child is considered for the study after undergoing a routine eye examination (as part of standard care) where myopia is identified, and the child appears to meet the eligibility criteria for enrollment. The study will be discussed with the child's guardian(s). Guardians who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent must be obtained from the guardians prior to performing any study-specific procedures that are not part of routine care.

Participants aged 5 to <13 years with myopia who meet all eligibility criteria will be enrolled in the study. Up to 72 participants will be enrolled and randomized in the study.

4.2 Inclusion Criteria

- Diagnosis of myopia (ICD-10-CM Diagnosis Code H52.13)
- Refractive error meeting the following by cycloplegic autorefraction:
    - Myopia -1.00D to -6.00D spherical equivalent (SE) in both eyes
    - Astigmatism <= 1.50D in both eyes
    - Anisometropia < 1.00D SE
- Complete eye exam with cycloplegic refraction within the past 12 months
- 5 to < 13 years of age
- Parent understands the protocol and is willing to accept randomization to 380 nm light or control.
- Parent has a phone (or access to phone) and is willing to be contacted by Investigator's site staff.
- Relocation outside of the area of CCHMC site within the next 12 months is not anticipated.

4.3 Exclusion Criteria

- Current or previous myopia treatment with atropine, pirenzepine or other antimuscarinic agent.
- Current or previous use of bifocals, progressive-addition lenses, or multi-focal contact lenses.
- Current or previous use of orthoK, rigid gas permeable, or other contact lenses being used to reduce myopia progression.
- Current or prior history of manifest strabismus, amblyopia, or nystagmus.
- Abnormality of cornea, lens, central retina, iris, or ciliary body.
- Prior eyelid, strabismus, intraocular, or refractive surgery.
- Down syndrome or cerebral palsy.

4.4 Sample Size

Up to 72 participants will be enrolled in this study. Up to 24 will be enrolled into the three experimental groups:

- Violet light experimental group with polycarbonate glasses

- Violet light experimental group with CR-39 glasses
- Non-violet control group with CR-39 glasses.

4.5 Historical Information

Historical information elicited will include the following: date of birth, sex, race, ethnicity, current refractive correction, iris color (brown or not brown), parental history of myopia (0, 1, or 2 parents), current medication use, history of and current medical conditions, and myopia treatment history.

4.6 Survey to Determine Lighting Schedule

To determine suitable dawn and dusk times for each participant, participants will be asked when they typically wake up, eat dinner, and sleep. Additionally, participants will be asked to detail their typical evening schedule and any activities that may negatively affect compliance.

4.7 Testing at the Enrollment/Randomization Visit

Testing at the enrollment/randomization visit will include the following:

1. Standard Refraction

The investigator may use his/her standard refraction technique (with or without cycloplegia) at any time during the visit to ensure that the participant meets eligibility criteria with respect to refractive correction as described in section 2.5.

2. Cycloplegic Autorefraction

Combination Drops (tropicamide 1%, cyclopentolate 1%, phenylephrine 2.5%) – one drop twice to each eye with 5 minutes between drops. The use of proparacaine prior to the cycloplegic drops is at investigator discretion. For each eye, three autorefraction measurements will be taken. For each measurement, the autorefractor will yield a final reading (either an individual reading or the mean/median of several individual readings, depending on the autorefractor) consisting of sphere, cylinder, and axis (see manual of procedures). Each final reading will be converted to a spherical equivalent refractive error (SER) and the mean of the 3 SER values for each eye will be used for confirming eligibility. A specific autorefractor model is not required for the study; however, each participant should have their autorefraction assessed using the same instrument during the entire study. The cycloplegic autorefraction should occur at 30 minutes ± 5 minutes from the time the second drop was instilled. If eyes are not sufficiently dilated/cyclopleged and/or if the dilation/cycloplegia has worn off before all cycloplegic procedures have been performed, another drop may be administered, followed by an additional 30-minute wait before testing. The use of proparacaine prior to this cycloplegic drop is at investigator discretion.

3. Axial Length Measurement and Additional Biometry

Axial length will be measured 3 times in each eye using optical biometry (e.g., IOLMaster, LENSTAR). The following will also be measured 3 times in each eye using optical biometry (e.g., IOLMaster, LENSTAR) at the same time as axial length.

- Mean corneal radius (mm to 100th)

- Anterior chamber depth (mm to 100th)
- Lens thickness, if available (mm to 100th)

A specific instrument is not required for the study; however, each participant should have axial length and additional biometry assessments made using the same instrument during the entire study.

If the Enrollment Visit occurs at a time or location that the IOLMaster or LENSTAR is unavailable, the Axial length measurement may be completed at the Equipment Pickup Visit.

4. Optical Coherence Tomography Angiography (OCTA)

OCTA will be utilized to image retinal vasculature. 3 x 3 mm OCT angiograms will be obtained for each eye.

OCTA will be performed using the Heidelberg HRA2 Spectralis device (Heidelberg Engineering, Germany). Using a standardized scanning protocol of 15 degree field of view, 4.4 × 2.9-mm X by Y dimension on the retina, 256 B-scans (12 µm between B-scans), a Z-dimension of 1.9 mm (496 pixels approximated to 3.87 µm/pixel), and automatic real-time tracking (ART) of 5; patients will be imaged with macular area OCTA images of superficial vascular complex, deep vascular complex, choriocapillaris and choroid, centered at the fovea.

If the Enrollment Visit occurs at a time or location that the Heidelberg HRA2 Spectralis Device is unavailable, the OCTA may be completed at the Equipment Pickup Visit.

4.8 Refractive Correction

To be eligible for randomization, the participant must be wearing refractive correction in each eye (single vision eyeglasses or soft, daily wear single vision contact lenses with any necessary adjustment for contact lens rotation and vertex distance) that meets the following criteria:

1. Myopia (by spherical equivalent) in both eyes must be corrected to within ±0.50 D the investigator's cycloplegic measurement of refractive error.

2. Cylinder power in both eyes must be within ±0.50 D of the investigator's standard refraction technique, which can be based on a cycloplegic or non-cycloplegic refraction.

3. Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's standard refraction when cylinder power is >= 1.00 D or within ±15 degrees when the cylinder power is < 1.00 D.

Measurement of refractive error for assessing the above criteria may be performed as an over refraction or without refractive correction. If the participant meets all eligibility criteria, but their current correction does not meet the requirements for randomization, then new refractive correction (or a change in refractive correction) can be prescribed to meet the requirements. A new (or change) in refractive correction can also be prescribed if the investigator elects to change a smaller amount of refractive error, but the resulting prescription must meet the criteria above. The prescribed correction can be single vision eyeglasses or contact lenses. Single vision lenses will be

paid for by the study; contact lenses will be at the participants' own expense. A pair of eyeglasses is recommended for all participants and may be ordered through Zenni by the study team.

5. Randomization

5.1 Randomization Process

Participants eligible for randomization will be randomly assigned in a 1:1:1 distribution respectively to:

- Violet light experimental group (BIOS SkyView Lamp) with polycarbonate glasses
- Violet light experimental group (BIOS SkyView Lamp) with CR-39 glasses
- Non-violet control group (Aooshine Bedside Lamp) with CR-39 glasses

The investigator will construct a separate Master Randomization List using a permuted block design stratified by the treatment group. A participant is considered randomized when REDCap randomization process is completed.

The participant, parents, testers, and investigators will be masked to treatment group. If the need arises, the investigator may become unmasked after discussion of a specific case with the study team in response to any adverse events**.** The study coordinator will remain unmasked to the treatment group in order to facilitate the type of equipment and lenses the participant will need.

6. Equipment Pickup Visit

6.1 Prescription Glasses

Participants will come back for their Equipment Pickup Visit once the study team has received the glasses shipment from Zenni. These lenses must be used in conjunction with the lamp, therefore must be picked up alongside the lamp.

6.2 Study Lamp

Participants will receive their lamp at this visit. Patients were randomized at the enrollment/randomization visit and are prepared to receive their respective lamp. The study coordinator will instruct the participant and guardian on the use and setup of the lamp. The HOBO sensor will be attached to the lamp, and participants and guardians will be instructed on how to remove the sensor from the lamp to bring to follow-up visits.

6.3 HOBO Sensor

Participants will receive the HOBO sensor attached to their lamp. The sensor will be removable to bring to follow-up visits. Participants and guardians will be instructed how to remove the sensor properly, and how to put it back on the lamp.

6.4 Automated Wall Plug-In

Participants will receive an outlet timer that will be set to the times the parent or guardian has specified to be their on (dawn) and off (dusk) times. It will be during these times that the child will be asked to be

in the room with the light on for at least one hour at dawn and one hour at dusk. This will allow the lamp to turn on and off automatically during the designated times.

6.5 Testing Not Completed at Enrollment

Participants that were unable to complete testing at the enrollment visit due to unavailability of equipment may have this testing performed at this visit.

- Axial length measurement (see 4.7.3)
- OCTA (see 4.7.4)

7. Follow-Up

7.1 REDCap Daily Surveys

Each day, the parent or guardian of the participant will receive a survey via email with two questions as to what times the lamp was used during the dawn hours and dusk hours that day. Parents and guardians will be reminded of the importance of this survey during telephone calls and follow-up visits.

This survey will serve as a second point of compliance data to compare to the data received from the HOBO sensor.

7.2 Telephone Calls

Telephone calls will be made by the study coordinators to the participants and guardians at 2 weeks (± 3 days), 3 months (± 1 month), and 9 months (± 1 month) post Equipment Pickup visit.

Coordinators will contact parents to confirm that the BIOS SkyView/Aooshine lamp is working properly, encourage compliance, and question the parent as to whether the child is experiencing any issues with treatment.

Additionally, these calls will help maintain direct contact with the parents of the participants, develop and maintain rapport with the family, and assist with scheduling of study visits if needed.

7.3 Follow-Up Visits: 6-Month and 12-Month

The following will be performed at Follow-Up Visits and recorded in the Follow-Up Visit CRF via Redcap.

- Medical History
    - Includes questioning about the occurrence of adverse effects of treatment. Concomitant medications will be recorded, as well as current eyeglasses or contact lenses correction.
- Compliance Assessment (HOBO sensor data collection)
    - App data will be reviewed and assessments of compliance will be recorded on the Follow-up Examination Form.
- Standard Refraction
    - The investigator may use their standard refraction technique (with or without cycloplegia) at any time during the visit to ensure that refractive correction meets study criteria at each visit.
- Cycloplegic Autorefraction
    - See 4.7.2

- Binocular Near Visual Acuity
    - Binocular near visual acuity is measured with participant wearing current refractive correction prior to administration of cycloplegia.
- Distance Visual Acuity
    - Monocular distance visual acuity tested at the start of the exam without cycloplegia in current correction.
    - Measurement of best corrected visual acuity in each eye by a study certified visual acuity tester using the E-ETDRS testing protocol.
    - If the vision is more than one line (>= 5 letters) worse than baseline, retest using trial frames or phoropter with the most recent subjective refraction.
- Monocular Amplitude of Accommodation
    - Measured in their current correction without cycloplegia with a study-specified and provided accommodation near-point rule.
    - Axial Length Measurement (12-Month Only)
    - See 4.7.3
- OCTA- Performed (12-Month Only)
    - See 4.7.4

7.4 Management of Refractive Error

Spectacle correction must be updated whenever the investigator's standard refraction technique reveals a change in refractive error. A change in refractive error is defined as any of the following amounts:

- A difference of >0.75D sphere
- A difference of >0.75D cylinder
- A difference of >0.50D in SE anisometropia
- A difference in axis of 6 degrees or more when the cylinder is ≥1.00D.

Whether to update the correction for smaller differences in refraction is at investigator discretion. updated, the refractive correction must meet the requirements described in section 4.7.

7.5 Non-Randomized Treatment Other than Refractive Correction

Non-randomized treatment for myopia other than changes in refractive error as described above is not permitted during the study. The investigator must call the principal investigator to discuss the case and obtain approval for an exception prior to initiating non-randomized treatment (including OrthoK, rigid gas permeable, and other contact lenses being prescribed for myopia management).

7.6 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic CRFs, which will be considered the source data.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations – a Risk-Based Approach to Monitoring" (August 2013).

8. Miscellaneous Considerations

8.1 Participant Withdrawals

Parents may withdraw their child from the study at any time. If the parents indicate that they want to withdraw their child from the study, the investigator should attempt to speak with the parents personally to determine the reason. If their interest is in transferring the child's care to another eye care provider, every effort should be made to comply with this and at the same time, try to keep the participant in the study under the new provider's care.

8.2 Discontinuation of Study

The study may be discontinued by the study team prior to the pre-planned completion of enrollment and follow-up for all participants.

8.3 Payment to Participants

The parent/guardian of each participant will be compensated $50 by ClinCard upon completion of the Enrollment/Randomization Visit, Equipment Pickup Visit, 6-Month Visit, and 12-Month Visits, for a maximum of $250.

8.4 Costs Covered by the Study

The study will pay for the office visits that are part of the study (Enrollment/Randomization Visit, Equipment Pickup Visit, 6-Month Visit, and 12-Month Visit).

The study will pay for the following:

- BIOS SkyView/Aooshine lamp will be provided to each participant at no cost.
- Eyeglasses will be ordered at enrollment (if needed).
- Frames and Lenses will be ordered by the study team from Zenni.
- Lens changes will be provided at 6 months if a change is required, and the lenses will be ordered by the study team through Zenni.

8.5 Costs Not Covered by the Study

The study will not pay for eyeglasses obtained elsewhere (the study pays for glasses if needed through Zenni only). The study will not pay for contact lenses.

9. Data Storage and Analysis

9.1 Analysis

<u>Primary Analyses</u>

The primary analysis will be an experimental vs control group comparison of change from baseline to 12 months in spherical equivalent refractive error (SER), as measured using cycloplegic autorefraction. At baseline and all follow-up visits, the mean of the three readings from autorefraction in each eye will be calculated and then the mean of both eyes for each participant will be used for the analysis. If fewer than 3 readings are available in each eye, the mean of available readings will be used for each eye to obtain the mean of both eyes for each participant.

The treatment group difference (violet vs. non-violet light) and a 95% confidence interval will be calculated based on the model estimates at 12 months.

Secondary Analyses

- Difference in change in axial length at 6 and 12 months between the violet and non-violet light group
- Compliance will be assessed at each follow up and described as excellent (76%-100%), good (51%-75%), fair (26%-50%) or poor (<25%).

9.2 Decision Guideline

The data collected in this short-term, pilot randomized clinical trial will primarily be used to determine whether to proceed to a full-scale, longer-term randomized trial of violet light vs control non-violet. The side effect profiles in the experimental and control groups will also be considered when deciding whether to proceed with a full-scale trial.

The decision guideline for determining whether to proceed to a full-scale randomized trial will be based on the primary and secondary outcomes at study conclusion.

9.3 Data Safety Monitoring Plan

The participants in this study are patients routinely seen by the investigator or his colleagues as part of standard clinical care at CCHMC, Division of Pediatric Ophthalmology. Participants will continue to be followed clinically by either the investigator or the referring clinicians in addition to attending the study visits.

During the study, participants are observed closely to detect occurrences of any adverse events or complications that may have arisen. At each study visit, the participants and their guardians will be asked questions regarding the occurrence of adverse events to determine whether any complications or adverse events might have occurred since the previous visit.

In the case of a suspected adverse event, further testing may be performed, and non-study treatment may be initiated to ensure patient safety.

9.4 Source Documents and Case Report Forms

Adequate records will be maintained for the study including participant medical records, test reports, signed informed consent forms, adverse event reports, and information regarding participant discontinuation and reasons for discontinuation. All original source documentation will be stored electronically in the password-protected CCHMC shared-drive or in a locked filing cabinet located in the investigator's office or research coordinator's workspace.

In accordance with 21 CFR 50, guardians will provide written informed consent for participation in this study.

9.5 Changes to Protocol

The investigator will notify the IRB of any unanticipated problem requiring a change in the protocol to eliminate apparent immediate hazard to a subject per CCHMC Research Policy, R-18. Changes that affect

the scientific soundness of the study or the rights, safety, or welfare of human subjects will be submitted to the IRB in an amendment prior to implementation.

10. References

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