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# **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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## TABLE OF CONTENTS

20		
21		
22	<b>CHAPTER 1: BACKGROUND AND SUMMARY .....</b>	<b>1-1</b>
23	1.1 Objective .....	1-1
24	1.2 Rationale for the Study.....	1-1
25	1.3 Prior PEDIG Studies .....	1-2
26	1.4 Levodopa.....	1-2
27	1.5 Tolerability and Adverse Effects.....	1-5
28	1.6 Objectives.....	1-10
29	1.7 Synopsis of Study Design .....	1-10
30	1.8 Study Summary Flow Chart.....	1-12
31	<b>CHAPTER 2: SUBJECT ENROLLMENT (BASELINE VISIT) .....</b>	<b>2-1</b>
32	2.1 Assessment and Informed Consent/Assent .....	2-1
33	2.2 Eligibility and Exclusion Criteria.....	2-1
34	2.2.1 Eligibility .....	2-1
35	2.2.2 Exclusions .....	2-2
36	2.3 Examination Procedures.....	2-3
37	2.3.1 Historical Information.....	2-3
38	2.3.2 Clinical Testing.....	2-3
39	2.3.3 Symptom Survey.....	2-4
40	2.3.4 Randomization .....	2-4
41	<b>CHAPTER 3: TREATMENT.....</b>	<b>3-1</b>
42	3.1 Treatment .....	3-1
43	3.2 Compliance.....	3-1
44	3.3 Adverse Events.....	3-2
45	3.4 Dose Changes .....	3-2
46	3.4.1 Overdosage .....	3-2
47	3.4.2 Discontinuation of Treatment .....	3-2
48	<b>CHAPTER 4: FOLLOW UP .....</b>	<b>4-1</b>
49	4.1 Follow-up Examinations .....	4-1
50	4.1.1 Post-enrollment Telephone Calls.....	4-1
51	4.1.2 Four-week Visit (Visit 1).....	4-1
52	4.1.3 Primary Outcome Visit (Visit 2).....	4-2
53	4.1.4 Off Treatment Visit (Visit 3) .....	4-2
54	<b>CHAPTER 5: MISCELLANEOUS CONSIDERATIONS .....</b>	<b>5-1</b>
55	5.1 Management of Optical Correction.....	5-1
56	5.2 Management of Strabismus.....	5-1
57	5.3 Worsening of Visual Acuity in the Amblyopic Eye .....	5-1
58	5.4 Subject Withdrawals .....	5-1
59	5.5 Subject Payments .....	5-1
60	5.6 Discontinuation of Study.....	5-1
61	5.7 Maintaining Subject Follow-up.....	5-1
62	<b>CHAPTER 6: ADVERSE EVENTS .....</b>	<b>6-1</b>
63	6.1 Definition .....	6-1
64	6.2 Recording of Adverse Events.....	6-1
65	6.3 Reporting Serious or Unexpected Adverse Events .....	6-1
66	6.4 Data and Safety Monitoring Committee Review of Adverse Events.....	6-2

67	6.5	Risks.....	6-2
68	6.5.1	Risks of Examination Procedures.....	6-2
69	6.5.2	Side Effects of Treatment.....	6-2
70	6.5.3	Reverse Amblyopia.....	6-3
71	6.5.4	Development of Strabismus.....	6-3
72	6.6	Risk Assessment.....	6-3
73	<b>CHAPTER 7: STATISTICAL CONSIDERATIONS .....</b>		<b>7-1</b>
74	7.1	Sample Size and Analysis.....	7-1
75	7.2	Decision to Proceed to Randomized Trial.....	7-1
76	7.2.1	Recruitment Potential.....	7-1
77	7.2.2	Pilot Study Outcomes.....	7-2
78	<b>CHAPTER 8: REFERENCES.....</b>		<b>8-1</b>
79			

## 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.<sup>1</sup> 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.<sup>1</sup>

124 **1.3 Prior PEDIG Studies**

125 PEDIG conducted a randomized trial of 507 subjects (age 7 to 17 years old) with amblyopic eye  
126 visual acuity ranging from 20/40 to 20/400 (ATS3).<sup>1</sup> Subjects were provided with optimal  
127 optical correction and then randomized to a Treatment Group (2 to 6 hours per day of prescribed  
128 patching of the sound eye combined with near visual activities for all subjects plus atropine one  
129 drop per day in the sound eye for 7 to 12 year olds) or an Optical Correction Group (optical  
130 correction alone). Subjects whose amblyopic eye acuity improved 10 or more letters (2 lines) by  
131 24 weeks were considered *responders*. In the 7 to 12 year-old subjects (N=404), 53% of the  
132 Treatment Group were responders compared with 25% of the Optical Correction Group  
133 (P<0.001). In the 13 to 17 year olds (N=103), the responder rates were 25% and 23%  
134 respectively overall (adjusted P=0.22), but 47% and 20% respectively among subjects not  
135 previously treated with patching and/or atropine for amblyopia (adjusted P=0.03). Most  
136 subjects, including responders, were left with a residual visual acuity deficit, as noted earlier.

137

138 ATS9 is a recently completed randomized trial comparing weekend atropine to patching 2 hours  
139 per day in children 7 to 12 years of age for both moderate and severe amblyopia.<sup>2</sup> The specific  
140 treatments were:

- 141 1. Atropine 1% once each weekend day in the sound eye plus near activities for at least one  
142 hour every day (with increase to daily atropine at 5 weeks if acuity not improved by at  
143 least 5 letters).
- 144 2. Patching 2 hours per day plus near activities for one hour while patching (with increase to  
145 4 or more hours per day at 5 weeks if acuity not improved by at least 5 letters).

146

147 Initial treatment was for 17 weeks with continued treatment until improvement stopped. At the  
148 5-week visit, visual acuity had improved from baseline by an average of 6.2 letters in the  
149 atropine group and by 6.8 letters in the patching group. At the 17-week primary outcome exam,  
150 visual acuity had improved from baseline by an average of 7.6 letters in the atropine group and  
151 8.6 letters in the patching group. Fifty-nine percent of the subjects in the atropine group and  
152 70% of those in the patching group achieved 20/40 visual acuity or better.

153

154 **1.4 Levodopa**

155 Many investigators have recognized that conventional therapies with patching and atropine have  
156 not been universally successful and have sought alternatives. PEDIG has discussed for several  
157 years the problem of residual amblyopia and how the remaining visual acuity deficit could be  
158 reduced. We are currently conducting a trial of combined daily atropine and patching 6 hours or  
159 more per day for children 3 to 9 years old with mild residual amblyopia (20/32 to 20/63). A  
160 number of research groups have evaluated the short term use of oral levodopa-carbidopa as an  
161 adjunct to patching therapy for older children.<sup>3-5</sup>

162

163 Levodopa is a medication used to treat adults with Parkinson disease and children with dopamine  
164 responsive dystonia. Dopamine is a neuro-transmitter that does not cross the blood brain barrier.  
165 Levodopa, which is an intermediate in the biosynthesis of dopamine, is used as pharmacological  
166 replacement therapy as it will cross the blood brain barrier, where it is converted to dopamine.  
167 Levodopa is typically used in combination with carbidopa. Carbidopa is a peripheral  
168 decarboxylase inhibitor that prevents the peripheral breakdown of levodopa. Concomitant

169 administration reduces the dose of levodopa required by about 75%, yet allows sufficient  
170 levodopa to enter the brain for the desired effect.<sup>6</sup>

171  
172 Dopamine is active in the retina and in the cortex. Dopamine appears to play an important role  
173 in the normal function of the retina and in central visual processing. The site of action of  
174 dopamine in the visual pathway is unknown, although both retinal and cortical sites have been  
175 suggested. Brandies and Yehuda have authored an extensive review of this subject, in which  
176 they reviewed the role of retinal dopaminergic system in visual performance.<sup>7</sup> They concluded  
177 that both the retina and visual cortex are involved in most visual sensory and perceptual  
178 functions, but that it is difficult to fully understand the interrelationships and therefore the site of  
179 dysfunction in the dopamine dependent portions of the visual system of amblyopic subjects  
180 (section 6.4 of article).

181  
182 For the retinal mechanism of action, two reports have suggested that increased dopamine levels  
183 lead to shrinkage in the size of the receptive field, thereby improving visual acuity.<sup>8,9</sup> For a  
184 cortical mechanism, it has been hypothesized that increased dopamine levels produce a reduction  
185 in the size of the suppression scotoma thereby improving visual acuity.<sup>10,11</sup> In a single dose  
186 administration, dopamine changes the volume of cortical activation measured by functional  
187 MRI.<sup>10</sup> Both improved visual acuity and VEP amplitudes have been reported following both  
188 single dose and 1 week of levodopa administration, but the improvement rapidly regressed with  
189 discontinuation of the drug.<sup>5,8</sup> The improvement of visual acuity in the amblyopic eye occurs  
190 within 1 hour of medication administration and then begins to decline 5 hours after  
191 administration.<sup>3,9,12</sup> This transient improvement in the acuity of the amblyopic eye has led  
192 Leguire and others to suggest that the lasting improvement of visual acuity that is found when  
193 levodopa is used for the treatment of amblyopia may not be a direct effect, but rather the  
194 levodopa may allow better vision in the amblyopic eye during treatment, thus facilitating  
195 compliance with conventional occlusion therapy.<sup>9,13</sup>

196  
197 A number of small case series using levodopa have been published (see below) suggesting  
198 immediate improvement in the amblyopic eye visual acuity, as well as a sustained benefit for  
199 some. Results of visual acuity improvement and maintenance of improvement have varied  
200 across the published case series that are abstracted below. Doses of levodopa are listed in  
201 parentheses.

- 202
- 203 • In a pilot study Leguire and colleagues evaluated side effects and visual acuity  
204 improvement. They found nausea and emesis with higher doses of levodopa  
205 (100mg/25mg and 400mg/100mg). These doses are substantially higher than that given  
206 in their subsequent trials. The investigators demonstrated a temporary improvement in  
207 visual acuity in both the amblyopic eye and the dominant eye within one hour of  
208 ingestion of the medication, and these improvements began to decrease within five hours  
209 of drug ingestion. These results suggest that some of the observed improvement in visual  
210 function may be a drug-mediated effect of ramping up the function of the visual system,  
211 primarily the retina, rather than due to a sustained cortical improvement.<sup>12</sup>
  - 212
  - 213 • Leguire and colleagues conducted a randomized longitudinal double masked placebo  
214 control trial of 10 amblyopic children aged 6 to 14 years. The dosing averaged 0.5 mg

215 per kg. Treatment lasted for three weeks. During that time visual acuity of the  
216 amblyopic eyes improved by 2.7 lines in the levodopa treated group, and by 1.6 lines in  
217 the subjects treated with placebo. One month after the termination of treatment, the  
218 levodopa-carbidopa group maintained a significant 1.2-line improvement in visual acuity.  
219 The placebo group did not maintain any improvement in visual acuity.<sup>14</sup>  
220

- 221 • In a double-blind non-randomized clinical trial of 14 subjects 24 to 63 years, visual  
222 acuity and visual fields were examined before and after 3 weeks of daily levodopa, as  
223 well as 1 and 2 months after completion of drug therapy (2 mg/kg/tid and 3 mg/kg/tid).  
224 A significant increase in visual acuity was found, mostly during the first week.  
225 Improvement of visual function persisted 2 months after the levodopa administration was  
226 completed. Increasing the dosage and the duration of use did not enhance the effect.<sup>4</sup>  
227
- 228 • An unmasked open-label clinical trial of 15 children at least 7 years of age who were no  
229 longer improving with standard treatment for amblyopia were treated for 7 weeks with a  
230 combination of levodopa-carbidopa (0.55 mg/kg/tid). The results showed visual acuity in  
231 the amblyopic eye improved from 20/170 baseline to 20/107. All of the improvement  
232 occurred in the first five weeks. Visual acuity also improved in the dominant eye from  
233 20/19 to 20/16. A concern is that the improvement observed may simply represent  
234 improvement that occurs as a result of retreatment i.e., these subjects had been at an end  
235 point and had stopped treatment. It is unclear whether the improvement was due to  
236 retreatment or an additional effect of levodopa.<sup>9</sup>  
237
- 238 • An unmasked clinical observational study was reported in the Chinese literature, with  
239 only the abstract available in English (we had the paper reviewed for side-effects  
240 description by a native Mandarin speaker). Thirty-six subjects with recalcitrant  
241 amblyopia who had not had any improvement for six months with daily occlusion had  
242 additional treatment with levodopa-carbidopa (1.5 mg/kg/day) for three months. The  
243 authors describe improvement in 90% of eyes, and a “cure rate” of 43%. The amount of  
244 improvement is not described in the English abstract, and the definition of cure rate is not  
245 provided.<sup>15</sup>  
246
- 247 • In a double-masked, placebo-controlled randomized study, 18 amblyopic children aged 4  
248 through 17 years were treated with levodopa of (2 mg/kg/day) without carbidopa or  
249 placebo. Improvement in the levodopa group was 1.4 lines of visual acuity compared  
250 with no improvement in the placebo group (n=14). However, Snellen acuity decreased to  
251 the baseline level within one week of cessation of levodopa treatment.<sup>5</sup>  
252
- 253 • A 1-week, randomized, double-blind, parallel, and placebo-controlled study was  
254 performed with 62 children with amblyopia who were between 7 and 17 years of age.  
255 Subjects were instructed to occlude the dominant eye for 3 hours per day. Visual acuity  
256 improved from 0.59 to 0.45 in the levodopa-carbidopa group (average dose 0.51  
257 mg/kg/day) and from 0.69 to 0.63 in the control group (P = 0.023). There were no  
258 complaints of adverse side effects.<sup>16</sup>  
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- 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.<sup>17</sup>
  - 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.<sup>3</sup>
  - 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.<sup>18</sup> 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.<sup>19</sup> 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).

## 294 **1.5 Tolerability and Adverse Effects**

295 Dopamine is used to treat movement disorders, most commonly those associated with Parkinson

296 disease (PD). The drug is of rapid onset and is taken at regular intervals, with marked

297 improvement in hypokinesia. PD is very rare in children. Moreover, since PD is degenerative

298 and induces post-synaptic striatal changes that would not be present in our study sample, the

299 relevance of CNS side effects seen in PD to our study sample is low.

300

301 Adult subjects receiving levodopa-carbidopa for the management of Parkinson's disease may

302 experience side effects, but these are usually reversible. Acute peripheral effects are nausea and

303 vomiting which may be caused by direct stimulation of the chemotrigger receptor zone in the

304 brain.<sup>20</sup> Tolerance to these symptoms rapidly develops in adults being treated. Other acute

305 effects include orthostatic hypotension, peripheral edema, and psychosis.

306  
307 Prolonged use of dopaminergic drugs in PD has been associated with the development of  
308 dyskinesias in adults and in children. These may include chewing, gnawing, twisting, tongue or  
309 mouth movements, head bobbing, or movements of the feet, hands, or shoulder. These may  
310 respond to a reduction in the dose. Muscle twitching, dizziness, muscle jerks during sleep, and  
311 hand tremor also may occur. Various psychiatric disturbances may occur during levodopa-  
312 carbidopa therapy, such as memory loss, anxiety, nervousness, agitation, restlessness, confusion,  
313 inability to sleep, nightmares, daytime tiredness, mental depression or euphoria.  
314 Pharmacological treatment with medications such as pyridoxine has been suggested, but has not  
315 been shown to be effective.

316  
317 Neuroleptic malignant syndrome is an uncommon, life-threatening side-effect of neuroleptic  
318 treatment which has also been reported in rare cases of adults during reduction or withdrawal of  
319 levodopa therapy for PD.<sup>6</sup> This syndrome is characterized by fever, muscle rigidity, involuntary  
320 movements, altered mental status, and autonomic signs such as tachycardia, sweating, and  
321 tachypnea. Treatment includes monitoring in the intensive care unit, with use of dopamine  
322 agonists such as bromocryptine.

323  
324 Levodopa has also been used for many years in children to treat dopa-responsive dystonia, also  
325 known as Segawa Disease.<sup>21-25</sup> This disease is extremely rare and occurs due to deficient  
326 synthesis of dopamine due to GTP cyclohydrolase deficiency. Typical doses of levodopa in  
327 children range from 50 mg on alternate days when used with carbidopa to 2 g daily when used  
328 without carbidopa.<sup>23</sup> Historically, chorea was noted to appear in several subjects early on in  
329 treatment which responded to dosage adjustment. A recent review noted that typical chronic  
330 dosing is 4-5 mg/kg/day in divided doses, though up to 20 mg/kg/day may be needed.<sup>24</sup>  
331 However, the relevance of dosing and associated side effects in this disease to our study sample  
332 is low, because of the substantially smaller doses used for amblyopia treatment and proposed for  
333 our study.

334  
335 A larger clinical experience with levodopa-carbidopa and with synthetic dopamine agonists is  
336 found in pediatric Tourette Syndrome, cerebral palsy, and Restless Leg Syndrome. In general in  
337 these populations, nausea is the most common side effect. This is reversible, treatable, and dose  
338 related.

339  
340 Gastrointestinal side effects are common in subjects receiving levodopa-carbidopa. Nausea,  
341 vomiting, loss of appetite, and weight loss may occur. Subjects may experience dizziness upon  
342 standing up that is associated with a transient drop in blood pressure. In general, tolerance to  
343 these side effects develops within a few months. Infrequently, subjects may develop a drop in  
344 white blood cell count during levodopa-carbidopa therapy.<sup>6</sup>

345  
346 The side-effects of nausea and emesis associated with administration of levodopa are minimized  
347 with the simultaneous administration of carbidopa, which allows use of lower dosages of  
348 levodopa. Carbidopa and dopamine do not cross the blood-brain barrier. Carbidopa inhibits  
349 dopamine decarboxylase and prevents the decarboxylation of levodopa in peripheral tissues, thus  
350 allowing sufficient levodopa to enter the CNS, yet reduces the total amount of levodopa  
351 administered. Peripheral dopamine decarboxylase is saturated by carbidopa at approximately 70

352 mg per day in adults (1 mg/kg/day). Subjects receiving less than this amount of carbidopa may  
353 experience nausea and vomiting.

354  
355 Levodopa has been used with carbidopa for amblyopia treatment since 1993. The medication  
356 has been well tolerated in the dose and duration typically prescribed.<sup>9, 16</sup> Levodopa-carbidopa is  
357 recognized as a Pregnancy Class C medication with uncertain safety. Safety in lactation is  
358 recognized as possibly unsafe. Reported adverse effects of oral levodopa-carbidopa during  
359 treatment of amblyopia have included nausea, headache, vomiting, dry mouth, mood changes,  
360 dizziness, and fatigue. In one study more than half of the subjects reported at least one  
361 symptom.<sup>9, 12</sup> Decreased body temperature was noted during a 7-week treatment course with the  
362 1.02 mg/kg/tid, but not with 0.55 mg/kg/tid.<sup>26</sup> Dyskinesias, to our knowledge, have not been  
363 reported with the short-term use for the treatment of amblyopia. Gottlob reported infrequent  
364 minor side effects in her group of adult subjects with amblyopia.<sup>4</sup>

365  
366 An analysis of serum chemistry, hematological tests, renal function tests, liver function tests and  
367 liver enzymes was undertaken in 32 children with an average age of 8.44 years across a number  
368 of studies by the Columbus group (Leguire et al, 2007, unpublished data). Blood samples were  
369 taken at baseline, before drug dosing, and after seven weeks of levodopa-carbidopa dosing with  
370 three different dosing regimens. The combined results showed that individual deviations from  
371 the normal range for 39 tests were similar at baseline and following seven weeks of levodopa-  
372 carbidopa dosing. Although some laboratory test means were different from baseline to the 7-  
373 week test session, the means remained well within the normal range for each individual test. In  
374 addition, the percent changes were so small as to have no clinical significance. Overall, based on  
375 the analysis of these 39 tests, levodopa-carbidopa was well tolerated in a pediatric population.

376  
377 Combined formulation tablets of levodopa-carbidopa are commercially available in a 1:4 ratio of  
378 carbidopa to levodopa (25-100) as well as 1:10 ratio (25-250 and 10-100). Tablets of the two  
379 ratios are combined as needed to provide the optimum dosage of both drugs in adults. Because  
380 higher doses are required for their neurological diseases, adequate levels of carbidopa are  
381 administered. For the management of amblyopia Leguire and colleagues have used the 1:4 ratio  
382 for their studies (personal communication, Larry Leguire, 11/12/2007), as have the other studies  
383 cited earlier.

384  
385 This pilot study will evaluate two different doses of levodopa (0.51 mg/kg/tid levodopa and 0.76  
386 mg/kg/tid levodopa, equivalent to 1.53 mg/kg/day and 2.28 mg/kg/day). Most of the literature  
387 published has used the lower dosage (Table 1). A few studies have used higher doses of  
388 levodopa. Leguire and colleagues have used doses ranging from 0.75 to 3.06 mg/kg/day.<sup>27, 3</sup>  
389 These were generally well tolerated. With the 3.06 mg/kg/day dose, there was a slight drop in  
390 body temperature (mean change 99.0 to 97.8 degrees) that was not symptomatic or clinically  
391 consequential.<sup>28</sup> Procyanoy and colleagues administered average doses of 0.51, 1.05, and 2.29  
392 mg/kg/day to three dosage groups with about 20 patients per group.<sup>16</sup> They found similar results  
393 in visual acuity change and side effects with both the lowest and highest doses. In each of these  
394 studies carbidopa was added in a ratio of 1 part to 4 of levodopa. The data from the current pilot  
395 study will help in our selection of the dose to be used in a future randomized clinical trial.

396

397 In this study, carbidopa will be prescribed at 0.17 mg/kg/tid for both levodopa dosages  
398 (equivalent to 1 part to 3 of levodopa for the lower levodopa dosage and about 1 part to 4.5 for  
399 the higher levodopa dosage). We acknowledge that the dose of carbidopa is less than the 1  
400 mg/kg/day recommended for adults and certainly less than the maximal dose possible in children  
401 according to child neurologists we have consulted. However, as noted in the preceding  
402 paragraphs this is more than the dosage of carbidopa used in prior studies of amblyopia where  
403 nausea was unusual with carbidopa 1:4. In this pilot study we will monitor side effects and  
404 determine whether the 1:3 ratio or the 1:4.5 ratio of carbidopa to levodopa is sufficient or should  
405 be increased in a future randomized trial. In addition to the study formulation, additional  
406 carbidopa may be prescribed at any time to control nausea in consultation with the study chair  
407 and neurologist serving as the medical monitor.

408 **Table 1: Side Effects Summary Levodopa for Amblyopia**

409

Author/ Year	Treatment Duration	Age	Number of amblyopic subjects	Levodopa Dosage	Side effects										Systemic Changes	Chemistry
					Emesis	Nausea	Headache	Fatigue	Mood changes	Dizziness	Dry mouth	Nightmares	Decreased Appetite			
Leguire 1992 <sup>12</sup>	1 day	7-12 years	5	100 to 400 mg	3	3		1								
Leguire 1993 <sup>14</sup>	3 weeks	6-14 yrs	10	mean 10 mg tid		0		1		1				none		elevated bilirubin - felt unrelated
Leguire 1995 <sup>9</sup>	7 weeks	7-14 yrs	15	0.55 mg/kg tid	3	9	9	5	8	4	4					no abnormalities
Leguire 1996 <sup>26</sup>	7 weeks	6-14 yrs	15	0.55 mg/kg tid												no change in body temperature
			13	1.02 mg/kg tid												slight reduction in body temperature
Leguire 2002 <sup>3</sup>	7 weeks	6-14 yrs (previously published)	22	0.55 mg/kg tid												
Leguire unpub	7 weeks	4.7-14.2 yrs	23	0.55 mg/kg tid												no changes in blood tests from baseline to 7 weeks in any of the groups
			24	1.02 mg/kg tid 0.25 mg/kg increasing to 0.75 mg/kg tid												
Gottlob 1995 <sup>4</sup>	3 weeks	> 16 yrs	14	2 mg/kg tid and 3 mg/kg tid	1	3		1								
Mohan 2001 <sup>17</sup>	7 weeks	4-22 yrs	72	0.50 mg/kg tid	0	0	0	0	0	0	0			none		
Wu 1998 <sup>15</sup>	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 <sup>5</sup>	1 week	4-17 yrs	18	2 mg/kg tid	Did not measure or report (reviewed by German speaker)											
Procyanoy 1999 <sup>16</sup>	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 <sup>27</sup>	7 weeks	7-12 yrs	13	1.02 mg/kg	1	2	4	2	2			0	1	none		none

410

Blank cells – side-effect not reported by authors,

411

412 **1.6 Objectives**

413 This pilot study is being conducted as a prelude to a randomized trial to compare levodopa/carbidopa  
414 plus patching versus patching alone. The purpose of the pilot study is to demonstrate recruitment  
415 potential, to provide prospective data on the tolerability of levodopa as a treatment for amblyopia, to  
416 provide limited data on its safety, to provide limited data on its efficacy, and to provide data to assist in  
417 selecting a dose to use in a subsequent phase 3 randomized trial. In addition, this study will provide the  
418 opportunity for investigators to gain experience in using levodopa prior to a randomized trial.  
419

420 **1.7 Synopsis of Study Design**

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

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

430  
431 Treatment

432 All subjects will have two hours of daily patching prescribed plus be randomized to one of two levodopa  
433 doses for about 8 weeks with a rapid taper prior to the primary outcome exam:  
434

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

438  
439 The subject, parents, and the site staff will be masked to treatment assignment.  
440

441 Sample Size

442 A sample of 30 subjects will be enrolled.  
443

444 Contact and Visit Schedule

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

450  
451

452 Analysis

453

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

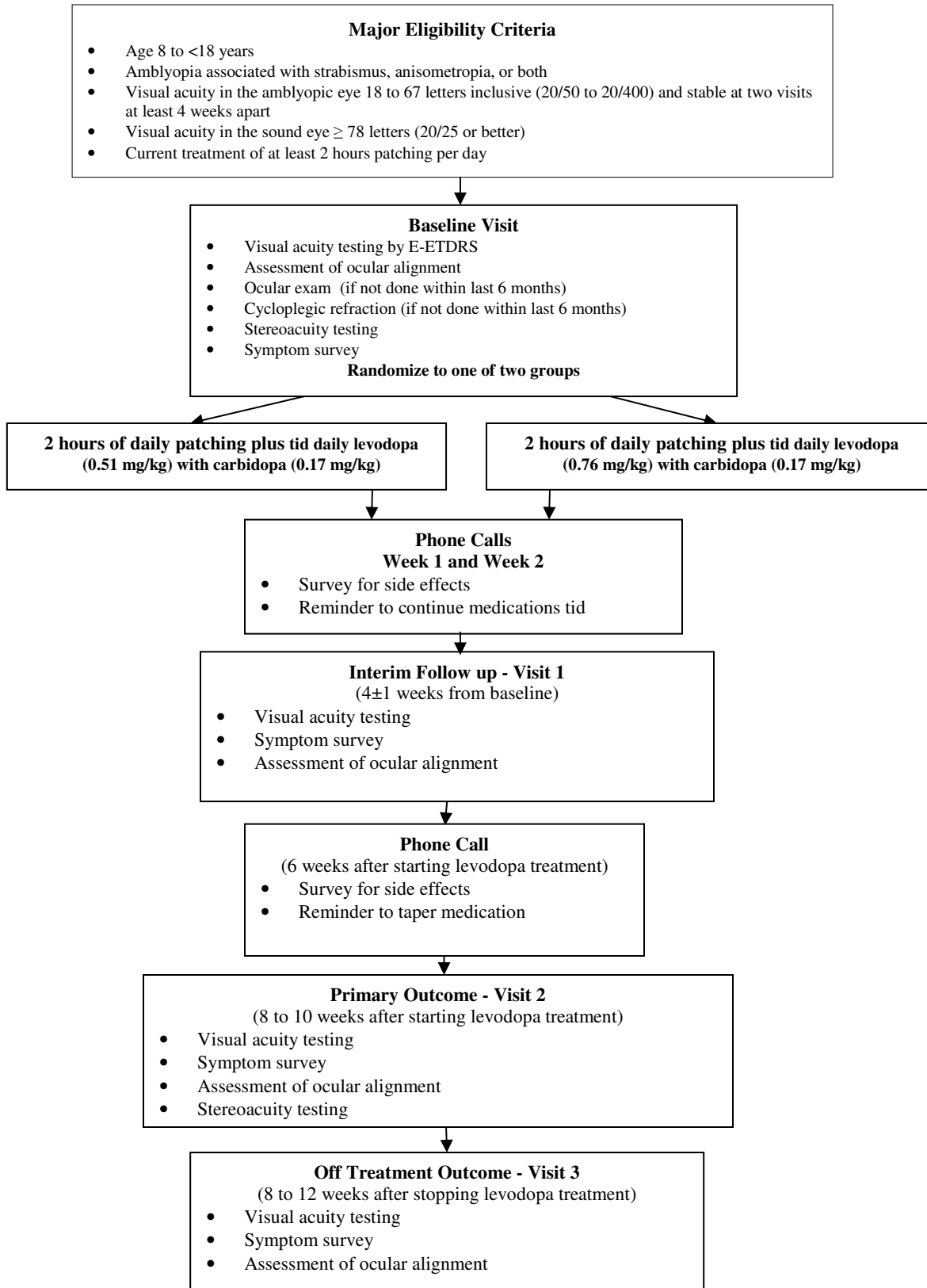
455

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

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462 **1.8 Study Summary Flow Chart**

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## 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:
    - $\geq 0.50$  D difference between eyes in spherical equivalent
    - $\geq 1.50$  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  $\geq 78$  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)

- 546 • At least two hours of occlusion per day prescribed for the sound eye and performed  
547 during the same period of time during which the two measurements of visual acuity at  
548 least 4 weeks apart were obtained (and visual acuity was not improved).
- 549 • Treatment with atropine during this period is not allowed.
- 550 • Any treatment prior to the current patching episode with stable acuity is acceptable.
- 551 5. Spectacle correction (if applicable) for measurement of enrollment visual acuity must meet  
552 the following criteria and be based on a cycloplegic refraction that is no more than 6  
553 months old:
- 554 a. Requirements for spectacle correction:
- 555 • Spherical equivalent must be within 0.50 D of fully correcting the anisometropia.
- 556 • Hypermetropia must not be undercorrected by more than 1.50 D spherical  
557 equivalent, and reduction in plus sphere from the most recent cycloplegic  
558 refraction must be symmetric in the two eyes.
- 559 • Cylinder power in both eyes must be within 0.50 D of fully correcting the  
560 astigmatism.
- 561 • Cylinder axis in both eyes is within 6 degrees of the axis in the spectacles when  
562 cylinder power is  $\geq 1.00$  D.
- 563 • Myopia of amblyopic eye greater than 0.50 D by spherical equivalent must be  
564 corrected, and the glasses must not undercorrect the myopia by more than 0.25 D  
565 or overcorrect it by more than 0.50 D.
- 566 b. Spectacles meeting above criteria must be worn either:
- 567 1) for 16 weeks immediately prior to enrollment, or
- 568 2) until visual acuity in amblyopic eye is stable (defined as two consecutive visual  
569 acuity measurements by the same testing method at least 4 weeks apart with no  
570 improvement of more than 4 letters or one logMAR line)
- 571 • An acuity measurement done any of the following ways may be considered the  
572 first of two consecutive measurements: 1) in current glasses, 2) in trial frames  
573 with full correction of hypermetropia with cycloplegia, or 3) by having the subject  
574 return in new glasses for first measurement. *Note: since this determination is a*  
575 *pre-study procedure, the method of measuring visual acuity is not mandated.*
- 576 6. Ocular examination within 6 months prior to enrollment
- 577 7. Parent available for at least 4 months of follow-up, has home phone (or access to phone),  
578 and willing to be contacted by clinical site staff and Jaeb Center staff
- 579 8. In the investigator's judgment, the subject is likely to comply with prescribed treatment  
580 (e.g., no history of poor compliance with patching treatment).

581  
582 **2.2.2 Exclusions**

- 583 1. Myopia more than -6.00 D (spherical equivalent) in either eye.

- 584 2. Current vision therapy or orthoptics  
585 3. Ocular cause for reduced visual acuity  
586 • nystagmus per se does not exclude the subject if the above visual acuity criteria are met  
587 4. Prior intraocular or refractive surgery  
588 5. History of narrow-angle glaucoma  
589 6. Strabismus surgery planned within 16 weeks  
590 7. Known allergy to levodopa-carbidopa  
591 8. History of dystonic reactions  
592 9. Current requirement to take oral iron supplements including multivitamins containing iron  
593 during treatment with levodopa-carbidopa  
594 10. Current use of antihypertensive, anti-depressant medications, phenothiazines,  
595 butyrophenones, risperidone and isoniazid, non-specific monoamine oxidase inhibitors  
596 11. Current use of medication for the treatment of attention deficit hyperactivity disorder  
597 12. Known gastrointestinal or liver disease  
598 13. History of melanoma  
599 14. Known psychological problems  
600 15. Known skin reactions to patch or bandage adhesives  
601 16. Prior levodopa treatment  
602 17. Current treatment with topical atropine  
603 18. Females who are pregnant, lactating, or intending to become pregnant within the next 16  
604 weeks.  
605 • A negative urine pregnancy test will be required for all females who have experienced  
606 menarche.  
607 • Requirements regarding the establishment of pregnancy status and monitoring for  
608 pregnancy over the course of the study as defined by each individual Institutional Review  
609 Board may supersede these criteria.

610

## 611 **2.3 Examination Procedures**

### 612 **2.3.1 Historical Information**

613 Historical information elicited will include the following: date of birth, gender, ethnicity, prior  
614 amblyopia therapy (e.g., glasses, patching, pharmacologic, Bangerter filters, combined therapies,  
615 near activities with treatment), corrected visual acuity before amblyopia treatment started (if  
616 available), current amblyopia therapy, current spectacle correction, and history of the following:  
617 allergy to adhesive skin patches, allergy to levodopa-carbidopa, narrow-angle glaucoma,  
618 dystonic reactions, gastrointestinal or liver disease, melanoma, psychological problems.

619

### 620 **2.3.2 Clinical Testing**

621 Examination procedures include:

- 622  
623 1. Measurement of body weight.  
624 2. Measurement of visual acuity in each eye (right eye first) by the E-ETDRS testing protocol  
625 on a study approved visual acuity tester.
- 626 • Testing of the amblyopic eye must be done without cycloplegia (with spectacles, if worn)  
627 no more than 7 days prior to enrollment.
  - 628 • Subjects currently wearing spectacles must have enrollment acuity measured while  
629 wearing spectacles; trial frames or phoropter cannot be used.
- 630 3. Ocular motility examination
- 631 • Measurement of alignment by Simultaneous Prism and Cover Test (SPCT) in primary  
632 position at distance and near
  - 633 • If performed within prior 7 days, alignment measurements do not need to be repeated at  
634 time of enrollment
- 635 4. Stereoacuity testing: Titmus fly, Randot Preschool test
- 636 5. Complete ocular examination, including dilated fundus examination, to rule out a cause for  
637 reduced visual acuity other than amblyopia.
- 638 • If performed within prior 6 months, the ocular examination does not need to be repeated  
639 at time of enrollment
- 640 6. Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine
- 641 • If performed within prior 6 months, the cycloplegic refraction does not need to be  
642 repeated at time of enrollment

643  
644 **2.3.3 Symptom Survey**

645 Each subject (or parent if subject is unable to complete) will complete a symptom survey to  
646 identify any symptoms they may be experiencing before beginning treatment. The questionnaire  
647 will be repeated at each follow-up visit.

648  
649 **2.3.4 Randomization**

650  
651 **Randomization of Eligible Patients**

- 652 1. Once a subject is randomized, that subject will be included in the analysis regardless of  
653 whether the assigned treatment is received or not. Thus, the investigator must not  
654 randomize a subject until he/she is convinced that the parent/guardian will accept and  
655 comply with either of the treatment regimens.
- 656 2. A subject should not be randomized until both the investigator and parent are ready to start  
657 protocol-mandated treatment.
- 658 3. The Jaeb Center will construct a Master Randomization List using a permuted block design  
659 stratified by visual acuity in the amblyopic eye as moderate 20/50 to 20/80 (53 to 67  
660 letters) versus severe 20/100 to 20/400 (18 to 52 letters), which will specify treatment  
661 group assignments. A subject is officially enrolled when the website randomization

662 process is completed. Both the subject and the site will be masked to treatment group  
663 assignment.

664

665 **Delay in Randomization**

- 666 1. Visual acuity testing and the ocular motility examination must be performed no more than  
667 7 days prior to randomization. If randomization is delayed beyond 7 days, then these tests  
668 must be repeated to confirm eligibility and establish the baseline measures for the study.
- 669 2. No other parts of the examination (including the refraction) need to be repeated if they  
670 were performed within 6 months prior to randomization.

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## Chapter 3: Treatment

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### 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

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

716  
717 Medication containers will be brought to the 4-week and primary outcome visits. The amount of  
718 remaining medication will be recorded.

719  
720 **3.3 Adverse Events**

721 Reporting of adverse events is described in Chapter 6.

722  
723 **3.4 Dose Changes**

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

727  
728 **3.4.1 Overdosage**

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

732  
733 **3.4.2 Discontinuation of Treatment**

734 Blepharospasm or dyskinesia may be an early indication of excess dosage.<sup>6</sup> The development of  
735 these signs should be discussed immediately with the protocol chair and medical monitor to  
736 determine if the drug should be discontinued.

737

**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)

<b>Test</b>	<b>Visit / Interaction</b>						
	<i>Baseline</i>	<i>1 week call</i>	<i>2 week call</i>	<i>4 week visit</i>	<i>6 week call</i>	<i>Primary Outcome Visit</i>	<i>Off-Treatment Visit</i>
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

775

776 **4.1.3 Primary Outcome Visit (Visit 2)**

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

779

780 Examination procedures will include the following:

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

789

790 **4.1.4 Off Treatment Visit (Visit 3)**

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

792

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

796

797 Examination procedures will include the following:

- 798 1. Questioning about the occurrence of adverse effects  
799 2. Completion of symptom survey  
800 3. Visual acuity
- 801 • Measured in each eye (right eye first) by a certified examiner using the Electronic  
802 ETDRS visual acuity protocol on a study certified visual acuity tester.
- 803 4. Ocular alignment at distance and near assessed with the SPCT  
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## Chapter 5: Miscellaneous Considerations

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### **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

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### 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.<sup>6</sup>

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.

894  
895 Each principal investigator is responsible for informing his/her IRB of serious, unexpected  
896 study-related adverse events and abiding by any other reporting requirements specific to their  
897 IRB.

898  
899 **6.4 Data and Safety Monitoring Committee Review of Adverse Events**

900 A Data and Safety Monitoring Committee (DSMC) will approve the protocol, template informed  
901 consent form, and substantive amendments and provide independent monitoring of adverse  
902 events. Cumulative adverse event data are semi-annually tabulated for review by the Data and  
903 Safety Monitoring Committee (DSMC). Data will be reviewed with the DSMC when 50% of  
904 subjects complete the study. Following each DSMC data review, a summary will be provided to  
905 IRBs. A list of specific adverse events to be reported to the DSMC expeditiously will be  
906 compiled and included as part of the DSMC Standard Operating Procedures document.

907  
908 The DSMC Chair will be notified within 24 hours of the coordinating center being notified of a  
909 serious adverse event.

910  
911 **6.5 Risks**

912  
913 **6.5.1 Risks of Examination Procedures**

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

917  
918 **6.5.2 Side Effects of Treatment**

- 919 1. Patching potentially could decrease the visual acuity in the sound eye, although this is  
920 almost always reversible. The diagnosis and management of reverse amblyopia is left to  
921 the investigator's judgment- see section 6.5.3.
- 922 2. If skin irritation occurs, the parent will be advised to put an emollient on the skin and  
923 discontinue use of the patch for a day. If a skin reaction to the patch or an allergic reaction  
924 occurs serious enough to discontinue patching prior to the primary outcome visit (Visit 2),  
925 the investigator will call the Protocol Chair to discuss the case. An alternative adhesive  
926 patch may be tried. If patching with adhesive patches is discontinued, then the subject  
927 should try a Patch Works occluder on glasses (using plano lenses if the subject is not  
928 wearing spectacles).
- 929 3. Patching could precipitate the development of an ocular deviation. See Section 6.5.4.
- 930 4. Short courses of 7 to 12 weeks with a dose of 0.51 mg/kg/tid of levodopa-carbidopa (4:1  
931 formulation) have been used in the treatment of amblyopia without significant problems  
932 (see Chapter 1). Levodopa-carbidopa has been associated with body hypothermia when  
933 administered at doses of levodopa 1.02 mg/kg/tid, but not at the lower doses being used for  
934 this study. Some children when treated with levodopa for amblyopia have reported  
935 headache, emesis, nausea, dry mouth, and fatigue.<sup>9, 13</sup> Nausea has been lessened by taking  
936 the medication with meals, building the dosage up gradually over several days to allow  
937 carbidopa levels to reach steady state and administering the lower doses of levodopa. Each  
938 of these approaches is being used in this study design.

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

943

### 944 **6.5.3 Reverse Amblyopia**

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

949

### 950 **6.5.4 Development of Strabismus**

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

956

957 If amblyopia treatment is to be discontinued prior to the primary outcome exam, then the  
958 Protocol Chair should be called to discuss the situation. The development of a new heterotropia  
959 is an accepted risk of standard-care amblyopia therapy. However, previous studies suggest that  
960 the resolution of pre-existing strabismus during amblyopia treatment occurs as often as the  
961 development of new strabismus. In ATS1, new strabismus occurred in 13% of patching subjects.  
962 Twenty-one percent of subjects had resolution of their preexisting strabismus with treatment.<sup>29</sup>  
963 In ATS3 there was no increase in the proportion of subjects with strabismus with patching for  
964 teens 13 to <18 years, and with patching plus atropine for children 7 to <13 years.<sup>1</sup> In ATS9  
965 there was no increase in the proportion of subjects with strabismus following 2 hours daily  
966 patching.<sup>2</sup> The risk of strabismus in this study is no greater than it would be with standard care  
967 of amblyopia.

968

969 In view of the short duration of the treatment phases of the study and the eligibility criterion that  
970 strabismus surgery is not planned in the 16 weeks following enrollment, it is unlikely that  
971 strabismus surgery will need to be performed prior to the end of the study.

972

## 973 **6.6 Risk Assessment**

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

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## Chapter 7: Statistical Considerations

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### 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.

1020 **7.2.2 Pilot Study Outcomes**

1021 Table 7-1 below provides a priori decision rules to evaluate tolerability and potential efficacy of  
 1022 levodopa treatment. Point estimates and 95% confidence intervals will be calculated for the  
 1023 proportion events described below within each levodopa dosage subgroup.

1024 **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  <i>(# completing primary outcome/# enrolled)</i>	If lower 95% CI $\geq 60\%$	If lower 95% CI between 30 and 60%	If lower 95% CI $<30\%$
Proportion of subjects stopping treatment due to side effects  <i>(# stopping tmt /# enrolled)</i>	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  <i>(#<math>\geq 10</math> letters improved /# enrolled)</i>	If upper 95% CI $\geq 50\%$	If upper 95% CI between 20 and 50%	If upper 95% CI $<20\%$

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1032 **Decision Tables for Each Outcome**

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1034 **Table 7-2: Observed proportion of subjects completing treatment course of levodopa:**

- 1035 ➤ Proceed if lower 95% CI  $\geq 60\%$
- 1036 ➤ Uncertain if lower 95% CI between 30 and 60%
- 1037 ➤ Don't Proceed if lower 95% CI  $< 30\%$
- 1038

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

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1040

1041 **Table 7-3: Observed proportion of subjects stopping treatment due to side effects:**

- 1042     ➤ Proceed if upper 95% CI <40%  
1043     ➤ Uncertain if upper 95% CI between 40 and 60%  
1044     ➤ Don't Proceed if upper 95% CI >60%

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<b>Number of Subjects Stopping Treatment</b>	<b>Proportion Subjects Stopping Treatment</b>	<b>95% Confidence Interval</b>		<b>Decision</b>
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

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1048 **Table 7-4: Observed proportion of subjects  $\geq 10$  letters improved at primary outcome**  
 1049 **visit:**

- 1050 ➤ Proceed if upper 95% CI  $> 50\%$
- 1051 ➤ Uncertain if upper 95% CI between 20 and 50%
- 1052 ➤ Don't Proceed if upper 95% CI  $< 20\%$

1053

<b>Number of Subjects Improved</b>	<b>Proportion Subjects Improved</b>	<b>95% Confidence Interval</b>		<b>Decision</b>
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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