ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 10, pp.74013-74018, October, 2018

DOI: https://doi.org/10.24941/ijcr.32349.10.2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

RANDOMIZED, MULTI-CENTRIC, DOUBLE-BLIND COMPARATIVE STUDY TO EVALUATE EFFICACY AND SAFETY OF BIOSIMILAR PEGFILGRASTIM AND REFERENCE PEGFILGASTRIM IN PATIENTS WITH CHEMOTHERAPY INDUCED NEUTROPENIA (CIN)

***Prasad Apsangikar, Manoj Naik, Sunil Chaudhry, Shashank Deosghare, Jamila Joseph**

Medical Affairs Group, Reliance Life Sciences, Navi Mumbai 400701, Maharashtra, India

ARTICLE INFO

Article History:
Received 20th July, 2018
Received in revised form
07th August, 2018
Accepted 24th September, 2018
Published online 30th October, 2018

Key Words:

Pegfilgrastim neutropenia chemotherapy cancer, ANC, Efficacy.

**Corresponding author:*

ABSTRACT

Background: Pegfilgrastim is the most widely used long-acting G-CSF available worldwide in the management of febrile neutropenia during chemotherapy.

Objective: The present multicentre study evaluated efficacy and safety of pegfilgrastim biosimilar against innovator reference pegfilgrastim, when given subcutaneously in patients with Chemotherapy Induced Neutropenia (CIN).

Methods: A prospective, multi-centre, randomized, double-blind, two-arm, parallel group, active-control, comparative clinical study to evaluate efficacy and safety of biosimilar pegfilgrastim (study arm)/ innovator pegfilgrastim (reference arm) in patients with Chemotherapy Induced Neutropenia. A total of 105 patients were enrolled in in two arms i.e. study pegfilgrastim and innovator pegfilgrastim. The primary objective of the study was to evaluate the duration of Grade 4 neutropenia in patients receiving study drug / reference drug in the 1st cycle of chemotherapy during the study and the secondary objectives of the study were to study the incidence of Grade 4 neutropenia, the incidence and duration of febrile neutropenia, time to ANC recovery after ANC nadir and the depth of ANC nadir in Cycles 1 to 4.

Results: Mean duration of Grade 4 neutropenia was 1.43 days in the study arm and 2.00 days in the reference arm. In the secondary efficacy analysis, most cases of Grade 4 neutropenia occurred in the first cycle. No cases of Grade 4 neutropenia were noted during cycle 2 in either of the treatment arms. The incidence of Grade 4 neutropenia in the study arm was 4.76% in cycle 3 and 1.11% in cycle 4. The incidence of Grade 4 neutropenia in the reference arm was 6.25% in cycle 3. There was no statistically significantly difference between the study and reference arm during cycle 3.(P= 0.759). No subject in either arm developed febrile neutropenia in any of the cycles other than this sporadic case. The depth of ANC nadir in study arm was lowest in cycle 1, (2.914 $x10^9$/L) and in reference arm, the depth of ANC nadir was lowest in cycle 4 (3.23 $x10^9$/L). The mean time to ANC recovery ($\geq$2.0$x10^9$/L) after the ANC nadir in study arm and in reference arm was comparable. Observed difference between two arms in 2nd, 3rd, and 4th cycle was statistically insignificant.

Conclusion: The biosimilar pegfilgrastim was found to be as effective and safe as reference pegfilgrastim product. The analysis of secondary endpoints were consistent with those of the primary endpoint, with reduction in incidence and duration of grade 4 neutropenia and febrile neutropenia.

Citation: ***Prasad Apsangikar, Manoj Naik, Sunil Chaudhry, Shashank Desghare, Jamila Joseph*****, 2018.** "Randomized, multi-centric, double-blind comparative study to evaluate efficacy and safety of biosimilar pegfilgrastim and reference pegfilgastrim in patients with Chemotherapy Induced Neutropenia (CIN)", *International Journal of Current Research*, 10, (10), 74013-74018.

INTRODUCTION

Febrile neutropenia (FN) is a serious side effect of many cancer treatments and can lead to infections and sepsis with potentially fatal consequences (Aapro *et al.,* 2010). The European Society of Medical Oncology defines FN as "an oral temperature of 38.3 °C or two consecutive readings of > 38.0 °C for 2 hours and an absolute neutrophil count (ANC) of < 0.5 × 10^9/L, or expected to fall below < 0.5 × 10^9/L" (Klastersky *et al.,* 2016). The Infectious Diseases Society of America defines it as an "ANC < 500 cells/mm^3 (or that is expected to decrease to < 500 cells/ mm3 during the next 48 hours) with a single oral temperature measurement of > 38.3 °C or a temperature of ≥ 38.0 °C sustained over a 1-hour period" (Alison Freifeld *et al.,* 2011). In patients receiving chemotherapy, development of FN can result in dose reduction and/or treatment delays, or treatment discontinuation, which may limit disease control (Li Wang *et al.,* 2015). Current guidelines recommend granulocyte colony-stimulating factors (G-CSF) for primary prophylaxis of chemotherapy-induced FN when the overall risk of FN among patients with non-myeloid malignancies receiving myelosuppressive chemotherapy is ≥ 20% (Thomas *et al.,* 2015). Pegfilgrastim is the most widely approved long-acting G-CSF available worldwide. Initially approved by FDA and

EMA in 2002, it is now the most commonly used. Pegfilgrastim has been shown to have a favorable efficacy and safety profile and may be preferred over short-acting G-CSF by both patients and physicians due to improved adherence and its convenient once-per-cycle subcutaneous administration, thereby improving patient compliance by reducing inconvenience of multiple injections (Matti Aapro *et al.,* 2017). Biosimilar products are biologic medicines that have highly similar physicochemical and functional characteristics with current regulations and high end characterization. The present study evaluated efficacy and safety of pegfilgrastim biosimilar against innovator reference pegfilgrastim, when given subcutaneously in patients with Chemotherapy Induced Neutropenia (Matti Aapro *et al.,* 2017).

MATERIALS AND METHODS

The study was a prospective, multi-centre, randomized, double-blind, two-arm, parallel group, active-control, comparative clinical study to evaluate efficacy and safety of biosimilar pegfilgrastim (study arm)/ innovator pegfilgrastim (reference arm) in patients with Chemotherapy Induced Neutropenia (CTRI/2015/03/005607). The study was conducted in compliance with the ethical principles that originated in the declaration of Helsinki and ICH-GCP and Indian Schedule-Y regulations. The purpose of the study was to assess the comparative efficacy and safety of biosimilar pegfilgrastim against the innovator pegfilgastrimin patients with chemotherapy-induced Neutropenia. The study was designed and conducted with the principles of good clinical practice, with applicable regulatory requirements. This study was approved by the respective Institutional Ethics Committee at each site and eligible patients provided written informed consent before participating in the study. A total of 105 patients were enrolled in the study across 15 centers in two arms i.e. Study pegfilgrastim and innovator pegfilgrastim in a 2:1 ratio. The centralized randomization sheet was provided by statistical team was followed across all sites and subjects were assigned to the treatment groups according to randomization. All subjects who had given written informed consent to participate in the study were assigned a sequential subject number at the screening visit. Subjects were randomly assigned to the 2 treatment groups in a 2:1 ratio. Once a subject was found to be eligible for randomization, the site requested a randomization code for the subject. Randomization was managed centrally. Subject identification number was a unique number having site number and subject number. After randomization, 70 patients were enrolled in study arm and 35 patients in reference arm. The primary objective of the study was to evaluate the duration of Grade 4 neutropenia in patients receiving study drug / reference drug in the 1stcycle of chemotherapy during the study. On Day 1 of the first four cycles in the study, chemotherapy was administered to all the patients and approximately 24 hrs later (on the day after chemotherapy) a single dose of biosimilar pegfilgastrim 6 mg (0.6 mL) was administered subcutaneously. Patients received study medication as primary or secondary prophylaxis once per cycle for the first four cycles in the study followed by therapeutic treatment as prescribed by the treating physician from the 5thcycle onward. All patients were assessed for Grade 4 neutropenia, incidence of febrile neutropenia and time to ANC recovery in the first 4 cycles of chemotherapy in the study. The primary endpoint of the study was to measure the duration of Grade 4 neutropenia (ANC<0.5x10^9/L) in days in patients receiving study drug / reference product in the first cycle of chemotherapy during the study. The secondary objectives of the study were to study the incidence of Grade 4 neutropenia in the 2nd, 3rdand 4thcycle of chemotherapy during the study, to assess the incidence and duration of febrile neutropenia, time to ANC recovery after ANC nadir and study the depth of ANC nadir in Cycles 1 to 4, to compare the safety of both arms and to study the immunogenicity of study and reference products.

Subject disposition

70 subjects were randomized in biosimilar pegfilgrastim or study arm and 35 subjects were randomized in reference arm. Intent to treat (ITT) population included all subjects who were randomized in the study while safety population included all subjects who were randomized and received at least a single dose of study medication. One subject withdrew consent and did not report on the day of dosing. Hence, a total of 104 subjects were included in safety population i.e. 69 subjects in study arm and 35 subjects in reference arm. In study arm, one subject was withdrawn due to adverse event after dosing, seven subjects withdrew consent after dosing, one subject was lost to follow-up, two subjects were discontinued in their interest to be withdrawn and one subject had a serious adverse event during the first cycle. In reference arm, three subjects withdrew consent, one subject had an adverse event and was withdrawn from the study and one subject was discontinued in subject's best interest. Out of 104 subjects, a total of 87 subjects. i.e. 57 subjects in study arm and 30 subjects in reference arm completed all four cycles in the study. Evaluable population for efficacy included all patients who received at least one dose of biosimilar pegfilgastrimin the first chemotherapy cycle and had pre- and post-dosing ANC data of at least Cycle 1. Hence 104 subjects were considered as evaluable subjects for efficacy analysis i.e. 69 subjects in study arm and 35 subjects in reference arm. Patient disposition, including reasons for discontinuation, is summarized below in Table 1. The primary endpoint analysis was based on duration of grade 4 neutropenia (ANC <0.5x10^9/L) measured in days in 1st cycle of chemotherapy during the study. The mean, median, range, standard deviation were presented for primary endpoint analysis. The secondary efficacy analysis was based on duration and incidence of ANC related efficacy assessment parameters which included febrile neutropenia, grade 4 neutropenia, ANC nadir and recovery time from ANC nadir. Safety assessment was based on incidence of treatment-emergent adverse events, and abnormal clinical as well as laboratory results from baseline to the end of the study. Antibody assessment was included as an additional safety parameter assessed at the baseline and at the end of third cycle. A full statistical analysis plan (SAP) was written to describe the statistical methods to be employed in the study and the data presentations required for this study. Statistical analyses were performed using the SAS® system. Comparative analysis of study and reference drug was performed for primary and secondary endpoint data.

RESULTS

Demographic and Other Baseline Characteristics

Out of 70 subjects randomized in study arm, 59 (84.29%) were female subjects and 11 (15.71%) were male subjects. Out of 35 subjects randomized in reference arm, 32 (91.43%) were female subjects and 3 (8.57%) were male subjects.

Table 1. Subject Disposition [N=104 (69 in study arm and 35 in reference arm)]

Parameter	Study arm	Reference arm
Study Completed	57 (82.61%)	30 (85.71%)
Reason for Early Termination		
The subject was non-compliant with protocol specifications	0 (0.00%)	0 (0.00%)
The subject was erroneously included in the study	0 (0.00%)	0 (0.00%)
Adverse Events	1 (1.45%)	1 (2.86%)
The investigator feels it is in the subject's best interest to be withdrawn	2 (2.90%)	1 (2.86%)
Subject Non Responder to IP Therapy	0 (0.00%)	0 (0.00%)
The study is terminated by the sponsor	0 (0.00%)	0 (0.00%)
Lost to follow–up	1 (1.45%)	0 (0.00%)
The subject withdrew consent	7 (10.14%)	3 (8.57%)
Serious adverse effect	1 (1.45%)	0 (0.00%)
Other	0 (0.00%)	0 (0.00%)

Table 2. Demographics and baseline characteristics

Parameters	Variable	Study arm (N=70)	Reference (N=35)	Total (N=105)
Age (yrs)	N	70	35	105
	Mean	46.3	47.7	46.8
	Std Dev	10.85	9.2	10.31
Sex	Female	59(84.29%)	32(91.43%)	91(86.67%)
	Male	11(15.71%)	3(8.57%)	14(13.33%)
Weight (Kg)	N	70	35	105
	Mean	53.2	57.6	54.6
	Std Dev	7.66	9.37	8.48
Height (cm)	N	70	35	105
	Mean	152.3	152.2	152.3
	Std Dev	8.14	6.26	7.54
Bmi (Kg/m2)	N	70	35	105
	Mean	23	24.8	23.6
	Std Dev	2.94	3.74	3.32
Anc result (..x109/l)	N	70	35	105
	Mean	5	6.4	5.5
	Std Dev	1.69	2.31	2.01
Ecog performance	0	27(38.57%)	9(25.71%)	36(34.29%)
	1	42(60.00%)	26(74.29%)	68(64.76%)
	2	1(1.43%)	.(.%)	1(0.95%)

Table 3. Duration of Grade 4 neutropenia in chemotherapy cycle 1 (Evaluable population N=104)

Primary Efficacy measure	Observations	Treatment Groups	
		Study arm	Reference arm
Duration of Grade 4 (severe) neutropenia	n/N	7/69	1/35
(Chemotherapy cycle 1)	Mean	1.43 days	2.00 days

Table 4. Incidence of grade 4 neutropenia in chemotherapy cycles 2nd, 3rd and 4th cycle of chemotherapy (Evaluable population N=104)

Primary Efficacy measure	Observations	Treatment Groups	
		Study arm	Reference arm
Incidence of Grade 4 neutropenia (Cycle 2)	n/N	0	0
	%	NA	NA
	OR(95% CI)	NA	NA
Incidence of Grade 4 neutropenia (Cycle 3)	n/N	3/63	2/32
	%	4.76	6.25
	OR(95% CI)	0.75	
	P value	0.759	
Incidence of Grade 4 neutropenia (Cycle 4)	n/N	1/60	0
	%	1.11%	NA
	OR(95% CI)	NA	
	P value	NA	

The mean age of subjects randomized in the study arm was 46.3 years and the mean weight of subjects was 53.2 kgs. The mean age of subjects randomized in the reference arm was 47.7 years and the mean weight of subjects was 57.6 kgs. The mean BMI of subjects was 23.0 kg/m^2in study arm and 24.8 kg/m^2in reference arm. The most common primary tumor in both treatment arms was breast cancer (72.46% in study arm and 77.14% in reference arm). The demographics and baseline characteristics of ITT population are given below and are noted to be comparable between the two arms.

The demographics and baseline characteristics of per-protocol (PP) population is given in the Table 2.

Efficacy analysis

The primary endpoint of the study was to measure the duration of Grade 4 neutropenia (ANC<$0.5x10^9$/L) in days in the first cycle of chemotherapy during the study. In the evaluable population, the mean duration of Grade 4 neutropenia was 1.43 days in the study arm and 2.00 days in the reference arm Table 3.

Table 5 Secondary efficacy results

Secondary Efficacy measure	Observations	Treatment Groups	
		Study arm (N=69)	Reference arm (N=35)
Depth of ANC nadir (Cycle 1)	Mean	2.914 x10^9/L	3.361 x10^9/L
	SD	1.838	1.510
	Median(Range)	2.960(0.060 – 8.78)	3.300(0.432 – 6.680)
	(95% CI)	(-0.225, 1.119)	
	P value	0.189	
Depth of ANC nadir (Cycle 2)	Mean	3.36 x10^9/L	4.15 x10^9/L
	SD	1.61	1.63
	Median(Range)	3.225(0.520 – 7.770)	3.805(1.080-8.140)
	(95% CI)	(0.092, 1.490)	
	P value	0.027	
Depth of ANC nadir (Cycle 3)	Mean	3.17 x10^9/L	3.46 x10^9/L
	SD	2.29	1.98
	Median(Range)	3.070(0.220 – 10.030)	3.095(0.420 – 10.240)
	(95% CI)	(-0.611, 1.197)	
	P value	0.520	
Depth of ANC nadir (Cycle 4)	Mean	3.32 x10^9/L	3.23 x10^9/L
	SD	1.61	1.76
	Median(Range)	2.930(0.456 – 11.080)	2.670(0.800-8.50)
	(95% CI)	(-0.864, 0.674)	
	P value	0.805	

Table 6. Mean time to ANC recovery in cycles 1 to 4

Secondary Efficacy measure	Observations	Treatment Groups	
		Study arm (N=69)	Reference arm (N=35)
Time to ANC recovery (Cycle 1)	Mean	2.222	1.86
	SD	1.396	1.069
	Median(Range)	2.00(1.00-7.00)	2.0(1.0-4.0)
	(95% CI)	(-1.481, 0.755)	
	P value	0.497	
Time to ANC recovery (Cycle 2)	Mean	2.27	1.5
	SD	1.421	0.707
	Median(Range)	2.0(1.0-6.0)	1.5(1.0-2.0)
	(95% CI)	(-3.606, 2.060)	
	P value	0.361	
Time to ANC recovery (Cycle 3)	Mean	2.67	2
	SD	1.923	0.632
	Median(Range)	2.0(1.0-7.0)	2(1.0-3.0)
	(95% CI)	(-1.980, 0.646)	
	P value	0.294	
Time to ANC recovery (Cycle 4)	Mean	1.71	2.29
	SD	0.756	2.138
	Median(Range)	2.0(1.0-3.0)	2.0(1.0-7.0)
	(95% CI)	(-1.455, 2.599)	
	P value	0.526	

The observed results were comparable in both treatment arms in terms of duration of Grade 4 neutropenia. In the secondary efficacy analysis (Table 4), most cases of Grade 4 neutropenia occurred in the first cycle. No cases of Grade 4 neutropenia were noted during cycle 2 in either of the treatment arms. The incidence of Grade 4 neutropenia in the study arm was 4.76% in cycle 3 and 1.11% in cycle 4. The incidence of Grade 4 neutropenia in the reference arm was 6.25% in cycle 3. None of the subjects had Grade 4 neutropenia in cycle 4 in the reference arm. In the per protocol (PP) population, the incidence of Grade 4 neutropenia was not statistically significantly different between the study and reference arm during cycle 3.(P= 0.759). In terms of the incidence & duration of febrile neutropenia in cycles 1 to 4 during the study, as per NCCN definition only documented grade 4 neutropenia was used to label the cases as febrile neutropenia and no cases with grade 3 neutropenia was included in analysis. In the evaluable population, one subject (1.45%) in study arm developed febrile neutropenia during cycle 1. The incidence of febrile neutropenia was very low. No subject in either arm developed febrile neutropenia in any of the cycles other than this sporadic case. The depth of ANC nadir for each cycle was defined as the minimal ANC value for a patient in each respective cycle.

The depth of ANC nadir in study arm was lowest in cycle 1. (2.914 x10^9/L) and in reference arm, the depth of ANC nadir was lowest in cycle 4 (3.23 x10^9/L). The observed depth of ANC nadir in study and reference arm were comparable in both treatment arms and the observed difference between two arms in each cycle is statistically insignificant (Table 5). The mean time to ANC recovery (≥2.0x10^9/L) in days after the ANC nadir was 2.22 days in the study arm and 1.86 days in reference arm in cycle 1 (P=0.497). The mean time to ANC recovery (≥2.0x10^9/L) in days after the ANC nadir in study arm and in reference arm arm was comparable. The observed difference between two arms in 2nd, 3rd, and 4th cycle was statistically insignificant (Table 6).

Safety analysis

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1. The safety evaluation was performed using safety population of 104 subjects who were dosed were considered for safety analysis. In this study, 547 adverse events were reported out of which, 320 were reported in 56 subjects in the study arm and 227 were reported in 26 subjects in the reference arm. All the AEs

reported in the study were treatment emergent adverse events (TEAE). There were 16 (23.19 %) subjects in the study arm and 10 (28.57 %) subjects in the reference arm with at least one treatment emergent adverse event related to study drug. There were 13 (18.84%) subjects and five (14.29%) subjects respectively in the study and reference arm with at least one treatment emergent severe adverse event in the study. In this study, two (2.90%) serious adverse events (SAEs) including one death were reported in study arm (the death was unrelated to study medication and was related to disease stage and complications). As per MedDRA coding, these two SAEs were coded into Blood and lymphatic system disorders and vascular disorder SOC. One (1.45%) subject from study arm and one (2.86%) subject from reference arm discontinued the study due to an adverse event. According to SOC (System Organ Class) in the study arm, the most commonly reported (incidence ≥ 5%) TEAEs were related to gastrointestinal disorders [30 (43.48%)] SOC followed by skin and subcutaneous tissue disorders [27 (39.13%)], General disorders and administration site conditions [26 (37.68%)], Blood and lymphatic system disorders [13 (18.84%)] SOC, Nervous system disorders [10 (14.49%)] and Musculoskeletal and connective tissue disorders [9 (13.04%)]. In the reference arm, the most commonly reported (incidence ≥ 5%) TEAEs were related to skin and subcutaneous tissue disorders [20 (57.14%)] followed by gastrointestinal disorders [18 (51.43%)], General disorders and administration site conditions [17 (48.57%)], Blood and lymphatic system disorders [7 (20.00%)], and Nervous system disorders [5 (14.29%)]. The observed mean bone pain score on numeric pain rating scale of 0-10 was 1.4 and 1.5 in study and reference arms respectively during cycle 1. Mean score showed a steady increase from day 2 onwards until day 6 and showed decline after day 8 and reached near baseline values by day 21 in cycle 1. A similar trend for mean bone pain score was observed in cycle 2, 3 and 4. The observed change in bone pain was comparable in both treatment arms. Immunogenicity analysis was done by sandwich enzyme immunoassay technique method, was based on the resulting presence of antibodies at the end of 3rdcycle against baseline assessment. A total of 196 samples were analyzed in six sets and it was established that the samples were negative for anti-drug antibodies (ADA).

DISCUSSION

Use of granulocyte-colony stimulating factor (G-CSF) agents, including the long-acting G-CSF pegfilgrastim, is recommended for both primary and secondary prophylaxis of chemotherapy-induced FN, and many providers and many patients prefer pegfilgrastim to short-acting therapeutic options because of its less frequent administration (Matti Aapro and Kelly Davio, 2017). According to Expert recommendations, Pegfilgrastim or short-acting G-CSF should be given for all cycles of chemotherapy in patients receiving chemotherapy or targeted agents with a FN risk of 20% of greater. For patients with a FN risk of 10% to 20%, if the factors that increase risks demonstrate that the overall risk of neutropenia-related complications is 20% or higher, the patient should receive pegfilgrastim or short-acting G-CSF (Alison Rodriguez, 2017). In this study, the duration of Grade 4 neutropenia observed in either treatment group was considerably shorter than values reported in previous clinical studies in patients who received myelosuppressive chemotherapy. The results of this study demonstrated the biosimilarity of biosimilar pegfilgrastim versus the reference product in patients on myelosuppressive chemotherapy. The analysis of secondary endpoints were consistent with those of the primary endpoint, with reduction in incidence and duration of grade 4 neutropenia and febrile neutropenia. Most cases of grade 4 neutropenia occurred in the first cycle. No cases of Grade 4 neutropenia were noted during cycle 2 in any of the treatment arms. The observed incidence of febrile neutropenia was very low and only one case was observed in biosimilar study arm. This may be attributed to strict criteria defined in the protocol as per NCCN for defining the febrile neutropenia (ANC below 0.5x109/L and fever). The depth of ANC nadir in cycle 1 was comparable in both treatment groups with no significant difference observed (P =0.189). In cycles 2 and 3 the mean depth of ANC nadir had higher absolute values for subjects treated with reference arm compared with those treated with biosimilar study arm. This was not observed in cycle 4. The depth of ANC nadir in all cycles was comparable in both treatment groups with no significant difference observed. The time to recovery from ANC nadir was shorter in cycle 4 and longer in cycle 1 for subjects treated with biosimilar pegfilgrastim compared with those treated with reference arm. The time to recovery from nadir in any cycle was comparable in both treatment arms with no significant differences observed. The results of this study demonstrate the non-inferiority of biosimilar pegfilgrastim versus the reference pegfilgrastim in patients on myelosuppressive chemotherapy.

Conclusion

This present phase III study has indicated a therapeutic equivalence between biosimilar pegfilgrastim and reference product based on efficacy and safety including immunogenicity assessment. Considering the data analyzed for efficacy and safety, the biosimilar pegfilgrastim was found to be as effective and safe as reference product. The effectiveness of pegfilgrastim is established in the setting of chemotherapy-induced neutropenia (CIN) across multiple indications and can provide an added benefit for patient safety. Mass usage of an economical biosimilar in clinical practice is further expected to improve treatment outcomes through added compliance.

Conflict of Interest statement: The authors declare that there is no conflict of interest.

Funding statement: This study was a multicentric phase III clinical study with the regulatory approval in India conducted and funded by Reliance Life Sciences Pvt. Ltd.

Acknowledgement

We acknowledge the investigators who participated in the study for completion of the data. Any opinions and conclusion expressed are those of the authors.

REFERENCES

Aapro, M.S., J. Bohlius, D.A. Cameron, Lissandra Dal Lago et al. 2010. update of EORTC guidelines for the use of granulocytecolony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *European Journal of Cancer,* 2011: 47; 8 –3 2.

Alison G. Freifeld, Eric J. Bow, Kent A. Sepkowitz, Michael J. Boeckh et al. 2011. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with

Cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical Practice Guideline,* CID 2011:52.

Alison Rodriguez, 2017. Expert Recommendations for Pegfilgrastim in Chemotherapy-Induced Febrile Neutropenia. Newsroom.

Clinical Study Report, Version 1.0, *Investigational Product:* R-TPR-029(Peg Filgrastim) Dated 17 Nov 2015.

Jihyoun Lee, Jong Eun Lee, Zisun Kim, Sun Wook Han, Sung Mo Hur, Sung Yong Kim et al. 2018. Pegfilgrastim for primary prophylaxis of febrile neutropenia in breast cancer patients undergoing TAC chemotherapy. *Annals of Surgical Treatment and Research,* 94(5); 223-228.

Li Wang, Onur Baser, LucieKutikova, John H. Page, Richard Barron, 2015. The impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia during chemotherapy: a systematic review and meta-analysis of randomized controlled trials. *Support Care Cancer,* 23; 3131–3140.

Klastersky, J., J. de Naurois, K. Rolston, B. Rapoport, G. Maschmeyer, M. and Aapro, et al. 2016. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Annals of Oncology,* 27 (Supplement 5); v111–v118.

Matti Aapro, Ralph Boccia, Robert Leonard, Carlos Camps, Mario Campone, Sylvain Choquet et al. 2017. Refining the role of pegfilgrastim (a long-acting G-CSF) for prevention of chemotherapy-induced febrile neutropenia: consensus guidance recommendations. *Support Care Cancer,* 25; 3295–3304.

MattiAapro, Kelly Davio, 2017. Consensus Recommendations on Pegfilgrastim for Prophylaxis of Febrile Neutropenia. October 23.

Thomas J. Smith, Kari Bohlke, Gary H. Lyman, Kenneth R. Carson, Jeffrey Crawford, Scott J. Cross et al. 2015. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology,* Vol 33 (28).

****