



REVIEW

Treatment Landscape of Macular Disorders in Indian Patients with the Advent of Razumab™ (World's First Biosimilar Ranibizumab): A Comprehensive Review

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ABSTRACT

Ranibizumab is approved for the treatment of several macular disorders, including wet age-related macular degeneration (wet AMD), diabetic macular edema (DME), retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV), among others. The unaffordability of the innovator ranibizumab among patients from developing countries such as India led to the development of the world's first biosimilar ranibizumab, which is a cost-effective alternative that does not compromise efficacy and safety. Razumab™, developed and produced by Intas Pharmaceuticals Ltd., India, is the world's first biosimilar of ranibizumab, and is approved in India for the treatment of various macular disorders, including wet AMD, DME, RVO and mCNV. The efficacy and safety of Razumab for the treatment of these macular

disorders have been evaluated in both prospective and real-world retrospective studies. Razumab has shown an efficacy similar to that of the innovator ranibizumab, achieving improved visual acuity, as measured by the best corrected visual acuity, and reduction in the central macular thickness, leading to improved patient outcomes. The safety profile of Razumab is comparable to that of the innovator ranibizumab and is well tolerated without any new safety concerns. Here, we review the clinical and real-world data of Razumab in the treatment of macular disorders.

Keywords: Razumab; Biosimilar ranibizumab; Wet age-related macular degeneration; Diabetic macular edema; Retinal vein occlusion; Myopic choroidal neovascularization

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Key Summary Points

Ranibizumab is approved for the treatment of several macular disorders.

The unaffordability of innovator ranibizumab among patients from developing countries has led to the development of Razumab™ (Intas Pharmaceuticals Ltd., India), the world's first biosimilar ranibizumab.

Razumab is approved by the 'Drugs Controller General of India (DCGI)—the apex regulatory authority in India, for the treatment of various macular disorders, including age-related macular degeneration (wet AMD), diabetic macular edema, retinal vein occlusion and myopic choroidal neovascularization.

Razumab is a cost-effective anti-vascular endothelial growth factor alternative for the treatment of macular disorders without compromise of efficacy and safety.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14744172>.

INTRODUCTION

Neovascularization of the eye is responsible for the loss of vision in numerous ocular disorders [1]. Of these, diabetic retinopathy (DR), diabetic macular edema (DME), neovascular age related macular degeneration (AMD) and retinal vein occlusion (RVO) are major contributors to blindness [2]. Globally, neovascular or wet AMD is the leading cause of vision impairment, accounting for approximately 9% of all cases of

blindness, with elderly (> 60 years) patients the most commonly affected [3–5]. Neovascularization expanding to the subretinal pigment epithelium and an increase in the intraretinal (IRF) or subretinal fluid (SRF) are the main characteristics of wet AMD [6–9]. Wet AMD has the potential to become a public health concern in India due to a rapidly increasing ageing population [10]. RVO, a significant factor leading to unilateral and painless vision loss [11–13], has a global prevalence of 0.7–1.6% [14], with an estimated 16 million people affected worldwide [15]. DME is the most common and vision-limiting condition in DR [16] and represents a major cause of vision loss in diabetic individuals [17]. Myopic choroidal neovascularization (mCNV) appears to be a rare disease, with an incidence of 0.017% [18], but may result in an irreversible vision loss [19].

VASCULAR ENDOTHELIAL GROWTH FACTORS IN MACULAR DISORDERS

The role of vascular endothelial growth factor (VEGF) and its receptors has been established in the etiopathogenesis of macular disorders, including wet AMD, DME, RVO and mCNV [20–23]. The pathogenesis of AMD is characterized by the overexpression of VEGF, which is secreted by hypoxic retinal pigmented epithelium (RPE) cells and induces neoangiogenesis through endothelial cell proliferation and vascular permeability [24–29]. In choroidal vasculature, VEGF may also regulate choroidal integrity by binding to its receptors on the adjacent choriocapillaris [29]. The VEGF protein may cause development of abnormal blood vessels under the retina, a condition also known as choroidal neovascularization (CNV). In the pathogenesis of RVO, hypoxia and several other stimuli upregulate VEGF expression, and the increased VEGF concentration in ocular fluid is positively correlated with the severity of macular edema [22, 30–32]. In addition, VEGF-A has an established role in the pathogenesis of RVO [33]. In DME, DR develops due to hyperglycemia leading to the triggering of pathophysiological mechanisms, including increased VEGF expression [34]. Although the

etiopathogenesis of DME and myopic CNV involve angiogenesis, it remains unclear whether the latter is due to the effects of VEGF overexpression [35, 36].

ANTI-VEGF AGENTS—MECHANISM OF ACTION

The advent of anti-VEGF biologics, such as ranibizumab, aflibercept, brolucizumab and bevacizumab (off-label), has revolutionized the management of macular disorders [20, 21, 37]. Anti-VEGF agents inhibit vascular permeability, endothelial cell proliferation and endothelial cell migration, and penetrate the retina to block isoforms of VEGF-A [38–40]. Ranibizumab is a human recombinant monoclonal antibody that inhibits VEGF-A binding to its receptors, thereby suppressing the neovascularization process [41]. Several studies have established the efficacy and safety of ranibizumab for the treatment of wet AMD [42, 43], RVO [44, 45], DME [46–52] and mCNV [36, 53, 54].

RAZUMAB IN MACULAR DISORDERS

Razumab™, developed and produced by Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat, India (referred to further as Intas), is the world's first biosimilar ranibizumab and has been approved for the treatment of several macular disorders by the Drugs Controller General of India (DCGI), which is the apex regulatory authority in India (dated 20 Feb 2015; MF-35/2015 BULK-36/2015) [55]. The approval of Razumab was based on the results of a phase III study involving patients with wet AMD ($n = 104$) which demonstrated that the proportion of patients who lost fewer than 15 letters in visual acuity (approximately 3 lines) from baseline to the end of the study was similar in patients on Razumab ($n = 78$) and the innovator ranibizumab ($n = 26$) (data on file). Razumab is approved for the treatment of wet AMD, DME, RVO and mCNV [55]. Several prospective as well as retrospective studies have established the efficacy and safety of Razumab for the treatment

of macular disorders [2, 56–61]. In this review article, we focus on the clinical and real-world data on Razumab in the treatment of macular disorders.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Table 1 provides an overview of the studies conducted with Razumab.

RAZUMAB—A COST EFFECTIVE ALTERNATIVE

The availability of innovator ranibizumab (Lucentis®) to many patients is limited due to its high cost, especially to patients in developing countries such as India [37]; it is this financial burden which is a major reason for patient non-compliance to the treatment [63]. The advent of a biosimilar agent has paved the way to democratize the existing expensive medical need [64]. Biosimilar agents are cost-effective as they are developed at approximately one-tenth of the cost of biologics, and their marketing price tag is 20–40% lower than that of biologics [64]. Biosimilars can potentially reduce healthcare expenditures, thus allowing a larger patient population to reap benefits [37].

Compared to parent biologic drugs, the use of biosimilar agents may lead to 25–50% decrease in the treatment cost [65]. For example, the cost of Razumab is approximately 40% lower than that of its innovator product [37]. In India, Razumab (US \$125) is an economical alternative to the innovator ranibizumab (US \$320), aflibercept (US \$760) and brolucizumab (US \$350) [65]. The total annual cost of treatment was estimated to be US \$2700–3700 for innovator ranibizumab versus US \$1600–1900 for Razumab in an analysis conducted by Verma et al. [37, 66]. An online VIBE survey evaluating the perceptions of retina specialists on the use of anti-VEGF biosimilars in India showed an increased acceptance of the efficacy and safety of Razumab from 2018 to 2020 [67]. The commercial sales of Razumab increased from 2842 vials in 2015 following the publications of the

Table 1 Summary of the studies on Razumab

Study name or first author	Type of study	Indications	No of patients/ eyes treated	Razumab dose and schedule	BCVA/CDVA	CRT/CMT/CFT/ CSFT
ASSET [55]	Prospective	Wet AMD	126 patients	0.5 mg every 4 weeks for 24 weeks	Baseline: 44 (16.27) letters Week 24: 53.7 (17.83) letters	Baseline: 384.8 ± 146.44 μm Week 24: 258.5 ± 74.77 μm
Sameera et al. [2]	Prospective	Wet AMD, DME, RVO	123 eyes of 95 patients	0.5 mg single dose	Baseline: 0.67 ± 0.41 logMAR Day 30: 0.57 ± 0.37 logMAR	Baseline: 345.90 ± 128.84 μm Day 30: 287.66 ± 90.28 μm
Gopal et al. [62]	Retrospective	Wet AMD, DME, RVO	309 eyes of 297 patients	0.5 mg single dose	Baseline: 0.66 ± 0.350 logMAR Day 30: 0.52 ± 0.488 logMAR	Baseline: 400.16 ± 102.360 μm Day 30: 315 ± 87.682 μm
CESAR study [37]	Retrospective	DME, RVO, mCNV	153 eyes of 141 patients	0.5 mg PRN	Baseline: 0.62 ± 0.44 logMAR 3-months: 0.42 ± 0.44 logMAR	Baseline: 405.68 ± 192.422 μm 3-months: 271 ± 104.24 μm
RE-ENACT study [61]	Retrospective	Wet AMD, DME, RVO	561 patients	0.5 mg PRN	Baseline: 0.75 ± 0.01 logMAR Week 12: 0.49 ± 0.01 logMAR	Baseline: 418.47 ± 4.78 μm Week 12: 301.17 ± 2.8 μm

Table 1 continued

Study name or first author	Type of study	Indications	No of patients/ eyes treated	Razumab dose and schedule	BCVA/CDVA	CRT/CMT/CFT/ CSFT
RE-ENACT 2 study [56]	Retrospective	Wet AMD, DME, RVO, mCNV	341 patients	0.5 mg PRN	Baseline: 0.89 ± 0.6 logMAR Week 48: 0.43 ± 0.3 logMAR	Baseline: 467.09 ± 159.6 µm Week 48: 296.56 ± 49.7 µm

AMD Age-related macular degeneration, *BCVA* best-corrected visual acuity, *CDVA* corrected distance visual acuity, *CFT* central foveal thickness, *CMT* central macular thickness, *CRT* central retinal thickness, *CSFT* central subfoveal thickness, *DME* diabetic macular edema, *logMAR* logarithm of the minimum angle of resolution, *mCNV* myopic choroidal neovascularization, *PRN* pro re nata (as needed), *RVO* retinal vein occlusion

RE-ENACT and RE-EANCT 2 studies, to 49,914 vials in 2019 and 120,582 vials in 2020 [65].

RAZUMAB IN POOLED PATIENT POPULATION OF WET AMD, DME AND RVO

In a prospective study, Sameera and colleagues evaluated the short-term (30 days) efficacy and safety of a single intravitreal injection of Razumab (0.05 mL) for the treatment of chorioretinal vascular diseases, such as DME, RVO and wet AMD, in 123 eyes of 95 patients [68]. These authors observed significant improvements from baseline to day 30 in best corrected visual acuity (BCVA, mean ± standard deviation [SD]; 0.67 ± 0.41 vs. 0.57 ± 0.37 logMAR; $p = 0.001$) and central macular thickness (CMT; 345.90 ± 128.84 vs. 287.66 ± 90.28 µm; $p < 0.0001$) in the pooled patient population. The subgroup analysis of patients with DME, RVO and wet AMD, respectively, also showed significant improvements in the BCVA and CMT. In treatment-naïve eyes, the results were similar, with marked improvements in the BCVA and CMT. The authors of this short-term pilot study concluded that the efficacy and safety profile of Razumab was similar to that of the innovator ranibizumab [2]. Sameera and

colleagues also presented their prospective analysis treatment data on Razumab at the APVRS, 2016 Congress, which showed significant ($p < 0.001$) improvements from baseline to day 30 in BCVA (0.680 ± 0.43 vs. 0.581 ± 0.361 logMAR) and CMT (355.66 ± 128.07 vs. 296.87 ± 92.93 µm) in 165 eyes of 143 patients with wet AMD, DME and RVO [68].

In comparison to results obtained in controlled clinical trials, innovator ranibizumab has demonstrated suboptimal treatment outcomes in real-world clinical practice [69, 70]. Hence, in addition to the prospective studies, several retrospective studies have also generated evidence on the effectiveness of Razumab in real-world setting. In a single-center, retrospective observation study, Gopal et al. demonstrated that a single-dose intravitreal Razumab injection significantly improved the visual acuity (BCVA) and markedly reduced the central foveal thickness (CFT) from baseline by the end of the first month of treatment in patients with wet AMD, DME and RVO (309 eyes of 297 patients) [62]. Intas conducted the multicenter, retrospective, observational RE-ENACT study, which demonstrated that treatment with Razumab significantly improved BCVA, CMT, IRF and SRF in patients with wet AMD, DME and RVO over the short-term (12 weeks) duration of the RE-ENACT study ($n = 561$) [61]. However,

the need for long-term data based on studies evaluating the anti-VEGF treatments in these macular disorders [71] led to the conceptualization and execution of the RE-ENACT 2 study.

RAZUMAB IN POOLED PATIENT POPULATION OF WET AMD, DME, RVO AND MCNV

The RE-ENACT 2 study enrolled patients with wet AMD, DME, RVO as well as those with mCNV ($n = 341$) and had a follow-up duration of 48 weeks. Treatment with Razumab resulted in significant improvements ($p < 0.001$) from baseline to week 48 in the BCVA (0.89 ± 0.6 vs. 0.43 ± 0.3 logMAR) and central subfoveal thickness (CSFT; 467.09 ± 159.6 vs. 296.56 ± 49.7 μm). In addition, there were insignificant ($p = 0.4307$) changes observed in the intraocular pressure (IOP; 14.92 ± 3.4 vs. 13.89 ± 2.2 mmHg), and the proportion of patients with IRF and SRF decreased [56].

RAZUMAB IN POOLED PATIENT POPULATION OF DME, RVO AND MCNV

The single-center, retrospective CESAR study evaluated the effects of Razumab treatment in a pooled population (153 eyes of 141 patients) of patients with DME, RVO and mCNV. There were significant ($p < 0.001$) improvements from baseline to 3 months in mean (\pm SD) corrected distance visual acuity (CDVA; 0.62 ± 0.44 vs. 0.42 ± 0.44 logMAR) and CFT (405.68 ± 192.422 vs. 271 ± 104.24 μm). The improvements in both of these efficacy parameters were significant as early as 1 month after initiating treatment [37]. At the American Society of Retina Specialists (ASRS) meeting 2018, Banker et al. reviewed the data from prospective, consecutive case series, who had received Razumab including 22,276 eyes, and showed a significant improvement from baseline to 3 months in the visual acuity (0.72 vs. 0.54 logMAR) and CMT (406.15 vs. 314.10 μm) in patients with DME, RVO and mCNV [72].

RAZUMAB IN PATIENTS WITH WET AMD

The prospective, postmarketing phase 4 ASSET study established the safety and efficacy of Razumab (0.5 mg intravitreal injections every 4 weeks for 24 weeks; 6 doses) in patients with wet AMD ($n = 126$) aged ≥ 50 years, with an active primary or recurrent sub-foveal lesion with CNV secondary to AMD, with foveal center involvement, and a BCVA of 20/40 to 20/320 [55]. From baseline to week 24, Razumab treatment significantly ($p < 0.0001$) improved the mean (\pm SD) BCVA (44 ± 16.27 vs. 53.7 ± 17.83 letters) and CRT (384.8 ± 146.44 vs. 258.5 ± 74.77 μm). Furthermore, 97.60% patients lost fewer than 15 letters and 31.20% patients showed improvement in the visual acuity by ≥ 15 letters at week 24. The dimensions of self-reported vision-related activities during day-to-day living activities were measured through the Visual Function Questionnaire-25 (VFQ-25) scores, which improved significantly ($p < 0.001$) from baseline to week 24 (60.9 ± 14.36 vs. 8.5 ± 13.04) [55].

In the study by Sameera et al. the subgroup of wet AMD patients (46 eyes) receiving Razumab showed a significant improvement from baseline to day 30 in BCVA (0.8 ± 0.4 vs. 0.6 ± 0.3 logMAR) and CMT (291.4 ± 103.6 vs. 272.6 ± 77.1 μm), although the difference was not statistically significant [2]. The subgroup analysis of patients with wet AMD ($n = 194$) in the RE-ENACT study demonstrated a significant ($p < 0.0001$) improvement with Razumab treatment from baseline to week 12 in BCVA (0.81 ± 0.03 vs. 0.55 ± 0.02 logMAR) and CMT (393.02 ± 7.32 vs. 293.5 ± 4.10 μm) together with a reduction in the proportion of patients with IRF (59.79 vs. 31.96%) and SRF (82.47 vs. 41.24%). [60] In the subgroup of wet AMD patients ($n = 103$) from the RE-ENACT 2 study, Razumab treatment was associated with significant improvements in visual acuity from baseline to week 48 as measured by BCVA (0.92 ± 0.6 vs. 0.51 ± 0.4 logMAR) and CSFT (430.83 ± 14.4 vs. 301.26 ± 11.6 μm) along with decreased proportions of patients having

IRF (63.6 vs. 15%) and SRF (82.3 vs. 5%) with similar results observed for the subgroups with occult and classic wet AMD [57].

RAZUMAB IN PATIENTS WITH RVO

The effectiveness of Razumab in the treatment of patients with RVO has been evaluated in the RE-ENACT and RE-ENACT 2 studies. In the RE-ENACT study, patients with RVO ($n = 160$) demonstrated significant ($p < 0.0001$) improvement from baseline to week 12 in the BCVA (0.76 ± 0.04 vs. 0.47 ± 0.02 logMAR) and CMT (447.60 ± 10.91 vs. 298.23 ± 6.68 μm), together with a significant decrease in the proportion of patients with IRF (70.63 vs. 30.00%) and SRF (65.63 vs. 24.38%). [59] The RE-ENACT 2 study also demonstrated significantly improved BCVA (0.89 ± 0.06 vs. 0.41 ± 0.08 logMAR) and CSFT (527.58 ± 19.9 vs. 307.47 ± 16.4 μm) from baseline to week 48 in the subgroup of patients with RVO ($n = 101$). A decrease in the proportion of patients with IRF (71.3 vs. 0%) and SRF (52.5 vs. 0%) was also observed [58]. The patients with branch RVO (BRVO) and central RVO (CRVO) showed similar improvements in the efficacy parameters in the RE-ENACT 2 study [58].

RAZUMAB IN PATIENTS WITH DME

Shrivastava and colleagues performed a retrospective comparative analysis of Razumab (20 eyes) versus innovator ranibizumab (12 eyes) in terms of improvements in vision and macular thickness in patients with DME ($n = 26$). Significant improvements were observed from baseline to 1 month in BCVA, as measured by ETDRS letters, for both the innovator ranibizumab (53 vs. 61 letters; $p = 0.010$) and Razumab (48 vs. 55 letters; $p = 0.011$); there was no significant difference between the groups ($p = 0.31$). Similarly, the improvements in CMT were significant in both groups (innovator ranibizumab: 428 vs. 301 μm ; $p = 0.032$; Razumab: 378 vs. 279 μm ; $p = 0.021$); again there was no significant between-group difference

($P = 0.21$). These results suggest a similar efficacy for both of these anti-VEGF agents [73].

RAZUMAB IN PATIENTS WITH OTHER INDICATIONS

The use of Razumab in indications other than the conditions mentioned above has also been reported. Razumab (0.5 mg/0.05 mL) demonstrated improved BCVA in a 50-year-old male patient who had vasculitic RVO secondary to COVID-19 [74]. In a patient with stage II Coats' disease, Razumab treatment led to significant reductions in the exudation, angioma-like lesions, CMT and edema in the retina, and improved the distant vision (BCVA 5/60 at baseline to 6/18 post-treatment) and near vision, which was 'not able to read' at baseline to N/12 post-treatment [75].

SWITCHING FROM INNOVATOR RANIBIZUMAB TO RAZUMAB

Sharma and colleagues reviewed the real-world effects of switching from innovator ranibizumab to Razumab on the efficacy and immunogenicity in a retrospective study of 30 eyes with wet AMD, DME and RVO. The reason for switching was financial constraints reported by all patients. The Mean Early Treatment Diabetic Retinopathy Study (ETDRS) letter score before switching was 49.5 ± 14.1 letters, and at 6 months after switching it was 59.8 ± 9.7 letters; there were no clinical signs of immunogenicity [76].

IMMUNOGENICITY ASSESSMENTS

Immunogenicity of Razumab was evaluated in the phase IV ASSET study ($n = 126$) through a validated bridging enzyme-linked immunosorbent assay (ELISA) in a total of nine 6-mL samples. Anti-ranibizumab antibodies were present in 7.94% of patients at baseline before Razumab administration whereas these were present in 7.14% patients at week 2 post Razumab treatment, in 3.97% at week 4, in 4.76% at week 6, in

3.97% at week 8, in 6.35% at week 12, in 7.14% at week 16, in 7.14% at week 20 and in 6.35% at week 24 [55]. No increase in the immunogenicity incidence was reported with increased number of Razumab injections [55]. These immunogenicity data are similar to data observed with innovator ranibizumab, with pre-treatment immunogenicity of 0–5% and post-treatment immunogenicity ranging from 1 to 9% after 6–24 months [77] up to 17.1% [78].

SAFETY

The most common ocular adverse events (AEs) reported with innovator ranibizumab are conjunctival hemorrhage, vitreous floaters, increased IOP, increased lacrimation, eye pain, blepharitis, intraocular inflammation, visual disturbance, dry eye, ocular hyperaemia, eye irritation and eye pruritus [77]. In the phase III trial of Razumab (data on file), a total of 13 AEs (10 in the Razumab arm and 3 in the innovator ranibizumab arm) were reported, all of which were mild to moderate in severity (data on file). The prospective, multicenter, phase IV ASSET study ($n = 126$) evaluated the safety of Razumab in patients with wet AMD using fundus fluorescein angiography, indirect ophthalmoscopy, laboratory assessments and slit-lamp examination. Of the 19 AEs in 16 (12.70%) patients in this study, 15 were mild, three were moderate and one was severe in nature. All AEs resolved with the exception of one AE which culminated in death; this AE was assessed as being unlikely to be linked to the study drug. [55] Iridocyclitis, corneal edema, ocular hyperaemia, dry eye, pyrexia and increased IOP were the AEs reported [55]. In a subgroup of wet AMD patients from the RE-ENACT 2 study, Razumab treatment resulted in minimal but not significant changes in IOP from baseline to 48 weeks (14.92 ± 3.2 vs. 14.50 ± 2.1 mmHg) [57]. Chakraborty et al reported the largest pooled safety data on intravitreal Razumab use, with 9406 injections administered in 6404 eyes of 6404 patients with chorioretinal disorders, including wet AMD (25.37%), DME (32.32%) and BRVO (23.34%) in a real-world setting. AEs were reported to be associated with 21.03% (1978) of the Razumab

injections administered; however, most (97.12%) of these were non-serious. Subconjunctival hemorrhage (8.2% of all injections), blurring of vision (6.5%) and ocular pain (5.27% of all injections) were the most common AEs. Infrequent (0.61%) serious ocular and systemic events reported were retinal pigment epithelial tears (0.33%), non-infectious vitritis (0.02%), endophthalmitis (0.01%), non-fatal myocardial infarction (0.12%) and non-fatal cerebrovascular accident (0.09%). There were no new systemic or ocular AEs reported with the use of Razumab, and the authors concluded that the use of intravitreal Razumab treatment is safe for the management of chorioretinal disorders [65]. In addition, the retrospective RE-ENACT and RE-ENACT 2 studies demonstrated that Razumab was well-tolerated in the real-world setting with no new safety concerns. Intas is planning to conduct prospective studies on Razumab to generate more controlled clinical data on the approved indications.

CONCLUSION

Overall, the efficacy and safety of Razumab™ has been consistently maintained, and it has been increasingly accepted by the ophthalmologists in India [79]. The efficacy and safety data of Razumab presented by several key retina specialists at multiple scientific platforms, including the American Society of Retina Specialists, EURETINA and the American Academy of Ophthalmology, among others [80] substantiate ophthalmologists' confidence in the efficacy and safety of Razumab. The overall choice of anti-VEGF agent may depend on the affordability [81], especially in countries with limited resources, such as India.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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