



# A Multicenter, Retrospective Study (RE-ENACT 2) on Razumab™ (World's First Biosimilar Ranibizumab) in Retinal Vein Occlusion

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## ABSTRACT

**Purpose:** The REal life assessmENT of safety And effeCTiveness of Razumab 2 (RE-ENACT 2) study evaluated the long-term effectiveness of biosimilar ranibizumab. We present the subgroup analysis of patients with retinal vein occlusion (RVO).

**Methods:** Data of patients who received pro re nata (PRN) biosimilar ranibizumab (November 2015 to December 2018, 17 centers) were analyzed. Endpoints were change from baseline in best corrected visual acuity (BCVA, Snellen's/logMAR), central subfield thickness (CSFT), intraocular pressure (IOP), and proportions of patients having intraretinal fluid (IRF) and subretinal fluid (SRF) at weeks 4, 8, 12, 16, 20, 24, 30, 36, and 48.

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**Results:** Of 101 patients, 48.51% were men, and the majority (79.21%) were treatment naïve and had received 3 (range 1–5) injections (53.5%). Significant improvements ( $P < 0.05$ ) were observed from baseline to all timepoints for BCVA [baseline,  $0.89 \pm 0.06$  ( $n = 94$ ); week 48,  $0.41 \pm 0.08$  ( $n = 14$ )] and CSFT [baseline,  $527.58 \pm 19.9$  ( $n = 85$ ); week 48,  $307.47 \pm 16.4$  ( $n = 15$ )]. Changes in IOP (mmHg) were non-significant [baseline,  $15.38 \pm 0.4$  ( $n = 94$ ); week 48,  $13.94 \pm 0.6$  ( $n = 16$ );  $P = 0.5575$ ]. Proportions of patients having IRF [baseline, 71.3% ( $n = 84$ ) vs week 48, 0% ( $n = 15$ )] and SRF [baseline, 52.5% ( $n = 83$ ) vs week 48, 0% ( $n = 15$ )] were decreased. Similar results for BCVA, CSFT, IOP, IRF, and SRF were observed for BRVO and CRVO subgroups. There were no new safety concerns.

**Conclusions:** Biosimilar ranibizumab demonstrated improvements in visual acuity and disease outcomes up to 48 weeks in patients with RVO without any new safety concerns.

**Keywords:** Anti-VEGF; Biosimilar ranibizumab; Razumab; Retinal vein occlusion; RVO

### Key Summary Points

Retinal vein occlusion (RVO) may result in irreversible vision loss despite availability of several treatment options.

Branch RVO (BRVO) occurs more commonly than central RVO (CRVO), up to sevenfold in Indian patients.

The 15-year cumulative incidence of BRVO and CRVO is 1.8% and 0.5%, respectively.

Ranibizumab is approved as an anti-VEGF agent by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of RVO.

Biosimilar ranibizumab, Razumab™, approved by the Drug Controller General of India (DCGI) in 2015, provides a cost-effective alternative to innovator ranibizumab.

This report presents the effectiveness of Razumab in patients with RVO treated in a real-world setting.

Razumab (biosimilar ranibizumab) demonstrated improvements in visual acuity and disease outcomes in patients with RVO without new safety issues.

## INTRODUCTION

Retinal vein occlusion (RVO), characterized by a thrombus obstruction in the fundus of the eye, is the second most common retinal vascular disorder after diabetic retinopathy [1, 2]. RVO is classified on the basis of the location of venous occlusion as central retinal vein occlusion (CRVO)—obstruction at optic nerve head; branch retinal vein occlusion (BRVO)—obstruction at a branch of the central retinal vein; and hemiretinal vein occlusion (HRVO)—occlusion at disc involving retinal venous

drainage (superior or inferior hemifield) [2]. BRVO occurs more commonly than CRVO, up to sevenfold in Indian patients [3], with a 15-year cumulative incidence of BRVO and CRVO at 1.8% and 0.5%, respectively, as per a large population-based study in the USA [4].

RVO may result in irreversible vision loss despite availability of several treatment options [5]. Among various treatment strategies attempted, laser therapy has been the gold standard for the treatment of RVO [6, 7]. The advent of intravitreal anti-vascular endothelial growth factor (VEGF) agents has reformed RVO management [6, 8, 9]. Ranibizumab has demonstrated efficacy and safety in the treatment of several retinal disorders including RVO [10–13], and is approved by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of RVO. The US FDA approval of ranibizumab for the treatment of visual impairment due to macular edema secondary to RVO was based on the results from the pivotal phase III BRAVO (BRANCH retinal Vein Occlusion) trial [12] and CRUISE (Central Retinal vein Occlusion Study) trial [13].

Razumab™, the world's first biosimilar ranibizumab developed by Intas Pharmaceuticals Ltd., Ahmedabad, India, is a cost-effective alternative, is easily accessible to patients, and was approved by the Drug Controller General of India in 2015 for the treatment of RVO, wet age-related macular degeneration (wet AMD), diabetic macular edema (DME), and myopic choroidal neovascularization (mCNV). The efficacy and safety of biosimilar ranibizumab have been also evaluated in a prospective study in Indian patients with chorioretinal vascular diseases including RVO [14].

The effectiveness of biosimilar ranibizumab for the treatment of retinal disorders in a real-world clinical setting was established in a previous retrospective, multicenter, observational REal life assessment of safety And effectiveNess of Razumab (RE-ENACT) study [15–17]. The RE-ENACT 2 study was conducted with the intent to generate long-term data on the usage of biosimilar ranibizumab in a real-world clinical setting in Indian patients. The current report

presents the subgroup analysis on patients with RVO from the RE-ENACT 2 study.

## METHODS

### Study Design, Population, Endpoints, and Statistical Considerations

The RE-ENACT 2 study design was similar to the RE-ENACT study, which is published elsewhere [16]. The RE-ENACT 2 study analyzed the medical records of adult (aged 18 years or more) patients of either sex who had RVO and who had received one or more intravitreal biosimilar ranibizumab injections as per routine clinical care for the management of macular disorders between November 2015 and December 2018 at 17 centers across India. RVO is defined as intraretinal hemorrhages, dilated veins and/or cotton wool spots, and there may be evidence of macular edema. Retinal capillary ischemia facilitates the classification of RVO as non-ischemic and ischemic. The pathogenesis, clinical manifestations, and the treatment of RVO are predisposed to the location of occlusion. Patients were administered one intravitreal injection of biosimilar ranibizumab followed by pro re nata (PRN) treatment regimen. Biosimilar ranibizumab PRN treatment regimen/retreatment criteria included logMAR best corrected visual acuity (BCVA) of no greater than 0.5 or mean central subfield thickness (CSFT) of 250  $\mu\text{m}$  or more in the study eye as compared to the previous follow-up visit. Patients were followed up every 4 weeks after biosimilar ranibizumab injection and the improvements in effectiveness parameters BCVA, CSFT, subretinal fluid (SRF) and intraretinal fluid (IRF) were recorded. Patients were evaluated at each follow-up visit for further treatment. The study included both treatment-naïve patients and patients previously treated with other anti-VEGF, steroids, or laser treatment. Patients were excluded if assessment of optical coherence tomography (OCT) was not available (i.e., dense cataract). This retrospective study was conducted after ethics committee (OM ethics committee, Ahmedabad, India) approval and in

accordance with the protocol and the principles of the Helsinki Declaration.

The study assessment parameters were BCVA, CSFT, intraocular pressure (IOP), IRF, and SRF. The study endpoints were change in the BCVA, CSFT, IOP, and decrease in proportion of patients with IRF and SRF from baseline to weeks 4, 8, 12, 16, 20, 24, 30, 36, and 48. The BCVA measurement were done using Snellen's chart or the logMAR chart. Spectral domain OCT (SD-OCT) was utilized to measure CSFT, IRF, and SRF. The BCVA and CSFT were analyzed using two-tailed paired *t* test, and IRF and SRF using  $\chi^2$  test. All statistical analyses were done using SAS® 9.4.

## RESULTS

### Patients Disposition and Demographics

A total of 101 patients with RVO were included in this subgroup analysis; 48.51% were men, and the majority (79.21%) were treatment naïve. The majority of the patients had received three biosimilar ranibizumab injections (53.5%); the median number of biosimilar ranibizumab injections in this study were 3 (range 1–5). The majority of the patients had hypertension (74.25%) and diabetes (26.73%). BRVO was the most common RVO type ( $n = 55$ , mean age  $58.8 \pm 11.1$  years, men 32.7%) followed by CRVO ( $n = 32$ , mean age  $55.3 \pm 10.8$  years, men 65.6%) and HRVO ( $n = 4$ , mean age  $59 \pm 10.8$  years, men 75%). The treatment effects were observed up to 48 weeks. Table 1 presents the patient disposition and baseline characteristics.

### Best Corrected Visual Acuity

A significant improvement ( $P < 0.05$ ) in the mean  $\pm$  SE BCVA was observed from baseline to all timepoints (baseline,  $0.89 \pm 0.06$ ; week 48,  $0.41 \pm 0.08$ ) indicating improved visual acuity. A slight decrease in BCVA improvements was observed from weeks 16 to 24 compared to previous weeks, though these improvements were significant when compared with baseline.

**Table 1** Patient disposition and baseline characteristics

Parameters	Biosimilar ranibizumab ( <i>N</i> = 101)
Age, years (mean ± SD)	57.9 ± 11.4
Gender, <i>n</i> (%)	
Men	49 (48.51)
Women	52 (51.49)
RVO subgroup, <i>n</i> (%) <sup>a</sup>	
BRVO	55 (54.46)
CRVO	32 (31.68)
HRVO	4 (3.96)
Eye treated, <i>n</i> (%)	
Left	47 (46.53)
Right	54 (53.47)
Phakic vs pseudophakic eye, <i>n</i> (%) <sup>a</sup>	
Phakic eye	68 (67.33)
Pseudophakic eye	30 (29.7)
Treatment, <i>n</i> (%) <sup>a</sup>	
Treatment naïve	80 (79.21)
Previously treated	15 (14.85)
Other anti-VEGF	10 (9.9)
Combined treatment (other anti-VEGF, laser, and steroid)	4 (3.96)
Steroid	1 (0.99)
Baseline BCVA score, [logMAR], mean ± SE <sup>b</sup>	0.89 ± 0.06
Baseline CSFT, μm, mean ± SE <sup>b</sup>	527.58 ± 19.9
Baseline IOP, mmHg, mean ± SE <sup>b</sup>	15.38 ± 0.4
Baseline SRF <sup>a</sup>	
Present, <i>n</i> (%)	53 (52.48)
Absent, <i>n</i> (%)	30 (29.7)
Baseline IRF <sup>a</sup>	
Present, <i>n</i> (%)	72 (71.29)

**Table 1** continued

Parameters	Biosimilar ranibizumab ( <i>N</i> = 101)
Absent, <i>n</i> (%)	12 (11.88)

BCVA best corrected visual acuity, BRVO branch retinal vein occlusion, CRVO central retinal vein occlusion, CSFT central subfield thickness, HRVO hemiretinal vein occlusion, IRF intraretinal fluid, RVO retinal vein occlusion, SD standard deviation, SE standard error, SRF subretinal fluid, VEGF vascular endothelial growth factor

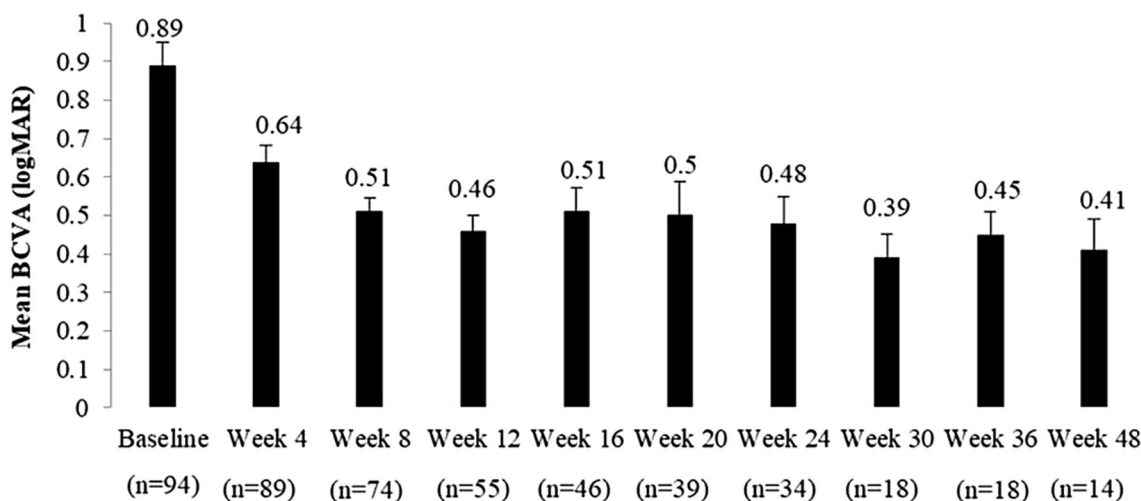
<sup>a</sup> Data not available for 10 patients for RVO subgroup, 3 patients for phakic vs pseudophakic eye, 6 patients for treatment-naïve vs previously treated eye, 18 patients for baseline SRF, and 17 patients for baseline IRF

<sup>b</sup> Baseline BCVA available in 94 patients, CSFT in 85 patients, and IOP in 94 patients

Similarly, after week 30, there was a slight decrease in BCVA improvement though the improvements were significant from baseline (Fig. 1). Figure 2 presents the mean change in BCVA from baseline at each timepoint. The majority (57.9%) of the patients had received three biosimilar ranibizumab injections with significant improvements ( $P < 0.05$ ) seen in BCVA from baseline to all timepoints. A maximum of five injections were administered and the improvements were observed up to 48 weeks. In the BRVO subgroup, the improvements (mean ± SE) in BCVA were significant ( $P < 0.05$ ) from baseline ( $0.85 \pm 0.07$ ) to 48 weeks ( $0.3 \pm 0.08$ ). The improvements in BCVA were also significant ( $P < 0.05$ ) for the CRVO subgroup from baseline ( $1.10 \pm 0.1$ ) to 48 weeks ( $0.6 \pm 0.08$ ) (Fig. 3). The mean change in BCVA did not differ significantly at all timepoints in a subgroup analysis of treatment-naïve vs previously treated patients (Table 2).

### Central Subfield Thickness

A significant ( $P < 0.05$ ) decrease in CSFT scores (mean ± SE) indicating improved disease condition was observed from baseline



**Fig. 1** Mean  $\pm$  SE BCVA at baseline and at each timepoint after biosimilar ranibizumab administration. BCVA best corrected visual acuity

(527.58  $\pm$  19.9) to 48 weeks (307.47  $\pm$  16.4) (Fig. 4). Improvements in CSFT were continuous till the 20th week, after which a slight decrease in the improvement was observed as compared with the previous weeks. But all the observations at all timepoints were significant when compared with baseline. There were significant ( $P < 0.05$ ) improvements in CSFT from baseline to all timepoints in patients who received three biosimilar ranibizumab injections. Figure 5 presents the mean change in CSFT from baseline at each timepoint. The decrease in CSFT (mean  $\pm$  SE) was significant ( $P < 0.05$ ) from baseline to 48 weeks when analyzed for BRVO (499.84  $\pm$  21.83 vs 313.33  $\pm$  63.4) and CRVO subgroups (597.42  $\pm$  37.7 vs 301.75  $\pm$  16.4) (Fig. 6). For a subgroup analysis of treatment-naïve vs previously treated patients, the mean change in CSFT did not differ significantly at all timepoints (Table 2).

### Intraretinal Fluid and Subretinal Fluid

A significant ( $P < 0.05$ ) reduction in the proportion of patients having IRF or SRF from baseline to all timepoints was observed, indicating improved disease condition. The proportion of patients having IRF and SRF at baseline and at each timepoint is presented in

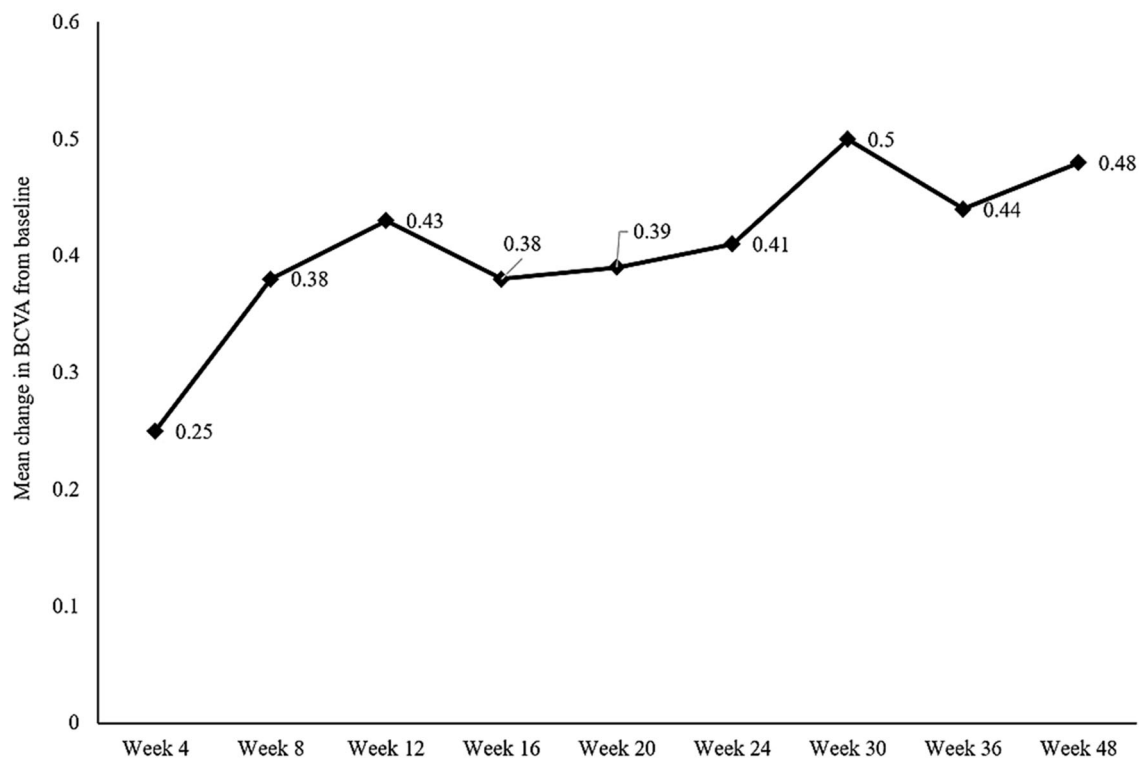
Table 3. Similar results were reported for the subgroup analysis of treatment-naïve vs previously treated patients.

### Intraocular Pressure

The changes in mean IOP scores observed from baseline [15.38  $\pm$  0.4 mmHg ( $n = 94$ )] to 48 weeks [13.94  $\pm$  0.6 mmHg, ( $n = 16$ )] were  $\pm 1$  mmHg at most of the timepoints and these changes were not significant. Similarly, the changes were not significant from baseline to all timepoints in patients who received three biosimilar ranibizumab injections. The changes in mean IOP from baseline to all timepoints were minimal and did not differ significantly when evaluated for a subgroup of treatment-naïve vs previously treated patients. The changes in IOP from baseline were minimal and they were not significant when analyzed for BRVO and CRVO subgroups.

## DISCUSSION

Ranibizumab, bevacizumab, and aflibercept have been extensively used for the treatment of RVO [18, 19]. A recent systematic review and network meta-analysis of 11 randomized controlled trials ( $n = 1130$ ) demonstrated no



**Fig. 2** Mean change in BCVA from baseline and at each timepoint after biosimilar ranibizumab administration. BCVA best corrected visual acuity

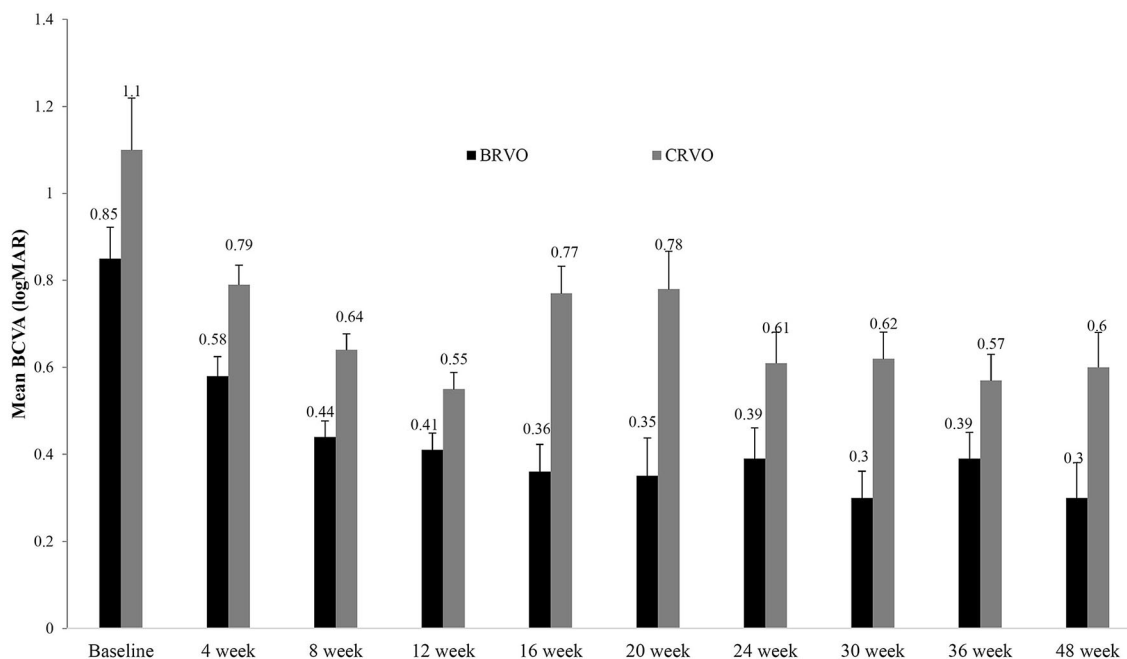
significant differences among bevacizumab, ranibizumab, and aflibercept for the treatment of macular edema secondary to RVO [20]. The recent LEAVO study compared ranibizumab (0.5 mg/0.05 mL,  $n = 155$ ), bevacizumab (1.25 mg/0.05 mL,  $n = 154$ ), and aflibercept (2.0 mg/0.05 mL,  $n = 154$ ) for the treatment of macular edema due to CRVO for 100 weeks and reported that aflibercept was noninferior (no worse than) whereas bevacizumab was not noninferior (may be worse or may not be worse) to ranibizumab for mean changes in vision. Also, bevacizumab treatment was not noninferior to aflibercept treatment in the post hoc exploratory analysis [21].

The pivotal BRAVO [12] and CRUISE [13] trials have demonstrated the efficacy and safety of ranibizumab in RVO treatment. Intas Pharmaceuticals Limited, Ahmedabad, India, has developed the world's first biosimilar ranibizumab—Razumab™, with an objective to provide a cost-effective (up to 25%) alternative to innovator ranibizumab [22].

Biosimilar ranibizumab has been used by leading ophthalmologists in India and has demonstrated efficacy and safety managing macular disorders in prospective and retrospective studies in Indian patients. The current RE-ENACT 2 study further established the effectiveness of biosimilar ranibizumab in the treatment of macular disorders. The previous multicenter, retrospective RE-ENACT [15] ( $n = 561$ ) study strengthened the effectiveness of biosimilar ranibizumab in macular disorders in Indian patients in a routine clinical setting with significant improvements in BCVA, central macular thickness, IRF, and SRF with the use of 4-weekly biosimilar ranibizumab injections (three injections) for a 3-month duration [16].

The RE-ENACT study evaluated the improvements in BCVA, CMT, IRF, and SRF with the use of biosimilar ranibizumab in patients with wet AMD, DME, and RVO for a short duration (12 weeks). The RE-ENACT 2 ( $n = 341$ ) study evaluated the long-term (48 weeks) use (effectiveness measured by





No of patients	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 30	Week 36	Week 48
BRVO	54	51	45	36	28	23	20	12	12	8
CRVO	29	29	24	17	16	13	12	4	4	4

**Fig. 3** Mean ± SE BCVA at baseline and at each timepoint after biosimilar ranibizumab administration in BRVO and CRVO subgroups. Note: Data for patients

with HRVO are not shown in graphs because of the small sample size of only 4 patients. BCVA best corrected visual acuity

improvements in BCVA, CSFT, IRF, and SRF) of biosimilar ranibizumab in patients with wet AMD, DME, RVO, and additionally in patients with mCNV. Furthermore, in the RE-ENACT study, three biosimilar ranibizumab injections were given to all patients but the RE-ENACT 2 study evaluated the patients who had received one to five biosimilar ranibizumab injections overall. Biosimilar ranibizumab resulted in marked improvements in BCVA, CSFT, IRF, and SRF parameters in patients with RVO in this subgroup analysis of the RE-ENACT 2 study. The results for the RE-ENACT 2 study for pooled analysis of the wet AMD, DME, RVO, and mCNV population [23] and a subgroup analysis on the wet AMD population [24] are published elsewhere.

The visual acuity and disease condition improvement in the RE-ENACT 2 study, as measured by logMAR BCVA, was significant

with biosimilar ranibizumab starting at week 4 and throughout 48 weeks, which was similar to the RE-ENACT study (weeks 4 to 12). These results are consistent with a study by Minami et al., which established the positive correlation of short-term effects of ranibizumab in predicting the long-term effects in patients with RVO [25]. The subgroup analysis in the current report demonstrated significant improvements in BCVA in patients with BRVO and patients with CRVO. The BRAVO [12] and CRUISE [13] studies also demonstrated similar results with significant improvements in BCVA sustained over 12 months in patients with BRVO and patients with CRVO, respectively. Several other studies [26] and case series [27] have demonstrated improved BCVA till 12 months. MARVEL [28] and ROCC [11] studies reported similar results with ranibizumab with significant improvements in BCVA at 6 months in patients with

**Table 2** Change in BCVA and CSFT at each timepoint after biosimilar ranibizumab administration in subgroup of treatment-naïve vs previously treated patients with RVO

Week	Subgroup	BCVA		CSFT	
		Mean change	<i>P</i> value	Mean change	<i>P</i> value
4	Treatment naïve	0.3097	0.113	168.9	0.1905
	Previously treated	0.16		105.8	
8	Treatment naïve	0.3692	0.8202	200	0.7821
	Previously treated	0.3956		212.1	
12	Treatment naïve	0.4954	0.8763	253.1	0.9222
	Previously treated	0.47		246.5	
16	Treatment naïve	0.5411	0.1742	288.5	0.5835
	Previously treated	0.2667		227.3	
20	Treatment naïve	0.4924	0.2038	290.7	0.8382
	Previously treated	0.2967		269.1	
24	Treatment naïve	0.4776	0.6567	292.6	0.8629
	Previously treated	0.392		270	
30	Treatment naïve	0.5514	0.7547	259.3	0.5102
	Previously treated	0.47		382	
36	Treatment naïve	0.5643	0.3224	240.4	0.4466
	Previously treated	0.4		383	
48	Treatment naïve	0.632	0.6317	250.4	0.4768
	Previously treated	0.49		382.8	

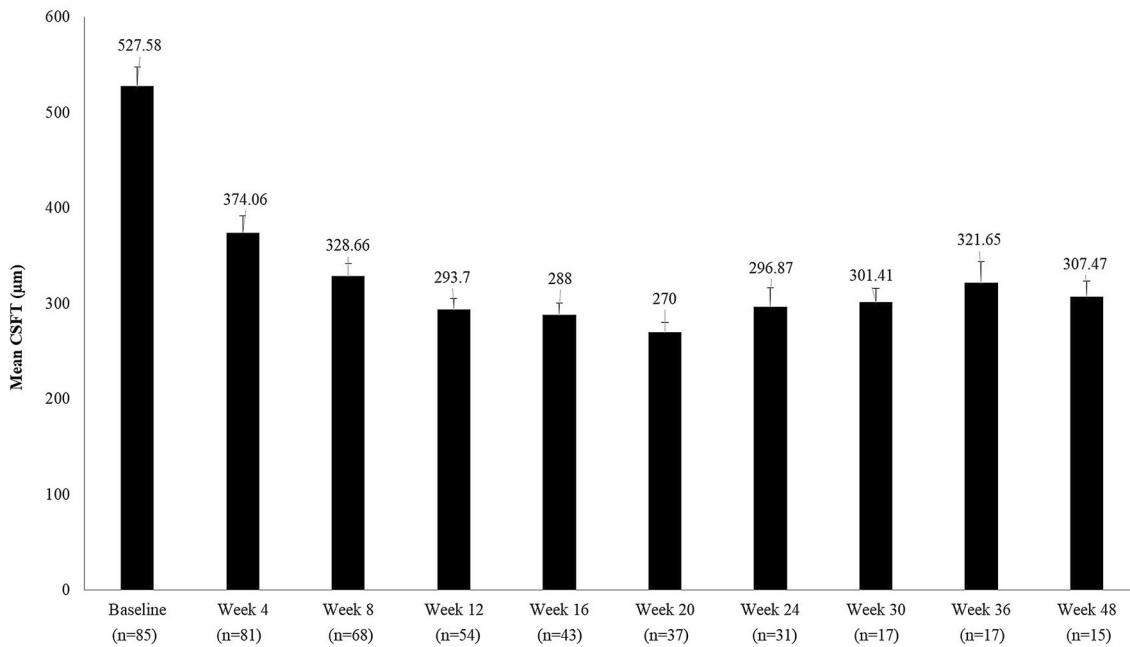
BRVO and patients with CRVO, respectively [29].

Biosimilar ranibizumab was also associated with significant reduction in CSFT in this subgroup analysis at all timepoints starting at week 4 to week 48. The subgroup analysis in patients with BRVO and patients with CRVO demonstrated similar results with a significant reduction in CSFT. The reduction in CSFT was observed as early as day 1 after ranibizumab administration in a case series ( $n = 3$ ) by Verma et al., suggesting early effects of ranibizumab on macular edema related to RVO [30]. Ranibizumab was associated with significant reduction in CSFT in patients with BRVO and patients with CRVO at 6 months in a previous

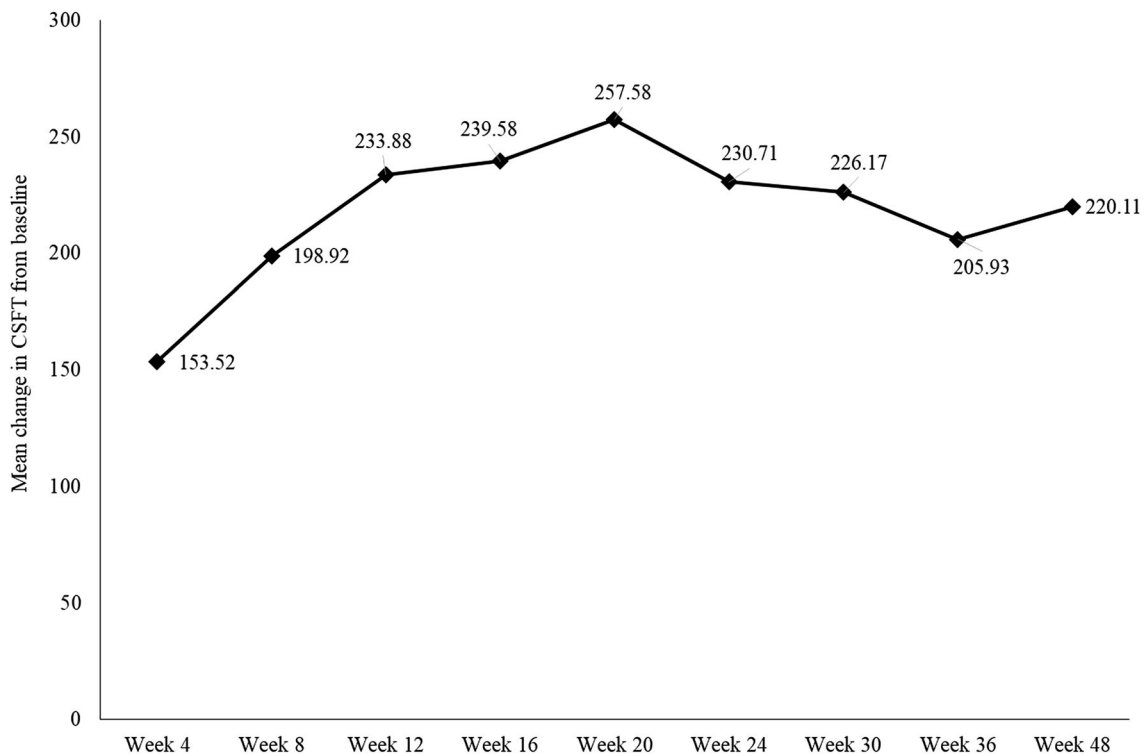
retrospective study by Son et al. [31] ( $n = 15$ , BRVO) and Yuan and colleagues ( $n = 26$ ; BRVO 12, CRVO 13, HRVO 1) [32]. The BRIGHTER study showed a decrease in CSFT at 3, 6, 9, and 12 months with ranibizumab treatment in patients with BRVO ( $n = 183$ ) that continued till 24 months [33].

The possible role of increased IOP in the pathogenesis of RVO was indicated by Frucht and colleagues [34]. Intravitreal injections are known to cause transient increase in IOP. However, information regarding long-term increase in IOP is varied in the literature [34]. Kampougeris and colleagues define a raise in IOP as an increase up to 5 mmHg from baseline [35]. In our study, the values of IOP were within

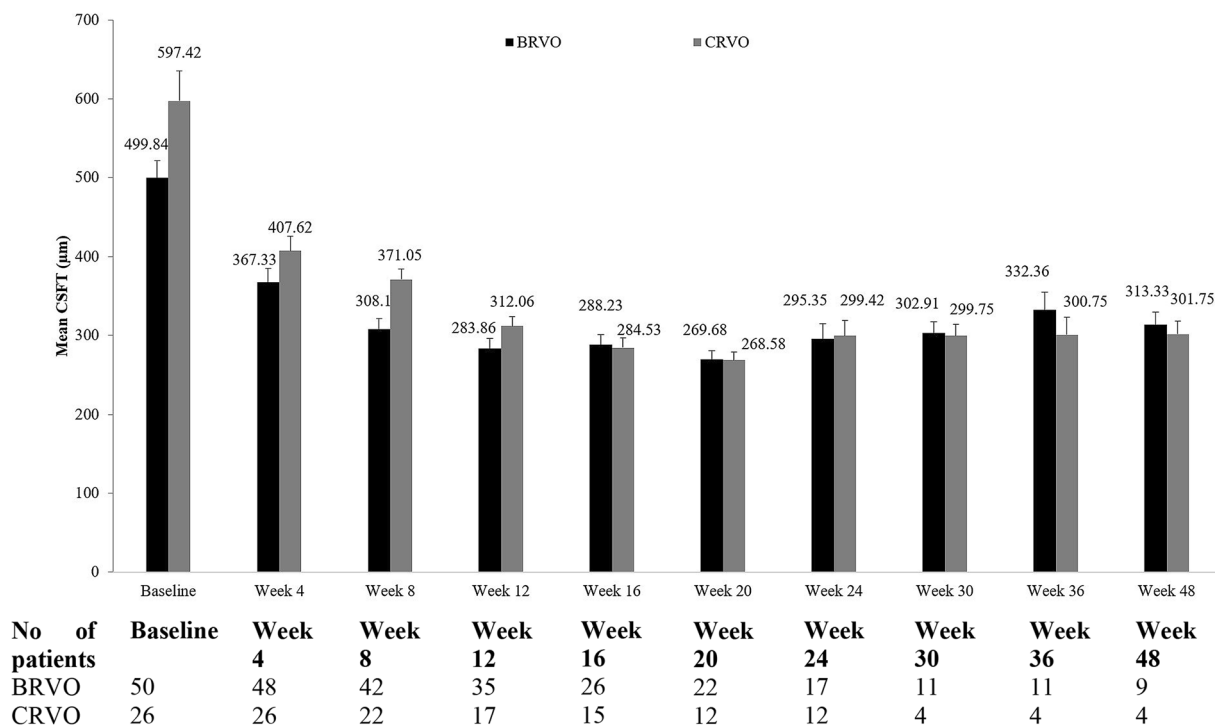




**Fig. 4** Mean  $\pm$  SE CSFT ( $\mu\text{m}$ ) at baseline and at each timepoint after biosimilar ranibizumab administration. CSFT central subfield thickness



**Fig. 5** Mean change in CSFT ( $\mu\text{m}$ ) from baseline at each timepoint after biosimilar ranibizumab administration. CSFT central subfield thickness



**Fig. 6** Mean  $\pm$  SE CSFT at baseline and at each timepoint after biosimilar ranibizumab administration in BRVO and CRVO subgroups. Note: Data for patients

with HRVO are not shown in graphs because of the small sample size of only 4 patients. CSFT central subfield thickness

**Table 3** Proportion of patients with IRF and SRF at baseline and at each timepoint

Timepoint	Total no. of patients with IRF available	IRF present (%)	Total no. of patients with SRF available	SRF present (%)
Baseline	84	71.3	83	52.5
Week 4	82	53.5	80	34.6
Week 8	70	41.6	69	15.8
Week 12	55	28.7	54	5.9
Week 16	42	10.9	44	3.0
Week 20	37	3.9	36	1.0
Week 24	31	2.0	31	2.0
Week 30	17	0	17	0
Week 36	18	2.0	18	2.0
Week 48	15	0	15	0

the normal limits at all timepoints, and  $\pm 1$  mmHg changes in mean IOP scores were seen from baseline to most timepoints; these changes were not significant, consistent with the aforementioned statement. Furthermore, none of the patients had received any medications to reduce IOP before/after biosimilar ranibizumab administration. Similar to our study, Gu et al. reported that IOP remained stable with ranibizumab treatment ( $n = 32$ ) with no statistical difference till 6 months with the mean IOP change at less than 1 mmHg [36]. One-year results from the COMRADE extension study revealed a relatively low IOP with ranibizumab, which was constant over time in patients with RVO when compared with dexamethasone implant, another commonly used agent for RVO treatment [37].

There is generally an accumulation of IRF and SRF in patients with RVO. The BRIGHTER study demonstrated a decrease in the proportion of patients with visible IRF and SRF with ranibizumab treatment at 6 months [38]. Post hoc analysis from the prospective randomized, controlled BRAVO and CRUISE trials showed resolution in SRF in almost all patients with BRVO/CRVO at 3 months after ranibizumab treatment [39]. SRF was effectively reduced through 24 months with ranibizumab treatment in the long-term CRYSTAL study [40]. Our study demonstrated a decrease in the proportion of patients with IRF and SRF throughout the study.

Overall, the current study demonstrated no significant differences in BCVA, CSFT, IOP, IRF, and SRF at most of the timepoints when evaluated for treatment-naïve vs previously treated patients. The major limitation of this study included its retrospective nature because of which complete information pertaining to severity of the disease, previous treatments, bilaterality ischemia, and adverse events could not be presented as it was not captured in medical records. Also, the data on effectiveness parameters were not available for all patients at all timepoints, and the number of patients at each timepoint is mentioned in the respective figures. Overall, no new safety concerns compared to the innovator ranibizumab were observed. The Early Treatment Diabetic

Retinopathy Study (ETDRS) chart is used commonly in controlled clinical studies for measurement of visual acuity. However, the visual acuity was measured with logMAR/Snellen's charts in this study, which is considered inferior to ETDRS charts [41].

## CONCLUSION

The current subgroup analysis of patients with RVO from the RE-ENACT 2 study reinforces Razumab<sup>TM</sup>, the world's first biosimilar of ranibizumab, as an effective treatment option in managing RVO by reducing macular thickness and improving visual acuity. However, larger numbers of patients with complete details at longer follow-up are desirable for a definitive interpretation of the study results.

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**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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