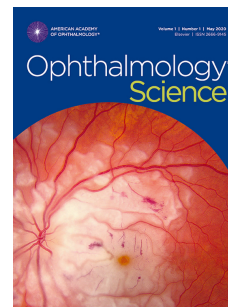


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Phase 1 Clinical Trial of Elamipretide in Intermediate Age-Related Macular Degeneration and High-Risk Drusen: ReCLAIM HRD Study

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Running head: ReCLAIM: Elamipretide in Intermediate AMD and High-Risk Drusen

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Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well tolerated in patients with intermediate age-related macular degeneration and high-risk drusen, 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 intermediate age-related macular
4 degeneration (AMD) and high-risk drusen (HRD) and to perform exploratory analyses of change
5 in visual function.

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

7 **Participants:** Adult patients, age ≥ 55 years, with intermediate AMD and HRD.

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), mesopic
13 microperimetry, dark adaptation, and low-luminance questionnaire (LLQ).

14 **Main Outcome Measure:** The primary endpoint was safety and tolerability. Prespecified
15 exploratory endpoints included changes from baseline in BCVA, LLVA, NLRA, LLRA, RPE-
16 drusen complex (RPE-DC) volume by OCT, FAF, mesopic microperimetry, dark adaptation, and
17 LLQ.

18 **Results:** Subcutaneous administration of elamipretide was highly feasible. All HRD participants
19 (n=21) experienced ≥ 1 adverse event but all were mild (57%) or moderate (43%) with the most
20 common events related to injection site reactions. There were no serious systemic AEs. One
21 participant discontinued due to injection site reaction, one participant withdrew because they did

22 not wish to continue study visits, and one participant withdrew after experiencing transient
23 visual impairment. Among the 18 participants who completed the study, mean change in BCVA
24 from baseline to 24 weeks was +3.6 letters ($P=0.014$) and LLVA was +5.6 letters ($P=0.004$).
25 Compared to baseline, mean NLRA improved by -0.11 logMAR units ($P=0.001$), and LLRA by
26 -0.28 logMAR units ($P<0.0001$). There were significant improvements in 6 of 7 subscales of the
27 LLQ ($P<0.0015$). No significant changes were observed for RPE-DC volume, FAF, mesopic
28 microperimetry, and dark adaptation.

29 **Conclusions:** Elamipretide appears to be generally safe and well tolerated in patients with
30 intermediate AMD and HRD. Exploratory analyses demonstrate a positive effect on visual
31 function, particularly under low luminance conditions. Further study of elamipretide for
32 treatment of intermediate AMD with HRD is warranted.

33 **Introduction**

34 Age-related macular degeneration (AMD) is the leading cause of vision loss in individuals 65
35 and older,¹ with an expected increase in prevalence to 10% among those 50 years and older by
36 the year 2050.^{1,2} Severe vision loss occurs among patients who develop advanced dry AMD with
37 central (i.e., foveal center-involving) geographic atrophy (GA) and those patients with untreated
38 or undertreated neovascular AMD.² While decreased vision in setting of intermediate AMD and
39 high-risk drusen (HRD) can occur in the setting of confluent, large-size drusen within the
40 macula, the majority of HRD patients retain preserved central visual acuity. However, a
41 significant number of HRD patients do experience difficulties with activities of daily living
42 despite preserved best-corrected visual acuity.³⁻⁷ Specifically, between 30-50% of HRD patients
43 experience moderate to profound impairment in low luminance visual function and activities of
44 daily living (e.g., driving at dusk, dim light reading, others).⁸⁻¹⁰ While there is some evidence
45 that supplements targeting enhancement of macular pigment might offer modest visual
46 benefits,^{11,12} these remain exploratory in nature. Thus, despite the progressive nature of AMD
47 and associated visual dysfunction, there are currently no approved therapeutic agents that can
48 improve vision (standard or low luminance) or that can alter the progression of AMD, in part
49 because mechanisms of disease are not fully understood.¹³

50 Risk factors associated with intermediate AMD and HRD include aging,^{14,15} genetic
51 polymorphisms (e.g., complement factor H),¹⁶ systemic health factors, and environmental risk
52 factors (especially cigarette smoking).^{14,17,18} Development of therapies for AMD is challenging,
53 in part because disease pathogenesis is multifactorial, including: mitochondrial dysfunction,^{19,20}
54 abnormal lipid metabolism and transport,^{21,22} oxidant injury,²³ complement overactivity,²⁴
55 inflammation,²⁵ accumulation of bisretinoids,²⁶ diminished autophagy,²⁷ and other mechanisms

56 of disease. A substantial body of evidence suggests that mitochondrial dysfunction plays a major
57 role in AMD pathobiology^{28–33} with numerous preclinical investigations demonstrating that
58 mitochondrial dysfunction and oxidant-induced cellular injury represents a major mechanism of
59 disease, particularly at the RPE.^{19,23,32–36} In histopathology studies, AMD is also associated with
60 damage to RPE mitochondrial DNA, and the effect occurs early in the course of the disease.³²
61 Human RPE isolated from patients with AMD exhibit mitochondrial dysmorphology and
62 markers of oxidative damage, and these are noted to progressively increase with more advanced
63 stages of disease.^{19,32,37} Further, other accepted risk factors for developing AMD—including
64 cigarette smoking, complement dysregulation and lipofuscin accumulation within RPE (though
65 the relative importance and contribution of lipofuscin to dry AMD is still debated^{31,38})—have
66 been shown to cause mitochondrial dysfunction in RPE cell culture models and in rodent models
67 of AMD-like sub-RPE deposit formation.^{30,31,33} Collectively, these findings provide a strong
68 rationale for the development of mitochondria targeted therapies for treatment of AMD.

69 Mitochondria are most well known as producers of adenosine triphosphate (ATP) in support of
70 certain energy-intensive cell functions. However, mitochondria also play roles in regulation of
71 calcium signaling, reactive oxygen species (ROS) generation, and key metabolic pathways such
72 as glutamate recycling.^{39–41} Thus, while the specific mechanisms by which dysfunctional
73 mitochondria mediate AMD pathobiology are not known, disrupted cellular bioenergetics,
74 increased ROS production, and/or loss of other mitochondrial functions may lead to dysfunction
75 at the RPE and photoreceptors, with subsequent disruption of the visual cycle, phototransduction,
76 or normal metabolism of affected cells.^{28,31,37}

77 Elamipretide is a first-in-class mitochondria-targeted tetrapeptide drug that increases cellular
78 ATP production and reduces mitochondria-derived oxidants in affected cells by stabilizing the

79 structure and function of the mitochondrial electron transport chain.⁴²⁻⁴⁵ This mechanism of
80 action suggests that elamipretide could improve mitochondrial dysfunction within RPE and
81 retina, ameliorating this component of AMD pathobiology.^{36,43} The ReCLAIM study was a phase
82 1 clinical trial with a primary objective of evaluating the safety and tolerability of
83 subcutaneously administered elamipretide in patients with nonexudative AMD, with exploratory
84 analyses for changes in measures of visual function and disease progression. The ReCLAIM
85 study included two prespecified cohorts of patients with nonexudative AMD: 1) patients with dry
86 AMD and noncentral, fovea-sparing GA (NCGA); and 2) patients with intermediate AMD and
87 high-risk drusen (HRD) without GA. The present report details the findings of the HRD cohort;
88 results of the NCGA cohort are included in a separate report.

89 **Materials and Methods**

90 *Study Design*

91 This was a Phase 1, single-center, 24-week, open-label clinical trial (ClinicalTrials.gov
92 Identifier: NCT02848313). The study was conducted in accordance with ICH GCP Guidelines
93 and the tenets of the Declaration of Helsinki and was approved by the Duke Health Institutional
94 Review Board (Durham, NC). Following informed consent and study enrollment, prospective
95 participants underwent a screening assessment (\leq 14 days prior to the baseline visit) to verify
96 study eligibility, which included physical and ophthalmic examination, measurement of Early
97 Treatment Diabetic Retinopathy Study (ETDRS) scale best-corrected visual acuity (BCVA)
98 under normal luminance (i.e., standard light) and low luminance conditions, spectral-domain
99 optical coherence tomography (OCT), fundus autofluorescence (FAF), fluorescein angiography,
100 and low-luminance questionnaire (LLQ) (adapted from Owsley, *et al.*,⁸ see Supplement 1).

101 ***Participants***

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

104 ***Inclusion criteria***

105 Males and nonpregnant or nursing females ≥ 55 years of age with 1 eye with intermediate AMD
106 with high-risk drusen without GA were eligible. High-risk drusen was defined as the presence of
107 either at least 1 large (≥ 125 μm) drusen or multiple medium-size (63-124 μm) drusen.

108 Participants were also required to have: 1) no evidence of choroidal neovascularization (active or
109 prior history) in the study eye; 2) normal luminance BCVA ≥ 55 ETDRS letters score (i.e.,
110 Snellen equivalent $\geq 20/70$); 3) low-luminance visual acuity (LLVA) deficit > 5 letters, wherein
111 LLVA deficit is defined as the difference BCVA and LLVA; and 4) at least two LLQ abnormal
112 subscale scores indicating impairment, wherein one of the abnormal subscales was either general
113 dim light vision or dim light reading (wherein abnormal subscale was defined as $\geq 50\%$ of
114 questions in that subscale with answers of 3 (some difficulty) or 4 (a lot of difficulty) with
115 specific low luminance tasks or functions). The fellow eye was permitted to have any stage of
116 AMD: intermediate AMD with high-risk drusen, AMD with NCGA, neovascular AMD, or
117 advanced AMD with center-involving GA. Ongoing treatment with anti-vascular endothelial
118 growth factor therapies in the fellow eye was permitted.

119 Participants were also required to have either no visually significant cataract or pseudophakia
120 without posterior capsular opacity, along with sufficiently clear ocular media, adequate pupillary
121 dilation, fixation to permit quality fundus imaging, and ability to cooperate sufficiently for
122 adequate ophthalmic visual function testing and anatomic assessment. When both eyes were

123 eligible for the study, the eye with the greater low luminance visual acuity deficit was chosen for
124 inclusion.

125 *Exclusion criteria*

126 Exclusion criteria included any of the following ocular conditions in the study eye: AMD with
127 any evidence of GA, where GA is defined as a well demarcated area of hypoautofluorescence on
128 FAF corresponding to an area of choroidal hypertransmission and loss of RPE and outer retina
129 on OCT, based on the assessment of the investigator; diagnosis of neovascular AMD or presence
130 of choroidal neovascularization; or macular atrophy due to causes other than AMD. Additional
131 macular / retinal exclusion criteria in the study eye included: presence of diabetic retinopathy,
132 macular pathology (i.e., hole, pucker), history of retinal detachment, presence of vitreous
133 hemorrhage. Nonmacular exclusion criteria in the study eye included: uncontrolled glaucoma,
134 advanced guttae indicative of Fuchs endothelial dystrophy; visually significant cataract, presence
135 of significant posterior capsular opacity in the setting of pseudophakia, aphakia, or significant
136 keratopathy that would alter visual function, especially in low light conditions. Prior treatment
137 exclusion criteria in the study eye included previous intravitreal injection of pharmacologic
138 agents or implants (including anti-angiogenic (anti-VEGF) drugs and corticosteroids), prior
139 vitreoretinal surgery (including vitrectomy surgery and submacular surgery), prior treatment with
140 macular laser, verteporfin, external-beam radiation therapy, or transpupillary thermotherapy, or
141 any ocular incisional surgery (including cataract surgery) in the study eye in the 3 months
142 preceding the baseline visit. Additional exclusion criteria included the presence of any of the
143 following ocular conditions in either eye: active uveitis and/or vitritis, history of uveitis, active
144 infectious disease (conjunctivitis, keratitis, scleritis, endophthalmitis, etc.). Finally, individuals
145 known to be immunocompromised, individuals receiving systemic immunosuppression for any

146 disease, and individuals with estimated glomerular filtration rate < 30 mL/minute were excluded
147 from study participation.

148 *Study Drug and Evaluations*

149 The study drug elamipretide was administered as a 40mg (1 mL) subcutaneous injection in the
150 abdominal area once daily for 24 weeks, beginning at baseline. Study drug was either self-
151 administered by the participant or by a caregiver, following training by study personnel at the
152 initial baseline visit. Participants were trained using a standard script explaining the importance
153 of proper administration of the drug on a daily basis for the 24-week study treatment period. The
154 first dose could be given by a qualified member of the study team, by the participant, or
155 caregiver at the investigator's discretion. The option of a home health nurse making visit(s) to
156 the participant and caregiver to oversee and verify proper study drug administration was offered
157 to each participant and provided to participants, as needed, and the number of nurse visits was
158 recorded for each participant. Assessments for safety and tolerability were performed throughout
159 the 24-week treatment period and at the follow-up visit (Week 28). Adverse events were
160 assessed by the investigator for severity and relationship to study drug. Participants were asked
161 to complete a diary documenting study drug administration and compliance. Compliance was
162 assessed by study personnel assessment of participant diary and inventory of used study drug
163 vials over the course of the active treatment period.

164 For ocular assessments, while only one eye of each eligible participant was designated as the
165 study eye, all specified ophthalmic testing was performed on both eyes at each time point.
166 Assessments for best-corrected visual acuity (ETDRS letter score) under normal luminance
167 (BCVA) and low luminance (LLVA) were performed at screening and baseline, during active

168 treatment period (Weeks 1, 4, 8, 12, 16, 20, 24), and at follow-up (Week 28). BCVA and LLVA
169 were measured as the correct number of letters read using standard ETDRS charts, lighting, and
170 procedures. For LLVA, participants were fitted with trial frames with their best-corrected
171 refraction and a 2.0-log unit neutral density filter to replicate low-luminance conditions under
172 standardized ambient lighting.

173 Normal light binocular reading acuity (NLRA) and low luminance binocular reading acuity
174 (LLRA) were measured at baseline, during study treatment (Weeks 4, 8, 12, 16, 20, 24), and at
175 follow-up (Week 28). Assessment of NLRA was done by standardized illumination using several
176 different standard MNREAD charts (MNREAD 1-W, 2-W and 3-W charts; Precision Vision,
177 Lasalle, IL) with charts rotated throughout the study to prevent a learning effect. To calculate
178 reading acuity, we used an adaptation of Gordon Legge's initially reported method⁴⁶ as follows:
179 participants were fitted with trial frames with best-corrected near acuity lenses in standardized
180 ambient lighting conditions, and results were recorded as the smallest font size read correctly
181 with ≤ 1 word mistake within 30 seconds. This approach was undertaken to optimize test-retest
182 consistency and reduce subjectivity related to assessment of reading error measurements. The
183 MNREAD reading chart is comprised of 19 distinct font sizes ranging from -0.5 logMAR
184 (smallest font size, Snellen equivalent 20/6) to 1.3 logMAR (largest font size, Snellen equivalent
185 20/400), total range in logMAR values of 1.9.

186 LLRA was performed in the same fashion as NLRA, with MNREAD 1-W, 2-W, and 3-W charts
187 rotated between visits to prevent a learning effect, except that a 2.0-log unit neutral density filter
188 was added to trial frames with best-corrected near acuity lenses to replicate low-luminance
189 conditions. Results were recorded as the smallest font size read correctly (logMAR value ranging
190 between -0.5 to 1.3) with ≤ 1 -word mistake within 30 seconds.

191 Additional tests including mesopic microperimetry, dark adaptometry, fundus autofluorescence
192 (FAF), and spectral domain optical coherence tomography (SD-OCT) were performed at
193 baseline and Weeks 4, 8, 12, 16, 20, 24 and follow-up (Week 28). Mesopic microperimetry
194 (MAIA microperimeter, iCare) was performed as previously described.⁴⁷ The mean 95% bicurve
195 ellipse area (BCEA), the mean threshold for reduced retinal sensitivity, and the number of loci
196 with reduced retinal sensitivity as defined by <25dB or <14dB below normal values were
197 quantified. Dark adaptometry (AdaptDx, Maculogix) was performed and the rod intercept was
198 calculated as previously described.⁴⁸ with some modification. Participants were initially exposed
199 to 100% bleach. If participants could not recover from 100% bleach defined as inability to detect
200 the stimulus after 20 minutes, testing was repeated at 75% bleach. For FAF, reading center
201 graders evaluated changes in hyperautofluorescence patterns in images taken at baseline and
202 week 24. Segmentation of SD-OCT was used to quantify the retinal pigment epithelium-drusen
203 complex (RPE-DC) as previously described,⁴⁹ The RPE-DC was defined as the volume
204 extending from the inner aspect of the RPE plus drusen material to the outer aspect of Bruch's
205 membrane. Evaluation of FAF and OCT was performed by masked graders.

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

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

216 *Endpoints*

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

221 Exploratory efficacy endpoints reported in the present study include changes from baseline in
222 BCVA, LLVA, NLRA, and LLRA, OCT (to determine changes in retinal pigment epithelium-
223 drusen complex (RPE-DC) volume, FAF, and LLQ. Mesopic microperimetry and dark
224 adaptometry were performed to assess retinal sensitivity and recovery of dim light vision
225 following bright light stress, respectively.

226 *Statistical Analysis*

227 For this phase 1, open-label study, a sample size of 40 evaluable participants was considered
228 sufficient to allow preliminary assessment of safety and tolerability, based on precedent set by
229 prior phase 1 studies of similar nature and design. The HRD and NCGA cohorts were preplanned
230 by study design and were enrolled with approximately equal number. Safety and efficacy
231 variables are summarized descriptively. All participants who received ≥ 1 dose of study drug
232 were included in assessment of safety as part of intention-to-treat analysis. Exploratory efficacy
233 endpoints were assessed in participants who completed the 24-week treatment period. All
234 statistical analyses and reporting were performed using the SAS® System Version 9.4 (SAS,
235 Cary, NC). Continuous variables analyzed in this study were summarized by the number of non-

236 missing observations (N), mean, standard deviation (SD), median, minimum, and maximum
237 values. For each continuous variable, statistical analysis of mean change from baseline value was
238 assessed by one-sample t-test and signed-rank test for parametric and non-parametric analysis,
239 respectively. To correct for multiple comparisons for changes in metrics from baseline, the Holm
240 method was applied to determine the statistically significant threshold (P value) for the α level
241 (Type I error rate) for each metric, based on the P value threshold $P < 0.05$ for the metric with the
242 highest P value.⁵⁰ For example, using the Holm method, for the four metrics BCVA, LLVA,
243 NLRA, and LLVA, the P values were ordered from lowest to highest to identify the statistically
244 significant threshold for each: $P < 0.0125$ for the lowest P value among the four metrics;
245 $P < 0.0167$ for the second lowest P value among the four metrics; $P < 0.025$ for the next to highest
246 P value among the four metrics; and $P < 0.05$ for the highest P value among the four metrics.⁵⁰

247 **Results**

248 *Study Participants*

249 A total of 21 participants were included in the high-risk drusen cohort (**Table 1**). The majority
250 were female (13/21), mean age was 71, and most (20/21) were Caucasian. One participant had
251 large drusen, pigment and reticular pseudodrusen (RPD); 1 had medium drusen, pigment and
252 RPD; 5 had large drusen and pigment; 2 had medium drusen and pigment; 4 had large drusen
253 and RPD; 1 had large drusen and subretinal hyperreflective material (SHRM); 1 had medium
254 drusen and SHRM; 5 had large drusen; and 1 had medium drusen. Eighteen of the 21
255 participants completed the 24-week treatment period. One participant in the HRD cohort
256 discontinued the study early (at week 8) due to intolerable injection site reaction. One participant
257 withdrew from the study (at week 12) because they did not wish to continue with study visits,

258 and one participant withdrew after experiencing transient visual impairment (following week
259 12). Mean baseline (SD) BCVA and LLVA values were 79.4 (7.4) and 63.8 (10.0), respectively.

260 *Feasibility and Compliance*

261 Subcutaneous administration of elamipretide was highly feasible following proper instruction of
262 participants and caregiver by study personnel and health nurse home visits to instruct and verify
263 proper drug administration. The mean (SD) number of home visits required to ensure proper
264 subcutaneous administration of elamipretide was 2.2 (0.54) visits. Mean (SD) treatment
265 compliance across the 24-week active study drug period was 98.4 (4.0) %.

266 *Safety and Tolerability*

267 Adverse events are summarized in **Table 2**. All patients experienced at least one adverse event
268 but all were either mild (57%) or moderate (43%) in intensity. The most common treatment-
269 emergent adverse events were related to the injection site and included pruritus, erythema,
270 induration and bruising. In most cases, these reactions were either self-limited or amenable to
271 local treatment. Only one participant discontinued study drug due to intolerance to injection-site
272 reaction. There were no deaths in the study, and there was one treatment emergent serious
273 adverse event (urinary calculus), which was of moderate intensity, was not considered related to
274 study drug, and resolved with full recovery of the participant. Eight participants experienced an
275 adverse event in the study eye (two participants each experienced two adverse events): one
276 participant had conversion to neovascular AMD and retinal hemorrhage, one participant had
277 mild intraretinal hemorrhage; one participant had reduced visual acuity and visual impairment;
278 one participant had borderline glaucoma, one participant had eyelid pruritis, one participant had
279 meibomian gland dysfunction, one participant had posterior capsular opacification, and one

280 participant had punctate keratopathy. Of the two participants who experienced retinal
281 hemorrhage in the study eye, the first was a mild intraretinal hemorrhage outside the arcades
282 which was not consistent with choroidal neovascularization (CNV), diabetes, or retinal vein
283 occlusion and which was attributed to the patient's longstanding hypertension. This was not
284 considered related to study drug. The second participant with intraretinal hemorrhage was
285 concurrently diagnosed with new CNV due to neovascular AMD at the final week 28 study visit
286 (4 weeks after having stopped study drug per protocol). This individual subsequently received
287 intravitreal anti-VEGF therapy as part of standard of care. Risk factors for the development of
288 neovascular AMD in this participant included large drusen and pigmentary changes in the study
289 eye and prior diagnosis of neovascular AMD in the fellow eye. This was similarly not considered
290 related to study drug.

291 As noted above, one participant experienced two ocular AEs of reduced visual acuity and visual
292 impairment in the study eye at the week 12 study visit. In this individual, measures of visual
293 function were stable through the week 8 study visit. At week 12, some visual function measures
294 were decreased compared to baseline while others were stable or improved compared to baseline
295 (-17 letters BCVA; -8 letters LLVA; NLRA was unchanged at 0.1 logMAR and LLRA was
296 improved by +0.3 logMAR). There was no change in clinical exam or imaging. The participant
297 voluntarily decided to withdraw from the study at the week 12 visit. At this participant's standard
298 of care follow up visit one month later, BCVA had recovered to baseline. These AEs were
299 considered mild and possibly related to study drug. Among other study eye AEs, one was
300 considered moderate in intensity (punctate keratopathy), and all others were mild in intensity.

301 Eight participants reported an ocular AE in the nonstudy eye. Six of these were considered mild
302 in intensity and two were considered of moderate intensity. Two AEs, reduced visual acuity and

303 visual impairment, occurred in the same participant who experienced these AEs in the study eye
304 and were considered mild in intensity and possibly related to study drug.

305 *Exploratory Efficacy Endpoints*

306 Mean (SD) BCVA at baseline was 79.4 (7.4) letters compared to 82.0 (6.9) at week 24. Effects
307 of the study drug on standard luminance BCVA are summarized in **Figure 1**. Among study
308 participants completing the 24-week treatment period, improvement in BCVA compared to
309 baseline were evident by week 4 which was maintained throughout the study period with mean
310 increase of 3.6 (6.4) letters at week 24 ($P=0.014$, Holm method threshold for statistical
311 significance $P < 0.05$) (**Figure 1A**). Scatterplot and categorical analyses showed that 14 of 18
312 patients experienced an increase in BCVA, 5 of 18 (26.3%) had a greater than 5-letter
313 improvement in BCVA, 2 of 18 (10.5%) had a greater than 10-letter increase and 1 of 18 (5.3%)
314 had a greater than 15-letter increase in BCVA. (**Figure 1B, 1C**). No participants had a greater
315 than 5-letter decrease in BCVA.

316 Mean (SD) LLVA at baseline was 63.8 (10.0) letters compared to 68.4 (11.5) at week 24. Effects
317 of the study drug on LLVA are summarized in **Figure 2**. Among study participants completing
318 the 24-week treatment period, improved LLVA was noted at all time points with mean increase
319 of 5.6 (7.8) letters at week 24 ($P=0.004$, Holm method threshold for statistical significance P
320 < 0.025) (**Figure 2A**). Nine of 18 participants (50%) had greater than 5-letter improvement, 3 of
321 18 (16.7%) had greater than 10-letter improvement and 2 of 18 (11.1%) had greater than 15-
322 letter increase in LLVA. One participant had a decline of > 5 letters in LLVA. (**Figure 2B, 2C**).

323 Mean (SD) NLRA at baseline was logMAR 0.01 (0.18) compared to -0.08 (0.186) at week 24,
324 with mean increase of -0.11 ± 0.15 ($P=0.001$, Holm method threshold for statistical significance

325 $P < 0.0167$), equivalent to an approximately 1-line gain in NLRA (**Figure 3**). Improvement in
326 NLRA was evident by week 4 and was maintained at weeks 8 through 24. Mean (SD) LLRA was
327 logMAR 0.39 (0.23) at baseline compared to 0.11 (0.21) at week 24, a mean increase of -0.28
328 (0.17) ($P < 0.0001$, Holm method threshold for statistical significance $P < 0.0125$), equivalent to
329 an approximately 3-line gain in LLRA (**Figure 4**). Improvement in LLRA was evident by week
330 4 and was maintained at weeks 8 through 24.

331 For the low luminance questionnaire (LLQ), subscale scores at week 24 as well as change in
332 subscale scale at week 24 from baseline are included in **Table 3**. Using Holm method
333 thresholds for statistical significance to correct for multiple comparisons of subscales on the
334 LLQ, mean changes from baseline were statistically significant in 6 of 7 parameters (dim
335 light reading; driving or riding in car; general dim light vision; light transitions and glare;
336 other activities of daily living; peripheral vision) at Week 24.

337 Examination of anatomic changes was performed by segmentation of RPE-DC volume on OCT.
338 Mean RPE-DC volume did not change significantly in any of the 9 fields of the ETDRS grid nor
339 globally across the macula from baseline at Week 24. FAF was assessed at 24 weeks as
340 compared to baseline, and no appreciable change in hyperautofluorescence signal, and no
341 appreciable development of new hypoautofluorescence indicating GA was observed at Week 24.

342 To assess potential alterations in retinal sensitivity, mesopic microperimetry was performed. The
343 mean 95% bicurve ellipse area (BCEA) was 8.06 log square minutes of arc at baseline and this
344 parameter did not change significantly from baseline at Week 24 (mean 1.47-log square minutes
345 of arc decrease; $P = 0.1901$). There was no significant change in the mean threshold for reduced
346 retinal sensitivity, nor in the number of loci with reduced retinal sensitivity as defined by $< 25\text{dB}$

347 or <14dB below normal values. The utility of this endpoint was further limited by problematic
348 test-retest variability present in nearly all participants.

349 Dark adaptometry was performed to assess recovery of dim light vision following bright light
350 stress. In the HRD cohort, results were limited by the fact that no patient could recover from
351 100% bleach within 20 minutes. Participants had a mean (SD) dark adaptation time at a 75%
352 bleach level of 7.121 (5.6128) minutes at the baseline visit, and this parameter did not change
353 significantly from baseline at Week 24.

354 **Discussion**

355 Along the spectrum of AMD, the most profound vision loss occurs in patients experiencing
356 central vision loss due to GA or due to inadequately treated or advanced neovascular AMD, and
357 this effect is evident by best-corrected visual acuity (BCVA) under standard luminance
358 conditions, the most frequently used measure of assessing visual function. However, BCVA
359 generally has poor sensitivity to detect visual dysfunction in HRD patients since these patients
360 frequently retain preserved central visual acuity under standard lighting conditions.⁴⁷ Instead,
361 patients with HRD suffer from debilitating visual impairment in low-light conditions, which can
362 have profound effects on nighttime activities and also increase risk of nighttime falls and
363 injury.^{4,7,8} Thus, measures of visual function in dim lighting conditions (e.g., low luminance
364 visual acuity (LLVA)) appear to be more useful for characterization of visual difficulties in
365 patients with intermediate AMD and HRD.^{47,51}

366 Decreased low luminance visual acuity may be associated with impaired short-wavelength cone
367 function and reduced retinal sensitivity that are evident in early and intermediate AMD
368 disease.^{47,51} Nevertheless, the mechanism(s) for low luminance visual impairment in AMD are

369 poorly understood, which has limited the development of therapies to treat visual dysfunction in
370 affected patients. The results of the present study suggest that mitochondrial dysfunction, likely
371 at the RPE and/or the neurosensory retina, is a major mediator of low luminance vision
372 impairment, and that drugs targeting mitochondrial dysfunction may be effective to improve low
373 luminance visual function.

374 Elamipretide is a small tetrapeptide drug which has been shown to prevent or reverse
375 mitochondrial dysfunction in a number of preclinical models.^{43,52,53} Elamipretide localizes to
376 mitochondria where it reversibly binds to cardiolipin, a unique phospholipid localized to the
377 hairpin turn of mitochondrial cristae where it is required for normal morphology of the cristae
378 and the electron transport complex.^{44,45,53,54} Elamipretide has been shown to bind cardiolipin in
379 dysfunctional mitochondria and restore normal ATP generation, respiration and reactive oxygen
380 species generation.^{44,45,53,54} Elamipretide has been studied in multiple preclinical models relevant
381 to AMD where it has been shown to ameliorate mitochondrial dysfunction in RPE.^{36,43}
382 Specifically, elamipretide has been shown to prevent mitochondrial dysfunction and improve
383 mitochondrial respiration in cultured RPE cells isolated from AMD donor eyes. Finally,
384 elamipretide was found to reverse morphologic, biochemical and functional signs of AMD
385 pathobiology in the ApoE4 mouse model of AMD,³⁶ including regression of subRPE deposits,
386 improved mitochondrial morphology, and restoration of ERG amplitudes, all of which provided
387 compelling support for the current clinical trial.³⁶

388 The current study demonstrates that subcutaneous daily elamipretide is generally well tolerated
389 in patients with AMD with the majority of adverse events related to local injection site reactions.
390 These events were all mild to moderate in severity and only one participant discontinued study
391 drug due to injection site reaction. There was one serious AE (urinary calculus) which was not

392 related to study drug. Ocular AEs were all of mild or moderate intensity and only two ocular AEs
393 in the study eye were considered possibly related to study drug, reduced visual acuity (n=1) and
394 visual impairment (n=1), both of which occurred in the same participant. Overall, the safety
395 profile of elamipretide was comparable to that previously observed in other clinical trials of
396 elamipretide.^{55,56}

397 Exploratory efficacy endpoints suggest that elamipretide may have a positive benefit on visual
398 function in intermediate AMD with HRD. While pharmacokinetics (PK) samples were not
399 collected and analyzed in this study, the PK profile of elamipretide has been extensively
400 characterized in other clinical trials (data on file, Stealth BioTherapeutics).⁵⁷ In rabbit PK
401 studies, subcutaneous dosing of elamipretide (1 mg / kg) produced measurable drug levels at the
402 choroid, RPE, and retina at C_{max} (30 min). The measured concentrations are expected to be
403 therapeutic, based on the exposure-response data from the mouse model of HQ-induced
404 oxidative injury (data on file, Stealth BioTherapeutics).

405 Small but statistically significant improvements in both BCVA and NLRA were observed in
406 participants with HRD. These gains may have been limited by a ceiling effect due to very good
407 normal light visual function at baseline in this cohort. Larger and statistically significant gains
408 were noted in low luminance visual function endpoints (LLVA and LLRA). Gains in visual
409 function evident as early as day 7, increased further by week 4 and were maintained across the
410 study period for all visual function endpoints. Additionally, significant improvements were noted
411 in 6 out of the 7 subscales of the LLQ at week 24, consistent with the observed improvements in
412 visual acuity endpoints.

413 The current study is limited by small sample size and the fact that it was an open-label study
414 without placebo control. In addition, the improvements in BCVA and LLVA may have been
415 influenced by a highly responsive subset of participants with a substantially greater benefit.
416 There were not statistically significant improvements in drusen volume (RPE-DC on OCT), dark
417 adaptometry, or mesopic microperimetry. Thus, improvements in the exploratory visual
418 endpoints must be interpreted with caution. Nevertheless, elamipretide showed good feasibility,
419 safety and tolerability in participants with intermediate AMD and HRD. The natural history
420 AMD is one of progressive vision loss in affected patients, with a high prevalence of low
421 luminance visual dysfunction in intermediate AMD with HRD.^{7,58} There is a relative lack of
422 clinical trials targeting the HRD stage of AMD compared to more advanced stages of the disease.
423 Given the encouraging safety profile and findings in some exploratory endpoints, a future study
424 of elamipretide in HRD patients is strongly justified.

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592 **Figure Legends**

593 **Figure 1.** Effects of elamipretide on best-corrected visual acuity (BCVA). (A) Mean change in
594 BCVA (ETDRS letters) from Baseline (Day 0) over 24-week active study period; bars indicate
595 standard deviation (SD). * ($P=0.014$, Holm method threshold for statistical significance P
596 <0.05). (B) Scatterplot for change in BCVA (ETDRS letters) from Baseline at week 24.
597 Horizontal solid line: mean value; vertical dashed line: SD. (C) Percentage of study participants
598 by categorical change in BCVA (ETDRS letters) from Baseline at week 24.

599 **Figure 2.** Effects of elamipretide on low luminance best-corrected visual acuity (LLVA). (A)
600 Mean change in LLVA (ETDRS letters) from Baseline (Day 0) over 24-week active study
601 period; bars indicate standard deviation (SD). * ($P=0.004$, Holm method threshold for statistical
602 significance $P <0.025$). (B) Scatterplot for change in LLVA (ETDRS letters) from Baseline at
603 week 24. Horizontal solid line: mean value; vertical dashed line: SD. (C) Percentage of study
604 participants by categorical change in LLVA (ETDRS letters) from Baseline at week 24.

605 **Figure 3.** Effects of elamipretide on normal luminance reading acuity (NLRA). Mean change in
606 NLRA (logMAR) from Baseline (Day 0) over 24-week active study period; bars indicate
607 standard deviation (SD). * ($P=0.001$, Holm method threshold for statistical significance P
608 <0.0167). (B) Scatterplot for change in NLRA (logMAR) from Baseline at week 24. Horizontal
609 solid line: mean value; vertical dashed line: SD.

610 **Figure 4.** Effects of elamipretide on low luminance reading acuity (LLRA). Mean change in
611 LLRA (logMAR) from Baseline (Day 0) over 24-week active study period; bars indicate
612 standard deviation (SD). * ($P < 0.0001$, Holm method threshold for statistical significance P
613 < 0.0125). (B) Scatterplot for change in LLRA (logMAR) from Baseline at week 24. Horizontal
614 solid line: mean value; vertical dashed line: SD.

Journal Pre-proof

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

Journal Pre-proof

Tables and Figure Legends**Table 1.** Characteristics of participants in the high-risk drusen study cohort

Characteristic	N=21
Age, mean (SD) (range)	70.9 (8.5) (59, 87)
Sex, n (%)	
Female	13 (61.9)
Male	8 (38.1)
Ethnicity, n (%)	
Hispanic/Latino	1 (4.8)
Caucasian	20 (95.2)
Former smoker*, n (%)	8 (38.1)
Baseline BCVA, mean (SD)	79.4 (7.4)
Baseline LLVA, mean (SD)	63.8 (10.0)

*Former smoker; no participants were current smokers

SD= standard deviation; BCVA= best-corrected visual acuity; LLVA= low luminance visual acuity

Table 2. Adverse events (AEs)* in patients with high-risk drusen

Event	N=21
<i>All Treatment-emergent events, n (%)</i>	
Any treatment-emergent AE	21 (100)
Injection site reactions	
Pruritis	21 (100)
Erythema	16 (76.2)
Induration	16 (76.2)
Bruising	16 (76.2)
Pain	9 (42.9)
Hemorrhage	6 (28.6)
Urticaria	5 (23.8)
Upper respiratory tract infection	7 (33.3)
Headache	2 (9.5)
Myalgia	2 (9.5)
Increased intraocular pressure	2 (9.5)
Procedural nausea	2 (9.5)
Seasonal allergy	2 (9.5)
AE by maximum intensity	
Mild	11 (52.4)
Moderate	10 (47.6)
Related to study drug	21 (100)
AE leading to study drug discontinuation	1 (4.8)
Any serious systemic AE	1 (4.8)
Urinary Calculus	1 (4.8)

All treatment-emergent ocular events in the study eye, n (%)

Any treatment-emergent AE	10*
Eye disorders	
Retinal hemorrhage	2 (9.5)
Borderline glaucoma	1 (4.8)
Eyelid pruritis	1 (4.8)
Meibomian gland dysfunction	1 (4.8)
Neovascular age-related macular degeneration	1 (4.8)
Posterior capsular opacification	1 (4.8)
Punctate keratitis	1 (4.8)
Visual acuity reduced	1 (4.8)
Visual impairment	1 (4.8)
AE by maximum intensity	
Mild	9 (42.8)
Moderate	1 (4.8)
Possibly related to study drug	2 (9.5)
Visual acuity reduced	1 (4.8)
Visual impairment	1 (4.8)
AE leading to study drug discontinuation by investigator	0
Any serious AE	0

* There were 10 total ocular AEs in 8 participants; two participants each experienced two AEs during the study (one participant experienced reduced visual acuity and visual impairment; one participant experienced neovascular AMD and retinal hemorrhage).

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	Holm threshold
Dim light reading	18	58.9	20.34	56.3	31.3	87.5	18	15.8	14.34	12.5	-6.3	43.8	0.0001	0.0083
Driving or riding in car	18	63.5	26.54	68.8	25.0	100.0	18	16.4	18.77	12.5	-12.5	75.0	0.0013	0.025
General dim light vision	18	71.1	22.09	75.0	34.4	100.0	18	15.6	15.17	12.5	-6.3	56.3	0.0003	0.010
Light transitions and glare	18	62.6	21.69	65.0	25.0	95.0	18	17.4	13.98	15.0	-5.0	45.0	<0.0001	0.0071
Mobility	18	74.6	21.60	83.3	41.7	100.0	18	9.6	20.27	8.3	-16.7	66.7	0.0526	0.05
Other ADLs	18	76.3	21.00	81.3	37.5	100.0	18	17.8	17.95	12.5	-6.3	68.8	0.0004	0.012
Peripheral vision	18	74.3	27.79	75.0	25.0	100.0	18	17.8	20.12	12.5	-12.5	50.0	0.0012	0.017

SD= standard deviation; ADLs= activities of daily living