

Safety and Efficacy of Intravitreal Risuteganib for Non-Exudative AMD: A Multicenter, Phase 2a, Randomized, Clinical Trial

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BACKGROUND AND OBJECTIVE: To evaluate the safety and efficacy of 1.0 mg risuteganib in subjects with nonexudative age-related macular degeneration (AMD).

PATIENTS AND METHODS: This was a phase 2a, prospective, double-masked, sham-controlled study. Eyes with nonexudative (dry) AMD and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 20/40 and 20/200 were included. Subjects were randomized to intravitreal 1.0 mg risuteganib or sham injection. At Week 16, subjects in the risuteganib group received a second 1.0-mg dose and the sham group crossed over to receive a dose of 1.0 mg risuteganib and were evaluated at Week 28. The primary endpoint was proportion of subjects with 8 letters ETDRS or more BCVA gain from baseline to Week 28 in the risuteganib group versus baseline to Week 12 for the sham group. BCVA was tested and subjects were observed for adverse events (AEs) every 4 weeks until completion of the study at 32 weeks.

RESULTS: Forty-five subjects (risuteganib, n = 29; sham, n = 16) were enrolled in the study, of whom 39 (risuteganib, n = 25; sham, n = 14) completed the study and were included in the per protocol efficacy analysis. At baseline, mean age was 78.8 and 75.9 years and mean BCVA was 67.1 and 64.4 letters in the sham and risuteganib groups, respectively. The primary endpoint was met by 48% of the risuteganib group at Week 28 and 7% of the sham group at Week 12 ($P = .013$). Of the risuteganib subjects, 20% gained 15 letters or more at Week 28, whereas no patients in the sham group at Week 12 achieved this visual acuity gain. The only ocular treatment-related treatment-emergent AE was vitreous floaters, which spontaneously recovered without sequelae. No drug-related serious AE was reported.

CONCLUSIONS: Risuteganib demonstrated significant BCVA improvement in patients with non-exudative AMD. No drug-related AEs were seen during a 32-week observation period.

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INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of legal blindness in individuals older than 65 years in the United States.¹ It is a progressive disease that results in significant visual dysfunction that severely affects quality of life.² Worldwide, the projected number of people with AMD in 2020 was 196 million.³

The pathogenesis of AMD is complex and multifactorial, and the exact molecular mechanisms of disease are not completely understood.⁴ Oxidative stress (OS) induces damage caused by reactive oxygen species (ROS).⁵ With age, decreased mitochondrial oxidative phosphorylation creates increased generation of ROS and decreased metabolic activity, resulting in an

imbalance that affects the cells' optimal bioenergetics and impairs the cytoprotective role of mitochondrial dynamics.^{6,7} Mitochondrial dysfunction in the retinal pigment epithelium (RPE) is thought to contribute to the chronic OS associated with AMD.⁸ Chronic OS results in modification of proteins and lipids in the posterior chamber, triggering activation and dysregulation of the complement system.⁹ Constant exposure to light and OS indirectly contributes to complement activation through lipid peroxidation.^{10,11} Complement inhibition has been identified as a candidate for therapeutic intervention in AMD.¹²⁻¹⁴

Risuteganib (Allegro Ophthalmics, San Juan Capistrano, CA) is a small peptide integrin regulator that has been shown to protect human RPE cells against OS-

associated cellular dysfunction. In human donor RPE cells, risuteganib was found to protect cells by reducing ROS level, upregulating cytoprotective heme oxygenase-1 protein level, and regulating genes in multiple disease-relevant pathways including inflammation, cell proliferation, cell adhesion and migration.¹⁵ In RPE cells containing mitochondria derived from AMD patients, risuteganib exposure was associated with reduced expression of genes associated with apoptosis (*BAX*), angiogenesis (*VEGFA*) and integrin function (*ITGB1*).¹⁶ Pharmacokinetics studies found risuteganib has a long half-life in the retina after intravitreal injection, whereas *ex vivo* studies suggest the peptide may be specifically localized to the RPE cells, where it may play a role in preserving and reversing the diseased cellular state.¹⁷ This is further supported by studies from multiple labs that demonstrated improved mitochondrial bioenergetics and metabolic activity after risuteganib treatment, indicating potential reactivation of patient RPE with diminished mitochondrial function.^{15,17,18} Studies of other antioxidants have also demonstrated reduction in retinopathy and improvement in visual parameters in animal models,¹⁹⁻²¹ suggesting pro-mitochondrial therapeutics can lead to both morphological and functional improvements. Collectively, pre-clinical studies demonstrated that risuteganib has cytoprotective, anti-inflammatory, and pro-mitochondria properties, which make it a potential candidate for use in the treatment of nonexudative AMD.

PATIENTS AND METHODS

Phase 2a, prospective, randomized, double-masked, sham-controlled, multicenter study, registered on ClinicalTrials.gov with Identifier NCT03626636, conducted at seven sites in the United States under the approval of institutional review boards. The study adhered to provisions of the Declaration of Helsinki and its amendments, and Good Clinical Practice.

Participants

Key inclusion criteria were adults between 50 and 85 years diagnosed with nonexudative AMD defined as 1) combination of areas of RPE disturbances and/or 1 or more large drusen (>125 µm) and/or multiple intermediate drusen (63-124 µm) in the macula, and 2) well-defined RPE and outer segment ellipsoid line on spectral domain optical coherence tomography (SD-OCT) examination of the central 1 mm of the macula, with ETDRS best-corrected visual acuity (BCVA) of 33 to 72 letters (Snellen equivalent 20/40 and 20/200), and history of symptomatic decrease in visual acuity (VA) in the previous 12 months not attributable to any other condition.

Key exclusion criteria included serous pigment epithelium detachment, history of exudative AMD, history of retina surgery, or coexistent ocular pathology that could interfere with measurement of BCVA, and visualization of the macula in the study eye. Subjects who received anti-VEGF intravitreal

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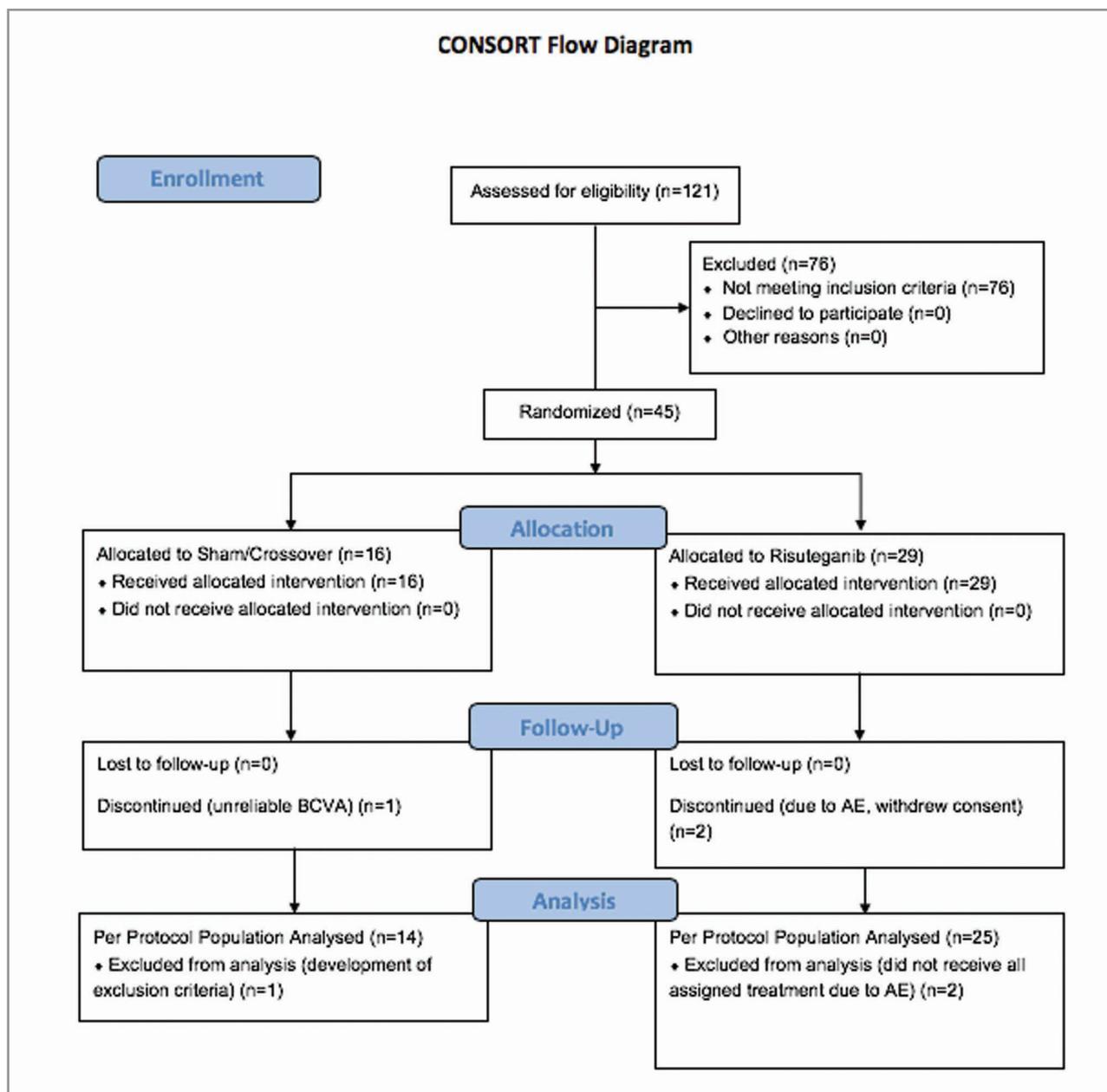


Figure 1. CONSORT flow diagram. BCVA = best-corrected visual acuity; AE = adverse event

injection in the fellow eye in the preceding 90 days and subjects with active exudative AMD in the fellow eye were excluded.

Study Design

After written informed consent, potential study participants were screened from 28 days to 2 days prior to randomization. Eligible subjects were enrolled by the principal investigator and assigned to experimental treatment group or sham group by the contract research organization using central electronic data capture randomization. Target sample

size was 40 subjects: 25 subjects in the risuteganib group and 15 subjects in the control group, resulting in a 1.7:1 ratio. Injecting unmasked investigators administered 1.0 mg/0.05 mL risuteganib as an intravitreal injection on Day 0 and Week 16 to the experimental treatment group, and a sham injection on Day 0 to the sham group. Masked investigators, photographers, and VA technicians examined all subjects every 4 weeks for 32 weeks. On week 16, subjects from the sham group crossed over and received one intravitreal 1.0 mg/0.05 mL risuteganib injection.

TABLE 1
Demographic Characteristics of Subjects

Variable	Sham (n = 14)	Risuteganib (n = 25)	P Value
Male	3 (21.4%)	9 (36.0%)	.48
Female	11 (78.6%)	16 (64.0%)	
Caucasian	14 (100%)	24 (96.0%)	1.00
Asian	0	1 (4.0%)	
Hispanic or Latino	2 (14.3%)	3 (12.0%)	1.00
Not Hispanic or Latino	12 (85.7%)	22 (88.0%)	
< 45 years old	0	0	.64
45-65 years old	1 (7.1%)	4 (16.0%)	
> 65 years old	13 (92.9%)	21 (84.0%)	
N	14	25	.32
Mean (SD)	78.8 (8.40)	75.9 (8.43)	
Median	80.0	77.0	
Min, Max	59, 91	57, 87	

SD = standard deviation; Min = minimum; Max = maximum

Outcome Measures

The prespecified primary efficacy endpoint was the percentage of subjects with 8 ETDRS letters or more of BCVA improvement from baseline to Week 28 in the risuteganib group compared to baseline to Week 12 in the sham group. Secondary efficacy endpoints were 1) percentage of subjects with 10 or greater and 15 or greater ETDRS letters of BCVA improvement, 2) mean change in BCVA from baseline to Week 28 in the risuteganib group and Week 12 in the sham group 3) maximum changes in BCVA between groups. Safety assessments included complete ocular examination and monitoring for occurrence of adverse events (AEs). Color vision, microperimetry, and SD-OCT data will be discussed in separate papers.

Statistical Methods

Descriptive statistics was used to tabulate and summarize study outcomes. Background and demographic characteristics were presented. Continuous variables were summarized by descriptive statistics. Discrete variables were summarized by frequencies and percentages; 95% confidence intervals were provided for the primary endpoint. AEs were summarized by presenting the number and percentage of having at least one such AE. Any other information collected was listed as appropriate. Any statistical tests performed to explore the data were used only to highlight any interesting comparisons that may warrant further consideration. All statistical analyses were programmed us-

ing SAS software version 09.4 or later (SAS Institute, Cary, NC). A *P* value of less than .05 was considered significant. Since this was a phase 2a exploratory clinical study, no formal hypothesis testing was performed. The sample size was determined based on establishing a reasonable number of subjects to provide adequate safety and efficacy results to proceed to the next phase of clinical development. In case of subject drop-out, more subjects could be enrolled.

RESULTS

Subjects

The study was conducted between June 23, 2017, and March 5, 2019. One hundred twenty-one subjects were screened (**Figure 1**). Most of these subjects had preexisting retinal lesions or did not meet the OCT anatomical criteria. Forty-five subjects from seven investigational sites were enrolled, included in the safety population, and randomized into two treatment groups: 29 risuteganib and 16 sham.

One subject in the sham group received only one (sham) injection. Three subjects in the risuteganib group received only one (risuteganib) injection. Following the specifications of the statistical analysis plan, one subject in the risuteganib group was excluded from the modified intent-to-treat population due to withdrawal of consent and lack of follow-up. Reasons for exclusion from the per protocol (PP) population were: did not receive all assigned treat-

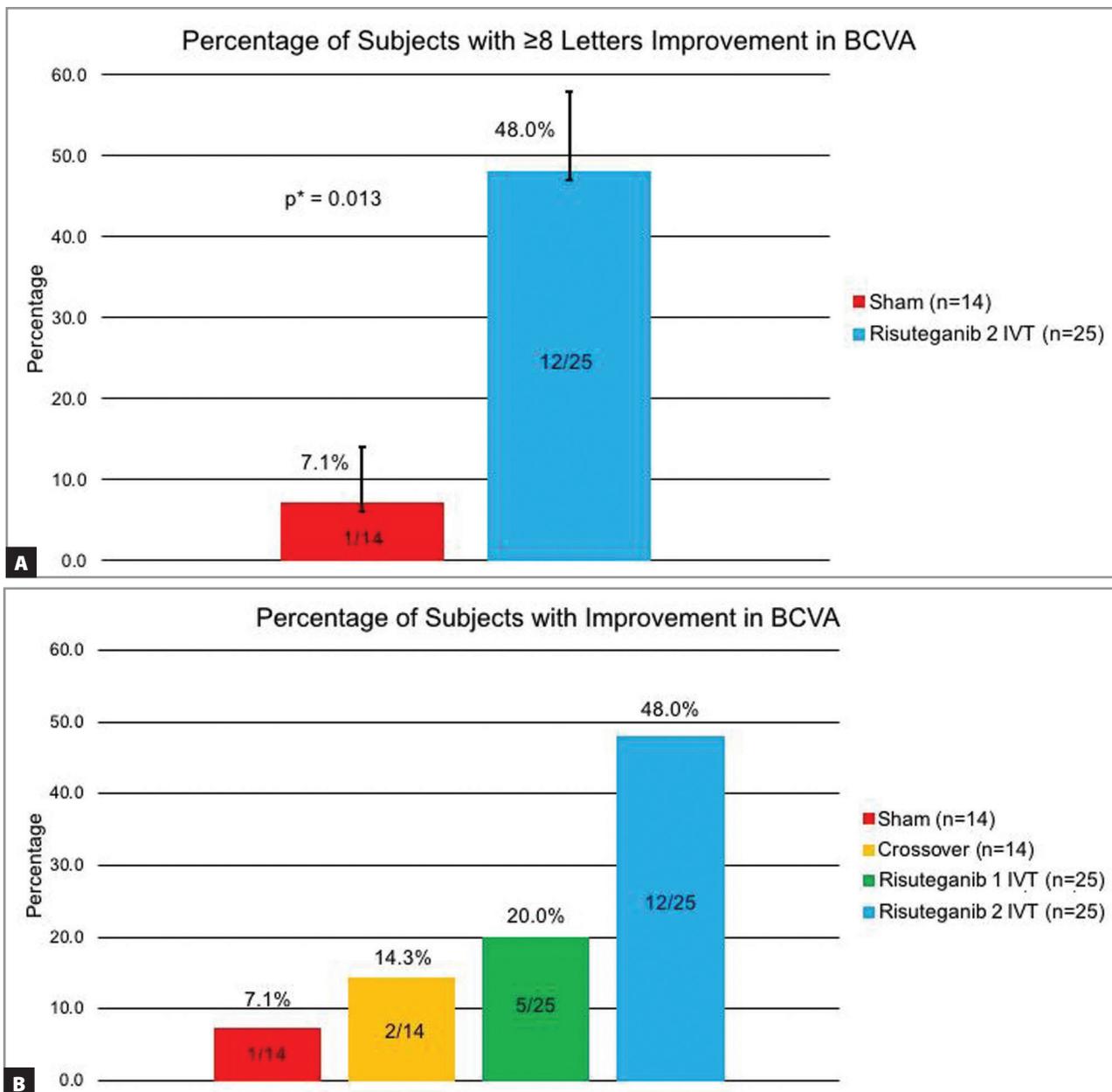


Figure 2. (A) Primary endpoint. Comparison of the percentage of subjects with ≥ 8 letters of improvement in best-corrected visual acuity (BCVA) from baseline: sham group at Week 12 versus risuteganib group at Week 28. (B) Comparison of the percentage of subjects with 8 or more letters of improvement in BCVA from baseline: sham group at Week 12, sham group after crossing over and receiving one risuteganib treatment at Week 28, risuteganib group after receiving one treatment at Week 12 and two treatments at Week 28.

ments due to AE (n = 3), development of an exclusion criteria (n = 1), subject withdrawal of consent and lack of any follow-up visit (n = 1), and subject's inability to follow instructions leading to unreliable BCVA measurement (n = 1). The PP population included a total of 39 subjects (25 risuteganib, 14 control). The demographics and baseline characteristics were similar between the two treatment groups (**Table 1**).

Efficacy

Primary Endpoint: The primary endpoint was met with 12 of 25 subjects (48%; confidence interval [CI] 27.8% - 68.69%) gaining 8 or more ETDRS letters at 28 weeks after receiving two intravitreal risuteganib injections at baseline and Week 16, compared to one of 14 subjects at Week 12 (7.1%; CI 0.18% - 33.87%) after sham injection at baseline (**Figure 2A**). Post hoc analysis using a two-sided Fisher's exact test showed

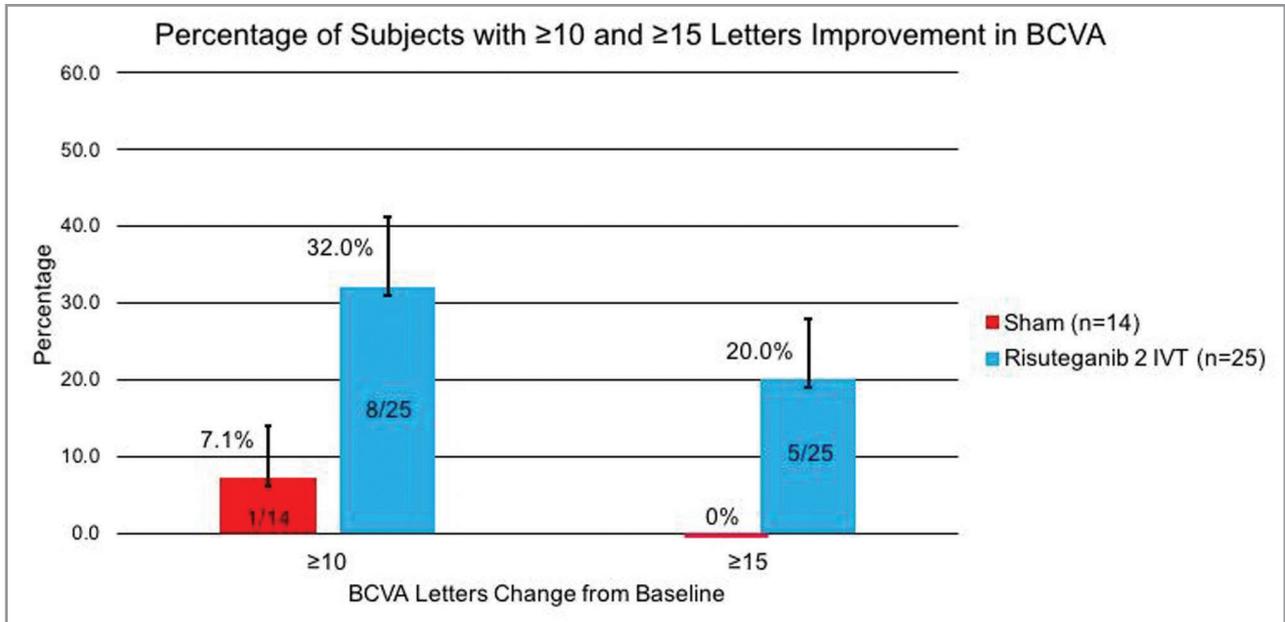


Figure 3. Comparison of the percentage of subjects with 10 or more and 15 or more letters of improvement in best-corrected visual acuity (BCVA) from baseline: sham at Week 12 versus risuteganib at Week 28.

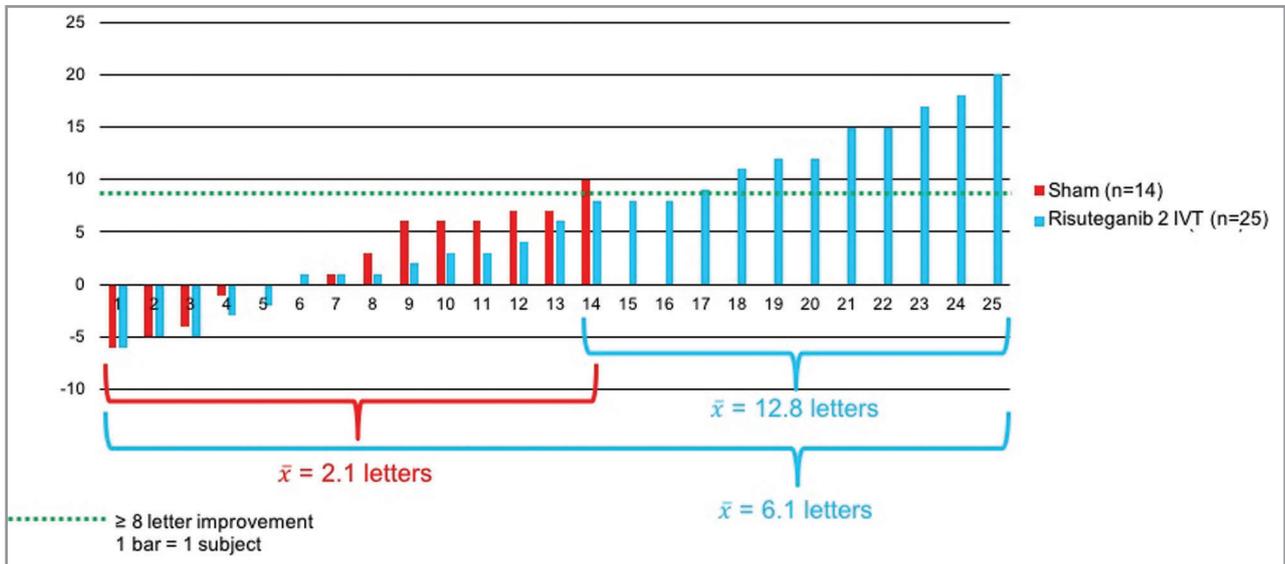


Figure 4. Change in best-corrected visual acuity from baseline for each subject: sham at Week 12 versus risuteganib at Week 28.

a statistically significant difference ($P = .013$).

Secondary Endpoints: The same data are shown for the sham cohort after crossing over and receiving one treatment of risuteganib, and for the risuteganib cohort after receiving only one treatment (**Figure 2B**).

The proportion of subjects with more than 10 ETDRS letter gain in BCVA was 32.0% in the risuteganib treatment group at 28 weeks compared to 7.1% in the control group at 12 weeks ($P = .12$) (**Figure 3**). The proportion of subjects with more than 15 ETDRS letter gain in BCVA was 20.0% in the risuteganib treat-

ment group at 28 weeks compared to 0% in the control group at 12 weeks ($P = .14$).

Change in BCVA from baseline for each subject in **Figure 4** showed a strong right shift in the risuteganib group, indicating more subjects gaining vision compared to the sham group. Although eight subjects in the control group showed a measurable improvement in BCVA, only one subject had a significant improvement 8 or more letters. The mean improvement in the risuteganib group was +6.1 letters compared to +2.1 letters in the sham group (**Figure 5**). The peak effect

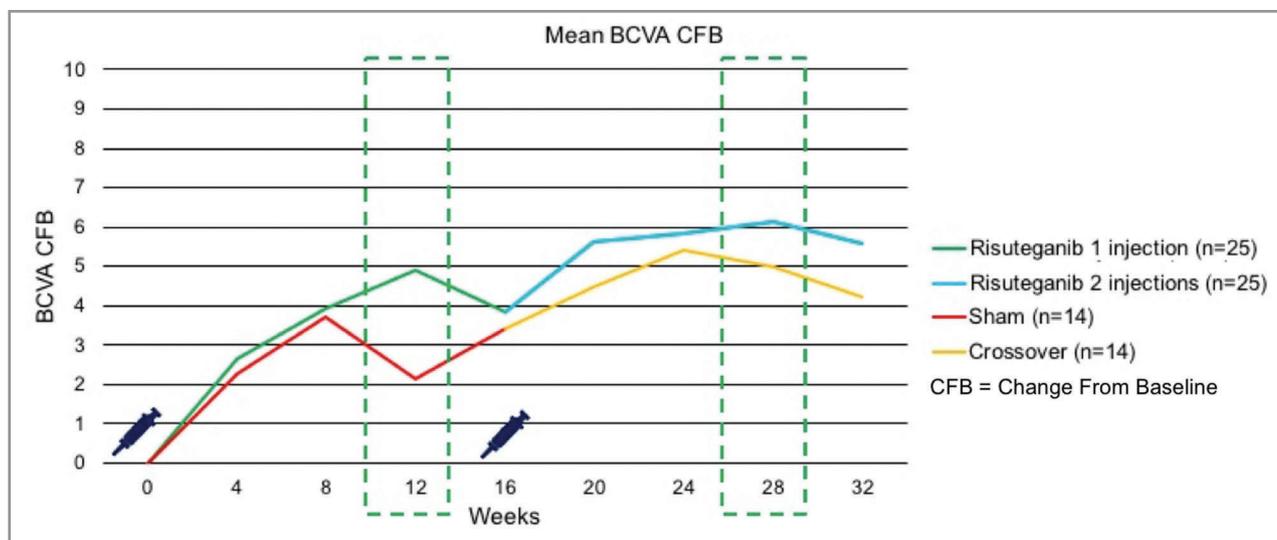


Figure 5. Mean best-corrected visual acuity (BCVA) change from baseline (CFB): sham group, sham group after crossing over and receiving one risuteganib treatment, and risuteganib group.

of a risuteganib injection was evident 12 weeks after each treatment, with a mild decrease in therapeutic effect at 16 weeks. Repeat dosing of risuteganib demonstrated an additive effect to the prior dose effect, again peaking at 12 weeks then showing a mild decrease in therapeutic effect after 16 weeks. Subjects who initially received a sham injection then crossed over to risuteganib treatment demonstrated an improvement in mean BCVA, which peaked at Week 8. Similar to the result of one injection in the risuteganib group, one injection in the crossover group was not enough to improve vision by 8 letters, but a second injection in the risuteganib group had an additive effect.

Safety

All subjects were included in the safety analysis. The only ocular treatment-related treatment-emergent AE was vitreous floaters of moderate intensity in a control subject, without other findings to suggest intraocular inflammation. This required no treatment and resolved without sequelae. No serious treatment-related AEs were reported. Slit-lamp examination and indirect ophthalmoscopy did not reveal any AEs. Two subjects in the risuteganib treatment group (6.9%) converted to exudative AMD during the observation period (30 and 53 days after the first risuteganib treatment); one of these subjects had a history of exudative AMD in the fellow eye. These subjects were treated with anti-VEGF and did not receive their second dose of risuteganib. No conversion to exudative AMD was observed in the sham/crossover group.

One subject in the sham/crossover group had perifoveal GA at baseline. This subject's BCVA dropped by

8 letters at Week 16, prior to receiving risuteganib treatment, and continued to drop at the subsequent visits. It was later discovered that the GA had encroached into the foveal center, with no other findings.

DISCUSSION

The long-established definition and classification of nonexudative AMD is based on anatomical abnormalities. It was only recently that functional abnormalities (ie, oxidative stress, mitochondrial dysfunction and complement-based inflammation) have been discovered to be part of the underlying cause of the disease. This discovery led to identifying potentially attractive targets for pharmaceutical agents such as risuteganib. To our knowledge, this is the first study to use a functional endpoint and demonstrate reversal of vision loss in a study population with less advanced dry AMD disease.

Natural history studies of nonexudative AMD show a mean decline in vision over time.²² Although an improvement in outcome after intervention in a chronic, degenerative disease such as AMD can, in itself, be considered indicative of a therapeutic effect, in a therapeutic trial, it is important to anticipate a placebo effect. Twelve weeks of observation for the control group was deemed to be adequate to establish the noise level, which would represent test-retest variability and placebo effect. Prior risuteganib dosing studies demonstrated an additive effect. In order to achieve maximum therapeutic benefit, subjects were given two intravitreal doses, and the primary endpoint for the treatment group was BCVA at Week 28. A crossover design allowed the control group to receive treatment after the noise level had been established.

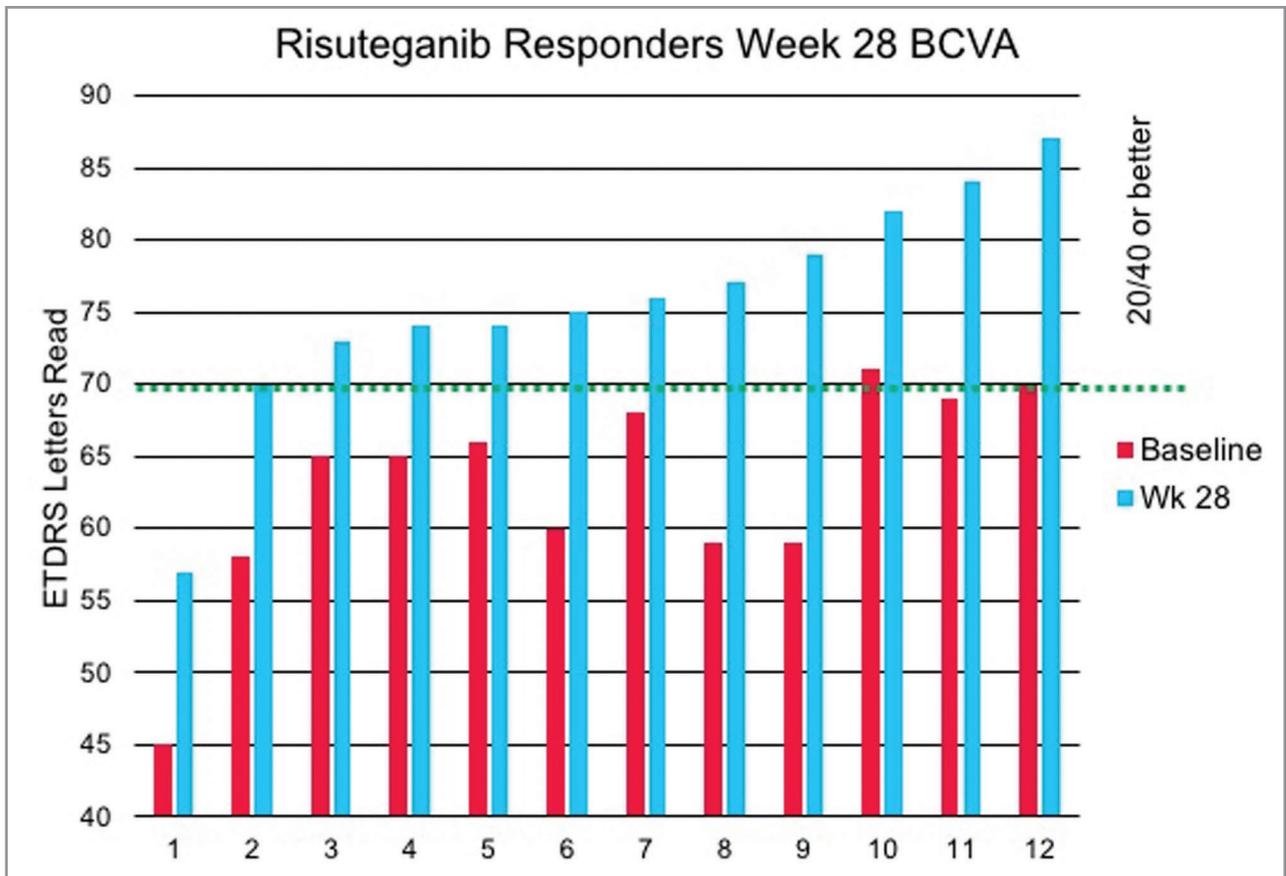


Figure 6. Comparison of best-corrected visual acuity (BCVA) at baseline versus Week 28 in risuteganib responders (≥ 8 letters of improvement).

Eight letters was used as the criteria for primary outcome as this represents a significant BCVA change based on literature review.^{23,24} Furthermore, a U.S. Food and Drug Administration endpoints meeting from November 2016 stated that a change of 5 or more letters in eyes with VA greater than 20/100 and a change of 10 or more letters in eyes with VA less than 20/100 is a real change in VA that is likely to be reproducible over time. Data were also analyzed to determine the percentage of subjects who achieved improvement of 10 or more and 15 or more letters. Results showed a trend similar to the improvement seen at the 8-letter threshold. Twenty percent of risuteganib treated subjects demonstrated a 15-letter or greater improvement in BCVA compared to 0% of controls. Although not significant, the natural history of this population of patients would likely have very few patients improving this amount.

Preclinical ocular distribution study of radiolabeled risuteganib after intravitreal injection revealed a half-life of 10.5 days (Pharmacokinetic Study performed by Charles River Laboratories, data on file, April 2018). A phase 2 clinical trial in DME demonstrated drug durability up to 12 weeks.²⁵ In comparison, ranibizumab and aflibercept, which are typically dosed every 4 to 8

weeks, have a retinal half-life of 2.6 and 2.425 days, respectively.²⁶ In this study, the peak treatment effect was observed 12 weeks after injection, with a mild decline in vision at 16 weeks. Repeat injection resulted in an apparent additive effect, which similarly peaked after 12 weeks. These data suggest that drug durability of risuteganib in dry AMD is every 12 weeks.

In patients with early to intermediate nonexudative AMD, the rate of natural conversion to exudative AMD has been reported as high as 28% over 5 years.²⁷ This study showed two patients who converted from nonexudative to exudative AMD in the treatment group, and none in the sham group. We do not believe that the conversion to exudative AMD is drug related, and it is difficult to interpret given the small sample size. However, choroidal neovascularization conversion will be closely monitored in a larger trial.

In this study, 48% of subjects who received two intravitreal risuteganib injections 16 weeks apart demonstrated an improvement of at least 8 letters of vision. Risuteganib responders (BCVA improvement ≥ 8 letters, $n = 12$) had a mean improvement of +12.8 letters at Week 28. Among the 12 risuteganib responders, 10 of them had a mean baseline BCVA of 20/63. At Week 28,

nine of 10 improved to 20/40 or better (**Figure 6**). The one subject that did not improve to 20/40 or better had a 12-letter gain but had a baseline BCVA of 20/80. This indicates that 90% of the responder subjects who had reduced functional vision (worse than 20/40) at baseline improved to functional vision after two quarterly treatments. This level of vision improvement allows patients to meet VA requirements for typical activities of daily living, which could provide increased independence and improved quality of life.

In conclusion, risuteganib 1.0 mg demonstrated significant improvement in BCVA in 48% (12/25) of subjects who received two intravitreal doses, with a drug durability of 12 weeks. No serious drug-related AEs were seen during the 32-week observation period. Positive results from this study warrant further investigation in a larger population with more frequent dosing and longer follow-up.

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