# Signature Page

# AMBLYOPIA TREATMENT STUDY

# A Randomized Trial of Dichoptic Treatment for Amblyopia in Children 4 to 7 Years of Age

# Protocol Identifying Number: ATS23

# Version Number: 1.0

# 01 April 2024

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| **Signature/Date** | |

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# KEY ROLES

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# VERSION HISTORY

| VERSION NUMBER | AUTHOR | APPROVER | EFFECTIVE DATE | REVISION DESCRIPTION |
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*Version in effect at study initiation

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# LIST OF ABBREVIATIONS

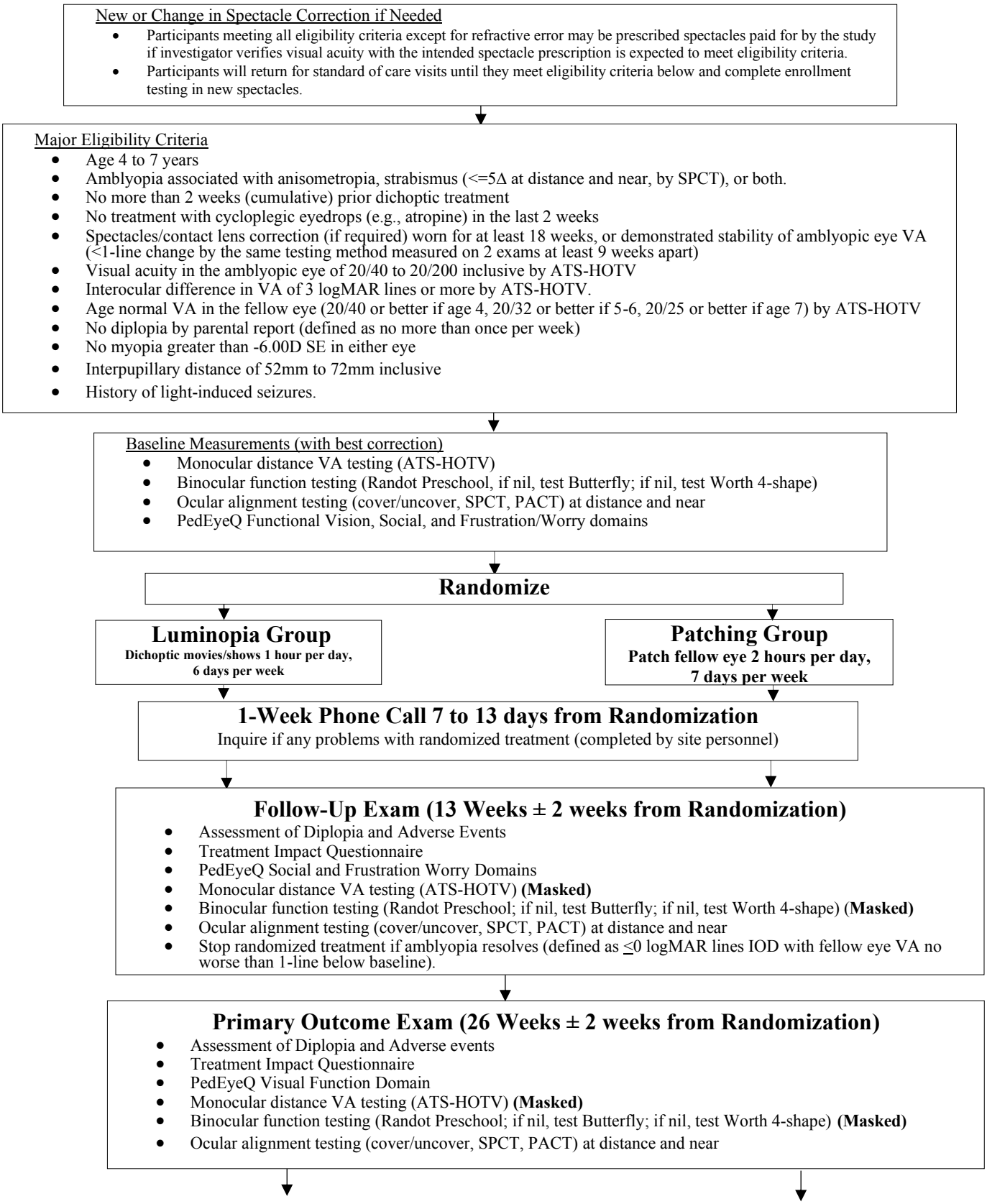
| ABBREVIATION | DEFINITION |
|---|---|
| ANCOVA | Analysis of covariance |
| ATS | Amblyopia Treatment Study |
| BCVA | Best corrected visual acuity |
| CI | Confidence interval |
| CFR | Code of Federal Regulations |
| CRF | Case report form |
| D | Diopter |
| DHHS | Department of Health and Human Services |
| DSMC | Data safety and monitoring committee |
| eCRF | Electronic case report form |
| FDA | Food and Drug Administration |
| GCP | Good clinical practice |
| ICH | International Council for Harmonisation |
| IOD | Interocular difference |
| IRB | Institutional Review Board |
| JCHR | Jaeb Center for Health Research |
| logMAR | Logarithm of the minimal angle of resolution |
| NIH | National Institutes of Health |
| ODM | Occlusion dose monitor |
| PACT | Prism and alternate cover test |
| PedEyeQ | Pediatric Eye Questionnaire |
| PEDIG | Pediatric Eye Disease Investigator Group |
| QA | Quality assurance |
| QC | Quality control |
| RBM | Risk based monitoring |
| RCT | Randomized clinical trial |
| SAP | Statistical Analysis Plan |
| SPCT | Simultaneous prism and cover test |
| VA | Visual Acuity |

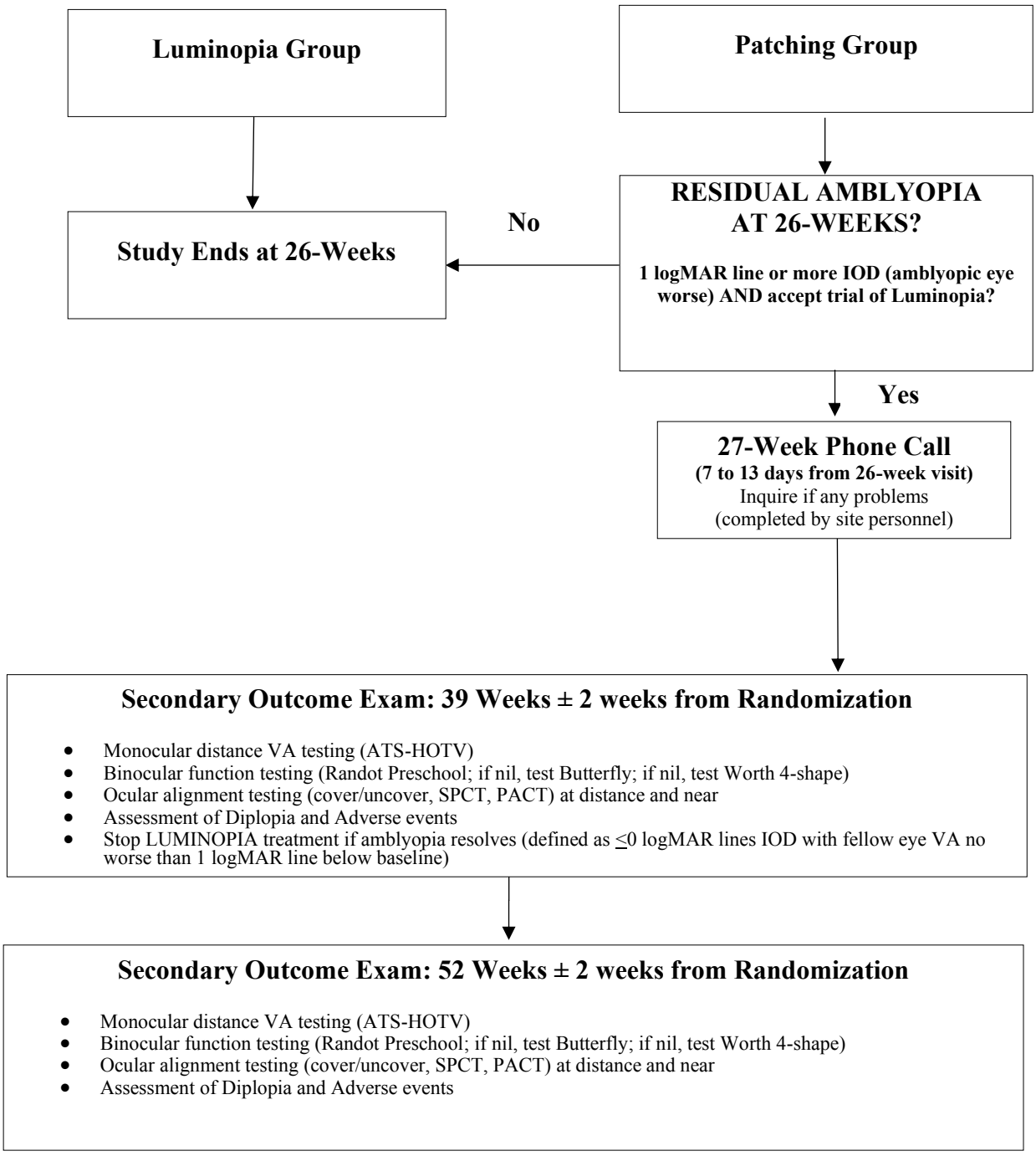
# PROTOCOL SUMMARY

| | |
|---|---|
| **Title** | A Randomized Trial of Dichoptic Treatment for Amblyopia in Children 4 to 7 Years of Age. |
| **Précis** | Current treatments for amblyopia have limited effectiveness in a notable proportion of young children. In addition, the standard treatment of patching may be associated with adverse psychosocial effects. Home-based dichoptic movies/shows present an appealing alternative to patching, but there are few data on comparative effectiveness.<br><br>Dichoptic movies/shows with Luminopia technology show promise of better adherence, and an easier treatment experience.<br><br>If dichoptic therapy using Luminopia is confirmed to be non-inferior to standard part-time patching for best-corrected visual acuity, this study will have provided evidence to support Luminopia as a reasonable alternative to patching in young children. In addition, we plan to assess treatment impact and quality of life to provide data on whether there are advantages to Luminopia. |
| **Investigational Device** | Luminopia digital therapeutic system. |
| **Primary Objective** | In children 4 to 7 years of age, to determine if treatment with 1 hour per day 6 days per week of watching dichoptic movies/shows wearing the Luminopia headset is non-inferior to treatment with 2 hours of patching per day 7 days per week with respect to change in amblyopic eye distance VA from randomization to 26 weeks. |
| **Study Design** | Multicenter, randomized clinical trial. |
| **Number of Sites** | The study is open to all clinical sites approved to participate in the PEDIG network. |
| **Endpoints** | Primary Efficacy Outcome:<br><br>• Change in amblyopic eye logMAR distance VA between randomization and 26 weeks.<br><br>Key Secondary Efficacy Outcomes:<br><br>• Functional Vision, Social, and Frustration/Worry quality of life domains as measured by the Pediatric Eye Questionnaire (PedEyeQ).<br><br>Key Safety Outcomes:<br><br>• Change in fellow eye logMAR distance VA between randomization and 26 weeks.<br>• Proportion of participants with no strabismus who develop a new strabismus.<br>• Proportion of participants with strabismus who develop a worsening strabismus ≥10Δ.<br>• Proportion of participants with parental report of diplopia more than once per week.<br>• Proportion of participants reporting headache, eyestrain, nausea, seizures, dizziness, increase in frequency of night terrors, or skin irritation. |

| | |
|---|---|
| **Population** | **Key Inclusion Criteria:**<br><br>• Age 4 to 7 years.<br>• Amblyopia associated with anisometropia, strabismus (<=5Δ at distance and near measured by SPCT), or both.<br>• Amblyopic-eye VA of 20/40 to 20/200 inclusive by ATS-HOTV.<br>• Age normal VA in the fellow eye by ATS-HOTV (20/40 or better if age 4 years, 20/32 or better if age 5-6 years, 20/25 or better if age 7 years).<br>• Interocular difference in VA of 3 logMAR lines or more by ATS-HOTV.<br>• Spectacles/contact lens correction (if required) worn for at least 18 weeks, or until stability of VA is demonstrated (<1-line change by the same testing method measured on 2 exams at least 9 weeks apart).<br>• Interpupillary distance of 52mm to 72mm inclusive.<br>• No treatment with cycloplegic eyedrops (e.g., atropine) in the last 2 weeks.<br>• No more than 2 weeks (cumulative) prior dichoptic treatment.<br>• No diplopia by parental report (defined as no more than once per week).<br>• No myopia greater than -6.00D SE in either eye. |
| **Sample Size** | 238 total participants (119 in each treatment group) |
| **Phase** | Phase III Randomized Clinical Trial |
| **Treatment Groups** | Random assignment (1:1) to:<br><br>• Luminopia Group: watching dichoptic movies/shows wearing the Luminopia headset prescribed 1 hour per day (treatment time can be split into shorter sessions totaling 1 hour each day) 6 days a week with optical correction, if needed.<br>• Patching Group: patching of the fellow eye 2 hours per day (treatment time can be split into shorter sessions totaling 2 hours each day) 7 days per week with optical correction, if needed. |
| **Participant Duration** | If randomized, participation in the study will last 1 year or less. |
| **Study Duration** | Thirty-seven (37) months from first enrollment to last participant visit (25 months to recruit, followed by 12 months of follow up). |
| **Protocol Overview/Synopsis** | Participants eligible for the study will be randomly allocated (1:1) to receive either dichoptic treatment while wearing the Luminopia headset or patching treatment of the fellow eye for amblyopia with clinical assessments at 13, and 26-weeks post-randomization.<br><br>At the 26-week primary outcome visit, participants who were randomly assigned to receive patching treatment with an IOD of 1 logMAR line or more, will be offered Luminopia dichoptic therapy and if they accept, followed forward with visits at 39- and 52-weeks post-randomization.<br><br>The study will end for all other participants. |

# STUDY SUMMARY FLOW CHART




Luminopia Group
Patching Group
RESIDUAL AMBLYOPIA AT 26-WEEKS?
1 logMAR line or more IOD (amblyopic eye worse) AND accept trial of Luminopia?
No
Study Ends at 26-Weeks
Yes
27-Week Phone Call
(7 to 13 days from 26-week visit)
Inquire if any problems
(completed by site personnel)
Secondary Outcome Exam: 39 Weeks ± 2 weeks from Randomization
Monocular distance VA testing (ATS-HOTV)
Binocular function testing (Randot Preschool; if nil, test Butterfly; if nil, test Worth 4-shape)
Ocular alignment testing (cover/uncover, SPCT, PACT) at distance and near
Assessment of Diplopia and Adverse events
Stop LUMINOPIA treatment if amblyopia resolves (defined as ≤0 logMAR lines IOD with fellow eye VA no worse than 1 logMAR line below baseline)
Secondary Outcome Exam: 52 Weeks ± 2 weeks from Randomization
Monocular distance VA testing (ATS-HOTV)
Binocular function testing (Randot Preschool; if nil, test Butterfly; if nil, test Worth 4-shape)
Ocular alignment testing (cover/uncover, SPCT, PACT) at distance and near
Assessment of Diplopia and Adverse events

# SCHEDULE OF STUDY VISITS AND PROCEDURES

| Visit | Informed Consent | Demographics / Medical History | Distance VA | Binocular Function Testing | Ocular Alignment | PedEyeQ Functional Vision | PedEyeQ Social/Frustration/Worry | Binocular Diplopia Questionnaire | Adverse Events Questionnaire | Treatment Impact Questionnaire |
|---|---|---|---|---|---|---|---|---|---|---|
| **Enrollment Visit** | X | X | X | X | X | X | X | X | | |
| **1-week Call** | | | | | | | | | | |
| **13-week Visit** | | | X masked | X masked | X | | X | X | X | X |
| **26-week Visit** | | | X masked | X masked | X | X | | X | X | X |
| **27-week Call*** | | | | | | | | | | |
| **39-week Visit†** | | | X | X | X | | | X | X | |
| **52-week Visit†** | | | X | X | X | | | X | X | |

*27-week phone call timed 7 to 13 days after the 26-week primary outcome only for participants assigned to patching who have residual amblyopia and accept treatment with Luminopia at the 26-week primary outcome.

†The 39-week and 52-week post-randomization visits are completed by any participant assigned to patching who has residual amblyopia and accepts treatment with Luminopia at the 26-week primary outcome.

# Chapter 1: Background Information

## 1.1 Epidemiology and Clinical Characteristics

Amblyopia is the most common cause of reduced monocular visual acuity (VA) in children and young adults, with estimates of prevalence ranging from 1% to 5%.[1,2] Common risk factors are uncorrected anisometropia, strabismus, or a combination of these. In addition to reduced VA, amblyopia may also be associated with dysfunctions of accommodation, fixation, binocularity, vergence, reading speed and fluency, and contrast sensitivity.[3-12]

## 1.2 Current Practice

### 1.2.1 Monocular Penalization

The current foundation of amblyopia treatment is optical correction (when there is uncorrected refractive error) followed, if needed, by part-time patching or atropine penalization of the fellow eye.[13-18] This treatment approach has been shown to be effective in many younger children (3 to <7 years),[13-18] but residual amblyopia (20/32 or worse) is present in approximately 54% at age 10 years[19] and 40% at age 15 years.[20]

A possible explanation for failure of part-time patching treatment in some younger children is poor adherence with prescribed treatment regimens.[21,22] Nevertheless, data from studies using occlusion dose monitors[23,24] indicate that many children who successfully adhere to prescribed part-time patching still fail to respond fully. Such data suggest that part-time patching may simply be inadequate in some young children with amblyopia.

### 1.2.2 Dichoptic Treatments

An alternative treatment approach that has gained momentum in recent years is dichoptic therapy.[25] Although monocular penalization has been the predominant amblyopia treatment approach for many years, some have advocated that a dichoptic (binocular) approach has additional value.[26] Dichoptic treatments for amblyopia provide simultaneous but separate and independent stimulation to each eye, incorporating binocular elements, but modifying the input to the sound eye by introducing blur, reduced contrast, and/or reduced luminance. Dichoptic treatment strategies may also differentially modify central versus peripheral vision. The neuro-physiological basis for dichoptic treatment is supported by evidence that binocular cortical mechanisms remain intact even in adults with strabismic amblyopia.[27]

Over the past 20 years, dichoptic treatments have evolved from office-based technologies[28-30] to those that can be conducted in the home. Home-based technologies have many advantages, including convenience and reduced cost associated with less in-office care-provider time. Current home-based dichoptic treatments typically utilize games, movies, or web-based content. Both dichoptic games and dichoptic movies have been previously studied to a limited extent in younger children with amblyopia.[25,31-34]

#### 1.2.2.1 Dichoptic Games

PEDIG has previously evaluated two dichoptic iPad games as treatment for amblyopia in RCTs in younger children. In ATS18,[31] the Tetris falling blocks game was found *not* to be non-inferior to patching; however, only 22% completed >75% of prescribed gameplay (objectively

monitored).[34] In the ATS20 younger cohort of 4- to 6-year-olds,[32] binocular Dig Rush treatment resulted in greater improvement in amblyopic-eye VA at 4 weeks but not at 8 weeks compared with continued spectacles alone. Only half of 46 participants (57%) completed >75% of prescribed gameplay (objectively monitored) over the entire 8 weeks.[32]

Another RCT of dichoptic game play reported similar problems with adherence in younger children.[33] Likewise, a study evaluating barriers to successful dichoptic video game play[35] reported that inability to understand game requirements was a significant barrier to successful treatment in children <5.5 years of age.

These previous data strongly suggest that poor comprehension and poor adherence with game play are factors that have likely contributed to failure to show a benefit of this modality of dichoptic treatment.

#### 1.2.2.2 Dichoptic Movies/Shows

Home-based dichoptic movies have been evaluated in younger children in a small number of previous randomized trials.[36,37] Luminopia is a dichoptic movie technology (often termed a digital therapeutic with software as the medical device) available for use in the USA since 2022 and has been approved by the FDA for the treatment of amblyopia in children 4 to 7 years of age.

Luminopia displays a large library of web-based video content through a virtual reality (VR) headset, utilizing computational algorithms to split the source video into 2 streams (one to each eye) and modify the input in real time. Contrast in the sound eye is reduced to 15% and a series of 6 different dichoptic masks overlay the video content, rotating every 30 seconds.

Xiao et al[36] conducted a randomized trial comparing dichoptic movies using the Luminopia device versus continued glasses alone. Of 103 enrolled children (aged 4 to 7 years) 52 were randomly assigned to continued glasses and 51 to dichoptic movies using Luminopia 1 hour/day, 6 days a week. At the 12-week outcome, mean amblyopic eye VA had improved 1.8 lines (95% CI: 1.4 to 2.3 lines; n=45) in the Luminopia group and 0.8 lines (95% CI: 0.4 to 1.3 lines; n=45) in the continued glasses group. At the planned interim analysis, the difference between groups was significant favoring Luminopia by 1.0 line (P=0.001; 96.14% CI: 0.3 to 1.6 lines) and the study was stopped early for success. Median adherence with Luminopia (objectively monitored by the device) was 88% over 12 weeks (IQR, 61 to 99%).

In a preceding non-randomized study,[38] Xiao et al prescribed Luminopia 1 hour/day for 12 weeks to 90 children 4- to 12-years of age (mean 6.7 ± 2.0 years) with amblyopia. Overall (n=74) the mean amblyopic-eye VA improved from 0.50±0.15 to 0.35±0.21 logMAR (1.5 logMAR lines, 95% CI: 1.2-1.8 lines, $P<0.001$) over 12 weeks.[38] Median adherence (objectively monitored by the device) was 86% (IQR, 70% to 97%).

### 1.3 Rationale for the Present Study

Current treatments for amblyopia have limited effectiveness in some young children. In a previous large, multicenter RCT, home-based dichoptic movies were shown to be superior to continued glasses alone, but treatment effectiveness compared with patching has not yet been

established. It is possible that dichoptic movies/shows are as effective as patching, in which case they would provide an appealing alternative treatment.

Standard patching treatment may also be associated with adverse effects including negative psychosocial experiences, bullying, and social stigma.[39-43] There are few direct measures of treatment impact and there is a need for instruments that assess the impact a treatment has on the child and their family. Such an assessment is of value especially for treatments that may be similar regarding effectiveness but differ regarding treatment experience. Dichoptic movies/shows with Luminopia technology show promise of better adherence and an easier treatment experience.

Treatment outcomes are typically measured only in terms of monocular VA despite evidence that amblyopia impacts many other visual functions.[3-12] An expanded assessment of amblyopia treatment outcomes, including evaluation of functional vision and quality of life, is important for future practice and research. Such testing will lead to an improved understanding of the wider-reaching benefits of amblyopia treatment and enable further exploration of possible differential treatment benefits with different modalities.

In summary, while current treatment approaches are moderately effective in many younger children with amblyopia, the high prevalence of residual amblyopia and the challenges associated with patching treatment call for consideration of alternative, age-appropriate treatments. Treatments less onerous than patching need to be considered even if treatment outcomes are only equally effective.

If dichoptic therapy using the Luminopia digital therapeutic system is confirmed to be non-inferior to standard part-time patching for improving amblyopic eye best-corrected VA, this study would provide evidence to support Luminopia as a reasonable alternative to patching in young children. In addition, we plan to assess: 1) treatment impact to provide data on whether there are advantages to Luminopia regarding treatment burden and treatment difficulty, 2) impact on functional vision and 3) impact on social and frustration / worry quality of life concerns.

## 1.4 Potential Risks and Benefits of Study Treatment

### 1.4.1 Known Potential Risks

#### 1.4.1.1 Patching

Patching treatment may potentially cause a decrease of VA in the non-amblyopic eye (reverse amblyopia), but this is extremely unlikely when the fellow eye has several hours without occlusion each day, and should it occur, is almost always reversible. If reverse amblyopia occurs, investigators should contact one of the protocol chairs to discuss future management.

Skin irritation may develop due to the adhesive patch, but this is expected to be rare with only 2 hours per day of patching. If irritation develops the participant will be provided with a fabric patch to wear on their glasses (plano glasses will be provided for children who are not already wearing glasses).

Diplopia with patching is expected to be rare based on our experience in ATS18 in which only 2% reported diplopia at a frequency of once per week (the maximum frequency reported).[31]

Likewise, the development of a new strabismus or worsening of a preexisting strabismus is expected to be rare with a rate of 5.9% found in the patching group in ATS18.[31]

#### 1.4.1.2 Luminopia

In a previous randomized clinical trial evaluating Luminopia vs continued glasses alone in children aged 4 to 7 years[36], 10 (20%) of 51 patients experienced non-serious adverse events in the treatment group vs. 7 (13%) of 54 patients in the continued glasses group. In the Luminopia treatment group adverse events were new heterotropia in 3 (6%), worsening VA in the amblyopic eye in 2 (4%), worsening VA in the fellow eye in 2 (4%), headache in 4 (8%), eyestrain in 1 (4%), with single cases each of dizziness, increase in frequency of night terrors, eye twitching, and facial redness.

In the continued glasses group adverse events were diplopia in 1 (2%), new heterotropia in 2 (4%), worsening heterotropia in 1 (2%), worsening VA in the amblyopic eye in 4 (7%), headache in 1 (2%) and pain from glasses in 1 (2%). No serious adverse events were reported. The most frequent non-serious adverse event potentially related to Luminopia was headache (8%).

In a preceding non-randomized study evaluating 90 participants aged 4 to 12 years,[40] the most common adverse events were headaches (n=6), eye strain (n=3), blurry vision (n=2), and worsening VA (n=2). One participant developed a new strabismus. All adverse events were graded as mild in severity.

The Luminopia headset may become warm during normal usage. If the surface touching the face feels hot, the participant should stop using the headset immediately and wait for it to cool down before re-using.

Luminopia treatment is considered "digital media" use for children. An American Academy of Pediatrics (AAP) policy statement recommends that children 2 to 5 years should be limited to no more than 1 hour per day of digital media use, noting that heavy media use during preschool years is associated with small but significant increases in BMI and sets the stage for weight gain later in childhood. During the informed consent process, parents of children aged 4 or 5 years will be advised of these potential risks associated with digital media if they are prescribed Luminopia therapy.

### 1.4.2 Known Potential Benefits

The potential benefit of treatment with patching or treatment with Luminopia is improvement in amblyopic eye VA.

### 1.4.3 Risk Assessment

Luminopia is a software-only digital therapeutic designed to be used with commercially available Head-Mounted Displays (HMDs) which are compatible with a software application. Luminopia is approved by the FDA and indicated for improvement in visual acuity in amblyopia patients, aged 4-7, associated with anisometropia and/or with mild strabismus, having received treatment instructions (frequency and duration) as prescribed by a trained eye-care professional.

The expected adverse events from Luminopia are summarized in 1.4.1.2 and do not pose a greater risk than what the typical child would experience in their normal day-to-day activities (e.g., wearing glasses, wearing small adhesives like band aids, watching television, playing videogames, etc.).

The safety of Luminopia beyond 12 weeks is unknown; however, the expected adverse events between 12 weeks and 26 weeks in the current study are expected to be similar in type and severity to the type and severity summarized in 1.4.1.2.

Since Luminopia does not pose a significant risk to participants, the Sponsor has determined that Luminopia is not a significant risk device.

The expected adverse events from patching are summarized in 1.4.1.1 and are non-significant.

The Sponsor has determined that the protocol's level of risk is consistent with 45 CFR 46.404 and 21 CFR 50.51, which indicates research not involving greater than minimal risk.

**1.5 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 (GCP).

The protocol is not considered a significant risk device study, since Luminopia is a non-invasive product that has been approved by the U.S. Food and Drug Administration (FDA) as treatment for amblyopia in children aged 4 to 7 years for up to 12 weeks. Therefore, an investigational device exemption (IDE) from the FDA is not required to conduct the study. However, the study must still comply with the abbreviated requirements of 21 CFR 812.2(b) as a non-significant risk device under an investigation to evaluate safety and efficacy as used specified in accordance with this protocol.

# Chapter 2: Study Enrollment and Screening

## 2.1 Participant Recruitment and Enrollment

The study plans to enroll a minimum of 238 participants. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants whose parents have signed an informed consent form (and child has signed assent form, if required) can be enrolled up until the end date, which means the recruitment goals might be exceeded; however, total recruitment will not exceed 250 participants.

Study participants will be recruited from approximately 70 clinical centers in North America. All eligible participants will be included without regard to sex, race, or ethnicity. There is no restriction on the number of participants to be enrolled or randomized by each site toward the overall recruitment goal.

### 2.1.1 Informed Consent and Authorization Procedures

A child is considered for the study after undergoing a routine eye examination as part of standard of care that identifies amblyopia appearing to meet the eligibility criteria. Children may also be referred to a study investigator from another eye-care or health-care provider. The study will be discussed with the child's parent(s) or legal guardian(s) (referred to subsequently as parent(s)). Parent(s) who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent and assent must be obtained from a parent prior to performing any study-specific procedures that are not part of the child's routine care and/or collecting any data for the study.

If the participant and/or parents are not fluent in written and spoken English, then the consent and/or assent forms must be translated into a language of fluence for the participant/parent. Further, a qualified interpreter must be available for the consent process and for all subsequent study-related interactions.

A participant is considered enrolled when the informed consent and assent forms have been signed, as applicable.

## 2.2 New or Change in Spectacle Correction If Needed

New spectacles or a change in spectacles may be prescribed for participants who have not had a cycloplegic refraction within 7 months *OR* if their current spectacles do not meet spectacle tolerance criteria (2.3 #6) *OR* in cases where the investigator determines that updating the spectacles is necessary for best clinical care, IF they ALSO meet ALL the other inclusion criteria (2.3) while wearing their current refractive correction.

The prescribed spectacles must be based upon a cycloplegic refraction performed on the day of enrollment or within 7 months and must meet eligibility criteria in 2.3 #6. If new spectacles are prescribed and paid for by the study, the investigator should ensure that visual acuity is still expected to meet eligibility criteria in 2.3 #2. As needed, VA should be measured (using the investigator's preferred VA testing method) in the intended spectacle prescription if the child is not cyclopleged or in the full cycloplegic refractive error if the child is cyclopleged.

The participant will return for standard of care visits until they meet eligibility criteria (including stability criteria) below in 2.3 #6.

Any new contact lenses or change to contact lenses will NOT be paid for by the study.

**2.3 Participant Inclusion Criteria**

At the time of enrollment, individuals must meet all the following inclusion criteria to be eligible to participate in the study.

1. Age 4 to 7 years.
2. Visual acuity, measured in each eye without cycloplegia in current refractive correction (if applicable) using the ATS-HOTV VA protocol on a study-approved device displaying single surrounded optotypes, as follows:
   a. VA in the amblyopic eye 20/40 to 20/200 inclusive.
   b. Age-normal VA in the fellow eye:[44,45]
      - 4 years: 20/40 or better; 5-6 years: 20/32 or better; 7 years: 20/25 or better
   c. Interocular difference ≥ 3 logMAR lines (i.e., amblyopic eye VA at least 3 logMAR lines worse than fellow eye VA).
3. Amblyopia associated with strabismus, anisometropia, or both (previously treated or untreated).
   a. Criteria <u>for strabismic amblyopia</u>: At least one of the following must be met:
      - Presence of a heterotropia on examination at distance or near fixation (with optical correction), must be <=5 prism diopters (Δ) by SPCT at distance and near fixation.
      - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia).
   b. Criteria <u>for anisometropia</u>: At least one of the following criteria must be met:
      - ≥1.00 D difference between eyes in spherical equivalent (SE).
      - ≥1.50 D difference in astigmatism between corresponding meridians in the two eyes.
   c. Criteria <u>for combined-mechanism</u>: Both of the following criteria must be met:
      - A criterion for strabismus is met (see above).
      - ≥1.00 D difference between eyes in spherical equivalent OR ≥1.50 D difference in astigmatism between corresponding meridians in the two eyes.
4. No more than 2 weeks (cumulative) of prior dichoptic treatment.
5. No treatment with cycloplegic eyedrops (e.g., atropine) in the past 2 weeks; other treatments allowed up to enrollment but then must be discontinued.
6. Refractive correction is required (single vision lenses or contact lenses) for any of the following refractive errors based on a cycloplegic refraction completed within the last 7 months:
   - Hypermetropia of 2.50 D or more by SE
   - Myopia of amblyopic eye of 0.50D or more SE
   - Astigmatism of 1.00D or more
   - Anisometropia of more than 0.50D SE

*NOTE: Monocular or binocular contact lens wear is allowed provided the contact lenses meet the refractive error correction requirements below. For each child, all testing must be performed using the same form of optical correction (i.e., no changing between contacts and spectacles).*

a. Spectacles/contact lens correction prescribing instructions referenced to the cycloplegic refraction completed within the last 7 months:
   - SE must be within 0.50D of fully correcting the anisometropia (if new glasses are prescribed, reduction in plus sphere must be symmetric in the two eyes).
   - SE must not be under corrected by more than 1.50D SE.
   - Cylinder power in both eyes must be within 0.50D of fully correcting the astigmatism.
   - Axis must be within +/- 10 degrees if cylinder power is ≤1.00D, and within +/- 5 degrees if cylinder power is >1.00D.
   - Myopia must not be under corrected by more than 0.25D or over corrected by more than 0.50D SE, and any change must be symmetrical in the two eyes.

b. Spectacles/contact lens correction (with or without other treatment such as patching) meeting the above criteria must be worn:
   - For at least 18 weeks (immediately prior to enrollment) ***OR*** until VA stability is documented (defined as <0.1 logMAR change by the same testing method measured on 2 consecutive exams at least 9 weeks apart).
     - For determining VA stability (non-improvement):
       - The **first** of two measurements may be made 1) in current correction, or 2) in trial frames with or without cycloplegia or 3) without correction (if new correction is prescribed),
       - The **second** measurement must be made without cycloplegia in the correct spectacles/contact lens correction that has been worn for at least 9 weeks.
       - *NOTE: Because this determination is a pre-randomization, the method of measuring VA is not mandated.*

7. Participant is willing to wear the Luminopia headset.
8. Participant is willing to continue full-time spectacles/contact lens wear (if needed).
9. Participant is willing to accept assignment to either dichoptic shows (view 1 hour per day 6 days per week) OR part-time patching (2 hours per day 7 days per week) for 26 weeks.
10. Interpupillary distance of 52mm to 72mm inclusive.
11. Investigator is willing to prescribe Luminopia or patching per protocol.
12. Parent understands the protocol and is willing to accept randomization.
13. Parent has phone (or access to phone) and is willing to be contacted by JAEB Center.
14. Relocation outside area of active PEDIG site within the next 52 weeks is not anticipated.

### 2.4 Participant Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from study participation.

1. Heterotropia more than 5Δ at distance or near (measured by SPCT in current correction)
2. Prism lenses or need of a prism prescription at enrollment.
3. Current bifocal spectacles (eligible only if bifocal discontinued 2 weeks prior to enrollment).

4. Myopia greater than -6.00D spherical equivalent in either eye.
5. Previous intraocular or refractive surgery.
6. Known skin reactions to patch or bandage adhesives.
7. Ocular co-morbidity that may reduce VA determined by an ocular examination performed within the past 7 months (*Note: nystagmus per se does not exclude the participant if the above visual acuity criteria are met using patch occlusion. Fogging is not permitted*).
8. Diplopia more than once per week over the last week prior to enrollment by parental report.
9. History of light-induced seizures.
10. Severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Participants with mild speech delay or reading and/or learning disabilities are not excluded.
11. Participation in a prior study involving patching for amblyopia
12. Immediate family member (biological or legal guardian, child, sibling, parent) of investigative site personnel directly affiliated with this study or an employee of the JAEB center for Health Research.

## 2.5 Procedures at Enrollment Visit

### 2.5.1 Historical Information

After informed consent has been signed, historical information elicited will include the following: date of birth, sex, race, ethnicity, history of allergy to patching, and prior amblyopia therapy including refractive correction.

### 2.5.2 Ability to Use Luminopia

Interpupillary distance will be measured using investigator's standard method or a PEDIG-provided IPD ruler. Participants with interpupillary distance <52mm or >72mm will not be eligible to participate in the study.

Site personnel will confirm that the participant is able and willing to wear the Luminopia headset by:

1. Showing the child the devices in the clinic and allowing them to try them on, if desired.
2. Asking the child if they are willing to wear the headset for up to an hour a day, 6 days a week.

### 2.5.3 Clinical Testing

Participants who meet all eligibility criteria in section 2.3 and 2.4 including visual acuity stability criteria in current spectacles/contract lens correction will complete the following tests and assessments.

All examination procedures must be tested on the day of enrollment, except the cycloplegic refraction and ocular examination, which may be performed within 7 months prior to enrollment.

The following procedures should be performed at the enrollment visit in the following order:

**Lensometry**:
Verify current refractive correction by lensometry. If a participant is wearing contact lenses, verify contact lens prescription.

**Questionnaires:**

1. Assessment of Binocular Diplopia:
   An estimate of the frequency of diplopia (if any) will be determined by asking the parent "has your child complained of double vision over the last week." If yes, the parent is asked how frequently during the last week the child has complained of double vision: "once per week," or "2 to 3 times per week," or "4 or more times per week." Any study personnel may assess diplopia. Children who have reported diplopia more than once over the past week are ineligible (see section 2.3).
2. PedEyeQ Functional Vision Domain[46]:
   A child questionnaire for children ages 5-7 years (inclusive), and a proxy questionnaire completed by the parent regarding their child's functional vision. The child questionnaire is administered to the child by study personnel. The Proxy questionnaire is completed by the parent.
3. PedEyeQ Social Domain and Frustration/Worry Domain[46]:
   Child questionnaire for children ages 5-7 years (inclusive), and proxy questionnaire completed by the parent regarding their child. The child questionnaire is administered to the child by study personnel. The Proxy questionnaire is completed by the parent.

**Clinical Testing** (in the following order) **is performed in the participant's current refractive correction, if required, without cycloplegia:**

4. Distance Visual Acuity Testing:
   Monocular distance VA testing will be performed in current refractive correction (if required) in each eye by a certified examiner using the electronic ATS-HOTV VA on a study-certified VA tester displaying single surrounded optotypes.
5. Binocular Function Testing (by a certified examiner):
   - Stereoacuity will be tested at 40cms in current refractive correction using the Randot Preschool Test.
   - If nil stereoacuity on the Randot Preschool Test, the Random Dot Butterfly test will be performed at 40cms.
   - If nil stereoacuity on the Random Dot Butterfly, the Worth 4-shape will be administered.
6. Ocular Alignment Testing:
   Ocular alignment will be assessed in current spectacle/contact lens correction by the cover test, simultaneous prism and cover test (SPCT) (in cases of strabismus detected by cover test), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter).
7. Additional Clinical Testing:
   Ocular examination as per investigator's clinical routine.

## 2.6 Randomization of Eligible Participants

The JAEB Center will construct a Master Randomization List using a permutated block design stratified by VA in the amblyopic eye as 20/40 to 20/80 (moderate impairment) versus 20/100 to 20/200 (severe impairment) and any previous treatment (glasses only versus other treatment in addition to glasses) which will specify the order of treatment group assignments.

All eligible participants enrolled in the study will be followed for up to 52 weeks. Participants will be randomly assigned in a 1:1 allocation to one of the following two treatment groups for 26 weeks:

- **Luminopia Group**: dichoptic movies/shows wearing the Luminopia headset prescribed 1 hour per day (treatment time can be split into shorter sessions totaling 1 hour each day) 6 days a week with optical correction, if needed.

- **Patching Group**: patching of the fellow eye 2 hours per day (treatment time can be split into shorter sessions totaling 2 hours each day) 7 days per week with optical correction, if needed.

Once a child is assigned to treatment, they will be included in the analysis regardless of whether the assigned treatment is received. Thus, the investigator must not randomly assign a participant to treatment unless convinced that the parent will accept either of the treatments.

# Chapter 3: Randomized Trial Procedures

## 3.1 Treatment

Investigators must not start any additional amblyopia treatment (other than that outlined below) prior to the 26-week primary outcome visit.

### 3.1.1 Luminopia Group

Participants randomized to the Luminopia group will be instructed to watch dichoptic movies/shows using the Luminopia device at home, for 1 hour/day, 6 days/week, for 26 weeks unless resolved at 13 weeks (see below), while continuing to wear any optical correction (including while wearing the Luminopia device).

Parents will be instructed that the 1 hour of daily treatment should be completed in a single 60-minute session, but if this is not possible for whatever reason, the treatment may be divided into shorter sessions totaling 1 hour per day. Adherence with Luminopia treatment will be recorded electronically throughout the study.

### 3.1.2 Patching Group

Participants assigned to the patching group will be instructed to wear an adhesive patch over the fellow eye (while continuing to wear any optical correction) for 2 hours per day, 7 days per week for 26 weeks. Parents of participants will be instructed that the 2 hours of daily patching should be completed in a single 2-hour session, but if this is not possible for whatever reason, the treatment may be divided into shorter sessions totaling 2 hours per day.

Adherence with prescribed patching treatment will be monitored throughout the study using a parental calendar. Parents will be asked to complete an adherence calendar by manually recording the number of minutes that the child wore the patch each day. The investigator will review the calendars at each follow-up visit.

## 3.2 Phone Call

Site personnel will call all participants 1 week (7 to 13 days) after randomization to encourage adherence and confirm that there are no problems with randomized treatment. Site personnel will also call participants in the patching group who switch to Luminopia treatment at the 26-week primary outcome visit (7 to 13 days after the 26-week visit), again to encourage adherence with treatment and to confirm that there are no problems with the Luminopia device.

## 3.3 Follow-up Schedule Through 26-Week Primary Outcome

The follow-up schedule through 26-week primary outcome is timed from randomization:

| Visit | Target Day Post-Randomization | Target Window Post-Randomization* | Allowable Window Post-Randomization |
|---|---|---|---|
| 1-Week Phone Call | 7 days | 7 to 13 days | 7 to 27 days |
| 13-Week Office Visit | 91 days | 77 days to 105 days | 56 days to 125 days |
| 26-Week Primary Outcome | 182 days | 168 days to 196 days | 126 days to 238 days |

* Target window for phone calls is 7 to 13 days from previous office visit. Target window for office visits is target day +/- 2 weeks.

### 3.3.1 Resolution of Amblyopia at 13-Week Office Visit

If amblyopia resolves at the 13-week visit (defined as ≤0 logMAR lines IOD with fellow eye VA no worse than 1 logMAR line below baseline), participants will discontinue Luminopia or patching treatment but return for the 26-week primary outcome visit. No other treatment should be prescribed before the 26-week outcome visit.

## 3.4 Continued Follow-up Post 26-Week Primary Outcome

Children originally randomized to Luminopia will end the study at 26 weeks.

Children originally randomized to Patching whose amblyopia HAS NOT resolved (1 or more logMAR lines IOD is present with the originally amblyopic eye worse than fellow eye) at the 26-week primary outcome visit, will be offered a trial of Luminopia treatment, and if accept treatment, will continue in follow-up as defined below. Otherwise, the study will end.

The follow-up schedule through 52-week outcome is timed from the 26-week visit:

| Visit | Target Day Post 26-week visit | Target Window Post-26-week* | Allowable Window Post-26-week |
|---|---|---|---|
| 27-Week Phone Call | 7 days | 7 to 13 days | 7 to 27 days |
| 39-Week Office Visit | 91 days | 77 days to 105 days | 56 days to 125 days |
| 52-Week Office Visit | 182 days | 168 days to 196 days | 126 days to 238 days |

* Target window for phone call is 7 to 13 days from previous office visit. Target window for office visits is target day +/- 2 weeks.

### 3.4.1 Resolution of Amblyopia at 39-Week Office Visit

If amblyopia resolves at the 39-week visit (defined as ≤0 logMAR lines IOD with fellow eye VA no worse than 1 logMAR line below baseline), participants will discontinue treatment with Luminopia, but continue follow-up until the 52-week visit.

## 3.5 Follow-up Visit Testing Procedures

Participants will be seen at follow-up visits as outlined in sections 3.3 and 3.4.

All procedures will be performed with the participant's current refractive correction without cycloplegia.

- If a participant currently wears spectacles or contact lenses but they are not available or are not within tolerance at the 13-week follow-up examination, testing may be performed with current correction in trial frames.
- Habitual refractive correction (meeting study requirements) must be worn for the primary outcome visit at 26 weeks.

A Masked Examiner must complete distance VA and binocular function testing at the 13, and 26-week visits. The masked examiner must be PEDIG certified for the required testing. All other assessments are unmasked. Prior to the Masked Examiner entering the room, participants and parents should be instructed not to discuss their treatment with the Masked Examiner.

The following procedures should be performed at each visit in the following order:

**Lensometry (unmasked)**:
Verify current refractive correction by lensometry. If a participant is wearing contact lenses, verify contact lens prescription.

**Questionnaires (all unmasked):**

1. Assessment of Binocular Diplopia (at 13, and 26 weeks; and at 39, and 52 weeks if treated with Luminopia):
   An estimate of the frequency of diplopia (if any) will be determined by asking the parent "has your child complained of double vision over the last week." If yes, the parent is asked how frequently during the last week the child has complained of double vision: "once per week," or "2 to 3 times per week," or "4 or more times per week." Any study personnel may assess diplopia.
2. Adverse Events (at 13, and 26 weeks; and at 39, and 52 weeks if treated with Luminopia):
   A standardized questionnaire will be administered to the parent to collect data on possible adverse events.
3. Treatment Impact Questionnaire (at 13, and 26 weeks):
   An item bank of participant-derived questionnaire items will be completed by the child themselves (for children ages 5-7 years inclusive) and by the child's parent (proxy rating regarding impact on their child and also questions regarding impact on the parent themselves). Questions pertain to the impact of the child's specific treatment on the child themselves and on the parent / family.
4. PedEyeQ Social Domain and Frustration/Worry Domain (at 13 weeks only):
   Child questionnaire for children ages 5-7 years (inclusive) and proxy questionnaire for the parent regarding their child. The Child questionnaire is administered to the child by study personnel and the Proxy questionnaire is completed by the parent.
5. PedEyeQ Functional Vision Domain (at 26 weeks only):
   A child questionnaire for children ages 5-7 years (inclusive), and proxy questionnaire for the parent regarding their child's functional vision. The child questionnaire is administered to the child by study personnel. The Proxy questionnaire is completed by the parent.

**Clinical Testing performed in the participant's current refractive correction (if required) without cycloplegia in the following order at ALL VISITS. Masked testing must be performed by a PEDIG certified examiner.**

- *Habitual refractive correction (meeting study criteria) is required for the 26-week primary outcome exam.*
- *Testing in trial frames with current Rx is allowed at 13, 39 and 52 weeks if current refractive correction is not available or does not meet study criteria.*

6. Distance VA Testing (**at 13, and 26 weeks masked**; at 39, and 52 weeks if applicable unmasked): Monocular distance VA testing will be performed in current refractive correction (if required) in each eye by a certified examiner using the electronic ATS-HOTV VA on a study-certified VA tester displaying single surrounded optotypes.

7. Binocular Function Testing by a certified examiner in current refractive correction if required (**at 13, and 26 weeks Masked**; at 39, and 52 weeks if applicable unmasked):
    - Stereoacuity will be tested at 40cms in current refractive correction using the Randot Preschool Test.
    - If nil stereoacuity on the Randot Preschool Test, the Random Dot Butterfly test will be administered at 40cms.
    - If nil stereoacuity on the Random Dot Butterfly, then the Worth 4-shape will be administered at 40cms.
8. Ocular Alignment Testing (Unmasked): Ocular alignment will be assessed by a certified examiner in current spectacle/contact lens correction by the cover test, SPCT (in cases of strabismus detected by cover test), and PACT in primary gaze at distance (3 meters) and at near (1/3 meter).
9. Adherence Monitoring (Unmasked): Adherence data Luminopia will be downloaded and patching adherence calendars will be reviewed.

### 3.5.1 Masked Examiner

The Masked Examiner must be certified to test VA and binocular function testing. Because the Masked Examiner must be masked to the participant's treatment group and be someone other than the managing clinician (in many cases the managing clinician will be the investigator, but this is not required).

## 3.6 Non-Study Visits and Treatment

Investigators may schedule additional visits at their own discretion. Participants will continue to follow the study-specified follow-up schedule regardless of any non-study visits. No data will be collected at non-study visits for the purpose of the study.

Investigators must not start any additional non-randomized amblyopia treatment or stop randomized treatment prior to the 26-week primary outcome visit without first contacting a protocol chair. As part of randomized treatment, if amblyopia is resolved at 13 weeks, randomized treatment can be discontinued.

For participants who continue in the study after 26 weeks, Luminopia treatment may be stopped at 39 weeks if amblyopia meets resolution criteria, but otherwise Luminopia treatment will continue up to the 52-week visit. No other treatment should be prescribed prior to the 52-week outcome visit.

## 3.7 Management of Refractive Error

No cycloplegic refraction is mandated during the study. Nevertheless, if the investigator suspects that refractive error may not be corrected according to study guidelines, a cycloplegic refraction should be performed. If the new cycloplegic refraction compared to the old cycloplegic refraction differs by $\geq$0.75 D sphere or $\geq$0.75 D cylinder or $\geq$0.75 D in SE anisometropia or axis change of 6 degrees or more when cylinder is 1.00 D or more; then a change in spectacles is required. Whether to update the spectacles for smaller changes in refraction is at investigator discretion.

When new spectacles are prescribed, the refractive correction prescribed must meet the requirements as described in section 2.3 #6. The updated spectacles will be paid for by the study.

### 3.8 Management of Strabismus

Because of the short duration of the primary outcome for the study and the age group being studied, strabismus surgery is not allowed prior to the 26-week primary outcome visit.

If surgery must be performed, a protocol chair should be contacted and a masked exam prior to surgery scheduled. The participant should remain in the study and complete all necessary visits. If surgery is performed, it must be recorded in the comment section of the Follow-up Examination Form.

# Chapter 4: Study Device

## 4.1 Description of the Luminopia Device

Luminopia is a software-only digital therapeutic designed to be used with commercially available Head-Mounted Displays (HMDs) which are compatible with the software application. The software application requires an internet connection for treatment. The Luminopia medical software application presents slightly different video content to each eye to encourage amblyopic eye usage. Treatment using Luminopia will be prescribed for 1 hour per day, 6 days per week, consistent with its FDA approval.

### 4.1.1 Headset

The study will provide each participant with a VR headset pre-loaded with Luminopia software. The VR headset has a screen resolution of 564 pixels per inch, which constitutes the minimum display resolution requirement. The Luminopia system has been approved by the FDA for the treatment of moderate or severe amblyopia in children 4 to 7 years of age.

The Luminopia device should only be used in accordance with the manufacturer's instructions. Use in a safe and stationary environment with the HMD connected to Wi-Fi. Luminopia should only be used with the participant seated or lying down. If the participant experiences discomfort because the Luminopia device feels too heavy, the participant should try to use the Luminopia device while lying down on their back.

The HMD should be kept away from heat sources, water, moisture, open flames, or direct sunlight. If the participant intends to use the Luminopia device away from home for an extended period of time, the parent should bring the charger provided with the HMD to charge the device as needed. The participant should not use the Luminopia device while the HMD is charging.

### 4.1.2 Internet Requirements

Wireless internet with Wi-Fi speed near the router that exceeds 5 Mbs is required to operate Luminopia. Faster network speeds will result in a better product experience. Potential study participants who do not have the required internet capabilities in their home will be provided Wi-Fi access using a Hotspot at no cost for the duration of the study.

## 4.2 Device Delivery and Return

Device Delivery and Return procedures will be detailed in the site instruction manual.

## 4.3 Device Accountability Procedures

Device accountability procedures will be detailed in the site instruction manual.

### 4.3.1 Device Failure

Parents will be provided with written instructions regarding the process to follow should the Luminopia device fail. If the device needs to be replaced PEDIG will provision a replacement.

### 4.3.2 Participant Access to Study Device After Primary Outcome Visit

Participants randomly assigned to receive patching treatment who have not resolved at the 26-week primary outcome visit, will be offered Luminopia therapy and if accepted, followed forward with a 27-week phone call and follow-up visits at 39-weeks and 52-weeks post-randomization. Luminopia therapy will NOT continue beyond the 52-week visit.

Participants randomly assigned to receive Luminopia will end treatment after the 26-week primary outcome visit.

# Chapter 5: Testing Procedures and Questionnaires

## 5.1 Questionnaires

1. Assessment of Binocular Diplopia:
   An estimate of the frequency of diplopia (if any) will be determined by asking the parent "has your child has complained of double vision over the last week." If yes, the parent is asked how frequently during the last week the child has complained of double vision: "once per week," or "2 to 3 times per week," or "4 or more times per week." Any study personnel may ask the parent to rate diplopia. Testing time is approximately 1 minute.

2. PedEyeQ Functional Vision Domain:
   A child questionnaire for children ages 5-7 years (inclusive) and a proxy questionnaire completed by the parent regarding their child's functional vision. The child questionnaire is administered by study personnel. The proxy questionnaire is completed by the parent. The questionnaires take about 3-4 minutes to complete.

3. PedEyeQ Social Domain:
   A child questionnaire for children ages 5-7 years (inclusive) and a proxy questionnaire completed by the parent regarding their child's social concerns. The child questionnaire is administered by study personnel. The Proxy questionnaire is completed by the parent. The questionnaires take about 3-4 minutes to complete.

4. PedEyeQ Frustration / Worry Domain:
   A child questionnaire for children ages 5-7 years (inclusive), a proxy questionnaire completed by the parent regarding their child's Frustration / Worry. The child questionnaire is administered by study personnel. The Proxy questionnaire is completed by the parent. The questionnaires take about 3-4 minutes to complete.

5. Treatment Impact Questionnaire:
   An item bank of participant-derived questionnaire items will be completed by the child themselves (for children ages 5-7 years inclusive) and by the child's parent (proxy rating regarding impact on their child and also questions regarding impact on the parent themselves). Questions pertain to the impact of the child's specific treatment on the child themselves and on the parent / family. Testing is anticipated to take 5-7 minutes.

6. Adverse Event Questionnaire:
   A standardized questionnaire will be administered to the parent to collect data on possible adverse events. The questionnaire is anticipated to take 1 minute to complete.

## 5.2 Clinical Assessments

The following procedures will be performed at each visit as defined in the *ATS Procedures Manual:*

7. Distance VA Testing:

Monocular distance VA testing will be performed in refractive correction in each eye by a certified examiner using the electronic ATS-HOTV VA protocol on a study-certified VA tester displaying single surrounded optotypes. The VA protocol used at enrollment will be used throughout the study regardless of age at follow-up. Testing time for both eyes typically is in the range of 5 to 15 minutes.

8. Binocular Function Testing (by a certified examiner):
   Stereoacuity will be tested at 40cms in current refractive correction using the Randot Preschool Test.
   - If nil stereoacuity on the Randot Preschool Test, then the Random Dot Butterfly test will be administered at 40 cm.
   - If nil stereoacuity on the Random Dot Butterfly, the hand-held Worth 4-Shape test will be performed at 40 cm.
   - Testing typically takes 3-5 minutes.

9. Ocular Alignment Testing: Ocular alignment will be assessed by a certified examiner in current spectacle correction by the cover test, simultaneous prism and cover test (SPCT) (in cases of strabismus detected by cover test), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter). Testing time is typically 1 to 3 minutes.

# Chapter 6: Miscellaneous Considerations

## 6.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided the parents' contact information. The Jaeb Center may contact the parents of the participants. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the participant's family and to help coordinate the scheduling of study visits, when needed.

## 6.2 Participant Compensation

Participant compensation will be specified in the informed consent form.

## 6.3 Cost of Treatment

Any new or changes to optical correction will be paid for during the study.

For those randomized to patching, patches will be paid for by the study for 26-weeks.

For those randomized to Luminopia, the cost of prescribed dichoptic treatment for 26-weeks will be paid for by the study.

For those randomized to patching who have residual amblyopia at 26 weeks, the cost of dichoptic treatment with Luminopia, if accepted, through 52-weeks will be paid for by the study.

For those randomized to Luminopia, the study will not pay for continued Luminopia treatment outside the study.

## 6.4 Participant Withdrawal

Participation in the study is voluntary and a participant may withdraw at any time. For participants who withdraw, their data collected prior to their withdrawal will be used. This stipulation is specified in the consent form.

## 6.5 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

# Chapter 7: Unanticipated Problem and Adverse Event Reporting

## 7.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Sites must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all three (3) of the following criteria:

1. Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document and (b) the characteristics of the participant population being studied
2. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
3. Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem that requires further reporting.

## 7.2 Adverse Events

### 7.2.1 Reportable Adverse Events

Because study treatment with patching and Luminopia are non-invasive and consistent with usual clinical care, it is not expected that there would be significant adverse events other than those already being captured as part of the clinical outcome assessments or questionnaire (e.g., worsening of fellow eye VA, development of new or worsening of strabismus, new diplopia, or report of headache, eyestrain, nausea, seizures, dizziness, increase in frequency of night terrors, or skin irritation).

### 7.2.2 Safety Oversight

A Data and Safety Monitoring Committee (DSMC) will review compiled safety data at periodic intervals, with a frequency of no less than twice a year. The DSMC can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMC review will be documented in a separate DSMC charter.

The objective of the DSMC review is to decide whether the study (or study treatment for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a

particular group, a particular study site, or for the entire study) is a potential outcome of a DSMC safety review.

### 7.2.3 Stopping Criteria

The study may be discontinued by the Steering Committee (with approval of DSMC) prior to the preplanned completion of follow-up for all study participants. No formal guidelines for stopping the study for futility or efficacy are pre-specified (see section 7).

### 7.2.4 Participant Discontinuation of Study Treatment

Rules for discontinuing study treatment use are one of the following:

- The investigator believes it is unsafe for the participant to continue to receive the treatment.
- The participant or parent requests that the treatment be stopped.

Even if the study treatment is discontinued, the participant will be encouraged to remain in the study through the 26-week Primary Outcome Visit with permission from the parent to allow ongoing data collection.

# Chapter 8: Statistical Considerations

## 8.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

## 8.2 Study Objective and Statistical Hypothesis

### 8.2.1 Primary Efficacy Outcome

The primary objective of the study is to determine if treatment by watching dichoptic movies/shows wearing the Luminopia One headset (subsequently referred to as LUMINOPIA) is non-inferior to treatment with 2 hours of patching per day 7 days per week (subsequently referred to as PATCHING) with respect to change in amblyopic eye distance VA from randomization to 26 weeks.

The primary efficacy outcome will be the change in amblyopic eye distance VA (measured as logMAR) from randomization to 26 weeks. Change in logMAR will be calculated as [outcome VA] – [randomization VA] such that a negative change indicates improvement in visual acuity, and a positive change indicates worsening.

The study is designed to test a one-sided null hypothesis that LUMINOPIA is inferior to PATCHING by 0.0625 logMAR (i.e., 5/8 of one line) or more in favor of the alternative hypothesis that LUMINOPIA is non-inferior to PATCHING.

$$H_0: \mu_{PATCHING} - \mu_{LUMINOPIA} \leq -0.0625 \text{ logMAR (LUMINOPIA inferior to PATCHING)}$$

$$H_a: \mu_{PATCHING} - \mu_{LUMINOPIA} > -0.0625 \text{ logMAR (LUMINOPIA not inferior to PATCHING)}$$

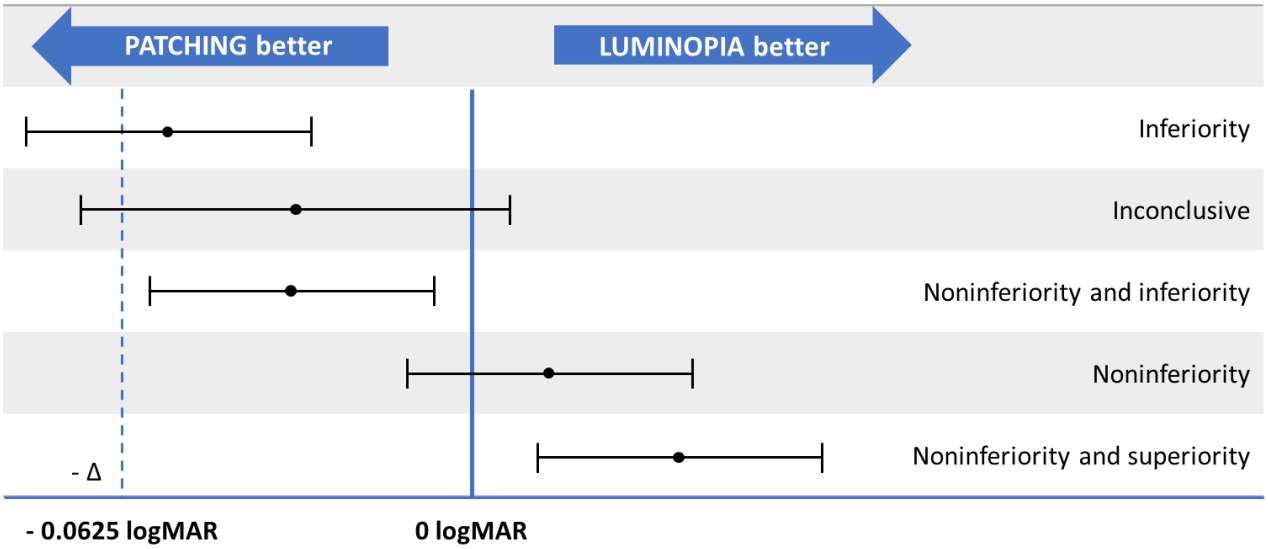
To represent the difference between treatment groups (PATCHING minus LUMINOPIA), a two-sided 95% confidence interval (CI) will be constructed. Since the LOWER limit of a two-sided 95% CI is equivalent to the LOWER limit of a one-sided 97.5% CI, this will allocate a significance level of 0.025 to be used in testing noninferiority.

Non-inferiority of LUMINOPIA to PATCHING will be declared if the LOWER limit of the two-sided 95% CI for the difference between treatment groups is greater than the non-inferiority limit of -0.0625 logMAR favoring PATCHING (Figure 1).

If non-inferiority is declared, a test of no difference (superiority test) for LUMINOPIA compared with PATCHING will be conducted.

**Figure 1. Depiction of Null and Alternative Hypotheses for Treatment Group Difference**

Mean difference (PATCHING – LUMINOPIA) and 95% CI of amblyopic eye distance VA




## 8.3 Sample Size

### 8.3.1 Effect of PATCHING

To estimate the treatment effect for those randomized to PATCHING, visual acuity data from participants prescribed 2 hours daily patching in a previous PEDIG study, ATS18,[31] were used. The data were limited to participants who met the eligibility criteria for the current study. In ATS18, 75 participants between the ages of 5 to 7 years experienced 0.17 logMAR (95% CI: 0.14 to 0.20) mean improvement in visual acuity after 16 weeks with a standard deviation of 0.13 logMAR (95% CI: 0.12 to 0.16).

### 8.3.2 Effect of LUMINOPIA

To estimate the treatment effect for those randomized to LUMINOPIA, visual acuity data from participants randomized to LUMINOPIA therapy were reviewed. Xiao et al[36] conducted a randomized trial comparing dichoptic movies using the Luminopia device versus continued glasses alone. Of 103 enrolled children (aged 4 to 7 years) 52 were randomly assigned to continued glasses and 51 to dichoptic movies using Luminopia 1 hour/day, 6 days a week. At the 12-week outcome, mean amblyopic eye VA had improved 0.18 logMAR (95% CI: 0.14 to 0.23; n=45) in the Luminopia group and 0.08 logMAR (95% CI: 0.04 to 0.13; n=45) in the continued glasses group. The study was stopped early for success having a difference between groups of 1.0 lines; P = 0.0011; 96.14% CI, 0.33-1.63 lines).

In a preceding non-randomized study,[38] Xiao et al prescribed Luminopia 1 hour/day for 12 weeks to 90 children 4- to 12-years of age (mean 6.7 ± 2.0 years) with amblyopia. Overall (n=74) the mean amblyopic-eye VA improved 0.15 logMAR (95% CI: 0.12 to 0.18) after 12 weeks.[38]

### 8.3.3 Selection of Noninferiority Margin

The non-inferiority (NI) margin for the primary outcome was determined by the Planning Committee using clinical judgment; based on simulated distributions of VA improvement corresponding to a mean difference between 2 populations of 0.025, 0.050, 0.0625, 0.075 and 0.10 logMAR. Side-by-side histograms illustrating the shift in the distribution for each mean were reviewed along with corresponding differences in proportions for clinically meaningful cut points, e.g., difference in percent improving by 0.2 logMAR or more (2 or more logMAR lines), or percent with final VA of 20/32 (0.2 logMAR) or better.

The consensus of the Planning Committee was that if LUMINOPIA was no worse than PATCHING by 0.0625 logMAR then LUMINOPIA would be considered non-inferior to PATCHING. This mean difference corresponded to a difference of 16% improving 2 or more logMAR lines (59% in the PATCHING group and 43% in the LUMINOPIA group).

As an alternative approach, the NI margin was calculated using statistical criteria, using half the lower limit of the 95% CI for change in VA after patching treatment in ATS18 as a guideline. In ATS18, half the lower limit of the 95% CI for change after 16 weeks was 0.07 logMAR; therefore, 0.0625 logMAR is a conservative choice as a noninferiority (NI) margin.

### 8.3.4 Sample Size Calculations and Assumptions

A common standard deviation (SD) of 0.14 logMAR and a true mean difference of 0.00 logMAR between LUMINOPIA and PATCHING groups were selected to calculate the required sample size for the current study. With the between-group difference of the change in logMAR VA calculated as PATCHING minus LUMINOPIA, the noninferiority margin would be -0.0625 logMAR to show directionality of the primary outcome hypotheses (Figure 1, section 8.2.1).

Using a noninferiority margin of -0.0625 logMAR and a one-sided Type 1 error rate of 0.025, the study would require 214 participants total (107 participants in each treatment arm) to complete the primary outcome to achieve 90% power to reject the null hypothesis that LUMINOPIA is not non-inferior to PATCHING (Table 1). With an anticipated 10% loss to follow up, the adjusted sample size to enroll is 238 total (214 ÷ 0.90).

**Table 1. Total Sample Size Estimates***

| SD of Change in VA (logMAR) | True Treatment Group Difference in Mean logMAR VA Change at 26-weeks [PATCHING – LUMINOPIA] | | | | |
|---|---|---|---|---|---|
| | **-0.025 Favoring PATCHING** | **-0.0125 Favoring PATCHING** | **0 No Difference** | **0.0125 Favoring LUMINOPIA** | **0.025 Favoring LUMINOPIA** |
| 0.13 | 508 | 288 | 184 | 130 | 96 |
| 0.14 | 588 | 332 | **214** | 150 | 110 |
| 0.15 | 676 | 382 | 246 | 172 | 126 |

*Cells reflect total sample size unadjusted for loss to follow up with NI -0.0625 logMAR, one-sided alpha of 0.025, and 90% power.

Positive values for the true difference indicate greater VA improvement with LUMINOPIA treatment as compared to PATCHING treatment. Negative values for the true difference indicate greater VA improvement with PATCHING than LUMINOPIA (Figure 1, Table 1).

### 8.3.5 Power for Superiority

If non-inferiority is declared, a two-sided test of no difference (superiority test) for LUMINOPIA compared with PATCHING will be conducted. Superiority of LUMINOPIA over PATCHING will be declared if the LOWER limit of the 95% CI is greater than zero. Conversely, superiority of PATCHING over LUMINOPIA will be declared if the UPPER limit of the 95% CI is less than zero; in this scenario, LUMINOPIA would be both inferior to PATCHING and non-inferior to PATCHING with a margin of -0.0625 logMAR distance VA (Figure 1).

Table 2 below shows the projected statistical power to reject a null hypothesis of no difference in favor of an alternative hypothesis that the treatment groups differ for various true differences and standard deviations with a two-sided alpha of 0.05 and a sample size of 214 participants completing the primary outcome.

If 214 participants complete the primary outcome, the study has 90% power to reject a null hypothesis of no difference in favor of an alternative hypothesis that the treatment groups differ if the true difference is as small as 0.0625 logMAR, assuming SD = 0.14 with a two-sided alpha of 0.05.

**Table 2. Power for Testing Superiority of Mean Change in VA (two-sided $\alpha$=0.05, N=214)**

| | True Difference 0.050 logMAR | True Difference 0.0625 logMAR | True Difference 0.075 logMAR |
|---|---|---|---|
| SD | Power | Power | Power |
| 0.12 | 85% | 96% | 99% |
| 0.13 | 80% | 93% | 98% |
| 0.14 | 73% | 90% | 97% |
| 0.15 | 68% | 85% | 95% |
| 0.16 | 62% | 81% | 92% |

### 8.4 Outcome Measures

*Primary Efficacy Endpoint:*

- Change in amblyopic eye distance VA from baseline at 26 weeks.

*Secondary Efficacy Endpoints:*

- Change in child and proxy PedEyeQ Functional Vision domain scores from baseline at 26 weeks.
- Change in child and proxy PedEyeQ Social domain scores from baseline at 13 weeks.
- Change in child and proxy PedEyeQ Frustration/Worry domain scores from baseline at 13 weeks.

*Exploratory Efficacy Endpoints:*

- Change in amblyopic eye distance VA from baseline at 13 weeks.
- Change in amblyopic eye distance VA over 26 weeks (area under the curve).
- Improvement of amblyopic eye distance VA by 2 or more lines (0.2 logMAR) at 13 and 26 weeks, respectively.
- Resolution of amblyopia at 13 and 26 weeks, respectively as defined in section 3.3.1 and 3.4.1.
- Change in binocular function score from baseline at 13 and 26 weeks.
- Child, proxy, and parent Treatment Impact Questionnaire scores at 13 weeks and 26 weeks.

**8.5 Analysis Datasets and Sensitivity Analyses**

Analyses will follow the intent-to-treat principle (ITT); all participants will be analyzed according to their randomized treatment group, irrespective of adherence or compliance. However, a per protocol analysis will be performed for the primary outcome to check sensitivity of the results (details to be outlined in the statistical analysis plan [SAP]). The intent-to-treat analysis is considered primary and if the results of the per-protocol analysis and intent-to-treat give inconsistent results, exploratory analyses will be performed to evaluate possible factors contributing to the differences.

**8.6 Analysis of the Primary Efficacy Outcome**

The primary outcome, change in amblyopic eye logMAR distance VA from baseline at 26 weeks, is a continuous outcome that will be analyzed using an analysis of covariance (ANCOVA) model to estimate the adjusted mean difference between PATCHING and LUMINOPIA. The model will adjust for baseline amblyopic-eye distance VA and prior treatment for amblyopia (glasses only vs other treatment in addition to glasses). The adjusted between-group mean difference and two-sided 95% confidence interval will be reported. If an imbalance of factors between treatment groups is observed, a sensitivity analysis may be performed, controlling for these potential confounders.

Non-inferiority of LUMINOPIA compared to PATCHING will be declared if the LOWER limit of the two-sided 95% CI for the difference between treatment groups in mean change in logMAR distance VA from baseline to 26 weeks (PATCHING minus LUMINOPIA) is greater than the non-inferiority limit of -0.0625 logMAR favoring PATCHING. Note that the LOWER limit of a two-sided 95% confidence interval is equivalent to the lower limit of a one-sided 97.5% confidence interval.

If non-inferiority is declared, superiority of LUMINOPIA over PATCHING will be declared if the LOWER limit of the 95% CI is greater than zero. Conversely, superiority of PATCHING over LUMINOPIA will be declared if the UPPER limit of the 95% CI is less than zero; in this scenario, LUMINOPIA would be both inferior to PATCHING and non-inferior to PATCHING with a margin of 0.0625 logMAR distance VA (Figure 1).

Participants who do not complete the 26-week visit will have their 26-week amblyopic eye distance VA imputed. Markov chain Monte Carlo multiple imputation with 100 imputations will be used to impute missing data; variables in the imputation model will include prior treatment for

amblyopia and amblyopic-eye VA at baseline, 13, and 26 weeks. Imputation will be carried out separately for PATCHING and LUMINOPIA.[47] Reasons for which a participant may not complete the 26-week visit are outlined in section 7.13, "Intercurrent Events."

The ANCOVA model assumptions of linearity, normality, and homoscedasticity (equal variance) will be verified with graphical methods. If assumptions are seriously violated, then transformation of dependent or independent variables, elimination or categorization of continuous covariates, a robust method, or a nonparametric method may be considered.

As a sensitivity analysis, the primary outcome will be analyzed using complete cases rather than the imputed data. If the results from these analyses are discordant, then differences between participants with and without complete visit data will be evaluated. Additional sensitivity analyses will be detailed in the SAP.

### 8.7 Analysis of the Secondary Efficacy Outcomes

Secondary analyses will test the null hypothesis of no difference between treatment groups. Both *p*-values and confidence intervals will be reported with adjustments for multiplicity (described in section 8.15).

#### 8.7.1 Pediatric Eye Disease Questionnaire (PedEyeQ)

Quality of life will be evaluated for children respondents aged 5 to 7 years in each treatment group using the PedEyeQ questionnaire. Additionally, the parent will answer on behalf of his/her child as a proxy for children 4 to 7 years of age. Scores on Functional Vision, Frustration/Worry, and Social domains will be assessed for both child and proxy at baseline as well as at the visit week indicated below (Table 3). Responses will be Rasch scored according to reference tables and standardized on a ratio scale ranging from 0 to 100.[46]

**Table 3. Structure of the PedEyeQ Analysis: Domains and Respondents**

| | | Domain | | | |
|---|---|---|---|---|---|
| **Participant Age** | **Respondent Level** | **Social (13 weeks)** | **Frustration/Worry (13 weeks)** | **Functional Vision (26 weeks)** | **Outcomes** |
| 4-7 years | Proxy | 1 | 1 | 1 | 3 |
| 5-7 years | Child | 1 | 1 | 1 | 3 |
| | | | | | Total = 6 |

Univariate analysis of covariance (ANCOVA) will be used to assess the difference between treatment groups across all domains and respondents (3 domains × 2 respondents = 6 outcomes) as shown in Table 3. Models will be adjusted for prior treatment for amblyopia and enrollment scores. The treatment effect will be summarized as a mean difference and 95% confidence interval. Similar to the primary outcome, missing data will be imputed using multiple imputation with prior treatment for amblyopia and baseline and outcome scores included in the imputation model and stratified by treatment group.

### 8.8 Intervention Adherence

At 13, and 26-weeks, the investigator will assess participant adherence to the assigned treatment. For each participant randomized to LUMINOPIA, the number of dichoptic treatment hours will be categorized according to percentage of prescribed treatment time as 75-100%, 50-75%, or

<50%. PATCHING calendar data will not be analyzed other than a subjective assessment by the investigator of adherence at 13, and 26-weeks as Excellent, Good, Fair, or Poor after review of calendar and interview with parent. The tabulation of data related to treatment adherence is intended for exploratory purposes only, and therefore formal comparisons between treatment groups will not be performed.

### 8.9 Protocol Adherence and Retention

Protocol deviations and visit completion rates (excluding participants who die before the end of the visit window) will be tabulated for each treatment group.

### 8.10 Intercurrent Events

If any of the following events take place before the 26-week outcome, missing follow-up data will be imputed for the participant experiencing the event in the primary ITT analysis.

- Death
- Lost to follow up
- Withdrawal

If any of the following events occur before the 26-week outcome, data will not be imputed for participants experiencing these events, since the event itself does not preclude completion of study visits. Thus, the observed data at the 26-week outcome visit will be utilized.

- Treatment discontinuation
- Treatment crossover
- Receipt of non-protocol treatment

### 8.11 Safety Analyses

The cumulative proportions of each of the following adverse events by treatment group will be assessed at the initial study phase (enrollment to 26 weeks) and during the LUMINOPIA treatment phase for those originally randomized to PATCHING (26 weeks to 52 weeks). During the initial study phase, the proportions will be compared statistically with Barnard's Unconditional Exact Test considering the number of participants per group as fixed. As type II error (false negative) is more of a concern than type I error (false positive) in safety analyses, we will use $p \leq 0.05$, without adjustment for multiplicity, to define statistical significance in all safety analyses. It is noted that this study is not powered for safety analyses and that absence of a significant effect cannot be taken as evidence that a difference does not exist. The proportion of adverse events occurring during the LUMINOPIA treatment phase for original PATCHING participants will be tabulated.

- Worsening of best-corrected fellow-eye distance VA of 0.2 logMAR or more
- New onset strabismus >5 Δ by SPCT in participants with no strabismus at baseline
- Strabismus >10 Δ by SPCT in participants with strabismus at baseline
- Parental report of diplopia occurring more than once per week
- Skin irritation
- Headache
- Seizures
- Eyestrain
- Dizziness

- Night terrors
- Eye twitching
- Facial redness

The PEDIG DSMC will review safety data tabulated by treatment group at each of its semi-annual meetings and can request formal statistical comparison of any safety outcome at any time if they have cause for concern.

### 8.12 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics will be tabulated by randomized treatment group, and summary statistics appropriate to their distributions will be reported.

### 8.13 Planned Interim Analyses

There is no plan for formal interim analyses. The Data and Safety Monitoring Committee will review tabulated and graphical displays of interim safety data at approximately 6-month intervals and will have the option to recommend stopping the study.

### 8.14 Subgroup Analyses

Subgroup analyses, i.e., assessments of effect modification, will be conducted for the primary outcome. These analyses will be considered exploratory. Missing data will be imputed like the primary analyses except that the subgroup factors of interest, specified below, will be included in the imputation model, which will be stratified by treatment group. Within-subgroup mean differences for the treatment effects with 95% confidence intervals will be estimated for each subgroup by adding an interaction term to the primary analysis models. Results will be presented as forest plots; *p*-values will not be presented.

The baseline factors to be evaluated in pre-planned exploratory subgroup analyses include amblyopic-eye distance VA (categorized), type of amblyopia, prior treatment for amblyopia, age 4 to 5 or >5 to 7), and binocularity. The SAP will provide specific details on categorizations. The subgroup analysis by amblyopic-eye distance VA is considered of greatest interest.

There are no data to suggest that the treatment effect will vary by sex, race, or ethnicity. However, each of these factors will be evaluated in exploratory subgroup analyses as mandated by National Institutes of Health (NIH) guidelines.

### 8.15 Multiple Comparison/Multiplicity

For the primary outcome, a 95% confidence interval for the treatment group difference will be constructed and used to evaluate the primary hypothesis of non-inferiority and also the possibility of superiority or inferiority (Figure 1).[48]

For the PedEyeQ questionnaire secondary outcomes, the adaptive false discovery rate (FDR) method with two-stage testing will control the FDR at 5% to adjust *p*-values and CIs for multiplicity.[49]

### 8.16 Exploratory Analyses

Exploratory analyses will test the null hypothesis of no difference between treatment groups. Both *p*-values and confidence intervals will be reported without adjustment for multiplicity.

#### 8.16.1 Mean Change in Distance VA at 13 Weeks

Change in amblyopic eye VA from baseline to 13 weeks is a continuous outcome. Analyses, including imputation of missing data, will mirror the primary outcome.

#### 8.16.2 Mean Change in Distance VA over 26 weeks (area under the curve)

The change in amblyopic eye distance VA from baseline over 26 weeks (area under the curve) will be calculated for each participant using the trapezoidal rule. The analysis, including imputation of missing data, will mirror the primary outcome.

#### 8.16.3 Improvement of Amblyopic-eye Distance VA by 2 or More Lines

Improvement of amblyopic-eye distance VA of 2 or more lines (reduction of 0.2 logMAR) at 13 and 26 weeks, respectively, will be analyzed as binary outcomes. For each time point, the proportions with improvement $\geq 2$ lines and 95% confidence interval will be calculated. The risk difference will be calculated using logistic regression with conditional standardization and adjusted for amblyopic-eye VA at baseline and prior treatment of amblyopia. The delta method will be implemented to construct a 95% CI on the risk difference and the model-based two-sided *p*-value will be reported. Missing data will be imputed as described for the primary outcome.

#### 8.16.4 Binocular Function

The change in binocular function score from enrollment to the 13- and 26-week visit is an ordinal outcome. Components of binocularity include results from the following 3 tests: Randot Preschool Stereoacuity (RPS), Random Dot Butterfly, and Preschool Worth 4-shape (W4S) at near. These tests will create a composite ordinal score of binocularity with 9 levels.[51]

The difference between LUMINOPIA and PATCHING for the change in binocularity from baseline to 13 and 26 weeks will be evaluated with the nonparametric Wilcoxon Rank-Sum test. The difference between groups will be estimated using the Hodges-Lehmann estimator with 95% CI. Analyses for binocular function score will be limited to complete case data at each respective outcome visit (13 weeks or 26 weeks).

In a sensitivity analysis, binocular function scores will be analyzed using ANCOVA with adjustment for prior treatment for amblyopia and baseline binocular function score and imputation of missing data. The baseline-adjusted mean difference and 95% CI in binocularity between the treatment groups will be presented.

#### 8.16.5 Resolution of Amblyopia at 13 weeks and 26 weeks

The cumulative probability of amblyopia resolution at 13 and 26 weeks will be calculated using Cox proportional hazards regression with adjustment for baseline IOD and prior treatment for amblyopia. For each visit, the rate of resolution (estimated using the survivor function) and 95% CI will be presented for each group using direct adjustment along with the difference in rates, 95% CI, and *p*-value (based on a Z test). Participants who are lost to follow up will be censored on the day of the last completed visit.

### 8.16.6 Treatment Impact Questionnaire

The Treatment Impact Questionnaire (TIQ) will be used as a quantitative measure to evaluate opinions regarding the burdens and impact of the randomized treatment at 13 weeks and 26 weeks (as questions for the child – the Child TIQ, for the parent about the child – the Proxy TIQ, and the parent themselves – the Parent TIQ.

The Child-TIQ, Proxy-TIQ, and Parent-TIQ will undergo separate factor analysis to determine the number of domains for each TIQ. Each domain will be refined through the evaluation of misfitting items and will then be Rasch scored.

Note that because the TIQ is not administered at baseline (because treatment has not been started), there will be no adjustment for baseline score in any analysis.

Additional methods to score and analyze the Treatment Impact Questionnaire will be detailed in a separate SAP.

### 8.16.7 Improvement with Dichoptic Therapy after PATCHING

Participants who were randomized to PATCHING who have 1 line or more IOD residual amblyopia will be offered dichoptic treatment with LUMINOPIA after 26 weeks. These participants will have visits at 39 weeks and 52 weeks to evaluate safety and efficacy. The same safety, binocular function, and VA outcomes evaluated at 13 and 26 weeks will be evaluated at 39 and 52 weeks with 26 weeks considered the baseline visit for the extended follow-up.

# Chapter 9: Data Collection and Monitoring

## 9.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs). When data are directly collected in real-time in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF; data not entered in real-time; etc.), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live participant must be recorded (e.g., office note, visit record, etc.)

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

## 9.2 Study Records Retention

Study documents should be retained for a minimum of 3 years after completion of the final grant reporting. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 9.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted appropriately, and the data are generated, documented, and reported in compliance with the protocol that adheres to Good Clinical Practice (GCP) and the applicable regulatory requirements. In addition, QC systems will be in place to ensure that the rights and well-being of trial participants are protected, and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the veracity and completeness of the key site data.

Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff
- Participant retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study site facilities at any time to maintain current and personal knowledge of the study through medical record review, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### 9.4 Protocol Deviations

A protocol deviation is any instance of noncompliance with the clinical trial protocol, GCP, or clinical procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI, protocol PI (if different) and all study staff are responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

# Chapter 10: Ethics/Protection of Human Participants

## 10.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 10.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the JCHR IRB for review and approval as the IRB of Record. Approval of both the protocol and the consent form must be obtained from the IRB before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; the IRB will determine whether previously consented participants need to be re-consented.

## 10.3 Informed Consent Process

### 10.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout that individual's study participation. Written IRB-approved consent materials and consent discussions must be in a language understandable to the participants and their parent(s). For example, if the parent(s) primary language is Spanish, then the Spanish consent form, as well as other participant/parent facing materials (e.g., questionnaires) must be in Spanish. Also, the use of a translator approved by the Coordinating Center is required to support not only the consent process, but also the participants and their parent(s) understanding and communication for the duration of the study.

Extensive discussion of risks and possible benefits of participation will be provided to participants and their families. Consent forms will be approved by the IRB and the parent/legal guardian will be asked to read and review the document. The investigator will explain the research study to the parent and participant and answer any questions that may arise. All parents and participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Parents and participants (old enough to sign per IRB) will have the opportunity to carefully review the written consent form and ask questions prior to signing.

Parents should have the opportunity to discuss the study with their partner or family physician or think about it prior to agreeing to participate. Written informed consent will be obtained from a parent and written or verbal assent from the child (depending on age and IRB requirements) prior to performing any study-specific procedures that are not part of the child's routine care. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the family for their records. The rights and welfare of the participants will be protected by emphasizing to them and their parent(s) that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 10.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or study data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Jaeb Center for Health Research staff will be secured and password protected.

At the end of the study, all study databases will be de-identified and archived at the Jaeb Center for Health Research.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

### 10.5 Future Use of Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. After the study is completed, the de-identified, archived data will be made available to the public.

# Chapter 11: References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