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Early Predictive Factors of Visual Loss at 1 Year in Neovascular Age-Related Macular Degeneration under Anti-Vascular Endothelial Growth Factor

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1 Early predictive factors of visual loss at 1-year in neovascular age-related macular degeneration
2 under anti-VEGF in the GEFAL study

3

4 **Short Title:** Predictive factors of visual loss in neovascular AMD under anti-VEGF

5

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36

37 **Conflict of interest**

38 Laurent Kodjikian is a consultant for Abbvie-Allergan, Bayer, Alimera-Horus, Roche, Thea
39 and Novartis; Thibaud Mathis is a consultant for Abbvie, Bayer, GSK and Novartis; Other
40 authors have nothing to declare.

41 **KEYWORDS:**

42 Age-related macular degeneration; anti-VEGF therapy; predictive factors; visual acuity.

43

44

45 **PRECIS**

46 This post-hoc analysis of the GEFAL study, evaluating predictive factors of visual loss in

47 neovascular AMD, found that only a large neovascularization area at baseline is significantly

48 associated with initial or secondary vision loss, despite anti-VEGF injection.

49 **ABSTRACT**

50 **Purpose:** To evaluate early predictive factors of visual loss in patients treated with anti-vascular
51 endothelial growth factor (VEGF) injections under as-needed regimen for neovascular age-
52 related macular degeneration (AMD).

53 **Design:** Post-hoc analysis from the randomized controlled trial GEFAL, comparing
54 ranibizumab versus bevacizumab for neovascular AMD.

55 **Participants:** 393 patients aged ≥ 50 years with neovascular AMD.

56 **Methods:** The present analysis is based on 1-year data from patients included in the study.
57 Patients were separately categorized according to the BCVA change at 3-months (M3) and 1-
58 year into three trajectories: i) patients with no vision loss ≥ 5 -letters at M3 and at 1-year (absence
59 of loss ≥ 5 -letters); ii) patients with no vision loss ≥ 5 -letters at M3 but loss ≥ 5 -letters at 1-year
60 (secondary loss ≥ 5 -letters); and iii) patients with vision loss ≥ 5 -letters at M3 and 1-year (initial
61 loss ≥ 5 -letters). The threshold of at least 5-letters loss was used as it is ordinarily considered as
62 clinically significant.

63 **Main outcome measures:** The following factors were evaluated at baseline and at M3: age,
64 sex, BCVA, presence of fluid, central macular thickness, angiographic choroidal
65 neovascularization (CNV) subtype, CNV area measured in disk area on fluorescein
66 angiography, and number of intravitreal injections.

67 **Results:** An absence of loss ≥ 5 -letters was found in 225 patients (57.3%), a secondary loss ≥ 5 -
68 letters after M3 was found in 109 patients (27.7%) and an initial loss ≥ 5 -letters of BCVA was
69 found in 59 patients (15%). Baseline characteristics were comparable between the three groups
70 except for the total CNV area which was larger in the initial and the secondary loss groups
71 ($p=0.0412$). At M3 a significant association was found between presence of subretinal fluid
72 ($p=0.0318$) and vision loss ≥ 5 -letters, and an even stronger significant association between the
73 presence of intraretinal fluid ($p=0.0066$) and vision loss ≥ 5 -letters.

74 **Conclusions:** In the present study, we found that a large CNV area at baseline was significantly
75 associated with initial or secondary loss of visual acuity ≥ 5 -letters despite anti-VEGF injection.
76 The presence of fluid, both subretinal fluid (SRF) and intraretinal fluid (IRF) at M3 was found
77 in patients with poorer trajectories.

78 **INTRODUCTION**

79 Neovascular age-related macular degeneration (AMD) is one of the main causes of severe and
80 irreversible vision loss, and can result in blindness.¹ The prognosis of patients with neovascular
81 AMD improved with the introduction of anti-vascular endothelial growth factor (VEGF) agents
82 in 2004, which have since been administered as the first-line therapy for treating and stabilizing
83 most cases of neovascular AMD.² Ranibizumab was introduced after the pivotal Anti-Vascular
84 Endothelial Growth Factor Antibody for the Treatment of Predominantly Classic Choroidal
85 Neovascularization in Age-related Macular Degeneration (ANCHOR) and Minimally
86 Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular
87 Age-Related Macular Degeneration (MARINA) studies which demonstrated the molecule's
88 superiority in comparison to placebo or photodynamic therapy.^{3,4} However the burden and cost
89 of a monthly treatment regimen led researchers to investigate the off-label use of bevacizumab
90 as a potential alternative. The Comparison of Age-Related Macular Degeneration Treatments
91 Trials (CATT) study aimed to compare both treatments and showed the non-inferiority of
92 bevacizumab under a monthly regimen, but also the more commonly used as-needed regimen
93 (Pro-Renata, PRN).⁵ Numerous clinical trials including the Groupe d'Evaluation Français
94 Avastin[®] versus Lucentis[®] (GEFAL) study in France have since confirmed these results,
95 establishing the PRN regimen following a three-month loading dose treatment phase as
96 effective for controlling the disease, for both molecules, with similar safety profiles.⁶⁻⁹
97
98 Despite a high rate of functional responders to anti-VEGF treatment administered under a PRN
99 regimen, 15-23% of patients lost 5 letters or more at 1 year.⁷⁻⁹ In the French study group
100 GEFAL, 8.9% of patients treated with bevacizumab and 9.8% of patients treated with
101 ranibizumab lost 15 letters or more.⁹ Early identification of these patients with worse 1-year

102 outcomes would make it possible to adapt their treatment regimens in order to prevent vision
103 loss.

104 The aim of this *post-hoc* analysis of the GEFAL study is to evaluate the early predictive factors
105 of visual loss at 1-year in patients treated with anti-VEGF injections under a PRN regimen for
106 neovascular AMD.

107 **MATERIAL AND METHODS**

108 **Study population**

109 The GEFAL study was a prospective, noninferiority, double-masked, randomized clinical trial
110 performed in 38 French ophthalmology centers between June 2009 and November 2011
111 (NCT01170767) in patients with active subfoveal neovascular AMD and baseline best-
112 corrected visual acuity (BCVA) between 20/32 and 20/320 (Snellen equivalent) measured on
113 Early Treatment of Diabetic Retinopathy Study (ETDRS) charts. The research adhered to the
114 Declaration of Helsinki. Patients gave written informed consent before inclusion, and the study
115 was authorized by the competent French health authority (Agence Française de Sécurité
116 Sanitaire des Produits de Santé) on July 22, 2008, and approved by the research ethics
117 committee (Comité de Protection des Personnes Sud Est IV) on September 9, 2008. The design
118 and methods for GEFAL have been published previously.⁹

119

120 **Study protocol**

121 Patients were randomized to one of two treatment arms: (1) intravitreal administration of a 1.25
122 mg dose of bevacizumab or (2) intravitreal administration of ranibizumab at a concentration of
123 0.50 mg in 0.05 ml of solution. Intravitreal injections were administered with a loading-dose
124 period (three injections at months 0, 1, and 2) and a maintenance period (9 months, i.e. months
125 3-12, starting 28-35 days after the last loading injection). During the loading-dose period,
126 patients received three monthly intravitreal injections (window, 28-35 days). A PRN regimen
127 was chosen for the maintenance period, in accordance with the European label regimen for
128 ranibizumab. Reinjections were performed when at least one of the following criteria was met:
129 (1) loss of ≥ 5 letters since the previous visit with no obvious atrophy or subretinal fibrosis and
130 with fluid on OCT; and/or (2) active exudation on OCT (subretinal fluid unless stable since the
131 last three monthly injections, macular edema with intraretinal fluid, or increase in central

132 subfield macular thickness of at least 50 μm compared with the previous examination); and/or
133 (3) increased CNV area or persistence of leakage on angiography since the previous visit;
134 and/or (4) new or persistent subretinal or intraretinal macular hemorrhage. The monthly follow-
135 up examinations were performed by an ophthalmologist and included clinical and slit-lamp
136 examination; best corrected visual acuity (BCVA; ETDRS score and Snellen equivalent acuity);
137 spectral-domain or time-domain Optical Coherence Tomography (OCT; depending on
138 availability in each center); fundus or color fundus photography; fluorescein (FA) and/or
139 indocyanine green angiography (ICGA), at the investigator's discretion (mandatory only at
140 baseline and 12 months – M12).

141

142 **Post Hoc Analysis**

143 To better understand the visual status at 1-year, we worked on trajectories which took into
144 account the visual status at 3 months (one month after the end of the loading-dose period) and
145 1-year. Therefore, the present analysis is based on the 1-year study data from patients included
146 in GEFAL who were randomized to treatment with ranibizumab or bevacizumab and for whom
147 a BCVA reading was available at 3-months (M3).

148 From these data, three trajectories were defined: i) patients with no vision loss ≥ 5 -letters at M3
149 and at 1-year (absence of loss ≥ 5 -letters); ii) patients with no vision loss ≥ 5 -letters at M3 but
150 loss ≥ 5 -letters at 1-year (secondary loss ≥ 5 -letters) and iii) patients with vision loss ≥ 5 -letters
151 at M3 and 1-year (initial loss ≥ 5 -letters). Absence of loss ≥ 5 -letters at 1-year was defined as a
152 loss of less than 5 letters compared to both baseline and M3 values. The threshold of at least 5-
153 letters loss was used as it is ordinarily considered as clinically significant.

154

155 **Outcome measures**

156 The following factors were evaluated at baseline and at M3: age, sex, baseline BCVA, presence
157 of fluid (intraretinal fluid (IRF), subretinal fluid (SRF) and pigmented epithelium detachment
158 (PED)), central macular thickness (CMT), choroidal neovascularization (CNV) angiographic
159 subtype (purely occult, minimally classic and predominantly classic), total area of CNV, and
160 number of intravitreal injections (IVI). Classic CNV was defined as a well-demarcated
161 hyperfluorescent lesion in the early phase with leakage through the late phases. Occult CNV
162 was defined as an irregular area of stippled hyperfluorescence starting in the middle phase with
163 persistent hyperfluorescence in the late phase. In this case, ICGA shows a hyperfluorescent
164 plaque in the late phases of the exam. Within the classic group, eyes with a classic component
165 accounting for $\geq 50\%$ of the lesion were assigned to the predominantly classic subgroup, and
166 those with a classic component accounting for $< 50\%$ of the lesion were assigned to the
167 minimally classic subgroup. The total area of CNV was assessed on FA. For classic CNV, early
168 frames were chosen in which the well-demarcated border of the CNV was visible. In occult
169 CNV, the area of leakage in late frames was used for analysis. Area was measured in disk area
170 (1 disk area = 2.54 mm^2 on the basis of a diameter of 1.8 mm).⁴

171

172 **Statistical methods**

173 The analysis was performed on the full analysis set for the GEFAL study that consisted of all
174 randomized patients with BCVA available at baseline and at 12 months after inclusion (or at
175 least 10 months after inclusion for patients with unavailable data). Presence of BCVA score at
176 3 months was an additional criterion for considering patients in this post-hoc analysis.
177 Categorical variables were described in terms of frequency and percentages, and continuous
178 variables as means and standard deviations. Comparisons of M3 and final values according to
179 the trajectory groups were made using ANOVA and chi-squared test.² The influence of baseline

180 variables on trajectories groups was assessed using univariate logistic regression. All analyses
181 were carried out using SAS software version 9.2 (SAS Inc, Cary, NC).

182 **RESULTS**

183 **Baseline Characteristics**

184 The GEFAL full analysis set population consisted of 404 patients. A total of 11 patients did not
185 have M3 BCVA values (five patients were lost to follow-up and six patients did not have BCVA
186 assessment at M3) the analysis therefore included 393 patients. The mean age at inclusion was
187 79.2 (+/- 7.1) years old; 67.4% were women. The mean baseline BCVA was 54.9 (+/- 14.0)
188 letters and the mean CMT was 357.4 (+/- 116.6) μm . CNV type was purely occult in 43.6% of
189 cases. The mean total area of CNV at baseline was 2.0 (+/- 1.5) disk areas (**Table 1**).

190

191 **Functional and anatomical outcomes according to the patient trajectories**

192 An absence of loss ≥ 5 -letters was found in 225 patients (57.3%), a secondary loss ≥ 5 -letters
193 after M3 was found in 109 patients (27.7%) and an initial loss ≥ 5 -letters of BCVA was found
194 in 59 patients (15%). Mean BCVA at M3 was 62.0 (+/-14.5), 64.1 (+/-16.0) and 43.8 (+/-17.2)
195 letters for the absence of loss ≥ 5 -letters, secondary loss ≥ 5 -letters and initial loss ≥ 5 -letters
196 groups respectively ($p < 0.0001$). Final BCVA was significantly different between the three
197 groups with 67.0 (+/- 14.4), 49.5 (+/- 20.8) and 45.5 (+/- 20.9) letters for the absence of loss
198 ≥ 5 -letters, secondary loss ≥ 5 -letters and initial loss ≥ 5 -letters groups respectively ($p < 0.0001$,
199 **Figure 1**).

200

201 Mean CMT at M3 was 247.5 (+/- 66.5), 244.2 (+/- 56.6) and 265.0 (+/- 82.6) μm for the absence
202 of loss ≥ 5 -letters, secondary loss ≥ 5 -letters and initial loss ≥ 5 -letters groups respectively
203 ($p = 0.2741$). Final CMT was significantly different between the three groups with 253.1 (+/-
204 82.8), 270.2 (+/- 83.8) and 263.6 (+/- 76.5) μm for the absence of loss ≥ 5 -letters, secondary
205 loss ≥ 5 -letters and initial loss ≥ 5 -letters groups respectively ($p = 0.0353$, **Figure 2**).

206

207 **Predictors of visual trajectories**

208 Baseline characteristics were comparable between the three groups except for the total CNV
209 area which was larger in the secondary loss ≥ 5 -letters and initial loss ≥ 5 -letters groups
210 ($p=0.0412$). Baseline BCVA ($p=0.6676$), and baseline CMT ($p=0.7024$) were not associated
211 with a particular trajectory, nor the presence of a specific fluid location or the CNV subtype
212 (**Table 2**).

213

214 At M3 the presence of SRF ($p=0.0286$) was significantly associated with profile groups but this
215 was not the case for IRF ($p=0.1113$). CMT ($p=0.2741$) and total CNV area ($p=0.1087$) were
216 not significantly associated with the profile group (**Table 3**). The presence of both IRF and SRF
217 at M3 were seen in 83 (36.9%), 30 (27.5%) and 31 (52.5%) of patients in the absence of loss
218 ≥ 5 -letters, secondary loss ≥ 5 -letters and initial loss ≥ 5 -letters groups respectively ($p=0.0066$).

219

220 The number of injections in one year did not differ between the three groups ($p=0.8603$) but
221 the early need for a fourth injection seems to be associated with worse visual outcomes
222 ($p=0.0006$). Patients with an initial loss ≥ 5 -letters needed this injection in the third month after
223 the first IVI in 70.6% of cases in comparison to 30.6% and 48.2% for the group with secondary
224 loss ≥ 5 -letters and the group with absence of loss ≥ 5 -letters, respectively (**Table 4**).

225 Finally, the treatment arm (ranibizumab or bevacizumab) was not statistically associated with
226 any specific outcomes ($p=0.0896$).

227

228 **DISCUSSION**

229 In the current study, patients were assigned to different groups according to their visual acuity
230 trajectories over time. Three groups of patients were defined: patients with no vision loss ≥ 5 -
231 letters at 3-months and at 1-year; patients with no vision loss ≥ 5 -letters at 3-months but with
232 loss ≥ 5 -letters at 1-year, and patients with vision loss ≥ 5 -letters at 3-months and 1-year.
233 Looking for predictive factors of vision loss that might determine whether the patient belongs
234 to one or other of these groups could allow for the early identification of a visual prognosis and
235 justify for more intensive treatment regimens for certain patients where relevant. We found
236 herein that only baseline CNV area correlated to the visual trajectory. Larger lesions were
237 associated with poorer visual outcomes in the two subgroups of patients who lost more than 5
238 letters, either initially or after the loading dose. Neither baseline BCVA nor baseline CMT were
239 associated with visual loss. A *post-hoc* analysis of the randomized controlled trial VEGF Trap-
240 Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) has also recently shown that
241 only CNV area, in addition to the leakage area, influenced vision loss under fixed-dose anti-
242 VEGF regimen (bi-monthly aflibercept or monthly ranibizumab).¹⁰ Unlike this previous study,
243 our results were extracted from the GEFAL study, analyzing anti-VEGF treatments under PRN
244 regimen (ranibizumab and bevacizumab). The similarity of our findings to the *post-hoc* analysis
245 of the VIEW study suggests that baseline CNV area is a predictive factor of vision loss,
246 independently of the treatment regimen and anti-VEGF molecule used.

247

248 In the present study, we found no association between neovascular subtype and visual loss.
249 However, it is well known from historical studies dating from before the anti-VEGF era that
250 the natural history of choroidal neovascularization differs according to the neovascular
251 membrane location. Occult neovascularization has better outcomes if left untreated and the
252 lesion can remain stable for months,^{11,12} in comparison to classic neovessels which more

253 frequently develop fibrotic scars.¹³⁻¹⁵ In the *post hoc* analysis of the VIEW study, occult
254 neovessels were associated with better final visual acuity, however, lower visual gain was found
255 in comparison to classic CNV. This result is explained by the fact that patients with occult CNV
256 have higher BCVA at baseline and therefore cannot achieve as large a gain as those with lower
257 visual acuity at baseline.¹⁰ The major drawback of these studies, including ours, is that they did
258 not consider the neovascular subtype classification, but only used the fluorescein angiography
259 to classify occult or classic CNV or retinal angiomatous proliferation. As such, some patients
260 could have been diagnosed incorrectly. Current studies should use spectral domain or even
261 swept-source OCT to classify neovascular subtype as recently described in an international
262 expert consensus.¹⁶

263

264 Neovascular AMD can decrease vision in a number of ways: fibrotic scars,¹⁷ long-term intra-
265 and subretinal fluid,¹⁸ or the onset of geographic atrophy.^{19,20} In our study, final CMT was
266 significantly different between subgroups, but this result is not clinically relevant and the onset
267 of macular atrophy in the subgroups of patients who lost 5 letters or more of vision is highly
268 unlikely. However, we cannot exclude the presence of a focal photoreceptor alteration in the
269 subfoveal lesion that could explain poor vision. Other early biomarkers of macular atrophy,
270 such as those defined in incomplete retinal pigment epithelium and outer retinal atrophy
271 (iRORA) cannot be excluded.²¹

272

273 At 3 months, only the presence of SRF alone or in combination with IRF were found to be
274 associated with patients who experienced early vision loss despite the injections. However,
275 mean CMT at 3 months was not significantly associated with vision loss. Conflicting results
276 have been published in the literature concerning fluid management in AMD. Although IRF is
277 associated with long-term visual loss,²² the presence of SRF and its tolerance under the retina

278 is largely debated.^{18,23,24} In addition to the presence of fluid, its location within the retina is
279 highly dependent on the CNV subtype and SRF is more frequently associated with occult
280 neovessels (type 1) than other subtypes,²⁵ especially when it is recalcitrant.²⁶ Moreover, the
281 CNV area was no longer associated with poorer visual outcomes, as the neovessel area
282 decreased after the loading dose.

283

284 We acknowledge several limitations to our study. Firstly, due to the *post hoc* design, other
285 biomarkers, that could have helped to explain vision loss in eyes treated with anti-VEGF in
286 AMD, might be missing. Presence of retinal pigment epithelium/ellipsoid alteration, choroidal
287 thickness, or hyperreflective foci are other OCT findings that might be associated with
288 recurrence and vision loss and should be analyzed in further studies using spectral domain or
289 swept source OCT.^{21,27} More recently, OCT-angiography imaging has also been found to
290 provide useful information on neovascular patterns that could potentially serve as a biomarker
291 for treatment resistance.²⁸ It has also been ascertained that patients with active disease have a
292 higher CNV area than patients in remission, probably explaining our main finding.²⁹ Secondly,
293 the follow-up of this study was only 12 months which is relatively short in comparison to the
294 natural history of the disease that develops over years. Thirdly, most of the randomized
295 controlled trials on neovascular AMD reported the number of patients that lost more than 15
296 letters during the follow-up period.^{3,4,9} However, here we deliberately chose to use the threshold
297 of a loss of 5 letters or more in order to include all the patients with a significant and clinical
298 drop in visual acuity from baseline. Nowadays, visual gain after anti-VEGF is the norm and
299 patients whose vision does not at least stabilize (i.e. absence of loss of 5 letters or more) should
300 be considered as non-responders. As previously recommended,^{30,31} we used the clinically
301 significant threshold of a loss of at least 5 letters to define patients within the poorer trajectories.
302 We could also have defined a group of patients who gained 5-letters or more to add a level of

303 comparison with patients who lost 5-letters or more. Nevertheless, our main goal was to assess
304 the predictive factors of vision loss at 1-year despite anti-VEGF therapy and we preferred to
305 compare patients with poor visual outcomes to patients that, at least, had no significant loss of
306 vision.

307

308 In conclusion, in this post-hoc analysis of the randomized controlled GEFAL study, we found
309 that a large CNV area at baseline was significantly associated with initial or secondary loss of
310 visual acuity ≥ 5 -letters, despite anti-VEGF injections, in wet AMD. Moreover, the presence of
311 fluid, both SRF and IRF at M3 was found in patients with poorer trajectories. Further studies
312 are needed to find other biomarkers of visual loss, especially those related to CNV subtypes, to
313 improve follow-up and adapt treatment regimens to specific patients and diseases.

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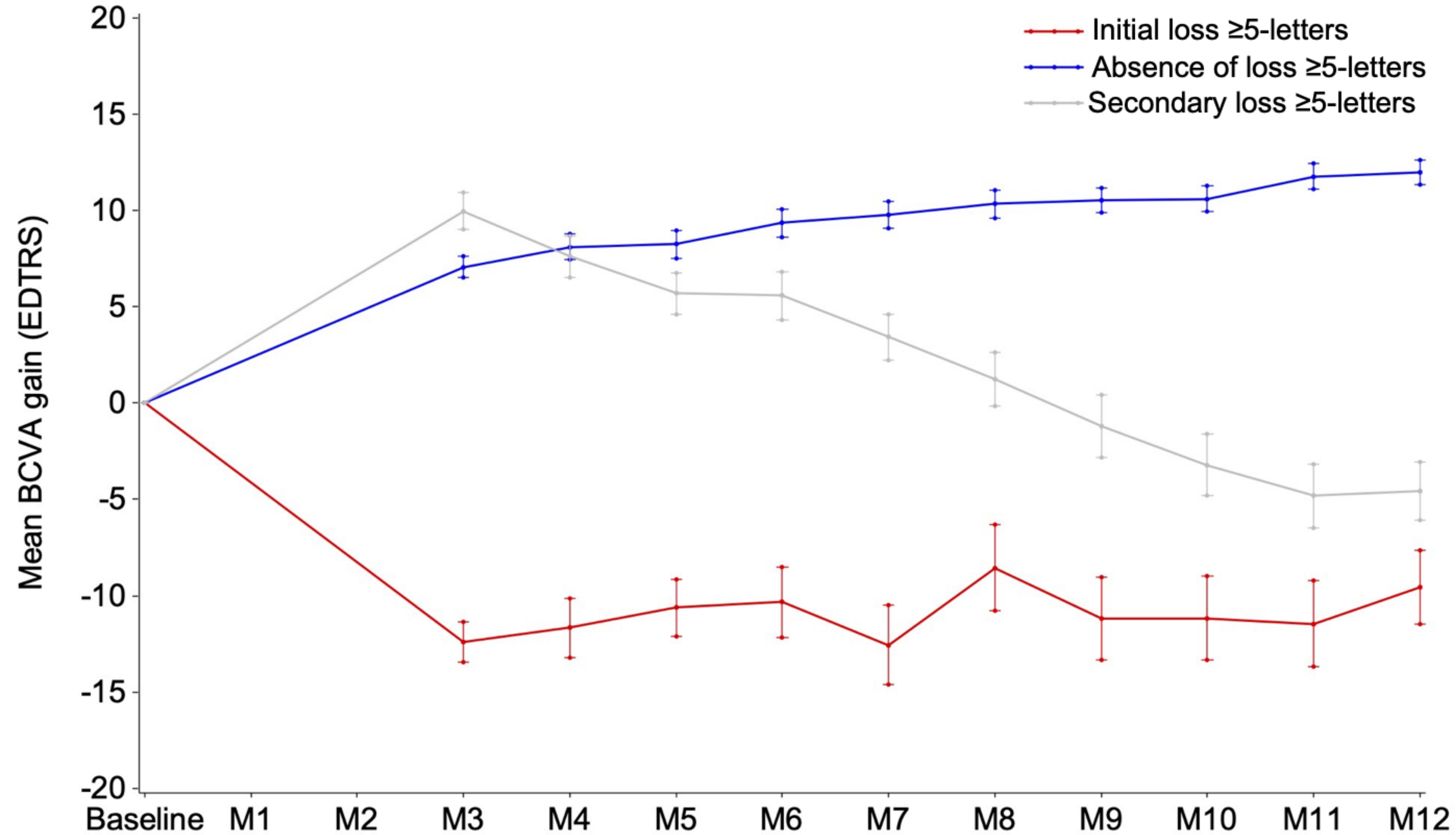
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411 **FIGURE CAPTIONS**

412 **Figure 1:** Mean visual acuity changes from baseline. Error bars represents standard deviations.

413

414 **Figure 2:** Evolution of mean central macular thickness from baseline. Error bars represents
415 standard deviations.



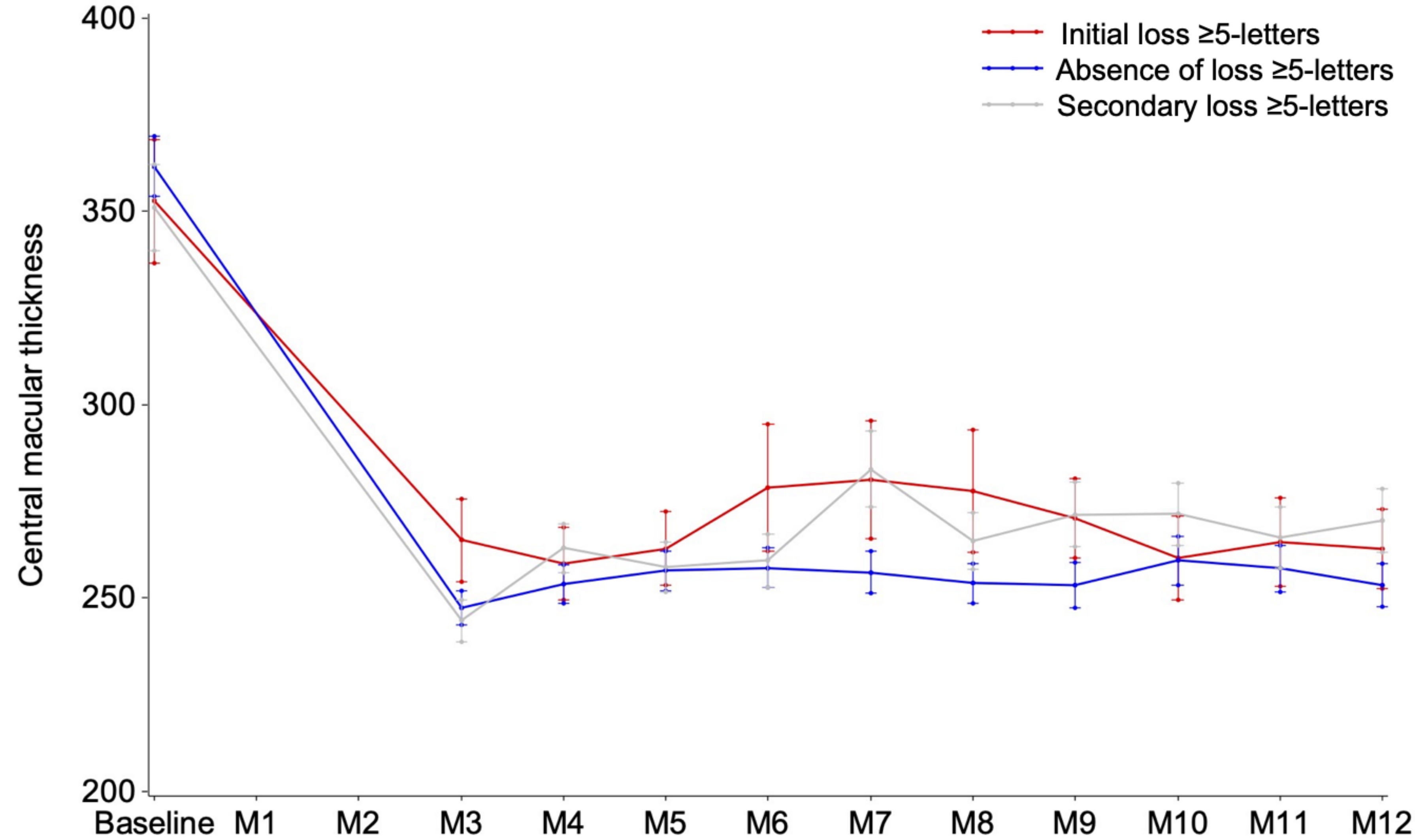


Table 1: Characteristics of the global population (n=393)

Sex Female, n (%)	265 (67.4)
Mean age, year (SD)	79.2 (7.1)
Mean baseline BCVA, ETDRS letters (SD)	54.9 (14.0)
Presence of fluid, n (%)	
IRF	216 (55.0)
SRF	309 (78.6)
PED	221 (56.2)
Mean CMT, μm (SD)	357.4 (116.6)
CNV type, n (%)	
Purely occult	170 (43.6)
Minimally classic	93 (23.8)
Predominantly classic	127 (43.6)
Total area of CNV, Disk area (SD)	2.0 (1.5)
Mean number of IVI in 1 year, n (SD)	6.6 (2.5)

BCVA: best-corrected visual acuity; CMT: central macular thickness; CNV: choroidal neovascularization; IRF: intraretinal fluid; IVI: intravitreal injection; PED: pigment epithelium detachment; SRF: subretinal fluid

Means were given with standard deviation

Table 2: Comparison of baseline characteristics between the trajectories

	Absence of loss ≥ 5 -letters (n=225)	Secondary loss ≥ 5 -letters (n=109)	Initial loss ≥ 5 -letters (n=59)	p-value
Sex Female, n (%)	147 (65.3)	75 (68.8)	43 (72.9)	0.5125
Mean age, year (SD)	79.0 (7.0)	79.6 (7.1)	79.2 (7.2)	0.8011
Mean baseline BCVA, ETDRS letters (SD)	55.0 (13.5)	54.2 (14.8)	56.2 (14.4)	0.6676
Presence of fluid, n (%)				
IRF	119 (52.9)	58 (53.2)	39 (66.1)	0.1802
SRF	181 (80.4)	81 (74.3)	47 (79.7)	0.4320
PED	121 (53.8)	65 (59.6)	35 (59.3)	0.5246
Mean CMT, μm (SD)	361.6 (115.7)	351.1 (116.1)	352.7 (122.5)	0.7024
CNV type, n (%)				
Purely occult	102 (45.7)	48 (44)	20 (34.5)	0.3089
Minimally classic	53 (23.8)	28 (25.7)	26 (44.8)	
Predominantly classic	68 (30.5)	33 (30.3)	12 (20.7)	
Mean total area of CNV, Disk area (SD)	1.8 (1.4)	2.2 (1.7)	2.2 (1.5)	0.0412

BCVA: best-corrected visual acuity; CMT: central macular thickness; CNV: choroidal neovascularization; IRF: intraretinal fluid; PED: pigment epithelium detachment; SRF: subretinal fluid

Table 3: Comparison of M3 characteristics between the trajectories

	Absence of loss \geq 5-letters (n=225)	Secondary loss \geq 5-letters (n=109)	Initial loss \geq 5-letters (n=59)	p-value
Mean BCVA, ETDRS letters (SD)	62.0 (14.5)	64.1 (16.0)	43.8 (17.2)	<0.0001
Presence of fluid, n (%)				
IRF	44 (19.6)	13 (11.9)	14 (23.7)	0.1113
SRF	52 (23.1)	21 (19.3)	22 (37.3)	0.0286
PED	63 (28.0)	32 (29.4)	18 (30.5)	0.9183
Mean CMT, μ m (SD)	247.5 (66.5)	244.2 (56.6)	265.0 (82.6)	0.2741
Mean total area of CNV, Disk area (SD)	1.4 (0.8)	1.7 (1.5)	2.1 (1.2)	0.1087

BCVA: best-corrected visual acuity; CMT: central macular thickness; CNV: choroidal neovascularization; IRF: intraretinal fluid; PED: pigment epithelium detachment; SRF: subretinal fluid

Table 4: Timing of the 4th injection

Month	Absence of loss ≥5-letters (n=225)	Secondary loss ≥5-letters (n=109)	Initial loss ≥5-letters (n=59)	p-value
M3, n (%)	93 (48.2)	30 (30.6)	36 (70.6)	0.0029
M4, n (%)	39 (20.2)	30 (30.6)	8 (15.7)	
M5, n (%)	32 (16.6)	13 (13.3)	1 (2)	
M6, n (%)	13 (6.7)	11 (11.2)	3 (5.9)	
M7-8, n (%)	13 (6.7)	8 (8.2)	1 (2)	
≥M9, n (%)	3 (1.6)	6 (6.1)	2 (3.9)	