NEW DRUG APPROVAL

Brand Name	Cimerli™
Generic Name	ranibizumab-eqrn
Drug Manufacturer	Coherus Biosciences INC

New Drug Approval

FDA approval date: August 2, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761165

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME) are leading causes of blindness and severe visual impairment. Effective therapies include intravitreal injection of a

vascular endothelial growth factor (VEGF) inhibitor. VEGF inhibitors reduce leakage from blood vessels, prevent the proliferation of new abnormal vessels, decrease swelling of the retina, and improve visual acuity in patients with neovascular (wet) AMD, DR, and DME. Most patients with AMD and many with DR and DME will receive treatment with intravitreal Avastin, Lucentis, or Eylea.

AMD is a common eye condition and a leading cause of vision loss among people 60 years of age and older. There are two types of AMD: dry and wet. Dry AMD is more common, but wet AMD is associated with a more sudden loss of central vision. AMD causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead. The loss of central vision in AMD can interfere with simple everyday activities, such as the ability to see faces, drive, read, write, or do close work, such as cooking or fixing things around the house. Approximately 11 million people in the United States have some form of AMD, and of those, about 1.1 million have wet AMD.

DR affects blood vessels in the light-sensitive tissue called the retina that lines the back of the eye. It is a leading cause of visual loss and the principal cause of impaired vision in patients between 25 and 74 years of age. DME is a consequence of DR that causes a buildup of fluid in the area of the retina called the macula. The incidence of DME increases with the severity and duration of diabetes, occurring in about 3% to 20% of patients with diabetes. About half of all people with DR will develop DME. It affects approximately 750,000 people in the United States, The number of people with DME is expected to grow as the prevalence of diabetes increases.

Figure 1. 2010 U.S. Prevalence Rates for Age-Related Macular Degeneration by Age and Race

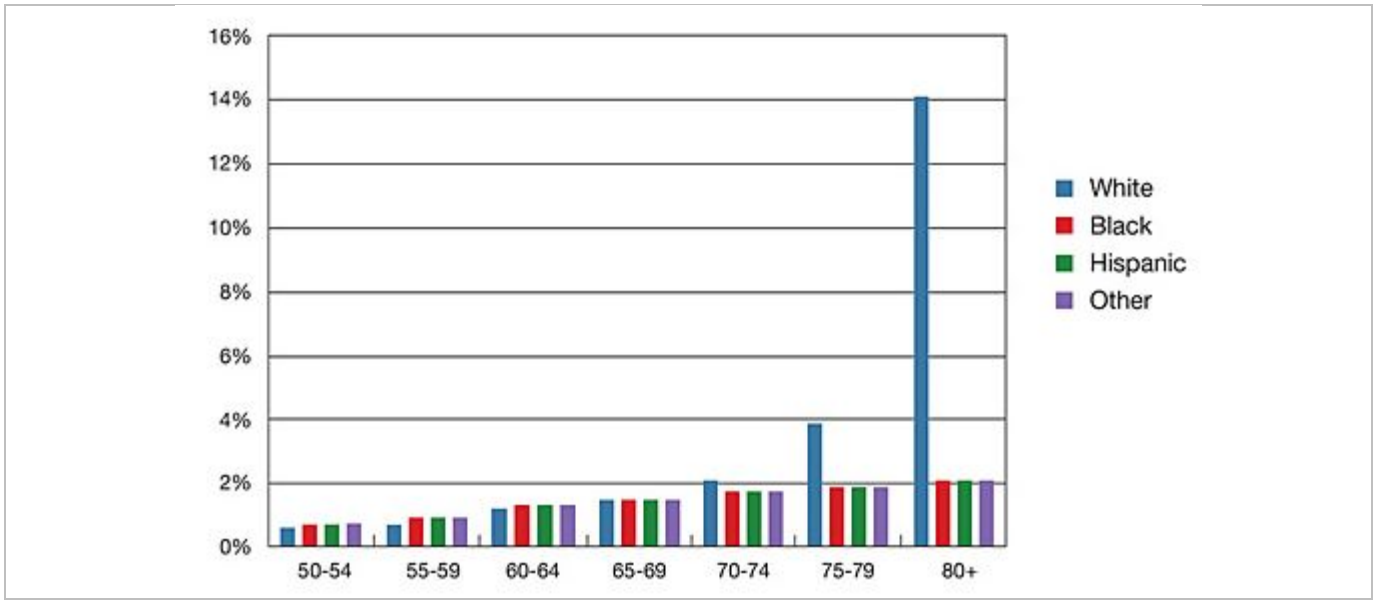
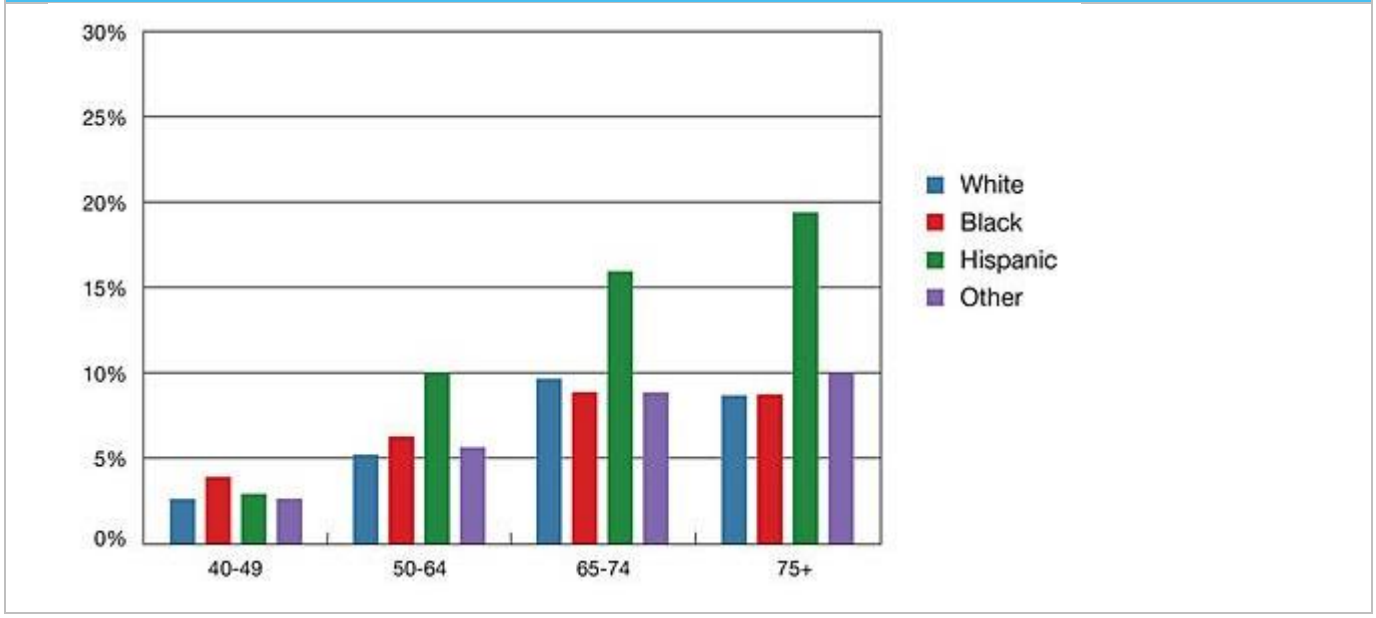


Figure 2. 2010 U.S. Prevalence Rates for Diabetic Retinopathy by Age and Race



Efficacy

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of ranibizumab were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (ranibizumab 879, control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2

In Study AMD-1, patients with minimally classic or occult (without classic) CNV lesions received monthly ranibizumab 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month

24. Patients treated with ranibizumab in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly ranibizumab 0.3 mg intravitreal injections and sham PDT; 2) monthly ranibizumab 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active PDT. Sham PDT (or active PDT) was given with the initial ranibizumab (or sham) intravitreal injection and every 3 months thereafter if FA showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with ranibizumab in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24. In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all ranibizumab-treated patients (approximately 95%) maintained their visual acuity. Among ranibizumab-treated patients, 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results.

Patients in the group treated with ranibizumab had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3-disc areas (DA) for ranibizumab versus 2.3-2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3-0.4 DA for

Table 2. Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	Month	Sham n = 99	Ranibizumab 0.5 mg n = 230	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)	12	60%	91%	30% (23%, 37%)
	24	56%	89%	33% (26%, 41%)
Gain of ≥15 letters in visual acuity (%)	12	6%	31%	25% (18%, 31%)
	24	4%	30%	25% (18%, 31%)
Mean change in visual acuity (letters) (SD)	12	-11.0 (17.9)	+6.3 (14.1)	17.1 (14.2, 20.0)
	24	-15.0 (19.7)	+5.5 (15.9)	20.1 (16.9, 23.4)

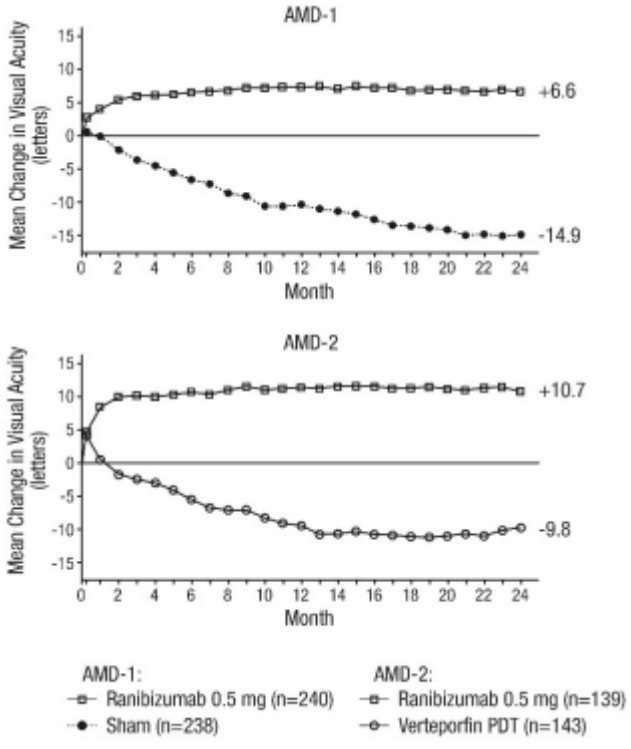
[a] Adjusted estimate based on the stratified model; $p < 0.01$

Table 3. Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	Month	Sham n = 99	Ranibizumab 0.5 mg n = 230	Estimated Difference (95% CI)[a]
Loss of <15 letters in visual acuity (%)	12	66%	98%	32% (24%, 40%)
	24	65%	93%	28% (19%, 37%)
Gain of ≥15 letters in visual acuity (%)	12	11%	37%	26% (17%, 36%)
	24	9%	37%	29% (20%, 39%)
Mean change in visual acuity (letters) (SD)	12	-8.5 (17.8)	+11.0 (15.8)	19.8 (15.9, 23.7)
	24	-9.1 (18.7)	+10.9 (17.3)	20.0 (16.0, 24.4)

[a] Adjusted estimate based on the stratified model; $p < 0.01$

Figure 3. Mean Change in Visual Acuity[a] from Baseline to Month 24 in Study AMD-1 and Study AMD-2



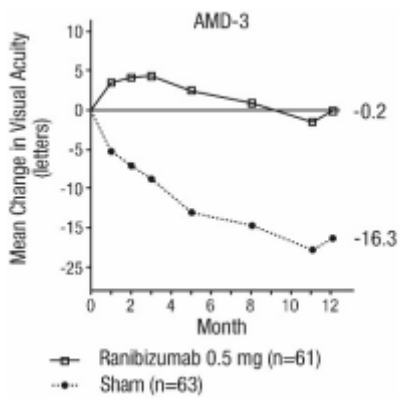
[a] Visual acuity was measured at a distance of 2 meters

Study AMD-3

Study AMD-3 was a randomized, double-masked, sham-controlled, 2-year study designed to assess the safety and efficacy of ranibizumab in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received ranibizumab 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for three consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (ranibizumab 0.3 mg, 60; ranibizumab 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with ranibizumab in Study AMD-3 received a mean of six total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was the mean change in visual acuity at 12 months compared with baseline.After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every 3 months with ranibizumab lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all ranibizumab-treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

Figure 4. Mean Change in Visual Acuity from Baseline to Month 12 in Study AMD-3



Study AMD-4

Study AMD-4 was a randomized, double-masked, active treatment-controlled, two-year study designed to assess the safety and efficacy of ranibizumab 0.5 mg administered monthly or less frequently than monthly in patients with neovascular AMD. Patients randomized to the ranibizumab 0.5 mg less frequent dosing arm received three monthly doses followed by monthly assessments where patients were eligible to receive ranibizumab injections guided by pre-specified re-treatment criteria. A total of 550 patients were enrolled in the two 0.5 mg treatment groups with 467 (85%) completing through Month 24. Data are available through Month 24; Clinical results at Month 24 remain similar to that observed at Month 12.

From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm.Over this 21-month period, patients in the 0.5 mg less frequent dosing and the 0.5 mg monthly arms averaged 10.3 and 18.5 injections, respectively. The distribution of injections received in the less frequent dosing arm.

Figure 5. Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-4

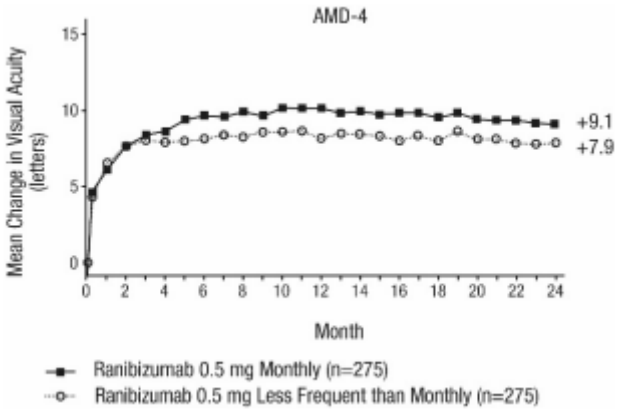
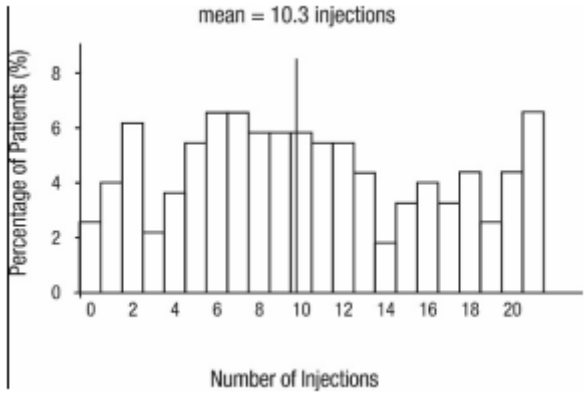


Figure 6. Distribution of Injections from Month 3 to Month 24 in the Less Frequent Dosing Arm in Study AMD-4



Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of ranibizumab were assessed in two randomized, double-masked, 1-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (ranibizumab 0.3 mg, 266 patients; ranibizumab 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were eligible to receive ranibizumab injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly ranibizumab 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 6-month treatment period. Macular focal/grid laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg ranibizumab and 71 of 132 (54%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly ranibizumab 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

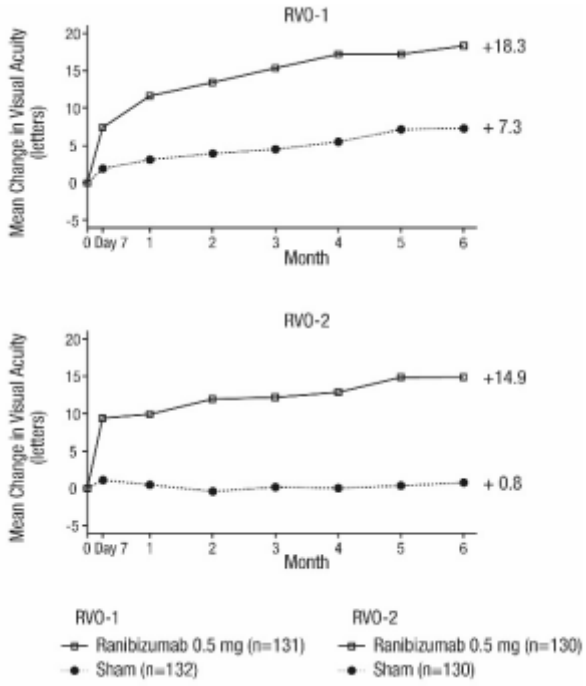
At Month 6, after monthly treatment with 0.5 mg ranibizumab, the following clinical results were observed:

Table 4. Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

Outcome Measure	Study[a]	Sham	Ranibizumab 0.5 mg	Estimated Difference (95% CI)[b]
Gain of ≥15 letters in visual acuity (%)	RVO-1	29%	61%	31% (20%, 43%)
Gain of ≥15 letters in visual acuity (%)	RVO-2	17%	48%	30% (20%, 41%)

[a] RVO-1: Sham, n=131; ranibizumab 0.5 mg, n=132
RVO-2: Sham, n=130; ranibizumab 0.5 mg, n=130
[b] Adjusted estimate based on stratified model; $p < 0.01$

Figure 7. Mean Change in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2



P<0.01 for all time points

Diabetic Macular Edema (DME)

The safety and efficacy of ranibizumab were assessed in two randomized, double-masked, 3-year studies. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (ranibizumab 0.3 mg, 250 patients; ranibizumab 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.

In Studies D-1 and D-2, patients received monthly ranibizumab 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly ranibizumab 0.5 mg and patients originally randomized to monthly ranibizumab 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for

macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or pan-retinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with ranibizumab 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with ranibizumab 0.3 mg and 30 of 257 (12%) patients treated with sham.

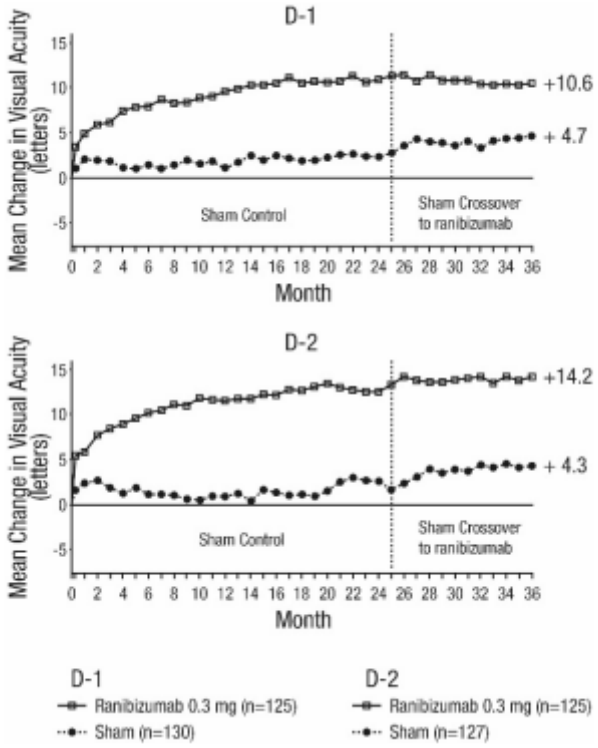
Compared to monthly ranibizumab 0.3 mg, no additional benefit was observed with monthly treatment with ranibizumab 0.5 mg. At Month 24, after monthly treatment with ranibizumab 0.3 mg, the following clinical results were observed:

Table 5. Visual Acuity Outcomes at Month 24 in Study D-1 and D-2

Outcome Measure	Study[a]	Sham	Ranibizumab 0.3 mg	Estimated Difference (95% CI)[b]
Gain of ≥15 letters in visual acuity (%)	D-1	12%	34%	21% (11%, 30%)
	D-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	D-1	92%	98%	7% (2%, 13%)
	D-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	D-1	2.3	10.9	8.5 (5.4, 11.5)
	D-2	2.6	12.5	9.6 (6.1, 13.0)

[a] D-1: Sham, n=130; ranibizumab 0.3 mg, n=125
D-2: Sham, n=127; ranibizumab 0.3 mg, n=125
[b] Adjusted estimate based on stratified model; $p \leq 0.01$

Figure 8. Mean Change in Visual Acuity from Baseline to Month 36 in Study D-1 and Study D-2



P<0.01 for all time points comparing ranibizumab 0.3 mg to sham through Month 24

Visual acuity outcomes observed at Month 24 in patients treated with ranibizumab 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received ranibizumab 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with ranibizumab at the beginning of the studies.

In Studies D-1 and D-2, patients received monthly injections of ranibizumab for 12 or 36 months, after which 500 patients opted to continue in the long-term follow-up study. Of 298 patients who had at least 12 months of follow-up from Month 36, 58 (19.5%) patients-maintained vision with no further therapy. The remaining 202 patients were followed for less than 12 months.

Diabetic Retinopathy (DR)

Efficacy and safety data of ranibizumab are derived from Studies D-1 and D-2 and D-3. All enrolled patients in Studies D-1 and D-2 had DR and DME at baseline. Study D-3 enrolled DR patients both with and without DME at baseline.

Of the 759 patients enrolled in Studies D-1 and D-2, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scores (ETDRS-DRSS) ranging from 10 to 75. At baseline, 62% of patients had non-proliferative diabetic retinopathy (NPDR) (ETDRS-DRSS less than 60) and 31% had proliferative diabetic retinopathy (PDR) (ETDRS-DRSS greater than or equal to 60). The ETDRS-DRSS could not be graded in 5% of patients at baseline, and 2% of patients had absent or questionable DR at baseline. Approximately 20% of the overall population had prior PRP.

After monthly treatment with ranibizumab 0.3 mg, the following clinical results were observed:

Table 6. ≥ 3-Step and ≥2-Step Improvement at Month 24 in Study D-1 and Study D-2

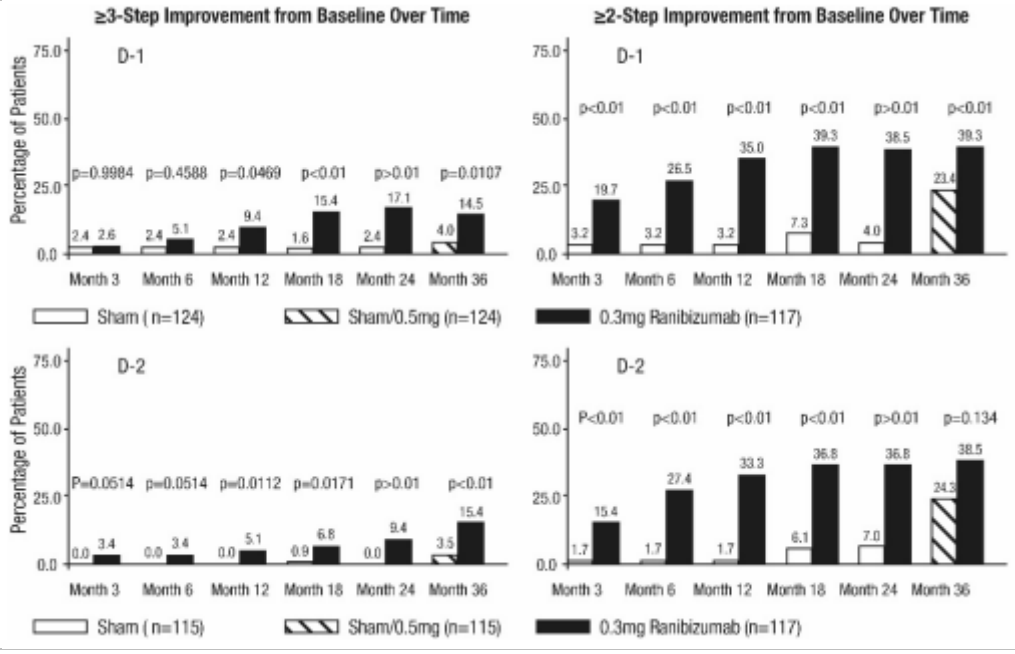
Outcome Measure	Study[a]	Sham	Ranibizumab 0.3 mg	Estimated Difference (95% CI)[b]
≥3-step improvement from baseline in ETDRS-DRSS [c]	D-1	2%	17%	15% (7%, 22%)
	D-2	0%	9%	9% (4%, 14%)
≥2-step improvement from baseline in ETDRS-DRSS [d]	D-1	4%	39%	35% (26%, 44%)
	D-2	7%	37%	31% (21%, 40%)

[a] D-1: Sham, n=124; ranibizumab 0.3 mg, n=117
D-2: Sham, n=115; ranibizumab 0.3 mg, n=117
[b] Adjusted estimate based on stratified model
[c] $p < 0.05$ for all time points comparing ranibizumab 0.3 mg to sham from Month 12 through Month 24
[d] $p < 0.05$ for all time points comparing ranibizumab 0.3 mg to sham from Month 3 through Month 24

At Month 24, DR improvement by ≥3-steps in ETDRS-DRSS from baseline in subgroups examined (e.g., age, gender, race, baseline visual acuity, baseline HbA1c, prior DME therapy at baseline, baseline DR severity (NPDR, PDR)) were generally consistent with the results in the overall population.

The difference in the proportion of patients treated with ranibizumab 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-DRSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.

Figure 9. Proportion of Patients with ≥ 3-Step and ≥ 2-Step Improvement from Baseline in ETDRS Diabetic Retinopathy Severity Level over Time in Study D-1 and Study D-2

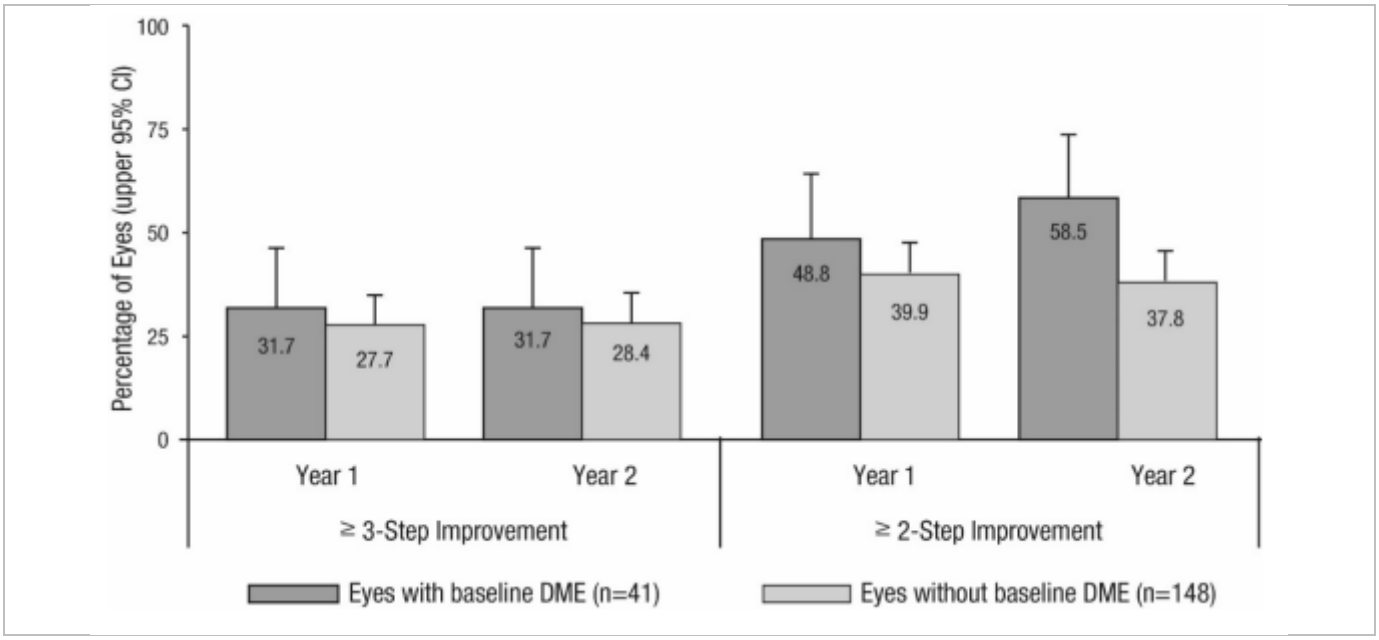


Study D-3 enrolled DR patients with and without DME; 88 (22%) eyes with baseline DME and 306 (78%) eyes without baseline DME and balanced across treatment groups. Study D-3 was a randomized, active-controlled study where patient age ranged from 20 to 83 with a mean age of 51 years. A total of 394 study eyes from 305 patients, including 89 who had both eyes randomized, were enrolled (ranibizumab, 191 study eyes; pan-retinal photocoagulation; 203 study eyes). All eyes in the ranibizumab group received a baseline 0.5 mg intravitreal injection followed by 3 monthly intravitreal injections, after which treatment was guided by pre-specified retreatment criteria. Patients had baseline ETDRS-DRSS ranging from 20 to 85. At baseline, 11% of eyes had NPDR (ETDRS-DRSS less than 60), 50% had mild-to-moderate PDR (ETDRS-DRSS equal to 60, 61, or 65), and 37% had high-risk PDR (ETDRS-DRSS greater than or equal to 71).

An analysis of data from Study D-3 demonstrated that at Year 2 in the ranibizumab group, 31.7% and 28.4% of eyes in the subgroups with baseline DME and without baseline DME, respectively, had ≥ 3-step improvement from baseline in ETDRS-DRSS.

Table 7. Proportion of Eyes with ≥ 3-Step and ≥ 2-Step Improvement from Baseline in ETDRS-DRSS at Year 2 in Study D-3

	Ranibizumab group	
Outcome Measure (in ETDRS-DRSS)	**Eyes with Baseline DME n = 41**	**Eyes without Baseline DME n = 148**
≥ 3-step improvement from baseline 95% CI for percentage	13 (31.7%) (17.5%, 46.0%)	42 (28.4%) (21.1%, 35.6%)
≥2-step improvement from baseline 95% CI for percentage	24 (58.5%) (43.5%, 73.6%)	56 (37.8%) (30.0%, 45.7%)



Myopic Choroidal Neovascularization (mCNV)

The efficacy and safety data of ranibizumab were assessed in a randomized, double-masked, active-controlled 3-month study in patients with mCNV. Patients age ranged from 18 to 87 years, with a mean age of 55 years. A total

of 276 patients (222 patients in the ranibizumab treated Groups I and II; 55 patients in the active control PDT group) were enrolled. Patients randomized to the ranibizumab groups received injections guided by prespecified re-treatment criteria. The retreatment criteria in Group I were vision stability guided, with the Best Corrected Visual Acuity (BCVA) at the current visit being assessed for changes compared with the two preceding monthly BCVA values. The retreatment criteria in Group II were disease activity guided, based on BCVA decrease from the previous visit that was attributable to intra- or sub-retinal fluid or active leakage secondary to mCNV as assessed by OCT and/or FA compared to the previous monthly visit.

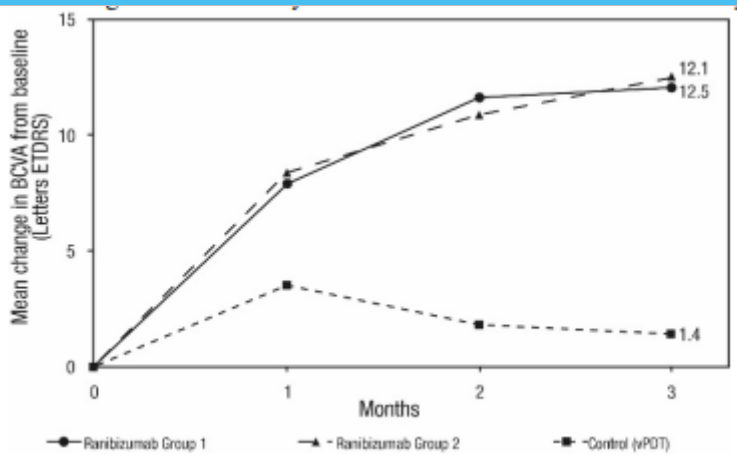
Visual gains for the two ranibizumab 0.5 mg treatment arms were superior to the active control arm. The mean change in BCVA from baseline at Month 3 was: +12.1 letters for Group I, +12.5 letters for Group II and +1.4 letters for the PDT group. . Efficacy was comparable between Group I and Group II.

Table 1. Mean Change in Visual Acuity and Proportion of Patients who Gained ≥15 letters from Baseline at Month 3

Study Arms	Mean change in BCVA from baseline (Letters)		Proportion of patients who gained ≥15 letters from baseline	
	Mean (SD)	Estimated Difference (95% CI)[a]	Percent	Estimated Difference (95% CI)[a]
Group I	12.1 (10.2)	10.9 (7.6, 14.3)	37.1	22.6 (9.5, 35.7)
Group II	12.5 (8.8)	11.4 (8.3, 14.5)	40.5	26.0 (13.1, 38.9)
Control (PDT)	1.4 (12.2)		14.5	

[a] Adjusted estimates based on stratified models; $p < 0.01$

Figure 10. Mean Change in Visual Acuity from Baseline to Month 3 in mCNV Study



The proportion of patients who gained ≥15 letters (ETDRS) by Month 3 was 37.1% and 40.5% for ranibizumab Groups I and II, respectively and 14.5% for the PDT group. The mean number of injections between baseline and

Month 3 was 2.5 and 1.8 for Groups I and II, respectively. 41% of patients received 1, 2 or 3 injections between baseline and Month 3 with no injections afterwards.

Safety

ADVERSE EVENTS

Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

Ocular Reactions

Figure 11. Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	Ranibizumab 0.3 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control
Conjunctival hemorrhage	32%		60%		50%		37%	
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions

Figure 12. Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	Ranibizumab 0.3 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control
	0		79		41		60	
	%							
Nasopharyngitis	11%	10%	8%	7%	4%	3%	1%	1%
Anemia	10%	9%	9%	6%	5%	5%	1%	2%
Nausea	9%	4%	9%	8%	5%	4%	1%	2%
Cough	8%	4%	5%	7%	3%	4%	0%	1%
Constipation	8%	4%	4%	4%	2%	2%	0%	2%
Seasonal allergy	7%	5%	5%	5%	3%	2%	1%	1%
Hypercholesterolemia	7%	3%	7%	5%	3%	2%	3%	2%
Influenza	7%	6%	1%	1%	0%	0%	0%	0%
Renal failure	7%	7%	9%	8%	5%	5%	2%	2%
Upper respiratory tract infection	6%	4%	4%	6%	3%	4%	1%	0%
Gastroesophageal reflux disease	6%	8%	12%	9%	6%	5%	3%	3%
Headache	6%	4%	3%	5%	2%	3%	0%	1%
Edema peripheral	6%	2%	0%	1%	0%	0%	0%	0%
Renal failure chronic	5%	3%	1%	1%	1%	0%	0%	0%
Neuropathy peripheral	5%	8%	8%	7%	5%	5%	3%	2%
Sinusitis	4%	4%	11%	9%	6%	5%	0%	2%
Bronchitis	3%	3%	5%	4%	2%	2%	1%	0%
Atrial fibrillation	3%	3%	11%	9%	5%	5%	2%	1%
Arthralgia	1%	1%	6%	3%	3%	1%	0%	0%
Chronic obstructive pulmonary disease	1%	0%	1%	1%	1%	0%	0%	0%
Wound healing complications								

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ranibizumab products may be misleading.

The pre-treatment incidence of immunoreactivity to ranibizumab was 0%-5% across treatment groups. After monthly dosing with ranibizumab for 6 to 24 months, antibodies to ranibizumab were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to ranibizumab products are unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

Additional Adverse Reactions Identified Post-Marketing

Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD**.**

WARNINGS & PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored following the injection.
- Increases in intraocular pressure (IOP) have been noted both pre- and postintravitreal injection.
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.
- Fatal events occurred more frequently in patients with DME and DR at baseline, who were treated monthly with ranibizumab compared with control.

CONTRAINDICATIONS

Ocular or Periocular Infections
Cimerli™ is contraindicated in patients with ocular or periocular infections.

Hypersensitivity
Cimerli™ is contraindicated in patients with known hypersensitivity to ranibizumab products or any of the excipients in Cimerli™. Hypersensitivity reactions may manifest as severe intraocular inflammation.

Clinical Pharmacology

MECHANISMS OF ACTION

Ranibizumab products bind to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, mCNV, DR, DME and macular edema following RVO. The binding of ranibizumab products to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Dose & Administration

ADULTS

For ophthalmic intravitreal injection only

Neovascular (Wet) Age-Related Macular Degeneration (AMD):

- Cimerli™ 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).
- Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment.
- Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly.

Macular Edema Following Retinal Vein Occlusion (RVO):

- Cimerli™ 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR):

- Cimerli™ 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Myopic Choroidal Neovascularization (mCNV):

- Cimerli™ 0.5 mg (0.05 mL) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to three months. Patients may be retreated if needed.

Preparation for Administration

Using aseptic technique, all of the Cimerli™ vial contents are withdrawn through a 5-micron (19-gauge x 1-1/2 inch), sterile filter needle attached to a 1 mL syringe (not included). The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge x ½ inch needle for the intravitreal injection.

Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve head immediately after the injection. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needles should be changed before Cimerli™ is administered to the other eye.

PEDIATRICS

The safety and effectiveness of ranibizumab products in pediatric patients have not been established.

GERIATRICS

No special dosage modification is required for any of the populations that have been studied; Refer to adult dose and administration.

RENAL IMPAIRMENT

In pharmacokinetic covariate analyses, 48% (520/1091) of patients had renal impairment (35% mild, 11% moderate, and 2% severe). Because the increases in plasma ranibizumab exposures in these patients are not considered clinically significant, no dosage adjustment is needed based on renal impairment status.

HEPATIC IMPAIRMENT

Information not provided in manufacturer's full prescribing information.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Single-dose glass vial designed to provide 0.05 mL for intravitreal injections: 10 mg/mL solution (Cimerli™ 0.5 mg), 6 mg/mL solution (Cimerli™ 0.3 mg).