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COMPARISON OF THE EFFECT OF A BIOSIMILAR BEVACIZUMAB WITH THE INNOVATORS' BEVACIZUMAB IN THE TREATMENT OF NON-SMALL-CELL LUNG CANCER

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ABSTRACT

Aim: The role of bevacizumab in combination with carboplatin/paclitaxel chemotherapy has been established in patients with non-small-cell lung cancer (NSCLC). This trial was designed to compare the effect of the Zydus biosimilar bevacizumab with the reference bevacizumab in patients with NSCLC. **Methods:** A multicentre, prospective, randomized, open-label, active controlled study was carried out on 248 subjects with advanced, unresectable, recurrent or metastatic NSCLC at 28 sites across India. Subjects were randomized in a 2:1 ratio to receive intravenous infusion of 15 mg/kg of test or reference bevacizumab, plus paclitaxel 175 mg/m^2 and carboplatin (AUC 5 mg/mL×min) every 3 weeks for 6 cycles. Overall response rate (ORR) after 6 cycles was assessed by using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Pharmacokinetics, safety and tolerability, and immunogenicity were also assessed. **Results:** The ORR was 60.82% responders in the Zydus bevacizumab and 58.82% responders in the reference bevacizumab and the 90% confidence interval (CI) for the difference of ORR fell within the ±20% equivalence margin (-11.96, 15.97). The pharmacokinetic assessment of the Ln-transformed bevacizumab after Cycle-1 data showed the 90% CI for the ratio of the test to reference geometric least square mean fell within the 80.00-125.00% limits for C_{max} (87.99%; 120.41%) and AUC_{0-t} (90.70%; 122.03%). The incidence of immunogenicity was marginally lower in the test group as compared to the reference group (72.16% vs. 76.47%). **Conclusion:** The results demonstrated biosimilarity between Zydus and reference bevacizumab with respect to efficacy, tolerability and safety in the patients with NSCLC.

KEYWORDS: NSCLC, bevacizumab, biosimilar, ORR, pharmacokinetics, immunogenicity.

INTRODUCTION

Lung cancer is one of the common malignancies and the leading cause of cancer deaths worldwide in men and women.[1] Therapeutically, lung cancer is classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). About 85% of all lung cancers are identified as non-small cell, and approximately 70% of these patients are metastatic, or advanced, at the time of diagnosis.[2]

Systemic chemotherapy is considered as the standard treatment for the advanced stage amongst the avaialble options,[3] as it improves both quality of life and survival.[4] Biological drug products have offered a novel treatment option and enhanced therapeutic outcomes in patients with NSCLC.[5] The platinum or non–platinum based, two-drug regimens were considered as the standard of care for advanced NSCLC patients until the finding of the Eastern Cooperative Oncology Group (ECOG) and AVAiL studies of bevacizumab,[6,7] which ultimately lead to the approval of bevacizumab plus carboplatin and paclitaxel regimen as a first-line therapy for the treatment of NSCLC.[8] Several studies have reported that the use of carboplatin and paclitaxel chemotherapy plus bevacizumab (at a dose of 15 mg/kg, every 3 weeks) increases the two year survival rate for patients diagnosed with advanced lung cancer as compared to chemotherapy.[6,9,10]

Bevacizumab is indicated for the treatment of a number of cancer indications, i.e., NSCLC, metastatic colorectal cancer (mCRC), glioblastoma, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, metastatic renal cell carcinoma (mRCC) at a dose of 5–15 mg/kg once every two weeks or once every three weeks.[10]

Cadila Healthcare Limited (CHL), the Zydus group, has developed a biosimilar of bevacizumab, which is a recombinant humanized monoclonal antibody (IgG1 isotype) produced by Chinese Hamster ovary (CHO) suspension cells, containing 93% human and 7% murine protein sequences, generated by humanization of the murine parent antibody. The pre-clinical profile of bevacizumab developed by CHL was comparable with the approved Avastin® (unpublished data). Therefore, the present study was designed to compare the efficacy, safety and tolerability of the biosimilar bevacizumab (Bryxta™) with the reference bevacizumab (Avastin®, Genentech/Roche) in patients with NSCLC.

MATERIALS AND METHODS

Study design

This prospective, multicentre, randomized, open-label, active controlled, phase 3 study was conducted at 28 Indian sites between 26 September 2015 and 23 March 2017. The study was conducted in accordance with Good Clinical Practice (GCP) and initiated after obtaining the approvals from the Drug Controller General of India (DCGI) and the Ethics Committees of each investigational site, and registered at the Clinical Trial Registry - India (ctri.nic.in) (CTRI/2015/08/006109). Written informed consent was obtained from each participant before initiation of any study related procedures.

Study population

Male or female subjects aged ≥18 years with a history of histologically or cytologically confirmed stage IIIB with malignant pleural effusion, stage IV, or recurrent NSCLC were eligible for the study. Additional inclusion criteria included; subjects suitability for the treatment of bevacizumab with carboplatin and paclitaxel therapy as a first line therapy with bi-dimensionally measurable lesions according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria, and had an ECOG Performance Status (PS) of ≤2 and a life expectancy of ≥3 months.

Subjects were excluded who had received prior chemotherapy, biotherapy or radiotherapy to an area of measurable disease (unless disease progression was documented following completion of the therapy) or radiotherapy within the past 2 weeks. Additional exclusion criteria included patients with central nervous system metastasis, absolute neutrophil count <1500/mm^3, platelets <100000/mm^3, creatinine level ≥1.5 mg/dL, bilirubin level ≥1.5 × upper limit of normal (ULN), aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) levels ≥2.5 × ULN (≥5 × ULN for patients with liver metastases), alkaline phosphatase level ≥5 × ULN, history of clinically significant cardiac diseases in the past six months, history of serious or severe arterial thrombotic events and/or venous thromboembolic events in the past three months, history of surgery in the past 4 weeks or planned elective surgery, fine needle biopsy, or an open biopsy within past one week, recent or current use of aspirin or oral and/or parenteral anticoagulants (except low dose coumadin 1 mg), known hypersensitivity to any components of the study medications and ingredients, gross hemoptysis or hematuria or hematemesis within 3 months, patients with non-healing wounds, ulcers or bone fractures, history of serious and / or severe infections such as hepatitis C virus, hepatitis B virus, HIV infections, tuberculosis, etc., and any other medical conditions (including mental illness, substance abuse) as deemed by the investigator.

Treatment protocol

Subjects were randomly assigned in a 2:1 ratio to receive intravenous infusion of 15 mg/kg of test bevacizumab or reference bevacizumab, plus paclitaxel (175 mg/m^2) and carboplatin (AUC 5 mg/mL×min) every 3 weeks for 6 cycles. After cycle 6 the compassionate reference bevacizumab monotherapy was given based on the Investigators discretion; however, this was not the part of study report/analysis. The randomization schedule was generated by using SAS® statistical software (Version: 9.3). The first five subjects were enrolled to the test group to assess the infusion toxicity and then randomization was started; however, these subjects were included in the total sample size.

Paclitaxel was administered over 3 hours. After 60 minutes, carboplatin was administered over 15 to 30 minutes as per the Calvet formula.[11] One hour after the above chemotherapy cycle, the recommended dose of bevacizumab (15 mg/kg) was administered by an intravenous infusion over 90 minutes. If the initial infusion was well tolerated, subsequent infusion times were shortened to 30 to 60 minutes. The dose of bevacizumab was not modified during the study period. Premedication such as analgesics/antipyretics, antihistamines and supportive concomitant medications i.e. pegfilgrastim were allowed during the study.

A total of eight visits were scheduled during this study including the screening visit i.e., Day 1, 22, 43, 64, 85, 106 and 127. Four additional visits i.e., Day 8, 15, 113 and 120, were planned for a cohort of subjects who participated in the pharmacokinetic assessment study.

The primary efficacy variable was overall response rate (ORR) after Cycle-6. ORR was assessed by using RECIST 1.1.[12] The secondary endpoints were comparison of pharmacokinetics and assessment of safety, tolerability and immunogenicity between the test and reference drug products.

Safety assessments included vital signs, physical examination, laboratory investigations, cardiac safety and assessment of adverse events (AEs).

Statistical analysis

Statistical analysis was performed using SAS®, version 9.4 software (SAS Institute Inc., USA). The sample size

calculation was based on the assumed ORR of 29% at the end of study[13] and an equivalence margin of 20% with 80% power and 5% level of significance. Including 10% dropouts, a total of 222 subjects were required to be randomized in a 2:1 treatment ratio out of which 40 subjects in a ratio (1:1) were planned to undergo pharmacokinetic analysis.

Any subject who had not completed two consecutive cycles after enrollment was replaced by an additional subject in the same treatment arm. Hence a total of 248 subjects were enrolled in the study.

The efficacy analysis was performed on the per protocol population, which included the set of all randomized subjects who had received the study medications and had completed the study in compliance with the protocol without major protocol violations. A safety analysis was performed on the safety population which included the subjects who were randomized and received at least a single dose of the study medication.

The demographic and baseline characteristics were summarized by the treatment groups. For continuous measurements such as the age, mean, and the median, standard deviation and range were tabulated. For categorical measurements such as gender, the counts (n) and percentage were computed.

Subjects with CR (complete response) or PR (partial response) were considered as responders for the primary efficacy analysis. The ORR at the End of study i.e. day 127 were analyzed using Chi-square with Yate's correction to check the significant difference between test and reference bevacizumab. To establish the equivalence between test bevacizumab and reference bevacizumab, the 90% confidence interval of the difference in ORR between treatments at the end of the study was established to fall within the predefined equivalence limit of (-0.20, 0.20).

For the secondary endpoint, the 90% confidence interval for the ratio of relative mean (Geometric mean) of the test and reference formulation for Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} was calculated. Descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum and maximum) was computed for pharmacokinetic parameters and individual time-concentration data for both Cycle-1 and Cycle-6.

Other secondary endpoints of the study were safety, tolerability and immunogenicity. All the AEs observed during the study period have been summarized. Immunogenicity analysis between the two treatments was performed using Chi-square test.

RESULTS

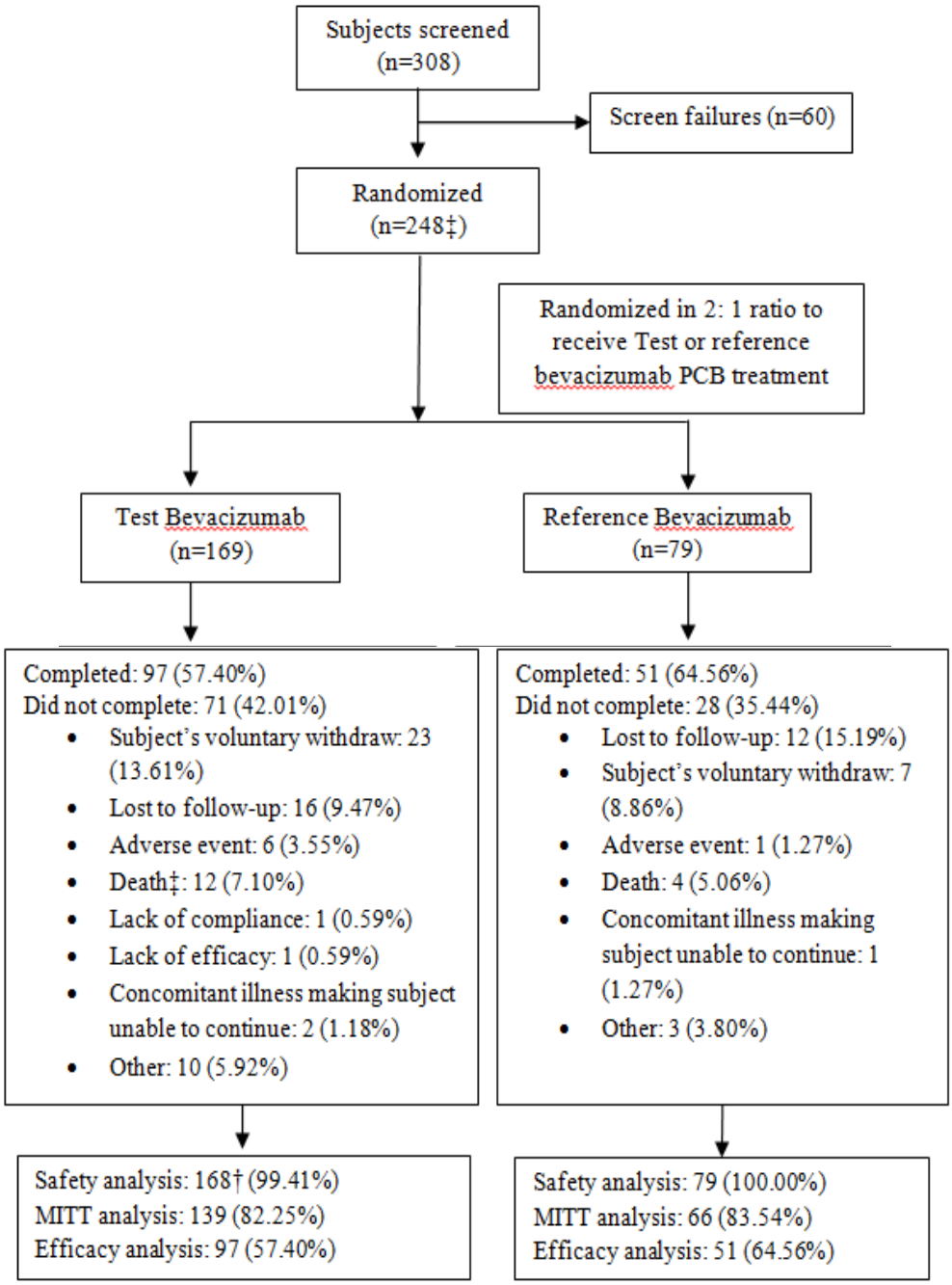
Patient characteristics

All the enrolled subjects were Asian in origin and the majority (>70%) comprised of male population in both the groups. The mean age was 57 ± 9.71 years in test bevacizumab and 58 ± 11.35 years in reference bevacizumab. All the subject's characteristics were balanced in both the study groups and no statistically significant difference was observed at baseline. Demographic and baseline characteristics are presented in Table 1. Disposition of subjects is presented in Figure 1.

Table 1: Summary of demographic characteristic (Safety population).

	Test Bevacizumab (N=168)	Reference Bevacizumab (N=79)	p-value*
Gender			
Male	122 (72.62%)	56 (70.89%)	0.7771
Female	46 (27.38%)	23 (29.11%)	
Race			
Asian	168 (100%)	79 (100%)	NE
Age (years)			
n	168	79	0.8154
Mean ± SD	57 ± 9.71	58 ± 11.35	
BMI (Kg/m^2)	20.81 ± 3.88	20.66 ± 4.30	0.7754
ECOG status			
0	38 (22.62%)	17 (21.52%)	0.956
1	103 (61.31%)	50 (63.29%)	
2	27 (16.07%)	12 (15.19%)	
Duration of cancer			
0-3 months	131 (77.98%)	66 (83.54%)	0.829
3-6 months	18 (10.71%)	6 (7.59%)	
6-9 months	5 (2.98%)	1 (1.27%)	
9-12 months	3 (1.78%)	1 (1.27%)	
>= 1 year	11(6.55%)	5 (6.33%)	

Abbreviations: N=number of subjects in the specified treatment group; n=number of subjects in the specified category; NE=Not Estimable.
*p-value for categorical variable is calculated using Chi-square test and for continuous variable p-value is calculated using ANOVA.



Note:

†One subject has withdrawn consent after administration of paclitaxel (Bevacizumab was not administered), hence not considered under safety population and for any further analysis.

‡ One subject in test treatment arm died after discontinuation from study due to adverse event, hence has been considered under adverse event and not under death.

Figure 1: Subject disposition.

Tumor response

Tumor response evaluation for target lesion for subjects assigned to test bevacizumab was comparable to that of subjects assigned to reference bevacizumab. Similarly, tumor response evaluation of non-target lesions was comparable between test and reference bevacizumab. The details of tumor response evaluation for target and non-target lesions are presented in Table 2.

Table 2: Summary of tumor response evaluation for target lesion and non-target lesion by treatment at visit 11 (End of study, Day 127 ± 3) - (Per protocol population).			
Lesion	**Tumor Response**	**Test Bevacizumab (N=97) n (%)**	**Reference Bevacizumab (N=51) n (%)**
Target lesion	Complete Response	6 (6.19)	0 (0.00)
	Partial Response	57 (58.76)	32 (62.75)
	Stable Disease	31 (31.96)	15 (29.41)
	Progressive Disease	3 (3.09)	4 (7.84)
	Missing	0 (0.00)	0 (0.00)
Non- target lesion	Complete Response	8 (8.25)	5 (9.80)
	Non-CR/Non-PD	50 (51.55)	34 (66.67)
	Non-PD	1 (1.03)	0 (0.00)
	Non-PD/Not Evaluated	0 (0.00)	0 (0.00)
	Not Evaluated	1 (1.03)	0 (0.00)
	Progressive Disease	2 (2.06)	0 (0.00)
	Missing	35 (36.08)	12 (23.53)
Abbreviations: N=number of subjects in the specified treatment group; n=number of subjects in the specified visit. Note: Visit 7 (Cycle 5) tumor response evaluation may be carried out as per the Investigator discretion; missing subjects will be considered as not performed.			

A sample size of 148 subjects was calculated to demonstrate equivalence in ORR at the end of study for test *vs* reference bevacizumab, defined as a 90% CI for the difference of ORR which fall within the equivalence margin (-11.96, 15.97). Subjects with CR or PR were considered as responders. The ORR was 60.82% (59 responders out of 97 subjects) in the test bevacizumab group and 58.82% (30 responders out of 51 subjects) responders in the reference bevacizumab group. There was no statistically significant difference (p>0.05) observed in the number of responders for ORR between test and reference bevacizumab (Table 2 and Figure 2).

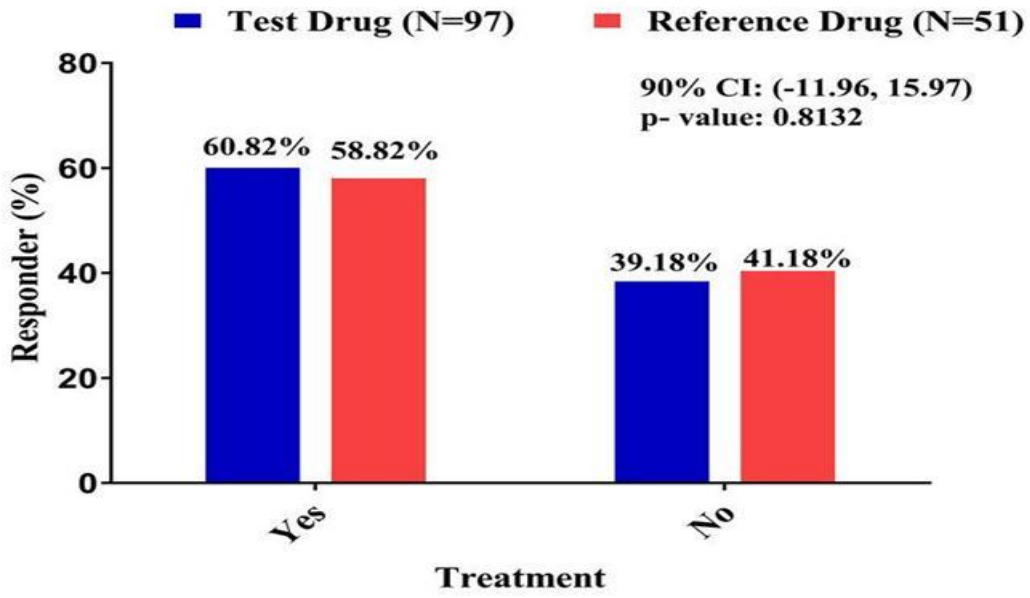


Figure 2: Analysis of overall response rate at the end of study (Per protocol population).

Pharmacokinetic assessment

Forty subjects who completed the sampling schedule till the 504 hours' time-point after the infusion of Cycle-1 of test or reference bevacizumab were included for pharmacokinetic and statistical analysis. However, out of the 40 subjects one subject had pre-dose concentration > 5% of the C_{max} in the Cycle-1 and therefore was excluded from the analysis.

Similarly, 28 out of 29 subjects who completed the sampling schedule after infusion of Cycle-6 were included for pharmacokinetic and statistical analysis.

Descriptive statistics (mean, standard deviation, coefficient of variation, minimum, median and maximum) were calculated for the pharmacokinetic parameters for both Cycle-1 and Cycle-6.

Descriptive statistics for the pharmacokinetic parameters by treatment groups after Cycle-1 and Cycle-6 is presented in Table 3.

The pharmacokinetic assessment of the Ln-transformed bevacizumab Cycle-1 data showed the 90% CI for the ratio of the test geometric least square mean to reference geometric least square mean as within the 80.00% to 125.00% limits for C_{max} (87.99%; 120.41%) and AUC_{0-t} (90.70%; 122.03%).

Table 3: Descriptive statistics of test and reference bevacizumab.

Parameters (Units)	Test Bevacizumab			Reference Bevacizumab		
	N	Mean ± SD	CV (%)	N	Mean ± SD	CV (%)
Cycle-1						
C_{max} (µg/mL)	19	375.82 ± 141.14	37.56	20	352.52 ± 106.35	30.17
AUC_t (h·µg/mL)	19	63490.90 ± 17030.82	26.82	20	60182.10 ± 16415.43	27.28
AUCi (hr·µg/mL)	13	122174.92 ± 124984.69	102.3	16	86638.58 ± 24317.00	28.07
T_{max} (hr)	19	4.03 ± 2.92	72.47	20	2.03 ± 1.12	55.2
Kel (1/hr)	13	0.00 ± 0.00	66.54	16	0.00 ± 0.00	35.91
$T_{1/2}$ (hr)	13	725.80 ± 1377.83	189.84	16	344.21 ± 131.09	38.08
Vd (mL)	13	5509.25 ± 3251.43	59.02	16	4914.63 ± 1636.88	33.31
Cl (mL/hr)	13	9.46 ± 3.07	32.49	16	10.65 ± 4.03	37.87
Cycle-6						
C_{maxss}(µg/mL)	13	455.96 ± 196.58	43.11	15	499.76 ± 128.75	25.76
AUC_{tau} (hr·µg/mL)	13	81572.70 ± 39932.95	48.95	15	100638.65 ± 25245.09	25.08
T_{maxss} (hr)	13	3.35 ± 2.88	86.14	15	3.90 ± 3.62	92.86
Kel_{ss} (1/hr)	12	0.00 ± 0.00	42.21	15	0.00 ± 0.00	31.35
$T_{1/2ss}$ (hr)	12	321.54 ± 189.49	58.93	15	417.57 ± 415.43	99.49
Vd_{ss} (mL)	12	5338.50 ± 3898.80	73.03	15	5443.77 ± 5587.27	102.64
Cl_{ss} (mL/hr)	13	12.48 ± 4.70	37.63	15	8.97 ± 3.33	37.16

Abbreviations: AUCi: area under the plasma concentration versus time curve from zero to infinity; AUC_t: area under the plasma concentration versus time curve; Cl: clearance; C_{max}: peak plasma concentration; Kel: terminal elimination rate constant; $T_{1/2}$: half-life; T_{max}: time to maximum plasma concentration; $_{ss}$: steady state; Vd: volume of distribution

Immunogenicity assessment

The incidence of immunogenicity in the test treated group was marginally lower compared to the reference treated subjects (72.16% vs. 76.47%). The titer values in both the treatment groups (test and reference) having ADA positive at post treatment with both baseline negative and positive were ranged from 20-20480 and 40-1280, respectively. Immunogenicity analysis between the two treatments was performed using Chi-square test. Analysis showed no statistically significant difference in immunogenicity of test and reference bevacizumab in the patients with NSCLC.

Safety assessment

Overall, the test and the reference bevacizumab were safe and well tolerated in this study. A total of 646 AEs and 63 serious adverse events (SAEs) were reported in 152 subjects in the study. There were 449 AEs reported in 103 (61.31%) subjects in the test group, whereas in the reference group, 197 AEs were reported by 49 (62.03%) subjects. The distribution of AEs was comparable between the treatment groups.

Commonly reported AEs across the groups were vomiting, asthenia, alopecia, pyrexia, decreased appetite, pain, pain in extremity, paraesthesia, diarrhoea, nausea and cough.

A total of 63 SAEs were reported in 42 subjects during the study. In the test bevacizumab group, 42 SAEs were reported in 29 (17.26%) subjects and in the reference bevacizumab group, 21 SAEs were reported in 13 (16.46%) subjects. Proportion of SAEs was similar in both the groups. Majority of the SAEs were of severe intensity (21, 50.00% vs 11, 52.38%), not related with study drug (33, 78.57% vs 15, 71.42%) and recovered/resolved (23, 54.76% vs 9, 42.85%) in both the groups. A total 18 deaths were reported during the study; 14 (8.33%) in the test group and 4 (5.06%) in the reference group. Three cases of deaths were considered as related to the drug product in the test group while two cases were considered related to the drug product in the reference group.

There were no persistent changes from baseline in laboratory parameters, vital signs, and were comparable between the test and reference bevacizumab.

DISCUSSION

A biosimilar product is a biological product that is highly similar in terms of quality, safety and efficacy to an approved reference biological product based on comparability.

The clinical development of a biosimilar is not as extensive as that of the reference biologic; however, confirmation of biosimilarity is based on a sequential process which includes characterization studies to compare the molecular and quality attributes with regard to the reference product, non-clinical (*in-vitro* and *in-vivo*) and clinical studies, and it is essential that the product meets acceptable levels of safety, efficacy and quality to ensure public health in accordance with international guidelines.[14,15]

The current guidelines on similar biologics in India require evaluation of the pharmacokinetic bioequivalence of the test product to the reference product in addition to efficacy and safety assessment.[16]

Cadila Healthcare Limited of the Zydus Group has developed a bevacizumab biosimilar with an aim to make essential medicines accessible both in terms of availability and affordability to the patients. Extensive physicochemical and biological comparability data showed high similarity of the Zydus bevacizumab to that of reference bevacizumab, therefore, the present clinical study was designed to compare the safety, tolerability and efficacy of test bevacizumab in patients with NSCLC.

In this study, efficacy, safety, tolerability and pharmacokinetics were evaluated and compared with the reference bevacizumab. Based on the DCGI recommendation, the infusion toxicity of the first five subjects was assessed and the results were reviewed by a data safety monitoring board (DSMB). Based upon the favorable safety recommendations from the DSMB, subsequent randomization of subjects was performed. Overall survival (OS) remains the gold standard for the demonstration of clinical benefit. This endpoint is unambiguous and is not subject to investigator interpretation. However, it is identified as the endpoint of choice to assess the efficacy of new treatments in cancer therapeutics. For a biosimilar trial of cancer therapeutics, the focus is to demonstrate biosimilarty of test product to the approved reference product. Therefore, surrogate endpoint was selected as a primary endpoint for this study in concurrence with the regulatory authority.

The primary endpoint of the study was to compare ORR, a surrogate marker, between the test and reference bevacizumab at the end of Cycle-6, as assessed by RECIST 1.1. Generally ORR is recommended as a primary endpoint as it reduces the number of subjects and shortens the duration of the study, therefore considered practically feasible in biosimilar cancer studies.[17-19]

The main finding of this study was that tumor response evaluation for target lesion and non-target lesions in subjects treated with test bevacizumab were comparable with that of the reference bevacizumab.[20] The ORR achieved for both the arms was comparable and the difference was statistically not significant. The response rate observed in our study is in line with the results of the Brazilian center experience[21] and BEYOND study[22]; however, higher when compared with 35% and 30.4% in E4599 and AVAiL.[6,7] The reason of differences in the response rate was not clear; however, one of the study justified the difference in response rate was due to methods of tumor assessments.[21]

The secondary efficacy endpoints were to evaluate pharmacokinetics following IV infusions of test or reference bevacizumab and immunogenicity assessment till the end of study.

Pharmacokinetic bioequivalence is demonstrated by applying the standard criteria that the two sided 90% CI for the geometric mean ratio must be within the pre-specified acceptance range of 0.8 and 1.25.[23] The pharmacokinetic assessment of the Ln-transformed bevacizumab after Cycle-1 showed the 90% CI for the ratio of the test to reference geometric least square mean were within the 80.00% to 125.00% limits for C_{max} and AUC_{0-t}. The study demonstrated similar pharmacokinetics between the test and reference products. Descriptive statistics for the pharmacokinetics parameters of test and reference bevacizumab was comparable after Cycle-6.

Immunogenicity refers to the ability of a protein antigen to elicit an immune response resulting in the production of ADA against itself.[24,25] In this study, at the baseline, prior to the dose administration, few subjects from both the test and reference groups were found to be ADA-positive (~12.37 vs 11.76%). Immunogenicity (ADA) was detected with both the test and reference drug product treated subjects. The incidence of immunogenicity in the test product treated group was marginally lower compared to the reference drug product treated subjects; however, incidence was much higher than reported values of 0.6%.[10] Comparison of the incidence of antibodies to bevacizumab in this study with previous studies may be misleading because detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Moreover, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, timing of sample collection, sample handling, concomitant medications, and underlying disease.[26]

The results support that there is no clinically meaningful difference in the immunogenicity risk between the test and reference products.There were no evident differences between the test and reference group with respect to the type, incidence or severity of AEs. The rate and

incidence observed in the current study cannot be directly compared with the previous studies as those studies were conducted in a different setting. However, the observed safety profile of test bevacizumab was comparable with the reference product in the present study.

This comparative trial enrolled the patient population from across India where ethnic diversity is predominant and therefore partially rules out the challenge of generalizability of the data.

The sample size and equivalence margin was based on the current Indian biosimilar regulatory guideline recommendation and discussions with the drug regulator. The actual biosimilarity was concluded based on 90% CI of the difference in treatments and was found to fall within a recommended equivalence margin of (+/-20%) with adequate power and significance level. Moreover, the sample size was much higher in general when compared to the other bevacizumab biosimilar studies conducted in India.

The study design was open-label where ORR was selected as a short term efficacy endpoint; and is in line with the planned development of biosimilars undertaken by various pharmaceutical companies for submission to global regulatory agencies. The ORR assessed through medical imaging is considered to be an objective assessment of the efficacy of the drug and also the responses were reviewed by Investigators and experts independent of the study. Therapeutic equivalence of the proposed bevacizumab was statistically supported by the primary efficacy.

CONCLUSION

In conclusion, the results demonstrate a high degree of biosimilarity with respect to efficacy, tolerability and safety of the test bevacizumab and reference bevacizumab in patients with NSCLC.

Biological agents have increased the treatment options and have improved outcomes for a number of cancers. Bevacizumab, a VEGF inhibitor, has been approved as a first-line therapy for metastatic NSCLC in combination with carboplatin and paclitaxel. But patients access to these biologics is limited in many countries mainly due to availability and affordability. The availability of a biosimilar bevacizumab can potentially lead to a lowering of the therapy cost and an increased access to patients with NSCLC.

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