BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA
Application Number	761212
Received Date	04/02/2021
BsUFA Goal Date	04/02/2022
Division/Office	Division of Nonmalignant Hematology
Review Completion Date	See DARRTS stamped date
Product Code Name	LUBT 004
Proposed Nonproprietary Name[1]	pegfilgrastim-unne
Proposed Proprietary Name[1]	ARMLUPEG
Pharmacologic Class	LEUKOCYTE GROWTH FACTOR
Applicant	Lupin Limited
Applicant Proposed Indication(s)	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.
Recommendation on Regulatory Action	Complete Response

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis

DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EOS	End of Study
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
LUBT 004	Lupin pegfilgrastim
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
US-Neulasta	U.S.-licensed Neulasta

Signatures

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1. Executive Summary

1.1. Product Introduction

Proposed Proprietary Name: ARMLUPEG

Proposed Nonproprietary Name: pegfilgrastim-unne

Code Name: LUBT004 (Lupin pegfilgrastim)

Dosage Forms: Solution for injection (6 mg/0.6 mL in a single dose prefilled syringe)

Pharmacologic Class: Leukocyte growth factor

Chemical Class: Recombinant Protein

ARMLUPEG (pegfilgrastim-unne) is a proposed biosimilar product to U.S.-licensed Neulasta (pegfilgrastim).

Proposed Indication: 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.

Limitations of Use:
Armlupeg is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Dosage/Administration: Single subcutaneous injection of 6 mg administered subcutaneously into the thigh, abdomen, buttocks, or upper arm once per chemotherapy cycle in adults.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

In its BPD Type 4 meeting package, the Applicant proposed excluding Module 4, Nonclinical Study Reports, from its BLA, and the Agency agreed with the applicant's proposal.

As described below, the Applicant's analytical and clinical studies supported a demonstration that LUBT004 is highly similar to U.S.-licensed Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between LUBT004 and U.S.-licensed Neulasta in terms of safety, purity, and potency. Accordingly, FDA has determined that animal studies are unnecessary in this 351(k) application.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

U.S.-licensed Neulasta (also referred to as US-Neulasta) is a leukocyte growth factor that binds to the granulocyte colony stimulating factor (G-CSF) receptor on hematopoietic cells leading to an increase in neutrophils via three processes including stimulating the proliferationand differentiation of neutrophils, inducing neutrophil maturation, and enhancing survive and function of mature neutrophils.

Comparative analytical assessment of LUBT004, including multiple orthogonal assays relevant to the mechanism of acton of U.S.-licensed Neulasta, demonstrated LUBT004 has the same mechanism of action as the U.S.-licensed Neulasta, to the extent known.

U.S.-licensed 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. The Applicant is seeking licensure for this previously approved indication. The Applicant is not seeking the licensure for the U.S.-licensed Neulasta indication of *"Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)."*.

The strength of LUBT004 in each pre-filled syringe (6mg/0.6ml) is the same as that of U.S.-licensed Neulasta. LUBT004 also has the same dosage form (injection) and route of administration (subcutaneous) as that of U.S.-licensed Neulasta. The proposed dose of LUBT004 is a single S.C. injection of 6 mg administered once per chemotherapy cycle in patients with cancer who are receiving myelosuppressive chemotherapy. LUBT004 is supplied as a single use prefilled syringe designed to deliver 6 mg of LUBT004 (10 mg/ml) for S.C. injection.The conditions of use for which the Applicant is seeking licensure have been previously approved for U.S.-licensed Neulasta.

1.4. Inspection of Manufacturing Facilities

An on-site inspection at Lupin Limited (Biotech Division) Pune, India (FEI 3010977634) was conducted from October 3 through October 15, 2022. At the conclusion of the inspection, a seventeen-item FDA Form 483 was issued. Based on the facility compliance review of the firm's response to the FDA Form 483, the Office of Pharmaceutical Manufacturing Assessment (OPMA) recommended a withhold for the facility and also recommended that the firm's capability and readiness to manufacture G-CSF intermediate, LUBT 004 drug substance, and drug product should be reevaluated during a re-inspection for BLA 761212. In addition, from microbiology perspective, an additional deficiency, that the container closure integrity test method had not been adequately validated to ensure sterility assurance of the final drug product, was identified. For details of the OPQ identified deficiencies, see Section 12.

Therefore, OPQ recommends a Complete Response for BLA 761212 during this assessment cycle due to deficiencies identified related to Lupin Limited (Biotech Division), Pune, India (FEI: 3010977634) facility and microbiology.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable

1.6. Biosimilarity Assessment

Table 1: **Summary and Assessment of Biosimilarity for LUBT004**

Comparative Analytical Studies	
Summary of Evidence	• The comparative analytical assessment of the LUBT004 and U.S.-licensed Neulasta supports a demonstration that LUBT004 is highly similar to U.S.-licensed Neulasta, notwithstanding minor differences in clinically inactive components. LUBT004 has the same strength, dosage form, and route of administration as U.S.-licensed Neulasta.
Assessment of Residual Uncertainties	• No residual uncertainties
Animal/Nonclinical Studies	
Summary of Evidence	• FDA determined that animal studies are unnecessary in this 351(k) application.
Assessment of Residual Uncertainties	• No residual uncertainties

Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• PK and PD (absolute neutrophil count) similarity between LUBT004 and US-Neulasta was demonstrated in healthy subjects (Study ARL/18/360/LBC-19-146). • Comparable incidence of immunogenicity was observed between LUBT004 and US-Neulasta in patients with breast cancer (Study LRP/PegGCSF/2016/004); the upper bound of the 90% CIs for the risk difference of the endpoint of the ADA incidence was within the prespecified bound of <10%. • In summary, the PK, PD, and immunogenicity results from Studies ARL/18/360/LBC-19-146 and LRP/PegGCSF/2016/004 support a demonstration of no clinically meaningful differences between LUBT004 and US-Neulasta.
Assessment of Residual Uncertainties	• There are no residual uncertainties based on the clinical pharmacology evaluation.
Additional Clinical Studies	
Summary of Evidence	• In Study LRP/PegGCSF/2016/004, the incidence of post-dose positive anti-drug antibody was comparable between the two groups (LUBT 004: 1.5%, US-Neulasta: 4.4%). The overall incidences of related AEs in these patients with treatment-emergent positive anti-drug antibody were comparable between the two groups. • The LUBT004 safety profile was comparable to that of US-Neulasta. The safety results from Studies ARL/18/360/LBC-19-146 and LRP/PegGCSF/2016/004 support a demonstration of no clinically meaningful differences between LUBT004 and US-Neulasta.

Assessment of Residual Uncertainties	• There are no residual uncertainties based on the clinical safety evaluation.
Extrapolation	
Summary of Evidence	• The Applicant has provided adequate scientific justification to support extrapolation of data and information submitted to support licensure of LUBT004 as a biosimilar, under Section 351 (k) of the PHS Act, for the following indication for which US-Licensed Neulasta has been previously approved: 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.
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding extrapolaton of data and information to support licensure of LUBT004 as a biosimilar to US-Neulasta for the indications being sought.

Source: FDA table

1.7. Conclusions on Approvability

A comparative analyitical assessment was performed and clinical PK, PD, and immunogenicity studies were conducted to support a demonstration that LUBT004 and U.S.-licensed Neulasta are highly similar, and that there are no clinically meaningful differences between LUBT004 and U.S.-licensed Neulasta.

The Office of Pharmaceutical Quality found the applicant provided results of the comparative analytical assessment that support the conclusion that LUBT004 is highly similar to U.S.-licensed Neulasta, notwithstanding minor differences in clinically inactive components. The proposed product will have the same strength, dosage form, route of administration as the U.S.-licensed Neulasta . However, based on the findings of the on-site manufacturing facilities inspection and the container closure deficiency, there is insufficient information to demonstrate that the manufacturing process and control strategy of LUBT004 is well-controlled and leads to a product that is safe, pure, and potent.

A Complete Response is recommended.

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CDTL

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The clinical development of LUBT004 was conducted outside the US. The relevant regulatory history pertaining to the development of LUBT004 is detailed in Table 2.

Table 2: Regulatory History

Dates	Milestone
November 4, 2016	Pre-IND meeting Biosimilar Product Development (BPD) Type 2 meeting was held to discuss the development plans for LUBT 004, a proposed biosimilar to U.S.-licensed Neulasta. • The FDA provided advice on the development program of LUBT004 pertaining to CMC, the nonclinical program, and a proposed pharmacokinetic/pharmacodynamics (PK-PD) study and immunogenicity study.
September 22, 2017	Submitted the initial IND # 131463: Under this IND the Applicant conducted PK/PD and immunogenicity studies.
November 15, 2019	Second BPD Type 2 meeting • Advice provided for comparative analytical assessment plan for LUBT004 with US-licensed Neulasta.
July 28, 2020	Third BPD Type 2 meeting • Advice was provided that there was no need to submit Human Factor (HF) study as part of the marketing application.
January 31, 2017	BPD Type 2 meeting • To discuss proposed comparative immunogenicity study.
June 30, 2020	Agreement was reached on the Initial Pediatric Study Plan (iPSP)
October 26, 2020	BPD Type 3 meeting • Advice was provided on the (b) (4) DS and DP process development and analytical method validations.

November 10, 2020	BPD Type 4 meeting • Advice was provided regarding the content and format of the planned BLA submission.

Source FDA Table

2.2. Studies Submitted by the Applicant

Refer to the Comparative Analytical Assessment (CAA) Chapter of the Integrated Quality Assessment (IQA) for additional information regarding comparative analytical data.

Table 3: Tabular Listing of Submited Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
ARL/18/360/LBC-19-146	No NCT	• To compare the relative bioavailability of LUBT004 and US-Neulasta. • To compare the pharmacodynamic effect of LUBT 004 and US-Neulasta.	Double-blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover comparative PK-PD study	Healthy Subjects	• LUBT004 6 mg/0.6 ml, s.c. injection N= 131 • US-Neulasta, 6 mg/0.6 ml s.c. injection N= 133
LRP/PegGCSF/2016/004	NCT0351 1378	To assess the immunogenicity of LUBT004 with US-Neulasta in patients with breast cancer.	Open-label, randomized, two-arm, comparative, parallel-group, multicenter to assess the immunogenicity of LUBT004 vs US-Neulasta in patients with breast cancer.	Patients with breast cancer receiving chemotherapy	• LUBT004 6 mg/0.6 ml, s.c. injection N= 70 • US-Neulasta, 6 mg/0.6 ml s.c. injection N= 68

Source: FDA Table

Authors:

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Clinical Reviewer

Ann T. Farrell, MD
Division Director

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

LUBT004 is a covalent conjugate of a non-glycosylated, recombinant methionyl human granulocyte-colony stimulating factor (G-CSF) produced in Escherichia coli (E. coli) (b) (4) cells called G-CSF intermediate and a 20 kDa PEG (polyethylene glycol). LUBT004 drug product (DP) is a sterile, clear, colorless, and preservative-free solution. Each pre-filled syringe (PFS) contains 6 mg/0.6 mL of LUBT004 at 10 mg/mL concentration in pH 4.0. Each DP injection of 0.6 mL dose for the PFS contains 6 mg LUBT 004, 30.0 mg (b) (4) sorbitol, (b) (4), 0.02 mg polysorbate 20 in water-for-injection, USP. The recommended dose for LUBT004 is same as the dose for U.S.-licensed Neulasta (i.e., 6 mg administered subcutaneously once per chemotherapy cycle). Review of manufacturing has identified that most of the methodologies used for G-CSF intermediate, LUBT004 DS and DP manufacturing, and release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. However, the container closure integrity test method has not been adequately validated.

The Applicant provided results of the comparative analytical assessment to support that LUBT004 is highly similar to U.S.-licensed Neulasta, notwithstanding minor differences in clinically inactive components. The proposed product will have the same strength, dosage form, route of administration as the U.S.-licensed Neulasta.

However, based on the findings of the on-site manufacturing facilities inspection and the container closure deficiency, there is insufficient information to demonstrate that the manufacturing process and control strategy of LUBT004 is well-controlled and leads to a product that is safe, pure, and potent. OPQ is recommending that a Complete Response letter be issued to Lupin Limited.

3.2. Devices

LUBT004 is supplied as a single-use, disposable, fix dose (b) (4) pre-filled syringe (PFS) with a 27G ½ inch fixed injection needle and a rigid needle shield. PFS is assembled with (b) (4) Ultrasafe plus passive needle safety guard.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH was consulted. Their review included an assessment of needle safety device constituent performance, needle safety stability, and needle safety control strategy. CDRH concluded that the pre-filled syringe from a device perspective was approvable.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA performed a risk assessment of the proposed Armlupeg container label, carton labeling, Prescriber Information (PI), Patient Information (PPO), and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors. DMEPA concluded

that the proposed PI, PPI, IFU, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. These recommendations were provided to DNH with advise that they be implemented prior to approval.

3.3. Office of Study Integrity and Surveillance (OSIS)

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below:

Accutest Research Labs in Ahmedabad, Gujarat, India.

The text below describing the rationale for this decision is from the review:

The Office of Regulatory Affairs (ORA) inspected the site in August 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: ANDA 213112.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Also, the Division requested inspection of the Lupin Bioresearch Center. However, because of the COVID-19 pandemic, an onsite inspection could not be conducted. Therefore, the Division of Generic Drug Study Integrity (DGDSI) in the Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of Study LBC-19-146 conducted at Lupin Bioresearch Center, Pune, Maharashtra, India.

OSIS review team observed objectionable conditions during the RRR. The review states that Lupin rejected study runs and performed repeat analysis of study samples without proper justification and contradictory to their established acceptance criteria. Lupin also reported extrapolated data outside the valid concentration range in a method validation run.

OSIS notified Lupin that OSIS had identified four objectionable observations. Lupin was given the opportunity to respond and take corrective action for each objection:

1. The firm rejected study runs in Study LBC-19-146 without proper justification.

2. The firm performed repeat analysis of study samples from Study LBC-19-146 without proper justification and reported data from the repeat analyses as the final sample concentration.

3. The firm did not treat calibration standards, QCs and study samples consistently in MV-20-007 and Study LBC-19-146.

4. The firm reported extrapolated data values for QCs with nominal concentrations outside the calibration range in method validation MV-20-007.

After review of Lupin's response, OSIS concluded for all observations, corrective and preventive actions taken by the Applicant were appropriate, and there were no impacts on the study outcome.

3.4. Office of Scientific Investigations (OSI)

Not applicable.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

As described in its BPD Type 4 meeting package, the Applicant proposed excluding Module 4, Nonclinical Study Reports, from its BLA, and the Agency agreed, as animal studies would be uninformative, and therefore unnecessary in this 351(k) application. In the absence of specific PK, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity.

Animal studies with LUBT004 and US-Neulasta were not required to support this 351(k) application.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The composition of the LUBT004 drug product (6 mg/0.6 mL) is qualitatively the same as U.S.-licensed Neulasta, see Table 4 and Table 5. In both drug products, polysorbate 20 is used as [redacted], sorbitol as [redacted] and glacial acetic acid as [redacted] and WFI as excipient. The sterile, colorless, preservative-free drug product solution is filled into a single-dose syringe (PFS) for subcutaneous injection with [redacted] UltraSafe plus passive needle safety guard.

Table 4 : LUBT004 Injection Drug Product Composition

Sr. No.	Name of ingredient	Quantity Per PFS (6mg/0.6mL)	Function	Reference to standards
1.	Pegfilgrastim	6 mg	Active pharmaceutical Ingredient	In-house
2.	Sorbitol	30 mg	[redacted]	USP-NF, IP, Ph.Eur., BP and JP
3.	*Glacial acetic acid	0.77 mg		USP, IP, Ph.Eur., BP and JP
4.	#Sodium acetate [redacted]	[redacted]		USP, IP, Ph.Eur., BP and JP
5.	Polysorbate 20	0.02 mg		USP-NF, IP, Ph.Eur. and BP
6.	Water for injection	q.s. to 0.6 mL		USP, In-House, IP, Ph.Eur, BP and JP

[redacted]

Table 5: U.S.-licensed Neulasta Product Composition

Composition	Concentration per 0.6 mL
Pegfilgrastim	6 mg
Sorbitol	30 mg
Acetate	0.35 mg
Sodium	0.02 mg
Polysorbate 20	0.02 mg
Water for Injection	q.s. to 0.6 mL

Source: Applicant Submission

Comments on Excipients

The excipients in LUBT004 are the same and present in the same levels as the excipients in U.S.-Licensed-Neulasta with minor difference in composition, see Tables 4 and 5.

Comments on Impurities of Concern

There are no impurities or degradants with toxicological safety concern.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 6: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• In Study ARL/18/360/LBC-19-146, PK similarity was demonstrated between LUBT004 and US-Neulasta. The 90% CI of the geometric mean ratio (GMR) for the primary PK endpoints C_{max}, AUC_{0-t} and AUC_{0-inf} were within the pre-specified margin of 80-125%.
Pharmacodynamics	• In Study ARL/18/360/LBC-19-146, PD (ANC) similarity was demonstrated between LUBT004 and US-Neulasta. The 90% CI of the GMR for the primary PD endpoints ANC_E_{max} and ANC_$AUEC_{0-t}$ were within the pre-specified margin of 80-125%.
Immunogenicity	• In Study LRP/PegGCSF/2016/004, a similar incidence of ADA formation was observed for LUBT004 and US-Neulasta in patients with breast cancer. The upper bound of the 90% CI for risk difference was <10%, and met the prespecified limit.

Source: FDA summary

The Applicant submitted pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity data from two clinical studies in healthy subjects and patients with

breast cancer to support demonstration of no clinically meaningful differences between LUBT004 and U.S.-Neulasta:

1. Study ARL/18/360/LBC-19-146 was a double-blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover study, to evaluate the PK and PD (absolute neutrophil count [ANC]) similarity of LUBT004 and US-Neulasta following a single 6 mg subcutaneous (S.C.) dose in healthy adult subjects. A total of 218 subjects completed both treatment periods. The results of the study established PK and PD similarity between LUBT004 and U.S.-Neulasta based on the primary PK (C_{max}, $AUC_{0-\infty,}$ and AUC_{0-t}) and PD (observed ANC_E_{max} and ANC_$AUCE_{0-t}$) endpoints.

2. Study LRP/PegGCSF/2016/004 was an open-label, randomized, comparative, parallel-group study to evaluate the immunogenicity of LUBT004 and US-Neulasta following multiple doses of 6 mg administered S.C. in each chemotherapy cycle for 4 cycles in patients with breast cancer. A total of 138 subjects were dosed at least once in the study. The observed antidrug antibodies (ADA) formation was similar between LUBT004 and US-Neulasta. The study results demonstrated non-inferiority of LUBT004 over US-Neulasta for the confirmed treatment induced ADA positive status.

Overall, the results from Study ARL/18/360/LBC-19-146 and Study LRP/PegGCSF/2016/004 support the demonstration of no clinical meaningful differences between LUBT004 and U.S.-Neulasta and add to the totality of the evidence to support a demonstration of biosimilarity between LUBT004 and U.S.-Neulasta (Table 7 and Table 8).

Table 7. Summary of statistical analyses for assessment of PK similarity (Study ARL/18/360/LBC-19-146)

Parameter	**Geometric Mean (%CV)**		**Geometric Mean Ratio* (90% CI)**
	LUBT004 (n=218)	**U.S.- Neulasta (n=218)**	**LUBT004 vs U.S.- Neulasta**
Primary			
AUC_{0-inf} (hr*pg/mL)	8350461 (34.3%)	8781283 (34.3%)	95.1 (90.2, 100.3)
AUC_{0-t} (hr*pg/mL)	8308295 (34.6%)	8742428 (34.6%)	95.0 (90.1, 100.2)
C_{max} (pg/mL)	232685 (34.4%)	246205 (34.4%)	94.5 (89.6, 99.7)

*Presented as percent. Source: FDA analysis

Table 8. Summary of statistical analyses for assessment of PD similarity (Study ARL/18/360/LBC-19-146)

Parameter	**Geometric Mean (%CV)**		**Geometric Mean Ratio* (90% CI)**
	LUBT004 (n=209)	**U.S.- Neulasta (n=209)**	**LUBT004 vs U.S.- Neulasta**

Primary			
ANC_AUEC$_{0-t}$ (hr*10^9/L)	5848 (10.5%)	5823 (10.5%)	100.4 (98.7, 102.2)
ANC_E_{max} (10^9/L)	36.7 (11.9%)	36.5 (11.9%)	100.6 (98.7, 102.5)

*Presented as percent. Source: FDA analysis

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

The clinical studies adequately showed PK and PD similarity between LUBT004 and U.S.- Neulasta and showed no increase in immunogenicity risk for LUBT004 when compared to U.S-Neulasta. There are no residual uncertainties from the clinical pharmacology assessment.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-licensed Comparator Product

Not Applicable

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1. Study ARL/18/360/LBC-19-146

Clinical Pharmacology Study Design Features

The Applicant conducted one clinical pharmacology PK/ PD similarity study comparing LUBT004 to US-Neulasta in healthy subjects. The study design of ARL/18/360/LBC-19-146 is considered adequate to demonstrate PK/PD similarity for the following reasons:

- A study in healthy subjects is considered safe and an appropriately sensitive study population.
- A single S.C. dose of 6 mg is the approved dose for U.S.-Neulasta and is within the linear range for PK. This dose range is also in the sensitive portion of the dose response curve for PD (ANC) assessments.
- A cross-over study design was used to assess the PK/PD similarity of LUBT004 and US- Neulasta.
- A target washout period of 42 - 45 days between each treatment was used. As per the U.S.-Neulasta labeling, the half-life of pegfilgrastim ranged from 15 to 80 hours (0.63 to 3.33 days) after subcutaneous injection. Based on observation, ANC returned to baseline by around Day 14 after each treatment.
- Absolute neutrophil count (ANC), the PD marker of drug efficacy, has been well characterized in patients with chemotherapy-induced myelosuppression in clinical studies.

Clinical Pharmacology Study Endpoints

In Study ARL/18/360/LBC-19-146, the prespecified PK endpoints were $C_{max,}$ AUC_{0-t}, and AUC_{0-inf}, and the prespecified PD endpoints were observed ANC_E_{max} and ANC_$AUEC_{0-t}$. PK and PD similarities were established if the 90% CI of GMR of each parameter between LUBT004 with U.S.-Neulasta were within the prespecified limits of 80-125%.

Blood sample measurements were as follows:

- PK – blood samples for PK measurement were collected at pre-dose, and 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336 hours post-dose during each study period.
- PD – blood samples for ANC measurements were collected at pre-dose, and 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336 hours post-dose during each study period.
- ADA – blood samples for ADA were collected at pre-dose (baseline), and 336 hours post dose for both study period 1 and period 2.

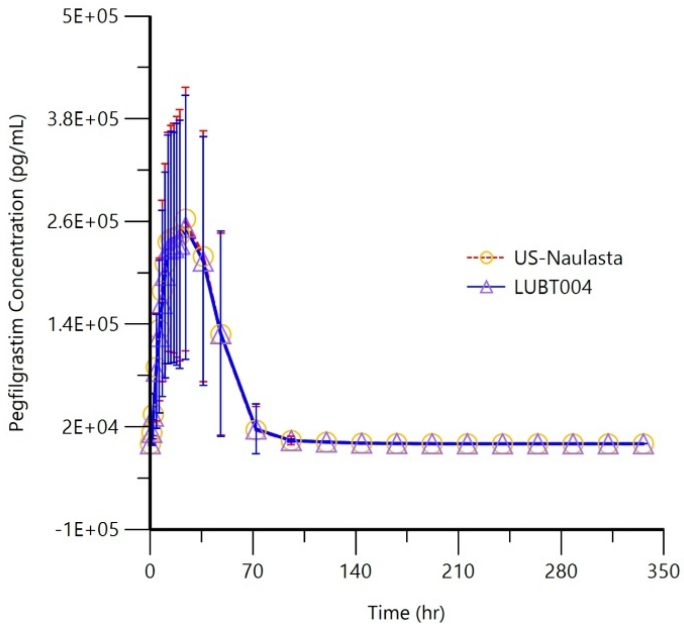
Bioanalytical PK Method and Performance

The bioanalytical method was validated and robust in supporting the PK similarity results and conclusions from Study ARL/18/360/LBC-19-146. See Section 14.4.1. for details.

PK Similarity Assessment

PK similarity between LUBT004 and US-Neulasta was demonstrated in the single-dose crossover Study ARL/18/360/LBC-19-146. The 90% CI of the GMR for PK (C_{max}, AUC_{0-inf}, and AUC_{0-t}) endpoints were within 80-125%. (Table 1). The mean concentration-time profiles and a summary of the calculated PK parameters are shown in Figure 1 and Table 1 (Section 5.1).

Figure 1: Mean Concentrations (pg/mL) versus Time (hr) from Study ARL/18/360/LBC-19-146



Source: Reviewer analysis

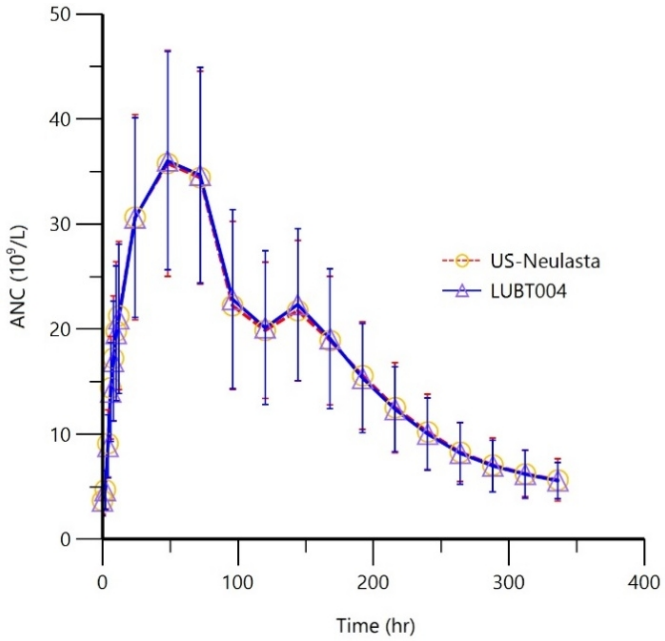
Bioanalytical PD Method and Performance

The bioanalytical method was validated and robust in supporting the PD similarity results and conclusions from Study ARL/18/360/LBC-19-146. See Section 14.4.1. for details.

PD Similarity Assessment

PD (ANC) similarity between LUBT004 and US-Neulasta was demonstrated in the single-dose crossover Study ARL/18/360/LBC-19-146. The 90% CIs of the GMR for PD (ANC_E_{max} and $AUEC_{0-t}$) endpoint were within 80-125%. The mean concentration-time profiles and a summary of the calculated PD parameters are shown in Figure 2 and Table 2 (Section 5.1).

Figure 2: Mean ANC Concentration (x 10^9/L) versus Time (hr) from Study ARL/18/360/LBC-19-146 (Error Bars – Standard Deviation)



Source: Reviewer analysis

5.4. Clinical Immunogenicity Studies

5.4.1. STUDY LRP/PegGCSF/2016/004

Immunogenicity incidence of LUBT004 and US-Neulasta was comparable in Study LRP/PegGCSF/2016/004. LUBT004 was noninferior to US-Neulasta based on the following assessment.

Design features of the clinical immunogenicity assessment

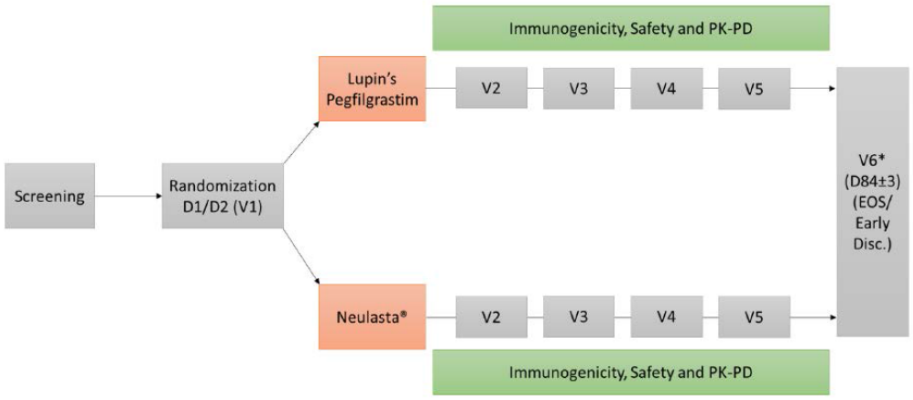
The Applicant conducted one parallel designed immunogenicity study (LRP/PegGCSF/2016/004) in patients with breast cancer. It was an open-label, randomized, parallel-group study to compare the immunogenicity and safety of LUBT004 and US-Neulasta in patients with breast cancer. Overall, 138 patients with breast cancer were randomized in either LUBT004 or US-Neulasta treatment arm for a total of 4 study drug injections in each chemotherapy cycle.

The study consisted of screening part (up to 7 days) and treatment and assessment part (approximately 84 days). The treatment and assessment part included 4 chemotherapy cycles (21 ± 3 days for each cycle). All eligible patients received chemotherapy on Day 1 of each cycle and were randomly assigned to LUBT004 or US-Neulasta treatment group on Cycle 1 Day 1 or Day 2 at a 1:1 ratio. Study drug was administrated on Day 2 or Day 3 of each Cycle. Each patient received a single dose of

subcutaneous injection of LUBT004 or US-Neulasta at 6 mg in each chemotherapy cycle. The study design schematic is represented in Figure 3.

Blood samples for immunogenicity assessments were collected at Day 1 pre-dose (baseline), Day 10 of Cycle 1, and Day 21 of each cycle. The primary immunogenicity endpoint was the accumulative ADA at Day 21 of Cycle 4 (Day 84 after the first dose). Immunogenicity assessments included presence of anti-study drug antibodies and anti-peg antibodies.

Figure 3. Study Schematic



Source: BLA Submission, module 5.3.5.1

The primary objective of this study was to demonstrate similarity of LUBT004 to US-Neulasta with respect to immunogenicity in patients with breast cancer. The primary endpoint was to compare of cumulative incidence of treatment-induced positive anti-study drug antibody and neutralizing antibody (NAb) status to study drug between treatment groups at the end of Cycle 4 (Day 84). The secondary objective of the study was to compare the safety and tolerability of LUBT004 and US-Neulasta. The secondary endpoint was assessed based on adverse events (AEs), vital signs, physical and systemic examinations, laboratory parameters of subjects receiving LUBT004 and US-Neulasta from the first dose until the end of study (EOS) assessment visit. Based on the study design described above, Study LRP/PegGCSF/2016/004 is considered adequate to assess immunogenicity risk.

Immunogenicity endpoints

The primary endpoint is patients' confirmed treatment-induced positive ADA (anti-study drug) status to LUBT004 or US-Neulasta at the End of Study Assessment Visit (Day 84) after a total of 4 injections of LUBT004 or US-Neulasta. The difference in cumulative incidence of anti-study drug antibodies (binding and neutralizing) to study drug between study groups (LUBT004 – U.S.-Neulasta) at the end of Cycle 4 (Day 84) was calculated, along with the two-sided 90% confidence interval (CI) for the difference in proportions. Noninferiority was assessed using a noninferiority margin of 10%. The binomial proportion using PROC FREQ and margin = 0.1 (10%) was used to present the

proportion difference along with two-sided 90% CI. Non-inferiority is demonstrated when the upper bound of the CI is less than or equal to 10%.

Table 9 displays the detailed definition for the Applicant's and FDA analysis sets and their differences. According to the applicant's analysis, Patient # (b) (6) who had 1 cycle of chemotherapy and received 1 dose of LUBT004 was excluded from the applicant's defined-ITT population because this patient had no postbaseline immunogenicity data. For a randomized study, the primary analysis should be based on all randomized subjects in order to protect the balance of covariates between arms to avoid potential bias.

Table 9. Comparison of immunogenicity analysis set defined by the applicant and the FDA statistical reviewer for Study LRP/PegGCSF/2016/004

	Applicant 1 (ITT)	Applicant 2 (PP)	FDA 1 (AR)	FDA 2 (RAR)
Analysis Set	**Intention-to-Treat (ITT) Population**: all patients who received at least one dose of study drug and subsequently provided any postbaseline immunogenicity variable data.	**Per-Protocol (PP) Population**: all patients who satisfactorily completed the study and complied with the requirements of the protocol.	**All Randomized (AR) Population:** all randomized patients irrespective of whether patient received any study drug.	**Reduced All Randomized (RAR) Population:** All randomized population excluding patients with positive baseline ADA.
# of Patients	137 69 (LUBT004) 68 (US-Neulasta)	130 64 (LUBT004) 66 ((US-Neulasta)	138 70 (LUBT004) 68 ((US-Neulasta)	117 61 (LUBT004) 56 ((US-Neulasta)
# of cumulative ADA-positive patients	10 (LUBT 004) 15 (U.S.-Neulasta)	9 (LUBT 004) 15 ((U.S.-Neulasta)	10 (LUBT 004) 15 ((U.S.-Neulasta)	1 (LUBT 004) 3 ((U.S.-Neulasta)
# of baseline ADA-positive patients	9 (LUBT004) 12 (US-Neulasta)	8 (LUBT004) 12 ((US-Neulasta)	9 (LUBT004) 12 ((US-Neulasta)	0
# of patients with incomplete visits	2 (LUBT004) 2 (US-Neulasta)	0	3 (LUBT004) 2 ((US-Neulasta)	3 (LUBT004) 2 ((US-Neulasta)

Source: FDA analysis

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of LUBT004 and US-Neulasta in the study samples

The immunogenicity assays were capable of detecting the ADA in the presence of LUBT004 and U.S.-Neulasta in the study samples. The sensitivity of the ADA assay was 4.8 ng/mL for anti-study drug antibodies and 7.3 ng/mL for anti-PEG antibodies. The anti-study drug antibody at 31.3 ng/mL can be detected in the presence of 1000 ng/mL of study drug (LUBT004 and US-Neulasta). The anti-US-Neulasta at 31.3 ng/mL can be detected in the presence of 1000 ng/mL of LUBT004 and 62.5 ng/mL can be detected in the presence of 1000 ng/mL of US-Neulasta. The anti-PEG at 62.5 ng/mL

can be detected in the presence of 1000 ng/mL of drug. The sensitivity of the Nab assay was 76.7 ng/mL. The drug tolerance of Nab assay was 1000 ng /mL (LPC) up to 4000 ng/mL (HPC) for anti-study drug antibody. The drug tolerance of Nab assay was 500 ng /mL (LPC) up to 4000 ng/mL (HPC) for anti-US-Neulasta antibody. Refer to the Immunogenicity Review by the Office of Biotechnology Products for details regarding the ADA assay methods.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

Sampling plan in Study LRP/PegGCSF/2016/004 was adequate to capture baseline, early onset, and the dynamic profile (transient or persistent) ADA formation. Samples for ADA assessment were collected at Day 1 pre-dose (baseline), Day 10 of Cycle 1, and Day 21 of each cycle (Day 21, Day 42, Day 63 post-first dose), till the end-of-study on Day 84.

Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

Table 10. Immunogenicity results for binding ADA and NAb in Study LRP/PegGCSF/2016/004 based on Applicant-ITT population

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
LUBT004	69	9/69 (13.0%)	1/69 (1.5%)	0
US-Neulasta	68	12/68 (17.7%)	3/68 (4.4%)	0

Source: Applicant analysis

The ADAs of patients with ADA post-dose status were summarized as the followings:

- 1 patients (1.5%) in the LUBT004 treatment arm had positive anti-PEG antibodies at around week 6 (Day 42, Cycle 2).
- 3 patients (4.4%) in US-Neulasta treatment arm had positive anti-study drug antibodies at around week 3 (Day 21, Cycle 1) to week 9 (Day 63, Cycle 3).

No patient had positive ADA detected at the end of the study (Day 84) and none of the binding antibodies were neutralizing in nature. Overall, the observed incidence of ADA in this study was low and responses were similar between patients receiving LUBT004 and US-Neulasta.

Anti-PEG antibodies

Anti-PEG antibody was detected in 1 patient (1.5%) in LUBT004 treatment arm, and not detected in any patient in US-Neulasta treatment arm. The Applicant's analysis

suggested that no meaningful differences were observed between the two treatment arms.

Statistical Results

Table 11. Immunogenicity results for binding ADA and NAb in study LRP/PegGCSF/2016/004 based on Applicant-ITT and PP populations

Analysis Set	Product	N	Anti-Drug Antibody			NAb
			Baseline	Treatment-Induced	Risk Difference (90% CI)	
ITT	LUBT004	69	9/69 (13.0%)	1/69 (1.5%)	-3.0% (-7.7%, 1.8%)	0
	US-Neulasta	68	12/68 (17.7%)	3/68 (4.4%)		0
PP	LUBT004	64	8/64 (12.5%)	1/64 (1.6%)	-3.0% (-7.9%, 2.0%)	0
	US-Neulasta	66	12/66 (18.2%)	3/66 (4.6%)		0

Source: Applicant analysis

The applicant's analysis results for binding ADA and NAb are shown in Table 11. For Applicant-ITT population, the risk difference between LUBT004 and US-Neulasta is -3.0% with a 90% two-sided confidence interval of (-7.7%, 1.8%). For PP population, the risk difference between LUBT004 and U.S.-Neulasta is -3.0% with a 90% two-sided confidence interval of (-7.9%, 2.0%). The upper bounds of the 90% two-sided confidence intervals for both ITT and PP population do not exceed 10% (a pre-specified margin for the noninferiority analysis), which demonstrates the non-inferiority of LUBT004 comparing with US-Neulasta.

The applicant's analysis was not based on all randomized patients because their Intent-to-treat definition requires patients receive study drug and provide postbaseline immunogenicity variable data. The applicant's analysis also counts baseline ADA-positive patients as non-responders regardless whether they are post-baseline ADA-positive.

To preserve balance of characteristics of the two arms, the FDA statistical reviewer performed re-analyses (Table 12) by including all randomized patients irrespective of whether patients receiving any study drug or having positive ADA or missing value at baseline (i.e., the FDA-ITT population). In particular, the following are the two imputations utilized.

- *Imputation 1*: Treat patients as ADA incidences for those who had positive baseline ADA or missing post-baseline visits
- *Imputation 2*: Treat patients as non-ADA incidences for those who had positive baseline ADA or missing post-baseline visits

Table 12. Immunogenicity results for binding ADA and NAb in study LRP/PegGCSF/2016/004 from FDA analysis on FDA-ITT population

Imputation method	Product	N	Anti-Drug Antibody			NAb
			Baseline	Treatment -Induced	Risk Difference (90% CI)	
Imputation 1	LUBT 004	70	9/70 (12.9%)	13/70 (18.6%)	-6.4% (-18.0%, 5.1%)	0
	U.S.-Neulasta	68	12/68 (17.7%)	17/68 (25.0%)		0
Imputation 2	LUBT 004	70	9/70 (12.9%)	1/70 (1.4%)	-3.0% (-7.7%, 1.7%)	0
	U.S.-Neulasta	68	12/68 (17.7%)	3/68 (4.1%)		0

Source: FDA analysis

For the FDA-ITT population, the risk difference between LUBT004 and US-Neulasta is -6.4% with a 90% two-sided confidence interval of (-18.0%, 5.1%) using Imputation 1, and the risk difference between LUBT004 and U.S.-Neulasta is -3.0% with a 90% two-sided confidence interval of (-7.7%, 1.7%) using Imputation 2. The upper bounds of the 90% two-sided confidence interval for both imputations do not exceed 10%.

To reduce the impact of positive baseline ADA patients to the analysis result, the FDA statistical reviewer also performed re-analyses (Table 13) on the FDA-RITT which includes all randomized population but exclude patients who had positive baseline ADA. In particular, the following are the two imputations FDA conducted.

- *Imputation 3*: Impute patients with missing post-baseline visits as ADA incidences
- *Imputation 4*: Impute patients with missing post-baseline visits as no ADA incidences

Table 13. Immunogenicity results for binding ADA and NAb in Study LRP/PegGCSF/2016/004 from FDA analysis on FDA-RITT population

Analysis Set	Product	N	Anti-Drug Antibody			NAb
			Baseline	Treatment-Induced	Risk Difference (90% CI)	
Imputation 3	LUBT 004	61	0/61 (0%)	4/61 (6.6%)	-2.4% (-10.5%, 5.8%)	0
	U.S.-Neulasta	56	0/56 (0%)	5/56 (8.9%)		0
Imputation 4	LUBT 004	61	0/61 (0%)	1/61 (1.6%)	-3.7% (-9.3%, 1.9%)	0
	U.S.-Neulasta	56	0/56 (0%)	3/56 (5.4%)		0

Source: FDA analysis

For the FDA-RITT population, the risk difference between LUBT004 and U.S.-Neulasta is -2.4% with a 90% two-sided confidence interval of (-10.5%, 5.8%) using Imputation 3, and the risk difference between LUBT004 and U.S.-Neulasta is -3.7% with a 90% two-sided confidence interval of (-9.3%, 1.9%) using Imputation 4. The upper bounds of the 90% two-sided confidence interval for both imputations do not exceed 10%.

In both of the two FDA analysis sets, the conclusion was not affected, which demonstrates the non-inferiority of LUBT004 comparing with US-Neulasta.

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

The incidence of ADA was low, in which 4 subjects tested ADA positive at any time during the study and none of ADA incidence reported at the end of study (Day 84). There is no significant difference of ADA incidence between the LUBT004 and US-Neulasta treatment arms in Study LRP/PegGCSF/2016/004 as discussed above. PK analysis was not conducted by the applicant. The impact of ADA on PK, PD, safety, and clinical outcomes are expected to be negligible from Study LRP/PegGCSF/2016/004.

Immunogenicity was also evaluated in Study ARL/18/360/ LBC-19-146, PK/PD crossover study in which 218 normal healthy subjects received single doses of both LUBT004 and US-Neulasta. Higher rates of antibody formation overall were noted in this study as compared to LRP/PegGCSF/2016/004; however, there was no statistically significant difference between subjects who receive LUBT004 in the first period as compared to subjects who received US-Neulasta in the first period, and the PK and PD results demonstrated similarity of the two treatments.

The data from these studies demonstrates that the formation of ADA or NAb is similar for LUBT004 and US-Neulasta. While the incidence of treatment emergent binding ADA differed between studies, the observed level of NAb formation was low in both studies

and no subjects or patients developed NAb specific to rh-GCSF during the studies.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The BLA submission contained two clinical studies, a comparative pharmacokinetics-pharmacodynamics (PK-PD) crossover study in healthy subjects (ARL/18/360/LBC-19-146) and a randomized, parallel, non-inferiority, comparative immunogenicity study (LRP/PegGCSF/2016/004) to support licensure of LUBT004 as a biosimilar product to U.S.-licensed Neulasta for the same approved indication 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 Applicant is not seeking the Hematopoietic Syndrome of Acute Radiation Syndrome indication.

The overall safety evaluation of LUBT004 was based primarily on 402 subjects who participated in the two comparative studies and received at least one dose of either LUBT004 or US-Neulasta. There were 264 healthy volunteers and 138 female patients with breast cancer who received at least one dose of LUBT004 or US-Neulasta.

In Study LRP/PegGCSF/2016/004, among patients with negative anti-drug antibody at baseline, the incidence of post-dose positive anti-drug antibody (ADA) was comparable between the two groups (LUBT004: 1.5%, US-Neulasta: 4.4%). No patient had positive ADA detected at the end of the study (Day 84), and none of the binding antibodies were neutralizing in nature.

Based on the review of the safety results, the overall safety profile of LUBT004 was similar to that of US-Neulasta. The safety results from the comparative clinical studies support a demonstration of no clinically meaningful differences between LUBT004 and US-Neulasta. There were no apparent impact of immunogenicity on safety in either study.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. Study ARL/18/360/LBC-19-146

The Applicant conducted one clinical pharmacology PK/ PD similarity study (Study ARL/18/360/LBC-19-146) comparing LUBT004 to US-Neulasta in healthy subjects.

Title: A Double-Blind, Balanced, Randomized, Single- Dose, Two-Treatment, Two-Sequence, Two-Period Crossover Comparative Pharmacokinetics-Pharmacodynamics (PK-PD) Study of Lupin's Pegfilgrastim 6mg/0.6ml subcutaneous injection manufactured by Lupin Limited, India and US-Neulasta (Pegfilgrastim 6mg/0.6ml) subcutaneous injection manufactured by Amgen Inc. US administered in Healthy, Adult, Human Subjects.

Study Initiation Date: November 04, 2019
Study Completion Date (Last Subject Last Visit): January 31, 2020
Study Site: The study was conducted at one site in India.

Study Design

The study was a single center, double-blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover PK/PD similarity study in healthy subjects designed to demonstrate equivalence with respect to the PK and PD (Absolute neutrophil count, ANC) profiles of LUBT004 and US-Neulasta.

The study was conducted at one site, Accutest Research Laboratories (I) Pvt. Ltd., Ahmedabad, India. A total of 268 healthy volunteers (171 males and 97 female) enrolled in 5 batches, with 264 subjects participating in Period-I and 223 subjects in Period-II. The washout period was at least 42 days between dosing in period-I and period-II. Subjects received a single dose from the single-use pre-filled syringe of 6mg/0.6 ml of either Lupin's pegfilgrastim (LUBT004) or US-Neulasta administered s.c. injection in the upper arm in each period. In Period-I, 131 and 133 subjects received LUBT004 or US-Neulasta, respectively. In Period-II, 110 and 113 subjects received LUBT004 or US-Neulasta, respectively.

Blood samples were collected at different time points for assessment of PKs/PDs and immunogenicity during the study.

In each period, a total of 27 blood samples were collected at pre-dosing and post-dosing at 1 hour and up to 336 hours postdosing.

The concentrations of study drug in human serum were measured by employing the validated sandwich ELISA method developed at Lupin Bioresearch Center, Pune. The study sample analysis was performed on ELISA reader (Synergy H1 Microplate reader). Absorbance mode color detection (OD) of end-point at 450nm wavelength and 630nm being referenced. During the analysis of the study samples for study drug the linearity ranged from 500.000pg/ml to 8000.000pg/ml.

Absolute neutrophil count (ANC) was determined using flow cytometry.

The Applicant performed the immunogenicity assessment in sequential format which is broadly classified into ADA assay and NAb assay. The detection, confirmation, characterization and titration of anti-study drug antibodies (ADA) was done by electrochemiluminescent (ECL) bridging immunoassay method based on MSD platform. The direct qualitative neutralizing cell-based assay method with an evaluation of NFS-60 cell proliferation as the functional endpoint was employed for Neutralizing Antibody Assay (NAb).

Population: Eligible subjects were adults, age 18 to 45 years, in good health at the time of screening, based on comprehensive medical history, physical examination, vital signs, clinical laboratory tests, and had no known hypersensitivity to any component of either pegfilgrastim products. Subjects should have body mass index (BMI) between 18.5 and 29.9 kg/m^2 and body weight between 60 kg and 100 kg (both inclusive). Subjects should have normal hepatic function tests and an estimated creatinine clearance (CrCL) of >90 mL/min and using the Cockcroft-Gault formula. Female subject of childbearing potential currently not pregnant, or lactating, or attempting to become pregnant should have a negative serum pregnancy test and agree to use an acceptable method of birth control for a period of 4 weeks before the screening visit, throughout the duration of the study, and 3 weeks after the subject's last study-related visit.

Objectives:
Pharmacokinetics (PKs) Evaluation: The primary objective was to compare the relative bioavailability of LUBT004 6mg/0.6ml subcutaneous injection to reference product (US-Neulasta, pegfilgrastim 6mg/0.6ml) subcutaneous injection in adult healthy subjects.

Pharmacodynamics (PDs) Evaluation: The objective was to compare the pharmacodynamic effect of LUBT004 6mg/0.6ml subcutaneous injection to reference product (US-Neulasta, Pegfilgrastim 6mg/0.6ml) subcutaneous injection in adult healthy subjects.

Endpoints:
Primary PK endpoints were to establish PK similarity based on area under the concentration time curve from time zero to infinity ($AUC_{0-\infty}$) and maximum serum concentration (C_{max}) of study drug. Primary PD endpoints were ANC_E_{max} and $AUEC_{0-t}$

Secondary PK endpoints were time to observe maximum drug concentration in plasma

(T_{max}), the terminal elimination rate constant (Kel), terminal half-life (t½), the volume of distribution (Vd) and total body clearance (Clt).

The secondary objective was to determine immunogenicity (presence of anti-study drug antibodies and anti-peg antibodies) and to monitor the safety and tolerability of a single subcutaneous dose of study drug.

Study Assessment

Safety Assessment: Safety was monitored by physical examination, vital signs, clinical laboratory examinations and 12-lead ECGs.

Vital signs (blood pressure, pulse rate, respiration rate and body temperature) were measured at 02, 04, 06, 12, 24, 48, 72, 96 hrs ± 45 minutes of scheduled time.

Table 14: Schedule of events (Study ARL/18/360/LBC-19-146)

Safety Parameters	Screening	Period I	Period II	Post study safety assessment
Demographic examination	X	-	-	-
Clinical History	X	-	-	-
Physical examination	X	X	X	X
Vital Signs	X	X	X	X
Well being Assessment	-	X	X	X
Biochemistry test	X	-	-	X
Hematology test (Including ANC test)	X	X	X	X
Immunological Investigation	X	-	-	-
Serological examination (HIV, Hepatitis B and C)	X	-	-	-
Urine analysis	X	-	-	X
Urine examination for drug of abuse	-	X	X	-
Breath alcohol test	X	X	X	X
12 Lead ECG	X	-	X	-
Serum (β) Beta- hCG	X	X	X	-
Adverse event Assessment	-	X	X	X
Tolerability assessment	-	X	X	-

"X" indicates the relevant activity performed.

Procedure	Within 21 days Screening	Admission Day	For Batch I to IV	Period I Day 1*15	Post-Study [d]	Discontinuation of Subject [d]
				Period II Day 43*57		
			For Batch V	Period I Day 1*15		
				Period II Day 46*60		
Informed consent	X	-	-		-	-
Medical history and Serology tests (HIV, hepatitis B, C and Syphilis)	X	-	-		-	-
Physical examination [a]	X	X	X		X	X
Weight	X	-	-		-	-
Height and BMI	X	-	-		-	-
Vital Signs [a]	X	X	X		X	X
Well Being Assessment [a]	-	-	X		X	X
Haemogram (Including ANC Test)	X	-	-		X	X
Creatinine clearance (CrCL) [a]	X	-	-		-	-
Biochemistry	X	-	-		X	X
Urinalysis	X	-	-		X	X
Urine examination for drug abuse	-	X	-		-	-
12 Lead ECG[f]	X	-	X		-	-
Breath alcohol test [b]	X	X	X		X	X
Admit to CPU	-	X	-		-	-
Study drug administration	-	-	X		-	-
Meal [c]	-	X	X		-	-
Serial blood samples collection [e]	-	-	X		-	-
Serum (β) Beta- hCG test (For female subjects)[g]	-	X	-		-	-
Tolerability assessment [h]	-	-	X		-	-

'X' indicates the occurrence, '*' indicates day starts from post-dose.

a. Physical examination and vital examination (Blood pressure, pulse rate, oral temperature and respiratory rate) done at the time of screening, check-in and check-out of each study period. Haemogram (Including ANC Test), biochemistry, urinalysis were done at the time of screening, and during post study safety assessment.
Additionally, Immunological Investigation was done at the time of screening.
Physical examination and vital examination of check out were started approximately 02.00 hours prior to the scheduled time in each study period.
Each subject's Intravenous cannula site was observed by principal investigator/sub-investigator/medical officer at the time of check-out, for any swelling or thrombophlebitis and well being was asked.
Well-being assessment, measurement of blood pressure and pulse rate were done at pre-dose and at 02.00, 04.00, 06.00, 12.00, 24.00, 48.00, 72.00 and 96.00 hours ± 45 minutes (except for pre-dose) of scheduled time in each study period.
Note: For each ambulatory blood sample visits, blood sample collection was preceded by wellbeing assessment in each study period.
b. Breath alcohol test was performed at each visit to the study center during the entire course of the study.
c. Standardized meal was given during check-in night (in such a way to maintain at least 10.00 hours fasting prior to drug administration) and breakfast was given 30 minutes prior to drug administration and at around 04.00, 08.00, 12.00, 24.00, 28.00, 32.00, 36.00, 48.00, 52.00, 56.00, 60.00, 72.00, 76.00, 80.00, 84.00, 96.00, 100.00, 104.00 and 108.00 hours post-dose in each study period.
d. Physical examinations including vital examinations, well-being assessment, haemogram, (Including ANC Test), biochemistry and urinalysis were done at the end of study or on discontinuation of subjects from the study.
e. Blood samples were collected at 01.00 hour (collected within 01.00 hour prior to dosing) and at 01.00, 02.00, 04.00, 06.00, 08.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00, 168.00, 192.00, 216.00, 240.00, 264.00, 288.00, 312.00 and 336.00 hours post-dose in each study period.
f. 12 - Lead ECG (Electrocardiogram) was done at the time of screening and during check-out of period-II.
g. For female subjects serum (β) Beta- hCG test was done during screening and at the time of check-in of each period.
h. Tolerability assessment (Injection site reactions) were done at pre dose and at 02.00, 04.00, 06.00, 12.00, 24.00, 48.00, 72.00, 96.00 hrs post dose ± 45 minutes of scheduled time (except pre-dose) in each study period.
Note: For each ambulatory sample visits, tolerability assessment were done in each study period.|

Source: Applicant submission, Module 5.3.4.1

Statistical Methodologies

PK similarity between LUBT004 and US-Neulasta was assessed by constructing the 90% confidence intervals (CIs) for the geometric mean ratio (GMR; test/reference) for C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$. PK similarity was concluded if the 90% CIs for all C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ were completely contained within the acceptance limits of 80%-125%.

PD (ANC) similarity between LUBT004 and US-Neulasta was assessed by constructing the 90% confidence intervals (CIs) for the geometric mean ratio (GMR; test/reference) for ANC_E_{max} and $AUEC_{0\text{-}t}$. PD similarity was concluded if the 90% CIs for both ANC_E_{max} and $AUEC_{0\text{-}t}$ were completely contained within the acceptance limits of 80%-125%.

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

6.2.2. Study LRP/PegGCSF/2016/004

Title: An Open-label, Randomized, Comparative, Parallel-Group Study to Assess the Immunogenicity of Lupin's Pegfilgrastim Versus Neulasta® as an Adjunct to Chemotherapy in Patients with Breast Cancer.

Study Initiation Date: April 04, 2018
Study Completion Date: January 08, 2019
Study Site: The study was conducted at 12 sites in India.

Study Design and Endpoints

Study design:

The study was a randomized, comparative, parallel-group, two-arm, open-label, multicenter clinical study conducted in India to compare the immunogenicity and safety of LUBT004 to that of US-Neulasta in patients with breast cancer who were scheduled to receive myelosuppressive chemotherapy (docetaxel/ paclitaxel/doxorubicin/ cyclophosphamide/epirubicin) and who were eligible to receive pegfilgrastim.

Eligible adult patients diagnosed with breast cancer who were planned to receive myelosuppressive chemotherapy for 4 cycles of 21 days each were enrolled. A total of 138 patients were randomized in a 1:1 ratio, and 70 patients received LUBT004, and 68 patients received US-Neulasta. Patients received a single dose 6 mg of study drug administrated s.c. on Day 2 or Day 3 of each Cycle for 4 Cycles. The primary endpoint was comparative cumulative incidence of binding and neutralizing anti-study drug antibodies between treatment groups at the end of C4, D84, see study schematic in Section 5.4.1, Figure 3.

Endpoints

Primary Endpoint:
The primary endpoint was comparison of cumulative incidence of anti-study drug antibodies (binding and neutralizing) to study drug between treatment groups at the end of Cycle 4 (Day 84).

Secondary Endpoints:

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

Secondary Safety Endpoints: Safety endpoints included AEs, vital signs, physical and systemic examinations, and laboratory parameters (hematology, biochemistry and urinalysis).

Eligibility Criteria

Inclusion Criteria:

1. Adult female patients age ≥18 years.
2. Patients with histologically or cytologically proven diagnosis of breast cancer who were eligible for neoadjuvant or adjuvant chemotherapy.
3. Patients who planned to receive/were receiving myelosuppressive chemotherapy regimen containing at least 1 chemotherapeutic agent from docetaxel/paclitaxel/doxorubicin/cyclophosphamide/epirubicin.
4. Patients who had not received any hematopoietic growth factors (e.g., G-CSF, PegGCSF, erythropoietin) or cytokines (e.g., interleukins, interferons) anytime in the past.
5. Patients with baseline white blood cell (WBC) ≥3.5 × 10^9/L, ANC of ≥1.5 ×10^9/L, platelet count ≥100 × 10^9/L, and hemoglobin ≥8.5 g/dL.
6. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
7. Patient who had estimated life expectancy of more than 6 months.
8. No evidence of hemorrhage.

Exclusion Criteria:

1. Male patients.
1. Hypersensitivity to any of the study drugs or its components such as E. coli proteins or similar product.
2. Patients who weighed < 45 kg.
3. Patients with myeloid malignancies and myelodysplasia or evidence of metastatic disease in bone marrow or brain.
4. Patients currently receiving radiation therapy or had completed radiation therapy within 4 weeks before study entry or was likely to receive radiotherapy during the study.
5. Patients with prior bone marrow or stem cell transplantation.
6. 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.
7. Patients with history of systemic antibiotic use (i.e., parenteral use) within 72 hours before chemotherapy.
9. Patients with any active infection, which might have required systemic antimicrobial therapy. Patients with inadequate hepatic and renal function (defined as alkaline phosphatase >2.5 × upper limits of normal [ULN], serum glutamic-oxaloacetic transaminase [SGOT] >2.5 × ULN, serum glutamic-pyruvic transaminase [SGPT] >2.5 × ULN, total bilirubin >1.5 × ULN and creatinine >1.5 × ULN of the reference range at the screening assessment).
10. Patients with seropositivity for human immunodeficiency virus (HIV) or hepatitis B virus (HBV) or hepatitis C virus (HCV).

11. Patients with 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 have compromised the patient's involvement in the study or overall interpretation of the data (e.g., uncontrolled hematologic, renal, hepatic, endocrine, neurologic, psychiatric, metabolic, pulmonary, cardiovascular disease/impaired functioning, or history of any autoimmune disease).
15. Patients who had participated in another therapeutic clinical study within the past 30 days prior to screening or were likely to simultaneously participate in another therapeutic clinical study.
16. Patients who were doubtful to comply with study procedures for mental, psychological, or social reasons.
17. Women of childbearing potential who were not willing to follow a reliable and effective contraceptive measure during the study and at least 3 months after the last dose of study drug.
18. Pregnant and breastfeeding women.

Study Assessment

Immunogenicity assessments included presence of anti-study drug antibodies and anti-peg antibodies. Safety assessments included adverse events (AEs), physical and systemic examinations, vital signs, and clinical laboratories. Serum study drug concentrations were measured during PK assessments and ANCs measured for PD assessments.

Assessments of immunogenicity, safety, and PK-PD were performed periodically during the study according to the following scheduling visits:

- Randomization Visit 1/ Day 1 of chemotherapy Cycle 1 (V1): Immunogenicity, safety, and PK-PD at baseline.
- Visit 2 (V2) - Day 10 ± 3 days of chemotherapy Cycle 1: Immunogenicity, safety, and PK-PD.
- Visit 3 (V3) - end of chemotherapy Cycle 1 (C1D21 ± 3 days)/ C2D1: Immunogenicity, safety, and PK-PD.
- Visit 4 (V4) - end of chemotherapy Cycle 2 (C2D42 ± 3 days)/ C3D1: Immunogenicity, safety, and PK-PD.
- Visit 5 (V5) - end of chemotherapy Cycle 3 (C3D63 ± 3 days)/ C4D1: Immunogenicity, safety, and PK-PD.
- Visit 6 (V6 End of Study (EOS)) - end of chemotherapy Cycle 4 (C4D84 ± 3 days)/EOS Visit or Early Discontinuation Visit: Immunogenicity, safety, and PK-PD.

Table 15: Study LRP/PegGCSF/2016/004 Schedule of Assessments

Period	Screening period (Max 7 days)	Treatment Period									
Cycle		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)		
Day		D1 (V1)	D2	Day 10 ±3 (V2)	C1-D21 or C2-D1 (V3)[1]	D2	C2-D21 or C3-D1 (V4)[1]	D2	C3-D21 or C4-D1 (V5)[1]	D2	D21/ EOS/ET (V6)[2]
Informed consent	X										
Demography	X										
Eligibility criteria	X										
Medical history	X										
Physical and systemic examination	X	X		X	X		X		X		X
Vital signs[3]	X	X		X	X		X		X		X
Weight	X				X		X		X		X
Blood sampling for lab investigations[4]	X	X[5, 6, 7]			X[7]		X[7]		X[7]		X
Urine sample for urine analysis	X	X[7]			X[7]		X[7]		X[7]		X
Urine pregnancy test[8]	X				X		X		X		X
Serum pregnancy test	X										
HIV, HBV, and HCV	X										
Chest X-ray	X										
ECG	X				X[6]		X[6]		X[6]		X
Abdominal USG[9]	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[10]		X									

Period	Screening period (Max 7 days)	Treatment Period									
Cycle		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)		
Day		D1 (V1)	D2	Day 10 ±3 (V2)	C1-D21 or C2-D1 (V3)[1]	D2	C2-D21 or C3-D1 (V4)[1]	D2	C3-D21 or C4-D1 (V5)[1]	D2	D21/ EOS/ET (V6)[2]
Chemotherapy administration[11]		X			X		X		X		
Study drug administration[12]			X			X		X		X	
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for immunogenicity assessment		X[13]		X	X[13]		X[13]		X[13]		X
Blood sampling for PK assessment		X[13]		X	X[13]		X[13]		X[13]		X
Blood sampling for ANC assessment		X[13]		X	X[13]		X[13]		X[13]		X

Abbreviations: ANC = absolute neutrophil count; D = day; V = visit; C = cycle; ECG = electrocardiogram; EOS = end of study; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; PD = pharmacodynamics; PK = pharmacokinetics; USG = ultrasonography.

1. Day 21 assessments of the previous cycle were allowed to be performed on Day 1 (Pre-chemotherapy) of next cycle.
2. In case of early discontinuations/premature termination of the study, all EOS investigations were to be done on the day of termination as far as possible.
3. Included body temperature, pulse rate, blood pressure, and respiratory rate.
4. Hematology included complete blood count (hemoglobin, hematocrit, red blood cells, white blood cells, platelets and differential white blood cell counts [neutrophils, lymphocytes, monocytes, eosinophils, and basophils including ANC]).
   Blood chemistry included bilirubin (total, direct, indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, total protein, albumin, globulin, uric acid, urea, creatinine, random glucose, and lactate dehydrogenase.
   Urinalysis included appearance, color, specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood (and microscopic examination, if abnormality was suspected). In case of early discontinuation/premature termination of the study, all EOS investigations were repeated on the day of termination as far as possible.
5. Hematology tests were to be repeated if the gap between screening laboratory investigations and Cycle 1 Day 1 was more than 7 days.
6. Assessments were done before chemotherapy.

Source: BLA submission, Module 5.3.5.1

Discontinuation Criteria

Patient discontinuation criteria: Patients were allowed to discontinue the study at any time for the following reasons:

- If the patient withdrew consent.
- After the first dose, it became apparent that the patient was ineligible.
- The patient needed emergency treatment or was unable to continue participation in the study because of exacerbation of their symptoms, at the discretion of the investigator.
- Inability of patient to comply with the protocol for any reason.
- The patient became pregnant during the study period.
- In the opinion of the investigator or sub-investigator, the patient was to be discontinued because of AEs (including progressing complications) or safety reasons.
- In the opinion of the investigator or sub-investigator the patient should be discontinued from the study.

Statistical Methodologies

Analysis Population: For definition of the Analysis Population, see Table 9.

Applicant's analysis of the primary endpoint: The difference in cumulative incidence of anti-study drug antibodies (binding and neutralizing) to study drug between study groups (LUBT004 vs. US-Neulasta) at the end of Cycle 4 (Day 84) was calculated, along with the two-sided 90% confidence interval (CI) for the difference in proportions. Noninferiority was assessed using a noninferiority margin of 10%. The binomial proportion using PROC FREQ and margin = 0.1 (10%) was used to present the proportion difference along with two-sided 90% CI. Non-inferiority is demonstrated when the upper bound of the CI is less than or equal to 10%.

FDA reviewer's analysis of the primary endpoint: The applicant's analysis was not based on all randomized patients because their Intent-to-treat definition requires patients receive study drug and provide postbaseline immunogenicity variable data. The applicant's analysis also counts baseline ADA-positive patients as non-responders, regardless whether they are post-baseline ADA-positive. To preserve balance of characteristics of the two arms, the FDA statistical reviewer performed re-analyses by including all randomized patients, irrespective of whether patients receiving any study drug or having positive ADA or missing value at baseline (i.e., the FDA-ITT population). In particular, the following are the two imputations utilized.

- *Imputation 1*: Treat patients as ADA incidences for those who had positive baseline ADA or missing post-baseline visits
- *Imputation 2*: Treat patients as non-ADA incidences for those who had positive baseline ADA or missing post-baseline visits

To reduce the impact of positive baseline ADA patients to the analysis result, the FDA statistical reviewer also performed re-analyses on the FDA-RITT population which includes all randomized population but exclude patients who had positive baseline ADA. In particular, the following are the two imputations FDA conducted.

- *Imputation 3*: Impute patients with missing post-baseline visits as ADA incidences
- *Imputation 4*: Impute patients with missing post-baseline visits as no ADA incidences

Protocol Amendments

There were 3 amendments to the original version 1.0 protocol (version 2.0, May 29, 2017, version 2.1, October 16, 2017, and version 2.2, July 02, 2018). According to the Applicant, the first executed protocol was version 2.1, dated October 16, 2017, which was amended once July 02, 2018. The key changes from protocol version 2.1 to protocol version 2.2 are as follows:

- Missing adverse events assessment details were added to the screening visit.
- Added clarification to exclusion criterion #8 that antibiotic use within 72 hours before chemotherapy referred to parenteral use.
- Sample processing method used for PK samples was updated to harmonized PK sample processing.

There were no changes made to the planned SAP in version 1.0, dated October 01, 2018.

Patient Disposition

From the total of 160 patients screened, 138 adult female patients were enrolled and randomized. Seventy patients were randomized to LUBT004 group and 68 patients were randomized to US-Neulasta group. Five patients prematurely discontinued the study (3 patients in the LUBT004 group and 2 patients in the US-Neulasta group). Among discontinued patients, 2 patients each group withdrew their consent forms, and one patient in the LUBT004 group withdrew due to non-compliance.

The patient disposition in study LRP/PegGCSF/2016/004 is summarized in Table 27.

Demographics and Baseline Characteristics

A total of 138 patients with breast cancer were randomized in a 1:1 ratio with 70 patients to LUBT004 group and 68 patients to US-Neulasta group. Baseline demographics characteristics were comparable between the two groups. The average age was 51.2 years, and all were female. At screening most of patients (74%) had an Eastern Cooperative Oncology Group (ECOG) status of Grade 1. The mean baseline weight was similar between the two groups at 67 Kg.

The demographic characteristics of safety analysis set is summarized in Table 21 in Section 6.3.2.

Concomitant Therapy

According to the Applicant, concomitant administration of 5-fluoro-2, 4 pyrimidinedione (5-FU) or other antimetabolites, lithium, radiotherapy, rescue medication for treating neutropenia and immunization were prohibited. Any other medications required by the patient and expected not to interfere with study drug assessments were allowed on a case-by-case basis and as deemed appropriate by the investigator.

Missing Data
There was no concern for potential effects of missing data for this study.

Analysis of Primary Clinical Endpoint(s)

The primary endpoint for Study LRP/PegGCSF/2016/004 was comparison of cumulative incidence of anti-study drug antibodies (binding and neutralizing) to study drug between treatment groups at the end of Cycle 4 (Day 84). Noninferiority of LUBT004 versus US-Neulasta was assessed using a noninferiority margin of 10%.

The primary endpoint is appropriate for a biosimilar application for determination of non-inferiority of LUBT004 to US-Neulasta in incidence of anti-study drug antibodies (binding and neutralizing).

Anti-PEG antibody was detected in 1 patient (1.5%) in the LUBT004 treatment group arm and not detected in any patient in the US-Neulasta treatment group. The cumulative incidence of binding anti-study drug antibodies at the end of Cycle 4 was 1.4% in the LUBT004 group and 4.1% in the US-Neulasta group. The incidence difference was -3% (95% CI of -7.7%, 1.7%). The upper bound of the 90% two-sided confidence interval do not exceed 10%, which demonstrates that LUBT004 is non-inferior to US-Neulasta. Based on the Applicant's analysis, no meaningful differences were observed between the two treatment groups.

For the results of the analysis of the primary endpoint, see Section 5.4.1 (Table 12).

Potential Effects of Missing Data

There was only one patient in the LUBT004 group (Patient # (b) (6) who withdrew from the study after Cycle 1 of chemotherapy and who had no postbaseline sample and thus was excluded from the applicant's analysis for immunogenicity. The FDA analysis, which includes patients with missing postbaseline immunogenicity testing, concluded that missing data did not impact the conclusion that LUBT004 was non-inferior to US-Neulasta. These results are summarized in Table 12.

The impact of positive baseline ADA patients on the analysis results of the primary endpoint by including all randomized population but excluding patients who had positive baseline ADA (Table 13) showed no effect on the conclusion that LUBT004 is noninferior to US-Neulasta.

There was no concern for potential effects of missing data for this study.

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The clinical review of the safety data was based on the safety data derived from Study ARL/18/360/LBC-19-146 conducted in healthy volunteers and Study LRP/PegGCSF/2016/004 study conducted female patients with breast cancer.

Information used in the safety review included:

- Clinical study reports and other relevant portions of the BLA
- Safety data was audited or reproduced

- Relevant published literature on US-Neulasta
- Regulatory history
- Existing labels

Clinical Studies Used to Evaluate Safety

The safety database comprised 402 subjects who received at least one dose of either LUBT004 or US-Neulasta in one of the two studies. There were 264 healthy volunteers and 138 female patients with breast cancer who received at least one dose of LUBT004 or US-Neulasta.

The overall safety database was adequate for an application for a biosimilar to US-Neulasta. There were no major concerns regarding data integrity. The overall quality of data was acceptable for safety evaluation. Safety data from the two studies was not pooled due to differences in study design, study population (healthy vs patients), and treatment duration.

Study ARL/18/360/LBC-19-146

The study was a single center, double-blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover comparative PK-PD study of LUBT004 6 mg/0.6 ml subcutaneous (s.c.) injection and U.S.-licensed Neulasta (pegfilgrastim 6 mg/0.6 ml) s.c. injection. The study was conducted in 268 healthy volunteers enrolled in 5 batches with 264 participated in Period 1 and 223 participated in Period 2. Subjects received a single dose of 6 mg/0.6 ml of either LUBT004 or US-Neulasta in each period administered SC.

Study LRP/PegGCSF/2016/004

The study was an open label, randomized trial designed to assess the immunogenicity of LUBT004 compared to US-Neulasta in patients with breast cancer receiving chemotherapy. Eligible adult patients diagnosed with breast cancer planned to receive myelosuppressive chemotherapy for 4 cycles of 21 days each were enrolled. A total of 138 patients were randomized in 1:1 ratio with 70 patients received LUBT004 and 68 patients received US-Neulasta. Patients received a single dose 6 mg of study drug administrated s.c. injection on Day 2 or Day 3 of each Cycle for 4 Cycles. The primary endpoint was comparative cumulative incidence of binding and neutralizing anti-pegfilgrastim antibodies between treatment groups at the end of C4, D84.

Table 16: Overall clinical studies

Trial	Trial Design	Subjects	Treatment	Study Endpoints
ARL/18/360/LBC-19-146	Double-blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover comparative PK-PD study	268 Healthy Volunteers	• LUBT004 6 mg/0.6 ml, s.c. injection • US-Neulasta, 6 mg/0.6 ml s.c. injection	• Primary: PK Cmax, AUC0-t and AUC0-∞ PD ANC_Cmax, $ANC\_AUEC_{0\text{-}tlast}$ • Secondary: PK Tmax, Kel, t½, Vd and Clt PD Parameters ANC_Tmax Adverse event (safety)
LRP/PegGCSF/2016/004	Open-label, randomized, two-arm, comparative, parallel-group, multicenter to assess the immunogenicity of LUBT 004's vs US-Neulasta in patients with breast cancer	138 Patients with breast cancer Peg =70 Neulasta= 68	• LUBT004 6 mg/0.6 ml, s.c. injection • US-Neulasta, 6 mg/0.6 ml s.c. injection	• Primary: Cumulative incidence of anti-pegfilgrastim antibodies (binding and neutralizing) at the end of Cycle 4 (Day 84) • Secondary: Safety and tolerability

Source: Reviewer Table

Overall Exposure

There were a total of 402 subjects who received at least one dose of either LUBT004 or US-Neulasta on Study ARL/18/360/ LBC-19-146 or Study LRP/PegGCSF /2016/004. The s.c. doses of LUBT004 administered were 6 mg.

Table 17: Subjects exposure to pegfilgrastim (Studies ARL/18/360/LBC-19-146 and LRP/PegGCSF/2016/004)

Study/ Population (N)	LUBT004	US-Neulasta
Study ARL/18/360/ LBC-19-146 Healthy volunteers (N=264)	241	246
Study LRP/PegGCSF/2016/004 Patients with breast cancer (N=138)	70	68
Total	311	314

Source: BLA submission, Module 2.7.4

Study ARL/18/360/LBC-19-146

In Study ARL/18/360/LBC-19-146, 264 healthy adult subjects received at least 1 dose of 6 mg/0.6 ml s.c. injection of LUBT004 or US-Neulasta. Of the 264 subjects, 131 were randomized to the LUBT004 group and 133 were randomized to the US-Neulasta group. In Period I, 131 subjects received a single dose of 6 mg/0.6 ml s.c. injection of

LUBT004, and 133 subjects received a single dose of 6 mg/0.6 ml s.c. injection of US-Neulasta. In Period II, 110 subjects received a single dose of 6 mg/0.6 ml s.c. injection of LUBT004, and 113 subjects received a single dose of 6 mg/0.6 ml s.c. injection of US-Neulasta. There was a washout period of at least 42 days between Period I and Period II. Overall, 264 subjects in Period I and 223 subjects in Period II exposed to the study drugs.

The extent of exposure in the individual group is summarized in Table 18 and Table 19.

Table 18: Drug exposure (Study ARL/18/360/LBC-19-146)

Period	LUBT 004	US-Neulasta	Total dosed
Period I	131	133	264
Period II	110	113	223
	241	246	Total

Source: BLA submission, Module 2.7.4

Table 19: Dose of Study Treatment (Study ARL/18/360/LBC-19-146)

	LUBT004 N=241	US-Neulasta N=246
Study period 1 (n)	131	133
Median (mg)	6.0	6.0
Range (mg)	6.0-6.0	6.0-6.0
Study period 2 (n)	110	113
Median (mg)	6.0	6.0
Range (mg)	6.0-6.0	6.0-6.0

Source: BLA submission, Module 2.7.4

Study LRP/PegGCSF/2016/004

In Study LRP/PegGCSF/2016/004,138 female patients with breast cancer received at least one dose of study drug. Seventy patients were randomized and received LUBT004, and 68 patients were randomized and received US-Neulasta. A total of 67 patients in each arm received a single dose of 6 mg/dose of either LUBT004 (95.7%) or US-Neulasta (98.5%) administered by s.c. injection per chemotherapy cycle for a total of 4 chemotherapy cycles. However, 3 patients in the LUBT004 group discontinued treatment after study initiation and received less than 4 doses as follows:

- Patient # (b) (6) discontinued after 1 dose of LUBT004
- Patient # discontinued after 2 doses of LUBT004
- Patient # discontinued after 3 doses of LUBT004

One patient in the US-Neulasta group discontinued treatment after receiving 2 doses (Patient # (b) (6)

The planned duration of treatment was approximately 84 days (up to 4 chemotherapy cycles of 21 ± 3 days each cycle).

Categorization of Adverse Events

According to the Applicant, all adverse events (AEs) were coded according to the Medical Dictionary for Regulatory activities (MedDRA) version 20.1 for Study LRP/PegGCSF/2016/004 and MedDRA version 23.0 for Study ARL/18/360/LBC-19-146. The severity of AEs was categorized as mild, moderate, or severe.

Treatment emergent adverse event (TEAE) was defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

Safety Analyses

Pooling of the safety data from the two studies for purpose of an integrated safety analysis was not performed due to the differences in study design, population (health subjects vs patients with breast cancer) and treatment duration (single dose administration in healthy volunteers vs 4 doses in patients with breast cancer). Therefore, adverse events were summarized in each study separately.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Study ARL/18/360/LBC-19-146

A total of 268 healthy subjects were enrolled in this study (males =171; females =97). However, only 264 subjects received at least one dose of study drug and are thus included in the safety analysis. Baseline demographics was balanced between the two groups. The majority of subjects were male (64%). The mean age was 34.5 years. The mean height, weight, and BMI were 162.2 cm, 67.2 kg and 25.7 kg/m^2, respectively. All subjects included in the study were from India.

The demographic characteristics of safety analysis set is summarized in Table 20.

Table 20: Baseline demographic characteristics (Study ARL/18/360/LBC-19-146)

Demographic	Lupin pegfilgrastim	US-Neulasta	Lupin pegfilgrastim	US-Neulasta
	Period-I		Period-II	
	(N = 131)	(N = 133)	(N = 110)	(N = 113)
Age (years)				
Mean (SD)	34.6 (5.8)	34.3 (6.1)	34.5 (6.2)	34.6 (5.9)
Median (Min, Max)	35 (20, 44)	35 (18, 44)	35 (18, 44)	35 (20, 44)
Gender, n (%)				
Female	47 (35.9)	48 (36.1)	42 (38.2)	36 (31.9)
Race, n (%)				
Asian (India)	131 (100)	133 (100)	110 (100)	113 (100)
Weight (kg)				
Mean (SD)	67.4 (6.9)	67.1 (6.8)	67.0 (7.1)	67.3 (6.8)
Median (Min, Max)	66.14 (60.01, 90.8)	65.29 (60.14, 91.54)	65.2 (60.1, 91.5)	66.1 (60.0, 90.8)
Height (cm)				
Mean (SD)	161.9 (9.1)	162.5 (8.5)	162.8 (8.4)	161.9 (9.1)
Median (Min, Max)	163.3 (161.9, 183.5)	162.6 (142.5, 182.6)	163.2 (142.5, 181.1)	163.3 (142.1, 183.5)
BMI (Kg/m^2)				
Mean (SD)	25.8 (2.9)	25.1 (2.7)	25.4 (2.6)	25.8 (2.8)
Median (Min, Max)	26.2 (18.86, 29.89)	25.6 (19.32, 29.69)	25.3 (19.3, 29.7)	25.9 (18.9, 29.9)

Source: Reviewer Analysis

Study LRP/PegGCSF/2016/004

A total of 138 patients with breast cancer were randomized in a 1:1 ratio with 70 patients randomized to LUBT004 group and 68 patients randomized to the US-Neulasta group. Baseline demographics characteristics were comparable between the two groups. All patients enrolled were female and from India. The average age was 53.4 years in LUBT004 group compared to 48.8 years in US-Neulasta group. At baseline, approximately 29% and 24% of patients in the LUBT004 and US-Neulasta, respectively, had an Eastern Cooperative Oncology Group (ECOG) status of Grade 0. The majority of patients, 71% in LUBT004 group and 76% in US-Neulasta group, had ECOG status of 1 at baseline. The mean baseline weight was similar between the two groups at 67 Kg.

The demographic characteristics of the safety analysis set are summarized in Table 21.

Table 21: Baseline demographic characteristics (Study LRP/PegGCSF/2016/004)

Demographic and Disease Characteristic	Lupin pegfilgrastim (N = 70)	US-Neulasta (N = 68)
Age (years)		
Mean (SD)	53.4 (11.59)	48.8 (8.73)
Median (Min, Max)	54 (29, 75)	48 (29, 72)
Gender, n (%)		
Female	70 (100)	68 (100)
Race, n (%)		
Asian (India)	70 (100)	68 (100)
Ethnicity, n (%)		
Not Hispanic or Latino	70 (100)	68 (100)
ECOG Status at Screening, n (%)		
Grade 0	20 (28.6)	16 (23.5)
Grade 1	50 (71.4)	52 (76.5)
Female with Child Bearing Potential, n (%)	13 (18.6)	26 (38.2)
Weight (kg)		
Mean (SD)	56.56 (9.74)	56.29 (10.63)
Median (Min, Max)	55.5 (46, 102)	53.45 (46, 102)

Source: Reviewer Analysis

Deaths

No deaths were reported in the Study ARL/18/360/ LBC-19-146 (comparative PK-PD study in healthy subjects) or Study LRP/PegGCSF/2016/004 (comparative immunogenicity study in patients with breast cancer).

Treatment Emergent Adverse Events

Study ARL/18/360/LBC-19-146

There were a total of 64 TEAEs reported in 57 subjects (23.7%) in LUBT004 group and 57 TEAEs reported in 52 subjects (21.1%) in US-Neulasta group. The majority of TEAEs were categorized as moderate in severity (89% [108/121] of all events). Two subjects in both groups experienced a severe TEAE. One subject in LUBT004 group experienced serious chest pain and one subject in US-Neulasta group experienced perspiration.

The percentage of subjects who discontinued study due to adverse events was comparable between groups (15 subjects (6%) in the LUBT004 group versus 12

subjects (5%) in the US-Neulasta group). The most common TEAEs leading to discontinuation were: vomiting (12 subjects: 3 subjects in LUBT004 vs 8 subjects in US-Neulasta); skin rash (5 subjects in LUBT 004), vomiting with burning pain in epigastrium (2 subjects: 1 in each arm), and body ache (2 subjects: 1 in each arm).

Table 22: Overall summary of safety in Study ARL/18/360/LBC-19-146

	Lupin pegfilgrastim N= 241 n (%)	**US-Neulasta N= 246** n (%)
Any TEAE	**57 (23.7)**	**52 (21.1)**
TEAE probably related	**50 (20.7)**	**39 (15.9)**
Mild TEAE	6 (2.5)	5 (2.0)
Mild TEAE propably related	6 (2.5)	5 (2.0)
Moderate TEAE	52 (21.6)	47 (19.1)
Moderate TEAE propably related	46 (19.1)	34 (13.8)
Severe TEAEs*	1 (0.4)	1 (0.4)
Fatal TEAEs	0 (0)	0 (0)
AE leading to discontinuation	15 (6.2)	12 (4.9)

* Chest burning pain in Lupin Peg and Chest pain (anterior wall MI) and prespiration in Neulasta (tests showed no abnormal findings)

Source: Reviewer Table

The most frequently reported TEAEs were pain and discomfort, headache, back pain, vomiting and rash. Pain and discomfort, headache and rash occurred in higher frequencies in subjects received LUBT004 compared to those who received US-Neulasta. However, back pain occurred in higher frequency in subjects received US-Neulasta than those received LUBT004. These slight differences were not considered to be meaningful.

Table 23 summarizes the most common TEAEs occurring in Study ARL/18/360/LBC-19-146.

Table 23: Common TEAEs, Study ARL/18/360/LBC-19-146

TEAE/PT	Lupin pegfilgrastim	US-Neulasta
N	N= 241	N= 246
	n (%)	n (%)
Back pain	9 (3.7%)	13 (5.3%)
Headache	17 (7.1%)	12 (4.9%)
Pain	3 (1.2%)	0 (0.0%)
Pain and discomfort	22 (9.1%)	13 (5.3%)
Pain in extremity	0 (0.0%)	1 (0.4%)
Pyrexia	1 (0.4%)	0 (0.0%)
Rash	5 (6.9%)	0 (0.0%)
Vomiting	6 (2.5%)	13 (5.3%)
Chest pain	1 (0.4%)	1 (0.4%)

Source: Reviewer Analysis

Study LRP/PegGCSF/2016/004

In Study LRP/PegGCSF/2016/004, the safety population comprised 138 patients of which 70 patients received LUBT004 and 68 patients received US-Neulasta.

There were a total of 175 TEAEs reported in 60 patients in the LUBT004 group compared to 218 TEAEs reported in 58 patients in the US-Neulasta group. The percentage of patients with at least one TEAE was similar between treatment groups (86% of patients in LUBT004 group vs 85% of patients in US-Neulasta group). The majority of TEAEs were categorized as mild or moderate in severity. There were 3 severe TEAES (2 caes of neutropenia and 1 case of anemia) occurring in two patients (2.9%) in the LUBT004 group compared to 11 severe TEAEs occurring in 8 patients (12%) in the US-Neulasta group. All severe and life-threatening TEAEs, except one case of pain, were hematologic disorders, including neutropenia, anemia, leukopenia, and increased neutrophil count.

The majority of TEAEs (83%) were assessed by the investigator to be unrelated to the study drug. Possibly treatment related adverse events were reported in 8 patients (11%) in the LUBT004 treatment group and 13 patients (19%) in US-Neulasta treatment group. There were no TEAEs that led to study drug discontinuation or study withdrawal in either group. No patients in the LUBT004 group experienced a serious AE while 2 patients (2.9%) in US-Neulasta group experienced serious AEs (neutropenia and anemia).

Table 24: Overall summary of safety in Study LRP/PegGCSF/2016/004

	Treatment Emergent Adverse Event	
	Lupin Pegfilgrastim (N = 70)	**US-Neulasta (N = 68)**
Patients with any TEAE, n (%)	60 (85.7)	58 (85.3)
Patients with any Serious TEAE, n (%)	0	2 (2.9)*
Patients with Mild TEAE, n (%)	37 (52.9)	27 (39.7)
Patients with Moderate TEAE, n (%)	21 (30.0)	23 (33.8)
Patients with Severe TEAE	2 (2.9)	8 (11.8)
Neutropenia or Leukopenia	2 (2.9)	4 (5.9)
Anemia	0	3 (4.4)
Neutrophil count increased	0	1 (1.5)
Patients with any possibly related TEAE	8 (11.4)	13 (19.1)
Patients who Discontinued from Study due to TEAE	0	0

* One patient had neutropenia and the other patient had anemia and neutropenia

Source: BLA Submission, Module 2.7.4.

The most common reported TEAEs were alopecia, vomiting, nausea, asthenia, neutropenia, and pain. Most common TEAE related to the study drug was pain.

Table 25 sumarizes the most common TEAEs reported in LRP/PegGCSF/2016/004 study.

Table 25: TEAEs occurrring in ≥ 2% of patients, Study LRP/PegGCSF/2016/004

TEAE PT	Lupin Pegfilgrastin N= 70 n (%)	US-Neulasta N= 68 n (%)
Alopecia	27 (38.6%)	22 (32.4%)
Vomiting	19 (27.1%)	21 (30.9%)
Nausea	15 (21.4%)	19 (27.9%)
Asthenia	13 (18.6%)	15 (22.1%)
Stomatitis	7 (10%)	5 (7.4%)
Cough	6 (8.6%)	6 (8.8%)
Neutropenia	6 (8.6%)	9 (13.2%)
Pain	6 (8.6%)	8 (11.8%)
Anemia	5 (7.1%)	7 (10.3%)
Headache	5 (7.1%)	9 (13.2%)
Decreased appetite	4 (5.7%)	1 (1.5%)
Diarrhoea	3 (4.3%)	3 (4.4%)
Mucosal inflammation	3 (4.3%)	1 (1.5%)
Pyrexia	3 (4.3%)	3 (4.4%)
Back pain	2 (2.9%)	4 (5.9%)
Bacterial infection	2 (2.9%)	0 (0%)
Constipation	2 (2.9%)	1 (1.5%)
Gastritis	2 (2.9%)	0 (0%)
Nasopharyngitis	2 (2.9%)	3 (4.4%)
Pyuria	2 (2.9%)	1 (1.5%)

Source: Reviewer Analysis

The incidence of TEAEs categorized by System Organ Class (SOC) groups was comparable between LUBT004 and US-Neulasta treatment groups. The most common TEAEs by SOC were gastrointestinal disorders (46% of patients in the LUBT004 group versus 52% of patients in US-Neulasta group), skin and subcutaneous tissue disorders (40% of patients in the LUBT004 group versus 34% of patients in the US-Neulasta group), and general disorders and administration site conditions (27% of patients in the LUBT004 group versus 35% of patients in the US-Neulasta group).

TEAE By System Organ Class	Lupin pegfilgrastim N=70 n (%)	US-Neulasta N=68 n (%)
Any TEAE	60 (85.7%)	58 (85.3%)
Gastrointestinal disorders	32 (45.7%)	35 (51.5%)
Skin and subcutaneous tissue disorders	28 (40%)	23 (33.8%)
General disorders and administration site conditions	19 (27.1%)	24 (35.3%)
Blood and lymphatic system disorders	10 (14.3%)	16 (23.5%)
Respiratory, thoracic and mediastinal disorders	8 (11.4%)	8 (11.8%)
Nervous system disorders	7 (10%)	12 (17.6%)
Infections and infestations	6 (8.6%)	10 (14.7%)
Metabolism and nutrition disorders	4 (5.7%)	3 (4.4%)
Musculoskeletal and connective tissue disorders	3 (4.3%)	7 (10.3%)
Eye disorders	2 (2.9%)	0 (0%)
Investigations	2 (2.9%)	3 (4.4%)
Psychiatric disorders	2 (2.9%)	0 (0%)
Immune system disorders	1 (1.4%)	0 (0%)
Reproductive system and breast disorders	0 (0%)	1 (1.5%)

Source: Reviewer Analysis

Serious Adverse Events

Study ARL/18/360/LBC-19-146

There were 2 SAEs reported in 2 subjects (one in each group). One subject in the LUBT004 group experienced severe chest pain and perspiration (PT: chest pain), and one subject in the US-Neulasta group experienced severe burning pain in chest (PT: chest pain). One patient was diagnosed with multivessel coronary atherosclerotic artery disease, and the second patient was diagnosed with acute allergic alveolitis. Both events were resolved on further follow up. Both events were assessed by the investigator to be unlikely to be related to study drugs. Narratives for these events are summarized below:

- Subject No. (b) (6) 37-year-old male who received a single dose of LUBT004 6mg/0.6ml administered s.c. on (b) (6) during Period-I. Approximately 17 days later (b) (6), he experienced burning chest and was admitted to the local hospital. His ECG findings were suggestive of anterior wall myocardial infarction. However, 2D Echo done on (b) (6) was normal and LVEF was 40%. Coronary angiography done on (b) (6) showed multi-vessel coronary artery atherosclerosis. On (b) (6), a percutaneous transluminal coronary angioplasty (PTCA) was performed, and a stent was placed in the distal left anterior descending (LAD) coronary artery. The patient recovered and was discharged from the hospital on (b) (6) On several followup visits were unremarkable with no patient complaints and no abnormal findings was reported. Final study assessment done on (b) (6) found no further abnormalities and

adverse event was reported as resolved and the patient was deemed fit to return to normal activities.

- Subject No. [redacted] 38-year-old female who received a single injection of US-Neulasta 6mg/0.6ml on [redacted], during Period-I. Approximately 6 days later [redacted] she complained of perspiration and chest pain. ECG showed T wave inversion and the patient was admitted to the hospital. 2D Echo revealed mild dilated right atrium and right ventricle and LVEF was 60% with reduced left ventricle compliance. Chest x-ray showed heterogenous soft tissue opacity in the right lower chest with blunting of the right costophrenic angle. Pulmonary angiography [redacted] showed areas suggestive of interstitial fibrosis with no evidence of pulmonary thromboembolism. Coronary angioplasty [redacted] showed normal coronariesarteries. The patient was discharged on [redacted] with a diagnosis of acute allergic alveolitis. On post study assessment [redacted] the patient had no complaint, and the event was reported as resolved.

Study LRP/PegGCSF/2016/004

There were no SAEs reported in the LUBT004 group and 3 SAEs reported in 2 patients in the US-Neulasta group. One patient experienced neutropenia and another patient experienced severe anemia and severe neutropenia. All three events were assessed to be unrelated to the study drugs. All events were resolved on further follow up.

Dropouts and/or Discontinuations

Subject Disposition Study ARL/18/360/LBC-19-146

Subject disposition is summarized in Table 26.

In Period I, a total of 51 subjects discontinued the study and did not continue into Period 2 (18 subjects received the LUBT004 and 23 subjects received US-Neulasta). Reasons for discontinuation were adverse events (23 subjects), personal reason (17 subjects) and non-compliance (1 subject).

In Period 2, a total of 5 subjects discontinued the study (4 subjects in the LUBT004 group and 1 in US-Neulasta group).

Table 26: Subject disposition, Study ARL/18/360/LBC-19-146

	Lupin Pegfilgrastim n (%)	Neulasta® n (%)
Screened	460	
Enrolled and randomized	268	
Discontinued before dosing in Period I due to personal reason	3	1
Period 1		
Total subjects dosed	131	133
Subjects discontinued after Period I dosing	18 (13.7)	23 (17.3)
· Adverse event	12 (9.2)	11 (8.3)
· Personal reason	5 (3.8)	12 (9.0)
· Protocol non-compliance	1 (0.8)	-
Period 2		
Total subjects dosed	110	113
Subjects discontinued after Period II dosing	4 (3.7)	1 (0.9)
· Adverse event	3 (2.8)	1 (0.9)
· Personal reason	1 (0.9)	-
Total subjects completed the study	109	109

Source: Reviewer Analysis

Discontinuation due to AEs in the LUBT004 group (12 subjects [9.2%] in Period-I and 3 [2.8%] in Period-2) was comparable to that in the US-Neulasta group (11 subjects [8.3%] in Period-1 and 1 [0.9%] in Period-2). Adverse events resulted in subject's discontinuation were vomiting (12 subjects); vomiting with burning pain in epigastrium (2 subjects), skin rashes (5 subjects) and body ache (2 subjects).

Subject Disposition Study LRP/PegGCSF/2016/004

From the total of 160 patients screened, 138 adult female patients were enrolled and randomized (LUBT004: 70,. US-Neulasta: 68) Five patients prematurely discontinued the study (3 in the LUBT004 group and 2 in the US-Neulasta group). Among discontinued patients, 2 patients each group withdrew their consent forms and one patient in the LUBT004 group withdrew due to non-compliance.

Table 27: Subjects disposition of (Study LRP/PegGCSF/2016/004)

	Lupin pegfilgrastim n (%)	US-Neulasta® n (%)
Screened	160	
Screen failure	22	
Reason for Screen failure		
• Deviation from inclusion criteria	13	
• Exclusion criteria	9	
Randomized Population	70	68
• Treated	70	68
• Subjects who completed the study	67 (95.7)	66 (97.1)
• Subjects who discontinued the study early	3 (4.3)	2 (2.9)
Primary reason for discontinuation		
➢ Withdrew consent	2 (2.9)	2 (2.9)
➢ Lost to follow-up	1 (1.4)	0

Source: Reviewer Analysis

No patients discontinued the study in either groups due to TEAE.

6.3.3. Additional Safety Evaluations

Laboratory Findings

The Applicant stated that laboratory assessment for serum chemistry, hematology (except for neutrophile), and urinalysis were performed on samples collected at the Screening visit and End of Study (EOS).

Study ARL/18/360/LBC-19-146

Hematology

In Study ARL/18/360/LBC-19-146, there were no clinically meaningful differences in hematology parameters observed across the two groups. The mean values of neutrophils and leukocytes increased after administration of each study drug were similar, peaking Day 2 and returning to baseline by the End of Study Assessment Visit.

Table 28: Summary of Hematology Laboratory Tests, Study ARL/18/360/LBC-19-146

		LUBT004	US-Neulasta
Neutrophils ($x10^9$/L)	N	241	246
	Mean baseline (SD)	4.9 (1.4)	4.87 (1.3)
	N	240	246
	Day 1, Mean (SD)	30.32 (9.3)	30.51 (9.59)
	N	239	244
	Day 2, Mean (SD)	35.69 (10.39)	35.72 (10.58)
	N	228	235
	Day 4, Mean (SD)	22.79 (8.4)	22.35 (8.15)
	N	220	225
	Day 7, Mean (SD)	18.89 (6.6)	18.78 (6.0)
	N	222	227
	Day 14, Mean (SD)	5.58 (1.71)	5.63 (2.15)
	Post study Safety Visit	N=263	
	Mean (SD)	5.52 (1.76)	
Leukocytes ($x10^9$/L)	N	241	246
	Baseline	8.14 (1.87)	7.93 (1.74)
	End of Assessment Visit	8.20 (1.9)	8.37 (2.1)
Hemoglobin (g/L)	N	241	246
	Baseline	13.23 (1.48)	13.06 (1.50)
	End of Assessment Visit	12.49 (1.79)	12.77 (1.74)
Platelets ($x10^9$/L)	N	241	246
	Baseline	327.31 (83.98)	340.6 (81.45)
	End of Assessment Visit	291.47 (82.93)	289.54 (73.52)

Source: Reviewer Analysis

Chemistry

In Study ARL/18/360/LBC-19-146, the changes in serum chemistry laboratory values from screening to the end of the study were generally similar between the LUBT004 and the US-Neulasta groups. No meaningful differences in laboratory abnormalities were reported between the two arms.

Study LRP/PegGCSF/2016/004

Hematology

In Study LRP/PegGCSF/2016/004, the changes in hematology laboratory values from baseline were generally similar between the LUBT004 and US-Neulasta groups. No meaningful differences in laboratory abnormalities were reported between the two groups.

The mean changes from baseline to the end of the study in hemoglobin level (-1 versus -0.9 g/dL), and hematocrit (-3.6% versus -3.1%) were similar in the LUBT004 group and the US-Neulasta group, respectively.

The mean changes from baseline to the end of the study in the leukocytes decreases (-455 versus -594 cell/mm^3), and neutrophils increases (176 versus 271 cell/mm^3) were comparable between the LUBT004 group and the US-Neulasta group, respectively.

Table 29 summarizes the changes from baseline to the end of study in hematology values in Study LRP/PegGCSF/2016/004.

Table 29: Hematology, Changes from baseline to end of study of hematology values, Study LRP/PegGCSF/2016/004

	Changes from Baseline (CFB) in Hematology Values			
	Lupin Pegfilgrastim N=70		US-Neulasta N=68	
Parameters (Unit)	Baseline Mean (SD)	End of Study CFB (SD)	Baseline Mean (SD)	End of Study CFB (SD)
Hemoglobin (g/dL)	11.9 (1.2)	-1.0 (1.2)	11.99 (1.3)	-0.9 (1.1)
Hematocrit (%)	38.1 (3.6)	-3.6 (4.2)	38.2 (4.7)	-3.1 (4.3)
White Blood Cells (cells/mm^3)	8252.7 (2021.8)	-454.5 (3498.1)	7893.8 (2420.6)	-594.2 (3163.9)
Neutrophils (cells/mm^3)	5216.6 (1837)	176.5 (3613.1)	4962.9 (2153)	271.7 (3073.3)
Lymphocytes (cells/mm^3)	2129.3 (803.2)	-728.9 (831.8)	2094.1 (726.4)	-901.3 (658.9)
Monocytes (cells/mm^3)	581.3 (252.8)	217.7 (335.9)	561.6 (280.5)	170.4 (377.5)
Eosinophils (cells/mm^3)	282.3 (379.7)	-125.3 (224.5)	279.3 (293.0)	-188.6 (264.4)
Basophils (cells/mm^3)	52.5 (43.2)	-3.9 (61.5)	55.7 (41.8)	-17.3 (58.9)
Platelets (x10^3/µL)	306.8 (74.7)	58.5 (88.9)	320.8 (86.4)	50.0 (97.2)

CFB: changes from baseline.

Source: Reviewer Analysis

Chemistry

In Study LRP/PegGCSF/2016/004, the changes in serum chemistry laboratory values from baseline to the end of the study were generally similar between the LUBT004 and US-Neulasta groups. No meaningful differences in laboratory abnormalities were reported between the two arms.

Table 30 summarizes the changes from baseline to the end of study in hematology values in Study LRP/PegGCSF/2016/004.

Table 30: Changes from baseline to end of study of serum chemistry values, Study LRP/PegGCSF/2016/004

	Changes from Baseline (CFB) in Serum Chemistry			
	Lupin Pegfilgrastim N=70		US-Neulasta N=68	
Parameters (Unit)	Baseline Mean (SD)	End of Study CFB (SD)	Baseline Mean (SD)	End of Study CFB (SD)
Albumin (g/dL)	4.1 (0.3)	0.04 (0.3)	4.2 (0.3)	0.09 (0.3)
Alkaline Phosphatase (U/L)	78.5 (19.3)	4.4 (18.2)	72.0 (19.2)	1.9 (18.3)
Alanine Aminotransferase (U/L)	20.5 (10.6)	0.7 (11.1)	22.0 (12.9)	2.9 (22.5)
Aspartate Aminotransferase (U/L)	21.6 (8.3)	2.1 (10.3)	23.2 (11.1)	3.5 (20.3)
Bilirubin (mg/dL)	0.5 (0.2)	- 0.02 (0.17)	0.5 (0.2)	- 0.03 (0.2)
Creatinine (mg/dL)	0.79 (0.11)	- 0.04 (0.11)	0.69 (0.09)	- 0.04 (0.09)
Globulin (g/dL)	3.08 (0.41)	- 0.31 (0.51)	3.11 (0.36)	- 0.23 (0.46)
Glucose (mg/dL)	126.6 (81.4)	- 0.7 (82.8)	115.6 (39.3)	6.1 (42.4)
Lactate Dehydrogenase (U/L)	228.7 (72.5)	2.9 (79.3)	239.9 (148.2)	- 10.4 (154.8)
Protein (g/dL)	7.2 (0.5)	-0.3 (0.7)	7.3 (0.5)	- 0.1 (0.6)
Urea (mg/dL)	20.1 (7.8)	- 2.9 (7.6)	19.9 (6.4)	- 3.4 (6.1)

Source: Reviewer Analysis

Vital Signs

In Study ARL/18/360/LBC-19-146, the mean vital sign results of blood pressure, heart rate and body temperature remained generally within normal limits with no remarkable observations in mean change from baseline values.

In Study LRP/PegGCSF/2016/004, there were no notable changes from baseline in average blood pressure, pulse rate, respiratory rate, and axillary body temperature in both treatment groups. However, significant finding was only observed in one patient in US-Neulasta group, reported as a non-serious TEAE (mild pyrexia).

Electrocardiograms

In Study ARL/18/360/LBC-19-146, there were no clinically meaningful changes in mean ECG parameters, and no subject had abnormal ECG findings at the end of study.

In Study LRP/PegGCSF/2016/004, there were no clinically significant abnormal findings in ECG were reported.

Product Specific Safety Concerns

The US-Neulasta (pegfilgrastim) U.S. Prescribing Information (USPI) includes warnings for the adverse reactions of fatal splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions, fatal sickle cell crisis, glomerulonephritis, leukocytosis, thrombocytopenia, and capillary leak syndrome. FDA assessed these adverse reactions as Adverse Events of Special Interest in both studies.

In Study ARL/18/360/LBC-19-146, there were no cases of leukocytosis, splenic rupture, ARDS, capillary leak syndrome, sickle cell crises, thrombocytopenia, neoplasms, aortitis or glomerulonephritis reported.

In Study LRP/PegGCSF/2016/004, there were no cases of splenic rupture, ARDS, capillary leak syndrome, sickle cell crises, thrombocytopenia, neoplasms, aortitis or glomerulonephritis reported. There were 5 cases of leukocytosis reported in the study (2 cases in the LUBT004 group and 3 cases in the US-Neulasta group). There were 3 (4.3%) subjects in the LUBT004 groups and 7 (10.3%) subjects in the US-Neulasta group with at least 1 TEAE in the Musculoskeletal and Connective Tissue Disorders SOC. There were no injection site related AEs reported in either groups.

6.4. Clinical Conclusions on Immunogenicity

For full details of the immunogenicity analysis, see Section 5.4.

The Applicant conducted one parallel designed immunogenicity study (LRP/ PegGCSF/ 2016/004) in patients with breast cancer. The incidence of ADA was low in both the LUBT004 group and the US-Neulasta group. In the LUBT004 group, of the 69 patients with negative ADA antibody at baseline, who received study drug, and who provided postbaseline immunogenicity data, 1 developed treatment-induced ADA (1.5%) at around week 6. In the US-Neulasta group, out of the 68 patients, 3 developed treatment-induced ADA (4.4%) at around week 3 to week 9. No patients had positive ADA detected at the end of the study (Day 84), and none of the binding antibodies were neutralizing in nature. The Division concludes that the incidence of post-dose positive anti-drug antibody (ADA) was comparable between the two groups (LUBT004: 1.5%, US-Neulasta: 4.4%).

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6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that LUBT004 is highly similar to US-Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between LUBT004 and US- Neulasta in terms of safety, purity and potency.

The Applicant is seeking licensure of LUBT004 as a biosimilar product to US-Neulasta for the following indication which has been previously approved for US-Neulasta and for which LUBT004 has not been directly studied:

- 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 Applicant has provided adequate scientific justification for extrapolation of data and information to support licensure of LUBT004 for the proposed indication above. However, because the application is receiving a complete response letter, this text about extrapolation should be revisited when the Sponsor has adequate manufacturing to produce a product which is safe, pure and potent.

6.5.1. Division of Nonmalignant Hematology (DNH)

Mechanism of Action
The Applicant provided data to support that LUBT004 has the same mechanism of action as U.S.-Neulasta, which support extrapolation for the sought indication. LUBT004 is highly similar to U.S.-Neulasta notwithstanding minor differences in clinically inactive components.

Pharmacokinetics (PK)
The comparative PK/PD Study ARL/18/360/ LBC-19-146 results demonstrated similar PK and bio-distribution of LUBT004 to US-Neulasta as concluded in Section 5. The 90% CI of the geometric mean ratio (GMR) for the primary PK endpoints Cmax, AUC0-t and AUC0-inf were within the pre-specified margin of 80-125%. The PD (ANC) similarity was demonstrated between LUBT004 and US-Neulasta. The 90% CI of the GMR for the primary PD endpoints ANC_Emax and ANC_AUEC0-t were within the pre-specified margin of 80-125%.

The bone marrow in healthy subjects, in contrast to myelosuppressed patients, is more responsive to pegfilgrastim, thereby making this population a more sensitive model for comparative PK and PD assessments. Available data do not indicate any major differences in PK based on indication. Therefore, it is reasonable to conclude that PK for LUBT004 is expected to be similar between patients in the indication being sought.

The Applicant provided adequate justification that a similar PK profile is expected between LUBT004 and US-Neulasta for the indication being sought.

Immunogenicity
The overall immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (single dose) and in patients with breast cancer (multiple doses), and an assessment of the impact of ADA on safety. The results from the comparative clinical immunogenicity study demonstrated that LUBT004 has comparable immunogenicity profile to that of US-Neulasta. There are no clinically meaningful differences in immunogenicity between proposed LUBT004 and US-Neulasta.

The Applicant provided adequate justification that similar immunogencity is expected between LUBT004 and US-Neulasta for the indication being sought.

Toxicity
The Applicant showed that the overall safety profile of LUBT004 was similar to that of US-Neulasta. The safety results from the comparative clinical studies in healthy subjects and patients with breast cancer supports demonstration of no clinically meaningful differences between LUBT004 and US-Neulasta.

The Applicant provided adequate justification that a similar safety profile would be expected between LUBT004 and US-Neulasta for the indication being sought.

Conclusions
DNH concludes that the Applicant has provided sufficient scientific justification based on the mechanism of action, PK/PD, immunogenicity and toxicity profile to support extrapolation of data and information in the application to support licensure of LUBT004 for the proposed indication.

However, the lack of adequate manufacturing facilities and a container closure integrity testing deficiency preclude approval of this product.

Authors:
Saleh Ayache, MD, Clinical Reviewer
Margaret Thompson, MD PhD, Clinical Team Leader
Ann T. Farrell, MD, Division Director

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, pegfilgrastim-unne, was found to be conditionally accepted by the the Division of Medication Error Prevention and Analysis (DMEPA). Refer to DMEPA's memorandum dated February 7, 2022.

7.2. Proprietary Name

The proposed proprietary name for LUBT004 is conditionally approved as Armlupeg. This name has been reviewed by DMEPA, who concluded the name was acceptable.

Stephanie DeGraw, PharmD archived her review on 6/25/2021. The review was also signed by her Team Leader, Hina Mehta, PharmD and the DMEPA Assoc. Director of Nomenclature and Labeling, Chi-Ming (Alice) Tu, PharmD. A Proprietary Name Granted letter was sent to the Applicant on 07/01/2021 by Linda Wu.

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

Lupin is seeking licensure for a subset of the approved indications of the U.S.-licensed Neulasta. They are only seeking the indication “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. They are NOT seeking the indication for “increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

There were minor edits made to the draft USPI.

- In Highlights, the section (b) (4) was deleted because this section is not relevant to newly approved biosimilar products.

- The Applicant was asked to remove the decimal point after the numbers of the main headings (1-17) per PLR format.

- Throughout all sections of the labeling, the naming of the product was revised to be consistent with the FDA Guidance: Labeling for Biosimilar Products.

- The format of cross-references throughout the USPI were corrected.

- Throughout the labeling, the non-proprietary drug name “pegfilgrastim” was capitalized unnecessarily in the proposed labeling. I revised the word “pegfilgrastim” to lower case unless presented as the first word in a sentence or a table title (both of which require capitalization).

Authors:

Virginia E. Kwitkowski, MS, ACNP-BC
Associate Director for Labeling

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

The Applicant has adequately disclosed financial arrangements with clinical investigators. The Application provided the FDA financial disclosure Form 3454 certifying that there were no financial arrangements with any of the investigators involved in the two clinical studies LRP/PegGCSF/2016/004 and ARL/18/360 / LBC-19-146. The document included a list of all investigators. The Applicant stated that none of the Principal Investigators reported financial interests or arrangements.

The Applicant reported that no clinical investigators were full-time or part-time employees of the Applicant for the covered studies.

Authors:
Saleh Ayache, MD
Clinical Reviewer

Ann T. Farrell, MD
Division Director

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting held for this application, as it was determined that there were no issues where the Agency needed input from the committee.

Author:
Saleh Ayache
Clinical Reviewer

10. Pediatrics

In view of the recommendation for a Complete Response, any recommendations for PREA post marketing requirement(s) are deferred until the next review cycle.

Authors:
Margaret Thompson, MD
Clinical Team Lead

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

In view of the recommendation for a Complete Repsonse, any recommendations for postmarket requirement(s) are deferred until the next review cycle.

Authors:
Margaret Thompson, MD
Clinical Team Lead

12. Comments to Applicant

The following deficiencies were conveyed to the Applicant in the CR letter.

1. The container closure integrity test method has not been adequately validated. The study results do not demonstrate that the limit of detection can be evaluated in the pre-filled syringe as only vials were used as breach controls. Comparability between breached vials and syringes was not demonstrated. In addition, the acceptance criterion for the positive controls in the repeatability experiments is not robust. The established criterion requires the absorbance of a minimum of only (b) (4) of 6 positive controls be greater than that of the spiked LUBT 004 drug product. Repeat the container closure integrity test method validation studies to include the appropriate controls and more robust acceptance criteria.

2. Following pre-license inspection of Lupin Limited (Biotech Division), Pune, Maharashtra, India (FEI 3010977634) listed in this application, FDA conveyed deficiencies to the representative of the facility. Your complete response should include the date of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

The following comments/recommendations, which that are not approvability issues, were also conveyed to the Applicant in the CR letter:

3. (b) (4)

4. [redacted] (b) (4)

13. Division Director Comments

13.1. Division Director (OND – Clinical) Comments

This application is receiving a complete response based on inspectional and microbial testing issues. I concur with this recommendation.

Author:
Ann T. Farrell, MD
Division Director

14. Appendices

14.1. Financial Disclosure

Covered Clinical Study: LRP/PegGCSF/2016/004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator : 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: ARL/18/360/ LBC-19-146

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator : 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2. Clinical Pharmacology Appendices

14.2.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity Study ARL/18/360/LBC-19-146, serum LUBT004 and US-Neulasta concentrations measured using a validated ELISA (MV-20-007) were suitable for assessment of PK similarity. Both the method validation entitled "Estimation of Pegfilgrastim in human serum by sandwich ELISA method for Pharmacokinetic evaluation." and sample analysis for the study were performed at Lupin Bioresearch Center, (Pune, Maharashtra, India). In this method, anti-human G-CSF (b) (4) coated in 96-well plate was used to capture serum LUBT 004, US-Neulasta, and anti-human G-CSF conjugate (b) (4) was used to detect the bound analytes. Table 32 shows the summary of ELISA method performance in quantification of serum LUBT004 and US-Neulasta during the method validation.

Table 31. Summary of the bioanalytical method validation and in-study performance for measurement of serum LUBT004 and US-Neulasta

Bioanalytical method review summary	Estimation of Pegfilgrastim in human serum by sandwich ELISA method for Pharmacokinetic evaluation
Materials used for calibration curve & concentration	LUBT 004 Batch No.: Y900006 Expiration: 31 Oct 2021
Validated assay range	500.000 – 8000.000 pg/mL
Material used for QCs & concentration	LUBT 004 Batch No.: Y900006 Expiration: 31 Oct 2021 US-Neulasta Batch No.:1099084 Expiration: 31 Jul 2021

	Upper Limit of Quantitation (ULOQ) : 8000.000 pg/ml High Quality Control (HQC): 6000.000 pg/ml Mid Quality Control (MQC): 4000.000 pg/ml Low Quality Control (LQC): 1500.000 pg/ml Lower Limit of Quantitation (LLOQ): 500.000 pg/ml		
Minimum required dilutions (MRDs)	1:10		
Source & lot of reagents (LBA)	Human G-CSF Microplate Source: (b) (4) Lot No.: P218339 Anti-human G-CSF Conjugate Source: (b) (4) Lot No.: P218343		
Regression model & weighting	Regression Model: non linear 4-parameter logistic Weighting: none		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ LUBT 004	-1.78% to 1.79%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ LUBT 004	1.87% to 8.47%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs US-Neulasta LUBT 004	-9.35% to -2.04% -8.52% to -2.42%	Yes
	Inter-batch %CV US-Neulasta LUBT 004	4.02% to 9.74% 3.76% to 9.75%	Yes
	Percent total error (TE) US-Neulasta LUBT 004	6.45% to 19.09% 6.01% to 18.27%	Yes
Selectivity & matrix effect	Ten total lots tested. Range of observed %bias at LLOQQC: LUBT 004: -13.76% to -0.86%		Yes

Interference & specificity	Six total concomitant medicine (Pheniramine, Ondansetron, Ibuprofen, Ranitidine, Diclofenac and Paracetamol) at concentrations of 2.000µg/mL in normal human serum tested. Observed %bias and %CV at LLOQQC: LUBT 004: -12.94% and 2.57%, respectively Observed %bias and %CV at ULOQQC: LUBT 004: 3.08% and 1.85%, respectively	Yes
Hemolysis effect	One lot tested. Observed %bias at LLOQQC: LUBT 004: -11.08% Observed %bias at HQC: LUBT 004: -8.62%	Yes
Lipemic effect	One lot tested. Observed %bias at LLOQQC: LUBT 004: -6.63% Observed %bias at HQC: LUBT 004: -9.38%	Yes
Dilution linearity & hook effect	Range of %bias and %CV for dilution linearity samples within the range of quantitation (up to 625-fold dilution): LUBT 004: %bias: -7.55 to -2.78%, %CV: 1.25% to 2.71%, Hook Effect: All hook effect samples tested produced values above the ULOQ for LUBT 004.	Yes
Bench-top/process stability	24.75 hours at room temperature. LUBT 004: HQC: 99.84%, LQC:96.70% US-Neulasta: HQC:98.29%, LQC:95.73%	Yes
Freeze-Thaw stability	2,4,6 cycles each at -75 10°C, and -20 5°C. 6 cycles freeze-thaw stability: LUBT 004: HQC: 8.87% (-75°C), 1.58% (-20°C) LQC: -5.69% (-75°C), -0.58% (-20°C) US-Neulasta: HQC: -0.02% (-75°C), -0.25% (-20°C) LQC: -0.25% (-75°C), -6.28% (-20°C)	Yes
Long-term storage	-75 10°C at 244 days: LUBT 004: HQC: 2.30%; LQC: 3.73% US-Neulasta: HQC: -0.19%; LQC: -0.41%	Yes

	-20 5°C at 244 days*: LUBT 004: HQC: -1.16%; LQC: -3.16% US-Neulasta: HQC: -4.32%; LQC: 2.19%	
Parallelism	Parallelism evaluation at five dilution levels (50, 60, 70, 80, 90-fold): Global %CV: 3.01% Global %bias: -4.62%	Yes
Carry over	Not evalucated	N/A
Method Performance in Study ARL/18/360/LBC-19-146 Determination of study drug in human serum samples from protocol ARL/18/360/LBC-19-146		
Assay passing rate	• Passed Runs: 513 (98.65%) • Failed Runs: 7 (1.35%) • Totol Number of Runs: 520	Yes
Standard curve performance	• Standard Curve Range: 500 – 8000 pg/mL • $R^2 \geq 0.99$ • Cumulative %bias range: -0.80 to 0.88% • Cumulative precision %CV range: 1.97% to 5.02%	Yes
QC performance	• Cumulative %bias range: -5.41% to -3.26% • Cumulative precision %CV range: 5.36% to 10.07% • Including values outside acceptance range criteria: ± 20.0% bias for all QC samples	Yes
Method reproducibility	Incurred sample reanalysis was performed in 877 samples (10% of first 1500 samples and 6.88% of the subsequent samples, thereafter) and 98.97% samples met the pre-specified criteria.	Yes
Study sample analysis/ stability	The interval from first sample draw date to last analysis date was 240 days. Adequate long-term stability (244 days) has been established to cover the storage period.	

Source: Reviewers' Table

Pharmacodynamics

Bioanalytical methods that were used to assess the PD biomarker(s) and/or the PD effect(s) of the study drug(s)

For pharmacodynamics (PD) determination, the Applicant provided the bioanalytical method used to determine Absolute Neutrophil Count (ANC) over time in the blood of the subjects included in Study ARL/18/360/LBC-19-146. The ANC was derived from measurements of the total number of WBC and is part of a larger blood panel (complete blood count (CBC)). The study samples analysis was performed on five part automated hematology analyzer (Make: Dymind, Model: DH76). The Analytical Measurement Range (AMR) of ANC is 0.0 to 100.0 $x10^3/\mu L$. Readymade calibrator and quality control

sample were used. Hematology quality control samples were performed on every day before starting of study samples. Study samples were analyzed once the hematology QC samples results found within acceptable ranges. The ANC testing report contains information on the method manual, SOPs of the DH76 auto hematology analyzer, and QC results in the individual analytical runs in the appendix section. The validation studies have been reviewed and the performance of the analyzer is considered acceptable for patient testing.

Authors:
Xiaomeng Xu, PhD
Clinical Pharmacology Reviewer

Anusha Ande, PhD
Clinical Pharmacology Team Lead

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/s/

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