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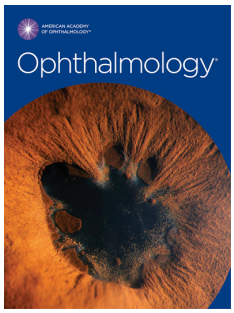

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An eye-tracking-based dichoptic home treatment for amblyopia: a multicenter randomized clinical trial

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Key Words: Amblyopia, lazy eye, binocular treatment, dichoptic treatment, eye-tracking, visual acuity, stereopsis, stereo acuity, adherence, patching

List of Abbreviations:

AE (adverse events), ATS (Amblyopia Treatment Study), BCVA (best-corrected visual acuity), CI (Confidence interval), D (Diopter), DMC (Data Monitoring Committee). FDA (Food and Drug Administration), GDPR (General Data Protection Regulation), HIPAA (Health Insurance Portability and Accountability Act), ITT (intent-to-treat), LS (least squares), mITT (modified intent-to-treat), PACT (Prism Alternate Cover Test), PD prism diopters, PI (Principal Investigator), PP (per-protocol), RCTs (Randomized Controlled Trials), SD (standard deviation),

SPCT (simultaneous prism and cover test), VA (visual acuity).

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Conflict of Interest

All authors have completed and submitted the ICMJE disclosures form. Authors with financial interests or relationships to disclose are listed prior to the references. TWJ is an unpaid scientific advisor. MB is a scientific advisor. TWJ and MB are shareholders, and have stock options in NovaSight LTD.; BJK is a scientific advisor and has stock options in NovaSight LTD. OY and AM are employees of and have stock options in NovaSight LTD. MB and OY are inventors to a patent for a novel amblyopia treatment titled “Screening, Diagnosing, Assessing, Monitoring and Treating Eye Diseases and Visual Impairments Using Eye Tracking” US 16/334666. None of the site investigators in the study besides TWJ had stock options in NovaSight LTD or served as paid consultants.

Abstract

Purpose:

To compare the effectiveness and safety of a novel binocular eye-tracking-based-home-treatment (CureSight) to patching.

Design:

Prospective, multi-center, randomized, masked, controlled non-inferiority pivotal trial.

Participants:

A total of 103 children aged 4 to ≤9 years with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia were enrolled at six clinical sites, randomized 1:1 to either CureSight treatment or patching.

Methods:

Binocular treatment group used the CureSight for 90 min/day, 5 days/week for 16 weeks (120 hours). The treatment combined anaglyph glasses and an eye tracker to induce dominant eye real-time blur around the fovea in dichoptic streamed video content. Patching group received 2-hour patching 7 days/week (224 hours). The pre-specified non-inferiority margin was 1 logMAR line.

Main outcome measures:

The primary outcome was the improvement in the amblyopic eye distance visual acuity (VA) from baseline at 16 weeks, modeled with a repeated measures ANCOVA. Secondary outcomes included stereoacuity, binocular VA, and treatment adherence rates, analyzed by a one-sample Wilcoxon-test within each group and a two-sample Wilcoxon-test comparing groups. Safety outcomes included the frequency and severity of study-related adverse events.

Results:

Binocular treatment group VA improvement at 16 weeks was found to be not inferior to patching group improvement (0.28 logMAR (±0.13, p<0.0001) and 0.23 logMAR (±0.14, p<0.0001) in binocular treatment group and patching group (90% CI of difference [-0.008, 0.076]), respectively)), since the lower confidence bound of -0.008 falls within the non-inferiority margin of -0.1 logMAR. Stereoacuity improvement of 0.40 log-arcseconds (p<0.0001) and improved binocular VA (0.13 logMAR, p<0.0001) was observed in binocular treatment group, with similar improvements in patching group in stereoacuity (0.40 log-arcseconds, p<0.0001) and binocular VA (0.09 logMAR, p<0.0001), with no significant difference between improvements in the two groups for both stereoacuity (difference 0 95% CI[-0.27, -0.27]; p=0.76) and binocular VA (difference 0.041 95% CI[-0.002, 0.085]; p=0.07). A significantly higher adherence was observed in treatment compared with patching group (91% vs. 83%, difference 8% 95% CI[-4.0%-21%]; p=0.011). No serious adverse events were found.

Conclusions:

Binocular treatment was well tolerated, noninferior to patching in amblyopic children aged 4 to ≤9 years. High adherence may provide an alternative treatment option for amblyopia.

Amblyopia can have a substantial impact on the quality of life, with estimates of prevalence ranging from 1% to 5%. Associated deficits involve visual sensitivity, fixation, stereopsis, and binocularity[1–6], which may result in poor academic performance[7]. The conventional amblyopia treatment is optical correction of the uncorrected refractive error, followed by part-time monocular deprivation by patching or penalizing the dominant eye to force the visual system to use the amblyopic eye[1,8,9]. The limitations of this treatment include poor adherence (44-57% for patchingr[6]), residual amblyopia, and recurrence of amblyopia (reported as about 25% of cases), even after successful treatment, as well as adverse psychological effects[10–12].

Over the last decade, binocular amblyopia therapy with dichoptic presentation has been developed as an alternative treatment approach with the potential benefit of improved adherence and better outcomes. Novel binocular treatments with dichoptic presentation adjust the visual stimuli between the amblyopic and fellow eyes, consequently, reducing interocular suppression[13–20]. New approaches that quantify the degree of interocular suppression, tested on larger samples of patients with amblyopia, demonstrated a direct relationship between the strength of suppression and the depth of amblyopia[19]. Dichoptic therapy has shown promise in pilot studies[15–18] and has been evaluated in randomized controlled trials (RCTs),[14,21–26] with mixed results. The efficacy of dichoptic therapy was successfully demonstrated in few large multi-center RCT performed versus continued spectacle correction[14,21,24,26,27]. However, to the best of our knowledge, no previous multicenter, long-term RCT that compared dichoptic therapy with patching has found dichoptic therapy to be either non-inferior or superior to patching. The need for stronger evidence to support the use of binocular treatment as a substitute for currently accepted therapies has been recognized by the American Academy of Ophthalmology[28].

CureSight is a novel investigational digital dichoptic device for binocular home treatment of

amblyopia (NovaSight, Israel) based on passive watching of video content. The treatment algorithm blurs the central vision of the non-amblyopic (fellow) eye in real-time using continuous gaze-tracking and is less obtrusive than conventional patching. This approach is designed to encourage adherence by allowing an unlimited choice of streamed video content that caters to a child's preference for an enjoyable home treatment. There are no limitations on which websites/streaming content can be used for training, as long as the link for the specific website was included in the device and was not blocked through the parental control function by the guardians. A monitoring center remotely tracks adherence and offers technical support and advice with respect to adherence as needed.

Following the initial results from a single-arm pilot study that showed significant improvements in amblyopic eye acuity and stereoacuity[29], the safety and effectiveness of CureSight were evaluated in a multi-center RCT for 16 weeks compared to part-time daily patching in children aged 4 to < 9 years with amblyopia associated with anisometropia and/or small angle strabismus.

Methods

Study Design

The study was a prospective, multi-center, randomized (1:1), evaluator masked, controlled trial conducted at six academic and community sites in Israel (Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer, Israel; Kaplan Medical Center, Rehovot, Israel; Maccabi Healthcare, Israel; Rambam health Care Campus, Haifa, Israel; Shaare Zedek Medical Center, Jerusalem, Israel; Soroka University Medical Center, Beer Sheva, Israel). The study was placed on a national registry (MOH_2020-08-10_009227, available at:

https://my.health.gov.il/CliniTrials/Pages/MOH_2020-08-10_009227.aspx) and listed on clinicaltrials.gov (NCT05185076). The study adhered to the tenets of the Declaration of Helsinki; Institutional Review Board/Ethics Committee approval was obtained at all participating sites, and both the parents or guardians of the study participants provided written informed consent prior to any study procedures.

Participants

Participants diagnosed with amblyopia were prospectively recruited from the outpatient clinics of the participating centers. Subjects were enrolled beginning August 18, 2020; the last subject completed the 16-week visit on February 15, 2022. The key entry criteria were amblyopia associated with small angle strabismus, anisometropia, or both (a combined mechanism) in subjects aged 4 to < 9 years, with a best corrected visual acuity (BCVA) of 20/32 to 20/100 in the amblyopic eye, a dominant eye BCVA of 20/40 or better for subjects aged 4 to 5 years, and 20/32 or better for those between 5 and 7 years, with an interocular difference of ≥ 2 lines. Strabismus was limited to a tropia of ≤5 prism diopters (PD) measured by the Simultaneous Prism and Cover Test (SPCT) at near fixation or heterophoria up to 10 PD measured by the Prism Alternate Cover Test (PACT). Participants were required to have stable visual acuity in their best refractive correction prior to enrollment, defined as wearing the same glasses for ≥16 weeks or until 2 consecutive VA measurements in the amblyopic eye 8 weeks apart did not change by >1 line. Anisometropia was defined as an interocular difference of at least 1.00 diopter (D) in spherical equivalent and/or at least 1.50 D in astigmatism. Both treatment-naive and previously treated subjects (i.e., patching, atropine penalization) were allowed. The list of inclusion and exclusion criteria is presented in Table 1.

CureSight™ System

CureSight is an eye-tracking-based system designed to treat amblyopia under dichoptic conditions that incorporate eye gaze tracking and separation of streamed visual stimuli presented on a monitor into two separate digital channels, one for each eye (the CureSight device was an investigational device when this study was performed and received an FDA clearance based on the outcomes of this study (K221375, September 29, 2022)). The treatment task consists of passively watching streamed video content presented by the system according to the child's personal preference from the web links approved by the parents. The main components of the system include the following: i) a computer with an 11.6-inch monitor used for stimulus presentation, ii) an eye-tracker that allows the continuous tracking of each eye gaze, iii) anaglyph glasses worn during the treatment to separate stimuli presented to each eye (Figure 1), and iv) proprietary software that uses the eye-tracking data to blur the central vision area of the visual stimuli presented to the non-amblyopic eye in order to encourage the brain to use the sharp, high-resolution information from the amblyopic eye's center of vision. The diameter and magnitude of the blur are adjusted automatically during treatment according to the VA of each eye, as measured at periodic follow-up visits at the clinic and registered on the CureSight cloud portal. Worse amblyopic eye distance visual acuity and greater differences in VA between eyes result in greater blur amplitudes and greater diameters being applied.

The system includes a Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR) compliant cloud web application that allows an eye care provider and the dedicated monitoring center to track the child's adherence and to intervene or provide technical support when needed.

Procedure

Each participant was randomly assigned to either the binocular treatment group or the control patching group using a permuted block design stratified by site with a 1:1 allocation ratio. Randomization was conducted by the Principal Investigator (PI) or study coordinator at each site using the secure EDC, web-based computer software. Allocation concealment was achieved by keeping the randomization sequences hidden. Examiners who performed primary outcome measurements were masked to the treatment group assignments at all follow-up visits.

Subjects assigned to the binocular treatment group were prescribed the CureSight home treatment for 90 minutes per day, 5 days a week for 16 weeks, for a total of 120 hours. At the beginning of each session, a positioning algorithm automatically guided the subject to sit at the optimal position for treatment (at a viewing distance of ~60 cm). Once optimal positioning was achieved, a brief eye-tracking calibration was performed. Subjects assigned to the patching control group were instructed to wear an adhesive patch (Ortopad - Pietrasanta Pharma, Italy) over the dominant eye for 2 hours per day, 7 days per week for 16 weeks (for a total of 224 hours).

Outcome assessments were performed at weeks 4, 8, 12, and 16 (±1 week). Outcome measures comprised the Amblyopia Treatment Study (ATS) Diplopia assessment and a Symptom Survey (5-question Ocular symptom survey from the ATS Miscellaneous Testing Procedures Manual[30]); masked examiners performed distance VA and stereoacuity testing.

Monocular and binocular VA testing were performed using the CTS software (M&S Technologies, Niles, IL, USA). Participants aged ≥7 years had VA assessed by the E-ETDRS protocol[31] using Lea numbers optotype, whereas participants aged 4 to <7 years were assessed by the HOTV protocol[31] using Lea symbols optotype[32] . The same VA protocol used at enrolment

were used throughout the study regardless of age at follow-up. Stereoacuity was assessed using the Randot Preschool Stereoacuity test (Stereo Optical Co, Inc., Chicago, IL, USA) at near (0.33 m). An SPCT and PACT were used to measure the ocular alignment. Adherence was objectively monitored by analyzing the treatment logs of screen gaze as recorded by the eye tracker for the binocular treatment group and was calculated using the guardians' manual self-reported logs for the patching group.

At the end of treatment (16-week), visiting patients' treatment satisfaction was assessed using a questionnaire.

Outcomes

The primary effectiveness outcome was defined as the mean improvement from baseline in amblyopic eye VA to week 16 in both study groups (a non-inferiority of no more than 0.10 logMAR). Secondary and additional outcomes included the change from baseline to week 16 in the stereoacuity test score, the amblyopic eye NVA, the binocular VA, and the binocular NVA. Safety was evaluated by the frequency, severity, and causality of adverse events (AEs). AEs were captured using a protocol-defined questionnaire of parents and participants for diplopia, headaches, and eye strain, and the exam data for new or worsening heterotropia (an increase of ≥10 prism diopters from baseline), worsening visual acuity in either eye (a decrease of ≥2 lines from baseline), and seizures. The mean change in the dominant eye BCVA from baseline to week 16 was also compared between groups.

Statistical Analyses

The statistical analysis plan was established *a priori*. The sample size for the study was calculated for the primary effectiveness endpoint A sample size of 90 subjects was calculated (45

per arm) to test the null hypothesis with 90% power at a 1-sided 5% level of significance based on a *t*-test of the non-inferiority using a prespecified non-inferiority margin of -0.1 logMAR, assuming a difference between the groups of zero (0) and a standard deviation of 0.16 logMAR. After adjusting for ~20% dropout, a total of up to 114 (57 per arm) subjects were to be recruited. We planned to use a sample size adaptive design (promising zone approach), which allowed for one interim analysis after approximately 80 subjects were recruited into the study. Based on the conditional power at the interim analysis (of the primary endpoint point), the study would either continue to the originally planned sample size if the result is "favorable," stop for futility if the result is "unfavorable," or increase the sample size to the maximum sample size of 200 subjects or the re-calculated value, whichever was lower, if the result is "promising." Following this principle does not inflate the Type I error.

The overall alpha level for this study is 5%. The primary endpoint was be tested with a one-sided 95% confidence interval. All other tests are tested at a 5% level of significance using two-tailed tests, except for the treatment by site interaction that was tested at a significance level of 15%. The hierarchy approach was adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. Thus, the primary endpoint was first analyzed and only if successful, the secondary endpoints were analyzed. Safety analyses were performed on the intent to treat (ITT) population and effectiveness analyses on the modified intent to treat population which was pre specified in the protocol to consist of all randomized subjects who also retrospectively met the inclusion criteria of the protocol, effectiveness analyses were also performed on the ITT and PP sets as sensitivity analyses. The improvement from baseline in amblyopic eye VA (in logMAR) to 16 weeks was compared between the treatment groups using repeated measures analysis of covariance (ANCOVA, SAS® MIXED procedure). The model

included the following fixed effects: treatment group, visit (4, 8,12 and 16 weeks as a categorical variable) and the treatment group by visit interaction term which is the parameter of interest. Baseline amblyopic eye VA, age (as a continuous variable), and site (as a categorical random effect) were entered as covariates. Baseline amblyopic eye VA was entered as a continuous variable so that the potential for co-linearity problems will be minimized. There was no differential dropout between the treatment groups, thus, any missing data at the 16 weeks' time point can most likely be considered missing at random. Since likelihood based repeated measures ANOVA is also an imputation method, for this evaluation no other method of imputation of missing data is considered beyond the model estimates. The principal statistical analysis was a comparison between the treatment groups, derived from the visit by treatment group interaction term from the model. The adjusted mean (LS Means) improvement from baseline in amblyopic eye VA at the 16-week visit was estimated from the model interaction term per group (with two-sided 95% confidence intervals) and for the difference between the groups (CureSight - patching) which was presented with one-sided 95% CI (equivalent to two-sided 90% CI) which was used as the pre-specified method for testing the non-inferiority hypothesis. The null hypothesis was rejected if the lower limit of the one-sided 95% CI of the LSmean difference in amblyopic eye VA between the treatment groups (binocular treatment- patching) at week 16 is greater than the non-inferiority margin fixed at -0.10 logMAR.

The treatment group by site interaction was evaluated as well, for assessment of poolability which confirmed that the primary outcome data could be pooled across sites (Table s2).

Secondary endpoints were analyzed with a one-sample t-test or a one sample Wilcoxon test for within group comparisons and a two-sample t-test sample or a two sample Wilcoxon test to

compare groups, depending on data distribution. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Stereoacuity was measured in current correction. For analysis, nil stereoacuity measurements were scored as 10000 arc seconds[33].

One interim analysis was planned after 90% of the original sample size was randomized to the study and had completed the 16-week follow-up period, in addition to those subjects who were terminated early. The interim analysis included an analysis of the primary efficacy end point and allowed for early cessation of the study only for futility. The interim analysis was performed in December 2021 by the independent external statistician who was contracted solely for this purpose and consisted of the data from 87 subjects. Based on the conditional power for the primary outcome at the interim analysis, the Data Monitoring Committee (DMC) and the unblinded independent statistician recommended continuing the trial with the original sample size planned for 90 subjects, without the need to adaptively increase the sample size. The DMC report with the decision to proceed to the original sample size of 90 subjects was signed on the 2nd of January 2022. Final database lock was performed on February 24th, 2022, with 95 evaluable subjects.

Results

Between August 18, 2020, and February 15, 2022, 103 children with amblyopia were randomized to one of two treatment groups: binocular treatment (n=51) and patching (n=52); see Figure 2. Ninety-five of the 103 participants had available 16-week outcome data and were included in the primary analysis. The groups were similar in age (binocular treatment group: 6.6±1.3 years; patching group: 6.9±1.4 years). Fifty percent of the overall subjects were female.

There was an even distribution of subjects who had not received prior patching treatment or atropine penalization (51%). Most subjects had anisometropic amblyopia (92%). Table 3 summarizes the demographics and baseline characteristics overall and per group.

Primary Effectiveness Outcomes (mITT Population)

At baseline, the mean amblyopic eye VA in the binocular treatment group was 0.37±0.15 logMAR and 0.37±0.14 logMAR in the patching group. The mean improvement from baseline at 16 weeks was 0.28± 0.13 logMAR in the binocular treatment group ($p<0.0001$) and 0.23±0.14 logMAR in the patching group ($p<0.0001$) (Figure 3).

The study met its primary effectiveness endpoint of non-inferiority of improvement in amblyopic eye VA in the binocular treatment group compared to patching. At 16 weeks, the LSmean change from baseline was 0.26 logMAR (SE 0.02) in the binocular treatment group and 0.23 logMAR (SE 0.02) in the patching group (Table s4). The difference between groups in LSmean improvement from baseline at 16 weeks was 0.034 logMAR (90% CI [-0.008, 0.076]) (See Table s4), fulfilling the success criterion of non-inferiority in relation to controls within a margin of -0.1 logMAR. These findings were consistent in the PP and ITT populations as well (see Table s4). Amblyopic eye VA demonstrated a statistically significant improvement in both treatment groups from baseline at weeks 4, 8, 12, and 16 ($p<0.001$).

Secondary Effectiveness Outcomes (mITT Population)

At baseline, the median stereoacuity was 2.3 log arcseconds for both groups. At week 16, the median stereo acuity was 1.78 log arcseconds for the binocular treatment group and 2.0 log arcseconds for the patching group (Figure 4). At 16 weeks, the binocular treatment was associated with a median improvement in the Randot stereo acuity of 0.40 log arcseconds

(Range: -0.65 to 1.78, Wilcoxon one-sample test, p<0.0001, Table 5). The improvement from baseline to week 16 was also significant in the patching group (p<0.0001), with a median improvement of 0.40 log arcseconds (Range: -0.60 to 1.95) and no significant difference between the groups in the magnitude of change (difference 0 95%CI[-0.27 - 0.27]; p=0. 76). As observed from the upper quartile (Q3), at week 16, 75% of the subjects had a Randot stereo acuity of better than 2.3 log arcseconds in the binocular treatment group and 2.6 log arcseconds in the patching group.

In addition, at 16 weeks, mean binocular VA had significantly improved from baseline by 0.13 logMAR (SD 0.09) in the binocular treatment group (one-sample *t*-test, p<0.0001), the difference between the groups was not found statistically significant (difference 0.041 95% CI:[-0.002, 0.085]; p=0.07). A significant improvement also observed at weeks 4 through 12 (p=0.0001 at week 4, p<0.0001 at other visits). A significant improvement from baseline was also observed at weeks 8 through 16 in the patching group (p<0.0001), by 0.09 logMAR (SD 0.12) at week 16, whereas the change from baseline at week 4 did not reach statistical significance (p=0.13).

Additional Effectiveness Outcomes (mITT Population)

Subgroup analysis did not reveal significant differences in the primary endpoint of improvement in amblyopic eye VA by the baseline covariates of the age group (4 to <7 years, 7 to <9 years), the type of amblyopia, previous amblyopia treatment, or the baseline VA levels (<0.3, from 0.3 to 0.5, >0.5 logMAR).

At the 16-week visit, the proportion of participants with 2 lines or more improvement from baseline of amblyopic eye VA was 79% (34/43) in the binocular treatment group and 61%

(30/49) in the patching group, with no significant difference between the groups (difference 17.9% 95%CI[-0.43%,36.1%]; chi-square test p=0.0635) (Figure 5 and Table s6).

At 16 weeks, the regimen adherence (as determined by the total treatment time) of the binocular treatment group was significantly greater than that of the patching group (median adherence of 91% (Range: 33% to 137%) in the binocular treatment group and 83% (Range: 22% to 130%) in the patching group; difference 8% 95% CI[-4-21%]; p=0.0114). In addition, 88% of parents reported satisfaction with the CureSight therapy and felt there was greater ease of use with that treatment therapy. The mean adherence in the binocular treatment group was also greater than that of the patching group being 93% versus 78% (Figure s6).

Safety Outcomes (ITT Population)

There were no serious AEs and no unanticipated AEs in the study. Non-serious AEs were reported in 27% (14/51) of the subjects in the binocular treatment group and 27% (14/52) in the patching group. The most commonly reported AEs were related to pathogens and allergies that are not related to the study (Table s7). Two out of 51 subjects (3.9%) in the binocular treatment group and 5 out of 52 subjects (9.6%) in the patching group had AEs that were possibly related to the treatment procedure. The majority of the AEs were mild and all were resolved without sequelae Other theoretical risks of a digital dichoptic system, such as diplopia, eye strain, and seizures, were not reported in the binocular treatment group.

There was no significant linear trend for change in the VA of the fellow eye for the type of treatment, CureSight or patching ($p>0.05$ at all visits; the Cochran-Armitage trend test). At week 16, 3 participants in the patching group had a worsening of fellow eye VA of greater than 1 line, as opposed to no participants in the binocular treatment group.

Discussion

We report that the novel digital, binocular, eye-tracking-based home treatment device was as effective as patching as a treatment for amblyopia stemming from anisometropia, small angle strabismus, or both, in an evaluator-masked multicenter RCT. The mean amblyopic eye distance VA improvement from the binocular treatment was 2.8 lines over 16 weeks. Importantly the benefit was seen in both age subgroups (4 to <7 and 7 to <9) with the advantage of significantly higher adherence rate for the binocular treatment users as compared to patching.

The improvement in the control patching group observed in our study is comparable to what has been reported in the literature for 2-hour patching in a similar age group[8,9,34]. The percentage of subjects with a 2-line or more improvement in the binocular treatment group was 79 % (34/43) versus 61% (30/49) in the patching group. Although this difference was not statistically significant (Fisher's exact test, p=0.0635), the improvement of the binocular treatment group appears to be higher than what was observed with patching group. Table s9 presents the distribution of line change from baseline in amblyopic eye VA in each treatment group for weeks 4 through 16 for the mITT set. Note that the distribution of subjects in our study was even between younger children aged 4 to < 7 years and slightly older children aged 7 to < 9 years and between those who had not received previous amblyopia treatment. Although some studies[23,24] have associated a younger age and no prior treatment with a better outcome from amblyopia therapy, we did not observe any statistically significant effect of age and prior amblyopia therapy in this study. One of the differences in the baseline characteristics in this study compared to other binocular treatment RCTs[24–26] was the interocular difference criterion of ≥ 2 logMAR lines (versus ≥ 3 logMAR lines). The improvement from baseline in the subset with 3-lines or a greater interocular difference (about 60% of the study subjects) was 3.1 (1.6) lines in the

binocular treatment group and 2.6 (1.4) lines in the patching group, reflecting the ability to reduce a 3-line interocular difference in VA and thereby increase the potential for binocularity. Importantly, although both groups improved similarly until week 12. At week 16 the binocular treatment group continued to demonstrate a significant improvement (p=0.0003), whereas the patching group had reached a plateau (p=0.62) (Table s10). This suggests the potential for further improvement with longer binocular treatment periods in the VA of the amblyopic eye. Future studies are needed to explore the value of longer treatment durations for maximum benefit from the investigated binocular treatment.

The improvement in amblyopic eye VA was coupled with significantly improved stereopsis and binocular VA, possibly demonstrating a positive effect of treatment on binocular interaction. These improvements were achieved progressively over the study period in both groups. Improvement in stereoacuity was observed in the binocular treatment group, both in the previous single-arm pilot study[29] and in the current evaluator-masked RCT. Results for stereoacuity in the literature on conventional patching therapy and the newer binocular approaches have been inconsistent, with some studies reporting a tendency for improvement[35–37] and others with no demonstrable improvement[15,22,23,26].

Adherence plays a key role in amblyopia treatment effectiveness, with higher regimen adherence being associated with greater amblyopic eye VA gains[38]. Poor adherence with patching is a significant risk factor affecting the child's final VA outcome[38–40]. It was estimated that only 50% of caregivers achieve the recommended patching times for their children[41]. Despite the closely monitored boundaries of a clinical study, the adherence with patching was similar to that of the binocular treatment group only in the initial follow-ups. The significantly greater adherence with to the binocular treatment regimen at week 16 (a median of 91% for binocular treatment vs. 83%

for patching) demonstrates the sustained benefit of our treatment in maintaining adherence throughout the assigned treatment period. In addition, unlike the subjective reporting of the adherence with patching that was recorded by subjective logbook entries by the guardians, the adherence monitoring for CureSight was accurately monitored by using the eye tracking data and only the actual screen watching time was considered in calculating adherence. If the patient's eye gaze was not on the screen or if the patient was not wearing the treatment glasses, the treatment was stopped, the patient was alerted, and the pause time was not calculated as treatment time. Holmes et al. found that the adherence could be substantially reduced even in the case of binocular treatment with iPad games, when the viewed content was repetitive for children[23]. Since our treatment offers children the choice of unlimited streamed visual content to keep them engaged and it is individually tailored, along with continued support from the monitoring center, the adherence e to treatment will likely remain high even outside the rigor of a clinical study.

The subjective satisfaction questionnaire also matched the objective measure of adherence, with 88% of parents reported being either "Very Satisfied" or "Satisfied" with the CureSight system as a treatment for amblyopia (see Table s8). The majority of parents answered favorably to questions regarding adherence (including the ability to track adherence data on the system), the ease of use, and satisfaction. Hence, our treatment may also be a beneficial option in young children whose resistance to wearing a patch, resulting from psychological and sensory factors, could adversely affect the treatment.[20,22]

The safety profile of the reported binocular treatment is comparable to the standard of care patching of the non-amblyopic eye. There was a lower incidence of headaches associated with the binocular treatment (4%), compared with patching (8%). Other notable risks, including diplopia, eye strain, and seizures were not observed.

The current study has several limitations that should be considered. The majority of the subjects were anisometropic amblyopes (90% of the subjects in this study vs. 50-60% in comparable RCTs[23,26]). Although the amblyopia type subgroup analysis showed no significant difference in subgroup analysis of the groups, further generalizability confirmation to strabismic and mixed amblyopia population should be explored. Moreover, future studies are needed to evaluate the impact of dosing on the rapidity of visual improvement and its durability, and the effect of subgroups on treatment effectiveness, compared to other binocular treatments. Tropia was limited to no more than 5 prism diopters. Finally, using a subjective self-logging compliance diary by the guardians of the patching group was another limitation in our study, as there is ample evidence for overestimating compliance in this type of patching monitoring[42,43].

In the current study we used a non-inferiority margin of one line (0.1 logMAR), which is greater than the other non-inferiority studies that used more conservative limits of either 0.05 or 0.075 logMAR. As shown in Table s4, if we had performed the statistical comparison using either of the more conservative non-inferiority margins, the study would have resulted in the same conclusion. Nevertheless, in retrospect, we believe that a more conservative non-inferiority limit should have been considered and we intend to use such margins when planning future studies.

Conclusions

To the best of our knowledge, this is the first successful multi-center RCT that demonstrated the effectiveness of a digital dichoptic amblyopia therapy delivered through passive video watching requiring no gaming skills, compared to the gold standard patching therapy. The evaluated novel binocular treatment was found to be non-inferior to patching following a 16-week trial period

and was associated with higher regimen adherence rates and parent preferences. Stereopsis and binocular acuity were also significantly improved, despite a 2-fold shorter overall treatment time than with patching. Hence, it is reasonable that this approach to amblyopia treatment will represent a safe, engaging, and personalized alternative to patching. It is yet to be investigated if this binocular treatment can apply for other forms of amblyopia and to older children and adults.

Figure Legends

Figure 1. Binocular treatment setup. Step 1: Streamed visual stimuli is converted into two anaglyph separate channels, blue for the amblyopic eye and red for the fellow eye and are presented super-imposed. Step 2: Illustration of the blurred fellow eye channel (red) central visual area: a high diameter blur area with a high amplitude blur (left); a small diameter blur area with a low blur amplitude (right). The amblyopic eye channel is not affected by the blur.

Figure 2. CONSORT diagram of the trial. ITT, intent-to-treat; mITT, modified intent-to-treat; PP, per-protocol.

Figure 3. Change in amblyopic eye distance visual acuity from baseline. Change in amblyopic eye distance visual acuity VA from the baseline at each follow-up visit, at 4, 8, 12, and 16 weeks for participants in the binocular treatment group, compared with the patching group (modified intent-to-treat [mITT] population).

Figure 4. Change from baseline in stereo acuity. Stereo acuity (Randot preschool test) in arcseconds from the baseline and at follow-up visits at 4, 8, 12, and 16 weeks for participants in the binocular treatment group, compared with the patching group (mITT population).

Figure 5. Improvement of ≥2 Lines

Proportion of participants with ≥2 lines of improvement in amblyopic eye VA at each follow-up visit.

Précis

CureSight, a binocular eye-tracking-based amblyopia treatment is non-inferior to conventional patching therapy for treating children aged 4-<9 with amblyopia. Hence, it might represent a safe, engaging, effective and personalized alternative to patching.

Footnotes and Disclosures

Conflicts of Interest

All authors have completed and submitted the ICMJE disclosures form. Authors with financial interests or relationships to disclose are listed prior to the references. TWJ and MB are scientific advisors, shareholders, and have stock options in NovaSight LTD.; BJK is a scientific advisor and has stock options in NovaSight LTD. OY and AM are employees of and have stock options in NovaSight LTD. MB and OY are inventors to a patent for a novel amblyopia treatment titled "Screening, Diagnosing, Assessing, Monitoring and Treating Eye Diseases and Visual Impairments Using Eye Tracking" US 16/334666. None of the site investigators in the study besides TWJ had stock options in NovaSight LTD or served as paid consultants.

CureSight Pivotal Trial Group

Sites are listed in order by number of participants enrolled into the study. The number of patients enrolled at each site is noted in parentheses and personnel are listed as: investigator (I), Sub investigator (SI) coordinator (C), and masked examiner (E). Sheba Medical Center, Ramat Gan,

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Table 1. Eligibility Criteria

Inclusion Criteria

The subjects met all of the following inclusion criteria in order to be eligible for the study:

1. Age 4 to <9 years, male and female
2. Amblyopia associated with strabismus, anisometropia, or both (untreated or previously treated) meeting one of the following conditions:
   - Newly diagnosed amblyopia no prior treatment)
   - Prior amblyopia treatment must have been discontinued with no treatment administered for a minimum of 8 weeks prior to the Screening Visit.

   a. Criteria for strabismic amblyopia (at least one of the following must be met):
      - The presence of heterotropia upon examination at a distance or near fixation (with or without optical correction; it must be no more than 5 PD by SPCT at near fixation).
      - A documented history of strabismus that is no longer present

   b. Criteria for anisometropia (at least one of the following criteria must be met):
      - ≥1.00 D difference between eyes in spherical equivalent
      - ≥1.50 D difference in astigmatism between the corresponding meridians in the two eyes

   c. Criteria for a combined-mechanism amblyopia (both of the following criteria must be met):
      - Criteria for strabismus
      - ≥1.00 D difference between eyes in a spherical equivalent OR ≥1.50 D difference in astigmatism between the corresponding meridians in the two eyes
3. Refractive error correction (based on a cycloplegic refraction completed within the last 7 months) if any of the following are true:
   - Hypermetropia of 2.50 D or more by Spherical Equivalent (SE)
   - Myopia of the amblyopic eye of 0.50D or more
   - Astigmatism of 1.00D or more
   - Anisometropia of more than 0.50D

   Note: Subjects with cycloplegic refractive errors that do not fall within the requirements above for spectacle correction may be given spectacles at the investigator's discretion, but must follow the study-specified prescribed guidelines, as detailed below.

a. Spectacle prescribed instructions in reference to the cycloplegic refraction must have been completed within the last 7 months:

   - SE must be within 0.50D of fully correcting the anisometropia.
   - SE must not be under corrected by more than 1.50D SE, and a reduction in the plus sphere must be symmetric in the two eyes.
   - The cylinder power in both eyes must be within 0.50D of fully correcting the astigmatism.
   - The axis must be within +/- 10 degrees if the cylinder power is ≤1.00D, and within +/- 5 degrees if the 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 both eyes.

b. Spectacle correction meeting the above criteria must be adhered to:
   - For at least 16 weeks OR

   until distance VA stability is documented (defined as <0.1 logMAR change by the same testing method measured on 2 consecutive exams at least 8 weeks apart).
      - For determining VA stability (non-improvement):
         - The first of two measurements may be made 1) in the current spectacles, or 2) in trial frames with or without cycloplegia or 3) without correction (if a new correction is prescribed),

- The second measurement must be made without cycloplegia in corrected spectacles that have been worn for at least 8 weeks.
  Note: Since this determination was a pre-study procedure, the method of measuring VA was not mandated.

4. VA, measured in each eye without cycloplegia in the current spectacle correction (if applicable) within 7 days prior to randomization using the Lea symbol per ATS VA protocol for children < 7 years and the E-ETDRS VA protocol for children ≥ 7 years on a study-approved device displaying single surrounded optotypes, was as follows:

   a. Visual acuity in the amblyopic eye 20/32 to 20/100 inclusive.
   b. Best-corrected dominant-eye VA meeting the following criteria:
      - If age 4, 20/40 or better by Lea symbols per ATS
      - If age 5 and older, 20/32 or better by ATS-HOTV using LEA symbols for age <7 and Lea numbers for > 7 years
   c. Interocular difference ≥ 2 logMAR lines (Lea symbols per ATS)

5. *Heterotropia with a near deviation of <5Δ (measured by SPCT) in habitual correction (Angles of ocular deviation >4Δ are not allowed because the large magnitudes of the deviation would compromise successful alignment of the dichoptic stimuli).
6. Passing a dedicated 10 min in-clinic performance ability test to assure suitable eye tracking performance.
7. Subjects and families eligible for clinic visits during the course of the study.
8. Subjects in general good health and able, as per investigator decision, to comply with the study visits and protocol procedures and to wear refractive correction and who have access to a wireless internet at home, which is able to support the CureSight treatment (loaned by the sponsor).
9. A signed and dated informed consent form.
10. Parents and participants understand, and willing to comply with the study procedures and are available for the duration of the study.

**Note: For criterion 5, heterotropia of 5 PD or less at near, as measured by SPCT, was allowed for inclusion in the study (although the protocol text reads <5 Δ). This is correctly specified in the study definition for strabismic amblyopia in criterion 2a.*

Exclusion Criteria

Individuals with any of the following characteristics were excluded from the study.

1. Myopia greater than -6.00 D spherical equivalent in either eye
2. Known skin reactions to patch or bandage adhesives
3. Any other condition that could be a potential cause for reduced BCVA according to the investigator
4. 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.
5. History of low adherence with amblyopia treatment, as assessed informally by the investigator
6. Subjects who do not wear their spectacles (as assessed by investigator)
7. A history of light-induced seizures
8. Wearing RGP contact lenses
9. Any reported anatomic ocular anomaly (e.g., a small lens opacity, a myelinated nerve fiber layer)
10. Previous intraocular or refractive surgery
11. Any condition that prevents the subject from completing a continuous treatment for 45-90 min per day while seated in front of a near screen. This includes children who do not like or cannot watch TV/movies for more than 60 min every day according to the parent's report.
12. Heterophoria with a total near deviation of ≥10Δ (measured by PACT)

Table 3. Demographics and baseline characteristics.

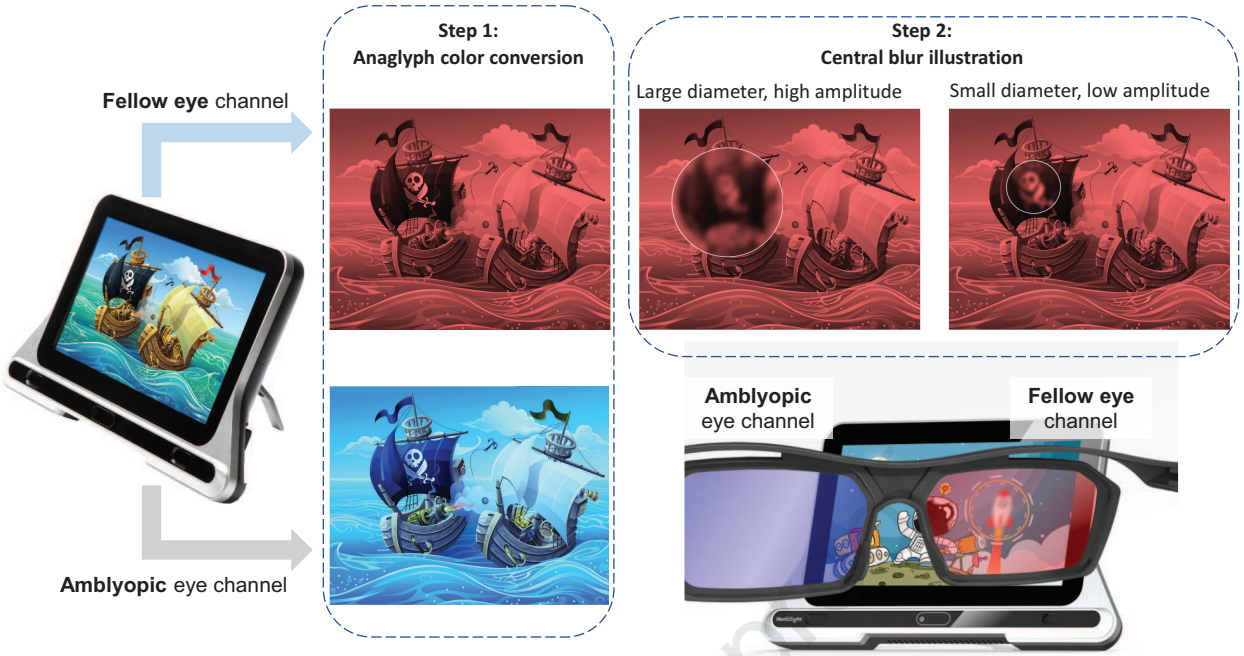
		Treatment (N=51)	**Control (N=52)**
Age (years)		6.63 ± 1.34	6.94 ± 1.43
Sex	Male	28 / 51 (54.90%)	23 / 52 (44.23%)
	Female	23 / 51 (45.10%)	29 / 52 (55.77%)
Amblyopic Eye	OD (Right) eye	17 / 51 (33.33%)	25 / 52 (48.08%)
	OS (Left) eye	34 / 51 (66.67%)	27 / 52 (51.9%)
Type of Amblyopia	Refractive	46 / 51 (90.20%)	49 / 52 (94.23%)
	Strabismic	0 / 51 (0.0%)	0 / 52 (0.0%)
	Both combined	5 / 51 (9.8%)	3 / 52 (5.77%)
Prior Amblyopia Treatment	None	24 / 51 (47.06%)	26 / 52 (50.00%)
	Patching	26 / 51 (50.98%)	26 / 52 (50.00%)
	Atropine + Patching	1 / 51 (1.96%)	0 / 52 (0.0%)
	Binocular treatment	0 / 51 (0.0%)	0 / 52 (0.0%)
Prior Strabismus Surgery		0 / 51 (0.0%)	0 / 52 (0.0%)
Duration in Current Correction (months)	Within the last 6 months	32 / 51 (62.75%)	33 / 52 (63.46%)
	More than 6 months	19 / 51 (37.25%)	19 / 52 (36.54%)
Cycloplegic Refraction Spherical Equivalent (diopters)	Amblyopic Eye	3.87 ± 3.51	4.70 ± 3.39
	Fellow Eye	2.20 ± 1.77	3.29 ± 2.12
Baseline Best Corrected Visual Acuity (logMAR)	Amblyopic Eye	0.370 ± 0.144	0.36 ± 0.14
	Fellow Eye	0.053 ± 0.11	0.043 ± 0.11

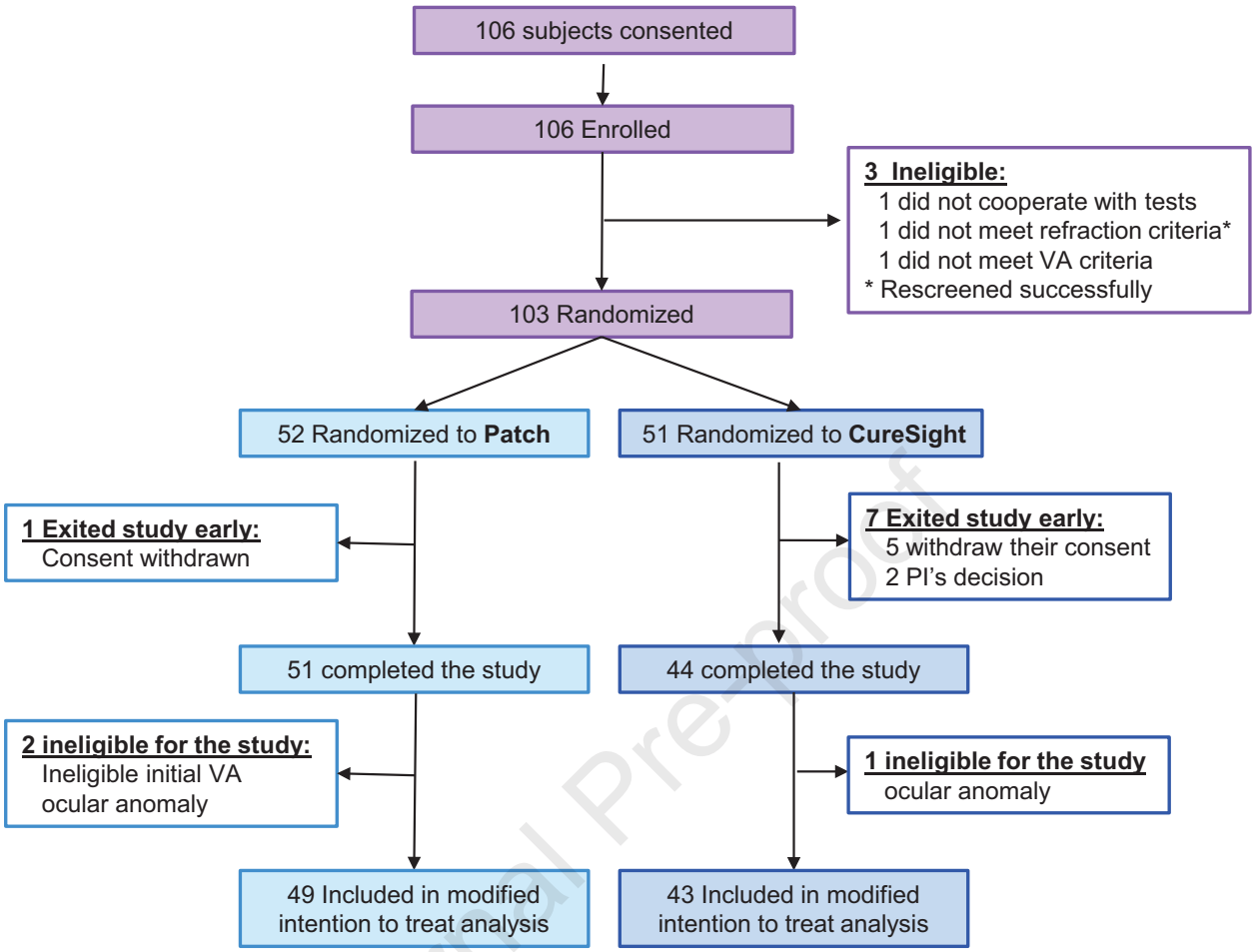
Categorical variables presented as n / N (%) and continuous variables presented as the mean ± standard deviation.

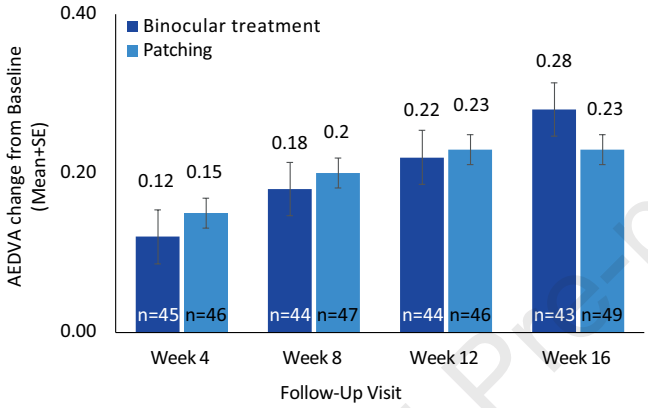
Table 7. Incidence of Adverse Events Observed in the Study Intervention

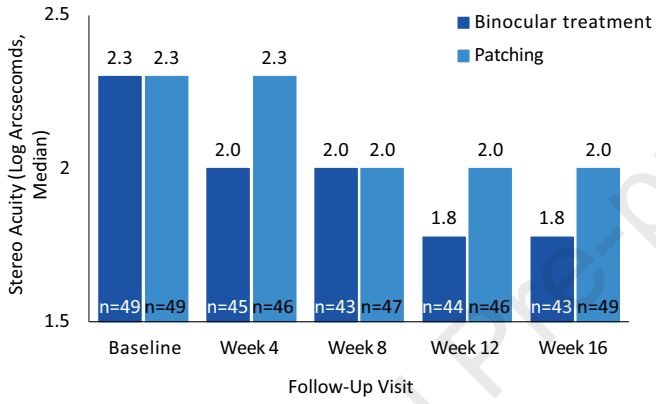
	Binocular treatment (N=51) *	Patching (N=52) *	Difference Between Groups (Binocular – Patching) **
Diplopia	0 (0.0%) [0] [0%, 6.98%]	0 (0.0%) [0] [0%, 6.85%]	0% (0%, 0.05%)
New heterotropia	0 (0.0%) [0] [0%, 6.98%]	2 (3.85%) [2] [0.47%, 13.21%]	-3.85% (-9.07%, 1.38%)
Worsening heterotropia	1 (1.96%) [1] [0%, 10.45%]	0 (0%) [0] [0%, 6.85%]	1.96% (0%, 10.45%)
Worsening of the VA amblyopic eye	2 (3.92%) [2] [0.48%, 13.46%]	0 (0%) [0] [0%, 6.85%]	3.92% (0.48%, 13.46%)
Worsening of the VA Fellow eye	0 (0%) [0] [0%, 6.98%]	1 (1.92%) [1] [0.05%, 10.26%]	-1.92% (-10.26%, -0.05%)
Headache	2 (3.92%) [2] [0.48%,13.46%]	4 (7.69%) [5] 2.14%, 18.54%]	-3.77% (-12.76%, 5.22%)
Eye strain	0 (0%) [0] [0%, 6.98%]	0 (0%) [0] [0%, 6.85%]	0% (0%, 0.05%)
Skin Irritation	0 (0%) [0] [0%, 6.98%]	0 (0%) [0] [0%, 6.85%]	0% (0%, 0.05%)
Seizures	0 (0%) [0] [0%, 6.98%]	0 (0%) [0] [0%, 6.85%]	0% (0%, 0.05%)
Pathogens and allergies	9 (23.53%) [12] [8.4%, 30.87%]	6 (11.54%) [6] [4.35%, 23.44%]	6.11% (-7.49%, 19.71%)
Other	0 (0%) [0] [0%, 6.98%]	2 (3.85%) [2] 0.47%,13.21%]	-3.84% (-13.21%, -0.47%)
Overall	14 (33.33%) [17] [15.20%, 41.74%]	14 (30.77%) [16] [15.57%, 41.02%]	0.53% (-16.66%, 17.71%)

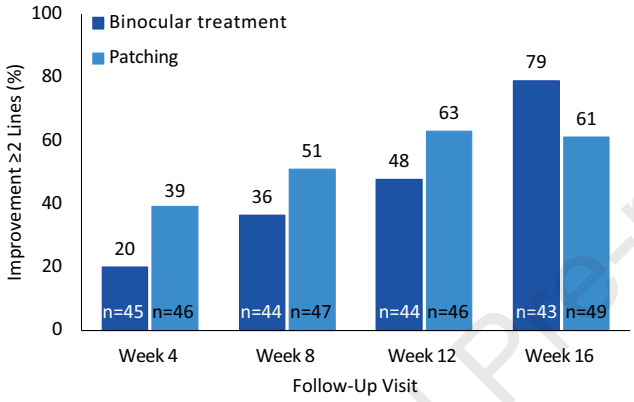
*Data presented as the no. (%) of participants [no. of events], [95% confidence interval].
**Data presented as the differences in % of participants (95% confidence interval).
Participants may experience more than 1 adverse event. Negative point estimates of the difference between groups indicate that the adverse event was observed more commonly in the control group than in the treatment group.
The adverse events categorized as "other" in the continued glasses group were uncharacteristic anger attack and syncope. VA (visual acuity)











CureSight Pivotal Trial Group

Sites are listed in order by number of participants enrolled into the study. The number of patients enrolled at each site is noted in parentheses and personnel are listed as: investigator (I), Sub investigator (SI) coordinator (C), and masked examiner (E). Sheba Medical Center, Ramat Gan, IL (n=36): Abraham Spierer, MD (I) Tamara Wygnanski-Jaffe MD (SI), Nethanel Zitzer (E), Dan Cohen (E), Ahuva Shpigelman (E), Maoz Hadash (E), and Ilya Ortenberg (E), Rinat Cohen (C). Kaplan Medical Center, Rehovot, IL (n=21) Hana Leib, MD (I), Majd Arow, MD (SI) Reut Parness MD (SI), Luba Rodov MD (SI), Alexandra Goz MD (SI). Haia Katz MD (SI), Anabel Bazov (C), Chaim Nissen (E), Gabriel Avraham (E), and Emad Borsha (E). Maccabi Healthcare Service, Tel Aviv, IL (n=18). Idit Keynann, MD (I) Tali Aviv (E), Nathalie Corcos (C) and Keren Roll (E). Rambam Medical Center, Haifa, IL (n=14) Eedy mezer MD (I), Vered Brucker (E), Meital Abecassis (C) and Shaare Zedek Medical Center, Jerusalem, IL (n = 9) Ronen Rabinovich, MD (I), Eran Laster (E), Ronit Politi (E) and Hila Givoni (C). Soroka Medical Center, Beer Sheva, IL (n=5). Ahed Amitirat MD (I), Chiya Robert Barrett, MD (SI), Adelina Zioni (E) and Katty Kuperman (C).Yael Crocus - clinical study manager

Précis

CureSight, a binocular eye-tracking-based amblyopia treatment is non-inferior to conventional patching therapy for treating children aged 4-<9 with amblyopia. Hence, it might represent a safe, engaging, and personalized alternative to patching.