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*APPLICATION NUMBER:*

**761075Orig1s000**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	18 May 2018
<b>From</b>	Nicole Gormley, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	BLA 761075
<b>Applicant</b>	Mylan GmbH
<b>Date of Submission</b>	4 Dec 2017
<b>BsUFA Goal Date</b>	4 Jun 2018
<b>Proprietary Name/ Nonproprietary Name</b>	Fulphila/ pegfilgrastim-jmdb*
<b>Dosage forms / Strength</b>	Injection: 6 mg/0.6 mL in a single-dose prefilled syringe
<b>Proposed Indication(s)</b>	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.
<b>Recommended:</b>	Approval

\* For purposes of this review, the proposed product is referred to by either the proprietary name, the proper (nonproprietary) name, or the Sponsor's descriptor MYL-1401H. The proposed proprietary name, Fulphila, and the proposed proper name, pegfilgrastim-jmdb, are conditionally accepted until such time that the application is approved.

<b>Material Reviewed/Consulted</b>	<b>Reviewer</b>
Clinical Review, Division of Hematology Products	Rachel Ershler, MD
Clinical Pharmacology Review, Office of Clinical Pharmacology	Saeho Chong, PhD, MS; Sarah Schrieber, Pharm.D.; and NamAtiqur Rahman, PhD.
Division of Hematology and Oncology Toxicology	Natalie Simpson, PhD; Christopher Sheth, PhD
Office of Biotechnology Products	Maria-Teresa Gutierrez-Lugo, PhD
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Nicole Garrison, Pharm.D, BCPS / Hina Mehta, Pharm. D.
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Casmir Ogbonna, Pharm.D, MBA, BCPS, SCGP/ Danielle Harris, Pharm. D, BCPS

## 1. Introduction

On December 9, 2016, Mylan GmbH (Applicant) submitted BLA 761075 for MYL-1401H as a proposed biosimilar product to US-licensed Neulasta (Amgen Inc.). BLA 761075 was submitted for the purpose of licensure of MYL-1401H under section 351(k) of the Public Health Service Act. The proposed indication for MYL-1401H is 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. US-licensed Neulasta is approved for this indication. Of note, US-licensed Neulasta also has an indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). However, the acute radiation syndrome indication was not sought by the Applicant as US-licensed Neulasta has unexpired orphan drug exclusivity for this indication.

The Application received a complete response on October 6, 2017 because of deficiencies identified during the facilities inspections and product quality deficiencies.

On December 4, 2017, the Applicant resubmitted the application.

## 2. Background

Granulocyte-colony stimulating factor (G-CSF) is an endogenous glycoprotein that regulates the survival, proliferation, differentiation, and function of cells in the neutrophil lineage. Neupogen(filgrastim) is a recombinant human G-CSF used therapeutically to stimulate the production of granulocytes in patients who are neutropenic subsequent to receiving myelosuppressive chemotherapy. Neupogen was first approved in the United States in 1991. Neulasta is a conjugate of a 20 kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionyl residue of filgrastim that was first approved in the United States in 2002. Neulasta has a considerably longer half-life than Neupogen (15-80 hours compared to 3-4 hours) and is advantageous in that it requires less frequent administration.

The Applicant's biosimilar development program consisted of an analytical similarity assessment and nonclinical and clinical programs.

For the analytical similarity assessment, up to 24 lots of US-licensed Neulasta, 12 of MYL-1401H drug product (DP), and 31 of EU-approved Neulasta were evaluated to support a demonstration that MYL1401H is highly similar to US-licensed Neulasta and to establish the analytical component of the scientific bridge to justify the relevance of the clinical data generated using EU-Neulasta from study MYL-401H-3001. .

For the clinical program, the applicant submitted data from three studies: Study MYL-1401H-1001, Study MYL-1401H-1002 and Study MYL-1401H-3001. These data support a demonstration that there are no clinically meaningful differences between MYL1401H and US-licensed Neulasta. Also, MYL-1401-1001 included a 3-way, pair-wise comparison of MYL-1401H, US-Neulasta, and EU Neulasta to establish the PK component of the scientific bridge to justify the relevance of the clinical data generated using EU-Neulasta from study MYL-401H-3001.

### 3. CMC

*Source: Derived in part from the OBP Executive Summary by Dr. Maria Gutierrez-Lugo.*

Mylan conducted analytical similarity studies to demonstrate that MYL-1401H is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. Up to 24 lots of US-licensed Neulasta, 12 of MYL-1401H drug product (DP), and 31 of EU-approved Neulasta were evaluated, including MYL-1401H lots used in the PK/PD similarity and additional clinical studies that were manufactured by the proposed commercial manufacturing process. The analytical similarity data support a determination that MYL-1401H is highly similar to US-licensed Neulasta notwithstanding minor differences in clinically inactive components. The pair-wise analytical comparisons of MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta, support the establishment of the analytical component of the scientific bridge to justify the relevance of the clinical data generated using EU-Neulasta from study MYL-401H-3001 .

The previously identified CR deficiencies were related to drug product manufacturing and cGMP deficiencies identified at [REDACTED] <sup>(b) (4)</sup> the proposed drug product manufacturing facility. The CR deficiencies and additional comments included in the CR letter were adequately addressed by the applicant in the December 4, 2017, resubmission.

The manufacturing data and information provided in the submission are sufficient to support a determination that the manufacturing process of MYL-1401H is well controlled and leads to a product that is safe, pure, and potent for the duration of the product shelf life. OPQ recommends MYL-1401H be approved for human use under the conditions specified in the package insert.

### 4. Nonclinical Pharmacology/ Toxicology

During the initial review cycle, the pharmacology/ toxicology review stated that the totality of the nonclinical data supports a demonstration that MYL1401 is similar to US-licensed Neulasta. The nonclinical review team did not identify any deficiencies in the initial review cycle. A subsequent review was not conducted for this response to CR. For further details, please refer to the initial nonclinical review dated September 5, 2017.

### 5. Clinical Pharmacology/ Biopharmaceutics

*Source: Derived in part from the clinical pharmacology review by Drs. Chong, Schrieber, and Rahman.*

During the initial review cycle, the clinical pharmacology review concluded that the PK and PD results support PK and PD similarity of MYL-1401H to US-licensed Neulasta and contribute to the data supporting a demonstration of no clinically meaningful differences between MYL-1401H and US-licensed Neulasta. In Study MYL-1401H-1001, the 90% confidence interval (CI) for the geometric mean ratios of the primary PK endpoints of  $C_{max}$  and  $AUC_{0-inf}$  and the primary PD endpoints of  $ANC_{max}$  and  $ANC_{AUEC_{last}}$  were within the pre-specified limits of 80% to 125% in the pairwise comparisons between MYL-1401H, US-

licensed Neulasta, and EU-approved Neulasta. The clinical pharmacology team concluded that the PK and PD results contribute to the totality of the data to support a demonstration of no clinically meaningful differences between MYL-1401H and US-licensed Neulasta.

The immunogenicity response for MYL-1401H and US-licensed Neulasta was compared in a multiple-dose, parallel-arm study in 50 healthy subjects (MYL-1401H-1002). The results of the studies indicate similar incidence and titers of anti-drug antibodies (ADAs) for MYL-1401H vs. US-licensed Neulasta. The incidence of ADAs was also compared in Study MYL-1401H-3001, a comparative clinical study, comparing MYL-1401H and EU-approved Neulasta in patients with stage II/III breast cancer receiving neoadjuvant or adjuvant chemotherapy.

The clinical pharmacology review team did not identify any deficiencies in the initial review cycle. A subsequent review was not conducted for this response to CR. For further details, please refer to the initial clinical pharmacology review dated August 8, 2017.

## 6. Clinical

*Source: Derived in part from the clinical review by Dr. Ershler.*

During the initial review, no clinical deficiencies were identified. Review of the studies MYL-1401H-1001, MYL-1401H-1002 and MYL-1401H-3001, supported that there were no clinically meaningful differences between MYL-1401H and US-licensed Neulasta. There were no clinical approvability issues.

The clinical efficacy of MYL-1401H compared to EU-Neulasta was assessed in 194 patients with Stage II/III breast cancer receiving chemotherapy (Study MYL-1401H-3001). The primary efficacy endpoint was the duration of severe neutropenia (DSN) in Cycle 1, defined as days with ANC  $<0.5 \times 10^9/L$ . In the MYL-1401H treatment group, the mean DSN ( $\pm$  SD) was 1.2 ( $\pm$  0.93) days. In the EU-Neulasta treatment group, the mean DSN ( $\pm$  SD) was 1.2 ( $\pm$  1.10) day. The primary endpoint of DSN was assessed by ANOVA and the equivalence margin was met. Based on the results and analysis, it was concluded that the data from Study MYL-1401H-3001 support a demonstration that there are no clinically meaningful differences between MYL-1401H and US-Neulasta.

The safety of MYL-1401H was assessed in two clinical studies in healthy subjects (MYL-1401H-1001 and MYL-1401H-1002) and in subjects with breast cancer (MYL-1401H-3001). MYL-1401H was generally well tolerated and the safety profile was acceptable. There were no deaths related to study treatment in any of the clinical studies. There were no events of splenomegaly, adult respiratory distress syndrome, capillary leak syndrome, or severe allergic reactions, which are rare but serious events known to be associated with pegfilgrastim treatment. The overall safety profile of MYL-1401H was similar to US-Neulasta, with bone pain reported as the most frequently occurring treatment-related TEAE.

The resubmission did not include any additional clinical information or a safety update. The clinical review team recommended approval. For further details, please refer to the initial clinical review dated September 6, 2017.

## **7. Advisory Committee Meeting**

This BLA was not presented to the Oncologic Drugs Advisory Committee.

## **8. Pediatrics**

The Applicant submitted a pediatric study plan. In order to comply with the Pediatric Research Equity Act, Mylan must develop a presentation that will allow administration of MYL- 1401H to patients weighing less than 45 kg. The Agency granted a deferral and required a PREA PMR for development of a pediatric presentation.

## **9. Other Relevant Regulatory Issues**

None.

## **10. Labeling**

The Prescribing Information is currently under negotiation. DMEPA, OPDP and the Division's Associate Director for Labeling participated in labeling discussions and provided recommendations.

DMEPA reviewed the suffix, -jmdb, for BLA 761075, which was found conditionally acceptable on July 28, 2017. During re-review, it was determined that the suffix -jmdb, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product. The proposed propriety name, Fulphila, was also conditionally accepted.

## **11. Recommendations/ Risk Benefit Assessment**

*Source: Derived in part from the reviews by Drs. Gutierrez-Lugo, Chong, Simpson, Ershler and Wang.*

MYL-1401H is a pegylated recombinant granulocyte colony stimulating factor (PEG-GCSF). GCSF is an endogenous glycoprotein that regulates the survival, proliferation, differentiation, and function of cells in the neutrophil lineage.

The OBP review noted that the analytical similarity data submitted by the applicant supported a determination that MYL-1401H is highly similar to US-licensed Neulasta notwithstanding minor differences in clinically inactive components. The CMC statistical review states that the statistical equivalence testing of protein content supported a demonstration that the proposed biosimilar MYL-1401H is highly similar to US-licensed Neulasta. The results also supported the analytical portion of the scientific bridge to justify the relevance of EU-approved Neulasta data from the comparative clinical study.

The pharmacology/toxicology review states that the totality of the nonclinical data supports a demonstration that MYL1401H is similar to US-licensed Neulasta.

The clinical pharmacology review concluded that the PK similarity and PD similarity were established between MYL-1401H and US-licensed Neulasta and the results contribute to the data supporting a determination of no clinically meaningful differences between MYL-1401H and US-licensed Neulasta. The results also supported the PK portion of the scientific bridge to justify the relevance of data derived from EU-approved Neulasta in the comparative clinical study.

The clinical/statistical review states that the clinical data supported a determination of no clinically meaningful differences between MYL-1401H and US-licensed Neulasta. The clinical data, including PK, PD, efficacy, safety, and immunogenicity data support the demonstration of no clinically meaningful differences in terms of the safety, purity, and potency of the product.

Overall the totality of the evidence supports a demonstration of biosimilarity between MYL-1401H and US-licensed Neulasta and support licensure of MYL-1401 as a biosimilar to US-licensed Neulasta for the indication requested.

Recommended Regulatory Action: Approval

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/s/  
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NICOLE J GORMLEY  
06/04/2018

## Cross-Discipline Team Leader Review

<b>Date</b>	29 September 2017
<b>From</b>	Nicole Gormley, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	BLA 761075
<b>Applicant</b>	Mylan GmbH
<b>Date of Submission</b>	9 Dec 2016
<b>BsUFA Goal Date</b>	9 Oct 2017
<b>Nonproprietary Name</b>	MYL-1401H* (also referred to as Fulphila by the Applicant)
<b>Dosage forms / Strength</b>	Injection: 6 mg/0.6 mL in a single-dose prefilled syringe
<b>Proposed Indication(s)</b>	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.
<b>Recommended:</b>	Complete Response

\* For purposes of this review, the proposed product is referred to by the Sponsor's descriptor MYL-1401H. FDA has not yet designated a nonproprietary name for Mylan's proposed biosimilar product that includes a distinguishing suffix (see Final Guidance on Nonproprietary Naming of Biological Products)

<b>Material Reviewed/Consulted</b>	<b>Reviewer</b>
Joint Clinical and Statistical Review, Division of Hematology Products and Division of Biometrics V	Rachel Ershler, MD Yaping Wang, PhD
Clinical Pharmacology Review, Office of Clinical Pharmacology	Saeho Chong, PhD, MS; Sarah Schrieber, Pharm.D.; and NamAtiqur Rahman, PhD.
CMC Statistical Review, Office of Biostatistics	Tianhua Wang, PhD; Meiyu Shen, PhD
Division of Hematology and Oncology Toxicology	Natalie Simpson, PhD; Christopher Sheth, PhD
Office of Biotechnology Products	Maria-Teresa Gutierrez-Lugo, PhD
Office of Process and Facilities/ Division of Inspectional Assessment	Laura Fontan; Zhihao Peter Qiu, PhD;
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Nicole Garrison, Pharm.D, BCPS; Lubna Merchant, Pharm.D.
Office of Study Integrity and Surveillance/ Division of New Drug Bioequivalence Evaluation	Gajendiran Mahadevan, PhD
Office of Scientific Investigations/ Division of Clinical Compliance Evaluation	Navid Homayouni, MD; Janice Pohlman, MD

## 1. Introduction

On December 9, 2016, Mylan GmbH (Applicant) submitted BLA 761075 for MYL-1401H as a proposed biosimilar product to US-licensed Neulasta (Amgen Inc.). BLA 761075 was submitted for the purpose of licensure of MYL-1401H under section 351(k) of the Public Health Service Act. The proposed indication for MYL-1401H is 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. This indication is approved for US-licensed Neulasta. Of note, US-licensed Neulasta also has an indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). However, the acute radiation syndrome indication is not being sought by the Applicant as US-licensed Neulasta has unexpired orphan drug exclusivity for this indication.

## 2. Summary

*Source: Derived in part from the reviews by Drs. Gutierrez-Lugo, Chong, Simpson, Ershler and Wang.*

MYL-1401H is a pegylated recombinant granulocyte colony stimulating factor (PEG-GCSF). GCSF is an endogenous glycoprotein that regulates the survival, proliferation, differentiation, and function of cells in the neutrophil lineage.

The OBP review notes that during a pre-license inspection of the [REDACTED] (b) (4) manufacturing facility for this BLA, the FDA identified deficiencies in MYL-1401H drug product manufacturing, including cGMP deficiencies. The review also states that the manufacturing data and information provided in the submission are insufficient to support a determination that the manufacturing process of MYL-1401H is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. The OBP review included the following summary of the issues:

1. The proposed MYL-1401H drug product manufacturing facility, [REDACTED] (b) (4) [REDACTED] has GMP deficiencies. Refer to Establishment Inspection Report and Form FDA 483 from a pre-license inspection associated with this application.
2. Insufficient assurance of drug product quality and control, including:
  - a. [REDACTED] (b) (4)
  - b. [REDACTED]

The OBP review noted that the analytical similarity data submitted by the applicant supported a determination that MYL-1401H is highly similar to US-licensed Neulasta notwithstanding minor differences in clinically inactive components. The CMC statistical review states that the statistical equivalence testing of protein content supported a demonstration that the proposed biosimilar MYL-1401H is highly similar to US-licensed Neulasta. The results also supported the analytical portion of the scientific bridge to justify the relevance of EU-approved Neulasta data from the comparative clinical study.

The pharmacology/toxicology review states that the totality of the nonclinical data supports a demonstration that MYL1401H is biosimilar to US-licensed Neulasta.

The clinical pharmacology review concluded that the PK and PD results supported a demonstration of no clinically meaningful differences between MYL-1401H and US-licensed Neulasta.

The clinical/statistical review states that the clinical data supported a demonstration of no clinically meaningful differences between MYL-1401H and US-licensed Neulasta.

### 3. Other Relevant Regulatory Issues

#### Inspections

##### CMC

*This section is derived in part from the reviews by Laura Fontan and Dr. Gutierrez-Lugo. Please see their reviews for further details.*

The Office of Pharmaceutical Quality/ Office of Process and Facilities/Division of Inspectional Assessment conducted pre-license inspection of (b) (4). The facility also underwent a surveillance inspection (b) (4). Observations from both inspections were reviewed to consider potential impact to the proposed operations for MYL-1401H drug product manufacturing. Corrective actions from the PLI conducted from (b) (4), were completed and deemed adequate.

However, corrective actions from the surveillance inspection conducted from (b) (4) are currently still in progress. Since critical corrective action preventative action (CAPAs) are still outstanding and the firm is currently not ready to manufacture, BLA 761075 for the manufacture of MYL-1401H is not recommended for approval. Since critical CAPAs are still outstanding and the firm is currently not ready to manufacture, BLA 761075 for the manufacture of MYL-1401H is not recommended for approval.

##### Clinical

*This section is derived from the reviews by Drs. Homayouni and Mahadeven. Please see their reviews for further details.*

The data from Study MYL-1401H-3001 was submitted to FDA in support of BLA 761075. Three clinical sites, Dzagnidze Giorgi, M.D. (Site 9901), Gia Nemsadze, M.D. (Site 9903), Zakaria Zautashvili, Ph.D. (Site 9906) and the Contract Research Organization (CRO), (b) (4) were selected for audit. There were no significant inspectional observations noted.

The data from studies MYL-1401H-1001 and MYL-1401H-1002 were submitted to the Agency in support of BLA 761075. An inspection was conducted at PRA Group B.V.,

Groningen, The Netherlands. The final inspection was classified as No Action Indicated (NAI).

### **Financial Disclosures**

The application includes financial disclosure form 3454 and indicates there were no financial arrangements with any of the investigators involved in clinical studies: MYL-1401H-1001, MYL-1401H-1002, and MYL-1401H-3001.

## **4. Recommendations/Risk Benefit Assessment**

Recommended Regulatory Action:

Due to the deficiencies noted by the Office of Pharmaceutical Quality, the CDTL recommendation is a complete response.

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NICOLE J GORMLEY  
10/06/2017