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CLINICAL TRIAL REPORT

Efficacy and Safety of Biosimilar Ranibizumab (OPTIMAB®) *versus* Innovator Ranibizumab in Patients with Neovascular (Wet) Age-Related Macular Degeneration: A Double-Blind, Randomized, Multicenter, Phase III Study

Parth J Rana[1], Himanshu Deshmukh[2], Urmil Shah[3], Vinod Kumar[4], Sanghamitra Kanungo[5], Deepika Singhal[6], Santosh Kumar Mahapatra[7], Ira Vakharia[8], Mukesh Jaiswal[9], Ajitkumar Gondane[10], Pooja Vaidya[10], Vinayaka Shahavi[9], Harish Shandilya[11], Dattatray Pawar[10], Akhilesh Sharma[12]

[1]Department of Retina and Trauma Surgery, Netralaya Superspeciallity Hospital, Ahmedabad, Gujarat, India; [2]Department of Retina; 'Daulat' Deshmukh Eye Hospital, Khaparde Gardens, Amravati, Maharashtra, India; [3]Department of Retina, P.N. Desai Eye Hospital, Ahmedabad, Gujarat, 380052, India; [4]Department of Ophthalmology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India; [5]Department of Retina, Kar Vision Eye Hospital, Bhubaneswar, Odisha, 751007, India; [6]Department of Ophthalmology, GMERS Medical College and Civil Hospital, Ahmedabad, Gujarat, India; [7]Department of Retina, JPM Rotary Club of Cuttack Eye Hospital and Research Institute, Cuttak, Odisha, 753014, India; [8]Department of Retina, Nirmal Hospital Pvt Ltd, Surat, Gujarat, 395002, India; [9]Clinical Research Department, Alkem Laboratories Ltd., Lower Parel, Mumbai, India; [10]Medical Affairs Department, Alkem Laboratories Ltd., Lower parel, Mumbai, India; [11]Global Product Development, IPM & Regulatory Affairs, Enzene Biosciences Ltd., Pune, India; [12]Medical Affairs and Clinical Research Department, Alkem Laboratories Ltd., Lower Parel, Mumbai, India

Correspondence: Ajitkumar Gondane, Medical Affairs, ALKEM Laboratories Ltd., ALKEM HOUSE, "Devashish", Adjacent to Matulya Centre, Senapati Bapat Marg, Lower Parel, Mumbai, 400 013, India, Tel +8983375722, Email ajitkumar.gondane@alkem.com

Objective: This study aimed to compare efficacy, safety, and immunogenicity of the biosimilar ranibizumab in comparison with the Innovator Ranibizumab in treatment-naive patients with neovascular (wet) age-related macular degeneration (nAMD or wAMD).

Materials and Methods: This comparative, double blind, multicentre, Phase III clinical study randomized eligible patients in a 3:1 ratio to receive either OPTIMAB® (Alkem Laboratories Ltd./ Enzene Biosciences Ltd.) or Innovator Ranibizumab. Intravitreal injections of Innovator Ranibizumab (0.5 mg in 0.05 mL) and OPTIMAB® (0.5 mg in 0.05 mL) were administered every four weeks for 12 weeks (three doses). Primary efficacy endpoints included loss of <15 letters from baseline, gain of ≥15 letters from baseline in visual acuity, mean change in best corrected visual acuity (BCVA) from baseline, and change in central subfoveal thickness (CSFT) from baseline at week 12. Safety was assessed through monitoring of adverse events (AEs) and serious adverse events (SAEs) throughout the study.

Results: Overall, of the 152 patients randomized, 141 (92.8%) patients (mean age, 66.6 ± 9.37 years) completed the study. Percentage of patients who lost < 15 letters in BCVA at week 12 from baseline was comparable in both the groups (100.0%, each). On secondary end point analysis, the two groups had comparable mean changes in BCVA (OPTIMAB®, 11.8 ± 9.18; innovator ranibizumab, 12.9 ± 10.29; P = 0.5509); proportion of patients who gained ≥ 15 letters in visual acuity (OPTIMAB®, 32.18%; innovator ranibizumab, 25.74%; P = 0.4785) and mean change in CSFT (OPTIMAB®, −76.6 ± 89.03; Innovator ranibizumab, −73.1 ± 92.23 µm; P = 0.8422) at week 12 as compared to baseline. OPTIMAB® and innovator ranibizumab demonstrated comparable safety over the 12-week treatment period and no patient expressed anti-ranibizumab antibody in either group patient.

Conclusion: Biosimilar ranibizumab (OPTIMAB®) was non-inferior to innovator ranibizumab in terms of efficacy, safety, and immunogenicity in the patients of nAMD.

Keywords: biosimilar ranibizumab, best corrected visual acuity, central subfoveal thickness, nAMD

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Introduction

The World Health Organization (WHO) reports that age-related macular degeneration (AMD), on a global scale, ranks third among the causes of blindness, contributing to 8.7% of total cases of vision impairment.[1,2] Untreated, neovascular AMD (nAMD) leads to irreversible loss of vision in a majority of patients.[3] The nAMD or wAMD, recognized as one of the most aggressive manifestations of AMD, stands as a prevalent cause of global blindness, afflicting more than 200 million individuals worldwide.[4] The overall prevalence of AMD in India ranges from 1.4% to 3.1%.[5] Further, the prevalence of AMD is projected to surge to 17.8 million cases by the year 2050.[2,6] Vascular endothelial growth factor (VEGF) stands as a potent endothelial-specific mitogen, provoking angiogenesis, vascular hyper permeability, and heightened expression levels in the retinal pigment epithelium (RPE) and vitreous of eyes afflicted with both non-neovascular and neovascular forms of AMD, particularly in response to hypoxia. These VEGF-driven processes play a pivotal role in the pathogenesis of AMD.[7]

Anti-VEGF agents are medications aimed at blocking the effects of VEGF-A. The introduction of these agents has revolutionized the treatment of nAMD.[7] VEGF-A inhibitors, exemplified by ranibizumab, represent recombinant, humanized, murine monoclonal antibody fragments specifically engineered to bind to and neutralize active isoforms of VEGF-A. This class of agents like ranibizumab, bevacizumab, aflibercept, pegaptanib, brolucizumab has established itself as the standard of care for the majority of newly diagnosed, symptomatic nAMD cases.[8–11] Even though these drugs have the same pharmacological target, they do not have the same structure and are not equivalent. Ranibizumab is known to have a lower dissociation rate with lower conformational fluctuations of the ranibizumab/VEGF-A complex and a higher number of contacts and hydrogen bonds in comparison to bevacizumab and aflibercept.[12] Intravitreal ranibizumab is a well-established treatment for nAMD, with high and rapid retinal penetration and a short half-life, which minimizes systemic effects.[13] Ranibizumab obtained regulatory approval for the treatment of nAMD from both the US Food and Drug Administration (FDA) in 2006 and the European Medicines Agency (EMA) in 2007.[14,15]

The application of anti-VEGF therapy in the treatment of nAMD presented a significant burden on both patients and healthcare systems in the past. This burden primarily arose from the substantial financial investment required for these pharmacological interventions.[16,17] The financial strain linked to the treatment mainly resulted from the necessity for frequent and economically high-cost injections, potentially limiting clinical effectiveness in practical clinical settings. Although off-label alternatives have reduced drug-related costs, patients continue to face significant financial burdens related to frequent appointments, including travel expenses, time away from work, and caregiver costs, which further contribute to the overall healthcare burden.[16,17] Furthermore, its impacts extended beyond the clinical domain affecting insurance entities and influencing their reimbursement policies, thereby contributing to the overall healthcare burden.[18,19]

Biosimilars refer to biological medicinal products that incorporate a version of the active ingredient found in an already licensed original biological medicinal product, referred to as the innovator medicinal product.[20] Biosimilars helps to decrease the costs and improve patient access for effective biological medicinal products.[20] Biosimilars are deemed to be comparable to an approved innovator product in regard to safety, efficacy, and immunogenicity. Furthermore, conducting clinical studies that compare the safety and efficacy profiles of biosimilars with innovator products can enhance the effective utilization of biosimilars.[21]

OPTIMAB®, a ranibizumab biosimilar developed by Enzene Biosciences Ltd., has identical primary structure and the active substance as the Innovator biological medicinal product LUCENTIS®. Building upon the aforementioned background and the favourable safety profile exhibited by OPTIMAB®, this comparative, double blind, randomized, multicentre phase III study was conducted to compare clinical efficacy and safety between OPTIMAB® and the innovator ranibizumab in patients with nAMD.

Materials and Methodology

Study Design

This was comparative, double-blind, randomized, multicenter, Phase III study conducted at 19 centers across India from Oct 2021 to Feb 2023. The study was conducted in accordance with the Good Clinical Practice guideline of the International Council for Harmonisation, the ethical principles of the Declaration of Helsinki, and the local regulatory

requirements. Institutional review board/ethics committee approval was obtained at each participating centre prior to initiation of study. The detailed list of all approving ethics committees is provided in Supplementary Table 1. The study was registered with the Clinical Trial Registry of India (https://ctri.nic.in/) with the number CTRI/2021/08/035907. Written informed consent was obtained from each patient before enrolment in the study.

Participants

Eligible patients were male or female aged ≥50 years with treatment-naive choroidal neovascularization (CNV) secondary to AMD. Key ocular inclusion criteria were CNV involving the foveal center, BCVA within the range of 20/40 to 20/320 in the study eye determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and Snellen equivalent measurements. Key exclusion criteria included prior treatment with any anti-VEGF therapy in last 6 months, treatment with an intravitreal drug, verteporfin, or photodynamic therapy in the study eye in the past (except for extrafoveal laser photocoagulation in the study eye) and/or non-study eye within the past 3 months, and/or laser photocoagulation in the study eye within 1 month before screening. Patients with vision only in one eye, sub foveal fibrosis or sub foveal atrophy in the study eye, polypoidal choroidal vasculopathy, history of retinal detachment or macular hole (stage 3 or 4) and/or vitreous haemorrhage in the study eye, CNV due to causes other than AMD, retinal pigment epithelial tear involving the macula in the study eye, active intraocular inflammation or active/suspected ocular or periocular infection in the study eye, and any other retinal pathology which may affect the outcome measures were excluded.

Randomization and Intervention

Randomization was performed using an Interactive Web Response System (IWRS) in a 3:1 ratio of treatment allotment for test and innovator products, respectively. The randomization schedule was generated using SAS® (SAS Institute Inc., USA). Patients who fulfilled the eligibility criteria were assigned a randomization code. The patients and the study team (investigators or their designee, sponsor or their designee, contract research organization or their designee, or any other relevant personnel involved in the conduct and interpretation of the study results) were blinded to the administration of the investigational product (IP).

Based on the randomization schedule, the IP was administered in a dose of 0.5 mg/0.05 mL by an intravitreal injection every 4 weeks for a total of 12 weeks (03 doses). The intravitreal injection procedure was carried out under aseptic conditions. Follow-up was planned every 4 weeks and final data was compared at 12 weeks. The study design was shown in Figure 1.

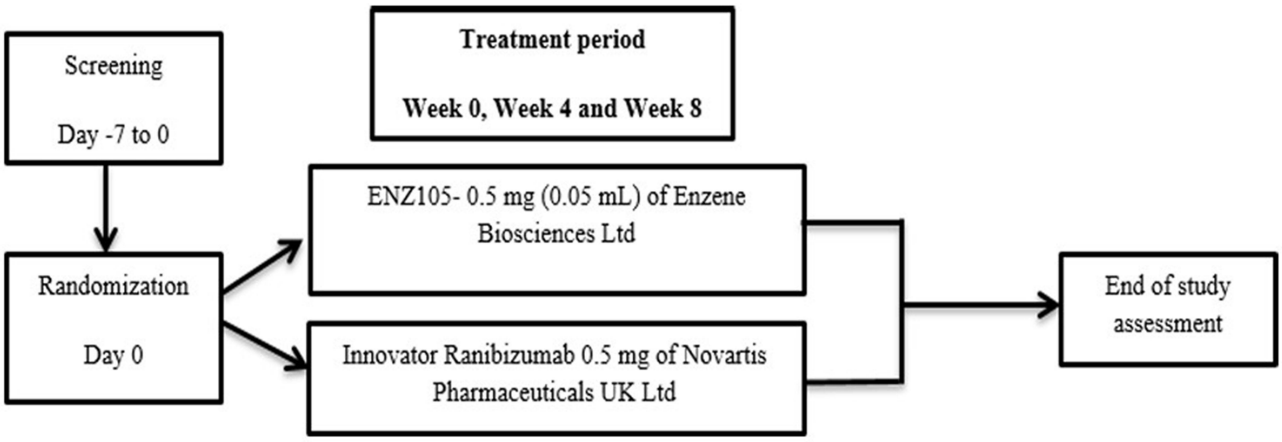

Figure 1 Study Protocol. Flowchart of the study protocol outlining screening, randomization, treatment period, and end-of-study assessment. Patients received either OPTIMAB® (ENZ105) (0.5 mg) or Innovator Ranibizumab (0.5 mg) at weeks 0, 4, and 8. End-of-study assessment was conducted at week 12 or at early discontinuation.

Outcome Measurements

The primary efficacy endpoint included the proportion of patients who lost < 15 letters (approximately three lines) in BCVA from baseline at the end of 12 weeks. The secondary efficacy endpoints included mean change in BCVA in the study eye from baseline to end of 12 weeks, change in CSFT assessed by Optical Coherence Tomography (OCT) at week 12, and proportion of patients gaining ≥ 15 letters in visual acuity at end of 12 weeks compared to baseline. Safety involved monitoring for treatment-emergent adverse events (TEAE) and serious adverse events (SAE) and was evaluated based on complete physical examination (vitals and systemic), ophthalmic examination, 12-lead ECG, and assessment of laboratory tests (hematology, biochemistry, serology, urinalysis, urine pregnancy test) throughout the study duration. Anti-ranibizumab antibody was measured by ELISA method for immunogenicity. Adverse events were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Analysis of Data Set

Both per protocol (PP) and intention-to-treat (ITT) data sets were analysed in the study. The results of ITT and PP population were similar; PP results have been described in the manuscript.

Sample Size and Statistical Analysis

The study assumed a 95% probability of observing a loss of <15 letters in BCVA (%) at week 12, with a statistical power of 90% to detect non-inferiority between OPTIMAB® and innovator ranibizumab. This assumption was made considering a non-inferiority margin of 20% and a one-sided confidence interval of 5%. To account for a drop-out rate of 10%, a total of 152 patients were required to be randomized, with 114 patients in the OPTIMAB® group and 38 patients in the Innovator treatment group, in order to achieve the required sample size of 136 patients. Continuous data are presented as mean ± standard deviation (SD) while categorical variables are presented as n (%). Unpaired *t*-test has been used to compare the two groups for continuous variables and Fischer's Exact test for continuous variable. P<0.05 was considered significant.

Results

A total of 152 patients of nAMD fulfilling the study selection criteria were randomized in the study at 19 sites across India in a 3:1 ratio to receive either OPTIMAB® (Test Group; n = 114) or innovator ranibizumab (Innovator Group, n = 38). Of the152 patients, 141 (92.8%) patients [106 (93.0%) in OPTIMAB® group and 35 (92.1%) in innovator group] completed the study and these comprised the PP population. The patient disposition is shown in Figure 2. Baseline and demographic characteristics were comparable between the test and innovator groups. Of the randomized patients, 57.9% were males and 42.1% were females. Mean age of patients in the OPTIMAB® group was 65.8 ± 9.04 years, while in the Innovator ranibizumab group was 68.8 ± 10.10 years. Other baseline characteristics of patients randomized in the study are shown in Table 1.

Efficacy Assessment

In the PP population, proportion of patients who lost less than 15 letters in BCVA at week 12 was comparable between OPTIMAB® (100%[n=106];90% CI:97.21, 100) and innovator ranibizumab groups (100%[n=35];90% CI: 91.80, 100) at Week 12, thereby establishing non-inferiority of OPTIMAB® compared to innovator. The actual and change in BCVA from baseline to week 12 in the PP Population has been depicted in Table 2.

The BCVA in the study eye improved significantly from 42.5± 11.42 letters at baseline to 54.3 ± 13.15 letters at week 12 in the OPTIMAB® group (P<0.001) and from 46.5± 12.01 letters at baseline to 59.4 ± 13.46 letters at week 12 in the innovator ranibizumab group (P<0.001). There was no significant difference in the change in BCVA at week 12 as compared to baseline in the two groups (OPTIMAB® – 11.8 ± 9.18 vs innovator ranibizumab – 12.9 ±10.29 letters; P = 0.5509).

The CSFT in the study eye significantly improved from baseline to week 12 in both the groups. In the OPTIMAB® group, it improved from 323.2± 125.82µm at baseline to 238.4 ± 84.50µm at week 12 (P<0.001); and, from 318.8± 94.51µm at

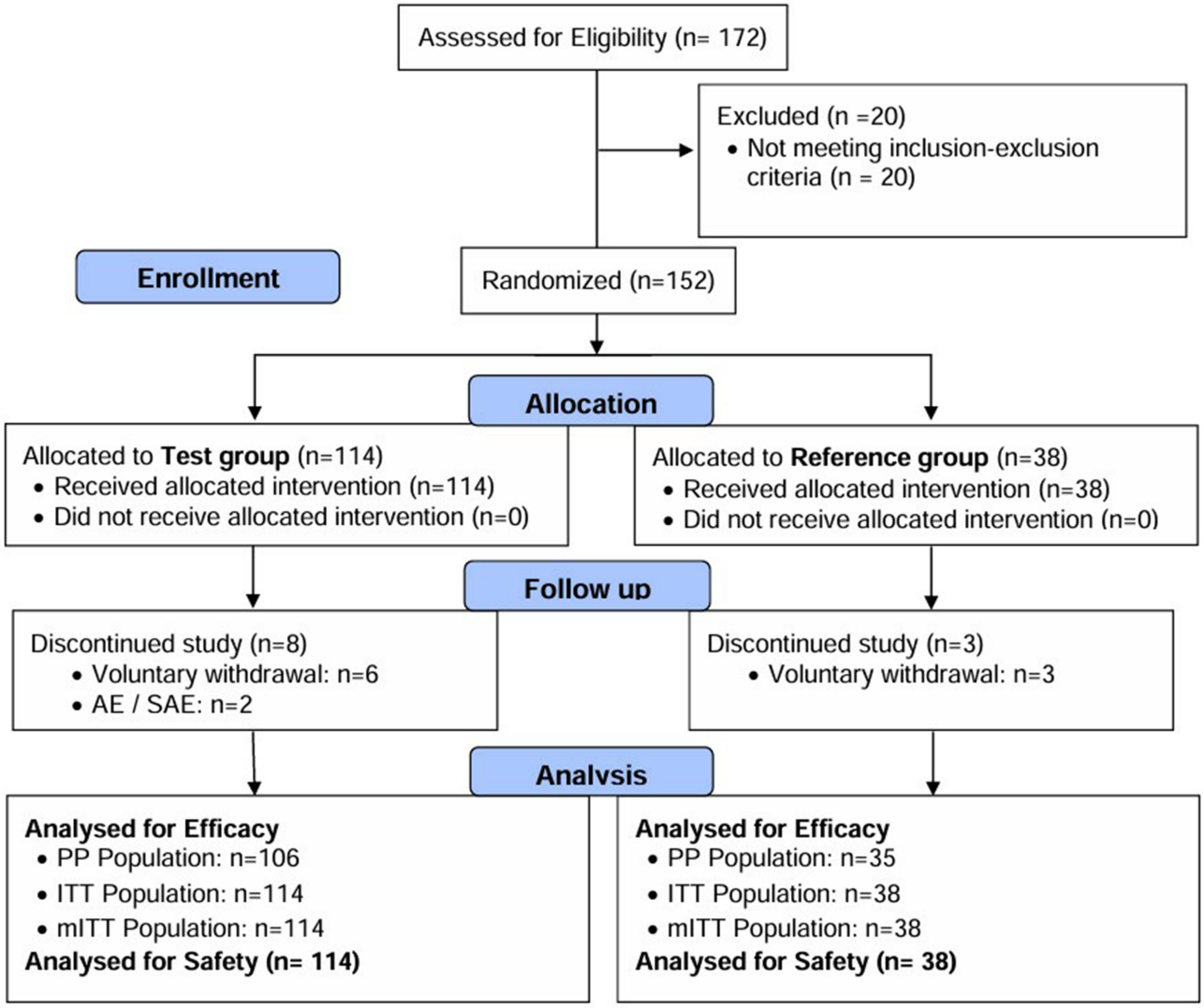

Figure 2 Flow of Subjects in the study. A total of 172 patients were assessed for eligibility, with 20 excluded due to not meeting inclusion-exclusion criteria. The remaining 152 patients were randomized, with 114 allocated to the test group and 38 to the reference group; all patients received the allocated intervention. During follow-up, 8 patients in the test group discontinued (6 due to voluntary withdrawal, 2 due to AEs/SAEs), while 3 patients in the reference group discontinued (all due to voluntary withdrawal). Efficacy was analyzed in PP, ITT, and mITT populations, and safety was analyzed for all patients in each group.

baseline to 245.7 ± 96.01 μm at week 12 in the innovator ranibizumab group (P<0.001). There was no significant difference in the change in CSFT from baseline to week 12 in both the groups (OPTIMAB®,−76.6 ± 89.03;innovatorranibizumab,−73.1 ± 92.23 μm; P = 0.8422). The change in CSFT at various time points in the study in the two groups is shown in Figure 3. The percentage of patients who gained ≥ 15 letters inBCVA in the study eye were 32.18% (n = 34) vs 25.74% (n = 9), respectively, in the OPTIMAB® vs innovator groups (Difference 6.36%; 90% CI: −8.40%, 21.12%; P = 0.4785).

Immunogenicity

None of the patients expressed anti-ranibizumab antibodies in OPTIMAB® and innovator ranibizumab groups, and neither any patient reported an increase in severity of intraocular inflammation or any clinical sign attributable to intraocular antibody formation.

Safety Assessment

In the safety population (N = 152), 20 (13.2%) patients reported at least one TEAE, with a total of 23 TEAEs reported collectively. Among the 20 patients reporting TEAEs, 17 patients (14.9%) in the OPTIMAB® group experienced 19

Table 1 Baseline and Demographics Characteristics of Study Population (N=152)

Parameters		OPTIMAB® (N=114)	Innovator Ranibizumab (N=38)	Overall (N=152)
Age (years)		65.8 ± 9.04	68.8 ±10.10	66.6 ±9.37
Gender	Male	66 (57.9%)	22 (57.9%)	88 (57.9%)
	Female	48 (42.1%)	16 (42.1%)	64 (42.1%)
Ethnicity	Asian	114 (100.0%)	38 (100.0%)	152 (100.0%)
	Non-Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)		160.7 ± 8.39	160.3 ± 7.24	160.6 ± 8.10
Weight (kgs)		63.3 ± 10.22	63.4 ± 9.41	63.3 ± 9.99

Notes: Data presented as mean ± SD for continuous variables and n(%) for categorical variables.

Table 2 Summary of Actual and Change in BCVA from Baseline to Week 12 (PP Population; N=141)

Visit	Actual Measurements			Change from Baseline		
	OPTIMAB® (N=106)	Innovator Ranibizumab (N=35)	P value*	OPTIMAB® (N=106)	Innovator Ranibizumab (N=35)	P value*
Visit2 (Baseline)	42.5 ± 11.42	46.5 ± 11.65	0.0815	NA	NA	NA
Visit3 (Week 1)	44.4 ± 12.08	49.4 ± 12.42	0.0367	1.9 ± 3.88^	3.0 ± 3.94^	0.1702
Visit4 (Week 4)	47.5 ± 12.30	52.4 ± 12.15	0.0427	5.0 ± 6.37^	5.9 ± 4.50^	0.3440
Visit5 (Week 8)	51.7 ± 12.24	55.8 ± 11.55	0.0823	9.2 ± 7.69^	9.3 ± 7.11^	0.9118
Visit6 (Week 12)	54.3 ± 13.15	59.4 ± 13.46	0.0517	11.8 ± 9.18^	12.9 ± 10.29^	0.5509

Notes: Data presented as mean ± SD. * P value calculated to test the difference between treatment arm using two sample *t*-test ^P < 0.001 (calculated to test the change from baseline within treatment arm using paired *t*-test).

TEAEs, while 3 patients (7.9%) in the innovator ranibizumab group reported 4 TEAEs. The majority of TEAEs were ocular in nature, with vitritis being the most frequently reported event, occurring in 8 patients (7.0%) in the OPTIMAB® group and 3 patients (7.9%) in the innovator group. Other ocular events, including retinal haemorrhage, retinal vasculitis, and uveitis, were observed in 2 patients (1.8%) in the OPTIMAB® group. Additionally, leukopenia was reported in 1 patient (2.6%) in the innovator ranibizumab group.

All the non-serious TEAEs in both the groups were mild to moderate in severity; and, one SAE of lower limb fracture, unrelated to the study treatment, was reported in 1 patient (0.7%) in the OPTIMAB group. All the AEs and SAE resolved during the study period. None of the patients in either treatment group exhibited any clinically significant abnormalities in biochemistry, urinalysis, vital signs, or physical examination parameters throughout the study duration. The overall summary of TEAE is shown in Table 3.

Discussion

This double-blind, randomized, multicenter, phase III study established non-inferiority between Enzene Biosciences'ranibizumab biosimilar OPTIMAB® and innovator ranibizumab (Lucentis) in the treatment of patients with nAMD. The primary endpoint was met and there was no clinically and statistically significant difference in

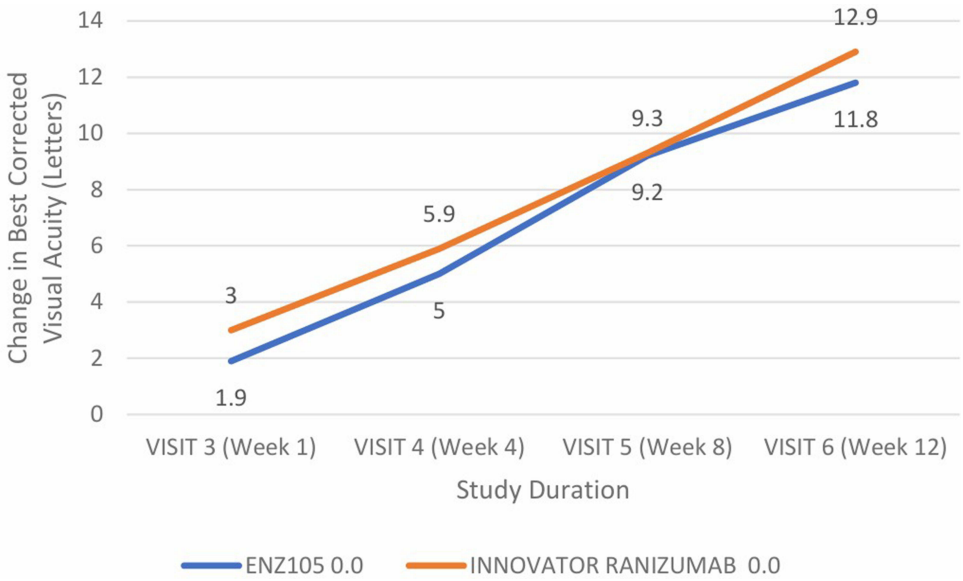

Figure 3 Change in BCVA at various time points in the study in the two groups. Mean change in Best Corrected Visual Acuity (BCVA) from baseline across visits at weeks 1, 4, 8, and 12 for patients treated with OPTIMAB® (ENZ105) and Innovator Ranibizumab.

proportion of patients who lost less than 15 letters in BCVA between OPTIMAB® and innovator ranibizumab when given over 12-week study duration (three dose regimen over 12 weeks). Moreover, the study also showed that the biosimilar ranibizumab ie, OPTIMAB® is similar to the innovator ranibizumab in terms of secondary endpoints like: proportion of

Table 3 Overall Summary of Adverse Events – Safety Population (N=152)

	Treatment Groups		
Parameter, category n (%) E [1]	**OPTIMAB® (N=114)**	**Innovator Ranibizumab (N=38)**	**Overall (N=152)**
Patients who reported at least one AE	17 (14.9%) [19]	3 (7.9%) [4]	20 (13.2%) [23]
Serious Adverse Event			
Yes	1 (0.9%) [1]	0 (0.0%) [0]	1 (0.7%) [1]
No	17 (14.9%) [18]	3 (7.9%) [4]	20 (13.2%) [22]
If yes,			
Persistent or significant disability /incapacity	1 (0.9%) [1]	0 (0.0%) [0]	1 (0.7%) [1]
Severity			
Mild	12 (10.5%) [12]	2 (5.3%) [3]	14 (9.2%) [15]
Moderate	6 (5.3%) [6]	1 (2.6%) [1]	7 (4.6%) [7]
Severe	1 (0.9%) [1]	0 (0.0%) [0]	1 (0.7%) [1]
Causality			
Related	10 (8.8%) [10]	2 (5.3%) [3]	12 (7.9%) [13]
Not related	8 (7.0%) [9]	1 (2.6%) [1]	9 (5.9%) [10]

(*Continued*)

Table 3 (Continued).

	Treatment Groups		
Parameter, category n (%) E [1]	**OPTIMAB® (N=114)**	**Innovator Ranibizumab (N=38)**	**Overall (N=152)**
Outcome			
Resolved	17 (14.9%) [19]	3 (7.9%) [4]	20 (13.2%) [23]
Action Taken			
No action taken	12 (10.5%) [13]	3 (7.9%) [4]	15 (9.9%) [17]
Dose delayed	3 (2.6%) [3]	0 (0.0%) [0]	3 (2.0%) [3]
Not applicable	2 (1.8%) [2]	0 (0.0%) [0]	2 (1.3%) [2]
Drug withdrawn	1 (0.9%) [1]	0 (0.0%) [0]	1 (0.7%) [1]

Notes: [1] The Percentage was calculated by taking the count of the respective column header as the denominator. General Note: • Zero frequencies were presented by "0" and percentage as "0 (0.0%)" and Event as "[0]" • Adverse events were represented as: patient count (Percentage of patients) [Event Count]. • Adverse events were coded using MedDRA version 25.0 or later. A patient might have reported more than one adverse event. Percentages are based on the total number of safety set patients in each treatment group.

patients gaining ≥ 15 letters on visual acuity, improvement in best corrected visual acuity, and reduction in CSFT over 12 weeks study duration (no statistically significant difference was observed in any of the endpoints between the two groups). The BCVA significantly improved by 1.9 ± 3.88, 5.0 ± 6.37, 9.2 ± 7.69, and 11.8 ± 9.18 letters at end of week 1, 4, 8, and 12 respectively as compared to baseline in the OPTIMAB® group, while the corresponding improvement in the innovator ranibizumab group was 3.0 ± 2.94, 5.9 ± 4.50, 9.3 ± 7.11, and 12.9 ± 10.29, respectively. There was no significant difference between the two groups at any of the 4 time points (P>0.05). A total of 34 (32.18%) subjects in OPTIMAB® group and 9 (25.74%) subjects in innovator ranibizumab group gained ≥15 letters in BCVA at visit 6 (week 12) from baseline with the difference of 6.36 (90% CI: −8.40, 21.12) which were comparable with better outcomes in OPTIMAB® group. The CSFT changed by −52.1 ± 82.80, −74.6 ± 80.37, and −76.6 ± 89.03 at end of week 4, 8, and 12, respectively, as compared to baseline in the OPTIMAB® group; while, it changed by −57.6 ±66.14, − 69.0 ±74.04, and −73.1 ±92.23 at similar time points in the innovator ranibizumab group (Figure 4).

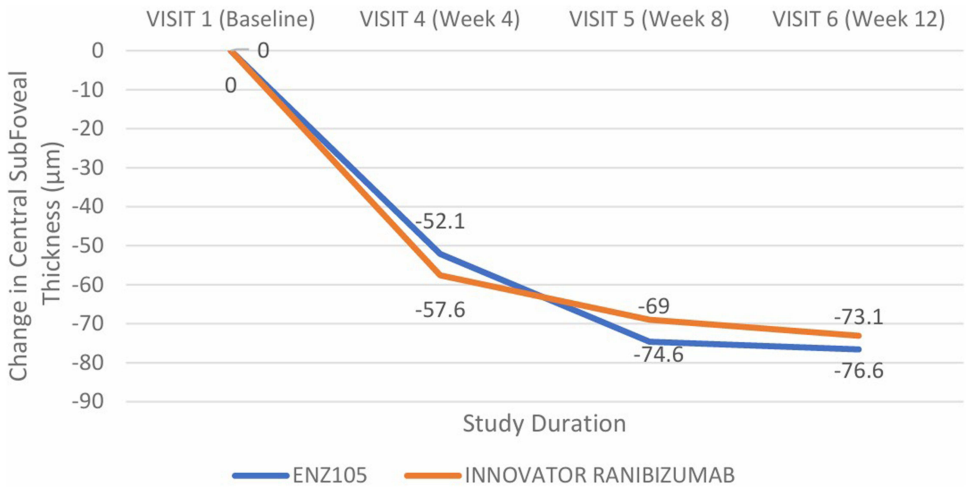

Figure 4 CSFT at various time points in the study in the two groups. Mean change in Central Subfoveal Thickness (CSFT) from baseline across visits at weeks 4, 8, and 12 for patients treated with OPTIMAB® (ENZ105) and Innovator Ranibizumab.

Further, both OPTIMAB® and innovator ranibizumab were well tolerated by the patients and comparable in terms of safety and immunogenicity. The most common ocular TEAE was vitritis in both the groups, with no significant difference in the number of patients reporting TEAEs in both the study groups. Other ocular events, such as retinal haemorrhage, retinal vasculitis, and uveitis, were infrequent and reported only in the OPTIMAB® group, each with a low incidence. Leukopenia, on the other hand, was observed in one patient from the innovator ranibizumab group. Most of the events were mild and unrelated to the study drug. Further, no anti-ranibizumab antibodies were detected in either group during the study. Overall, OPTIMAB® was found to be similar to the innovator ranibizumab in terms of both efficacy, safety, and immunogenicity. The availability of biosimilar ranibizumab will be of paramount importance as it will expand patient access to effective treatments for sight-threatening conditions, such as AMD, while simultaneously addressing cost and resource allocation challenges in the healthcare systems.

The current Phase 3 clinical study used a randomization ratio of 3:1 and followed up the subjects for 12 weeks. The 3:1 design increased the exposure to the biosimilar test product (OPTIMAB®), thereby generating more safety data prior to its regulatory approval. Further, considering the expectation that biosimilars should closely resemble the reference drug at their peak effectiveness, a study period of three months is justified; and, that could also function as a surrogate for assessing their efficacy similarity over a more extended timeframe. Although the 12-week study period and the 3:1 randomization ratio were appropriate for initial assessments, these factors present certain limitations. The short duration restricts the ability to fully assess the long-term safety and efficacy of both products, and the 3:1 randomization ratio, while increasing biosimilar exposure, may introduce potential biases that could affect the generalizability of the findings. Therefore, longer-term studies with a more balanced design are recommended to confirm these results and provide more comprehensive data on long-term safety and efficacy outcomes.

The management guidelines for nAMD endorsed by the Royal College of Ophthalmologists emphasize the utilization of both visual function and morphological indicators to inform the diagnosis and treatment of this condition.[22,23] Additionally, guidance and consensus documents authored by Mitchell et al[24] and Pauliekhoff et al[25] have been published. Visual function alterations are evaluated through the measurement of visual acuity and accurate assessment of macular morphology is achieved through the use of optical coherence tomography, specifically the spectral domain or more advanced variants. In accordance with these guidelines, our study was designed to evaluate visual function through the measurement of VA and to assess morphological characteristics using OCT. The evaluation of VA was performed utilizing ETDRS charts, a methodology endorsed by multiple research investigations.[26–28]

Ranibizumab, a humanized monoclonal antibody fragment, was the pioneer among anti-VEGF agents in demonstrating improvements in VA for patients afflicted with nAMD.[29–31] Regulatory approvals for ranibizumab's utilization were based on data derived from the MARINA and ANCHOR studies. These data indicated mean VA gains ranging from 7 to 11 letters over a span of 12 months when administered on a monthly basis.[27,29–33] Moreover, during this timeframe, as many as 40% of patients experienced an enhancement of more than 15 letters in VA, with only a small number demonstrating a decline in vision.[27] The ANCHOR study demonstrated that 96.4% of patients receiving 0.5 mg of Lucentis® lost less than 15 letters from their baseline visual acuity, while the MARINA study showcased an enhancement in BCVA score in 94.6% of patients.[28] In the current study, 100% of patients administered the innovative ranibizumab and 100% receiving OPTIMAB® lost <15 letters, aligning closely with the findings from the pivotal clinical studies on innovator ranibizumab.[27,28] The concordance between the results of this study and historical ranibizumab data, coupled with the fulfillment of primary and secondary efficacy endpoints, furnishes compelling evidence of the biosimilarity of OPTIMAB® in the context of nAMD.

Given that ranibizumab's mechanism of action remains consistent across all its approved indications, the extrapolation of study outcomes to other approved applications of ranibizumab, such as macular edema, diabetic retinopathy, and myopic choroidal neovascularization, can be considered in accordance with the regulatory guidelines for "similar biologics" set forth by the Central Drugs Standard Control Organization (CDSCO).[34]

The safety profile of OPTIMAB® as exhibited in this study is also in line with previously published literature on innovator and other biosimilar ranibizumab. No new safety concerns were identified during the study period. No significant variation in the occurrence of ocular TEAEs was observed. While there was a minor numerical difference, it lacked statistical or clinical significance. To ascertain whether these slight numerical differences were coincidental or genuinely reflected a minor difference in the incidence of ocular TEAEs, a considerably larger number of participants

would be required. The common (> 10%) ocular AEs reported for ranibizumab are conjunctival hemorrhage, eye pain, vitreous detachment or floaters, increase in intraocular pressure, intraocular inflammation, visual disturbance, eye irritation, increased lacrimation, blepharitis, dry eye, ocular hyperemia, and eye pruritus.[27] Non-ocular AEs associated with systemic VEGF inhibition, such as arterial thromboembolic events, hypertension, proteinuria, and non-ocular hemorrhage are of particular interest, but none of these was reported during the study period.[35–38]

The outcomes of this study, encompassing efficacy, safety and immunogenicity, provide robust and compelling evidence supporting the overall biosimilarity of OPTIMAB® to the innovator ranibizumab. These findings suggest that OPTIMAB® could be a valuable option in real-world clinical practice, offering a cost-effective alternative while maintaining similar therapeutic benefits, thereby improving access to effective treatments for patients with nAMD.

Conclusion

The investigational biosimilar ranibizumab OPTIMAB® exhibited comparable efficacy, safety, and immunogenicity to innovator ranibizumab in patients with nAMD, establishing its potential utilization as a biosimilar product for ranibizumab. By offering a cost-effective and sustainable alternative to innovator anti-VEGF treatments, OPTIMAB® has the potential to improve access to treatment for a broader population of patients with nAMD while reducing the overall financial burden on healthcare systems.

Data Sharing Statement

Individual deidentified participant data, along with the study protocol, statistical analysis plan, and informed consent form, will be available upon request to the corresponding author at ajitkumar.gondane@alkem.com.

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Disclosure

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