

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761458Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 3, 2025

To: Juliannae Lee
Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

Through: Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Quyn-Nhu Capasso, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EXDENSUR (depemokimab-ulaa)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761458

Applicant: GlaxoSmithKline LLC

1 INTRODUCTION

On December 16, 2024, GlaxoSmithKline LLC (GSK) submitted for the Agency's review an original New Biologic Drug License (BLA 761458) for depemokimab-ulaa injection, for subcutaneous use. GSK proposed the following indications:

- add on-maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older.

(b) (4)

A Proprietary Name Review Request was submitted to IND 146742 on 27 September 2023 for the proposed proprietary name EXDENSUR. FDA communicated conditional acceptance in the Proprietary Name Request Granted Letter dated 23 September 2024. On 18 December 2024, GSK submitted to request the proprietary name review of EXDENSUR (depemokimab-xxxx) Injection 100 mg/mL. On 27 February 2025, the proprietary name was granted.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Critical Care (DPACC) on January 6, 2025 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EXDENSUR (depemokimab-ulaa) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft EXDENSUR (depemokimab-ulaa) PPI received on December 16, 2024, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on November 24, 2025.
- Draft EXDENSUR (depemokimab-ulaa) Prescribing Information received on December 16, 2024, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on November 24, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if

(b) (4)

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: December 2, 2025

To: Julianne Lee, Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for EXDENSUR® (depemokimab-ulaa) injection, for subcutaneous use

BLA: 761458

Background:

In response to DPACC's consult request dated January 6, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original BLA submission for EXDENSUR® (depemokimab-ulaa) injection, for subcutaneous use.

Of note, OPDP was initially consulted to also review (b) (4), (b) (4), OPDP was notified on November 29, 2025 that (b) (4) the product is administered only by a healthcare provider, DPACC has asked the applicant (b) (4)

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 24, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on November 24, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov

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/s/

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**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13**

Date:	November 20, 2025
Product Name(s):	Exdensur (depemokimab)
Application Type/Number(s):	761458
Submission Number:	BLA
Sponsor/Applicant:	GlaxoSmithKline (GSK)
NEXUS Task Tracking Tool ID #:	2025-15409
Reviewer:	Huei-Ting Tsai, PhD Division of Epidemiology II
Master Epidemiologist:	Natasha Pratt, PhD Division of Epidemiology II
Division Director:	Monique Falconer, MD, MS Division of Epidemiology II
Director of Sub-Office:	Judy Zander, MD Office of Pharmacovigilance and Epidemiology
Associate Director for Sentinel:	Patricia Bright, PhD Office of Surveillance and Epidemiology



1. BACKGROUND INFORMATION

1.1. Medical Product

Exdensur (depemokimab) is an immunoglobulin G1 (IgG1) kappa monoclonal antibody that targets the interleukin-5 (IL-5) pathway for the treatment of eosinophilic inflammatory conditions. The drug is proposed as an add-on maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium- to high-dose inhaled corticosteroids plus another asthma controller.

A modification (M252Y/S254T/T256E) in the fragment (Fc) domain distinguishes depemokimab from other approved anti-IL-5 monoclonal antibodies. This modification increases binding to the neonatal Fc receptor (FcRn), thereby increasing depemokimab's elimination half-life to 38-53 days and enabling a dosing regimen of 100 mg subcutaneously every 6 months.

Current standard of care for eosinophilic asthma includes inhaled corticosteroids as first-line therapy and immunotherapy through biologic options including the anti-IL-5 therapies that lack the YTE modification for patients with severe asthma.

1.2. Describe the Safety Concern

The safety concern for depemokimab pregnancy exposure stems from three converging factors described below.

- (i) Asthma affects 3-8% of pregnant women and treatment with depemokimab will be needed when other treatment for refractory severe eosinophilic asthma is unavailable. Due to depemokimab's extended half-life (can persist for up to 6 half-lives of 53 days, i.e. 318 days) exposure during pregnancy can occur while receiving treatment or for months after treatment has stopped.
- (ii) During drug development programs, seven depemokimab-exposed pregnancies were reported, three of the six known outcomes resulting in spontaneous abortions (SAB), two early termination of pregnancy and one live birth without anomalies. There is insufficient data to inform pregnancy safety of depemokimab use due to small numbers.
- (iii) A pharmacovigilance analysis in the WHO VigiBase database¹ found that mepolizumab, a related anti-IL-5 monoclonal antibody without YTE modification, showed about 2-3 times higher reporting frequencies for spontaneous fetal death (reporting odds ratio, ROR, 1.87, 95% CI 1.05-3.36) and SABs (ROR 2.75, 95% CI 1.51-5.00) compared to non-biologic asthma medications.

The safety signal represents a potential increased risk of adverse pregnancy outcomes,

¹ Jang W, Jo H, Park J, Kim S, Cho H, Jeong YD, Son Y, Pizzol D, Papadopoulos NG, Yon DK. Use of Biologics to Treat Asthma during Pregnancy and Adverse Events in Pregnant Women and Newborns: A Global Pharmacovigilance Analysis. *Int Arch Allergy Immunol*. 2025 Jan 17:1-14. doi: 10.1159/000543490. Epub ahead of print. PMID: 39827867



particularly SABs, in pregnant women exposed to depemokimab. The signal's strength is considered moderate due to limited clinical data and confounding factors. However, the unknown impact on placental transfer and on the developing fetus due to substantially increased half-life through the YTE modification is concerning.

Asthma is associated with increased risks of preeclampsia, preterm birth, and low birth weight when poorly controlled, creating a complex risk-benefit scenario where treatment discontinuation could also pose maternal and fetal risks. These factors support the importance to obtain pregnancy safety data of depemokimab use.

Current risk management strategies include pregnancy labeling in Section 8, subsection 8.1 stating " The impact of YTE modification on placental transfer is uncertain" and text to warn an increased impact on fetus during the (b) (4) third trimester of pregnancy. The labeling also recommends that pregnant women exposed to depemokimab report their exposure through a designated phone number and webpage. A descriptive pregnancy safety study (DPSS) is also requested as a post-market requirement (PMR) to assess embryo safety of depemokimab.

The regulatory gap exists because depemokimab is the first anti-IL-5 monoclonal antibody with YTE modification approved for use in women of reproductive potential, and no reproductive toxicology studies have been conducted specifically with depemokimab. The PMR study is anticipated to address the regulatory gap by collecting detailed information on adverse maternal, pregnancy and infant outcomes among depemokimab-exposed pregnancies to facilitate causality assessment based on human data.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication in pregnant women, but practitioners may use product off-label in pregnant women
- ☒ No approved indication in pregnant women, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication in pregnant women, but use in women of childbearing age is a general concern



2.2. Regulatory Goal²

- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest.*
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome.*
- ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a **targeted or multiple** safety concern(s)/health outcome(s).*
 - ☐ Targeted evaluation of specific safety concern
 - ☒ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Descriptive Pregnancy Safety Study

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	Explanation on ARIA insufficiency
☐ Study Population	
☐ Exposures (and Comparators)	
☒ Outcomes	ARIA lacks access to detailed narratives. This study requires collection of outcomes in both the pregnant women and the resultant offspring. Given that the study is considered for broad-based surveillance of pregnancy and infant outcomes, descriptive design without sample size requirements and a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and conduct causality assessments.
☒ Covariates	ARIA does not have detailed information on potential

² Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. *Pharmacoepidemiol Drug Saf.* 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.



	confounders. The DPSS being considered can collect detailed narratives with information on potential covariates, such as history of any complications in prior pregnancy event(s), lifestyle factors (e.g. smoking, drinking), and prenatal supplement use etc.
☐ Analytic Tools	
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to depemokimab during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 18, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761458
Product Name, Dosage Form, and Strength:	Exdensur (depemokimab-ulaa) injection, 100 mg/mL
Applicant Name:	GlaxoSmithKline, LLC (GSK)
FDA Received Date:	May 5, 2025, and November 12, 2025
TTT ID #:	2025-12444-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP

1 PURPOSE OF MEMORANDUM

GlaxoSmithKline, LLC submitted revised container label and carton labeling received on May 5, 2025 and November 12, 2025, for Exdensusur. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Exdensusur (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

GlaxoSmithKline, LLC implemented all of our recommendations and we have no additional recommendations at this time.

^a Owens, L. Label and Labeling Review for Exdensusur (BLA 761458). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 APR 28. TTT ID: 2025-12444.

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Clinical Inspection Summary

Date	November 12, 2025
From	Suyoung Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Abhilasha Banerjee, M.D., Clinical Reviewer, DPACC Stacy Chin, M.D., Team Leader, DPACC Julianne Lee, Regulatory Project Manager, DPACC Division of Pulmonology, Allergy, and Critical Care (DPACC)
BLA #	761458
Applicant	GlaxoSmithKline LLC
Drug	Exdensur (depemokimab)
NME (Yes/No)	Yes
Proposed Indication(s)	Add-on-maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium-to high-dose inhaled corticosteroids (ICS) plus another asthma controller (b) (4)
Consultation Request Date	February 25, 2025
Summary Goal Date	November 13, 2025
Action Goal Date	December 16, 2025
PDUFA Date	December 16, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Adolfo de Luis Martinez, Pulka, De Salvo, Cornet, and the contract research organization (CRO) (b) (4) were inspected in support of BLA 761458, covering (b) (4) SWIFT-1 and SWIFT-2. Based on the inspection results, the studies appear to have been conducted adequately, and the data generated by the inspected clinical investigator sites and the CRO appear acceptable in support of the respective indication.

II. BACKGROUND

According to the sponsor, depemokimab is a humanized, IgG1 kappa anti-interleukin-5 (anti-IL-5) monoclonal antibody developed as a long-acting subcutaneous therapy. The drug was designed to provide efficacy and safety comparable to current anti-IL-5 therapies while reducing dosing frequency to once every 26 weeks. The sponsor has submitted BLA 761458

for (b) (4) Add-on-maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium-to high-dose inhaled corticosteroids (ICS) plus another asthma controller (b) (4)

(b) (4). The Sponsor submitted two replicate studies, 206713 (SWIFT-1) and 213744 (SWIFT-2), to support the treatment of asthma (b) (4)

(b) (4). Four BIMO-Review-Based clinical investigator inspections and a directed CRO inspection of (b) (4) were requested for (b) (4) SWIFT-1, SWIFT-2, (b) (4). The following describes (b) (4) studies:

Protocol 206713 (SWIFT-1): “A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype.”

Study SWIFT-1 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy of depemokimab 100 mg subcutaneously every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy.

Sites: Subjects were randomized at 144 sites in 12 countries including Canada, China, Czechia, France, Germany, Ireland, Italy, Poland, Russia, Spain, United Kingdom, and United States.

Subjects: A total of 382 subjects were randomized (i.e., 132 received placebo, 250 subjects received depemokimab), and 359 subjects completed the study (i.e., 122 who received placebo, 237 subjects who received depemokimab).

Study initiation and completion dates: March 17, 2021 (date first subject enrolled); November 21, 2023 (date last subject completed the last visit)

eDC/External vendor data lock date; restricted study unblinding date; GSK Database lock date: December 12, 2023; December 18, 2023; December 20, 2023

Reviewer’s comment: *GSK’s initial response to the February 10, 2025, information request provided dates suggesting study unblinding occurred before database lock, prompting a follow-up clarification request dated November 5, 2025. Upon further review, GSK clarified that their pivotal studies* (b) (4)

ensuring study integrity throughout the process.

This study had four phases: 0–2-week Pre-Screening Period, 1–6-week Screening Period, 52-

week Treatment Period, and 4-week follow-up phase. During the 52-week treatment period, subjects were randomized 2:1 to receive either add-on depemokimab 100 mg subcutaneous (SC) injection administered once every 6-months, at Week 0 (Visit 2) and at Week 26 (Visit 10), or matching placebo.

Key inclusion criteria: Male and female subjects ≥ 12 years of age. Subjects were to be ≥ 18 years of age in the UK, Russia, and Germany. Subjects also had to have a documented physician diagnosis of asthma for ≥ 2 years, a previously confirmed history of ≥ 2 asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Visit 1 despite the use of medium to high-dose inhaled corticosteroids (ICS). In addition, subjects also had to have eosinophilic asthma as documented by an elevated peripheral blood eosinophil count of ≥ 300 cells/ μL demonstrated in the past 12 months prior to Visit 1 or an elevated peripheral blood eosinophil count of ≥ 150 cells/ μL at Screening Visit 1. Subjects ≥ 18 years of age needed to demonstrate persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 $< 80\%$ predicted at Visit 1. Subjects 12-17 years of age had to demonstrate a pre bronchodilator FEV1 $< 90\%$ predicted, or an FEV1: FVC ratio < 0.8 at Visit 1. Subjects had to have a well-documented requirement for regular treatment with medium to high-dose ICS in the 12 months prior to Visit 1 [with or without maintenance oral corticosteroids] and current treatment with at least one additional controller medication besides ICS, for at least 3 months. The maintenance ICS dose must be 440 mcg FP HFA daily, or clinically comparable. Subjects who were treated with medium dose ICS also had to be treated with long-acting beta agonist to qualify for inclusion. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Annualized rate of clinically significant asthma exacerbations over 52 weeks.

Protocol 213744 (SWIFT-2): “A 52-week, randomized, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype.”

Study SWIFT-2 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy of depemokimab 100 mg SC every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy.

Sites: Subjects were randomized at 187 sites in 11 countries including Australia, Canada, Czechia, France, Hungary, Italy, Japan, Poland, Spain, Taiwan and United States.

Subjects: A total of 1797 subjects were randomized (i.e., 579 subjects received placebo, 595 subjects received brensocatib 10 mg, and 593 subjects received brensocatib 25 mg), and 1381 subjects completed the Treatment Period (i.e., 457 subjects who received placebo, 458 subjects who received brensocatib 10 mg, 466 subjects who received brensocatib 25 mg).

Study initiation and completion dates: February 4, 2021 (date first subject enrolled); April 11, 2024 (date last subject completed the last visit)

eDC/External vendor data lock date; restricted study unblinding date; GSK Database lock date; study unblinding date: April 29, 2024; May 2, 2024; May 7, 2024

SWIFT-1 and SWIFT-2 had similar study designs.

Key inclusion criteria: Similar to SWIFT-1. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Annualized rate of clinically significant asthma exacerbations over 52 weeks.

(b) (4)



(b) (4)



III. RESULTS (by site):

(b) (4)



3. Dr. Gustavo Adolfo de Luis Martinez

Avda. De los Argonautas s/n

29631 Benalmadena

Malaga

Spain

Protocol 206713 (SWIFT-1), Site 251016

Protocol 213744 (SWIFT-2), Site 259373

PDUFA Inspection Dates: June 16-20, June 23, 2025

For Protocol SWIFT-1, 33 subjects were screened, 25 subjects were enrolled and randomized, and all 25 randomized subjects completed the study. For Protocol SWIFT-2, 16 subjects were screened, 12 subjects were enrolled and randomized, and all 12 randomized subjects completed the study.

An audit of the study records was conducted for all 25 enrolled subjects for SWIFT-1 and all 12 enrolled subjects for SWIFT-2. Records reviewed included, but were not limited to, protocol and amendments, training records for study personnel, informed consent forms, delegation of authority logs, ethics committee correspondence and approvals, subject eligibility, investigational product administration records, monitoring reports, laboratory assessments, financial disclosures, concomitant medications, protocol deviations, adverse event reporting, and electronic source records for verification of primary efficacy endpoint.

The primary efficacy endpoint was verified by comparing clinically significant asthma exacerbation data from paper source documents with the sponsor's data listings, including onset and resolution dates, primary cause, systemic corticosteroid use, hospitalization status, emergency department visits, and intubation status. No discrepancies were identified. There were no unreported adverse events.

4. Dr. Grazyna Pulka

Grazyna Pulka Centrum Medyczne All Med Spolka Komandytowa
ul. Henryka Sienkiewicza 23
30-033 Krakow
Poland
Protocol 206713 (SWIFT-1), Site 250201
Protocol 213744 (SWIFT-2), Site 259220
PDUFA Inspection Dates: March 25-28, 2025

For Protocol SWIFT-1, 39 subjects were screened, 34 subjects were enrolled and randomized, and all 34 randomized subjects completed the study. For Protocol SWIFT-2, 20 subjects were screened, 19 subjects were enrolled and randomized, and 18 randomized subjects completed the study. One subject withdrew consent.

An audit of the study records was conducted for all enrolled subjects in both protocols. Records reviewed included, but were not limited to, protocol and amendments, Ethics Committee approval letters and correspondence, monitoring reports, informed consent forms, financial disclosure reports, Investigator Agreement Forms, case report forms, test article accountability records, delegation of authority logs, site training documentation, subject eligibility, laboratory reports, protocol deviations, adverse event reporting, and electronic source records for verification of primary efficacy endpoint

The primary efficacy endpoint was verified by comparing clinically significant asthma exacerbation data from paper source documents with the sponsor's data listings, including onset and resolution dates, primary cause, systemic corticosteroid use, hospitalization status, emergency department visits, and intubation status. No discrepancies were identified. There were no unreported adverse events.

5. CRO:

(b) (4)

(b) (4)

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	10/22/2025		
To:	NOWRIN KAKON		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Choose an item.
From	Bingjie Liang OPEQ/OHT3/DHT3C		
Through (Team)	Kyrán Gibson, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Office)	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761458, DEPEMOKIMAB ICC2500024 ICCR01042516		
Recommendation	Filing Recommendation Date: 2/28/2025 ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Mid-Cycle Recommendation Date: 4/17/2025 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☒ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 10/22/2025 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Bingjie Liang -S Digitally signed by Bingjie Liang -S Date: 2025.10.22 11:30:42 -04'00'	Kyrán Gibson -S Digitally signed by Kyrán R. Gibson -S Date: 2025.10.22 12:19:32 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761485
Sponsor	GLAXOSMITHKLINE LLC
Drug/Biologic	DEPEMOKIMAB
Indications for Use	(b) (4)
Device Constituent	Safety Syringe and Auto-Injector
Related Files	ICC2500031

Review Team		
Lead Device Reviewer		Bingjie Liang
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
N/A		

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	5/19/2025
Interim Due Dates	Meeting/Due Date
Filing	Jan 30, 2025/Feb 14, 2025
74-Day Letter	Feb 28, 2025
Mid-Cycle	May 23, 2025/May 30, 2025
Primary Review	Aug 8, 2025
Internal Meeting(s)	Aug 15, 2025
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

Approvable – the device constituent of the combination product is approvable for the proposed indication.

Approvable with PMC or PMR, [See Section 2.3](#)

Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	x			
Labeling	x			
Design Controls	x			The CAPA procedure was provided in sequence 00020.
Risk Analysis	x			The hazard analysis was provided in sequence 00020.
Design Verification	x			The design verification report, shipping/transport study report, and biocompatibility test reports were provided in sequence 00020.
Consultant Discipline Reviews			x	
Clinical Validation			x	Defer to CDER/Clinical
Human Factors Validation			x	Defer to CDER/DMEPA
Facilities & Quality Systems			x	A Pre-Approval Inspection (PAI) was recommended and completed. No concerns with the quality system documentation. Please refer to ICC2500031 for additional information.

2.1. **Comments to the Review Team**

CDRH does not have any further comments to convey to the review team.

CDRH has the following comments to convey to the review team:

Comment #1: CDRH defers the reviews for Clinical Validation and Human Factors Validation to CDER Clinical and DMEPA, respectively.

2.2. **Complete Response Deficiencies**

There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market Commitments or Requirements	
CDRH does not have Post-Market Commitments or Requirements	

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3. PURPOSE/BACKGROUND

3.1. Scope

GLAXOSMITHKLINE LLC is requesting approval of DEPEMOKIMAB. The device constituent of the combination product is a Safety Syringe and Auto-Injector.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

We request CDRH consult for this BLA original application/ BLA-761458-ORIG-1 because this submission contains information regarding a prefilled syringe assembled with a safety syringe device or autoinjector. We request CDRH consult for the “Technical engineering/Device design” by 04/18/2025 (Fri).

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

- the needle safety device (NSD) performance, i.e. NSD activation, lockout, etc.
- Autoinjector (AI)

This review will not cover the following review areas:

The prefilled syringe – Safety Syringe (PFS-SS) performance such as dose accuracy and break-loose and glide force will not be addressed within this review. Per the ICCR agreement [Do I Need to Request an Intercenter Consult \(i.e., Intercenter Agreements\)?](#), review of the performance of the pre-filled syringe is deferred to CDER CMC.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

CDRH has not previously consulted on this BLA.

3.2.1. *Related Files:*

ICC2500031: QS & facilities review for this BLA

3.3. Indications for Use

Combination Product	Indications for Use
DEPEMOKIMAB	(b) (4)
Safety Syringe and Auto-Injector	
	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	1.14 Labeling
	3.2.P.2 Pharmaceutical Development
	3.2.P.3 manufacture
	3.2.P.3.5 Process Validation and/or Evaluation
	3.2.P.5 Control of Drug Product
	3.2.P.7 Container Closure System
	3.2.P.8 Stability
	3.2.R. Regional Information
0020	1.11.1 Quality Information Amendment

4. DEVICE DESCRIPTION

4.1. Device Description

4.1.1 Safety Syringe Device (SSD)

The safety syringe device (SSD) has been developed by (b) (4) The SSD is a single-use, disposable device designed to enable manual delivery of depemokimab by a patient, caregiver or healthcare professional, while providing a needle shielding feature (post-use) and enhanced ergonomics.

Letters of authorization are provided as Figures 1, 2 and 3 in Section 1.4.2, which are summarized in Table 1.

m1.4.2. Statement of Right of Reference

LETTERS OF AUTHORIZATION

Table 1 Letters of Authorization

DMF Number	DMF Holder	Description	Reference
(b) (4)	(b) (4)	Drug Product Container Closure System Component: (b) (4) Glass Prefillable Syringe (PFS)	Figure 1
		Drug Product Container Closure System Component: Elastomeric Formulations, (b) (4)	Figure 2
		Drug Product Container Closure System Component: (b) (4) Needle Guard 1ml	Figure 3

The safety syringe employs the Pre-Filled Syringe (PFS) as the primary container closure described in P.7.3 Container Closure System PFS.



Figure 2 Representative Illustration of SSD Before and After Use

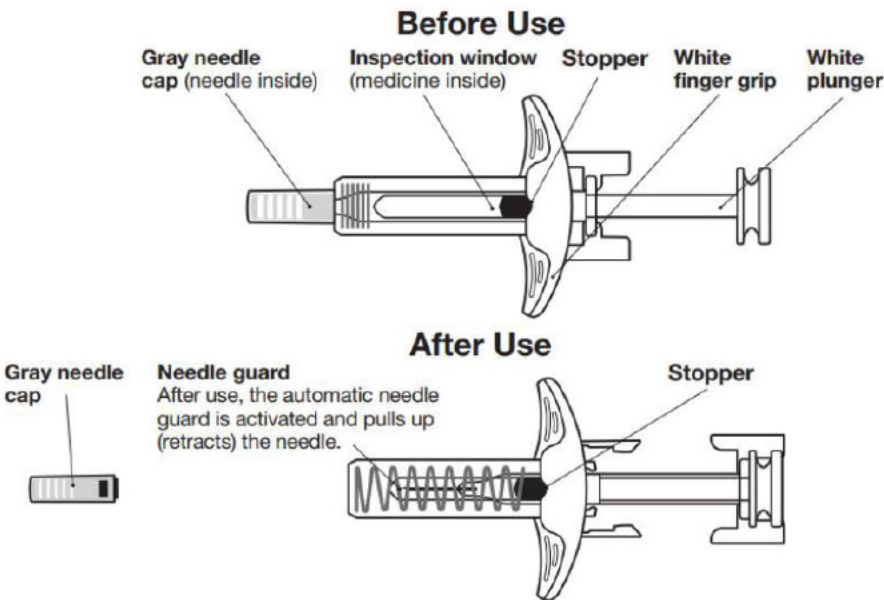


Table 2 Materials and Functions of SSD Components

Component / Sub-Assembly	Subcomponent	Material of Construction	Function
Needle Guard	(b) (4)		
Plunger Rod	(b) (4)		
Add-on Finger Flange	(b) (4)		

4.1.2 Autoinjector

The autoinjector (AI) has been developed by (b) (4). The autoinjector is a single-use, disposable device designed to provide a convenient and safe means for administration of depemokimab by a patient or via a caregiver or healthcare professional. The AI employs the PFS as the primary container closure described in the Section P.7.3 Container Closure System_PFS.

Figure 1 **Representative diagram of the final assembled Autoinjector**



The autoinjector consists of [REDACTED] (b) (4)
[REDACTED] (b) (4). An exploded view of the autoinjector is shown in Figure 2.

These subassemblies are supplied to GSK by [REDACTED] (b) (4) nested together, but not yet assembled, as shown in Figure 3.

Figure 2 **Representative Exploded Diagram of the Autoinjector Device Assembly**



Figure 3 Representative illustrations of Autoinjector Subassembly Components, Supplied to GSK



Table 2 **Materials and Functions of** (b) (4) **Components**

(b) (4)

4.2. Steps for [Using the Device](#)

4.2.1 Safety Syringe Device

Figure 3 Operation of the SSD

Operation Description	Operation Illustration
Prior to using the safety syringe device, the user prepares the device by removing it from the refrigerator and allowing it to equilibrate to room temperature. Once equilibrated to room temperature the device can be used. To perform the injection, the user first removes the needle cap (rigid needle shield) by pulling it straight off.	(b) (4)
The user pinches a fold of skin and inserts the entire needle into the pinched area of the skin at approximately 45°.	
The user then manually pushes the plunger rod down until all the solution in the prefilled syringe is injected. The user can monitor the progress of the injection by looking at the white plunger rod in the window. The end of injection is determined when the plunger stopper is at the bottom of the syringe and the user cannot push the plunger rod any further.	
Upon completion of the injection and slowly releasing pressure on the plunger rod (by slowly moving the thumb back), the needle will automatically retract into the needle guard and lock so that the needle is shielded.	
The user removes the safety syringe away from the injection site and disposes of it in an appropriate sharps container.	

4.2.1 Auto Injector

Figure 3 Operation of the AI

Operation Description	Operation Illustration
Prior to using the AI, the user prepares the device by removing it from the refrigerator and allowing it to equilibrate to room temperature. Once equilibrated to room temperature the device can be used. To perform the injection, the user first removes the needle cap.	(b) (4)
The user then positions the cover sleeve straight onto the injection site.	
The injection is started by pressing the AI all the way down onto the injection site and holding it in place. This will manually insert the needle and start drug delivery. An audible "click" and movement of the indicator in the inspection window signal the start of the injection.	
The user continues to hold the AI down until a second "click" and the indicator reaches the end of the viewing window and stops moving.	
Operation Description	
When the injection is complete, the user lifts the AI from the injection site. The cover sleeve will automatically move back over the needle and lock in place.	(b) (4)
The user then disposes of the AI in an appropriate sharps container.	

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
Reviewer Comments The device description is ADEQUATE.								
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No

5. FILING REVIEW

CDRH performed Filing Review	
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	

5.1. Filing Review Checklist

Filing Review Checklist			
Description	Present		
	Yes	No	N/A
Description of Device Constituent	X		
Device Constituent Labeling	X		
Letters of Authorization	X		
Essential Performance Requirements defined by the application Sponsor	X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor	X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor	X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities	X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X	
	Reliability	X	
	Biocompatibility	X	
	Sterility	X	
	Software		X
	Cybersecurity		X
	Electrical Safety		X
	EMC/RF Wireless		X
	MR Compatibility		X
	Human Factors	X	
	Shelf Life, Aging and Transportation	X	
	Clinical Validation	X	
	Human Factors Validation	X	
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X	
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X	
	CAPA Procedure	X	
	Control Strategy provided for EPRs	X	

Reviewer Comment

Design verification summary reports for safety syringe device and autoinjector are provided in section 3.2.R. However, full test reports for verification and validation testing are not provided to support the design verification and validation in the submission. The sponsor should provide the following full test reports for design verification, transportation study and stability study.

VQD-RPT-199176
VQD-RPT-276495
VQD-RPT-288579
VQD-RPT-241315
VQD-RPT-048231
VQD-RPT-276494
VQD-RPT-276496
VQD-RPT-276497
VQD-RPT-276498
VQD-RPT-421984
VQD-RPT-221633
VQD-RPT-221678
VQD-RPT-221681

The following information request is identified.

- You provided the design verification summary reports for safety syringe device and autoinjector in section 3.2.R. However, the full verification test reports are not provided in the submission. Please provide the full verification test reports to support that the design verification is complete and adequate.

Please refer to the FDA Guidance Titled “Design Control Guidance for Medical Device Manufacturers” issued on March 11, 1997 (<https://www.fda.gov/media/116573/download>) for more details.

Update: In the response provided in sequence 0020 received on 4/28/2025, the sponsor provided the following updated Design Verification Summary Reports (DVSRs) for both SSD and AI to include test method references and test lab report references for each applicable test line.

- Depemokimab (GSK3511294) SSD Design Verification Summary Report (DVSR) (VQD-RPT-229163)
- Depemokimab (GSK3511294) (b) (4) 1ml (AI) - Design Verification Summary Report (DVSR) (VQD-RPT-242883)

In the updated DVSRs, the sponsor includes the sample size, reliability, raw data (mean, standard deviation, minimum, maximum), and lower tolerate limit and upper tolerate limit. All test results are within the tolerance interval. No further information is required.

5.2. Facilities Information

Firm Name:	Glaxo Operations UK Ltd
Address:	Harmire Road, Barnard Castle County Durham, DL12 8DT United Kingdom
FEI:	3002807078
Responsibilities:	Drug product manufacture, Storage of drug product, Assembly of Autoinjector and/or Safety Syringe Device, Release testing, Stability testing and Labelling and packaging.
Inspectional History An analysis of the firm’s inspection history: Inspection was conducted 3/9/2023 to 3/16/2023. The inspection covered drug CGMP and was classified VAI. An analysis of the firm’s inspection history over the past 2 years showed that it has never been inspected.	

N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

A pre-approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part.
- A medical device inspection of the firm has not been performed.
- The last inspection conducted in 2023 covered cGMP.
- The firm is not on the active Medical Device Single Audit Program (MDSAP) Master List

An inspection is not required because Choose an item.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	Yes	No	UNK
Is the device constituent a PMA or class III device?	Yes	No	UNK
Is the final combination product meant for emergency use?	Yes	No	UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	Yes	No	UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	Yes	No	UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	Yes	No	UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	Yes	No	UNK
cGMP Risk:			
Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.			
High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.			

Reviewer Comment

Both devices have low to moderate risk of cGMP issues given that the devices are relatively simple manufacturing/assembly processes.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION			
Acceptable for Filing:	Yes	No (Convert to a RTF Memo)	N/A
Facilities Inspection Recommendation:			
(PAI) Pre-Approval Inspection		Post-Approval Inspection	Routine Surveillance
No Inspection	N/A		

Site(s) needing inspection: Glaxo Operations UK Ltd (FEI 3002807078)			
Reviewer Comments The Pre-Approval Inspection (PAI) recommendation was communicated to CDER. The RRA has been completed. Please refer to ICC2500031 for additional information on the QS and facilities review associated with this BLA.			
Refuse to File Deficiencies:	Yes	No	N/A
74-Day Letter Deficiencies:	Yes	No	N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		
Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications			X
(b) (4)			
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments The sponsor noted no reported serious hypersensitivity reactions. Therefore, per FDA Guidance, there are no Contraindications relating to hypersensitivity on page 3 of Prescribing Information in section 1.14.1.2.
--

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
1.14.1.1 Carton Label 100mg Prefilled Pen	x		

1.14.1.1 Container Label 100mg Prefilled Pen	x		
1.14.1.1 Carton Label 100mg Prefilled Syringe	x		
1.14.1.1 Container Label 100mg Prefilled Syringe	x		
1.14.1.1 Container Label Back 100mg Prefilled Syringe	x		
1.14.1.1 Container Label Front 100mg Prefilled Syringe	x		
(b) (4)			

The Sponsor provided the PFS container and carton labels in section 1.14.1.1 as shown below.



Container Label Back 100mg Prefilled Syringe



Container Label Front 100mg Prefilled Syringe

The sponsor provided the (b) (4)

(b) (4)

Reviewer Comments

The carton and container labels of the PFS and AI contains necessary components. CDRH defers to CDER/DMEPA to review human factors validation to support that the (b) (4) device design are adequately validated.

6.3. Labeling Review Conclusion

LABELING REVIEW CONCLUSION

Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
Reviewer Comments								
The Labeling (b) (4) are Adequate.								
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial	x		
Bioequivalence Study utilized to-be-marketed device	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	x		
Traceability demonstrated for specifications to performance data	x		

Reviewer Comments

It should be noted that per the ICCR agreement [Do I Need to Request an Intercenter Consult \(i.e., Intercenter Agreements\)?](#), Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. is deferred to CDER CMC. The PFS-SS performance such as dose accuracy and break loose and glide force will not be addressed within this review.

In section 5.3.1.2, the sponsor summarized that the relative bioavailability between the liquid drug product administered by AI or SSD was investigated in the PK comparability study and concluded that statistical comparability between the 2 devices was demonstrated, and 90% CI of the geometric mean treatment ratios for Cmax and AUCs were well within the conventional bioequivalence limits of 0.80, 1.25. CDRH defers the review to CDER/Clinical.

7.2. Design Inputs and Outputs

(b) (4)

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
FDA Regulation of Combination Products (21 CFR Part 4)	Y	

ISO 13485 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes	Y	
ISO 14971 Medical devices – Application of risk management to medical Devices	Y	
ISO 11608 Needle-based injection systems for medical use — Requirements and test Methods	Y	
ISO 23908 Sharps injury protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling.	Y	

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
<u>Reviewer Comments</u>								
The Design Control information is adequate.								
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: Yes No								

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

Reviewer Comments

The risk analysis is adequate.

8.2. Hazard Analysis and Risk Summary Report

(b) (4)

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
<u>Reviewer Comments</u>								
The risk analysis is adequate. The risk management activities have been conducted for the SS-PFS and AI in accordance with ISO 14971.								
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

- Safety Syringe

As stated previously in the review memo, per the ICCR agreement [Do I Need to Request an Intercenter Consult \(i.e., Intercenter Agreements\)?](#) review of Prefilled Syringe functionalities outside of the needle safety device (NSD) performance, i.e. NSD activation, lockout, etc. is deferred to CDER CMC. The PFS-SS performance such as dose accuracy and break-loose and glide force will not be addressed within this review.

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Needle Safety Distance	$D \geq (b) (4) \text{ mm}$	Y Measure the needle safety distance for SSD	Y Simulated use study	Y	Y
Force to remove RNS	$(b) (4) \leq F \leq (b) (4) \text{ N}$	Y Force testing (force cell) to measure force	Y All acceptance criteria met.	Y All acceptance criteria met up to 24 months at the storage condition.	Y All acceptance criteria met.
Lockout Mechanism (Force to overcome lockout and needle guard lockout) ²	$F \geq (b) (4) \text{ N}$	Y The verified method for post use needle guard lock-out is VQD-OPS-023175. GSK3511294 DP (SSD) was used in the experiments.	Y All acceptance criteria met.	Y All acceptance criteria met up to 24 months at the storage condition.	Y All acceptance criteria met.

² Verification testing of force to overcome lockout (DIR-107) also confirms needle guard lockout.

Reviewer Comment

Pharmaceutical development for container closure system – safety syringe is provided in section 3.2.P.2. The method for post use needle guard lock-out is provided in the document “Validation of Analytical Procedures Compendial Conshohocken VQD VGQ-RPT-197938” in section 3.2.R.

The proposed Essential Performance Requirements (EPRs) are provided in Table 4 in accordance with ISO 11608-1:2022 and ISO 23908. The proposed specifications for Force to remove RNS and Lockout force highlighted in orange are comparable to the similar market products. They appear adequate.

Table 4 Depemokimab SSD EPRs

Design Input	EPRs	Acceptance Criteria (Design Output)	Method	Verification	Aging / Stability	Shipping Transportation	Validation	Control Strategy
Delivered Volume	Yes	(b) (4) $V \leq$ (b) (4) mL	Balance measures delivered weight, from which delivered volume is calculated.	All acceptance criteria met. See Section 5.2	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated. See Section 6.3	See Section 9.2
Force to remove Rigid Needle Shield (RNS)	Yes	(b) (4) $F \leq$ (b) (4) N	Force testing (force cell) to measure force.	All acceptance criteria met. See Section 5.2	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated. See Section 6.3	See Section 9.2
Maximum break loose force:	Yes	$F \leq$ (b) (4) N	Force testing (force cell) to measure force.	All acceptance criteria met. See Section 5.2	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated. See Section 6.3	See Section 9.2
Maximum glide force:	Yes	$F \leq$ (b) (4) N	Force testing (force cell) to measure force.	All acceptance criteria met. See Section 5.2	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated. See Section 6.3	See Section 9.2

Depemokimab SSD EPRs(Cont'd)

Design Input	EPRs	Acceptance Criteria (Design Output)	Method	Verification	Aging / Stability	Shipping Transportation	Validation	Control Strategy
Force to overcome lockout	Yes	$F \geq$ (b) (4) N	Force testing to measure the override force.	All acceptance criteria met. See Section 5.2	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated. See Section 6.3	See Section 9.2

Design verification testing was conducted according to ISO 23908:2011 and FDA Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features. Complete testing documentation is provided in "(b) (4) Needle Guard 1 ml" (b) (4), sequence 0001, Section 3.2.P.7). Testing evaluated three key areas with results summarized in Table 7:

- Activation of sharp injury prevention features - including activation cycle force, triggering test, and plunger action force
- Challenge testing in safe mode - comprising compression force and separation force assessment
- Access to sharp in safe mode - verification of protective barrier integrity

Results demonstrated that activation force, override force, and access to sharps in safe mode are maintained over a real-time 5-year period.

We note that while ISO 23908:2024 (second edition) has superseded the 2011 version, FDA continues to recognize ISO 23908:2011 during a transition period ending July 4, 2027. No justification for using the previous ISO standard revision is required currently.

The simulated use study results are summarized in Table 12. Validation testing confirmed that the device met all predetermined design validation requirements:

- Safety feature performance: 0 failures out of 500 simulations for triggering and activating the safety feature with device lock maintained until safe disposal
- User detection: 86% of users detected activation of the safety feature, meeting the acceptance criteria of (b) (4)0%

The baseline and aged testing of the NSD for the PFS is acceptable. The Sponsor has assessed activation, override, sharps access in safe mode and simulated clinical use testing for the PFS+NSD. The results of the clinical study and human factors validation study support the use of the NSD.

- Autoinjector

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	(b) (4) ≤ V ≤ (b) (4) mL	Y Uses ISO 11608-5 methodology to test dose accuracy using a membrane. Preconditions from ISO11608-1 of standard, cool, warm, free-fall, dry-heat, cold-storage, vibration, transport and stability were all tested	Y	Y All Passed – 50 samples were tested. Dose accuracy testing was completed, and all met specification	Y All Passed –30 samples were tested. Dose accuracy testing was completed, and all met specification.

Needle safe distance	$L \geq (b) (4) \text{ mm}$	Y A sphere with diameter 12 mm, simulating a fingertip shall not contact the extremity of the needle point when positioned against the needle shield (Cover Sleeve) before and after injection	Y	Y All acceptance criteria met.	Y All acceptance criteria met.
Force to remove cap	$(b) (4) \leq F \leq (b) (4) \text{ N}$	Y Uses force testing (force cell) to measure force. Uses preconditions as designated in ISO	Y	Y All acceptance criteria met.	Y All acceptance criteria met.
Actuation force	$(b) (4) \leq F \leq (b) (4) \text{ N}$	Y Uses force testing (force cell) to measure force. Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	Y	Y All acceptance criteria met.	Y – All acceptance criteria met.
Holding Force	$F \leq (b) (4) \text{ N}$	Y The peak force during the hold time is measured.	Y	Y All acceptance criteria met.	Y All acceptance criteria met.
Delivery Time	$t \leq (b) (4) \text{ s}$	Y Measures time for full dose to be delivered.	Y	Y All acceptance criteria met.	Y All acceptance criteria met.
Lockout Mechanism (Force to overcome lockout and needle guard lockout)	$F \geq (b) (4) \text{ N}$	Y Uses force testing to measure the override force. Uses preconditions as designated in ISO 11608-1: 2014 for verification testing. The verified method for post use needle guard lock-out is VQD-OPS-023175. GSK3511294 (AI) was used in the experiments.	Y	Y All acceptance criteria met.	Y All acceptance criteria met.

Reviewer Comment

Pharmaceutical Development Depemokimab Injection 100 mg/mL Container Closure System_Autoinjector is provided in section 3.2.P.2.4.5. The proposed ERPs are provided in Table 4 as shown below in accordance with ISO 11608-1:2022 and ISO 23908. The proposed specifications are comparable to the similar market products. They appear adequate.

Table 4 Depemokimab AI Critical Functions

Design Input	EPRs	PFs	Acceptance Criteria (Design Output)	Method	Verification	Aging/Stability	Shipping/ Transportation	Validation	Control Strategy
Force to Remove Cap	Yes	No	(b) (4) ≤ F ≤ (b) (4) N	Force testing (force cell) to measure force	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9
Actuation Force	Yes	Yes	(b) (4) ≤ F ≤ (b) (4) N	Force testing (force cell) to measure force	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9

Depemokimab AI Critical Functions(Cont'd)

Design Input	EPRs	PFs	Acceptance Criteria (Design Output)	Method	Verification	Aging/Stability	Shipping/ Transportation	Validation	Control Strategy
Needle Extension	Yes	Yes	(b) (4) ≤ L ≤ (b) (4) mm	The needle length distance is measured when the cover sleeve is fully depressed.	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9
Holding Force	Yes	Yes	F ≤ (b) (4) N	The peak force during the hold time is measured.	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9
Delivery Time	Yes	Yes	t ≤ (b) (4) s	Measures time for full dose to be delivered.	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9
Lockout Mechanism (Force to Overcome lockout and Needle guard lockout)	Yes	No	F ≥ (b) (4) N	Uses force testing to measure the override force.	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9
Dose Accuracy	Yes	Yes	(b) (4) ≤ V ≤ (b) (4) mL at a depth of ≥ (b) (4) mm	Uses ISO 11608-5 methodology to test dose accuracy using a membrane.	All acceptance criteria met. See Section 5	All acceptance criteria met. See Section 5.3	All acceptance criteria met. See Section 5.4	Validated See Section 6	See Section 9

The baseline and aged testing of the AI is acceptable. Regarding the needle safety feature, the Sponsor has assessed activation, override, and sharps access in safe mode. The results of the clinical study and human factors validation study support the use of the AI.

9.1.2. Verification of Design Inputs Evaluation

- Safety Syringe

(b) (4)

9.1.3. *Evaluation of Test Methods*

Title:	Methods Validation – Summary Information is provided in section 3.2.R.2.
Scope/Objective & Acceptance Criteria:	A summary of the analytical methods, analytical validation reports and method transfer reports is provided in Table 2 for depemokimab drug product testing.

	The analytical methods for injection volume, post use needle guard lock-out, injection force and injection time are shown below.				
	Analytical Method	Method Validation		Method Transfer	
		Method Validation or Compendial Method Verification Laboratory	Method Validation Report(s) or Compendial Verification Report(s)	Receiving Laboratory	Method Transfer Report(s)
	Injection Volume Determination Ph. Eur. 2.9.17, USP <697>, JP 6.05	GSK Conshohocken	VQD-RPT-197938	N/A	N/A
		GSK Parma	VQD-RPT-202706		
	Post Use Needle Guard Lock-Out Determination ISO 23908	GSK Conshohocken	VQD-RPT-197938	N/A	N/A
		GSK Parma	VQD-RPT-202706		
	Injection Forces Determination	GSK Barnard Castle	Not provided, site will not perform release testing	GSK Parma	VQD-RPT-221563
		GSK Conshohocken	VQD-RPT-436237	N/A	N/A
	Delivery Time Determination	GSK Barnard Castle	Not provided, site will not perform release testing	GSK Parma	VQD-RPT-221563
GSK Conshohocken		VQD-RPT-436237	N/A	N/A	
Methods	Volume of Injection in Containers Post Use Needle Guard Lock-Out Injection Force Delivery Time				
Results:	All results met the specifications.				
Conclusions/ Reviewer Comments:	These methods are suitable for release and stability testing of the finished product.				
Acceptable:	☒ Yes ☐ No				

Reviewer Comment

The following validation of analytical procedures are provided in section 3.2.R

 [\[000\]](#) Validation of Analytical Procedures Compendial Conshohocken VQD-RPT-197938

It reports the verification results of compendial methods, including Volume of Injection in Containers, Post Use Needle Guard Lock-Out used to test depemokimab (GSK3511294) drug product (DP), i.e., PFS, SS and AI. The individual results, average result, and total average results for both analysts conform to the current depemokimab (GSK3511294) drug product specification VQD-SPEC-028563 v7.0. The repeatability and intermediate precision criteria met the pre-defined acceptance criteria outlined in the protocol, demonstrating the successful verification of the compendial methods for testing depemokimab drug product at GSC UMBL, thereby qualifying the GSC UMBL to test depemokimab commercial drug product.

 [0001] Verification Report for IF and DT UMBL_VQD-RPT-436237

It reports the verification (VQD-PRTL-146375) of the Injection Force and Delivery Time Analytical Methods for safety syringe and AI at GSK Biopharm Upper Merion (UMBL) for depemokimab drug product release and stability testing. The injection force and delivery time method, VQD-SOP-070749, is suitable for release and stability testing of depemokimab drug product.

 [0001] Validation of Analytical Procedures-General characteristics - IF and DT_VQD-RPT-221563

It is Injection Force Abbreviated Confirmation and Delivery Time verification report on GSK3511294 Depemokimab DP for the Analytical Method Transfer from GSK Barnard Castle to GSK Parma. All the experimental runs required by the Confirmation/Verification design outlined in VQD-PRTL-086340 (v2.0) for the Depemokimab Injection Force and Delivery Time methods were performed at GSC Parma. For both methods all the system suitability and transfer acceptance criteria have been met, and the obtained results are compliant to the product specifications.

The analytical methods procedure and validation of volume of injection in containers, delivery time and post-use needle guard lock-out are provided in section 3.2.P.2, 3.2.P.5.3 and 3.2.R. However, the rest of analytical methods, e.g., Needle Safe Distance, Force to remove cap, Actuation Force, Needle Extension, Holding Force are not provided in the submission.

The analytical procedure and validation for safety syringe injection force is provided in section 3.2.P.5.2 and 3.2.p.5.3, respectively, but analytical method for AI injection force is not provided.

However, the analytical method procedure and validation for some EPRs, e.g., Force to remove Rigid Needle Shield (RNS) for safety syringe force, and Extended Needle Length for autoinjector, are not provided in the submission. The following IR is identified.

- You identified Essential Performance Requirements (EPRs) per ISO 11608-1 in section 3.2.P.2 Container Closure System Safety Syringe and Container Closure System Autoinjector. However, you did not provide the procedure and validation of all functional performance testing method for the following EPRs, e.g., Force to remove Rigid Needle Shield (RNS) for the safety syringe, and Needle Safe Distance, Force to remove cap, Actuation Force, Needle Extension and Holding Force for autoinjector in the submission. The failure to meet these identified EPRs could result in unacceptable harm to the patent, e.g. delay of delivery and/or medication error, and these testing methods for these EPRs are critical to ensure devices perform as intended according to ISO 23908:2011 and ISO 11608-1:2022. Please provide the analytical method procedure and validation for these EPRs to demonstrate that the functional performance testing methods are suitable for the intended use.

Update: In the response provided in sequence 0020 received on 4/28/2025, the sponsor provided analytical method procedure and validation for SSD EPRs and AI EPRs listed in Tables 12 and 14.

Table 12 Safety Syringe Device (SSD) EPRs, test method and method validation

EPR	Test Method	Test Method Validation
Delivered Volume	VQD-OPS-029296 ¹	VQD-RPT-092045
Glide Force	Universal Test Method (UTM) VQD-OPS-022413	VQD-RPT-220831
Peak Break-Loose Force		
Force to remove RNS		
Force to overcome lockout		
Needle Safe Distance	VQD-OPS-045784	VQD-OPS-045784 Appendix 1

¹ This document contains various test methods, however, only the ‘Volume of injection (deliverable volume)’ test method is applicable for the delivered volume design verification testing for the SSD.

Safety syringe device universal test method validation for Force to remove RNS, and Force to overcome lockout demonstrated acceptable performance across all device tests as shown in Table 13, and the repeatability and reproducibility are in accordance with ISO 11609-1:2022.

Table 13 – SSD UTM Method Validation Result Summary

Device Test	Device Test Acceptance Criteria	Method Validation Acceptance Criteria (Std Deviation)	Std Deviation	Method Validation Outcome
Force to remove RNS	(b) (4)			Pass
Peak Break-Loose Force				Pass
Glide Force				Pass
Force to Overcome Lockout				Pass

Table 14 Autoinjector (AI) EPRs

EPR	(b) (4)	Test Method	Test Method Validation
Dose Accuracy	(b) (4)	VQD-RPT-553046	VQD-RPT-553025
Force to Overcome Lockout		VQD-RPT-553043	VQD-RPT-553033
Force to remove cap			
Actuation Force			
Holding Force			
Delivery Time			
Needle Extension			
Needle Safe Distance			

The test method validation was completed involving two testing individuals at (b) (4). The results showed that the p-values were greater than 0.05, suggesting no significant differences between the means and variances of the results from the two individuals. The test method was consistent and reliable across different testing individuals. The test methods for the autoinjector appear adequate.

9.2. Discipline Specific Sub-Consulted Review Summary

No Additional Discipline Specific Sub-Consults were requested

The following additional Discipline Specific Sub-Consults were requested:

<u>Discipline-Specific Design Verification / Validation adequately addressed</u>						
Discipline	Consult needed			Consultant	Section	Adequately Addressed (Y/N/NA)
	Yes	No	N/A			
Engineering (Materials, Mechanical, General)		x				
Biocompatibility		x				
Sterility			x			
Software / Cybersecurity			x			
Electrical Safety / EMC			x			
Human Factors		x			<u>11</u>	<u>Defers to CDER/DMEPA</u>
Clinical		x				Defers to CDER/Clinical

Notes:

- The device components are (b) (4) and this is deferred to CDER.
- A cursory review will be conducted to address validation of the usability related specifications. The adequacy of the human factors study is deferred to CDER/DMEPA.
- Clinical is deferred to CDER/Clinical.

CDRH sent <u>Deficiencies or Interactive Review Questions</u> to the Sponsor	Yes	No
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9.3. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
<u>Reviewer Comments</u> The Design Verification is adequate. Information requests identified for design verification, shipping/transport validation, stability study, biocompatibility and device functional performance testing method have been addressed in the response provided in sequence 0020 received on 4/28/2025.								
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor:							Yes	No

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

There is no device related clinical studies for review

There are clinical studies for review

In section 2.2, the sponsor stated that both PFS-SSD and AI products have been designed and tested to support administration by healthcare professionals (HCPs). Following approval, the sponsor intends to initially launch only the SSD. In section 2.5, the sponsor stated that all Phase 3 studies were conducted with a pre-filled safety syringe

assembled to an SSD. In section 5.3.1.2, the sponsor provided the relative bioavailability between the AI and SSD in the PK biocompatibility study. There were no observations of device performance issues. CDRH defers the review to CDER/Clinical.

11.HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	
Human Factors deferred to DMEPA	

Human factors studies were conducted on both AI and PFS finished products. The study reports are provided in sequence 0001, section 5.3.5.4. Reported issues included use errors, close calls, and use difficulties. DMEPA concluded that risks have been mitigated to an acceptable level, and no further user interface changes are likely to provide additional risk mitigation.

- 100 mg/mL, single-dose, prefilled pen with attached 29-gauge, half-inch needle in cartons of 1 (NDC 0173-0927-31).
- 100 mg/mL, single-dose, prefilled syringe with attached 29-gauge, half-inch needle with a needle guard in cartons of 1 (NDC 0173- 0927-42)

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	
CDRH Facilities Inspection Review was not conducted	

Facility Regulatory History Review	
Firm Name:	Glaxo Operations UK Ltd
Address & FEI:	Harmire Road, Barnard Castle County Durham, DL12 8DT United Kingdom FEI: 3002807078
Responsibilities:	The firm is responsible for Drug product manufacture, Storage of drug product, Assembly of Autoinjector and/or Safety Syringe Device, Release testing, Stability testing and Labelling and packaging. Based on the responsibilities, the site is then subject to applicable QS requirements.
Site Inspection Recommendation:	VAI per Remote Regulatory Assessment (RRA) — FACTS/eNSpect OP #320156

Reviewer Comments

A pre-approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed per [OSAR FIRM360](#).
- The firm is not on the active [MDSAP Master List](#) dated 1/24/2025.

CDER decided to pursue a RRA in lieu of CDRH's PAI recommendation (ICC2500031) for coverage of the medical device cGMP regulations called out under 21 CFR Part 4: Management Controls (21 CFR 820.20); Design Controls (21 CFR 820.30); CAPA Controls (21 CFR 820.100); and Purchasing Controls (21 CFR 820.50).

Glaxo Operations U.K. Ltd.

Harmire Road Barnard Castle County Durham DL12 8DT GB · Phone: (0)183 369 3258 Fax: (0)183 369 2300

Surviving FEI: 3002807078 Merged FEI: 117 Merged Firm(s) DUNS: 228472833 Match Confidence: 10

Executive Summary
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Remote Regulatory Assessments 1

Detail	RRA FEI	FACTS Asgmt	FACTS Op ID	Inspection ID	eNSpect Op ID	District/ Division	Start Date	End Date	Basis	FACTS Status	Lead Invs
<a>ins	3002807078	12437813	12810215	1274361	320156	DMDRHGO	07/02/2025	07/11/2025	Compliance	Completed	Joshua Silvestri

Assessment Processes: 1

PAC	PAC Description	Etab Type	Process	Final Outcome (Y/N)	Outcome	Outcome Description	Outcome Remarks	Outcome Org Abbrv	Outcome Made By	Outcome Date
828458	MEDICAL DEVICE LEVEL II (BASELINE) INSPECTIONS	M	80	N	rVAI			FOR-DEVICE	Akbar Zaidi	09/01/2025

Assessment Products Covered: 1

Assessment Summary:

Assessment Endorsement Text:

Assessment Document(s): 67

This was the initial inspection of the factory assessing current GMP for medical devices as defined under the Quality System Regulation, 21 CFR 820. Per OII, OMDHRI conducted 704 assessments from 7/2/25 - 7/14/25 with acceptable outcome. The outcome was VAI as shown above. There was one (1) Observation; "Procedures to ensure that all purchased or otherwise received products and services conform to specified requirements have not been adequately established." As part of the device constituent review, we reviewed the EPR control strategy which demonstrates that all EPRs for the final finished combination product are adequately controlled through release. As such, CDRH does not have any concerns with this observation. Please refer to the document "RRA-GLAXO Operations UK Ltd FEI 3002807078 (11-Jul-2025) for more details. No further action is required.

Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	Yes	No
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12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	
CDRH Quality Systems Documentation Review was not conducted	

12.2.1. Description of the Device Manufacturing Process

(b) (4)

Device Manufacturing Process Conclusion

The Sponsor provided adequate information for the summary of the manufacturing process / production flow.

☒ Yes

☐ No

12.2.2. cGMP Review

(b) (4)

Reviewer Comments

The Sponsor provided adequate summary information about the GMP compliance activities.

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities	Yes	No
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12.2.3. Corrective and Preventive Action Review

(b) (4)

(b) (4)

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

☒ Yes

☐ No

12.3. Control Strategy Review

(b) (4)

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒ Yes	☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
<u>Reviewer Comments</u> There are no concerns with the quality system documentation. CDER pursued a RRA for medical device level II (baseline) inspection between 7/2/2025 and 7/12/2025, and the 9/1/2025 outcome is VAI as shown in section 12.1. No further action is required.								
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor:							Yes	No

<<END OF REVIEW>>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NOWRIN S KAKON
10/22/2025 05:14:16 PM
CDRH review is uploaded on behalf of CDRH assessors.

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 21, 2025

TO: Kelly Stone, MD, Ph.D.
Supervisory Physician
Division of Pulmonology, Allergy and Critical Care
Office of Immunology and Inflammation
Office of New Drugs

FROM: Monica Javidnia, Ph.D.
Pharmacokineticist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Julia Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of PPD Development L.P.,
Austin, TX, USA

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study 214099 (BLA 761458) conducted at Clinical Inspection of PPD Development L.P., Austin, TX, USA.

Form FDA 483 was not issued at the inspection close-out. There was one discussion item for an unreported adverse event (Attachment 1). I recommend that the review division consider the adverse event and associated medication in their review of subject (b) (6).

2. Inspected Study**BLA 761458**

Study Number: 214099

Study Title: "An Open-Label, Randomized, Single-Dose, Multicenter, Parallel-Group Study to Compare the Pharmacokinetics of Subcutaneous Depemokimab When

Delivered with a Safety Syringe Device or an
Autoinjector in Healthy Adult Participants”

Dates of study conduct: 12/06/2022 - 10/23/2023

Clinical site: PPD Development L.P.
7551 Metro Center Dr Ste 200
Austin, TX 78744-1645
CI: Brian Spears, MD

3. Inspectional Findings

PPD Development L.P., Austin, TX, USA

OII investigator Iris C. MacInnes inspected PPD Development L.P., 7551 Metro Center Dr Ste 200, Austin, TX 78744-1645 from August 04-07, 2025.

3.1 Previous Inspection

The previous OSIS inspection of PPD Development L.P. was conducted from October 07-11, 2024. At the conclusion of the inspection, Form FDA 483 was not issued, and there were no discussion items. The final classification was NAI.

3.2 Current Inspection

The current inspection included auditing the following items:

- Informed consent forms
- Subject records, including adverse events (AEs)
- Randomization
- Training records
- Drug accountability
- Institutional review board approvals

3.3 Inspection Findings

At the conclusion of the inspection, investigator MacInnes did not issue Form FDA 483 to the clinical site. There was one discussion item.

3.3.1 Discussion Items

Discussion Item 1: One AE was not transcribed into the electronic data capture (EDC).

OSIS Evaluation: Per the protocol, the investigator must review all documentation related to the AE then record all relevant

information. Subject (b) (6) experienced a toothache (onset (b) (6)). This AE was documented in the source records but was not entered into the EDC and ultimately not reported as part of the submission. I recommend the review division review the subject's AE record and associated medications (**Attachment 1**) as part of their review process.

Firm's Response: The firm stated the AE was left open because the subject was lost to follow up (**Attachment 1, page 3**) and that it was missed when entering data into the EDC.

Attachment

Attachment 1: Subject (b) (6) AE report

Monica Javidnia, Ph.D.
Pharmacokineticist

Draft: MJ 08/20/2025, 08/21/2025
Edit: MO 08/20/2025; JC 8/21/2025

OSIS File #: BE 10502

AMS Assignment ID: 260025
eNSpect OpID: 312962

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONICA JAVIDNIA
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08/21/2025 02:00:37 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 7/29/2025 **Date consulted:** 2/27/2025

From: Katherine Kratz, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: CDR Miriam Dinatale, DO, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Pulmonology, Allergy and Critical Care (DPACC)

Drug: Exdensur (depemokimab-xxxx)

BLA: 761458

Applicant: GlaxoSmithKline (GSK)

Subject: Pregnancy and Lactation Labeling

Indication:¹ “Add-on maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium- to high-dose inhaled corticosteroids (ICS) plus another asthma controller.

(b) (4)

¹ BLA 761458, Sequence Number (SN) 0001, Module 1.14.1.2, Annotated Draft Labeling Text, under review by DPACC.

Materials

Reviewed:

- DPMH consult request dated 2/27/2025. DARRTS Reference ID: 5539265
- Applicant's submitted background package and proposed labeling for BLA 761458 Sequence Number (SN) 0001, dated 12/16/2025.
- BLA 761458, SN 0018, 120-Day Safety Update, dated 4/9/2025.
- Response to FDA Information Request (IR), BLA 761458, SN 0025, dated 6/13/2025.

Consult Request: "Based on depemokimab's MOA of neonatal FcR binding, it is unclear whether this would increase placental transfer of depemokimab if used during pregnancy. Has DPMH considered if additional safety monitoring and/or studies (e.g., pregnancy registry) are needed in pregnant women for biologic products containing a YTE modification? Does DPMH have recommendations (e.g., labeling, PMRs, etc.) for this application?"

Reviewer comment:

The YTE modification (M252Y/S254T/T256E) involves the introduction of amino acid mutations in the crystallizable fragment (Fc) domain of an immunoglobulin G (IgG) monoclonal antibody (mAb). The "Y" stands for tyrosine (Y) replacement of methionine (M) at position 252 of the heavy chain; the "T" stands for threonine (T) replacement of serine (S) at position 254 of the heavy chain; and the "E" stands for glutamic acid (E) replacement of tyrosine (Y) at position 256 of the heavy chain.^{2,3} The YTE modification increases binding to the neonatal Fc receptor (FcRn) and extends the elimination half-life.

I. INTRODUCTION AND BACKGROUND

On December 16, 2024, the Applicant, GlaxoSmithKline, submitted a new Biologics License Application (BLA) pursuant to 351(a) for Exdensus (depemokimab-xxxx) for (b) (4) add-on maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium- to high-dose inhaled corticosteroids (ICS) plus another asthma controller (b) (4).

(b) (4). DPACC consulted the DPMH MHT on February 18, 2025, to assist with the Pregnancy and Lactation subsections of labeling and to provide recommendations related to pregnancy safety studies.

Relevant Regulatory History

- FDA has approved other anti-interleukin-5 (IL-5) mAbs without a YTE modification, including mepolizumab (Nucala, approved 2015) and reslizumab (Cinqair, approved

² Abdeldaim DT, Schindowski K. Fc-Engineered Therapeutic Antibodies: Recent Advances and Future Directions. *Pharmaceutics*. 2023 Sep 28;15(10):2402. doi: 10.3390/pharmaceutics15102402. PMID: 37896162; PMCID: PMC10610324.

³ Rosenberg YJ, Lewis GK, Montefiori DC, LaBranche CC, Lewis MG, Urban LA, Lees JP, Mao L, Jiang X. Introduction of the YTE mutation into the non-immunogenic HIV bnAb PGT121 induces anti-drug antibodies in macaques. *PLoS One*. 2019 Feb 20;14(2):e0212649. doi: 10.1371/journal.pone.0212649. PMID: 30785963; PMCID: PMC6437720.

2016), which are indicated as add-on maintenance treatment of severe asthma with an eosinophilic phenotype.

- DPMH reviewed mepolizumab in 2015.⁴ At the time of approval, the Applicant agreed to voluntarily conduct a pregnancy surveillance study. According to the FDA Office of Women's Health (OWH) website,⁵ this study is called The Mepolizumab Pregnancy Exposure Registry: OTIS [Organization of Teratology Information Specialists] and Vaccines and Medications in Pregnancy Surveillance Study (VAMPSS). The study completion date was estimated to be in 2023. At this time, the OTIS website states that the study is closed to recruitment, and no further information is available. Since no study reports have been submitted to FDA, an IR was sent to the Applicant requesting data from the registry. In the IR response,⁶ the Applicant explained that 23 subjects were enrolled in the mepolizumab-exposed cohort. According to the Applicant, "there was no evidence of pattern of major structural birth defects in the mepolizumab-exposed cohorts, there were no stillbirths, one spontaneous abortion, and one termination. However, due to the small sample size in the mepolizumab-exposed pregnancies in this study, the findings are limited in interpretability regarding safety in pregnancy."
- GSK, the Applicant for the proposed biologic product, markets mepolizumab.
- DPMH reviewed reslizumab in 2016.⁷ No pregnancy safety studies or clinical lactation studies were issued as PMRs for reslizumab.
- The labelings for mepolizumab and reslizumab do not contain a contraindication for pregnancy or lactation or a warning and precaution (W&P) for embryofetal toxicity (EFT). There are no human pregnancy or lactation data for these drug products.
- (b) (4)
- There is one mAb, nirsevimab (Beyfortus, approved 2023), that contains a YTE modification. Nirsevimab, an IgG1 kappa (κ) that targets the respiratory syncytial virus (RSV) F protein, is indicated for the prevention of RSV lower respiratory tract disease in 1) neonates and infants born during or entering their first RSV season and 2) children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Given that nirsevimab is not indicated for use in females of reproductive potential, it was not reviewed by the DPMH MHT.

⁴ DPMH Memorandum for BLA 125526 by Dr. Miriam Dinatale, dated 6/8/2015. DARRTS Reference ID: 3775784

⁵ <https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries> Accessed 5/23/25.

⁶ Response to FDA Information Request (IR), BLA 761458, SN 0025, dated 6/13/2025.

⁷ Division of Pediatric and Maternal Health Memo for BLA 761033 by Dr. Carol Kasten, dated 1/4/2016. DARRTS Reference ID: 3867119

Drug Characteristics⁸

Drug class	IgG 1 kappa (κ) anti-interleukin-5 (IL-5) mAb
Mechanism of action	Targets human IL-5 and blocks IL-5 binding to the IL-5 receptor alpha
Dosage forms	Subcutaneous (SC) injection
Dose and Administration	100 mg SC every 6 months
Molecular weight	149 kDa
Half-life	(b) (4) days
% protein bound	Not specified
Bioavailability	Not specified
Warnings and Precautions	Hypersensitivity reactions

II. REVIEW

PREGNANCY

Eosinophilic Asthma

Asthma is a chronic inflammatory disease of the airways. Eosinophilic asthma, a subtype of asthma, is characterized by high levels of eosinophils in the airways, peripheral blood and sputum.⁹ IL-5 triggers a cascade of intracellular signaling events that are associated with eosinophil recruitment, maturation, activation, and survival, and induces eosinophilic inflammation in the airways. Eosinophilic asthma is estimated to represent 50% of severe asthma cases¹⁰ or approximately one million adults in the U.S.¹¹

Asthma During Pregnancy

Asthma is the most common pulmonary disease during pregnancy, occurring in 3-8% of pregnant women.¹² Asthma is reported to worsen in approximately 40% of women during pregnancy and remain the same in the other 60% of women during pregnancy.¹³ Publications suggest an association between asthma during pregnancy and an increased risk of spontaneous abortion and ante- and post-partum hemorrhage,¹⁴ preeclampsia, preterm birth and pulmonary

⁸ BLA 761458, SN 0001, Module 1.14.1.2, Annotated Draft Labeling Text, under review by DPACC.

⁹ Hussain M, Liu G. Eosinophilic Asthma: Pathophysiology and Therapeutic Horizons. *Cells*. 2024 Feb 23;13(5):384. doi: 10.3390/cells13050384. PMID: 38474348; PMCID: PMC10931088.

¹⁰ Ibid (Hussain)

¹¹ Based on 20 million adults in the U.S. having asthma (American College of Allergy, Asthma and Immunology, Asthma Facts. <https://acaai.org/asthma/asthma-101/facts-stats/>) and 10% of those cases being severe (i.e., 2 million adults with severe asthma) and 50% of those severe cases being due to eosinophilic asthma.

¹² Weinberger S, Schatz M. Asthma in pregnancy: Clinical course and physiologic changes. *UpToDate*. Topic 555 Version 25.0. Accessed 4/21/25.

¹³ Stevens DR, Perkins N, Chen Z, Kumar R, Grobman W, Subramaniam A, Biggio J, Grantz KL, Sherman S, Rohn M, Mendola P. Determining the Clinical Course of Asthma in Pregnancy. *J Allergy Clin Immunol Pract*. 2022 Mar;10(3):793-802.e10. doi: 10.1016/j.jaip.2021.09.048. Epub 2021 Oct 14. PMID: 34656801; PMCID: PMC9082822.

¹⁴ Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, West J, Hubbard RB. A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med*. 2007 May 15;175(10):991-7. doi: 10.1164/rccm.200611-1641OC. Epub 2007 Feb 1. PMID: 17272783.

embolism,¹⁵ low birthweight¹⁶ and congenital malformations.¹⁷ The goal of asthma therapy during pregnancy is prevention of maternal hypoxic episodes and maintenance of adequate fetal oxygenation.¹⁸ Treatment of asthma in pregnant women is similar to treatment in nonpregnant women, including inhaled glucocorticoids (budesonide is preferred) as first-line controller therapy for persistent asthma, rescue therapy (albuterol preferred), continuation of immunotherapy for patients who are at or near a maintenance dose, and use of oral corticosteroids for severe asthma.¹⁹

(b) (4)

Nonclinical Data

For this BLA, the Applicant relied on the reproductive toxicology data from the mepolizumab development program. Standard reproductive toxicity studies in rodents and rabbits could not be

¹⁵ Mendola P, Laughon SK, Männistö TI, Leishear K, Reddy UM, Chen Z, Zhang J. Obstetric complications among US women with asthma. *Am J Obstet Gynecol*. 2013 Feb;208(2):127.e1-8. doi: 10.1016/j.ajog.2012.11.007. Epub 2012 Nov 15. PMID: 23159695; PMCID: PMC3557554.

¹⁶ Abdullah K, Zhu J, Gershon A, Dell S, To T. Effect of asthma exacerbation during pregnancy in women with asthma: a population-based cohort study. *Eur Respir J*. 2020 Feb 12;55(2):1901335. doi: 10.1183/13993003.01335-2019. PMID: 31772000.

¹⁷ Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, Schatz M. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG*. 2013 Jun;120(7):812-22. doi: 10.1111/1471-0528.12224. Epub 2013 Mar 26. Erratum in: *BJOG*. 2014 Apr;121(5):652. PMID: 23530780.

¹⁸ Dombrowski MP, Schatz M; ACOG Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists number 90, February 2008: asthma in pregnancy. *Obstet Gynecol*. 2008 Feb;111(2 Pt 1):457-64. doi: 10.1097/AOG.0b013e3181665ff4. PMID: 18238988.

¹⁹ Ibid (Dombrowski)

(b) (4)

conducted with mepolizumab due to the absence of IL-5 binding in these species.²⁵ Mepolizumab is pharmacologically active in cynomolgus monkeys.²⁶ Therefore, the Applicant conducted a pre- and post-natal development (PPND) study in cynomolgus monkeys. In the PPND study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times the maximum recommended human dose (MRHD) on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks. The Applicant reported that mepolizumab did not elicit adverse effects on fetal or neonatal growth or immune function up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Although mepolizumab was detectable in infant plasma, it did not affect physical, hematologic or immunologic development of the offspring. A low incidence of anti-mepolizumab antibodies was observed which did not affect the pregnancy outcome or the offspring.

The reader is referred to the Pharmacology/Toxicology (P/T) review by Dr. David Klein.

Reviewer comment:

The PPND conducted by the Applicant using mepolizumab was an enhanced PPND (ePPND) study. The ePPND study was discussed with the P/T team. The P/T team explained that FDA communicated with the Applicant during the IND phase of development and told the Applicant that nonclinical studies with depemokimab were not needed based on the ePPND study conducted with mepolizumab.

As explained under the Nonclinical Data section above, mepolizumab did not cause embryofetal toxicity at 9-times the MRHD based on the AUC. Per the P/T team, the YTE modification in depemokimab should not impact embryofetal development because the high doses used in the mepolizumab ePPND study make up for the effect of the YTE modification in depemokimab. It is also possible that placental transfer of depemokimab will be limited by saturation of the FcRns,²⁷ and the remaining unbound depemokimab will be digested by lysosomal enzymes within endosomes responsible for placental transport.²⁸ The worst-case scenario would be that the YTE modification in depemokimab results in a high level of placental transfer and complete IL-5 inhibition in the developing fetus. Complete inhibition of IL-5 was studied in a fertility, early embryonic and embryofetal development study in pregnant IL-5 deficient mice. Embryofetal development in IL-5 deficient mice was generally unaffected relative to wild-type mice (see mepolizumab labeling, subsection 8.1, Animal Data). Thus, the P/T team explained that complete inhibition of IL-5 did not appear to place the mouse fetus at risk.

²⁵ BLA 761458, SN 0001, Module 2.4, Nonclinical Overview, p. 23.

²⁶ BLA 761458, SN 0001, Module 4.3, Literature References, Final Study report for SB-240563: Intravenous Study for Effects on Pre- and Postnatal Development in Cynomolgus Monkeys.

²⁷ Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646. doi: 10.1155/2012/985646. Epub 2011 Oct 1. PMID: 22235228; PMCID: PMC3251916.

²⁸ Ibid (Palmeira)

Based on the mepolizumab reproductive toxicology data, DPMH concludes that inhibition of IL-5 in animal studies did not result in embryofetal toxicity. It is not clear whether these findings with mepolizumab can be confidently translated to depemokimab or applied to humans. Without nonclinical studies conducted with depemokimab, the effect of the YTE modification on placental transfer is unknown.

The Applicant reported that an *in silico* placental transfer model was developed, and monkey and human distribution profiles were compared between mepolizumab and depemokimab.²⁹ The model predicted mepolizumab monkey fetal exposures based on neonatal plasma exposures from the ePPND study conducted with mepolizumab in cynomolgus monkeys. The model predicted up to a 2-fold difference in pharmacokinetic (PK) parameters in the fetus with depemokimab compared with mepolizumab. The Applicant did not consider these increases to be clinically significant, as the mepolizumab ePPND study achieved exposures 30-fold higher than those achieved with the maximum recommended human dose. The Applicant concluded that the monkey and human fetal exposure modeling estimated minor increases on fetal exposures with depemokimab compared to the ePPND study with mepolizumab, where there were no developmental effects observed.

The reader is referred to the reviews by the Clinical Pharmacology (CP) and P/T teams.

Reviewer comment:

The in silico transfer model was discussed with both the CP and the P/T teams. Per the CP team, the model that the Applicant described is reasonable for the stated purpose. The Applicant verified the model by confirming that it could accurately predict monkey PK data for both mepolizumab and depemokimab from the toxicology studies for each respective drug by simply changing the FcRn binding affinity input. Additionally, the Applicant confirmed that the model could accurately predict the mepolizumab PK data observed from the mepolizumab ePPND study within 2- to 3-fold.

Clinical Data from Drug Development

Females of reproductive potential were eligible for enrollment in the phase 3 clinical trials if they had a negative pregnancy test and used effective contraception from at least 14 days prior to the first dose of the study intervention and until at least 30 weeks after the last dose of the study intervention. Females who were pregnant were excluded from clinical trials during drug development. Female subjects who became pregnant during the trials were discontinued from the study intervention.

Seven pregnancies were reported in participants who received depemokimab. No congenital anomalies were reported. The outcomes of the seven pregnancies are shown in the reviewer-generated table 1 below:³⁰

²⁹ BLA 761458, SN 0001, Module 2.4, Nonclinical Overview, p. 23.

³⁰ BLA 761458, SN 0001, Module 2.7.4, Summary of Clinical Safety, pp. 106-107 and Module 2.5, Clinical Overview, pp. 68-69.

Table 1. Reviewer-generated table of pregnancies during drug development

Subject number	Pregnancy outcome	# of doses of depemokimab/timing of dose in relation to LMP or hcg test
(b) (6)	FT, live birth, no anomalies	1/261 days prior to LMP
	ToP at 20 5/7 weeks' gestation	1/Positive hcg 273 days after dose
	ToP at ~7 weeks' gestation	2/Last dose 7 days after LMP
	SAB in first trimester (occurred 7 days after dose)	1/Positive hcg on day of dose
	SAB in first trimester (occurred 56 days after dose)	1/Positive hcg 28 days after dose
	SAB in first trimester (occurred 233 days after dose)	1/Positive hcg 201 days after dose
	Ongoing pregnancy	1/118 days before LMP

FT = full-term; ToP = termination of pregnancy; SAB = spontaneous abortion; LMP = last menstrual period; hcg = human chorionic gonadotropin

Reviewer comment:

Among the seven pregnancies that occurred during the drug development program, all were exposed to depemokimab even when the pregnancy occurred 273 days after dosing or 118 days before the LMP. This is because the half-life of depemokimab may be as long as 53 days. Some exposure is expected for at least 6 half-lives, which is 318 days.

Although three of the six known outcomes for these pregnancies resulted in SABs, the records from these pregnancies do not provide data related to risk factors for SAB, so it is not possible to attribute the SABs to drug exposure. In general, the data are too limited to draw conclusions about the use of depemokimab during pregnancy.

Review of Literature

Applicant's review:

The Applicant did not provide a review of the literature related to anti-IL-5 mAbs and pregnancy.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms “anti-IL-5” or “IL-5 inhibition” or “IL-5 inhibitors” or “mepolizumab” or “reslizumab” and “pregnancy,” “pregnancy outcomes,” “birth defects,” “malformations,” “stillbirth,” or “spontaneous abortion.” The results of the literature search are as follows:

- Couillard et al.³¹ published an article to update obstetric providers on the stratification and management of pregnant women and asthma. In this publication, the authors stated that mAbs targeting IL-5 have had a significant impact on clinical practice in severe

³¹ Couillard S, Connolly C, Borg C, Pavord I. Asthma in pregnancy: An update. *Obstet Med.* 2021 Sep;14(3):135-144. doi: 10.1177/1753495X20965072. Epub 2020 Nov 1. PMID: 34646341; PMCID: PMC8504309.

asthma and conclude that there have been no concerns of teratogenicity despite being trialed and used in humans for more than two decades.

- Ozden et al.³² published a case report of a patient with asthma who received mepolizumab preconception through 5 weeks of gestation at which time mepolizumab was discontinued. The patient delivered a healthy infant without congenital anomalies.
- Jang et al.³³ published an observational study based on reports to Vigibase, the World Health Organization global database of safety reports, between 1980 and 2023. The authors performed a case-non-case disproportionality analysis to evaluate the association between the use of biologics for asthma during pregnancy and maternal, fetal and neonatal outcomes compared with the use of non-biologic asthma medications. Reports were extracted from Vigibase if they mentioned one or more pregnancy-related reactions and identified one or more asthma medications as “suspected” or “interacting.” A total of 15,715 pregnancy-related reports were used for disproportionality analysis. In this observational study, the severity of asthma was unknown and was not adjusted for, and the authors could not account for the gestational age at which the drug was administered. The authors reported these findings for the anti-IL5 mAbs:
 - Mepolizumab: There were 154 pregnancy-related reports for mepolizumab. Compared to non-biologic asthma medications, mepolizumab showed higher reporting frequency for spontaneous fetal death (reporting odds ratio (ROR), 1.87; 95% confidence interval (CI) 1.05-3.36), spontaneous abortion (ROR, 2.75; 95% CI 1.51-5.00) and a lower frequencies for preterm birth (ROR, 0.10; 95% CI 0.03-0.34).
 - Reslizumab: There were 25 pregnancy-related reports for reslizumab. Reslizumab did not show significant differences in any specific outcomes compared to those in asthma medications other than biologics, however, the reporting frequency for reslizumab was low.

Reviewer comment:

The publications reviewed by DPMH do not suggest a clear safety signal associated with use of anti-IL-5 mAbs for the treatment of asthma during pregnancy; however, the publication by Jang et al. along with the pregnancies reported during drug development highlight the potential for an increased risk of SAB associated with anti-IL5 mAbs. Due to the lack of information about the severity of asthma in the Jang et al. publication and the lack of information from the pregnancies that occurred during drug development, the association between anti-IL5 mAbs and SABs is not clear. To obtain more information about adverse pregnancy outcomes with depemokimab, DPMH recommends a postmarketing pregnancy safety study as outlined in the Discussion and Conclusions section below.

³² Ozden G, Pinar Deniz P. May mepolizumab used in asthma correct subfertility? Ann Med. 2021 Dec;53(1):456-458. doi: 10.1080/07853890.2021.1900591. PMID: 33739210; PMCID: PMC7993371.

³³ Jang W, Jo H, Park J, Kim S, Cho H, Jeong YD, Son Y, Pizzol D, Papadopoulos NG, Yon DK. Use of Biologics to Treat Asthma during Pregnancy and Adverse Events in Pregnant Women and Newborns: A Global Pharmacovigilance Analysis. Int Arch Allergy Immunol. 2025 Jan 17:1-14. doi: 10.1159/000543490. Epub ahead of print. PMID: 39827867.

LACTATION

Nonclinical Data

According to the mepolizumab prescribing information, mepolizumab was detected in the milk of monkeys. Levels of mepolizumab in milk were $\leq 0.5\%$ of maternal serum concentration. According to the Applicant, treatment of monkeys with mepolizumab throughout pregnancy did not compromise lactation or milk production post-partum as there were no body weight effects and offspring survival was not affected.³⁴

The reader is referred to the P/T review by Dr. David Klein.

Reviewer comment:

The nonclinical data do not suggest drug-associated toxicity related to use during lactation.

Clinical Data from Drug Development

According to the Applicant, there were no reports of depemokimab exposure during lactation in any of the studies in the depemokimab program. However, depemokimab is a humanized mAb (IgG1 kappa), and IgG is present in human milk in small amounts.³⁵

Review of Literature

Applicant's review:

The Applicant did not provide a review of the literature related to anti-IL-5 mAbs and lactation.

DPMH review:

DPMH conducted a search for published human studies in PubMed and Embase, using the search terms: “anti-IL-5” or “IL-5 inhibition” or “IL-5 inhibitors” or “mepolizumab” or “reslizumab” and “lactation” and “breastfeeding.” A review by Ramos et al. was found,³⁶ but the full text was not able to be retrieved. According to the abstract for the Ramos et al. publication, “Insufficient safety data exist on mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab use during pregnancy and lactation.”

In addition, DPMH conducted a search for mepolizumab and benralizumab in Hale's *Medications and Mothers' Milk*,³⁷ Reprotox, the Drugs and Lactation Database (LactMed),³⁸ and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.³⁹ The results are as follows:

³⁴ BLA 761458, SN 0001, Module 2.4 Nonclinical Overview, p. 24.

³⁵ BLA 761458, SN 0001, Module 2.5, Clinical Overview, p. 69.

³⁶ L Ramos C, Namazy J. Monoclonal Antibodies (Biologics) for Allergic Rhinitis, Asthma, and Atopic Dermatitis During Pregnancy and Lactation. *Immunol Allergy Clin North Am*. 2023 Feb;43(1):187-197. doi: 10.1016/j.iac.2022.07.001. PMID: 36411004.

³⁷ Hale, Thomas W. *Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology*. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com

³⁸ Drugs and Lactation Database (LactMed). Accessed 5/27/25.

³⁹ Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. *Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk*. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

- Hale's related to mepolizumab: L3 – no data – presumed compatible; poorly transferred into human milk and would be poorly absorbed orally by the infant.
- LactMed related to mepolizumab and reslizumab:
 - Because they are large protein molecules, 149,000 Da (mepolizumab) and 147,000 Da (reslizumab), the amount in milk is likely to be very low.
 - They are also likely to be partially destroyed in the infant's gastrointestinal tract and absorption by the infant is probably minimal.
 - A task force of respiratory experts from Europe, Australia and New Zealand found that mepolizumab is possibly acceptable during breastfeeding and an international consensus panel concluded that if the patient is in agreement, and the risks and benefits have been discussed, asthma biologics can be initiated or continued while breastfeeding.
 - Waiting for at least 2 weeks postpartum to resume therapy may minimize transfer to the infant.
- No data were found in Briggs.

Reviewer comment:

There are no clinical data related to depemokimab use during lactation. Hale's and LactMed state that transfer to human milk and absorption by the breastfed infant is likely to be minimal for mepolizumab and reslizumab. Given that depemokimab has similar characteristics to mepolizumab and reslizumab in terms of mechanism of action, large molecular weight and poor oral absorption, transfer of depemokimab to human milk and absorption by the breastfed infant is likely to be minimal.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Data

The Applicant conducted male and female fertility and early embryofetal development studies in mice using mepolizumab.⁴⁰ In mice, a top dose of 50 mg/kg was used because it was the highest achievable dose based on the formulation. No reproductive or postnatal developmental effects were observed.

In sexually mature monkeys, there were no findings in the reproductive organs with treatment with mepolizumab or depemokimab for 6 months.⁴¹

In terms of genotoxicity, the Applicant reported that, in general, antibodies and amino acids such as depemokimab do not interact with, nor are they reactive with, DNA or other chromosomal elements and hence they are not genotoxic. For this reason, the Applicant did not conduct genotoxicity studies with depemokimab.⁴²

According to the Applicant, depemokimab is not believed to possess an inherent carcinogenic potential since humanized or human monoclonal antibodies, proteins and amino acids are not considered to be associated with cancer risks unless they cause significant immunosuppression,

⁴⁰ BLA 761458, SN 0001, Module 2.4, Nonclinical Overview, p. 23.

⁴¹ Ibid (Nonclinical Overview), p. 24.

⁴² Ibid (Nonclinical Overview), pp. 21-22.

which depemokimab does not.⁴³

The reader is referred to the P/T review by Dr. David Klein.

Drug-Drug Interactions (DDIs)

According to the Applicant, depemokimab is deemed to have a low potential for drug-drug interactions since the clearance mechanism for depemokimab is proteolytic and therefore does not overlap with those of small molecules. In addition, cytochrome (CYP) P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of depemokimab.⁴⁴

The reader is referred to the CP review by Dr. James Mease.

Reviewer comment:

The DDI information submitted by the Applicant was discussed with the CP team. The CP team agrees with the Applicant that there are no DDI concerns for depemokimab.

Clinical Data from Drug Development

There were no reports of depemokimab exposure related to fertility during the depemokimab program.

Review of Literature

Applicant's review:

The Applicant did not provide a review of the literature related to anti-IL-5 mAbs and fertility.

DPMH review:

DPMH conducted a literature search for published human studies in PubMed and Embase, using the search terms “anti-IL-5” or “IL-5 inhibition” or “IL-5 inhibitors” or “mepolizumab” or “reslizumab” and “fertility,” “contraception,” “oral contraceptives,” and “infertility.” One publication was found as follows:

- Ozden et al.⁴⁵ reported a case series in which two women with unexplained infertility were treated with mepolizumab for severe eosinophilic asthma and became pregnant. The authors concluded that unexplained infertility in people with severe eosinophilic asthma may be corrected by mepolizumab treatment but insufficient data are available regarding the use of mepolizumab during pregnancy.

Reviewer comment:

Nonclinical data suggest that depemokimab will not adversely affect fertility, is not genotoxic or carcinogenic, and will not interact with hormonal contraceptives. There are limited published clinical data that suggest that mepolizumab may improve fertility in women with unexplained infertility and severe eosinophilic asthma; however, the data are insufficient to draw conclusions.

⁴³ Ibid (Nonclinical Overview), p. 22.

⁴⁴ Ibid (Nonclinical Overview), p. 18.

⁴⁵ Ozden G, Pinar Deniz P. May mepolizumab used in asthma correct subfertility? Ann Med. 2021 Dec;53(1):456-458. doi: 10.1080/07853890.2021.1900591. PMID: 33739210; PMCID: PMC7993371.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

There are no nonclinical data related to pregnancy for depemokimab. The available nonclinical data pertain to mepolizumab. The P/T team recommends including the nonclinical data from the mepolizumab program under the Animal Data section in the labeling of subsection 8.1 for depemokimab. DPMH recommends adding a modification to the Animal Data section to address placental transfer and discussed this with the P/T team. Ultimately, DPMH and the P/T team agreed to add a statement at the end of the Animal Data section stating that the impact of the YTE modification on placental transfer is uncertain.

In terms of clinical data, there were seven human pregnancies that occurred during the depemokimab development program from which conclusions cannot be drawn. This information should be included in the labeling of subsection 8.1 as follows: “Available data from clinical trials with [TRADENAME] use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.”

Given the risks of adverse pregnancy outcomes associated with asthma, DPMH recommends a Clinical Considerations section under subsection 8.1 to align with labeling for other products indicated to treat asthma.

In terms of postmarketing requirements (PMRs), DPMH recommends issuing a descriptive pregnancy safety study (DPSS) due to uncertainty about the impact of the YTE modification on placental transfer and on the developing fetus and to evaluate for adverse pregnancy outcomes such as SAB that occurred in the reported pregnancies during drug development and were observed in mepolizumab-exposed pregnancies.⁴⁶ A DPSS is recommended instead of a pregnancy exposure registry because DPMH is not anticipating significant exposure during pregnancy based on the results of the mepolizumab registry in which only 23 subjects were enrolled and a sufficient comparative analysis could not be conducted. In addition, utilization of depemokimab was discussed with the DPACC clinical team. They explained that they do not expect depemokimab to be used preferentially over other biologic products in females of reproductive potential (FRPs) due to comparable efficacy to other marketed biologic products.

Lactation

There are no nonclinical or clinical data specific to the use of depemokimab during lactation. In the labeling of subsection 8.2, DPMH recommends the following statement to explain this lack of data: “There is no information regarding the presence of depemokimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production.” However, since depemokimab is a humanized IgG, and IgG is present in human milk in small amounts, DPMH recommends including information about the presence of IgG in milk in subsection 8.2. Finally, DPMH recommends a risk/benefit statement in subsection 8.2 because no risks have been

⁴⁶ Jang W, Jo H, Park J, Kim S, Cho H, Jeong YD, Son Y, Pizzol D, Papadopoulos NG, Yon DK. Use of Biologics to Treat Asthma during Pregnancy and Adverse Events in Pregnant Women and Newborns: A Global Pharmacovigilance Analysis. *Int Arch Allergy Immunol*. 2025 Jan 17:1-14. doi: 10.1159/000543490. Epub ahead of print. PMID: 39827867.

identified that would preclude breastfeeding. The risk/benefit statement is as follows: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for [TRADE NAME] and any potential adverse effects on the breastfed infant from depemokimab or from the underlying maternal condition.”

Based on the lack of available data and the anticipated use of depemokimab in females of reproductive potential including lactating women, DPMH also recommends issuing a PMR for a clinical lactation study (milk only) to assess concentration of depemokimab in human milk and to assess the effects on the breastfed infant.

Females and Males of Reproductive Potential

DPMH recommends omitting subsection 8.3 of depemokimab labeling. Nonclinical data suggest that depemokimab will not adversely affect fertility, is not genotoxic or carcinogenic, and will not interact with hormonal contraceptives. There are limited published clinical data that suggest that mepolizumab may improve fertility in women with unexplained infertility and severe eosinophilic asthma; however, the data are insufficient to draw conclusions. Pregnancy testing and contraception subheadings are not applicable because there are no available data to suggest depemokimab use is associated with embryo-fetal toxicity.

IV. LABELING RECOMMENDATIONS

DPMH recommends the following text for subsections 8.1 and 8.2 of labeling. DPMH discussed our labeling recommendations with DPACC on 7/17/2025. DPMH recommendations are below and reflect the discussions with DPACC. DPMH refers to the final BLA action for final labeling.

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE G KRATZ
07/29/2025 12:20:02 PM

MIRIAM C DINATALE
07/29/2025 12:41:40 PM

LEYLA SAHIN on behalf of LYNNE P YAO
07/29/2025 07:49:23 PM

HUMAN FACTORS STUDY RESULTS REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 24 , 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761458
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form and Strength:	Exdensur ^a (depemokimab-xxxx) ^b injection, 100 mg/mL
Device Constituent:	Autoinjector (AI) ^c and Prefilled Syringe (PFS) ^d
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKline LLC (GSK)
FDA Received Date:	December 16, 2024; January 16, 2025; February 12, 2025; March 21, 2025
TTT #:	2024-12147
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

^a The proposed proprietary name Exdensur was found conditionally acceptable by DMEPA 1 on January 30, 2024. PNR#2023-1044725355.

^b Since the nonproprietary name suffix has not yet been determined, the nonproprietary name placeholder, depemokimab-xxxx, is used throughout this review to refer to the non-proprietary name for this product and not intended to be included in the final labels and labeling.

^c GSK used the term "Autoinjector" (AI) in their HF validation study results report, and the term "Prefilled Pen" (PFP) in their prescribing information (PI), container label and carton labeling. However, for consistency we used the term autoinjector (AI) throughout this review.

^d GSK used the term "Safety Syringe Device" (SSD) in their HF validation study results report, and the term "Prefilled Syringe" (PFS) in their prescribing information (PI), container label and carton labeling. However, for consistency we used the term prefilled syringe (PFS) throughout this review.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results reports submitted under BLA 761458 for Exdensur (depemokimab-xxxx) injection.

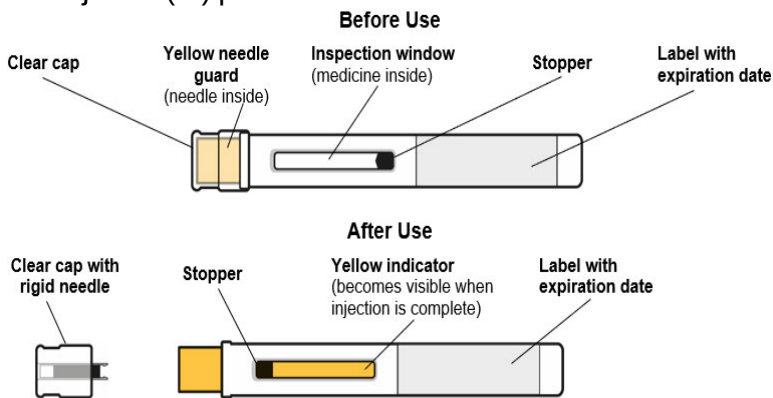
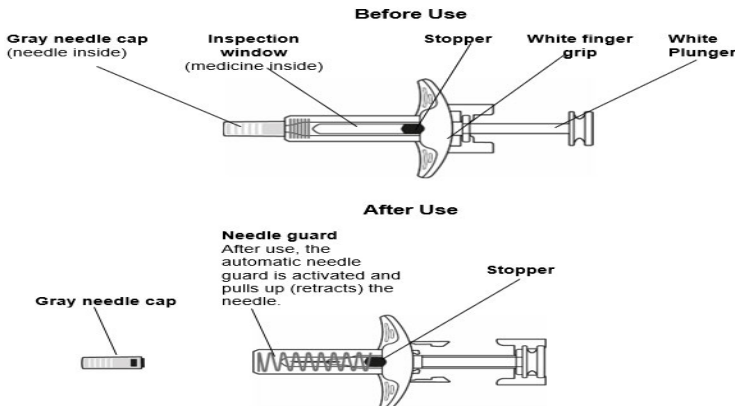
We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Considered	Section/Appendix
Product Information	Section 1.1
Relevant Regulatory History Related to the Proposed Product's Human Factors Development Program	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Labels, Labeling, and Packaging	Appendix C
Tasks Involving Use Errors, Use Difficulties, and Close Calls for Section 3.1	Appendix D

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Exdensur that GlaxoSmithKline LLC submitted on December 16, 2024.

Table 2. Relevant Product Information for Exdensur	
Initial Approval Date	N/A
Active Ingredient	Depemokimab-xxxx
Indication	Add-on-maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium-to high-dose inhaled corticosteroids (ICS) plus another asthma controller. (b) (4)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	100 mg/mL
Dose and Frequency	100 mg administered subcutaneously once every 6 months

How Supplied	100 mg/mL, single-dose, <u>prefilled pen</u> with attached 29-gauge, half-inch needle in cartons of 1 (NDC 0173-0927-31). 100 mg/mL, single-dose, <u>prefilled syringe</u> with attached 29-gauge, half-inch needle with a needle guard in cartons of 1 (NDC 0173-0927-42).
Storage	- The recommended storage condition is 36°F to 46°F (2°C to 8°C), protected from light. - The prefilled pen or prefilled syringe can be removed from the refrigerator and kept in the unopened carton, protected from light for up to 7 days at room temperature up to 86°F (30°C). Discard if left out of the refrigerator for more than 7 days. - The prefilled pen or prefilled syringe must be administered within 8 hours once the carton is opened. Discard if not administered within 8 hours. - Do not freeze. Do not shake. - Avoid exposure to heat.
Container Closure/ Device Constituent (including figure)	Prefilled pen (also referred as Autoinjector (AI)): (b) (4) 1.0 mL autoinjector (AI) platform  Before Use Clear cap, Yellow needle guard (needle inside), Inspection window (medicine inside), Stopper, Label with expiration date After Use Clear cap with rigid needle, Stopper, Yellow indicator (becomes visible when injection is complete), Label with expiration date Prefilled Syringe (PFS):  Before Use Gray needle cap (needle inside), Inspection window (medicine inside), Stopper, White finger grip, White Plunger After Use Gray needle cap, Needle guard (After use, the automatic needle guard is activated and pulls up (retracts) the needle), Stopper

Intended Users	Healthcare professionals (HCPs) In GSK's January 16, 2025 response to the Agency's January 15, 2025, information request (IR), GSK stated <i>"The HF validation studies were conducted to support all potential users globally, including HCPs. GSK would like to clarify the intended users of depemokimab injection in the US are Health Care Professionals."</i> ^e
Intended Use Environment	Clinical (i.e., Hospital or HCP Office)

1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On February 5, 2025, we searched for previous DMEPA reviews and FDA/GSK interactions relevant to this current review using the terms, "IND 146742", "depemokimab" and "BLA 761458". The identified DMEPA reviews and FDA/GSK interactions are provided below.

- On March 03, 2023, GSK submitted their HF validation study protocols for their proposed depemokimab-xxxx injection 100 mg/mL, autoinjector (AI) and prefilled syringe (PFS) under IND 146742. Furthermore, GSK notified us on October 3, 2023, via email, that they had completed their HF validation studies, but they still requested we provide feedback on their submitted HF validation study protocol.^f
 - On April 16, 2024, we finalized our high-level review of the HF validation study protocols, in which we stated, *"we have identified concerns with the methodology, for both HF validation studies, that could make interpretation of the HF study results difficult. These concerns will require you to submit additional information/data to address the data gap and deficiencies."*^g
 - On April 19, 2024, Human Factors (HF) Validation Study Protocol Advice Letter was sent to GSK.^h

^e BLA 761458 Response to Information Request. Philadelphia (PA): GlaxoSmithKline LLC. 2025 JAN 16. Available from: [\CDSESUB1\EVSPROD\bla761458\0003\m1\us\111-information-amendments\response-ir-15jan25.pdf](https://cdsesub1\evsprod\bla761458\0003\m1\us\111-information-amendments\response-ir-15jan25.pdf)

^f Attinello, C. FW: [EXTERNAL] IND 1466742 depemokimab HF Validation Study Protocols. Silver Spring (MD): FDA, CDER, OSE (US); IND 146742; 2024 JAN 03. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80717458>

^g Barlow, M. Memorandum Human Factors Validation Study Protocol for depemokimab-xxxx injection (IND 146742). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2024 APR 16. TTT No.: 2023-3995.

^h Attinello, C. Human Factors Validation Study Protocol Advice for depemokimab-xxxx injection (IND 146742). Silver Spring (MD): FDA, CDER, OSE, PMS (US); 2024 APR 19. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8073c9dd>

- o On May 17, 2024, GSK submitted their Response to HF Validation Study Protocol Advice dated April 19, 2024.ⁱ
- o On June 24, 2024, we finalized our review of GSK's Response to HF Validation Study Protocol Advice in which we concluded that *"the Applicant responded to each of our recommendations and confirmed that they will provide the requested data in their planned marketing application. We find their plan to be acceptable and we have no additional recommendations at this time."*^j
- On December 16, 2024, GSK submitted their HF validation study results reports under BLA 761458 for their proposed Exdensur (depemokimab-xxxx) injection 100 mg/mL, AI and PFS, which are the subject of this review.

2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study (HFVS) design and our discussion of methodology concerns (as applicable). See Appendix A for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study for Autoinjector and Prefilled Syringe	
Study Design Elements	DMEPA Discussion of Methodology Concerns
User Group(s)	
Autoinjector Study: A total of 105 participants representative of the intended user groups (Patients, Caregivers and HCPs) participated in the validation study. • 30 Adolescent (12-17 years old) Asthma or Surrogate Condition Patients: - o Injection Experienced (EXADP*): n=15 - o Injection Naïve (NADP*): n=15 • 30 Adult Asthma Patients: - o Injection Experienced (EXAP*): n=15 - o Injection Naïve (NAP*): n=15	We note that in the HF validation study results reports the proposed intended users of the proposed product (AI and PFS) are patients, their caregivers, and HCPs. However, the Prescribing Information (PI) (b) (4) of GSK's draft labelling states "EXDENSUR (b) (4) be administered by a healthcare professional" (b) (4). (b) (4). To clarify this discrepancy in the intended users of the proposed product, on January 15, 2025, the Agency sent an

ⁱ IND 1466742 Response to HF Validation Study Protocol Advice. Philadelphia (PA). GlaxoSmithKline LLC. 2024 MAY 17. Available from: [\\CDSESUB1\EVSPROD\ind146742\0157\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5354-other-stud-rep\hf-protocol\depemokimab-fda-response-to-human-factors-advice-april-2024.pdf](#)

^j Barlow, M. Memorandum Response to Human Factors Advice for depemokimab-xxxx injection (IND 146742). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2024 JUN 24. TTT No.: 2023-3995-1.

Table 3. Study Methodology for Human Factors (HF) Validation Study for Autoinjector and Prefilled Syringe

Study Design Elements	DMEPA Discussion of Methodology Concerns
30 Caregivers who care for/ support Asthma or Surrogate Condition: - Injection Experienced tested (EXCG*): n=15 - Injection Naïve tested (NCG*): n=15 15 Healthcare Professionals – Nurses (HCP) *GSK’s acronyms: Naïve Adolescent Patient Participant (NADP); Naïve Adult Patient (NAP); Naïve Caregiver Participant (NCG); Experienced Adolescent Participants (EXADP); Experienced Adult Patient Participant (EXAP); Experienced Caregiver Participant (EXCG) Prefilled Syringe Study: A total of 91 participants, representing distinct user groups (patients and caregivers) participated in the validation study. Further GSK stated, “<i>Out of scope were HCPs, who have not been included in this study because due to their professional background it is expected they have extensive expertise in administering injections with SSD or similar injector devices.</i>” 31 Adolescent (12-17 years old) Asthma or Surrogate Condition Patients: - Injection Experienced (EXADP): n=16 - Injection Naïve (NADP): n=15 30 Adult Asthma Patients: - Injection Experienced (EXAP): n=15 - Injection Naïve (NAP): n=15 30 Caregivers who care for/ support Asthma or Surrogate Condition: - Injection Experienced tested (EXCG): n=15 - Injection Naïve tested (NCG): n=15	information request (IR) to GSK. On January 16, 2025, GSK submitted their response to the IR in which GSK stated that “<i>The HF validation studies were conducted to support all potential users globally, including HCPs. GSK would like to clarify the intended users of depemokimab injection in the US are Health Care Professionals.</i>”^k As per the aforementioned clarification by GSK, the intended users of the proposed product are HCPs only, therefore we do not have any comments regarding the patient or caregiver user populations included in both of the HF validation studies. We note that HCPs were not included in the HF study for the PFS presentation, based on our review of the use-related risk analysis for the PFS, we agree with GSK’s approach and justification for not including HCPs in the HF validation study for the PFS presentation. See Section 3.3 for additional details.
Training	
The study participants did not receive any training.	
Test Environment & Materials	
The test rooms, used in the study included a table to represent a kitchen table, a refrigerator, and a chair where the participant could sit while giving themselves or the manikin an injection. For the caregiver participants, a manikin, simulating the patient, was situated in a spare chair. Supplemental injection supplies (i.e.: alcohol wipes, cotton buds, gloves, plasters, sharps container) as indicated in the	

^k BLA 761458 Response to Information Request. Philadelphia (PA): GlaxoSmithKline LLC. 2025 JAN 16. Available from: <https://cdsesub1.evspod\bla761458\0003\m1\us\111-information-amendments\response-ir-15jan25.pdf>

Table 3. Study Methodology for Human Factors (HF) Validation Study for Autoinjector and Prefilled Syringe	
Study Design Elements	DMEPA Discussion of Methodology Concerns
IFU associated with the use scenario were made available to the participants. Alcohol gel was provided to replace a sink for the participant to wash their hands.	
Sequence of Study	
1. Study Orientation 2. Product Differentiation (between Nucala and depemokimab) 3. Procedure Based Assessment (IFU optional) 4. Procedure Based Assessment Debrief 5. Knowledge Based Assessment (IFU optional) 6. Knowledge Based Assessment Debrief 7. Close Session	

3 RESULTS AND ANALYSIS

We note GSK included the lay user participant user groups (i.e., adult patient user groups, pediatric patient user groups, and caregiver user groups) as well as HCP user groups. However, based on GSK's January 16, 2025 information request (IR) response confirming they intend this product to be only administered by HCPs, our review of the HF validation study results focused on the HCP data (i.e., use issues, subjective feedback, and root cause analysis). Thus, we did not review the lay user participant data provided in HF validation study results reports for AI and PFS presentations.

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), GSK's URRAs, the HCP participants' subjective feedback, GSK's RCA, and GSK's comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. We provide a discussion of the identified use tasks below where we agree with GSK's conclusions and have no further recommendation or comment.

3.1 ANALYSIS OF THE IDENTIFIED ISSUES FOR AUTOINJECTOR

The HF validation study report showed issues with the tasks evaluated by simulated use and knowledge task assessments. Based on our review of the available assessment of the identified issues, the available HCP participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), GSK's root cause analysis, GSK's post-HF validation study mitigations, and our evaluation of the residual risks, we find the proposed user interface has been appropriately designed. We did not identify recommendations to address the identified issues with the tasks in Appendix D, and we find that the labels and labeling mitigations in place support the safe and effective use of the product.

3.2 HF VALIDATION STUDY RESULTS FOR PREFILLED SYRINGE

Per GSK, HCPs were not included in the HF validation study for the proposed product's PFS presentation because of their professional background and experience of using PFS and similar injection devices.

GSK submitted a URR for their proposed product.

We reviewed the URR for the proposed product and, based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what GSK proposes for the design and intended use of this product. We did not identify any additional use-related issues that were not analyzed, and we determined the risks are mitigated by the proposed labels and labeling.

4 LABELS AND LABELING

We note GSK submitted (b) (4) per GSK's clarification that the intended users for the proposed product are only HCPs, (b) (4). We provide our recommendations for the labels and labeling in Section 5 below.

We note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under separate cover and label and labeling comments have been sent to GSK based on the outcome of that review.¹

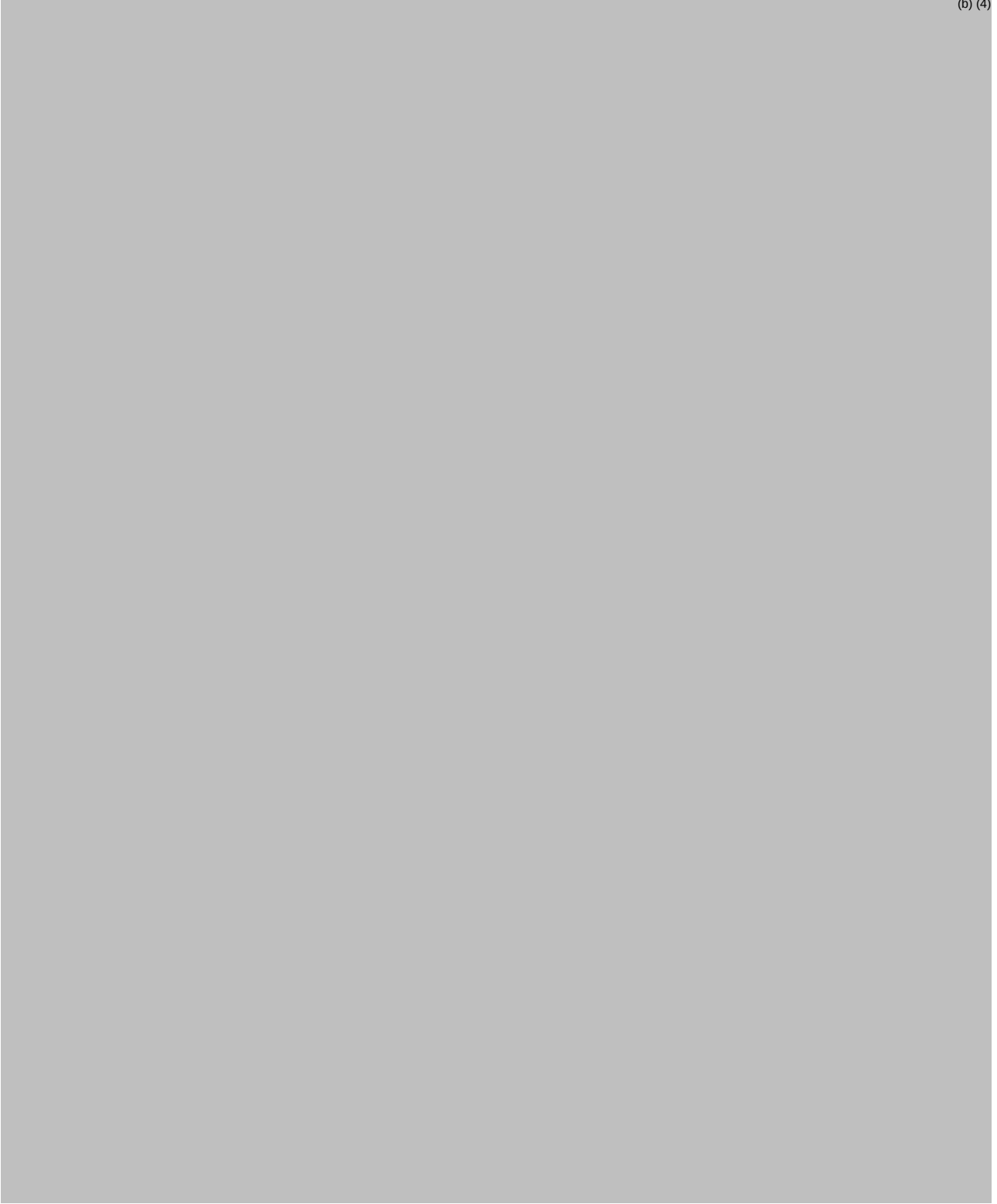
5 RECOMMENDATIONS FOR DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

GSK included (b) (4) As discussed previously, GSK clarified that HCPs are the intended users for the proposed product. (b) (4). Additionally, below, we have provided our recommendations to the proposed PI's section "2.4 Preparation

¹ Pringle-Owens, L. Label and Labeling Review for Exdensus (depemokimab-xxxx) injection (BLA 761458). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2025 APR 28. TTT No.: 2025-12444.

and Administration Instructions for EXDENSUR” for the division. These changes can be implemented without submitting additional HF validation testing results for Agency review.

(b) (4)



6 CONCLUSION

The results of the HF validation study for the autoinjector presentation of the proposed product demonstrated several use errors, close calls, and use difficulties with critical tasks that may result in harm. However, based on our review of the available HCP participants' subjective feedback, and root cause analysis and GSK's post-HF validation study mitigations, we did not identify additional risk controls to address the use errors, close calls, and use difficulties. Further, for the PFS presentation, based on our review of the URRRA, we find that the tasks evaluated appear to be comprehensive and appropriate for the design and intended use and intended users of the proposed product's PFS presentation, and we did not identify any additional use-related issues that were not analyzed.

Thus, based on our overall review, we find that the risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. As such, we have no HF recommendations for this marketing application.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report and background information for Autoinjector can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761458\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5354-other-stud-rep\human-factors\gsk-design-validation-report-autoinjector.pdf>
- The HF study results report and background information for Prefilled Syringe can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761458\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5354-other-stud-rep\human-factors\gsk-design-validation-report-safety-syringe-device.pdf>
- The use-related risk analysis for Autoinjector (AI) and Prefilled Syringe (PFS) (received on February 12, 2025, as a response to IR) can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761458\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5354-other-stud-rep\human-factors\depemokimab-safety-syringe-device-ssd-ai-ufmea.xlsx>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 15, 2025, DPACC issued an Information Request (IR) requesting to clarify the intended user of the proposed product. On January 16, 2025, GSK provided a response that can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761458\0003\m1\us\111-information-amendments\response-ir-15jan25.pdf>

On February 10, 2025, we issued an Information Request (IR) to submit the URRAs for the AI and PFS presentations. On February 12, 2025, GSK provided a response that can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761458\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\asthma\5354-other-stud-rep\human-factors\response-to-human-factors-ir-february-2025.pdf>

On March 19, 2025, we issued an IR to submit HF validation study protocol and moderator script for each of the HF validation study results reports submitted. On March 21, 2025, GSK provided a response that can be accessed in EDR via: <\\CDSESUB1\EVSPROD\bla761458\0015\m1\us\111-information-amendments\response-human-factors-ir-19mar2025.pdf>

APPENDIX C. LABELS, LABELING, AND PACKAGING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^m along with postmarket medication error experiences with similar products, we reviewed the following Exdensusur labels and labeling submitted by GlaxoSmithKline LLC .

- Container label(s) received on December 16, 2024
- Carton labeling received on December 16, 2024
-  (b) (4)
- Prescribing Information (Image not shown) received on December 16, 2024, available from: <\\CDSESUB1\EVSPROD\bla761458\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf>

C.2 Label and Labeling Images

Container label for Autoinjector:



^m Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX D. TASKS INVOLVING USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FOR SECTION 3.1

- AI simulated use tasks:
 - o Peel the sealed tray
 - o Wash hands
 - o Remove clear cap—User does not touch the yellow needle guard: One HCP participant encountered a use error with this task, specifically this participant touched and moved the yellow needle guard. GSK stated that, “Participant (b) (6) explained that they thought the (b) (4) (b) (4) had to align with the (b) (4) on the yellow needle guard to unlock the device before injecting as they have seen “locking mechanisms that you have to engage” on other devices. Participant stated that if the (b) (4) was not in line with the inspection window, they would not have noticed it. The participant realized when the needle guard did not turn, that they just needed to be pushed against the injection pad to be actuated.” The root cause analysis indicated that the use error was due to negative transfer of knowledge (previous experience with other devices which require an unlocking mechanism before administration of an injection). Further to note, this participant did not use the IFU. Based on our review of the subjective feedback, root cause analysis, and user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
 - o Position the device at a 90-degree angle: Three HCP participants encountered a use error with this task, specifically they pinched the skin during the injection. The root cause analysis indicated that the use error was due to negative transfer of knowledge (participants past experience/training they were taught/learned to pinch the skin and applied this experience to this device). Further, to note, one participant used the IFU, and the two other participants did not use the IFU. Based on our review of the subjective feedback, root cause analysis, and user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
 - o Ensure the inspection window is visible: One HCP participant encountered a use error with this task, specifically the participant did not ensure the inspection window was visible during the injection. GSK stated that, “Participants (b) (6), (b) (6) stated that they were not aware that there was an inspection window on the device until the second injection and that they were not familiar with autoinjectors that had inspection windows, so did not think to look for an inspection window on this device.” Further, GSK stated that, “Participant (b) (6) suggested making the inspection window larger to catch their attention.”

The root cause analysis indicated that the use error was due to *“device design is not intuitive – participants’ attention was not drawn to the inspection window, so they did not ensure it was visible to them.”* Further to note, the HCP participant did not use the IFU. Additionally, we note that the proposed GSK’s AI device used (b) (4) 1.0 mL autoinjector is a platform device. Based on our review of the subjective feedback, root cause analysis, and user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

- o Hold pen down firmly against the skin until injection is complete: Two HCP participants encountered two use errors with this task, specifically one participant (b) (6) lifted the device before the injection was complete, and the other participant (b) (6) lifted the device prematurely. GSK stated that, *“Participant (b) (6) stated they initially thought the injection was complete because they had ‘pushed’ the device, which is all they need to do with their current device.”* Further GSK stated that, *“Participant (b) (6) stated that they would expect to see information about how long they should hold the device down for on the carton.”* Additionally, GSK stated that, *“Participant (b) (6) was aware that they did not deliver their full dose and stated that they did not look at the inspection window or focus on the clicks during the injection. They explained that they believed the injection would have been quicker based on their experience with other devices and assumed this would be the same.”* The root cause analysis indicated that the use errors were due to negative transfer of knowledge (participants assumed that this device would work the same as their current/past devices). Further to note, both of the HCP participants did not use the IFU. Based on our review of the subjective feedback, root cause analysis, and user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
 - o Dispose of the needle cap in sharps disposal.
- Knowledge task assessment:
 - o Where should you store the device? Answer: store at room temperature for maximum 7 days and/or store in a refrigerator in the original carton until you are ready to use it.
 - o Between what temperatures should you store the device? Answer: The carton can be stored at room temperature for a period of 7 days prior to opening or in a refrigerator between 36°F to 46°F (2°C to 8°C).
 - o How long can a carton be kept at room temperature for? Answer: The carton can be stored at room temperature for a period of 7 days prior to opening.

- o If you take the device out of the carton, what is the maximum amount of time you can leave the device out of the carton? Answer: The device can be stored at room temperature for a period of 8 hours out of the carton, before use.
- o What should you check on the device packaging before use? Answer: Check the expiration date.
- o What, if anything, should you check about the liquid medication appearance before using it. Answer: check if the medication is clear and colorless.
- o What should you do if you see (b) (4) in the medication? Answer: You don't need to do anything about it.
- o What should you do after removing the device from the refrigerator? Answer: allow the device to warm up to room temperature for 30 minutes.
- o Why do you need to wait for 30 minutes? Answer: Cold medicine is more painful to inject.
- o Where should you place the device while you wait? Answer: on a clean, flat surface.
- o What methods are inappropriate for warming the device? Answer: microwave, hot water, or direct sunlight.
- o Where are the allowable injection sites for this device and medication? Answer: into the upper arm, thigh, or abdomen.
- o If you needed another injection to complete the dose, where would you next inject? Answer: not within 2 inches (5 cm) of the belly button.
- o What should you do if you see a droplet of medication at the end of the needle, prior to administering the injection. Answer: This is normal. Nothing to do.
- o Once you have removed the clear cap from the device, how long can the device be uncapped for before it's no longer safe to use? Answer: less than 5 minutes.
- o What should you do if the needle guard does not slide up into the pen? Answer: Dispose of the pen.
- o What are the indicators that signal the injection is complete? Answer: the second click, the inspection window is filled with the yellow indicator and the black stopper has stopped moving.

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/s/

AVINASH KONKANI
07/24/2025 12:11:19 PM

MATTHEW J BARLOW
07/24/2025 12:33:38 PM

JASON A FLINT
07/24/2025 12:56:19 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 28, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761458
Product Name, Dosage Form, and Strength:	Exdensur (depemokimab-xxxx) ^a injection, 100 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	GlaxoSmithKline, LLC (GSK)
FDA Received Date:	December 16, 2024
TTT ID #:	2025-12444
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP

^a The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder depemokimab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

As part of the approval process for Exdensur (depemokimab-xxxx) injection, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Exdensur Prescribing Information (PI), Patient Package Insert (PPI), (b) (4) container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Exdensur Prescribing Information (PI), Patient Package Insert (PPI), (b) (4) container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Pulmonology, Allergy, and Critical Care (DPACC) in Section 4 and for GlaxoSmithKline, LLC in Section 5.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and, based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR THE DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

Table 2. Identified Issues and Recommendations for the Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The nonproprietary name suffix is denoted by the placeholder “-xxxx”.	An undefined nonproprietary name suffix placeholder may lead to identification medication errors.	Replace “-xxxx” with the conditionally acceptable nonproprietary name suffix when it is determined.
Full Prescribing Information – Section 2 Dosage and Administration			

Table 2. Identified Issues and Recommendations for the Division of Pulmonology, Allergy, and Critical Care (DPACC)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, under the heading, (b) (4) the route of administration is abbreviated as “SC”.	Presenting the route of administration as an abbreviation may lead to misinterpretation of the intended route of administration.	We recommend revising “SC” to “subcutaneous”.
2.	(b) (4)		
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the route of administration is abbreviated as “SC”.	Presenting the route of administration as an abbreviation may lead to misinterpretation of the intended route of administration.	We recommend revising “SC” to “subcutaneous”.
Patient Package Insert (PPI)			
1.	The nonproprietary name suffix is denoted by the placeholder “-xxxx”.	An undefined nonproprietary name suffix placeholder may lead to	Replace “-xxxx” with the conditionally acceptable nonproprietary name suffix when it is determined.

^b <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dosage-and-administration-section-labeling-human-prescription-drug-and-biological-products-content>

Table 2. Identified Issues and Recommendations for the Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		identification medication errors.	
(b) (4)			

5 RECOMMENDATIONS FOR GLAXOSMITHKLINE, LLC

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

Table 3. Identified Issues and Recommendations for GlaxoSmithKline, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The nonproprietary name suffix is denoted by the placeholder “-xxxx”.	An undefined nonproprietary name suffix placeholder may lead to identification medication errors.	Replace “-xxxx” with the conditionally acceptable nonproprietary name suffix when it is determined.
2.	The route of administration statement contains the word (b) (4)	We reserve the use of the word (b) (4) when there is a (b) (4)	We recommend revising the route of administration statement so that it reads “For subcutaneous use”.
Container Label (Prefilled Pen)			
1.	The route of administration is not present on the principal display panel.	Failure to include the route of administration on the principal display panel may lead to wrong route errors.	We recommend relocating the route of administration [“For subcutaneous use”] to the principal display panel of the prefilled pen.
Carton Labeling			

Table 3. Identified Issues and Recommendations for GlaxoSmithKline, LLC
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The placement of the (b) (4) competes with the legibility of the proprietary name, which may lead to misinterpretation because (b) (4) in the proprietary name or detract from legibility.	(b) (4) can lead to misinterpretation of the proprietary name.	Consider relocating or decreasing the prominence of (b) (4)

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Exdensur received on December 16, 2024 from GlaxoSmithKline, LLC.

Table 4. Relevant Product Information for Exdensur	
Initial Approval Date	N/A
Nonproprietary Name	depemokimab-xxxx
Indication	Add-on maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium- to high-dose inhaled corticosteroids (ICS) plus another asthma controller. (b) (4)
Dosage Form	injection
Strength	100 mg/mL
Route of Administration	subcutaneous
Dose and Frequency	- Asthma: 100 mg administered subcutaneously once every 6 months. (b) (4)
How Supplied	100 mg/mL, single-dose, pre-filled pen with attached 29-gauge, half-inch needle in cartons of 1 (NDC 0173-0927-31). 100 mg/mL, single-dose, pre-filled syringe with attached 29-gauge, half-inch needle with a needle guard in cartons of 1 (NDC 0173-0927-42).
Storage	The recommended storage condition is 36°F to 46°F (2°C to 8°C), protected from light. Do not freeze.
Container Closure	Pre-filled Pen: The autoinjector employs the Pre-Filled Syringe (PFS) as the primary container closure. Pre-filled Syringe: The primary container closure is a prefilled syringe (PFS).

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

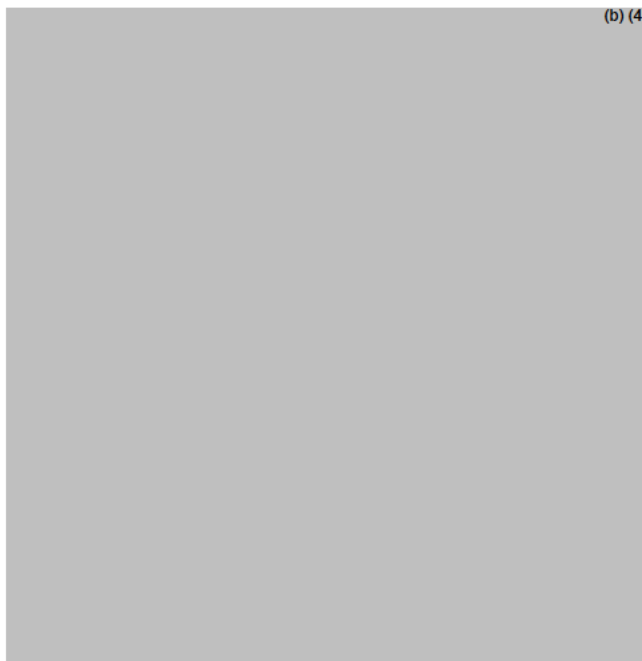
Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Exdensur labels and labeling submitted by GlaxoSmithKline, LLC.

- Prescribing Information received on December 16, 2024, available from <\\CDSESUB1\EVSPROD\bla761458\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf>
- Patient Package Insert received on December 16, 2024, available from <\\CDSESUB1\EVSPROD\bla761458\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf>
-  (b) (4)
- Container labels received on December 16, 2024
- Carton labeling received on December 16, 2024

B.2 Container Labels and Carton Labeling Images

Container Labels:

Prefilled Pen



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISSA C PRINGLE-OWENS
04/28/2025 10:52:38 AM

DAMON A BIRKEMEIER
04/28/2025 12:23:10 PM

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 3/20/2025

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761458

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS received an inspection request consult from the Office of Immunology and Inflammation (OII) on January 7, 2025, for the below site. OSIS determined that an inspection or remote regulatory assessment (RRA) is not needed for the site. The rationale for this decision is noted below.

Although OSIS has no inspection history for the site, OSIS has planned an inspection for another clinical site listed on the consult. Notably the selected clinical site enrolled a large number of subjects for the study.

As such, an inspection of the site below is not possible at this time.

Site

Facility Type	Facility Name	Facility Address
Clinical	PPD Development, L.P.	100 West Gore Street, Suite 202, Orlando, FL

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/s/

NICOLA M FENTY-STEWART
03/20/2025 09:59:04 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/26/2025

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: BLA 761458

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

PPD Development, L.P., Austin, TX: The Office of Inspections and Investigations (OII) conducted an inspection for the clinical site in October 2024. The inspection was conducted under the following submission: NON-RESPONSIVE.

OSIS concluded that data from the reviewed studies were reliable.

PPD Development, L.P., Las Vegas, NV: OII conducted an inspection for the clinical site in June 2022. The inspection was conducted under the following submission: NDA 216951.

OSIS concluded that data from the reviewed studies were reliable.

(b) (4) OSIS conducted an inspection for the analytical site in (b) (4) The inspection was conducted under the following submission: NON-RESPONSIVE

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	PPD Development, L.P.	7551 Metro Center Drive, Suite 200, Austin, TX
Clinical	PPD Development, L.P.	8285 West Arby Avenue, Suite 331, Las Vegas, NV
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
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