AMBLYOPIA TREATMENT STUDY

ATS8

A Randomized Trial Comparing Atropine to Atropine Plus a Plano Lens for the Sound Eye As Prescribed Treatments for Amblyopia in Children 3 to <7 Years Old

PROTOCOL

Version 1.4

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Chapter 1: Background and Summary

1.1 Overview

ATS8 will evaluate two atropine treatment regimens for amblyopia (20/40 to 20/400) in children 3 to <7 years old:

- weekend atropine 1%
- weekend atropine 1% plus a plano lens for the sound eye

The study is being coordinated by the Jaeb Center for Health Research in Tampa, Florida and funded through a cooperative agreement from the National Eye Institute. The organizational structure of the study group and study policies are detailed in the PEDIG Bylaws document.

1.2 Rationale for the Study

Amblyopia is the most common cause of monocular visual impairment in both children and young and middle-aged adults. Patching has been the mainstay of amblyopia therapy. It is generally held that the response to treatment is best when it is instituted at an early age. Atropine has been used as an alternative to patching for the treatment of amblyopia for more than a century. Through its cycloplegic effect, atropine prevents accommodation, blurring the sound eye at near fixation, presumably forcing the patient to use the amblyopic eye at near.

There are a number of studies including at least two randomized studies which have evaluated atropine as a treatment for moderate amblyopia. ATS1, a randomized trial of 419 children meeting entry criteria similar to primary group of interest in ATS8, found that both atropine 1% (one drop daily) and patching (6 hours to full time daily) produced visual acuity improvement of similar magnitude and concluded that both are appropriate treatment modalities for the management of moderate amblyopia in children.[1] Patching had the advantage of a more rapid improvement in visual acuity and possibly a slightly better acuity outcome, whereas atropine had the advantage of easier administration and lower cost.

ATS4 is a recently completed randomized trial comparing daily and weekend-only atropine for moderate amblyopia (20/40 to 20/80). [2] This study demonstrated that the improvement with both daily atropine and weekend-only atropine was 2.3 lines after 4 months. This treatment was of similar magnitude to that reported with patching either 2 or 6 hours per day for 4 months.[3]

Although a randomized treatment trial of atropine for severe amblyopia has not been conducted, there are several published case series on the outcome of pharmacological penalization that specifically discusses the outcomes for patients with severe amblyopia. In nearly all of the following studies atropine was prescribed daily. Ron and Nawratzki reported on 16 patients with initial acuities of 20/200 and 13 patients with initial acuities of 20/100. [4] In all but two children the vision improved and in 18 improved to 20/30 or better. North and Kelly included only one such case in their series of 20 patients with longitudinal follow-up.[5] Repka and Ray reported on 79 patients treated with atropine.[6] They stratified patients on the basis of initial amblyopic eye acuity, 20/100 or worse, 20/80 to 20/50, and 20/40 or better. They found that the 20/100 or worse group improved the most. Of those children who improved an octave or more, the initial mean acuity was 20/113. Foley-Nolan and colleagues reported a prospective randomized study of occlusion versus atropine.[7] The treatments appeared equally effective. Ten of the 18 patients randomized to atropine had acuity worse than 20/100. After treatment all 10 children were better than 20/80 and 7 were 20/40 or better. Simons and coworkers specifically mentioned that they observed visual acuity improvement with atropine treatment for initial amblyopic eye acuities of <20/100. [8] Eight patients

with 20/200 to 20/600 best corrected initial visual acuity (geometric mean = 20/287) were managed recently at the Wilmer Institute with atropine penalization and best glasses correction (unpublished data – Michael X. Repka). Visual acuity testing was not masked. The acuity of 6 of 8 patients improved, with the mean geometric acuity of 20/80 at outcome for all 8 patients.

The therapeutic approach of reducing the hypermetropic refractive correction before the sound eye in combination with atropine has been part of the clinical approach to amblyopia treatment for a long time.[9] When the sound eye is hypermetropic, the penalization effect can be augmented by prescribing less than full hypermetropic spectacle correction for the sound eye, effectively blurring the eye at near and distance fixation. Some pediatric eye care providers prescribe a plano or reduced-plus lens concurrent with the initiation of atropine treatment believing that this will accelerate the visual improvement and provide a better visual acuity outcome than atropine alone.[10] Kaye and colleagues took patients who were failing occlusion therapy after a mean of 36 weeks and prescribed atropine 1% and a plano lens for the sound eye. After 10 weeks they found an improvement in geometric mean acuity from 20/113 to 20/37. In ATS1, a plano lens was prescribed for the sound eye only if the patient had not improved to 20/30 or at least 3 lines after 4 months of daily atropine use.[1, 11] Among the 55 patients in ATS1 who were prescribed a plano lens for the sound eye during follow up, the distance optical blur from the plano lens induced by cycloplegia was >0.50 to ≤1.00 D for 2 patients, >1.00 to ≤2.00 D for 9 patients, >2.00 to ≤3.00 D for 11 patients, and >3.00 D for 33 patients. The mean improvement in acuity prior to the use of the plano lens was 1.0 line compared with 1.6 lines after prescribing the plano lens (P=0.11 by paired t-test). While using the plano lens, the amount of improvement was not related to the amount of optical induced blur; patients with induced blur >3.00 D had 1.7 mean lines of improvement and patients with induced blur ≤3.00 D had 1.5 mean lines of improvement (P=0.93 evaluating induced blur as a continuous variable in linear regression model). ATS8 will assess whether prescribing a plano lens concurrently with initiating atropine therapy will produce a faster or a better visual acuity outcome by 17 weeks than prescribing atropine alone.

In ATS1, a reduction in sound eye visual acuity (2 or more lines) occurred at 6 months more frequently when a plano lens was prescribed in addition to atropine (7 of 43, 16%) compared with treatment with atropine alone (4 of 123, 3%; P=0.01). However, after longer follow-up the sound eye of only one patient treated with atropine alone and no patient treated with atropine plus the plano lens was worse than baseline.

In ATS4 the use of atropine was associated with the loss of two lines in the sound eye of only 1 of 85 patients in the weekend only treatment group and 1 of 83 patients in the daily group. [2] This lower frequency of sound eye acuity reduction in this study is likely due to the study design which required the patients to be tested at least two weeks after the drops were stopped and by having the investigators retest any sound eyes with vision loss. The finding could also reflect the study design that a plano lens was prescribed for some patients in ATS1 but not in ATS4.

1.3 Summary of Rationale for the Trial

Atropine is an effective treatment of moderate amblyopia. Reduction of the plus sphere for the sound eye is an accepted method of enhancing and possibly accelerating the treatment effect. Demonstrating additional value of the plano lens in terms of speed of improvement will shorten the treatment period, possibly improving child and parental compliance, leading to improved overall outcomes for patients with amblyopia. If the plano lens leads to greater improvement, then there will be less permanent visual impairment in patients with a history of amblyopia. It also is important to determine if the use of a plano lens in conjunction with atropine has a deleterious effect on the sound eye, and if yes, how often this occurs.

Little is known about the pharmacologic treatment of severe amblyopia. This study will provide important prospectively determined outcome data at little additional expense.

In ATS4, the use of weekend atropine for moderate amblyopia was as effective as daily treatment. Intermittent atropine use (such as using it only on the weekends) has the theoretical potential benefit of the sound eye having some time each week during which cycloplegia is only partial. It is possible that allowing some loss of the cycloplegic effect over the course of each week may be safer for the sound eye.

1.4 Study Objectives

- To compare the effectiveness and safety of weekend atropine augmented with a plano lens for the sound eye versus weekend atropine alone for moderate amblyopia (20/40 to 20/100) in children 3 to <7 years old.

- To provide data on the response of severe amblyopia (20/125 to 20/400) to atropine treatment with and without a plano lens.

1.5 Synopsis of Study Design

Major Eligibility Criteria *(see section 2.2 for a complete listing)*

- Age 3 to < 7 years
- Amblyopia associated with strabismus, anisometropia, or both
- Visual acuity in the amblyopic eye between 20/40 and 20/400 inclusive
- Visual acuity in the sound eye 20/40 or better and inter-eye acuity difference ≥3 logMAR lines
- No prior amblyopia therapy or if there has been prior therapy, it must meet certain criteria (see section 2.2)
- Hypermetropic spherical equivalent refractive error in the sound eye at least +1.50 D
- No myopia in amblyopic eye
- Spectacles, if needed, worn for at least 16 weeks or visual acuity documented to be stable

Treatment Groups

The two treatment regimens for the 18 week primary treatment period are:

- Atropine 1% once each weekend day in the sound eye

- Atropine 1% once each weekend day in the sound eye plus a plano lens for the sound eye

Sample Size

Moderate Amblyopia (20/40 to 20/100): 172 patients

Severe Amblyopia (20/125 to 20/400): patients to be enrolled until enrollment ends in the moderate amblyopia trial.

Visit Schedule

- Visits at 5 weeks, 10 weeks, and 18 weeks
- Partial responders (see section 3.3 for definition) will continue to be followed at 8-week intervals after the 18-week visit until there is no further improvement

At each visit, distance visual acuity will be assessed in each eye. At the 18-week visit, the visual acuity testing using the ATS HOTV protocol will be done by a masked examiner.

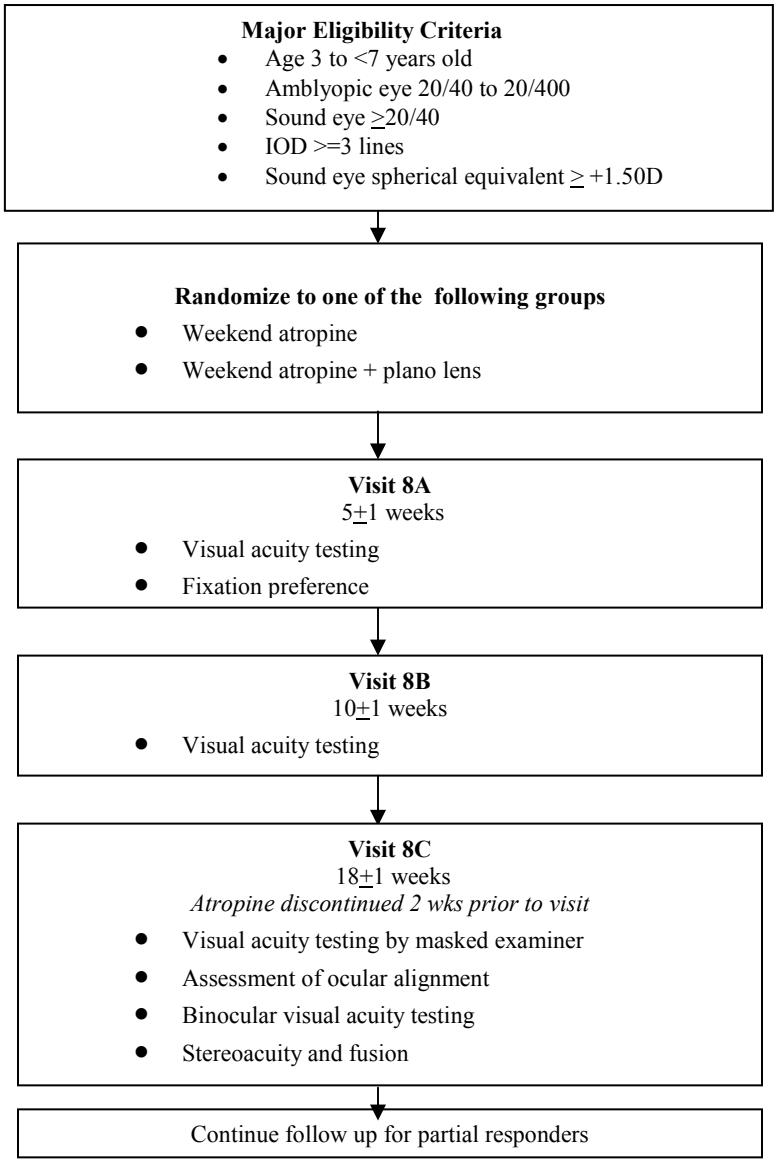
Primary Analysis

The primary outcome assessment is visual acuity at 18 weeks for both the amblyopic and sound eyes.

The primary analytic approach for the amblyopic eye acuity will involve a treatment group comparison of logMAR visual acuity scores adjusted for baseline visual acuity scores in an analysis of covariance (ANCOVA) model.

Sound eye acuity data will be reported for each treatment regimen at the 18-week visit as mean change from baseline and as the distribution of the numbers of lines of change from baseline.

1.6 Study Summary Flow Chart



Chapter 2: Patient Enrollment

2.1 Eligibility Assessment and Informed Consent

A patient is considered for the study after undergoing a routine eye examination by an investigator (as part of standard care) that identifies amblyopia meeting the eligibility criteria. As noted in subsequent sections, refractive error must be corrected with glasses (as is the case in standard patient care) in most cases before a patient can be enrolled into the trial.

For patients who appear eligible for the study following a "standard-care" or preliminary examination, the study will be discussed with the child's parent(s) or guardian. Parents or guardians who express an interest in the study will be given a patient brochure and a copy of the informed consent form to read. Written informed consent must be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the patient's routine care.

2.2 Eligibility and Exclusion Criteria

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

1. Age 3 to < 7 years
2. Amblyopia associated with strabismus (comitant or incomitant), anisometropia, or both
   - Criteria for strabismus: At least one of the following criteria must be met:
     - Heterotropia at distance and/or near fixation on examination (with or without spectacles)
     - History of strabismus surgery (or botulinum)
     - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)
   - 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
   - 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. Sound eye with a spherical equivalent of +1.50 D or greater
4. Amblyopic eye with no myopia.
5. Visual acuity, measured in each eye without cycloplegia within 7 days prior to randomization using the ATS single-surround HOTV letter protocol on Electronic Visual Acuity Tester, as follows:
   a. Visual acuity in the amblyopic eye between 20/40 and ≥20/400 inclusive
   b. Visual acuity in the sound eye 20/40 or better
   c. Inter-eye acuity difference ≥3 logMAR lines (i.e., amblyopic eye acuity at least 3 lines worse than sound eye acuity)
6. No prior amblyopia therapy or if there has been prior therapy, it must meet the following criteria:

- no atropine treatment within 6 months of enrollment and no other amblyopia treatment of any type (other than normal spectacle lenses) used within one month of enrollment
- any treatment more than 6 months prior to enrollment is acceptable

7. Spectacle correction for measurement of enrollment VA must meet the following criteria and be based on a cycloplegic refraction that is no more than 6 months old;

a. Requirements for spectacle correction:

1) For patients meeting criteria for strabismus (see #2 above)
   - Hypermetropia if corrected must not be undercorrected by more than +1.50 D spherical equivalent, and the reduction in plus sphere must be symmetric in the two eyes. Otherwise, spectacle correction is at investigator discretion.

2) For patients meeting criteria for anisometropia or combined-mechanism (see #2 above)
   - Spherical equivalent must be within 0.50 D of fully correcting the anisometropia
   - Hypermetropia must not be undercorrected by more than +1.50 D spherical equivalent, and reduction in plus must be symmetric in the two eyes
   - Cylinder power in both eyes must be within 0.50 D of fully correcting the astigmatism
   - Cylinder axis in the spectacle lenses in both eyes must be within 6 degrees of the axis of the cycloplegic refraction when cylinder power is $\geq$ 1.00 D

Note: if NEW spectacles are being prescribed in anticipation of study enrollment, it is advisable to fully correct the anisometropia, fully correct astigmatism, and symmetrically reduce the hypermetropic correction by no more than +0.50 D to avoid having to replace the lenses immediately following randomization (see section 2.4.2)

b. Spectacles meeting above criteria must be worn either:

1) for 16 weeks immediately prior to enrollment, or

2) until visual acuity in amblyopic eye is stable (defined as two consecutive visual acuity measurements by the same testing method at least 4 weeks apart with no improvement of one logMAR line or more)
   - An acuity measurement done any of the following ways may be considered the first of two consecutive measurements: 1) in current glasses , 2) in trial frames with full correction of hypermetropia with cycloplegia, or 3) by having the patient return in new glasses for first measurement. *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*

8. No current vision therapy or orthoptics
9. No ocular cause for reduced visual acuity
   - nystagmus per se does not exclude the patient if the above visual acuity criteria are met
10. Cycloplegic refraction within 6 months prior to enrollment
11. Ocular examination within 6 months prior to enrollment
12. No prior intraocular or refractive surgery
13. No known allergy to atropine or other cycloplegic drugs

14. Down Syndrome not present

15. Parent willing to accept randomized treatment, available for 6 months of follow-up, has home phone (or access to phone), and willing to be contacted by Jaeb Center staff

2.3 Examination Procedures

2.3.1 Historical Information

Historical information elicited will include the following: date of birth, gender, ethnicity, iris color, prior amblyopia therapy (e.g., glasses, patching, pharmacologic, filters), spectacle correction, and history of allergy to cycloplegic eye drops.

2.3.2 Clinical Testing

Examination procedures include:

1. Measurement of visual acuity in each eye (right eye first) by the ATS single-surround HOTV testing protocol on the Electronic Visual Acuity Tester. The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual. Aspects of the testing protocol that are specific to this study are indicated below:
   - Testing must be done <u>without cycloplegia</u> (with spectacles, if worn) no more than 7 days prior to randomization.
   - Since the patient needs to be wearing spectacles that provide best visual acuity to be enrolled, trial frames/phoropter with a different correction cannot be used to measure acuity at enrollment.
   - If the patient has difficulty with the acuity testing, often he or she will perform better when the testing is repeated. At the investigator's discretion, acuity can be retested on the same or a subsequent day to assess eligibility.

2. Measurement of binocular acuity with the ATS single-surround HOTV testing protocol on the Electronic Visual Acuity Tester

3. Ocular motility examination
   - Measurement of predominant alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near; and recording of the presence of primary position nystagmus (with and without monocular occlusion).
   - If performed within prior 7 days, do not need to repeat at time of enrollment

4. Ocular examination as per investigator's clinical routine to rule out a cause for reduced visual acuity other than amblyopia.
   - If performed within prior 6 months, do not need to repeat at time of enrollment

5. Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine
   - If performed within prior 6 months, do not need to repeat at time of enrollment.

6. Binocularity testing (prior to cycloplegia): Titmus fly, Randot Preschool test

2.4 Randomization of Eligible Patients

1. Once a patient is randomized that patient will be included regardless of whether the assigned treatment is received or not. Thus, the investigator must not randomize a patient until he/she is convinced that the parent/guardian will accept either of the treatment regimens.
2. Treatment must commence within 48 hours following randomization; therefore, a patient should not be randomized until both the investigator and parent are ready to start treatment.

3. The Jaeb Center will construct a separate Master Randomization List for moderate amblyopia and severe amblyopia using a permuted block design stratified by site and by visual acuity (20/40 to 20/100 and 20/125 to 20/400), which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed.

2.4.1 Delay in Randomization

1. Visual acuity testing must be performed within 7 days prior to randomization. If patient randomization is delayed beyond 7 days, the visual acuity testing must be repeated to confirm eligibility and establish the baseline acuity for the study.
2. The ocular motility examination must be performed within 7 days prior to randomization. If patient randomization is delayed beyond 7 days, the ocular motility examination must be repeated.
3. No other parts of the examination (including the refraction) need to be repeated if they were performed within 6 months prior to randomization.

2.4.2 New Spectacles Prescription Upon Randomization

All patients will be offered new, study-paid spectacles (frames and lenses) upon randomization. The cost of all spectacle changes prior to randomization is not covered by the study.

1. For patients in whom the eyes are underplussed by more than +0.50 D spherical equivalent (but, to be eligible, underplussed by no more than +1.50 D) upon randomization:
   - If the patient is randomized to the atropine only group, the prescription for both lenses in the new frames will be exactly underplussed by +0.50 D spherical equivalent.
   - If the patient is randomized to the atropine plus plano lens group, the amblyopic eye lens prescription will be exactly underplussed by +0.50 D spherical equivalent and the sound eye lens prescription will be "plano".

Note: to have an eligible VA measurement for enrollment the current lenses must have already met criteria specified in section 2.2., e.g., underplussed by no more than +1.50 and stability of VA must have been documented (as described in section 2.2) or the glasses worn for at least 16 weeks, as described above.

2. For patients whose current spectacles are already within +0.50 D of cycloplegic refraction and have met the other eligibility criteria described in section 2.2.:
   - If the patient is randomized to atropine only, the correction prescribed for the new spectacles will be identical to the current correction.
   - If the patient is randomized to atropine plus plano lens, the amblyopic eye lens prescription will be identical to the current correction and the sound eye lens prescription will be "plano".

The parents of children receiving new glasses with the plano lens will be encouraged to go to the study optician within 48 hours to have the glasses made. Every effort should be made to have the child wearing his/her new glasses within 4 days.

Parents of all patients randomized to the atropine plus plano lens group will be instructed to keep the old spectacles, and bring them back to the site at the 5-week visit. The site will keep the old spectacles for use at the 18-week outcome exam.

Chapter 3: Treatment and Follow Up

3.1 Treatment Groups

Each patient is randomly assigned to one of the two treatment groups:

- Atropine 1% once each weekend day in the sound eye
- Atropine 1% once each weekend day in the sound eye plus a plano lens for the sound eye

For both treatment groups:

- Atropine is discontinued after 16 weeks (2 weeks prior to visit 8C).
- If acuity in amblyopic eye becomes the same or better than acuity in the sound eye, the frequency of atropine should be maintained through 16 weeks.
- If reverse amblyopia is suspected or strabismus develops or worsens, treatment is at investigator discretion.
- If an allergy to atropine develops, the patient can be switched to homatropine 5% after discussion with a Protocol Chair.

Notes

1. The study will be providing atropine drops and sunglasses (or flip-ups) for the patients. The dispensing of atropine will be recorded on the ATS Atropine Accountability Log.
2. Wearing a hat with a brim for outdoor activities is to be encouraged.
3. Morning is the preferred time for administration of the atropine. However, if there is an overriding reason why the parent/guardian wants to administer the atropine at night, this will be acceptable.
4. If a patient is noncompliant with treatment, the parents should be encouraged to persist with the treatment to the best of their ability.
5. Deviations from the treatment protocols or prescribing non-protocol treatment should be discussed with a Protocol Chair prior to initiating.
6. Discontinuation of therapy due to reverse amblyopia, strabismus, or atropine allergy should be discussed with a Protocol Chair.
7. Both treatment groups will receive atropine in the sound eye, which should help tolerance of wear of the full or near-full cycloplegic correction. Therefore, bilateral atropine to relax accommodation for two days is not likely necessary, and will not be allowed.

3.1.1 Compliance

A calendar log will be maintained by patients on treatment. The preprinted calendar will contain customized instructions about treatment.

1. An adhesive sticker will be placed by the child on the log on days when the atropine was used.
2. These logs will be turned in to the investigator at each of the protocol visits. At each visit, the logs will be reviewed. The investigator's assessment of compliance will be recorded on the Follow-up Examination Form.

3.2 Follow-up Examinations

All patients will have the following study visits:

- Visit 8A: 5 ± 1 week
- Visit 8B: 10 ± 1 week
- Visit 8C: 18 ± 1 week

Test	Visit		
	8A *5±1 wk*	**8B** *10 ± 1 wk*	**8C** *18 ± 1 wk*
Distance acuity each eye*	X	X	X
Binocular distance acuity			X
Ocular alignment**			X
Fixation Preference testing	X		
Stereoacuity and fusion***			X

*using ATS single-surround HOTV acuity testing protocol on the EVA. The testing at visit 8C will be done by a masked examiner

**Assessed at each visit but only quantified at visit 8C after atropine discontinued (at other visits, the development of a new or increased deviation will be reported)

***Titmus fly, Randot Preschool Test, and Randot Suppression Test

Additional visits can be performed at the discretion of the investigator. A Follow-up Examination Form should be completed on the study website for every exam (not just the minimum required exams).

Two weeks prior to visit 8C (18 weeks) after 16 weeks of treatment, atropine treatment will be discontinued in all patients. The parents of patients who were randomized to receive atropine plus a plano lens will be instructed to bring the old glasses to a visit prior to 8C, which will be used during the outcome exam.

3.2.1 Visual Acuity Testing

At each visit, visual acuity is measured in each eye (right eye first) by a certified examiner using the ATS single-surround HOTV acuity protocol on the Electronic Visual Acuity Tester.

- While atropine is being used, the sound eye will be tested with the full cycloplegic correction in trial frames.
- The visual acuity measurement at visit 8C (18 weeks) will be done by a masked examiner.

3.2.2 Fixation Preference Testing

At visit 8A (5 weeks), a test of fixation preference at near under the treatment conditions will be conducted after acuity testing. The procedures for the strabismic and non-strabismic patients are described in the PEDIG procedures manual.

3.2.3 Visit 8C Exam

Visit 8C will occur at 18±1 week, 2 weeks after the discontinuation of atropine.

The parents of patients who were randomized to receive atropine plus a plano lens will be instructed to bring the old glasses to a visit prior to 8C. The old glasses used at enrollment will be retained at the site and used during the outcome exam. They will be returned to the family at the end of the

study. If a plano group patient's refraction has changed in the sound eye prior to visit 8C, visual acuity may be tested in trial frames with the new correction instead of the enrollment glasses. In addition to visual acuity testing, testing will include the following:

- Titmus fly and Randot Preschool test
- Randot Suppression Test
- Binocular distance acuity
- Ocular alignment assessed with the SPCT
- Retesting of visual acuity in the amblyopic eye
    - Only performed if visual acuity is worse than 20/25, acuity is not improved from baseline by at least 2 lines, or acuity is not improved from the last visit by at least one line
- Retesting of visual acuity in the sound eye
    - Only performed if the sound eye acuity is reduced by 1 or more lines from its baseline acuity.
    - If it is still decreased after retesting, then a cycloplegic refraction should be performed, lenses adjusted in trial frames/phoropter, and then the acuity should be tested again, modifying the refractive correction in trial frames if indicated.
    - If acuity is still reduced by one or more lines from pretreatment baseline and there has been a change in refraction from the spectacle wear, a change in spectacle lens should be prescribed (*the study will pay for this change*).
    - If the best sound eye acuity at visit 8C is decreased 1 or more lines from baseline (and worse than 20/20), the patient should return in 1 to 4 weeks (visit 8C-2) to recheck the sound eye acuity (with the new spectacles, if a change was prescribed). The patient should remain off atropine and should not start any other amblyopia therapy for either eye.

Patients who have not discontinued atropine at least 2 weeks prior to visit 8C may use the enrollment correction or the full cycloplegic correction for the testing of the sound eye. All binocularity testing must be done in trial frames correcting the residual hypermetropic deficit plus +3.00D to account for the near distance in the atropinized eye.

3.3 Additional Follow-up for Partial Responders

After visit 8C, follow up will end for all patients except for the patients who meet both of the following criteria:

- amblyopic eye acuity (better of test and retest, if done) worse than 20/25, improved 2 or more lines from baseline and improved at least one line from visit 8B (if missed, then one line from 8A)

AND

- amblyopic eye acuity worse than best visit 8C (18 weeks) sound eye acuity

Patients continuing in follow up will resume using the randomized treatment (for patients in the 'plano' group, the spectacles with the plano lens will continue to be used) and will have a follow-up visit every 8± 1weeks until:

(1) amblyopic eye acuity reaches 20/25 or better,
(2) treatment is discontinued because the sound eye worsened, or
(3) there is no further improvement in the amblyopic eye acuity.

- 'No further improvement' is defined as visual acuity in the amblyopic eye that is no better than the measured acuity at the prior visit on two tests of acuity at the same visit. At the first 8-week visit, the better amblyopic eye acuity at visit 8C is used as the 'baseline' for evaluating improvement. At subsequent visits, the acuity from the prior visit is used (or better acuity if acuity was tested twice at that visit).

At each visit, distance visual acuity will be measured in each eye using the ATS single-surround HOTV acuity protocol on the Electronic Visual Acuity Tester. If the amblyopic eye acuity is not improved by 1 or more lines from the prior visit, the visual acuity test will be repeated.

For patients remaining in the study after 6 months from enrollment, a cycloplegic refraction is encouraged.

When study participation ends for patients in the 'plano' group, the plano lens in their study-paid spectacles may be replaced with a lens of proper correction purchased by the study.

Chapter 4: MISCELLANEOUS CONSIDERATIONS

4.1 Management of Optical Correction

A refraction should be performed at any time the investigator suspects that refractive error may not be optimally corrected.

4.2 Management of Strabismus

Strabismus surgery is allowed at the discretion of the clinician. These will be recorded in the comment section of the Follow-up Examination Form.

4.3 Intercurrent Events

If visual acuity should worsen in the amblyopic eye (or in the sound eye and does not recover with cessation or reversal of treatment), the investigator should evaluate this condition using best clinical judgment and perform whatever work up is clinically indicated to assess for an alternate cause (i.e., other than amblyopia) for the visual loss. Patients found to have a cause other than amblyopia that fully explains the visual loss (i.e., amblyopia was never present) will be dropped from the study. This will be reported on the Patient Final Status Form.

Eye injuries or the development of an eye problem that might affect vision will be reported on the Follow-up Examination Form. Likewise, the development of a serious medical problem that might affect the patient's study participation will be recorded.

4.4 Patient Withdrawals

A patient (and in this case the parents or guardian) may withdraw from the trial at any time. This is expected to be a very infrequent occurrence in this trial in view of the testing procedure's similarity to routine clinical practice. If the parents or guardian indicate that they want to withdraw the child from the study, the investigator personally should attempt to speak with them to determine the reason. If a plano group patient with high hypemetropia is intolerant to atropine and the plano lens, it is preferred that the patient wear his/her enrollment glasses and continue on atropine rather than withdraw from the study. The decision to restart the enrollment glasses should be discussed with a protocol chair.

Patients who receive alternate treatment, e.g. patching, for at least one week, will be dropped from the study after completion of the main outcome exam (8C).

4.5 Risks

There are no risks involved in this study that would not be part of usual care.

4.6 Risks of Examination Procedures

The procedures in this study are part of daily pediatric eye care practice in the United States and pose no known risks. As part of a routine usual-care exam, the patient may receive cycloplegic/dilating eye drops.

4.7 Adverse Events/Risks

The risks involved in the study are identical to those that would be present for a patient treated with the study treatment regimens who is not participating in the study.

4.7.1 Side Effects of Treatment

1. Local side effects of minimal severity include allergic lid reactions, local irritation, conjunctival hyperemia, and follicular conjunctivitis. Potential systemic side effects include dry skin and mouth, tachycardia, fever, flushing and irritability. These effects occur very uncommonly in the dosage schedule (one drop a day) suggested in this protocol as noted in the previous studies of atropine treatment. Simons and coworkers[8] found the risk of allergic reactions to be less than 1%. Additional safety data can be derived from the literature describing the chronic topical atropine treatment for the attempted prevention of myopia. In the study by Brodstein and colleagues,[12] 253 patients were treated for an average of 33 months with daily atropine 1% drops. Neither local nor systemic side effects of any significance were noted. This therapy lasted 5 times as long and involved twice as much drug as in the proposed protocol. In ATS1,[1] among 204 patients, an ocular side effect was reported at least once for 26% of patients, most commonly light sensitivity (18%), lid or conjunctival irritation (4%), and eye pain or headache (2%). Facial flushing was reported for two patients, one of whom remained on atropine with no further problems and one of whom was switched to homatropine. Atropine was not discontinued because of side effects in any other patients. No other systemic side effects of atropine were reported. In ATS4 ocular side effects, most commonly light sensitivity, were reported by 13 (16%) patients in the daily group and 25 (29%) patients in the weekend group. [2] However, these symptoms did not lead to a change in treatment. Facial flushing and fever were reported for 2 patients in the daily group, one of whom remained on atropine and the other was switched to homatropine.

2. Atropine produces dilation of the pupil, which can increase the light that enters the eye. Although it has not been demonstrated that atropine used for several months will have harmful ocular effects, excessive exposure to light theoretically could be toxic to the retina. Atropine has been used long-term to prevent the progression of myopia without an apparent adverse effect on acuity.[12-15] To minimize risk from pupil dilation, sunglasses (or flip-ups) will be provided for patients who do not require glasses. Hats with brims or visors will be encouraged.

3. When a patient develops adverse effects serious enough to discontinue atropine, the investigator should call a Protocol Chair to discuss the case. If atropine is discontinued, then the patient should be switched to homatropine 5%. Such a change in the treatment regimen will be recorded on a follow-up examination form. Homatropine, if needed, will be sent directly to the patient from the Jaeb Center.

4.7.2 Reverse Amblyopia

Atropine could decrease the visual acuity in the sound eye, although this is almost always reversible. In ATS1, as noted in section 1.2, results were inconclusive as to whether atropine produced a transient decrease in sound eye acuity. However, the results did not indicate that treatment caused a permanent reduction in sound eye acuity. After two years of follow up, there was no difference in sound eye acuity comparing the two treatment groups. As noted in section 1.2, there is uncertainty as to whether the use of a plano lens increases the risk of reverse amblyopia compared to atropine alone. One of the objectives of the study is to determine this.

The diagnosis and management of reverse amblyopia at the interim visits is left to the investigator's judgment. At visit 8C a protocol for testing the sound eye with reduced vision should be followed (see section 3.2.3).

4.7.3 Development of Strabismus

The study treatment could precipitate the development of a manifest ocular deviation. If treatment precipitates the development of an ocular deviation (e.g., esotropia), the parent will be advised to have the patient see the investigator as soon as possible. If the deviation is confirmed on examination, the decision as to whether to continue or discontinue therapy will be left to the investigator's and parent's decision. If amblyopia treatment is to be discontinued during the treatment period of the study, a Protocol Chair should be called to discuss the case. The development of a new heterotropia is an accepted risk of amblyopia therapy as part of standard care. Such an event occurred with both patching and atropine therapy with atropine in about 18% of cases in ATS1. About 13% of patients had resolution of their preexisting strabismus with treatment. In ATS4, 2 of 168 patients developed a new esotropia >8 D, while 5 patients had resolution of a small angle esotropia. This risk in this study is no greater than it would be with standard care of amblyopia.

In view of the short duration of the study, it is preferred that strabismus surgery be deferred until the patient completes the study; however, such surgery is allowed at the discretion of the clinician if medically indicated. Performance of strabismus surgery will be reported in the comment section of the Follow-up Exam Form.

4.8 Reporting of Adverse Events

Each investigator is responsible for informing his/her IRB of serious treatment-related adverse events and for abiding by any other reporting requirements specific to his or her IRB.

Data on the complications of the study treatments will be tabulated regularly by the Coordinating Center for review by the Steering Committee. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

4.9 Patient Payments

The parent/guardian of each patient will be compensated $25 per visit for completion of the 5-week, 10-week, and 18-week visits. For patients remaining in follow up after the 18-week visit, $25 will be paid for each 8-week interval visit, up to a maximum of $75 (maximum of $150 for the entire study). If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

4.10 Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of enrollment and follow-up for all patients.

4.11 Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent/guardian's contact information. The Jaeb Center will maintain direct contact with the parents or guardian of each patient. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the family and to help coordinate scheduling of the outcome examination. One phone contact is planned for each patient in the first month after enrollment. Additional phone contacts will be made

692 if necessary to facilitate the scheduling of the patient for follow-up visits. A patient newsletter,
693 study updates, and a study logo item may be sent. Patients will be provided with a summary of the
694 study results in a newsletter format after completion of the study by all patients.
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Chapter 5: Sample Size Estimation and Statistical Analysis

The estimation of sample size and statistical analysis plan are summarized below and detailed in separate documents.

5.1 Sample Size Estimation

The primary analysis will include only patients with moderate amblyopia (visual acuity of 20/40 to 20/100); therefore the sample size was estimated in order to have the needed power for analysis of these patients. Based on data from previous studies (ATS1 and ATS4), we assumed a standard deviation for the 18-week outcome score of 0.16 logMAR and a correlation between baseline and 18-week week outcome score of 0.40. We decided to use a two-sided alpha of 0.05, with 90% power to detect a 0.075 logMAR difference between treatment groups in the mean improvement in acuity from baseline. With these assumptions, and accounting for 5% loss to follow up, we have selected a necessary sample size of 172 patients with moderate amblyopia.

During the time period of recruitment of patients with moderate amblyopia, patients with severe amblyopia (visual acuity 20/125 to 20/400) will be enrolled without a limit or formal sample size/power estimation. Based on enrollment in our previous studies, it is predicted that ¼ of recruited patients with amblyopia in the range of 20/40 to 20/400 will have severe amblyopia. Thus, during recruitment of the 172 patients with moderate amblyopia, it is expected that 58 patients will be recruited with severe amblyopia.

5.2 Primary Analysis for Efficacy

All primary analyses will include the cohort of patients with moderate amblyopia (20/40 to 20/100). The primary analysis will be a treatment group comparison of logMAR visual acuity scores in the amblyopic eye obtained 18 weeks after randomization, adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model.

As a secondary analysis, acuity at 18 weeks will categorized as $\geq$20/25 vs <20/25. Patients who receive alternate treatment, e.g. patching, for at least one week, will be categorized in the group which did not reach the better visual acuity. The outcomes in each group will be analyzed by a Fisher's exact test for association with treatment group.

To explore whether there is a difference in the initial effect of treatment, the visual acuity data from the 5-week and 10-week visits will be used to compare the treatment groups in an analysis of covariance similar to that described for the primary analysis. To explore differences in rate of improvement, a repeated measures regression analysis will be performed.

The effect of fixation preference at 5 weeks on the primary outcome (logMAR acuity in amblyopic eye at 18 weeks) without respect to treatment group will be evaluated in an ANCOVA model, adjusting for baseline acuity score. Additionally, the possibility of interaction between fixation preference and treatment group will be evaluated in an ANCOVA model.

The treatment effect in subgroups based on baseline factors will be assessed in preplanned secondary analyses. The subgroups of most interest will be those based on baseline amblyopic eye visual acuity ($\geq$20/50, <20/50), cause of amblyopia, age, and prior treatment.

5.3 Primary Safety Analysis

The primary safety analysis will be a treatment group comparison of logMAR sound eye visual acuity score obtained 18 weeks after randomization (after atropine has been discontinued for at least two weeks), adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model.

A second analysis will compare the proportion of subjects with a 3 or more line decrease from baseline to 18 weeks in sound eye acuity with a Fisher's exact test.

5.4 Severe Amblyopia

In an exploratory analysis, data from patients with severe amblyopia (20/125-20/400) will be evaluated in a treatment group comparison of logMAR visual acuity scores obtained 18 weeks after randomization, adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model. The primary safety analysis will be repeated as well.

5.5 Interim Analyses

No formal interim efficacy analyses of the outcome data are planned in view of the timing of its collection as it seems unlikely that there would be sufficient data and reason to terminate the trial early. However, an efficacy and safety report will be provided to the DSMC twice a year. DSMC reports also will include tabulations of local and systemic adverse effects of atropine. Nevertheless, a minimal amount of alpha spending (0.001) will be allocated for each DSMC review of the data. There are projected to be two DSMC data reviews prior to the end of the trial. The final alpha level at the end of the trial will be accordingly adjusted to 0.048 for the overall statistical comparisons of the two treatment groups.

Chapter 6: References

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