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Phase 1 Clinical Trial of Elamipretide in Dry Age-Related Macular Degeneration and Noncentral Geographic Atrophy: ReCLAIM NCGA Study

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Running head: ReCLAIM: Elamipretide in Dry AMD and NCGA

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Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well tolerated in patients with dry age-related macular degeneration and noncentral geographic atrophy, with positive effect on visual function, particularly under low luminance conditions.

1 **Abstract**

2 **Purpose:** To assess safety, tolerability, and feasibility of subcutaneous administration of
3 mitochondrial targeted drug elamipretide in patients with dry age-related macular degeneration
4 (AMD) and noncentral geographic atrophy (NCGA) and to perform exploratory analyses of
5 change in visual function.

6 **Design:** Phase 1, single-center, open-label, 24-week clinical trial with preplanned NCGA cohort.

7 **Participants:** Adult patients, age ≥ 55 years, with dry AMD and NCGA.

8 **Methods:** Participants received subcutaneous elamipretide 40 mg daily, with safety and
9 tolerability assessed throughout the study. Ocular assessments included normal luminance best-
10 corrected visual acuity (BCVA), low-luminance best-corrected visual acuity (LLVA), normal
11 luminance binocular reading acuity (NLRA), low luminance binocular reading acuity (LLRA),
12 spectral-domain optical coherence tomography (OCT), fundus autofluorescence (FAF), and
13 patient self-reported function by low luminance questionnaire (LLQ).

14 **Main Outcome Measures:** The primary endpoint was safety and tolerability. Prespecified
15 exploratory endpoints included changes in BCVA, LLVA, NLRA, LLRA, GA area, and LLQ.

16 **Results:** Subcutaneous administration of elamipretide was highly feasible. All participants
17 (n=19) experienced ≥ 1 non-ocular adverse events (AEs), but all AEs were either mild (73.7%)
18 or moderate (26.3%); no serious AEs were noted. Two participants exited the study due to AEs
19 (conversion to neovascular AMD (n=1); intolerable injection site reaction (n=1)), one participant
20 discontinued due to self-perceived lack of efficacy, and one participant chose not to continue
21 with study visits. Among participants completing the study (n=15), mean change (standard
22 deviation (SD)) in BCVA from baseline to week 24 was +4.6 (5.1) letters ($P=0.0032$), while
23 mean change (SD) in LLVA was +5.4 (7.9) letters ($P=0.0245$). While there was minimal change

24 in NLRA, mean change (SD) in LLVA was -0.52 (0.75) logMAR units ($P=0.005$). Mean change
25 (SD) in GA area (SQRT) from baseline to week 24 was 0.14 (0.08) mm by FAF and 0.13 (0.14)
26 mm by OCT. Improvement was observed in LLQ for dim light reading and general dim light
27 vision.

28 **Conclusions:** Elamipretide appears to be well tolerated without serious AEs in patients with dry
29 AMD and NCGA. Exploratory analyses demonstrate possible positive effect on visual function,
30 particularly under low luminance. A Phase 2b trial is underway to further evaluate elamipretide
31 in dry AMD and NCGA.

32 **Introduction**

33 Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people
34 aged 50 years and older, affecting an estimated 11 million individuals in the United States, with
35 AMD prevalence expected to double to 22 million individuals by 2050 (10% of those 50 years
36 and older).^{1,2} The most profound visual impairment occurs in untreated neovascular AMD or in
37 advanced dry AMD with foveal center-involving geographic atrophy (GA), both of which can
38 cause severe central vision loss.¹ However, patients with patients with noncentral GA (NCGA)
39 (as well as patients with high-risk drusen) also experience significant visual impairment.³⁻⁷ In
40 spite of good best-corrected visual acuity (i.e., often 20/40 or better), these patients frequently
41 experience moderate to profound impairment in low luminance visual function and activities of
42 daily living (e.g., driving at dusk, dim light reading, others).⁸ Low luminance vision impairment
43 affects up to 50% of NCGA patients,^{9,10} thus representing a significant clinical unmet need.

44 An emerging body of evidence suggests an important role for retinal mitochondrial dysfunction
45 in AMD pathobiology.¹¹⁻¹³ Multiple risk factors associated with AMD—including cigarette
46 smoke, lipofuscin accumulation within retinal pigment epithelium (RPE), and complement
47 dysregulation—have been identified as triggers of mitochondrial dysfunction.¹⁴⁻¹⁶ Oxidant-
48 induced modifications as well as mutations in mitochondrial DNA of RPE cells are more
49 prevalent in human eyes with AMD than in eyes of age-matched controls, and the morphology of
50 RPE mitochondria in eyes with AMD is often enlarged and dysmorphic (indicating dysfunction),
51 as compared to RPE mitochondria of control eyes.^{13,16,17} Additionally, certain genetic
52 mitochondrial disorders, especially maternal inherited diabetes and deafness (MIDD) and
53 mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), often develop
54 GA or other signs of macular degeneration.¹⁸⁻²⁰ The mechanisms of visual impairment in the

55 setting of mitochondrial dysfunction have not been clearly elucidated but may be related to
56 alterations in cellular bioenergetics (i.e., diminished ATP production) and/or aberrant oxidant
57 production at the RPE and/or photoreceptors, leading to altered phototransduction, impaired
58 visual cycle, or insufficient metabolic support.^{11,16,21}

59 Elamipretide is a first-in-class investigational drug and mitochondria-targeted tetrapeptide that
60 has been previously evaluated in mitochondrial diseases such as primary mitochondrial
61 myopathy and Barth syndrome.²² Elamipretide increases cellular ATP production and reduces
62 mitochondria-derived oxidants in affected cells by stabilizing the structure and function of the
63 mitochondrial electron transport chain.^{23–26} Elamipretide's mechanism of action suggests that it
64 could modulate the mitochondrial-mediated pathophysiologic processes involved in dry
65 AMD.^{24,27} The ReCLAIM study was a phase 1 clinical trial with the primary objective to
66 evaluate the safety and tolerability of elamipretide in two preplanned cohorts of patients with dry
67 AMD: 1) patients with dry AMD and noncentral, fovea-sparing GA (NCGA); and 2) patients
68 with intermediate AMD: high-risk drusen (HRD) without GA. Exploratory objectives included
69 evaluation of changes from baseline in measures of visual function and in GA area. The study
70 protocol prespecified relevant inclusion criteria for each cohort and that the two cohorts would
71 be analyzed separately. This report will detail the findings of the NCGA cohort; results of the
72 high-risk drusen cohort will be included in a companion report.

73

74 **Methods**

75 *Study Design*

76 This was a Phase 1, single-center, 24-week, open-label clinical trial (ClinicalTrials.gov

77 Identifier: NCT02848313). The study was conducted in accordance with ICH GCP Guidelines

78 and the tenets of the Declaration of Helsinki and was approved by the Duke Health Institutional
79 Review Board (Durham, NC). Following informed consent and study enrollment, prospective
80 participants underwent a screening assessment (≤ 14 days prior to the baseline visit) to verify
81 study eligibility, which included physical and ophthalmic examination, measurement of Early
82 Treatment Diabetic Retinopathy Study (ETDRS) scale best-corrected visual acuity (BCVA)
83 under normal luminance (i.e., standard light) and low luminance conditions, spectral-domain
84 optical coherence tomography (OCT), fundus autofluorescence (FAF), fluorescein angiography,
85 and low luminance questionnaire (LLQ) (adapted from Owsley, *et al.*,⁸ see Supplement 1).

86 *Participants*

87 Detailed list of eligibility criteria is included in Supplement 2. Key inclusion and exclusion
88 criteria are summarized below.

89 *Inclusion criteria*

90 For the NCGA cohort, males and females ≥ 55 years of age with dry AMD and NCGA were
91 eligible for enrollment, with a single eye designated as study eye. NCGA was defined as well-
92 demarcated area(s) of GA by FAF, sparing the foveal center (i.e., center having intact RPE and
93 outer retinal ellipsoid zone layer) by OCT. The cumulative GA lesion size (solitary or
94 multifocal) was required to be: 1) $\geq 1.27 \text{ mm}^2$ (approximately ≥ 0.5 disc area) and $< 10.16 \text{ mm}^2$
95 (approximately < 4 disc area); and 2) to reside completely within the FAF imaging field (30
96 degree image centered on the fovea). There were no other size requirements for a single GA
97 lesion as long as the above specified size criteria were met. Participants were also required to
98 have: 1) detectable rim area hyper-autofluorescence adjacent to the area of GA by FAF; 2) no
99 evidence of choroidal neovascularization (active or prior history) in the study eye; 3) normal
100 luminance BCVA ≥ 55 ETDRS letters score (i.e., Snellen equivalent $\geq 20/70$); 4) low-luminance

101 visual acuity (LLVA) deficit > 5 letters, wherein LLVA deficit is defined as the difference
102 BCVA and LLVA; and 5) at least two low luminance questionnaire (LLQ) abnormal subscale
103 scores indicating impairment, wherein one of the abnormal subscales was either general dim
104 light vision or dim light reading (where abnormal subscale was defined as $\geq 50\%$ of questions in
105 that subscale with answers of 3 (some difficulty) or 4 (a lot of difficulty) with specific low
106 luminance tasks or functions). The fellow eye was permitted to have any stage of AMD:
107 intermediate AMD with high-risk drusen, AMD with NCGA, neovascular AMD, or advanced
108 AMD with center-involving GA. Ongoing treatment with anti-vascular endothelial growth factor
109 therapies in the fellow eye was permitted.

110 Participants were also required to have either no visually significant cataract or pseudophakia
111 without posterior capsular opacity, along with sufficiently clear ocular media, adequate pupillary
112 dilation, fixation to permit quality fundus imaging, and ability to cooperate sufficiently for
113 adequate ophthalmic visual function testing and anatomic assessment. When both eyes were
114 eligible for the study, the eye with the greater low luminance visual acuity deficit was chosen for
115 inclusion.

116 *Exclusion criteria*

117 Exclusion criteria included any of the following ocular conditions in the study eye: AMD with
118 any evidence of central GA (i.e., involving the foveola by OCT), diagnosis of neovascular AMD,
119 or macular atrophy due to causes other than AMD. Additional macular / retinal exclusion criteria
120 in the study eye included: presence of diabetic retinopathy, macular pathology (i.e., hole,
121 pucker), history of retinal detachment, presence of vitreous hemorrhage. Nonmacular exclusion
122 criteria in the study eye included: uncontrolled glaucoma, advanced guttae indicative of Fuchs
123 endothelial dystrophy; visually significant cataract, presence of significant posterior capsular

124 opacity in the setting of pseudophakia, aphakia, or significant keratopathy that would alter visual
125 function, especially in low light conditions. Prior treatment exclusion criteria in the study eye
126 included previous intravitreal injection of pharmacologic agents or implants (including anti-
127 angiogenic (anti-VEGF) drugs and corticosteroids), prior vitreoretinal surgery (including
128 vitrectomy surgery and submacular surgery), prior treatment with macular laser, verteporfin,
129 external-beam radiation therapy, or transpupillary thermotherapy, or any ocular incisional
130 surgery (including cataract surgery) in the study eye in the 3 months preceding the baseline visit.
131 Additional exclusion criteria included the presence of any of the following ocular conditions in
132 either eye: active uveitis and/or vitritis, history of uveitis, active infectious disease
133 (conjunctivitis, keratitis, scleritis, endophthalmitis, etc.). Finally, individuals known to be
134 immunocompromised, individuals receiving systemic immunosuppression for any disease, and
135 individuals with estimated glomerular filtration rate < 30 mL/minute were excluded from study
136 participation.

137 *Study Drug and Evaluations*

138 The study drug elamipretide was administered as a 40mg (1 mL) subcutaneous injection in the
139 abdominal area once daily for 24 weeks, beginning at baseline. Study drug was either self-
140 administered by the participant or by a caregiver, following training by study personnel at the
141 initial baseline visit. Participants were trained using a standard script explaining the importance
142 of proper administration of the drug daily for the 24-week study treatment period. The first dose
143 could be given by a qualified member of the study team, by the participant, or caregiver at the
144 investigator's discretion. The option of a home health nurse making visit(s) to the participant and
145 caregiver to oversee and verify proper study drug administration was offered to each participant
146 and provided to participants, as needed, and the number of nurse visits was recorded for each

147 participant. Assessments for safety and tolerability were performed throughout the 24-week
148 treatment period and at the follow-up visit (week 28). Adverse events were assessed by the
149 investigator for severity and relationship to study drug. Participants were asked to complete a
150 diary documenting study drug administration and compliance. Compliance was assessed by
151 study personnel assessment of participant diary and inventory of used study drug vials over the
152 course of the active treatment period.

153 For ocular assessments, while only one eye of each eligible participant was designated as the
154 study eye, all specified ophthalmic testing was performed on both eyes at each time point.
155 Assessments for best-corrected visual acuity (ETDRS letter score) under normal luminance
156 (BCVA) and low luminance (LLVA) were performed at screening and baseline, during active
157 treatment period (weeks 1, 4, 8, 12, 16, 20, 24), and at follow-up (week 28). BCVA and LLVA
158 were measured as the correct number of letters read using standard ETDRS charts, lighting, and
159 procedures. For LLVA, participants were fitted with trial frames with their best-corrected
160 refraction and a 2.0-log unit neutral density filter to replicate low-luminance conditions under
161 standardized ambient lighting.

162 Best-corrected binocular reading acuity (BCRA) and low luminance binocular reading acuity
163 (LLRA) were measured at baseline, during study treatment (weeks 4, 8, 12, 16, 20, 24), and at
164 follow-up (week 28). Assessment of BCRA was done by standardized illumination using several
165 different standard MNREAD charts (MNREAD 1-W, 2-W, and 3-W charts; Precision Vision,
166 Lasalle, IL). Charts were rotated at visits throughout the study, and a single chart was not
167 utilized at consecutive visits, to reduce the likelihood of learning effect. Participants were fitted
168 with trial frames with best-corrected near acuity lenses in standardized ambient lighting
169 conditions, and results were recorded as the smallest font size read correctly with ≤ 1 word

170 mistake within 30 seconds. The MNREAD reading chart is comprised of 19 distinct font sizes
171 ranging from -0.5 logMAR (smallest font size, Snellen equivalent 20/6) to 1.3 logMAR (largest
172 font size, Snellen equivalent 20/400), total range in logMAR values of 1.9.

173 LLRA was performed in the same fashion as BCRA, with MNREAD 1-W, 2-W, and 3-W charts
174 again rotated at visits throughout the study, and a single chart was not utilized at consecutive
175 visits, to reduce the likelihood of learning effect. For LLRA, a 2.0-log unit neutral density filter
176 was added to trial frames with best-corrected near acuity lenses to replicate low-luminance
177 conditions. Results were recorded as the smallest font size read correctly (logMAR value ranging
178 between -0.5 to 1.3) with ≤ 1 -word mistake within 30 seconds. If participants were unable to
179 read the 1.3 logMAR line (i.e., largest font size) using the 2.0-log unit neutral density filter, then
180 LLRA was repeated using a 1.0-log unit neutral density filter. The final adjusted logMAR value
181 for measurements obtained with 1.0-log unit neutral density filter was derived by adding 1.9 to
182 the measured value, such that the adjusted logMAR value ranged between 1.4 logMAR (smallest
183 font size) to 3.2 logMAR (largest font size).

184 Low luminance questionnaire (LLQ) (adapted from Owsley, *et al.*,⁸ see Supplement 1) was
185 performed at baseline as described and was subsequently repeated at weeks 12 and 24, and at
186 follow-up (week 28). LLQ was scored and analyzed as previously described.⁸ In brief, items in
187 the LLQ had a difficulty response scale and corresponding scores: (1) no difficulty at all; (2) a
188 little difficulty; (3) some difficulty; and (4) a lot of difficulty. option of “X”, does not apply to
189 me, was included in case a particular item was not applicable for a participant, and in this case,
190 the item was not included in determining the subscale score. The subscale score was calculated
191 by scaling each item response from 0 to 100, wherein 100 reflects the highest functional level

192 and 0 the lowest functional level; the mean value was determined for the applicable items
193 comprising each subscale.

194 For assessment of geographic atrophy (GA), OCT of the macula and FAF were performed at
195 screening, baseline, during study treatment (weeks 4, 8, 12, 16, 20, 24), and at follow-up (week
196 28), with measurement of GA area assessed on each imaging modality performed by masked
197 graders, who were masked to the date of performance / study visit. For FAF, masked graders
198 demarcated the margins of GA lesions, defined as discrete regions of hypoautofluorescence
199 within the FAF imaging field (field 2- to 30-degree image centered on the fovea), determined
200 lesion areas, and determined the cumulative GA lesion area (in square millimeters). For OCT,
201 graders assessed OCT B-scan images to identify the margins of GA lesion, defined as the
202 presence of choroidal hypertransmission, absence or disruption of RPE, and overlying
203 photoreceptor loss (ellipsoid zone loss, absence of external limiting membrane, outer nuclear
204 layer thinning). GA margin was identified as the transition point between intact and disrupted or
205 absent / attenuated RPE. OCT B-scans were registered to OCT infrared images, and the margin
206 points were identified on infrared images to determine the cumulative GA area (in square
207 millimeters). Square root transformation (SQRT) was performed on GA area measurements to
208 eliminate the dependence of growth rates on baseline GA lesion measurements.

209 ***Endpoints***

210 The primary study endpoint was safety and tolerability as assessed by the incidence and severity
211 of adverse events and changes from baseline in vital sign measurements, ECGs, clinical
212 assessments, and clinical laboratory evaluations. Assessment of adverse events was performed at
213 each study visit and included both investigator-assessed and participant-reported events.

214 Exploratory efficacy endpoints reported in the present study include changes from baseline in
215 BCVA, LLVA, NLRA, LLRA, LLQ, and GA area.

216 *Statistical Analysis*

217 For this phase 1, open-label study, a sample size of 40 evaluable participants was considered
218 sufficient to allow preliminary assessment of safety and tolerability, based on precedent set by
219 prior phase 1 studies of similar nature and design. As mentioned, the HRD and NCGA cohorts
220 were preplanned by study design. Safety and efficacy variables are summarized descriptively.
221 All participants who received ≥ 1 dose of study drug were included in assessment of safety as part
222 of intention-to-treat analysis. As this was an open-label study without a control or comparator
223 group, analyses of exploratory efficacy endpoints were limited to descriptive analyses. Analyses
224 of change in each metric from baseline to 24 weeks were limited to participants who completed
225 the 24-week study period. Missing data was not imputed (e.g., by last observation carried
226 forward) to avoid making assumptions about the outcomes of study participants that did not
227 complete the study. All statistical analyses and reporting were performed using the SAS®
228 System Version 9.4 (SAS, Cary, NC). Continuous variables analyzed in this study were
229 summarized by the number of non-missing observations (N), mean, standard deviation (SD),
230 median, minimum, and maximum values. Statistical analysis of mean change from baseline
231 value was assessed by signed-rank test. Pearson's correlation coefficient was utilized to assess
232 the correlation between GA area at baseline and the change in LLVA at week 24 from baseline.
233 To correct for multiple comparisons for changes in metrics from baseline, the Holm method was
234 applied to determine the statistically significant threshold (P value) for the α level (Type I error
235 rate) for each metric, based on the P value threshold $P < 0.05$ for the metric with the highest P
236 value.²⁸ For example, using the Holm method, for the four metrics BCVA, LLVA, NLRA, and

237 LLVA, the P values were ordered from lowest to highest to identify the statistically significant
238 threshold for each: $P < 0.0125$ for the lowest P value among the four metrics; $P < 0.0167$ for the
239 second lowest P value among the four metrics; $P < 0.025$ for the next to highest P value among
240 the four metrics; and $P < 0.05$ for the highest P value among the four metrics.²⁸

241

242 **Results**

243 *Study Participants*

244 A total of 19 participants were included in the NCGA cohort (**Table 1**). The mean age was 76
245 and the majority were female (11/19) and current or former smokers (11/19). Of the 19 enrolled,
246 15 participants completed the 24-week treatment period. Of the four individuals who did not
247 complete the study, one participant discontinued participation due to study drug intolerance in
248 the form of pruritis and discomfort at injection site (prior to the week 4 visit), one participant was
249 discontinued by study investigator due to conversion to neovascular AMD (just after the week 8
250 visit), one participant chose to withdraw from the study due to the participant's perceived lack of
251 efficacy of the study drug (at week 12), and one participant withdrew from the study (at week
252 20) because they did not wish to continue with study visits.

253 *Feasibility and Compliance*

254 Subcutaneous administration of elamipretide was highly feasible following proper instruction of
255 participants and caregiver by study personnel and health nurse home visits to instruct and verify
256 proper drug administration. The mean (SD) number of home visits required to ensure proper
257 subcutaneous administration of elamipretide was 2.5 (1.02) visits. Mean (SD) treatment
258 compliance across the 24-week active study drug period was 97.3 (6.7) %.

259 *Safety and Tolerability*

260 Adverse events are summarized in **Table 2**. All study participants experienced at least one
261 adverse event, which were all either mild (73.7%) or moderate (26.3%) in intensity. The most
262 common treatment-emergent adverse events were injection site reactions, defined as a local
263 reaction at the site of subcutaneous administration (including pruritus, erythema, discomfort,
264 swelling, induration, and bruising). In most cases, these reactions were mild, self-limited and/ or
265 amenable to local treatment; one participant discontinued study drug due to intolerance to
266 injection-site reaction, pruritis, which in this instance was considered moderate intensity.
267 There were two treatment-emergent serious adverse events and no deaths in the study. Both
268 serious adverse events, urinary tract infection [n=1] and sepsis [n=1], occurred in the same
269 participant, were of moderate intensity, and were not considered related to study drug; both
270 events resolved with full recovery of the participant. Two study participants experienced ocular
271 adverse events in the study eye; conversion to neovascular AMD [n=1] (moderate intensity) and
272 vitreous floaters [n=1] (mild intensity), but both events were not considered related to study drug
273 (**Table 2**). As noted above, the participant with conversion to neovascular AMD was withdrawn
274 from the study by the study investigator. Two participants reported an ocular adverse event in the
275 nonstudy eye, both of which were of mild intensity and not related to study drug.

276 *Exploratory Efficacy Endpoints*

277 Mean (SD) normal luminance BCVA was 77.9 (12.7) letters at week 24, as compared to 73.7
278 (9.5) letters at baseline. Normal luminance BCVA over the course of the study period are
279 summarized in **Figure 1**. Among the 15 participants who completed the active study period, the
280 mean change in BCVA from baseline progressively increased over time, with a mean (SD)
281 increase of 4.6 (5.1) letters ($P=0.0032$, Holm method threshold for statistical significance

282 $P<0.0125$) at week 24 (**Figure 1A, 1B**). Six of 15 participants (40%) had at least a 6-letter
283 increase in BCVA at week 24, and two of 15 participants (13.3%) had greater than 10-letter
284 increase in BCVA at week 24; no individuals had greater than 5-letter decrease in BCVA
285 (**Figure 1B, 1C**).

286 Mean (SD) LLVA was 51.5 (21.8) letters at week 24, as compared to 44.0 (19.8) letters at
287 baseline. LLVA over the course of the study period are summarized in **Figure 2**. Mean increase
288 in LLVA from baseline was observed at all study visits throughout the study period, with a mean
289 (SD) increase of + 5.4 (7.9) letters ($P=0.0245$, Holm method threshold for statistical significance
290 $P<0.025$) at 24 weeks (**Figure 2A, 2B**). Eight of 15 participants (53.3%) had at least a 6-letter
291 increase in LLVA, five of 15 participants (33.3%) had greater than 10-letter increase in LLVA,
292 and one of 15 participants (6.7%) had greater than 15-letter increase in LLVA. (**Figure 2B, 2C**).

293 Two of 15 participants (13.3%) had at least a 6-letter decrease in LLVA (**Figure 2B, 2C**).

294 Mean (SD) NLRA at week 24 (0.13 (0.26) logMAR) was not appreciably different from
295 baseline (0.15 (0.25) logMAR); mean change from baseline -0.02 logMAR ($P=0.55$, Holm
296 method threshold for statistical significance $P<0.05$). In contrast, mean (SD) LLRA at week
297 24 was 0.79 (0.97) logMAR as compared to baseline value of 1.28 (1.07) logMAR. Increase
298 in LLRA was observed at all study visits throughout the study period, with a mean LLRA
299 change from baseline in the smallest line read correctly of -0.52 logMAR at week 24
300 ($P=0.005$, Holm method threshold for statistical significance $P<0.0167$) (**Figure 3**),

301 equivalent to an approximately 5-line gain in LLRA.

302 For the low luminance questionnaire (LLQ), subscale scores at week 24 as well as change in
303 subscale scale at week 24 from baseline are included in **Table 3**. Using Holm method
304 thresholds for statistical significance to correct for multiple comparisons of subscales on the

305 LLQ, mean changes from baseline were not statistically significant, though there were
306 notable improvements in general dim light vision ($P=0.0292$) and dim light reading
307 ($P=0.0271$) that trended toward clinical significance.

308 For change in GA lesion size, mean (SD) change in GA area at week 24 was increased at 0.50
309 (0.49) mm^2 by FAF and 0.45 (0.61) mm^2 by OCT. Mean (SD) change from baseline in GA area
310 at week 24, measured by square root transformation (i.e., calculation performed to eliminate
311 dependence of growth rates on lesion measurements), was increased at 0.14 (0.08) mm by FAF
312 and 0.13 (0.14) mm by OCT. There was good correlation between baseline GA area (mm^2) by
313 OCT and change in LLVA at week 24 from baseline (correlation coefficient: -0.6555 ; $P=0.008$).
314 In general, eyes with smaller GA area at baseline experienced greater increase in LLVA at week
315 24, with all instances of ≥ 6 -letter increase in LLVA ($N=8$) occurring in eyes with baseline GA
316 area $< 4 \text{ mm}^2$ (approximately 1.6 disc areas) and intact foveal ellipsoid zone.

317

318 **Discussion**

319 Dry AMD with geographic atrophy (GA) represents an advanced form of AMD disease,
320 characterized by foci of cell death at the RPE, attenuation of underlying choriocapillaris, and loss
321 of overlying and marginal photoreceptors.¹² While the disease is variably progressive, the extent
322 of associated visual deficit is related to several factors, including size and location of GA relative
323 to the fovea as well as the rate and direction of GA enlargement.²⁹ Progression of AMD disease
324 produces increasing impairment in health-related quality of life (QoL), with a QoL in moderate
325 AMD (i.e., AMD with NCGA) comparable to that following a moderate stroke and QoL in
326 severe AMD (i.e., AMD with center-involving GA) similar to that found in patients with total
327 renal failure on home dialysis.³⁰ Currently, there are no approved treatments to prevent GA, limit

328 its progression, or improve vision for affected patients. The lack of efficacious therapies for dry
329 AMD carries significant public health and societal burden, estimated at a total financial cost
330 (direct and indirect) of \$30 billion.³⁰

331 Declines in visual function experienced by dry AMD patients are especially apparent under low
332 luminance conditions, including difficulty reading in dimly lit conditions and driving at dusk /
333 nightfall or in poor ambient light environments.⁸⁻¹⁰ These deficits in activities of daily living
334 profoundly impact affected patients, in many cases causing loss of independence and social
335 withdrawal. Low luminance vision dysfunction is quantified by clinical endpoints of LLVA and
336 LLRA, which assess central cone-mediated function under standardized conditions.^{10,31,32}
337 Therapies that specifically improve low luminance visual function and boost LLVA and LLRA
338 would thus represent a paradigm shift for AMD patients.

339 Mitochondrial dysfunction at the RPE and neurosensory retina, characterized by excessive
340 production of cellular oxidants (superoxide, singlet oxygen, others) and diminished ATP
341 production, appears to be an important contributor to AMD pathobiology.^{11,13,21} RPE cells in
342 eyes from patients with AMD exhibit mitochondrial dysmorphology and oxidative damage with
343 the effect proportional to disease severity.^{13,17,21} Preclinical mouse models of dry AMD, which
344 are characterized by dysmorphic RPE and subRPE deposit formation, have abnormal RPE
345 mitochondria along with biochemical evidence of mitochondrial dysfunction and increased
346 superoxide production at the RPE.^{27,33,34} Additionally, induction of the ApoE4 dry AMD mouse
347 model triggers neurosensory retina mitochondrial dysfunction in the setting of diminished ERG
348 amplitudes and disrupted photoreceptor-bipolar cell synapses.²⁷ These data strongly support
349 mitochondrial dysfunction as a key disease paradigm for dry AMD.

350 The investigational drug elamipretide is a small peptide that reversibly binds cardiolipin, a
351 phospholipid found only in the inner mitochondrial membrane that is responsible for establishing
352 the cristae architecture and optimizing the function of the electron transport chain for ATP
353 generation.²³⁻²⁶ Binding of elamipretide to cardiolipin restores the efficiency of the electron
354 transport chain in dysfunctional mitochondria, improving cellular respiration and ATP
355 production and reducing production of oxidants.²³⁻²⁶ The net effect is to restore niche cellular
356 functions requiring high levels of ATP and to downregulate cellular response to injury pathways
357 that are triggered by oxidants. Elamipretide has been shown to have significant activity in
358 preclinical models of eye disease, with *in vitro* studies showing reduced oxidative stress,
359 decreased apoptosis, and improved cell survival in cultured human RPE cells.^{24,35} Further, in
360 RPE cells cultured from dry AMD donor eyes, elamipretide treatment improved mitochondrial
361 function, as measured by maximal respiration and spare respiratory capacity.²⁴ Finally, treatment
362 of the ApoE4 mouse model of dry AMD, using a rigorous drug intervention strategy following
363 induction of the model (as opposed to a pretreatment strategy prior to or concurrent with model
364 induction), promoted reversal of mitochondrial dysfunction, regression of subRPE deposits,
365 restoration of RPE cellular morphology, improvement in neurosensory retinal function by ERG,
366 and restoration of phototransduction and synaptic integrity and function.²⁷ It was on the basis of
367 these compelling preclinical data that the elamipretide clinical development program was
368 initiated for dry AMD.

369 Results from the present phase 1 ReCLAIM study demonstrate that subcutaneous administration
370 of elamipretide is generally well tolerated without serious drug-related adverse events (AEs) in
371 patients with AMD and NCGA. Treatment-emergent adverse events, which were primarily
372 comprised of injection site reactions, were mild or moderate in severity, with only one

373 participant discontinuing study participation due to injection site reaction (pruritis). There were
374 two serious AEs (urinary tract infection [n=1] and sepsis [n=1]) that occurred in the same
375 patient, but neither of these was deemed to be related to study drug, and both serious AEs
376 resolved with recovery of the participant. Among ocular AEs occurring in the study eye (n=2),
377 none were severe or thought to be related to study drug, and only one, conversion to neovascular
378 AMD [n=1], led to study drug discontinuation. The overall safety profile of elamipretide was
379 comparable to that previously observed in other clinical trials of elamipretide.^{36,37}

380 Elamipretide dose and frequency was selected based on maximally tolerated subcutaneous
381 dosing from prior safety studies in adults. While pharmacokinetics (PK) samples were not
382 collected and analyzed in the present study, the PK profile of elamipretide administered via
383 infusion has been characterized in other clinical trials (data on file, Stealth
384 BioTherapeutics).³⁸ In rabbit PK studies, subcutaneous dosing of elamipretide (1 mg / kg)
385 produced measurable drug levels at the choroid, RPE, and retina at C_{max} (30 min). The measured
386 concentrations are expected to be therapeutic, based on the exposure-response data from the
387 mouse model of HQ-induced oxidative injury (data on file, Stealth BioTherapeutics). Studies on
388 the pharmacokinetics of subcutaneous elamipretide in AMD patients are included in the
389 forthcoming Phase 2 clinical trial.

390 Exploratory efficacy endpoints suggest that elamipretide may have a possible positive benefit on
391 visual function in dry AMD and NCGA, particularly under low luminance conditions. We
392 observed increased mean change in both LLVA and LLRA that was evident at early visits (i.e.,
393 day 7 and week 4) and subsequently sustained over the duration of the study, suggestive of a
394 possible drug treatment effect. The phenomenon of short-term learning effect has been described
395 in studies of other measures of visual function (e.g., microperimetry) in dry AMD patients.³⁹ It is

396 possible that short-term learning effect could have contributed to observed changes in LLVA and
397 LLRA at early visits. However, as described in the methods, for LLRA (and NLRA), MNREAD
398 charts were rotated at visits throughout the study, such that single chart was not utilized at
399 consecutive visits, to reduce the likelihood of a testing-specific learning effect. Furthermore, as
400 the methodology for LLVA testing does not include added psychovisual aspects beyond what is
401 encountered in the testing of normal luminance BCVA, a learning effect specifically attributable
402 to LLVA would be unexpected. The recent GA natural history study Proxima B (NCT02399072)
403 demonstrated that patients with NCGA (with fellow eye intermediate AMD) had mean visual
404 acuity loss of approximately 3-5 letters at the similar 6 month (24 week) assessment interval;
405 there was neither a short-term learning effect for LLVA nor a spontaneous improvement in
406 LLVA at later points for patients in this study.⁹ This is of relevance since Proxima B had eyes of
407 similar disease state and baseline LLVA as compared to those included in the NCGA cohort of
408 the present ReCLAIM study.

409 In contrast, in the sham control arms of GATHER1, the Phase 2b/3 clinical trial of avacincaptad
410 pegol (IVERIC Bio), mean change in LLVA from baseline to month 12 was -1.4 (standard error
411 (SE) 3.3) in the sham group for the 2 mg arm and +3.0 (SE 3.4) for the sham group for the 4 mg
412 arm.⁴⁰ In a natural history study of a cohort (n=8) of NCGA patients, Wu, et al., observed
413 minimal change in LLVA from baseline to 12 months.⁶ The findings from these studies suggest
414 the possibility that LLVA may not substantially decline over time or may demonstrate short-term
415 improvement in some dry AMD patients. Further, the coefficient of repeatability for LLVA in
416 patients with intermediate AMD was found to be 9.34 letters by Chandramohan, et al.,⁴¹ and
417 approximately 6.5 letters and Wu and colleagues.⁴² While the present study describes findings in
418 a cohort of NCGA patients rather than intermediate AMD patients, visit-to-visit variation in

419 LLVA and LLRA must be taken into account when considering the potential for true differences
420 attributable to study drug. The data from available and relevant literature highlight the
421 importance of careful study design, endpoint measurement methodology, and patient selection in
422 assessing change in low luminance visual function in AMD patients over time, and most
423 importantly, underscore the critical need for a placebo control group to understand the true
424 nature and magnitude of drug effect on low luminance visual function in NCGA patients.

425 With respect to effects on GA area, similarly, multiple caveats apply in interpreting observations,
426 including the relatively short 24-week duration of the study, selection of NCGA patients, and the
427 normal variability across AMD populations for changes in GA size over time. We observed
428 mean increase in GA area (SQRT) of 0.14 mm by FAF and 0.13 mm by OCT. Previously
429 published studies of GA natural history at 6 months (24 weeks) have included increases in GA
430 area (SQRT) ranging from 0.17 – 0.19 mm.^{9,43,44} The limitations inherent in making cross-trial
431 comparisons to other studies preclude substantive conclusions for NCGA patients in ReCLAIM.
432 If a reduced rate of GA progression is affirmed for elamipretide-treated patients in a placebo-
433 controlled study, this would suggest the hypothesis that retinal and/or RPE mitochondrial
434 dysfunction may contribute to progression of GA over time and would further suggest that rate
435 of GA progression could serve as an additional clinical efficacy endpoint for mitochondria-
436 targeted drugs. Further evaluation in a placebo-controlled study is needed to address this
437 possibility.

438 While the study produced an acceptable safety profile as well as intriguing efficacy signals, care
439 must be taken not to overinterpret the presented exploratory efficacy analyses. As we have noted,
440 the lack of placebo control group represents the most significant limitation for this study in
441 considering the implications of the efficacy analyses. As this was an open-label uncontrolled

442 Phase 1 safety with small sample size, there were also limitations in the statistical approach, as
443 there were not prespecified rules for handling missing data. As such, efficacy analyses were
444 restricted to the 15 participants who completed the study, to avoid making assumptions about the
445 outcomes of those individuals who discontinued study participation. The inability to account for
446 the impact of the four participants withdrawals on efficacy analyses represents an additional
447 limitation of the present study. However, we did adjust analyses for multiple comparisons to
448 determine appropriate thresholds for statistical significance, following which, the observed
449 changes from baseline to week 24 for BCVA, LLVA, and LLRA remained statistically
450 significant.

451 The observed, potentially positive effects of elamipretide on visual function are thus highly
452 promising and provide substantial support and justification for further investigation of
453 elamipretide in clinical trials of dry AMD. Based on the results of this prespecified cohort
454 analysis of NCGA patients, a randomized, double-masked, multicenter Phase 2b clinical trial
455 (ReCLAIM-2, NCT03891875) is ongoing to continue the evaluation of safety and efficacy of
456 subcutaneous administration of elamipretide in patients with dry AMD with NCGA.

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570 **Figure Legends**

571 **Figure 1.** Effects of elamipretide on best-corrected visual acuity (BCVA). (A) Mean change in
572 BCVA (ETDRS letters) from Baseline (Day 0) over 24-week active study period; bars indicate
573 standard deviation (SD). $**P=0.0032$ for mean change value at week 24 vs. Baseline, Holm
574 method threshold for statistical significance $P<0.0125$. (B) Scatterplot for change in BCVA
575 (ETDRS letters) from Baseline at week 24. Horizontal solid line: mean value; vertical dashed
576 line: SD. (C) Percentage of study participants by categorical change in BCVA (ETDRS letters)
577 from Baseline at week 24.

578 **Figure 2.** Effects of elamipretide on low luminance best-corrected visual acuity (LLVA). (A)
579 Mean change in LLVA (ETDRS letters) from Baseline (Day 0) over 24-week active study
580 period; bars indicate standard deviation (SD). $**P=0.0245$ for mean change value at week 24 vs.
581 Baseline, Holm method threshold for statistical significance $P<0.025$. (B) Scatterplot for change
582 in LLVA (ETDRS letters) from Baseline at week 24. Horizontal solid line: mean value; vertical
583 dashed line: SD. (C) Percentage of study participants by categorical change in LLVA (ETDRS
584 letters) from Baseline at week 24.

585 **Figure 3.** Effects of elamipretide on low luminance reading acuity (LLRA). Mean change in
586 LLRA (logMAR) from Baseline (Day 0) over 24-week active study period; bars indicate
587 standard deviation (SD). $**P=0.005$ for mean change value at week 24 vs. Baseline, Holm

588 method threshold for statistical significance $P < 0.0167$.

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Table 1. Characteristics of patients with noncentral geographic atrophy (NCGA)

Characteristic	N=19
Age, mean (SD) (range)	76.0 (8.22) (64, 96)
Sex, n (%)	
Female	11 (57.9)
Male	8 (42.1)
Ethnicity, n (%)	
Hispanic/Latino	1 (5.3)
Caucasian	18 (94.7)
Former smoker*, n (%)	11 (57.9)
Baseline BCVA, mean (SD)	73.7 (9.5)
Baseline LLVA, mean (SD)	43.9 (19.8)
Baseline NCGA area by FAF, mean (SD)	3.46 (3.39)
Baseline NCGA area by OCT, mean (SD)	3.28 (3.23)

*Former smoker - no participants were active smokers

SD= standard deviation; BCVA= best-corrected visual acuity; LLVA= low luminance visual acuity; FAF= fundus autofluorescence; OCT= spectral domain-optical coherence tomography

Table 2. Adverse events (AEs) in patients with noncentral geographic atrophy

Event	N=19
<i>All Treatment-emergent events, n (%)</i>	
Any treatment-emergent AE	19 (100)
Injection site reactions	
Pruritis	17 (89.5)
Erythema	14 (73.7)
Induration	14 (73.7)
Bruising	13 (68.4)
Hemorrhage	7 (36.8)
Pain	6 (31.6)
Urticaria	4 (21.1)
Extravasation	2 (10.5)
Swelling	1 (5.3)
Upper respiratory tract infection	3 (15.8)
Headache	2 (10.5)
Dizziness	2 (10.5)
Pyrexia	2 (10.5)
Nausea	2 (10.5)
Gastroenteritis, viral	2 (10.5)
AE by maximum intensity	
Mild	14 (73.7)
Moderate	5 (26.3)
Related to study drug	18 (94.7)

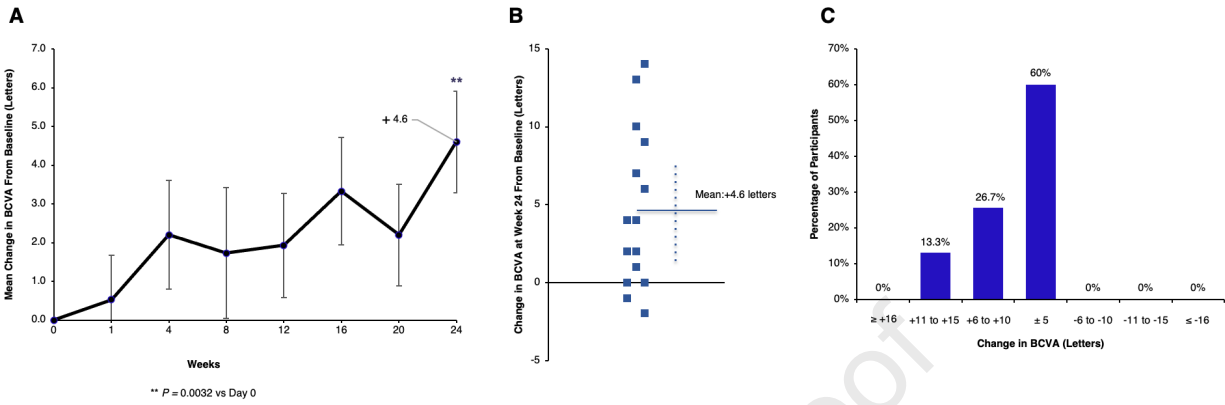
AE leading to study drug discontinuation	2 (10.5)
Any serious systemic AE*	
Urinary tract infection	1 (5.3)
Sepsis	1 (5.3)
<i>All treatment-emergent ocular events in study eye, n (%)</i>	
Any treatment-emergent ocular AE	2 (10.5)
Neovascular AMD	1 (5.3)
Vitreous floaters	1 (5.3)
AE by maximum intensity	
Mild	1 (5.3)
Moderate	1 (5.3)
Related to study drug	0
AE leading to study drug discontinuation	2 (10.5)
Any serious ocular AE	0

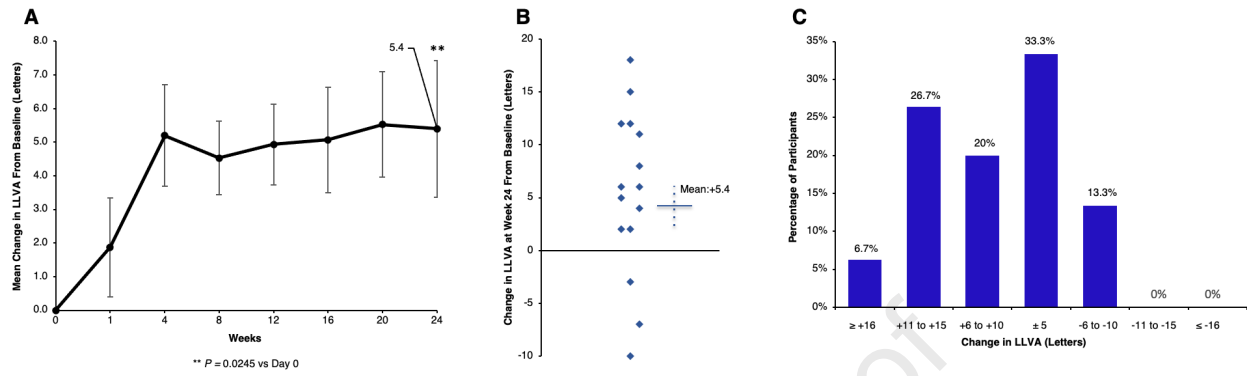
*Both serious systemic AEs occurred in the same participant.

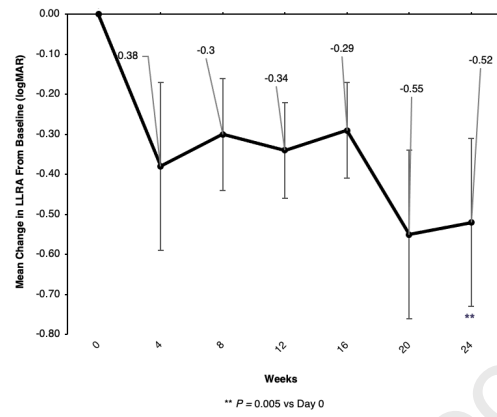
Table 3. Low Luminance Questionnaire Scores at Week 24

Subscale Score	Observed Score at Week 24						Change from Baseline at Week 24						
	n	Mean	SD	Median	Minimum	Maximum	n	Mean	SD	Median	Minimum	Maximum	<i>P</i> value
Dim light reading	15	40.8	16.00	37.5	25.0	81.3	15	7.1	11.30	6.3	-12.5	25.0	0.0292
Driving or riding in car	15	48.9	26.86	37.5	25.0	93.8	15	4.2	14.11	0.0	-25.0	31.3	0.2719
General dim light vision	15	58.4	20.38	53.1	31.3	93.8	15	7.7	12.10	6.3	-18.8	25.0	0.0271
Light transitions and glare	15	51.0	20.98	45.0	25.0	95.0	15	6.7	13.71	5.0	-25.0	30.0	0.0807
Mobility	15	71.1	22.02	75.0	25.0	100.0	15	2.8	16.57	0.0	-25.0	33.3	0.5266
Other ADLs	15	64.6	24.96	68.8	25.0	100.0	15	10.4	20.82	12.5	-37.5	43.8	0.0731
Peripheral vision	15	61.7	32.55	50.0	25.0	100.0	15	5.8	24.03	0.0	-50.0	50.0	0.3630

SD= standard deviation; ADLs= activities of daily living







Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well-tolerated in patients with dry age-related macular degeneration and noncentral geographic atrophy, with possible positive effect on visual function, particularly under low luminance conditions.

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