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Natural History of Geographic Atrophy Secondary to Age-Related Macular Degeneration

Results from the Prospective Proxima A and B Clinical Trials

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Purpose: To better characterize visual function decline and geographic atrophy (GA) progression secondary to age-related macular degeneration (AMD).

Design: Proxima A (NCT02479386)/Proxima B (NCT02399072) were global, prospective, noninterventional, observational clinical trials.

Participants: Eligible patients were aged ≥50 years. Patients in Proxima A had bilateral GA without choroidal neovascularization (CNV) in either eye (N = 295). Patients in Proxima B had GA without CNV in the study eye and CNV±GA in the fellow eye (fellow eye CNV cohort, n = 168) or GA without CNV in the study eye, no CNV/GA in the fellow eye (fellow eye intermediate AMD cohort, n = 32).

Methods: Changes in visual function and imaging/anatomic parameters were evaluated over time using a mixed model for repeated measurement accounting for key baseline characteristics.

Main Outcome Measures: Prespecified end points included change in GA area from baseline, best-corrected visual acuity (BCVA) score assessed by Early Treatment Diabetic Retinopathy Study (ETDRS), and visual acuity under low-luminance (LLVA).

Results: At 24 months, adjusted mean (standard error) change in GA lesion area from baseline was 3.87 (0.15) mm^2 in participants with bilateral GA (Proxima A), 3.55 (0.16) mm^2 in the fellow eye CNV cohort (Proxima B), and 2.96 (0.25) mm^2 in the fellow eye intermediate AMD cohort (Proxima B). Progression of GA was greater in patients with baseline nonsubfoveal (vs. subfoveal) GA lesions and tended to increase as baseline low-luminance deficit increased (all patients). Conversion to GA or CNV in the fellow eye occurred in 30% and 6.7% of participants, respectively, in the Proxima B intermediate AMD cohort at month 12. Adjusted mean (standard error) changes in BCVA and LLVA (ETDRS letters) in the study eye from baseline to 24 months were −13.88 (1.40) and −7.64 (1.20) in Proxima A, −9.49 (1.29) and −7.57 (1.26) in Proxima B fellow eye CNV cohort, and −11.48 (3.39) and −8.37 (3.02) in Proxima B fellow eye intermediate AMD cohort, respectively.

Conclusions: The prospective Proxima A and B studies highlight the severe functional impact of GA and the rapid rate of GA lesion progression over a 2-year period, including in patients with unilateral GA at baseline. *Ophthalmology 2020;127:769-783 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss in people aged ≥50 years.[1] The majority of this visual loss occurs in the advanced stage of AMD, which has 2 typical clinical forms: geographic atrophy (GA) and neovascular AMD.[2-4] The nonexudative form of (GA) is characterized by loss of choriocapillaris, retinal pigment epithelium, and photoreceptors.[4,5] In comparison, the exudative form (neovascular AMD) is characterized by the occurrence of choroidal neovascularization (CNV).[6] Geographic atrophy secondary to AMD is a significant unmet medical need,[2,7,8] with no approved therapeutic strategies to fully prevent its onset or progression. Despite strong genetic and physiologic evidence implicating complement cascade dysregulation in the development of GA,[9,10] several clinical trials of agents targeting this pathway have been unsuccessful in slowing GA enlargement.[11,12]

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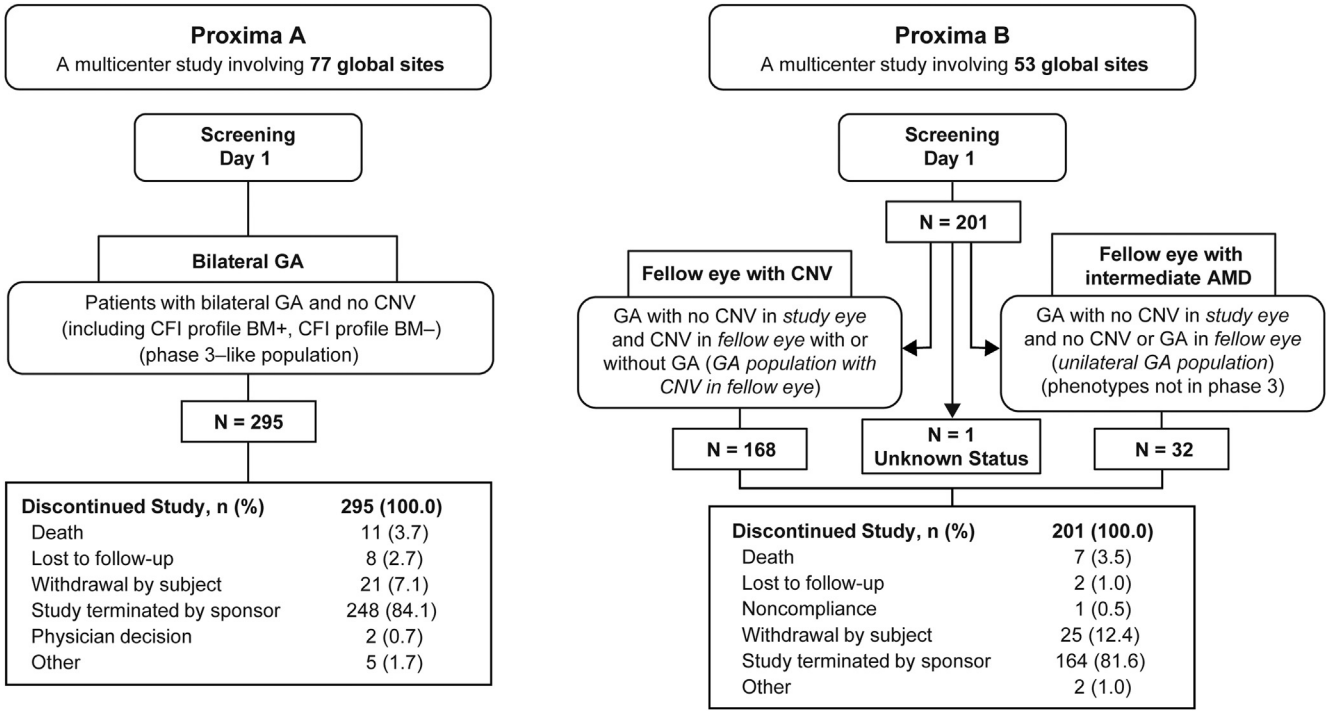


Figure 1. Participants enrolled in Proxima A and B. AMD = age-related macular degeneration; BM− = biomarker-negative; BM+ = biomarker-positive; CFI = complement factor I; CNV = choroidal neovascularization; GA = geographic atrophy.

Although substantial natural history data exist on the development and progression of GA lesions from prospective, longitudinal studies,[2,3,13-16] there are less data on the decline of visual function in patients with GA.[13,16-18] In addition, a number of outstanding questions remain unanswered concerning the interrelationship between GA and CNV[19] and the functional impact of GA (both as an isolated entity and in association with CNV). Further research is also needed on the differentiation of clinical phenotypes and associated implications for severity and rates of disease progression.

The Proxima program involved 2 global, prospective, noninterventional observational clinical trials that were part of the lampalizumab clinical trial program[11] and were designed to better characterize visual function decline associated with progression of GA secondary to AMD. Proxima A enrolled participants with bilateral GA without CNV at baseline and was designed to reflect the patient population recruited into the interventional phase 3 Chroma and Spectri clinical trials.[11] Proxima B enrolled those with unilateral GA with or without CNV in the fellow eye at baseline and was designed to capture phenotypic variations of GA not captured by the Proxima A study population.

Methods

Study Design and Participants

Proxima A and B were global, multicenter, prospective, observational studies involving, respectively, 77 sites in 15 countries (Proxima A; ClinicalTrials.gov, NCT02479386) and 53 sites in 11 countries (Proxima B; ClinicalTrials.gov, NCT02399072). The studies were originally planned to enroll 360 and 200 patients and have a follow-up period of 48 and 60 months, respectively, in the absence of an approved therapy. These studies were terminated on November 20, 2017 (last patient visit: January 31, 2018), after the primary analyses of the lampalizumab phase 3 trials did not show efficacy benefit of lampalizumab.[11] Consequently, none of the recruited patients completed the planned follow-up (Fig 1).

No investigative treatment was evaluated in Proxima A and B; rather, they were natural history studies. The changes in visual function parameters and imaging and anatomic characteristics were followed over time. The studies were approved by the institutional review board or ethics committee at each participating site and conducted according to the provisions of the Declaration of Helsinki[20] and the Good Clinical Practice Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,[21] as well as all applicable local, state, and federal laws.

Three cohorts were enrolled in the studies. Patients enrolled in Proxima A had bilateral GA without CNV in either eye, and the population was enriched for the complement factor I (CFI) biomarker-positive participants (defined below) at a 2:1 ratio.[11] Patients were enrolled in Proxima B in 1 of 2 cohorts: GA with no CNV in the study eye, and CNV in the fellow eye with or without GA (fellow eye CNV cohort); or GA with no CNV in the study eye, and no CNV or GA in the fellow eye (i.e., unilateral GA [fellow eye intermediate AMD cohort]). Across both studies, participants eligible for enrollment were consenting men and women, aged ≥50 years, with the ability and willingness to return for all scheduled visits and assessments. A full list of inclusion/exclusion criteria can be found in Table S1 (available at www.aaojournal.org).

One eye was chosen as the study eye on the basis of several inclusion criteria. In Proxima A, the study eye must have had an

Table 1. Participant Demographics and Baseline Characteristics in Proxima A and B (All Enrolled Participants)

Characteristic	Proxima A	Proxima B		
	All Participants (*N* = 295)	*Fellow Eye CNV** (*n* = 168)	*Fellow Eye Intermediate AMD*† (*n* = 32)	*All Participants* (*N* = 201‡)
Mean age, yrs (SD)	78.1 (8.1)	79.5 (7.3)	75.1 (8.4)	78.7 (7.7)
Age group, n (%)				
<75 yrs	97 (32.9)	38 (22.6)	14 (43.8)	53 (26.4)
75–84 yrs	128 (43.4)	86 (51.2)	14 (43.8)	100 (49.8)
≥85 yrs	70 (23.7)	44 (26.2)	4 (12.5)	48 (23.9)
Sex, n (%)				
Male	115 (39.0)	52 (31.0)	13 (40.6)	65 (32.3)
Female	180 (61.0)	116 (69.0)	19 (59.4)	136 (67.7)
Race, n (%)				
American Indian or Alaskan Native	2 (0.7)	1 (0.6)	0	1 (0.5)
Asian	1 (0.3)	0	0	0
Black or African American	1 (0.3)	0	0	0
White	287 (97.3)	165 (98.2)	32 (100.0)	198 (98.5)
Unknown	4 (1.4)	2 (1.2)	0	2 (1.0)
Ethnicity, n (%)				
Hispanic or Latino	33 (11.2)	16 (9.5)	2 (6.25)	18 (9.0)
Not Hispanic or Latino	249 (84.4)	150 (89.3)	30 (93.75)	181 (90.0)
Not stated	7 (2.4)	1 (0.6)	0	1 (0.5)
Unknown	6 (2.0)	1 (0.6)	0	1 (0.5)

AMD = age-related macular degeneration; CNV = choroidal neovascularization; SD = standard deviation.
*Fellow eye with CNV with or without geographic atrophy (GA).
†Fellow eye without GA or CNV.
‡One patient was of unknown status (with regard to fellow eye).

Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letter score of ≥49 letters (Snellen equivalent of 20/100 or better). If the BCVA letter score was ≥79 letters (Snellen equivalent of 20/25 or better), ≥1 GA lesion must have been within 250 μm of the foveal center. In addition, the study eye must have had well-demarcated area(s) of GA secondary to AMD with no evidence of prior or active CNV and with a total GA lesion size of 2.54–17.78 mm^2 (1–7 disc areas [DAs]) residing completely within the blue-light fundus autofluorescence (FAF) imaging field (field 2–30 degrees, image centered on the fovea), with perilesional banded or diffuse hyperautofluorescence patterns. If the GA was multifocal, ≥1 focal lesion must have been ≥1.27 mm^2 (≥0.5 DAs).

In Proxima B, the study eye must have had an ETDRS BCVA letter score of ≥19 letters (Snellen equivalent of 20/400 or better) and no evidence of prior or active CNV. In addition, the study eye must have had well-demarcated areas of GA secondary to AMD residing completely within the FAF imaging field (field 2–30 degrees, image centered on the fovea) with perilesional banded or diffuse hyperautofluorescence patterns observed on FAF. For the fellow eye CNV cohort, a total lesion size of 1.27–17.78 mm^2 (0.5–7 DAs) was required in the study eye. For the fellow eye intermediate AMD cohort, the study eye was required to have a total lesion size of 0.3–17.78 mm^2 (~0.1–7 DAs) or, if multifocal, ≥1 focal lesion of ≥0.3 mm^2. Morphological inclusion and exclusion criteria were confirmed by the reading center before enrollment.

If both eyes met the eligibility criteria for the study eye, the eye with the worse visual function as determined by the investigator and the participant was designated as the study eye. If both eyes had the same visual function, the eye with the larger area of GA was selected as the study eye.

In Proxima A and B, the *CFI* profile biomarker-positive participants were defined as risk-allele carriers of *CFI* who were also risk-allele carriers at *complement factor H (CFH)* and/or *complement C2/complement factor B (C2/CFB)*, and the *CFI* profile biomarker-negative participants were defined as noncarriers of the *CFI* risk allele or carriers of the *CFI* risk allele who are noncarriers of the risk alleles at both *CFH* and *C2/CFB*.

Assessments and Outcomes

Prespecified outcome end points for Proxima A and B included change in GA area from baseline as assessed by FAF; BCVA score, as assessed by ETDRS chart at a starting distance of 4 m; and BCVA score, as assessed by ETDRS chart under low-luminance conditions (low-luminance visual acuity [LLVA]) at a starting distance of 4 m using a 2 log unit neutral density filter (Kodak Wratten 2.0 Neutral Density Filter). Geographic atrophy lesion area (by FAF), BCVA, and LLVA were measured at baseline (i.e., screening for GA area; day 1 for visual acuity assessments) and at 6-monthly assessments thereafter, up to an anticipated 48 months (in Proxima A), 60 months (in Proxima B), and at the early termination visit held within 2 months of their last visit (for participants who discontinued before study completion).

Fundus images of the study and fellow eyes at screening and at specified visits were evaluated at the Doheny Image Reading Center (Los Angeles, CA) for Proxima A and at the GRADE Reading Center (Bonn, Germany) for Proxima B. The diagnosis and measurement of GA were based on FAF imaging. Other imaging modalities such as near-infrared reflectance, OCT, and fluorescein angiography were used to confirm key features of the GA lesion, such as the exact boundaries for precise measurement and foveal involvement.

The diagnosis of active or previous CNV was based on a qualitative assessment of multimodal imaging at baseline. The image biomarkers suggesting presence of CNV varied according to the image modality; for example, leakage on fluorescein

Table 2. Ocular Baseline Characteristics in the Study Eye in Proxima A and B (All Enrolled Participants)

Characteristic	Proxima A	Proxima B		
	All Participants (N = 295)	*Fellow Eye CNV* (n = 168)*	*Fellow Eye Intermediate AMD† (n = 32)*	*All Participants (N = 201)*
GA lesion area (mm^2)				
n	291	167	32	200
Mean (SD)	8.1 (4.0)	6.8 (3.7)	3.6 (2.7)	6.4 (3.9)
Square root of GA area (mm)				
n	291	167	32	200
Mean (SD)	2.7 (0.7)	2.5 (0.7)	1.8 (0.6)	2.4 (0.8)
GA lesion size category, n (%)				
n	291	167	32	200
<4 DAs	204 (70.1)	134 (80.2)	30 (93.75)	164 (82.0)
≥4 DAs	87 (29.9)	33 (19.8)	2 (6.25)	36 (18.0)
GA lesion location, n (%)				
n	291	168	32	201
Subfoveal	140 (48.1)	92 (54.8)	19 (59.4)	112 (55.7)
Nonsubfoveal	151 (51.9)	76 (45.2)	13 (40.6)	89 (44.3)
GA lesion contiguity, n (%)				
n	291	168	32	200
Multifocal	229 (78.7)	132 (78.6)	18 (56.25)	150 (75.0)
Nonmultifocal	62 (21.3)	36 (21.4)	14 (43.75)	50 (25.0)
Presence of reticular pseudodrusen, n (%)				
n	291	168	32	201
Yes	130 (44.7)	147 (87.5)	24 (75.0)	172 (85.6)
No	133 (45.7)	NA	NA	NA
Not determinable	28 (9.6)	21 (12.5)	8 (25.0)	29 (14.4)
Distance to central fovea for participants with nonsubfoveal lesion, μm				
n	151	74	13	87
Mean (SD)	252.4 (190.7)	467.9 (286.1)	442.9 (184.8)	464.2 (272.6)
Lens status, n (%)				
n	294	168	32	201
Phakic	133 (45.2)	64 (38.1)	17 (53.1)	82 (40.8)
Pseudophakic	160 (54.4)	104 (61.9)	15 (46.9)	119 (59.2)
Other	1 (0.3)	0	0	0
Hyperautofluorescence pattern, n (%)				
n	291	168	32	201
Banded	9 (3.1)	6 (3.6)	0	6 (3.0)
Diffuse	280 (96.2)	161 (95.8)	31 (96.9)	192 (95.5)
Focal	1 (0.3)	0	0	0
Not determinable/not available	1 (0.3)	1 (0.6)	1 (3.1)	3 (1.5)
Years since first diagnosis of GA in study eye at day 1				
n	241	156	31	188
Mean (SD)	4.4 (4.7)	3.8 (3.2)	2.6 (3.2)	3.6 (3.2)
Medical history, n (%)				
n	295	168	32	201
Glaucoma	24 (8.1)	12 (7.1)	3 (9.4)	15 (7.5)
Ocular hypertension	11 (3.7)	1 (0.6)	1 (3.1)	2 (1.0)

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DA = disc area; GA = geographic atrophy; NA = not applicable; SD = standard deviation.
*Fellow eye with CNV with or without GA.
†Fellow eye without GA or CNV.

angiography and fibrovascular pigment epithelium detachment on OCT. The presence of reticular pseudodrusen was based on a qualitative assessment whereby the reviewer used all available images (i.e., color fundus images, near-infrared reflectance, and FAF) to look for interlacing ill-defined networks with soft drusen-like appearance. The reader could then determine the presence of pseudodrusen as no, questionable (i.e., grader was >50% but <90% sure that pseudodrusen are present), yes (i.e., >90% certain pseudodrusen are present), or undeterminable (i.e., presence cannot be evaluated). Foveal involvement was

Table 3. Visual Function Baseline Characteristics in the Study Eye in Proxima A and B (All Enrolled Participants)

Characteristic	Proxima A	Proxima B		
	All Participants (N = 295)	*Fellow Eye CNV* (n = 168)*	*Fellow Eye Intermediate AMD† (n = 32)*	*All Participants (N = 201)*
BCVA, ETDRS letters				
n	293	168	32	201
Mean (SD)	66.3 (9.6)	63.1 (15.6)	56.6 (19.5)	61.9 (16.5)
BCVA categories, ETDRS letters, n (%)				
n	293	168	32	201
<64 (worse than 20/50)	108 (36.9)	80 (47.6)	17 (53.1)	98 (48.8)
≥64 (20/50 or better)	185 (63.1)	88 (52.4)	15 (46.9)	103 (51.2)
BCVA categories, approximate Snellen equivalent, n (%)				
n	293	168	32	201
Worse than 20/100	3 (1.0)	26 (15.5)	12 (37.5)	39 (19.4)
20/100 to <20/80	36 (12.3)	18 (10.7)	4 (12.5)	22 (10.9)
20/80 to <20/40	116 (39.6)	54 (32.1)	3 (9.4)	57 (28.4)
20/40 or better	138 (47.1)	70 (41.7)	13 (40.6)	83 (41.3)
LLVA, ETDRS letters				
n	287	167	32	200
Mean (SD)	36.5 (18.8)	39.8 (16.7)	42.1 (15.7)	40.1 (16.5)
LLD (BCVA − LLVA), ETDRS letters				
n	287	167	32	200
Mean (SD)	29.8 (17.5)	23.3 (14.7)	14.5 (13.5)	21.8 (14.8)
By quartile, n (%)				
Min − Q1	73 (25.4)	36 (21.6)	17 (53.1)	53 (26.6)
Q1 − Q2	74 (25.8)	48 (28.7)	6 (18.75)	54 (27.1)
Q2 − Q3	70 (24.4)	39(23.4)	6 (18.75)	45 (22.6)
Q3 − max	70 (24.4)	44 (26.3)	3 (9.4)	47 (23.6)

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; LLD = low-luminance deficit; LLVA = low-luminance visual acuity; max = maximum; min = minimum; Q = quartile; SD = standard deviation.
*Fellow eye with CNV with or without geographic atrophy (GA).
†Fellow eye without GA or CNV.

determined by multimodal imaging anchored on OCT, and the GA lesion boundary had to affect the foveal center point to be considered subfoveal.

Mesopic microperimetry (retinal sensitivity and number of scotomatous points) was also assessed at baseline and at yearly assessments thereafter in Proxima A but will not be reported in this publication dedicated to topline results. In Proxima A and Proxima B, *CFI* biomarker status was determined using the Cobas CFI Profile Clinical Trial Assay, a real-time polymerase chain reaction test developed by Roche Molecular Systems (Pleasanton, CA). Participants were assessed at screening for CFI biomarker status based on risk alleles at single nucleotide polymorphisms rs4698775 (*CFI*), rs429608 (*C2/CFB*), and rs1329428 (*CFH*).

Statistical Methods

In Proxima A, the proposed sample size of a total of 360 participants enabled estimates to be made with reasonable precision; with a sample of 360, the width of 95% confidence interval (CI) of mean BCVA change from baseline at 24 months would be within 3−4 letters (assumed standard deviation [SD] of 15 BCVA ETDRS letters), the minimal clinically meaningful difference.[22,23] In Proxima B, the proposed sample size of a total of 200 participants (n = 50 in fellow eye intermediate AMD cohort and n = 150 in fellow eye CNV cohort) enabled estimates to be made with reasonable precision; with a sample of 200, the width of 95% CI (0.4−0.5 mm^2) of mean GA lesion size change from baseline at 12 months would be within an assumed SD of 1.5−2.0 mm^2.

All participants who had ≥1 postbaseline assessment were included in the analysis. Descriptive statistics are presented for the demographic and baseline characteristics. In both Proxima A and B, the end points included changes from baseline in GA area in the study eye, BCVA, and LLVA. Low-luminance deficit (LLD) was calculated as BCVA minus LLVA. The change from baseline in anatomic and visual function end points at months 6, 12, 18, and 24 was analyzed using a linear model (mixed model for repeated measurement [MMRM]) adjusting for key baseline characteristics: categoric covariates of visit, GA location, and GA contiguity; and continuous covariates of baseline GA area, baseline visual functions (BCVA and LLVA, as appropriate), and years since first diagnosis of GA in the study eye at day 1. An unstructured covariance was used to account for within-patient correlation. There was no formal correction of type I error for multiple testing. Least-square means with the corresponding 2-sided 95% CIs are presented.

Subgroup analyses of GA progression based on baseline risk factors including baseline quartile LLD were also conducted. These analyses were adjusted only for categoric covariates of corresponding baseline risk factor and continuous covariates of baseline GA area. Following the work of Feuer et al,[24] we

investigated whether baseline GA area was predictive of progression in square-root transformed GA area. Additionally, an analysis of the impact of baseline visual acuity measured using the ETDRS BCVA chart on the decline in LLD was undertaken. In Proxima B only, in the fellow eye intermediate AMD cohort, conversion to advanced AMD in the fellow eye was also analyzed as an end point (occurrence of CNV or GA). Conversion to CNV was not analyzed for the study eye in Proxima A or B and will not be reported in this publication.

Results

Patient Population (Proxima A and Proxima B)

Between May 2015 and February 2017, 295 participants were enrolled in Proxima A, and 201 participants were enrolled in Proxima B (fellow eye CNV cohort, n = 168; fellow eye intermediate AMD cohort, n = 32; 1 patient was of unknown status with respect to fellow eye; Fig 1). Because of early termination of the lampalizumab program, the follow-up time for both Proxima A and B varied across the month 6, 12, 18, and 24 assessments.

Baseline participant demographics, ocular characteristics, and visual function in the study eye (Tables 1–3) were consistent with the advanced AMD populations recruited into Proxima A and B. Overall, the majority of participants were white (Proxima A: 97.3%; Proxima B: 98.5%), and more than half of participants were female (Proxima A: 61.0%; Proxima B [both cohorts]: 67.7%). There were, however, some differences between the Proxima B fellow eye intermediate AMD cohort and the other 2 cohorts, reflecting an earlier disease state in this cohort. Participants in Proxima A and in the Proxima B fellow eye CNV cohort were similar in age (mean age, 78.1 and 79.5 years, respectively), whereas participants in the Proxima B fellow eye intermediate AMD cohort tended to be younger (mean age, 75.1 years). Participants in Proxima A and the Proxima B fellow eye CNV cohort also tended to have larger baseline GA areas than those in the Proxima B fellow eye intermediate AMD cohort (mean, 8.1 and 6.8 vs. 3.6 mm^2, respectively), reflecting the entry criteria for this cohort. There was also a higher proportion of patients in Proxima A with BCVA of ≥64 letters (Snellen equivalent: 20/50) or better than in the Proxima B cohorts, again reflecting the different entry criteria between the 2 studies (Table 3).

The majority of participants in both studies had multifocal GA lesions (Proxima A, 78.7%; Proxima B fellow eye CNV cohort, 78.6%; and Proxima B fellow eye intermediate AMD cohort, 56.3%), and approximately half had subfoveal GA lesions (Table 2). Most of the participants in Proxima A (96.2%) and Proxima B (95.5%) had a diffuse hyperautofluorescence FAF pattern. Overall, the mean (SD) ETDRS BCVA letter scores ranged from 56.6 (19.5) letters in the Proxima B fellow eye intermediate AMD cohort to 66.3 (9.6) letters in Proxima A, and approximately half of all participants had ≥64 (20/50 or better) ETDRS BCVA letter score at baseline in both studies (Table 3). Participants in Proxima A also tended to have lower LLVA scores than the other 2 cohorts (Table 3).

Geographic Atrophy Progression in the Study Eye over Time (Proxima A and Proxima B)

As shown in Table 4 and Figure 2, GA lesion area in the study eye showed a marked increase in each of the cohorts over the 2-year follow-up period. At 24 months of follow-up, the adjusted mean change in GA lesion area (MMRM data) from baseline was 3.87 mm^2 (95% CI, 3.58–4.16) in participants with bilateral GA (Proxima A), 3.55 mm^2 (95% CI, 3.24–3.86) in the fellow eye CNV cohort (Proxima B), and 2.96 mm^2 (95% CI, 2.46–3.46) in the fellow eye intermediate AMD cohort (Proxima B). The unadjusted means were similar to the means adjusted for baseline variables in the Proxima A and B studies (Table 4). Change in GA lesion area following square root transformation is presented in Table 4 and Figure 2B.

Conversion to Geographic Atrophy in the Fellow Eye (Proxima B)

In Proxima B, GA occurrence in the fellow eye intermediate AMD cohort participants was higher than in the fellow eye CNV cohort, with GA occurring in 30% (9/30 fellow eyes) versus 1.4% (2/141 fellow eyes) within the first 12 months of follow-up in these respective groups (Fig 3). At month 24, the cumulative rate of conversion to GA was 40% (4/10 fellow eyes) in the fellow eye intermediate AMD cohort and 3.2% (3/95 fellow eyes) in the fellow eye CNV cohort (Fig 3). This analysis excluded 2 patients in the fellow eye CNV cohort who had GA at baseline and 1 patient with the fellow eye unclassified.

Conversion to Choroidal Neovascularization in the Fellow Eye (Proxima B)

Of participants in the Proxima B fellow eye intermediate AMD cohort, 6.7% (2/30) developed CNV in the fellow eye within the first 12 months of follow up; at 24 months, the cumulative conversion to CNV was 20% (2/10 fellow eyes).

Change in Visual Function in the Study Eye (Proxima A and Proxima B)

As illustrated in Figure 4, visual function as assessed by ETDRS BCVA and LLVA deteriorated in all cohorts over the 2-year follow-up period. The adjusted mean change (95% CI) in BCVA (ETDRS letters) from baseline to 24 months (MMRM data) was −13.88 (−16.64 to −11.11) in Proxima A, −9.49 (−12.03 to −6.94) in the Proxima B fellow eye CNV cohort, and −11.48 (−18.51 to −4.46) in the Proxima B fellow eye intermediate AMD cohort. For LLVA (ETDRS letters), the adjusted mean change (95% CI) from baseline to 24 months (MMRM data) was −7.65 (−10.02 to −5.28) in Proxima A, −7.57 (−10.06 to −5.07) in the Proxima B fellow eye CNV cohort, and −8.37 (−14.88 to −1.86) in the Proxima B fellow eye intermediate AMD cohort. The adjusted mean change (95% CI) in LLD

Table 4. Unadjusted and Adjusted Geographic Atrophy Lesion Size in the Study Eye at Baseline, Month 12, and Month 24 in Proxima A and B (All Enrolled Participants)

	Baseline	Change at Month 12	Change at Month 24	Change at Month 12	Change at Month 24
	Unadjusted GA Area, mm²			*Adjusted GA Area, mm²**	
Proxima A (all participants)					
n	291	246	99	246	99
Mean (SE)	8.05 (0.24)	2.09 (0.08)	3.95 (0.22)	2.07 (0.09)	3.87 (0.15)
95% CI	7.59–8.52	1.94–2.24	3.52–4.38	1.90–2.24	3.58–4.16
Proxima B (fellow eye CNV)†					
n	167	139	91	138	91
Mean (SE)	6.82 (0.28)	1.90 (0.08)	3.60 (0.20)	1.87 (0.08)	3.55 (0.16)
95% CI	6.27–7.38	1.75–2.06	3.22–3.99	1.71–2.03	3.24–3.86
Proxima B (fellow eye intermediate AMD)‡					
n	32	29	10	29	10
Mean (SE)	3.55 (0.47)	1.42 (0.19)	2.61 (0.52)	1.58 (0.19)	2.96 (0.25)
95% CI	2.59–4.51	1.03–1.81	1.43–3.79	1.20–1.97	2.46–3.46
	Unadjusted Square Root of GA Area, mm			**Adjusted Square Root of GA Area, mm***	
Proxima A (all participants)					
n	291	246	99	246	99
Mean (SE)	2.75 (0.04)	0.36 (0.01)	0.63 (0.03)	0.35 (0.01)	0.62 (0.02)
95% CI	2.66–2.83	0.33–0.38	0.57–0.69	0.32–0.37	0.58–0.66
Proxima B (fellow eye CNV)†					
n	167	139	91	138	91
Mean (SE)	2.52 (0.05)	0.36 (0.01)	0.63 (0.03)	0.35 (0.01)	0.62 (0.03)
95% CI	2.41–2.63	0.33–0.39	0.56–0.69	0.32–0.38	0.57–0.67
Proxima B (fellow eye intermediate AMD)‡					
n	32	29	10	29	10
Mean (SE)	1.78 (0.11)	0.36 (0.05)	0.63 (0.13)	0.38 (0.04)	0.65 (0.09)
95% CI	1.55–2.01	0.27–0.45	0.34–0.92	0.29–0.47	0.45–0.84

AMD = age-related macular degeneration; CI = confidence interval; GA = geographic atrophy; SE = standard error.
*Least-squares values derived from model including categoric covariates of visit, GA location, GA contiguity, and continuous covariates of baseline GA area, baseline best-corrected visual acuity, baseline low-luminance visual acuity, and years since first diagnosis of GA in study eye at day 1. To model the absolute value at baseline visit, a first-order autoregressive covariance structure was assumed. To model the change from baseline at postbaseline visit, an unstructured covariance structure was assumed.
†Fellow eye with CNV with or without GA.
‡Fellow eye without GA or CNV.

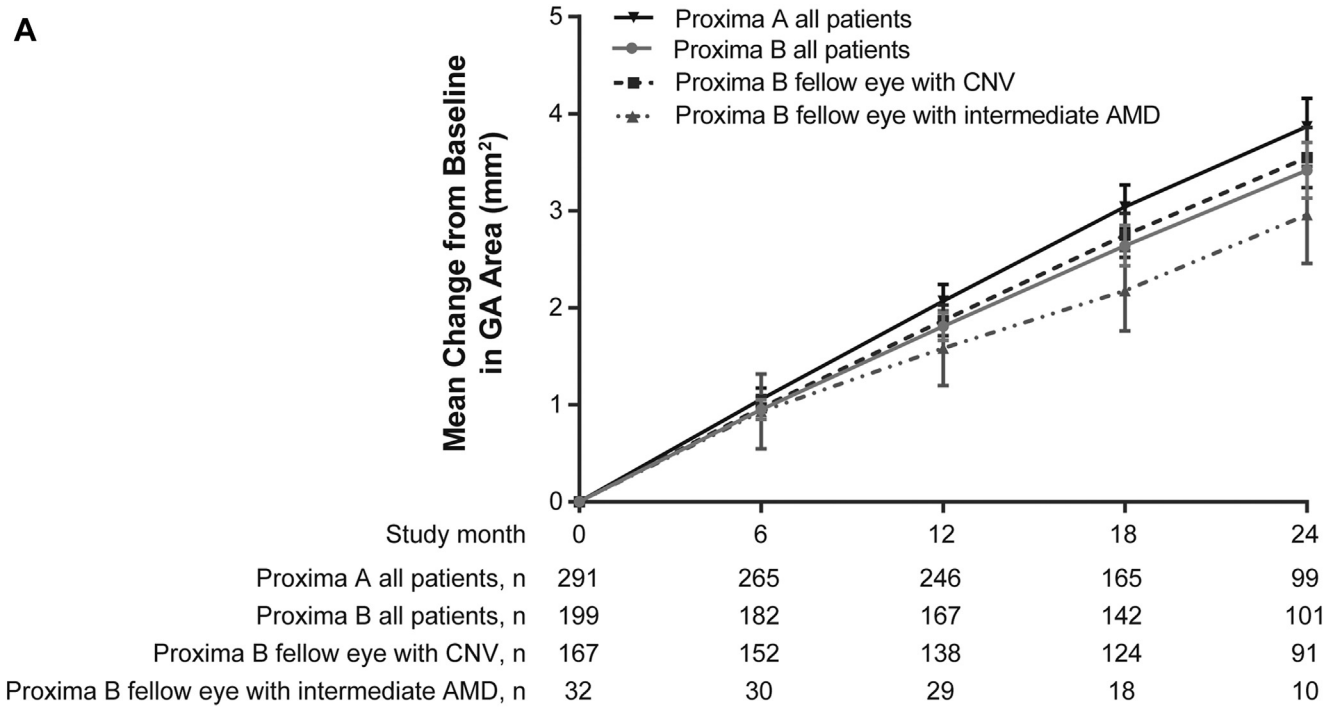
(ETDRS letters) from baseline to 24 months (MMRM data) was −5.78 (−8.70 to −2.85) in Proxima A, −1.80 (−4.73 to 1.13) in the Proxima B fellow eye CNV cohort, and −4.05 (−9.34 to 1.24) in the Proxima B fellow eye intermediate AMD cohort (Fig 5).

The proportion of patients experiencing a ≥15 letter deterioration in BCVA (i.e., moderate vision loss) at 2 years was 20.0% in the Proxima B fellow eye intermediate AMD cohort, 23.7% in the Proxima B fellow eye CNV cohort, and 34.6% in Proxima A. Within these respective cohorts, the proportions with ≥30 letter loss (i.e., severe vision loss) at 2 years were 8.3%, 10.0%, and 10.3%, respectively. Three and 4 patients in Proxima A and B, respectively, reached a Snellen equivalent of 20/200 at 2 years: in each of the trials, 2 of these patients had a BCVA of <64 (Snellen equivalent of 20/50) at baseline. Participants with lower visual function at baseline (BCVA <64, worse than 20/50) tended to have lower LLD letter scores at any point during the study compared with those with a higher visual function (≥64, 20/50 or better; Table S2, available at www.aaojournal.org).

Subgroup Analysis of Geographic Atrophy Progression in the Study Eye (Proxima A and Proxima B)

Figure 6 presents GA progression rates at month 12 in Proxima A and Proxima B (both cohorts combined) stratified by baseline risk factors. Similar trends were observed for subgroup analyses of the Proxima B fellow eye CNV cohort and fellow eye intermediate AMD cohort at month 24, as well as for GA progression rates at month 24 in the Proxima A and B studies (data not shown).

In both studies, there were apparent differences in GA progression (based on least-squares mean change) between subgroups of baseline GA lesion size, location, and contiguity, BCVA, and LLD (Fig 6). Least-squares mean change from baseline in GA lesion area at 12 months was greater in the subgroup with baseline GA lesion size <4 DA than in those with a GA lesion size ≥4 DA. However, no association was found between baseline GA area and square-root transformed GA area over the 2-year



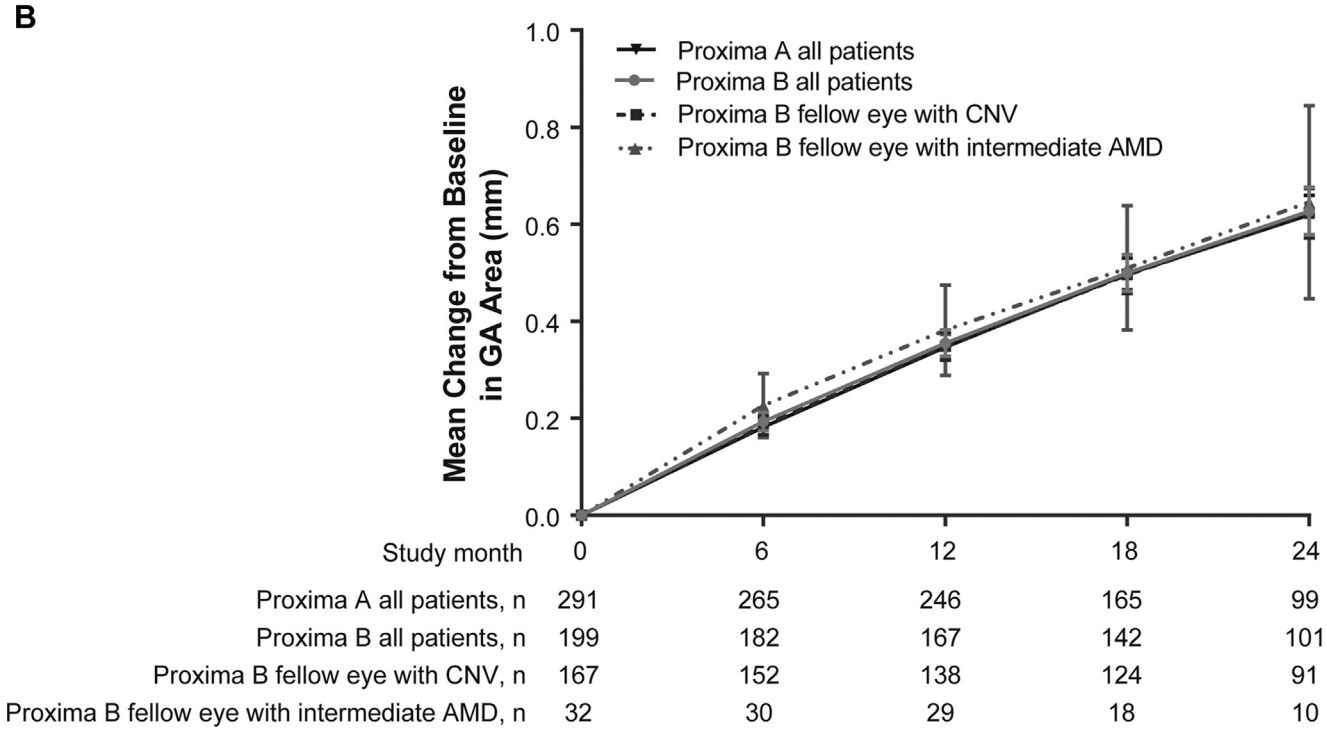


Figure 2. Geographic atrophy (GA) progression over time in Proxima A and B (study eye only). **A,** Change in GA area (mm^2) over time. **B,** Change in GA area (square-root transformed; mm) over time. n represents number of patients contributing to summary statistics; all enrolled patients. For postbaseline visits, only patients with data at baseline and visit were included. Least-squares values and corresponding 95% confidence intervals (CIs) derived from mixed model for repeated measurement including categoric covariates of visit, GA location, GA contiguity, and continuous covariates of baseline GA area, baseline best-corrected visual acuity, baseline low-luminance visual acuity, and years since first diagnosis of GA in study eye at day 1. Error bars represent 95% CIs. AMD = age-related macular degeneration; CNV = choroidal neovascularization.

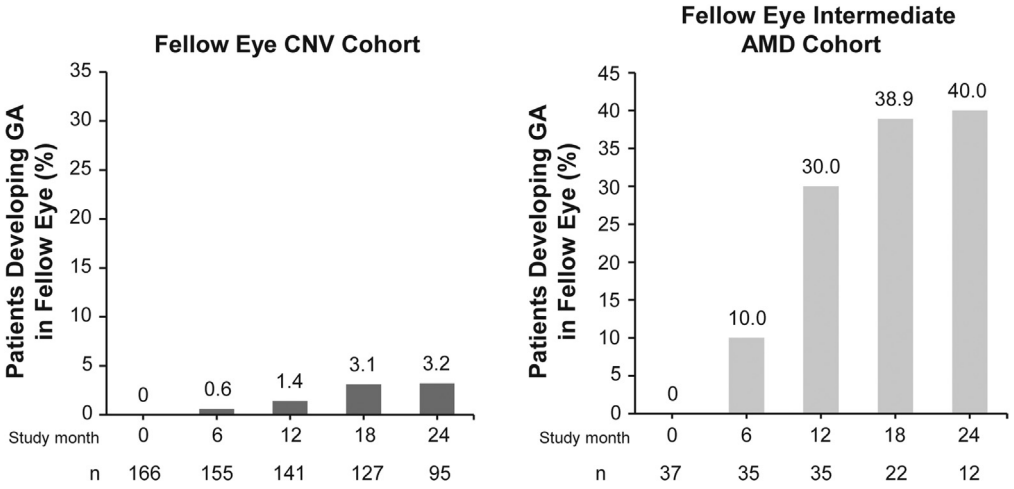


Figure 3. Cumulative rate of geographic atrophy (GA) occurrence in fellow eye in Proxima B (excluding baseline GA). n represents number of patients contributing to summary statistics; all enrolled patients. Two patients in the fellow eye choroidal neovascularization (CNV) cohort with baseline GA were excluded. For postbaseline visits, only patients with data at baseline and visit were included. Bars represent number of patients (%). AMD = age-related macular degeneration.

follow-up period in any of the cohorts (Table S3, available at www.aaojournal.org). Least-squares mean changes in GA lesion area at 12 months were greater in those with nonsubfoveal (vs. subfoveal) and multifocal (vs. nonmultifocal) GA lesions at baseline. Progression of GA also tended to increase as baseline BCVA and LLD increased.

Biomarker (CFI) status did not appear to impact GA lesion progression in either of the studies. Other risk factors evaluated (e.g., sex and presence of reticular pseudodrusen) did not appear to affect GA lesion progression in Proxima A. However, these factors presented a slightly different pattern in Proxima B. Geographic atrophy lesion progression from baseline to 12 months was greater in female than in male patients, as well as in those with presence of reticular pseudodrusen at baseline in Proxima B.

Discussion

The prospective Proxima A and Proxima B observational clinical trials contribute to our knowledge of the natural history of GA secondary to AMD by quantifying visual function decline and GA lesion progression using a variety of assessments. Findings from both studies highlight the substantial rate of disease progression and its impact on visual function in participants with GA over a 2-year period, including in those with an earlier disease state, such as those with intermediate AMD in the fellow eye.

The Proxima A trial recruited patients with bilateral GA and was designed to emulate the patient population recruited into the lampalizumab phase 3 Chroma and Spectri interventional trials.[11] It is not surprising, therefore, that participants in Proxima A had a similar rate of GA progression over 12 months as those in the Chroma and Spectri trials (adjusted mean of ~2 mm^2). These findings are also similar to those observed in other epidemiologic studies involving patients with bilateral GA (Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) study: median, 1.5 mm^2/year; Geographic Atrophy Progression Study: mean, 1.9 mm^2/year; Sunness natural history study: mean, 2.5 mm^2/year).[14-16]

The Proxima B trial recruited 2 separate participant cohorts: one in which participants had CNV (with or without GA) in the fellow eye and another in which participants had intermediate AMD in the fellow eye (i.e., no GA or CNV in the fellow eye). The rate of GA progression at the 24-month follow-up varied across the Proxima A and B cohorts, ranging from approximately 3 mm^2 in the fellow eye intermediate AMD cohort to approximately 4 mm^2 in participants with bilateral GA (Proxima A). The range of baseline GA areas across the 3 cohorts (mean, 3.6−8.1 mm^2) may have affected these results, because large baseline GA areas may artifactually be associated with faster GA progression (as discussed next). Nevertheless, our findings support those from previous studies, which have demonstrated the impact of fellow eye status on GA progression in the study eye.[16,18,25-27] In an analysis of Age-Related Eye Disease Study 2 (AREDS2) data, including patients with GA at baseline or who developed GA during the study, significantly faster GA enlargement ($P < 0.0001$) occurred with bilateral versus unilateral GA (1.50 vs. 0.91 mm^2/year or 0.31 vs. 0.23 mm/year following square root transformation, respectively), although the presence or absence of neovascular AMD had no effect on GA progression.[18] The AREDS2 analysis, however, involved patients with smaller mean baseline GA area (mean, 2.2 mm^2) than those in the Proxima studies, and a lower proportion of patients in the AREDS2 trial had central foveal involvement than in the Proxima cohorts. Sunness et al[16] and Fleckenstein et al[25] (FAM study) reported greater rates of GA progression when the fellow eye had GA (bilateral GA), lower rates when the fellow eye had early/intermediate AMD, and intermediate rates when

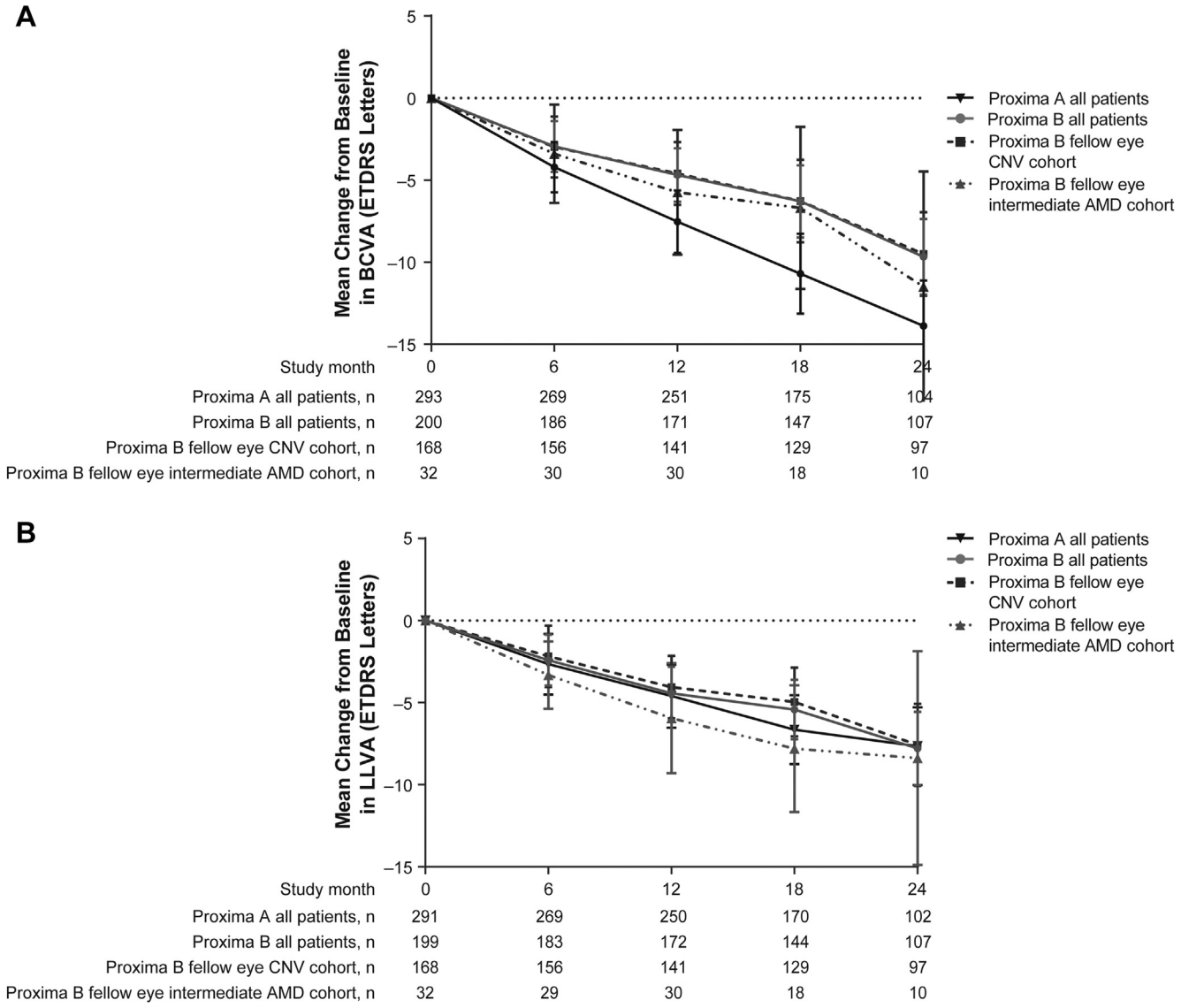
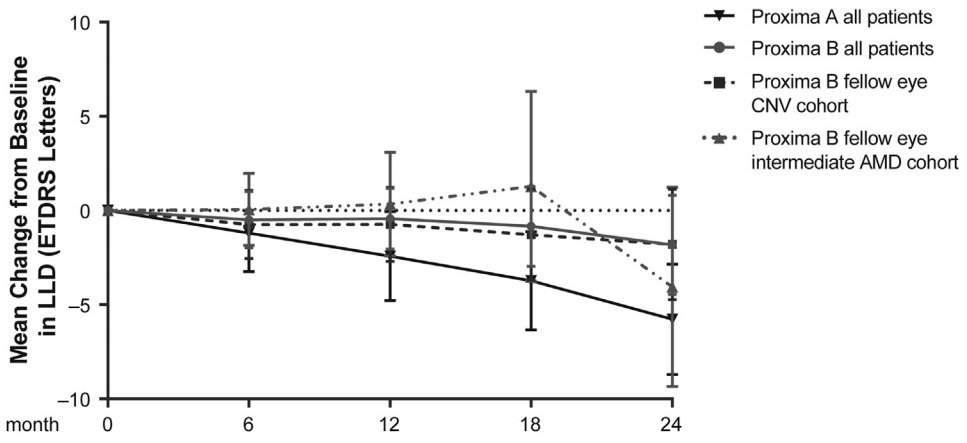


Figure 4. Mean change in (**A**) best-corrected visual acuity (BCVA) and (**B**) low-luminance visual acuity (LLVA) in study eye in Proxima A and Proxima B. n represents number of patients contributing to summary statistics; all enrolled patients. For postbaseline visits, only patients who had data at baseline and the visit are included in the summary. Least-squares mean and corresponding 95% confidence interval (CI) values derived from a mixed model for repeated measurement including categoric covariates of visit, geographic atrophy (GA) location, GA contiguity, and continuous covariates of baseline GA area, baseline BCVA, baseline LLVA, and years since first diagnosis of GA in study eye at day 1. Error bars represent 95% CIs, unadjusted analysis. AMD = age-related macular degeneration; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study.

the fellow eye had CNV. In the FAM study, which involved patients with similar baseline GA area (mean, 3.5−7.0 mm^2 across the cohorts) as those in the Proxima studies, GA progression was significantly greater in the bilateral GA group than in the fellow eye early/intermediate AMD group (mean, 1.64 vs. 0.74 mm^2/year).[25] Likewise, a meta-analysis of the FAM (discovery and replicate) and AREDS studies found a highly significant association between the presence of bilateral GA and lesion growth (size based on a random effects model; slope, 0.317 [95% CI, 0.148−0.485]; adjusted $P = 0.0037$).[26] Data presented from the UK electronic medical record study also show that progression to GA and CNV in patients with early/intermediate AMD is related to the disease state of the fellow eye. The rate of GA progression was more rapid in patients with GA in the fellow eye (adjusted hazard ratio [HR], 4.5) than in those with CNV in the fellow eye (adjusted HR, 1.7) or GA and CNV in the fellow eye (adjusted HR, 2.9).[27]

Also notable from the Proxima B data were the rates of GA or CNV occurrence in the fellow eye. Approximately one-third of participants with unilateral GA (fellow eye intermediate AMD cohort) developed bilateral GA during the first 12 months of follow-up, compared with a rate of 1.4% in those with CNV in the fellow eye. This highlights the unrelenting nature of GA. Considering that the mean time



Study month	0	6	12	18	24
Proxima A all patients, n	287	260	246	168	100
Proxima B all patients, n	199	182	170	144	106
Proxima B fellow eye CNV cohort, n	167	153	140	126	96
Proxima B fellow eye intermediate AMD cohort, n	32	29	30	18	10

Figure 5. Mean change in low-luminance deficit (LLD) in study eye in Proxima A and Proxima B. n represents number of patients contributing to summary statistics; all enrolled patients. For postbaseline visits, only patients who have data at baseline and the visit are included in the summary. Least square values derived from a mixed model for repeated measurement including categoric covariates of visit, geographic atrophy (GA) location, GA contiguity, and continuous covariates of baseline GA area, baseline best-corrected visual acuity, baseline low-luminance visual acuity, and years since first diagnosis of GA in study eye at day 1. Error bars represent 95% confidence intervals. AMD = age-related macular degeneration; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study.

from diagnosis of GA in the study eye to study entry was <3 years in the Proxima B fellow eye intermediate AMD cohort, this would suggest that progression from unilateral to bilateral GA may be quicker than has previously been reported (median estimate of 7 years based on data from AREDS).[2] These findings, however, should be interpreted with caution because of the small number of participants in the Proxima B fellow eye intermediate AMD cohort (n = 30 at 12 months) and the different imaging modalities used in the trials; development of GA was assessed in AREDS by color fundus photography, whereas multimodal imaging anchored on FAF was available in the Proxima studies.[2] In addition, approximately 7% of participants with fellow eye intermediate AMD converted to CNV in the fellow eye during the first 12 months of follow-up, with CNV conversion rates comparable to those reported in other intermediate AMD trials.[27,28] Data from a UK electronic medical record study demonstrated CNV progression rates of 8.5% per patient-year in those with early/intermediate AMD in 1 eye and GA in the contralateral eye.[27] In AREDS2, a 9.2% CNV conversion rate was reported over a median 5-year follow-up in eyes with bilateral large drusen or late AMD in 1 eye and large drusen in the fellow eye.

As previously reported, in the Proxima studies, GA progression was accompanied by deterioration in visual acuity as assessed by BCVA and LLVA across the 3 cohorts.[11,29,30] These data also support the findings from a retrospective analysis of a multicenter electronic medical record database, in which mean visual acuity (as measured by ETDRS letters) declined by 6.1 letters from baseline in the worse-seeing (study) eye at 2 years in patients with bilateral GA.[30] The BCVA letter score can underrepresent functional deficits, especially early on in the disease course, because individuals with foveal sparing may be able to read high-contrast individual letters and thus have relatively preserved visual acuity on standard testing. In Proxima A and B, half of participants had subfoveal lesions at baseline, and thus, visual acuity appears to worsen as the disease progresses irrespective of the degree of foveal sparing, as previously reported by Sunness et al.[16]

Patients with baseline BCVA of 64 letters or better (Snellen equivalent of 20/50) had significantly greater LLD scores (i.e., BCVA − LLVA or the extent of worsening in BCVA with a filter imposed) than those with baseline BCVA of less than 64 letters throughout the Proxima A and B trials, which is in line with previous findings reported by Sunness et al.[31] Low-luminance deficit captures cone function under reduced illumination,[31] and higher LLD scores at baseline have been shown to predict subsequent visual acuity loss, as well as being associated with increased GA lesion progression.[12,29,31] A subanalysis of GA progression in Proxima A and B by baseline risk factors supports the observation that GA progression varies according to baseline LLD; patients with higher LLD at baseline tended to have more rapid GA progression. This subanalysis also identified other factors, potentially affecting GA progression, with trends observed in both trials for greater GA progression in patients with nonsubfoveal (vs. subfoveal) GA lesions, which is in line with previously reported data.[14,15,18] In both Proxima trials, greater mean changes in GA lesion area were observed in those with baseline GA lesion areas of <4 DAs (vs. ≥4 DAs). Also, as has been previously reported,[18,24,32] no association was observed between baseline GA area and GA progression after square root

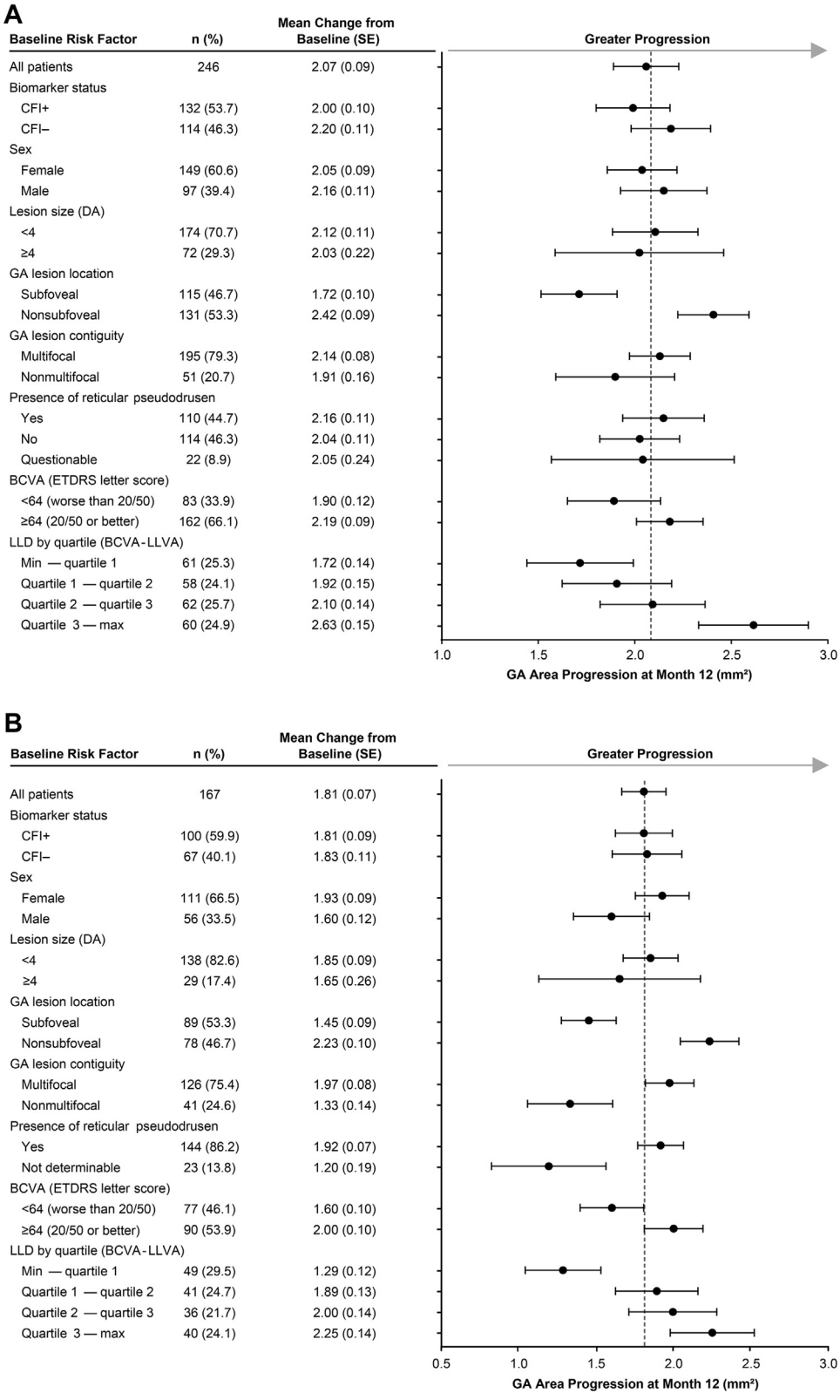


Figure 6. Mean change from baseline in geographic atrophy (GA) lesion area of study eye at month 12 by baseline risk factors. **A,** Proxima A. **B,** Proxima B (fellow eye choroidal neovascularization and fellow eye intermediate age-related macular degeneration cohorts combined). The vertical dotted line represents the mean for all patient groups. BCVA = best-corrected visual acuity; CFI− = complement factor I-negative; CFI+ = complement factor I-positive; DA = disc area; ETDRS = Early Treatment Diabetic Retinopathy Study; LLD = low-luminance deficit; LLVA = low-luminance visual acuity; max = maximum; min = minimum; SE = standard error.

transformation. Square root transformation has been used to remove any artifactual increase in GA progression with larger versus smaller GA lesions.[32] It has been suggested that although the lesion radius may expand at a constant rate, this will be accompanied by an exponential increase in area over time due to the relationship between radius and area (πr^2).[32] The remaining baseline risk factors evaluated presented slightly different patterns in Proxima A and B. In Proxima A, GA lesion progression did not appear to vary according to sex, baseline GA contiguity, and presence of reticular pseudodrusen, whereas in Proxima B, GA lesion progression was greater in female than in male patients and in those with multifocal (vs. nonmultifocal) GA lesion at baseline. There also appeared to be a trend for greater GA progression in those with reticular pseudodrusen at baseline in Proxima B. However, this latter finding may reflect the more conservative approach used by the reading center used in Proxima B, whereby pseudodrusen was graded as present or indeterminable, whereas in Proxima A it could be present, absent, or indeterminable. Overall, these findings suggest that the presence of reticular pseudodrusen may have less of impact on progression than on the development of GA.

There are a number of limitations of the Proxima studies, including the relatively small number of participants in the Proxima B fellow eye with intermediate AMD cohort in comparison with the other cohorts. This arm was challenging to recruit, perhaps reflecting that the majority of patients with GA have bilateral disease[9] and that patients with unilateral GA are not referred to retina specialists because they are asymptomatic and they may have small GA lesions. Furthermore, as a result of early termination of the program, none of the patients completed the full planned duration of 48 and 60 months for Proxima A and Proxima B, respectively, with the number of participants discontinuing from the trial increasing during the later assessments, so that not all planned analyses were performed. Overall baseline characteristics were well balanced across the 3 cohorts, although some differences between groups were noted. A higher percentage of patients in Proxima A had a baseline visual acuity of 20/40 or better (Snellen equivalent), perhaps reflecting the differences between the inclusion/exclusion criteria across the 2 trials.

The strengths of the Proxima A and B clinical trials are that they were large, prospective, observational studies including multiple anatomic and functional assessments. The studies were also conducted across a broad GA population, and information was collected on GA and CNV occurrence in the fellow eye. Findings from Proxima A and B contribute to the understanding of the natural history of GA and are valuable in considering the design of future clinical trials.

In conclusion, the Proxima A and B studies demonstrate the severe functional impact of GA and the rapid rate of GA lesion progression over a 2-year period, even in those with an earlier disease state (i.e., unilateral GA) at baseline. The magnitude of functional decline was consistent across end points, demonstrating the potential impact on a patient's quality of life. These advances in our understanding of the natural progression of GA should assist with future efforts to find an effective therapy for GA.

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Footnotes and Financial Disclosures

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Analysis and interpretation: Holekamp, Wykoff, Schmitz-Valckenberg, Monés, Souied, Lin, Rabena, Cantrell, Henry, Tang, Swaminathan, Martin, Ferrara, Staurenghi

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **AREDS2** = Age-Related Eye Disease Study 2; **BCVA** = best-corrected visual acuity; **C2/CFB** = complement C2/complement factor B; **CFH** = complement factor H; **CFI** = complement factor I; **CI** = confidence interval; **CNV** = choroidal neovascularization; **DA** = disc area; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **HR** = hazard ratio; **LLD** = low-luminance deficit; **LLVA** = low-luminance visual acuity; **MMRM** = mixed model for repeated measurement; **SD** = standard deviation.

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