CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761122Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

BLA 761122
Review

Date: April 1, 2019

From: Jennifer Swisher, Ph.D.
Team Leader, DBRR I/OBP/OPQ

Through: Rachel Novak, Ph.D.
Review Chief, DBRR I/OBP/OPQ

Drug Name/Dosage Form	**Nucala (mepolizumab)/injection**
Strength/Potency	**100 mg/1.0 mL prefilled syringe**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indications	**Add-on maintenance treatment in patients with severe eosinophilic asthma; treatment of adult patients with eosinophilic granulomatosis with polyangiitis**
Applicant/Sponsor	**GlaxoSmithKline Inc.**

Product Overview

Mepolizumab is a human IgG1κ monoclonal antibody produced in CHO cells and was approved in the lyophilized presentation (100 mg/vial) under BLA 125526. BLA 761122 describes a liquid presentation of mepolizumab in a pre-filled syringe (PFS), which is then assembled into an autoinjector (AI) or safety syringe device (SSD). Mepolizumab binds and neutralizes soluble interleukin 5 (IL-5), preventing the binding of IL-5 to its receptor and subsequent downstream signaling, leading to a reduction in eosinophil levels. The mepolizumab drug product described in this BLA is supplied at 100 mg/1.0 mL as a sterile, single-dose, preservative-free solution for subcutaneous (SC) injection in a PFS; it is proposed as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype, and as a treatment for adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), both of which are approved indications for the lyophilized presentation.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Lymarie Maldonado-Baez	DBRR I/OBP/OPQ
Drug Product	Lymarie Maldonado-Baez	DBRR I/OBP/OPQ
Labeling	Scott Dallas	OBP/OPQ

Facility	Michael Shanks	DIA/OPF/OPQ
Microbiology (DS)	Madushini Dharmasena	DMA/OPF/OPQ
Microbiology (DP)	Monica Commerford	DMA/OPF/OPQ
Business Process Manager	Florence Aisida	RBPMBI/OPRO/OPQ
Team Lead for OBP	Jennifer Swisher	DBRR I/OBP/OPQ
Tertiary Reviewer for OBP	Rachel Novak	DBRR I/OBP/OPQ
Microbiology Quality Assessment Lead	Reyes Candau-Chacon	DMA/OPF/OPQ
Facilities Team Lead	Zhihao Peter Qiu	DIA/OPF/OPQ

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Ji Hyun LaRose	DPARP/OND
Cross-disciplinary Team Lead	Stacy Chin	DPARP/OND
Medical Officer	Xu Wang	DPARP/OND
Pharm/Tox	Wei Sun and Tim Robison (TL)	DPARP/OND
Clinical Pharmacology	Renu Singh, Anshu Marathe (TL)	OTS/OCP/DCPII
Stats	Jade Wang, Yongman Kim (TL)	OTS/OB/DBII

a. Names
   i. Proprietary Name: Nucala
   ii. Trade Name: Nucala
   iii. Non-Proprietary/USAN: mepolizumab
   iv. INN Name: mepolizumab
   v. OBP systematic name: MAB HUMAN (IGG1) ANTI P01579 (IFNG_HUMAN) [NI0501]

b. Pharmacologic category: Interleukin 5-directed neutralizing monoclonal antibody

Quality Review Team – Signature Block

DISCIPLINE	REVIEWER	SIGNATURE
Quality Assessment Lead OPF/DMA	Reyes Candau-Chacon	See Panorama
Facilities Branch Chief OPF/DIA	Peter Qiu	See Panorama
Team Lead OBP/DBRRI	Jennifer Swisher	See Panorama
Review Chief OBP/DBRRI	Rachel Novak	See Panorama

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
STN 761122/1	8/7/2018	OBP, DMA, DIA
STN 761122/2	8/27/2018	DIA
STN 761122/3	9/12/2018	DMA, OBP
STN 761122/4	9/17/2018	DMA
STN 761122/6	10/3/2018	DMA, OBP
STN 761122/7	11/9/2018	DMA
STN 761122/11	1/9/2019	OBP
STN 761122/12	1/11/2019	OBP(updated stability)
STN 761122/13	1/16/2019	DMA, OBP
STN 761122/14	1/25/2019	DMA
STN 761122/19	3/6/2019	DMA
STN 761122/20	3/20/2019	DMA
STN 761122/21	3/29/2019	OBP
STN 761122/23	4/11/2019	DMA
STN 761122/25	4/17/2019	OBP
STN 761122/27	4/23/2019	DMA
STN 761122/28	4/26/2019	OBP

B. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]
(b) (4)	Type III		(b) (4)	3	Adequate
	Type III			3	N/A
	Type III			3	N/A
	Type III			3	N/A

[1] Action codes for DMF Table: 1 – DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: The following documents represent BLA and IND files for mepolizumab, which are all held by GSK and are cross-referenced in their entirety.

DOCUMENT	DESCRIPTION
BLA 125526	Mepolizumab, 100 mg/vial, lyophilized presentation; approved add-on maintenance treatment in patients with severe eosinophilic asthma and treatment of adult patients with EGPA

IND 006971	Mepolizumab for asthma, EGPA, nasal polyposis, and mepolizumab liquid drug product
	(b) (4)

3. **CONSULTS:** CDRH, syringe system

Discipline/Topic	Date Requested	Status	Recommendation	Reviewer/TL
CDRH/ODE/DAGID/GHDB Review of the device component of the combination product, including • Device performance • Release specifications for the device constituent • Biocompatibility of the syringe components as the barrel is the primary container closure	4/22/2019	Complete	CDRH GHDB is recommending approval of the device constituent of the combination product for the proposed indication. See approval letter for PMC language regarding ongoing stability studies.	Sapana Patel, Primary Reviewer Sarah Mollo, TL

Product Quality Review

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761122 for Nucala (mepolizumab), liquid formulation, manufactured by GlaxoSmithKline. The data submitted in this application are adequate to support the conclusion that the manufacture of mepolizumab liquid drug product is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Approval action letter language

- Manufacturing locations:
  - Drug Substance – (b) (4)
  - Drug Product manufacturing, labeling, and packaging– Glaxo Operations UK Ltd. (County Durham, United Kingdom)
- Fill size and dosage form – 100 mg/mL, injection, in single-dose prefilled syringe
- Dating period:
  - Drug Substance: (b) (4) months; (b) (4) °C
  - Drug Product: 24 months; 2-8°C; may be stored up to 7 days at 20-25°C
  - Protocols for the extension of DS and DP expiry periods are approved
- Exempt from lot release
  - Yes. Exemption of specified products according to 601.2a

c. Benefit/Risk Considerations

Mepolizumab in the lyophilized presentation is approved for add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype, and as a treatment for adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). While the formulation is different than that of the lyophilized product in order to support the stability of the liquid PFS presentation, the drug substance in the approved formulation and the proposed formulation are essentially unchanged. BLA 761122 cross-references BLA 125526 because the (b) (4) are identical. Mepolizumab has demonstrated efficacy for the indications listed above and the PFS presentation will allow the convenience of home usage for patients who are prescribed mepolizumab.

The overall control strategy for the manufacture of the mepolizumab liquid formulation incorporates control over (b) (4) release of Drug Substance (DS) and Drug Product (DP), and stability of these materials. The currently proposed manufacturing control strategy, in-process controls, process monitoring tests, release and stability testing are sufficient to ensure process consistency and that DS and DP are of adequate quality and are free of (b) (4).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if Approvable

DMA:

To conduct a microbial retention study using mepolizumab drug product under conditions that do not impact the viability of the challenge organism.

Final study report due October 31, 2019.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance and drug product.

APPEARS THIS WAY ON ORIGINAL

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Drug Substance (DS) and Drug Product (DP) CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other notes
Antigen Binding	MOA (Efficacy)	Intrinsic to the molecule. Impacted by oxidation, deamidation, aggregation and fragmentation. Minimal change is expected during storage through expiry.	(b) (4)	
IL-5 Neutralization	MOA (Efficacy)	Intrinsic to the molecule. Impacted by oxidation, deamidation, aggregation and fragmentation.		
Deamidation	Efficacy and PK/PD	(b) (4)		
Oxidation	Efficacy and PK/PD	(b) (4)		

			(b) (4)
Aggregates	Efficacy, PK/PD, immunogenicity and safety	(b) (4) Minimal increase expected during storage through expiry	
Particulate matter (visible and sub-visible)	Safety and efficacy	DS Manufacture	
Fragments (LMW species)	Efficacy and PK, immunogenicity and safety	Manufacturing process and (b) (4) Minimal change is expected during storage through expiry.	
Primary Sequence	Efficacy	(b) (4)	
Secondary and Tertiary Structure	PK/PD and immunogenicity		

			(b) (4)	

B. Drug Substance [mepolizumab] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes. Because the drug substance manufacturing process is identical to that of the drug substance for the lyophilized presentation, much of the following table is identical to what is found in BLA 125526.

APPEARS THIS WAY ON ORIGINAL

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other notes
Appearance: Color and opalescence (general)	Safety and immunogenicity	May be formed (b) (4)	(b) (4)	
Particulate matter (visible and sub-visible)	Safety and efficacy	DS Manufacture		
Protein Quantity (general)	Efficacy	DS manufacture, (b) (4)		
Host Cell Protein (Process-related impurity)	Safety, Immunogenicity	Cell Culture		
Host Cell DNA (Process-related impurity)	Safety, Immunogenicity	Cell Culture		
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process related impurity (b) (4)		

(b) (4) (Process-related impurity)	Safety, immunogenicity	(b) (4)	(b) (4)
(b) (4) (Process Impurity)	Impact on safety, immunogenicity, and allergenicity		
(b) (4) (Process Impurity)	Safety		
(b) (4) (Process Impurity)	Safety		
Endotoxin (contaminant)	Safety, purity and immunogenicity	Endotoxin can be introduced through (b) (4) throughout the manufacturing process	

Bioburden (contaminant)	Safety, purity and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced through (b) (4) throughout the manufacturing process	(b) (4)	N/A

APPEARS THIS WAY ON ORIGINAL

a. Description

Mepolizumab is a humanized IgG1, kappa anti-IL-5 monoclonal antibody produced in CHO cells. The molecular weight of the most common glycovariant (G0F/G1F) is 148,758 Da. It has the typical structure of an IgG1 antibody with (b) (4)

Mechanism of action

Mepolizumab binds with high affinity to soluble IL-5 (KD = $<2.29 \times 10^{-11}$ M) and blocks IL-5 binding to the IL-5α chain of the IL-5 receptor on eosinophils and other cells expressing the IL-5 receptor. Furthermore, the on rate (association constant) is fast (ka = 4.37×10^{5} Ms^{-1}) while the off rate (dissociation constant) is slow (kd = $<1.00 \times 10^{-5}$ s^{-1}), so once mepolizumab is bound to IL-5, it stays bound and is not released to become available for binding the receptor. Once IL-5 is bound to either mepolizumab or the IL-5 receptor, steric hindrance prevents binding of the other.

IL-5 is a soluble dimer and is not expressed on cell surfaces. Therefore, Fc effector function does not contribute to the mepolizumab MOA. In addition, since IL-5 cannot bind to both mepolizumab and its receptor at the same time, mepolizumab will not bind to any IL-5 already bound to the receptor and therefore, cannot exhibit Fc receptor effector function due to cell surface bound IL-5.

b. Potency Assay

There are two potency assays. The surface plasmon resonance (SPR) assay is used for DS and DP release and stability. The IL-5 neutralization assay is used for DP release.

SPR: Increasing concentrations of mepolizumab (0 – 20 µg/mL for a standard curve and 10 µg/mL of the reference standard as a positive control and the test sample) are captured on a Protein A sensor chip, IL-5 is captured by the immobilized mepolizumab. The IL-5/mepolizumab complex is compared to the Protein A/mepolizumab complex to determine the response. The specific binding activity is determined by interpolation of the rhIL-5 binding response against a standard curve of known concentrations of mepolizumab reference standard (RS).

IL-5 Neutralization Bioassay: The bioassay uses the IL-5 dependent human bone marrow erythroleukaemia TF-1.28 cell line. A mixture of TF-1.28 cells, IL-5 and increasing concentrations of mepolizumab are added to microtiter plates and incubated for 43-45 hours. Mepolizumab inhibits IL-5 signaling in the cells, and metabolic activity and cell proliferation decreases. AlamarBlue is added to each well, which fluoresces in metabolically active cells. Fluorescence of each plate is measured and the relative activity of the test samples are reported as the ratio of the ED50 of the mepolizumab RS to the ED50 of the mepolizumab DP release.

c. Reference Standard(s)

A two-tier reference standard system is in place, which is consistent with ICH Q6B. (b) (4)

(b) (4)

(b) (4)

d. Critical starting materials or intermediates

(b) (4)

e. Manufacturing process summary

(b) (4)

g. Container closure

The container closure system is a (b) (4) Total organic carbon, volatile, semi-volatile, non-volatile, and metal extractables or leachables were below reporting thresholds. The container closure system is suitable for mepolizumab storage based on stability data. This is supported by several years of stability data for the mepolizumab lyophilized product in the same container closure, albeit a lower concentration and different formulation.

h. Dating period and storage conditions

The dating period for the DS will be (b) (4) months when stored at (b) (4) °C.

C. Drug Product [mepolizumab] Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that are derived from the liquid PFS drug product manufacturing process and general drug product attributes.

APPEARS THIS WAY ON ORIGINAL

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance (Color and clarity) (General)	Measure of purity; potential impact on product safety and immunogenicity	Input materials, BDS; BP manufacture	(b) (4)	
pH	Product stability, conformation	DS manufacture Input materials and BDS		
Osmolality	Safety, impact on therapeutic dose	DS manufacture Input materials and BDS, DP manufacture		N/A
Particulate matter (visible and sub-visible)	Safety and efficacy	DP manufacture Input materials, BDS (b) (4)		(b) (4)
(b) (4)	Affects half-life (PK)	DP manufacture, exposure to heat and light stress (oxidation, deamidation)		Well controlled for normal storage and temperature and light excursions
Bacterial endotoxin (contaminant)	Safety, purity, and immunogenicity	Raw materials, manufacturing process, or failure of container closure integrity		N/A

Sterility (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout DP-manufacturing process or failure of container closure integrity.	(b) (4)	N/A
Container Closure Integrity	Safety (maintenance of sterility during shelf life)	Container closure breaches during storage		
Injection Force	Impact on efficacy	Materials (PFS components, (b) (4), DP manufacture		
Delivered Volume (general)	Efficacy/Dosing	Manufacturing process		N/A
Leachables* (process-related impurities)	Safety	Manufacturing equipment and container closure		Based on the extractables studies and stability data, as well as 6 month leachable study on the CCS, the risk from leachables is low; (b) (4)

				(b) (4)
Tungsten*	Safety	Manufacturing process and CCS	(b) (4)	
Silicone Oil*	Safety and immunogenicity	Manufacturing process and CCS		

*Sponsor did not name this attribute as a CQA. However, the risk assessment, (b) (4) and control strategy are adequate.

APPEARS THIS WAY ON ORIGINAL

a. Potency and Strength

Mepolizumab is supplied at 100 mg/1.0 mL syringe. Potency is defined as the percent activity relative to the current mepolizumab RS. The potency assays are the same as described in the DS section of this memo.

b. Summary of Product Design

Mepolizumab is supplied as a sterile, single-dose, preservative-free solution in a clear glass pre-filled syringe (PFS) that delivers 100 mg of mepolizumab for subcutaneous injection. The primary container closure consists of a 1 mL Type (b) (4) glass (b) (4) barrel with a staked 29G thin wall x 12.7 mm stainless steel needle with (b) (4) needle shield covered by rigid plastic shield sealed with a (b) (4) plunger stopper. Mepolizumab DP is formulated in (b) (4) sucrose, (b) (4) polysorbate 80, (b) (4) EDTA disodium dihydrate, (b) (4) sodium phosphate dibasic heptahydrate and (b) (4) citric acid monohydrate at pH 6.3. A minimum fill volume of (b) (4) mL is provided in the PFS to ensure the required 1.0 mL volume is delivered.

c. List of Excipients

Excipients include sucrose, polysorbate 80, EDTA, disodium dihydrate, sodium phosphate dibasic heptahydrate and citric acid monohydrate. All excipients are compendial and are in compliance with the United States Pharmacopeia (USP).

d. Reference material(s)

The same reference material is used for DS and DP.

e. Manufacturing process summary

The DP is manufactured at Glaxo Operations UK, Ltd., Barnard Castle, UK

(b) (4)

f. Container closure

The primary container closure system for mepolizumab DP consists of a 1 mL long syringe barrel with (b) (4) with a staked stainless steel 29 gauge thin wall ½ in needle, a (b) (4) stopper with a (b) (4) coating, and a rigid needle shield.

g. Dating period and storage conditions
The dating period for mepolizumab DP will be 24 months when stored at 2-8ºC; DP may be stored for up to 7 days at 25ºC within that period, but must be used within that 7 days.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations

- Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).
- Store in original carton until time of use.
- Protect from light until use.
- Do not freeze.
- Do not shake.

APPEARS THIS WAY ON ORIGINAL

F. Establishment Information

OVERALL RECOMMENDATION: Approve				
DRUG SUBSTANCE				
Site Name	**Address**	**FEI/DUNS Number**	**Responsibility**	**Final Recommendation**
(b) (4)			Drug Substance manufacture and storage; Drug Substance release testing; MCB and WCB storage	Acceptable based on PAI of (b) (4)
GlaxoSmithKline LLC	893 River Road, (b) (4) Conshohocken, PA 19428, USA	FEI# 3004055938	Drug Substance and Drug Product release and stability testing; BDS storage; MCB and WCB storage	Approve based on facility profile
Glaxo Operations UK Ltd.	BioCTL Medicines Research Center, Stevenage, Hertfordshire SG1 2NY United Kingdom	FEI# 3009763376	Drug Substance and Drug Product release and stability testing; MCB and WCB storage	Approve based on facility profile
(b) (4)				Approve based on facility profile
DRUG PRODUCT				
Site Name	**Address**	**FEI Number**	**Responsibility**	**Final Recommendation**
Glaxo Operations UK Ltd. Harmire Road, Barnard Castle, County Durham, United Kingdom DL 12 8DT	Harmire Road, Barnard Castle, County Durham DL12 8DT United Kingdom	FEI# 3002807078	Manufacture of the Syringe Drug Product (PFS), Analytical Testing (Release), Assembly of PFS inside autoinjector or safety syringe device, Visual inspection, Labelling and Packaging of Supply, Batch Release	Approve based on facility profile
GlaxoSmithKline LLC	893 River Road, Building 40, Conshohocken, PA 19428, USA	FEI# 3004055938	Drug Substance and Drug Product release and stability testing; BDS storage; MCB and WCB storage	Approve based on facility profile
Glaxo Operations UK Ltd.	BioCTL Medicines Research Center, Stevenage, Hertfordshire SG1 2NY United Kingdom	FEI# 3009763376	Drug Substance and Drug Product release and stability testing; MCB and WCB storage	Approve based on facility profile

(b) (4)	CCI testing, DP stability	Approve based on facility profile

APPEARS THIS WAY ON ORIGINAL

G. Facilities

The BLA proposes commercial manufacture of mepolizumab DS and DP at (b) (4) GSK Operations Ltd., Barnard Castle, UK (FEI: 3002807078), respectively. DS and DP release and stability testing will also occur at GlaxoSmithKline LLC , Conshohocken, PA (FEI: 3004055938), GSK Operations Ltd., Stevenage, UK (FEI: 3009763376), (b) (4)

A pre-licensure inspection (PLI) of the drug substance manufacturing facility was conducted at (b) (4) The initial field recommendation for the firm is VAI and approval of BLA 761122/0. A one-item FDA-483 was issued. An OPF/DIA review of the inspection deemed the firm's 483 response adequate and recommended approval of the facility in regard to BLA 761122. The inspection was classified as VAI. The compliance status of this mepolizumab DS manufacturing facility is acceptable. The DP manufacturing site, GSK Operations Ltd., Barnard Castle, UK (FEI: 3002807078), currently has an acceptable (b) (4) profile for the proposed (b) (4) for the subject application. The pre-license inspection for the facility has been waived for the subject application. This submission is recommended for approval from a facility perspective.

H. Lifecycle Knowledge Management

a. Drug Substance
   i. Annual stability protocol for Drug Substance
   ii. Stability extension protocol for Drug Substance
   iii. Protocols approved: (b) (4) annual stability and protocol for extension of expiry
   iv. Outstanding review issues/residual risk: None
   v. Future inspection points to consider: None

b. Drug Product
   i. (b) (4) Drug Product
   ii. Annual stability protocol for Drug Product
   iii. Stability extension protocol for Drug Product
   iv. Outstanding review issues/residual risk: None
   v. Future inspection points to consider: Continue to monitor the ability to assemble the autoinjector and safety syringe device at Glaxo Operations UK Ltd., Barnard Castle, FEI# 3002807078. (b) (4) .

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 5/08/2019 05:11:49PM
GUID: 508da6d7000262dc015dcdc5f6541612

Rachel Novak

Digitally signed by Rachel Novak
Date: 5/08/2019 10:02:19PM
GUID: 52e163f70002ba9e745b4e39384c76d7

Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 5/09/2019 07:04:13AM
GUID: 508da7480002bfb5825e149b2b4eb91d

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 5/10/2019 12:56:20PM
GUID: 508da7160002977f7ca389c8f849b707

BLA STN 761122

Product [Mepolizumab; Liquid Formulation of Mepolizumab (NUCALA)]

GlaxoSmithKline (GSK)

OBP, DS/DP Reviewer
Lymarie Maldonado-Báez

ATL Reviewer
Jennifer Swisher

Division of Biotechnology Review and Research I

OBP CMC Review Data Sheet

1. **BLA#:** STN 761122

2. **REVIEW DATE:** April 24th, 2019

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Xu Wang
Pharm/Tox: Wei Sun and Tim Robison (TL)
Product Quality Team: Lymarie Maldonado-Báez (PR) and Jennifer Swisher (ATL)
BMT or Facilities: Michael Shanks
Clinical Pharmacology: Renu Singh, Anshu Marathe (TL)
Statistics: Jade Wang and Yongman Kim (TL)
OBP Labeling: Scott Dallas
RPM: Ji Hyun LaRose

4. **MAJOR GRMP DEADLINES**
Filing Meeting: October 10th, 2018
Mid-Cycle Meeting: January 10th, 2019
Wrap-Up Meeting: May 2nd, 2019
Primary Review Due: April 29th, 2019
Secondary Review Due: May 7th, 2019
CDTL Memo Due: May 17th, 2019
PDUFA Action Date: June 7th, 2019

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Teleconference 1	October 1st, 2018
Information Request #1	December 26th, 2018
Information Request #2	March 22nd, 2019
Information Request #3	April 5th, 2019
Information Request #4	April 19th, 2019

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 761122/0 (Original Submission)	August 13th, 2018	Yes
STN 761122/0011 (Response to IR #1)	January 9th, 2019	Yes
STN 761122/0021 (Response to IR #2)	March 29th, 2019	Yes
STN 761122/0025 (Response to IR #3)	April 17th, 2019	Yes
STN 761122/0027 (Response to IR #4)	April 26th, 2019	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: NUCALA
b. Trade Name: Mepolizumab
c. Non-Proprietary/USAN: Mepolizumab
d. CAS name: 196078-29-2
e. Common name:
f. INN Name: Mepolizumab
g. Compendial Name:
h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P05113 (IL5_HUMAN) [SB240563]
i. Other Names: Recombinant humanized monoclonal antibody specific for human IL-5

8. PHARMACOLOGICAL CATEGORY: Monoclonal Antibody

9. DOSAGE FORM: Liquid Formulation for Injection

10. STRENGTH/POTENCY: 100 mg/ml

11. ROUTE OF ADMINISTRATION: Subcutaneous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			N/A	Type (b) (4) Sufficient information was provided in the BLA for its intended use.
			N/A	Type (b) (4) Sufficient information was provided in the BLA for its intended use
			N/A	Type (b) (4) Sufficient information was provided in the BLA for its intended use
			N/A	Type (b) (4) Sufficient information was provided in the BLA for its intended use

13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the biologics drug substance manufacturing facility was conducted at [redacted] (b) (4) The site is responsible for the manufacture of drug substance (DS) and DS release testing. One 483 observation was issued at the end of the inspection. The recommendation of the inspection team was VAI.

14. CONSULTS REQUESTED BY OBP

CDRH; syringe systems (PFS, AI and SSD)

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Design of Experiments studies were performed as part of process development.

16. PRECEDENTS

Although this 351(a) application is within the scope of the final guidance entitled Nonproprietary Naming of Biological Products issued on January 13, 2017, the recommendation of the review team is that the proper name for this drug should not be issued a suffix due to potential confusion for patients. The mepolizumab lyophilized vial presentation, approved under BLA 125526, was named prior to the finalization of this guidance. As there will be a single USPI for mepolizumab that would include both the lyophilized powder and liquid mepolizumab formulations, and as the drug substance is essentially unchanged, it is the recommendation of the review team, captured in a memo authored by Lubna Merchant, current Acting Director of DMEPA, that the proper name of the drug product for BLA 761122 should be allowed to remain identical to that of mepolizumab approved under BLA 125526.

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Rachel Novack, Ph.D. Review Chief Office of Biotechnology Products Division of Biotechnology Review and Research 1	
Jennifer Swisher, Ph.D. Team Leader and ATL Office of Biotechnology Products Division of Biotechnology Review and Research 1	
Lymarie Maldonado-Báez, Ph.D. Primary Reviewer Office of Biotechnology Products Division of Biotechnology Review and Research 1	

APPEARS THIS WAY ON ORIGINAL

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The information and data submitted in this Biologics License Application support the conclusion that the manufacture of Nucala (Mepolizumab) Injection is well controlled and leads to a product that is pure and potent. The product does not contain detectable endogenous and adventitious infectious agents and is sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs utilizing the intended commercial manufacturing process. It is recommended that Nucala (Mepolizumab) Injection be approved for human use under conditions specified in the Prescribing Information.

II. List of Deficiencies to Be Communicated

N/A

III. List of Post-Marketing Commitments/Requirement: None

IV. Review of Common Technical Document-Quality Module 1

Environmental Assessment or Claim of Categorical Exclusion

A categorical exclusion from the requirement of an environment assessment was requested by GlaxoSmithKline (GSK) under 21 CFR Part 25.31(b).

Reviewer comment: *The claim of a categorical exclusion is appropriate.*

V. Primary Container Labeling Review

The OBP review of the DP labeling was performed separately by Scott Dallas (see review in Panorama).

VI. Review of Common Technical Document-Quality Module 3.2

This document contains the review of the information provided for mepolizumab drug substance for liquid formulation (Section 3.2.S), drug product (Section 3.2.P), the adventitious agent safety evaluation (Section 3.2.A), and the method validation package and batch records (Section 3.2.R).

VII. Review of Immunogenicity Assays – Module 5.3.1.4

A review of the immunogenicity assays was not required for this BLA as the sponsor cross-referenced the approved BLA 125526 for information on the assays used to evaluate immunogenicity and the immunogenicity data for Mepolizumab.

Contents

121 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2.P.7 Container Closure System

Primary Container Closure System - PFS

The PFS is the primary container closure for Mepolizumab Injection, 100 mg/mL; the PFS use for commercial purposes are the same as the PFS used in clinical trials (studies 205958, 204959, and 205667). The components, composition and specifications for the PFS primary container are summarized in the table below.

Table 1 Primary Container Closure - Syringe Materials and Function

Component	Subcomponent	Supplier	Material Description	Color	Function
Syringe	Glass barrel	(b) (4)	(b) (4) glass Type (b) (4) Ph. Eur., USP and JP (b) (4)	Colorless transparent	Container closure, (b) (4) surface reduces friction to enable plunger stopper to move through the barrel during delivery
	Staked hypodermic needle		29G TW x ½" (b) (4)	Grey (Stainless steel)	Penetrates the skin into the subcutaneous space and enables flow of product for subcutaneous injection
	Rigid needle shield (RNS) – insert			Black	Maintains container closure integrity Protects needle
	Rigid needle shield (RNS) – outer cover		(b) (4) outer cover)	Colorless translucent	Protects needle and prevents it from penetrating through the insert and causing accidental needle sticks
Plunger stopper		(b) (4)	(b) (4)		Maintains container closure integrity and enables movement for injection of product

Note: Abbreviations (b) (4) Rigid Needle Shield (RNS); (b) (4) Thin-wall (TW)

Reviewer comment: *Review of the design features, verification, validation and risk management for the Mepolizumab Injection, 100 mg/mL PFS container closure system is deferred to CDRH.*

7 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
In support of the liquid clinical development program, measurement of mepolizumab plasma concentrations, as well as incidence of immunogenicity were carried out using the same validated bioanalytical methods to that used in the clinical development program of the lyophilized drug product as described in the initial application.

Reviewer comment: *The validated and approved bioanalytical methods used to evaluate immunogenicity of Mepolizumab LYO DP were used in the clinical development program of the LIQ DP. No new immunogenicity assays were introduced in this BLA.*

APPEARS THIS WAY ON ORIGINAL

Lymarie Maldonado-Baez

Digitally signed by Lymarie Maldonado-Baez
Date: 4/29/2019 05:02:08PM
GUID: 5ac7de300070e5e69fb599e6b33f405e

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 4/29/2019 05:07:45PM
GUID: 508da6d7000262dc015dcdc5f6541612

U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 26 April 2019

To: Administrative File, **STN 761122/0**

From: Monica Commerford, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV

Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV

Subject: New Biologics License Application

Applicant: GlaxoSmithKline LLC

US License: 1727

Product: NUCALA® (mepolizumab)

Dosage: 100 mg/mL pre-filled syringe for subcutaneous injection

Indication: Treatment of severe asthma, eosinophilic granulomatosis with polyangiitis, (b) (4)

Facilities: Glaxo Operations UK Ltd, Harmire Road, Barnard Castle, County Durham, UK DL12 8DT (FEI: 3002807078)

Receipt Date: 7 August 2018

Action date: 7 June 2019

Recommendation for Approvability: The drug product section of BLA 761122/0, as amended, was reviewed from a sterility assurance and microbiology product quality perspective and is recommended for approval with the following post-marketing commitment:

> To conduct a microbial retention study using mepolizumab drug product under conditions that do not impact viability of the challenge organism. The study results will be submitted by 31 October 2019.

Review Summary

GlaxoSmithKline LLC has submitted this new 351(a) Biologics License Application for liquid drug product injection of NUCALA® (mepolizumab), a humanized monoclonal antibody that binds to IL-5. The drug substance is manufactured at (b) (4) The drug product is manufactured at Glaxo Operations UK Ltd in Barnard Castle, UK. This application contains CMC information in an eCTD format. The BLA was originally submitted on 7 August 2018. Module 2 contains a Quality Overall Summary. Module 3 contains sections

describing manufacturing, characterization, control of drug product, stability, and drug product information.

This review contains an assessment of the drug product manufacturing process of mepolizumab from a sterility assurance and product quality microbiology perspective and may reference the Drug Master Files (DMFs) listed in the table below.

DMFs associated with BLA 761116/0

DMF	DMF Holder	Subject of DMF	Reviewed	Determination
[redacted] (b) (4)			Yes (4/22/2019)	Adequate
			No	N/A
			No	N/A
			No	N/A

Amendments associated with this review memo are also listed in the table below. FDA information requests are listed at the end of this review memo.

Amendments Reviewed for Drug Product Quality Microbiology

Document Type	eCTD Sequence	Date
Original submission	0001	8/7/2018
Response to Filing IR	0004	9/17/2018
Information Request Response #1	0014	1/25/2019
Information Request Response #2	0025	4/17/2019
Information Request #3	0027	4/23/2019
T-con with applicant	N/A	4/25/2019

Product Quality Microbiology Assessment: Drug Product

MODULE 1

Labeling review: Prescribing information

NUCALA injection is a clear to opalescent, colorless to pale yellow solution for SC use, and each syringe is designed to deliver 100 mg mepolizumab per 1 mL of solution. Before dispensing, mepolizumab should be refrigerated and protected from light. NUCALA must be administered within 8 hours after removal from carton. Otherwise, discard.

The description is satisfactory.

MODULE 3.2.P DRUG PRODUCT

P.1 Description and Composition of the Drug Product (DP)

100 mg/mL mepolizumab drug product (DP) is formulated in [redacted] (b) (4) sucrose, [redacted] (b) (4) polysorbate 80, [redacted] (b) (4) EDTA disodium dihydrate, [redacted] (b) (4) sodium phosphate dibasic heptahydrate, and [redacted] (b) (4)

(b) (4) citric acid monohydrate, pH 6.3. The liquid DP is filled in a single-use, clear pre-filled syringe (PFS). The PFS consists of a 1 mL long Type (b) (4) glass (b) (4) barrel with a staked 29G thin wall x 12.7 mm stainless steel needle with a (b) (4) needle shield. A rigid plastic shield is sealed with (b) (4) rubber plunger stopper. This PFS can be assembled into a safety syringe device or an autoinjector (opaque housing, a clear window, a yellow needle guard, and a translucent cap). NUCALA injection is a clear to opalescent, colorless to pale yellow solution for SC use, and each syringe is designed to deliver 100 mg mepolizumab per 1 mL of solution. Before dispensing, mepolizumab should be refrigerated and protected from light. NUCALA must be administered within 8 hours after removal from carton. Otherwise, discard.

The description is satisfactory.

P.2 Pharmaceutical Development

(b) (4)

33 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Satisfactory

Conclusion

I. The drug product section of BLA 761122/0 was reviewed from a sterility assurance and microbiology product quality perspective and is recommended for approval as amended. There is one post-marketing commitment:
   a. To conduct a microbial retention study using mepolizumab drug product under conditions that do not impact viability of the challenge organism. The study results will be submitted by 31 October 2019.

II. The non-microbial aspects of the BLA should be reviewed by the OBP reviewer.

III. The pre-license inspection at Glaxo Operations UK Ltd in Barnard Castle, UK was waived. Refer to Panorama for the compliance status of the facility.

APPEARS THIS WAY ON ORIGINAL

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Monica Commerford (Markovski)

Digitally signed by Monica Commerford (Markovski)
Date: 4/26/2019 04:05:31PM
GUID: 56c21fb00023a450a9d1733bdf21bc80

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 4/26/2019 04:32:48PM
GUID: 508da7160002977f7ca389c8f849b707

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761122/0**
From: Madushini Dharmasena, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead, DMA Branch IV
Subject: New BLA for the treatment of Severe Asthma and Eosinophilic Granulomatosis with Polyangiitis (EGPA)
US License: 2099
Applicant: GlaxoSmithKline LLC (GSK)
Product: Liquid formulation of Mepolizumab (NUCALA)
Dosage: 100 mg in 1 mL pre-filled syringe for subcutaneous injection
Facilities: (b) (4)
Receipt Date: 08/07/2018
Action Date: 06/07/2019

Conclusion: The drug substance (DS) portion of STN 761122/0 was reviewed from a product quality microbiology /sterility assurance perspective and is recommended for approval. The DS release and in-process (b) (4) qualification using two additional batches will be reviewed in an addendum review memo.

Review Summary

GlaxoSmithKline LLC (GSK) submitted a new Biologics License Application (BLA) for the liquid formulation of NUCALA® (mepolizumab) at a dose of 100 mg in 1ml to be administered subcutaneously (SC) via an Autoinjector (AI) or a Safety Syringe Device (SSD). The currently approved product, Nucala (mepolizumab), is a lyophilized powder (100 mg) manufactured in the GSK manufacturing facilities in Conshohoken, PA (original submission) and (b) (4) (prior approval supplement-8 under sequence #0104) under BLA 125526. The new BLA for liquid mepolizumab cross references BLA 125526. GSK is the Sponsor and license holder for BLA 125526.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0001	08/07/2018	Original BLA

0003	09/12/2018	Response to information request sent on 09/05/2018
0006	10/03/2018	Response to information request sent on 09/21/2018
0007	11/09/2018	Response to information request sent on 10/26/2018
0013	01/16/2019	Response to information request sent on 01/11/2019
0019	03/06/2019	Response to information request sent on 03/01/2019
0020	03/20/2019	Response to information request sent on 03/11/2019
0023	04/11/2019	Response to information request sent on 04/04/2019

3.2.S DRUG SUBSTANCE

3.2.S.1 GENERAL INFORMATION

3.2.S.2 MANUFACTURE

3.2.S.2.1 Manufacturer

The following table provided in the submission lists DS manufacturing, testing and release sites.

8 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

cGMP Status
Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval. The DS release and in-process (b) (4) qualification using two additional batches will be reviewed in an addendum review memo.

II. Information and data in this submission not related to microbial control should be reviewed by OBP.

III. Inspectional follow-up items were not identified.

Information request sent on September 5, 2018

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPEARS THIS WAY ON ORIGINAL

Madushini Dharmasena

Digitally signed by Madushini Dharmasena
Date: 4/24/2019 02:40:43PM
GUID: 5aecc01b00af3fb623ee1f6f17a576ea

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 4/24/2019 04:01:50PM
GUID: 508da7160002977f7ca389c8f849b707