

# A prospective, randomized, parallel group, double blind, multicenter study to compare the efficacy, safety and immunogenicity of Lupin's Ranibizumab with Lucentis® in patients with neovascular age-related macular degeneration

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**Purpose:** The present study compares the efficacy, safety, and immunogenicity of Lupin's biosimilar ranibizumab with that of Lucentis® in patients with neovascular age-related macular degeneration.

**Methods:** This prospective, double-blind, multi-centric phase-III study was conducted across 19 centers in India. A total of 202 patients with neovascular age-related macular degeneration were randomized (1:1) to receive either Lupin's biosimilar ranibizumab or Lucentis®, 0.5 mg, as an intravitreal injection once every month for 3 months. The primary efficacy endpoint was the proportion of patients who lost fewer than 15 letters from baseline in best-corrected visual acuity. The safety profile included assessment of adverse events, ophthalmic examination, physical and systemic examination, and vital parameters. The immunogenicity assessment was based on evaluation of anti-drug antibodies. **Results:** Overall, 174 patients (87 [86.14%] in each group) completed the study. The demographics and baseline characteristics were comparable between the treatment groups. The proportion of patients losing fewer than 15 letters from baseline best corrected visual acuity score in the study eye was comparable between two groups. The difference between Lupin's ranibizumab and Lucentis® for the proportion of patients who lost fewer than 15 letters was within the predefined equivalence margin (intention-to-treat population: 1.0%; 95% confidence interval [CI], -3.3% to 5.4% and per protocol population: 1.2%; 95% CI, -3.2% to 6.4%). The incidence of treatment-emergent adverse events was comparable, and 11 (10.89%) patients in Lupin's ranibizumab and 19 (18.81%) patients in Lucentis® group had at least one treatment-emergent adverse event. The immunogenicity incidence as assessed by proportion of patients with positive anti-drug antibodies was numerically lower in Lupin's ranibizumab (4.95%) than Lucentis® (12.87%). **Conclusion:** Lupin's biosimilar ranibizumab demonstrated therapeutic equivalence, desirable safety, and favorable immunogenicity profile compared to Lucentis®.

**Key words:** Biosimilar, immunogenicity, Lucentis®, neovascular age-related macular degeneration (n-AMD), ranibizumab

Age-related macular degeneration (AMD) is a chronic disease that causes vision impairment in people aged 50 years or more.<sup>[1]</sup> It accounts for one-third of vision impairment cases in developed countries. The World Health Organization (WHO) reports that, globally, AMD ranks third as the cause of blindness and contributes to 8.7% of the overall cases of blindness.<sup>[2,3]</sup> Though the prevalence of AMD is estimated to escalate to 17.8 million by 2050, literature also indicates a fall in blindness due to AMD during the past three decades. This can be attributed to the extensive research in the anti-VEGF (vascular endothelial growth factor) therapy.<sup>[1,3]</sup> VEGF-A is the most

prominent cytokine playing a vital role in angiogenesis through endothelial cell proliferation and migration, causing injury and inflammation in choroidal neovascularization. The introduction of anti-VEGF-A inhibitors was a game changer in the management of AMD;<sup>[4]</sup> neovascular (wet) AMD (nAMD or wAMD), one of the most aggressive forms of AMD. Ranibizumab, a recombinant, humanized monoclonal antibody fragment that binds to all active isoforms of VEGF-A and inhibits its action<sup>[5]</sup> was approved for management of nAMD by the US Food and Drug Administration (FDA) in 2006 and the European Medicines Agency (EMA) in 2007.<sup>[6,7]</sup> Ranibizumab was studied for its efficacy, safety, and tolerability (phase I-IV clinical trials) in the management of nAMD; however, its high cost limits its utilization.<sup>[5]</sup>

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Alternative to the innovator product, Lupin has developed an investigational biosimilar ranibizumab. Biosimilars are considered to be comparable with an approved reference product in terms of safety, efficacy, and immunogenicity. Previously published clinical studies demonstrated that biosimilars can offer multiple, yet affordable treatment options for patients and physicians, thereby improving access to care for a wider population.<sup>[8]</sup> Further, clinical studies comparing the safety and efficacy profiles of biosimilars with the reference products can improve the utilization of biosimilars in an effective manner.<sup>[9]</sup> Based on this background and the favorable safety profile of ranibizumab presented in its preclinical program, this phase-III randomized clinical study was designed to compare the efficacy, safety, and immunogenicity of a biosimilar, Lupin's ranibizumab with that of the reference product, Lucentis® in patients with neovascular AMD.

## Methods

### Study design

This was a prospective, randomized, comparative, parallel group, double-blinded, multi-centric phase-III therapeutic equivalence study conducted across 19 centers in India from June 2019 to October 2020 (CTRI/2019/03/018322). The study protocol was approved by the institutional review boards (IRB) and the study was conducted in accordance with the major ethical principles specified in the Declaration of Helsinki and good clinical practice (GCP) guidelines. Written informed consent was obtained from each subject before enrolment in the study.

### Randomization and intervention

The study comprised two phases, that is, screening phase of 14 days and treatment and assessment phase of 3 months. After initial screening, eligible patients were randomized in 1:1 ratio, to receive either Lupin's ranibizumab or Lucentis® as an intravitreal injection using the randomization list produced by interactive web recognition system (IWRS). This randomization list was not accessible to the investigators or participants involved in the study. The subjects were then followed up for administration of injection once every month for 3 months. The dosage of Lucentis® or Lupin's ranibizumab was 0.5 mg. In total, three injections were administered to each patient.

### Study population

Subjects of either gender ≥50 years with neovascular AMD; primary or recurrent active choroidal neovascularization (CNV) lesions in any one of the eyes and with best corrected visual acuity (BCVA) in the study eye between 20/40 and 20/320 (Snellen equivalent) using early treatment diabetic retinopathy study (ETDRS) testing, were eligible for the study. Patients with a history of known allergy to fluorescein dye or having coexisting CNV lesions secondary to AMD in the non-study eye that required treatment were excluded from the study. Patients previously treated with intravenous bevacizumab (Avastin®), or intravitreal ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea®), or pegaptanib (Macugen®) in either of the eyes were also excluded. Patients with seropositivity for hepatitis B, hepatitis C, human immunodeficiency virus (HIV), serious uncontrolled concomitant disease, or any other immunodeficiency disease were excluded from the study.

### Outcome measures

The primary efficacy endpoint included proportion of patients who lost fewer than 15 letters (approximately three lines) from baseline at the end of 3 months. The secondary efficacy endpoint included the mean change in BCVA in study eye from baseline at the end of 3 months.

The safety outcome measures included assessment of adverse events (AEs) (as per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.03), ophthalmic examination, physical and systemic examination, vital signs (blood pressure, pulse rate, respiratory rate and body temperature), 12-lead electrocardiogram (ECG), laboratory parameters (hematology, biochemistry, and urinalysis) and systemic VEGF inhibition.

The safety endpoints also involved immunogenicity outcome measure and included the proportion of patients with anti-drug antibodies (ADA).

### Analysis of data sets

This study was conducted to evaluate the therapeutic equivalence of Lupin's ranibizumab with Lucentis®. Intention-to-treat (ITT) population comprised all the randomized patients (RND) enrolled in the study. Per protocol (PP) population were patients who were administered all the doses and successfully completed the follow-up of 3 months without any protocol deviation. Safety population (SAF) received at least one dose of study medication and provided post-baseline safety variable data. Immunogenicity population (IMP) received at least

**Table 1: Demographics and baseline characteristics of subjects**

Parameters	Lupin's ranibizumab group (n=101)	Lucentis® group (n=101)
Gender (n* [%])†		
Male	64 (63.37)	59 (58.42)
Female	37 (36.63)	42 (41.58)
Age (years) (Mean [SD])‡	67.2 (10.29)	67.2 (10.52)
Height (cm) (Mean [SD])	161.05 (9.37)	160.04 (9.22)
Weight (Kg) (Mean [SD])	63.113 (9)	61.532 (10.48)
Race (n [%])		
Asian	101 (100)	101 (100)
Others	0	0
Ethnicity (n [%])		
Hispanic or Latino	0	0
Not Hispanic or Latino	101 (100)	101 (100)
Not reported	0	0
Unknown	0	0
Study eye		
Left	56 (55.45)	47 (46.53)
Right eye	45 (44.55)	54 (53.47)
Fluorescein angiography performed?		
Yes	101 (100)	101 (100)
No	0	0

\*n, number of patients; †%, percentage of patients; ‡SD, standard deviation

one dose of study medication and provided post-baseline immunogenicity variable data.

### Statistical analysis

All statistical tests were performed two-sided using the SAS® System version 9.1.3 or higher and evaluated at a 5% level of significance.

**Sample size:** Based on the equivalence margin of 8.5%, an assumed 97% response rate of ranibizumab treatment and 15% dropout rate of randomized subjects from the literature, a sample size of 170 (85 per treatment group) was calculated to attain a 5% significance level and 80% power to demonstrate bio similarity.

### Statistical analysis plan

Descriptive statistics were performed to summarize baseline demographics and safety data.

**Efficacy analysis:** All efficacy parameters were analyzed in both ITT and PP population. PP was primary efficacy analysis population for this study. Equivalence based on 95% (two-sided) confidence interval (CI) for BCVA from baseline to the end of 3 months was calculated. The mean change in BCVA score was compared between two treatment arms using the Analysis of covariance (ANCOVA) model.

**Safety analysis:** Safety data was analyzed in the SAF population. All AEs that occurred after the time of informed consent until the final visit (Day 90) were reported. All AEs were coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or higher.

**Immunogenicity analysis:** Immunogenicity testing was performed using a validated and highly sensitive electrochemiluminescence immunoassay, which is the reference standard for testing in clinical trials.<sup>[10]</sup> All patients provided samples for immunogenicity assessment, which was performed at day 1, day 30, and day 60. The data were analyzed

in IMP population and the proportion of ADA patients was calculated on the basis of the number of patients found positive for ADA in respective treatment groups.

## Results

### Disposition of participants

A total of 256 patients were screened; of these, 202 patients (54 participants did not fulfil the eligibility criteria) were randomized to receive at least one dose of the study drug and were included in ITT, safety, and immunogenicity population. Among the randomized patients, 92 (91.09%) patients in Lupin's ranibizumab and 91 patients (90.10%) in the Lucentis® group received all three injections. Overall, 174 patients (87 of 101 in each treatment group [86.14%]) successfully completed the study of 3 months, and 28 patients (14 in each group [13.86%]) were lost to follow-up [Fig. 1].

### Demographics and baseline characteristics of participants

The demographics and baseline characteristics were comparable between the treatment groups [Table 1]. Most of the patients were in the age group of 65 to 70 years (mean age = 67.02 ± 10.52) years. The majority of the patients were males in both the groups and of Asian origin. The ratio of left and right eye of patients studied in Lupin's ranibizumab and Lucentis® groups was 56:45 and 47:54, respectively. Baseline BCVA score was analyzed in 199 and 172 patients from ITT and PP analysis set, respectively. No patient reported known allergy to fluorescein dye.

### Efficacy

At the end of 3 months, the visual acuity of the study eye improved in both ITT and PP populations as measured by the primary and secondary efficacy end points.

The proportion of patients losing fewer than 15 letters on the ETDRS chart, on day 90 from baseline BCVA score in the study eye was comparable between Lupin's ranibizumab and

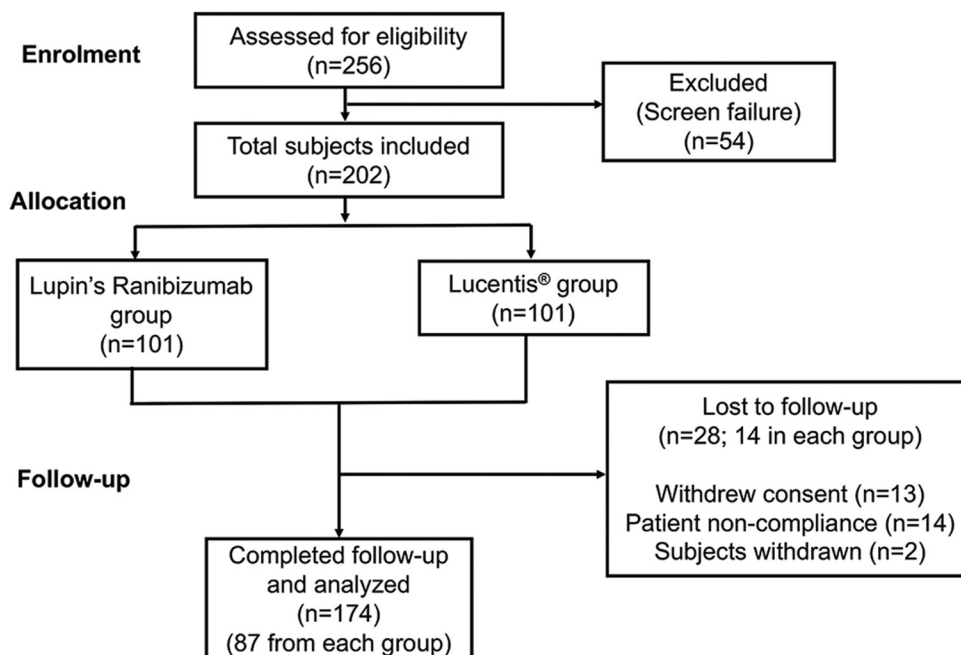


Figure 1: Study flow chart

**Table 2: Analysis of primary and secondary efficacy end point**

Outcome (Day 90)	Lupin's ranibizumab group (%) <sup>*</sup>	Lucentis® group (%)	Difference (95% CI) <sup>†</sup>	P
Proportion of patients losing fewer than 15 letters				
ITT <sup>‡</sup>	99.9	98.9	1.0 (-3.3-5.4)	
PP <sup>§</sup>	100	98.82	1.2 (-3.2-6.4)	
Mean change in BCVA <sup>¶</sup> from baseline				
ITT	8.9	7.6	1.33 (-1.39-4.04)	0.3380
PP	9.3	7.7	1.46 (-1.38-4.30)	0.3123

\*%, percentage of patients; †CI, confidence interval; ‡ITT, Intention-to-treat population; §PP, per-protocol population; ¶BCVA, best corrected visual acuity

**Table 3: Evaluation of adverse events**

Adverse Events; n* (%) <sup>†</sup>	Lupin's ranibizumab group (n=101)	Lucentis® group (n=101)
TEAEs <sup>‡</sup>	18	31
Ocular TEAEs	8	15
Non-ocular TEAEs	10	16
Non-serious TEAEs	17	30
Treatment-related AE	0	1
TESAEs <sup>§</sup>	1	1
Treatment-related SAEs	0	0
Patients having at least one Ocular TEAE in study eye	2 (1.98)	3 (2.97)
Patients having at least one ocular TEAE in the fellow eye	4 (3.96)	5 (4.95)
Patients having at least one non-ocular TEAE	6 (5.94)	14 (13.86)
Myocardial infarction	1 (0.99)	0
Gastrointestinal disorders	1 (0.99)	2 (1.98)
General disorders and administration site conditions	3 (2.97)	1 (0.99)
Urinary tract infection	1 (0.99)	3 (2.97)
Injury and procedural complications	0	2 (1.98)
Musculoskeletal and connective tissue disorders	0	4 (3.96)
Nervous system disorders	1 (0.99)	2 (1.98)
Respiratory, thoracic and mediastinal disorders	1 (0.99)	1 (0.99)
Skin and subcutaneous tissue disorders	1 (0.99)	0

\*n, number of patients; †%, percentage of patients; ‡TEAE, treatment emergent adverse events; §TESAE, treatment emergent serious adverse events. \*n, number of patients; †%, percentage of patients; ADA<sup>‡</sup>, anti-drug antibodies

**Table 4: Analysis of immunogenicity**

Immunogenicity; n* (%) <sup>†</sup>	Lupin's ranibizumab group (n=101)	Lucentis® group (n=101)
ADA <sup>‡</sup> Positive patients at any time point during the study	5 (4.95%)	13 (12.87%)
Pre-treatment ADA at Day 1	4 (3.96%)	8 (7.92%)
Treatment emergent ADA at any timepoint	1 (0.99%)	5 (4.95%)
Treatment emergent ADA at Day 61	0	1 (0.99%)
Treatment emergent ADA at Day 90	1 (0.99%)	5 (4.95%)

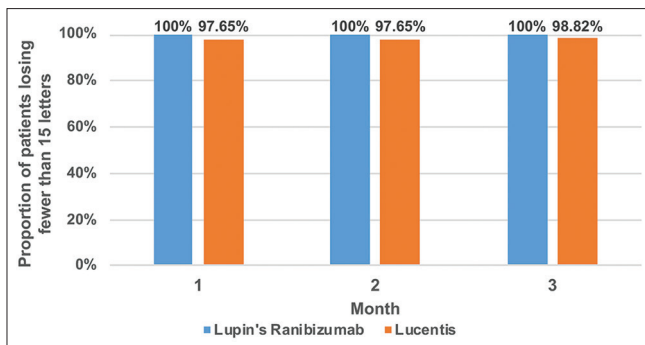
Lucentis® group [Fig. 2]. On day 90, the estimated treatment difference between Lupin's ranibizumab and Lucentis® group was well within the predefined equivalence margin of 8.5% (ITT: 1.0% [95% confidence interval [CI]: -3.3% to 5.4%] and PP: 1.2% [95% CI: -3.2% to 6.4%]) for the proportion of patients who lost fewer than 15 letters.

A consistent improvement was reported in the mean BCVA score at days 31, 61, and 90 as compared to the baseline score in both the treatment groups [Fig. 3]. The difference in least-square (LS) mean change in BCVA score from the baseline to day 90 were comparable between the treatment groups and

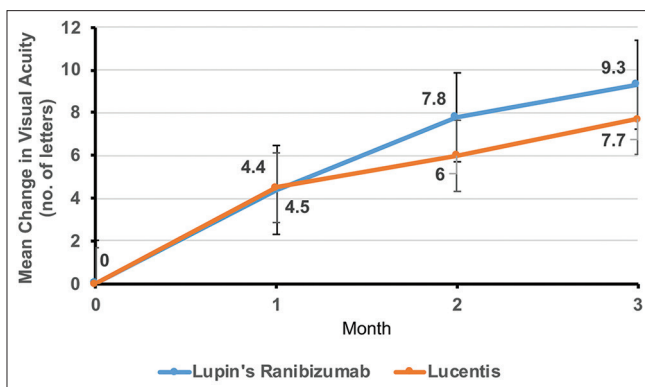
was found to be 1.33 (95% CI: -1.39 to 4.04;  $P = 0.33$ ) for ITT population and 1.46 (95% CI: -1.38 to 4.30;  $P = 0.31$ ) for PP population, which was non-significant [Table 2].

### Safety

The incidence of AEs in the study was 24.25% ( $n = 49/202$ ), of which 47 were non-serious treatment-emergent AEs (TEAEs) and two were serious TEAEs. The most common TEAEs included conjunctival hemorrhage, retinal tear and vitreous disorder, hyphema and vitreous hemorrhage. AE related to treatment during the study period was reported in only one patient who belonged to the Lucentis® group and neither of



**Figure 2:** Proportion of patients losing fewer than 15 letters on ETDRS chart



**Figure 3:** Mean ( $\pm$ SE) changes in Visual Acuity from baseline through 3 months

'the' treatment-emergent serious AEs (TESAEs) were associated with the study drug.

The incidence of ocular and non-ocular TEAEs was comparable between the study groups. [Lupin's ranibizumab group vs. Lucentis® group: Ocular: 5.94 vs. 7.92%, non-ocular: 5.94 vs. 13.86%]. Also, 2/101 (1.98%) patients from Lupin's ranibizumab group and 3/101 (2.97%) patients from Lucentis® group reported at least one ocular TEAE in the study eye. 3.96% of patients ( $n = 4/101$ ) from Lupin's ranibizumab group, and 4.95% of patients ( $n = 5/101$ ) from Lucentis® group reported minimum one ocular TEAE in the fellow eye. A total of 20 patients reported non-ocular TEAE such as gastrointestinal disorders ( $n = 3/202$  [1.4%]), urinary tract infections ( $n = 4/202$  [1.98%]), pyrexia, arthralgia, pain and headache ( $n = 2/202$  [0.99%]). Most of the TEAEs were mild in nature and considered by investigators as "not related" to the study drug [Table 3]. No patient discontinued from the study due to AEs. Also, no clinically meaningful trend was observed in laboratory parameters, physical examinations, and vital signs between both the treatment groups. Levels of systemic VEGF in both the groups did not significantly differ at the end of the study.

### Immunogenicity

Out of 18 (8.91%) anti-ranibizumab antibody-positive patients, 12 patients (5.94%) reported pre-treatment ADA and six patients (2.97%) developed treatment emergent ADA during the study (Lupin's ranibizumab group:  $n = 5/101$  [4.95%] and Lucentis® group:  $n = 13/101$  [12.87%]). The incidence

of treatment emergent ADA was comparable between the treatment groups at the end of 3 months. However, numerically lesser incidence of ADA was reported with Lupin's ranibizumab when compared to the Lucentis® group [Table 4].

### Discussion

This study met the primary and secondary efficacy end points, demonstrating equivalence in efficacy between Lupin's ranibizumab and Lucentis® when administered intravitreally every month for 3 months for the treatment of neovascular AMD (n-AMD). The proportion of patients who lost fewer than 15 letters from baseline BCVA score in study eye was comparable between both the groups and the treatment difference was well within the predefined equivalence margins of  $\pm 8.5\%$ . The BCVA score also showed similar gains over baseline at each visit in both treatment groups, which taken together with primary endpoint, indicates that similar to Lucentis®, Lupin's ranibizumab not only stops the progression of vision loss but also improves vision in nAMD. The reported AEs were consistent with ranibizumab's known safety profile with comparable ocular and non-ocular TEAEs between the treatment groups. Most of the TEAEs were not related to the drug and mild in nature. Similar safety and immunogenicity profiles were observed in Lupin's ranibizumab and Lucentis® groups.

The RCOphth (Royal College of Ophthalmologists') guidelines for the management of nAMD with anti-VEGF therapy recommend the use of visual function and morphological parameters for assessing the treatment response with anti-VEGF therapy. After the initiation of anti-VEGF therapy in n-AMD, it is recommended that patients are followed up at pre-determined intervals, and VA is the most important tool to monitor the response to therapy with reference to the visual function.<sup>[11]</sup> Pivotal studies such as ANCHOR, MARINA, and CATT,<sup>[12]</sup> along with real-world findings, suggest that baseline BCVA is the strongest predictor of visual outcomes. VA was also assessed using the ETDRS chart, the gold standard for assessment of vision in clinical studies for n-AMD, and the process has been standardized across all study centers. The functional and morphological parameters in n-AMD are not correlated,<sup>[12]</sup> and hence, the OCT-based biomarkers viz. central retinal thickness (CRT) and central subfield thickness (CST)<sup>[13]</sup> were not assessed to establish treatment response in our study. The efficacy of Lucentis® in AMD is well established in ANCHOR and MARINA trials.<sup>[14,15]</sup> The ANCHOR trial showed that 96.4% of patients receiving 0.5 mg Lucentis® lost fewer than 15 letters from baseline, whereas the MARINA trial demonstrated an improvement in BCVA score in 94.6% of patients. In present study, 98.9% of patients receiving 0.5 mg Lucentis® and 99% receiving Lupin's ranibizumab lost fewer than 15 letters, which is in concordance with the observations of the pivotal trials of Lucentis®.<sup>[14,15]</sup> The comparability of results obtained in this study with historic data on Lucentis in addition to the trial meeting its primary and secondary efficacy endpoints provides robust evidence of biosimilarity of Lupin's ranibizumab in nAMD. Because the mechanism of action of ranibizumab is similar across all its approved indications, extrapolation of results from this study to other approved indications of ranibizumab such as macular edema, diabetic retinopathy, and myopic choroidal neovascularization is possible as per the Central Drugs

Standard Control Organization (CDSCO) regulatory guidelines for “similar biologics.”<sup>[16]</sup>

It is well known that generic drugs and biosimilars are not the same; biosimilars constitute recombinant proteins that have the structural nuances, folding characteristics, and post-translational changes identical to the generic drugs, and hence necessitate characterization by specialized analytical tests and also require randomized controlled trials to prove therapeutic equivalence. For biosimilars to be injected intravitreally, there have been additional concerns pertaining to the occurrence of sterile endophthalmitis for specific batches of another ranibizumab biosimilar in the past, raising the level of regulatory scrutiny for such products.<sup>[17]</sup> In the present study, there was a pleasant departure from such concerns where, only 18 patients showed AEs from Lupin's ranibizumab group, whereas 31 patients from Lucentis<sup>®</sup> group displayed AEs. Moreover, the ocular events in Lupin's ranibizumab vs. Lucentis<sup>®</sup> were 5.94 vs. 7.92%, which is also similar to the findings of the pivotal trials of Lucentis.<sup>[18]</sup>

Another potential risk perceived with biosimilars in comparison to reference products is the immunogenicity. Biosimilars are proteins with potential differences from the innovator product due to enzymatic post-translational modifications (e.g., glycosylation) and antigenic variations. They may lead to stronger immune responses that can be further compounded by various other patient- and disease-related factors. This response to therapeutic proteins is complex and, the potential adverse reactions or reduced efficacy may be attributed to antibody neutralization or T-cell activation. The suspected consequence of such responses could range from clinically insignificant transient development of ADA to larger safety issues.<sup>[19]</sup> However, in present study, <1% of patients receiving the study drug reported positive for anti-ranibizumab antibody, which is very similar to the recent study published on another ranibizumab biosimilar (SB11).<sup>[20]</sup> The immunogenicity profiles of marketed drugs such as Lucentis<sup>®</sup> and biosimilar products such as Lupin's ranibizumab are comparable, albeit with numerically lower incidence of anti-drug antibodies in Lupin's ranibizumab compared to Lucentis.

The development of biosimilars is associated with numerous challenges such as proprietary nature of the production processes and the complexity of biologic molecules.<sup>[21]</sup> Moreover, changes in the biological and environmental factors such as pH, temperature, pressure, and storage conditions may influence the quality, potential, and clinical performance of a biosimilar.<sup>[9]</sup> The totality of evidence for biosimilarity has been demonstrated right from the bench (all *in vitro* comparison) to the bed-side (clinical phase III trial) under stringent manufacturing and regulatory controls. The present clinical study was designed in conformance with guidelines on biosimilar development of the CDSCO and was directed by the subject expert committee (SEC) appointed by the DCGI.<sup>[16]</sup> The study duration was decided to be 3 months considering the fact that the maximum efficacy is achieved within first 3 months of treatment, followed by plateauing of the effect in subsequent months.<sup>[22]</sup> Because biosimilars are expected to show similarity to the reference drug during the phase of maximum efficacy, study duration of 3 months is justified and can further be considered as a surrogate to assess similarity of efficacy in the long term. The outcome of this study in terms

of safety, efficacy, and immunogenicity along with extensive similarity in quality attributes provides substantial and robust evidence to support biosimilarity of Lupin's ranibizumab to Lucentis in its entirety.

## Conclusion

Lupin's ranibizumab has demonstrated therapeutic equivalence to Lucentis<sup>®</sup> in terms of changes in VA to show comparisons in proportion of patients losing fewer than 15 letters from baseline as well as improvement in functional endpoint of visual acuity in patients with nAMD. Furthermore, Lupin's ranibizumab has demonstrated comparable safety and immunogenicity profile, supporting its use as a proposed ranibizumab biosimilar product.

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## Conflicts of interest

There are no conflicts of interest.

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