AMBLYOPIA TREATMENT STUDY ATS17

A Randomized Trial of Levodopa as Treatment for Residual Amblyopia

PROTOCOL

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CHAPTER 1: BACKGROUND

The study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and is being coordinated by the Jaeb Center for Health Research in Tampa, Florida. The study is funded through a cooperative agreement from the National Eye Institute. It is one of a series of randomized trials and observational studies that address management issues related to the treatment of amblyopia in children. This study is designed to evaluate the efficacy and safety of oral levodopa and patching versus oral placebo and patching as treatment for residual amblyopia in children 7 to <13 years old with visual acuity of 20/50 or worse in the amblyopic eye.

1.1 Rationale for the Study

Amblyopia is the most common cause of monocular visual impairment in both children and young and middle-aged adults. Both patching and atropine are accepted treatment modalities for the management of moderate amblyopia in children.[1] Despite best efforts with conventional amblyopia treatment, many older children and teenagers with amblyopia fail to achieve normal visual acuity in the amblyopic eye. In a previous PEDIG study (ATS3, results detailed below) where children 7 to 12 years old were treated with atropine and patching, only 36% of the children with moderate amblyopia and only 23% of the children with severe amblyopia achieved 20/40 or better acuity.[1]

1.2 Prior PEDIG Amblyopia Studies

PEDIG conducted a randomized trial of 507 subjects (7 to 17 years old) with amblyopic eye visual acuity ranging from 20/40 to 20/400 (ATS3).[1] Subjects were provided with optimal optical correction and then randomized to a Treatment Group (2 to 6 hours per day of prescribed patching of the fellow eye combined with near visual activities for all subjects plus atropine one drop per day in the fellow eye for 7 to 12 year olds) or an Optical Correction Group (optical correction alone). Subjects whose amblyopic eye acuity improved 10 or more letters (2 lines) by 24 weeks were considered *responders*. In the 7 to 12 year-old subjects (N=404), 53% of the Treatment Group were responders compared with 25% of the Optical Correction Group (P <0.001). In the 13 to 17 year olds (N=103), the responder rates were 25% and 23% respectively overall (adjusted P=0.22), but 47% and 20% respectively among subjects not previously treated with patching and/or atropine for amblyopia (adjusted P=0.03). Most subjects, including responders, were left with a residual visual acuity deficit, as noted earlier.

ATS9 was a PEDIG-conducted randomized trial comparing weekend atropine to patching 2 hours per day in children 7 to 12 years of age for both moderate and severe amblyopia.[2] The specific treatments were:

1. Atropine 1% once each weekend day in the fellow eye plus near activities for at least one hour every day (with increase to daily atropine at 5 weeks if acuity not improved by at least 5 letters).
2. Patching 2 hours per day plus near activities for one hour while patching (with increase to 4 or more hours per day at 5 weeks if acuity not improved by at least 5 letters).

Initial treatment was for 17 weeks with continued treatment until improvement stopped. At the 5-week visit, visual acuity had improved from baseline by an average of 6.2 letters in the

atropine group and by 6.8 letters in the patching group. At the 17-week primary outcome exam, visual acuity had improved from baseline by an average of 7.6 letters in the atropine group and 8.6 letters in the patching group. Fifty-nine percent of the subjects in the atropine group and 70% of those in the patching group achieved 20/40 visual acuity or better.

1.3 Levodopa

Many clinicians have recognized that conventional therapies with patching and atropine have not been universally successful and have sought alternatives. PEDIG has discussed for several years the problem of residual amblyopia and how the remaining visual acuity deficit could be reduced. A number of research groups have evaluated the short term use of oral levodopa-carbidopa as an adjunct to patching therapy for older children.[3-5]

Levodopa is a medication used to treat adults with Parkinson disease and children with dopamine responsive dystonia. Dopamine is a neuro-transmitter that does not cross the blood brain barrier. Levodopa, which is an intermediate in the biosynthesis of dopamine, is used as pharmacological replacement therapy as it will cross the blood brain barrier, where it is converted to dopamine. Levodopa is typically used in combination with carbidopa. Carbidopa is a peripheral decarboxylase inhibitor that prevents the peripheral breakdown of levodopa. Concomitant administration reduces the dose of levodopa required by about 75%, yet allows sufficient levodopa to enter the brain for the desired central effect.[6] The reduced dose of levodopa reduces the peripherally-mediated side effects such as nausea and emesis.

Dopamine is active in the retina and in the cortex. Dopamine appears to play an important role in the normal function of the retina and in central visual processing. The site of action of dopamine in the visual pathway is unknown, although both retinal and cortical sites have been suggested. Brandies and Yehuda have authored an extensive review of this subject, in which they reviewed the role of retinal dopaminergic system in visual performance.[7] They concluded that both the retina and visual cortex are involved in most visual sensory and perceptual functions, but that it is difficult to fully understand the interrelationships and therefore the site of dysfunction in the dopamine dependent portions of the visual system of amblyopic subjects (section 6.4 of article).

For the retinal mechanism of action, two reports have suggested that increased dopamine levels lead to shrinkage in the size of the receptive field, thereby improving visual acuity.[8, 9] For a cortical mechanism, it has been hypothesized that increased dopamine levels produce a reduction in the size of the suppression scotoma thereby improving visual acuity.[10, 11] In a single dose administration, dopamine changes the volume of cortical activation measured by functional MRI.[10] Both improved visual acuity and VEP amplitudes have been reported following both single dose and 1 week of levodopa administration, but the improvement rapidly regressed with discontinuation of the drug.[5, 8] The improvement of visual acuity in the amblyopic eye occurs within 1 hour of medication administration and then begins to decline 5 hours after administration.[3, 9, 12] This transient improvement in the acuity of the amblyopic eye has led Leguire and others to suggest that the lasting improvement of visual acuity that is found when levodopa is used for the treatment of amblyopia may not be a direct effect, but rather the levodopa may allow better vision in the amblyopic eye during treatment, thus facilitating compliance with conventional occlusion therapy.[9, 13]

Several studies using levodopa have been published (see below) suggesting immediate improvement in the amblyopic eye visual acuity, as well as a sustained benefit for some. Results of visual acuity improvement and maintenance of improvement have varied across the published case series that are abstracted below. Doses of levodopa are listed in parentheses.

- In a pilot study Leguire and colleagues evaluated side effects and visual acuity improvement. They found nausea and emesis with higher doses of levodopa/carbidopa (100mg/25mg and 400mg/100mg). These doses are substantially higher than that given in their subsequent trials. The investigators demonstrated a temporary improvement in visual acuity in both the amblyopic eye and the dominant eye within one hour of ingestion of the medication, and these improvements began to decrease within five hours of drug ingestion. These results suggest that some of the observed improvement in visual function may be a drug-mediated effect of ramping up the function of the visual system, primarily the retina, rather than due to a sustained cortical improvement.[12]
- Leguire and colleagues conducted a randomized longitudinal double masked placebo controlled trial of 10 amblyopic children aged 6 to 14 years. The dosing averaged 0.5 mg per kg. Treatment lasted for three weeks. During that time visual acuity of the amblyopic eyes improved by 2.7 lines in the levodopa treated group, and by 1.6 lines in the subjects treated with placebo. One month after the termination of treatment, the levodopa-carbidopa group maintained a significant 1.2-line improvement in visual acuity. The placebo group did not maintain any improvement in visual acuity.[14]
- In a double-blind non-randomized clinical trial of 14 subjects 24 to 63 years of age, visual acuity and visual fields were examined before and after 3 weeks of daily levodopa, as well as 1 and 2 months after completion of drug therapy (2 mg/kg/tid and 3 mg/kg/tid). A significant increase in visual acuity was found, mostly during the first week. Improvement of visual function persisted 2 months after the levodopa administration was completed. Increasing the dosage and the duration of use did not enhance the effect.[4]
- An unmasked open-label clinical trial of 15 children at least 7 years of age who were no longer improving with standard treatment for amblyopia were treated for 7 weeks with a combination of levodopa-carbidopa (0.55 mg/kg/tid). The results showed visual acuity in the amblyopic eye improved from 20/170 baseline to 20/107. All of the improvement occurred in the first five weeks. Visual acuity also improved in the dominant eye from 20/19 to 20/16. A concern is that the improvement observed may simply represent improvement that occurs as a result of retreatment i.e., these subjects had been at an end point and had stopped treatment. It is unclear whether the improvement was due to retreatment or an additional effect of levodopa.[9]
- An unmasked clinical observational study was reported in the Chinese literature, with only the abstract published in English (we had the entire paper reviewed for side-effects description by a native Mandarin speaker). Thirty-six subjects with recalcitrant amblyopia who had not had any improvement for six months with daily occlusion had additional treatment with levodopa-carbidopa (1.5 mg/kg/day) for three months. The authors describe improvement in 90% of eyes, and a "cure rate" of 43%. (The amount of improvement is not described in the English abstract.) The definition of cure rate was not provided in either abstract or text.[15]

- In a double-masked, placebo-controlled randomized study, 18 amblyopic children aged 4 through 17 years were treated with 2 mg/kg/day of levodopa (without carbidopa) or placebo. Improvement in the levodopa group was 1.4 lines of visual acuity compared with no improvement in the placebo group (n=14). However, Snellen acuity decreased to the baseline level within one week of cessation of levodopa treatment.[5]
- A 1-week, randomized, double-blind, parallel, and placebo-controlled study was performed with 62 children with amblyopia who were between 7 and 17 years of age. Subjects were instructed to occlude the dominant eye for 3 hours per day. Visual acuity improved from 0.59 to 0.45 logMAR in the levodopa-carbidopa group (average dose 0.51 mg/kg/day) and from 0.69 to 0.63 in the control group (P=0.023). There were no complaints of adverse side effects.[16]
- In a prospective randomized controlled trial, 72 subjects with amblyopia were distributed into three groups of 24. Group A subjects received levodopa alone, group B received levodopa (0.50 mg/kg/tid) and part-time occlusion (3 hours/day), and group C received levodopa and full-time occlusion (during all waking hours) of the dominant eye. Visual acuity was recorded before treatment, at weeks 1, 3, 5, and 7 after starting treatment, and every 6 weeks for 1 year after the completion of treatment. Though 53/72 subjects (74%) had an improvement in visual acuity (maximum=4.6 Snellen lines; mean 1.6 Snellen lines, ≤ 10years; mean 1.1 Snellen lines, >10 years) after treatment, 52% of those who improved had regression in visual acuity when measured after 1 year.[17]
- A follow-up report of three longitudinal studies (9 to 27 months) using Levodopa (0.55 mg/kg/tid) plus occlusion for treatment of amblyopia included 30/33 (91%) of participating subjects. Subjects who received levodopa plus occlusion demonstrated significant regression of visual acuity after stopping the levodopa. On average, the amount of regression over approximately six months of follow-up averaged 1.4 lines. This recurrence was similar in magnitude to that experience by those receiving occlusion only.[3]
- Forty children 6 to <18 years of age were randomized to 4 weeks of levodopa (1.86 mg/kg/day (1.33-2.36 mg/kg/day) plus full-time occlusion or full-time occlusion only.[18] No difference in visual acuity outcome (ETDRS charts) between treatments was found. The medication was well tolerated.
- Thirty children 3 to 12 years old were randomized to patching plus placebo or 0.50 mg/kg levodopa with 1.25 mg/kg carbidopa tid.[19] The authors observed more than 2 lines of improvement that was greater in the levodopa group (15 of 15) than in the placebo group (9 of 15). The medication was reported to be well tolerated with only one case of nausea.
- PEDIG recently completed a pilot study evaluating recruitment potential and safety of levodopa (ATS14). Thirty-three subjects 8 to <18 years old were randomized between two dosages of levodopa (0.51 mg/kg and 0.76 mg/kg, both with carbidopa) and followed for 8 weeks. At the 8-week primary outcome, visual acuity in the amblyopic eye had improved an average of 4 letters in the 15 subjects randomized to the 0.51 mg/kg dosage, and an average of 6 letters in the 17 subjects randomized to the 0.76 mg/kg dosage. All subjects completed their treatment course of levodopa and the medication was well tolerated (*Appendix 1*).

- An alternative to oral levodopa has been parenteral citicoline. Citicoline is used to compliment levodopa in subjects with movement disorders such as Parkinson Disease. Subjects received intramuscular injections of citicoline (1gm IM daily) for 15 days in an open (non-randomized, unmasked) clinical trial. Ten additional subjects were studied in a randomized double-masked design. They demonstrated a significant improvement in visual acuity in both the amblyopic (mean 1.7 lines) and the fellow (mean 1.0 lines) eyes which remained stable for at least four months.[20] This drug requires intra muscular injection and would not currently be acceptable in a study group such as PEDIG. An oral formulation is currently being studied in Europe (personal communication, E. Campos, May 2007).

1.4 Tolerability and Adverse Effects

Dopamine is used to treat movement disorders, most commonly those associated with Parkinson Disease (PD). The drug is of rapid onset and is taken at regular intervals, with marked improvement in hypokinesia. PD is very rare in children. Moreover, since PD is degenerative and induces post-synaptic striatal changes that would not be present in our study sample, the relevance of CNS side effects seen in PD to our study sample is low.

Adult subjects receiving levodopa-carbidopa for the management of PD may experience side effects, but these are usually reversible. Acute effects are nausea and vomiting which may be caused by direct stimulation of the chemotrigger receptor zone in the brain.[21] Tolerance to these symptoms rapidly develops in adults being treated. Other acute effects include orthostatic hypotension, peripheral edema, and psychosis.

Prolonged use of dopaminergic drugs in PD has been associated with the development of dyskinesias in adults and in children. These may include chewing, gnawing, twisting, tongue or mouth movements, head bobbing, or movements of the feet, hands, or shoulder. These may respond to a reduction in the dose. Muscle twitching, dizziness, muscle jerks during sleep, and hand tremor also may occur. Various psychiatric disturbances may occur during levodopa-carbidopa therapy, such as memory loss, anxiety, nervousness, agitation, restlessness, confusion, inability to sleep, nightmares, daytime tiredness, mental depression or euphoria. Pharmacological treatment with medications such as pyridoxine has been suggested, but has not been proven to be effective.

Neuroleptic malignant syndrome is an uncommon, life-threatening side-effect of neuroleptic treatment which has also been reported in rare cases of adults during reduction or withdrawal of levodopa therapy for PD.[6] This syndrome is characterized by fever, muscle rigidity, involuntary movements, altered mental status, and autonomic signs such as tachycardia, sweating, and tachypnea. Treatment includes monitoring in the intensive care unit, with use of dopamine agonists such as bromocryptine.

Levodopa has also been used for many years in children to treat dopa-responsive dystonia, also known as Segawa Disease.[22-26] This disease is extremely rare and occurs due to deficient synthesis of dopamine due to GTP cyclohydrolase deficiency. Typical doses of levodopa in children range from 50 mg on alternate days when used with carbidopa to 2 g daily when used without carbidopa.[24] Historically, chorea was noted to appear in several subjects early on in

treatment which responded to dosage adjustment. A recent review noted that typical chronic dosing is 4-5 mg/kg/day in divided doses, though up to 20 mg/kg/day may be needed.[25] However, the relevance of dosing and associated side effects in this disease to our study sample is low, because of the substantially smaller doses used for amblyopia treatment and proposed for our study. It is preferred to administer the drug separate from meals. Levodopa competes with some amino acids for absorption.

A larger clinical experience with levodopa-carbidopa and with synthetic dopamine agonists is found in pediatric Tourette Syndrome, cerebral palsy, and Restless Leg Syndrome. In general in these populations, nausea is the most common side effect.

Gastrointestinal side effects are common in subjects receiving levodopa-carbidopa. Nausea, vomiting, loss of appetite, and weight loss may occur. Subjects may experience dizziness upon standing up that is associated with a transient drop in blood pressure. In general, tolerance to these side effects develops within a few months. Infrequently, subjects may develop a drop in white blood cell count during levodopa-carbidopa therapy.[6]

The side-effects of nausea and emesis associated with levodopa are minimized with the simultaneous administration of carbidopa, which allows use of lower dosages of levodopa.[6] Carbidopa and dopamine do not cross the blood-brain barrier. Carbidopa inhibits dopamine decarboxylase and prevents the decarboxylation of levodopa in peripheral tissues, thus allowing sufficient levodopa to enter the CNS, yet reduces the total amount of levodopa that needs to be administered. Peripheral dopamine decarboxylase is saturated by carbidopa at approximately 70 mg per day in adults (1 mg/kg/day). Subjects receiving less than this amount of carbidopa may experience nausea and vomiting.

Levodopa has been used with carbidopa for amblyopia treatment since 1993, with doses considerably lower than the doses prescribed for Parkinson disease and dystonia. The medication has been well tolerated in the dose and duration typically prescribed.[9, 16] Levodopa-carbidopa is recognized as a Pregnancy Class C medication with uncertain safety. Safety in lactation is recognized as possibly unsafe. Reported adverse effects of oral levodopa-carbidopa during treatment of amblyopia have included nausea, headache, vomiting, dry mouth, mood changes, dizziness, and fatigue. In one study more than half of the subjects reported at least one symptom.[9, 12] Decreased body temperature was noted during a 7-week treatment course with the 1.02 mg/kg/tid, but not with 0.55 mg/kg/tid.[27] Dyskinesias, to our knowledge, have not been reported with the short-term use for the treatment of amblyopia. Gottlob reported infrequent minor side effects in her group of adult subjects with amblyopia.[4]

An analysis of serum chemistry, hematological tests, renal function tests, liver function tests and liver enzymes was undertaken in 32 children with an average age of 8.44 years across a number of studies by the Columbus group (Leguire et al, 2007, unpublished data). Blood samples were taken at baseline, before drug dosing, and after seven weeks of levodopa-carbidopa dosing with three different dosing regimens. The combined results showed that individual deviations from the normal range for 39 tests were similar at baseline and following seven weeks of levodopa-carbidopa dosing. Although some laboratory test means were different from baseline to the 7-week test session, the means remained well within the normal range for each individual test. In

addition, the percent changes were so small as to have no clinical significance. Overall, based on the analysis of these 39 tests, levodopa-carbidopa was well tolerated in a pediatric population.

Combined formulation tablets of levodopa-carbidopa are commercially available in a 1:4 ratio of carbidopa to levodopa (25-100) as well as 1:10 ratio (25-250 and 10-100). Tablets of the two ratios are combined as needed to provide the optimum dosage of both drugs in adults. Because higher doses are required for their neurological diseases, adequate levels of carbidopa are administered. For the management of amblyopia Leguire and colleagues have used the 1:4 ratio for their studies (personal communication, Larry Leguire, 11/12/2007), as have the other studies cited earlier.

The present study will evaluate one dose of levodopa (0.76 mg/kg tid levodopa, equivalent to 2.28 mg/kg/day). Most of the literature published has used a dose of about 0.51 mg/kg tid (*Appendix 1*). A few studies have used higher doses of levodopa. Leguire and colleagues have used doses ranging from 0.75 to 3.06 mg/kg/day.[28, 3] These were generally well tolerated. With the 3.06 mg/kg/day dose, there was a slight drop in body temperature (mean changed from 99.0 to 97.8 degrees) that was not symptomatic or clinically consequential.[29] Procianoy and colleagues administered average doses of 0.51, 1.05, and 2.29 mg/kg/day to three dosage groups with about 20 subjects per group.[16] They found similar results in visual acuity change and side effects with both the lowest and highest doses. In each of these studies carbidopa was added in a ratio of 1 part to 4 of levodopa. In the PEDIG pilot study we randomized between 0.51 mg/kg tid levodopa and 0.76 mg/kg tid levodopa, equivalent to 1.53 mg/kg/day and 2.28 mg/kg/day. Carbidopa was prescribed at 0.17 mg/kg/tid. The medications at both doses were well tolerated.

In the present study, carbidopa will be prescribed at 0.17 mg/kg/tid (equivalent to 1 part to 4.5 parts levodopa). The dose of carbidopa is less than the 1 mg/kg/day recommended for adults and certainly less than the maximal dose possible in children according to child neurologists we have consulted. However, as noted in the preceding paragraphs this is more than the dosage of carbidopa used in prior studies of amblyopia where nausea was unusual with carbidopa 1:4. In addition to the study formulation, additional carbidopa may be prescribed at any time to control nausea in consultation with the study chair and neurologist serving as the medical monitor.

1.5 Primary Objectives

The primary objective of the study is to compare the efficacy and safety of oral levodopa and patching versus oral placebo and patching at 18 weeks, after 16 weeks of treatment for amblyopia in children 7 to <13 years old followed by a two-week taper of oral medication.

1.6 Secondary Objectives

Secondary objectives are:

1. To evaluate maximum improvement in visual acuity with oral levodopa plus patching versus oral placebo plus patching through 26 weeks.
2. To evaluate the frequency of recurrence of amblyopia after 13 weeks of no therapy, among subjects from both randomized treatment groups who have improved from baseline by 10 or more letters in amblyopic eye visual acuity at 26 weeks and are ready to stop amblyopia treatment.

1.7 Synopsis of Study Design

1.7.1 Randomized Trial

The Randomized Trial is divided into two phases: the Randomized Treatment Phase (weeks 0 to 18) and the Post Primary Outcome Phase (weeks 18 to 26).

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

1. Age 7 to <13 years
2. Amblyopia associated with strabismus, anisometropia, or both
3. Visual acuity in the amblyopic eye 18 to 67 letters inclusive (20/50 to 20/400)
4. Visual acuity in the fellow eye ≥78 letters (20/25 or better)
5. Current amblyopia treatment (other than spectacles) of at least two hours occlusion per day for at least 12 weeks during the immediate pre-enrollment period
6. While on current treatment, visual acuity has not improved one line (5 letters) or more since a non-study visit at least 6 weeks ago. Both acuity measurements to define no improvement must have been done using the same testing method.

1.7.1.2 Randomized Treatment Groups

All subjects will have two hours of daily patching prescribed plus be randomized to one of two oral treatment regimens for 16 weeks with a rapid taper prior to the primary outcome exam two weeks later (18 weeks):

- Oral levodopa 0.76 mg/kg tid with carbidopa 0.17 mg/kg tid
- Oral placebo tid

1.7.1.3 Sample Size

Approximately 138 subjects will be randomized in a 2:1 ratio to the two treatment groups (92 subjects to levodopa plus patching and 46 subjects to patching plus placebo).

1.7.1.4 Randomized Treatment Phase - Follow-up Visit and Phone Contact Schedule

All contacts and visits are timed from randomization.

- Phone Call 1: 2 weeks (± 3 days)
- Office Visit 1: 4 weeks (± 1 week)
- Phone Call 2: 7 weeks (± 1 week)
- Office Visit 2: 10 weeks (± 1 week)
- Phone Call 3: 13 weeks (± 1 week)
- Office Visit 3: 16 weeks (± 1 week)
- Office Visit 4 (Primary Outcome): 18 weeks (± 1 week) following rapid taper of study medicine

1.7.1.5 Primary Outcome and Analysis

The primary outcome is amblyopic eye visual acuity measured at the 18-week primary outcome visit (Visit 4) following rapid taper of study medicine beginning at week 16. The primary analytic approach will be a treatment group comparison of the mean amblyopic eye acuity adjusted for baseline acuity using an analysis of covariance.

1.7.2 Post Primary Outcome Phase (Weeks 18 through 26)

Upon completion of the primary outcome visit (18 weeks from randomization) all subjects will enter the Post Primary Outcome Phase (Weeks 18-26). Subjects will remain masked to treatment group during this phase.

1. Treatment between 18 and 26 weeks after randomization will depend upon whether or not visual acuity in the amblyopic eye has improved 5 or more letters between baseline and the 16-week visit (*see Chapter 3 for additional details*).
    - If the amblyopic eye visual acuity has improved 5 or more letters between baseline and the 16-week visit subjects will restart randomized treatment
        - They will resume the medication once daily for three days, twice daily for three days and then three times daily.
        - At the end of week 24 and two weeks prior to the scheduled 26-week outcome visit for this phase, subjects will begin a tapering regimen. The tapering schedule will be twice daily dosing for three days, once daily for three days and then off-treatment with a follow-up visit one week later. Patching will remain unchanged prior to the 26-week visit.
        - If the improvement is less than 5 letters between baseline and the 16-week visit, treatment is at investigator discretion, except that study medication will stop and levodopa may not be prescribed until after the 26-week visit. Prescribed spectacles are continued. The parent and investigator will remain masked to randomized treatment throughout this phase.
2. Visit and Phone Call Schedule in the Post Primary Outcome Phase
    - Phone Call 4: 23 weeks (± 1 week) – notify parents to begin study medication taper one week prior to visit
    - Office Visit 5: 26 weeks (± 1 week)

1.7.3 Extension Studies

Study participation beyond the 26-week visit is based on whether the amblyopic eye visual acuity has improved by 10 or more letters from baseline to the 26-week visit, the treatment group assignment, and future treatment plans of the investigator for the subject.

The possibilities are:

1. Improved ≥ 10 letters and both investigator and subject are ready to stop. Enter Post 26-week Observation Extension Study (*see Section 1.7.3.1*).
2. Improved ≥ 10 letters and either investigator or subject are <u>not</u> ready to stop. Study participation concludes.
3. Improved < 10 letters in the levodopa group or placebo group with no plan for further therapy. Study participation concludes.

4. Improved < 10 letters in the levodopa group with a plan for further therapy. Study participation concludes.
5. Improved < 10 letters and in the placebo group and elect Levodopa. Enter optional Levodopa Treatment Extension Study for the Placebo Group (*see Section 1.7.3.2*) or study participation concludes.

1.7.3.1 Post 26-week Observation Extension Study

1. Subjects entering this Study will have visual acuity in the amblyopic eye improved 10 or more letters from baseline to 26 weeks and both the investigator and subject are ready to stop amblyopia therapy.
    a. Treatment will be discontinued and the subject will be followed off treatment in the Post 26-week Observation Extension Study, with a visit 39 weeks (± 1 week) from randomization (Visit 6).
    b. Subjects will remain masked to their treatment group assignment until the 39-week visit.
    c. After completion of this Post 26-week Extension Study subjects who were in the placebo treatment group may elect to begin levodopa and enter the Levodopa Extension Study for the Placebo Group (*see Section 1.7.3.2*)

1.7.3.2 Levodopa Treatment Extension Study for the Placebo Group

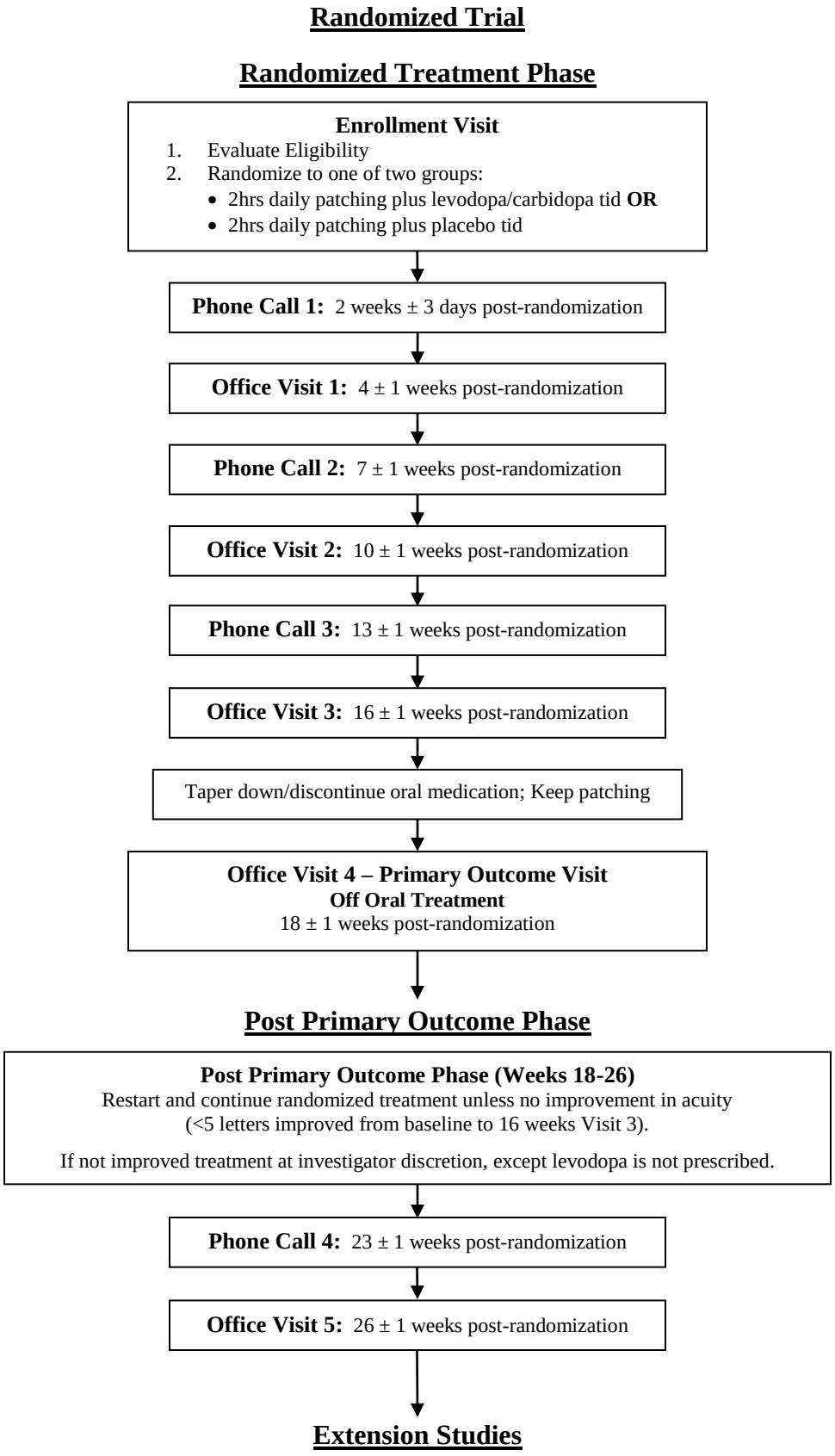
Subjects in the placebo group may enter the extension study. If the subjects move to this phase, they are started on levodopa at either the 26-week visit (*see Section 1.7.3, #5*) or, if the subject completed the Post 26-week Observation Extension Study (*see Section 1.7.3.1, #1c*), at the 39-week visit.

Subjects will be treated with 16 weeks of levodopa as described above for the randomized trial.

Phone contacts and follow-up visits in the extension study are timed from the last visit.

- Phone Call 1E: 2 weeks (± 3 days)
- Office Visit 1E: 4 weeks (± 1 week)
- Phone Call 2E: 7 weeks (± 1 week)
- Office Visit 2E: 10 weeks (± 1 week)
- Phone Call 3E: 13 weeks (± 1 week)
- Office Visit 3E: 16 weeks (± 1 week)
- Office Visit 4E: 18 weeks (± 1 week) following taper of study medicine beginning at week 16

1.7.4 Study Flowchart



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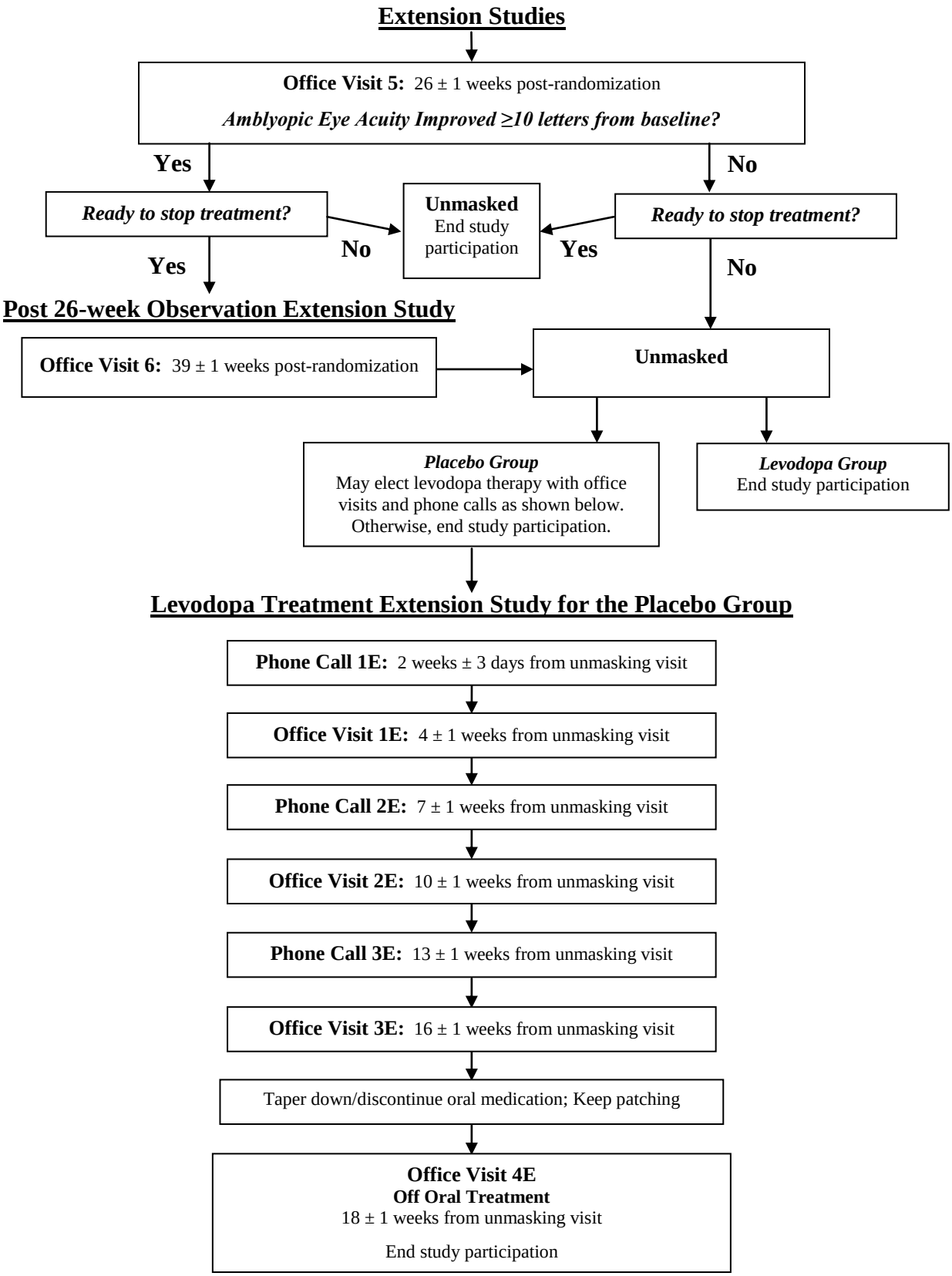
Extension Studies
Office Visit 5: 26 ± 1 weeks post-randomization
Amblyopic Eye Acuity Improved ≥10 letters from baseline?
Yes
No
Ready to stop treatment?
No
Unmasked
End study participation
Yes
Ready to stop treatment?
Yes
No
Post 26-week Observation Extension Study
Office Visit 6: 39 ± 1 weeks post-randomization
Unmasked
Placebo Group
May elect levodopa therapy with office visits and phone calls as shown below. Otherwise, end study participation.
Levodopa Group
End study participation
Levodopa Treatment Extension Study for the Placebo Group
Phone Call 1E: 2 weeks ± 3 days from unmasking visit
Office Visit 1E: 4 ± 1 weeks from unmasking visit
Phone Call 2E: 7 ± 1 weeks from unmasking visit
Office Visit 2E: 10 ± 1 weeks from unmasking visit
Phone Call 3E: 13 ± 1 weeks from unmasking visit
Office Visit 3E: 16 ± 1 weeks from unmasking visit
Taper down/discontinue oral medication; Keep patching
Office Visit 4E
Off Oral Treatment
18 ± 1 weeks from unmasking visit
End study participation

CHAPTER 2: SUBJECT ENROLLMENT (BASELINE VISIT)

2.1 Assessment and Informed Consent/Assent

A minimum of 138 subjects are expected to be enrolled with a goal to enroll an appropriate representation of minorities. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the minimum recruitment goal might be exceeded. The maximum number of randomized subjects will be 150.

An individual is considered for the study after undergoing an 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 before a subject can be enrolled into the trial.

For individuals who appear eligible for the study following a "standard-care" 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 brochure and a copy of the consent form. Written informed consent will be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the subject's routine care. Written assent will be obtained from children as required by Institutional Review Boards.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

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

1. Age 7 to <13 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
     - 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
3. Visual acuity, measured in each eye (amblyopic eye without cycloplegia) within 7 days prior to enrollment using the E-ETDRS protocol by a study certified visual acuity tester as follows:
   - Visual acuity in the amblyopic eye 18 to 67 letters inclusive (20/50 to 20/400)
   - Visual acuity in the fellow eye ≥78 letters (20/25 or better)
4. Current amblyopia treatment (other than spectacles)
   - A minimum of 12 weeks of at least two hours of occlusion per day prescribed for the fellow eye during the immediate pre-enrollment period.

- While on current treatment, visual acuity has not improved one line (5 letters) or more since a non-study visit at least 6 weeks ago. Both acuity measurements to define no improvement must have been done using the same testing method. *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*
- Treatment with atropine at any time during this pre-enrollment period is not allowed.
- Any treatment prior to the current patching episode with stable acuity is acceptable.

5. Spectacle correction (if applicable) for measurement of enrollment visual acuity 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:
      - Spherical equivalent must be within 0.50 D of fully correcting the anisometropia.
      - Hypermetropia of 3.00D or more must be corrected.
      - Hypermetropia must not be under corrected by more than 1.50 D spherical equivalent, and reduction in plus sphere 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 both eyes is within 6 degrees of the axis in the spectacles when cylinder power is ≥1.00 D.
      - Myopia of amblyopic eye greater than 0.50 D by spherical equivalent must be corrected, and the glasses must not under correct the myopia by more than 0.25 D or overcorrect it by more than 0.50 D.
   b) Spectacles meeting above criteria must be worn
      - 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 line (5 letters) 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) in new glasses. *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*
6. Eye examination within 6 months prior to enrollment
7. Parent available for at least one year of follow-up, has home phone (or access to phone), and willing to be contacted by clinical site staff and Jaeb Center staff
8. In the investigator's judgment, the subject is likely to comply with prescribed treatment (e.g., no history of poor compliance with patching treatment) and unlikely to continue to improve by using 2 hours of patching per day alone.

2.2.2 Exclusions

1. Myopia more than -6.00 D (spherical equivalent) in either eye.
2. Current vision therapy or orthoptics
3. Ocular cause for reduced visual acuity
   - nystagmus per se does not exclude the subject if the above visual acuity criteria are met

4. Prior intraocular or refractive surgery
5. History of narrow-angle glaucoma
6. Bronchial asthma or severe pulmonary disease
7. Strabismus surgery planned within 26 weeks
8. Known allergy to levodopa or carbidopa
9. History of dystonic reactions
10. Current use of oral iron supplements including multivitamins containing iron during treatment with levodopa-carbidopa
11. Current use of antihypertensive, anti-depressant medications, phenothiazines, butyrophenones, risperidone or isoniazid, non-specific monoamine oxidase inhibitors, or medication for the treatment of attention deficit hyperactivity disorder
12. Known liver disease
13. History of melanoma
14. Known psychological problems
15. Known skin reactions to patch or bandage adhesives
16. Prior levodopa treatment
17. Treatment with topical ophthalmic atropine within the past 12 weeks
18. A physician-prescribed diet high in protein
19. Females who are pregnant, lactating, or intending to become pregnant within the next 34 weeks.
    - A negative urine pregnancy test will be required for all females who have experienced menarche.
    - Requirements regarding pregnancy testing prior to enrollment and monitoring for pregnancy over the course of the study may be further defined by each individual Institutional Review Board.

2.3 Examination Procedures

2.3.1 Historical Information

Historical information elicited will include the following: date of birth, gender, ethnicity, prior amblyopia therapy (e.g., glasses, patching, pharmacologic, Bangerter filters, combined therapies, near activities with treatment), current amblyopia therapy, current medications being used, visual acuities before or during current cycle of patching treatment, current spectacle correction, and other medical conditions including a history of the following: allergy to adhesive skin patches, allergy to levodopa-carbidopa, narrow-angle glaucoma, dystonic reactions, gastrointestinal or liver disease, melanoma, psychological problems.

2.3.2 Clinical Testing

Examination procedures include:

1. Measurement of body weight.
2. Measurement of visual acuity in each eye (right eye first) by the E-ETDRS testing protocol on a study approved visual acuity tester.

- Testing of the amblyopic eye must be done without cycloplegia (with spectacles, if worn) no more than 7 days prior to randomization.
- Subjects currently wearing spectacles must have enrollment acuity measured while wearing spectacles; trial frames or phoropter cannot be used.

3. Ocular motility examination
   - Measurement of alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near
   - If performed within prior 7 days, alignment measurements do not need to be repeated at time of enrollment
4. Stereoacuity testing: Titmus fly, Randot Preschool test
   - If performed within prior 7 days, it does not need to be repeated at time of enrollment
5. Complete eye examination, including dilated fundus examination, to rule out a cause for reduced visual acuity other than amblyopia.
   - If performed within prior 6 months, the eye examination does not need to be repeated at time of enrollment
6. Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine
   - If performed within prior 6 months, the cycloplegic refraction does not need to be repeated at time of enrollment

2.3.3 Symptom Survey

Each subject and parent will complete a symptom survey to identify any symptoms the subject may be experiencing before beginning the study medicine. The questionnaire will be repeated at each office visit while using study medicine.

2.4 Randomization

2.4.1 Randomization of Eligible Subjects

1. A subject should not be randomized until both the investigator and the parent(s) are ready to start the study medicine.
2. The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by site and by visual acuity in the amblyopic eye as moderate 20/50 to 20/80 (53 to 67 letters) versus severe 20/100 to 20/400 (18 to 52 letters), which will specify the order of treatment group assignments.
   a. Subjects will be randomized in a 2:1 ratio, with 2 subjects randomized to levodopa plus patching for every 1 subject randomized to placebo plus patching. A subject is officially enrolled when the website randomization process is completed. Both the subject and the site will be masked to treatment group assignment.
3. Once a subject is randomized, that subject will be included in the analysis regardless of whether the assigned treatment is received or not. Thus, the investigator must not randomize a subject until he/she is convinced that the parent/guardian will accept and comply with either of the treatment regimens.

2.4.2 Delay in Randomization

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

CHAPTER 3: TREATMENT AND FOLLOW UP IN RANDOMIZED TRIAL

The Randomized Trial is divided into two phases: the Randomized Treatment Phase (weeks 0 to 18) and the Post Primary Outcome Phase (weeks 18 to 26).

3.1 Randomized Treatment Phase

All subjects will have two hours of daily patching prescribed plus be randomized to one of two oral treatment regimens for 16 weeks with a rapid taper prior to the primary outcome exam two weeks later (18 weeks):

- Oral levodopa 0.76 mg/kg tid with carbidopa 0.17 mg/kg tid
- Oral placebo tid

A central pharmacy will compound study medicine as gelatin capsules. Levodopa with carbidopa capsules will be filled with methylcellulose (filler) plus levodopa and carbidopa powder based upon body weight. Placebo capsules will be filled with methylcellulose (filler) alone. Capsules will be dispensed in masked prescription bottles and will be shipped to the subject who will begin study medicine upon receipt.

3.1.1 Study Medication Dosing in Randomized Treatment Phase

After receipt of study medicine, subjects will build up to a daily dose over one week by taking oral medication once daily for three days, twice daily for three days and then three times daily until an office visit 16 ± 1 weeks after randomization (Visit 3).

- Study medicine should be given at least 30 minutes before meals with water. Milk should not be taken with the medication.
- For school-age children the midday dose may be given in school if feasible or by administering the midday dose in mid-afternoon after dismissal from school, with the third dose given after dinner.
- Capsules may be crushed if necessary.

After the 16-week visit subjects will continue 2 hours of daily patching. They will also begin and complete a rapid taper of medication during the following week in anticipation of the primary outcome visit 2 weeks later at 18 weeks from randomization. The tapering schedule is twice daily dosing for three days, once daily for three days and then off-treatment before the exam.

3.2 Post Primary Outcome Phase

Subjects who enter this phase will have two hours of daily patching prescribed plus continue their randomized oral treatment as in the Randomized Treatment Phase.

3.2.1 Study Medication Dosing in Post Primary Outcome Phase

Upon completion of the primary outcome visit (18 weeks from randomization) all subjects will enter the Post Primary Outcome Phase (Weeks 18-26). Subjects will remain masked to treatment group during this phase.

Treatment between 18 and 26 weeks will depend upon whether or not visual acuity in the amblyopic eye has improved 5 or more letters between baseline and the 16-week visit.

- If the amblyopic eye visual acuity has improved 5 or more letters between baseline and the 16-week visit, subjects will restart randomized treatment and build up to three-times-a-day over one week by taking the medication once daily for three days, twice daily for three days and then three times daily.
    - At week 24, those subjects on oral medication will begin a tapering regimen. The dosing schedule will be twice daily for three days, once daily for three days and then off-treatment with a follow-up visit one week later.
    - Patching will remain 2 hours per day prior to the 26-week visit.
- If the improvement of the amblyopic eye is less than 5 letters between baseline and the 16-week visit treatment is at investigator discretion, except that study medication will stop and levodopa may not be prescribed until after the 26-week visit. Prescribed spectacles are continued. The parent and investigator remain masked to randomized treatment.

3.3 Compliance

In the randomized trial a calendar log will be maintained by all subjects on the daily completion of the prescribed patching treatment and consumption of the study medication. These logs will be reviewed by the investigator at each of the protocol visits. Medication containers will be brought to all visits while on randomized treatment. The amount of remaining study medicine will be recorded as a measure of treatment compliance.

If a subject is noncompliant with study medicine, the parents should be encouraged to persist with their efforts to treat to the best of their ability

3.4 Side Effects of Treatment

Reporting of adverse events is described in Chapter 6. Prior to deviating from the treatment protocol or prescribing non-protocol treatment, the situation should be discussed with the Protocol Chair. In the case of pregnancy during this study, the levodopa-carbidopa medicine will be discontinued.

A pediatric neurologist with experience using levodopa-carbidopa in children will serve as consultant expert for the investigators and Protocol Chair for review of side-effects and provide consultations for dosage adjustments. In addition to the study formulation, additional carbidopa may be prescribed at any time to prevent nausea in consultation with the study chair and neurologist serving as the medical monitor, to be paid for by the study.

3.4.1 Overdosage

Supportive measures along with gastric lavage and monitoring for cardiac arrhythmias are recommended. Pyridoxine has been suggested to reverse the actions of levodopa, but is not considered effective.

3.4.2 Discontinuation of Treatment

Blepharospasm or dyskinesia may be an early indication of excess dosage.[6] The development of these signs should be discussed immediately with the protocol chair and the medical monitor to determine if the medicine should be discontinued.

3.5 Phone and Visit Schedule in Randomized Trial

Protocol-specified contacts and follow-up visits will occur at the following times. All contacts and visits are timed from randomization.

Randomized Treatment Phase

- Phone Call 1: 2 weeks (± 3 days)
- Office Visit 1: 4 weeks (± 1 week)
- Phone Call 2: 7 weeks (± 1 week)
- Office Visit 2: 10 weeks (± 1 week)
- Phone Call 3: 13 weeks (± 1 week)
- Office Visit 3: 16 weeks (± 1 week)
- Office Visit 4 (Primary Outcome): 18 weeks (± 1 week) following rapid taper of study medicine

Post Primary Outcome Phase

- Phone Call 4: 23 weeks (± 1 week)
- Office Visit 5: 26 weeks (± 1 week)

Additional visits may be completed at investigator discretion.

3.6 Testing and Study Procedures in Randomized Trial

3.6.1 Telephone Calls

Each subject will be contacted by the physician's office via telephone 2, 7, 13, and 23 weeks post-randomization. During each call the parent will be questioned about side-effects (nausea, emesis, headache, fatigue, dyskinesias), and reminded of the importance of completing all aspects of the treatment. Parents will be reminded to bring their study medication containers to the office visits.

3.6.2 Visits 1, 2, and 3

Follow-up visits will occur 4 ± 1 weeks (Visit 1), 10 ± 1 weeks (Visit 2), and 16 ± 1 weeks (Visit 3) following randomization.

Testing will include the following:

1. Medical history will be updated including questioning about the occurrence of adverse effects of treatment. Any concomitant medications will be recorded.
2. Completion of symptom survey by subject and parent
3. Evaluation of treatment compliance

4. Visual acuity
    - Measured in each eye (right eye first) by a study-certified visual acuity tester using the Electronic ETDRS visual acuity protocol.
5. Retesting of visual acuity in the amblyopic eye (if indicated at Visit 3 only)
    - If amblyopic eye visual acuity has not improved from baseline (<5 letters better), then it will be re-tested.
    - The results of the re-test, if necessary, will be used to determine if the subject will continue on randomized treatment after the primary outcome at 18 weeks (Visit 4) as they enter the Post Primary Outcome Phase.

3.6.3 Primary Outcome – Visit 4

The primary outcome visit will occur 18 ± 1 weeks (Visit 4) following randomization after a rapid taper of study medicine.

Testing will include the following:

1. Medical history will be updated including questioning about the occurrence of adverse effects of treatment. Any concomitant medications will be recorded.
2. Completion of symptom survey by subject and parent
3. Evaluation of treatment compliance
4. Visual acuity
    - Measured in each eye (right eye first) by a study-certified visual acuity tester using the Electronic ETDRS visual acuity protocol.
6. Ocular alignment at distance and near assessed with the SPCT
7. Titmus fly and Randot Preschool Stereoacuity test

3.6.4 Visit 5

All subjects will have an office visit at 26 ± 1 weeks (Visit 5) post-randomization during the Post Primary Outcome Phase.

Testing will include the following:

1. Medical history will be updated including questioning about the occurrence of adverse effects of treatment. Any concomitant medications will be recorded.
2. Completion of symptom survey by subject and parent
3. Evaluation of treatment compliance (if on treatment)
4. Visual acuity
    - Measured in each eye (right eye first) by a study-certified visual acuity tester using the Electronic ETDRS visual acuity protocol.
5. Retesting of visual acuity in the amblyopic eye (if indicated)
    - If at 26 weeks (Visit 5), amblyopic eye acuity has not improved 10 or more letters from baseline then acuity will be retested.
    - The results of the re-test will be used to determine if the subject will continue into the Observational Phase off treatment with a visit at 39 ± 1 weeks.

CHAPTER 4: TREATMENT AND FOLLOW UP IN THE EXTENSION STUDIES

Study participation beyond the 26-week visit is based on whether the amblyopic eye visual acuity has improved by 10 or more letters from baseline to the 26-week visit, the treatment group assignment, and future treatment plans of the investigator for the subject.

The possibilities are:

1. Improved ≥ 10 letters and both investigator and subject are ready to stop. Enter Post 26-week Observation Extension Study (*see Section 4.1*).
2. Improved ≥ 10 letters and either investigator or subject are not ready to stop. Study participation concludes.
3. Improved < 10 letters in the levodopa group or placebo group with no plan for further therapy. Study participation concludes.
4. Improved < 10 letters in the levodopa group with a plan for further therapy. Study participation concludes.
5. Improved < 10 letters and in the placebo group and elect Levodopa. Enter optional Levodopa Treatment Extension Study for the Placebo Group (*see Section 4.2*) or study participation concludes.

4.1 Post 26-week Observation Extension Study

1. Subjects entering this Study will have visual acuity in the amblyopic eye improved 10 or more letters from baseline to 26 weeks and both the investigator and subject are ready to stop amblyopia therapy.
   a. Treatment will be discontinued and the subject will be followed off treatment in the Post 26-week Observation Extension Study, with a visit 39 weeks (± 1 week) from randomization (Visit 6).
   b. Subjects will remain masked to their treatment group assignment until the 39-week visit.
   c. After completion of this Post 26-week Extension Study subjects who were in the placebo treatment group may elect to begin levodopa and enter the Levodopa Extension Study for the Placebo Group (*see Section 4.2*).

4.2 Levodopa Treatment Extension Study for the Placebo Group

Subjects in the placebo group may enter the extension study. If the subjects move to this phase they are started on levodopa at either the 26-week visit (*see #5 above*) or, if the subject completed the Post 26-week Observation Extension Study (*see Section 4.1, #1a*), at the 39-week visit.

Subjects will be treated with 16 weeks of levodopa as described for the randomized trial.

Phone contacts and follow-up visits in the extension study are timed from the last visit.

- Phone Call 1E: 2 weeks (± 3 days)
- Office Visit 1E: 4 weeks (± 1 week)

- Phone Call 2E: 7 weeks (± 1 week)
- Office Visit 2E: 10 weeks (± 1 week)
- Phone Call 3E: 13 weeks (± 1 week)
- Office Visit 3E: 16 weeks (± 1 week)
- Office Visit 4E : 18 weeks (± 1 week) following taper of study medicine beginning at week 16

Testing and study procedures for the extension study phone calls and visits are the same as described for the randomized trial; except that re-testing of visual acuity is not required by protocol.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Management of Optical Correction

A refraction should be performed at any time the investigator suspects that refractive error may not be optimally corrected. A change in spectacle correction is at investigator discretion, the cost of which will not be paid for by the study.

5.2 Management of Strabismus

Strabismus surgery should not be done before completion of the 26-week visit (Visit 5). If performed, surgery will be recorded in the comment section of the Follow-up Examination Form.

5.3 Worsening of Visual Acuity

If visual acuity should worsen in the amblyopic eye (or in the fellow 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. Subjects 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.

5.4 Subject Withdrawals

A parent or guardian may withdraw a subject from the trial at any time. If the parent or guardian indicates that they want to withdraw the child from the study, the investigator should attempt to speak with them to determine the reason.

The investigator can withdraw the subject if he/she believes that continued participation in the study would be harmful to the subject.

5.5 Subject Payments

The parent/guardian of each subject will be compensated $30 per visit for completion of each office visit up to a maximum of $300 (10 visits). If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $30 and the subject will be unable to complete the visit without the reimbursement of the travel expenses. All payments will be made by the Jaeb Center by the end of the month following the date of each completed visit.

5.6 Study Costs

The following will be provided by the study at no charge:

- Patches.
- Custom compounded oral levodopa/carbidopa or placebo capsules.
- Additional carbidopa if needed

The study will cover the costs of up to 10 office visits. Any visits that are part of routine care will be the subject's or his/her insurance company's responsibility.

5.7 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 subjects.

5.8 Maintaining Subject Follow-up

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent/guardian's contact information. Permission for contacts will be included in the Informed Consent Form. The principal purpose of these contacts will be to help coordinate scheduling of the follow-up examinations.

A prescription for oral medication will be sent to a central compounding pharmacy, Professional Arts Pharmacy. The pharmacy will mail the oral medication directly to the subject. In order to mail the prescription, the subject's name, weight, address, phone number, and study identification number will be given to the pharmacist who is compounding the study medication.

CHAPTER 6: ADVERSE EVENTS

6.1 Definition

An adverse event is any untoward medical occurrence in a study subject, irrespective of whether or not the event is considered to be related to treatment.

6.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the subject at each visit and complete an adverse event form if necessary. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the treatment.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the subject's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

6.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity (e.g., sight threatening)

Unexpected adverse events are those that are not identified in nature, severity, or frequency in the package insert for levodopa.[6]

Serious or unexpected, related adverse events must be reported to the Coordinating Center immediately via completion of the adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related and unexpected. Notification will be made within 7 days after the Coordinating Center becomes aware of the event.

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

6.4 Data and Safety Monitoring Committee Review of Adverse Events

A Data and Safety Monitoring Committee (DSMC) will approve the protocol, template informed consent form, and substantive amendments and provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the Data and Safety Monitoring Committee (DSMC). Following each DSMC data review, a summary will be provided to IRBs.

The DSMC Chair will be notified within 24 hours of the coordinating center being notified of a treatment-related serious adverse event.

6.5 Risks

6.5.1 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 subject may receive cycloplegic/dilating eye drops.

6.5.2 Side Effects of Treatment

6.5.2.1 Study Medicine

Short courses with a dose of 0.51 mg/kg/tid of levodopa-carbidopa (4:1 formulation) have been used in the treatment of amblyopia without significant problems (*see Chapter 1 and Appendix 1*). Levodopa-carbidopa has been associated with body hypothermia when administered at doses of levodopa 1.02 mg/kg/tid, but not at the lower doses being used for this study. Some children when treated with levodopa for amblyopia have reported headache, emesis, nausea, dry mouth, and fatigue.[9, 13] Nausea has been lessened by taking the medication with meals, building the dosage up gradually over several days to allow carbidopa levels to reach steady state and administering the lower doses of levodopa. Each of these approaches is being used in this study design. In a pilot study we found that all 33 subjects completed their treatment course of levodopa and the medication was well tolerated. Headaches were reported by 6 subjects and nausea by 2 subjects.[30]

Dyskinesias have been found with long-term treatment using levodopa-carbidopa for Parkinson's disease, but not reported with short-term use for amblyopia. Parents will be surveyed at every contact for the onset of dyskinesias. Should those occur the study medication will be discontinued.

6.5.2.2 Patching

Patching potentially could decrease the visual acuity in the fellow eye, although this is almost always reversible. Reverse amblyopia is unheard of with 2 hours of daily patching in this age group. The diagnosis and management of reverse amblyopia at each of the study visits is left to the investigator's judgment.

If skin irritation occurs, the parent will be advised to put an emollient on the skin and discontinue use of the patch for a day. If a skin reaction to the patch or an allergic reaction occurs serious enough to discontinue patching prior to the primary outcome visit (Visit 4), the investigator will call the Protocol Chair to discuss the case. An alternative adhesive patch may be tried. If patching with adhesive patches is discontinued, then the subject should try a Patch Works occluder on glasses (using plano lenses if the subject is not wearing spectacles).

Patching could precipitate the development of a new manifest ocular deviation. If treatment precipitates the development of strabismus (e.g., esotropia) the parent(s) will be advised to have the subject see the investigator as soon as possible. If the development of a new manifest deviation is confirmed on examination, the decision as to whether to continue or discontinue therapy will be left to the investigator.

If amblyopia treatment is to be discontinued prior to the primary outcome exam, then the Protocol Chair should be called to discuss the situation. The development of a new heterotropia is an accepted risk of standard-care amblyopia therapy. However, previous studies suggest that the resolution of pre-existing strabismus during amblyopia treatment occurs as often as the development of new strabismus. In ATS1, new strabismus occurred in 13% of patching subjects. Twenty-one percent of subjects had resolution of their preexisting strabismus with treatment.[31] In ATS3 there was no increase in the proportion of subjects with strabismus with patching for teens 13 to <18 years, and with patching plus atropine for children 7 to <13 years.[1] In ATS9 there was no increase in the proportion of subjects with strabismus following 2 hours daily patching.[2] The risk of strabismus in this study is no greater than it would be with standard care of amblyopia.

In view of the short duration of the treatment phases of the study and the eligibility criterion that strabismus surgery is not planned within 26 weeks of enrollment, it is unlikely that strabismus surgery will need to be performed prior to the end of the study.

6.5.3 Risk Assessment

It is the investigators opinion that this protocol falls under DHHS 46.405, which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with amblyopia.

CHAPTER 7: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The approach to sample size and statistical analyses are summarized below. The analysis plan synopsis in this chapter contains the framework of the final analysis plan.

7.1 Sample Size Estimation

The primary analysis will be a treatment group comparison of mean visual acuity letter scores obtained at the 18 week primary outcome exam (Visit 4) adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model.

7.1.1 Patching Plus Placebo Group Projection

Outcome for the control group can be estimated using amblyopic eye visual acuity data from previous studies.[2, 32]

- In 23 ATS9 subjects 7 to <13 randomized to patching with no improvement from baseline after 5 weeks, the mean (SD) change between 5 and 17 weeks was 3.8 (7.5) letters; 2 (9%) improved 10 or more letters
- In 60 ATS6 subjects 3 to <7 treated with patching with no improvement from baseline after 5 or 8 weeks, the mean (SD) change between 8 and 17 weeks was 3.5 (7.0) letters; 13 (22%) improved 10 or more letters.

As the current study is evaluating continued patching treatment for residual amblyopia after patching treatment has been deemed to have stopped working, we estimate that the average improvement in the patching plus placebo group may be less than that observed in the prior ATS6 and ATS9 studies. In the current study, we estimate a mean (SD) improvement of 2.0 (7.0) letters in the control group treated with patching and placebo; and estimate that 10% may improve 10 or more letters.

7.1.2 Levodopa Plus Patching Group Projection

After enrollment into the ATS14 pilot study,[30] 33 subjects were seen again after 9 weeks of treatment with levodopa and patching. The mean (SD) change in visual acuity while on levodopa and patching was 4.9 (4.8) letters (95% confidence interval for change=2.7 to 7.3 letters); and 7 (21%) improved 10 or more letters (95% confidence interval for proportion=4% to 55%).

7.2 Sample Size Selection

Sample size estimates in Table 1 were based upon estimating the amount of change from baseline to the primary outcome exam in amblyopic eye visual acuity. To collect more safety data from subjects taking levodopa, sample size was estimated based upon a 2:1 allocation (2 subjects will be randomized to the levodopa plus patching group for every 1 subject randomized to the patching plus placebo group).

Table 1: Sample Size Estimates for Various Treatment Group Differences*

Cells reflect total sample size needed assuming a 2:1 randomization.
(Numbers in parenthesis reflect number needed in each group levodopa:placebo)

Standard Deviation Mean Change from Baseline to Outcome (Visit 4) in Letters	**True Treatment Group Difference (in letters) Mean Change from Baseline to Outcome**		
	3 letters	**4 letters**	**5 letters**
3.9 letters Lower 95% CI from ATS14 Pilot	69 (46:23)	39 (26:13)	27 (18:9)
4.8 letters Observed from ATS14 Pilot	102 (68:34)	57 (38:19)	39 (26:13)
6.3 letters Upper 95% CI from ATS14 Pilot	174 (116:58)	99 (66:33)	63 (42:21)
7.0 letters Estimate from ATS6/ATS9	213 (142:71)	120 (80:40)	78 (52:26)

*Sample sizes based on a t-test to evaluate a difference between treatment groups in mean change from baseline at primary outcome, with 1-sided alpha=0.05 prior to adjustment for interim analysis, and power=90%.

Based upon data from previous studies, we assumed a standard deviation for the amount of change from baseline to outcome of 7.0 letters. After discussion with clinicians, a mean difference of 5 letters (one logMAR line) between the levodopa plus patching group and the patching plus placebo group in the amount of change from baseline to primary outcome in amblyopic eye visual acuity is considered clinically meaningful.

If the true difference between treatment groups in the mean change from baseline to outcome is 5 or more letters (favoring levodopa), a sample size of 78 subjects (52 in the levodopa plus patching group and 26 in the patching plus placebo group) will provide at least 90% power to reject the null hypothesis that the mean change in visual acuity from baseline to outcome is the same in both treatment groups (in favor of the alternative that the mean change is higher in the levodopa plus patching group), assuming a standard deviation of 7 letters and one-sided alpha=0.05 (prior to adjustment for interim analysis).

In order to better evaluate the safety of levodopa by having more subjects on study medicine, and to have sufficient power for binary outcomes, we have selected a larger sample size of 129 subjects (86 in the levodopa plus patching group and 43 in the patching plus placebo group). A sample of 129 will provide 80% power to reject the null hypothesis of no difference between groups in a comparison of binary outcomes if the true difference between groups is 20% in favor of the levodopa plus patching group (30% in the levodopa plus patching group compared to 10% in the patching plus placebo group).

With this effective sample size of 129, statistical power will be 98% for the primary analysis comparing the mean change in visual acuity between groups. The actual power will be somewhat lower than 98% after adjustment for interim monitoring (*Section 7.3.2*), but will not be lower than 90%. The type I error rate for the final analysis also will be adjusted to account for interim monitoring (*Section 7.3.2*), with the overall type I error rate maintained at no higher than 5%.

Assuming 5% of randomized subjects may be lost to follow-up before completion of the primary outcome exam, the final sample size was raised to 138 subjects (92 in the levodopa plus patching group and 46 in the patching plus placebo group).

As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomized subjects will be 150.

7.2.1 Power for Analysis of Adverse Effects

Treatment groups will be compared with respect to the proportion of subjects experiencing adverse effects. With a final sample of 129 subjects completing the primary outcome (86 subjects in the levodopa plus patching group and 43 subjects in patching plus placebo group), for a true control group event rate of 10%, statistical power will be 80% to reject a null hypothesis of no difference in the proportion of subjects experiencing a specific adverse event if the true levodopa group rate is 30% or greater (with a one-sided alpha =0.05). For a control group rate of 5%, there will be 80% power to detect a difference if the true levodopa group rate is 24%.

For rarer side effects, Table 2 below specifies the chance of observing at least 1 adverse event in the levodopa group for various event rates in the population; Table 3 specifies the upper limit of the 95% confidence interval for the true proportion given observed adverse event proportions in the study of 1-5%.

Table 2: Chance of Observing at Least One Event in the Levodopa plus Patching Group

Actual Probability of an Event	Chance of observing at least one event in the study
	Number of Subjects in Levodopa Plus Patching Group N=86
1%	58%
2%	82%
3%	93%
4%	97%
5%	99%

Table 3: Width of 95% Confidence Interval for Observed Adverse Event Proportions in the Levodopa plus Patching Group

Observed Proportion	Upper Limit of 95% Confidence Interval
	Number of Subjects in Levodopa Plus Patching Group N=86
1%	6%
2%	8%
3%	10%
5%	11%

Hence, with the proposed sample size of 86 subjects in the levodopa plus patching group, the study has a high probability (>90%) for observing at least one event for adverse events with 3% or higher occurrence in the levodopa plus patching group, with expected precision of no worse than +7% for rare events.

7.3 Efficacy Analysis Plan

The primary analysis will be a treatment group comparison of mean visual acuity letter scores obtained at the 18 week primary outcome exam (Visit 4) adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model.

7.3.1 Principles to be Followed in Primary Analysis

The primary analysis will follow the "intent-to-treat" principle. The data of all randomized patients completing the visit will be included in the analysis regardless of whether the assigned treatment was actually received. Data from patients who receive alternative treatment or are non-compliant with treatment will be analyzed according to randomization group.

Multiple imputation using the Markov chain Monte Carlo method[33] will be used to impute the visual acuity outcomes that are missing. The primary analysis will be repeated including data from subjects who complete the exam with no imputation. The results will be compared with those using imputation to verify that conclusions are not sensitive to the method for handling missing data.

7.3.2 Interim Analysis

The current plan is to conduct one interim analysis when primary outcome data are available for 50% of the subjects, and a final analysis when primary outcome data are available for all subjects (assuming no early stopping of the trial). At the designated analysis times, an analysis of the primary outcome data will be conducted as described above.

The primary analysis for this protocol consists of a treatment group comparison of mean visual acuity at 18 weeks adjusted for baseline visual acuity in an analysis of covariance. Results will be compared against the stopping guidelines in Table 4 below.

Table 4. Stopping Guidelines for Interim Analysis of Primary Outcome Data

Analysis	% of planned sample size with 1° outcome data	Efficacy Threshold	Futility Threshold
1	50%	$Z \geq 2.54$ ($p<0.0055$)	$CP_{trend} \leq 0.30$
2 (final)	100%	$Z \geq 1.66$ ($p<0.0485$)	--

CP=conditional power

The efficacy thresholds correspond to those defined by the O'Brien-Fleming test.[34] The futility threshold consists of a conditional power calculation at the interim monitoring time under the assumption that the future data conform to the current observed trend.
The conditional power projects the power of the final analysis to detect a difference in favor of levodopa given the data collected as of the time of interim analysis and the assumption regarding the future data yet to be collected.

Under this plan, consideration will be given to stopping the study for futility if the conditional power for detecting a difference between treatments is 30% or less at the interim analysis, given the data at the time of analysis and assuming that future data conform to the current trend. Consideration will be given to stopping for efficacy if the p-value at the interim analysis is 0.0055 or less favoring levodopa. This corresponds to an approximate observed treatment effect at the interim analysis of a 4.7 letters or greater difference between the 2 treatment groups in mean change in visual acuity from baseline to the primary outcome exam. The observed treatment effect required for early stopping is less than the designed treatment effect because the study sample size was chosen based on a binary outcome and hence the study is 'overpowered' for the primary continuous outcome. If the designed treatment effect of 5 letters truly exists, the study has a 56% chance of crossing the efficacy threshold at the 1st analysis. If there is no difference between treatments, the chance of a type I error, i.e., crossing the efficacy threshold, is 0.55% at the first analysis and 3.37% at the final analysis (conditional on not stopping at the interim analysis) for a total overall type I error of 3.92%.

With the proposed futility stopping guideline, the futility threshold has 82% chance of being crossed at the first analysis if there is no difference between treatments. The chance of a type II error, i.e., crossing the futility threshold when a 5 letter treatment effect actually exists is 3.6%. The overall power of the study for the primary analysis accounting for the interim monitoring is 95.6%.

7.3.3 Secondary Efficacy Analyses

Secondary analyses will include treatment group comparisons adjusted for baseline acuity scores using logistic regression of (1) the proportion of subjects who have improved from baseline by 10 or more letters at the primary outcome exam, and (2) the proportion of subjects with 20/25 or better visual acuity.

Both the primary and secondary efficacy analyses will be conducted at the other time points (4, 10, 16, and 26 weeks) and will mirror the analyses of visual acuity at the primary outcome visit.

7.3.4 Treatment Effect in Subgroups/Assessment of Interaction

The treatment effect at the primary outcome visit (Visit 4) in subgroups based on baseline factors will be assessed in pre-planned secondary analyses. These analyses will be conducted to determine whether a similar trend of the overall treatment effect is seen in these subgroups. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction.

There are no data to suggest that the treatment effect will vary by gender or race/ethnicity. However, in accordance with NIH guidelines, a subgroup analysis of treatment effect according to gender, as well as race/ethnicity, will be conducted.

The general approach for these exploratory analyses will be to perform analyses within each subgroup similar to the methods described earlier for the overall primary and secondary efficacy analyses.

The planned subgroups for analyses are as follows:

- Visual acuity at time of randomization (20/50 to 20/80 vs. 20/100 to 20/400)
    - Letter score 53 to 67 letters vs. 18 to 52 letters
- Gender (male vs. female)
- Race/Ethnicity ('white non-Hispanic' vs. 'non-white or Hispanic')
- Age at randomization (7 to 9 years old vs. 10 to 12 years old)

7.3.5 Recidivism of Amblyopia

To evaluate recidivism of amblyopia, subjects who improve 10 or more letters from baseline at the 26-week visit and who are ready to stop treatment, will continue off treatment and have a final follow-up visit at 39 weeks. The visual acuity scores at 39 weeks will be compared with the scores at 26 weeks.

An estimate and 95% confidence interval by treatment group for the proportion of subjects with a recurrence of amblyopia at 39 weeks (defined as a worsening of 10 or more letters from the end of treatment 26 weeks confirmed by a retest) will be calculated using the exact binomial method. The number of subjects expected to be available for this analysis is small. No between treatment group comparison will be made. The ability to monitor both groups for recurrence or additional side effects warrants this short 13 week extension to allow for a more complete characterization of the treatment benefit.

7.3.6 Additional Tabulations and Analyses

The following will be tabulated according to treatment group unless otherwise stated:

1) Baseline demographic and clinical characteristics
2) Evaluate baseline visual acuity data for completers vs. non-completers of the primary outcome visit
3) Compliance with study drug as evidenced by pill counts and investigator impression over follow-up visits; compliance with patching as evidenced by investigator impression over follow-up visits.
4) Protocol deviations

A flow chart will be constructed that accounts for all subjects. Visit completion rates will be tabulated according to treatment group for each visit. The percentage of subjects with visits completed in window, out of window, and missed for each visit will be tabulated.

7.4 Safety Analysis Plan

7.4.1 Adverse Events

Adverse events will be coded using the MedRA system. They will be tabulated by treatment group.

An estimate and 95% confidence interval by treatment group of the following proportions will be obtained using the exact binomial method and a Fisher's exact test will be used to evaluate whether there is a treatment group difference in the proportion of subjects with events, although the power for some of the comparisons is expected to be low.

- Proportion reporting at least one event
- Proportion with an adverse event thought by investigator to be related to study drug
- Proportion who stopped study drug in response to an adverse event

The mean, standard deviation, and median for the following will be tabulated by treatment group and an exact Wilcoxon-Rank-Sum Test will be used to evaluate whether there is a difference between groups.

- Total number of events reported
- Total number of new events reported
- Number of serious events reported
- Number of non-serious adverse events reported

7.4.2 Fellow Eye Visual Acuity

Levodopa is not expected to have a negative effect on visual acuity in the fellow eye. Both groups will be prescribed 2 hours per day of patching. Two hours per day of patching has not been associated with a negative effect on fellow eye visual acuity in any previous PEDIG study.[1, 2, 32, 35-40] Nonetheless, the distribution of the amount of change in visual acuity from baseline to the primary outcome exam (Visit 4) will be evaluated. An analysis of covariance (ANCOVA) will evaluate whether or not there is a treatment group difference in fellow eye acuity similar to the analysis done for the amblyopic eye.

7.4.3 Ocular Alignment and Stereoacuity

Development of new strabismus (no tropia at baseline and the presence of near and/or distance tropia at follow-up) or an increase from baseline ≥10 pd at the primary outcome visit will be tabulated by treatment group. Similarly, disappearance of a heterotropia and a decrease in the angle of a preexisting strabismus by ≥10 pd will be tabulated.

Differences between treatment groups in stereoacuity and change in stereoacuity from baseline at the primary off-treatment outcome (Visit 4) will be assessed using a comparison of the distributions with the exact Wilcoxon-Rank-Sum test.

7.4.4 Analyses of Symptom Survey Data

Responses to the symptom survey will be obtained from both the child and parent at enrollment, and at the 4, 10, 16, and 26-week follow-up visits. A secondary analysis will be a treatment group comparison of symptom scores obtained on the survey at each visit. Separate analyses will be conducted for both the child and parent scores from each follow-up visit. The average of the overall item responses will be calculated and compared by treatment group with a t-test for difference in means.

7.5 Analyses of Data from Levodopa Treatment Extension Study for Placebo Group

7.5.1 Tabulations and Analyses

The following will be calculated for subjects in the placebo group who elect to start levodopa treatment after the 26-week or 39-week visit:

1) Adverse events reported while on levodopa treatment will be tabulated as described in the randomized trial (*see Section 7.4.1*).
2) The mean and 95% confidence interval will be calculated for the amount of change in amblyopic eye visual acuity at each visit while on levodopa treatment (baseline is the visit at which levodopa started).
3) Adverse events reported among placebo group patients who choose to initiate levodopa treatment at the end of the study will be tabulated.

CHAPTER 8: APPENDIX 1—SIDE EFFECTS SUMMARY LEVODOPA FOR AMBLYOPIA

Author / Year	Treatment Duration	Age	Number of amblyopic subjects	Levodopa Dosage	Side effects: Emesis	Nausea	Head-ache	Fatigue	Mood changes	Dizzi-ness	Dry mouth	Night-mares	Decreased appetite	Systemic changes	Other
Leguire 1992[12]	1 day	7-12 years	5	100 to 400 mg	3	3		1							
Leguire 1993[14]	3 weeks	6-14 yrs	10	mean 10 mg tid		0		1		1				none	elevated bilirubin - felt unrelated
Leguire 1995[9]	7 weeks	7-14 yrs	15	0.55 mg/kg tid	3	9	9	5	8	4	4				no abnormalities
Leguire 1996[27]	7 weeks	6-14 yrs	15 13	0.55 mg/kg tid 1.02 mg/kg tid										no change in body temperature slight reduction in body temperature	
Leguire 2002[3]	7 weeks	6 -14 yrs (previously published)	22	0.55 mg/kg tid											
Leguire Unpub	7 weeks	4.7-14.2 yrs	23 24	0.55 mg/kg tid 1.02 mg/kg tid 0.25 mg/kg increasing to 0.75 mg/kg tid											no changes in blood tests from baseline to 7 weeks in any of the groups
Gottlob 1995[4]	3 weeks	>16 yrs	14	2 mg/kg tid and 3 mg/kg tid	1	3		1							
Mohan 2001[17]	7 weeks	4-22 yrs	72	0.50 mg/kg tid	0	0	0	0	0	0	0			none	
Wu 1998[15]	3 months	4.5-14 yrs	36	1.5 mg/kg daily divided doses	5			1	1				1		all side-effects said to be mild.
Basmak 1999[5]	1 week	4-17 yrs	18	2 mg/kg tid	Did not measure or report (reviewed by German speaker)										
Procianoy 1999[16]	1 week	7-17 yrs	62	0.51, 1.05, and 2.29 mg/kg divided doses per day	Questioned for side effects – None reported										
Leguire 1998[28]	7 weeks	7-12 yrs	13	1.02 mg/kg	1	2	4	2	2		0	1		none	none
Bhartiya 2002[18]	4 weeks	6-18 yrs	19	0.62 mg/kg tid		1	3	1	1						Giddiness (2), Diarrhea (1), nocturnal incontinence (1), local complaints (allergy)(3)
Dadeya 2009[19]	3 months	3-12yrs	15	0.50 mg/kg tid		1									
PEDIG ATS14 Pilot Study[30]	9 weeks	8-17 yrs	33	0.51 mg/kg tid 0.76 mg/kg tid	2		12	3		2		1	1		Cold/URI/Cough/Flu (11), Rash (4), conjunctivitis (1), muscle pain (2), stomach ache (2), ear ache (1), fever (1), knee injury (1), sinus infection (1), weight loss (1), constipation (1), finger injury (1), pulled muscle (1)

Blank cells – side-effect not reported by authors

CHAPTER 9: REFERENCES

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