AMBLYOPIA TREATMENT STUDY

ATS14

A Pilot Study to Evaluate Levodopa as Treatment for Residual Amblyopia in 8 to 17 Year Olds

PROTOCOL

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Chapter 1: Background and Summary

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 clinical trials and observational studies that address management issues related to the treatment of amblyopia in children.

1.1 Objective

This study is a pilot study designed to evaluate two doses of levodopa as adjunctive treatment to patching for residual amblyopia (20/50 or worse) in older children and teenagers ages 8 to 17 years old. All subjects will be treated with 2 hours of daily patching plus oral administration of a combination of levodopa and carbidopa for about 8 weeks. Subjects will be randomized to receive either 0.51 mg/kg/tid levodopa with 0.17 mg/kg/tid carbidopa or 0.76 mg/kg/tid levodopa with 0.17 mg/kg/tid carbidopa.

The objectives of the pilot study are to:

- Demonstrate recruitment potential, including the willingness of parents and subjects to participate in a levodopa study
- Collect prospective data on the tolerability of two different dosages of levodopa as a treatment for amblyopia and provide limited data on its safety
- Collect prospective data on the visual acuity response to treatment of two different dosages of levodopa to estimate the magnitude of effect that might be seen in a randomized trial (if no improvement in acuity is seen, this might be sufficient evidence to decide not to conduct a randomized trial)
- Provide the opportunity for investigators to gain experience in using levodopa prior to a randomized trial

In the future, we propose to perform a randomized clinical trial in this subject population comparing patching treatment (2 hours of daily patching) plus oral administration of levodopa-carbidopa with a control group that will be treated with patching (2 hours daily) and oral placebo. The information from this study will be evaluated to determine the feasibility of a trial as well as which dosage of levodopa to use in the future randomized trial.

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. 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 detailed below) where children 7 to 13 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]

1.3 Prior PEDIG Studies

PEDIG conducted a randomized trial of 507 subjects (age 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 sound eye combined with near visual activities for all subjects plus atropine one drop per day in the sound 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 is a recently completed 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 sound 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.

1.4 Levodopa

Many investigators 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. We are currently conducting a trial of combined daily atropine and patching 6 hours or more per day for children 3 to 9 years old with mild residual amblyopia (20/32 to 20/63). 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 effect.[6]

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]

A number of small case series 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 (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 control 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, 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 available in English (we had the 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, and the definition of cure rate is not provided.[15]

- In a double-masked, placebo-controlled randomized study, 18 amblyopic children aged 4 through 17 years were treated with levodopa of (2 mg/kg/day) 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 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 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.

- 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 sound (mean 1.0 lines) eyes which remained stable for at least four months.[19] 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).

1.5 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 Parkinson's disease may experience side effects, but these are usually reversible. Acute peripheral effects are nausea and vomiting which may be caused by direct stimulation of the chemotrigger receptor zone in the brain.[20] 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 shown 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.[21-25] 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.[23] 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.[24] 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.

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. This is reversible, treatable, and dose related.

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 administration of levodopa are minimized with the simultaneous administration of carbidopa, which allows use of lower dosages of levodopa. 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 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. 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.[26] 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.

This pilot study will evaluate two different doses of levodopa (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). Most of the literature published has used the lower dosage (Table 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.[27, 3] These were generally well tolerated. With the 3.06 mg/kg/day dose, there was a slight drop in body temperature (mean change 99.0 to 97.8 degrees) that was not symptomatic or clinically consequential.[28] Procianoy and colleagues administered average doses of 0.51, 1.05, and 2.29 mg/kg/day to three dosage groups with about 20 patients 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. The data from the current pilot study will help in our selection of the dose to be used in a future randomized clinical trial.

In this study, carbidopa will be prescribed at 0.17 mg/kg/tid for both levodopa dosages (equivalent to 1 part to 3 of levodopa for the lower levodopa dosage and about 1 part to 4.5 for the higher levodopa dosage). We acknowledge that 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 this pilot study we will monitor side effects and determine whether the 1:3 ratio or the 1:4.5 ratio of carbidopa to levodopa is sufficient or should be increased in a future randomized trial. 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.

Table 1: Side Effects Summary Levodopa for Amblyopia

					Side effects										
Author/ Year	**Treatment Duration**	**Age**	**Number of amblyopic subjects**	**Levodopa Dosage**	**Emesis**	**Nausea**	**Headache**	**Fatigue**	**Mood changes**	**Dizziness**	**Dry mouth**	**Nightmares**	**Decreased Appetite**	**Systemic Changes**	**Chemistry**
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[26]	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 per day	Questioned for side effects – None reported										
Leguire 1998[27]	7 weeks	7-12 yrs	13	1.02 mg/kg	1	2	4	2	2		0	1		none	none

Blank cells – side-effect not reported by authors,

1.6 Objectives

This pilot study is being conducted as a prelude to a randomized trial to compare levodopa/carbidopa plus patching versus patching alone. The purpose of the pilot study is to demonstrate recruitment potential, to provide prospective data on the tolerability of levodopa as a treatment for amblyopia, to provide limited data on its safety, to provide limited data on its efficacy, and to provide data to assist in selecting a dose to use in a subsequent phase 3 randomized trial. In addition, this study will provide the opportunity for investigators to gain experience in using levodopa prior to a randomized trial.

1.7 Synopsis of Study Design

Major Eligibility Criteria *(see section 2.1 for a complete listing)*

- Age 8 to < 18 years
- Amblyopia associated with strabismus, anisometropia, or both
- Visual acuity in the amblyopic eye 18 to 67 letters inclusive (20/50 to 20/400)
- Visual acuity in the sound eye ≥ 78 letters (20/25 or better)
- Current amblyopia treatment of at least 2 hours patching per day
- No improvement in best-corrected amblyopic eye visual acuity between two consecutive visits at least 4 weeks apart using the same testing method and optimal spectacle correction (if needed), with no improvement of more than 4 letters or one logMAR line.

Treatment

All subjects will have two hours of daily patching prescribed plus be randomized to one of two levodopa doses for about 8 weeks with a rapid taper prior to the primary outcome exam:

- Oral levodopa 0.51 mg/kg/tid with carbidopa 0.17 mg/kg/tid (3 to 1 formulation)
- Oral levodopa 0.76 mg/kg/tid with carbidopa 0.17 mg/kg/tid (approximately 4.5 to 1 formulation)

The subject, parents, and the site staff will be masked to treatment assignment.

Sample Size

A sample of 30 subjects will be enrolled.

Contact and Visit Schedule

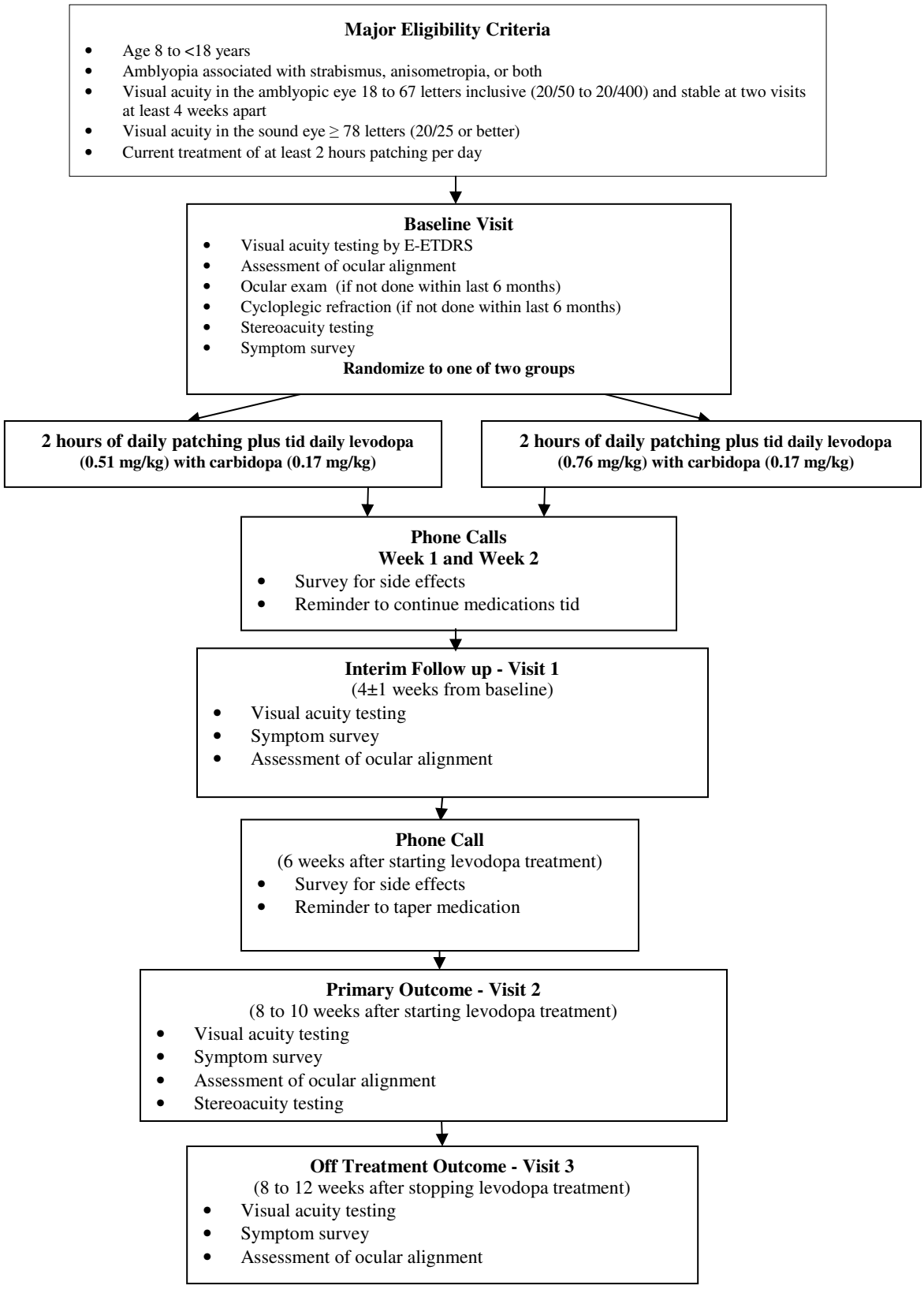
- Phone calls at 1 and 2 weeks post-enrollment
- Office visit 4 weeks post-enrollment (Visit 1)
- Phone call 6 weeks after starting levodopa treatment
- Office visit 8 to 10 weeks after starting levodopa treatment (Visit 2)
- Office visit 8 to 12 weeks after stopping levodopa treatment (Visit 3)

Analysis

The following analyses will be completed within each levodopa dosage subgroup.

- The proportion of subjects who were able to tolerate the full course of levodopa will be computed as will the proportion in whom treatment was discontinued due to side effects. All adverse effects will be tabulated.
- For each visit, the proportion of subjects with 10 or more letters improvement in amblyopic eye visual acuity will be calculated and an exact 95% confidence interval will be computed.

1.8 Study Summary Flow Chart



Chapter 2: Subject Enrollment (Baseline Visit)

2.1 Assessment and Informed Consent/Assent

A subject 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, if applicable, refractive error must be corrected with glasses (as per standard care) before a subject can be enrolled into the trial.

For subjects 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 copy of the consent form. Written informed consent will be obtained from the parent or guardian and assent from appropriately-aged subjects prior to performing any study-specific procedures that are not part of the subject's routine care. Sites will keep a log of the number of subjects who were eligible but not enrolled.

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 8 to < 18 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 on 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 sound eye ≥ 78 letters (20/25 or better)
   - No improvement in best-corrected amblyopic eye visual acuity between two consecutive visits at least 4 weeks apart using the same testing method and optimal spectacle correction (if needed), with no improvement of more than 4 letters or one logMAR line
4. Current amblyopia treatment (other than spectacles)

- At least two hours of occlusion per day prescribed for the sound eye and performed during the same period of time during which the two measurements of visual acuity at least 4 weeks apart were obtained (and visual acuity was not improved).
- Treatment with atropine during this 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 must not be undercorrected by more than 1.50 D spherical equivalent, and reduction in plus sphere from the most recent cycloplegic refraction 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 $\geq$ 1.00 D.
- Myopia of amblyopic eye greater than 0.50 D by spherical equivalent must be corrected, and the glasses must not undercorrect 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 either:

1) for 16 weeks immediately prior to enrollment, or

2) until visual acuity in amblyopic eye is stable (defined as two consecutive visual acuity measurements by the same testing method at least 4 weeks apart with no improvement of more than 4 letters or one logMAR line)

- An acuity measurement done any of the following ways may be considered the first of two consecutive measurements: 1) in current glasses, 2) in trial frames with full correction of hypermetropia with cycloplegia, or 3) by having the subject return in new glasses for first measurement. *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*

6. Ocular examination within 6 months prior to enrollment

7. Parent available for at least 4 months 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).

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. Strabismus surgery planned within 16 weeks
7. Known allergy to levodopa-carbidopa
8. History of dystonic reactions
9. Current requirement to take oral iron supplements including multivitamins containing iron during treatment with levodopa-carbidopa
10. Current use of antihypertensive, anti-depressant medications, phenothiazines, butyrophenones, risperidone and isoniazid, non-specific monoamine oxidase inhibitors
11. Current use of medication for the treatment of attention deficit hyperactivity disorder
12. Known gastrointestinal or liver disease
13. History of melanoma
14. Known psychological problems
15. Known skin reactions to patch or bandage adhesives
16. Prior levodopa treatment
17. Current treatment with topical atropine
18. Females who are pregnant, lactating, or intending to become pregnant within the next 16 weeks.
    - A negative urine pregnancy test will be required for all females who have experienced menarche.
    - Requirements regarding the establishment of pregnancy status and monitoring for pregnancy over the course of the study as defined by each individual Institutional Review Board may supersede these criteria.

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), corrected visual acuity before amblyopia treatment started (if available), current amblyopia therapy, current spectacle correction, and 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 enrollment.
   - 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
5. Complete ocular examination, including dilated fundus examination, to rule out a cause for reduced visual acuity other than amblyopia.
   - If performed within prior 6 months, the ocular 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 (or parent if subject is unable to complete) will complete a symptom survey to identify any symptoms they may be experiencing before beginning treatment. The questionnaire will be repeated at each follow-up visit.

2.3.4 Randomization

Randomization of Eligible Patients

1. 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. A subject should not be randomized until both the investigator and parent are ready to start protocol-mandated treatment.
3. The Jaeb Center will construct a Master Randomization List using a permuted block design stratified 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 treatment group assignments. 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.

Delay in Randomization

1. Visual acuity 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 these tests 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

3.1 Treatment

Subjects will be prescribed two hours of daily patching plus be randomized to one of two levodopa doses:

- Oral levodopa 0.51 mg/kg/tid with carbidopa 0.17 mg/kg/tid (3 to 1 formulation)
- Oral levodopa 0.76 mg/kg/tid with carbidopa 0.17 mg/kg/tid (approximately 4.5 to 1 formulation)

All subjects will build up to this daily dose over one week with a rapid taper of medication before a primary outcome visit 8 to 10 weeks after starting levodopa/carbidopa treatment. Subjects will continue with the prescribed 2 hours daily patching between the primary outcome visit #2 and the off-treatment visit #3, 8 to 12 weeks after stopping levodopa/carbidopa treatment.

Notes

1. The study will provide patches.
2. A central pharmacy will compound levodopa-carbidopa capsules based upon body weight and ship the study drug to the subject.
3. During the initiation of levodopa-carbidopa therapy, the drugs will be given once daily for three days, twice daily for three days, and three times daily on day 7 of week 1. The drugs will be administered three times daily up until one week prior to the primary outcome visit 8 to 10 weeks after starting treatment.
4. One week prior to the primary outcome visit, the subject will take the drug twice daily for two days, once daily for two days, and then off for three days.
5. Study medications should be administered with meals. 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.
6. 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.
7. If a subject is noncompliant with treatment, the parents should be encouraged to persist with their efforts to treat to the best of their ability.
8. Prior to deviating from the treatment protocols or prescribing non-protocol treatment, the situation should be discussed with the Protocol Chair.
9. In the case of pregnancy during this study, the levodopa-carbidopa medicine will be discontinued.

3.2 Compliance

A calendar log will be maintained by all subjects on the daily completion of the prescribed patching treatment and consumption of the oral medication. These logs will be reviewed by the investigator at each of the protocol visits. The investigator's assessment of compliance will be

recorded on the Follow-up Examination Form. In addition, compliance will be queried during the phone calls at weeks 1, 2, and 6.

Medication containers will be brought to the 4-week and primary outcome visits. The amount of remaining medication will be recorded.

3.3 Adverse Events

Reporting of adverse events is described in Chapter 6.

3.4 Dose Changes

A pediatric neurologist with experience using levodopa-carbidopa in children will serve as consultant expert for the investigators and protocol chairman for review of side-effects and provide consultations for dosage adjustments.

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 medical monitor to determine if the drug should be discontinued.

Chapter 4: Follow Up

4.1 Follow-up Examinations

The subject will have the following study visits / interactions:

- Phone calls at 1 and 2 weeks post-enrollment
- Office visit 4 weeks post-enrollment (Visit 1)
- Phone call 6 weeks after starting levodopa treatment
- Office visit 8 to 10 weeks after starting levodopa treatment (Visit 2)
- Office visit 8 to 12 weeks after stopping levodopa treatment (Visit 3)

	Visit / Interaction						
Test	*Baseline*	*1 week call*	*2 week call*	*4 week visit*	*6 week call*	*Primary Outcome Visit*	*Off-Treatment Visit*
Telephone call		X	X		X		
Distance acuity each eye*	X			X		X	X
Ocular alignment	X			X		X	X
Titmus Fly	X					X	
Randot Preschool Test	X					X	
Symptom survey	X			X		X	X

*Using Electronic ETDRS acuity testing protocol.

Additional visits are performed at the discretion of the investigator. A form should be completed on the study website for every exam (not just the minimum required exams).

4.1.1 Post-enrollment Telephone Calls

Each subject will be contacted by their physician's office via telephone 1 and 2-weeks post-enrollment and again at 6-weeks after starting levodopa treatment. 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. At the 6-week phone call, parents will be reminded to bring their study medication containers to the primary outcome visit and to taper medication the week before the primary outcome (the subject will take the drug twice daily for two days, once daily for two days and then off for three days).

4.1.2 Four-week Visit (Visit 1)

A follow-up visit will occur 4 weeks ($\pm$1 week) following enrollment.

Testing will include the following:

1. Questioning about the occurrence of adverse effects of treatment
2. Completion of symptom survey
3. Evaluation of medication compliance
4. Visual acuity
   - Measured in each eye (right eye first) by a certified examiner using the Electronic ETDRS visual acuity protocol on a study certified visual acuity tester.
5. Ocular alignment at distance and near assessed with the SPCT

4.1.3 Primary Outcome Visit (Visit 2)

A primary outcome visit will occur 8 to 10 weeks after starting levodopa treatment, 1 week after beginning the prescribed taper of oral therapy.

Examination procedures will include the following:

1. Questioning about the occurrence of adverse effects
2. Completion of symptom survey
3. Evaluation of medication compliance
4. Visual acuity
    - Measured in each eye (right eye first) by a certified examiner using the Electronic ETDRS visual acuity protocol on a study certified visual acuity tester.
5. Titmus fly and Randot Preschool Stereoacuity test
6. Ocular alignment at distance and near assessed with the SPCT

4.1.4 Off Treatment Visit (Visit 3)

A follow-up visit will occur 8 to 12 weeks after stopping levodopa treatment.

Two-hours of prescribed patching should be continued between the primary outcome and off treatment visit. If the visual acuity in the sound eye is reduced by 10 or more letters from baseline at Visit #2, patching can be discontinued.

Examination procedures will include the following:

1. Questioning about the occurrence of adverse effects
2. Completion of symptom survey
3. Visual acuity
    - Measured in each eye (right eye first) by a certified examiner using the Electronic ETDRS visual acuity protocol on a study certified visual acuity tester.
4. Ocular alignment at distance and near assessed with the SPCT

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 during the study. If performed, surgery will be recorded in the comment section of the Follow-up Examination Form.

5.3 Worsening of Visual Acuity in the Amblyopic Eye

If visual acuity should worsen in the amblyopic eye (or in the sound eye and does not recover with cessation or reversal of treatment), the investigator should evaluate this condition using best clinical judgment and perform whatever work-up is clinically indicated to assess for an alternate cause (i.e., other than amblyopia) for the visual loss. 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 the three office 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 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.

5.7 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.

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 treatment-related.

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 (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). Data will be reviewed with the DSMC when 50% of subjects complete the study. Following each DSMC data review, a summary will be provided to IRBs. A list of specific adverse events to be reported to the DSMC expeditiously will be compiled and included as part of the DSMC Standard Operating Procedures document.

The DSMC Chair will be notified within 24 hours of the coordinating center being notified of a 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

1. Patching potentially could decrease the visual acuity in the sound eye, although this is almost always reversible. The diagnosis and management of reverse amblyopia is left to the investigator's judgment- see section 6.5.3.

2. 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 2), 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).

3. Patching could precipitate the development of an ocular deviation. See Section 6.5.4.

4. Short courses of 7 to 12 weeks 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). 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.

5. 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 they occur, the study medications will be discontinued.

6.5.3 Reverse Amblyopia

Patching could decrease the visual acuity in the sound 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.

6.5.4 Development of Strabismus

The study treatment could precipitate the development of a new manifest ocular deviation. If treatment precipitates the development of an ocular deviation (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 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.[29] 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 in the 16 weeks following enrollment, it is unlikely that strabismus surgery will need to be performed prior to the end of the study.

6.6 Risk Assessment

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: Statistical Considerations

7.1 Sample Size and Analysis

This pilot study is being conducted as a prelude to conducting a randomized trial. The purpose of the pilot study is to evaluate two different dosages of levodopa and provide prospective data on the tolerability of levodopa as a treatment for amblyopia and to provide limited data on its safety. In addition, this study will address whether oral levodopa with patching improves the visual acuity of subjects with residual amblyopia.

Approximately 30 subjects will be enrolled by participating sites (each site will enroll no more than 5 subjects). Recruitment will continue until a fixed date. If a subject signs informed consent they will be allowed to enroll into the study. Subjects will be randomized to one of two levodopa dosage subgroups (0.51 mg/kg versus 0.76 mg/kg) in a 1 to 1 ratio.

Tabulations and computations will be done within the two dosage subgroups and will include the following:

- Proportion of subjects completing the treatment course and proportion discontinuing treatment due to side effects, with 95% confidence intervals.
- Listing of all reported adverse events.
- For each visit, proportion of subjects with improvement in amblyopic eye visual acuity of 10 or more letters, with 95% confidence interval; to be used to estimate magnitude of treatment effect for a subsequent RCT. Subjects who drop from the study will be considered to have not improved.
- The number of subjects per site enrolled will be calculated to estimate recruitment potential for a subsequent randomized trial.
- The proportion of eligible subjects enrolled will be calculated to estimate recruitment potential and the willingness of parents and subjects to participate.

7.2 Decision to Proceed to Randomized Trial

The data collected in this pilot study will be used to determine whether to proceed to a randomized trial. Data from the pilot study will also be used to make a decision on a dosage to use for a future randomized clinical trial. Given the small numbers of subjects in this pilot no formal statistical comparisons between the two dosage subgroups are planned, rather a qualitative assessment of the data including visual acuity and side effects will be used.

7.2.1 Recruitment Potential

The average number of subjects per site per month will be calculated and used to estimate the recruitment potential in a subsequent randomized trial with 30 sites recruiting for a period of two years. When estimating the recruitment potential, the average will be adjusted to account for the likelihood that fewer subjects would participate and accept randomization in a subsequent RCT.

7.2.2 Pilot Study Outcomes

Table 7-1 below provides a priori decision rules to evaluate tolerability and potential efficacy of levodopa treatment. Point estimates and 95% confidence intervals will be calculated for the proportion events described below within each levodopa dosage subgroup.

Table 7-1: Pilot Study Decision Table for Proceeding to RCT

Event	**Proceed to RCT**	**Uncertain**	**Don't Proceed**
Proportion of subjects completing treatment course *(# completing primary outcome/# enrolled)*	If lower 95% CI >= 60%	If lower 95% CI between 30 and 60%	If lower 95% CI <30%
Proportion of subjects stopping treatment due to side effects *(# stopping tmt /# enrolled)*	If upper 95% CI <40%	If upper 95% CI between 40 and 60%	If upper 95% CI >60%
Proportion of subjects improving 10 or more letters at primary outcome exam *(#≥10 letters improved /# enrolled)*	If upper 95% CI >=50%	If upper 95% CI between 20 and 50%	If upper 95% CI <20%

Decision Tables for Each Outcome

Table 7-2: Observed proportion of subjects completing treatment course of levodopa:

- Proceed if lower 95% CI >=60%
- Uncertain if lower 95% CI between 30 and 60%
- Don't Proceed if lower 95% CI <30%

Number of Subjects Completing Treatment Course	Proportion Subjects Completing Treatment Course	95% Confidence Interval		Decision
1	7%	0	19%	Don't Proceed
2	13%	0	35%	Don't Proceed
3	20%	0	40%	Don't Proceed
4	27%	4%	50%	Don't Proceed
5	33%	10%	57%	Don't Proceed
6	40%	15%	65%	Don't Proceed
7	47%	21%	72%	Don't Proceed
8	53%	28%	78%	Don't Proceed
9	60%	45%	85%	Uncertain
10	67%	43%	90%	Uncertain
11	73%	51%	95%	Uncertain
12	80%	60%	100%	Proceed
13	87%	70%	100%	Proceed
14	93%	80%	100%	Proceed
15	100%			Proceed

Table 7-3: Observed proportion of subjects stopping treatment due to side effects:

- Proceed if upper 95% CI <40%
- Uncertain if upper 95% CI between 40 and 60%
- Don't Proceed if upper 95% CI >60%

Number of Subjects Stopping Treatment	Proportion Subjects Stopping Treatment	95% Confidence Interval		Decision
1	7%	0	19%	Proceed
2	13%	0	35%	Proceed
3	20%	0	40%	Uncertain
4	27%	4%	50%	Uncertain
5	33%	10%	57%	Uncertain
6	40%	15%	65%	Don't Proceed
7	47%	21%	72%	Don't Proceed
8	53%	28%	78%	Don't Proceed
9	60%	45%	85%	Don't Proceed
10	67%	43%	90%	Don't Proceed
11	73%	51%	95%	Don't Proceed
12	80%	60%	100%	Don't Proceed
13	87%	70%	100%	Don't Proceed
14	93%	80%	100%	Don't Proceed
15	100%			Don't Proceed

Table 7-4: Observed proportion of subjects >=10 letters improved at primary outcome visit:

- Proceed if upper 95% CI >50%
- Uncertain if upper 95% CI between 20 and 50%
- Don't Proceed if upper 95% CI <20%

Number of Subjects Improved	Proportion Subjects Improved	95% Confidence Interval		Decision
1	7%	0	19%	Don't Proceed
2	13%	0	35%	Uncertain
3	20%	0	40%	Uncertain
4	27%	4%	50%	Uncertain
5	33%	10%	57%	Proceed
6	40%	15%	65%	Proceed
7	47%	21%	72%	Proceed
8	53%	28%	78%	Proceed
9	60%	45%	85%	Proceed
10	67%	43%	90%	Proceed
11	73%	51%	95%	Proceed
12	80%	60%	100%	Proceed
13	87%	70%	100%	Proceed
14	93%	80%	100%	Proceed
15	100%			Proceed

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