

Visual Acuity Change over 12 Months in the Prospective Progression of Stargardt Disease (ProgStar) Study (*ProgStar Report No 6*)

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Running head: Visual Acuity Change over One Year in Stargardt Disease

1 **Abstract**

2 **Purpose:** To estimate the yearly rate of change of best corrected visual acuity (BCVA) and
3 the risk of loss ≥ 1 lines over one year, and to identify risk factors for BCVA loss in patients
4 with Stargardt disease (STGD1).

5 **Design:** Multi-center *prospective* cohort study.

6 **Participants:** 259 patients (489 study eyes) with molecularly confirmed STGD1 enrolled at
7 nine centers in the USA and Europe.

8 **Methods:** Participants were followed every six months, and data at baseline, six and 12-
9 month visits were analyzed. BCVA was measured using the ETDRS protocol. Standardized
10 reporting forms were used to collect participants' characteristics and clinical observations.
11 Linear mixed effects models were used to estimate the rate of BCVA loss. Linear models with
12 generalized estimating equations were used to identify risk factors for BCVA loss ≥ 1 lines
13 over one year.

14 **Main Outcome Measures:** BCVA change over one year.

15 **Results:** Cross-sectional analysis at baseline showed that earlier symptom onset and longer
16 duration since onset was associated with worse BCVA. Longitudinal analysis showed no
17 overall significant change of BCVA within 12 months, but the rate of BCVA change was
18 significantly different by baseline BCVA ($p < .001$). BCVA of eyes with baseline BCVA better
19 than or equal to 20/25 declined at a rate of 2.8 ETDRS letters per year ($p = .10$); eyes with
20 baseline BCVA between 20/25 and 20/70 declined at a rate of 2.3 ETDRS letters per year
21 ($p = .002$); eyes with baseline BCVA between 20/70 and 20/200 declined at a rate of 0.8
22 ETDRS letters per year ($p = .08$); and eyes with baseline BCVA worse than 20/200 showed a
23 significant improvement of 2.3 ETDRS letters per year ($p < .001$). Overall, 12.9% eyes lost ≥ 1
24 lines, and the risk of such BCVA loss was different by baseline BCVA level ($p = .016$).
25 Smoking and vitamin A use was not significantly associated with baseline BCVA, nor with
26 rate of BCVA loss over one year.

27 **Conclusions:** BCVA change in STGD1 over a 12 month period was small, but the change
28 varied depending on baseline BCVA. Given the slow change during one year, BCVA is
29 unlikely to be a sensitive outcome measure for STGD1 treatment trials with one year
30 duration.

31

32 **Introduction**

33 Stargardt disease (STGD1; OMIM: 248200) is the most common juvenile macular dystrophy
34 with a prevalence of 10-12.5 per 100,000 persons¹, and is inherited as an autosomal-recessive
35 trait associated with mutations in the *ABCA4* gene². It is characterized by the appearance of
36 yellowish-white lesions called fundus flecks at the level of the retinal pigment epithelium
37 (RPE) and by the development of macular atrophic lesions. Patients with STGD1 are known
38 to experience impairment of visual acuity progressively and at various ages. Currently there is
39 no approved treatment for the disease. Understanding the natural history of STGD1 and
40 determining the rate of disease progression using multiple functional or structural methods is
41 of great interest for determining appropriate outcome measures in clinical trials of potential
42 treatments³⁻⁸.

43

44 Prior studies reporting the rate of change of visual acuity (VA) in STGD1⁹⁻¹⁵ were all based
45 on *retrospective* review of medical records. In this study, we used data from the *prospective*
46 international multi-center study of the natural history of the Progression of Atrophy
47 Secondary to Stargardt Disease (ProgStar), to assess the rate of VA change and identify
48 participants' demographic, clinical and behavioral characteristics associated with VA loss
49 over one year.

50

51 **Participants and Methods**

52 Data for this analysis are from the prospective ProgStar study which was approved by the
53 Western Institutional Review Board, the local institutional review boards, and the Human
54 Research Protection Office of the United States Army Medical Research and Materiel
55 Command. The study was registered at www.clinicaltrials.gov (identifier, NCT01977846).

56

57

58 Details of the prospective ProgStar study have been described in detail elsewhere⁷. In brief,
59 from September of 2014 to March 2015, eligible STGD1 patients were enrolled into the
60 ProgStar study at nine participating sites from the USA, United Kingdom, France and
61 Germany. Eligibility of participants included: age \geq 6 years; willingness to undergo ocular
62 examinations every 6 months for up to 24 months; having two pathogenic mutations in the
63 *ABCA4* gene, or, having one pathogenic mutation in the *ABCA4* gene together with a typical
64 Stargardt phenotype such as flecks at the level of the RPE (further inclusion and exclusion
65 criteria are described in ProgStar Report #1)⁷. The particularly relevant inclusion criteria for
66 analysis herein are that study eyes had to have a best corrected visual acuity (BCVA) \geq 20
67 ETDRS letters (i.e. 20/400 Snellen equivalent or better); have at least one well-demarcated
68 area of atrophy on fundus autofluorescence imaging with a diameter \geq 300 microns and the
69 sum of all lesions \leq 12 mm²; and have clear ocular media and adequate pupillary dilation per
70 site investigators' assessment. All participants gave written informed consent prior to
71 enrollment in the study.

72

73 Participants were followed every six months. At each visit, participants underwent detailed
74 ophthalmic examinations; refraction and best corrected visual acuity (BCVA) was obtained
75 following the ETDRS (Early Treatment of Diabetic Retinopathy Study) protocol¹⁶ at all sites.
76 For data collection, a standardized demographic form and clinical report form (CRF) was
77 used at all sites to record age, sex, race, age of symptom onset and clinical information on
78 BCVA, results from the biomicroscopy of the anterior segments and dilated fundus
79 examination, and behavioral characteristics (use of vitamin supplementation, smoking
80 history) at each study visit. All data were double entered by study coordinators into the
81 REDCap (Research Electronic Data Capture) system ([http://www.project-](http://www.project-redcap.org/cite.php)
82 [redcap.org/cite.php](http://www.project-redcap.org/cite.php)), and transferred to Data Coordinating Center for data quality control and
83 management.

84

85 **Statistical analysis**

86 Data from the baseline, 6 month and 12 month visits were used in this analysis. Participant
87 demographic and clinical characteristics at baseline visit were first summarized. Baseline
88 BCVA was also categorized in referencing the World Health Organization's International
89 Classification of Diseases, 10th revision¹⁷ and as (1) VA $\geq 20/25$ (i.e logarithm of the
90 minimum angle of resolution [logMAR] ≤ 0.1 or ETDRS letters ≥ 80) (i.e., no visual
91 impairment [VI]); (2) worse than 20/25 to 20/70 (logMAR 0.1 – 0.54, i.e. ETDRS letters 58-
92 80) (i.e., mild VI); (3) worse than 20/70 to 20/200 (logMAR 0.54 – 1.0, i.e. ETDRS letters
93 35-58) (i.e., moderate VI); (4) worse than 20/200 to 20/400 (logMAR 1.0–1.3, i.e. ETDRS
94 letters 20-35) (i.e., severe VI); and (5) worse than 20/400 (logMAR >1.3 , i.e. ETDRS letters
95 <20) (i.e., blindness).

96

97 For all analyses, ETDRS letter scores were converted to the logMAR scale. Baseline data of
98 participants and study eyes were used to explore the cross-sectional association of BCVA
99 with participant demographic and behavioral characteristics including age (categorized as
100 ≤ 18 , $>18-50$, $50+$ years), sex, race (white vs. non-white), smoking status and vitamin A use,
101 and with clinical characteristics including age at symptom onset (categorized into ≤ 14 , 15-20,
102 21-30, 30+ years upon considering data distribution and prior publications) and duration since
103 symptom onset at baseline (categorized as 0-2, $>2-6$, $>6-11.5$ and $>11.5-53$ years upon
104 considering data distribution and prior publications). Age, age of symptom onset, and
105 duration since onset were also modeled as continuous variables in separate models. Eye-level
106 clinical characteristics included observations from biomicroscopy of the anterior segments
107 and dilated fundus examination. Univariate linear models with generalized estimating
108 equations (GEE) were used to estimate the unadjusted cross-sectional associations while

109 accounting for between-eye correlation, followed by multivariate linear models with GEE to
110 estimate the associations adjusting for variables associated with BCVA in univariate analyses
111 with $p < 0.1$.

112

113 To estimate the longitudinal change of BCVA, a linear mixed effects model (LMM) was used
114 to estimate the yearly change rate: the mean of participants' BCVA was modeled as a linear
115 function of time since baseline visit, with the intercept and slope parameters assumed to be
116 normally distributed random effects. Additionally, BCVA change from baseline to year 1 was
117 further dichotomized as whether or not there was a loss of one or more lines (i.e. loss of 5 or
118 more ETDRS letters), and the proportion of such loss was estimated. Univariate log-binomial
119 models with GEE were used to estimate the risk ratios of baseline variables (for the
120 behavioral variable of vitamin A use, the report at year 1 visit was considered) in association
121 with the risk of one or more lines of BCVA loss during the year. Multivariate log-binomial
122 models with GEE were used to estimate the adjusted risk ratios for variables associated with
123 risk of BCVA loss of one or more lines in univariate analysis with $p \leq 0.10$ and for variables
124 associated with baseline BCVA with $p \leq 0.10$.

125

126 All analyses were conducted in SAS 9.3, and two-sided p-values from Wald-tests were
127 reported. For analyses using GEE models, model fit was assessed using aggregated
128 residuals¹⁸, and for the longitudinal analysis using LMMs, model fit was inspected visually
129 and based on plots of scaled residuals.¹⁹

130

131 **Results**

132 There were 259 participants with 489 study eyes enrolled in the prospective ProgStar study.
133 Follow-up rate was 92% at Month 6 and 93% at Month 12 (Figure 1). Table 1 summarizes
134 characteristics of participants and their study eyes. The median age at baseline was 31

135 (interquartile range [IQR] 21-44) years, and 54% (N=141) were female. Most participants
136 were white (N=222, 86%), 7.7% were black (N=20), and 4% were Asian (N=10). The median
137 age of self-reported age of symptom onset was 19 (IQR 12-29) years, and the median duration
138 since symptom onset at the baseline visit was 9 (IQR 5-15) years. Vitamin A use was reported
139 by 37 (14%) participants (a summary of dosage and frequency is presented in Supplemental
140 Table 1). Current smoking was reported in 29 (11%) participants, and 35 (14%) were former
141 smokers.

142

143 At baseline, the median BCVA of the study eyes was 41 (IQR 35-52, range 20-88) ETDRS
144 letters (i.e. median LogMAR=0.88), and 21% eyes had no or mild visual impairment (VI),
145 55% were moderately impaired, and 25% were severely impaired. Lens change or
146 abnormalities of the anterior segment were rare. Clinical exam data showed that 9.5% eyes
147 had nerve pallor, 93% eyes had RPE atrophy, and 67% eyes had RPE pigmentary abnormality
148 (i.e. hypo- and/or hyper-pigmentations at the level of the RPE). Most eyes (92%) had flecks
149 present within the arcades, and 46% eyes had flecks outside the arcades (Table 1).

150

151 *Cross-sectional associations of participant characteristics with baseline BCVA*

152 Table 2 presents the baseline BCVA in subgroups by participant characteristics, and the
153 difference of BCVA between subgroups. Compared to participants with age ≤ 18 years, the
154 BCVA of those aged 18-50 years and those aged >50 years was better by 4.5 and 10.5
155 ETDRS letters (i.e. ~ 0.09 and 0.21 LogMAR difference) respectively. Such differences
156 however were not significant in adjusted analysis. When age was modeled as a continuous
157 variable, older age was associated with better BCVA in univariate analysis ($p=.007$). But in
158 multivariate analysis controlling for age of symptom onset, older age was associated with
159 worse BCVA (adjusted $p=0.02$). There was no significant difference in BCVA by sex or by
160 race. Older age of symptom onset was significantly associated with better BCVA ($p<.001$):

161 for example, compared to participants with onset age ≤ 14 years, the BCVA of those with
162 onset age > 30 years was 11.5 ETDRS letters better (i.e. adjusted logMAR difference -0.23).
163 Such an association was also significant when age of onset was modeled as a continuous
164 variable (adjusted $p < .001$). Longer duration of symptoms was significantly associated with
165 worse BCVA ($p < .001$): e.g. compared to participants with symptoms ≤ 2 years, the BCVA of
166 those with symptoms for > 11.5 years was 13 ETDRS letters worse (i.e. adjusted LogMAR
167 difference 0.26). The association was also significant when duration was modeled as a
168 continuous variable (adjusted $p < .001$). For behavioral variables, vitamin A use was not
169 associated with BCVA ($p = 0.34$). The BCVA of current smokers was 5 ETDRS letters (i.e.
170 logMAR difference 0.1) worse than never smokers, but this difference was not statistically
171 significant ($p = 0.26$)

172

173 For eye-level clinical characteristics, having nerve pallor and flecks within the arcades was
174 not associated with worse BCVA. BCVA of eyes with RPE pigmentary abnormalities was 5
175 ETDRS letters (i.e. LogMAR difference 0.1, adjusted $p = .003$) worse than eyes without this
176 abnormality; BCVA of eyes with flecks outside the arcades was 6 ETDRS letters (i.e.
177 LogMAR difference 0.12, adjusted $p < .001$) worse than eyes without flecks outside the
178 arcades. Associations of BCVA with other fundus examination variables were not assessed
179 due to the small sample sizes in certain subgroups.

180

181 Longitudinal analysis of the yearly change of BCVA

182 Overall there was no statistically or clinically significant change of mean BCVA over 12
183 months (Figure 2): the rate of change was -0.36 ETDRS letters (0.007 LogMAR)/year (95%
184 CI: (-1.18, 0.46) ETDRS letters; $p = 0.38$). However, the change was statistically significantly
185 different by baseline BCVA level ($p < .001$) (Table 3 and Figure 3): eyes with no VI at
186 baseline ($N = 17$) had a non-significant BCVA change of -2.8 ETDRS letters (0.056

187 LogMAR)/year (95% CI: -6.01, 0.49 ETDRS letters); eyes with mild VI (N=83) showed a
188 significant BCVA change of -2.3 ETDRS letters (0.047 LogMAR)/year (95% CI: -3.86, -0.83
189 ETDRS letters); eyes with moderate VI (N=267) showed a non-significant BCVA change of -
190 0.8 ETDRS letters (0.015 LogMAR)/year (95% CI: -1.59, 0.09 ETDRS letters); and eyes with
191 severe VI (N=122) had a statistically significant gain of 2.3 ETDRS letters (-0.045
192 LogMAR)/year (95% CI: 1.00, 3.52 ETDRS letters). These change rates (Table 3) suggested
193 a dose-response relationship between baseline BCVA level and the rate of BCVA change. We
194 therefore modeled baseline BCVA as continuous in the linear mixed effects model which
195 confirmed that the better the baseline BCVA, the larger the BCVA decline over one year
196 ($p < .001$).

197

198 Longitudinal analysis of the factors associated with risk of loss of one or more lines from
199 baseline to 12 month visit

200 Among the 456 study eyes observed at baseline and month 12, the proportion losing one or
201 more lines was 12.9% (59/456). The risk of such loss was significantly different by baseline
202 BCVA level (adjusted $p=0.02$): it was 11.8%, 25%, 12.7% and 5.5%, respectively, in eyes
203 without VI, with mild, moderate, or severe VI at baseline (Table 4). The risk of BCVA loss
204 was also significantly different by age of symptom onset (adjusted $p=0.03$): in particular,
205 compared to participants with symptom onset age ≤ 14 years, the risk of BCVA loss was 66%
206 lower in participants with symptom onset age between 15 and 20 years (adjusted risk ratio
207 [RR]=0.34, 95%CI: 0.14-0.82). BCVA loss of one or more lines at one year was not
208 associated with duration of symptoms at baseline, vitamin A use (at year 1), smoking status,
209 and having nerve pallor, RPE pigmentary abnormalities, or flecks within the arcades. Having
210 flecks outside arcades was associated with lower risk of BCVA loss in univariate analysis, but
211 the association was not significant in adjusted analysis.

212

213 **Discussion**

214 We reported the demographic and clinical characteristics and change of BCVA during one
215 year for STGD1 patients enrolled in the multi-center ProgStar prospective study. Our
216 longitudinal analysis found that the rate of BCVA change was significantly different by
217 baseline BCVA level, but overall there was no significant change over one year of follow-up
218 (estimated rate=0.007 LogMAR/year). This finding differs from our ProgStar retrospective
219 cohort²⁰ where BCVA declined at a small but statistically significant rate of 0.03
220 LogMAR/year. The difference between these two findings may be due in part to the
221 differences in the length of follow-up between our two cohorts: the current analysis on the
222 prospective cohort focused on data during one year of follow-up, whereas the retrospective
223 study had variable but longer follow-up, with a median of 3.6 years. The difference in the two
224 findings may also be due to the fact that the retrospective cohort had better baseline VA than
225 the prospective cohort, especially considering that both studies found that the rate of VA
226 change was significantly different by baseline VA, with better baseline VA associated with a
227 greater yearly rate of decline. These findings suggest that VA loss in STGD1 is not a linear
228 process, where loss is greatest at an early stage when a degree of foveal vision is still present
229 despite accompanying parafoveal degeneration²¹⁻²³, then BCVA loss slows after foveal vision
230 is lost and fixation becomes eccentric.

231

232 For eyes without any visual impairment at baseline, there was a loss of VA over one year but
233 it was not statistically significant. This may be due to the small sample size in the group. The
234 estimated rates of change in eyes without impairment (0.056 LogMAR/year) and eyes with
235 mild impairment (0.047 LogMAR/year) were smaller than the estimates in the ProgStar
236 retrospective cohort (0.096 and 0.094 LogMAR/year, respectively)²⁰. This difference again is
237 most likely due to the difference in length of follow-up and due to the non-linear process of
238 BCVA loss in STGD1. The rates of change in eyes with moderate or severe impairment at

239 baseline were similar to those estimated in the retrospective study (~0.02 loss and 0.05 gain
240 LogMAR/year, respectively), suggesting that VA change may be relatively constant at these
241 stages.

242

243 In particular, similar to our findings in the ProgStar retrospective study and in our analysis
244 with ProgStar participants with recent onset of symptoms^{11,20}, we found that eyes with severe
245 impairment (VA worse than 20/200) at baseline showed a small (~0.5 lines/year) but
246 statistically significant improvement in VA over time. The improvement may be due to
247 regression to the mean, where patients with poor vision tested poorly at baseline, and tested
248 slightly better at subsequent visits reflecting normal variation. Additionally, VA is known to
249 vary to a greater extent in patients with more severe visual impairment. However, it is also
250 plausible for VA to improve as a result of change of the location of the preferred retinal locus
251 (PRL), as has been observed in participants with geographic atrophy and inherited macular
252 dystrophies²⁴⁻²⁷. Also, fixation stability may improve over time²⁸. In the case of STGD1, it is
253 possible for the PRL to move from a superior retinal locus to the parapapillary region as the
254 central scotoma expands with disease progression.²⁹ This hypothesis will be tested in
255 conjunction with the microperimetry data from the ProgStar prospective study.

256

257 In clinical trials, loss of 15 ETDRS letters (equivalent to three Snellen lines) or more are
258 considered clinically significant³⁰. However, such loss was rare in our cohort during the 12
259 months: 12 eyes lost three or more lines from baseline to year 1, i.e. a risk of 2.6%.

260 Clinically, loss of one or more lines may be concerning for patients and their physicians, and
261 such loss was not rare in our cohort, occurring in 59 (12.9%) eyes. Consistent with the
262 findings regarding the yearly rates of BCVA change, baseline BCVA level was the strongest
263 predictor for BCVA loss of one or more lines, with eyes with severe impairment at baseline
264 having the lowest risk of such loss. For the variable of age of symptom onset, results from the

265 multivariable model were similar to those from our retrospective ProgStar study: older age of
266 symptom onset was associated with lower risk of BCVA loss of one or more lines during the
267 year. However, in this prospective cohort, the risk of BCVA loss of one or more lines in the
268 oldest onset age group of (>30 years) was not significantly lower than the youngest onset age
269 group (≤ 14 years). This discrepancy could be due to the difference in outcomes in the two
270 studies: the current analysis considered the dichotomized outcome of BCVA loss of one more
271 lines during one year (which was of clinical relevance), whereas the retrospective study was
272 assessing the yearly change rate which used the actual BCVA values (rather than
273 dichotomized) and which was based on data of variable follow-up lengths among participants.

274

275 Similar to the retrospective study, duration of symptoms, presence of RPE pigmentary
276 changes, flecks within the arcades and flecks outside the arcades were not associated with the
277 one-year risk of BCVA loss of one or more lines. We are not aware of prior studies that
278 assessed the effects of smoking and vitamin A use in STGD1 patients. Our longitudinal
279 analysis did not find a higher risk of loss of BCVA during the year associated with smoking
280 and vitamin A use. Since few people used vitamin A (14%) or smoked (11%) in this cohort, it
281 is possible that the study was underpowered to detect small effects.

282

283 Examination of the brand names of the supplement showed that the supplementation was
284 often through multivitamin use. The cross-section analysis at baseline showed that baseline
285 BCVA was not significantly different by smoking or vitamin A use. Other results from the
286 baseline cross-sectional analysis are similar to prior published studies and to our earlier
287 findings in the retrospective ProgStar cohort^{11, 13, 14, 31}:

288 a younger age of symptom onset and a longer duration since symptom onset was associated
289 with worse VA; and older age was associated with worse VA, which is compatible with the
290 finding that the longer the duration since symptom onset the poorer is VA.

291

292 The ProgStar prospective study is a large-scale and the first study of STGD1 with prospective
293 data collection under a pre-designed standardized study protocol involving multiple sites from
294 both the US and Europe, greatly increasing generalizability. One limitation of the study herein
295 is that we inferred that the VA loss trajectory was non-linear in STGD1. However, this
296 inference was not based on directly observing the VA trajectory over many years from the
297 same individuals; rather, it was based on data from multiple participants with different current
298 VA levels and who showed different rates of VA change during one year. Nonetheless,
299 considering the small rate of change per year, it is reasonable to use linear models to describe
300 the BCVA change during one year.

301

302 STGD1 patients may present with distinct phenotypes, such as macular atrophy surrounded
303 by flecks, patchy/mottled foveal changes, bull's eye maculopathy, foveal sparing, and others⁸.
304 ³². These phenotypes may be associated with different genetic variants and may have different
305 VA progression patterns³³⁻³⁵, for example, the foveal sparing phenotype is known to be on the
306 milder end of the spectrum of the disease, and VA of patients with such phenotype may be
307 maintained longer^{34, 36, 37}. However, since our clinical data did not record specific phenotype
308 information, we were unable to assess VA change associated with each phenotype in our
309 cohort. Nevertheless, utilizing information from fundus autofluorescence image grading, we
310 will evaluate VA in patients with no foveal involvement at baseline in a subsequent ProgStar
311 report. Another limitation of this report is that at baseline, the study only tested participants
312 BCVA once using ETDRS protocol, and thus did not control for any potential learning effect
313 associated with the ETDRS chart. However, at least 56% of participants had received ETDRS
314 VA testing during their routine clinical visits before this study enrollment, and thus learning
315 effect should be minimal in these participants.

316

317 BCVA is an important visual function outcome directly related to participants daily activities,
318 ³⁸ and is the most common outcome measure for efficacy studies of retinal diseases ³⁰.
319 However, our data suggest that the change of BCVA in STGD1 was small and not statistically
320 significant during one year. . Since it will be difficult for trials aiming to prevent or slow VA
321 loss to show a difference over a one year period, VA is not sensitive enough to serve as a
322 primary outcome. Nevertheless, we found that the change of BCVA depended on the starting
323 level of BCVA, and faster progression was observed in patients with baseline BCVA better
324 than 20/70. This information may inform planning of future trials that target on patients who
325 are most likely to show VA loss in 12 months.

326

327 In summary, we found that there was no significant change of BCVA during one year, but
328 baseline BCVA level was associated with different rates of subsequent BCVA change. We
329 found that patients with poor vision at baseline showed a small, but statistically significant
330 gain in visual acuity. Smoking and vitamin A use was not associated with worse BCVA at
331 baseline, nor associated with higher risk of BCVA loss during the one year follow-up. BCVA
332 appears to be relatively insensitive to detect changes in a reasonable time period. Therefore, it
333 is important to explore other potentially more sensitive outcome measures derived from
334 functional or morphological analysis, such as microperimetry, optical coherence tomography,
335 adaptive optics, or fundus autofluorescence imaging.

336

337 List of Figure Legends:

338 Figure 1. Flowchart of enrollment and follow-up of the prospective ProgStar study.

339

340 Figure 2. Spaghetti plot showing visual acuity of the participants during their one year follow-
341 up. Each gray line is data for one eye. The blue line represents the estimated average VA
342 change: -0.36, 95% CI: (-1.18, 0.46) letters (i.e. 0.007 LogMAR) per year.

343

344 Figure 3. Spaghetti plots showing visual acuity change during one year follow-up by baseline
345 VA level. Each gray line is data for one eye. The blue line represents the estimated average
346 VA change. (VI: visual impairment.)

347 3A. Visual acuity change in eyes with no visual impairment (i.e. Snellen VA 20/25
348 or better) at baseline. Rate of change: -2.77 (95% CI -6.02, 0.49) letters/year (i.e.
349 0.056 LogMAR/year).

350
351 3B. Visual acuity change in eyes with mild visual impairment (Snellen VA between
352 20/25 and 20/70) at baseline. Rate of change -2.35 (95% CI -3.96, -0.83) letters/year
353 (i.e. 0.047 LogMAR/year).

354
355 3C. Visual acuity change in eyes with moderate visual impairment (Snellen VA
356 between 20/70 and 20/200) at baseline. Rate of change -0.75, (95% CI -1.59, 0.09)
357 letters/year (i.e. 0.015 LogMAR/year).

358
359 3D. Visual acuity change in eyes with severe visual impairment (Snellen VA worse
360 than 20/200) at baseline. Rate of change 2.26 (95% CI 1.00, 3.52) (i.e. -0.045
361 LogMAR/year).

362

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