AMBLYOPIA TREATMENT STUDY

ATS4

A Randomized Trial Comparing

Daily Atropine Versus Weekend Atropine

for Moderate Amblyopia

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PROTOCOL

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CHAPTER 1: BACKGROUND AND SUMMARY

1.1 Overview

ATS4 will evaluate two atropine treatment regimens for moderate amblyopia (20/40 to 20/80) in children <7 years old:

- daily atropine 1%
- weekend only atropine 1%

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 and is poor when attempted after eight years of age.

ATS1, a randomized trial of 419 children meeting entry criteria similar to ATS4, found that both atropine 1% (one drop daily) and patching (6 hours to full time daily) produced visual acuity improvement of similar magnitude and that both are appropriate treatment modalities for the management of moderate amblyopia in children. Patching has the potential advantage of a more rapid improvement in visual acuity (especially if prescribed as full-time) and possibly a slightly better acuity outcome, whereas atropine has the potential advantage of easier administration and lower cost.

Through its cycloplegic effect, atropine prevents accommodation, blurring the sound eye at near fixation. The blurring effect can be augmented by reducing the spectacle correction of hyperopia in the sound eye. The cycloplegic effect lasts at least partially for a week or longer. Therefore, some pediatric eye care providers believe that daily use of atropine is unnecessary and treatment may be effective at a dosage of as little as once a week. One advantage of less frequent dosing is a potential reduction in side effects, including any potential adverse effect on the vision in the sound eye (reverse amblyopia), on ocular alignment, and on binocularity. ATS4 will assess whether prescribing atropine once a day produces a better visual outcome than does atropine used only on the two weekend days.

In ATS1, the 6-month outcome data showed that more patients treated with atropine had a reduction in visual acuity of 1 or more lines in the sound eye than did patients treated with patching. Visual acuity was decreased from baseline by 1 line in 15% of the atropine group compared with 7% of the patching group and by 2 or more lines in 9% of the atropine group and 1% of the patching group. Only one patient (in the atropine group) was actively treated for a presumed treatment-related decrease in sound eye acuity, with return of acuity to its baseline level. Some of the cases of reduced acuity were unequivocally due to the use of improper refractive correction for the sound eye testing (including nine cases in which the testing was done with a plano lens prescribed for therapeutic effect rather than the proper corrective lens). In other cases, we speculated that there was a residual cycloplegic effect of atropine combined with improper refractive correction related to previously latent hyperopia becoming manifest hyperopia during the period of atropine treatment, although there were not data to fully document this in all cases. All 47 atropine group patients with a decrease of one or more lines at six months have had subsequent follow-up exams. Acuity on the subsequent testing was the same or better than that at baseline in 42 of the 47 patients: 22 while still

on atropine treatment (11 with the same refractive correction and 11 with a different refractive correction) and 20 after atropine was discontinued (6 with the same refractive correction and 14 with a different refractive correction). In the other five patients, acuity on subsequent testing was decreased from baseline by one line (3 on atropine, 2 off atropine). Thus, there did not appear to be a long-term safety concern for atropine, but the data were inconclusive as to whether atropine caused an actual, though transient, treatment-related decrease in sound eye acuity. One of the objectives of ATS4 will be to provide additional data on the effect of atropine on the sound eye.

1.3 Study Objectives

1.3.1 Effect of Treatment on the Amblyopic Eye

Primary Objective: To compare the visual acuity outcome in the amblyopic eye after 17 weeks of daily use of atropine versus weekend-only use of atropine.

Secondary Objective: To compare the proportion of patients achieving a *complete* treatment response (defined as amblyopic eye acuity $\geq$20/25 or equal to that of the sound eye in the absence of a reduction in the sound eye acuity from baseline) with daily atropine versus weekend-only atropine.

1.3.2 Effect of Treatment on the Sound Eye

To assess the frequency of reduction of the sound eye visual acuity in patients treated with daily atropine and in those treated with weekend atropine.

1.4 Synopsis of Study Design

Major Eligibility Criteria

- Age < 7 years
- Able to measure surrounded single optotype visual acuity using the ATS single-surround HOTV protocol *(this will in effect exclude all patients <2 years old and many <3 years old)*
- Amblyopia associated with strabismus, anisometropia, or both
- If anisometropia present (as per protocol definition), refractive error corrected with spectacles for a minimum of 4 weeks
- Visual acuity in the amblyopic eye $\leq$ 20/40 and $\geq$20/80
- Visual acuity in the sound eye $\geq$ 20/40 and inter-eye acuity difference $\geq$3 logMAR lines
- No amblyopia treatment (other than spectacles) in the past month and no more than one month of amblyopia treatment in the past 6 months
- No myopia more than a spherical equivalent of -6.00 D in the amblyopic eye
- No myopia more than a spherical equivalent of -0.50 D in the sound eye

Treatment Groups

- Atropine 1% once daily in the sound eye
- Atropine 1% twice a week on the weekend (Saturday and Sunday) in the sound eye

Sample Size

Approximately 160 patients will be enrolled (80 per group)

Visit Schedule

- Visits at 5 weeks (visit 4A) and 17 weeks (visit 4B)
- Visit 2 to 4 weeks after 17-week visit (visit 4C) to assess sound eye acuity and binocularity after atropine has been discontinued for at least 2 weeks
- Follow Up after Visit 4C
  - Patients categorized as a *partial responder* at visit 4C will continue in follow up as described in the Responder Classification section below.
  - Patients classified as a complete responder, nonresponder, or unclassified responder whose sound eye acuity is decreased at visit 4C will have an additional follow-up visit in 2 to 4 months to reassess the sound eye at which time follow up will end.
  - Patients classified as a complete responder, nonresponder, or unclassified responder whose sound eye acuity is not decreased at visit 4C will have no further follow up.

Testing Procedures

- At each visit, distance visual acuity will be assessed in each eye using the ATS single-surround HOTV testing protocol.
- In addition:
  - At the 5-week visit (visit 4A), the Amblyopia Treatment Index will be completed by the parent or guardian.
  - At the 17-week visit (visit 4B), the visual acuity testing will be done by a masked examiner.
  - At the post-17-week visit (visit 4C, after atropine has been discontinued for at least two weeks), binocularity, near acuity, and ocular alignment will be assessed.

Responder Classification

At visit 4C (2 to 4 weeks after the 17-week visit), each patient will be classified as one of the following based on the best distance acuity achieved in the amblyopic eye at either visit 4B or 4C and in the sound eye at visit 4C.

Nonresponder	(1) amblyopic eye acuity improved no more than 1 line from baseline or (2) amblyopia treatment other than the randomization-assigned treatment (e.g., patching or greater frequency of atropine) used for 7 or more days
Complete responder	(1) amblyopic eye acuity 20/25 or better or (2) amblyopic eye acuity equal to or better than sound eye acuity ➢ *note: if sound eye acuity is worse than baseline, then amblyopic eye acuity must be equal to or better than baseline sound eye acuity*
Partial responder	(1) amblyopic eye acuity worse than 20/25 but improved 2 or more lines from baseline and (2) amblyopic eye acuity worse than best visit 4C sound eye acuity ➢ *note: the criteria for partial responder could also be stated as patient does not meet criteria for nonresponder or complete responder and amblyopic eye acuity less than best visit 4C sound eye acuity* ➢ *note: if criteria for partial responder are met, but sound eye acuity has worsened from baseline such that the investigator suspects reverse amblyopia and discontinues the randomized treatment, then the patient will be considered an unclassified responder*
Unclassified responder	(1) amblyopic eye acuity worse than 20/25 but improved 2 or more lines from baseline and (2) amblyopic eye acuity equal to or better than best visit 4C sound eye acuity but worse than baseline sound eye acuity ➢ *note: this scenario can only occur if the sound eye acuity at visit 4C (following retesting) is less than it was at baseline. An unclassified responder is in essence a partial responder whose sound eye acuity has worsened such that amblyopic eye acuity is the same or better than the sound eye acuity at visit 4C.* ➢ *note: see 2nd note above for partial responder*

After completion of visit 4C (2 to 4 weeks after the 17-week visit), study participation will end for *complete responders* and *nonresponders* whose sound eye acuity has not worsened from baseline. Those whose sound eye acuity has worsened and those who are classified as *unclassified responder* will have an additional follow-up visit in 2 to 4 months to reassess the sound eye acuity.

Partial responders will resume using the randomized treatment (daily or weekend atropine) and have a follow-up visit every 8 weeks until either criteria are met for *complete responder* or there is no further improvement in visual acuity in the amblyopic eye.

Primary Analysis

The primary outcome assessment is at 17 weeks for the amblyopic eye and 2 to 4 weeks later (after atropine has been discontinued for at least 2 weeks) for the sound eye. The primary analytic approach for the amblyopic eye acuity will involve a comparison of the 17-week logMAR visual

acuity scores adjusted for baseline visual acuity scores in analysis of covariance (ANCOVA) models. A secondary analysis will compare the proportion of *complete responders* in each treatment group.

Sound eye acuity data will be reported for each treatment regimen at the post-17-week visit as mean change from baseline and as the distribution of the numbers of lines of change from baseline.

CHAPTER 2: PATIENT ENROLLMENT

2.1 Eligibility Assessment and Informed Consent

1. A patient is considered for the study after undergoing a routine eye examination (by a study 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) before a patient can be enrolled into the trial.

2. 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(s). Parent(s) or guardian(s) 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

1. Age < 7 years

2. Able to perform surrounded single optotype visual acuity using the ATS single-surround HOTV protocol
   - this will in effect exclude all patients <2 years old and many <3 years old

3. 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 (and which in the judgment of the investigator is the cause of amblyopia)

   - Criteria for anisometropia: One or both of the following must be present:
     - ≥0.50 D difference between eyes in spherical equivalent
     - ≥1.50 D difference between eyes in astigmatism in any meridian

4. If above criteria for anisometropia are met, spectacle correction worn for at least 4 weeks prior to enrollment as detailed in section 2.3.2.

5. Visual acuity, measured in both eyes without cycloplegia within 7 days prior to randomization using the ATS single-surround HOTV letter protocol on the Electronic Visual Acuity Tester (or study-approved alternative instrument), as follows:
   a. Visual acuity in the sound eye ≥20/40
   b. Visual acuity in the amblyopic eye ≤20/40 and ≥20/80
   c. Inter-eye acuity difference ≥3 logMAR lines

6. No amblyopia treatment (other than spectacles) in the past month and no more than one month of amblyopia treatment in the past 6 months
   - any treatment more than 6 months prior to enrollment is acceptable.

7. No current vision therapy or orthoptics

8. No ocular cause for reduced visual acuity
   - nystagmus per se does not exclude the patient if the above visual acuity criteria are met

9. Cycloplegic refraction and ocular examination within 2 months prior to enrollment

10. No myopia more than a spherical equivalent of -6.00 D in the amblyopic eye

11. No myopia more than a spherical equivalent of -0.50 D in the sound eye

12. No bifocals being used

13. No prior intraocular surgery

14. No known allergy to or development of systemic side effects (e.g., confused mental state, somnolence, skin flushing, exacerbation of asthma) with prior use of atropine or other cycloplegics

15. Down Syndrome not present

16. Parent willing to accept randomized treatment, available for a minimum of 5 months (through visit 4C) of follow-up, has home phone (or access to phone), and willing to be contacted by Jaeb Center staff

2.3 Correction of Refractive Error

2.3.1 Patients with Strabismic Amblyopia Only

For patients not meeting the anisometropia criteria in section 2.2 (i.e., there is <0.50 difference between eyes in spherical equivalent and <1.50 D difference between eyes in astigmatism), the refractive error of the amblyopic eye can be corrected according to the investigator's usual routine.

2.3.2 Patients Meeting Criteria for Anisometropic Amblyopia

For patients meeting the anisometropia criteria in section 2.2 (i.e., there is ≥ 0.50 D difference between eyes in spherical equivalent or ≥ 1.50 D difference between eyes in astigmatism, with or without strabismus):

1. For patients not currently wearing spectacles, anisometropia >0.50 D in spherical equivalent or ≥1.50 D of meridional difference must be corrected with spectacle wear for at least 4 weeks prior to enrollment.
   - Lesser degrees of refractive error can be corrected at the investigator's discretion.
   - Suggested guidelines for spectacles:
     - Full correction of anisometropia
     - Hypermetropia > 3.00 D corrected by either prescribing the maximum-tolerated hyperopic correction in a noncycloplegic refraction or by reducing the cycloplegic refraction by up to +1.50
     - Astigmatism ≥ 1.50 D corrected (full correction of astigmatism is preferred)
     - Myopia >0.50 D fully corrected in the amblyopic eye

2. If a patient is already wearing spectacles, a new prescription is not necessary as long as (1) both the spherical equivalent and cylinder are within 0.50 D of fully correcting the anisometropia and (2) the cylinder axis in both eyes is within 10 degrees of the axis in the spectacles when cylinder power is ≥ 1.00 D (if cylinder power is < 1.00 D, spectacle change is at the investigator's discretion); if these limits are exceeded, then a lens change must be prescribed and worn for at least 4 weeks before the patient can be considered for study enrollment.

3. If 4 or more weeks of spectacle wear have improved the visual acuity in the amblyopic eye, investigator discretion is used to determine whether to continue the patient on spectacle therapy alone or whether to consider the patient for enrollment into the study.

2.4 Examination Procedures

2.4.1 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/intolerance to cycloplegic eye drops.

2.4.2 Clinical Testing for Enrollment

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 or study-approved substitute.
   - Testing must be done without cycloplegia (with spectacles, if worn) no more than 7 days prior to randomization.
   - Prior to the formal measurement of visual acuity, a binocular screening test can be performed on the Electronic Visual Acuity Tester, at investigator discretion, to determine whether the patient is capable of having visual acuity measured by the ATS protocol.
   - For all acuity testing, an adhesive patch is to be placed on the skin over the nontested eye. If the child will not wear the patch, he or she is ineligible.
   - 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.
   - Use of the HOTV (with surround bars) matching card facilitates the testing.
   - 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 near acuity in each eye prior to cycloplegia using the ATS4 complete-scale logMAR HOTV near acuity card (ATS4 Near Acuity Test).
   - The near test consists of a series of flip cards with single-surrounded HOTV optotypes beginning at 20/400 and ending at 20/20 in 1 logMAR line intervals. A matching card is attached so that the child can either verbalize a response or point to the surrounded HOTV letter on the matching card. Spectacles are worn, if prescribed. The testing distance is 40 cm (measured with attached string). The right eye is tested first with optotype set #1 and then the left eye with optotype set #2.
   - The testing procedure consists of:
     - A screening phase asking the patient to identify the first HOTV optotype on each line starting with 20/400 until a letter is missed.
     - A threshold phase begins at the lowest correct line on screening: if 3 of 3 or 3 of 4 correct, continue to test downward until 2 on a line are missed; otherwise test upward until 3 of 3 or 3 of 4 on a line are correct. This line is recorded as the near visual acuity.
   - Near acuity is tested prior to cycloplegia in order to obtain a baseline near acuity for the amblyopic eye and to be able to compare pre- and post-cycloplegic near acuity in the sound eye.

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).

  The SPCT is performed at both distance and near fixation on an accommodative target (never a fixation light). The fixating eye is determined by inspection and/or a cover test. A cover is positioned before the fixating eye, while at the same time a prism is placed before the deviating eye. The examiner watches for movement of the non-fixating eye. The cover and prism are quickly removed and the binocular state reestablished. The power of the prism is increased until there is no movement of the deviating eye needed to fixate the target.

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 2 months, does not need to be repeated at time of enrollment.
5. Binocularity testing (prior to cycloplegia): Titmus fly, Preschool Randot test, Randot Suppression Test (*methods are described on the exam form; results will be used as baseline to assess for adverse effect of treatment)*
6. Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine.
   - if performed within prior 2 months, do not need to repeat at time of enrollment but sound eye will need to be cyclopleged to test acuity after cycloplegia (see #7 and #8 below).
7. Repeat distance acuity testing of the sound eye after cycloplegia (with cyclopentolate 1%), with spectacle correction (i.e., refractive correction the patient will be wearing at home) using the ATS single-surround HOTV testing protocol on the Electronic Visual Acuity Tester or study approved substitute (as an aid for monitoring patients for reverse amblyopia and to be assessed as a predictor variable in analysis).
8. Repeat near acuity testing of the sound eye after cycloplegia (with cyclopentolate 1%), with spectacle correction using the ATS4 Near Acuity Test.

2.5 Enrollment of Eligible Patients

1. Once a patient is randomized that patient will be included in the data analysis 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 any 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 Master Randomization List using a permuted block design stratified by site, which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed (see ATS4 Enrollment Form for steps to follow).

2.5.1 Delay in Enrollment

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

CHAPTER 3: TREATMENT AND FOLLOW-UP

3.1 Treatment Regimens

Each patient will be randomized to one of the following two treatment groups in a 1:1 allocation:

- Atropine 1% once a day in the sound eye
- Atropine 1% twice a week on the weekend (Saturday and Sunday) in the sound eye

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. Spectacle changes prior to enrollment are not covered. A lens change needed for the sound eye at visit 4C will be covered (see section 3.2.2.3).
3. Wearing a hat with a brim for outdoor activities will be encouraged.
4. The 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.
5. If a patient is noncompliant with treatment, the parent(s) should be encouraged to persist with the treatment to the best of their ability.
6. If reverse amblyopia is suspected or strabismus develops or worsens, treatment is at investigator discretion (a Protocol Chair should be contacted to discuss the case).
7. If side effects to atropine develop that the investigator considers sufficient to discontinue treatment, the patient can be switched to homatropine 5%. A Protocol Chair should be contacted to discuss the switch and the Jaeb Center will provide the homatropine for the patient .
8. For patients in the daily atropine group, if acuity in the amblyopic eye becomes the same as the acuity in the sound eye, the frequency of atropine can be reduced at investigator discretion to no less than twice a week.

3.1.1 Treatment After 17-week Primary Outcome Visit (Visit 4B)

All patients will discontinue treatment following completion of visit 4B (17 weeks) for at least 2 weeks and then return for visit 4C (2 to 4 weeks after visit 4B) at which time the acuity in the sound eye will be measured and binocular testing performed (see section 3.2.2.3).

Patients who are categorized as *partial responders* (see section 3.3) will restart the randomization-assigned treatment following visit 4C. Section 3.5 describes the follow up for these patients.

3.1.2 Compliance

A daily 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 is 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 4A: 5 ± 1 week
- Visit 4B: 17 ± 1 week
- Visit 4C: 2-4 weeks after visit 4B

At visit 4B (17 weeks), atropine treatment will be discontinued in all patients in preparation for visit 4C, which will occur 2 to 4 weeks after the discontinuation of atropine.

	Visit			
Test	**Baseline**	**4A** *5±1 wk*	**4B** *17 ± 1 wk*	**4C** *2-4 wks after 4B*
Distance acuity each eye*	X	X	X	X
Near acuity each eye**	X			X
Ocular alignment***	X			X
Amblyopia Treatment Index		X		
Cycloplegic refraction****	X			
Stereoacuity and fusion*****	X			X

*using ATS single-surround HOTV acuity testing protocol on the EVA (or approved alternative). The testing at visit 4B will be done by a masked examiner.
**using ATS4 Near Acuity Test
***Assessed at each visit but only quantitated at visit 4C after atropine discontinued (at other visits, the development of a new or increased deviation will be reported).
****baseline cycloplegic refraction must be within 2 months prior to enrollment
*****Titmus fly, Randot Preschool Test and Randot Suppression Test
Note: additional testing at baseline includes testing of sound eye acuity at distance and near after cycloplegia

Patients categorized at visit 4C as *partial responders* will continue in follow-up, with visits every 8 weeks as long as there is continued improvement in the amblyopic eye acuity, criteria for *complete responder* have not been met (see section 3.4), and the sound eye has not worsened.

Additional visits can be performed at the discretion of the investigator. A Follow-up Examination Form should be faxed to the Jaeb Center for every exam (not only the protocol-specified exams).

3.2.1 Visual Acuity Testing at All Visits (protocol-specified and unspecified visits):

Visual acuity (distance) 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 (or study-approved alternative instrument).

- While atropine is being used, the sound eye acuity can be measured either with spectacles or trial frames/phoropter at investigator discretion.

3.2.2 Additional Testing at Specific Visits

3.2.2.1 Visit 4A (5 weeks)

The Amblyopia Treatment Index (questionnaire) is completed by a parent or guardian.

- The questionnaire consists of 18 questions concerning the effect of the atropine on the child and parent. It is self-administered and does not require instructions from the site staff.
- The questionnaire should be completed prior to the examination (i.e., before the parent will be aware of the results of the visual acuity testing), sealed in the self-addressed postage-paid envelope by the parent, and given to clinic staff for mailing to the Jaeb Center.
- The questionnaire is meant to be completed by the child's parent or guardian who is responsible for administering the atropine drop. If the child is brought to the visit by an

individual who is not involved in the treatment, this is indicated on the questionnaire and it is not completed. In addition, the questionnaire is not completed if the parent/guardian does not have a sufficient comprehensiion of English.

3.2.2.2 Visit 4B (17 weeks)

This is the primary outcome exam for the amblyopic eye. The visual acuity testing will be done by a masked examiner.

3.2.2.3 Visit 4C (2 to 4 weeks after visit 4B)

Visit 4C will occur 2 to 4 weeks after the discontinuation of atropine at visit 4B (17-week visit).

Testing in addition to measurement of distance visual acuity will include the following:

1. Titmus fly and Preschool Randot test of stereoacuity
2. Randot Suppression Test
3. Near acuity in each eye (right, then left) using ATS4 Near Acuity Test
4. Ocular alignment measured with the SPCT

If the sound eye distance acuity at visit 4C is reduced by 1 or more lines from its baseline acuity, it should be retested. If it is still decreased, then a cycloplegic refraction should be performed. If there is a change indicated for the refractive correction, sound eye acuity should be measured again, using the new correction placed over the spectacles or in trial frames or a phoropter. If acuity is still reduced by one or more lines from the pretreatment baseline (noncycloplegic acuity at baseline) and there has been a change in refraction from the spectacle prescription, a change in the spectacle lens should be prescribed (the study will pay for this change) and the patient should return in 1 to 4 weeks for visit 4C-2 to recheck the sound eye acuity with the new spectacles (remaining off atropine).

3.3 Responder Classification

If the patient is to return to retest acuity in the sound eye at visit 4C-2, completion of the responder classification is deferred until that time.

After visit 4C (2 to 4 weeks after the 17-week visit) and visit 4C-2 (return visit to recheck sound eye acuity), the responder status of each patient will be determined. For purposes of the classification, the amblyopic eye acuity is considered to be the best acuity achieved at either visit 4B or visit 4C/4C-2 and the sound eye acuity is considered to be the best acuity achieved at visit 4C/4C-2.

The classification is as follows:

Nonresponder	(1) amblyopic eye acuity improved no more than 1 line from baseline or (2) amblyopia treatment other than the randomization-assigned treatment (e.g., patching or greater frequency of atropine) used for 7 or more days
Complete responder	(1) amblyopic eye acuity 20/25 or better or (2) amblyopic eye acuity equal to or better than sound eye acuity ➢ *note: if sound eye acuity is worse than baseline, then amblyopic eye acuity must be equal to or better than baseline sound eye acuity*
Partial responder	(1) amblyopic eye acuity worse than 20/25 but improved 2 or more lines from baseline and (2) amblyopic eye acuity worse than best visit 4C sound eye acuity ➢ *note: the criteria for partial responder could also be stated as patient does not meet criteria for nonresponder or complete responder and amblyopic eye acuity less than best visit 4C sound eye acuity* ➢ *note: if criteria for partial responder are met, but sound eye acuity has worsened from baseline such that the investigator suspects reverse amblyopia and discontinues the randomized treatment, then the patient will be considered an unclassified responder*
Unclassified responder	(1) amblyopic eye acuity worse than 20/25 but improved 2 or more lines from baseline and (2) amblyopic eye acuity equal to or better than best visit 4C sound eye acuity but worse than baseline sound eye acuity ➢ *note: this scenario can only occur if the sound eye acuity at visit 4C (following retesting) is less than it was at baseline. An unclassified responder is in essence a partial responder whose sound eye acuity has worsened such that amblyopic eye acuity is the same or better than the sound eye acuity at visit 4C.* ➢ *note: see 2nd note above for partial responder*

3.4 Additional Follow-up for Complete Responders, Nonresponders, and Unclassified Responders

Unclassified responders, complete responders, and *nonresponders* whose sound eye distance acuity has worsened from baseline to visit 4C/4C-2 will have a visit in 2 to 4 months for further follow-up of the sound eye, at which time distance visual acuity will be measured using best correction in both eyes.

Complete responders and *nonresponders* whose sound eye acuity has not worsened from baseline will end study participation after visit 4C.

3.5 Additional Follow-up for Partial Responders

Patients categorized at visit 4C as *partial responders* will resume using the randomized treatment (daily or weekend atropine) and have a follow-up visit every 8 weeks until criteria are met for

complete responder, treatment is discontinued because the sound eye worsened, or there is no further improvement in the amblyopic eye acuity.

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 (or study-approved alternative instrument). If the acuity is not improved by 1 or more lines from the prior visit, it will be repeated.

'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 visits 4B and 4C 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).

As long as the visual acuity in the amblyopic eye tests at least 1 line better than it did at the prior visit, follow-up will continue. The majority of patients will have only one or two 8-week interval visits before follow-up ends. The maximum number of 8-week interval visits is three (for a patient who was 20/80 at baseline and 20/50 at visit 4C).

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

3.5.1 Reclassification of Partial Responders after Continued Follow-Up

As noted in the prior section, follow-up of patients who are categorized at visit 4C as *partial responders* will end when either (1) criteria are met for *complete responder, (2)* there is no further improvement in amblyopic eye visual acuity, or (3) there is continued improvement (but not to the *complete responder* level) and the sound eye has worsened such that amblyopic eye acuity is the same or better than sound eye acuity

- If criteria for *complete responder* are met, the patient will be so classified.
- If the *complete responder* criteria are not met and there is no further improvement in amblyopic eye acuity, the patient's final classification will be *partial responder*.
- If *complete responder* criteria are not met, there is continued improvement in the amblyopic eye acuity but the sound eye has worsened such that amblyopic eye acuity is now the same or better than sound eye acuity, the patient's classification will be *unclassified responder*.
- A patient also will have a final classification of *partial responder* if $\geq$7 days of nonprotocol amblyopia treatment was received since visit 4C or the patient drops from the study before the protocol-specified end of follow-up.

3.6 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.

3.6.1 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, irritability, mental confusion, constipation, aggravation of asthma, and seizures. 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[1] 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,[2] 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. In ATS1,[3] 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%). Parents were queried about the occurrence of a systemic side effect at each follow-up visit during atropine treatment. 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.

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 a several month duration 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.[2, 4-6]

   To minimize risks, the following steps will be taken:
   - The identification and management of atropine toxicity will be reviewed with the investigators.
   - Drugs will be dispensed in childproof containers and parents will be instructed to keep the drug away from children.
   - To minimize risk from pupil dilation, sunglasses will be provided for patients who do not require glasses. Hats with 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 protocol to follow. If atropine is discontinued, then the patient should be switched to homatropine 5% once a day. 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.

3.6.1.1 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.

The diagnosis and management of reverse amblyopia is left to the investigator's judgment.

If reverse amblyopia is suspected, a suggested routine for evaluation is the following:

1. If not already done, recheck acuity using full hyperopic correction from the most recent cycloplegic refraction.
2. If acuity is still decreased, perform a refraction and recheck acuity if testing was not done with proper hyperopic correction.
3. If acuity is still worse, stop atropine and repeat visual acuity testing in one week.
4. If the visual acuity has returned to enrollment level, resume treatment as per protocol.

5. If still reduced after one week, contact a Protocol Chair to discuss the case and further treatment. Amblyopic treatment, other than that specified in the protocol, should not be prescribed prior to discussing the case with a Protocol Chair.

3.6.1.2 Development of Strabismus

The study treatment could precipitate the development of an 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 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.

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 such strabismus surgery will be reported in the comment section of the follow-up exam form.

3.6.2 Risks of Examination Procedures

The procedures in this study are part of daily ophthalmologic and optometric practice in the United States and pose no additional known risks. Dilating/cycloplegic eye drops may be used as part of an exam.

3.6.3 Reporting of Adverse Events

1. Side effects of treatment, worsening of visual acuity, and development of strabismus are to be noted on the Follow-up Examination Form. In addition to recording complications on this form, the following serious complications must be reported to the Jaeb Center within 24 hours as a narrative by FAX or e-mail.
   - Patient death
   - Angle-closure glaucoma
   - Any serious suspected systemic atropine toxicity

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

Adverse effects of treatment are recorded on each follow-up exam form. These data will be tabulated regularly by the Data Coordinating Center. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee (DSMC), which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRB's.

3.7 Miscellaneous Considerations

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 (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 Follow-up Exam Form.

3.8 Maintaining Patient Follow-up

The Jaeb Center will maintain direct contact with the parent(s) or guardian(s) 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 if necessary to facilitate the scheduling of the patient for follow-up visits.

3.8.1 Patient Withdrawals

1. A patient (and in this case the parent(s) or guardian(s)) may withdraw from the trial at any time. This is expected to be a very infrequent occurrence in this trial in view of the study design's similarity to routine clinical practice. If the parent(s) or guardian(s) 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 their interest is in transferring the child's care to another eye care provider, every effort should be made to comply with this and at the same time try to keep the patient in the study under the new provider's care.
2. Discontinuation or alteration in the protocol-specified treatment regimen is not a reason to withdraw the patient from the study. Patients who stop or change treatment will continue to follow the study protocol for the follow-up/outcome examinations through visit 4C.

CHAPTER 4: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The sample size estimation and analysis plan are summarized herein and will be detailed in a separate document.

4.1 Sample Size

The sample size requirement for the study was estimated to be a minimum of 80 patients per group. This number may be exceeded since patient enrollment will be planned to end on a fixed calendar date rather than ending with the enrollment of the 160th patient.

Monte Carlo simulations were used to estimate the sample size from projected baseline and outcome visual acuity data assuming a standard deviation of 0.153 for the 17-week acuity scores and correlation between the baseline and outcome scores of 0.47 (based on ATS1 data).

In selecting the sample size for the trial, we have decided to have a 2-sided alpha of 0.05, with at least 90% power to detect a 0.075 logMAR difference between groups in the mean improvement in acuity from baseline. The sample size of 80 per group accounts for 5% losses to follow-up and provides 80% power to detect approximately a 50% relative treatment effect in a secondary analysis comparing *complete responder* proportions between the two treatment groups.

4.2 Statistical Analysis for Efficacy

The primary analysis will be a treatment group comparison of logMAR visual acuity scores obtained 17 weeks after randomization, adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model. The primary analysis will follow the "intent-to-treat" principle.

As a secondary analysis, the proportion of patients in each group who are classified as *complete responders* over the entire follow-up period will be determined. The difference in the proportions and the exact 2-sided 95% confidence interval will be computed using StatExact software (Cytel, Inc.).

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, a formal data report will be provided to the Data and Safety Monitoring Committee twice a year.

4.3 Data Analysis Plan to Assess Safety

The primary safety outcome is visual acuity in the sound eye. Sound eye acuity will be evaluated at all visits. However, the primary treatment group comparisons will be made at visit 4C (approximately 20 weeks after enrollment), after atropine has been discontinued for at least two weeks. Data from the visit 4C exam will be tabulated by treatment group as the change in acuity from baseline and statistically compared with a t-test. The data on patients whose sound eye acuity was decreased from baseline by 2 or more lines at any visit also will be evaluated as individual case reports to assess the likelihood that a case represents reverse amblyopia.

Ocular alignment and binocularity will be assessed at visit 4C and compared with baseline measurements. Development of a new strabismus or an increase from baseline of $\geq$ 10 pd will be tabulated by treatment group as will cases of strabismus surgery prior to six months.

DSMC reports also will include tabulations of local and systemic adverse effects of atropine.

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