

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

CLINICAL STUDY PROTOCOL

Title: An open-label, randomized, comparative, parallel group study to assess the Immunogenicity of Lupin's Peg-filgrastim versus Neulasta® as an Adjunct to Chemotherapy in Patients with Breast Cancer

Protocol No. LRP/PegGCSF/2016/004
Version No.: 2.2, Dated 02 Jul 2018;
Supersedes: Version No.: 2.1, Dated 16 Oct 2017

Name of Study Drug: Pegfilgrastim (PegGCSF)

Development Phase: Phase 4 (In India)

Sponsor: Lupin Limited (Biotechnology Division)
Gat No: 1156, Village-Ghotawade,
Taluka-Mulshi, Pune. Pin: 412115
Maharashtra, India

Sponsor Signatory: Dr. Dhananjay Bakhle/ Dr. Akshaya Odak

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This study will be conducted according to the protocol and in compliance with the International Conference on Harmonization - Good Clinical Practice (ICH - GCP) and applicable regulatory requirements.




Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: An open-label, randomized, comparative, parallel group study to assess the Immunogenicity of Lupin's Peg-filgrastim versus Neulasta® as an Adjunct to Chemotherapy in Patients with Breast Cancer

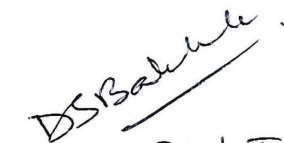
PROTOCOL NUMBER: LRP/PegGCSF/2016/004

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2nd July 2018
Signature & Date



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

STUDY SYNOPSIS

Name of Sponsor/Company: Lupin Limited	Protocol No. LRP/PegGCSF/2016/004	
Name of Active Ingredient: Pegfilgrastim		
Title of Study: An open-label, randomized, comparative, parallel group study to assess the Immunogenicity of Lupin's Peg-filgrastim versus Neulasta® as an Adjunct to Chemotherapy in Patients with Breast Cancer		
Study Site(s): Approximately 30 sites, in India, having qualified Investigators (Oncologists or other qualified clinicians).		
Planned Study Period: Q4 2017 to Q4 2018	Development Phase: Phase 4 (In India)	
Objectives: Primary Objective: To assess the immunogenicity of Lupin's Peg-filgrastim with Neulasta® in patients with breast cancer. Secondary Objectives: To assess the safety of Lupin's Peg-filgrastim with Neulasta® in patients with breast cancer		
Study Design: Randomized, Open-Label, Two-Arm, Parallel, Multi-Center study		
Methodology: This study will be conducted in India. Patients with breast cancer who are eligible to receive Pegfilgrastim and willing to give informed consent will be randomized to receive either Lupin's Pegfilgrastim or Neulasta® in 1:1 ratio. Pegfilgrastim will be administered subcutaneously once per chemotherapy cycle (of 21± 3 days) for up to 4 cycles. The myelosuppressive chemotherapy (like docetaxel/ paclitaxel/doxorubicin/ cyclophosphamide/ epirubicin) will be given on Day 1 of each cycle and Pegfilgrastim will be administered on Day 2/ Day 3 of each cycle (at least 24 hrs after chemotherapy administration). Blood samples for detection of anti-pegfilgrastim-antibodies against Pegfilgrastim, anti-peg antibodies, safety laboratory assessments, pharmacokinetic assessment (serum drug concentrations at baseline and trough [pre-dose]) and pharmacodynamic assessments (absolute neutrophil count [ANC]) will be collected at randomization (pre-dose) and on Day 10, Day 21 of cycle 1 and at the end of cycle 2 (Day 42), cycle 3 (Day 63) and cycle 4 (Day 84). Adverse events will be monitored at all cycles during the study. Day 84 will be the End of Study (EOS) visit.		
Number of Patients: Approximately 150 patients will be randomized in this study. However, sample size will be re-estimated based on interim analysis of ADA rate in first 75 patients.		
Diagnosis and Main Criteria for Inclusion: Ambulatory female patients aged ≥ 18 years with histologically or cytologically proven breast cancer receiving myelosuppressive chemotherapy that contains at least one chemotherapeutic agent from docetaxel/ paclitaxel / doxorubicin/ cyclophosphamide/ epirubicin and who are naïve to hematopoietic growth factors (e.g. G-CSF, PegGCSF) will be randomized in the study.		
Investigational Product (IP): The investigational products will be supplied as:		



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Name of Sponsor/Company: Lupin Limited	Protocol No. LRP/PegGCSF/2016/004	
Name of Active Ingredient: Pegfilgrastim		
Test Product: Lupin's Pegfilgrastim supplied as single-use, pre-filled syringe containing 6 mg of pegfilgrastim designed to deliver 6 mg pegfilgrastim Reference Product: Neulasta® supplied as single-use, pre-filled syringe containing 6 mg of pegfilgrastim designed to deliver 6 mg pegfilgrastim		
Dose and Administration: Pegfilgrastim 6 mg (Neulasta® or Lupin's Pegfilgrastim) will be administered once every chemotherapy cycle of 21 days for 4 cycles, as a subcutaneous injection to each patient.		
Study Duration: 91 days <ul style="list-style-type: none"> Screening Period: Maximum 7 full days Treatment and Subsequent Assessments: up to 4 chemotherapy cycles (84 days) 		
Study Endpoints: Primary Endpoint: Comparison of cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups at the end of cycle 4 (Day 84). Secondary Endpoint: Secondary Immunogenicity Endpoints: <ul style="list-style-type: none"> Comparison of cumulative incidence of anti-peg antibodies (binding & neutralizing) between treatment groups at the end of cycle 4 (Day 84). Comparison of incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84. Comparison of incidence of anti-peg antibodies (binding & neutralizing) between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84. Secondary Safety Endpoint: Safety during the study based on following assessment: <ul style="list-style-type: none"> Adverse Events (AE) assessment Vital signs Physical & systemic examination Laboratory parameters: Blood (hematology & biochemistry) and urinalysis 		
Statistical Methods: Statistical analyses will be performed using SAS version 9.1.3 or higher. Immunogenicity will be assessed in the intent to treat (ITT) and per protocol (PP) populations. The ITT will be the primary immunogenicity analysis population. Primary analysis The difference in the proportion of patients with cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between study groups at the end of cycle 4 (Day 84) will be calculated, along with the one-sided 95% confidence interval for the difference in proportions. Noninferiority will be assessed using a noninferiority margin of 10 percentage points. Sample size justification Noninferiority of Lupin's Pegfilgrastim versus Neulasta® will be assessed based on the one-sided 95% confidence interval for the difference between proportions using a noninferiority margin of 10 percentage points. For a two-arm, parallel-group trial with 1:1 randomization, and assuming true		



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Name of Sponsor/Company: Lupin Limited	Protocol No. LRP/PegGCSF/2016/004	
Name of Active Ingredient: Pegfilgrastim		
<p>rates of 2% in each of the two arms, the required total sample size for 90% power is 128 patients (Farrington and Manning, 1990). The expected rate for incidence of anti-pegfilgrastim antibodies is based on the various studies with Neulasta® conducted across the globe. In order to allow for a 15% dropout rate, the planned total sample size is 150 patients.</p>		
<p>Interim analysis</p> <p>An interim analysis will be conducted when primary endpoint data are available for approximately 50% of the planned total sample size (approximately 75 patients). The overall proportion of patients with anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim and anti-peg antibodies at the end of cycle 4 (Day 84) will be estimated at interim analysis. Based on the overall proportion, the sample size required for 90% power will be re-estimated using the approach of Farrington and Manning (1990). Safety of the drug will be also evaluated, in above set of patients, before the sample size re-estimation to rule out any drug related safety concerns. Descriptive statistics will be provided for safety analysis.</p>		
<p>During interim analysis, if any neutralizing anti-pegfilgrastim antibody activity is observed in the “Lupin Pegfilgrastim” arm or if the results from interim analysis clearly suggest that “Lupin Pegfilgrastim” has increased anti-pegfilgrastim antibody responses (greater than pre-specified amount of 2%) compared to Neulasta® then appropriate decision about the continuation/discontinuation of the study will be taken by sponsor.</p>		



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Table 1 Schedule of Assessment

D = Days, V = Visit C = Cycle EOS = End of Study Early Disc= Early Discontinuation	Screening period (Max 7 days)	Treatment Phase									
		Cycle 1 (Study Days 1-21±3)			Cycle 2 (Study Days 22-42±3)		Cycle 3 (Study Days 43-63±3)		Cycle 4 (Study Days 64-84±3)		
		D1 (V1)	D2	Day 10 ±3 (V2)	C1-D21 or C2-D1 (V3) *	D2	C2-D21 or C3-D1 (V4) *	D2	C3-D21 or C4-D1 (V5) *	D2	D21/ EOS/ Early Disc. (V6) ¹²
Informed consent	X										
Demography	X										
Eligibility criteria assessment	X										
Medical history	X										
Physical and systemic examination	X	X		X	X		X		X		X
Vital signs ¹	X	X		X	X		X		X		X
Weight	X				X		X		X		X
Blood sampling for lab investigations ²	X	X ^{3, 9, 10}			X ¹⁰		X ¹⁰		X ¹⁰		X
Urine sample for urine analysis ²	X	X ¹⁰			X ¹⁰		X ¹⁰		X ¹⁰		X
Urine pregnancy test ⁴	X				X		X		X		X
Serum Pregnancy test ⁴	X										
HIV, HBV and HCV	X										
Chest X-ray	X										

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Page 6 of 60



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

D = Days, V = Visit C = Cycle EOS = End of Study Early Disc= Early Discontinuation	Screening period (Max 7 days)	Treatment Phase									
		Cycle 1 (Study Days 1-21±3)			Cycle 2 (Study Days 22-42±3)		Cycle 3 (Study Days 43-63±3)		Cycle 4 (Study Days 64-84±3)		
		D1 (V1)	D2	Day 10 ±3 (V2)	C1-D21 or C2-D1 (V3) *	D2	C2-D21 or C3-D1 (V4) *	D2	C3-D21 or C4-D1 (V5) *	D2	D21/ EOS/ Early Disc. (V6) ¹²
ECG	X				X ⁹		X ⁹		X ⁹		X
Abdominal Ultrasonography (USG) ⁵	X										
Concurrent illnesses	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/treatment	X	X	X	X	X	X	X	X	X	X	X
Randomization ⁶		X									
Chemotherapy Administration ⁷		X			X		X		X		
Study Drug Administration ⁸			X			X		X		X	
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for immunogenicity assessments		X ¹¹		X	X ¹¹		X ¹¹		X ¹¹		X
Blood sampling for PK assessments		X ¹¹		X	X ¹¹		X ¹¹		X ¹¹		X
Blood sampling for		X ¹¹		X	X ¹¹		X ¹¹		X ¹¹		X

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Page 7 of 60



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

D = Days, V = Visit C = Cycle EOS = End of Study Early Disc= Early Discontinuation	Screening period (Max 7 days)	Treatment Phase									
		Cycle 1 (Study Days 1-21±3)			Cycle 2 (Study Days 22-42±3)		Cycle 3 (Study Days 43-63±3)			Cycle 4 (Study Days 64-84±3)	
		D1 (V1)	D2	Day 10 ±3 (V2)	C1-D21 or C2-D1 (V3) *	D2	C2-D21 or C3-D1 (V4) *	D2	C3-D21 or C4-D1 (V5) *	D2	D21/ EOS/ Early Disc. (V6) ¹²
ANC assessments											

Explanation of symbols used:

- * Day 21 assessments of previous cycle can be done on Day 1 (Pre chemotherapy) of next cycle.
- 1 Includes body temperature, pulse rate, blood pressure, and respiratory rate.
- 2 **Hematology:** Complete blood count (CBC) [hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), platelets and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils)], Absolute Neutrophil count
Blood chemistry: Bilirubin (total, direct, indirect), alkaline phosphatase, ALT, AST, BUN, total protein, albumin, globulin, uric acid, urea, creatinine, random glucose, LDH.
Urinalysis: Appearance, color, specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood (and microscopic examination, if abnormality is suspected).
In case of premature termination of the study, these investigations should be repeated on the day of termination as far as possible
- 3 Hematology tests to be repeated if the gap between screening laboratory investigations and Cycle 1-Day 1 is more than 7 days.
- 4 In female patients of child-bearing potential. UPT should be repeated anytime during the study, if pregnancy is suspected.
- 5 Only in cases with clinically suspected splenomegaly. Abdominal USG should be repeated anytime during study if splenomegaly is suspected.
- 6 Randomization to be performed on the Day 1/2 of chemotherapy Cycle 1.
- 7 The chemotherapy to be started on Day 1. Chemotherapy may be given for 2 days as per site practice.
- 8 To be administered not less than 24 h after chemotherapy in each cycle (on day 2/3). In addition Pegfilgrastim treatment will not be given within 14 days period before the next chemotherapy.
- 9 Assessments to be done pre chemotherapy
- 10 Sampling for laboratory tests to be done on Day 1 (predose) and Day 21(of previous cycle) or Day 1(predose) of subsequent cycle.
- 11 Blood sampling for immunogenicity, PK and PD assessments will be done on Day 1 before the start of each chemotherapy cycle.
- 12 In case of early discontinuations/ premature termination of the study all EOS investigations should be done on the day of termination as far as possible

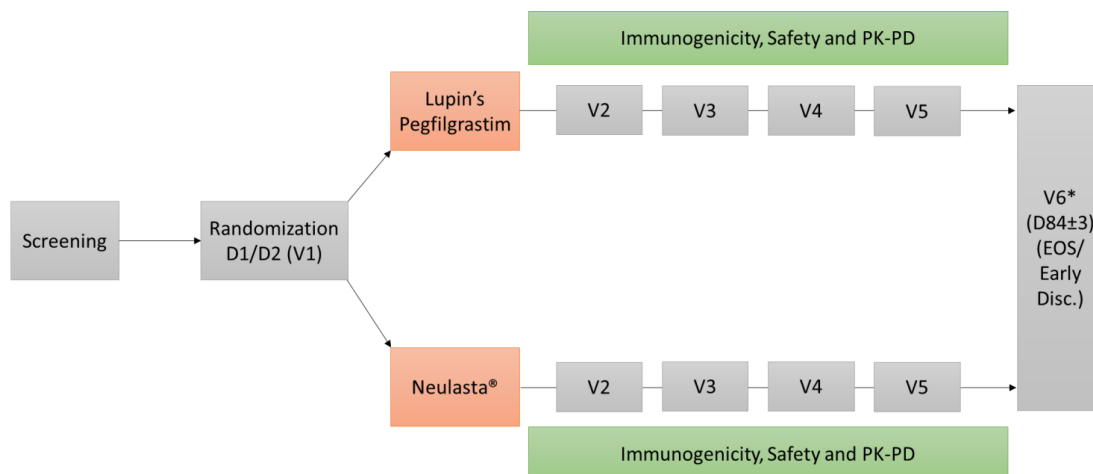
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Page 8 of 60



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Figure 1 Study Flow Chart



Visits & Assessments

Screening: Eligibility

Rand. V1– Randomization (Visit 1/ Day 1 of cycle 1): Immunogenicity at baseline

Visit 2 (V2) – Day 10±3 of chemotherapy cycle 1: Immunogenicity, safety & PK-PD

Visit 3 (V3) - end of chemotherapy cycle 1 (C1D21± 3)/ C2D1: Immunogenicity, safety & PK-PD

Visit 4 (V4) - end of chemotherapy cycle 2 (C2D42± 3)/ C3D1: Immunogenicity, safety & PK-PD

Visit 5 (V5) - end of chemotherapy cycle 3 (C3D63± 3)/ C4D1: Immunogenicity, safety & PK-PD

Visit 6 (V6 EOS)* - end of chemotherapy cycle 4 (C4D84± 3)/End of Study visit or Early discontinuation visit: Immunogenicity, safety & PK-PD

C=Cycle, D=Day, EOS=End of Study, Early Disc=Early Discontinuation, PK= Pharmacokinetics, PD=Pharmacodynamics



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

1 TABLE OF CONTENTS

SPONSOR SIGNATURE PAGE	2
STUDY SYNOPSIS	3
1 TABLE OF CONTENTS	10
1.1 List of Tables	14
1.2 List of Figures	14
2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	15
3 INTRODUCTION	17
3.1 Background	17
3.2 Scientific Findings	18
3.3 Rationale	19
4 STUDY OBJECTIVES	21
4.1 Primary Objective	21
4.2 Secondary Objectives	21
5 STUDY ENDPOINTS	22
5.1 Primary Endpoints	22
5.2 Secondary Endpoints	22
5.2.1 Secondary Immunogenicity Endpoint	22
5.2.2 Secondary Safety Endpoint	22
6 INVESTIGATIONAL PLAN	23
6.1 Overall Study Design and Plan	23
6.2 Discussion of Study Design	24
6.2.1 Choice of Study Population	24
6.2.2 Appropriateness of Measurements	24
6.2.3 Control Group	25
6.2.4 Duration of Study	25
6.2.5 Risk/ Benefit Ratio	25
6.3 Schedule of Assessments	26
6.3.1 Detailed Study Assessments	26
6.4 Selection of Study Population	30
6.4.1 Inclusion Criteria	30
6.4.2 Exclusion Criteria	31
6.4.3 Withdrawal of Patients	32
6.4.4 Rescreening of Patients	32
6.4.5 Other Patient Restrictions	32
6.4.6 Early Termination of Study/ Site	33



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

7	TREATMENT OF PATIENTS AND INVESTIGATIONAL PRODUCT MANAGEMENT	34
7.1	Treatment of Patients.....	34
7.1.1	Dosages & Treatment Regimen.....	34
7.1.2	Precautions while Administering Investigational Product (IP).....	34
7.1.3	Randomization of Study Treatment(s).....	35
7.1.4	Blinding of Study Treatment	35
7.1.5	Patient Compliance	35
7.1.6	Concomitant Therapy	35
7.2	IP MANAGEMENT.....	36
7.2.1	IP Dosage Form and Strength.....	36
7.2.2	IP Packaging and Labeling	36
7.2.3	Storage	36
7.3	IP Supply, Handling and Accountability	37
8	ASSESSMENT OF IMMUNOGENICITY	38
8.1	Immunogenicity Endpoints	38
8.2	Immunogenicity Variables	38
8.3	Anti-Pegfilgrastim and Anti-Peg Antibodies Detection.....	38
8.3.1	Collection, Handling and Analysis of Immunogenicity Samples	38
9	ASSESSMENT OF SAFETY	40
9.1	Adverse Events	40
9.1.1	Definitions	40
9.1.2	Recording and Collection of Adverse Events.....	41
9.1.3	Evaluation of Adverse Events.....	42
9.2	Physical and Systemic Examination.....	44
9.3	Vital Signs	44
9.4	Electrocardiogram Assessments (ECGs).....	45
9.5	Clinical Laboratory Examinations.....	45
9.5.1	Central Laboratory Samples	45
9.6	Pregnancy	46
10	ASSESSMENT OF PHARMACOKINETICS.....	47
10.1	PK Parameters	47
10.2	Blood Sampling.....	47
10.3	Bioanalysis	47
11	ASSESSMENT OF PHARMACODYNAMICS.....	48
11.1	PD Parameters	48
11.2	Blood Sampling.....	48



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

12	STATISTICAL EVALUATION	49
12.1	Sample Size and Power	49
12.2	Statistical Methods	49
12.3	Handling of Missing Data	49
12.4	Patient Disposition.....	49
12.5	Analysis Population.....	49
12.5.1	Intention to Treat (ITT).....	50
12.5.2	Per Protocol (PP)	50
12.5.3	Immunogenicity Population.....	50
12.5.4	Safety Population.....	50
12.5.5	Pharmacokinetic Population	50
12.5.6	Pharmacodynamic Population	50
12.6	Immunogenicity Analysis.....	50
12.6.1	Primary Endpoint.....	50
12.6.2	Secondary Immunogenicity Endpoint	50
12.7	Safety Analysis.....	51
12.7.1	Parameters for Assessment of Safety.....	51
12.8	Exploratory Analysis	52
12.9	Interim Analysis for sample size adaptation	52
13	DATA MANAGEMENT	53
13.1	Data Handling.....	53
14	CLINICAL STUDY MANAGEMENT	54
14.1	Conduct of the Study.....	54
14.2	Direct Access to Source Data	54
14.3	Amendments to the Protocol	54
14.4	Guidance and Supervision of Sub-Investigators	54
14.5	Archiving Study Records	54
15	QUALITY ASSURANCE AND QUALITY CONTROL	55
15.1	Monitoring.....	55
15.2	Agreement and Compliance with the Protocol.....	55
15.3	Audits and Inspections	55
16	ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS	56
16.1	IEC/ IRB Approval.....	56
16.2	Written Informed Consent.....	56
16.3	Confidentiality	56
16.4	Liability and Insurance	56
16.5	Publication Policy.....	57
17	APPENDICES	58
17.1	Appendix 1: Study Management Details.....	58



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

17.2	Appendix 2: Investigator's Signature Page	59
18	REFERENCE LIST	60



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

1.1 List of Tables

Table 1	Schedule of Assessment	6
Table 2	Doses and Treatment Regimen	34
Table 3	IP Details	36
Table 4	Clinical Laboratory Parameters	45
Table 5	Projected sample size adaptations for different proportions of anti-pegfilgrastim antibodies (actual data) at interim analysis	52

1.2 List of Figures

Figure 1	Study Flow Chart	9
----------	------------------------	---



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Full form
AC	Doxorubicin and Cyclophosphamide
ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
AE	Adverse Events
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CIN	Chemotherapy-induced neutropenia
CMF	Cyclophosphamide, Methotrexate, and Fluorouracil
CRA	Clinical Research Associate
CRF/ eCRF	Case Report Form/ electronic Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DNA	Deoxyribose Nucleic Acid
ECG	Electrocardiogram
EOS	End of Study
FN	Febrile Neutropenia
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
hrs	Hours
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
Ltd.	Limited
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
°C	Degree Celsius
°F	Degree Fahrenheit
PCT	Pre-clinical Toxicity
PFS	Pre filled syringe
RP	Reference Product
SAE	Serious Adverse Events

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Page 15 of 60



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Abbreviation	Full form
SMP	Safety Management Plan
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TEAE	Treatment Emergent Adverse Events
UPT	Urine Pregnancy Test
WHO	World Health Organization
WHO-DD	World Health Organization –Drug Dictionary



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

3 INTRODUCTION

3.1 Background

The current treatment of cancer with combination of cytotoxic therapy targeting proliferating cells invariably leads to bone marrow damage, anaemia, thrombocytopenia and most importantly, neutropenia resulting in impaired host defence. Neutropenia is a significant hematologic complication induced by cancer chemotherapy. The clinical consequences of chemotherapy induced neutropenia are often severe and can be potentially life-threatening. Febrile neutropenia (FN) and other infectious complications are the most serious treatment-related toxicities of chemotherapy, with a mortality rate up to 21%.¹

Chemotherapy-induced neutropenia (CIN) is the most common toxicity caused by the administration of anticancer drugs. In breast cancer patients, FN is relatively common. Up to 23% of them experience at least 1 episode of FN secondary to standard chemotherapy, and this figure increase rapidly to 98% in patients exposed to high-dose chemotherapy regimens. An analysis of over 1,100 breast cancer patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF), or doxorubicin and cyclophosphamide (AC), or other regimens showed that CIN was the most frequent cause of dose reductions and delays. In a large prospective registry, 37% of the breast cancer patients experienced an absolute neutrophil count (ANC) lower than 500 cells/mm³ over the first 4 cycles of treatment, and approximately 70% of the initial episodes occurred in cycle 1.²

Neutropenic complications associated with myelosuppressive chemotherapy are a significant cause of morbidity and mortality, possibly compromised treatment outcomes, and excess healthcare costs. The recovery of the bone marrow is stimulated by various growth factors. The prophylactic growth factors is recommended with such myelosuppressive drugs (e.g. docetaxel/ doxorubicin/ cyclophosphamide) where the risk of febrile neutropenia is approximately 20% or higher.³ Granulocyte colony stimulating factor (G-CSF) is one of the most important growth factor playing a role in recovery of neutrophils.⁴

Pegfilgrastim (PegGCSF) is an approved, long-acting, next generation of granulocyte colony stimulating factor that has similar clinical benefits to Filgrastim but has novel pharmacokinetic properties. The "peg" in Pegfilgrastim refers to a polyethylene glycol, "PEG," unit that is added to enlarge the Filgrastim protein. This enlargement prolongs the length of time it stays in the body, and this allows for administration in a single dose per chemotherapy cycle. Various clinical trials have shown that once-per-cycle administration of Pegfilgrastim provides neutrophil support with safety and efficacy similar to that provided by daily injections of Filgrastim.⁵

As per regulatory requirements, quality parameters have been established, a Pre-clinical Toxicity (PCT) studies has shown that Lupin's Pegfilgrastim is safe in doses tested in this study and well tolerated. A Phase 3 comparative, clinical study to assess efficacy and safety of Lupin's Pegfilgrastim versus Amgen's Neulastim® as an adjunct to chemotherapy in patients with non-myeloid malignancies was conducted in India. This study compared the relative efficacy of Lupin's Pegfilgrastim and Amgen's Neulastim® and monitored the safety of patients. Based on the primary and secondary endpoint analysis, the efficacy & safety profile of Lupin's Pegfilgrastim and Amgen's Neulastim® were found to be comparable. DCGI (letter No.MF-186/ dated 03 September 2013) has given approval to market the product in India based on the result of Phase 3 study. **Lupin is marketing its biosimilar product in India under the brand name Lupifil-P since 2015.** Lupin, further intends to conduct a clinical study to market



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

its product in US. A PK- PD study and an immunogenicity & safety study are planned by Lupin in its development path of Lupin's Pegfilgrastim. As, most of the biologic drug products elicit some level of anti- drug antibody. Hence, Lupin intends to know the immunogenicity and safety of Lupin's Pegfilgrastim and Neulasta® in breast cancer patients.

3.2 Scientific Findings

Innovator's Pegfilgrastim (Neulasta®)/ the Reference Product (RP) was approved in 2002 in US. Neulasta® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia and also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). It is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim.

Neulasta® is supplied as prefilled syringe for manual subcutaneous injection or the On-body Injector containing 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution. It is recommended to store at 36- 46 °F (2- 8 °C). Pegfilgrastim 6 mg (10 mg/ml) single dose is administered subcutaneously (SC) once in each chemotherapy cycle after at least 24 hrs of myelosuppressive chemotherapy. No Pegfilgrastim treatment is given within 14 days period before and within 24 hrs period after the chemotherapy.

The pharmacokinetics of innovator's pegfilgrastim was studied in patients with cancer. The pharmacokinetics of pegfilgrastim was nonlinear and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of pegfilgrastim ranged from 15 to 80 hrs after subcutaneous injection. In healthy volunteers, the pharmacokinetics of pegfilgrastim was comparable when delivered subcutaneously.

Renal dysfunction has no effect on PK of innovator's pegfilgrastim thus; no special dose adjustment is required in renal impaired patients. In paediatric patients weight based dose adjust is required in patients below 45 kg weight. There are no adequate and well-controlled studies in pregnant women. Thus, Pegfilgrastim should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus. Caution should be exercised when administered to a nursing woman as it is not known whether pegfilgrastim is secreted in human milk.

The most common adverse reactions ($\geq 5\%$) (reported more frequently in innovator's pegfilgrastim-treated subjects than control subjects) are bone pain and pain in extremity. Serious adverse events observed with pegfilgrastim administration are splenic rupture, Acute respiratory distress syndrome, Serious allergic reactions, Allergies to acrylics, Sickle cell crisis, Glomerulonephritis, Leucocytosis, Capillary leak syndrome, Potential for tumour growth stimulatory effects on malignant cells.

The efficacy and safety data in patients with cancer receiving myelosuppressive chemotherapy is derived from three clinical trials. The results showed that the mean days of severe



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

neutropenia of innovator's pegfilgrastim-treated patients did not exceed that of filgrastim treated patients by more than 1 day in cycle 1 of chemotherapy.

The investigational biosimilar of Lupin Limited is also supplied as single-dose, pre-filled syringes containing fixed dose of 6 mg/0.6 ml (10 mg/ml) subcutaneous injection of Pegfilgrastim. The Pre-clinical Toxicity (PCT) study that has been conducted with Lupin's Pegfilgrastim includes acute toxicity studies, repeated dose 28-day tests, skin sensitization test, and primary skin irritation test.

Lupin's pegfilgrastim was compared head-to-head with Neulastim[®] as a part of extensive characterization program. Various non-clinical studies conducted so far, have established similarity of Lupin's pegfilgrastim to Neulastim[®].

In Phase 3 open-label, multi-centre, randomized study conducted in India, in 170 patients with non-myeloid malignancies, the efficacy and safety of Lupin's pegfilgrastim versus Neulastim[®] was found to be comparable. The primary endpoint, mean DSN in cycle 1 (0.127 days in Lupin's pegfilgrastim arm and 0.197 days in Neulastim[®] arm) did not differ significantly ($p = 0.5167$, unpaired t-test) between two treatment arms. The 95% CI of the differences in mean DSN between the two groups laid well within the predefined interval (-1 to +1 day) for equivalence [-0.2796, 0.1481 ANCOVA for PP population]. The 95% CI of the differences in mean DSN between the two groups for mITT population also laid well within the predefined interval. The two groups were found to be comparable and demonstrated equivalence with respect to secondary efficacy endpoints such as DSN for Cycle 2, proportions of patients with severe neutropenia, time to ANC recovery, incidence of febrile neutropenia, rates of hospitalization and antibiotics use due to febrile neutropenia and depth of ANC nadir.

The incidence of AEs and AE profile were comparable between both the treatment groups across all cycles. The common ADRs experienced in Lupin's Pegfilgrastim group were neutrophilia, bone pain, musculoskeletal pain, constipation, pain, pyrexia, pancytopenia, and leukocytosis. In Neulastim[®], the ADRs observed were neutrophilia & musculoskeletal pain. The musculoskeletal pain of severe degree was the only ADR noted once in each arm. Out of SAEs reported, there was one fatal event (diseases related complications) in each of the treatment 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 Lupin's Pegfilgrastim and Amgen's Neulastim[®].

Therefore, Lupin, further intends to conduct a clinical study to market its product in US.

3.3 Rationale

Pegfilgrastim is the pegylated form of recombinant methionyl human Filgrastim. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilo Daltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of *Escherichia coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce Pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of Filgrastim. The average molecular weight of Pegfilgrastim is approximately 39 kD.

Pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Pegfilgrastim is a valuable treatment option for patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Pegfilgrastim is an approved, long-acting, next generation of G-CSF that has similar clinical benefits to Filgrastim but has novel pharmacokinetic properties. The safety and tolerability of Innovator's Pegfilgrastim has been studied in various Phase I –IV clinical studies. The results have demonstrated well accepted efficacy and safety profile. The pegfilgrastim is approved and available in the market globally since 2002. Therefore, the risks are well known and the benefits outweigh the risks for the treatment of incidence of febrile neutropenia.

As with all therapeutic proteins, there is a potential for immunogenicity. Most biological drug products elicit some level of anti-drug antibody (ADA) response. This antibody response can, in some cases, lead to potentially serious side effects and/or loss of efficacy although no such effect was observed with Innovator's product. In humans, ADA often causes no detectable clinical effects, but in the instances of some therapeutic proteins these antibodies have been shown to cause a variety of clinical consequences ranging from relatively mild to serious adverse events.⁶ The US FDA⁷ and EMEA⁸ in its guidelines recommend for evaluating and mitigating immune responses to or adverse immunologically related responses associated with therapeutic protein products that affect their safety and efficacy.

The immunogenicity studies of binding antibodies to innovator's pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay was 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.^{9,10}

Lupin Limited has developed an investigational product similar to Pegfilgrastim. Pre-clinical studies of Lupin's Pegfilgrastim were found to be safe and well tolerated. Phase 3 study conducted in India proved the efficacy & safety profile of Lupin's Pegfilgrastim and Amgen's Neulastim[®] were comparable. Lupin, further intends to conduct a clinical study to market its product in US. As, most of the biologic drug products elicit some level of anti- drug antibody. Thus, Lupin intends to know the immunogenicity and safety of Lupin's Pegfilgrastim and Neulasta[®] in breast cancer patients.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

4 STUDY OBJECTIVES

4.1 Primary Objective

To assess the immunogenicity of Lupin's Peg-filgrastim with Neulasta® in patients with breast cancer

4.2 Secondary Objectives

To assess the safety of Lupin's Peg-filgrastim with Neulasta® in patients with breast cancer



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

5 STUDY ENDPOINTS

5.1 Primary Endpoints

- Comparison of cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups at the end of cycle 4 (Day 84).

5.2 Secondary Endpoints

5.2.1 Secondary Immunogenicity Endpoint

- Comparison of cumulative incidence of anti-peg antibodies (binding & neutralizing) between treatment groups at the end of cycle 4 (Day 84).
- Comparison of incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84.
- Comparison of incidence of anti-peg antibodies (binding & neutralizing) between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84.

5.2.2 Secondary Safety Endpoint:

- Adverse event (AE) assessment
- Vital signs
- Physical & systemic examinations
- Laboratory parameters: Blood (hematology & biochemistry) and urinalysis



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

This is a randomized, comparative, parallel group, two arms, open label, multi-center clinical study will be conducted in India. The objective of the study is to compare the immunogenicity and safety of Lupin's Pegfilgrastim to that of Neulasta® in patients with breast cancer who are scheduled to receive myelosuppressive chemotherapy (like docetaxel/ paclitaxel/ doxorubicin/ cyclophosphamide/ epirubicin) and who are eligible to receive Pegfilgrastim.

Approximately 30 sites in India, having qualified investigators (Oncologists or other qualified clinicians). Study will be initiated only after receipt of regulatory and EC approval. Screening investigations on patient will be done only after signing of written informed consent. Initially, approximately 150 patients will be randomized in the study. However, sample size will be re-estimated based on interim analysis of ADA rate in first 75 patients (Section 12.9).

Total 4 injections (Neulasta® or Lupin's Pegfilgrastim 6 mg subcutaneous injection, once per chemotherapy cycle) will be given to each patient during the study. The chemotherapy cycle will be of 21 ± 3 days each. The duration of the treatment will be of 84 days (up to 4 chemotherapy cycle) during which the immunogenicity, safety, PK-PD (Peg-GCSF serum trough [pre-dose] concentrations and ANC) assessments will be done. The total study duration for each patient would be around 91 days. It will include 7 days of screening period and 84 days of treatment & assessment period.

The study consists of following parts (Figure 1):

- Screening Period (maximum 7 full days)
- Treatment and assessment period (84 days) which consists of 4 chemotherapy cycles where each chemotherapy cycle will be of 21 ± 3 days.
 - Day 1: First day of each cycle & also first day for chemotherapy
 - Randomisation Day: Day 1/2 of first chemotherapy cycle.
 - Day 2/ Day 3 of each cycle: Pegfilgrastim administration day
 - Day 10 of Cycle 1: Assessment of immunogenicity, safety and PK-PD
 - Day 21 of each cycle: Assessment of immunogenicity, safety and PK-PD (this can be clubbed with Day 1 of next cycle and can be done pre-dose of Day 1 of next cycle)
 - Day 84 i.e. Day 21 of cycle 4 (End of Study/Early Discontinuation)

After signing the informed consent form, the patients will undergo screening assessments to confirm eligibility as mentioned in Section 6.3.1.1 and Table 1.

Screening period will be of maximum 7 full days. The eligible patients will receive the chemotherapy on Day 1/ 2. The patients will be randomized in 1:1 ratio on Day 1/ 2 to receive either Lupin's Pegfilgrastim or Neulasta® as a subcutaneous injection once per chemotherapy cycle on Day 2/ 3. The patients will visit the clinical facility on Day 21 of each chemotherapy cycle for blood sampling for immunogenicity and safety assessment. In addition in cycle 1, patient will visit the clinical facility on Day 10 for immunogenicity, safety and PK-PD assessments. Day 21 of each chemotherapy cycle can be clubbed with Day 1 of subsequent cycle and assessments of Day 21 will be done prior to chemotherapy administration on Day 1



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

of next cycle. The investigational product will be administered by the investigator/ qualified person designated by the site.

Assessment of immunogenicity and safety will be done periodically during the study as given in the schedule of assessment table (Table 1).

Safety includes adverse event (AE) assessment, physical and systemic examination and assessment of vital signs and laboratory parameters.

6.2 Discussion of Study Design

This is a prospective, open label, randomized, two arms, parallel group, multicenter, interventional study to be carried out in patients with breast cancer. The present study is designed in conformance with guidelines on biosimilar development which requires assessment of immunogenicity and safety between investigational biologic and the reference product, thus, Neulasta® has been chosen as a comparator. Randomization method will be used to avoid selection and evaluation bias.

Breast cancer patients eligible for neo-adjuvant or adjuvant chemotherapy will be randomized in the study. The dose chosen for the study is 6 mg subcutaneous injection once per chemotherapy cycle which is also the approved and recommended dose of the Neulasta® for this indication.

Therefore, to assess immunogenicity and safety of Lupin's Pegfilgrastim with Neulasta® a randomized, open-label, two-arm, parallel, multi-center study design is deemed to be most appropriate.

6.2.1 Choice of Study Population

Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The efficacy, safety and immunogenicity of Neulasta® are well studied in breast cancer patients. Pre-existing binding antibodies were detected in patients with metastatic breast cancer with Neulasta®. Although, 0-6% incidence of binding anti-pegfilgrastim antibody was observed in various studies with Neulasta® conducted across the globe, none of the studies reported incidence of neutralizing anti-pegfilgrastim antibodies⁹⁻¹³. While conducting such a study may be possible in healthy subjects, it would require parallel group design doubling the healthy subjects and may not extrapolate real-life clinical setting. Therefore, conducting the study in breast cancer patients is well justified. As Lupin aims to assess immunogenicity and safety of its investigational product with Neulasta® and to have a homogenous patient population in accordance with the guidelines thus, breast cancer patients are chosen as study population in this study.

Considering these factors, the chosen study population is appropriate for the study.

6.2.2 Appropriateness of Measurements

The primary & secondary endpoints chosen for the study are the ones used during development of Neulasta® and well accepted by various regulatory agencies. Similarly, other safety parameters proposed are also in line with the conventional endpoints used in such type of studies. Biologic drugs commonly elicit immune responses, resulting in anti-drug antibodies. Formation of anti-drug antibodies can have a number of effects like reduced efficacy, rapid clearance etc. Pegfilgrastim is a biologically derived product thus, formation of antibodies



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

(both binding and neutralizing) to pegfilgrastim or anti-peg antibodies and safety are considered as appropriate endpoint for this study.

6.2.3 Control Group

The biosimilar development requires a comparative similarity with reference product at all steps of development. Accordingly, present study has reference product Neulasta® as the active control arm.

6.2.4 Duration of Study

Since this study is designed to evaluate immunogenicity and safety of pegfilgrastim, the dosage schedule in this study is Pegfilgrastim single dose of 6 mg subcutaneous injection per chemotherapy cycle. The treatment period includes 4 chemotherapy cycles of 21 ± 3 days each cycle, which is considered to be sufficient for assessing the immunogenicity.

Including the screening period of up to 7 days, the total duration is expected to be around 91 days. Hence, treatment duration of 4 chemotherapy cycle (84 days) is proposed for the study.

6.2.5 Risk/ Benefit Ratio

Neulasta® which is reference product for this study, approved first in 2002 by US-FDA, is well established for treatment of decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs which have a clinically significant incidence of febrile neutropenia; therefore, the risks and benefits are well known. The recommended dose is 6 mg to be administered subcutaneously once per chemotherapy cycle (each cycle of 21 days) after at least 24 hours of myelosuppressive chemotherapy.

The efficacy and safety data is derived from three clinical studies in cancer patients receiving myelosuppressive chemotherapy. The results showed that the mean days of severe neutropenia of peg-filgrastim treated patients did not exceed than that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy.

The most common adverse reactions ($\geq 5\%$) (reported more frequently in innovator's Peg-filgrastim-treated subjects than control subjects) are bone pain and pain in extremity. Serious adverse events observed with innovator's peg-filgrastim administration are splenic rupture, acute respiratory distress syndrome, serious allergic reactions, allergies to acrylics, sickle cell crisis, glomerulonephritis, leukocytosis, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells. In Phase 3 study conducted in India, the common ADRs experienced in Lupin's Pegfilgrastim group were neutrophilia, bone pain, musculoskeletal pain, constipation, pain, pyrexia, pancytopenia, and leukocytosis. The SAE reported in Lupin's Pegfilgrastim group were hemoptysis, gastroenteritis, abdominal discomfort, cellulitis of neck, musculoskeletal pain, asthenia, febrile neutropenia, pancytopenia, severe aspiration due to tumoral bleed, pyrexia.

The purpose of this study is to compare the immunogenicity and safety of Lupin's Pegfilgrastim versus Neulasta® in breast cancer patients. Based on the available preclinical information, Lupin's pegfilgrastim is expected to show similarity in terms of immunogenicity and safety. Therefore, participation in study is expected to yield benefit to the patients during the study similar to innovator i.e. preventing from febrile neutropenia. Besides, the safety of each patient will be monitored periodically by assessing vitals, laboratory and physical examination to minimize the risks. The cost of pegfilgrastim treatment and the investigations done for the study will be borne by the Sponsor. As confirmed from the preclinical and clinical

CONFIDENTIAL

Page 25 of 60



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Phase 3 study conducted in India, risks due to Lupin's Pegfilgrastim treatment is expected to be similar to those known to Neulasta[®] provided precautions are taken care of. Lupin's Pegfilgrastim has been evaluated in a Phase 3 study in India and based on this marketing authorization has been granted by DCGI. Lupin's Pegfilgrastim is available in Indian market and hence its safety has been well established. Thus, the risk benefit ratio seems favourable and the study is ethically justified. Additionally, the approval of biosimilar helps indirectly to whole society as it will open an additional cost-effective therapeutic option for patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

6.3 Schedule of Assessments

The schedule of assessments to be performed at each visit is indicated in [Table 1](#). For details, refer Section [6.3.1](#) given below.

6.3.1 Detailed Study Assessments

The objective of this clinical study is to study immunogenicity and safety of Lupin's Pegfilgrastim in comparison with Neulasta[®].

The following assessments will be performed at each study visit:

6.3.1.1 Screening Visit (Maximum 7 full days)

Screening procedures are as follows:

- Obtain written informed consent as per regulatory requirement
- Record demographic data
- Record medical and surgical history
- Record concomitant medication/ treatment.
- Record concurrent illness
- Vital signs assessment
- Perform physical & systemic examination
- Record weight
- Perform ECG
- Perform chest X-ray
- Perform abdominal ultrasonography
- Perform clinical laboratory assessment (hematology and biochemistry)
- Perform urinalysis
- Assessment of serological tests for human immunodeficiency virus (HIV), Hepatitis B virus (HBsAg), Hepatitis C virus (HCV)
- Perform urine pregnancy test and serum pregnancy test in females of child bearing potential only



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

- Adverse event assessment
- Assess patient eligibility against inclusion and exclusion criteria.
- The eligible patients will be informed about Randomization

6.3.1.2 Treatment Period (84 days)

The treatment period consist of 4 chemotherapy cycles (each cycle of 21 ± 3 days)

6.3.1.2.1 CYCLE 1 (Study days 1-21 \pm 3)

6.3.1.2.1.1 Visit 1: Day 1 (Randomization and Chemotherapy Administration)

- Perform physical & systemic examination
- Vital signs
- Blood sampling for Lab investigations (hematology and biochemistry) [Hematology tests not to be repeated if the gap between screening laboratory investigations and Cycle 1-Day 1 is less than 7 days.]
- Blood sampling for immunogenicity and PK-PD assessments (before chemotherapy administration)
- Perform urinalysis
- Randomization
- Record concurrent illness
- Record changes in concomitant medication/ treatment
- Chemotherapy administration
- Adverse event assessment

6.3.1.2.1.2 Day 2 of Cycle 1 (Study drug administration day)

- Record concurrent illness
- Randomization (If not done on Day 1)
- Record changes in concomitant medication/ treatment
- Study drug administration
- Adverse event assessment

6.3.1.2.1.3 Visit 2: Day 10 of Cycle 1

- Perform physical & systemic examination
- Vital signs
- Record concurrent illness
- Blood sampling for immunogenicity and PK-PD assessments



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

- Record changes in concomitant medication/ treatment
- Adverse event assessment

6.3.1.2.1.4 Visit 3: Day 21 of cycle 1/ Day 1 of cycle 2

- Pre-chemotherapy administration
 - Perform physical & systemic examination
 - Vital signs
 - Record weight
 - Perform ECG
 - Blood sampling for Lab investigations (hematology and biochemistry)
 - Blood sampling for immunogenicity and PK-PD assessments
 - Perform urinalysis
 - Perform urine pregnancy test
 - Record concurrent illness
- Chemotherapy administration
- Record changes in concomitant medication/ treatment
- Adverse event assessment

6.3.1.2.2 CYCLE 2 (Study days 22-42 ± 3)

6.3.1.2.2.1 Day 2 of cycle 2 (Day 23± 3)

- Record concurrent illness
- Record changes in concomitant medication/ treatment
- Study drug administration
- Adverse event assessment

6.3.1.2.2.2 Visit 4: Day 21 of cycle 2/ Day 1 of cycle 3

- Pre-chemotherapy administration
 - Perform physical & systemic examination
 - Vital signs
 - Record weight
 - Blood sampling for Lab investigations (hematology and biochemistry)
 - Blood sampling for immunogenicity and PK-PD assessments
 - Perform urinalysis



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

- Perform urine pregnancy test
- Record ECG
- Record concurrent illness
- Chemotherapy administration
- Record changes in concomitant medication/ treatment
- Adverse event assessment

6.3.1.2.3 CYCLE 3 (Study days 43-63 ± 3)

6.3.1.2.3.1 Day 2 of cycle 3 (Day 44± 3)

- Record concurrent illness
- Record changes in concomitant medication/ treatment
- Study drug administration
- Adverse event assessment

6.3.1.2.3.2 Visit 5: Day 21 of cycle 3/ Day 1 of cycle 4

- Pre-chemotherapy administration
 - Perform physical & systemic examination
 - Vital signs
 - Record weight
 - Perform ECG
 - Blood sampling for Lab investigations (hematology and biochemistry)
 - Blood sampling for immunogenicity and PK-PD assessments
 - Perform urinalysis
 - Perform urine pregnancy test
 - Record concurrent illness
- Chemotherapy administration
- Record changes in concomitant medication/ treatment
- Adverse event assessment

6.3.1.2.4 CYCLE 4 (Study days 64- 84 ± 3)

6.3.1.2.4.1 Day 2 of cycle 4 (Day 65 ± 3)

- Record concurrent illness
- Record changes in concomitant medication/ treatment



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

- Study drug administration
- Adverse event assessment

6.3.1.2.4.2 Visit 6: Day 21 of cycle 4 (Day 84 ± 3): End of Study /Early Discontinuation Visit

- The following investigation should be done pre-chemotherapy administration (planned if any, for the further treatment of patients out of the study)
 - Perform physical & systemic examination
 - Vital signs
 - Record weight
 - Blood sampling for Lab investigations (hematology and biochemistry)
 - Blood sampling for immunogenicity and PK-PD assessments
 - Perform urinalysis
 - Perform urine pregnancy test
 - Record ECG
- Record concurrent illness
- Record changes in concomitant medication/ treatment
- Adverse event assessment

6.4 Selection of Study Population

6.4.1 Inclusion Criteria

Patients satisfying all of the following criteria will be included in the study:

1. Patients must be able and willing to give written informed consent prior to any study related procedures
2. Ambulatory, female patients with an age ≥ 18 years
3. Patients with histologically or cytologically proven diagnosis of breast cancer who are eligible for neoadjuvant or adjuvant chemotherapy.
4. Patients who are planned and eligible to receive/ receiving myelosuppressive chemotherapy regimen that contains at least one chemotherapeutic agent from docetaxel/ paclitaxel / doxorubicin/ cyclophosphamide/ epirubicin
5. Patients who have not received any hematopoietic growth factors (e.g. G-CSF, PegGCSF, erythropoietin) or cytokines (e.g. interleukins, interferons) anytime in the past
6. Patients with baseline WBC \geq LLN/ $3.5 \times 10^9/L$, ANC of $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$ and hemoglobin ≥ 8.5 g/dL
7. Patients with ECOG Performance status of ≤ 2 .



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

8. Patient who have estimated life expectancy of more than six months
9. No evidences of hemorrhage

6.4.2 Exclusion Criteria

Patients who meet any of the following criteria should be disqualified from entering the study:

1. Male patients
2. Hypersensitivity to any of the study drugs or its components like E.coli proteins or similar product.
3. Patients weighing <45 Kg
4. Patients with myeloid malignancies and myelodysplasia or evidence of metastatic disease in bone marrow or brain
5. Patients currently receiving radiation therapy or have completed radiation therapy within 4 weeks before study entry or likely to receive radiotherapy during the study
6. Patients with prior bone marrow or stem cell transplantation
7. Patients with chronic use of oral corticosteroids (Except ≤ 20 mg/day dose of prednisolone/ equivalent steroids), immunotherapy, monoclonal antibody therapy and/or biological therapy or use of any other pegylated drug.
8. Patients with history of systemic antibiotic use within 72 hours prior to chemotherapy*
9. Patients with any active infection which may require systemic antimicrobial therapy. Patients with inadequate hepatic and renal function [defined as Alkaline Phosphatase $> 2.5 \times$ Upper limits of normal (ULN), serum SGOT $> 2.5 \times$ ULN, SGPT $> 2.5 \times$ ULN, Total bilirubin $> 1.5 \times$ ULN and Creatinine $> 1.5 \times$ ULN of the reference range at the screening assessment]
10. Patients with seropositivity for HIV or HBV or HCV
11. Known cases of Sickle Cell Anemia
12. Patients with radiographic evidence of active pulmonary infections and/or recent history of pneumonia within 1 month of screening
13. Patients with clinically evident splenomegaly confirmed subsequently by ultrasonography
14. Patients with any other clinically significant disease(s) which, in the opinion of the investigator, could compromise the patient's involvement in the study or overall interpretation of the data. [for e.g. uncontrolled hematologic, renal, hepatic, endocrine, neurologic, psychiatric, metabolic, pulmonary, cardiovascular disease/impaired functioning or history of any autoimmune disease]
15. Patients who have participated in another therapeutic clinical study within the past 30 days prior to screening, or are likely to simultaneously participate in another therapeutic clinical study
16. Patients who are doubtful to comply with study procedures for mental, psychological or social reasons.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

17. Women of child-bearing potential who are not willing to follow a reliable & effective contraceptive measure during the course of the study & at least 3 months after the last dose of study drug.
18. Pregnant and Breast feeding women.

*Refers to parenteral use

6.4.3 Withdrawal of Patients

In accordance with the Declaration of Helsinki and the informed consent form, patients may discontinue the study at any time without any penalty or loss of benefits to which the patient is otherwise entitled. For all patients withdrawn from the study, efforts will be made to ascertain the reason for withdrawal.

A withdrawn patient is one who meets any of the following withdrawal criteria stated below and whose study participation is discontinued. The reasons for patient withdrawal will be recorded in the case report form, signed and dated at the last assessment visit.

General Criteria:

- The patient is not willing to continue participation in the study (withdraws consent).
- After the first dose, it becomes apparent that patient was ineligible.
- The patient needs emergency treatment or is unable to continue participation in the trial due to the exacerbation of their symptoms at discretion of the investigator.
- Inability of patient to comply with the Protocol for any reason.
- The patient becomes pregnant during the study period.
- In the opinion of the investigator or sub-investigator, the patient should be discontinued due to AEs (including progressing complications) or safety reasons.
- Other reasons due to which the patient should be discontinued, in the opinion of the investigator or sub-investigator.

The treatment options will be discussed with all patients who have discontinued or completed study (EOS) and the patients will be continued on/ shifted to appropriate standard therapy by the Investigator depending on the disease condition.

6.4.4 Rescreening of Patients

Rescreening of a previously screen failed patient will be allowed for patients determined as screen failure due to inclusion and/ or exclusion criteria that could transiently change and do not compromise the patient's safety. Rescreens may occur until the sites are open for recruitment. Only one rescreen is allowed per patient. When a rescreen is authorized by the Sponsor or its designee, patient is to be consented again and all screening procedures should be completed (serology not required to be repeated (HIV, HBV, HCV), if rescreened within one month). Patients who discontinue the study after randomization and after receiving study medication are not eligible for rescreening.

6.4.5 Other Patient Restrictions

Patients may not participate in another clinical study that involves an IP during this study.

Females patient currently pregnant or breast feeding or planning to conceive are not allowed to be included in the study. Females should refrain from becoming pregnant during the study period and should use adequate contraception during the study and 3 months after the last dose of study drug.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

For concomitant medications/ treatments which are restricted during the study, please see Section [7.1.6](#)

6.4.6 Early Termination of Study/ Site

This study may be terminated at any time by the Sponsor if any safety concerns arise, the Investigator does not adhere to the protocol, non-performance or inability to achieve recruitment or in the Sponsor's judgment there are no further benefits to be achieved from the study or if Sponsor does not wish to continue the development of drug for any reason. In this event, the Sponsor will inform about the decision along with reason to the study Investigators, Institutions, ECs and all applicable regulatory authorities.

In such cases, patients will be continued on/ shifted to appropriate standard therapy by the Investigator depending on the disease condition.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

7 TREATMENT OF PATIENTS AND INVESTIGATIONAL PRODUCT MANAGEMENT

7.1 Treatment of Patients

7.1.1 Dosages & Treatment Regimen

Lupin's Pegfilgrastim/ Neulasta® is supplied as single-use pre-filled syringe (PFS) designed to deliver 6 mg pegfilgrastim. Pegfilgrastim will be administered as subcutaneous injection once per chemotherapy cycle. Patients will be randomized to one of the two arms viz. Lupin's Pegfilgrastim or Neulasta® arm (As per [Table 2](#))

Table 2 Doses and Treatment Regimen

Treatment Arm	Dose	Route	Duration & Frequency
Lupin's Pegfilgrastim	6 mg	Subcutaneous injection	Total four injections, one per chemotherapy cycle;
Neulasta®	6 mg	Subcutaneous injection	Total four injections, one per chemotherapy cycle;

7.1.2 Precautions while Administering Investigational Product (IP)

Pegfilgrastim will be administered by investigator or designee at the site to the patient. Pegfilgrastim will be given no less than 24 hours after the chemotherapy is administered. Pegfilgrastim treatment will not be given within 14 days period before and within 24 hours period after the chemotherapy.

Pegfilgrastim is provided in a prefilled syringe. Pegfilgrastim should be stored in its carton to protect from light until use. Before administering pegfilgrastim injection, always check to see that the expiration date on the prefilled syringe has not passed. The pegfilgrastim liquid should always be clear and colorless. Do not use pegfilgrastim if the contents of the prefilled syringe appear discolored or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

Before administration of drug remove the carton containing the prefilled syringe of pegfilgrastim from the refrigerator. Allow pegfilgrastim to reach room temperature. Remove the syringe from the carton before injection. Each prefilled syringe should be used only once. Do not shake the prefilled syringe. Shaking may damage pegfilgrastim. If the prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.

Remove the prefilled syringe from the package and the tray. Check to see that the plastic needle guard is covering the barrel of the glass syringe. Do not push the needle guard over the needle cover before injection. This may activate or lock the needle guard. If the needle guard is covering the needle that means it has been activated. Do not use that syringe. Check the syringe for air bubbles. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

of the syringe. After injection do not throw the container in the household trash. Do not recycle. Do not put the needle cover (the cap) back on the needle.

7.1.3 Randomization of Study Treatment(s)

The treatment arm (test or reference) for each patient during the study will be determined according to randomization list. This randomization list will not be accessible to the study team involved in the study conduct. The treatment will be assigned at the time of randomization, after confirming patient's eligibility. Patients will be randomized in a 1:1 ratio to either Lupin's Pegfilgrastim or Neulasta[®]. Patients who qualify for study randomization will have a unique randomization number. Equal allocation of patients will be ensured in the study. After completion of required number (150 patients), some patients who qualify in screening may not be randomized in the study.

7.1.4 Blinding of Study Treatment

Since the reference product is already a marketed formulation, achieving complete blinding is not possible. Hence, this study is an open label study.

7.1.5 Patient Compliance

For this study-purpose the per protocol compliance to study medication will be defined as all those randomized patients who receive subcutaneous injections of 6 mg pegfilgrastim post chemotherapy up to 4 cycles.

7.1.6 Concomitant Therapy

Prohibited Medications:

Concomitant administration of 5-FU or other antimetabolites is prohibited. Immunization is prohibited as they may interfere with immune status of the patient. Concomitant use of Lithium is not allowed as Lithium may potentiate release of neutrophils. The details of concomitant medications used during the study will be entered in the CRF.

Radiotherapy is prohibited in study patients during the study period. In case if the investigator decides to give radiotherapy patient should be discontinued from the study.

Allowable Medications:

No concomitant and rescue medication for treating neutropenia will be allowed during the study. Any other medications required by the patient and expected not to interfere with study drug assessments will be allowed on a case-by-case basis and as deemed appropriate by the investigator. The details of concomitant medications used during the study will be entered in the Case Report Form (CRF)



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

7.2 IP MANAGEMENT

7.2.1 IP Dosage Form and Strength

Lupin's Pegfilgrastim/ Neulasta® for subcutaneous injection is supplied as single-use pre-filled syringe (PFS) designed to deliver 6 mg pegfilgrastim. The details of the study medications are given in [Table 3](#)

Table 3 IP Details

Study Medication	Dosage Form and Strength	Manufacturer
Lupin's Pegfilgrastim	Supplied as Single-dose, pre-filled syringes containing fixed dose of 6 mg (10 mg/ml) subcutaneous injection of Pegfilgrastim	Lupin Limited (Biotech Division), Gat No: 1156, Village Ghotawade, Taluka Mulshi, Pune, Maharashtra, India – 412 115
Neulasta®	Supplied as a single-dose, pre-filled syringes containing fixed dose of 6 mg (10 mg/ml) subcutaneous injection of Pegfilgrastim.	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320-1799

7.2.2 IP Packaging and Labeling

The 6 mg carton containing a single-use, pre-filled syringe (Lupin's Pegfilgrastim or Neulasta®) are packaged individually. The packs will be labelled as per regulatory requirements. Each pack will have unique identification number.

Each patient will be assigned a randomization number and IP pack containing either Lupin's Pegfilgrastim or Neulasta® will be dispensed.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels shall contain appropriate information as per the local regulatory requirements including but not limited to product content and strength, batch No, manufacture date, retest/ expiry date, storage information, route of administration, statements like "For Clinical Trial Purpose Only".

7.2.3 Storage

Pegfilgrastim injection should be stored under refrigeration at 2°- 8 °C (36°- 46 °F) at all times. The following instructions will be given to the sites:

- Keep the product in the original carton to protect from light until the time of use.
- Do Not Freeze, if frozen, thaw in the refrigerator before administration. However, if it is frozen a second time, do not use.
- Prior to use, the unopened PFS may be kept at room temperature (25°C) for up to 48 hours. Do not use beyond the expiry date which is stated on the carton.
- Do not use any pack if it is damaged. Pegfilgrastim prefilled syringe should be used once only and any unused portion left in the syringes should not be used.
- Do not shake.
- Do not leave Pegfilgrastim syringe in direct sunlight.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

7.3 IP Supply, Handling and Accountability

The Sponsor/ designee will arrange for the supply, handling and management of IPs. Lupin Limited (Biotechnology Division) will supply sufficient quantity of IPs, for administration to randomized patients at each site. IP will be shipped under appropriate storage conditions to the Investigator sites.

The designated study personnel must take the responsibility to keep a record of the IP management.

Sites will receive IP with appropriate documents and store according to the storage requirements. Adequate records of IP for receipt, accountability, usage and disposal or return to sponsor will be maintained at respective Investigator site. Investigational product will be administered to eligible patients according to randomization schedule.

Pharmacist/ designated study personnel will dispense the IP for administration. The unused IP will be kept in their original containers. The sites will return any unused IP to the sponsor, or destroy on site (as mutually agreed between sponsor & sites), once the site's monitor has reviewed and confirmed drug accountability or at the end of the study.

Used IPs will also be kept in the original packing and will be returned/ destroyed on site (as mutually agreed) to sponsor after confirmed drug accountability.

The IPs will not be used for purposes other than those conforming to this protocol.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

8 ASSESSMENT OF IMMUNOGENICITY

8.1 Immunogenicity Endpoints

Primary endpoint: Comparison of cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups at the end of cycle 4 (Day 84).

Secondary Immunogenicity endpoint:

1. Comparison of cumulative incidence of anti-peg antibodies (binding & neutralizing) between treatment groups at the end of cycle 4 (Day 84).
2. Comparison of incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84.
3. Comparison of incidence of anti-peg antibodies (binding & neutralizing) between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84.

8.2 Immunogenicity Variables

Presence of anti-pegfilgrastim antibodies and anti-peg antibodies at the end of each cycle will be analyzed for each patient. Those samples confirmed to be positive for binding antibodies will be analyzed for presence of neutralizing antibodies to Pegfilgrastim

8.3 Anti-Pegfilgrastim and Anti-Peg Antibodies Detection

Immunogenicity will be assessed in patients at selected time points as mentioned in [Table 1](#). Blood samples for immunogenicity will be collected from all sites and an appropriate validated single assay format will be used for immunogenicity assessments. Immunogenicity assay will be done in a sequential format which is broadly classified into ADA assay and Neutralizing Antibody (NAb) assay:

ADA assay followed by NAb assays (if required), will be performed in the below mentioned sequential 3-Tier approach:

1. Screening Assay: All samples will be subjected to screening assay to detect the anti-Pegfilgrastim antibodies.
2. Confirmatory Assay: Samples identified positive under screening assay will be analysed in confirmatory tier, to identify anti-pegfilgrastim and anti-peg antibodies.
3. Titration Assay: All confirmed positive samples will be subjected to Titration assay.

Neutralizing Antibody Assay (NAb): All samples found to be confirmed positive in ADA assay will be subjected to Neutralization assay.

ADA assay will be done at Lupin Bioresearch Centre and NAb assay will be outsourced at a pre-qualified and sponsor-approved laboratory.

8.3.1 Collection, Handling and Analysis of Immunogenicity Samples

For immunogenicity assessments, a 6mL of blood sample will be collected in a plain blood collection vacutainer (with clot activator) by vein puncture as per the scheduled time points mentioned in [Table 1](#). Samples will be kept on bench for 45 ± 15 minutes to enable clotting and will be centrifuged at around 3800 ± 20 rpm for 10 minutes at $10 \pm 2^\circ\text{C}$.

Serum will be separated and transferred into three aliquots of equal volume for storage at $-75 \pm 10^\circ\text{C}$.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

The samples will be shipped to Lupin Bioresearch Center, Pune with dry ice shipment & data logger with proper documentation related to the shipped samples.

Anti-pegfilgrastim antibodies and anti-peg antibodies will be assayed and analyzed using an appropriate and validated single assay format.

Note: Samples of different subjects can be stored interim at clinical facility below -75°C and shipped at regular intervals. All samples collected during the conduct of clinical trial (including dropout/withdrawals) will be analysed. The analysis of the samples will be done in sets which will be decided by the bioanalytical team based on the number of samples in periodic intervals.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

9 ASSESSMENT OF SAFETY

Following safety parameters will be assessed,

- Adverse event assessment (as per NCI CTCAE)
- Physical & systemic examination
- Vital signs
- Laboratory parameters: Blood (hematology & biochemistry) and urinalysis

9.1 Adverse Events

9.1.1 Definitions

The definitions for AEs and SAEs are given in Sections 9.1.1.1 and 9.1.1.2, respectively. It is of the utmost importance that staff involved in the study is familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

9.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavourable and unintended sign, symptom or disease (including intercurrent illness), deterioration of a pre-existing illness, accident, any suspected drug reaction, or a clinically relevant change of laboratory values temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product and/ or study treatment.

A treatment emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

See Section 9.6 below for the instances where a pregnancy should be reported as an AE.

9.1.1.2 Serious Adverse Event (SAE)

An SAE is defined as, any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
An adverse event or adverse reaction is considered “life-threatening” if, in view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of hospitalization
- Results in persistent or significant disability/ incapacity.
- Is a congenital anomaly/ birth defect.
- Consists of any other medically important condition.

According to ICH E2A, CPMP/ICH/377/95: ‘Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.’



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Hospitalization or prolongation of hospitalization in following situations will not be considered as SAE:

- Disease-related investigations (e.g., biopsy, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

9.1.2 Recording and Collection of Adverse Events

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) derived from spontaneous, unsolicited reports of patients, by observation and by routine open questions.

AE reporting will extend from date of informed consent until completion of the final visit (EOS). Any ongoing AE at end of study visit should be followed until the outcome is evident and resolved, clinically stabilized or a plausible explanation has been found.

Pre-existing diseases (before participating in the study) are not considered to be AEs, unless the disease worsens during the study period. Concomitant diseases prior to randomization will be recorded in the CRF/ eCRF.

Signs and symptoms clearly associated with the disease under study (including symptoms of disease progression) should be reported as AEs if they are newly emergent (i.e., findings not previously observed in the patients), or are determined by the investigator as severe or a worsening, or if the investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug.

Abnormal laboratory values/ ECGs/ vital signs/ physical & systemic examination should be reported as AEs only if the Investigator considers the abnormality as clinically relevant or significant or believes that the abnormality should be reported as an AE.

Any dose (and associated symptoms) given to the patient that exceeds the dose prescribed to the patient has, at a minimum, to be recorded as a non-serious AE in the patient file and CRF/ eCRF. Any case of overdose leading to an AE or SAE should be reported to Medical Monitor according to reporting requirements.

After completion of all scheduled visit assessments, the Investigator must document any AEs arising from these assessments. In case of an SAE, the Investigator must also complete an SAE report form and report it to safety contact, as described in Section 9.1.3.3.

All AEs will be recorded in case report form (CRF/ eCRF) regardless of the causal relationship to the study drug.

All AE records should contain AE term/ AE diagnosis, date of onset, severity, relationship to the study drug, outcome, date of recovery or outcome, action taken with the study drug, action taken with AE, AE leading to discontinuation of patient from study and whether the event is classified as serious.

Breast cancer progression should not be recorded as AE/SAE. In cases of disease progression the relevant signs, symptoms and complications should be reported as an AE unless they meet the seriousness criteria. If any of the signs, symptoms and complications meets any of the seriousness criteria, they should be reported as an SAE.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

The categorization of action taken with IP, outcome and action taken for AE is described below:

Categories of Actions Taken with IP	Categories of Outcome*	Categories of action taken for AE
<ul style="list-style-type: none"> • Drug withdrawn permanently • Unknown • Not applicable 	<ul style="list-style-type: none"> • Recovered/ resolved • Recovered/ resolved with sequelae • Recovering/ resolving • Not recovered • Fatal • Unknown 	<ul style="list-style-type: none"> • None • Medication • Hospitalization • Non drug treatment • Patient withdrawn • Other
*If there is more than one AE, only the AE leading to death will be attributed with a fatal outcome.		

In cases where multiple symptoms and signs can be described as one diagnosis (disease), the name of the diagnosis is reported as the name of the adverse event.

For example, running nose, cough, sore throat: The 3 symptoms can be described as a series of symptoms of "common cold"

⇒ Common Cold or Upper Respiratory Tract Infection (URTI)

The investigator must continue to follow-up the patient with all AEs regardless of the causal relationship to the study drug until the AE has resolved or until the condition stabilizes to an acceptable level or is determined to pose no issue, or until follow-up is no longer feasible.

9.1.3 Evaluation of Adverse Events

Each adverse event is evaluated depending on the following categories by the investigator.

9.1.3.1 Definition of severity of an AE

Wherever possible, all observed AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.03. The severity of the AE shall be classified using the following grading.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care (bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to an AE.

Semicolon (;) indicates "or".



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Record the maximum intensity for AE occurring frequently than once a day. If the intensity category changes over a number of days, then those changes should be recorded as a new AE with the onset date of the new intensity.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.1.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

9.1.3.2 Relationship to the Study Drug

The assessment of the relationship of an adverse event to the administration of study drug is based on the presence or absence of a “reasonable possibility” that investigational drug has caused the AE. An AE is considered to be “related” to the study medication if a causal relationship between the IP and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). An AE related to the study drug is referred to as an adverse drug reaction (ADR).

The expression “reasonable causal relationship” is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline) based on relationship to time of onset & drug administration, temporary withdrawal, not attributable to any other drug or condition, dechallenge & rechallenge information as available.

The causal relationship between an adverse event and the study drug will be defined as below:

Unrelated: Clinical event with an incompatible time relationship to drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IP.

Unlikely: Clinical event whose time relationship to drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.

Possible: Clinical event with a reasonable time relationship to IP administration, but that could also be explained by concurrent disease or other drugs or chemicals.

Definite: Clinical event with plausible time relationship to IP administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

In final evaluation for reporting, the relationship will be converted into “Binary Determination”. Unrelated and Unlikely will be clubbed into “Unrelated” and Possible and Definite will be clubbed into “Related” for final reporting purpose.

9.1.3.3 Reporting of Serious Adverse Events

All SAEs occurring after the time of informed consent until the final visit (End of Study visit or Early Discontinuation Visit) must be reported.

All SAEs should be reported by the investigator to the Safety Contact via Email or telephone within 24 hours, regardless of the causal relationship with the IPs (following knowledge of the SAE). After receiving reports of the SAEs, the Safety Contact should communicate with the investigator to get additional information for evaluation of SAEs.

The Investigator is responsible for reporting SAE (initial report, analysed report as well as follow up information) to the Ethics Committee and/ or applicable regulatory authority as per



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

applicable local regulatory requirements of participant countries. All SAEs shall be reported by investigator/ Sponsor/ sponsor designee as per applicable regulatory requirements.

The Details of Safety Contact:

Name: Dr. Prabhat Singh
Designation: Medical and Safety Monitor
Address: Drug Safety & Risk Management
(DSRM), Lupin Limited,
Kalpataru Inspire, 5th Floor,
Off Western Express Highway,
Santacruz (East). Mumbai 400055
Contact Details:
Mobile: +91 7045 347 051
Tel/Fax: +91 22 6640 2833
Email: prabhatsingh@lupin.com

9.1.3.4 Follow-Up of Serious Adverse Events (SAEs)

The investigator must continue to follow the patient until the SAE has resolved or until the condition stabilizes to an acceptable level or is determined to pose no issue, or until follow-up is no longer feasible. Any ongoing SAE at end of study visit should be followed until the outcome is evident and resolved, clinically stabilized or a plausible explanation has been found.

9.1.3.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

An SAE that is also an unexpected adverse drug reaction is called a Suspected Unexpected Serious Adverse Drug Reaction (SUSAR). Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product or the Summary of Product Characteristics for an authorized medicinal product or available literature).

SUSARs will be reported in compliance with regulatory reporting requirements of participating countries. The details of reporting of SAE, significant AEs & SUSARs will be captured in the Safety Management Plan (SMPs).

9.2 Physical and Systemic Examination

A physical and systemic examination will be performed at the time of screening and after screening according to the schedule of procedures described in [Table 1](#).

Physical examinations will include, but are not limited to, the below items:

General findings, HEENT exam (head, eyes, ears, nose and throat), assessment of respiratory, cardiovascular, gastrointestinal, nervous, musculoskeletal and renal/ urinary systems, lymph nodes and dermatologic examination (including skin appendages) and other findings/ physical conditions of note. Any abnormal findings will be evaluated for clinical significance.

9.3 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate and axillary body temperature will be measured at screening and after screening according to the schedule of procedures described in [Table 1](#). These parameters are measured in a sitting position after resting for at least 3 minutes. Any abnormal findings will be evaluated for clinical significance.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

9.4 Electrocardiogram Assessments (ECGs)

A 12-lead ECG will be performed at screening and after screening according to the schedule of procedures described in Table 1. It will be recorded by qualified personnel after the patient has been resting in the supine position for at least 3 minutes. Any abnormal findings will be evaluated for clinical significance. QTc \geq 500 msec or any change from baseline of > 60 msec will be considered significant.

9.5 Clinical Laboratory Examinations

Hematology tests, biochemistry tests including serological test (HIV, HBV, and HCV) and urine analysis tests for safety assessment will be performed at screening and after screening according to the schedule of procedures described in Table 1.

The list of tests for safety laboratory assessment is shown in Table 4.

Serum and Urine Pregnancy test for females of child bearing potential will be performed at screening and as scheduled in Table 1.

9.5.1 Central Laboratory Samples

Sample collection and handling for laboratory tests will be conducted in accordance with the laboratory manuals and collected samples will be sent to the central laboratory. Not more than 200 mL of blood will be collected during this study for planned study assessments (until EOS).

Table 4 Clinical Laboratory Parameters

Hematology	Biochemistry	Urinalysis	Serology
Hematocrit	Albumin	Routine Examination	HIV
Hemoglobin	Globulin	Color	HBV (HBsAg)
Platelet count	Total protein	Appearance	HCV
Red blood cell count	Alkaline phosphatase	pH	
White blood cell count	ALT	Urobilinogen	
Differential white blood cell count:	AST	Occult blood	
Neutrophils	Bilirubin (total, Direct & Indirect)	Glucose	
Basophils	BUN	Protein	
Eosinophils	Urea	Ketone	
Lymphocytes	Uric Acid	Specific gravity	
Monocytes	Creatinine	Microscopic Examination (if abnormality is suspected)	
Absolute neutrophil count	Random Glucose	Red Blood Cells	
	LDH	Pus cells	
		Crystals	
		Cast	
		Bacteria	
		Yeast	
		Other	

Serum and urine pregnancy test will be done in females of child bearing potential.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

Any clinical test results outside the reference value range are evaluated for clinical significance. After dosing, laboratory abnormalities considered by the investigator to have worsened compared to that prior to dosing will be recorded as AEs.

9.6 Pregnancy

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy new born should not be considered an SAE.

If a pregnancy or a positive pregnancy test is reported for a patient during study participation, the study drug must be immediately discontinued.

Pregnancies occurring during the study until EOS must be reported. All pregnancies must be reported to the sponsor within 24 hours after becoming aware of the pregnancy, using the initial pregnancy report form. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and possible effects on the fetus. The investigator must follow up and document the course and outcome of all pregnancies, even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the investigator to the sponsor on the pregnancy outcome report form within 30 days after he/ she becomes aware of the outcome.

Any SAE that occurs during a pregnancy must be recorded on the SAE report form (e.g. maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defects) and reported in accordance with the procedure for reporting of SAEs.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

10 ASSESSMENT OF PHARMACOKINETICS

10.1 PK Parameters

Serum drug concentrations for Lupin's Peg-filgrastim and Neulasta® will be measured at Day1 (baseline/pre-dose) Day 10 and at trough (pre-dose) on Day 21 of cycle 1 and at the end of cycle 2 (Day 42), cycle 3 (Day 63) and cycle 4 (Day 84).

10.2 Blood Sampling

Blood samples (approximately 1 x 4 mL) will be collected by venipuncture or cannulation at the selected time points as mentioned in Schedule (Table 1) into vacutainers with clot activator.

The blood samples in vacutainers with clot activator will be kept aside for 45 ± 15 minutes so as to allow the coagulation process. Then the blood samples will be centrifuged at 3800 ± 20 rpm for 10 minutes at $10 \pm 2^\circ\text{C}$ to separate serum.

The separated serum will be collected in 2 tubes/aliquots. The serum samples will be stored - $75 \pm 10^\circ\text{C}$. The samples will be transported in dry ice to Lupin Bioresearch Center,, Pune for further analysis.

For details about sample processing and methodology, refer bioanalytical protocol.

10.3 Bioanalysis

Serum Pegfilgrastim concentrations will be measured using an appropriate validated quantitative sandwich enzyme immunoassay method at Lupin Bioresearch Centre. Enzyme immunoassay method will be developed and validated as per Global Bioanalytical Method Validation Guidelines^{8,11} and in house SOP of LBC.

In sandwich enzyme immunoassay, initially serum sample will be added to the wells of microtiter plate. Specific monoclonal antibody for human Peg G-CSF will be used as a capture antibody to which Peg-G-CSF will bind. An enzyme-linked polyclonal antibody specific for human Peg G-CSF shall be added in each well. The solution will be washed to remove unbound antibodies and then a suitable substrate solution will be added to quantify the primary antibody through a color change. The concentration of primary antibody present in the serum samples will be measured using suitable 96-well micro plate reader. The concentration of primary antibody present in the serum directly correlates with the intensity of the color.

A baseline level subtraction will be applied to normalize Peg-GCSF concentrations measured in study samples (If required).

For details about sample processing and methodology, refer bioanalytical protocol.

Note:

- PK samples will be assayed and data will be analyzed only in the case of an imbalance in the frequency of ADA between Lupin's Pegfilgrastim and Neulasta® arm.
- Samples of different subjects can be stored interim at clinical facility below -75°C and shipped at regular intervals. All samples collected during the conduct of clinical trial (including dropout/withdrawals) will be analyzed. The analysis of the samples will be done in sets which will be decided by the bioanalytical team based on the number of samples in periodic intervals.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

11 ASSESSMENT OF PHARMACODYNAMICS

11.1 PD Parameters

Absolute neutrophil count (ANC) will be assessed at Day1 (pre-dose), Day 10, Day 21 of cycle 1 and at the end of cycle 2 (Day 42), cycle 3 (Day 63) and cycle 4 (Day 84).

11.2 Blood Sampling

Blood samples (approximately 1 x 3 mL) for PD assessments will be collected by venipuncture or cannulation at the selected time points as mentioned in Schedule ([Table 1](#)) into K2EDTA vacutainers. Collected blood samples for pharmacodynamic evaluation will be transferred to central pathology laboratory for further analysis.

For the details of sample processing and storage, refer central laboratory manual.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

12 STATISTICAL EVALUATION

12.1 Sample Size and Power

The primary endpoint is comparison of cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim at the end of cycle 4 (Day 84). Noninferiority of Lupin's Pegfilgrastim versus Neulasta® will be assessed based on the one-sided 95% confidence interval for the difference between proportions using a noninferiority margin of 10 percentage points. For a two-arm, parallel-group trial with 1:1 randomization, and assuming true rates of 2% in each of the two arms, the required total sample size for 90% power is 128 patients.¹⁴ The expected rate for incidence of anti-pegfilgrastim antibody is based on the various studies with Neulasta® conducted across the globe.^{9,10,12,13} In order to allow for a 15% dropout rate, the planned total sample size is 150 patients.

12.2 Statistical Methods

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses will be provided in a Statistical Analysis Plan (SAP) as applicable.

All statistical analyses will be performed using SAS version 9.1.3 or higher. Continuous variables will be presented in summary statistics of number of patients (n), mean, SD, median, minimum and maximum by appropriate group and time point. Categorical variables will be described using the frequency count of the events, and the number and proportion of responding patients.

Detailed methodology on summary and statistical analysis of the data collected in this study will be provided in the SAP which will be finalized prior to the database lock.

All statistical tests will be one-sided and evaluated at a 5 % level of significance.

12.3 Handling of Missing Data

There are many possible reasons for missing data (e.g. patient refusal to continue in the study, treatment failures and successes, adverse events etc.), not all of which are related to the IP. Different degrees of data incompleteness can occur i.e. measurements may be available only at baseline, or may be missed for one or several follow up assessments. Such missing data will be handled by using LOCF (Last Observation Carried Forward) or other appropriate methods. These methodologies will be described in details in the SAP.

12.4 Patient Disposition

A detailed description of the patient disposition will be provided. It will include the number of patients screened, randomized, completed, as well as the number of dropouts, with reasons for discontinuation and major protocol deviations. All patients entered in the study will be accounted for this.

12.5 Analysis Population

The analysis populations are described below. The study being conducted at multiple sites, the data collected from individual sites will be pooled for analysis. Detailed listings will be produced for all relevant immunogenicity and safety data by treatment and by visits wherever applicable.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

12.5.1 Intention to Treat (ITT)

The Intention-to-Treat (ITT) population will include all patients who receive at least one dose of study medication and subsequently provide any post-baseline immunogenicity variable data. The ITT population will be used for all immunogenicity analyses.

12.5.2 Per Protocol (PP)

The Per Protocol (PP) population will include all patients who satisfactorily complete the study and comply with the requirements of the protocol. It is a subset of the ITT population without any major protocol deviations. The PP population will also be used for all immunogenicity analyses.

12.5.3 Immunogenicity Population

Immunogenicity will be assessed in the ITT and PP populations. The ITT will be the primary immunogenicity analysis population.

12.5.4 Safety Population

Safety population will include all patients who receive at least one dose of study medication and subsequently provide any post-baseline safety variable data. The Safety population will be used for all safety analyses.

12.5.5 Pharmacokinetic Population

The Pharmacokinetic population will include all patients who receive at least one dose of study medication and have evaluable PK data without any major deviations or events that may impact the quality of the data or alter the evaluation of the PK.

12.5.6 Pharmacodynamic Population

The Pharmacodynamic population will include all patients who receive at least one dose of study medication and have evaluable pharmacodynamics measurements.

12.6 Immunogenicity Analysis

12.6.1 Primary Endpoint

Comparison of cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between study groups at the end of cycle 4 (Day 84).

The difference in cumulative incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between study groups at the end of cycle 4 will be calculated, along with the one-sided 95% confidence interval for the difference in proportions. Noninferiority will be assessed using a noninferiority margin of 10 percentage points.

12.6.2 Secondary Immunogenicity Endpoint

- Comparison of cumulative incidence of anti-peg antibodies (binding & neutralizing) between treatment groups at the end of cycle 4 (Day 84).
- Comparison of incidence of anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84.
- Comparison of incidence of anti-peg antibodies (binding & neutralizing) between treatment groups on Day 10, Day 21, Day 42, Day 63 and Day 84.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

12.7 Safety Analysis

The safety data will be summarized and listed. Detailed statistical methodology will be described in SAP.

12.7.1 Parameters for Assessment of Safety

12.7.1.1 Adverse Events

All AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or higher. Events will be classified as TEAEs if they start on or after the date of the first dose of study medication. The number of AEs and the number and percentage of patients experiencing AEs will be summarized by severity and relationship to the study medication. SAEs and AEs leading to premature study discontinuation will be summarized. The corresponding listings will be provided. Study drug injection sites will be observed during the assessment of injection sites in each arm and the characteristics of injection site reactions/ inflammatory reactions will be observed and assessed at each study visit.

12.7.1.2 Physical & Systemic Examinations and Electrocardiogram Measurements

Changes in the physical & systemic examinations from screening to the end of IP will be listed.

12.7.1.3 Electrocardiogram Measurements

Changes in the 12-lead ECG findings from screening to the end of IP will be listed.

12.7.1.4 Laboratory Data

Descriptive statistics will be performed for laboratory parameters at each visit and for the changes from baseline. In addition, shift tables for hematology and biochemistry laboratory parameters comparing values (low, normal, high) using the standard reference ranges will be presented for the baseline laboratory measurements vs. EOS measurements. Abnormal values in each treatment arm will be determined and listed using reference ranges provided by the central laboratory. Patients with an incidence of clinically significant abnormalities occurring during treatment, as well as those that occur prior to the start of the IP will be listed. All laboratory results will be listed, including data from the unscheduled visits.

12.7.1.5 Vital Signs

Changes in vital signs (pulse rate, respiratory rate, body temperature, blood pressure) from screening to each vital signs assessment will be summarized. The corresponding listing will be provided.

12.7.1.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO-DD classification and a listing will be prepared. All concomitant medications received after the start of dosing will be summarized.

12.7.1.7 Extent of Exposure

Study compliance and the extent of exposure to the study medication will be summarized



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

12.7.1.8 Patient Discontinuation

All patients who discontinued from treatment and study will be listed and the reasons for discontinuation will be tabulated.

12.7.1.9 Baseline and Demographic Characteristics

Demographic data and other baseline characteristics will be summarized for the safety population. Categorical data will be summarized as frequencies, percentages and continuous data as descriptive statistics (number of patients, mean, SD, median, minimum value and maximum value). Demographic data will include age, gender, race, ethnicity, weight etc. and disease specific baseline characteristics including presence of anti-pegfilgrastim antibodies to Pegfilgrastim and anti-peg antibodies that will be detailed in SAP.

12.8 Exploratory Analysis

PK-PD analysis will be performed only in the case of an imbalance in the frequency of ADA between Lupin's Pegfilgrastim and Neulasta® arm. Analyses of PK-PD data will be described in a separate PK-PD analysis plan.

12.9 Interim Analysis for sample size adaptation

An interim analysis will be conducted when primary endpoint data are available for approximately 50% of the planned total sample size (approximately 75 patients). The overall proportion of patients with anti-pegfilgrastim antibodies (binding & neutralizing) to Pegfilgrastim at the end of cycle 4 will be estimated at interim analysis. Based on the overall proportion, the sample size required for 90% power will be re-estimated using the approach of Farrington and Manning (1990)¹⁴, as mentioned in Table 5. Safety of the drug will be also evaluated, in above set of patients, before the sample size re-estimation to rule out any drug related safety concerns. Descriptive statistics will be provided for safety analysis.

Table 5 Projected sample size adaptations for different proportions of anti-pegfilgrastim antibodies (actual data) at interim analysis

Blinded		Pegfilgrastim Rate <Neulasta® Rate					Pegfilgrastim Rate >Neulasta® Rate				
<u>Overall ADA Rate</u>	0%	1%	2%	3%	4%	5%	1%	2%	3%	4%	5%
1%	98	84					118				
2%	128	108	94	80			154	188	236		
3%	154	130	112	98	86	76	186	230	292	384	532
4%	180	152	130	112	98	86	218	272	346	458	640
5%	206	174	148	128	112	98	250	312	400	532	746
6%	232	194	166	142	124	110	282	352	452	604	854
7%	258	216	182	158	136	120	314	392	506	678	960
8%	282	236	200	172	150	132	346	432	558	750	1066
9%	308	256	218	186	162	142	376	472	610	822	1170
10%	332	276	234	200	174	152	408	512	662	892	1272



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

13 DATA MANAGEMENT

13.1 Data Handling

Data will be recorded at the site in source documents / CRF/ eCRFs promptly in English and the investigator shall verify the accuracy of data in the CRF/ eCRF.

The Investigator shall maintain source documents, such as laboratory reports, ECGs, consultation reports, and complete medical history and physical examination.

Data from external sources (such as laboratory data) will be appropriately handled into the database. Medical information will be coded using MedDRA and WHO DD.

The monitor assigned to the site will verify the data recorded in the CRF/ eCRF with source documents. The monitor confirms whether reporting is complete and that there are no contradictions by inspecting the CRF/ eCRF. The monitor checks for contradictions between documents based on data in the CRF/ eCRF by source data verification. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the CRF/ eCRF system.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

14 CLINICAL STUDY MANAGEMENT

14.1 Conduct of the Study

Lupin Limited/ designee will conduct the study according to written standard operating procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

14.2 Direct Access to Source Data

During the course of the study, the monitor will visit study sites to review protocol compliance, compare CRF/ eCRFs and individual patient medical records, assess drug accountability records and ensure that the study is being conducted according to applicable regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

A review of the CRF/ eCRFs for completeness, accuracy, legibility, timeliness and clarity, as well as with source documents will be required to monitor the progress of the study. Moreover, the applicable regulatory authorities, Institutional Review Boards (IRBs), Institutional Ethics Committees (IECs) and/ or the sponsor designated Clinical Quality Assurance team may perform source data checks and/ or on-site audits/ inspections to confirm the validity of the trial conduct and the integrity of data collected. Direct access to the source data will be required for these inspections and audits; these will be carried out giving due consideration to data protection and medical confidentiality. The investigator must ensure provision of the necessary support to the sponsor/ sponsor's representative, regulatory or IEC/ IRBs at all times.

14.3 Amendments to the Protocol

Important changes to the protocol and study design require a mutual agreement between the investigator and sponsor and will be effective following approval of the IRB/ IEC and regulatory authorities (as necessary). These changes are to be described in the revised protocol and a list of changes detailing the pre-change and post-change versions will be prepared.

14.4 Guidance and Supervision of Sub-Investigators

The principal investigator shall maintain the list of appropriately qualified sub-investigators and study support staff (e.g. pharmacists, nurses and other staff) to whom significant trial-related duties have been delegated.

The principal investigator shall ensure that all sub-investigators and study support staff participating in the trial are adequately trained on the protocol, the IP(s) and their trial-related duties and functions and they are timely informed of any new information pertaining to the study.

14.5 Archiving Study Records

The essential study documents should be retained and archived until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. However, these documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/ institution as to when these documents no longer need to be retained.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

15 QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor/ designee will implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, applicable regulatory requirements and institutional research policies and procedures.

15.1 Monitoring

The investigator acknowledges that the monitor has the responsibility to review the clinical trial data for verification of proper recording and to verify the source data against the CRF/ eCRF and to review the conduct of the clinical trial in compliance with the protocol and GCP. The Investigator will permit the site monitor to review study data as frequently as deemed necessary.

The Investigator may not recruit patients into the study until such time that a visit has been made by a Sponsor monitor/ representative, or with the agreement of the Sponsor/ formal training by Sponsor, to conduct a detailed review of the protocol and CRF/ eCRF.

The investigator must cooperate with the sponsor to ensure that the conduct of the clinical trial is GCP compliant.

15.2 Agreement and Compliance with the Protocol

Prior to trial initiation, the protocol/ other related documents must be approved by the IEC/ IRB/ regulatory authority in compliance with applicable regulatory requirements. Before the first patient is allowed to participate in the clinical trial, the sponsor/ designee must ensure that all the ethical and legal requirements are met.

The investigator should not deviate from the protocol approved by the IRB/ IEC, except when the changes are necessary to eliminate a risk to the patients. This trial must accurately comply with the protocol. If changes to the protocol are required the changes must be made in writing and notified or submitted for approval by the IRB/ IEC/ regulatory authorities (as necessary).

15.3 Audits and Inspections

An auditor from the sponsor/ designee, the regulatory authorities, or the IEC/ IRBs may conduct an audit or inspect the clinical sites.

The purpose of audits and inspections is to systematically and independently verify that study-related activities are performed, data in clinical studies are accurately recorded, analyzed and reported and that the study has been conducted in accordance with protocol, ICH- GCP guidelines and the applicable regulatory requirements.

Regulatory authorities will communicate the purpose of the audit to the investigator and the investigator should notify the sponsor/ designee of the audit. The sponsor/ designee may provide support to the investigator so that the site is inspection ready.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

16 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

This study will be conducted in compliance with the protocol and with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for Technical Requirements for Registration of Pharmaceuticals for Human use, the World Medical Association Declaration of Helsinki (2013) and in compliance to the specific local regulatory requirements wherever applicable and required.

16.1 IEC/ IRB Approval

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol, informed consent document and other applicable study documents have been reviewed and approved by an EC. The EC will be appropriately constituted and perform its functions in accordance with ICH GCP and local requirements as applicable.

16.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each patient (or their legally responsible guardian). Before each patient is randomized into the study, informed consent will be obtained from the patient (or his/ her legally authorized representative) according to the most current applicable regulatory and legal requirements. The consent will be obtained on the IEC/ IRB approved and most recent version of consent form in language best comprehended by the patient. The consent documents to be used for the study will include all the elements of informed consent as outlined in the applicable regulatory guideline and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki and be reviewed and approved by the appropriate EC prior to use at each site.

The patients should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The patients will be re-consented as required.

16.3 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/ her research team must not disclose such information without the prior written approval from the sponsor. The anonymity of the participating patients must be maintained. Patients will be identified on the CRF/ eCRF and other documents submitted to the CRO or the independent data management center by unique coded patient identification/ registration number but not by name. The confidentiality of records that could identify patients (e.g., the signed informed consent) should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s) and should only be disclosed to the authorized study personnel/ sponsor representative/ IEC/ Regulatory authorities if required.

16.4 Liability and Insurance

The sponsor will obtain a reasonable third-party liability insurance coverage in accordance with all local legal regulatory requirements.

The sponsor will provide for insurance coverage with respect to liability caused by trial-related injuries caused by IPs being tested or by study-related procedures/ medical steps taken in the course of the study in accordance with the applicable regulatory requirement(s). The terms and conditions will apply as specified in the insurance policy document.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

16.5 Publication Policy

Lupin shall retain the sole and exclusive ownership of any and all Data arising (whether directly or indirectly) out of the conduct of clinical trials in relation to the study ("Data"). Upon completion of the Study, Lupin may, at its sole discretion, arrange the analysis and tabulation of the Data. Lupin shall be entitled to utilize the Data and CSR in any manner whatsoever including using the same for publication, presentation at scientific meetings or for submission with regulatory authorities in the manner it deems fit. Investigator hereby agrees and acknowledges that it shall not use and/or publish the Data and/or any reports, presentation, information arising out of or in relation to the clinical trial without prior written approval of Lupin.

Since such studies are published with data of all patients pooled and analyzed together, isolated and independent publications at study center/country level may provide inaccurate representation of safety, efficacy or immunogenicity of the investigational product. Hence, if the Investigators would like to publish/present any paper/poster, the Investigators should provide Lupin the draft material to review for approval any such proposed publication/presentation or other type of disclosure before it is submitted or disclosed in order to ensure against any inadvertent disclosure of confidential information or unprotected invention. For approval by Lupin, the Investigator shall send such reports, presentation, information and/or Data for Lupin review and approval at least 90 (ninety) days prior. It is hereby agreed that all proposed publications based on the study shall be subject to Lupin's written approval with a possibility of denial for any reason including the reasons given above. If approved with comments from Lupin, the Investigator shall incorporate all such comments suggested by Lupin in the publication. By signing this Protocol, the Investigator agrees to unequivocally release the Data from the study to the Lupin without conditions and acknowledges this publication policy.



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

17 APPENDICES

17.1 Appendix 1: Study Management Details

Study management/ study administrative details are provided below

Sponsor Lupin Limited (Biotech Division), Gat No. 1156, Village Ghotawade, Taluka Mulshi, Pune. 412115, Maharashtra, (India), Office Telephone: +91 66549800	Medical Expert Dr. Chirag Shah Lupin Limited (Research Park), 46A/47A, Nande Village, Mulshi Taluka, Pune 412115, Maharashtra, (India) Telephone: +91-020-66749068
Central Laboratory Metropolis Healthcare Ltd, 250-D Udyog Bhavan, Hind Cycle Marg, Worli, Mumbai – 400030, Maharashtra, India	Laboratory Analysis of Immunogenicity and Pharmacokinetics Lupin Bioresearch Center, Sai Trinity A Wing, Unit 1, 2, 3 & 4, Survey No. 146/2/1B, Pashan, Pune – 411021, Maharashtra, India Telephone: +91-20-66219200 OR Appropriate Laboratory
Clinical Data Management Syneos Health 3201 Beechleaf Ct, Raleigh, North Carolina, USA, 27604	Project Management Lupin Limited (Research Park), 46A/47A, Nande Village, Mulshi Taluka, Pune 412115, Maharashtra, (India) AND Syneos Health 3201 Beechleaf Ct, Raleigh, North Carolina, USA, 27604
Safety Monitoring Drug Safety & Risk Management (DSRM), Lupin Limited, Kalpataru Inspire, 5th Floor, Off Western Express Highway, Santacruz (East). Mumbai 400055	Medical Writing and Statistics Lupin Limited (Research Park), 46A/47A, Nande Village, Mulshi Taluka, Pune 412115, Maharashtra, (India) AND Syneos Health 3201 Beechleaf Ct, Raleigh, North Carolina, USA, 27604
Manufacturer of Investigational Bio-similar Product Lupin Limited (Biotech Division) Gat No: 1156, Village Ghotawade, Mulshi Taluka, Pune. Pin: 412115 Maharashtra, (India) Telephone: +91 66549800	Packaging Bilcare Limited, Global Clinical Services 1028, Shirol, Rajgurunagar, Pune 410505 Maharashtra, India



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

17.2 Appendix 2: Investigator's Signature Page

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: An open-label, randomized, comparative, parallel group study to assess the Immunogenicity of Lupin's Peg-filgrastim versus Neulasta® as an Adjunct to Chemotherapy in Patients with Breast Cancer

PROTOCOL NUMBER: LRP/PegGCSF/2016/004

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients. I agree to conduct this study in full accordance with the protocol, all applicable regulations and Good Clinical Practice (GCP) guidelines.

Principal Investigator Name and Job Title: _____

Institution/Clinic: _____

Address: _____

Signature: _____

Date (day/month/year)



Protocol Number: LRP/PegGCSF/2016/004
Ver. No.: 2.2; Dated 02 Jul 2018

18 REFERENCE LIST

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SoC for Protocol Version 2.2

Confidential

Summary of changes (SoC) made in the Clinical Study Protocol: LRP/PegGCSF/2016/004 Version 2.1 Dated 16 Oct 2017

This document indicates the summary of changes made to the Clinical Study Protocol No.: LRP/PegGCSF/2016/004 Version 2.1, Dated 16 Oct 2017. These changes will be reflected in Protocol No.: LRP/PegGCSF/2016/004 Version 2.2, Dated 02 Jul 2018.



SoC for Protocol Version 2.2

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Protocol Sec No (pg. No)	Current Text	Updated Text	Reason For Change
Synopsis (Page 4); Section 6.1 Overall Study Design and Plan (Page 23); Section 6.3.1.1 Screening Visit (Page 26)	Screening Period (Maximum 7 Days)	Screening Period (Maximum 7 <i>full</i> Days)	Corrections have been made for better clarity.
6.3.1.1 Screening Visit (Page 26)		Adverse Event assessment details are added at screening visit.	Missing assessment has been added.
6.4.2 Exclusion Criteria (Page 31)	8. Patients with history of systemic antibiotic use within 72 hours prior to chemotherapy	8. Patients with history of systemic antibiotic use within 72 hours prior to chemotherapy* *Refers to parenteral use	The definition of systemic as envisaged in the original protocol has been clarified to mean parenteral.
Section 7.2.2 IP Packaging and Labeling (Page 36)	Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label text will be translated into local language. The labels shall contain appropriate information as per the local regulatory requirements including but not limited to product content and strength, batch No, manufacture date, retest/ expiry date, storage information, route of administration, statements like "For Clinical Trial Purpose Only".	Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label text will be translated into local language. The labels shall contain appropriate information as per the local regulatory requirements including but not limited to product content and strength, batch No, manufacture date, retest/ expiry date, storage information, route of administration, statements like "For Clinical Trial Purpose Only".	Since the product is marketed and the same pack being used in an open label study, translation in local language is not required.
Section 8.3.1 Collection, Handling and Analysis of Immunogenicity Samples (Page 38)	For immunogenicity assessments, a 6mL of blood sample will be collected in a plain blood collection vacutainer (with clot activator) by vein puncture as per the scheduled time points mentioned in Table 1. Samples will be kept on bench for 30-45 minutes to enable	For immunogenicity assessments, a 6mL of blood sample will be collected in a plain blood collection vacutainer (with clot activator) by vein puncture as per the scheduled time points mentioned in Table 1. Samples will be kept on bench for 45±15 minutes to enable clotting and will be	To bring in consonance with the sample processing method used for PK samples as it has no consequences on immunogenicity assay. Based on the communication from the bioanalytical laboratory to this effect,



SoC for Protocol Version 2.2

Confidential

Protocol Sec No (pg. No)	Current Text	Updated Text	Reason For Change
	clotting and will be centrifuged at around 3000 rpm for 10 minutes at 10°C. Serum will be separated and transferred into three aliquots of equal volume for storage below -75°C.	centrifuged at around 3800 ± 20 rpm for 10 minutes at $10 \pm 2^\circ\text{C}$. Serum will be separated and transferred into three aliquots of equal volume for storage at $-75 \pm 10^\circ\text{C}$	the change was implemented at all sites (Relevant communication from the Bioanalytical laboratory enclosed).
Section 9.1.3.3 Reporting of Serious Adverse Events (Page 44)	The Details of Safety Contact: Name: Dr. Anish Sule Designation: Medical and Safety Monitor Address: Drug Safety & Risk Management (DSRM), Lupin Limited, Kalpataru Inspire, 5th Floor, Off Western Express Highway, Santacruz (East). Mumbai 400055 Contact Details: Mobile: +91 7045 347 051 Tel/Fax: +91 22 6640 2731 Email: anishsule@lupin.com	The Details of Safety Contact: Name: <i>Dr. Prabhat Singh</i> Designation: Medical and Safety Monitor Address: Drug Safety & Risk Management (DSRM), Lupin Limited, Kalpataru Inspire, 5th Floor, Off Western Express Highway, Santacruz (East). Mumbai 400055 Contact Details: Mobile: +91 7045 347 051 Tel/Fax: +91 22 6640 2833 Email: prabhatsingh@lupin.com	Administrative change
10.2 Blood Sampling (Page 47)	The blood samples in vacutainers with clot activator will be kept aside for 45 ± 15 minutes so as to allow the coagulation process. Then the blood samples will be centrifuged at 3800 ± 20 rpm for 10 minutes at $10 \pm 2^\circ\text{C}$ to separate serum. The collected blood sample will be centrifuged at $10 \pm 2^\circ\text{C}$ at 3800 rpm for 10 minutes and the separated serum will be collected in 2 tubes/aliquots. The serum samples will be stored -75 ± 10	The blood samples in vacutainers with clot activator will be kept aside for 45 ± 15 minutes so as to allow the coagulation process. Then the blood samples will be centrifuged at 3800 ± 20 rpm for 10 minutes at $10 \pm 2^\circ\text{C}$ to separate serum. The collected blood sample will be centrifuged at $10 \pm 2^\circ\text{C}$ at 3800 rpm for 10 minutes and The separated serum will be collected in 2 tubes/aliquots. The serum samples will be stored -75 ± 10	Redundant text is removed.



SoC for Protocol Version 2.2

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Protocol Sec No (pg. No)	Current Text	Updated Text	Reason For Change
Across all document		<ul style="list-style-type: none"> Logistic and administrative changes are made. Typographical errors and inconsistencies have been corrected. 	<p>Administrative changes: Due to finalization of vendors.</p> <p>Corrections have been made for better clarity.</p>
Across all document		Page No. updated and formatting done.	Page No. updated across the document.
Across all document	<p>Protocol No.: LRP/PegGCSF/2016/004</p> <p>Version No.: 2.1, Dated 16 Oct 2017;</p> <p>Supersedes: Version No. 2.0, Dated 29 May 2017</p>	<p>Protocol No.: LRP/PegGCSF/2016/004</p> <p>Version No.: 2.2, Dated 02 Jul 2018;</p> <p>Supersedes: Version No.: 2.1, Dated 16 Oct 2017</p>	Version, date in header and page numbering updated.