

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761367Orig1s000

OTHER REVIEW(S)



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Instructions		Submission Information	
Date	4/30/2025		
To:	HANNAH LEE		
Requesting Center/Office	CDER/OPQ	Clinical Review Division	Other
From	Sarah Hanif OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA761367, Garadacimab (CSL 312) ICC2500027 Case 01042826		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. 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 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. 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: Click or tap to enter a date. 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)

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA761367
Sponsor	CSL Behring LLC
Drug/Biologic	Garadacimab (CSL 312)
Indications for Use	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Device Constituent	Pre-Filled Syringe with NSD and Autoinjector
Related Files	ICC2300938 – complete review
	ICC2300621- Facilities review. ICC2400990 – meeting request to discuss CR letter comment

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](#).

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:

Under the previous review, CDRH had the following CR comment that was relayed to the sponsor (Note that the following comment was listed as a non-CR comment, but during an internal meeting CDER decided that the non-CR comment should be included in the CR letter):

Comment #:

In an Information Request (IR) dated January 29, 2024, FDA requested device performance testing (either real time or accelerated aged testing) on a total of 3 batches of the subject prefilled syringe (PFS) with needle safety device (NSD) to include dose accuracy, peak force, injection force, and NSD activation force to demonstrate that the device will perform as intended to the end of its proposed shelf life of 36 months. The Agency also requested testing for a total of 3 batches of the subject autoinjector (AI) to include dose accuracy, injection time, activation force, extended needle length, and lockout force to demonstrate that the device will perform as intended to the end of its proposed shelf-life of 36-months. In the response dated February 5, 2024, it is noted that two additional batches of CSL 312 DP NSD and CSL 312 DP AI will be placed on stability and this data will be provided in an annual report. In your resubmission, please provide the results of the additional stability data rather than in an annual report.

The sponsor provided their response to the comment and included accelerated aging data for T12. They also stated that they will report the T36 data with their annual report. **This is acceptable. No concerns remain from CDRH perspective.**

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	

3. PURPOSE/BACKGROUND

3.1. Scope

CSL Behring LLC is requesting approval of Garadacimab. The device constituent of the combination product is a Pre-Filled Syringe with NSD and Autoinjector presentation.

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

The Applicant proposes to formulate a prefilled syringe (PFS) with a needle safety device (NSD) and a PFS with an autoinjector (AI). We kindly request CDRH's review and feedback for both PFS with NSD and AI presentations. We kindly request CDRH technical engineering/device design consult review by 04/30/2025. The review due date is tentative. If possible, we kindly request the previous assigned CDRH assessor, Shruti Mistry and Janice Ferguson, who were assigned to the previous CDRH technical engineering/ device design consult (ICCR #00950756).

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](#):

Device performance PFS/AI
Stability-device performance PFS/AI
Essential Performance Requirements (EPR) PFS/AI
Quality Assessment

This review will not cover the following review areas:

- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors (deferred to DMEPA)

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](#)

This is a resubmission. The device was previously reviewed in August 2023 under ICC2300938, ICCR00950756. Lead Reviewer was Janice Ferguson. CDRH had Information Requests at the Mid-Cycle. Final recommendation was that the device constituents of the combination product were approvable with a non-CR comment included in the CR letter. The comment asked for more information on their stability data.

3.2.1. [Related Files](#)

ICC2300938 – complete review
ICC2300621- Facilities review.
ICC2400990 – meeting request to discuss CR letter comment
IND139936 – related IND

3.3. Indications for Use

Combination Product	Indications for Use
Garadacimab (CSL 312)	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Pre-Filled Syringe with NSD and Auto-injector	Delivery of the Drug Product

4. DEVICE DESCRIPTION

4.1. Device [Description](#)

CSL312 (garadacimab) was developed as a combination product for subcutaneous (SC) administration.

The formulated CSL312 active substance is presented as a sterile liquid solution in a (b) (4) is defined as the CSL312 SFP 200mg. After assembly of the CSL312 semifinished product (SFP) 200mg with the plunger rod, extended finger flange, and NSD, the final combination product is manufactured, which is referred to as CSL312 DP 200 mg NSD. The CSL312 DP 200 mg AI refers to the CSL312 SFP 200 mg assembled into the AI.

The CSL312 DP 200 mg NSD and CSL312 DP 200 mg AI include protection from needle-stick injury. The CSL312 DP 200 mg AI includes an automated injection system. Both DP presentations are intended to administer the same single fixed dose of the CSL312 SFP 200 mg. The AI for CSL312 is a customized version of the (b) (4).

The CSL312 DP 200 mg NSD was used in the phase 3 clinical studies (Study CSL312_3001 and Study CSL312_3002). As of June 2023, the CSL312 DP 200 mg AI was introduced to patients enrolled in the ongoing Study CSL312_3002 following completion of the PK Study CSL312_1004 in adherence to the previous recommendation by the Agency. CSL submitted both versions of the combination product for review by the Agency as part of the original BLA 761367 in 2023.

CSL Behring is requesting approval of Garadacimab (CSL312). The drug product will be provided in two device presentations.

- A Prefilled Syringe (PFS) 200 mg assembled with a needle safety device (NSD)
- An Auto-injector (AI) 200 mg which also has a needle safety feature.

Both devices begin with the CSL312 Semi-Finished Product (SFP) 200mg, (b) (4). The (b) (4) is added to the syringe to make the CSL312 DP200 mg NSD or assembled with the (b) (4) to make the CSL312 DP200mg AI. Both presentations contain a fixed subcutaneous dose 200 mg/1.2 mL of drug product.

Figure 2 Schematic Representation of the Device Assembly Process with the CSL312 SFP 200 mg to Manufacture CSL312 DP 200 mg NSD or CSL312 DP 200 mg AI



Pre-filled Syringe CSL312 DP200 mg with Needle Safety Device (NSD)

Figure 3.2.P.3.3-1 CSL312 DP 200mg NSD assembly content (schematic representation)



Figure 2.3.R.3-1 CSL312 DP 200mg NSD before (left) and after (right) conclusion of the injection



Table 3.2.P.7-1 Device Components used for the CSL312 DP 200mg NSD

Item	Attribute	Description
CSL312 SFP 200mg ^a	Section 3.2.P.7-CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.	
Plunger rod ^{b,c}	(b) (4)	
Needle safety device ^{b,c}		
Extended finger flange ^{b,c}		

a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
b Not in contact with the liquid.
c Direct contact with user.

Needle Safety Component ((b) (4))

(b) (4)

(b) (4)

With this submission, the following design changes were included:

1. Increased fill volume from (b) (4) mL to (b) (4) mL – (b) (4). Dose accuracy, the only ERP impacted by the volume change, was re-assessed with three batches after the design change.

Auto-injector (CSL312 DP200mg AI):



Figure 2.3.R.3-1 CSL312 DP 200mg AI (without the label)



Figure 2 CSL312 Autoinjector (AI)

Figure 3.2.R.3.2-2 CSL312 DP 200mg AI Operating Position for Injection and Post-injection Safe State

(b) (4)



Table 3.2.P.7-1 Components for the Autoinjector used for CSL312 DP 200mg AI

Item	Attribute	Description
CSL312 SFP 200mg ^a		Section 3.2.P.7-CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.
(b) (4)		

- a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
b Not in contact with the liquid.
c Direct contact with user.

Figure 3.2.P.2.4-1 Components of CSL312 DP 200mg AI



4.2. Design Requirements

Basic Syringe Description/Requirements

Requirement	Reviewer Comment
-------------	------------------

Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-administration, caregiver
Injection Site	Arms for caregiver only Abdomen and thigh for self-administration
Injection tissue and depth of injection	(b) (4) mm (b) (4) mm
Type of Use (e.g. single use, disposable, reusable, other)	Single-use
Environments of use (e.g. home, clinic)	Home and clinic
Storage conditions and expiry	Between 2C and 8C, 36 month shelf-life
Needle connection (e.g. luer, slip tip, staked)	(b) (4)
Syringe Volume	(b) (4) mL
Device materials including lubricant	Glass syringe, (b) (4) plunger rod, (b) (4) and stainless steel NSD.



Simulated Use Study for NSD:



(b) (4)



4.3. Steps for Using the Device

Pre-filled Syringe NSD

(b) (4)



4.4. 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 has been adequately described. The steps for administering the drug via the PFS/NSD and the Autoinjector are provided. The instructions are adequate; however, we defer to DMEPA for the acceptability of the final labeling.								
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: Yes No								

5. Labeling

5.1. General Labeling Review

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		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors (deferred to DMEPA)			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

5.2. Device Specific Labeling Review

	YES	NO	N/A
Storage conditions on carton	X		
Remove syringe and Auto-Injector from the refrigerator	X		
Preparing for the Injection	X		
Cleansing of the injection site	X		
Injection of medication (including holding AI for 15 sec)	X		
Activation of needle safety feature	X		

Reviewer Comments:

The device instructions for both the Prefilled syringe and autoinjector are adequate.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by:

☐ Insert Consultant Name ; The full memo is located in [Appendix B.](#)

☒ The Lead Reviewer

Below is a summary of the review & [recommendation](#):

6.4. Labeling Review Conclusion**LABELING REVIEW CONCLUSION****Filing Deficiencies:**

☐ Yes ☒ No ☐ N/A

Mid-Cycle Deficiencies:

☐ Yes ☒ No ☐ N/A

Final Deficiencies:

☐ Yes ☒ No ☐ N/A

Reviewer Comments

The sponsor provided adequate device labeling of both the Prefilled Syringes NSD and Auto-Injector.

CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No

6. DESIGN CONTROL SUMMARY**6.1. 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:

Hazard analysis, design inputs/outputs and design verification and validation provided (See below).

6.2. Design Inputs and Outputs

(b) (4)

Reviewer Comments:

The device specifications are provided and are acceptable.

6.3. 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 D4169-16	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
IEC 62366-1:2015Applying 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)
----------------------	---------------------	----------------------

ISO 11040-4:2015 Pre-filled Syringes-Glass Barrels for Injectables	Y	Y
ISO 11040-8:2016 Prefilled Syringes-Requirements and test methods for finished prefilled syringes	Y	Y
ISO 11608-1:2022 Needle-based injection systems for medical use-Requirements and test methods-Part 1: Needle- injection systems	Y	Y
ISO 11608-3:2012 Needle-based injection systems for medical use-Requirements and test methods Par-3: Containers and integrated fluid paths	Y	NA
ISO 11608-5:2012 Needle-based injection systems for medical use- Requirements and test methods -Part 5: Automated Functions	Y	Y
ISO 23908:2011 Needle Safety	Y	Y

6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Essential Performance Requirements are provided along with appropriate standards for this device types. (PFS with NSD and Autoinjector).		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. RISK ANALYSIS

8.1. Risk Analysis

Conforms with ISO 14971:2019 Medical devices - Applications of risk management to medical devices.

8.2. Risk Management Plan

Information found in Seq. 0001 3.2.R



Reviewer Comments:

The risks assessed are appropriate for these device types. No outstanding concerns.

8.3. Hazard Analysis and Risk Summary Report

Reviewer Comments:

Risk Analysis provided for the PFS/NSD and AI in assessment provided in Seq. 0001 3.2.P.2.3.2, which outlined the potential failure modes and potential harm that can occur in the manufacturing of the Pre-filled syringe and Auto injector. A hazard analysis and risks associated with use of the device was provided in the HF study in Seq. 5.4.5.4. The potential hazards, harms and risk control measures were appropriately assessed for each device type.

8.4. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> Hazards assessed appropriately for the prefilled syringe and autoinjector device types.		
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

PREFILLED SYRINGE

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)
Deliverable Volume	$\geq$ (b) (4) mL	Y	Y	Y	Y
Peak Force (Break loose Force)	$\leq$ (b) (4) N	Y	Y	Y	Y
Injection Force (Glide Force)	$\leq$ (b) (4) N	Y	Y	Y	Y
NSD Activation Force	$\leq$ (b) (4) N	Y	Y	Y	Y
NSD Override Force	$\geq$ (b) (4) N	Y	Y	Y	Y

Reviewer Comment:

Device verification methods were described in 3.2.P.5.2 and the methods for establishing the specifications were independently validated.

Additional design verification testing was done on attributes that are not identified as EPR for the PFS/NSD such as: Needle-pull out forces per ISO 7864:2016 req. 4.12 performed (b) (4)

Rigid Needle Shield removal Force per ISO 11040-4:2015 (b) (4).

Originally the sponsor had provided stability data on two batches only. However a non-CR comment was issued asking the sponsor to provide stability data on at least 3 batches to demonstrate that the device will perform as intended to the end of its proposed shelf-life. In response to this non-CR comment, the sponsor had stated that they would be putting an additional two batches of both the NSD and the AI on stability. The data on all four batches is reported with this submission. **The sample size was adequate at 210 devices. All devices met their acceptance criteria.**

Table 3.2.R.3.1.7.2-7: Overview of Additional Two Batch EPR Stability Testing

Batch	Aging Type	Essential Performance Requirement			
		Dose Accuracy (Deliverable Volume)	Peak Force (Break Loose Force)	Injection Force (Glide Force)	NSD Activation Force
P100727019	RTA: 5°C	Table 3.2.R.3.1.7.2-8	Table 3.2.R.3.1.7.2-10	Table 3.2.R.3.1.7.2-12	Table 3.2.R.3.1.7.2-14
P100727904	RTA: 5°C	Table 3.2.R.3.1.7.2-8	Table 3.2.R.3.1.7.2-10	Table 3.2.R.3.1.7.2-12	Table 3.2.R.3.1.7.2-14
P100727019	AA: 25°C 60% RH	Table 3.2.R.3.1.7.2-9	Table 3.2.R.3.1.7.2-11	Table 3.2.R.3.1.7.2-13	Table 3.2.R.3.1.7.2-15
P100727904	AA: 25°C 60% RH	Table 3.2.R.3.1.7.2-9	Table 3.2.R.3.1.7.2-11	Table 3.2.R.3.1.7.2-13	Table 3.2.R.3.1.7.2-15

Auto-Injector

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	$\leq$ (b) (4)mL	Y	Y	Y	Y
Actuation Force	(b) (4) N	Y	Y	Y	Y
Injection Time	$\leq$ (b) (4)	Y	Y	Y	Y
Injection Depth	(b) (4)	Y	Y	Y	Y
Lock Out Force Needle Shield Override Force	$\geq$ (b) (4) N	Y	Y	Y	Y
Cap Removal Force (not listed as an EPR)	$\leq$ (b) (4) N	Y	Y	Y	Y

9.1.2 Verification of Design Inputs Evaluation

(b) (4)

9.2. Device Performance Review Conclusion

DEVICE PERFORMANCE REVIEW CONCLUSION								
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:		
Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
Reviewer Comments Provided device performance testing is adequate. Originally, the stability testing of the PFS and AI EPRs was not conducted on 3 lots at real time conditions to demonstrate the 36-month shelflife. A non-CR comment was included and the sponsor stated that they would place 2 additional batches of both the PFS and AI on stability and the results are included with the submission.. Provided test results are adequate.								
CDRH sent Device Performance Deficiency or Interactive Review Questions to the Sponsor:							Yes	No

10.APPENDIX B: FACILITIES & QUALITY SYSTEMS REVIEW

10.1. Facility Inspection Report Review

Facilities review was not part of this consult. Facilities review was completed under ICC2300937. A pre-approval inspection was recommended in November 2023 because a recent inspection had not been performed.

10.2. Quality Systems Documentation Review

N/A

10.3. 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
Reviewer Comments								
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/

FDSA BOT1
05/02/2025 04:33:59 PM
bot-userName-FDSABOT1

**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: April 23, 2025

To: Nina Phuong Ton
Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Nyedra Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): ANDEMBRY (garadacimab-gxii)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761367

Applicant: CSL Behring

1 INTRODUCTION

On 13 October 2023 CSL Behring (CSL) submitted for the Agency's review a novel BLA for CSL312 (garadacimab; FXIIa inhibitor monoclonal antibody) under BLA 761367 for the indication of prophylaxis to prevent attacks of hereditary angiodedema (HAE) in patients 12 years and older.

On 7 October 2024 , CSL received a Complete Response Letter (CRL) indicating that the application could not be approved in its present form and identified specific deficiencies to address.

On 17 December 2024, CSL resubmitted the application including addressing all deficiencies. Additionally, included with the resubmission is a change in contact for the Applicant. The nonproprietary suffix (gardacimab-gxii) and proprietary name (ANDEMBRY) were previously considered conditionally acceptable.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Critical Care (DPACC) on January 13, 2025 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ANDEMBRY (gardacimab-gxii) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed September 24, 2024.

2 MATERIAL REVIEWED

- Draft ADEMBRY (gardacimab-gxii) injection for subcutaneous use PPI and IFU received on December 17, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on April 9, 2025.
- Draft ADEMBRY (gardacimab-gxii) injection for subcutaneous use Prescribing Information (PI) received on December 17, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on April 9, 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. We reformatted the PPI and IFU] document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/

SHARON W WILLIAMS
04/23/2025 01:46:31 PM

NYEDRA W BOOKER
04/23/2025 01:57:37 PM

MEETA N PATEL
04/25/2025 06:25:37 AM

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:	April 23, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761367
Product Name, Dosage Form, and Strength:	Andembry (garadacimab-gxii) injection, 200 mg/1.2 mL
Applicant Name:	CSL Behring LLC
FDA Received Date:	December 17, 2024; April 1, 2025
TTT ID #:	2023-5433-1
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFUs) received on December 17, 2024 for their proposed Andembry (garadacimab-gxii) autoinjector (AI) and prefilled syringe (PFS). The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised IFUs for Andembry (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 human factors (HF) validation study results review.^a

2 DISCUSSION AND CONCLUSION

- Our recommendation for the Applicant to “*ensure that the [autoinjector and prefilled syringe] IFU submitted in the Application is the same as the IFU finalized in ‘Summative Study #2’*” (specifically regarding the fact that ‘Summative Study #2’ IFUs included (b) (4), but the IFUs that the Applicant submitted under this application did not):
 - The Applicant stated that, “CSL has not added the (b) (4) information back in as (b) (4) was removed from the USPI by FDA.” On March 18, 2025, we reached out to the Office of Product Quality Assessment III (OPQAI) regarding the removal of (b) (4). OPQAI confirmed that the Applicant did not (b) (4) and thus removed the (b) (4) from the IFUs and other parts of the labeling. Based in this information, we have no further comments regarding this recommendation.
- Our recommendation for the Applicant to “*Ensure that the [autoinjector and prefilled syringe] IFU leaflet can be identified. For example, in the carton, include the IFU leaflet folded such that the IFU title is face up and visible to users. For example, fold the IFU leaflet so that the upper left corner is visible upon opening the carton.*”
 - Based on the Applicant’s December 17, 2024 resubmitted IFUs, it was not clear whether the Applicant implemented this recommendation. Thus, on March 27, 2025, we sent the Applicant an information request asking the Applicant to confirm whether they implemented this recommendation. On April 1, 2025, the Applicant submitted their information request response that included their confirmation that they implemented the recommendation.^b Thus, we have no further comments regarding this recommendation.
- The Applicant implemented all of our remaining recommendations, and we have no additional recommendations at this time.

^a Kumar, N. Human Factors Study Results Review for Andembry (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 SEP 24. TTT ID: 2023-5433.

^b Response to FDA IR Dated 27Mar2025 for Andembry (garadacimab-gxii) BLA 761367. King of Prussia (PA): CSL Behring LL. 2025 APR 1. Available from: <\\CDSESUB1\EVSPROD\bla761367\0048\m1\us\111-information-amendment\clinical-info-amend.pdf>.

APPENDICES

APPENDIX A. INSTRUCTIONS FOR USE RECEIVED DECEMBER 17, 2024

The instructions for use are accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761367\0045\m1\us\114-labeling\draft-labeling-text.docx>

APPENDIX B. INFORMATION REQUEST ISSUED

On March 27, 2025, we issued an information request asking the Applicant to confirm whether they implemented our October 4, 2024 labeling comment. The Applicant provided a response on April 1, 2025 that is accessible in EDR via:

<\\CDSESUB1\EVSPROD\bla761367\0048\m1\us\111-information-amendment\clinical-info-amend.pdf>

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/

NEHA KUMAR
04/23/2025 01:25:38 PM

MATTHEW J BARLOW
04/23/2025 02:03:54 PM

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

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

Memorandum

Date: April 11, 2025

To: Nina Phuong Ton, Project Manager, DPACC

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for ANDEMBRY® (garadacimab-gxii) injection,
for subcutaneous use

BLA: 761367

In response to DPACC's consult request dated October 27, 2023, OPDP has reviewed the proposed product labeling (PI), patient prescribing information (PPI), Instructions for Use (IFU), and carton/container labeling for Andembry.

Labeling: OPDP has no comments on the proposed labeling based on the draft labeling received by electronic mail from DPACC on April 9, 2025.

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

Carton/Container: OPDP has no comments on the proposed carton and container labeling for Andembry.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

37 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

MEETA N PATEL
04/22/2025 02:54:11 PM

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:	February 28, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761367
Product Name, Dosage Form, and Strength:	Andembry (garadacimab-gxii) injection, 200 mg/1.2 mL (167 mg/mL)
Applicant Name:	CSL Behring LLC
FDA Received Date:	December 17, 2024
TTT ID #:	2023-5414-3
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

CSL Behring LLC submitted revised container labels, carton labeling, prescribing information (PI), Patient Package Insert (PPI), and Instructions for Use (IFU) received on December 17, 2024 for Andembry. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels, carton labeling, prescribing information (PI), Patient Package Insert (PPI), and Instructions for Use (IFU) for Andembry (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 REGULATORY HISTORY

On June 29, 2023, CSL Behring submitted BLA 761367. However, BLA 761367 received a refusal to file on August 28, 2023, because it was not sufficiently complete to permit a substantive review.^b

Thus, on October 13, 2023, CSL Behring submitted a Class 2 resubmission for BLA 761367. However, on October 7, 2024, the Agency issued a Complete Response (CR) letter^c due to facility inspection, microbiology, and product quality deficiencies.

Thus, On December 17, 2024, CSL Behring submitted a class II resubmission addressing the above deficiencies.

3 CONCLUSION

We evaluated the proposed Andembry container labels, carton labeling, and prescribing information (PI) and determined that they are acceptable from a medication error perspective.

However, the Patient Package Insert (PPI) and Instructions for Use (IFU) for the Autoinjector are unacceptable from a medication error perspective. As currently presented, there are instances where the nonproprietary name is referenced without a suffix. The nonproprietary name for biosimilars must include a suffix.

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

A. Patient Package Insert (PPI)

1. In instances where the PPI refers to the nonproprietary name, ensure it includes the conditionally acceptable nonproprietary name suffix, '-gxii'. Specifically, at the end of the document under the title, 'What are the ingredients in ANDEMBRY?'

^a Owens, L. Review of Revised Label and Labeling for Andembry (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 FEB 19. TTT ID: 2023-5414-2.

^b Won K. Refusal to File for garadacimab-xxxx (BLA 761367). Silver Spring (MD): FDA, CDER, OND, DPACC (US). 2023 AUG 08. Available from: <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af806ee737>.

^c Ton, P. Complete Response Letter for Andembry (BLA 761367). Silver Spring (MD): FDA, CDER, OND, DPACC (US). 2024 OCT 7. Available from: <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af807736c4>.

- B. Instructions for Use (IFU) for the Autoinjector
 - 1. In instances where the IFU refers to the nonproprietary name, ensure it includes the conditionally acceptable nonproprietary name suffix, '-gxii'. Specifically, at the top under the title, 'Instructions for Use'.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON DECEMBER 17, 2024

- Prescribing Information, Patient Package Insert, and Instructions for Use available from <\\CDSESUB1\EVSPROD\bla761367\0045\m1\us\114-labeling\annotated-draft-labeling-1-14-12.pdf>

Container Labels:

Prefilled Syringe



Autoinjector



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

LISSA C PRINGLE-OWENS
02/28/2025 03:20:07 PM

DAMON A BIRKEMEIER
02/28/2025 03:23:56 PM

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:	February 19, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761367
Product Name, Dosage Form, and Strength:	Andembry (garadacimab-gxii) Injection 200 mg/1.2 mL
Applicant Name:	CSL Behring
FDA Received Date:	September 12, 2024
TTT ID #:	2023-5414-2
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

This is a corrected review that does not change the overall recommendations of the original review dated September 24, 2024

1 PURPOSE OF MEMORANDUM

CSL Behring submitted revised container labels and carton labeling, prescribing information (PI), and Instructions for use (IFU) received on September 12, 2024 for Andembry. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Andembry (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

CSL Behring implemented all of our recommendations and we have no additional recommendations at this time.

^a Owens, L. Label and Labeling Review for Andembry (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 21. TTT ID: 2023-5414-1.

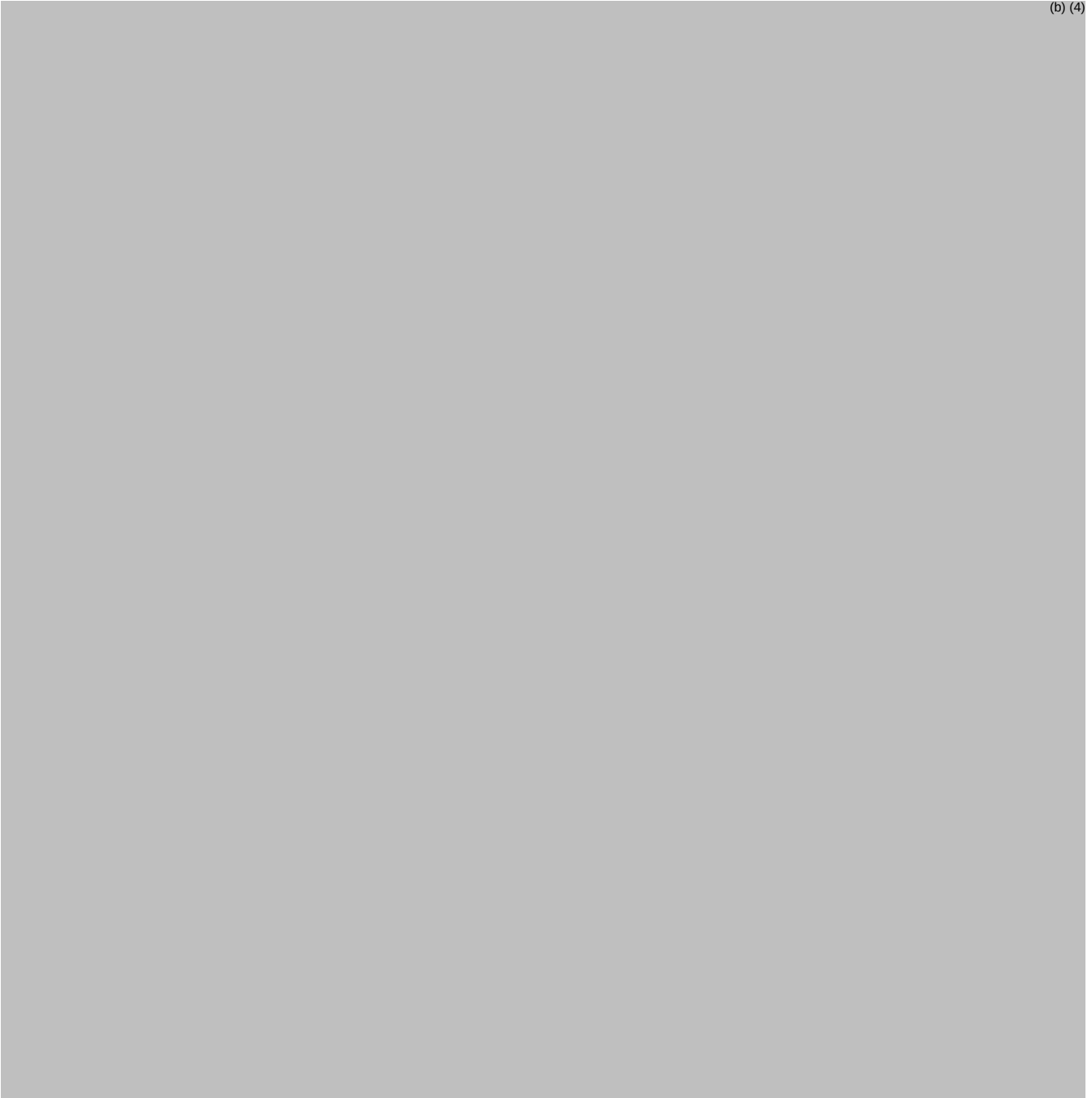
APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON SEPTEMBER 12, 2024

Prescribing Information and Instructions for Use

<\\CDSESUB1\EVSPROD\bla761367\0042\m1\us\114-labeling\annotated-draft-labeling-1-14-12.pdf>

Container Labels

(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/

LISSA C PRINGLE-OWENS
02/19/2025 04:31:45 PM

DAMON A BIRKEMEIER
02/20/2025 07:45:42 AM

HUMAN FACTORS STUDY 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:	September 24, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761367
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form ^a and Strength:	Andembry (garadacimab-gxii) ^a injection, 200 mg/1.2 mL
Device Constituent:	Autoinjector and prefilled syringe
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CSL Behring LLC
FDA Received Date:	June 29, 2023
TTT #:	2023-5433
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

^a The proprietary name, Andembry, was found conditionally acceptable on April 12, 2024 (PNR ID# 2024-1044725568) and the nonproprietary name suffix, gxii, was found conditionally acceptable on August 6, 2024 (Nexus NPNS ID# 2023-196).

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports and labels and labeling submitted under BLA 761367 for Andembry (garadacimab-gxii) injection.

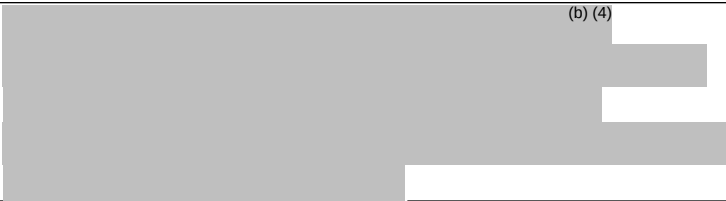
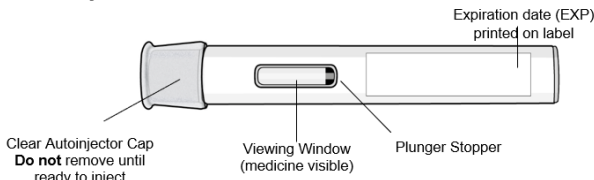
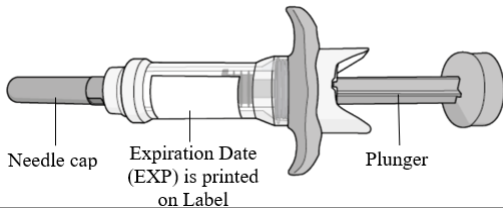
We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information	Section 1.1
Background Information Previous DMEPA HF Reviews	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 and Labeling	Appendix C
Detailed List of Use Errors, Use Difficulties, And Close Calls for Sections 3 and 5	Appendix D

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Andembry that CSL Behring LLC submitted on September 12, 2024.

Table 2. Relevant Product Information for Andembry	
Initial Approval Date	N/A
Active Ingredient	garadacimab-gxii
Indication	prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	200 mg/1.2 mL
Dose and Frequency	Initial loading dose of 400 mg (two 200 mg injections), followed by 200 mg once monthly
How Supplied	Each carton contains either one single-dose autoinjector or one single-dose prefilled syringe with needle safety device
Storage	Store the autoinjector and prefilled syringe with needle safety device refrigerated at 36°F to 46°F (2°C - 8°C).

	•  (b) (4)
Container Closure/ Device Constituent (including figure)	Autoinjector:  Prefilled syringe: 
Intended Users	Patient, caregivers, healthcare professionals (HCPs)
Intended Use Environment	Home, clinic

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

On August 26, 2024, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, “garadacimab”, “IND 139936” and “BLA 761367”. The identified reviews and FDA/Applicant interactions are provided below.

- On July 14, 2021, the Applicant submitted their garadacimab prefilled syringe HF validation study protocol for Agency review. Our review of the HF validation study protocol identified several areas of concern.^b We provided recommendations and informed the Applicant to implement all recommendations before commencing their HF validation study.
- December 15, 2021, the Applicant submitted their garadacimab autoinjector HF validation study protocol for Agency review. Our review of the HF validation study protocol identified several areas of concern.^c We provided recommendations and informed the Applicant to implement all recommendations before commencing their HF validation study.

^b Barlow, M. Human factors validation study protocol review for garadacimab prefilled syringe (IND 139936). FDA, CDER, OSE, DMEPA 1 (US); 2021 OCT 12. OSE RCM No.: 2021-1406

^c Oguntimein, O. Human factors validation study protocol review for garadacimab autoinjector (IND 139936). FDA, CDER, OSE, DMEPA 1 (US); 2022 FEB 9. OSE RCM No.: 2021-1406

- On December 22, 2022, the Applicant requested a pre-BLA meeting and asked, “Does the Agency agree with the proposed Human Factors (HF) validation package submission plan and timeline for the autoinjector (AI) including submission of the supplementary study no later than 30 days after submission of the original BLA?” We responded, “We generally expect that the submission to be complete at the time of filing. As such, we request that you submit that HF validation package for the AI presentation when you submit your original BLA for the AI presentation.”^d
- On the June 29, 2023, the Applicant submitted the Andembry autoinjector and prefilled syringe HF validation study results. The HF validation study results are the topics of this review. We note that Applicant implemented our October 21, 2021^b and February 9, 2022^c recommendations.

2 OVERALL ASSESSMENT OF THE AUTOINJECTOR HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study designs, 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 DESIGNS

Tables 3 and 4 present a summary of the HF study designs. See Appendix A for more details on the study designs.

Table 3. Autoinjector HF Study Methodology (named “Summative Study #1” in the Applicant’s Submission)						
Study Design Elements	Details submitted by Applicant					
Participants	Distinct groups	Untrained injection experienced	Untrained injection naïve	Trained injection experience	Trained injection naïve	
	HAE patients or surrogates ages 12-17 years old	9	9	7	8	
	Adult HAE patients or surrogates	13	7	17	10	
	Caregivers of HAE patients or surrogates	8	7	9	6	
	HCPs	15	N/A	N/A	N/A	
	Total participants = 125					

^d Sit, E. Pre-BLA Meeting minutes for garadacimab. Silver Spring (MD): FDA, CDER, OND, DPACC (US); 2023 MAR 17. IND 139936.

Training	Untrained cohort - untrained participants attended two visits of approximately 60 mins in duration per visit. • Visit 1: First unassisted usage of the autoinjector. Usability data were collected during Visit 1. Root cause assessment for any potential issues observed as well as a final debriefing was done. • Visit 2: After a decay time of 14 days (± 2 days), participants returned for a second unassisted use respectively. Also, at this visit, usability data were collected, and root-cause assessments for any potential issues observed was executed. Then, the knowledge-based assessment (KBA) was performed. Following that, the inspection scenario (INSP), which, for example, for the task to check for damage the Applicant provided participants with two cartons (an open carton and a sealed carton) and asked if they could discern the difference between the two carton), was performed. Lastly, a root cause assessment and final debriefing was performed before the participant was dismissed. Trained cohort – Trained participants attended a total of three sessions. Each visit was approximately 60 minutes in duration. • Visit 1: A training session, in which participants completed an assisted injection with the support of the nurse trainer. Upon completion of the assisted injection, the nurse trainer determined in their professional judgment, whether the user was deemed suitable for independent home usage. Only if a participant was deemed so, they returned for Visit 2 and 3. • Visit 2: After 14 days (± 2 days), participants who were deemed suitable by their nurse trainer to use the product independently at home returned for an assessment visit (first unassisted use). Usability data were collected during Visit 2. Root-cause assessment for any potential issues observed as well as a final debriefing were done. • Visit 3: There was a 14-day memory decay period (± 2 days) before the trained participants return for a second assessment visit (second unassisted use). Also, in visit 3, usability data were collected and root-cause assessments for any potential issues observed was executed. The KBA was performed. Following that, the INSP scenario was performed. Lastly, a root cause assessment and final debriefing was done.
Test Environment & Materials	• The study was performed in an environment representative of a typical domestic or clinical environment. The room included a table and 2 chairs, a flat table surface, and participants were anonymously monitored through a 1-way mirror from an adjacent observation room. The test sessions were video recorded.

- The test room was illuminated by typical incandescent and/or overhead lights typical of a domestic or clinical environment. Depending on local weather conditions and time of day, additional light filtered into the test room through windows. No extremes of the lit environment were expected or included in the study.
- The test room was relatively quiet. However, there were occasional acoustic distractions in the research facility; these noises were not controlled as they may represent noises and distractions that users and patients may encounter when performing an injection in the intended use environments.
- The test room was under climate-controlled conditions representative of typical domestic or clinical environments. No extremes of temperature or humidity were expected or included in the study.



Study Sequence

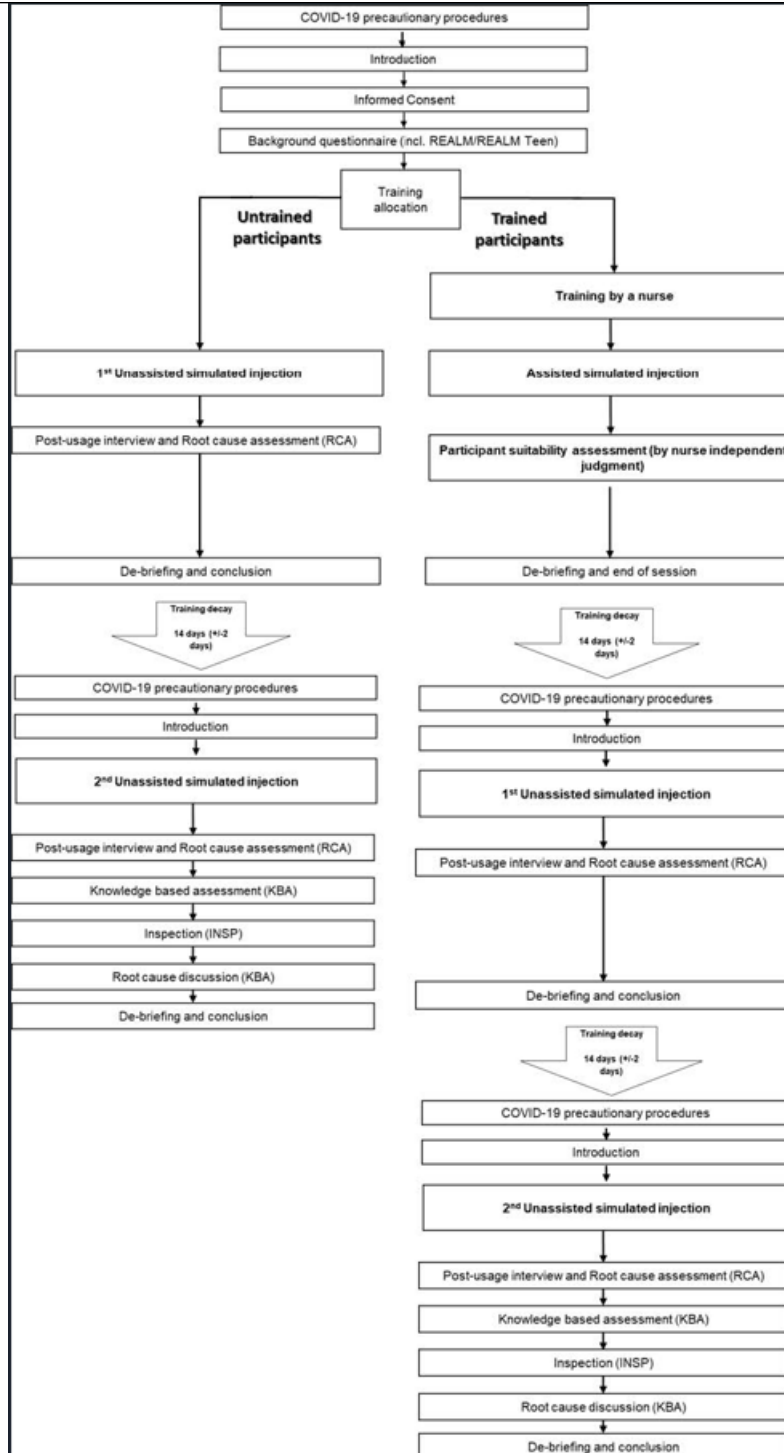
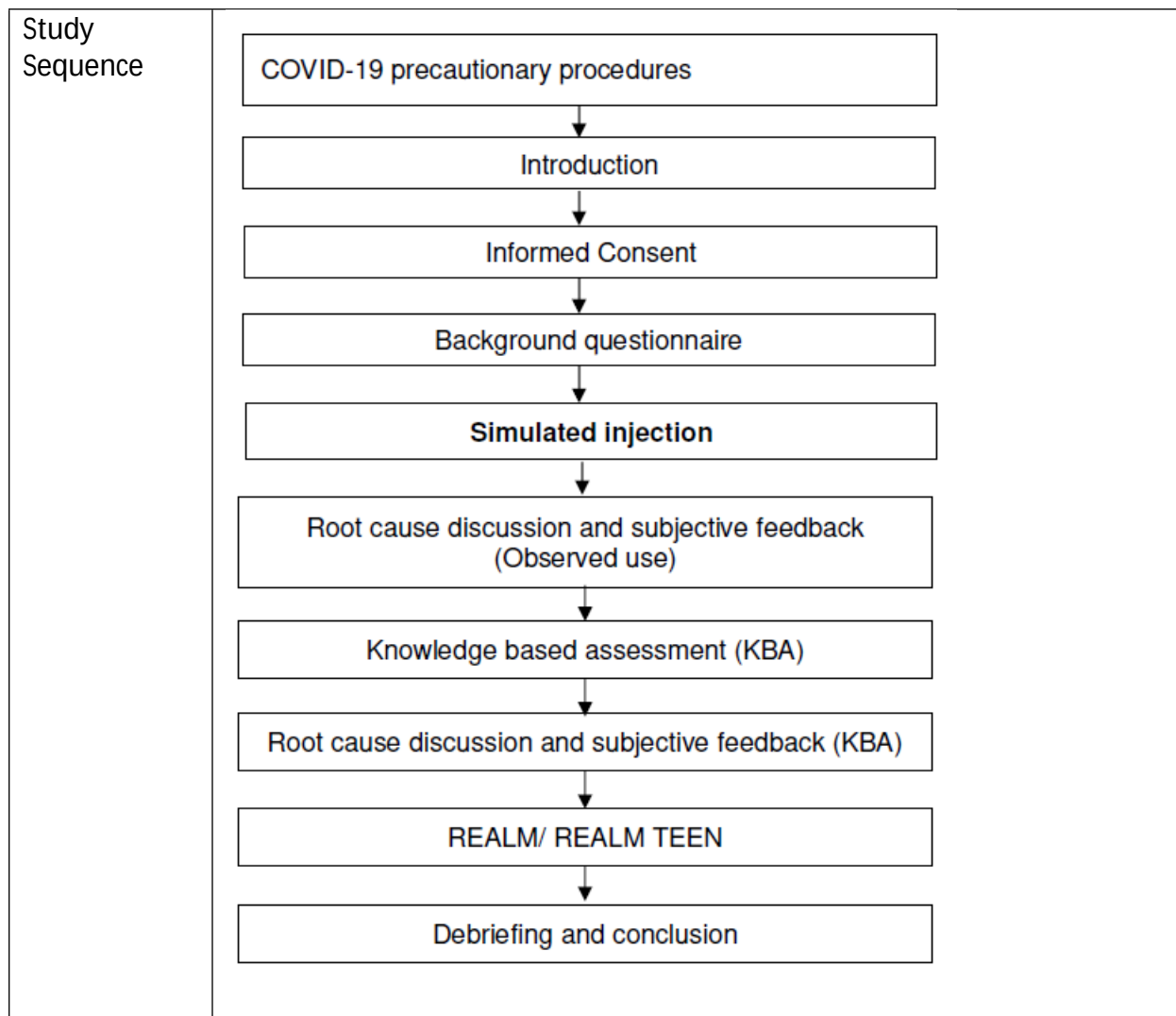


Table 4. Autoinjector Supplemental HF Study Methodology (named “Summative Study #2” in the Applicant’s Submission)				
Study Design Elements	Details submitted by Applicant			
Study Overview	The Applicant made changes, based on the subjective feedback and root cause analysis from “Summative Study #1”, to the IFU, including making the images more “realistic”, ensuring all terms were consistent, implementing plain language, labeling parts of images that were previously unlabeled, and increasing prominence of text. After making these changes, the Applicant conducted “Summative Study #2” and focused on assessing critical tasks.			
Participants	Distinct groups	Injection experienced	Injection naive	
	HAE patients or surrogates ages 12-17 years old	6	9	
	Adult HAE patients or surrogates	12	7	
	Caregivers of HAE patients or surrogates	8	7	
	HCPs	15	N/A	
	Total participants = 64			
Training	The participants were untrained.			
Test Environment & Materials	• The study was performed in an environment representative of a typical domestic or clinical environment. The room included a table and 2 chairs, a flat table surface, and participants were anonymously monitored through a 1-way mirror from an adjacent observation room. The test sessions were video recorded. • The test room was illuminated by typical incandescent and/or overhead lights typical of a domestic or clinical environment. Depending on local weather conditions and time of day, additional light filtered into the test room through windows. No extremes of the lit environment were expected or included in the study. • The test room was relatively quiet. However, there were occasional acoustic distractions in the research facility; these noises were not controlled as they may represent noises and distractions that users and patients may encounter when performing an injection in the intended use environments. • The test room was under climate-controlled conditions representative of typical domestic or clinical environments. No			

extremes of temperature or humidity were expected or included in the study.





3 RESULTS AND ANALYSIS OF THE AUTOINJECTOR HUMAN FACTORS STUDIES

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), the Applicant's URR, the participants' subjective feedback, the Applicant's root cause analysis (RCA), and the Applicant's comments and proposed mitigations 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. In Table 5 below, we document our points of dissent with the Applicant's findings. Additionally, Appendix D provides the observed use task and knowledge task issues where we agree with the Applicant's conclusions and have no further recommendations or comments.

Table 5. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: **UE** = use error; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study; **EXA** = injection experienced adolescent patient; **NAA** = injection naïve adolescent patient; **EXCG** = injection experienced caregiver; **NACG** = injection experienced caregiver; **EXP** = injection experienced adult patient; **NAP** = injection naïve adult patient; **HCP** = healthcare professional

Summary of Information Supplied by Applicant		DMEPA’s Identified Areas of Dissent and Recommendations		
Task: Remove the contents from the carton Scenario: simulated use from summative studies #1 and #2				
Summative study #1 reported issues:	Participant type(s):			
	Trained participants			Untrained participants
UE (n = 1)				NAA = 1
Summative study #2 reported issues:	Untrained participant type(s):			
UE (n = 1)	EXA = 1			
Observed event(s): Participants discarded the IFU leaflet.				
Risk associated with errors associated with this task: No dose, which may lead to partial loss in efficacy.				
Relevant RCA/Subjective Feedback: Participants were unaware of what the leaflet was and focused on removing the autoinjector.				
Applicant’s Comments and Proposed Post-HFVS Mitigations: None		Our review of the IFU leaflet indicates that it is folded in the carton in such a way that users do not see any text stating what the leaflet is (see image below). (b) (4)		

	Based on the subjective feedback and our overall assessment, we find the IFU leaflet can be improved by folding such that the IFU title is face up and visible to users. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.										
Task: Hold the autoinjector firmly in place until injection completion. Scenario: Simulated use from summative studies #1 and #2											
<table><tr><td>Summative study #1 reported issues:</td><td colspan="2">Participant type(s):</td></tr><tr><td></td><td>Trained participants</td><td>Untrained participants</td></tr><tr><td>UE (n = 21)</td><td>NACG = 1 EXA = 3 NAP = 2 EXP = 2</td><td>NACG = 3 EXCG = 2 NAA = 2 EXA = 2 NAP = 2 EXP = 1 HCP = 1</td></tr></table>	Summative study #1 reported issues:	Participant type(s):			Trained participants	Untrained participants	UE (n = 21)	NACG = 1 EXA = 3 NAP = 2 EXP = 2	NACG = 3 EXCG = 2 NAA = 2 EXA = 2 NAP = 2 EXP = 1 HCP = 1		
Summative study #1 reported issues:	Participant type(s):										
	Trained participants	Untrained participants									
UE (n = 21)	NACG = 1 EXA = 3 NAP = 2 EXP = 2	NACG = 3 EXCG = 2 NAA = 2 EXA = 2 NAP = 2 EXP = 1 HCP = 1									
<table><tr><td>Summative study #2 reported issues:</td><td>Untrained participant type(s):</td></tr><tr><td>UE (n = 2)</td><td>NACG = 1; HCP = 1</td></tr></table>	Summative study #2 reported issues:	Untrained participant type(s):	UE (n = 2)	NACG = 1; HCP = 1							
Summative study #2 reported issues:	Untrained participant type(s):										
UE (n = 2)	NACG = 1; HCP = 1										
Observed event(s): Users lifted the autoinjector before injection completion.											
Risk associated with errors associated with this task: Underdose and loss in efficacy.											
Relevant RCA/Subjective Feedback: - Negative transfer: participants were experienced with using other autoinjectors in which click significance and timing differ from the proposed product. - Incorrect mental model (when not referring to the IFU or overlooking the relevant steps in the IFU): participants believed 1st click or 2nd click signified injection completion. - Participants thought they counted five seconds after the 2nd click, but in actuality five second had not elapsed.											

One participant did not hear the 2nd click and could not identify the alternate cue (i.e., yellow plunger filling the window) for injection completion.	
Applicant's Comments and Proposed Post-HFVS Mitigations: After summative study #1, the Applicant made the following changes to Figure K "Step 9. Inject Medicine" (see Appendix A, "Summative Study #2, pages 287-288): <i>The hand grip design conveys a much stronger grip to indicate that the device has to be held firmly against the skin.</i> <i>Under each pictorial (three in Figure K), text provides in bullet points the detailed description of what cues appear and what they denote (i.e., clicks and movement of the yellow plunger through the window). The text also provides redundant instruction to keep pressing down.</i> <i>The first image has a title: "Press down to start" for clarification and to link the first click to the AI start. This instruction is also redundantly placed above each pictorial the text "Keep Pressing Down".</i> <i>The verb "press" is consistently used for both images and text.</i> <i>The second pictorial has a visual element reminding the user to pay attention to the window being filled with yellow.</i> <i>The third pictorial has clearer text requiring users to press down for 5 more seconds to ensure the full dose is delivered.</i>	Based on our review of the IFU, subjective feedback, and root cause analysis, we agree with the Applicant's IFU changes to mitigate the errors and close calls. However, based on subjective feedback from one participant who could not hear the second click and could not identify the alternate cue (i.e., yellow plunger filling the window) for injection completion, and our assessment of the IFU, we find the IFU can be improved. We identified that the third image from the left in Figure K (see below) does not identify the yellow plunger filling the viewing window and stop moving as a cue for completion. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review. (b) (4)

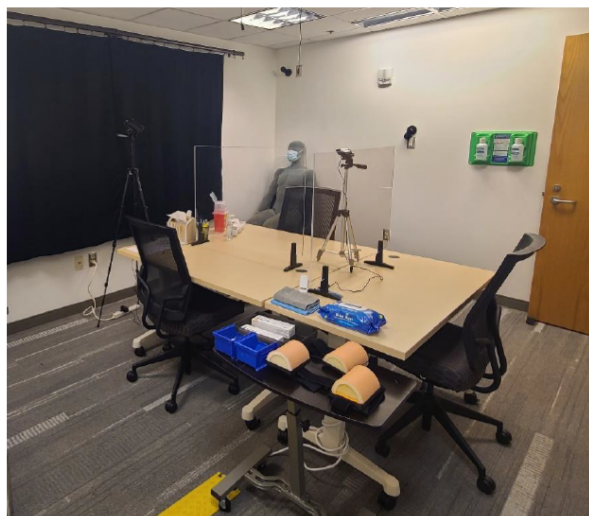
4 OVERALL ASSESSMENT OF PREFILLED SYRINGE HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

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.

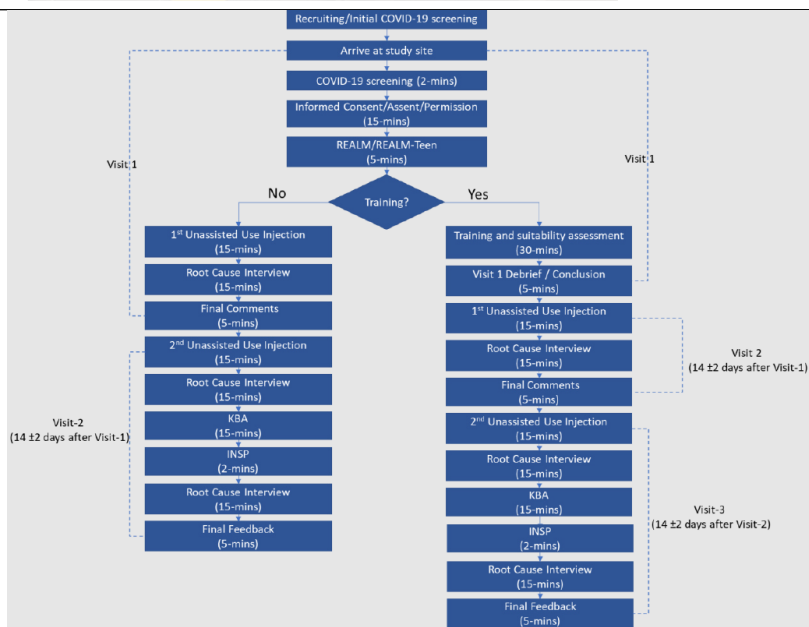
4.1 SUMMARY OF STUDY DESIGNS

Table 6 presents a summary of the HF study design. See Appendix A for more details on the study design.

Table 6. Autoinjector HF Study Methodology (named “Summative Study #1” in the Applicant’s Submission)						
Study Design Elements	Details submitted by Applicant					
Participants	Distinct groups	Untrained injection experienced	Untrained injection naïve	Trained injection experience	Trained injection naïve	
	HAE patients or surrogates ages 12-17 years old	3	14	5	10	
	Adult HAE patients or surrogates	10	6	11	4	
	Caregivers of HAE patients or surrogates	7	8	7	8	
	HCPs	16	N/A	N/A	N/A	
	Total participants = 109					
Training	The study included a trained and untrained arm. A registered nurse trained the participants and there a 14 day ± 2 days training decay period between the training and first simulated use scenario. See the “Study Sequence” row below for more information.					
Test Environment & Materials	The environment was aimed at matching the intended use conditions of the product. Therefore, this study was performed in an environment representative of a typical home or clinical environment. Study rooms were illuminated by incandescent and fluorescent lights (overhead lights) typical of a domestic or clinical environment. Depending on local weather conditions and time of day, additional light may have filtered into the test room through windows. There were no extremes of the lit environment in the study. The study rooms were under climate-controlled conditions common in a home or clinic. No extremes of temperature or humidity were included in the study.					



Study Sequence



Methodology concern: during review of the of the human factors validation study results we identified that the moderator directed participants to the IFU during the knowledge-based assessment. We did not identify this in our human factors validation study protocol review for the protocol submitted on June 14, 2021. However, our review of the human factor validation study results identified that the tasks evaluated in the knowledge-based assessment were also observed and evaluated via simulated use. Thus, we find this methodology acceptable in this case.

5 RESULTS AND ANALYSIS OF THE PREFILLED SYRINGE HUMAN FACTORS STUDY

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), the Applicant's URR, the participants' subjective feedback, the Applicant's root

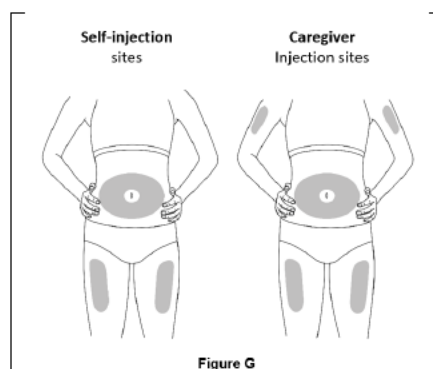
cause analysis (RCA), and the Applicant's comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. In Table 7 below, we document our points of dissent with the Applicant's findings. Additionally, Appendix D provides the observed use task and knowledge task issues where we agree with the Applicant's conclusions and have no further recommendations or comments.

Table 7. Detailed Analysis of Use Related Events and DMEPA’s Recommendations				
Legend: UE = use error; URRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study; EXA = injection experienced adolescent patient; NAA = injection naïve adolescent patient; EXCG = injection experienced caregiver; NACG = injection experienced caregiver; EXP = injection experienced adult patient; NAP = injection naïve adult patient; HCP = healthcare professional				
Summary of Information Supplied by Applicant		DMEPA’s Identified Areas of Dissent and Recommendations		
Task: Select the injection site. Scenario: Simulated use				
Summative study #1 reported issues:	Participant type(s):			
	Trained participants			Untrained participants
UE (n = 9)	NACG =2 EXA = 1			NAA = 5 HCP = 1
Observed event(s): Patient participants selected their arm to self-inject and caregivers and HCPs selected their bicep or deltoid.				
Risk associated with errors associated with this task: Underdose and loss of efficacy.				
Relevant RCA/Subjective Feedback: • Confusion with IFU: Based on the Figure H (see image below) one participant thought that the IFU lists the arm for self-injection. • Negative transfer: participants have experience with their HCP injecting in the arm, including the deltoid, or they have learned from school to inject in the arm.				

(b) (4)

Applicant's Comments and Proposed Post- HFVS Mitigations: None.

Based on subjective feedback from the prefilled HF study (one participant saw the arm highlighted in Figure H and believed that they could self-inject there), as well as subjective feedback from the autoinjector "Summative Study #1" (seven participants (5 untrained and 2 trained) stated that they could inject in the arm; these errors were due to confusion with the IFU image similar to Figure H), we identified that Figure H should be revised using the same modifications the Applicant used for Figure G in the autoinjector IFU (see below and Appendix D for more information). **We provide our recommendation in Table A to address this concern.** We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.



6 LABELS AND LABELING

Table A below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

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 Applicant based on the outcome of that review.^{e,f,g}

Table A. Identified Issues and Recommendations for CSL Behring LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
AUTOINJECTOR			
Instructions for Use (IFU)			
1.	The IFU leaflet is folded in such a way that it does not identify what it is.	Per the use-related risk analysis (URRA), if the user does not remove and use the IFU, there is risk of no dose, which may lead to partial loss in efficacy. The human factors validation study results identified subjective feedback that indicated that participants discarded the IFU since they were unaware of what the leaflet was and instead focused on removing the autoinjector.	Ensure that the IFU leaflet can be identified. For example, in the carton, include the IFU leaflet folded such that the IFU title is face up and visible to users. For example, fold the IFU leaflet so that the upper left corner (see image below) is visible upon opening the carton. (b) (4)
2.	The IFU you included in your revised labeling submission to the	We expect that the IFU evaluated and the IFU	Aside from IFU recommendations in Table A, ensure that IFU submitted in the Application is the

^e Owens, L. Label and Labeling Review for Andembry injection (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 APR 15. TTT No.: 2024-5414.

^f Owens, L. Label and Labeling Review for Andembry injection (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 JUN 21. TTT No.: 2024-5415-1.

^g Owens, L. Label and Labeling Review for Andembry injection (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2024 SEP 24. TTT No.: 2024-5415-2.

	Agency on September 12, 2024 differs from the IFU evaluated and finalized in your “Summative Study #2”. For example (please note that this example may not be all-inclusive), the IFU evaluated in “Summative Study #2” includes an (b) (4) section, but the IFU submitted to the Agency with revised labeling on September 12, 2024 does not.	submitted in the Application match.	same as the IFU finalized in “Summative Study #2”.
3.	The text under the third image from the left in Figure K does not identify the yellow plunger filling the viewing window and stopping moving as one of the cues for injection completion.	Per the use-related risk analysis (URRA), if the user removes the autoinjector before injection completion, there is risk of underdose and loss in efficacy. The human factors validation study results identified subjective feedback that indicated that a participant could not hear the second click and could not identify the alternate cue (i.e., yellow plunger filling the window) for injection completion.	In the text under the third image from the left in Figure K, provide information regarding the yellow plunger filling the viewing window and stopping moving as a cue for injection completion.
PREFILLED SYRINGE			
Instructions for Use			
1.	The IFU you included in your revised labeling submission to the Agency on September 12, 2024 differs from the	We expect that the IFU evaluated and the IFU submitted in the Application match.	Aside from IFU recommendations in Table A, ensure that IFU submitted in the Application is the same as the IFU finalized in in the human factors validation study.

	IFU evaluated and finalized in your human factors validation study. For example (please note that this example may not be all-inclusive), the IFU evaluated your human factors validation study includes an “ (b) (4) ” section, but the IFU submitted to the Agency with revised labeling on September 12, 2024 does not.		
2.	The “<i>Step 9. Inject the Medicine</i>” sentence, “<i>Pushing firmly on the plunger until the end of the injection (see Figure M)</i>” in the bullet, “<i>Press the plunger all the way down until it stops to get the full dose. Pushing firmly on the plunger until the end of the injection (see Figure M)</i>” is not grammatically correct.	Grammatical errors may cause confusion.	Revise the statement so that it is grammatically correct. For example, state, “<i>Push firmly on the plunger until the end of the injection (see Figure M)</i>”,
3.	The IFU leaflet is folded in such a way that it does not identify what it is.	Per the use-related risk analysis (URRA), if the user does not remove and use the IFU, there is risk of no dose, which may lead to partial loss in efficacy. Although the autoinjector human factors validation study results identified subjective feedback that indicated that participants discarded the IFU since they	Ensure that the IFU leaflet can be identified. For example, in the carton, include the IFU leaflet folded such that the IFU title is face up and visible to users. For example, fold the IFU leaflet so that the upper left corner (see image below) is visible upon opening the carton.

		were unaware of what the leaflet was and instead focused on the autoinjector, we note that the IFUs for both the autoinjector and prefilled syringe IFUs are currently folded in a similar manner.	(b) (4)
--	--	---	--------------------

7 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant so that recommendations are implemented for BLA 761367. These changes can be implemented without submitting additional HF validation testing data for Agency review.

APPENDICES:

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

The HF study results report and background information can be accessed in EDR via:

- Autoinjector
 - o “Summative Study #1”: <\\CDSESUB1\EVSPROD\bla761367\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5354-other-stud-rep\p-175b-p1\report-body.pdf>
 - o “Summative Study #2”: <\\CDSESUB1\EVSPROD\bla761367\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5354-other-stud-rep\p-175b-p1\report-body-summary.pdf>
- Prefilled syringe
 - o HF validation study results: <\\CDSESUB1\EVSPROD\bla761367\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5354-other-stud-rep\10-0059-36-0001\report-body.pdf>
 - o HF study background: <\\CDSESUB1\EVSPROD\bla761367\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5354-other-stud-rep\10-0059-36-0001\report-body-mdd021549.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

Information requests were not issued during the review.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^h along with postmarket medication error experiences with similar products, we reviewed the following Andembry labels and labeling submitted by CSL Behring LLC on September 12, 2024.

Prescribing Information and Instructions for Use (images not shown), available from <\\CDSESUB1\EVSPROD\bla761367\0042\m1\us\114-labeling\draft-labeling-text.docx>

C.2 Label and Labeling Images

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

APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTIONS 3 AND 5

FROM SECTION 3 (RESULTS AND ANALYSES OF THE AUTOINJECTOR HUMAN FACTORS STUDIES)

Simulated use scenarios:

- Allow the autoinjector to reach room temperature.
- Open the carton.
- Place the autoinjector on clean and flat surface.
- Check for expiration, medicine liquid, and device.
- Wash hands.
- Select the injection site.
 - o Summative study #1: Eight participants (six untrained, injection naïve adolescents, one untrained injection experienced adolescent, and one untrained, injection naïve adult patient) chose an incorrect injection site during the first simulated use scenario only. All use errors were due to negative transfer where participants had experience with injections, such as flu shots, administered in their arms.
 - o Summative study #2: Four adolescent participants (two injection experienced and two injection naïve) chose an incorrect injection site or were influenced by unsolicited advice from their parents. One participant selected their arm due to negative transfer and another participant selected their arm because they thought it would “make the injection pad stable” (study artifact). Two participants received unsolicited parental advice; however, one of these participants had already selected the abdomen.
- Clean the injection site.
- Remove autoinjector cap to inject.
 - o Summative study #1: Eleven participants (eight untrained and three trained in either the first or second simulated use scenario) tried injecting without removing the autoinjector cap due to various reasons (i.e.: negative transfer – participants had experience with injectables, such as EpiPen, which do not contain caps; patients stated that they would don’t usually refer to the IFU and therefore did not realize they had to remove a cap; participants referred to the autoinjector label, which included images for the tasks associated with pressing the autoinjector against the skin (see below) only, and removed by the Applicant after summative study #1; study artifact in which one participant did not have their glasses and could not see well and one participant’s hands were wet with hand sanitizer so they have difficulty removing the cap). One untrained injection experience adult patient who removed the cap during the first simulated use scenario, but was unable to do so in the second simulated use scenario stated, “*I forgot to take off the cap. I thought I did it.*” And that the “*cap looks like part of the whole thing because it is transparent.*” All adult participants were able to self-correct, since the autoinjector will not

administer the dose until the cap is removed. Two adolescent participants received help from their parent/guardian, including one participant whose parent started spontaneously helping. This participant thought that since the autoinjector is in the carton, it was already “protected” and therefore assumed that the autoinjector did not contain a cap. The other participant referred to the container label to provide them instructions.

Container label image evaluated in summative study #1:



- o Summative study #2: An injection naïve adolescent patient tried to inject with the cap on, but self-corrected when they realized the autoinjector would not activate. However, instead of pulling off the cap they gently wiggled the cap back and forth multiple times.

Although a participant stated that “*cap looks like part of the whole thing because it is transparent.*” we note that a clear cap may facilitate a user seeing the needle shield under the clear cap and therefore locating and removing the cap. Furthermore, multiple marketed autoinjectors and prefilled pens contain clear caps to facilitate cap removal. Additionally, this participant was able to remove the cap in the first simulated use scenario. Overall, based on the risks, mitigations and overall user interface, we have no recommendations at this time.

- Dispose of the autoinjector cap.
- Do not recap the autoinjector.
- Do not touch the gray needle shield.
- o Summative study #1: Six patients (five untrained and one trained in either the first or second simulated use scenario) touched the needle shield. Four participants, including the trained participant, touched the gray needle shield inadvertently when

picking up the autoinjector after setting it on the table. One participant tried to pull off the gray needle shield, since they assumed it was intended to be removed. Another participant tried to move the gray needle shield since the injectable device they use at home is a 3-step process in which they remove the needle cap and the “secondary cover”.

- o Summative study #2: Two injection experienced participants, one adult patient and the one caregiver, touched the needle shield due to negative transfer. Both participants used injectables in which they could see the needle, so they tried to pull/remove the needle guard on the autoinjector to reveal the needle. The caregiver’s autoinjector activated, but the adult patient’s did not.

We note that needle shield covers and expands past the needle and thus may mitigate the risk of needle sticks.

- Start injection administration immediately after cap removal without leaving it (i.e., putting the uncapped autoinjector down).
- Pinch the injection site.
 - o Summative study #1: There were 64 instances in either the first or second simulated use scenario, or both, in which participants (untrained, trained, and HCPs), did not pinch the injection site for various reasons (negative transfer since participants did not pinch their skin when administering their injectables at home, lapse in memory since the training and not referring to the IFU, study artifact with the injection pad, and assuming that they have enough fat to not have to pinch the skin).
 - o Summative study #2: Thirteen participants, including injection naïve and injection experienced caregivers, adolescents, and caregivers, did not pinch the injection site for various reasons (negative transfer since participants did not pinch their skin when administering their injectables at home, lapse in memory since first reading the IFU, study artifact with the injection pad, and assuming that they have enough fat to not have to pinch the skin).

We note that the URRRA states that not pinching the skin may lead to: intramuscular dose, which has no clinical significance; intradermal dose which may lead to pain, discomfort, itching, swelling, and redness; blood vessel (vein, artery) dose which may lead to bleeding, but no clinical relevance. The Applicant also stated that they mitigated these risks through device design in which the autoinjector injection depth is (b) (4) mm. Studies referenced evaluated the skin and subcutaneous tissue thickness of four injection sites (arm, thigh, abdomen, buttocks) used for adolescents aged 14-17 years old (mean age 15.8±1.43 years and mean BMI 21.4 ±3.8kg/m²). The subcutaneous tissue thickness was determined to be 8.1mm ±2.8 mm. Based on the risks, mitigations and overall user interface, we have no recommendations at this time.

- Push the needle shield at a 90° angle firmly against the skin to start the injection.
 - o Summative study #1: In the second simulated use scenario, due to negative transfer, an untrained, injection experienced caregiver assumed the autoinjector had a

button that they continuously tried to “push”, rather than pushing firmly against the skin to activate the autoinjector. A right-handed trained, injection experienced caregiver in the second simulated use scenario held the autoinjector at an approximately 45° angle. Although the participant knew to inject at a 90° angle and was able to do so during the first simulated use scenario, they used their left hand due to having a steel bar in their right hand. This combined with not properly adjusting their chair in a way that they could push the autoinjector led to a 45° angle.

- o Summative study #2: One HCP depressed the device at about a 45° angle, but then moved the autoinjector to a 90° angle, as that is how they administer subcutaneous injections.

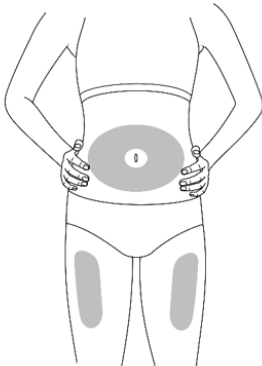
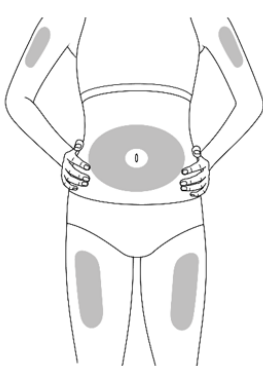
We note that the URRAs states not pushing the needle shield at a 90° angle may lead to: intradermal dose which may lead to pain, discomfort, itching, swelling, and redness and blood vessel (vein, artery) dose which, may lead to bleeding, but no clinical relevance. Based on the risks, mitigations, and overall user interface, we have no recommendations at this time.

- Release the pinch.
- Remove the autoinjector from the skin.
- If there is a little bleeding at the injection site, press a cotton ball or gauze over the injection site.
- Dispose of the autoinjector.
- Record the date of treatment.

Knowledge-based assessments:

- Question: How should you store your autoinjector? Answer: In its original carton box to protect from light until usage, in a refrigerator at 36-46°F (or at 2-8°C) and do not freeze.
- Questions: Imagine that you froze the device but now it has thawed. What should you do with the device? Answer: Do not use if frozen even it is thawed.
-  (b) (4).
- Question: What supplies should you have available when you are ready to perform an injection. Answer: autoinjector, alcohol pad, cotton ball/gauze/pad, sharps container or puncture resistant contact.
- Question: How do you know until when you can use this autoinjector? Can you tell me when that is? Answer: Points out and/or reads expiration date.
- Question: Other than the expiration date, what else should you check before using the Autoinjector to ensure it is safe to use? Answer: Autoinjector device and medicine.
- Question: What appearance of medicine inside the autoinjector would not be safe to use? What would you do in this case? Answer: Discolored and contains particles or not clear. Dispose of the autoinjector and get a new one.

- Question: What should you do if you see bubbles inside the autoinjector? Answer: Nothing, air bubbles are normal.
- What should you do if the autoinjector looks damaged or had dropped onto a hard surface? Answer: Safely dispose of the autoinjector and get a new one.
- Question: After you have removed the cap should you put it back on? Answer: No; do not recap.
- Question: Where on your body could you inject this medication if you were injecting yourself? Answer: Abdomen or thigh.
 - o Summative study #1: Seven participants (5 untrained and 2 trained) stated that they could inject in the arm. These errors were due to confusion with the IFU Figure G (participants missed the small text stating “ (b) (4) . See Figure G below, left.
 - o Summative study #2: After summative study #1, the Applicant included two separate images, one for self-injection and one for caregivers, and (b) (4) (see below, right). One injection naïve adult patient did not know where to inject and said they would ask their doctor. Another injection naïve adult participant said they would inject based on the injection sites they have seen their friend inject themselves. Both participants were able to successfully select the correct injection site during simulated use.

IFU image evaluated in summative study #1	IFU image evaluated in summative study #2
(b) (4)	Self-injection sites  Caregiver Injection sites  Figure G

- Question: If a caregiver is giving an injection, where could they inject? Answer: Abdomen, thigh, or back of arm.

- o Summative study #1: 10 participants (4 untrained, 6 trained, and one HCP) thought that the IFU Figure G (see above) indicated that caregivers could inject in the arm only.
 - o Summative study #2: One injection adult patient participant stated other areas including the buttocks and hips. However, they successfully completed the simulated use scenario task of selecting the injection site and also successfully answered the knowledge-based question of where to self-inject as a patient.
- Question: When should you rotate (change) your injection sites? Answer: If the skin is damaged. The answer is also acceptable if user says they would change it every time.
- Question: What area of your body should you avoid injecting into? Answer: The 1-inch area around the navel, the belly button.
- Question: What type of skin should you avoid injecting into with this autoinjector? Answer: Moles, scars or bruises, or into areas where the skin is tender, red, hard, or injured; skin damaged/not clear also acceptable.
- Question: How do you know when the injection has started? Answer: Hear a first click, yellow plunger starts moving.
- Question: After starting the injection how would you ensure that the full dose is injected. Answer: The yellow plunger has stopped moving and filled the viewing window and five seconds has passed after the 2nd click.
 - o Summative study #1: Three untrained participants, an injection naïve adolescent, injection experienced adult patient, and an injection naïve caregiver did not successfully respond to the question. The adolescent mentioned the 2nd click, but not the yellow in the viewing window, as they had highlighted the text regarding the 2nd click for previous knowledge-based questions. The adult patient and caregiver did not understand what the 2nd click indicates. The adult patient focused on the yellow in the viewing window during the simulated use scenario, and thus did not think about the 2nd click. The caregiver stated that 2nd clicks means injection start, even though they did not experience this error in the simulated use scenario.
 - o Summative study #2: One injection experienced caregiver could not verbalize the correct response and instead stated, “*Just by looking at the little medicine window, also you can kind of feel it going in when you’re holding it, you can almost feel the weight, the medicine leaving cos you’re obviously holding it in your hand.*” However, during simulated use, the Applicant successfully held the autoinjector at the injection site until the yellow plunger stopped moving and filled the viewing window and five seconds had passed after the 2nd click.
- Question: What should you do if you noticed that the viewing window is not completely filled by the yellow indicator? Answer: Contact your HCP right away, you might not have received a full dose.
 - o Summative study #1: Not asked during this study.
 - o Summative study #2: Two injection naïve adolescent participants did not refer to the IFU and assumed that they could just dispose of the autoinjector. One of these participants said that if the viewing window is not completely filled that

this is probably a manufacture defect. An injection naïve adult patient and caregiver stated that they would get a new autoinjector.

- Question: How many times can you use this autoinjector? Answer: Autoinjector is single use only.
- Question: How many doses are in an autoinjector? Answer: One.

For each observed issue, we considered the participants' subjective feedback, the Applicant's URR, RCA, our evaluation of the overall residual risks, the implementation of best practice standards and the Applicant's proposed mitigations (including any post-HFVS changes to the user interface). As a result, in this particular instance we find the proposed user interface has been appropriately designed and we did not identify recommendations to address the identified issues with these tasks.

FROM SECTION 5 (RESULTS AND ANALYSES OF THE PREFILLED SYRINGE HUMAN FACTORS STUDY)

Simulated use scenarios:

- Open the carton.
- Remove the contents of the carton.
- Place the prefilled syringe on clean and flat surface.
- Wash hands.
- Clean the injection site.
- Remove needle cap.
- Dispose of the needle cap.
- Do not recap the needle.
- Pinch the injection site. 27 participants (16 untrained and 11 trained) did not pinch the injection site in simulated use scenario one, two, or both. Participants did not pinch the injection site due to negative transfer (participants were experienced using their non-injecting hand to either stabilize the injection site or to hold the cotton swab, one participant was experienced with injecting into a fatty area like the buttocks, one participant was taught not to touch the injection site while injecting because they "*did not want to get hurt.*"), lapse (participants pinched during the first simulated use scenario, but forgot to during the second simulated use scenario or they read to pinch the skin, but when they arrived at the step during the administration, they forgot), study artifact (participants were experienced pinching their own skin, but were unsure of pinching the injection pad; one participant thought the injection pad was thick enough to inject without pinching), participants did not know they had to pinch the skin and did not refer to the IFU or were focused on other areas of the IFU.

Although the Applicant categorizes this task as critical, we note that the URR states that not pinching the skin may lead to minor/temporary bleeding injection site reactions (pain, discomfort, itching, swelling, redness), and no clinical significance. Based on the

risks, subjective feedback/root cause analysis, and overall user interface, we have no recommendations at this time.

- Do not remove air from the prefilled syringe. Five participants (2 HCPs, and three untrained participants) pushed the plunger after cap removal to prime or remove air due to negative transfer (participants had seen HCPs remove air from the prefilled syringe or had experience removing air from prefilled syringes in clinical practice).
- Insert the needle between a 45° and 90° angle. Two participants (both untrained) did not insert the needle between a 45° and 90° angle due to negative transfer (one of the participants observed doctors inject “IV shots” in this way) and incorrect mental model (the other participant did not refer to the IFU and felt that the angle was appropriate for injection “*under the skin*”).
- Start injection administration immediately after cap removal without leaving it (i.e., putting the uncapped prefilled syringe down).
- Hold the prefilled syringe in place and push the plunger down completely to deliver the full dose. Five participants (four trained and one untrained) did not push the plunger fully. Three untrained participants thought they pushed the plunger all the way down, however, the plunger was not pushed all the way to the bottom. During the subsequent use scenario, all three participants were able to successfully complete this task. One trained and one untrained participant had difficulty pushing the plunger due to their grip of the prefilled syringe that caused the prefilled syringe to shake.
- After full dose is delivered, slowly remove the thumb from the plunger. Twelve participants (eight untrained, three trained, and one HCP) kept their thumb on the plunger after removing from the injection site. Two of the participant’s needle shield did not activate due to the previous task of holding the prefilled syringe in place and pushing the plunger down completely to deliver the full dose. Participants experienced negative transfer from using prefilled syringes without needle shields and were not used to releasing their thumb. Other participants wanted to ensure that all the medication was administered, so they decided to continue pressing the plunger with thumb.
- Release the skin pinch.
- Remove the prefilled syringe from the injection site.
- Dispose of the prefilled syringe.

Knowledge-based assessment:

- Question: How should Sally protect the syringe from light? Answer: Keep it its original carton.
- Question: At what moment is Sally allowed to remove the needle cap from the syringe? Answer: When ready to inject.
- Question: Sally has been prescribed the device from the pharmacy. Where should Sally store the product when she arrives home? Answer: Store the prefilled in refrigerator at 36-46°F (or at 2-8°C) and do not freeze.
- Question: How many doses does each syringe have? [If necessary, follow up with: How many times can you use the same syringe?]. Answer: 1 dose [once; do not reuse].

- Question: Sally froze the device but now it has thawed. Is it okay for her to use the device?
Answer: Do not use the prefilled syringe even if it is thawed.
- Question: If Sally is traveling and cannot store the device in a fridge, how could she store the device? (b) (4)

- Question: What are the supplies that Sally needs to give an injection? Answer: alcohol wipes, sharps bin, prefilled syringe, cotton balls/gauze pads.
- Question: It's time for Sally's injection – what things should she check once she opens the carton and allows the device to reach room temperature? Answer: Check the expiration date, check the prefilled syringe for damaged, inspect the medicine inside the prefilled syringe.
- Question: When Sally is looking at the medicine in the syringe what should she see and what should she not see? Answer: It should not be discolored. Do not use if the medicine appears discolored.
- Question: What should Sally do if the prefilled syringe is expired or damaged? Answer: Do not use, dispose of the PFS, and get a new PFS.

For each observed issue, we considered the participants' subjective feedback, the Applicant's URR, RCA, our evaluation of the overall residual risks, the implementation of best practice standards and the Applicant's proposed mitigations (including any post-HFVS changes to the user interface). As a result, in this particular instance we find the proposed user interface has been appropriately designed and we did not identify recommendations to address the identified issues with these tasks.

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/

NEHA KUMAR
09/24/2024 03:40:58 PM

JASON A FLINT
09/24/2024 04:09:29 PM

The Clinical Inspection Summary

Date	August 22, 2024
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Canting Guo, M.D., Clinical Reviewer Stacy Chin, M.D., Team Leader Nina Ton, PharmD, Regulatory Health Project Manager Division of Pulmonology, Allergy, and Critical Care
BLA #	761367
Applicant	CSL Behring LLC
Drug	Garadacimab (CSL 312)
NME (Yes/No)	Yes
Proposed Indication(s)	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Consultation Request Date	November 8, 2023
Summary Goal Date	August 27, 2023
Action Goal Date	October 11, 2024
PDUFA Date	October 13, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Joshua Jacobs, Timothy Craig, and the sponsor, CSL Behring, LLC, were inspected in support of BLA 761367, covering two clinical studies, CSL312_3001 and CSL312_3002. Based on the inspection results, the study overall appears to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the sponsor appear acceptable in support of this BLA.

However, during Dr. Jacob's inspection, there were several discrepancies pertaining to the location of the hereditary angioedema (HAE) attack and trigger when comparing the source documents with the sponsor's subject data line listings. Some of these discrepancies were due to a limitation within the case report form and the electronic data capture system (EDC), which only allowed three entries per anatomical location. As a result, some of the attack locations were grouped into general body areas. The details of the discrepancies for Dr. Jacob's inspection are described for the review division's consideration in Table 1 below. Dr. Craig's inspection was conducted before Dr. Jacob's inspection, and the attack location was not reviewed. There were no discrepancies in the number of HAE attacks recorded for both inspections.

II. BACKGROUND

According to the sponsor, garadacimab (CSL312) is a fully human immunoglobulin IgG4 /

lambda recombinant monoclonal antibody, which binds to the catalytic domain of the plasma protein of activated factor XII (FXIIa) to inhibit its catalytic activity and prevent attacks of hereditary angioedema (HAE). BLA 761367 was submitted for prophylaxis to prevent attacks of hereditary angioedema in patients 12 years and older. The sponsor submitted two Phase 3 studies, CSL312_3001 and CSL312_3002, to support this BLA. The following describes the studies:

CSL312_3001: “A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema.”

Protocol CSL312_3001 was a Phase III, randomized, double-blind, parallel arm, placebo-controlled safety and efficacy study. The primary objective was to evaluate the efficacy of subcutaneous (SC) administration of CSL312 as prophylaxis to prevent hereditary angioedema (HAE) attacks in subjects with HAE.

Sites: A total of 28 study sites randomized study subjects in 7 countries including: Canada (4 sites), Germany (6 sites), Hungary (1 site), Israel (1 site), Japan (6 sites), Netherlands (1 site), and United States (9 sites).

Subjects: A total of 65 subjects were randomized (i.e., 39 subjects who received CSL312, 26 subjects who received placebo), and 60 subjects completed Treatment Period (i.e., 38 who received CSL312, 22 who received placebo).

Study initiation date: 27 January 2021 (first patient, first visit); 07 June 2022 (last patient, last visit)

Database lock date and study unblinding date: 24 June 2022 (database lock date) and 27 June 2022 (study unblinding date)

The study consisted of a Screening Period (up to one month), a Run-in Period (up to two months), a Treatment Period (six months), and a Follow-up Period (two months). During the Run-in Period, subjects who had experienced at least two HAE attacks during the first month of the Run-in Period could enter the Treatment Period. Subjects who did not experience an HAE attack during the first month of the Run-in Period could remain in the Run-in Period for up to an additional month, during which time they would be required to experience at least 2 attacks to be eligible to enter the Treatment Period. During the Treatment Period, eligible subjects were randomized 3:2 to either CSL312 or Placebo. The duration of the Treatment Period was 6 months. For subjects who received CSL312, a loading dose of 400 mg of CSL312 was administered subcutaneously as two 200 mg injections. Then, 200 mg doses of CSL312 were administered subcutaneously once monthly. For subjects who received placebo, a volume-matched loading dose of placebo as 2 injections was administered with subsequent volume-matched injections once monthly. Subjects who successfully completed the study CSL312_3001 had the option to roll over into the open-label safety study, CSL312_3002. Subjects who chose not to participate in study CSL312_3002 were required to complete the Follow-up Visit, Day 242, which was approximately three months after the last dose of the

investigational product.

Key inclusion criteria: To enter the Run-in Period, male or female subjects had to be at least 12 years of age at the time of providing written informed consent or assent for minors and diagnosed with clinically confirmed C1 esterase inhibitor (C1-INH) HAE. Subjects should have also experienced at least three or more HAE attacks during the three months before Screening, as documented in the subject's medical record. To enter the Treatment Period, subjects had to have participated in the Run-in Period for at least one month, experienced at least two HAE attacks during the Run-in Period, did not have laboratory clinical abnormalities assessed as clinically significant by the investigator in results of hematology, chemistry, or urinalysis assessments, and verified C1-INH functional activity and antigen, and C4 antigen concentration levels verified prior to randomization. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Time-normalized number of HAE attacks during treatment from Day 1 through Day 182

Data Flow for Primary Efficacy Endpoint: At the onset of a symptom of a potential HAE attack, subjects were instructed to enter information about the symptom in an eDiary and were to contact the site within 72 hours of the onset of symptoms. The site would also receive an email alert from the eDiary portal indicating that a subject experienced symptoms of a potential HAE attack. The clinical investigator or designate were to review the reported symptoms and confirm whether the symptoms represented an HAE attack. After the investigator or delegate reviewed the symptoms that were reported by the subject in the eDiary, they were to record any confirmed HAE attacks in the electronic case report form (eCRF). The data was uploaded and continuously accessible to investigators or delegates in the electronic data capture system (EDC) which was stored in the (b) (4) database and then uploaded to the CSLB Clinical Data Warehouse via monthly data transfers.

CSL312_3002: "An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema."

Protocol CSL312_3002 was an open-label study. The primary objective of the study was to evaluate the long-term safety of subcutaneous (SC) administration of CSL312 in the prophylactic treatment of subjects with C1 esterase inhibitor (C1-INH) hereditary angioedema (HAE).

Sites: A total of 28 study sites randomized study subjects in 7 countries including: Canada (4 sites), Germany (6 sites), Hungary (1 site), Israel (1 site), Japan (6 sites), Netherlands (1 site), and United States (9 sites).

Subjects: A total of 161 subjects entered the Treatment Period.

Study initiation date: 29 March 2021 (first patient, first visit)

Database lock date: 22 November 2022 (initial database lock date); the long-term safety study was ongoing at the time of inspections.

The study consisted of four periods: Screening, Run-in (at least one month and up to two months), Open-label Treatment (twelve months), and Follow-up (two months) period. During the Treatment Period, all subjects were assigned to one dose, 200 mg CSL312 subcutaneously (SC) once per month for at least twelve months. For CSL312-naïve subjects, a loading dose of 400 mg (two 200 mg doses) was administered SC on Visit Day 1, then 200 mg per month in subsequent months. Dose increases in 200 mg increments could be implemented for safety reasons after consultation between the investigator and CSL, with CSL approval. The maximum allowed dose for C1-INH HAE subjects was 400 mg per month. The maximum allowed dose for normal C1-esterase inhibitor FXII mutation subjects was 600 mg per month.

Key inclusion criteria: Similar criteria as those stated for study CSL312_3001.

Primary safety endpoint: Treatment-emergent adverse events in subjects with C1-INH HAE.

III. RESULTS (by site):

1. Dr. Joshua Jacobs

Site # 8400228

370 N. Wiget Lane

Ste. 210

Walnut Creek, CA 94598-3047

PDUFA Inspection Dates: January 22-26, 2024

For Protocol CSL312_3001, four subjects were screened, and all four subjects were randomized and completed the study.

For Protocol CSL312_3002, eight subjects were screened, and all eight subjects were randomized. At the time of inspection, none of the subjects had completed the study, and all eight subjects remained in the study.

An audit of the study records was conducted for all randomized subjects for both studies. Records reviewed included, but were not limited to, protocol versions, IRB approval letters and correspondence, subject medical records, financial disclosure reports, FDA1572s, drug accountability records, monitoring reports, informed consent forms, site signature and responsibility logs, site training documentation, eligibility records, and adverse event reports. Source documents for verification of primary efficacy endpoint were reviewed for Study CSL312_3001. Source records for subjects were in paper and electronic (subject eDiaries) format.

For study CSL312_3001, although there were no discrepancies in the number of HAE attacks, several discrepancies were noted pertaining to the location of the HAE attack and trigger for the attack for two subjects when comparing the source documents, which included the paper

Attack Verification Forms and eDiaries, against the EDC and subject data line listings. Details of the discrepancies are described in Table 1 below.

Table 1

Subject # (Treatment group)	Start/End Date	Paper Attack Verification Form		EDC/Subject Data Line Listings	
		Attack Location	Stressor	Attack Location	Stressor
(b) (6) (placebo)	(b) (6)	Both eyelids, both arms, right buttock, and <i>abdomen</i>	Seasonal allergy symptoms, occipital headache, neck pain	Cutaneous head; cutaneous extremities; and <i>throat</i>	Seasonal allergy symptoms
	(b) (6)	Right buttocks, right leg	None	Cutaneous trunk; cutaneous extremities	Cannot identify trigger
	(b) (6)	Tongue, throat, neck, trunk, internal and external abdomen, vaginal, left leg	None	Cutaneous head; cutaneous trunk; cutaneous genitourinary	Cannot identify trigger
	(b) (6)	Nasal cavity, tongue, neck, trunk, internal and external abdomen, vaginal area, left leg	Stress, <i>COVID-19 vaccine</i>	Cutaneous head; abdomen; genitourinary	Stress
	(b) (6)	Trunk, abdomen, left leg	Stress	Cutaneous trunk; abdomen; cutaneous extremities	Stress
	(b) (6)	Head (pushing on eyeballs), throat, nose, ears, no tongue swelling	None	Cutaneous head; throat	Cannot identify trigger

	(b) (6)	Back, right shoulder, right side of neck, abdominal	Stress	Cutaneous trunk; abdomen; right shoulder	Stress
	(b) (6)	Right hand, left shoulder, back, abdomen	None	Abdomen; cutaneous Trunk; right hand, left shoulder	Cannot identify trigger
	(b) (6)	Stomach, lower back swelling, lower abdomen "colon"	Stress	Abdomen; cutaneous trunk	Stress
	(b) (6)	Back of neck, facial sinus, throat swelling, left shoulder, right hand	Stress, physical exercise with moving	Throat; shoulder	Stress
	(b) (6)	Right periorbital areas, right side of neck	Stress	Cutaneous head; neck	Stress
(b) (6) (CSL312 200 mg)	(b) (6)	Abdomen	none	Cutaneous extremities	Cannot identify trigger
	(b) (6)	Abdomen, hands, feet, under chin, neck, periorbital	Physical activity	Abdomen; cutaneous head; cutaneous extremities	Physical activities
	(b) (6)	Throat, neck, internal abdomen	Stress	Cutaneous head; abdomen	Stress
	(b) (6)	Abdomen, vaginal area	Stress, walking on vacation	Abdomen	Cannot identify trigger

Reviewer's comment: For Subject # (b) (6)'s HAE attack that started on (b) (6), Dr. Jacobs confirmed that the "abdomen" should have been included and the "throat" should

not have been included in the EDC. For Subject # (b) (6) (randomized to CSL312 200 mg), the HAE attack that started on (b) (6), the paper attack verification form listed the location as the abdomen. However, it was reported in the EDC as "cutaneous extremities." For Subject # (b) (6)'s HAE attack that started on (b) (6), the location was reported in the vaginal area and abdomen but only the abdomen was reported in the line listings. For the rest of the HAE attacks listed in the table, there was a limitation within the case report form and EDC in that it only allowed three entries for the anatomical location; some of the attack locations were grouped into general body areas. For example, for Subject # (b) (6)'s HAE attack that started on (b) (6), the paper Attack Verification Form listed the "tongue, throat, neck, trunk, internal and external abdomen, vaginal, left leg." The attack locations were grouped into "Cutaneous head; cutaneous trunk; cutaneous genitourinary," and this was commonly done for the attack location for the other HAE attacks where there were multiple attack locations. Table 1 above is provided for the review division's consideration. Since the primary efficacy endpoint was the time-normalized number of HAE attacks during treatment from Day 1 through Day 182, these discrepancies regarding the location of the HAE attacks and the specific triggers should not have an impact on the efficacy data.

There was no evidence of underreporting of adverse events in either study.

2. Dr. Timothy Craig

Site #8400186
Penn State Milton S. Hershey Med Center
500 University Dr., C#5860
Hershey, PA 17033

PDUFA Inspection Dates: January 31 to February 8, 2024

For Protocol CSL312_3001, four subjects were screened, and three subjects were randomized and completed the study.

For Protocol CSL312_3002, three subjects were screened, and all three subjects were randomized. At the time of inspection, none of the subjects had completed the study, and all three subjects remained in the study.

An audit of the study records was conducted for all randomized subjects for both studies. Records reviewed included, but were not limited to, protocol versions, IRB approval letters and correspondence, subject medical records, financial disclosure reports, FDA1572s, drug accountability records, monitoring reports, informed consent forms, site signature and responsibility logs, site training documentation, eligibility records, and adverse event reports. Source documents for verification of primary efficacy endpoint were reviewed for Study CSL312_3001. Source records for subjects were in paper and electronic format.

For study CSL312_3001, the number of HAE attacks reported during the treatment period were compared with the source documents at the clinical investigator site with the sponsor's data line listings. No discrepancies were noted. There was no evidence of underreporting of

adverse events in either study.

3. CSL Behring LLC

1020 First Avenue

King of Prussia, PA 19406-1310

PDUFA Inspection Dates: April 17-25, 2024

This was a joint inspection with the EMA inspection team and covered the sponsor's conduct and oversight of Protocols CSL312_3001 and CSL312_3002.

Documents reviewed included, but were not limited to, organizational charts, standard operating procedures, monitoring plans, monitoring records for 6 clinical investigator sites (sites #12400004, #8400900, #3920146 for Protocol CSL312_3001 and sites # 8400140, #3760042, and #5540025 for Protocol CSL312_3002), contract agreements, vendor/site selection and qualifications, Form FDA 1572 (Statement of Investigators), Financial Disclosures forms, Independent Data Monitoring Committee (IDMC) Meeting Minutes, protocol deviations and adverse events.

The inspection found the site monitoring and general oversight by the sponsor to be adequate. The sponsor did not identify any serious noncompliance at any of the active clinical investigator sites, and none of the sites were terminated. In general, the sponsor appeared to be in compliance with Good Clinical Practice and FDA regulations. No significant concerns regarding the conduct or oversight of study were identified.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
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/

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/

SUYOUNG T CHANG
08/22/2024 10:53:44 AM

PHILLIP D KRONSTEIN
08/22/2024 11:59:39 AM

JENN W SELLERS
08/22/2024 06:57:11 PM

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

Date	8/21/2024		
To:	Phuong Nina Ton, OND RPM Hannah Le, OPRO RBPM Arnold Seo, OBP Lei Zhang, OBP, ATL		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	OPRO/DRBPM1/RBPMB2
From	Shruti Mistry Janice Ferguson, RN OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Gang Peng Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA761367, Garadacimab (CSL 312) ICC2300938 ICCR00950756		
Recommendation	Filing Recommendation Date: 12/12/2023 ☐ 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: 1/24/2024 ☐ 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: 8/21/2024 ☒ Device Constituent Parts of the Combination Product are Approvable with a non-CR (non-approvability) additional comment to be included in the CR letter. ☐ 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)

Please note that this memo has been updated by Shruti Mistry based on the BLA761367 CMC Wrap Up Meeting held with CDER on August 13, 2024 as the previous lead reviewer, Janice Ferguson has retired.

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA761367
Sponsor	CSL Behring, LLC
Drug/Biologic	Garadacimab (CSL 312)
Indications for Use	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Device Constituent	Pre-Filled Syringe and Auto-Injector
Related Files	NA

Review Team	
Lead Device Reviewer	<i>Janice Ferguson, RN</i>

Important Dates	
Final Lead Device Review Memo Due	5/30/2024
Interim Due Dates	Meeting/Due Date
Filing	12/4/2023 mtg. 12/12/2023
74-Day Letter	12/26/2023
Mid-Cycle	3/11/2024
Primary Review	5/30/2024
Internal Meeting(s)	2/20/2024
PDUFA	October 11, 2024 October 13, 2024 (Sunday)

Text in *italics* comes directly from submission/sponsor.

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			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	No consultants
Clinical Validation			X	
Human Factors Validation			X	
Facilities & Quality Systems	X			

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

As the sponsor has indicated that they would place an additional two batches of CSL 312 DP NSD and CSL 312 DP AI on stability and will provide data in an annual report, CDRH defers to CDER as to whether this needs to be written up as a post market commitment of whether the firm could/will just submit the data in the annual review. (SEE Section 2.3 BELOW)

In the CMC Wrap Up meeting held on August 13, 2024, CDER decided that a non-CR additional comment should be included in the CR letter reminding the sponsor of their commitment for the additional stability data for the NSDF and AI. CDRH will update the memo to note that we do not have any approvability concerns. The sponsor will be reminded of this commitment and will be advised to include this additional stability data in their response to the CR letter rather than an annual report. Please note that the additional stability data is not a CR or approvability concern, but just a reminder to the sponsor, as an additional comment, to submit the additional stability data for FDA review.

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. **Non Complete Response Additional Comment**

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☒ The following non-CR additional comment should be communicated to the Sponsor as part of the CR Letter:

In Seq. 0016 the firm indicated that they would place an additional two batches of CSL 312 DP NSD and CSL 312 DP AI on stability and will provide these data when available in an annual report.

This was not requested by CDRH but was communicated in the response to the CDRH information request received on 2/5/2024 in lieu of providing additional stability data.

In an Information Request (IR) dated January 29, 2024, FDA requested device performance testing (either real time or accelerated aged testing) on a total of 3 batches of the subject prefilled syringe (PFS) with needle safety device (NSD) to include dose accuracy, peak force, injection force, and NSD activation force to demonstrate that the device will perform as intended to the end of its proposed shelf life of 36 months. The Agency also requested testing for a total of 3 batches of the subject autoinjector (AI) to include dose accuracy, injection time, activation force, extended needle length, and lock-out force to demonstrate that the device will perform as intended to the end of its proposed shelf-life of 36-months. In the response dated February 5, 2024, it is noted that two additional batches of CSL 312 DP NSD and CSL 312 DP AI will be placed on stability and this data will be provided in an annual report. In your resubmission, please provide the results of the additional stability data rather than in an annual report.

2.4. Recommended Post-Market Commitments/Requirements

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

TABLE OF CONTENTS

1. SUBMISSION OVERVIEW	2
2. EXECUTIVE SUMMARY AND RECOMMENDATION	3
2.1. Comments to the Review Team.....	3
2.2. Complete Response Deficiencies	3
2.3. Recommended Post-Market Commitments/Requirements	4
3. PURPOSE/BACKGROUND	7
3.1. Scope	7
3.2. Prior Interactions	7
3.2.1. Related Files.....	7
3.3. Indications for Use.....	7
3.4. Materials Reviewed	8
4. DEVICE DESCRIPTION.....	8
4.1. Device Description.	8
4.2. Steps for Using the Device	15
Instructions for Use -Prefilled syringe NSD.....	15
4.3. Device Description Conclusion	34
5. FILING REVIEW.....	35
5.1. Filing Review Checklist	35
5.2. Facilities Information	36
5.3. Quality System Documentation Triage Checklist	37
5.4. Filing Review Conclusion	37
6. LABELING	38
6.1. General Labeling Review	38
6.2. Device Specific Labeling Review	40
6.3. Clinical Labeling Review	41
6.4. Labeling Review Conclusion.....	41
7. DESIGN CONTROL SUMMARY	41
7.1. Summary of Design Control Activities	41
7.2. Design Inputs and Outputs	42
7.3. Applicable Standards and Guidance Documents.....	42
7.4. Design Control Review Conclusion	43
8. RISK ANALYSIS	43
8.1. Risk Analysis.....	43
8.2. Risk Management Plan.....	43
8.3. Hazard Analysis and Risk Summary Report	43
8.4. Risk Analysis Review Conclusion	44
9. DESIGN VERIFICATION REVIEW	45
9.1. Performance/Engineering Verification.....	45
9.1.1. Essential Performance Requirement Evaluation.....	45
9.1.2. Verification of Design Inputs Evaluation	45
9.1.3. Verification of Design Inputs Evaluation	55
9.2. Design Verification Review Conclusion	67
9.3. Discipline Specific Sub-Consulted Review Summary	72
10. CLINICAL VALIDATION REVIEW	72
10.1. Review of Clinical Studies Clinical Studies.....	72

11.	HUMAN FACTORS VALIDATION REVIEW	72
12.	FACILITIES & QUALITY SYSTEMS	73
12.1.	Facility Inspection Report Review	73
12.2.	Quality Systems Documentation Review	73
12.2.1.	Description of the Device Manufacturing Process.....	74
12.2.2.	cGMP Review	78
12.2.3.	Corrective and Preventive Action Review	81
12.3.	Control Strategy Review	82
12.4.	Facilities & Quality Systems Review Conclusion.....	84
13.	APPENDIX A (INFORMATION REQUESTS)	89
13.1.	Filing/74-Day Information Requests	89
13.3	Interactive Information Requests.....	91
13.3.1	Interactive Information Requests sent on Click or tap to enter a date.	91
14.	APPENDIX B (CONSULTANT MEMOS)	91

3. PURPOSE/BACKGROUND

3.1. Scope

CSL Behring is requesting approval of Garadacimab (CSL312). The device constituent of the combination product is a Pre-Filled Syringe (PFS) 200 mg assembled in a needle safety device (NSD) and an autoinjector (AI) which also has a needle safety feature. Both devices contain a fixed subcutaneous (SC) dose 200 mg/1.2 mL of drug product in a single SC injection.

CSL312 DP 200mg NSD manufacturing is at CSL Behring, Germany. CSL 312 Semi-finished product (SFP) 200mg with Auto Injector manufacturing is by (b) (4).

Of Note: This submission received a Refuse to File letter on August 28, 2023, for lack of Pyrogen Rabbit Testing-CMC deficiency. CSL Behring resubmitted the BLA on 10/28/2023 which reset the PDUFA review timeline.

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

The applicant proposes to formulate a prefilled syringe (PFS) with a needle safety device (NSD) and a PFS with an autoinjector (AI), also referred to as a prefilled pen in the application. We kindly request CDRH's review and feedback for both the prefilled syringe with an autoinjector with Needle Safety Device and the autoinjector presentations.

We kindly request CDRH technical engineering/ device design consult review by 02/29/2024. The review due date is tentative.

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](#):

Device performance PFS/AI
Stability-device performance PFS/AI
Essential Performance Requirements (EPR) PFS/AI
Quality Assessment

This review will not cover the following review areas:

Compatibility of the drug product with the primary container closure (defer to CDER)
Biocompatibility of the primary container closure, including needle (defer to CDER)
Sterility of the primary container closure (defer to CDER)
Human Factors (Defer to DMEPA)

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

NA

3.2.1. [Related Files](#)

ICC2300621 Facilities review.

3.3. Indications for Use

Combination Product	Indications for Use
Garadacimab (CSL 312)	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Pre-Filled Syringe and Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed		
Sequence	Module(s)	
Seq. 0001	1.2	Cover Letter-Reviewer Guide
	1.4.1	LOA -MAF (b) (4)
	1.6.3	Correspondence regarding meetings-Attachment 3 Type C WRO
	1.14.1.1	Draft Labeling
	2.3P	Quality Overall Summary- Drug Product (NSD/AI)
	3.2.P.2	Pharmaceutical Development (NSD/AI)
	3.2.P.5	Control of Drug Product (NSD/AI)
	3.2.P.7	Container Closure (NSD/AI)
	3.2.P.8	Stability (NSD/AI)
	3.2.R	Regional Information (NSD/AI)
	5.4.5.4	Clinical Study Reports- PFS/HF & Simulated Use HF
Image 2000 Amendment 1	MAF (b) (4)	Volume 009 -3.2.P.2 Development 2.25 mL
		Volume 039 -Simulated Clinical Use study 2.25mL
Seq. 0009	1.14.1.3	Labeling
	3.2.P.2	Pharmaceutical Development [Manufacturing Process Development PFS/AI]
	3.2.P.3.5	Process Validation and/or Evaluation [PFS/AI]
	3.2.P.5.1	Specifications [PFS/AI]
	3.2.P.7	Container Closure System
	3.2.P.8	Stability (NSD/AI)
	3.2.P.8.3	Stability Data (NSD/AI)
Seq. 0016	3.2.R	Regional Information-Design Verification (NSD/AI)
	1.11.1	Quality Information Amendment
	3.2.P.8.1	Stability Summary and Conclusion (NSD & AI)
	3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment (NSD & AI)
	3.2.P.8.3	Stability Data (NSD & AI)
	3.2.R.3.1.3.2	Design Verification Summary
Email from Hamet Toure	OPF User Commented: re: inspection of CSL Behring Marburg, Germany	
	OPF User Commented: re inspection of	

4. DEVICE DESCRIPTION

4.1. Device Description.

Information found in Seq. 0001 3.2.P.1 [Description] & 1.2 [Reviewers Guide]

CSL Behring is requesting approval of Garadacimab (CSL312). The drug product will be provided in two device presentations.

- A Prefilled Syringe (PFS) 200 mg assembled with a needle safety device (NSD)
- An Auto-injector (AI) 200 mg which also has a needle safety feature.

Both devices begin with the CSL312 Semi-Finished Product (SFP) 200mg. (b) (4)
(b) (4). The (b) (4) is added to the syringe to make the CSL312 DP200 mg NSD or assembled with the (b) (4) to make the CSL312 DP200mg AI.

Both presentations contain a fixed subcutaneous dose 200 mg/1.2 mL of drug product.

Figure 2 Schematic Representation of the Device Assembly Process with the CSL312 SFP 200 mg to Manufacture CSL312 DP 200 mg NSD or CSL312 DP 200 mg AI



The combination product is presented in two forms. The Semi-finished product consists of

A. PRE-FILLED SYRINGE CSL312 DP200mg Needle Safety Device (NSD)

Seq. 0001 2.3.P [Quality Overall Summary]

Figure 3.2.P.3.3-1 CSL312 DP 200mg NSD assembly content (schematic representation)



Information found in Seq.0001 2.3.R.3.1 [Overview of device information CSL 312 DP 200 mg NSD]

Figure 2.3.R.3-1 CSL312 DP 200mg NSD before (left) and after (right) conclusion of the injection



Information found in 3.2.P.7-1 [Container Closure System]

Table 3.2.P.7-1 Device Components used for the CSL312 DP 200mg NSD

Item	Attribute	Description
CSL312 SFP 200mg ^a		Section 3.2.P.7-CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.
Plunger rod ^{b,c}		(b) (4)
Needle safety device ^{b,c}		
Extended finger flange ^{b,c}		

- a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
b Not in contact with the liquid.
c Direct contact with user.

B. NEEDLE SAFETY COMPONENT (

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

A large rectangular area of the document is completely redacted with a solid gray fill.

C. **AUTO INJECTOR (CSL312 DP200mg AI)**

Information found in Seq. 0001 3.2.P.3.5-3 [Package performance]

(b) (4)

A large rectangular area of the document is completely redacted with a solid gray fill.

Information found in Seq.0001 2.3.R.3.2 [Overview of device information CSL 312 DP 200 mg AI]

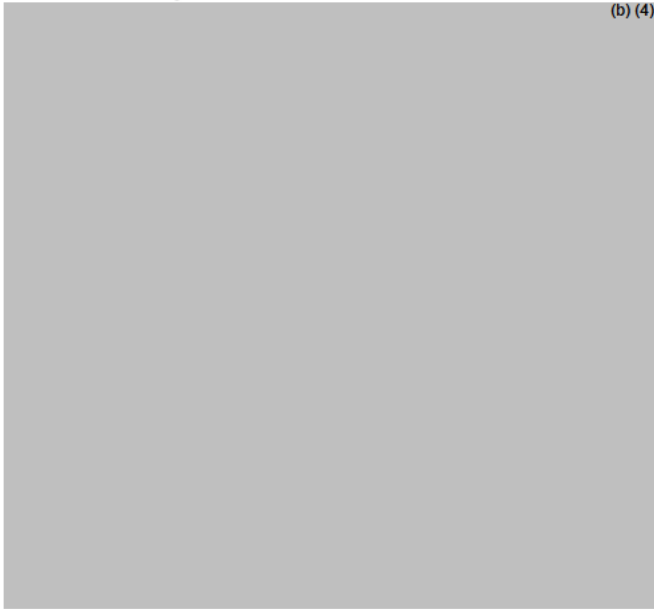
Figure 2.3.R.3-1 CSL312 DP 200mg AI (without the label)

(b) (4)

A large rectangular area of the document is completely redacted with a solid gray fill.

Figure 2 CSL312 Autoinjector (AI)

Figure 3.2.R.3.2-2 CSL312 DP 200mg AI Operating Position for Injection and Post-injection Safe State



Information found in 3.2.P.7-1 [Container Closure System]

Table 3.2.P.7-1 Components for the Autoinjector used for CSL312 DP 200mg AI

Item	Attribute	Description
CSL312 SFP 200mg ^a	Section 3.2.P.7 -CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.	
(b) (4)		

- a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
- b Not in contact with the liquid.
- c Direct contact with user.

Information found in Seq. 0001 3.2.P.2 Pharmaceutical Development [3.2.P.2.4 Container Closure]

Figure 3.2.P.2.4-1 Components of CSL312 DP 200mg AI

(b) (4)



4.2. Steps for Using the Device

Instructions for Use -Prefilled syringe NSD

Information found in Seq. 0001 1.14.1.3 [Draft Labeling Text]

(b) (4)



(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments: The device has been adequately described. The steps for administering the drug via the PFS/NSD and the Autoinjector are provided. The instructions are adequate; however, we defer to DMEPA for the acceptability of the final labeling.		
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 [“x” PFS and “o” Auto-Injector]				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		xo		
Device Constituent Labeling		xo		
Letters of Authorization		xo		
Essential Performance Requirements defined by the application Sponsor		xo		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		xo		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		xo		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		xo		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		xo		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	xo		
	Shipping 3.2.P.3.5-2 D4169			
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability			X
	Biocompatibility	xo		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors (however, defer to DMEPA)	xo		
	Shelf Life, Aging and Transportation	xo		
	Clinical Validation (Subject PFS/NSD used in clinical study)	x	o	
	Human Factors Validation	xo		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	xo		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	xo		
	CAPA Procedure (IR sent 1/29/2024)	xo		
	Control Strategy provided for EPRs	xo		

Reviewer Comment:

The submission is acceptable for filing.

5.2. Facilities Information

Firm Name:	CSL Behring GmbH
Address:	Emil-von Behring-Strasse 76 3504 Marburg Germany
FEI:	3003098680
Responsibilities:	- Manufacture (Device assembly), release, labelling, packaging, and storage of CSL312 (Drug Product) DP 200mg Needle Safety Device (NSD). - Release of final combination product CSL312 DP 200mg Auto-Injector (AI)

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☒ Inspection was conducted 2/21/2022 to 3/4/2022. The inspection covered drug CGMP and was classified VAI.

The following 483 observations were issued: 1) Written records of investigations do not always meet the appropriate conclusions and follow up; multiple deviations were reported but not properly investigated or followed up.(this included deviation report of mold *Purpureocillium lilacinum* found during IPC sampling of three (b) (4) bulk lots) 2) Product technical complaint (PTC) record did not include sufficient rationale for why investigations of retained samples not necessary such as atypical product appearance/ characteristics (particles/strands of string) 3) Buildings used in manufacture, processing, packing and holding US licensed plasma, bulk drug substances and drug products not always maintained in a state of good repair or cleanliness; 4) Procedures designed to prevent microbiological contamination of drug products purported to be sterile are insufficient; 5) Practice of cleaning validations of lyophilizes inadequate; 6) Procedures for crimping vials for filled sterile products/diluents are insufficient in that it leads to more than 50 complaints and deviations for crimped caps;

Per the EIR report page 30 there was a 1.b. noted a lack of follow up on a deviation regarding bioburden count for mold/yeast which was not followed up and no CAPA or Non-CAPA actions were initiated.

It does NOT appear that any device related inspections were performed during this inspection. This site is responsible for assembly of the PFS and release and final testing of the combination product as well as release of the Auto-injector. The last drug inspection was classified as VAI and the 483 noted a lack of follow up for Non-CAPA deviations.

Of note: the previous inspection was conducted 4/30/2018-05/17/2018 was a cGMP surveillance inspection and was classified as OAI with 13 483 observations. This did not appear to be a device related inspection.

☐ 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; and,
A recent medical device inspection of the firm has not been performed.

☐ 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:

Although HAE would normally be an “emergency” condition, this drug is used to prophylactically treat HAE and would not be used in an emergent situation. Thus, classified as “low/moderate risk”.

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: CSL Behring GmbH Emil-von Behring-Strasse 76 3504 Marburg Germany 3003098680	
Reviewer Comments: Facilities review memo was provided to CDER on 11/30/2023 under ICC2300937. CDRH recommended pre-approval inspection. Inspection results per CDER: <u>CSL Behring, Marburg, Germany</u> The full inspection report was not available for review however per Hamet Toure the following information was conveyed via email. ORA conducted a device inspection 4/15-18/2024 which resulted in one observation for complaint handling, an approval decision was recommended (EJS 4/23/3034).	

(b) (4)
CDRH did not recommend inspection of this site as it was not responsible for major activities related to the manufacturing and development of the final combination product (only device functionality performance for release testing). This site had never had an FDA inspection therefore, CDER made the decision to conduct a preapproval inspection of the site (b) (4). The full inspection report is not available for review, however per communication with Hamet Toure via email, the decision was made without EIR, classified as NAI and approval was recommended
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		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

6.2. Device Specific Labeling Review

	YES	NO	N/A
Storage conditions on carton	X		
Remove syringe and Auto-Injector from the refrigerator	X		
Preparing for the Injection	X		
Cleansing of the injection site	X		
Injection of medication (including holding AI for 15 sec)	X		
Activation of needle safety feature	X		

Reviewer Comments:

The device instructions for both the Prefilled syringe and autoinjector are adequate.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by:

- ☐ Insert Consultant Name ; The full memo is located in [Appendix B.](#)
☒ The Lead Reviewer

Below is a summary of the review & [recommendation](#):

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The sponsor provided adequate device labeling of both the Prefilled Syringes NSD and Auto-Injector.		
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:

Hazard analysis, design inputs/outputs and design verification and validation provided (See below).

7.2. Design Inputs and Outputs

(b) (4)

Reviewer Comments:

The device specifications are provided and are acceptable.

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 D4169-16	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
IEC 62366-1:2015Applying 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)
ISO 11040-4:2015 Pre-filled Syringes-Glass Barrels for Injectables	Y	
ISO 11040-8:2016 Prefilled Syringes-Requirements and test methods for finished prefilled syringes	Y	

ISO 11608-1:2022 Needle-based injection systems for medical use-Requirements and test methods-Part 1: Needle- injection systems	Y	
ISO 11608-3:2012 Needle-based injection systems for medical use-Requirements and test methods Par-3: Containers and integrated fluid paths	Y	
ISO 11608-5:2012 Needle-based injection systems for medical use- Requirements and test methods -Part 5: Automated Functions	Y	
ISO 23908:2011 Needle Safety	Y	

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Essential Performance Requirements are provided along with appropriate standards for this device types. (PFS with NSD and Autoinjector).		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

8. RISK ANALYSIS

8.1. Risk Analysis

Conforms with ISO 14971:2019 Medical devices - Applications of risk management to medical devices.

8.2. Risk Management Plan

Information found in Seq. 0001 3.2.R

(b) (4)

Reviewer Comments:

The risks assessed are appropriate for these device types.

8.3. Hazard Analysis and Risk Summary Report

Reviewer Comments:

Risk Analysis provided for the PFS/NSD and AI in assessment provided in Seq. 0001 3.2.P.2.3.2, which outlined the potential failure modes and potential harm that can occur in the manufacturing of the Pre-filled syringe and Auto-

injector. A hazard analysis and risks associated with use of the device was provided in the HF study in Seq. 5.4.5.4. The potential hazards, harms and risk control measures were appropriately assessed for each device type.

8.4. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Hazards assessed appropriately for the prefilled syringe and autoinjector device types.		
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

PREFILLED SYRINGE

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)
Deliverable Volume	$\geq$ (b) (4) mL	Y	Y	Y	Y
Peak Force (Break loose Force)	$\leq$ (b) (4) N	Y	Y	Y	Y
Injection Force (Glide Force)	$\leq$ (b) (4) N	Y	Y	Y	Y
NSD Activation Force	$\leq$ (b) (4) N	Y	Y	Y	Y
NSD Override Force	$\geq$ (b) (4) N	Y	Y	Y	Y

Reviewer Comment:

Device verification methods were described in 3.2.P.5.2 and the methods for establishing the specifications were independently validated.

Additional design verification testing was done on attributes that are not identified as EPR for the PFS/NSD such as:

Needle-pull out forces per ISO 7864:2016 req. 4.12 performed (b) (4)

Rigid Needle Shield removal Force per ISO 11040-4:2015 (b) (4).

The sponsor did not provide stability testing on the EPR on 3 batches/lots of devices. [IR #1 Q#2] Testing requested.

IR #1 Q#2 Response: the sponsor has provided testing on 3 lots of devices, real time aged to the shelf-life of 36-months. In addition, they have committed to placing an additional 2 batches of device on stability hold to be reported in an annual report. The sample size was adequate at 210 devices. All devices met their acceptance criteria. [IR #1 Q#2

DEFICIENCY RESOLVED]

9.1.2. Verification of Design Inputs Evaluation

(b) (4)

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The sponsor has not provided adequate stability testing for the subject devices. [IR#1 Q#2] Requested testing for the Prefilled syringe with NSD was requested. [IR# 1 Q#2 RESOLVED] [IR#1 Q#3] Requested testing for the Autoinjector requested.[IR#1Q#3 RESOLVED] Stability testing of the PFS EPRs was conducted on 3 lots at real time conditions to demonstrate the 36-month shelf-life. Stability testing of Auto-injector EPRs was conducted on 2 lots accelerated aged to the 36-months and 2 lots real time to 26 months, to demonstrate the 36-month shelf-life. Additionally, the sponsor has committed to provided 2 additional batches of both the PFS and AI on stability with the results to be provided in an annual report to further demonstrate the shelf-life of 36 months.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		
	Date Sent: 1/29/2024	Date/Sequence Received: 2/5/2024
Information Request #1 Question #2	(b) (4)	
Sponsor Response Q#2 a. and b.		

		(b) (4)
Reviewer Comments	The sponsor has provided 36-month Shelf-life testing on 3 lots of PFS/NSD in the following conditions: -Real time aging at 5°C - (b) (4) -Accelerated Aged to 25°C	

	Peak force (Break loose force), Injection force (Glide force), NSD Activation force, Needle pull out force, override force and Deliverable Volume tested. All of the results met their acceptance criteria. In addition, the sponsor has committed to placing additional 2 batches of devices on stability with the results to be reported with the annual report. This response is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 1/29/2024	Date/Sequence Received: 2/5/2024
Information Request #1 Question #3	(b) (4)	
Sponsor Response Q#3 a. and b.		

Reviewer Comments	The sponsor has provided Dose accuracy testing and injection time testing for 2 batches (lots) to the proposed shelf-life accelerated aged to 36 months. Actuation force was provided on two lots accelerated aged to 36 months. Additional real time testing was conducted up to 26 months on 2 additional lots. The results of the testing that was conducted on the subject auto-injector meet the acceptance criteria and is acceptable. The sponsor proports that the number of batches that were tested during all design verification testing in all conditions, time points and after simulated shipping account for product variability and was sufficient. However, the sponsor has committed to placing an additional 2 batches of CSL 312DP200 mg AI on stability with the results to be provided in an annual report. Discussed with AD, CDRH would not be able to hold approval of the BLA just because 3 lots of devices were not tested.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

9.3. Discipline Specific Sub-Consulted Review Summary

- ☒ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

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

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

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:	CSL Behring GmbH
Address & FEI:	Emil-von Behring-Strasse 76 35041 Marburg Germany FEI# 3003098680
Responsibilities:	Manufacture (Device assembly), release, labelling, packaging, and storage of CSL312 (Drug Product) DP 200mg Needle Safety Device (NSD). Release of final combination product CSL312 DP 200mg Auto-Injector (AI)
Site Inspection Recommendation:	VAI

Reviewer Comments:

See above information in Section 5.2.

CSL Behring, Marburg, Germany

The full inspection report was not available for review however per Hamet Toure the following information was conveyed via email. ORA conducted a device inspection 4/15-18/2024 which resulted in one observation for complaint handling, an approval decision was recommended (EJS 4/23/3034).

(b) (4)

CDRH did not recommend inspection of this site as it was not responsible for major activities related to the manufacturing and development of the final combination product (only device functionality performance for release testing). This site had never had an FDA inspection therefore, CDER made the decision to conduct a preapproval inspection of the site (b) (4). The full inspection report is not available for review, however per communication with Hamet Toure via email, the decision was made without EIR, classified as NAI and approval was recommended

Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable. [SEE ABOVE]	☒ Yes	☐ No
--	---	-----------------------------

12.2. Quality Systems Documentation Review

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

(b) (4)

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments: The sponsor has provided QS information regarding their manufacturing and CAPA processes. Device inspection was conducted (b) (4). The full inspection report is not yet available, however via an email provided by Hamet Toure, from CDER, ORA provided a final recommendation. A PAI resulted in one observation for complaint handling, an APPROVAL decision is recommended.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 1/29/2024	Date/Sequence Received: 2/5/2024	(b) (4)
Information Request #1 Question #1			

	(b) (4)
Reviewer Comments	The sponsor has provided a detailed description of the firms CAPA process per 21 CFR 820.100. This information is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

<<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/

HANNAH A LEE

08/21/2024 01:18:42 PM

CDRH review addendum is uploaded on behalf of CDRH assessors

Clinical Outcome Assessment Review Memorandum

From	Ji Li, MD, PhD Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Onyeka Illoh, OD, MPH COA Team Leader, DCOA
To	Division of Pulmonology, Allergy and Critical Care (DPACC)
COA tracking number	C2023354
BLA#	761367
Drug Sponsor	CSL Bering, LLC
Meeting type	Not applicable
Proposed Indication	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older Please check all that apply: ☒ Rare Disease/Orphan Designation (#19-7154) ☒ Pediatric
Instrument(s) reviewed	1. Subject's Global Assessment of Response to Therapy (SGART) 2. Angioedema Quality of Life Questionnaire (AE-QoL) ☒ Patient-reported outcome (PRO)

Executive Summary

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by the Division of Pulmonology, Allergy and Critical Care (DPACC) on October 31, 2023 (DARRTS Reference ID: 5270048) for BLA 761367 regarding garadacimab (CSL312), a novel, first-in-class, fully-human recombinant monoclonal antibody targeting activated factor XIIIa, proposed for the indication of prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. The Applicant provided data from 5 completed studies (three phase 1 studies, one phase 2 study, and one pivotal phase 3 study) and 1 ongoing long-term phase 3b study to evaluate the efficacy, safety, pharmacokinetic, and pharmacodynamic profiles of garadacimab in support of this BLA submission.

This COA consult response reviews the fitness-for-purpose¹ of the Subject's Global Assessment of Response to Therapy (SGART) and the Angioedema Quality of Life Questionnaire (AE-QoL) for deriving secondary and exploratory endpoints, respectively, used in the pivotal phase 3 Study CSL312_3001 (b) (4).

The Applicant did not provide a patient-reported outcome (PRO) evidence dossier for the SGART and AE-QoL. However, based on review of the clinical study report and existing

¹ Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>)

literature, this review concludes that the SGART and AE-QoL are not well-defined and reliable to inform regulatory decision making (b) (4).

Regulatory Background and Materials Reviewed

The Applicant was granted Orphan Drug designation for garadacimab for the treatment of bradykinin-mediated angioedema on April 30, 2020, and granted Fast Track designation for garadacimab on December 14, 2021. On June 29, 2023, the Applicant submitted a novel BLA for garadacimab under BLA 761367 with the proposed indication for prophylaxis to prevent attacks of HAE in adult and pediatric patients aged 12 years and older. Upon the initial filing review, FDA identified that Rabbit Pyrogen Testing (RPT) was not conducted on 3 batches of garadacimab, and thus issued a Refuse to File (RTF) letter on August 28, 2023 (DARRTS Reference ID: 5234072). In response to the Applicant's Type A meeting request dated September 5, 2023, FDA confirmed that the RPT study results were the only RTF issue as conveyed in the Meeting Preliminary Comments dated September 27, 2023 (DARRTS Reference ID: 5251503). The Applicant completed the required testing with no evidence of a pyrogenic effect, and resubmitted the BLA to seek approval of garadacimab for the same indication on October 13, 2023.

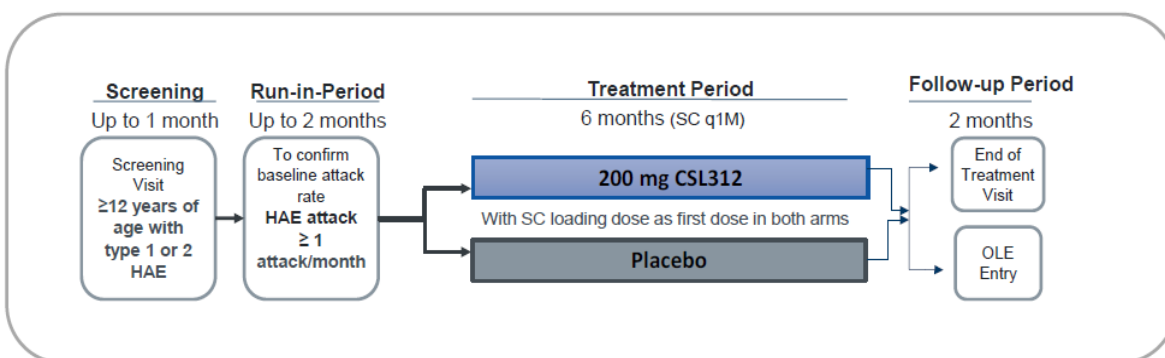
Document	SDN	eCTD#	Date Received
Clinical Overview	9	0009	10/13/2023
Summary of Clinical Efficacy	9	0009	10/13/2023
Clinical Study Report for CSL312 3001	1	0001	06/29/2023
Clinical Study Report for CSL312 3001 Erratum	1	0001	06/29/2023
Study Protocol for CSL312 3001	1	0001	06/29/2023
Study Protocol for CSL312 3001 Amendment 1	1	0001	06/29/2023
Clinical Study Report for CSL312 3002	9	0009	10/13/2023
Communications and Reviews	DARRTS Ref ID	Date	
Refuse to File letter	5234072	08/28/2023	
Meeting Preliminary Comments	5251503	09/27/2023	
Filing Review Issues Identified letter	5291954	12/12/2023	
IND (b) (4) COA Review Memo	(b) (4)		
IND (b) (4) COA Review Memo			
Publications			
Weller, K., Groffik, A., Magerl, M., Tohme, N., Martus, P., Krause, K., Metz, M., Staubach, P., & Maurer, M. (2012). Development and construct validation of the angioedema quality of life questionnaire. <i>Allergy</i> , 67(10), 1289–1298. https://doi.org/10.1111/all.12007			

Weller, K., Magerl, M., Peveling-Oberhag, A., Martus, P., Staubach, P., & Maurer, M. (2016). The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. *Allergy*, 71(8), 1203–1209. <https://doi.org/10.1111/all.12900>

Trial Design and Study Endpoints

The completed pivotal phase 3 Study CSL312_3001 provided the primary evidence to support the safety and efficacy of garadacimab for prophylaxis to prevent HAE attacks in adult and adolescent subjects (≥ 12 years and older). Specifically, Study CSL312_3001 was a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of 200 mg garadacimab administered subcutaneously once a month for the prophylaxis to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with C1-esterase inhibitor HAE. The study consisted of a screening period of up to 1 month, a run-in period of 1 to 2 months, a 6-month treatment period, and a follow-up period of 2 months (Figure 1).

Figure 1. Study CSL312_3001 Overview



Abbreviations: HAE = hereditary angioedema; OLE = open-label phase 3b Study CSL312_3002; q1M = once a month; SC = subcutaneous.

Source: Figure 2 of 16.1.1 Study Protocol for CSL312_3001 dated August 4, 2020.

The primary endpoint of this study was specified as time-normalized number of HAE attacks during treatment from Day 1 through Day 182. Secondary efficacy endpoints were listed as follows:

1. The reduction in the attack rate during the Treatment Period compared to the Run-in Period.
2. The time-normalized number of HAE attacks requiring on-demand treatment.
3. The time-normalized number of moderate and/or severe HAE attacks.
4. Time-normalized number of HAE attacks at various time points during the treatment period.
5. SGART: comparison of the proportions of subjects with an "excellent, good, fair, poor or none" response to therapy between CSL312 and placebo at the end of the Treatment Period.

Exploratory endpoints included the following:

- The time to first attack after Day 1 and after Day 15.
- CSL312 concentrations at scheduled time points.

- FXII concentration and FXIIa-mediated kallikrein activity at scheduled time points.
- Subject reported outcome measures:
 - Angioedema Quality of Life (AE-QoL)
 - EuroQoL-Group 5-Dimension 5-Level (EQ-5D-5L)
 - Work Productivity and Activity Impairment: General Health (WPAI:GH).
- Investigator's Global Assessment of Response to Therapy (IGART).

The Applicant is conducting an on-going, phase 3b, multicenter, open-label Study CSL312_3002 to evaluate the long-term safety and efficacy of garadacimab. Interim analysis results of Study 3002 were provided to support the US BLA and global submission plan.

[Reviewer's comments:

(b) (4)

(b) (4)

. From a measurement perspective, patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown. In settings where blinding is not feasible, lack of blinding will need to be overcome by demonstrating a large and durable magnitude of effect in the setting of strict adherence to a carefully conducted clinical trial.]

COA Descriptions

The Subject's Global Assessment of Response to Therapy (SGART)

The SGART is a self-reported instrument completed electronically via a provisioned electronic device (e.g., tablet) at the study site to measure patient's overall treatment response to the investigational product based on the question, "Considering all of the ways HAE affects you, please rate your response to the study medication you were given to prevent HAE attacks during this Treatment Period." Specifically, patients of all ages responded to the single-item question using a 5-point verbal rating scale, i.e., none (worse or no response at all, not acceptable), poor (very little response, not acceptable), fair (some response, acceptable but could be better), good (good response, acceptable), and excellent (excellent response, as good as can be imagined) on Days 91 and 182, respectively.

The Angioedema Quality of Life (AE-QoL) Questionnaire

The AE-QoL questionnaire ([Appendix A.1](#)) was developed to assess quality of life impairment in recurrent angioedema (RAE) patients, including patients with HAE.² It is a 17-item instrument that uses a 5-point Likert scale with response options of never, rarely, sometimes, often, and very often as well as a recall period of the last 4 weeks. The 17 items within the AE-QoL are organized into 4 distinct domains labeled as follows: functioning, fatigue/mood, fears/shame, and food/nutrition ([Table 1](#)):

² Weller, K., Groffik, A., Magerl, M., Tohme, N., Martus, P., Krause, K., Metz, M., Staubach, P., & Maurer, M. (2012). Development and construct validation of the angioedema quality of life questionnaire. *Allergy*, 67(10), 1289–1298. <https://doi.org/10.1111/all.12007>

Table 1. Conceptual framework of the AE-QoL

Item	Domain	General Concept
Item 1: Restrictions in work because of swelling episodes	Functioning	Functioning limitations associated with swelling episodes
Item 2: Restrictions in physical activity because of swelling episodes		
Item 3: Restrictions in leisure time because of swelling episodes		
Item 4: Restrictions in social relations because of swelling episodes		
Item 6: Difficulty falling asleep	Fatigue/Mood	Fatigue or mood difficulties associated with swelling episodes
Item 7: Waking up during the night		
Item 8: Being tired during the day		
Item 9: Difficulty concentrating		
Item 10: Feeling depressed	Fears/Shame	Fears or shame associated with swelling episodes
Item 12: Burden associated with swelling episodes		
Item 13: Afraid of swelling episodes that occur suddenly		
Item 14: Afraid of increased frequency of swelling episodes		
Item 15: Ashamed to go out in public because of swelling episodes		
Item 16: Feeling embarrassed or self-conscious because of swelling episodes		
Item 17: Afraid of negative long-term treatment effects	Food	Food limitations associated with swelling episodes
Item 5: Restrictions in eating and drinking because of swelling episodes		
Item 11: Limited food or beverage choices because of swelling episodes		

Source: DCOA reviewer.

Each domain has its own score, and a total score can also be calculated. The items are scored 0 to 4, and they are summed to provide raw domain scores, which are then transformed into linear scores ranging from 0 to 100. The total score is the sum of all 17 items. Higher scores in the AE-QoL domain and total scores indicate greater levels of impairment of quality of life. In Study CSL312_3001, patients ≥ 18 years were asked to complete the AE-QoL via a provisioned electronic device at the study site on Days 1, 31, 61, 91, 121, 151, and 182, respectively.

[Reviewer's comments: *The Applicant did not provide an exact copy of the SGART and AE-QoL as they were administered during the clinical trial and any associated training materials and user manuals for review; nor did the Applicant provide a PRO evidence dossier to support the fitness-for-purpose of the SGART and AE-QoL intended for this context of use.]*

Content Validity of the COAs

Content Validity of the SGART

[Reviewer's comments: *To construct the key secondary endpoint, the SGART asks patients to respond based on their experience in the past 6 months, making it susceptible to recall error. A global impression score may be influenced by factors outside of the disease process, is unable to characterize the drug's effect on individual signs/symptoms, and may mask the fact that overall improvement in score may be achieved by improvement in some signs/symptoms with concurrent worsening in other signs/symptoms. In addition, the SGART appears to assess some aspect of treatment satisfaction based on phrasing of its item and response options. From a regulatory perspective, it more appropriate to assess whether patients experienced a meaningful improvement in symptoms rather than satisfaction with treatment. In general, the SGART does not appear to be content valid for the context of use* (b) (4).]

Content Validity of the AE-QoL

The Applicant referenced the Weller et al. 2012³ article for information on the development history of this instrument. The original 29-item instrument used to develop the final AE-QoL was generated based on systematic literature review, clinical expert opinions, and exploratory semi-structured interviews with 10 RAE patients (i.e., four patients with HAE 1 & 2, three patients with chronic spontaneous urticaria, and 3 patients with other conditions). Item reduction was further performed by using means of impact analysis and factor analysis of data from 110 angioedema patients (66% women, mean age: 53 years, age range: 19–85 years, 21 (19%) of 110 adult RAE patients had a diagnosis of HAE), which yielded the final 17-item AE-QoL questionnaire.

[Reviewer's comments: *There is inadequate qualitative evidence published in the Weller et al 2012 paper to support the content validity of the AE-QoL for use in the Applicant's drug development program. In addition, the domains of the AE-QoL are not well-defined and reliable to inform regulatory decision making. Specifically, for the AE-QoL functioning domain, we note that asking patients about restrictions swelling episodes have on their daily lives regardless of whether or not they have actually experienced swelling episodes during a 4-week period will not provide useful information for assessing treatment benefit in the context of Study CSL312_3001. While the core concepts of disease-related symptoms and physical function are reasonable PRO measurement strategies for demonstrating treatment benefit, emotional impacts (such as anxiety and embarrassment) as assessed by the AE-QoL fears/shame domain are distal concepts that may be affected by factors external to HAE disease or effect of the investigational product. In addition, we do not agree that the 4-week recall period of the AE-QoL is appropriate as patients may not reliably recall the occurrence of their HAE attacks during this timeframe. As such, we do not believe that the AE-QoL is content valid for the context of use.]*

Measurement Properties of the COAs

The Applicant did not conduct psychometric analyses to establish the measurement properties of SGART and AE-QoL in their development program. However, the Applicant referenced the Weller et al. 2012 article to support the quantitative measurement properties of the AE-QoL. The AE-QoL total score and all four domains showed good internal consistency with Cronbach's alpha >0.8. Test-retesting indicated a good reliability of the AE-QoL total score and domain scores with the interclass correlation coefficients ≥ 0.68 . The AE-QoL scores were positively correlated with the Dermatology Life Quality Index scores ($p < 0.05$) and negatively correlated with SF-36 scores ($p = 0.05$), indicating acceptable convergent validity. The convergent validity of

³ Weller, K., Groffik, A., Magerl, M., Tohme, N., Martus, P., Krause, K., Metz, M., Staubach, P., & Maurer, M. (2012). Development and construct validation of the angioedema quality of life questionnaire. *Allergy*, 67(10), 1289–1298. <https://doi.org/10.1111/all.12007>

the AE-QoL was further confirmed in the Weller et al. 2016 article.⁴ The AE-QoL total score changes also correlated significantly with changes in the patients' global self-assessment of quality of life impairment (PGA-QoL), changes in the PGA disease activity, and changes in the SF-12 physical health composite score and mental health composite score, suggesting the sensitivity of the AE-QoL to QoL impairment.

[Reviewer's comments: *While findings from existing literature demonstrated acceptable psychometric properties of the AE-QoL, this will not replace or rectify problems with its content validity. In general, the content validity of a COA needs to be established prior to establishing its quantitative psychometric properties. As such, neither SGART nor AE-QoL is deemed fit-for-purpose for the context of use based on the available evidence and construction of the instruments.]*

Interpretation of Responder Threshold and Meaningful Within-Patient Score Change

The Applicant proposed a 6-point change as a minimal clinically important difference (MCID) in the AE-QoL total and domain scores, positioned as exploratory endpoints in Study CSL312_3001. The Applicant did not conduct anchor-based analyses to interpret meaningful within-patient score changes in PRO endpoints scores in Study CSL312_3001 as no external anchor scales (e.g., a Patient Global Impression of Severity or Patient Global Impression of Change) were included in Study CSL312_3001. Instead, the Applicant referenced the 6-point MCID threshold reported in the Weller et al 2016 publication.⁴

The Weller et al. 2016 article⁴ cited by the Applicant: The MCID for the AE-QoL was identified using data from 278 RAE patients (70.5% female) with a mean age of 47.8 years. In addition to the AE-QoL, all patients were asked to rate the PGA-QoL during the past 4 weeks on a 4-point Likert scale with response options of "none", "mild", "moderate", and "severe". Specifically, the mean AE-QoL total score change was -12.5 points for a one-step PGA-QoL improvement and 6.3 points for a one-step PGA-QoL worsening, respectively. The receiver operating characteristic (ROC) analysis demonstrated that 5.5 points as a cut-off provided a balanced sensitivity and specificity. In addition, the distributional criterion approach yielded a MCID of 10.5 points for the AE-QoL total score. The authors favored the anchor-based approach as a more direct and patient-centered method; because the interquartile range of AE-QoL total score changes in patients with unchanged angioedema-related QoL ranged from -5.8–6 points, that is only 25% of the 'stable' population exhibited AE-QoL total score changes of more than six points in either direction, the authors recommended 6 points to be used as the MCID for the AE-QoL total score for both, improvement and worsening of angioedema-related QoL impairment.

[Reviewer's comments: *Given issues with the content validity of the AE-QoL, it is premature to evaluate meaningful score changes for the AE-QoL. While anchor-based method is the primary method for deriving a range of thresholds that would constitute a meaningful within-patient change in target PRO scores, it should be supplemented with empirical cumulative distribution function and probability density function curves. In addition, estimation of clinically meaningful within-patient change thresholds should be confirmed in the specific context of the drug development trial. Detailed recommendations on the conduct of anchor-based analyses including properties of appropriate anchor scales can be found in FDA's PFDD Discussion Document: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making.⁵]*

⁴ Weller, K., Magerl, M., Peveling-Oberhag, A., Martus, P., Staubach, P., & Maurer, M. (2016). The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. *Allergy*, 71(8), 1203–1209. <https://doi.org/10.1111/all.12900>

⁵ <https://www.fda.gov/media/166830/download>

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/

JI LI

07/12/2024 06:52:23 PM

ONYEKACHUKWU A ILLOH

07/12/2024 07:01:46 PM

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:	February 19, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761367
Product Name, Dosage Form, and Strength:	Andembry (garadacimab-xxxx ^a) Injection 200 mg/1.2 mL
Applicant Name:	CSL Behring
FDA Received Date:	June 6, 2024
TTT ID #:	2023-5414-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

This is a corrected review that does not change the overall recommendations of the original review dated June 21, 2024

^a Since the nonproprietary name suffix for this BLA has not yet been determined, the nonproprietary name placeholder, “garadacimab-xxxx”, is used throughout this review.

1 PURPOSE OF MEMORANDUM

CSL Behring submitted revised container labels and carton labeling and prescribing information (PI) received on June 6, 2024 for Andembry. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Andembry (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.^b

2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. We note that some of our previous recommendations were implemented, but not all. Additionally, we note CSL Behring implemented updates to the prescribing information which makes for inconsistencies in the instructions for use (IFU). Therefore, we have included the additional recommendations in Section 3. We note that the nonproprietary name suffix for this BLA has not yet been determined.

3 RECOMMENDATIONS FOR CSL BEHRING

A. General Comments (Container Labels & Carton Labeling)

1. Replace the nonproprietary name suffix placeholder “-xxxx” with the conditionally acceptable nonproprietary name suffix when it is determined and use the intend-to-market presentation of the nonproprietary name and suffix (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2. For the autoinjector presentation: the product strength is expressed as a total quantity per total volume (b) (4)

so that the product strength reads as “200 mg/1.2 mL”.

B. Container Labels

1. Add the product’s linear barcode to the prefilled syringe and pen container labels in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text, and in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). Additionally, ensure the barcode is oriented on the container label such that it is not distorted or obstructed by the container curvature (i.e., oriented in a vertical position) in order to improve scannability.

C. Carton Labeling

^b Owens, L. Label and Labeling Review for Andembry (BLA 761367). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 APR 15. TTT ID: 2023-5414.

1. We recommend revising the statement of dosage to read, “Recommended dosage: see Prescribing Information”.

D. Instructions for Use (IFU)

1. We note you updated the term “prefilled pen” to “autoinjector” throughout the prescribing information, container labels, and carton labeling. Update the instructions for use (IFU) accordingly to reflect consistency between labeling.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JUNE 6, 2024

Prescribing Information

<\\CDSESUB1\EVSPROD\bla761367\0030\m1\us\114-labeling\annotated-draft-labeling-1-14-12.pdf>

Container Labels



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

LISSA C PRINGLE-OWENS
02/19/2025 04:29:37 PM

DAMON A BIRKEMEIER
02/20/2025 07:45:15 AM

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

Date	5/28/2024		
To:	Phuong Nina Ton, OND RPM Hannah Le, OPRO RBPM Arnold Seo, OBP Lei Zhang, OBP, ATL		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	OPRO/DRBPM1/RBPMB2
From	Janice Ferguson, RN OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA761367, Garadacimab (CSL 312) ICC2300938 ICCR00950756		
Recommendation	Filing Recommendation Date: 12/12/2023 ☐ 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: 1/24/2024 ☐ 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: 5/21/2024 ☐ 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)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA761367
Sponsor	CSL Behring, LLC
Drug/Biologic	Garadacimab (CSL 312)
Indications for Use	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Device Constituent	Pre-Filled Syringe and Auto-Injector
Related Files	NA

Review Team	
Lead Device Reviewer	<i>Janice Ferguson, RN</i>

Important Dates	
Final Lead Device Review Memo Due	5/30/2024
Interim Due Dates	Meeting/Due Date
Filing	12/4/2023 mtg. 12/12/2023
74-Day Letter	12/26/2023
Mid-Cycle	3/11/2024
Primary Review	5/30/2024
Internal Meeting(s)	2/20/2024
PDUFA	October 11, 2024 October 13, 2024 (Sunday)

Text in *italics* comes directly from submission/sponsor.

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			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	No consultants
Clinical Validation			X	
Human Factors Validation			X	
Facilities & Quality Systems	X			

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

As the sponsor has indicated that they would place an additional two batches of CSL 312 DP NSD and CSL 312 DP AI on stability and will provide data in an annual report, CDRH defers to CDER as to whether this needs to be written up as a post market commitment of whether the firm could/will just submit the data in the annual review. (SEE Section 2.3 BELOW)

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	☐

In Seq. 0016 the firm indicated that they would place an additional two batches of CSL 312 DP NSD and CSL 312 DP AI on stability and will provide these data when available in an annual report.

This was not requested by CDRH but was communicated in the response to the CDRH information request received on 2/5/2024 in lieu of providing additional stability data

TABLE OF CONTENTS

1. SUBMISSION OVERVIEW	2
2. EXECUTIVE SUMMARY AND RECOMMENDATION	3
2.1. Comments to the Review Team.....	3
2.2. Complete Response Deficiencies	3
2.3. Recommended Post-Market Commitments/Requirements	3
3. PURPOSE/BACKGROUND	6
3.1. Scope	6
3.2. Prior Interactions	6
3.2.1. Related Files.....	6
3.3. Indications for Use.....	6
3.4. Materials Reviewed	7
4. DEVICE DESCRIPTION.....	7
4.1. Device Description.	7
4.2. Steps for Using the Device	14
Instructions for Use -Prefilled syringe NSD	14
4.3. Device Description Conclusion	33
5. FILING REVIEW.....	34
5.1. Filing Review Checklist	34
5.2. Facilities Information	35
5.3. Quality System Documentation Triage Checklist	36
5.4. Filing Review Conclusion	36
6. LABELING	37
6.1. General Labeling Review	37
6.2. Device Specific Labeling Review	39
6.3. Clinical Labeling Review	40
6.4. Labeling Review Conclusion.....	40
7. DESIGN CONTROL SUMMARY	40
7.1. Summary of Design Control Activities	40
7.2. Design Inputs and Outputs	41
7.3. Applicable Standards and Guidance Documents.....	41
7.4. Design Control Review Conclusion	42
8. RISK ANALYSIS	42
8.1. Risk Analysis.....	42
8.2. Risk Management Plan.....	42
8.3. Hazard Analysis and Risk Summary Report	42
8.4. Risk Analysis Review Conclusion	43
9. DESIGN VERIFICATION REVIEW	44
9.1. Performance/Engineering Verification.....	44
9.1.1. Essential Performance Requirement Evaluation.....	44
9.1.2. Verification of Design Inputs Evaluation	44
9.1.3. Verification of Design Inputs Evaluation	54
9.2. Design Verification Review Conclusion	66
9.3. Discipline Specific Sub-Consulted Review Summary	71
10. CLINICAL VALIDATION REVIEW	71
10.1. Review of Clinical Studies Clinical Studies.....	71

11.	HUMAN FACTORS VALIDATION REVIEW	71
12.	FACILITIES & QUALITY SYSTEMS	72
12.1.	Facility Inspection Report Review	72
12.2.	Quality Systems Documentation Review	72
12.2.1.	Description of the Device Manufacturing Process.....	73
12.2.2.	cGMP Review	77
12.2.3.	Corrective and Preventive Action Review	80
12.3.	Control Strategy Review	81
12.4.	Facilities & Quality Systems Review Conclusion.....	83
13.	APPENDIX A (INFORMATION REQUESTS)	88
13.1.	Filing/74-Day Information Requests	88
13.3	Interactive Information Requests.....	90
13.3.1	Interactive Information Requests sent on Click or tap to enter a date.	90
14.	APPENDIX B (CONSULTANT MEMOS)	90

3. PURPOSE/BACKGROUND

3.1. Scope

CSL Behring is requesting approval of Garadacimab (CSL312). The device constituent of the combination product is a Pre-Filled Syringe (PFS) 200 mg assembled in a needle safety device (NSD) and an autoinjector (AI) which also has a needle safety feature. Both devices contain a fixed subcutaneous (SC) dose 200 mg/1.2 mL of drug product in a single SC injection.

CSL312 DP 200mg NSD manufacturing is at CSL Behring, Germany. CSL 312 Semi-finished product (SFP) 200mg with Auto Injector manufacturing is by (b) (4).

Of Note: This submission received a Refuse to File letter on August 28, 2023, for lack of Pyrogen Rabbit Testing-CMC deficiency. CSL Behring resubmitted the BLA on 10/28/2023 which reset the PDUFA review timeline.

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

The applicant proposes to formulate a prefilled syringe (PFS) with a needle safety device (NSD) and a PFS with an autoinjector (AI), also referred to as a prefilled pen in the application. We kindly request CDRH's review and feedback for both the prefilled syringe with an autoinjector with Needle Safety Device and the autoinjector presentations.

We kindly request CDRH technical engineering/ device design consult review by 02/29/2024. The review due date is tentative.

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](#):

Device performance PFS/AI
Stability-device performance PFS/AI
Essential Performance Requirements (EPR) PFS/AI
Quality Assessment

This review will not cover the following review areas:

Compatibility of the drug product with the primary container closure (defer to CDER)
Biocompatibility of the primary container closure, including needle (defer to CDER)
Sterility of the primary container closure (defer to CDER)
Human Factors (Defer to DMEPA)

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

NA

3.2.1. [Related Files](#)

ICC2300621 Facilities review.

3.3. Indications for Use

Combination Product	Indications for Use
Garadacimab (CSL 312)	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Pre-Filled Syringe and Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed		
Sequence	Module(s)	
Seq. 0001	1.2	Cover Letter-Reviewer Guide
	1.4.1	LOA -MAF (b) (4)
	1.6.3	Correspondence regarding meetings-Attachment 3 Type C WRO
	1.14.1.1	Draft Labeling
	2.3P	Quality Overall Summary- Drug Product (NSD/AI)
	3.2.P.2	Pharmaceutical Development (NSD/AI)
	3.2.P.5	Control of Drug Product (NSD/AI)
	3.2.P.7	Container Closure (NSD/AI)
	3.2.P.8	Stability (NSD/AI)
	3.2.R	Regional Information (NSD/AI)
	5.4.5.4	Clinical Study Reports- PFS/HF & Simulated Use HF
Image 2000 Amendment 1	MAF (b) (4)	Volume 009 -3.2.P.2 Development 2.25 mL
		Volume 039 -Simulated Clinical Use study 2.25mL
Seq. 0009	1.14.1.3	Labeling
	3.2.P.2	Pharmaceutical Development [Manufacturing Process Development PFS/AI]
	3.2.P.3.5	Process Validation and/or Evaluation [PFS/AI]
	3.2.P.5.1	Specifications [PFS/AI]
	3.2.P.7	Container Closure System
	3.2.P.8	Stability (NSD/AI)
	3.2.P.8.3	Stability Data (NSD/AI)
Seq. 0016	3.2.R	Regional Information-Design Verification (NSD/AI)
	1.11.1	Quality Information Amendment
	3.2.P.8.1	Stability Summary and Conclusion (NSD & AI)
	3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment (NSD & AI)
	3.2.P.8.3	Stability Data (NSD & AI)
	3.2.R.3.1.3.2	Design Verification Summary
Email from Hamet Toure	3.2.R.3.2.3.2	Design Verification Summary
	OPF User Commented: re: inspection of CSL Behring Marburg, Germany	
	OPF User Commented: re inspection of	

4. DEVICE DESCRIPTION

4.1. Device Description.

Information found in Seq. 0001 3.2.P.1 [Description] & 1.2 [Reviewers Guide]

CSL Behring is requesting approval of Garadacimab (CSL312). The drug product will be provided in two device presentations.

- A Prefilled Syringe (PFS) 200 mg assembled with a needle safety device (NSD)
- An Auto-injector (AI) 200 mg which also has a needle safety feature.

Both devices begin with the CSL312 Semi-Finished Product (SFP) 200mg. (b) (4)
(b) (4). The (b) (4) is added to the syringe to make the CSL312 DP200 mg NSD or assembled with the (b) (4) to make the CSL312 DP200mg AI.

Both presentations contain a fixed subcutaneous dose 200 mg/1.2 mL of drug product.

Figure 2 Schematic Representation of the Device Assembly Process with the CSL312 SFP 200 mg to Manufacture CSL312 DP 200 mg NSD or CSL312 DP 200 mg AI



(b) (4)

The combination product is presented in two forms. The Semi-finished product consists of

(b) (4)

A. PRE-FILLED SYRINGE CSL312 DP200mg Needle Safety Device (NSD)

Seq. 0001 2.3.P [Quality Overall Summary]

Figure 3.2.P.3.3-1 CSL312 DP 200mg NSD assembly content (schematic representation)



(b) (4)

Information found in Seq.0001 2.3.R.3.1 [Overview of device information CSL 312 DP 200 mg NSD]

Figure 2.3.R.3-1 CSL312 DP 200mg NSD before (left) and after (right) conclusion of the injection



Information found in 3.2.P.7-1 [Container Closure System]

Table 3.2.P.7-1 Device Components used for the CSL312 DP 200mg NSD

Item	Attribute	Description
CSL312 SFP 200mg ^a		Section 3.2.P.7 -CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.
Plunger rod ^{b,c}		(b) (4)
Needle safety device ^{b,c}		
Extended finger flange ^{b,c}		

- a

Only the

(b) (4) of the CSL312 SFP 200mg have direct contact with user.
- b

Not in contact with the liquid.
- c

Direct contact with user.

B. NEEDLE SAFETY COMPONENT

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

C. **AUTO INJECTOR (CSL312 DP200mg AI)**

Information found in Seq. 0001 3.2.P.3.5-3 [Package performance]

(b) (4)

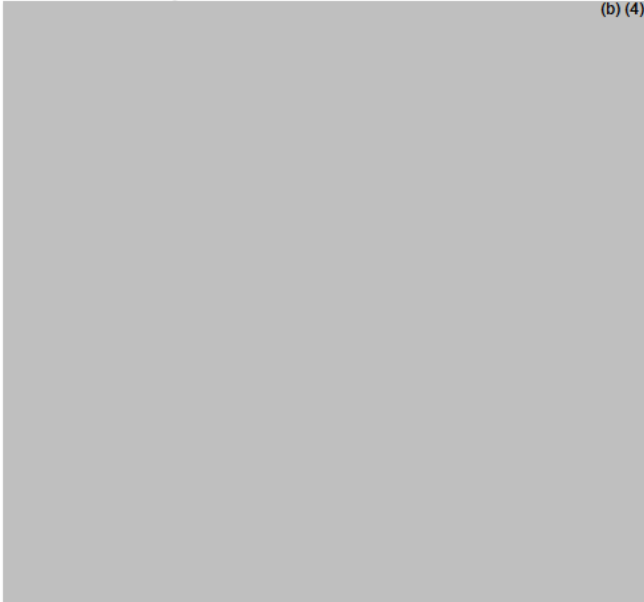
Information found in Seq.0001 2.3.R.3.2 [Overview of device information CSL 312 DP 200 mg AI]

Figure 2.3.R.3-1 CSL312 DP 200mg AI (without the label)

(b) (4)

Figure 2 CSL312 Autoinjector (AI)

Figure 3.2.R.3.2-2 CSL312 DP 200mg AI Operating Position for Injection and Post-injection Safe State (b) (4)



Information found in 3.2.P.7-1 [Container Closure System]

Table 3.2.P.7-1 Components for the Autoinjector used for CSL312 DP 200mg AI

Item	Attribute	Description
CSL312 SFP 200mg ^a	Section 3.2.P.7 -CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.	
(b) (4)		

a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
b Not in contact with the liquid.
c Direct contact with user.

Information found in Seq. 0001 3.2.P.2 Pharmaceutical Development [3.2.P.2.4 Container Closure]

Figure 3.2.P.2.4-1 Components of CSL312 DP 200mg AI



4.2. Steps for Using the Device

Instructions for Use -Prefilled syringe NSD

Information found in Seq. 0001 1.14.1.3 [Draft Labeling Text]



(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments: The device has been adequately described. The steps for administering the drug via the PFS/NSD and the Autoinjector are provided. The instructions are adequate; however, we defer to DMEPA for the acceptability of the final labeling.		
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 [“x” PFS and “o” Auto-Injector]				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		xo		
Device Constituent Labeling		xo		
Letters of Authorization		xo		
Essential Performance Requirements defined by the application Sponsor		xo		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		xo		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		xo		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		xo		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		xo		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing Shipping 3.2.P.3.5-2 D4169	xo		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability			X
	Biocompatibility	xo		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors (however, defer to DMEPA)	xo		
	Shelf Life, Aging and Transportation	xo		
	Clinical Validation (Subject PFS/NSD used in clinical study)	x	o	
	Human Factors Validation	xo		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	xo		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	xo		
	CAPA Procedure (IR sent 1/29/2024)	xo		
	Control Strategy provided for EPRs	xo		

Reviewer Comment:

The submission is acceptable for filing.

5.2. Facilities Information

Firm Name:	CSL Behring GmbH
Address:	Emil-von Behring-Strasse 76 3504 Marburg Germany
FEI:	3003098680
Responsibilities:	- Manufacture (Device assembly), release, labelling, packaging, and storage of CSL312 (Drug Product) DP 200mg Needle Safety Device (NSD). - Release of final combination product CSL312 DP 200mg Auto-Injector (AI)

Inspectional History
An analysis of the firm's inspection history over the past 2 years:

☒ Inspection was conducted 2/21/2022 to 3/4/2022. The inspection covered drug CGMP and was classified VAI.

The following 483 observations were issued: 1) Written records of investigations do not always meet the appropriate conclusions and follow up; multiple deviations were reported but not properly investigated or followed up. (this included deviation report of mold *Purpureocillium lilacinum* found during IPC sampling of three (b)(4) bulk lots) 2) Product technical complaint (PTC) record did not include sufficient rationale for why investigations of retained samples not necessary such as atypical product appearance/ characteristics (particles/strands of string) 3) Buildings used in manufacture, processing, packing and holding US licensed plasma, bulk drug substances and drug products not always maintained in a state of good repair or cleanliness; 4) Procedures designed to prevent microbiological contamination of drug products purported to be sterile are insufficient; 5) Practice of cleaning validations of lyophilizes inadequate; 6) Procedures for crimping vials for filled sterile products/diluents are insufficient in that it leads to more than 50 complaints and deviations for crimped caps;

Per the EIR report page 30 there was a 1.b. noted a lack of follow up on a deviation regarding bioburden count for mold/yeast which was not followed up and no CAPA or Non-CAPA actions were initiated.

It does NOT appear that any device related inspections were performed during this inspection. This site is responsible for assembly of the PFS and release and final testing of the combination product as well as release of the Auto-injector. The last drug inspection was classified as VAI and the 483 noted a lack of follow up for Non-CAPA deviations.

Of note: the previous inspection was conducted 4/30/2018-05/17/2018 was a cGMP surveillance inspection and was classified as OAI with 13 483 observations. This did not appear to be a device related inspection.

☐ 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; and,
A recent medical device inspection of the firm has not been performed.**

☐ 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:

Although HAE would normally be an “emergency” condition, this drug is used to prophylactically treat HAE and would not be used in an emergent situation. Thus, classified as “low/moderate risk”.

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: CSL Behring GmbH Emil-von Behring-Strasse 76 3504 Marburg Germany 3003098680	
Reviewer Comments: Facilities review memo was provided to CDER on 11/30/2023 under ICC2300937. CDRH recommended pre-approval inspection. Inspection results per CDER: CSL Behring, Marburg, Germany The full inspection report was not available for review however per Hamet Toure the following information was conveyed via email. ORA conducted a device inspection 4/15-18/2024 which resulted in one observation for complaint handling, an approval decision was recommended (EJS 4/23/3034).	

(b) (4)
CDRH did not recommend inspection of this site as it was not responsible for major activities related to the manufacturing and development of the final combination product (only device functionality performance for release testing). This site had never had an FDA inspection therefore, CDER made the decision to conduct a preapproval inspection of the site (b) (4). The full inspection report is not available for review, however per communication with Hamet Toure via email, the decision was made without EIR, classified as NAI and approval was recommended
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		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

6.2. Device Specific Labeling Review

	YES	NO	N/A
Storage conditions on carton	X		
Remove syringe and Auto-Injector from the refrigerator	X		
Preparing for the Injection	X		
Cleansing of the injection site	X		
Injection of medication (including holding AI for 15 sec)	X		
Activation of needle safety feature	X		

Reviewer Comments:

The device instructions for both the Prefilled syringe and autoinjector are adequate.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by:

- ☐ Insert Consultant Name ; The full memo is located in [Appendix B.](#)
☒ The Lead Reviewer

Below is a summary of the review & [recommendation](#):

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The sponsor provided adequate device labeling of both the Prefilled Syringes NSD and Auto-Injector.		
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:

Hazard analysis, design inputs/outputs and design verification and validation provided (See below).

7.2. Design Inputs and Outputs

(b) (4)

Reviewer Comments:

The device specifications are provided and are acceptable.

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 D4169-16	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
IEC 62366-1:2015Applying 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)
ISO 11040-4:2015 Pre-filled Syringes-Glass Barrels for Injectables	Y	
ISO 11040-8:2016 Prefilled Syringes-Requirements and test methods for finished prefilled syringes	Y	

ISO 11608-1:2022 Needle-based injection systems for medical use-Requirements and test methods-Part 1: Needle- injection systems	Y	
ISO 11608-3:2012 Needle-based injection systems for medical use-Requirements and test methods Par-3: Containers and integrated fluid paths	Y	
ISO 11608-5:2012 Needle-based injection systems for medical use- Requirements and test methods -Part 5: Automated Functions	Y	
ISO 23908:2011 Needle Safety	Y	

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Essential Performance Requirements are provided along with appropriate standards for this device types. (PFS with NSD and Autoinjector).		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

8. RISK ANALYSIS

8.1. Risk Analysis

Conforms with ISO 14971:2019 Medical devices - Applications of risk management to medical devices.

8.2. Risk Management Plan

Information found in Seq. 0001 3.2.R



Reviewer Comments:

The risks assessed are appropriate for these device types.

8.3. Hazard Analysis and Risk Summary Report

Reviewer Comments:

Risk Analysis provided for the PFS/NSD and AI in assessment provided in Seq. 0001 3.2.P.2.3.2, which outlined the potential failure modes and potential harm that can occur in the manufacturing of the Pre-filled syringe and Auto-

injector. A hazard analysis and risks associated with use of the device was provided in the HF study in Seq. 5.4.5.4. The potential hazards, harms and risk control measures were appropriately assessed for each device type.

8.4. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Hazards assessed appropriately for the prefilled syringe and autoinjector device types.		
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

PREFILLED SYRINGE

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)
Deliverable Volume	$\geq$ (b) (4) mL	Y	Y	Y	Y
Peak Force (Break loose Force)	$\leq$ (b) (4) N	Y	Y	Y	Y
Injection Force (Glide Force)	$\leq$ (b) (4) N	Y	Y	Y	Y
NSD Activation Force	$\leq$ (b) (4) N	Y	Y	Y	Y
NSD Override Force	$\geq$ (b) (4) N	Y	Y	Y	Y

Reviewer Comment:

Device verification methods were described in 3.2.P.5.2 and the methods for establishing the specifications were independently validated.

Additional design verification testing was done on attributes that are not identified as EPR for the PFS/NSD such as:

Needle-pull out forces per ISO 7864:2016 req. 4.12 performed (b) (4)

Rigid Needle Shield removal Force per ISO 11040-4:2015 (b) (4).

The sponsor did not provide stability testing on the EPR on 3 batches/lots of devices. [IR #1 Q#2] Testing requested.

IR #1 Q#2 Response: the sponsor has provided testing on 3 lots of devices, real time aged to the shelf-life of 36-months. In addition, they have committed to placing an additional 2 batches of device on stability hold to be reported in an annual report. The sample size was adequate at 210 devices. All devices met their acceptance criteria. [IR #1 Q#2

DEFICIENCY RESOLVED]

9.1.2. Verification of Design Inputs Evaluation

(b) (4)

Reviewer Comment:

Appropriate biocompatibility testing was done on the syringe and autoinjector. Summary and test reports provided in the submission. **The testing is acceptable.**

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> The sponsor has not provided adequate stability testing for the subject devices. [IR#1 Q#2] Requested testing for the Prefilled syringe with NSD was requested. [IR# 1 Q#2 RESOLVED] [IR#1 Q#3] Requested testing for the Autoinjector requested.[IR#1Q#3 RESOLVED] Stability testing of the PFS EPRs was conducted on 3 lots at real time conditions to demonstrate the 36-month shelf-life. Stability testing of Auto-injector EPRs was conducted on 2 lots accelerated aged to the 36-months and 2 lots real time to 26 months, to demonstrate the 36-month shelf-life. Additionally, the sponsor has committed to provided 2 additional batches of both the PFS and AI on stability with the results to be provided in an annual report to further demonstrate the shelf-life of 36 months.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		
	Date Sent: 1/29/2024	Date/Sequence Received: 2/5/2024
Information Request #1 Question #2	(b) (4)	
Sponsor Response Q#2 a. and b.		

(b) (4)

Reviewer Comments

The sponsor has provided 36-month Shelf-life testing on 3 lots of PFS/NSD in the following conditions:

-Real time aging at 5°C

(b) (4)

-Accelerated Aged to 25°C

	Peak force (Break loose force), Injection force (Glide force), NSD Activation force, Needle pull out force, override force and Deliverable Volume tested. All of the results met their acceptance criteria. In addition, the sponsor has committed to placing additional 2 batches of devices on stability with the results to be reported with the annual report. This response is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 1/29/2024	Date/Sequence Received: 2/5/2024
Information Request #1 Question #3	(b) (4)	
Sponsor Response Q#3 a. and b.		

	(b) (4)
Reviewer Comments	The sponsor has provided Dose accuracy testing and injection time testing for 2 batches (lots) to the proposed shelf-life accelerated aged to 36 months. Actuation force was provided on two lots accelerated aged to 36 months. Additional real time testing was conducted up to 26 months on 2 additional lots. The results of the testing that was conducted on the subject auto-injector meet the acceptance criteria and is acceptable. The sponsor proports that the number of batches that were tested during all design verification testing in all conditions, time points and after simulated shipping account for product variability and was sufficient. However, the sponsor has committed to placing an additional 2 batches of CSL 312DP200 mg AI on stability with the results to be provided in an annual report. Discussed with AD, CDRH would not be able to hold approval of the BLA just because 3 lots of devices were not tested.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

9.3. Discipline Specific Sub-Consulted Review Summary

- ☒ No Additional Discipline Specific Sub-Consults were requested
- ☐ The following additional Discipline Specific Sub-Consults were requested:

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

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

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:	CSL Behring GmbH
Address & FEI:	Emil-von Behring-Strasse 76 35041 Marburg Germany FEI# 3003098680
Responsibilities:	Manufacture (Device assembly), release, labelling, packaging, and storage of CSL312 (Drug Product) DP 200mg Needle Safety Device (NSD). Release of final combination product CSL312 DP 200mg Auto-Injector (AI)
Site Inspection Recommendation:	VAI

Reviewer Comments:

See above information in Section 5.2.

CSL Behring, Marburg, Germany

The full inspection report was not available for review however per Hamet Toure the following information was conveyed via email. ORA conducted a device inspection 4/15-18/2024 which resulted in one observation for complaint handling, an approval decision was recommended (EJS 4/23/3034).

(b) (4)

CDRH did not recommend inspection of this site as it was not responsible for major activities related to the manufacturing and development of the final combination product (only device functionality performance for release testing). This site had never had an FDA inspection therefore, CDER made the decision to conduct a preapproval inspection of the site (b) (4). The full inspection report is not available for review, however per communication with Hamet Toure via email, the decision was made without EIR, classified as NAI and approval was recommended

Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable. [SEE ABOVE]	☒ Yes	☐ No
--	---	-----------------------------

12.2. Quality Systems Documentation Review

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

(b) (4)

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments: The sponsor has provided QS information regarding their manufacturing and CAPA processes. Device inspection was conducted (b) (4). The full inspection report is not yet available, however via an email provided by Hamet Toure, from CDER, ORA provided a final recommendation. A PAI resulted in one observation for complaint handling, an APPROVAL decision is recommended.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 1/29/2024	Date/Sequence Received: 2/5/2024	(b) (4)
Information Request #1 Question #1			

(b) (4)

Reviewer Comments	The sponsor has provided a detailed description of the firms CAPA process per 21 CFR 820.100. This information is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

<<END OF REVIEW>>

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

HANNAH A LEE

05/28/2024 05:03:52 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
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: April 25, 2024
From: Interdisciplinary Review Team for Cardiac Safety Studies
Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN
To: Phuong (Nina) Ton
DPACC
Subject: QT Consult to BLA 761367 (SDN 1)

Note: Any text in the review with a light background should be inferred as copied from the Applicant's document.

This memo responds to your consult to us dated 3/27/2024 regarding the Division's QT related question. We reviewed the following materials:

- Applicant's proposed label (BLA 761367/ 009; [link](#));
- Applicant's Clinical Study Report CSL312_1001(BLA 761367/ 001; [link](#));
- Applicant's Clinical Study Report CSL312_1003(BLA 761367/ 001; [link](#));
- Applicant's Clinical Study Report CSL312_3001(BLA 761367/ 001; [link](#)); and
- Applicant's Summary of Clinical Pharmacology (BLA 761367/ 009; [link](#))

1 CS IRT Response

Division's Question: Review division is asking for our review and comments on the Applicant's proposed labeling submitted for their product (Garadacimab) which is a novel fully human recombinant immunoglobulin G4 (IgG4) monoclonal antibody (mAb). (b) (4)

Since it is a mAB, the Applicant didn't perform a dedicated QT study, but according to review division the Applicant measured ECGs in studies 1001, 1003 and 3001 and based on the data (b) (4)

IRT's response: The clinical and nonclinical ECG findings for garadacimab are consistent with the fact that large, targeted proteins and antibodies have a low likelihood of direct ion channel interaction and therefore not expected to cause concentration dependent prolongation of the QTc

interval. We recommend (b) (4) which is consistent with our labeling practices for large molecular weight proteins for which a dedicated QT study is generally not needed and when one has not been conducted.

According to the ICH E14 Q&A 6.3 (R3), “Large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies.”

1.1 Proposed label

(b) (4)

*Reviewer’s comment: We propose to use labeling language for this product consistent with the “QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry” draft guidance ([link](#)). **For drugs that do not need a QTc interval assessment (e.g., most monoclonal antibodies), the Cardiac Electrophysiology heading, and related information may be omitted from this subsection.***

2 BACKGROUND

2.1 Product Information

Garadacimab (CSL312) is a fully human immunoglobulin IgG4 / lambda recombinant monoclonal antibody, which binds to the catalytic domain of the plasma protein of activated factor XII (FXIIa) to inhibit its catalytic activity. Garadacimab is proposed for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. The proposed therapeutic dose consists of an initial loading dose of 400 mg (two 200 mg subcutaneous injections), followed by 200 mg once monthly administered subcutaneously.

2.2 Applicant’s position related to the question

No thorough QT study has been conducted for garadacimab. Garadacimab is a mAb with a low likelihood of a direct ion channel interaction. In addition, no potential proarrhythmic risks are suggested by the mechanistic considerations or based on the data from clinical and nonclinical studies.

Electrocardiograms were taken in Studies 1001, 1003, and 3001. There were no clinically relevant trends over time or differences across the garadacimab doses (across the IV and SC doses, respectively, or between the IV and SC doses) or between garadacimab and placebo for heart rate, PR duration, QRS duration, QT interval, or heart rate-corrected QT interval.

Reviewer's Comment: The ECG data collected by the Applicant cannot serve as substitute for thorough QT study per ICH E14 Q&A 5.1. Despite the limitations, garadacimab is not expected to directly interact with hERG channel to cause concentration dependent inhibition of cardiac repolarization. Given that garadacimab is a monoclonal antibody, a thorough QT/QTc study is not warranted.

2.3 Clinical Pharmacology

The Applicant did not submit the highlights of clinical pharmacology and clinical safety. However, the summary of clinical pharmacology notes the following:

- The primary elimination pathways for garadacimab are protein catabolism or target-mediated disposition, not via hepatic or renal elimination.
- Body weight was identified as an important covariate in the final PopPKPD model, however after exposure-response analysis the impact of body weight was not considered to be clinically relevant.
- Effect of age, sex and ethnicity were not considered to be clinically relevant.

Table 1: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	400 mg, SC	24.5 µg/mL
Applicant's High clinical exposure scenario	400 mg, SC (no exposure beyond therapeutic dose is anticipated)	24.5 µg/mL
Highest dose in QT assessment*	10 mg/kg, IV	410 µg/mL
C_{max} Ratio	17	

*Clinical trial dosing producing highest C_{max} -healthy subjects in Study 1001; [Table 12 Summary of Clinical Pharmacology](#)

Reviewer's Comment: The highest C_{max} observed in studies that evaluated safety ECGs provides a 17-fold margin over the maximum exposure at therapeutic doses. Despite the high exposure margin, the data cannot be used as substitute for TQT study (See Section 2.5).

2.4 Nonclinical Cardiac Safety

Electrocardiogram assessments in cynomolgus monkeys found no QT/QTc prolongation at IV doses up to 100 mg/kg and SC doses up to 200 mg/kg.

2.5 Clinical Cardiac Safety

The Applicant reports ECGs were collected in Studies 1001, 1003, and 3001.

Study 1001 (CSL312_1001): This was a single-center, randomized, double-blind, placebo-controlled, single ascending dose, phase 1 study in 48 healthy subjects. Subjects were administered a single IV infusion of 0.1, 0.3, 1, 3, or 10 mg/kg garadacimab or placebo or a single SC injection of 1, 3, or 10 mg/kg garadacimab or placebo.

- PK sampling: Predose, 0.5, 1, 6, 24, and 48 hours for IV cohorts, and for SC cohorts at predose, 6, 12, 24, 32, and 48 hours.
- ECG Sampling: A single ECG at Day -1. Triplicate ECGs at Screening, predose and at 1 hour (IV) or 48 hours (SC). Single ECGs were also taken at 96 hour (Day 5) and at end of study (EoS) on day 85. Real time cardiac monitoring (ECG telemetry, Lead II monitoring) was conducted during the first 24 hours after IV administration only. No monitoring was conducted after subcutaneous dosing.

There were no clinically relevant trends over time or differences across the CSL312 doses (across the IV and SC doses, respectively, or between the IV and SC doses) or between CSL312 and placebo for heart rate, PR duration, QRS duration, QT interval, QTcB, and QTcF.

Reviewers' comments: *Despite adequate exposure margin, ECG collection schedule and sample size at individual dosing groups do not support adequate characterization of garadacimab QTc effects and therefore cannot be used as a substitute for TQT study (ICH E14 Q&A 5.1.).*

The ECG schedule is adequate for evaluation of QT effect at high exposure - but not adequate for capturing any potential delay in QT effects. The data cannot be evaluated using concentration-QTc analysis since garadacimab is a large protein which is not expected to cause concentration dependent block of hERG channel. Moreover, due to small sample sizes in individual dose-groups, by-time analysis will not have enough power to characterize QT effects.

Despite the limitations, being less likely to block hERG channel and with non-clinical studies suggesting no proarrhythmic, a dedicated QT study for garadacimab is not required.

Study 1003 (CSL312_1003): This was a 2-part, phase 1, open-label, single-center, single ascending dose study in 37 healthy adult Japanese and White subjects.

In Part A of the study, 12 Japanese subjects were administered a single SC dose of 200 mg garadacimab, 13 White subjects were administered a single SC dose of 200 mg garadacimab, and 4 Japanese subjects were administered a single SC dose of 600 mg garadacimab.

In Part B of the study, 4 Japanese subjects were administered a single IV dose of 3 mg/kg garadacimab and 4 Japanese subjects were administered a single IV dose of 10 mg/kg garadacimab.

Part A:

- PK sampling: Predose, 1, 8, 24, 32, and 48 hours post injection.
- ECG Sampling: A single ECG at Day -1. Triplicate ECGs at Screening, predose and at 48 hours post injection.

Part B:

- PK sampling: Predose, 0.5, 1, 8, 24, and 48 hours post injection.
- ECG Sampling: A single ECG at Day -1. Triplicate ECGs at Screening, predose, at the end of infusion (1 hour), and at 48 hours post injection.

There were no clinically relevant trends in ECGs over time or differences across the CSL312 cohorts.

No patient in Study 1003, had a QTcF Increase from baseline (Δ QTcF) >60 msec or >500 msec at any visit.

Table 14.3.6.4 12-lead ECG: Number (Percent) Subjects with QTcF Increase from Baseline >60 msec or >500 msec by Visit (Safety Analysis Set)

Subcutaneous (SC) Subjects						
Visit (Day)	Value		Cohort 1a Japanese & 200 mg SC CSL312 (N=12)	Cohort 1b Caucasian & 200 mg SC CSL312 (N=13)	Cohort 2 Japanese & 600 mg SC CSL312 (N=4)	SC Total (N=29)
Day 3	CFB >60 msec	Yes	0	0	0	0
		No	12 (100.0)	13 (100.0)	4 (100.0)	29 (100.0)
	CFB >500 msec	Yes	0	0	0	0
		No	12 (100.0)	13 (100.0)	4 (100.0)	29 (100.0)
Day 5	CFB >60 msec	Yes	0	0	0	0
		No	12 (100.0)	13 (100.0)	4 (100.0)	29 (100.0)
	CFB >500 msec	Yes	0	0	0	0
		No	12 (100.0)	13 (100.0)	4 (100.0)	29 (100.0)
Day 85 (EOS)	CFB >60 msec	Yes	0	0	0	0
		No	12 (100.0)	12 (92.3)	4 (100.0)	28 (96.6)
	CFB >500 msec	Yes	0	0	0	0
		No	12 (100.0)	12 (92.3)	4 (100.0)	28 (96.6)

N = number of subjects in the treatment group and n = number of subjects who provided data at the visit.
Percentages are based on the number of subjects in the treatment group (N) as the denominator.
Baseline is defined as the last available, valid, nonmissing assessment before CSL312 administration.
CFB = Change from Baseline.

Source: 16.2.8.6.1 (ADSL, ADEG); Produced: 05AUG2021 17:41; Program: t_eg_qtcx_inc.sas

Source: [Clinical Study Report CSL312_1003](#), pg. 1275

Table 14.3.6.4 12-lead ECG: Number (Percent) Subjects with QTcF Increase from Baseline >60 msec or >500 msec by Visit (Safety Analysis Set)

Intravenous (IV) Subjects					
Visit (Day)	Value		Cohort 3 Japanese & 3 mg/kg IV CSL312 (N=4)	Cohort 4 Japanese & 10 mg/kg IV CSL312 (N=4)	IV Total (N=8)
Day 1	CFB >60 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
	CFB >500 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
Day 3	CFB >60 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
	CFB >500 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
Day 5	CFB >60 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
	CFB >500 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
Day 85 (EOS)	CFB >60 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)
	CFB >500 msec	Yes	0	0	0
		No	4 (100.0)	4 (100.0)	8 (100.0)

N = number of subjects in the treatment group and n = number of subjects who provided data at the visit.
Percentages are based on the number of subjects in the treatment group (N) as the denominator.
Baseline is defined as the last available, valid, nonmissing assessment before CSL312 administration.
CFB = Change from Baseline.

Source: 16.2.8.6.1 (ADSL, ADEG); Produced: 05AUG2021 17:41; Program: t_eg_qtcx_inc.sas

Source: [Clinical Study Report CSL312_1003](#), pg. 1276

Reviewers' comments: Despite reasonable ECG collection schedule and adequate exposure margin, the study lacks placebo control and does not include enough sample size to be used as a substitute for TQT study (ICH E14 Q&A 5.1.).

Study 3001 (CSL312_3001): This was a multicenter, double-blind, randomized, placebo-controlled, parallel-arm, phase 3 study in adolescent (12 to 17 years, inclusive) and adult subjects with HAE.

Subjects were randomized 3:2 to receive either 200 mg garadacimab SC once monthly (Q1M) or placebo SC Q1M for 6 months. Subjects on active treatment received an initial loading dose of 400 mg (2 × 200 mg dose) and subjects on placebo received an initial 2 injections of placebo.

- PK Sampling: Only sparse PK samples were collected (Days 1, 31, 61, 91, 121, 151, and 182)
- ECG sampling: Standard 12-lead ECGs were performed on Day 1 and 182(EOT)

No clinically significant changes in ECG findings from baseline values were reported in the study. There were no reported cases of QT prolongation during the study.

CSL Behring LLC (CSLB)

Confidential
Final Analysis (Database lock: 24Jun2022)

CSL312_3001

Table 14.3.6.1: ECG Results and Changes from Baseline by Study Visit (Safety Analysis Set)

Parameter (unit)	Visit/ Time Point	Statistics	CSL312 200mg (N=39)		Placebo (N=25)	
			Actual	Change[1]	Actual	Change[1]
QTcF Interval, Aggregate (msec)	Visit Day 1	Number Observed	38		25	
		Mean (SD)	401.5 (23.84)		394.5 (24.90)	
		Median	401.5		402.0	
		1st Quartile, 3rd Quartile	385.0, 415.0		371.0, 411.0	
		Minimum, Maximum	361, 472		350, 440	
		95% Confidence Interval	(393.7, 409.3)		(384.2, 404.8)	
	Baseline	Number Observed	38		25	
		Mean (SD)	401.5 (23.84)		394.5 (24.90)	
		Median	401.5		402.0	
		1st Quartile, 3rd Quartile	385.0, 415.0		371.0, 411.0	
		Minimum, Maximum	361, 472		350, 440	
		95% Confidence Interval	(393.7, 409.3)		(384.2, 404.8)	
	Visit Day 182	Number Observed	38	38	25	25
		Mean (SD)	402.7 (22.52)	1.2 (14.43)	387.0 (20.92)	-7.5 (17.03)
		Median	404.5	2.5	388.0	-8.0
		1st Quartile, 3rd Quartile	384.0, 418.0	-8.0, 11.0	370.0, 397.0	-15.0, 0.0
		Minimum, Maximum	353, 463	-45, 26	351, 446	-38, 33
		95% Confidence Interval	(395.3, 410.1)	(-3.6, 5.9)	(378.4, 395.6)	(-14.5, -0.5)

CSL Behring / CSL312_3001: /projects/csbbeh253590/stats/primary/prog/tables/t_ecg01.sas
Produced: 29AUG2022 10:28
Source: 16.2.9.2; UNBLINDED

Page 6 of 7

[1] Change = Change from Baseline, where baseline is defined as the most recent, non-missing value prior to the first study treatment administration (including unscheduled visits) for all assessments. Change from Baseline derived as: visit value - baseline value.

Source: [Clinical Study Report CSL312_3001](#), pg. 576

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrdcrpqt@fda.hhs.gov

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/

ELIFORD N KITABI
04/25/2024 03:34:38 PM

OLUSEYI A ADENIYI
04/25/2024 03:37:39 PM

CHRISTINE E GARNETT
04/25/2024 03:40:25 PM

This is a corrected review that does not change the overall recommendations of the original review dated April 15, 2024

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:	February 19, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761367
Product Name, Dosage Form, and Strength:	Andembry (garadacimab-xxxx ^a) Injection 200 mg/1.2 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CSL Behring
FDA Received Date:	June 29, 2023 and October 13, 2023
TTT ID #:	2023-5414
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

^a Since the nonproprietary name suffix for this BLA has not yet been determined, the nonproprietary name placeholder, "garadacimab-xxxx", is used throughout this review.

1 REASON FOR REVIEW

As part of the approval process for Andembry Injection, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the Andembry prescribing information (PI) and patient information, instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

CSL Behring submitted BLA 761367 on June 29, 2023. However, BLA 761367 received a refusal to file on August 28, 2023, because it was not sufficiently complete to permit a substantive review.^b Thus, CSL Behring submitted a Class 2 resubmission for BLA 761367 on October 13, 2023.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI) and patient information, instructions for use (IFU), container labels, and carton labeling may be improved to promote the 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 in Section 5 for the Division and in Section 6 for CSL Behring. Note that DMEPA 1 is

^b Won K. Refusal to File for garadacimab-xxxx (BLA 761367). Silver Spring (MD): FDA, CDER, OND, DPACC (US). 2023 AUG 08. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ee737>.

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.

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

Table 2. Identified Issues and Recommendations for 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.
2.	There are instances where the nonproprietary name is referenced without a suffix.	The nonproprietary name for biosimilars must include a suffix.	In instances where the PI refers to the nonproprietary name, ensure it includes the conditionally acceptable nonproprietary name suffix when it is determined.

6 RECOMMENDATIONS FOR CSL BEHRING

Table 3. Identified Issues and Recommendations for CSL Behring (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, the proprietary name is denoted by the placeholder “Tradename”.	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our Proprietary Name Request Conditionally Acceptable letter dated April 15, 2024, informing you that the proprietary name, Andembry, was found conditionally acceptable. We recommend replacing the placeholder “Tradename” with the conditionally acceptable proprietary name, Andembry, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2.	For the prefilled syringe presentation: The strength is not expressed as a total quantity per total volume followed by the concentration per mL.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. A number of overdoses have occurred with small-volume parenterals because of health care practitioner or patient confusion when determining the quantity of drug in the container. In most cases, the user noticed the quantity per milliliter or concentration (e.g., 10 mg/mL) but failed to see the net quantity (e.g., 10 mL), which often	Express the product strength as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7>. For example, “200 mg/1.2 mL (167 mg/mL)”

Table 3. Identified Issues and Recommendations for CSL Behring (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		appears in a different location on the container label.	
3.	For the prefilled pen presentation: As currently presented, the volume is not listed in collaboration with the strength.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling.	Revise the strength presentation the read: “200 mg/1.2 mL”
4.	The nonproprietary name suffix is missing from the container labels and carton labeling.	The nonproprietary name for biosimilars must include a suffix.	Include the nonproprietary name suffix placeholder “-xxxx” on your container labels and carton labeling. Subsequently, replace the nonproprietary name suffix placeholder “-xxxx” with the conditionally acceptable nonproprietary name suffix when it is determined and use the intend-to-market presentation of the nonproprietary name and suffix (font, color, etc.) so that we may adequately evaluate your labels and labeling.
5.	The route of administration statement contains the word “(b) (4)”.	We reserve the use of the word “(b) (4)” when there is a safety concern or data that supports the product must be given by a specific route.	We recommend revising the route of administration statement from “(b) (4)” to “For subcutaneous use”.
6.	The “Rx only” statement appears as prominent as other critical information [(e.g., proprietary name, established name, strength, route of	The “Rx only” statement should not compete in size and prominence with critical information on the principal display panel.	Revise the “Rx only” statement so that it does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations

Table 3. Identified Issues and Recommendations for CSL Behring (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	administration)] on the principal display panel.		for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). ^c
Container Labels			
1.	The linear barcode is missing on the prefilled syringe and pen container labels.	The linear barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	Add the product's linear barcode to the prefilled syringe and pen container labels in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text, and in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation). Additionally, ensure the barcode is oriented on the container label such that it is not distorted or obstructed by the container curvature (i.e., oriented in a vertical position) in order to improve scannability.
Carton Labeling			
1.	As currently presented, there is limited distinction between the prefilled syringe and the prefilled pen carton presentations.	A lack of differentiation between cartons may lead to dispensing errors.	Utilize different color fonts, color blocking and/or boxing to increase the prominence of the device platform 'syringe,' and 'pen.'
2.	The statement of dosage currently reads "(b) (4)"	To ensure consistency with the prescribing information.	We recommend revising the statement of dosage to read,

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: <https://www.fda.gov/media/158522/download>.

Table 3. Identified Issues and Recommendations for CSL Behring (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) .”		“Recommended dosage: see Prescribing Information”.
3.	The net quantity statement does not appear on the principal display panel of the container labels and carton labeling where the information is needed for clarity.	Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the container and carton.	Revise “Single-dose prefilled Syringe” and “Single-dose Prefilled Pen” to: “1 Single-dose Prefilled Syringe” and “1 Single-dose Prefilled Pen”.
4.	The storage statement “Storage: Store between 36°F to 46°F (2°C to 8°C). Do not freeze...” could be improved.	It is not immediately clear that the product should be refrigerated.	Revise the storage statement to state to include “refrigerate” verbiage. For example, “Storage: Store refrigerated between 36°F to 46°F (2°C to 8°C). Do not freeze...” Consider bolding this important storage information.
5.	We note the word “(b) (4)” is misspelled.	Correcting the typo will help alleviate confusion.	Correct the statement to “(b) (4)”

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Andembry that CSL Behring submitted on October 13, 2023.

Table 4. Relevant Product Information for Andembry	
Initial Approval Date	N/A
Active Ingredient	garadacimab-xxxx
Indication	prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older
Route of Administration	subcutaneous
Dosage Form	injection
Strength	200 mg/1.2 mL
Dose and Frequency	Initial loading dose of 400 mg (two 200 mg injections), followed by 200 mg once monthly
How Supplied	single-dose prefilled pen or prefilled syringe with needle safety device
Storage	- Store the prefilled pen and prefilled syringe with needle safety device refrigerated at 36°F to 46°F (2°C - 8°C). (b) (4)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error experiences with similar products, we reviewed the following Andembry labels and labeling submitted by CSL Behring.

- Container label(s) received on June 29, 2023
- Carton labeling received on June 29, 2023
- Instructions for Use received on October 13, 2023, available from <\\CDSESUB1\EVSPROD\bla761367\0009\m1\us\114-labeling\annotated-draft-labeling-1-14-12.pdf>
- Prescribing Information and Patient Information(Image not shown) received on October 13, 2023, available from <\\CDSESUB1\EVSPROD\bla761367\0009\m1\us\114-labeling\annotated-draft-labeling-1-14-12.pdf>

F.2 Label and Labeling Images

Container labels

Prefilled Syringe



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/

LISSA C PRINGLE-OWENS
02/19/2025 04:27:30 PM

DAMON A BIRKEMEIER
02/20/2025 07:44:25 AM

MEMORANDUM

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

DATE: December 5, 2023

TO: Debra Birnkrant, M.D.
Director
Division of Antivirals (DAV)
Office of New Drugs (OND)

Sally Seymour, M.D.
Director
Division of Pulmonology, Allergy, and Critical
Care (DPACC)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI, OSIS

SUBJECT: Review of Analytical Inspection of (b) (4)
(b) (4)

Inspection Summary

Per the requests of OND/DAV and OND/DPACC, OSIS conducted an inspection of analytical portion of (b) (4) **NON-RESPONSIVE** (b) (4) **NON-RESPONSIVE** and **CSL312-1004** (BLA 761367, Garadacimab/CSL312) conducted at (b) (4) (b) (4).

At the closeout of inspection, objectional conditions were observed and a two-item Form FDA 483 was issued for under-reporting of sample reanalysis and inaccurate reporting of study activities for Study CSL312-1004. No objectional conditions were observed for Study (b) (4) **NON-RESPONSIVE**.

Based on the inspectional findings and the firm's responses, I conclude that the observations are unlikely to have an impact on study data reliability of Study CSL312-1004. However, the

reported value of one subject sample (Subject # (b) (6), Day 85, 2016 hours; Custom ID (b) (6)) was invalid due to unacceptable variability between replicate wells and should be removed. Additionally, I recommend the review division to verify if the amended bioanalytical report of Study CSL312-1004 (not provided at the time of this review) includes the revisions indicated in the firm's responses.

Inspected Studies

NON-RESPONSIVE

BLA 761367

Study #2: CSL312-1004

Study Title: "A Phase 1, Randomized, Open-label, Parallel-group Study to Compare the Pharmacokinetic Properties of CSL312 Administered by Subcutaneous Prefilled Syringe Assembled to Autoinjector to Prefilled Syringe Assembled to needle Safety Device in Healthy Adult Subjects"

Dates of Study Conduct: October - November 2022

Analytical Site:

(b) (4)

OSIS scientist Yiyue Zhang conducted an inspection of (b) (4)

(b) (4)

- Previous inspection

This was the site's first BIMO analytical BA/BE inspection at the current location after relocation to (b) (4).

(b) (4)

The previous BIMO analytical BA/BE inspection of the site was conducted at the former location ((b) (4)) from (b) (4) . At the conclusion of the previous inspection, Form FDA 483 was not issued and the final classification was NAI.

- Current inspection

The current inspection included a thorough examination of study records (electronic and paper) of method validation and sample analysis, standard operating procedures (SOPs), facility, calibration and maintenance records and audit trails of instruments used in the reviewed studies, as well as interviews with the site's management and staff.

- Inspection findings

At the conclusion of the current inspection, I observed objectionable conditions and issued a two-item Form FDA 483. The Form FDA 483 observations (**Attachment 1**), the firm's response dated (b) (4) (**Attachment 2**), the follow-up response dated (b) (4) (**Attachment 3**), and my evaluations are presented below.

(b) (4)

Yiyue Zhang, Ph.D.
Senior Staff Fellow

Attachments:

Attachment 1. Form FDA 483, Inspectional Observations, issued to

(b) (4)

Attachment 2. (b) (4) written response to Form FDA 483 dated

(b) (4)

Attachment 3. (b) (4) follow-up written response to Form FDA 483 dated (b) (4)

Attachment 4. Summary table of repeat analysis of deactivated samples of Study CSL312-1004

Attachment 5. Concentration results of subject samples analyzed in Run 106 of Study CSL312-1004

Attachment 6. Summary table of repeat analysis of samples from rejected runs of Study CSL312-1004

Attachment 7. Summary table of repeat analysis of samples from rejected Run 65 of Study CSL312-1004

Attachment 8. Concentration results of subject samples analyzed in Run 103 of Study CSL312-1004

Draft: YZ 11/29/2023, 12/01/2023

Edit: GB 12/01/2023, 12/01/2023; AD 12/04/2023

OSIS File#: BE (b) (4) (BLA 761367),

NON-RESPONSIVE

eNSpect Assignment ID:

(b) (4)

eNSpect Op ID: (b) (4)

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

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/

YIYUE ZHANG
12/05/2023 08:27:07 AM

GOPA BISWAS
12/05/2023 08:35:17 AM

ARINDAM DASGUPTA
12/05/2023 08:44:38 AM

ICCR FACILITIES REVIEW MEMO

Date: November 30, 2023

To: Hamet Toure, OPMA DP (facilities assessor)
Hamet.toure@fda.hhs.gov

Maria Scott, OPMA DS (facilities assessor)
Maria.scott@fda.hhs.gov

RPM: Hannah Lee
Hannah.lee@fda.hhs.gov

Office of Combination Products at combination@fda.gov

From: Janice Ferguson, RN, Injection Team, OHT3/DHT3C
OPEQ/CDRH

Through: Shruti Mistry, Assistant Director, Injection Team, OHT3/DHT3C
OPEQ/CDRH

Applicant: CSL Behring GMBH
1020 First Avenue
King of Prussia, PA 19406
FEI# 3003098680

Application # **BLA761367**

Consult # ICC#2300937 ICCR#00950741

Product Name: Garadacimab (CSL312)

Combination Product Intended Use: Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older

Pre-Approval Inspection: **YES (See below)**

For site: CSL Behring GmbH
Emil-von Behring-Strasse
76 35041 Marburg
Germany
FEI# 3003098680

The Office of Health Technology 3 at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA 761367 which will require a device inspection. The following information was provided by the sponsor regarding the manufacture of the CSL312 Pre-filled Syringe with NSD.



Table 3.2.P.3.1-1 Manufacturing and Testing Facilities for CSL312 DP 200mg NSD

Name and Address of Site/Facility and Registration Number	Responsibility/Unit operations	Constitution
CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	Refer to Section 3.2.P.3.1-CSL312 SFP 200mg .	Drug only
	Manufacture (device assembly), release, labelling, packaging and storage of CSL312 DP 200mg NSD	Drug-device combination
CSL Behring AG Wankdorfstrasse 10 3014 Bern Switzerland DUNS Number: 481152762 FEI Number: 3002806716	Device functionality performance stability testing	Drug-device combination
(b) (4)	Device functionality performance release testing	Drug-device combination (device test only)
CSL Behring GmbH Görzhäuser Hof 1 35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	Tryptic digestion and RP-HPLC Peptide Map (Identity test) (refer to Section 3.2.P.5.1-CSL312SFP 200mg) conducted on final labeled and packaged combination product consistent with 21 CFR 610.14.	Drug-device combination (drug test only)



Table 3.2.P.3.1-1 Manufacturing and Testing Facilities for CSL312 DP 200mg AI

Name and Address of Site/Facility and Registration Number	Responsibility/Unit operations	Constitution
CSL Behring GmbH Emil-von-Behring-Strasse 76 D-35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	For CSL312 SFP 200mg, refer to Section 3.2.P.3.1-CSL312 SFP 200mg .	Drug only
	Release of final combination product CSL312 DP 200mg AI.	Drug-device combination
(b) (4)	Assembly of AI sub-assemblies and CSL312 SFP 200mg to manufacture CSL312 DP 200mg AI	Drug and device
	Final labelling, packaging and storage of CSL312 DP 200mg AI	Drug-device combination
	Device functionality performance testing for release	Drug-device combination (device test only)
CSL Behring AG Wankdorfstrasse 10 3014 Bern Switzerland DUNS Number: 481152762 FEI Number: 3002806716	Device functionality performance stability testing	Drug-device combination
CSL Behring GmbH Görzhäuser Hof 1 35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	Tryptic digestion and RP-HPLC Peptide Map (Identity test) (refer to Section 3.2.P.5.1-CSL312SFP 200mg) conducted on final labelled and packaged combination product consistent with 21 CFR 610.14.	Drug-device combination (drug test only)

PRODUCT DESCRIPTION

CSL Behring is requesting approval of Garadacimab (CSL312). The device constituent of the combination product is a Pre-Filled Syringe 200 mg assembled in a needle safety device (NSD) and an autoinjector (AI) which also has a needle safety feature. Both devices contain a fixed subcutaneous dose 200 mg/1.2 mL of drug product.

Figure 2 Schematic Representation of the Device Assembly Process with the CSL312 SFP 200 mg to Manufacture CSL312 DP 200 mg NSD or CSL312 DP 200 mg AI

(b) (4)



Figure 2.3.P-1 CSL312 DP 200mg NSD assembly content (schematic representation)

(b) (4)



Table 3.2.P.7-1 Device Components used for the CSL312 DP 200mg NSD

Item	Attribute	Description
CSL312 SFP 200mg ^a		Section 3.2.P.7-CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.
Plunger rod ^{b,c}		(b) (4)
Needle safety device ^{b,c}		
Extended finger flange ^{b,c}		

- a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
- b Not in contact with the liquid.
- c Direct contact with user.

(b) (4)

Table 3.2.P.7-1 Components for the Autoinjector used for CSL312 DP 200mg AI

Item	Attribute	Description
CSL312 SFP 200mg ^a		Section 3.2.P.7-CSL312 SFP 200mg contains the components, attributes and description/specification for Item CSL312 SFP 200mg.
(b) (4)		

- a Only the (b) (4) of the CSL312 SFP 200mg have direct contact with user.
b Not in contact with the liquid.
c Direct contact with user.

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the finished combination product in Application #BLA761367

- CSL Behring GmbH**
Emil-von Behring-Strasse
76 35041 Marburg
Germany
FEI# 3003098680

Responsibility – *Manufacture (Device assembly), release, labelling, packaging, and storage of CSL312 (Drug Product) DP 200mg Needle Safety Device (NSD).*
Release of final combination product CSL312 DP 200mg Auto-Injector (AI)

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted to 2/21/2022-3/4/2022. The inspection covered drug GMP QS and was classified VAI. The following 483 observations were issued: 1) Written records of investigations do not always meet the appropriate conclusions and follow up; multiple deviations were reported but not properly investigated or followed up.(this included deviation report of mold *Purpureocillium lilacinum* found during IPC sampling of three (b) (4) bulk lots) 2) Product technical complaint (PTC) record did not include sufficient rationale for why investigations of retained samples not necessary such as atypical product appearance/ characteristics (particles/strands of string) 3) Buildings used in manufacture, processing, packing and holding US licensed plasma, bulk drug substances and drug products not always maintained in a state of good repair or cleanliness; 4) Procedures designed to prevent microbiological contamination of drug products purported to be sterile are insufficient; 5) Practice of cleaning validations of lyophilizes inadequate; 6) Procedures for crimping vials for filled sterile products/diluents are insufficient in that it leads to more than 50 complaints and deviations for crimped caps;

Per the EIR report page 30 there was a l.b. noted a lack of follow up on a deviation regarding bioburden count for mold/yeast which was not followed up and not CAPA or Non-CAPA actions were initiated.

It does NOT appear that any device related inspections were performed during this inspection. This site is responsible for assembly of the PFS and release and final testing of the combination product as well as release of the Auto-injector. The last drug inspection was classified as VAI and the 483 noted a lack of follow up for Non-CAPA deviations.

Of note: the previous inspection was conducted 4/30/2018-05/17/2018 was a cGMP surveillance inspection and was classified as OAI with 13 483 observations. This did not appear to be a device related inspection.

Inspection Recommendation:

(1) An 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.

**2. CSL Behring
AG Wankdorfstrasse 10
3014 Bern
Switzerland
FEI# 3002806716**

Responsibility – *Device functionality performance stability testing (PFS)*
Device functionality performance stability testing (AI)

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted 2/10/2020 to 2/18/2020. The inspection covered drug GMP was classified as VAI. The following 483 observations were issued; 1) Written records of investigations for specific deviations did not always include appropriate conclusions or follow-up; 2) appropriate written procedures, designed to prevent microbial contamination of drug products purporting to be sterile were not established or followed; 3) Electronic production and laboratory blank forms/worksheets used were not adequately controlled by the quality control unit or by another document control method (forms not reconciled); 4) Procedures describing the calibration of instruments, apparatus, gauges and recording devices are deficiently written or followed.

It does NOT appear that any device related inspections were performed during this inspection. However, this site is not responsible for major activities related to manufacturing or development of the final combination product only

testing of both the Auto-injector and PFS during stability testing. The devices would be most similar to a Class II device, the drug substance is not high risk, and the drug treats a chronic illness and is not for emergency use.

Inspection Recommendation:

(1) An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

3. [REDACTED] (b) (4)

Responsibility – PFS -Device functionality performance release testing

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted unknown start to [REDACTED] (b) (4). [REDACTED] (b) (4) This facility is a contract testing laboratory. There is no EIR on record to review. The inspection covered drug GMP and was classified VAI. This is named as a testing facility for sterile and non-sterile product. This inspection covered quality, facilities and equipment and laboratory systems. Inspected products covered: [REDACTED] NON-RESPONSIVE [REDACTED] (b) (4). The inspection reported 27 deficiencies to include Majors: [REDACTED] (b) (4)

. Others: [REDACTED] (b) (4)

Previous Inspections: [REDACTED] (b) (4) by [REDACTED] (b) (4) was classified as VAI. And an inspection by FDA was done in [REDACTED] (b) (4) which was classified as NAI.

It does not appear that any device related inspections were conducted during this inspection. However, the firm has had a drug GMP inspection by [REDACTED] (b) (4) in the last 2 years which was classified as VAI. The device is most similar to a class II device (prefilled syringe, the device is not a high-risk substance, and the drug is not for treatment of a chronic condition or emergency condition (for prophylaxis not a rescue treatment).

Inspection Recommendation:

(1) An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or device constituent part, only release performance testing of the PFS.

4. [REDACTED] (b) (4)

(b) (4)

Responsibility – *Assembly of AI sub-assemblies and CSL312 SFP 200 mg to manufacture CSL312 DP 200 mg AI, Final labeling, packaging, and storage of CSL 312 DP200 mg AI.*

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4) to (b) (4). The inspection covered drug GMP and was classified as VAI. The following observations were issued on the 483; 1) (b) (4)

An inspection was conducted (b) (4) to (b) (4). The inspection covered medical device QS and was classified as VAI. The inspection was a pre-approval inspection of a contract assembler of the device constituent part (Autoinjector) of a drug combination product. The firm assembles PFS into an autoinjector device constituent part of for Drug Product Manufacturer and BLA NON-RESPONSIVE and BLA NON-RESPONSIVE. A 483 was issued for the following: (b) (4)

Inspection Recommendation:

(1) An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

5.

(b) (4)

Responsibility – *(AI only) Device functionality performance for release*

Inspectional History –

An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. However, the firm performs performance testing of the Auto-injector at release and not major manufacturing or development of the final combination product. The device is most similar to a Class II device and the drug product is not a high-risk substance and the drug product does not treat a chronic illness or for emergency condition (for prophylaxis not a rescue treatment).

Inspection Recommendation:

(1) An inspection is not required because:

- The firm is not responsible for major activities related to manufacturing and development of the final combination product.

Janice Ferguson, RN, BSN, CRNI

Inspectional Assignment

CDRH recommends a pre-approval inspection under the applicable Medical Device Regulations of CSL Behring GmbH, located in Marburg, Germany (FEI #3003098680).

Firm to be inspected:

- 1. CSL Behring GmbH**
Emil-von Behring-Strasse
76 35041 Marburg
Germany
FEI# 3003098680

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the CSL 312/Garadacimab BLA761367.

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

Inspectional Guidance

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Janice Ferguson, RN
Nurse Consultant
Injection Team
DHT3C
OHT#3: Division of Drug Delivery, General Hospital, and Human Factors

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Shruti Mistry
Assistant Director
Injection Team
DHT3C
OHT#3: Division of Drug Delivery, General Hospital, and Human Factors

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/

HANNAH A LEE

11/30/2023 03:01:18 PM

CDRH review is uploaded on behalf of CDRH assessors.

ICCR FACILITIES REVIEW MEMO

Date: August 22, 2023

To: Candace Gomez-Broughton OPMA/BC
Candace.gomez-broughton@fda.hhs.gov

Yan Wang, OBP RC/TL
Yan.wang1@fda.hhs.gov

RPM: Hannah Lee
Hannah.lee@fda.hhs.gov

Office of Combination Products at combination@fda.gov

From: Janice Ferguson, RN, Injection Team, OHT3/DHT3C
OPEQ/CDRH

Through: Courtney Evans, TL, Injection Team, OTH3/DHT3C
OPEQ/CDRH

Through: Alan Stevens, Assistant Director, Injection Team, OHT3/DHT3C
OPEQ/CDRH

Applicant: CSL Behring GMBH
1020 First Avenue
King of Prussia, PA 19406
FEI# 3003098680

Application # **BLA761367**

Consult # ICC#2300621

Product Name: Garadacimab (CSL312)

Combination Product Intended Use: Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older

Pre-Approval Inspection: **YES (See below)**

The Office of Health Technology 3 at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA 761367 which will require a device inspection. The following information was provided by the sponsor regarding the manufacture of the CSL312 Pre-filled Syringe with NSD.



Table 3.2.P.3.1-1 Manufacturing and Testing Facilities for CSL312 DP 200mg NSD

Name and Address of Site/Facility and Registration Number	Responsibility/Unit operations	Constitution
CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	Refer to Section 3.2.P.3.1-CSL312 SFP 200mg .	Drug only
	Manufacture (device assembly), release, labelling, packaging and storage of CSL312 DP 200mg NSD	Drug-device combination
CSL Behring AG Wankdorfstrasse 10 3014 Bern Switzerland DUNS Number: 481152762 FEI Number: 3002806716	Device functionality performance stability testing	Drug-device combination
(b) (4)	Device functionality performance release testing	Drug-device combination (device test only)
CSL Behring GmbH Görzhäuser Hof 1 35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	Tryptic digestion and RP-HPLC Peptide Map (Identity test) (refer to Section 3.2.P.5.1-CSL312SFP 200mg) conducted on final labeled and packaged combination product consistent with 21 CFR 610.14.	Drug-device combination (drug test only)



Table 3.2.P.3.1-1 Manufacturing and Testing Facilities for CSL312 DP 200mg AI

Name and Address of Site/Facility and Registration Number	Responsibility/Unit operations	Constitution
CSL Behring GmbH Emil-von-Behring-Strasse 76 D-35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	For CSL312 SFP 200mg, refer to Section 3.2.P.3.1-CSL312 SFP 200mg .	Drug only
	Release of final combination product CSL312 DP 200mg AI.	Drug-device combination
	(b) (4) Assembly of AI sub-assemblies and CSL312 SFP 200mg to manufacture CSL312 DP 200mg AI	Drug and device
	Final labelling, packaging and storage of CSL312 DP 200mg AI	Drug-device combination
	Device functionality performance testing for release	Drug-device combination (device test only)
CSL Behring AG Wankdorfstrasse 10 3014 Bern Switzerland DUNS Number: 481152762 FEI Number: 3002806716	Device functionality performance stability testing	Drug-device combination
CSL Behring GmbH Görzhäuser Hof 1 35041 Marburg Germany DUNS Number: 326530474 FEI Number: 3003098680	Tryptic digestion and RP-HPLC Peptide Map (Identity test) (refer to Section 3.2.P.5.1-CSL312SFP 200mg) conducted on final labelled and packaged combination product consistent with 21 CFR 610.14.	Drug-device combination (drug test only)

PRODUCT DESCRIPTION

CSL Behring is requesting approval of Garadacimab (CSL312). The device constituent of the combination product is a Pre-Filled Syringe 200 mg assembled in a needle safety device (NSD) and an autoinjector (AI) which also has a needle safety feature. Both devices contain a fixed subcutaneous dose 200 mg/1.2 mL of drug product.

Figure 2 Schematic Representation of the Device Assembly Process with the CSL312 SFP 200 mg to Manufacture CSL312 DP 200 mg NSD or CSL312 DP 200 mg AI

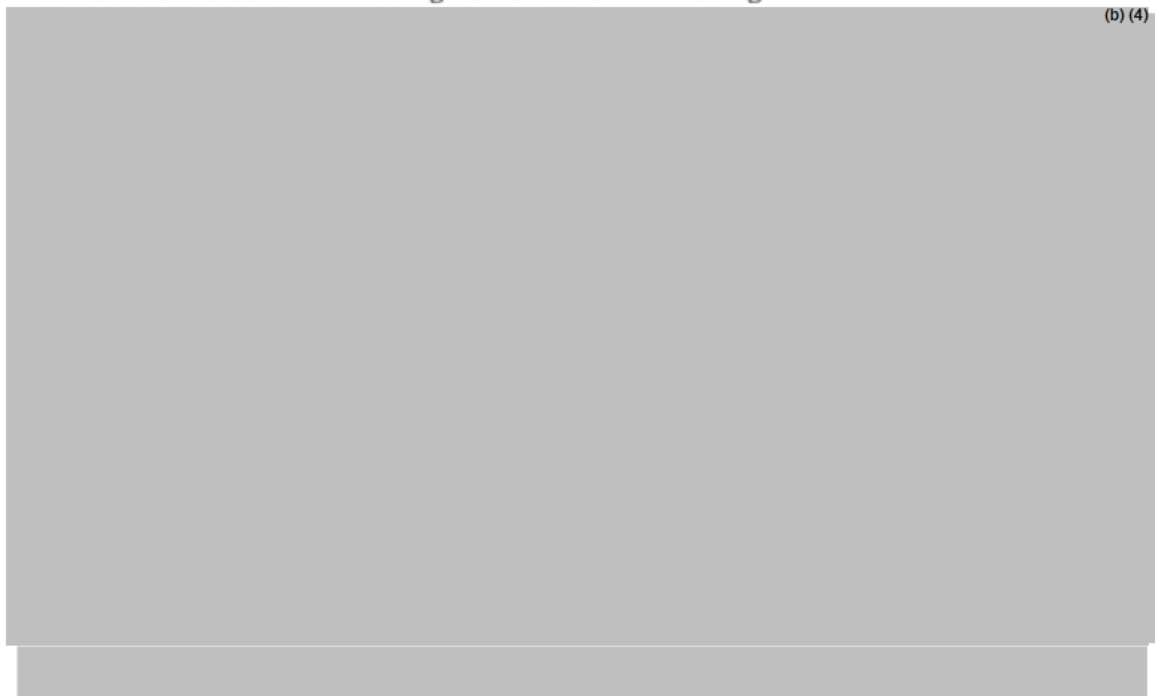


Figure 2.3.P-1 CSL312 DP 200mg NSD assembly content (schematic representation)



REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the finished combination product in Application #BLA761367

- 1. CSL Behring GmbH**
Emil-von Behring-Strasse
76 35041 Marburg
Germany
FEI# 3003098680

Responsibility – *Manufacture (Device assembly), release, labelling, packaging, and storage of CSL312 (Drug Product) DP 200mg Needle Safety Device (NSD).
Release of final combination product CSL312 DP 200mg Auto-Injector (AI)*

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted to 2/21/2022-3/4/2022. The inspection covered drug GMP QS and was classified VAI. The following 483 observations were issued: 1) Written records of investigations do not always meet the appropriate conclusions and follow up; multiple deviations were reported but not properly investigated or followed up. (this included deviation report of mold *Purpureocillium lilacinum* found during IPC sampling of three (b) (4) bulk lots) 2) Product technical complaint (PTC) record did not include sufficient rationale for why investigations of retained samples not necessary such as atypical product appearance/ characteristics (particles/strands of string) 3) Buildings used in manufacture, processing, packing and holding US licensed plasma, bulk drug substances and drug products not always maintained in a state of good repair or cleanliness; 4) Procedures designed to prevent microbiological contamination of drug products purported to be sterile are insufficient; 5) Practice of cleaning validations of lyophilizes inadequate; 6) Procedures for crimping vials for filled sterile products/diluents are insufficient in that it leads to more than 50 complaints and deviations for crimped caps;

Per the EIR report page 30 there was a 1.b. noted a lack of follow up on a deviation regarding bioburden count for mold/yeast which was not followed up and not CAPA or Non-CAPA actions were initiated.

It does NOT appear that any device related inspections were performed during this inspection. This site is responsible for assembly of the PFS and release and final testing of the combination product as well as release of the Auto-injector. The last drug inspection was classified as VAI and the 483 noted a lack of follow up for Non-CAPA deviations.

Of note: the previous inspection was conducted 4/30/2018-05/17/2018 was a cGMP surveillance inspection and was classified as OAI with 13 483 observations. This did not appear to be a device related inspection.

Inspection Recommendation:

(1) An 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

2. CSL Behring
AG Wankdorfstrasse 10
3014 Bern
Switzerland
FEI# 3002806716

Responsibility – *Device functionality performance stability testing (PFS)*
Device functionality performance stability testing (AI)

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 2/10/2020 to 2/18/2020. The inspection covered drug GMP was classified as VAI. The following 483 observations were issued; 1) Written records of investigations for specific deviations did not always include appropriate conclusions or follow-up; 2) appropriate written procedures, designed to prevent microbial contamination of drug products purporting to be sterile were not established or followed; 3) Electronic production and laboratory blank forms/worksheets used were not adequately controlled by the quality control unit by another document control method (forms not reconciled); 4) Procedures describing the calibration of instruments, apparatus, gauges and recording devices are deficiently written or followed.

It does NOT appear that any device related inspections were performed during this inspection. However, this site is not responsible for major activities related to manufacturing or development of the final combination product only testing of both the Auto-injector and PFS during stability testing. The devices would be most similar to a Class II device, the drug substance is not high risk, and the drug treats a chronic illness and is not for emergency use.

Inspection Recommendation:

(1) An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

3.

(b) (4)

Responsibility – *PFS -Device functionality performance release testing*

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted XX/XX/20XX to (b) (4). (b) (4). This facility is a contract testing laboratory. There is no EIR on record to review. The inspection covered drug GMP and was classified VAI. This is named as a testing facility for sterile and non-sterile product. This inspection covered quality, facilities and equipment and laboratory systems. Inspected products covered: **NON-RESPONSIVE**. The inspection reported 27 deficiencies to include Majors: (b) (4)

Others:

(b) (4)

Previous Inspections: (b) (4) by (b) (4) was classified as VAI. And an inspection by FDA was done in (b) (4) which was classified as NAI.

It does not appear that any device related inspections were conducted during this inspection. However, the firm has had a drug GMP inspection by (b) (4) in the last 2 years which was classified as VAI. The device is most similar to a class II device (prefilled syringe, the device is not a high-risk substance, and the drug is not for treatment of a chronic condition or emergency condition (for prophylaxis not a rescue treatment)).

Inspection Recommendation:

(1) An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or device constituent part, only release performance testing of the PFS.

4.

(b) (4)

Responsibility – Assembly of AI sub-assemblies and CSL312 SFP 200 mg to manufacture CSL312 DP 200 mg AI, Final labeling, packaging, and storage of CSL 312 DP200 mg AI.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4) to (b) (4). The inspection covered drug GMP and was classified as VAI. The following observations were issued on the 483; 1) (b) (4)

An inspection was conducted (b) (4) to (b) (4). The inspection covered medical device QS and was classified as VAI. The inspection was a pre-approval inspection of a contract assembler of the device constituent part (Autoinjector) of a drug combination product. The firm assembles PFS into an autoinjector device constituent part of for Drug Product Manufacturer and BLA NON-RESPONSIVE and BLA NON-RESPONSIVE. A 483 was issued for the following: (b) (4)

Inspection Recommendation:

(1) An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

5.

(b) (4)

Responsibility – (AI only) Device functionality performance for release

Inspectional History –

An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. However, the firm performs performance testing of the Auto-injector at release and not major manufacturing or development of the final combination product. The device is most similar to a Class II device and the drug product is not a high-risk substance and the drug product does not treat a chronic illness or for emergency condition (for prophylaxis not a rescue treatment).

Inspection Recommendation:

(1) An inspection is not required because:

- The firm is not responsible for major activities related to manufacturing and development of the final combination product.

Janice Ferguson, RN

Prepared: Janice Ferguson: 8/22/2023
ICC2300621
BLA 761367

Inspectional Assignment

CDRH recommends a pre-approval inspection under the applicable Medical Device Regulations of CSL Behring GmbH, located in Marburg, Germany (FEI #3003098680).

Firm to be inspected:

- 1. CSL Behring GmbH**
Emil-von Behring-Strasse
76 35041 Marburg
Germany
FEI# 3003098680

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the CSL 312/Garadacimab BLA761367.

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

Inspectional Guidance

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Janice Ferguson, RN
Nurse Consultant
Injection Team
DHT3C
OHT#3: Division of Drug Delivery, General Hospital, and Human Factors

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Courtney Evans
Team Leader
Injection Team
DHT3C
OHT#3: Division of Drug Delivery, General Hospital, and Human Factors

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/

HANNAH A LEE
08/28/2023 08:23:57 AM