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A Randomized Trial Of A Binocular iPad Game Versus Part-Time Patching In Children 5 To 12 Years Of Age With Amblyopia

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Abstract

Importance—A binocular approach to treating anisometropic and strabismic amblyopia has recently been advocated. Initial studies have yielded promising results, suggesting that a larger randomized clinical trial is warranted.

Objective—To compare visual acuity (VA) improvement in children with amblyopia treated with a binocular iPad® game versus part-time patching.

Design—Randomized, non-inferiority clinical trial.

Setting—Multicenter, community and institutional practices

Participants—385 participants 5 to <13 years of age (mean 8.5 years) with amblyopia (20/40 to 20/200, mean 20/63) resulting from strabismus, anisometropia, or both.

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*A complete list of participating members of the Pediatric Eye Disease Investigator Group (PEDIG) can be found in the Acknowledgements.

Trial Registration: Listed on www.clinicaltrials.gov, identifier NCT02200211.

Access to Data: Elizabeth Lazar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest: No conflicting relationships exist for any of the authors.

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Interventions—Participants were randomly assigned to either 16 weeks of a binocular iPad game, prescribed for 1 hour a day (n=190, binocular group) or patching of the fellow eye prescribed for 2 hours a day (n=195, patching group). Study follow-up visits were scheduled at 4, 8, 12, and 16 weeks.

Main outcome measure—Change in amblyopic-eye VA from baseline to 16 weeks.

Results—At 16 weeks, mean amblyopic-eye VA improved 1.05 lines (2-sided 95% confidence interval (CI): 0.85 to 1.24 lines) in the binocular group and 1.35 lines (2-sided 95% CI: 1.17 to 1.54 lines) in the patching group, with an adjusted treatment group difference of 0.31 lines favoring patching (upper limit of the 1-sided 95% CI 0.53 lines). This upper limit exceeded the pre-specified non-inferiority limit of 0.5 lines. Only 22% of participants randomized to the binocular game performed >75% of the prescribed treatment (median 46%, interquartile range 20% to 72%). In younger participants age 5 to <7 years old, without prior amblyopia treatment, amblyopic-eye VA improved 2.5 ± 1.5 lines in the binocular group and 2.8 ± 0.8 in the patching group. Adverse effects (including diplopia) were uncommon and of similar frequency between groups.

Conclusions and Relevance—In children 5 to <13 years of age, amblyopic-eye VA improved with binocular game play and with patching, particularly in younger children age 5 to <7 years without prior amblyopia treatment. Although the primary non-inferiority analysis was indeterminate, a post-hoc analysis suggested VA improvement with this particular binocular iPad treatment was not as good as with 2 hours of prescribed daily patching.

Introduction

A binocular approach to treating anisometropic and strabismic amblyopia has recently been advocated,[1–6] without patching,[7, 8] atropine drops,[9] or Bangerter filters[10] applied to the fellow eye. In such binocular therapy, images are presented dichoptically, with high-contrast images presented to the amblyopic eye and low-contrast images to the fellow eye, to achieve a binocular percept.[11] Recently, this binocular treatment has been adapted to an iPad® device as a “falling blocks” game, which uses red-green anaglyphic glasses. Initial studies have yielded promising results,[3–5] suggesting that a larger randomized clinical trial is warranted.

The purpose of the present randomized clinical trial was to establish whether treatment of amblyopia with a binocular iPad game (prescribed 1 hour per day for 16 weeks) was not substantially worse (non-inferior) than treatment with patching of the fellow eye (prescribed 2 hours per day) in children age 5 to <13 years, with 20/40 to 20/200 amblyopic-eye VA

Methods

The study was conducted at 78 institution- or community-based clinical sites and approved by the respective institutional review boards (IRB). A parent or guardian (referred to subsequently as “parent”) of each study participant gave written informed consent, and each participant assented to participation as required. The study is listed on www.clinicaltrials.gov, under identifier NCT02200211, accessed 5/27/16. The complete

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study protocol is available on the PEDIG website (www.pedig.net, accessed 5/27/16). Eligibility criteria are listed in Table 1.

Study Visits and Testing Procedures

Visual acuity was measured in each eye with optimal refractive correction (if applicable), and without cycloplegia by a study-certified examiner (masked at follow up). We used a consistent method throughout the study for each participant; either the Amblyopia Treatment Study single-surround HOTV protocol (ATS-HOTV©)[12] for participants age 5 to <7 years or the Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS©) protocol[13] for participants age 7 to <13 years. Visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) scale. Additional testing at all study visits included measurement of ocular alignment with a simultaneous prism and cover test (SPCT), and a prism and alternate cover test (PACT), and stereoacuity (masked at follow-up) using the Randot Butterfly and Randot Preschool stereoacuity tests (Stereo Optical Co., Chicago IL).

Follow-up visits occurred at 4, 8, 12, and 16 weeks (± 1 week) after randomization (± 1 week), with the primary outcome visit at 16 weeks. At each visit, a standardized questionnaire was administered to participants and their parents to assess the presence and frequency of diplopia.

Randomization and Treatment

Participants were randomly assigned via the PEDIG website with equal probability, using a permutated block design stratified by age group (5 to <7 years, 7 to <13 years) and site, to receive either binocular treatment or patching (subsequently referred to as the “binocular” and “patching” groups, respectively), administered via the PEDIG website.

The patching group was prescribed 2 hours of daily patching (allowing division into shorter sessions) with an adhesive style patch (Coverlet/3M Opticlude/Ortopad), 7 days a week for 16 weeks. The binocular group was prescribed the binocular falling blocks iPad game for 1 hour a day (allowing division into shorter sessions), 7 days a week for 16 weeks, with instructions to perform therapy a minimum of 4 days a week if unable to play for 7 days per week. The differing durations per day (2 hours versus 1 hour) were chosen to reflect commonly used regimes with each treatment. Compliance was calculated based on an intended treatment of 7 days a week for 16 weeks.

The game was played on a study-supplied iPad device at the participants’ habitual reading distance while wearing red/green anaglyphic glasses (over the spectacles if applicable) with the green filter placed over the amblyopic eye. Participants played the game by moving the falling blocks to form solid lines, with the level of difficulty (easy, medium, hard) set at the participant’s discretion. While the contrast of the falling blocks for the amblyopic eye was always 100%, the contrast for the fellow eye was initially set to 20% and automatically increased/decreased by 10% increments (with a lowest level of 10%), or left unchanged from the last contrast level, based on previous day game play duration and performance. The contrast only changed if ≥ 30 minutes of game play occurred the previous day, increasing if ≥1000 points were scored or decreasing otherwise.

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Parents recorded the number of hours the participant played the game or wore the patch each day using calendars. The iPad device automatically recorded the duration of game play, contrast and performance.

Statistical Analyses

The trial was designed as a non-inferiority study. The sample size of 346 participants was computed to have 90% power with a type I error of 5% for a non-inferiority limit of 0.05 logMAR (0.5 lines), assuming a standard deviation of change of 0.15 logMAR (1.5 lines) based on prior PEDIG studies,[10, 14–17] and no more than 10% loss to follow-up. This non-inferiority margin represents a conservative estimate of the treatment benefit of part-time patching compared with optical correction alone (based on previous studies[14, 15]), chosen so the effect of binocular treatment, if found non-inferior to patching, would very likely be greater than that of optical correction alone.

The primary outcome measure was change in amblyopic-eye VA from baseline to 16 weeks (14 to <20 week window). The upper limit of a 1-sided 95% confidence interval (CI) was computed on the treatment group difference, using an analysis of covariance (ANCOVA) model, adjusted for baseline age and VA, including only participants completing the 16-week outcome in a modified intent-to-treat analysis. Alternative approaches to the primary analysis are specified in eTable 1. The primary analysis was repeated with computation of a 2-sided 95% CI for the adjusted treatment group difference as a post-hoc analysis to estimate the range of plausible values of the treatment group difference.

In a post-hoc analysis, we compared the 16-week outcomes in those who were compliant (completing >50% prescribed treatment) and successfully played the game (fellow-eye contrast increased to >95%) with those who were not.

Statistical methods for additional analyses are described in the relevant tables and figures (including online tables and figures). Analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC).

Results

Baseline Characteristics

Between September 2014 and August 2015, 385 participants were randomly assigned to the binocular group (n=190) or to the patching group (n=195). Baseline characteristics were similar in the two groups (Table 2). Seven patients were subsequently found to be ineligible (reasons listed in Table 2).

Visit Completion and Treatment Adherence

The 16-week primary outcome was completed by 182 (96%) in the binocular group and 188 (96%) in the patching group (Figure 1), with masking maintained at 99% of visits.

During the 16-week follow-up period, 118 (67%) in the binocular group and 172 (92%) in the patching group reported completing >75% of prescribed treatment based on calendars. However, for the binocular group, the iPad device indicated only 22% of participants

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achieved >75% (median 46%, interquartile range 20% to 72%) of prescribed treatment. Only two participants in the binocular group had been prescribed less than the 1 hour/d 7 days/ week intended dose during follow-up. In the binocular group, 100% contrast in the fellow eye was achieved for 35 participants (20%) at 4 weeks and for 86 participants (49%) at 16 weeks. Thirty-one (18%) participants had 20% contrast or worse, to the fellow eye, at 16 weeks. Non-protocol alternative treatment was received by no participants in the patching group and 4 participants in the binocular group (1 atropine, 3 patching, one of whom received patching in addition to protocol binocular therapy).

Amblyopic-Eye Visual Acuity

At 16 weeks, mean amblyopic-eye VA improved from baseline by 1.08 lines (2-sided 95% confidence interval (CI): 0.86 to 1.29 lines) in the binocular group and by 1.32 lines (2-sided 95% CI: 1.14 to 1.51 lines) in the patching group (Figure 2, eFigure 1, eTable 2, Table 3). After adjusting for baseline covariates of age and VA, mean amblyopic eye VA improved from baseline by 1.05 lines (95% CI: 0.85 to 1.24 lines) and 1.35 lines (95% CI: 1.17 to 1.54 lines) in the patching and binocular groups respectively, resulting in a treatment group difference of 0.31 lines favoring the patching group. The upper limit of the 1-sided 95% CI of the treatment difference was 0.53 lines, which exceeded the pre-specified non-inferiority limit of 0.5 lines. Because we were unable to reject the null hypothesis (that binocular treatment was inferior to patching), our primary analysis was indeterminate. In a post-hoc analysis, the 2-sided 95% CI for the adjusted treatment group difference was 0.04 to 0.58 lines, favoring the patching group. Results of alternative analyses were consistent with the primary analysis (eTable 1).

At 16-weeks, amblyopic-eye VA improved ≥ 2 lines from baseline for 65 (35%) and 51 (29%) participants in the patching and binocular groups, respectively (adjusted difference: 5%, 2-sided 95% CI: −4% to 13%), and amblyopia resolved (VA of 20/25 or better and within 1 logMAR line of fellow eye) for 18 (10%) and 8 (5%) participants in the patching and binocular groups, respectively (adjusted difference: 2%, 2-sided 95% CI: −1% to 5%). The rate of amblyopic-eye VA improvement was not statistically different between treatment groups (P = 0.83, Figure 2).

Treatment effect by baseline characteristics

The overall reduced effect of binocular treatment compared with patching on improvement of amblyopic-eye VA was paralleled in baseline subgroups (eTable 3). For both treatment groups, there was a particularly noticeable improvement in younger participants (5 to <7 years) with no prior treatment (2.5 ± 1.5 lines in the binocular group and 2.8 ± 0.8 lines in the patching group) (eTable 3).

VA improvement in binocular group by compliance

At both 4 and 16 weeks, improvement in amblyopic-eye VA was not associated with objective measures of total hours of treatment or change in fellow-eye contrast for the binocular group, overall (eFigure 2, eFigure 3), or within baseline subgroups of age (5 to <7 years, 7 to <13 years) with or without previous treatment (eFigure 4, eFigure 5). In addition, mean improvement in 16-week amblyopic-eye VA for participants who completed >50% of

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prescribed treatment and achieved >95% fellow-eye contrast was 0.9 ± 1.4 line (n=51) compared with 1.2 ± 1.5 lines (n=125) in those who did not fulfill these criteria.

Stereoacuity

Change in stereoacuity did not differ significantly between treatment groups for the overall cohort (P = 0.66) or for participants with no history of strabismus at baseline (P = 0.19) (eTable 4). The median change in stereoacuity from baseline to 16 weeks was 0 in both groups, and there was a similar lack of an effect of binocular treatment and patching on change in stereoacuity in baseline subgroups (eTable 5).

At both 4 and 16 weeks, improvement in stereoacuity was not associated with either total hours of completed binocular treatment or change in fellow-eye contrast, either overall (eFigure 2, eFigure 3) or within baseline subgroups of age (5 to <7 years, 7 to <13 years) with or without previous treatment (eFigure 6, eFigure 7). At 16 weeks, median stereoacuity improvement was 0 for participants who completed >50% prescribed binocular treatment and achieved >95% fellow-eye contrast (n=51) and 0 for those who did not fulfill these criteria (n=124).

VA of Fellow Eye at 16 weeks

Mean improvement in fellow-eye VA, adjusted for baseline VA, differed by 0.16 lines (95% CI: 0.02 to 0.30 lines) favoring the binocular group (eTable 6).

Adverse Events at 16 weeks

The number of participants with a new tropia and/or worsening of a pre-existing deviation of ≥ 10 Δ was 16 (9%) and 11 (6%) in the binocular and patching groups, respectively (Fisher exact test: P = 0.32). Diplopia was rare in both groups (eTable 7).

Three participants (2%) in the patching group reported moderate/severe skin irritation with patching during follow-up.

Discussion

In children 5 to 12 years of age, amblyopic-eye VA improved in both the binocular and patching groups, particularly in younger participants (5 to 6 years) without prior amblyopia treatment. VA improvement in the binocular group did not meet the pre-specified definition for non-inferiority compared with 2 hours of prescribed daily patching, and therefore our primary analysis was indeterminate. Nevertheless, a post-hoc analysis suggested VA improvement with this particular binocular iPad treatment was not as good as with 2 hours of prescribed daily patching.

Mean improvement in amblyopic-eye VA with binocular treatment over our 16-week study was similar in magnitude (approximately 1 logMAR line) to that previously reported in non-randomized studies prescribing 4 hours/week of binocular treatment for 4 weeks in 4 to 12 year-olds,[3, 5] and in 3 to 6 year-olds.[4] These previous studies[3–5] of binocular iPad treatment included 4 different games, one of which was the falling blocks game, and allowed concurrent patching at a different time of day at the eye care provider's discretion, although

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a sub-analysis of those only treated with binocular games yielded a similar magnitude of effect.[4] Knox et al[2] also found a similar magnitude of improvement in children (mean age 8.5 years) treated with an analogous game, using a head-mounted display in a supervised setting for 1 hour/day for 5 sessions over one week. The rate of improvement in amblyopic-eye VA was slower in the present study than in these previous studies,[3–5] which may have been due to a larger proportion of older participants in the present study.

When treating adults with amblyopia using binocular therapy in a supervised setting for 1 hour/day over 2 weeks, Li et al[6] reported a mean improvement of approximately 2 logMAR lines, greater than that found in the present study of children. Nevertheless, this treatment in adults was in a laboratory setting using a head-mounted display, so results cannot be directly compared.

In our study, investigators noted participants often lost interest in the game after a number of days or weeks, well before the prescribed 16-week course was completed. Only 22% of our children achieved greater than 75% compliance, suggesting that compliance should be reviewed more frequently and games need to be more appealing such as more engrossing children's games, binocular first person action games,[18] and binocular movie viewing.[19]

Another reason why we may not have found a greater effect of binocular treatment was the timing of the initial and final assessments. Previous studies of binocular therapy have evaluated patients after a shorter duration of treatment. It is unclear whether active progression through contrast levels is necessary for treatment to be ongoing, or whether treatment is ongoing even when equal contrast has been achieved. If active progression is needed, many of our children who achieved 100% contrast to the fellow eye would have completed treatment well before our primary outcome (49%) and even before 4 weeks (20%). We also found that 18% of participants failed to progress in contrast to the fellow eye, suggesting that the contrast starting point was not optimally set for each participant, and that the initial contrast should be based on an individual measurement of suppression rather than the arbitrary 20% used here.

Regarding improvement of stereoacuity, it has been suggested that the mechanism of binocular treatment of amblyopia is by reducing suppression and increasing binocularity. Stereoacuity outcomes differ between studies, with some reporting improvement[1, 2] and others (like ours) reporting no improvement for most subjects.[3, 4] It is possible that these differences may be due to the type of stereoacuity test used. Improvements might be more easily detected using the Frisby test or contour tests, rather than random dot tests.[20, 21]

It remains unclear that the binocular iPad treatment used in our study was actually better than optical treatment alone (if needed) and, as such, whether binocular iPad treatment is actually better than sham therapy. Nevertheless, the large magnitude of the VA improvement in the younger participants (5 to <7 years old) in the binocular group, who had not received previous treatment, (2.5 ± 1.5 lines) suggests that binocular treatment produced a real effect, greater than would be expected with continued optical treatment alone after achieving stable VA in spectacles.[15] Regarding the effect of patching in our study, our overall mean improvement (1.3 logMAR lines) was less than we expected, but this was most likely due to

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a large proportion (63%) of participants who were both older (7 to <13 years) and who had received previous treatment.

There has been some concern that binocular treatment might be associated with new-onset diplopia because its mechanism of action may be via anti-suppression. Nevertheless, In our study, and in previous studies of this particular form of binocular treatment,[3–5] diplopia was rare.

Our study has a number of limitations regarding assessing compliance. For patching, we did not use occlusion dose monitors. Our compliance data relied on parental report (for patching and, in part, for binocular treatment) which may have been inaccurate. The electronic recording of compliance by the binocular game may have also included time when the game was not actually being played, but this would be expected to be minimal because the game sessions automatically ended after about 1 minute of inactivity. For binocular treatment, we allowed participants to play a minimum of 4 days per week, if they could not play 7 days per week, but reduced game play was only prescribed in 2 subjects. Finally, we did not monitor compliance with wearing the red-green glasses required to play the game.

In summary, in children 5 to 12 years of age, amblyopic-eye VA improved with binocular game play and with patching, but VA improvement with this particular binocular iPad treatment, when prescribed 1 hour a day, failed to meet our study's pre-specified definition for non-inferiority compared with 2 hours of prescribed daily patching, and therefore our primary analysis was indeterminate. Nevertheless, a post-hoc analysis suggested VA improvement with this particular binocular iPad treatment was not as good as with 2 hours of prescribed daily patching.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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No funding organization had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix

Clinical Sites

Sites are listed in order by number of participants enrolled. Personnel are listed as (I) for Investigator, (C) for Coordinator or (E) for Examiner.

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Norfolk, VA - Virginia Pediatric Eye Center (31)

Earl R. Crouch, Jr. (I); Earl R. Crouch III (I); Stacy R. Martinson (I); Gaylord G. Ventura (C); Candice C. Brown (E); Cynthea M. Carlton (E); Carolina A. Escala (E)

Miami, FL - Bascom Palmer Eye Institute (19)

Susanna M. Tamkins (I); Carolina Manchola-Orozco (C); Kara M. Cavuoto (E); Isaura Gomez Tamayo (E); Maria D. Martinez (E); Eva M. Olivares (E); Oriel Spierer (E); Erin Yanowitch (E)

Gainesville, FL - Accent Physicians (17)

Nausheen Khuddus (I); Kathy Bryan (C); Tammy Toskes Price (E)

Rockville, MD - Stephen R. Glaser (17)

Stephen R. Glaser (I); Tara G. Missoi (I); Nancy A. Morrison (I); Kasey L. Yost (C); Deandra B. Andrade (E); Odalis R. Flores (E)

Poland, OH - Eye Care Associates, Inc. (15)

S. Ayse Erzurum (I); Beth J. Colon (C); Diana C. McOwen (C); Guy C. Barrett (E); Zainab Dinani (E)

Cranberry TWP, PA - Everett and Hurite Ophthalmic Association (14)

Darren L. Hoover (I); Pamela A. Huston (C); Christine J. Deifel (E); Jody L. Desiderio (E); Pamela M. Racan (E); Kari E. Soros (E)

Chattanooga, TN - Pediatric Eye Specialists (11)

Edward A. Peterson (I); Zachary S. McCarty (I); Charla H. Peterson (C); Amie Jenkins (E)

Fullerton, CA - Southern California College of Optometry (11)

Susan A. Cotter (I); Angela M. Chen (I); Raymond H. Chu (I); Silvia Han (I); Catherine L. Heyman (I); Kristine Huang (I); Sue M. Parker (C); Reena A. Patel (I); Maureen D. Plaumann (I); Carlee Y. Young (I); Carmen N. Barnhardt (E)

Houston, TX - University of Houston College of Optometry (11)

Karen D. Fern (I); Heather A. Anderson (I); Debra C. Currie (I); Dashaini V. Retnasothie (I); Sylvia Landa (C); Fawn M. Candelari (C)

Portland, OR - Casey Eye Institute (11)*, †

Allison I. Summers (I); Paula K. Rauch (C); Yelena M. Bubnov (E); Grant A. Casey (E); Rhea N. Nelson (E); Kevin M. Woodruff (E)

The Woodlands, TX - Houston Eye Associates (11)

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Aaron M. Miller (I); Jorie Jackson (C); Angela C. Dillon (C); Kathleen M. Curtin (E); Maria N. Olvera (E); Starla J. Skaggs (E)

Birmingham, AL - University of Alabama at Birmingham School of Optometry (10)

Marcela Frazier (I); Kristine T. Hopkins (I); Sarah D. Lee (I); Katherine K. Weise (I); Paul Christian Spain (C); Michelle B. Bowen (C)

Baltimore, MD - Wilmer Institute (9)*

Michael X. Repka (I); Courtney Kraus (I); Anya A. Trumler (I); Xiaonong Liu (C); Alex X. Christoff (E); Kyle Pearce Harrold (E); Colin Patrick Kane (E)

Cincinnati, OH - Cincinnati Children's Hospital (9)

Michael E. Gray (I); Melissa L. Rice (I); Daniele P. Saltarelli (I); Corey S. Bowman (C); Shemeka R. Forte (E); Amanda R. Johnson (E); Erica M. Setser (E); Miqua LThomas (E); Felicia J. Timmermann (E)

Boise, ID - St Luke's Hospital (7)

Katherine A. Lee (I); Daniel R. Brooks (I); Bonita R. Schweinler (C); Lori Lynne McDaniel (E); Larry W. Plum (E)

Grand Rapids, MI - Helen DeVos Children's Hospital Pediatric Ophth. (7)

Brooke E. Geddie (I); Elisabeth T. Wolinski (C); Kimberly J. Hubbard (E); Michael N. Patton (E)

Rochester, MN - Mayo Clinic (7)*

Jonathan M. Holmes (I); Suzanne M. Wernimont (C); Matthew W. Heiderscheit (E); Anita R. Hermanson (E); Julie A. Holmquist (E); Jordan J. Huisman (E); Melissa J. Hunemuller (E); Lindsay D. Klaehn (E); Marna L. Levisen (E); Laura Liebermann (E); Rebecca A. Nielsen (E); Debbie M. Priebe (E); Casandra M. Turri (E)

Spokane, WA - Northwest Pediatric Ophthalmology, P.S. (7)

George F. Whitehead (I); Christina N. Nye (I); Caroline J. Shea (I); SueAnn M. Stillman (C)

Atlanta, GA - The Emory Eye Center (6)

Scott R. Lambert (I); Amy K. Hutchinson (I); Phoebe D. Lenhart (I); Judy L. Brower (C); Jayne M. Brown (E); Linda T. Curtis (E); Melanie K. Fowler (E); Marla J. Shainberg (E)

Lancaster, PA - Conestoga Eye (6)

David I. Silbert (I); Noelle S. Matta (C); Karen L. Delgado (E); Prucilla R. Shady (E)

Waterbury, CT - Eye Care Group, PC (6)

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Tara H. Cronin (I); Andrew J. Levada (I); Susan H. Heaton (C); Cheryl Capobianco (E); Lindsay Gill (E)

Big Rapids, MI - Michigan College of Optometry at Ferris State Univ (5)

Paula S. McDowell (I); Alison M. Jenerou (I); Kerrie Rachelle Currie (C); Emily Jean Aslakson (E); Sarah B. Hinkley (E)

Chicago, IL - Illinois College of Optometry (ICO) (5)

Yi Pang (I); Huizi Yin (I); Elyse Nylin (C)

Erie, PA - Pediatric Ophthalmology of Erie (5)

Nicholas A. Sala (I); Allyson Sala (C); Catherine Johnson (E); V. Lori Zeto (E)

Grand Rapids, MI - Pediatric Ophthalmology, P.C. (5)

Patrick J. Droste (I); Robert J. Peters (I); Jan Hilbrands (C); Leslie J. Bileth (E); Andrew P. Droste (E); Jennifer L. Mooney (E)

Rochester, NY - University of Rochester Eye Institute (5)

Benjamin P. Hammond (I); Matthew D. Gearinger (I); Andrea Czubinski (C); Rebecca K. Gerhart (E)

Silverdale, WA - Jason C. Cheung, M.D., PS (5)

Jason C. Cheung (I); Tiffany M. Parypa (C); Jacque J. Ferro (E)

West Des Moines, IA - Wolfe Clinic (5)

Myra N. Mendoza (I); Sara D. Khan (I); Jill J. Frohwein (C); Lisa M. Fergus (E); Susan K. Hayes (E); Rhonda J. Countryman (E)

Chicago Ridge, IL - The Eye Specialists Center, L.L.C. (4)

Benjamin H. Ticho (I); Megan Allen (I); Birva K. Shah (I); Deborah A. Clausius (C); Sharon L. Giers (E); Micaela N. Quebbemann (E)

Cleveland, OH - Cole Eye Institute (4)

Fatema F. Ghasia (I); Diana C. McOwen (C); Susan W. Crowe (C); Angela M. Borer (E); Rachael Briggs (E)

Fall River, MA - Center for Eye Health, Inc. (4)

John P. Donahue (I); Samantha J. Pape (C); Danielle K. Berry (E); Linda M. Cabeceiras (E); Mary E. Silvia (E); Samantha Teixeira (E)

Houston, TX - University of Texas- Robert Cizik Eye Clinic (4)

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Kartik S. Kumar (I); Ephrem K. Melese (C); Laura A. Baker (E)

Marlton, NJ - Michael F. Gallaway, O.D., P.C. (4)

Michael F. Gallaway (I); Debbie L. Killion (C); Tammy Lynn Thomas (E); Beth Zlock (E)

Portland, OR - Pacific University College of Optometry (4)

Richard London (I); Ryan C. Bulson (I); Jayne L. Silver (C); James J. Kundart (E)

Rio Rancho, NM - City of Vision Eye Care (4)

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References

1. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. Restor Neurol Neurosci. 2010; 28(6): 793–802. [PubMed: 21209494]
2. Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. Invest Ophthalmol & Vis Sci. 2012; 53(2):817–824. [PubMed: 22169103]
3. Li SL, Jost RM, Morale SE, et al. A binocular iPad treatment for amblyopic children. Eye (Lond). 2014; 28(10):1246–1253. [PubMed: 25060850]
4. Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. J AAPOS. 2015; 19(1):6–11. [PubMed: 25727578]
5. Li SL, Jost RM, Morale SE, et al. Binocular iPad treatment of amblyopia for lasting improvement of visual acuity. JAMA Ophthalmol. 2015; 133(4):479–480. [PubMed: 25611129]
6. Li J, Thompson B, Deng D, Chan LY, Yu M, Hess RF. Dichoptic training enables the adult amblyopic brain to learn. Curr Biol. 2013; 23(8):R308–R309. [PubMed: 23618662]
7. Pediatric Eye Disease Investigator Group. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol. 2003; 121(5):603–611. [PubMed: 12742836]
8. Pediatric Eye Disease Investigator Group. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. Ophthalmology. 2003; 110(11):2075–2087. [PubMed: 14597512]
9. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs patching for treatment of moderate amblyopia in children. Arch Ophthalmol. 2002; 120(3):268–278. [PubMed: 11879129]
10. Pediatric Eye Disease Investigator Group. A randomized trial comparing Bangerter filters and patching for the treatment of moderate amblyopia in children. Ophthalmology. 2010; 117(5):998–1004. 15. [PubMed: 20163869]
11. To L, Thompson B, Blum JR, Maehara G, Hess RF, Cooperstock JR. A game platform for treatment of amblyopia. IEEE Trans Neural Syst Rehabil Eng. 2011; 19(3):280–289. [PubMed: 21335317]
12. Holmes JM, Beck RW, Repka MX, et al. The Amblyopia Treatment Study visual acuity testing protocol. Arch Ophthalmol. 2001; 119(9):1345–1353. [PubMed: 11545641]
13. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. Am J Ophthalmol. 2003; 135(2):194–205. [PubMed: 12566024]
14. Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. Arch Ophthalmol. 2005; 123(4):437–447. [PubMed: 15824215]
15. Pediatric Eye Disease Investigator Group. A randomized trial to evaluate 2 hours of daily patching for strabismic and anisometropic amblyopia in children. Ophthalmology. 2006; 113(6):904–912. [PubMed: 16751033]
16. Pediatric Eye Disease Investigator Group. A randomized trial of near versus distance activities while patching for amblyopia in children aged 3 to less than 7 years. Ophthalmology. 2008; 115(11):2071–2078. [PubMed: 18789533]
17. Pediatric Eye Disease Investigator Group. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. Arch Ophthalmol. 2008; 126(12):1634–1642. [PubMed: 19064841]
18. Vedamurthy I, Nahum M, Huang SJ, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. Vision Res. 2015; 114:173–187. [PubMed: 25917239]
19. Li SL, Reynaud A, Hess RF, et al. Dichoptic movie viewing treats childhood amblyopia. J AAPOS. 2015; 19(5):401–405. [PubMed: 26486019]
20. Leske DA, Birch EE, Holmes JM. Real depth vs randot stereotests. Am J Ophthalmol. 2006; 142(4):699–701. [PubMed: 17011876]
21. Levi DM, Knill DC, Bavelier D. Stereopsis and amblyopia: A mini-review. Vision Res. 2015; 114:17–30. [PubMed: 25637854]

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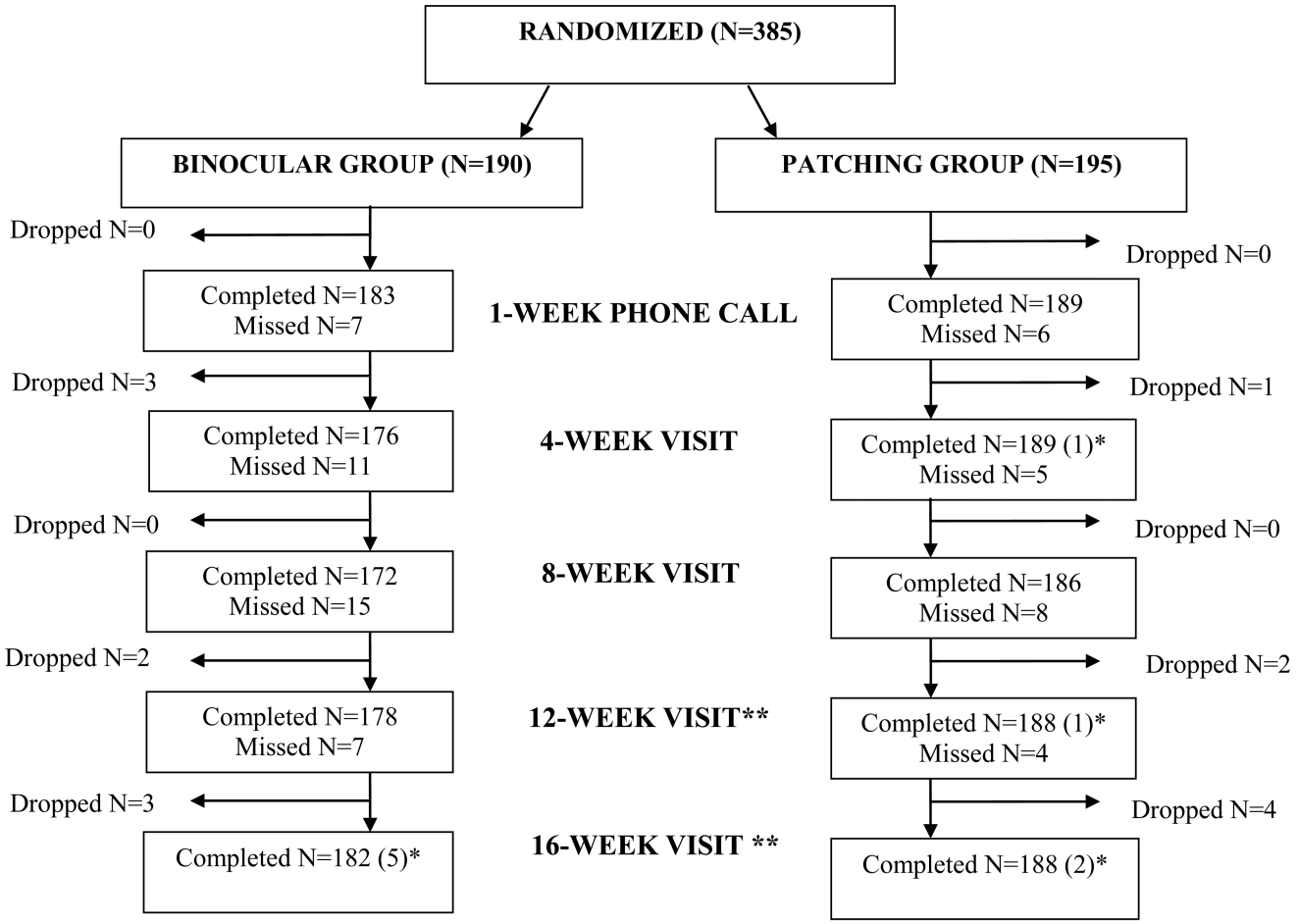

* In the patching group, one participant completed the 4-week visit outside of the analysis window (21 to <42 days after randomization) at 20 days after randomization and one participant completed the 12-week visit outside of the analysis window (70 to <98 days after randomization) at 104 days after randomization.

** There were 7 participants (5 binocular group, 2 patching group) that completed the 16-week visit outside of the analysis window (98 to <140 days after randomization). In the binocular group, the participants completed the 16-week visit at 140 (2 participants), 147, 154 and 164 days after randomization. In the patching group, the participants completed the 16-week visit at 148 and 196 days after randomization.

Figure 1. Visit completion by treatment group
Flowchart showing study completion in each treatment group.

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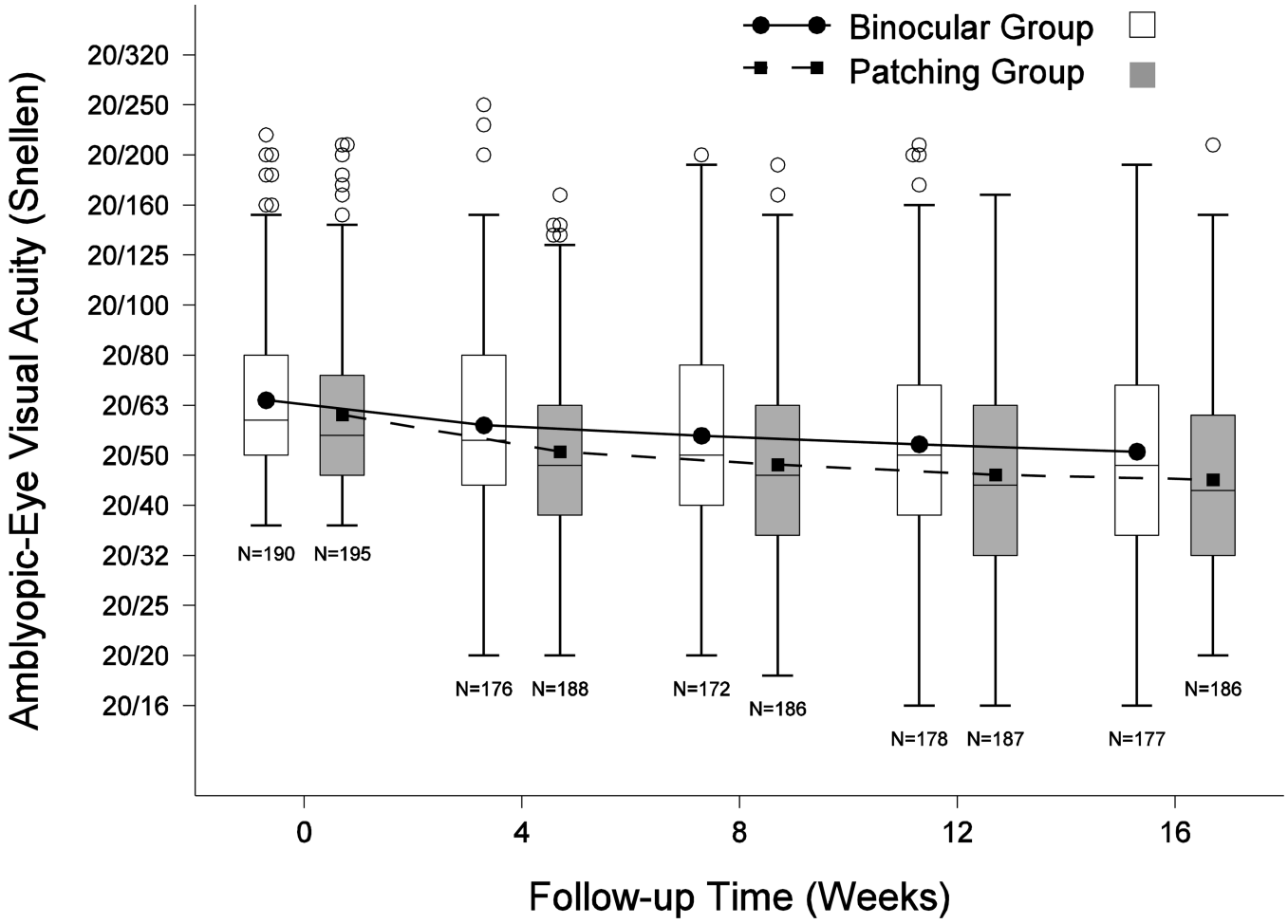

Figure 2. Visual acuity (VA) in amblyopic eyes from baseline to 16 weeks

At each time point, the left box represents the binocular group (joined by solid line) and the right represents the patching group (joined by dashed line). Bottom and top of each box represents the 25th and 75th percentiles. Line in the box is the median and dot the mean. Bars above and below extend to the closest observed data point inside 1.5 times the interquartile range and open circles represent near statistical outliers and the asterisks indicate far outliers.

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Table 1

Study Inclusion and Exclusion Criteria

ELIGIBILITY CRITERIA
The following criteria must be met for the patient to be enrolled in the study:

1 Age 5 to <13 years

2 Amblyopia associated with strabismus, anisometropia, or both (previously treated or untreated)

a. Criteria for strabismus: At least one of the following must be met:

- Presence of a heterotropia on examination at distance or near fixation (with or without spectacles)
- Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)

b. Criteria for anisometropia: At least one of the following criteria must be met:

- ≥0.50 D difference between eyes in spherical equivalent
- ≥1.50 D difference between eyes in astigmatism in any meridian

c. Criteria for combined-mechanism amblyopia: Both of the following criteria must be met:

- Criteria for strabismus are met (see above)
- ≥1.00 D difference between eyes in spherical equivalent OR ≥1.50 D difference between eyes in astigmatism in any meridian
- Note: the spherical equivalent requirement differs from that in the definition for refractive/anisometropic amblyopia

3 No amblyopia treatment in the past 2 weeks (patching, atropine, Bangerter, vision therapy)

4 Requirements for refractive error correction (*based on a cycloplegic refraction that is not more than 7 months old*):

- Hypermetropia of 3.00D or more by spherical equivalent (SE)
- Myopia of amblyopic eye of 0.50D or more SE
- Astigmatism of 1.50D or more
- Anisometropia of more than 0.50D SE
- *Note: Subjects with cycloplegic refractive errors that do not fall within the requirements above for spectacle correction may be given spectacles at investigator discretion but must follow the study-specified prescribing guidelines, as detailed below.*

a. Refractive error correction prescribing instructions:

- SE must be within 0.50D of fully correcting the anisometropia.
- SE must not be under corrected by more than 1.50D SE, and reduction in plus sphere must be symmetric in the two eyes.
- Cylinder power in both eyes must be within 0.50D of fully correcting the astigmatism.
- Cylinder axis must be within +/− 10 degrees if cylinder power is ≤1.00D, and within +/− 5 degrees if cylinder power is >1.00D. This criterion does not apply for dry over-refractions performed for subjects with contact lens correction.
- Myopia must not be undercorrected 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. Refractive error correction meeting the above criteria must be worn:

- 16 weeks ***OR*** until visual acuity stability is documented (defined as <0.1 logMAR change by the same testing method measured on 2 consecutive exams at least 4 weeks apart).

c. For determining visual acuity stability (non-improvement):

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- 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 that have been worn for at least 4 weeks.
- Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated
- The same form of correction must be worn throughout the entire study (i.e., no changing between contacts and spectacles). Monocular or binocular contact lens wear is allowed provided that the over refraction with the contact lenses meets the above requirements. Safety glasses are not required for patients wearing contact lenses, but investigators are encouraged to suggest safety glasses be worn over contact lenses.

5 Visual acuity, measured in each eye without cycloplegia in current refractive correction (if applicable) within 7 days prior to randomization using the ATS-HOTV© visual acuity protocol for children < 7 years and the E-ETDRS© visual acuity protocol for children ≥ 7 years on a study-approved device displaying single surrounded optotypes, as follows:

- **a.** Visual acuity in the amblyopic eye 20/40 to 20/200 inclusive (33 to 72 letters if E-ETDRS©)
- **b.** Visual acuity in the fellow eye 20/25 or better (≥ 78 letters if E-ETDRS©)
- **c.** Interocular difference ≥ 3 logMAR lines (≥ 15 letters if E-ETDRS©) (i.e., amblyopic-eye acuity at least 3 logMAR lines worse than fellow-eye acuity)

6 Heterotropia or heterophoria with a total near deviation of ≤ 10Δ (measured by PACT).

7 Ability to align the nonius cross on the binocular game system (angles of ocular deviation >10Δ would require the nonius cross to be adjusted to such an extent that playing of the game would be compromised).

8 Subject is able to play the special game on the study iPad® (on easy setting) under binocular conditions (with red-green glasses), as demonstrated by scoring at least 1 line in the office.

9 Investigator is willing to prescribe computer game play or patching per protocol.

10 Parent understands the protocol and is willing to accept randomization.

11 Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff.

12 Relocation outside of area of an active PEDIG site for this study within the next 16 weeks is not anticipated.

EXCLUSION CRITERIA

1 Prism in the refractive correction at time of enrollment (eligible only if prism is discontinued 2 weeks prior to enrollment).

2 Myopia greater than −6.00D spherical equivalent in either eye.

3 Previous intraocular or refractive surgery.

4 Known skin reactions to patch or bandage adhesives

5 Any treatment for amblyopia (patching, atropine, Bangerter filter, or vision therapy) during the past 2 weeks. Previous amblyopia therapy is allowed regardless of type, but must be discontinued at least 2 weeks immediately prior to enrollment.

6 Ocular co-morbidity that may reduce visual acuity determined by an ocular examination performed within the past 7 months (*Note: nystagmus per se does not exclude the subject if the above visual acuity criteria are met*).

7 No Down syndrome or cerebral palsy

8 No severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delay or reading and/or learning disabilities are not excluded.

9 Heterotropia or heterophoria with a total ocular deviation >10Δ (phoria plus tropia >10Δ) at near (measured by PACT).

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Table 2

Baseline Characteristics of Randomized Participants by Treatment Group [a]

	Binocular (N=190)		Patching (N=195)	
	N	%	N	%
Gender				
Female	98	52	89	46
Race/Ethnicity				
White	134	71	145	74
Black/African American	11	6	12	6
Hispanic	33	17	24	12
Asian/American Indian/Alaskan Native	9	5	6	3
More than one race	2	1	5	3
Unknown/not reported	1	<1	3	2
Age at enrollment (Years)				
5 to <7	43	23	50	26
7 to <9	78	41	62	32
9 to <13	69	36	83	43
Mean (SD) Years	8.4 (1.8)		8.6 (2.0)	
Prior Amblyopia Treatment				
None	45	24	40	21
Patching	89	47	89	46
Other (Not Patching) [b]	5	3	7	4
Patching Plus Other Treatment [b]	51	27	59	30
Distance Amblyopic-Eye Visual Acuity				
20/200 (33–37 Letters)	5	3	4	2
20/160 (38–42 Letters)	6	3	7	4
20/125 (43–47 Letters)	8	4	4	2
20/100 (48–52 Letters)	16	8	12	6
20/80 (53–57 Letters)	30	16	24	12
20/63 (58–62 Letters)	37	19	46	24
20/50 (63–67 Letters)	61	32	52	27
20/40 (68–72 Letters)	27	14	46	24
Mean (SD) LogMAR	0.51 (0.17)		0.48 (0.17)	
Mean Snellen Equivalent	$20/63^{-1}$		$20/63^{+1}$	
Distance Fellow-Eye Visual Acuity				
Mean (SD) LogMAR	−0.03 (0.09)		−0.03 (0.08)	
Mean Snellen Equivalent	$20/20^{+2}$		$20/20^{+2}$	
Interocular Difference				
Mean (SD) (Lines)	5.5 (1.8)		5.1 (1.8)	

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	Binocular (N=190)		Patching (N=195)	
	N	%	N	%
Baseline Stereoacuity (Seconds of Arc)[c]				
Nil	69	36	57	29
2000	28	15	37	19
800	18	9	26	13
400	17	9	19	10
200	23	12	18	9
100	23	12	23	12
60	10	5	9	5
40	2	1	6	3
Median (Seconds of Arc)	2000		800	
Amblyopia Cause				
Strabismus	22	12%	44	23%
Anisometropia	107	56	92	47
Strabismus/Anisometropia combined	61	32	59	30
Maximum Magnitude of Tropia Deviation at Distance Measured by SPCT (pd)				
Orthotropic	140	74	123	63
1 to 9	44	23	66	34
≥ 10	6	3	6	3
Maximum Magnitude of Tropia Deviation at Near Measured by SPCT (pd)				
Orthotropic	132	69	125	64
1 to 9	54	28	63	32
≥ 10	4	2	7	4
Amblyopic-Eye Spherical Equivalent (Diopters)				
Mean (SD) Diopters	+4.74 (2.41)		+4.20 (2.65)	
Fellow-Eye Spherical Equivalent (Diopters)				
Mean (SD) Diopters	+2.39 (2.04)		+2.31 (2.21)	
Spherical Equivalent Anisometropia (Diopters)				
Mean (SD) Diopters	+2.52 (1.74)		+2.11 (1.76)	

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation, SPCT = simultaneous prism and cover test

[a] Of the 12 participants who wore contact lens(s) during the study, an over-refraction was not performed for 7 participants and the contact lens over-refraction did not meet eligibility criteria for 1 participant. An over-refraction was not initially required for study eligibility but later added as an amendment to the protocol.

[a] Seven participants (3 in the binocular group and 4 in the patching group) were later found to be ineligible for the study based on the following pre-enrollment criteria: spectacles did not meet refractive correction guidelines (n=1), no over-refraction performed when required (n=1) or over-refraction was outside of the pre-specified tolerance limits (n=1) for contact lens wear, failure to meet visual acuity stability criteria for corrective wear (n=3), and the most recent cycloplegic refraction was performed more than 7 months prior to enrollment (n=1). These 7 participants were included in the primary analysis, but were excluded in a separate analysis as an additional approach to the primary analysis (eTable 1).

[b] Other treatment includes atropine, plano (or reduced plus) lens wear, fogging (Bangerter filter, tape, optical), vision therapy (home or office) or levodopa treatment for amblyopia.

[c] Results of the Randot Butterfly stereoacuity test were analyzed as 2000 seconds of arc (if correct response). Nil was defined as an incorrect response on the butterfly (n=67 and n=56 in binocular and patching groups, respectively), or on the 800 seconds of arc level of the Randot Preschool stereoacuity test if the butterfly was not attempted (n=2 and n=1 in binocular and patching groups, respectively)

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Table 3

Amblyopic-eye Visual Acuity Outcomes at 16 Weeks by Treatment Group [a]

	Binocular Group (N=177)		Patching Group (N=186)	
	N	%	N	%
Distribution of Amblyopic-eye Visual Acuity				
20/200 (33–37 Letters)	2	1	1	<1
20/160 (38–42 Letters)	2	1	3	2
20/125 (43–47 Letters)	10	6	2	1
20/100 (48–52 Letters)	12	7	7	4
20/80 (53–57 Letters)	18	10	17	9
20/63 (58–62 Letters)	25	14	22	12
20/50 (63–67 Letters)	30	17	38	20
20/40 (68–72 Letters)	32	18	37	20
20/32 (73–77 Letters)	33	19	27	15
20/25 (78–82 Letters)	8	5	22	12
20/20 (83–87 Letters)	3	2	10	5
20/16 (88–92 Letters)	2	1	0	0
Mean (SD) LogMAR	0.41 (0.21)		0.35 (0.20)	
Snellen Equivalent	$20/50^{-1}$		$20/50^{+2}$	
Distribution of Amblyopic-eye Visual Acuity Change				
≥ 3 lines (≥ 15 letters) better	19	11	29	16
2 lines (10–14 letters) better	32	18	36	19
1 line (5–9 letters) better	47	27	46	25
0 line (within 4 letters)	64	36	69	37
1 line (5–9 letters) worse	12	7	6	3
2 lines (10–14 letters) worse	1	<1	0	0
≥ 3 lines (≥ 15 letters) worse	2	1	0	0
Unadjusted Mean (95% CI) Lines	1.08 (0.86 to 1.29)		1.32 (1.14 to 1.51)	
Adjusted Mean (95% CI) Lines	1.05 (0.85 to 1.24)		1.35 (1.17 to 1.54)	
Participants with Amblyopic-eye Improvement of ≥ 2 Lines (≥ 10 Letters) from Baseline	51	29	65	35
Treatment Group Difference (95% CI) [c]	5% (−4% to 13%)			
Participants with Amblyopia Resolution[b]	8	5	18	10
Treatment Group Difference (95% CI) [c]	2% (−1% to 5%)			

SD = standard deviation, CI = confidence interval

[a] Visual acuity analyses only included data from participants who completed the 16-week visit within the pre-defined analysis window (14 to <20 weeks after randomization).

[b] Amblyopia resolution was defined as having an amblyopic-eye visual acuity of 20/25 or better (≥ 78 letters) and an interocular difference within 1 line (≤ 5 letters).

[c] Binomial regression was used to compute the treatment group difference, which was adjusted for baseline age group (5 to <7, 7 to <13 years) and baseline visual acuity. For the treatment group comparison of amblyopic-eye visual acuity of ≥ 2 lines, the baseline amblyopic-eye visual acuity

was treated as a continuous covariate in the model whereas this variable was included as a categorical factor (20/40, 20/50 or worse) for the treatment group comparison of amblyopia resolution. Due to model convergence issues, age was included as a categorical factor in the model (and baseline visual acuity for amblyopia resolution). Positive values favor the patching group.

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