MODULE 10.7
Clinical Studies and Treatment Data - RISE and RIDE

RISE and RIDE

Study Name	Ranibizumab for Diabetic Macular Edema: Results from 2 Phase III Randomized Trials: RISE and RIDE
Purpose of study	To evaluate the efficacy and safety of intravitreal ranibizumab in patients with diabetic macular edema (DME)
Study authors	Nguyen QD, Brown DM, Marcus DM et al on behalf of the RISE and RIDE Research Group
Published in	*Ophthalmology.* 2012;119:789-801.
Study also known as	RIDE/RISE
Subsequent studies	Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013-2022.

Study Overview

RIDE and RISE were parallel, 24-month, multinational, double-masked, sham injection - controlled, randomized phase 3 studies designed to evaluate the efficacy of ranibizumab in patients with DME. The studies enrolled 759 patients (RISE enrolled 377 patients; RIDE enrolled 382 patients) with confirmed vision loss as a result of DME. All enrolled patients had a best-corrected visual acuity (BCVA) between 20/40 and 30/320, and all enrolled patients had central subfield thickness of at least 275 µm (as confirmed on optical coherence tomography [OCT]).[1]

Patients were randomized as follows (numbers in parentheses represent the number of patients enrolled from RISE and RIDE, respectively): sham injection (127, 130); monthly ranibizumab 0.3 mg (125, 125); and monthly ranibizumab 0.5 mg (125, 127). The primary outcome was the proportion of patients gaining at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters of BCVA at 24 months.[1] Secondary outcomes included mean change in BCVA, the percentage of patients with a Snellen equivalent of 20/40 or better, the proportion of patients who lost 3 lines of vision, the mean change from baseline in central foveal thickness, and the mean number of laser treatments over time. The study also evaluated the proportion of patients with resolved leakage (verified by fluorescein angiography [FA]) and the proportion of patients with at least a 3-step progression in retinopathy severity (as determined by fundus photographs).[1]

Baseline characteristics between the 2 groups were generally the same, although more patients in the RISE 0.3-mg arm had BCVAs worse than 20/200, and more patients in both 0.5-mg groups has previously undergone steroid treatment.[1]

All patients were allowed to undergo laser rescue therapy if warranted; in both study arms, patients in the sham group underwent significantly more laser treatments than those in either ranibizumab arm (1.8 laser treatments in RISE, 1.6 in RIDE, compared to less than 1 injection in either ranibizumab arm in either study). A significantly greater proportion of ranibizumab-treated patients had ≥15 letter gains in vision compared with the placebo group, with 44.8% (RISE) and 33.6% (RIDE) for the 0.3-mg ranibizumab groups, 39.2% (RISE) and 45.7% (RIDE) for 0.5-mg ranibizumab groups, versus 18.1% (RISE) and 12.3% (RIDE) for the placebo groups ($P < .0001$). The mean change in vision was similar between the 2 groups regardless of treatment arm, although patients in RISE tended to have better vision outcomes: +12.5 letters (RISE) and +10.9 (RIDE) for the 0.3-mg ranibizumab groups, +11.9 letters (RISE) and +12 letters (RIDE) for the 0.5-mg ranibizumab groups versus +2.6 letters (RISE) and +2.3 letters (RIDE) in the placebo group.[1] By month 24, patients in the ranibizumab groups gained an average or 8.5 to 9.9 ETDRS letters over the sham

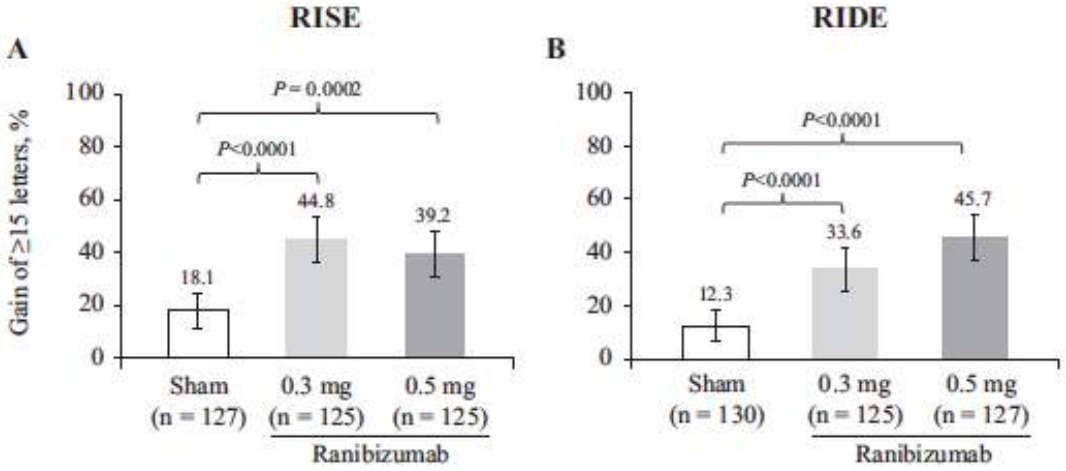


Figure 1. Mean change in central foveal thickness from baseline through 24 months.[1]

group after adjusting for baseline variables.[1] See Figure 1.

Similarly, the improvements (reductions) in macular edema were noticed as early as the first post-injection visit (day 7) as measured by OCT and continued throughout the study. Resolution of leakage (as confirmed by FA) and macular edema (confirmed by OCT) were statistically significantly more common among the ranibizumab-treated patient (see Figure 2).

Patients in the ranibizumab groups had a low incidence of postinjection endophthalmitis. There was no significant increase in the incidence of deaths, nonfatal myocardial infarction, or cerebrovascular accidents, which were known possible systemic side effects of anti-VEGF therapy. Most ocular side effects were considered mild or moderate, with increased intraocular pressure (IOP) post-injection much higher in the ranibizumab groups than the sham groups (which was expected, as the latter did not receive injections).[1] In both studies, serious adverse events (AEs) potentially related to systemic VEGF concentrations occurred in 5.6% to 11.9% of the ranibizumab-treated patients and in 9.4% to 10.6% of the sham-treated patients.[1] In both studies, hypertension was the leading AE. These results led to the US approval in August 2012 of ranibizumab for the treatment of DME.[2]

Study Implications

The results from these 2 studies supported the FDA's decision to approve the drug for the treatment of DME in August 2012.[3] This landmark approval is often heralded as the key in altering DME treatments away from laser and toward anti-VEGFs; although pegaptanib had been approved before ranibizumab, it was not as efficacious and has fallen out of favor with retina specialists. The 3-year results confirmed the 2-year findings: during year 3, patients initially assigned to the sham group were allowed to cross over to active treatment with ranibizumab 0.5 mg.[3] At 36 months, 19.2% of patients in the original sham group in RIDE and 22% of the patients in the original sham group in RISE gained at least 15 ETDRS letters from baseline. Comparatively, 36.8% and 51.2% of patients in the ranibizumab 0.3-mg groups of RIDE/RISE, respectively, and 40.2% and 41.6% of patients in the ranibizumab 0.5-mg

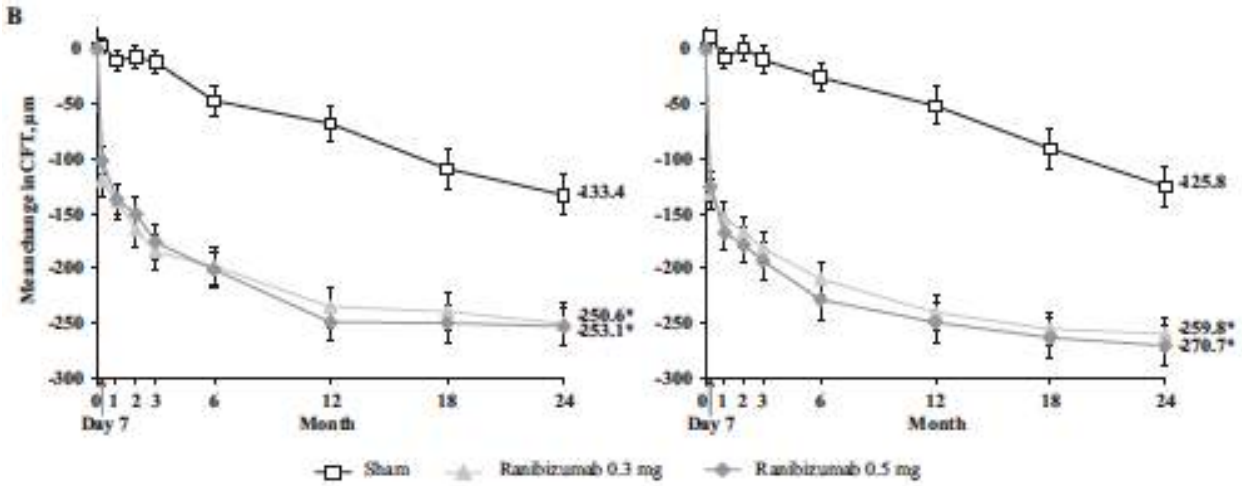


Figure 2. Visual acuity results from RISE/RIDE; percentage of patients who gained at least 15 ETDRS letters in each treatment arm at 24 months.

groups of RIDE/RISE, respectively, gained at least 15 ETDRS letters.[3]

It is important to note that the FDA approved a lower-dose version of ranibizumab for the treatment of DME (0.3 mg) than it had for age-related macular degeneration (AMD) (0.5 mg). This decision was primarily because of similar efficacy and safety outcomes between the 2 arms coupled with the known possible systemic side effects of anti-VEGF therapy. (Conversely, in the AMD studies, there was a clear benefit for those dosed with 0.5 mg).[3] The study authors also made a point of noting that people with worse baseline vision are more likely to have positive changes in vision than patients with better baseline vision.[1]

Similarly, once the patients completed the RISE/RIDE 24-month evaluation, those in the sham group could be crossed over to receive ranibizumab treatment. But the "relatively limited improvements in vision" in the crossed-over group "suggest that chronic retinal edema may result in a certain amount of potential vision gain being irreversibly lost."[3]

Another consideration is that the stringent criteria for study participation may not be realistic in a real-world setting. This includes the continuous monthly dosing schedule that, while providing the best efficacy, may not be sustainable in practices or by patients. This is particularly concerning for patients with bilateral disease.

Both studies are visualized at the end of this module.

Take-Home Points

- RISE/RIDE showed substantial improvements in vision and anatomy in patients with DME.
- RISE/RIDE was one of the longest-term controlled studies in patients with DME at the time of its publication.
- Patients who were crossed over after 2 years of sham treatment did not have the same level of improvement as well as those who were initially treated with ranibizumab, suggesting that earlier treatment is more beneficial.

References

1. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology.* 2012;119(4):789-801.

2. Lucentis [package insert]. South San Francisco, CA: Genentech Inc; 2014.

3. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. -2013;120(10):2013-2022.

DIABETIC VISION LOSS & ITS TREATMENTS

The Angiogenesis Foundation

RISE June 2007 - November 2010

A Phase III, Double-masked, Multicenter, Randomized, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus

Phase 3

Sponsor: Genentech

UNITED STATES & SOUTH AMERICA
Multiple Sites

TRIAL AGENT

Ranibizumab (Intravitreal Ranibizumab Injection (IRI)) VS Placebo (Sham Injection)

STUDY POPULATION

377 eyes, from 377 patients

INCLUSION CRITERIA

- Central Diabetic Macular Edema involvement with Optical Coherence Tomography (OCT) Central Subfield Thickness ≥275 µm
- Best-corrected Visual Acuity (BCVA) 24≤ x ≤74 Letters on Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart

ENDPOINTS (measured at 24 months)

PRIMARY

% of Eyes that gained ≥15 ETDRS Letters

SECONDARY

- Mean change in ETDRS Letters
- % of Eyes with ≥73 ETDRS Letters
- Mean change in ETDRS Letters in Eyes with Focal Edema, as assessed by Fluorescein Angiography (FA)
- % of Eyes that lost <15 ETDRS Letters
- Mean change in OCT Central Foveal Thickness (CFT)
- % of Eyes with a ≥3-step progression in ETDRS retinopathy severity on Fundus Photography (FP)
- % of Eyes with resolution of leakage on FA
- Mean number of macular laser treatments

TRIAL DESIGN

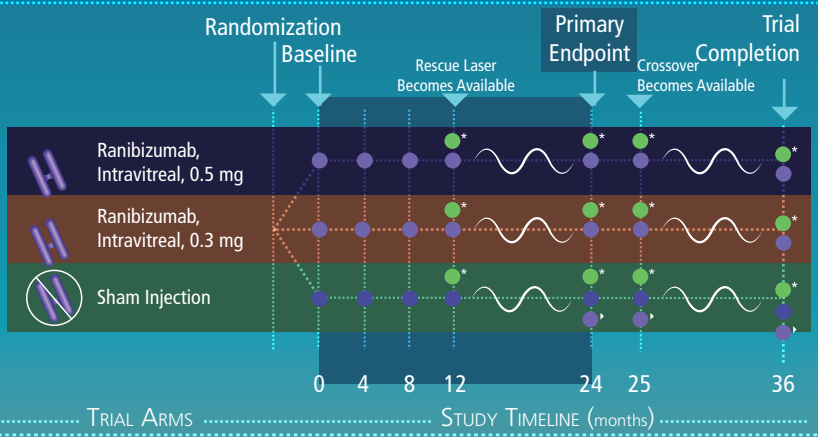
Double-Blind

- Ranibizumab (IRI)
- Sham Injection
- Laser
- Repeating Regimen

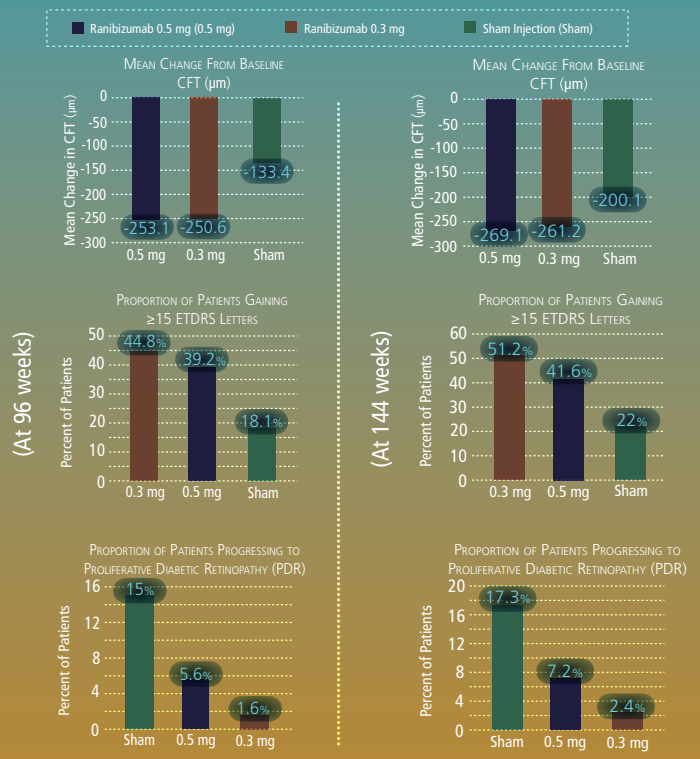
* Rescue Laser: Patients were evaluated monthly, beginning at month 3, for the need for Macular Laser Therapy, and were given laser if Central Foveal Thickness (CFT) ≥ 250 µm with a <50 µm change from the previous month, with no prior macular laser therapy in the previous 3 months. Patients were also eligible to receive panretinal photocoagulation if PDR was present.

▸ Crossover: Patients in the Sham Injection group were eligible to crossover into the 0.5 mg group if they were experiencing persistent edema and vision loss. An amendment to the protocol in mid-2010 allowed patients to crossover earlier than the 25-month mark. Patients who did crossover continued to be masked.

- 1 patient crossed over early (before
- 87% of patients in the Sham group crossed into the 0.5 mg Ranibizumab group during the third year (between months 24 and 36)



RESULTS



The 96-weeks results showed that Ranibizumab intravitreal injection proved more efficacious in improving vision and preventing vision loss for a greater number of people compared to sham injections. Furthermore, the 144-weeks results support those of the primary endpoint of 96 weeks.

Since the majority of patients in the sham group crossed over into the 0.5 Ranibizumab treatment arm during the third year, the 144-weeks results between the sham and 0.3 mg and 0.5 mg groups show a comparison between a delayed, one-year treatment with Ranibizumab versus a rapid, two-year treatment with Ranibizumab.

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IMPACT

Provides the longest term controlled evidence for efficacy and safety of ranibizumab for DME to date.

- Demonstration of efficacy in treatment-naïve and pre-treated eyes
- Demonstration of efficacy in eyes with focal edema

SUPERIOR OUTCOMES using RANIBIZUMAB

* SOURCE - Nguyen QD et al. Ranibizumab for Diabetic Macular Edema. *Ophthalmology.* 2012 Apr;119(4):789-801. doi: 10.1016/j.ophtha.2011.12.039. Epub 2012 Feb 11.
* SOURCE - Brown et al. Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two Phase III Trials. *Ophthalmology.* 2013 Oct;120(10):2013-22. doi: 10.1016/j.ophtha.2013.02.034. Epub 2013 May 22.

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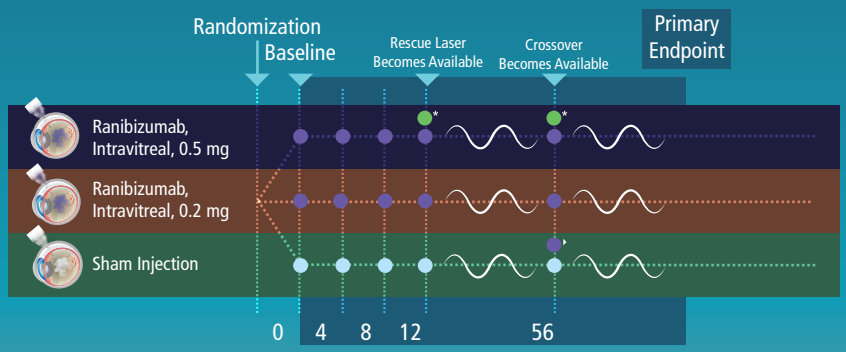
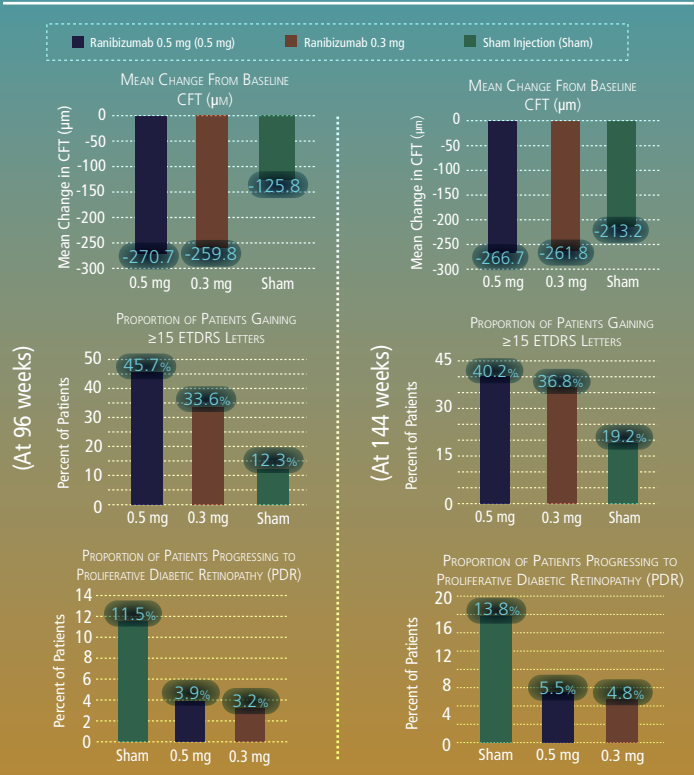
- 3 patient crossed over early (before Week 56)
- 94% of patients in the Sham group crossed into the 0.5 mg Ranibizumab group during the third year (between week 96 and 144)



TRIAL ARMS ..... STUDY TIMELINE (weeks)

RESULTS



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