MODULE 10.10
Clinical Studies and Treatment Data - RESTORE

RESTORE[1]

Study Name	The RESTORE Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema
Purpose of study	To determine superiority of Lucentis 0.5mg alone or combined with laser over laser alone in BCVA after 12 months.
Study authors	Mitchell P, Bandello F, Schmidt-Erfurht U, Lang GE, Massin P, Schlingemann RO, Sutter F, Simader C, Burian G, Gerstner O, Weichselberger A on behalf of the RESTORE Study Group
Published in	*Ophthalmology.* 2011;118:615-625.
Study also known as	RESTORE
Subsequent studies	Lang GE, Berta A, Eldem BM et al on behalf of the RESTORE Extension Study Group. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema. *Ophthalmology.* 2013;120:2004-2012. Schmidt-Erfurth U, Lang GE, Holz FG et al on behalf of the RESTORE Extension Study Group. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema. *Ophthalmology.* 2014;121:1045-1053.

Study Overview

Investigators in this study assessed if either ranibizumab 0.5-mg monotherapy or ranibizumab 0.5-mg and laser therapy would be more efficacious than laser monotherapy.

The core RESTORE study was a 12-month, phase 3, randomized, double-masked, laser-controlled, multicenter trial conducted at 73 centers in 10 European countries, Turkey, Canada, and Australia.[1] The study randomized 345 patients to ranibizumab 0.5-mg monotherapy (n = 116), ranibizumab 0.5 mg and laser therapy (n = 118) or sham injection and laser (n = 111). Key inclusion criteria included a best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score between 78 and 39 with the decreased vision caused solely by the diabetic macular edema (DME).

Primary outcomes were the mean average change in BCVA from baseline to month 12. Notable secondary outcomes included determining if ranibizumab 0.5 mg was superior to laser as either an adjunctive or monotherapy at month 12 in the proportion of patients with visual acuity (VA) improvement and a BCVA of 20/40 or better, and the proportion of patients with a central retinal thickness (CRT) either above or below the 275-µm level.

The ranbizumab or sham injections were given monthly for the first 3 months (months 0-2), and then moved to PRN dosing. Participants received the first laser treatment (active or sham) on day 1, with the option of splitting the treatment into 2 sessions, each separated by 4 weeks, if needed. Retreatments were based on ETDRS guidelines at intervals of 3 months or more from the previous treatment. For each participant, the eye with the worst VA was treated as the study eye. Treatment could be suspended if the investigator felt no further vision gain was attributable to treatment during the patient's last 2 visits or a BCVA ETDRS letter score of at least 84 (approximately 20/20 Snellen equivalent) had been noted at the last 2 visits. Injections were resumed if DME progressed

(as confirmed on optical coherence tomography [OCT]) or if vision decreased.

In this study, the researchers found the mean average change in BCVA ETDRS letter score from baseline to month 12 was significantly superior with ranibizumab (6.1 ± 6.4; P < .0001) and ranibizumab plus laser (5.9 ± 7.9; P < .0001) compared to laser plus sham/monotherapy (0.8 ± 8.6) (see Figure 1). The percentage of patients with a gain in BCVA ≥ 15 letters was similar between both ranibizumab groups and far greater than the percentage in the laser group. Thus, combining laser to ranibizumab did not have any additional benefit compared to treatment with ranibizumab alone. The mean change in central retinal thickness (CRT) significantly decreased in both ranibizumab groups, with benefits superior to that of the laser monotherapy group. There was a higher proportion of patients with a CRT <275 µm in the ranibizumab monotherapy (49.1%) and ranibizumab + laser groups (55.1%) than in the laser monotherapy group (39.1%) (see Figure 2).

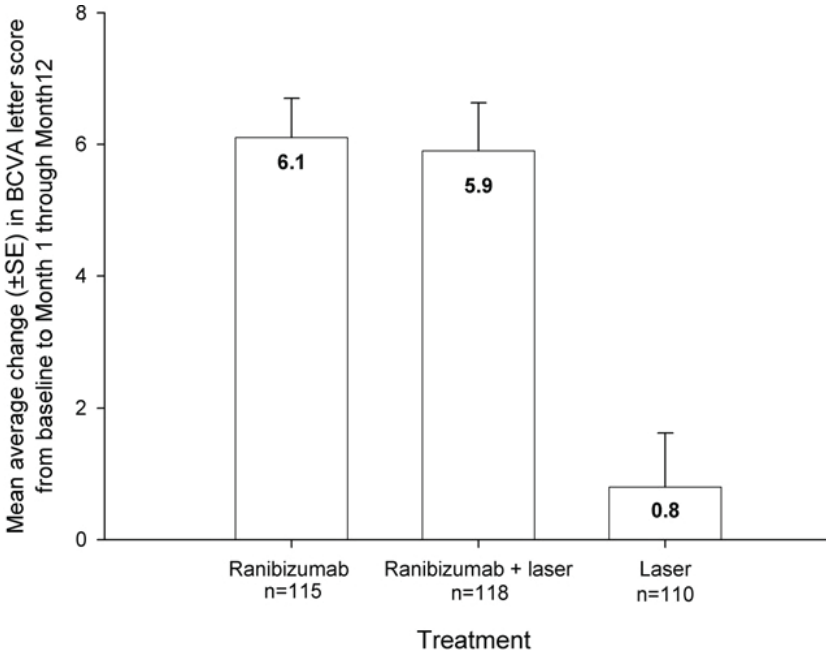


Figure 1: Mean average change in BCVA letter score from baseline to month 12.

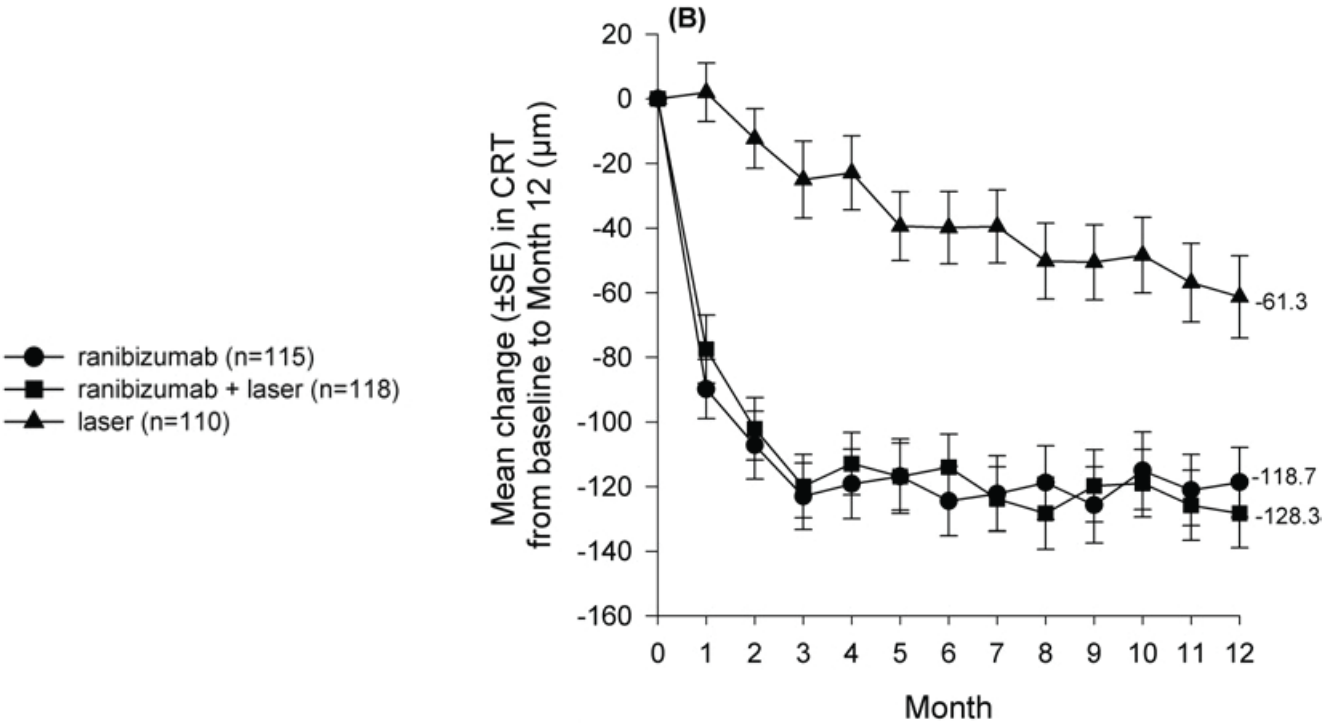


Figure 2: Mean change in CRT from baseline to month 12.

RESTORE May 2008 - January 2012

A Randomized, Double-masked, Multicenter, Laser-controlled Phase III Study Assessing the Efficacy and Safety of Ranibizumab (Intravitreal Injections) as Adjunctive and Mono-therapy in Patients With Visual Impairment Due to Diabetic Macular Edema

Phase 3

NOVARTIS

TRIAL AGENT

Ranibizumab
Intravitreal Ranibizumab Injection (IRI)

VS

Laser
(Focal/grid Laser Photocoagulation (LP))

STUDY POPULATION

345 eyes, from 345 patients, 240 of which enrolled in extension study

INCLUSION CRITERIA

- Focal or diffuse DME
- Best-corrected Visual Acuity (BCVA) 39 ≤ x ≤ 79 Letters on Early Treatment of Ciabetic Retinopathy Study (ETDRS) Chart

ENDPOINTS

PRIMARY

Mean Change in BCVA on ETDRS Chart

EXTENSION STUDY

- % of patients with Ocular Adverse Events
- % of patients with Non-Ocular Adverse Events

SECONDARY

- Categorized change in ETDRS Letters
- Mean change in ETDRS letters over time
- Mean change in Central Retinal Thickness (CRT)
- Mean Change in patient-reported Visual Functioning, measured by National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25)

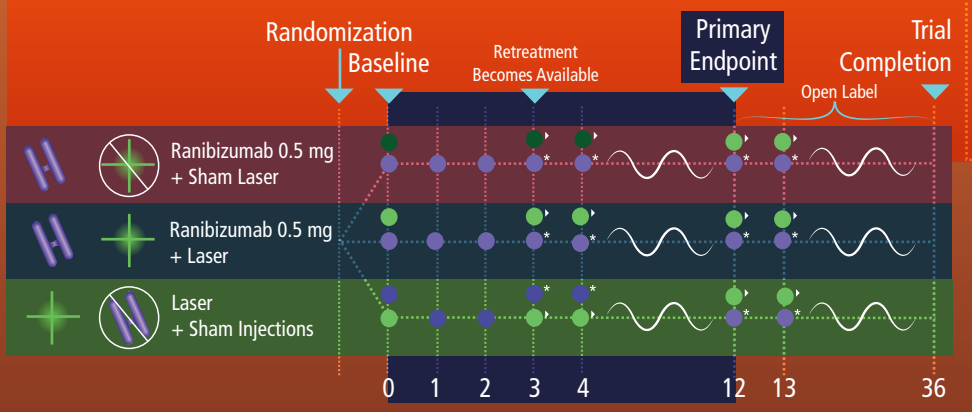
EXTENSION STUDY

- % of Patients with Ocular Adverse Events
- % of Patients with Non-Ocular Adverse Events
- Mean change in BCVA on ETDRS Chart from Baseline to 36 Months.
- Mean change in BCVA on ETDRS Chart from 12 Months to 36 Months.

TRIAL DESIGN

Double-Blind

Ranibizumab
Sham Injection
Laser
Sham Laser
Repeating Regimen



* **Ranibizumab Retreatment:** Monthly ranibizumab (or sham) injections were discontinued from their monthly schedule if no further BCVA improvement was seen from the last 2 consecutive visits or if BCVA ≥ 84 ETDRS Letters was seen at the last 2 consecutive visits.

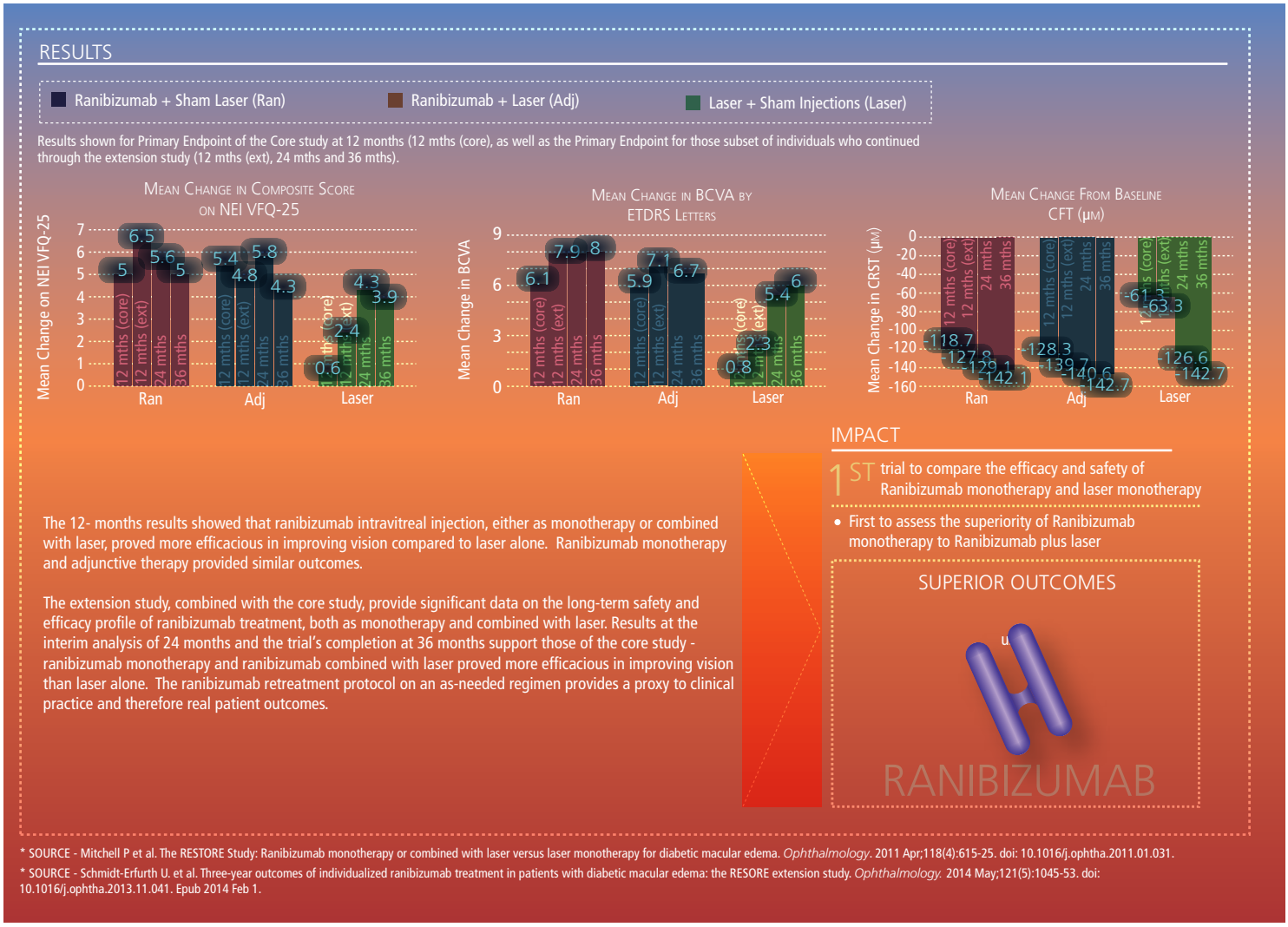
▶ **Laser Retreatment:** Laser (or sham laser) was given, if deemed necessary by the investigator using ETDRS criteria, at intervals no shorter than every 3 months.

Ranibizumab alone and in combination with laser was well tolerated in DME patients throughout the first 12 months. There were no cases of endophthalmitis or glaucoma throughout the study. No ocular serious adverse events (SAEs) were reported in the ranibizumab arm. Increased intraocular pressure (IOP) occurred in 1 patient in each of the ranibizumab arms, but these cases were mostly due to the injection procedure and they resolved naturally without treatment. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

The mean number of ranibizumab/sham injections (6.8/7.3 injections), and the mean number of active/sham laser treatments (1.7/2.1 administrations) were similar for all groups.

The researchers also evaluated the quality of life (per National Eye Institute [NEI] VFQ-25 composite scores), which improved for both ranibizumab and ranibizumab plus laser groups, but degraded for the laser group (all $P < 0.05$).

Two extension studies were undertaken as a result of the findings from the initial RESTORE study - a 2-year and a 3-year follow-up.[2,3] Both of the extension studies confirmed the original findings - that ranibizumab was well tolerated with no new safety concerns. Overall, an average of 3.8 ranibizumab injections was sufficient to maintain or improve outcomes in year 2;[2] at year 3, the original laser group had a mean of 6.5 injections from months 12 to 35 and the ranibizumab groups had a mean of 6.8 injections



The 12- months results showed that ranibizumab intravitreal injection, either as monotherapy or combined with laser, proved more efficacious in improving vision compared to laser alone. Ranibizumab monotherapy and adjunctive therapy provided similar outcomes.

The extension study, combined with the core study, provide significant data on the long-term safety and efficacy profile of ranibizumab treatment, both as monotherapy and combined with laser. Results at the interim analysis of 24 months and the trial's completion at 36 months support those of the core study - ranibizumab monotherapy and ranibizumab combined with laser proved more efficacious in improving vision than laser alone. The ranibizumab retreatment protocol on an as-needed regimen provides a proxy to clinical practice and therefore real patient outcomes.

* SOURCE - Mitchell P et al. The RESTORE Study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011 Apr;118(4):615-25. doi: 10.1016/j.ophtha.2011.01.031.
* SOURCE - Schmidt-Erfurth U. et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESORE extension study. *Ophthalmology.* 2014 May;121(5):1045-53. doi: 10.1016/j.ophtha.2013.11.041. Epub 2014 Feb 1.

(ranibizumab alone) and 6.0 injections (ranibizumab and laser).[3]

Study Implications

The RESTORE study is the first trial to compare the efficacy and safety of ranibizumab monotherapy and laser monotherapy, and the first to assess the superiority of ranibizumab monotherapy toranibizumab plus laser combined therapy.[1] It is important to note, however, that this study used the 0.5-mg dosing, which is the approved dose in Europe. Most US studies included both the 0.5-mg and the 0.3-mg dosing (the latter of which is approved for the DME indication in the US).

This is also the first study to evaluate ranibizumab treatment on quality of life (using the NEI's VFQ-25 questionnaire). The subjective results were overwhelmingly in favor of either ranibizumab alone or with laser in terms of quality of life improvement. The authors noted that ranibizumab showed progressive and sustained improvements in health-related quality of life assessments similar to what had been reported with ranibizumab in other retinal disorders (namely, age-related macular degeneration). This is also the first study to show stable vision and CRT with declining needed injections.

There remains ongoing debate about optimal treatment for DME patients, and these studies seem to suggest a higher dose than what is approved in the US may be able to reduce treatment burden.

Take-Home Points

- Ranibizumab 0.5 mg (with or without laser) is clearly superior in efficacy over laser alone.
- There was a steadily declining rate of necessary injections during the 2 extension studies, even in the group that was initially laser-only.
- This is the first study to evaluate treatment and its effects on quality of life, and it showed a clear benefit to treatment.

References

1. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology.* 2011;118:615-625.

2. Lang GE, Berta A, Eldem BM, et al. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE extension study. *Ophthalmology.* 2013;120:2004-2012.

3. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology.* 2014;121:1045-1053.