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Original Article

Oncology Section

Comparison of Efficacy and Safety of Lupin's Pegfilgrastim with Neulastim® as an Adjunct to Chemotherapy in Patients with Non Myeloid Malignancies: A Randomised Phase III Clinical Study

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ABSTRACT

Introduction: Pegfilgrastim is indicated in patients receiving myelosuppressive anticancer drugs to reduce the Duration of Severe Neutropenia (DSN) and incidence of Febrile Neutropenia (FN). The efficacy and safety of a proposed Pegfilgrastim biosimilar should be compared with an approved biologic drug to establish therapeutic equivalence.

Aim: To compare the efficacy of Lupin's biosimilar Pegfilgrastim versus Neulastim® (Amgen Inc.) as an adjunct to chemotherapy in patients with non-myeloid malignancies.

Materials and Methods: The present prospective, open-label, randomised phase III clinical study was conducted on a total of 170 patients with histologically or cytologically confirmed non-myeloid malignancies eligible to receive a myelosuppressive chemotherapy regimen. The participants were administered Lupin's Pegfilgrastim (n=86) or Neulastim® (n=84) 6 mg by subcutaneous injection, once in each chemotherapy cycle for a maximum of three cycles. Patients were chemotherapy naive or had not received myelosuppressive chemotherapy within last 12 months of screening. The primary efficacy endpoint was DSN (number of days on which absolute neutrophil count <0.5×10^9/L) in cycle 1 of chemotherapy. Equivalence was confirmed, if 95% Confidence Intervals (CI) were within the equivalence margin of ±1 day. Safety evaluation included assessment of Adverse Events (AEs), rate of discontinuation due to AEs, vital signs, and laboratory parameters. Statistical analysis were done using SAS Enterprise guide 9.4 (SAS Institute Inc., Cary, 2000).

Results: Of the 170 patients balanced for demographic characteristics, 161 patients completed cycle 1, 151 patients completed cycle 2, and 142 patients completed cycle 3. The mean±Standard Deviation (SD) DSN in cycle 1 was 0.127±0.5533 days with Pegfilgrastim (n=63) and 0.197±0.6615 days with Neulastim® (n=66) in the Per Protocol (PP) assessment; and 0.174±0.636 days with Pegfilgrastim and 0.193±0.671 days with Neulastim® in the modified Intent-to-Treat (mITT) assessment. The mean DSN between the groups did not differ significantly (PP: p=0.5167, mITT: p=0.8554). The 95% CI of difference in mean DSN in PP (-0.2796 to 0.1481) and mITT (-0.2103 to 0.1889) assessments was contained within the predefined equivalence margin of ±1 day. Secondary outcomes and safety profiles were also comparable between the two groups.

Conclusion: The present study establishes Lupin's Pegfilgrastim as a therapeutically equivalent biosimilar alternative to Neulastim® in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy.

Keywords: Absolute neutrophil count, Biosimilars, Febrile neutropenia, Granulocyte colony-stimulating factor, Therapeutic equivalence

INTRODUCTION

Biologics show great therapeutic potential but are mostly limited in terms of their availability and cost. Biosimilar development may reduce therapy costs and provide easy access to medicines [1]. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) established guidance for biosimilar development and approval, where biochemical, immunological, safety and efficacy studies are recommended to demonstrate equivalence to a reference product [2,3].

Lupin's Pegfilgrastim has been approved as a biosimilar to innovator's product Neulastim® (Pegfilgrastim of Amgen Inc.) in India in 2013 and is currently under active development for advanced markets [4]. Pegfilgrastim is used for chemotherapy-induced neutropenia and to reduce the incidence of FN in patients treated with cytotoxic chemotherapy for malignancy [5].

The FN is characterised by Absolute Neutrophil Count (ANC) <1×10^9/L and temperature of ≥38.3°C or a sustained temperature of ≥38°C for more than 1 hour [6]. FN and other infectious complications are the most serious treatment-related toxicities of chemotherapy, with a mortality rate upto 11% [7]. FN occurs in 10-50% of patients with solid tumours and >80% of patients with blood malignancies receiving chemotherapy [7]. Real-world data indicate that the FN rates are significantly higher than those observed in clinical trials [8]. FN and other infectious complications require hospitalisations, reducing the quality of life, and increasing costs [8]. Moreover, FN also restricts the full dose and schedule of chemotherapy, thereby compromising treatment efficacy and outcomes [6].

Granulocyte Colony-Stimulating Factors (G-CSFs) help in the recovery of neutrophils and the prevention of potentially life-threatening FN, thus, reducing the risk of chemotherapy-induced neutropenia and its complications [9]. Furthermore, there is no need for chemotherapy dose reductions and delays that may restrict chemotherapy dose intensity [5]. Thus, the prophylactic use of G-CSFs increases the potential for prolonged disease-free and overall survival in the curative setting. The 2020 National Comprehensive Cancer Network (NCCN) [10] and 2015 American

Society of Clinical Oncology (ASCO) [11] guidelines recommend G-CSFs for patients above an FN risk threshold of 20%.

Filgrastim is a G-CSF that regulates granulopoiesis and enhances the functions of normal mature neutrophils. Pegfilgrastim is a sustained-duration form of filgrastim created by the addition of a Polyethylene Glycol (PEG) moiety to filgrastim [6]. It is comparable to filgrastim with respect to clinical benefits but has novel pharmacokinetic properties, allowing a single dose administration per chemotherapy cycle as opposed to daily dose administrations of filgrastim [12-14].

Biosimilar clinical studies are designed to demonstrate equivalent efficacy and comparable safety versus the reference product. Clinical equivalence provides adequate scientific justification for the approval of a biosimilar for the specific indication studied [1]. The present phase III study from India was conducted as per protocol approved by Central Drugs Standard Control Organisation (CDSCO) [15], India and aims at assessing the comparative efficacy and safety of subcutaneous injection of Lupin's Pegfilgrastim versus Neulastim® as an adjunct to chemotherapy in subjects with non-myeloid malignancies receiving myelosuppressive chemotherapy to establish therapeutic equivalence. This is one of the first biosimilar trials conducted in India with stringent protocols before CDSCO and the Department of Biotechnology (DBT) recommended equivalence study designs for biosimilar approval [15].

MATERIALS AND METHODS

This was a prospective phase III, open-label, randomised, multi-centre, comparative, active-controlled, parallel, two-arm study in patients with non-myeloid malignancies, comparing equal doses of Lupin's Pegfilgrastim and Neulastim® (Pegfilgrastim manufactured and marketed by F. Hoffmann-La Roche Ltd, Switzerland under license from Amgen Inc.). The study was conducted across 11 centres in India from 16th January 2012 to 11th September 2012. The study protocol was approved by Drugs Controller General of India (DCGI) and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the participating sites. The study complied with the ethical principles specified in the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and Schedule Y 'Guidelines for Clinical Trials on Pharmaceutical Products in India' issued by CDSCO, India. Patients provided written informed consent before enrolling in the study. The present study is registered with the Clinical Trials Registry- India, CTRI/2012/01/002338.

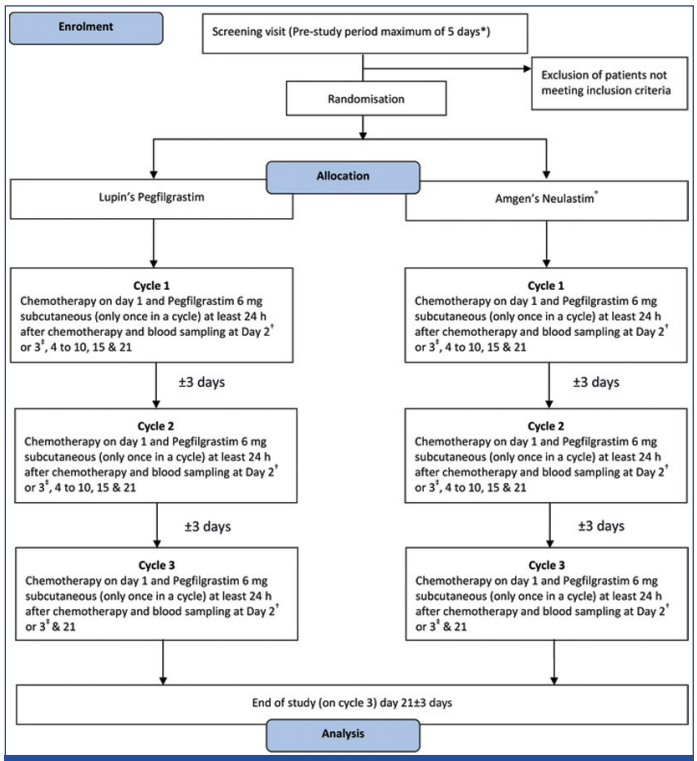
Sample size calculation: A sample size of 63 patients per treatment group was computed assuming clinical equivalence between biosimilar Pegfilgrastim and Neulastim®, the two-sided 95% Confidence Interval (CI) for the difference in Duration of Severe Neutropenia (DSN) within the equivalence range (±1 day), 80% power for rejecting the null hypothesis, and assuming an expected difference in mean DSN of <0.1 days and a Standard Deviation (SD) of 1.4 days [16,17].

Inclusion criteria: The study included male and non-pregnant/non-lactating female patients between 18 to 75 years of age with histologically or cytologically confirmed non-myeloid malignancies. Cancer staging was done using the TNM (Tumour, Nodes, Metastasis) method [18]. Patients included were eligible to receive a myelosuppressive chemotherapy regimen that contained atleast one chemotherapeutic agent viz. docetaxel, paclitaxel, doxorubicin, or epirubicin. Patients were chemotherapy naive or had not received myelosuppressive chemotherapy within last 12 months of screening; had a baseline ANC of ≥1.5×10^9/L and platelet count ≥100×10^9/L; with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 [19].

Exclusion criteria: Patients weighing <45 kg; with history of hypersensitivity to study drugs; components or similar products; with myeloid malignancies and myelodysplasia; receiving radiation therapy during the study duration or had completed radiation therapy within four weeks before study initiation; with prior bone marrow or stem cell transplantation; with chronic use of oral corticosteroids (except ≤20 mg/day dose of prednisolone); with history of systemic antibiotic use within 72 hours prior to chemotherapy; with any active infection which may require systemic antimicrobial therapy; who had received haematopoietic growth factors or cytokines within last one month of screening; with congestive heart failure class III/IV as per New York Heart Association (NYHA) classification [20] were excluded from the study.

Study Procedure

The study had a screening period of a maximum of five days, after which eligible patients were randomised as per the randomisation list across all centres to one of the two treatment arms (Lupin's Pegfilgrastim or Neulastim®) in a 1:1 ratio. The randomisation list was prepared in-house by using block design. Once patient eligibility was confirmed, a sequential unique randomisation number was assigned to the patients and they received treatment corresponding to the randomisation number. The study flow chart is outlined in [Table/Fig-1].



[Table/Fig-1]: Study flowchart.
*Haematology was repeated in pre-study period if duration between screening and day 1 was >48 h; †Only when chemotherapy was over on day 1 of the cycle
‡Only when chemotherapy extended till day 2 of the cycle

Study endpoints: DSN, defined as the number of days on which ANC <0.5×10^9/L) [7], in cycle 1 of chemotherapy was the primary efficacy endpoint. Secondary efficacy endpoints included DSN in cycle 2, the incidence of severe neutropenia, depth of ANC nadir and time to ANC recovery in cycles 1 and 2, the incidence of FN, rate of hospitalisations due to FN and the proportion of patients requiring systemic antibiotics for FN in cycles 1, 2 and 3. Assessments were performed during the 21 days of each chemotherapy cycle [Table/Fig-1].

Safety evaluation included assessing Adverse Events (AEs) at every visit, rate of discontinuation due to AEs, vital signs, and laboratory parameters. Additionally, patients were assessed for the occurrence of FN by measuring daily body temperature. Other assessments included recording of medical history, physical examination, and review of concomitant medications.

For data analyses, the treatment groups were divided into modified Intent-to-Treat (mITT) population, Per Protocol (PP) population, and ITT population [21].

The mITT population, a subset for efficacy population (defined for each cycle) comprised patients who were randomised, had received assigned Investigational Product (IP), had one post-dose ANC, and had received the correct chemotherapy regimen. The PP population (defined for each cycle) comprised patients who completed the respective chemotherapy cycles or other procedures as PP without any major protocol deviations. The ITT population comprised patients who received atleast one dose of IP in the treatment period, had a baseline and atleast one post-baseline assessment. Efficacy was analysed in mITT and PP populations. Safety was analysed in the ITT population.

STATISTICAL ANALYSIS

Statistical analyses were done using SAS Enterprise guide 9.4 (SAS Institute Inc., Cary, 2000). Variables measured on a continuous scale were compared using a t-test, the proportions data were compared using Fisher's-Exact test, and stratified data were compared using the Cochran-Mantel-Haenszel (CMH) test. Analysis of Covariance (ANCOVA) was applied using "DSN in cycle 1" as a dependent variable, including the factors such as but not limited to "treatment", and with the baseline ANC value as a covariate. Equivalence of biosimilar Pegfilgrastim and Neulastim® was assessed based on the PP set, using the ANCOVA model to calculate a two-sided 95% CI for "Lupin's Pegfilgrastim minus Neulastim®". Equivalence was concluded, if the 95% CI lay within the equivalence range (±1 day).

RESULTS

A total of 201 patients were screened in the study out of which 170 were randomly assigned to receive either Lupin's Pegfilgrastim (n=86; mean age 49.02±11.69 years) or Neulastim® (n=84; mean age 51.11±10.32 years). Out of 170 randomised patients, 56 (32.94%) were males and 114 (67.06%) were females. All patients were Asian. There were no significant between-group differences in demographic characteristics [Table/Fig-2]. The patients presented different cancer types-breast cancer [n=86 (50.59%)] and head and neck cancer [n=53 (31.18%)] were most common. There was no significant between-group difference in cancer stages, baseline ECOG status and baseline mean ANC. Most of the patients in this trial were on paclitaxel [n=91 (53.52%)], followed by doxorubicin [n=60 (35.29%)], epirubicin [n=9 (5.29%)] and docetaxel [n=10 (5.89%)]. Other chemotherapeutic agents used were cyclophosphamide, 5-fluorouracil (5-FU), carboplatin, cisplatin, rituximab, and vincristine (as a part of the chemotherapy regimen).

Demography and baseline characteristics	Pegfilgrastim (n=86)	Neulastim® (n=84)	Comparisons between treatment arms (p-value)
Gender, n (%) [a]			
Male	27 (31.40%)	29 (34.52%)	0.7447
Female	59 (68.60%)	55 (65.48%)	
Age, years, mean±SD [b]	49.02±11.69	51.11±10.32	0.2199
Weight, kg, mean±SD [b]	57.62±10.64	57.17±8.795	0.7676
Height, cm, mean±SD [b]	156.0±8.359	155.2±8.378	0.5750
ECOG status, n (%) [a]			
0	55 (63.95%)	56 (66.67%)	0.7489
1	31 (36.05%)	28 (33.33%)	
Baseline ANC, $\times 10^9$/L, mean±SD [b]	6.462±3.135	5.921±2.638	0.2262
Chemotherapy regimen, n (%) [a]			
Doxorubicin	28 (32.56%)	32 (38.10%)	0.4146
Docetaxel	7 (8.14%)	3 (3.57%)	
Epirubicin	6 (6.98%)	3 (3.57%)	
Paclitaxel	45 (52.33%)	46 (54.76%)	
Cancer type, n (%) [a]			
Breast cancer	46 (53.49%)	40 (47.62%)	0.7234
Head and neck cancer	27 (31.40%)	26 (30.95%)	
Non-Hodgkin's lymphoma	2 (2.33%)	3 (3.57%)	
Non-small cell lung cancer	6 (6.98%)	5 (5.95%)	
Ovarian cancer	5 (5.81%)	9 (10.71%)	
Stomach cancer	0 (0.00%)	1 (1.19%)	
Cancer stages, n (%) [a]			
I	2 (2.33%)	4 (4.76%)	0.7020
II	18 (20.93%)	20 (23.81%)	
III	36 (41.86%)	36 (42.86%)	
IV	30 (34.88%)	24 (28.57%)	

[Table/Fig-2]: Patient demographics and baseline characteristics.
SD: Standard deviation; ECOG: Eastern cooperative oncology group; ANC: Absolute neutrophil count; p-values were obtained by performing [a] Fisher's exact test and [b] t-test

A total of 147 patients (86.47%) were chemotherapy-naive, whereas 23 (13.53%) had received chemotherapy 12 months prior to screening. All patients received a single dose of the drug on either day 2 or day 3 of respective cycles depending on the duration of chemotherapy administration. Patient disposition and analysis of population are outlined in [Table/Fig-3].

Efficacy

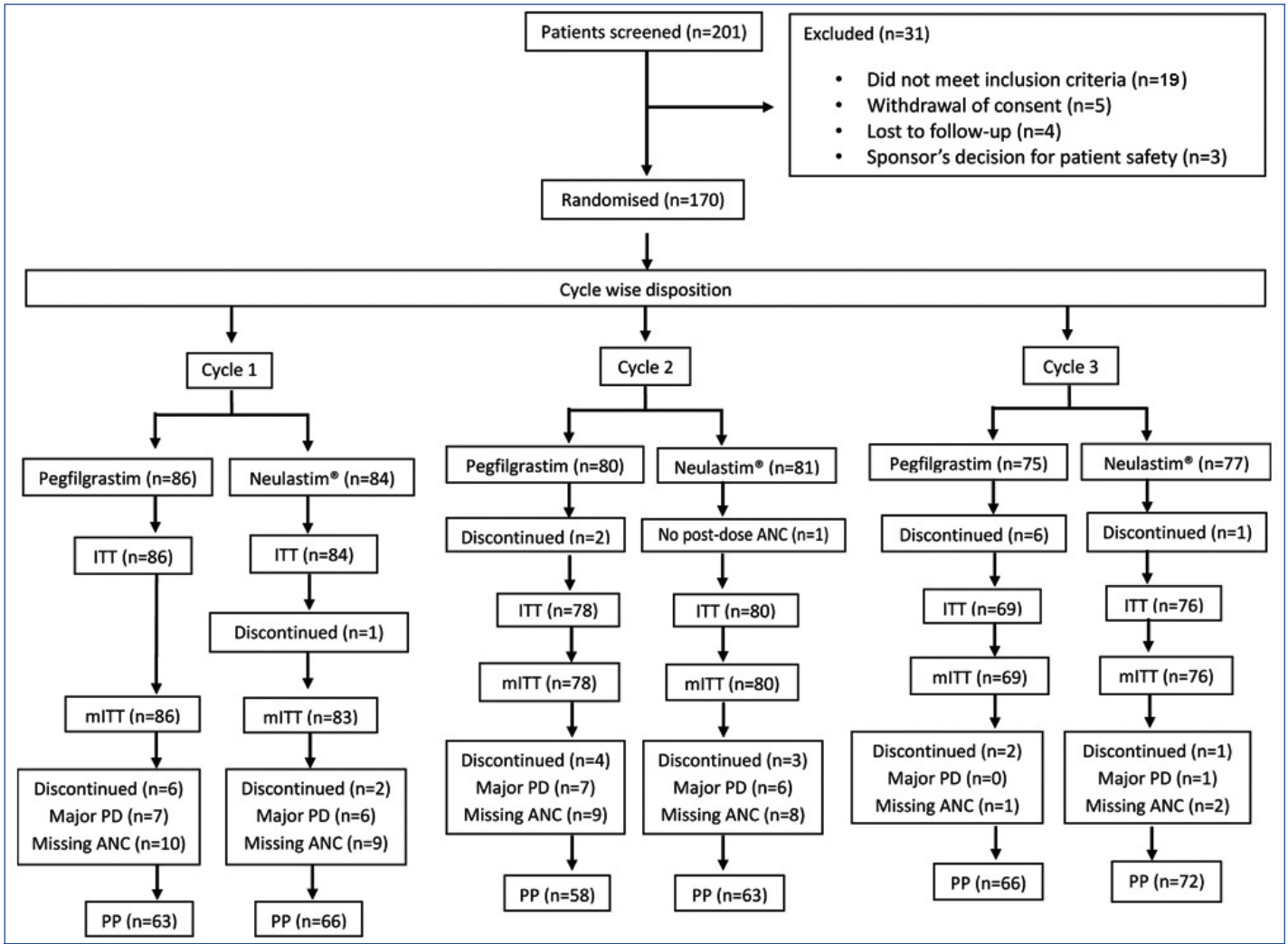
Efficacy was analysed in protocol-defined mITT and PP populations.

Primary endpoint: In the PP analysis, the mean±SD DSN in cycle 1 was 0.127±0.5533 days in the Pegfilgrastim arm and 0.197±0.6615 days in the Neulastim® arm, whereas in the mITT analysis, it was 0.174±0.636 days in the Pegfilgrastim arm and 0.193±0.671 days in Neulastim® arm. In cycle 1, the mean DSN was comparable between the Pegfilgrastim and Neulastim® arms (PP: p=0.5167, mITT: p=0.8554) [Table/Fig-4]. The maximum DSN observed in both the arms was 3 days. The difference of mean DSN between both the groups in the PP population was -0.0657 (95% CI: -0.2796 to 0.1481) and in the mITT population was -0.0107 (95% CI: -0.2103 to 0.1889), which lie in the predefined interval (±1 day) for equivalence.

Secondary endpoints: In cycle 2, the mean DSN was comparable between the Pegfilgrastim and Neulastim® arms (PP: p=0.5317, mITT: p=0.5056) [Table/Fig-4]. The maximum DSN observed was 2 days in the Pegfilgrastim arm and 3 days in the Neulastim® arm. The difference of mean DSN between both the groups in cycle 2 in the PP population was -0.05854 (95% CI: -0.2440 to 0.1269) and in the mITT population was -0.0490 (95% CI: -0.1926 to 0.0946) which lie in the predefined interval (±1 day) for equivalence.

The results of secondary efficacy endpoints such as the proportion of patients with severe neutropenia, depth of ANC nadir, time to ANC recovery, the incidence of FN, rates of hospitalisation due to FN, and proportion of patients requiring systemic antibiotic(s) were comparable between the Pegfilgrastim and Neulastim® arms [Table/Fig-4].

In the PP population, FN was observed in 1 patient (1.59%) in cycle 1 and none in cycle 2 in the Pegfilgrastim arm. In the mITT population, FN was observed in 1 patient (1.16%) in cycle 1 and 1 patient (1.28%) in cycle 2 in the Pegfilgrastim arm. These patients were hospitalised and received antibiotic for FN. No FN was observed in the Neulastim® arm. However, the incidence of FN was not statistically significant between the two arms (PP: p=0.3061, cycle 1 mITT: p=0.3259, cycle 2 mITT: p=0.3112) [Table/Fig-4].



[Table/Fig-3]: Patient disposition and analysis sets. The reasons for discontinuation include loss to follow-up, withdrawal of consent, patient death (2 cases), or sponsor's decision. The patients discontinued by the sponsor were mainly due to non compliance to protocol (n=2) and not meeting eligibility criteria (n=2) as discovered during site monitoring visits. Two patients (1.18 %) discontinued due to death, 1 patient in the Neulastim® arm during cycle 1 and 1 patient in the Pegfilgrastim arm during cycle 1. In cycle 3, 75 participants were included in Lupin's pegfilgrastim arm because one patient randomised to this arm in cycle 1 did not complete cycle 2 but entered cycle 3.
ITT: Intent-to-treat; mITT: Modified intent-to-treat; PP: Per protocol; PD: Protocol deviation; ANC: Absolute neutrophil count

	Analysis sets					
	Per Protocol Population (PP)			Modified Intent-to-treat Population (mITT)		
Efficacy endpoints	Pegfilgrastim	Neulastim®	p-value	Pegfilgrastim	Neulastim®	p-value
Number of patients						
Cycle 1	63	66	NA	86	83	NA
Cycle 2	58	63	NA	78	80	NA
DSN, days, mean±SD [b]						
Cycle 1	0.127±0.5533	0.197±0.6615	0.5167	0.174±0.636	0.193±0.671	0.8554
ANCOVA (95% CI)*	-0.0657 (-0.2796 to 0.1481)		NA	-0.0107 (-0.2103 to 0.1889)		NA
Cycle 2	0.086±0.3877	0.143±0.5918	0.5317	0.077±0.352	0.125±0.5366	0.5056
ANCOVA (95% CI)*	-0.05854 (-0.2440 to 0.1269)		NA	-0.0490 (-0.1926 to 0.0946)		NA
Proportion of patients with severe neutropenia, n (%) [a]						
Cycle 1	4 (6.35%)	6 (9.09%)	0.7446	7 (8.14%)	7 (8.43%)	1.0000
Cycle 2	3 (5.17%)	4 (6.35%)	1.0000	4 (5.13%)	5 (6.25%)	1.0000
Depth of ANC nadir, $\times 10^9$/L, mean±SD [b]						
Cycle 1	3.807±3.019	3.502±2.556	0.5380	4.076±3.437	3.672±3.115	0.4238
Cycle 2	3.577±2.554	3.594±2.744	0.9719	3.748±2.541	3.690±2.807	0.8919
Time to ANC recovery, days, mean±SD [b]						
Cycle 1	3.0952±4.9407	3.7879±5.4871	0.4521	3.1744±5.1317	3.6145±5.3302	0.5852
Cycle 2	2.9138±5.4363	3.7143±5.777	0.4338	2.6026±5.0177	3.55±6.0335	0.2855
Incidence of FN, n (%) [c]						
Cycle 1	1 (1.59%)	0	0.3061	1 (1.16%)	0	0.3259
Cycle 2	0	0	NA	1 (1.28%)	0	0.3112
Across cycles	1 (1.59%)	0	0.3061	2 (2.33%)	0	0.1635

Rates of hospitalisation due to FN, n (%) [b]						
Cycle 1	1 (1.59%)	0	0.4884	1 (1.16%)	0	1.0000
Cycle 2	0	0	NA	1 (1.28%)	0	0.4937
Proportion of patients requiring systemic antibiotic(s), n (%) [b]						
Cycle 1	1 (1.59%)	0	0.4884	1 (1.16%)	0	1.0000
Cycle 2	0	0	NA	1 (1.28%)	0	0.4937

[Table/Fig-4]: Results of all efficacy endpoints.
SD: Standard deviation; CI: Confidence interval; ANC: Absolute neutrophil count; FN: Febrile neutropenia; NA: Not applicable
p-values were obtained by performing [a] Fisher's exact test, [b] Unpaired t-test, [c] CMH test
*ANCOVA, analysis of covariance and 2-sided 95% CI difference in treatment arms

In cycle 3, none of the patients experienced FN. The incidence of FN, rates of hospitalisation due to FN, and proportion of patients requiring systemic antibiotic(s) were nil for both treatment arms and for both PP and mITT populations.

Thus, both treatments successfully prevented FN in subsequent cycles and avoided the complication of FN in patients receiving myelosuppressive chemotherapy with comparable efficacy.

Safety

The common AEs observed in both treatment groups with a frequency of >5% were anaemia, leukopenia, neutropenia, constipation, diarrhoea, nausea, vomiting, asthenia, pain, pyrexia, back pain, weight decrease, pain in extremity, and headache.

The ADRs common to both groups were neutrophilia and musculoskeletal pain. Musculoskeletal pain of severe degree was the only serious ADR noted once in each arm.

No patient was withdrawn from the study due to AE in any of the arms. There were no statistically significant differences in the incidence of AE, ADR or SAEs in any of the cycles between the groups [Table/Fig-5]. Both the groups were comparable in terms of vitals and laboratory parameters also.

Number of patients	AEs, n (%)	ADRs, n (%)	SAEs, n (%)
Cycle 1			
Pegfilgrastim (n=86)	54 (62.79%)	6 (6.98%)	5 (5.81%)
Neulastim® (n=84)	55 (65.48%)	1 (1.19%)	2 (2.38%)
p-value	0.7500	0.1170	0.4430
Cycle 2			
Pegfilgrastim (n=78)	45 (57.69%)	6 (7.69%)	6 (7.69%)
Neulastim® (n=80)	40 (50.00%)	1 (1.25%)	1 (1.25%)
p-value	0.3430	0.0610	0.0610
Cycle 3			
Pegfilgrastim (n=69)	19 (27.54%)	0	0
Neulastim® (n=76)	23 (30.26%)	0	0
p-value	0.8540	NA	NA

[Table/Fig-5]: Safety results.
AE: Adverse events; ADR: Adverse drug reaction; SAE: Serious adverse event; NA: Not applicable
p-values were obtained by performing Fisher's-Exact test

DISCUSSION

In this prospective, randomised, multi-centre, comparative study, Lupin's Pegfilgrastim was shown to be equivalent in terms of efficacy and safety to Amgen's Neulastim® in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy. In the PP analysis, the mean DSN in cycle 1 was 0.127 days in the Pegfilgrastim arm and 0.197 days in the Neulastim® arm, whereas in the mITT analysis, it was 0.174 days in the Pegfilgrastim arm and 0.193 days in Neulastim® arm. The mean DSN was comparable between the Pegfilgrastim and Neulastim® arms in cycles 1 and 2. The 95% CI for the difference in cycle 1 was within the equivalence range of ±1 day, thus meeting the primary endpoint.

The DSN is dependent on G-CSF efficacy; a difference in DSN signifies clinical differences in the activity of the reference product and biosimilar. Previous studies by Blackwell K et al., Harbeck N et al., and Desai K et al., comparing a Pegfilgrastim biosimilar with a reference product have used similar endpoints, both primary and secondary [22-24]. Moreover, FN and risk of infection are directly proportional to DSN, making it a sensitive and clinically relevant endpoint [25]. This indicates that Lupin's Pegfilgrastim has a G-CSF efficacy similar to Neulastim®. In addition, the other endpoints assessed in these studies viz. DSN in cycle 2, the incidence of severe neutropenia, depth of ANC nadir, time to ANC recovery, the incidence of FN, rate of hospitalisations due to FN, the proportion of patients requiring systemic antibiotics for FN were also analysed and were comparable between Lupin's Pegfilgrastim and Neulastim®.

Results from established studies have reported a mean DSN in cycle 1 ranging from 1.19 to 1.4 days and depth of ANC nadir of $<1\times10^9$/L [22-24]. In the present study, the mean DSN in cycle 1 was <1 day and depth of ANC nadir was $>3.5\times10^9$/L. While these studies enrolled a homogenous patient population for the study, the present study enrolled a heterogenous patient population-six different cancers, four stages of cancer, and four different chemotherapy regimens. This difference in patient populations may have contributed to the difference in values. Blackwell K et al., reported a time to ANC recovery ranging from 2.04 to 2.11 days, Harbeck N et al., reported 1.72 to 1.76 days, and Desai K et al., reported 9.2 to 9.5 days, while the present study reports 2.9 to 3.6 days [22-24]. Blackwell K et al.,and Harbeck N et al,. have recorded the proportion of patients with ≥1 fever episodes and they report as high as 34.5% of patients; Desai K et al., report rates of FN <10% [22-24]. In the present study, only two patients experienced FN in the mITT population. While comparing values across different studies offer insights about the clinical implications of the drug, in case of biosimilars, the efficacy and safety comparisons must be with the reference biologic in a head-to-head trial [15].

Very few patients experienced severe neutropenia (<10%) in the present study. Similarly, the incidence of FN, rates of hospitalisation, and proportion of patients requiring systemic antibiotic(s) were also low. This could be due to the successful prophylaxis provided by Pegfilgrastim and Neulastim® in majority of patients randomised in the present study. With regards to safety endpoints, the Pegfilgrastim arm did not show any new and significant safety concerns. The safety profile of Pegfilgrastim was comparable to that of Neulastim®.

The present phase III study was amongst the first few well-controlled therapeutic equivalence trials for the biosimilar Pegfilgrastim approval in Indian patients conducted prior to the introduction of Indian Biosimilar Guidelines by CDSCO and the DBT which recommends use of equivalence study designs for biosimilar approval in India [15]. The study assessed 129 subjects in PP population and showed that, the difference in DSN in cycle 1 is well within the equivalence range of ±1 day. Similarity in efficacy

was also demonstrated for all the secondary efficacy endpoints in both the PP and mITT populations.

Most of the biosimilar G-CSF trials have demonstrated clinical equivalence in one or a few cancer types. However, in clinical practice, G-CSFs are prescribed in patients with diverse non-myeloid malignancies, receiving various myelosuppressive anticancer agents. The evidence of therapeutic equivalence demonstrated in the present study in patients with various non-myeloid malignancies receiving different myelosuppressive chemotherapies is relevant for extrapolation to real-world clinical practice where diversity of cancer types and chemotherapy regimens is a norm. Also, various myelosuppressive chemotherapeutic agents used in this study have >20% risk of FN, which is the recommended risk threshold for prophylactic use of G-CSFs [5,26]. This gives the results of the present study a scope for extrapolation to all non-myeloid malignancies and makes it relevant to routine clinical practice [27].

Limitation(s)

Indian Biosimilar Guidelines recommend immunogenicity assessment in biosimilar clinical trials. Since, the authors initiated the present study prior to the introduction of Indian Biosimilar Guidelines, immunogenicity was not planned in the present study, which is one of the limitations of this trial. However, a dedicated immunogenicity study was planned subsequently after the product was introduced in India (ClinicalTrials.gov Identifier NCT03511378).

CONCLUSION(S)

Lupin's Pegfilgrastim is equivalent in efficacy with comparable safety profile to Neulastim® as an adjunct to chemotherapy in Indian patients with non-myeloid malignancies receiving myelosuppressive chemotherapy. Lupin's Pegfilgrastim can be potentially used as a therapeutically equivalent biosimilar alternative to Neulastim® when used in routine clinical practice to reduce the DSN and incidence of FN. Indian healthcare providers can opt for this economically viable and easily accessible Pegfilgrastim biosimilar for supportive care.

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