CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761262Orig1s000

OTHER REVIEW(S)

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	3/22/2022		
To:	Jay Fajiculay		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	Other
From	Kyran Gibson OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Division Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761105, Skyrizi (Risankizumab) ICC2100802 00787990		
Recommendation	**Filing Recommendation Date: 10/14/2021** ☐ 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: 12/28/2021 ☐ 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: 3/21/2022 ☐ 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	BLA 761105
Sponsor	ABBVIE INC.
Drug/Biologic	Skyrizi (risankizumab)
Indications for Use	Crohn's disease
Device Constituent	Other: On-Body Delivery System
Related Files	BLA 761262, DMF (b) (4)

Review Team		
Lead Device Reviewer	*Kyran Gibson*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	
Interim Due Dates	**Meeting/Due Date**
Filing	
74-Day Letter	
Mid-Cycle	
Primary Review	
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

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

☑ Approvable with PMC or PMR, See Section 2.3

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

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			A post-market requirement has been provided regarding verification of the "click" heard once the activation button has been fully pressed.
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	
Facilities & Quality Systems	X			A post-market commitment has been provided regarding implementation of release testing for the Button Activation Force EPR.

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:

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

Post-Market Commitment or Requirement: CDRH has Post-Market Commitments or Requirements	☑
CDRH does not have Post-Market Commitments or Requirements	☐

1. You stated in your response to the Information Request (IR) sent January 17, 2022, that "*a button activation force test will be implemented at* (b) (4) *for release testing of the OBDS device*". Please ensure the release testing procedure is implemented prior to commercialization and distribution of the OBDS device.

2. As a method to mitigate the risk of "Activation button not fully pressed", you have implemented labeling in the Instructions for Use that inform the user they should hear a "click" indicating the button has been fully pressed and the needle is locked out. However, there is no verification testing or acceptance criteria related to this audible

feedback (click, timing, correlation with dose delivery, click decibels) function of your device. Your intended user may solely rely on the audible feedback to indicate the device is ready to injection and the needle is locked out. Provide verifiable design input requirements and testing for your audible click indicating the activation button has been fully pressed.

APPEARS THIS WAY ON ORIGINAL

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3. PURPOSE/BACKGROUND

3.1. Scope

ABBVIE INC. is requesting approval of Skyrizi (risankizumab). The device constituent of the combination product is a Other: On-Body Device.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

CDER has requested CDRH review the BLA supplement submission that includes an on-body delivery system.

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:

Labeling, Risk Analysis, Device Performance, Clinical Study Review, QS, EPR Control Strategy

This review will not cover the following review areas:

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

Risankizumab is available in other configurations such as prefilled pens and prefilled syringes. These have been approved in prior supplements of this submission.

3.2.1. Related Files

BLA 761262, DMF (b) (4)

3.3. Indications for Use

Combination Product	Indications for Use
Skyrizi (risankizumab)	Crohn's disease
Other: On-Body Delivery System	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0139	3.2.P.7 Container Closure System
0136	1.14.1 Draft Labeling 3.2.P.7 Container Closure System 3.2.R Regional Information 5.3 Clinical Study Reports
DMF (b) (4)	3.2.R Regional Information
0171	1.14.1 Draft Labeling 3.2.R Regional Information
0181	1.14.1 Draft Labeling 3.2.P.7 Container Closure System
0198	1.11.4 Multiple Module Information Amendment
0203	1.11.4 Multiple Module Information Amendment

4. DEVICE DESCRIPTION

4.1. Device Description

The device utilized for the delivery of Skyrizi (risankizumab) is the [redacted] (b) (4) On-Body Delivery System (OBDS) developed by and obtained from [redacted] (b) (4) There are two configurations of the OBDS for the delivery volumes of 180 mg/1.2mL and 360 mg/2.4mL. Both configurations are compatible with their respective telescopic screw assembly (TSA) for each pre-filled cartridge (PFC) fill volume. A Letter of Authorization has been provided for the device component DMF provided by [redacted] (b) (4) The OBDS device is co-packaged with the TSA-PFC assembly. The [redacted] (b) (4) OBDS is intended for use by patients or caregivers in a non-healthcare environment or by healthcare professionals in a clinical setting. The treatment is intended to be administered once every eight (8) weeks.

OBDS Device Overview

The OBDS device is a sterile, single use, electromechanical on-body injector that administers a fixed dose of drug product from the PFC into the subcutaneous tissue of the abdomen or thigh. The device contains mechanical, electrical, and software elements.

The device has an integrated adhesive patch for adhesion to the patient's skin. When activated, the device inserts the 29G needle to a nominal 5mm depth and begins drug delivery. The device delivers the entirety of the drug substance contained within the PFC over a time of approximately 5 minutes at a constant delivery rate.

[redacted] (b) (4)

(b) (4)

[redacted]

4.2. Steps for Using the Device

1. Check expiration dates, let cartridge warm to room temperature, gather supplies, wash hands, remove OBDS from packaging and inspect.
2. Open OBDS door, inspect cartridge, insert cartridge, close OBDS door.
3. Choose injection area, clean, expose adhesive, place on skin.
4. Start injection, wait to finish, remove OBDS from skin.
5. Inspect OBDS and dispose.

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 sponsor has provided a comprehensive, detailed device description within Supplement 0136 in BLA 761105 and the manufacturer, [redacted] (b) (4) has provided additional documentation located in DMF [redacted] (b) (4) The device description includes the indications for use, method of injection, drug/biologic information, dose capability, packaging configuration, environment of use, engineering drawings/images, safety features, and materials.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☑
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist			
Description	**Present**		
	Yes	**No**	**N/A**
Description of Device Constituent	X		
Device Constituent Labeling	X		
Letters of Authorization	X		
Essential Performance Requirements defined by the application Sponsor	X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor	X		

Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing		X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility	X		
	Software	X		
	Cybersecurity			X
	Electrical Safety	X		
	EMC/RF Wireless	X		
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

The sponsor has not provided the following/the documentation is difficult to find:

- CAPA Procedure
- Control Strategy for EPRs

A reviewer guide has also been requested to navigate the documentation easily to ensure all information is present and adequate for filing. The sponsor has provided the documentation and location of documentation in response to the information request.

The sponsor has provided summary reports for design verification and validation. The reports contain the necessary information for an attribute analysis; however, raw data is not provided for the samples tested. The full reports can be requested as a review issue.

5.2. Facilities Information

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Component receiving, incoming inspection, assembly, packaging, testing, storage, final release TSA and OBDS manufacture; OBDS labeling, packaging (blister), release testing, storage

Inspectional History

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

☑ Inspection was conducted (b) (4). The inspection covered medical device QS and was classified NAI. The inspection was a Level I abbreviated inspection of a (b) (4) contract manufacturer was conducted as part of the Medical Device Division 3 work plan for (b) (4)

☐ 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 choose an item 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 Choose an item.

☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	OBDS device design and design verification testing

Inspectional History
☐ An analysis of the firm's inspection history over the past 2 years:
Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ 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 choose an item 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 Choose an item.

☑ An inspection is not required because the device verification testing will be analyzed as part of the review.

Firm Name:	AbbVie Inc.
Address:	1401 Sheridan Road North Chicago, IL 60064
FEI:	1411365
Responsibilities:	Design verification testing, release, and stability of the OBDS combination product

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 8/14/2018 to 8/24/2018. The inspection covered drug CGMP and was classified NAI.

☐ 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 choose an item 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 Choose an item. ☑ An inspection is not required because the verification, release, and stability testing will be analyzed during review.

Firm Name:	AbbVie Inc.
Address:	1 North Waukegan Road North Chicago, IL 60064
FEI:	3009751352
Responsibilities:	OBDS combination product design, design verification testing, assembly of TSA to the bulk PFC, labeling of TSA-PFC assembly, in-process testing of the TSA-PFC assembly, labeling of the OBDS combination product blister, TSA-PFC assembly insertion in blister, secondary packaging of OBDS combination product, storage of bulk PFC, TSA, blistered OBDS device and the OBDS combination product
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☑ Inspection was conducted 2/11/2019 to 2/15/2019. The inspection covered drug CGMP and was classified NAI. ☐ 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.	

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Sterilization of blistered OBDS device
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☑ Inspection was conducted (b) (4) The inspection covered medical device QS and was classified NAI. This was a preannounced inspection of a contract sterilizer; conducted as a Post-market Approval Inspection for PMA Post Market (b) (4) ☐ 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 choose an item 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 Choose an item. ☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Sterilization of blistered OBDS device
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☑ Inspection was conducted (b) (4) The inspection covered medical device QS and was classified NAI. The Premarket Approval (PMA) inspection of this contract sterilizer was requested by CDRH to cover sterilization of the (b) (4) (b) (4) referenced in a PMA (b) (4) ☐ 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 choose an item 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 Choose an item. ☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.	

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
The remaining facilities provided in the sponsor's 356h form were not reviewed for inspection requirement as activities do not relate to CDRH review.

The manufacturing process for the OBDS was unclear in the original documentation provided by the sponsor. An information request was sent to determine the manufacturing and packaging process of the OBDS. In Sequence 0139, the sponsor stated the device is obtained from (b) (4) and undergoes an incoming QA inspection prior to co-packaging with the TSA-PFC assembly. The sponsor responded to the IR with information regarding the facilities and manufacturing process to finalize review of the outlined device facilities.

The intended use of the drug + device combination product is treatment for patients diagnosed with Crohn's disease.

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:

AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Reviewer Comments
The information and documentation that could not be located during the filing review was resolved via an Information Request with the sponsor. The documentation has been located and the sponsor supplied a Reviewer Guide to locate information relating to the submission.

Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A

74-Day Letter Deficiencies: ☐ Yes ☑ No ☐ N/A

	Date Sent: **10/6/2021**	**Date/Sequence Received:** **10/8/2021**
Information Request #1	Your submission has identified several facilities as involved in the manufacturing of the OBDS final combination product. However, the manufacturing process of the OBDS and associated facility responsibilities are unclear. Please provide the following:	

	a. Identify the facility or facilities responsible for designing, fabricating, assembling, labeling, packaging, holding, and storing the finished combination product. For each facility identified, please include the detailed responsibilities correlating to the manufacturing process of the OBDS combination product. b. From your documentation provided, the OBDS final assembly step is performed at AbbVie Inc. It is unclear what assembly steps are conducted at AbbVie and what prior manufacturing process steps for the OBDS are conducted at the supplier level. Please clarify the manufacturing steps at each facility at which the OBDS is manufactured and/or assembled. c. If applicable, explain how the AbbVie manufacturing sites identified will control the manufacturing of the combination product through receiving and/or incoming acceptance activities from the OBDS supplier. d. Specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. Please describe each of these activities. e. Please ensure that you provide an up-to-date 356h form to include all sites involved in the manufacturing of your OBDS product.
Sponsor Response	Reviewed in Filing Review Section.

	Date Sent: **10/7/2021**	**Date/Sequence Received:** **10/12/2021**
Information Request #2	The CAPA documentation and Control Strategy for your device's EPRs are unable to be located within your submission. Please provide the location of these documents or submit the requested documents. Please provide a reviewer guide for the device constituent that includes the locations of documents such as Essential Performance Requirement specifications, verification and validation testing, verification testing completed after stability and shelf-life testing, transportation testing, and quality systems documentation.	
Sponsor Response	Reviewed in Quality Systems/Manufacturing Controls Section.	

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
MRI Labeling/Symbols	X		
RF/Wireless Labeling/Symbols			X

Reviewer Comments
The labeling provided includes images of proposed labels for the carton and container. The images have been provided for the 2.4mL PFC fill volume. Labeling between the two configurations should be the same except for the PFC volumes.

The annotated labeling text includes the PI. In this document, the information consist of indications and usage, dosage forms and strengths, warnings and precautions, use in specific populations, clinical pharmacology, nonclinical toxicology, clinical studies, storage and handling, patient counseling information, medication guide, and instructions for use for each presentation of the drug substance.

The instructions for use for the OBDS contains "Important information you need to know before injecting SKYRIZI" which include warnings for the operation and handling of the device. The instructions also contain a section for storage and preparation for use for the OBDS. Diagrams of the OBDS and TSA-PFC are provided for users to read. After the step-by-step instructions, there is a symbol key for the visual indications within the device (i.e., LED colors and meanings). There is a section containing FAQs and another section for the disposal of the OBDS. There is a glossary of symbols present on the labeling. Additional information states the device is a Type BF applied part.

However, the labeling does not include Electrical Safety, EMC, or MRI labeling. The labeling does not require Software Version or RF/Wireless labeling. The sponsor should include the appropriate labeling components for the device. See Mid-Cycle Deficiency 1 – Not resolved [EMC labeling], IR #2 – Resolved.

The BE and HF studies were conducted in parallel with some changes deriving from the complaints within the BE study implemented before initiation of the HF study. The sponsor states the HF expert review conducted concluded that "the IFU changes are logical and rationale improvements, and that additional post summative testing was not necessary". Any issues with the HF studies will be conveyed by DMEPA.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Type-of-use (e.g., personal, professional, single-use, reusable, labeled and sold for only one patient)	X		
Intended patient population	X		
Areas of the body for injection	X		
Target tissue and injection sites	X		
Dose setting and administering an injection	X		
How to ensure a full dose is delivered	X		
Injection depth	X		
Environmental conditions of use and storage	X		
Proper disposal	X		

Reviewer Comments
Device-specific labeling is acceptable.

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:

The sponsor has revised their labeling to include Electrical Safety, EMC, and MRI labeling for the device constituent. Other disciplines in the review team will also review the adequacy of the labeling.

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 See *6.3 Clinical Labeling Review* comments above.		

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

	Date Sent: **12/28/2021**	**Date/Sequence Received:** **1/10/2022**
Mid-Cycle Deficiency #1	You have provided proposed labeling for the OBDS including carton and container labels, Prescribing Information, and Instructions for Use. However, the labeling does not include elements for Electrical Safety, EMC, and MRI Safety. This information is needed to ensure use of the device in its intended environments. Please provide the following: • Electrical Safety: You should include the standards to which the device was tested. • EMC: The FDA-recognized standard 60601-1-2 includes specifications for testing and labeling. EMC labeling informs users about your intended environment of use, essential performance, EMC test levels, limitations, and precautions that supplement EMC testing to help assure and maintain Basic Safety and essential performance. This information is important so that users can use your device safely and for the purposes for which it is intended (21 CFR 801.5 and 801.109(c)). Please provide EMC information in the device labeling as specified in Clause 5 of 60601-1-2 and recommended by Section 2.I of the FDA guidance document "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically - Powered Medical Devices" (https://www.fda.gov/media/94758/download). In addition, the labeling should help users to identify and mitigate electromagnetic interference if it is encountered. • MRI: You should include whether the OBDS is MR Unsafe, MR Conditional, or MR Safe. Please refer to the FDA guidance titled "Understanding MRI Safety Labeling" (https://www.fda.gov/media/101221/download) for further information on MRI safety labeling.	
Sponsor Response	*AbbVie has revised the Instructions for Use (IFU), carton, and blister cover labeling to address electrical safety, EMC, and MRI safety (refer to the revised and redlined IFU in Module 1.14.1.3 included in this submission. The updated carton and blister cover labeling will be located in Module 1.14.1.1 of the planned submission under BLA 761105/S-016 (eCTD Sequence 0172) on January 11, 2022.* *The IFU for the OBDS combination product has been revised to include the following statements (refer to the revised and redlined labeling test provided in Module 1.14.1.3):* • *Electrical Safety – Under Additional Information of the IFU the following statement was added: "On-body injector complies with ISO 11608-1:2014 and IEC 60601-1-2:2014"* • *EMC – In step 3 of the IFU, the following statement was added: "Keep electronic devices including cell phones at least 12 inches (30 cm) from On-Body Injector until injection is complete". Under Additional Information of the IFU, the following statement was added: "Keep electronic devices including cell phones at least 12 inches (30 cm) from the On-Body Injector until injection is complete. The potential impact of electronic interference is unknown when the On-Body Injector is operated within 12 inches (30 cm).* • *MRI – Under Additional Information of the IFU, the following statement was added: "Do not expose the on-body injector for Skyrizi to Magnetic resonance (MR) Environment (e.g., MRI)". In addition, the MR Unsafe symbol has been added to the carton labeling as well as the blister cover labeling.*	

Reviewer Comments	The sponsor's updates to the Electrical Safety and MRI labeling are appropriate. However, the information added to the labeling regarding EMC is not adequate. The sponsor should include intended environment of use, essential performance, EMC test levels, limitations, and precautions that supplement EMC testing.
Response Adequate:	☐ **Yes** ☑ **No, See IR # Sent on 1/14/2022**

Follow-On Deficiency	**Date Sent: 1/14/2022**	**Date/Sequence Received: 1/21/2022**
Information Request #2	You have updated your labeling to include statements for Electrical Safety, EMC, and MRI. However, the EMC labeling does not include the information contained in Clause 5 of IEC 60601-1-2. According to the standard, the Instructions for Use shall include the intended use environment, essential performance, applicable warning statement(s). The labeling should also include a technical description including the compliance for each emissions and immunity standard or test specified by the standard. You should revise your labeling to include the required information outlined in the standard.	
Sponsor Response	*AbbVie has updated the Instructions for Use (IFU) to include:* • *The intended use environment* • *Essential Performance* • *Applicable warning statements* • *A technical description including the compliant for each emissions and immunity standard or test specified by the standard*	

Electromagnetic Compatibility (EMC) of the On-Body Injector

The On-Body Injector is intended for home use or use in a professional healthcare environment and complies with ISO 11608-1:2014 and IEC 60601-1-2:2014.

Care should be taken to use the On-Body Injector within the following specific limits and environments to avoid adversely impacting the performance (missed or incomplete SKYRIZI dose).

- Keep electronic devices including cell phones at least 12 inches (30 cm) from the On-Body Injector until injection is complete. The potential impact of electronic interference is unknown when the On-Body Injector is operated within 12 inches (30 cm).
- Do not expose the On-Body Injector to Magnetic Resonance (MR) Environment (e.g., MRI).
- If it is used adjacent to other electrical equipment, observe the On-Body Injector and other equipment to ensure it is operating normally.

Emissions

Emissions test name	Test levels
Radiated Radio frequency electromagnetic fields	Per CISPR 11, class B

Electromagnetic Immunity

Test Name	Test Levels
Electrostatic discharge (ESD)	± 8 kV contact ± 2 kV, ± 4 kV, ± 8 kV, ± 15 kV air
Radio frequency electromagnetic field	10 V/m 80 MHz – 2.7 GHz
Power frequency 50 Hz magnetic field	30 A/m

The enclosure port immunity to RF wireless communications equipment complies with IEC 60601-1-2:2014.

Reviewer Comments	The labeling changes are acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

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
The to-be-marketed device was not used in the Phase 3 clinical study. The sponsor has performed a BE bridging study. The sponsor has conducted an HF study for the OBDS device. The performance of the OBDS in the BE and HF studies will be reviewed in their respective sections.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Delivered Volume Accuracy	(b) (4)
Delivery Time	
Audible/Visual Feedback	

	(b) (4)
Adhesion Force	
Needle Extension Length	
Button Activation Force	

Reviewer Comments
The sponsor has submitted a document containing the EPRs for the device. The document contains AbbVie and (b) (4) specifications. The output specifications for the above EPRs are aligned. The purpose is for the incoming acceptance and release activities reviewed in *Section 12.3*.

The recommended EPRs for OBDS injectors are listed below:

- Delivered Volume Accuracy
- Activation Force
- Injection Time
- Extended Needle Length
- Adhesive/Adhesion Peel Force
- Audible/Visual Feedback

The EPRs recommended have been established by the sponsor quantitatively. The design inputs are acceptable. The adequacy of these specifications and the device's ability to meet these specifications will be reviewed.

7.3. 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 The sponsor has provided the necessary documentation for review. The EPRs identified are aligned with expectations from the Agency. The adequacy of the specifications will be reviewed in *Section 9*.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

Risk analysis documentation was obtained from BLA 761105 Supplement 0136 and DMF (b) (4) The documentation provided in Supplement 0136 was provided by AbbVie which included a Risk Management Plan, Risk Management Report, SRA, UERA, and pFMEA. The documentation provided in DMF (b) (4) was provided by (b) (4) (b) (4) which included a Risk Management Plan, Risk Management Report, Risk Assessment, dFMEA, and hazard analyses associated with software.

8.1. Risk Management Plan

(b) (4)

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(b) (4)

The RMPs provided by AbbVie and (b) (4) Pharma are acceptable.

8.2. Hazard Analysis and Risk Summary Report

(b) (4)

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(b) (4)

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8.3. 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 The risk documentation provided by AbbVie and (b) (4) are adequate.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification – Device Performance, Mechanical, & Environmental

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation Method Acceptable (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Delivered Volume Accuracy	1.2 mL: (b) (4) mL 2.4 mL: (b) (4) mL	95% Confidence 97.5% Reliability N = 60, 124 1.2mL and 2.4mL configurations	Y – Standard Conformance	Y	Y
Delivery Time	1.2 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds 2.4 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds	95% Confidence 95% Reliability N=45, 60, 124 Attribute test 0 failures 1.2mL and 2.4mL configurations	Y – Tested with Dose Accuracy	Y	Y
Audible/Visual Feedback	Buzzer shall operate at the state of Delivery Completion Visual notification of delivery completion shall be denoted by Green Solid LED	Type test N=1, no rejects	Y – BE, HF, Adhesive Study	Y	Y
Adhesion Force	(b) (4) N (removal)	95% Confidence 95% Reliability N=93 per lot (three lots tested) Variable	Y – Adhesive Study	Y	Y
Needle Extension Length	(b) (4) mm, (b) (4) mm	95% Confidence 95% Reliability N=30 Variable 2.4mL configuration	Y – BE, HF, Adhesive Study	Y	Y
Button Activation Force	(b) (4) N (b) (4) N	95% Confidence 95% Reliability N=30	Y – BE, HF, Adhesive Study	Y	Y

		Variable 2.4mL configuration			
Vibration	Device shall retain functionality when subjected to vibration per ISO 11608-1 (2014) clause 10.9; (b) (4) mm @ (b) (4) Hz	95% Confidence 95% Reliability Delivery Volume – Variable Delivery Time - Attribute N=20 for all configurations (old buzzer + old battery, old battery + new buzzer) 1.2mL and 2.4mL configurations	Y – Standard Conformance	N	N
Dry-Heat, Cold Storage	**Delivered Volume Accuracy** 1.2 mL: (b) (4) mL 2.4 mL: (b) (4) mL **Delivery Time** 1.2 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds 2.4 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds	95% Confidence 95% Reliability Delivery Volume – Variable Delivery Time - Attribute N=60 for all configurations (old buzzer + old battery, old buzzer + new battery) 1.2mL and 2.4mL configurations	Y – Standard Conformance	N	N
Device Transportation Altitude	**Delivered Volume Accuracy** 1.2 mL: (b) (4) mL 2.4 mL: (b) (4) mL **Delivery Time** 1.2 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds 2.4 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds	95% Confidence 95% Reliability Delivery Volume – Variable Delivery Time - Attribute N=60, 20 for all configurations (old buzzer + old battery, old buzzer + new battery) 1.2mL and 2.4mL configurations	Y – Standard Conformance	N	N
Cool, Standard, & Warm	**Delivered Volume Accuracy** 1.2 mL: (b) (4) mL 2.4 mL: (b) (4) mL	95% Confidence 95% Reliability Delivery Volume – Variable Delivery Time - Attribute	Y – Standard Conformance	N	N

	Delivery Time 1.2 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds 2.4 mL: (b) (4) seconds ≤ t ≤ (b) (4) seconds	N=60 for all configurations (old buzzer + old battery, old buzzer + new battery) 1.2mL and 2.4mL configurations			

9.1.2. Additional Design Input Evaluation

(b) (4)

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9.1.5. Adhesive Study

AbbVie conducted a clinical study with healthy subjects to evaluate the quality of the adhesion of the OBDS on human skin over a range of conditions including placement location and duration of wear. The F20-282 study was conducted according to a randomized, open label design. The study enrolled 36 volunteers – 12 males and 24 females. Applications to the abdomen (regimen A) and upper thigh (regimen B) were tested. Subjects were requested to follow a movement protocol after adherence in two periods. The first period was five minutes in duration and period 2 was thirty minutes in duration. Subjects were instructed to walk, sit, reach, and bend to mimic physical activities.

		Regimens	
Sequence Group	**Number of Subjects**	**Period 1**	**Period 2**
I	18	A	B
II	18	B	A
Regimen A:	Application to the abdomen		
Regimen B:	Application to the upper thigh		

	Regimen A	**Regimen B**	**Period 1**	**Period 2**
Mean % Surface Area of Device Adherence to Skin	67%	59%	61%	65%

	Period 1		**Period 2**	
Movement Protocol Step	**Regimen A N = 18**	**Regimen B N = 18**	**Regimen A N = 18**	**Regimen B N = 18**
Initial Contact	100%	100%	100%	100%
Walking	100%	94.4%[1]	100%	100%
Bending	100%	100%	100%	100%
Reaching	100%	94.4%[1]	100%	100%
Sitting	100%	100%	100%	94.4%[2]
End of 5 minutes	100%	94.4%[1]	--	--
End of 30 minutes	--	--	100%	94.4%[2]

Reviewer Comments
The adhesive study was performed to determine the adherence of the OBDS to the skin in the locations indicated in the labeling. There were some observations of an experience of no full adhesion on the outer edges for two participants. The peeling was not localized to a specific area and did not occur near the area of

needle insertion. However, the OBDS remained adhered for the time allotted. The sponsor states that when full OBDS device adherence was not observed, it did not result in dislodgement of the device.

9.1.6. Biocompatibility

The (b) (4) DMF contained biocompatibility testing according to ISO 10993-1:2018 *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*. The OBDS can be separated into two different types of patient contact – **surface contact** (adhesive patch and shells) and **externally communicating with tissue contact**. The sponsor states the device used as intended (approximately 5 minutes once every 8 weeks for up to 25 years) would be a cumulative exposure of 14.6 hours over the lifetime of a patient calculating a total **limited contact duration** over the lifetime of the patient. The manufacturer has categorized the device into three groups and tested them independently:

- Shell Assembly (with Pad Printed Cover): Surface Device, Intact Skin Contact
  - Cytotoxicity, Irritation, Sensitization
- Adhesive Patch Assembly: Surface Device, Intact Skin Contact
  - Cytotoxicity, Irritation, Sensitization
- Fluid Path Assembly: Externally Communicating Device, Tissue Contact
  - Cytotoxicity, Irritation, Sensitization, Chemical Characterization, Acute Systemic Toxicity, Material Mediated Pyrogenicity, Subchronic Toxicity, Genotoxicity, Hemocompatibility

Endpoint	Test Method	Extraction and Test Method Acceptability	Test Result
Shell Assembly			
Cytotoxicity – ISO 10993-5	ISO MEM elution using L-919 Mouse Fibroblast Cells	Extraction: MEM with (-) HDPE, (+) Latex; 37C for 24 hours; triplicates Test method acceptable	No reactivity for test article or negative control Positive control had severe reactivity
Sensitization – ISO 10993-10	ISO Guinea Pig Maximization Sensitization Test	Extraction: SC, SO; 50C for 72 hours 10 test, 5 control Assessed at 24 & 48 hours Positive control study (DNCB) Test method acceptable	No dermal reactions
Irritation – ISO 10993-10	ISO Intracutaneous Irritation Test	Extraction: SC, SO; 50C for 72 hours 3 rabbits	SC: 0.0 (negligible) SO: 0.0 (negligible)

		Tested at 1, 24, 48, & 72 hours Test method acceptable	
Adhesive Assembly			
Cytotoxicity – ISO 10993-5	ISO MEM elution using L-919 Mouse Fibroblast Cells	Extraction: MEM with (-) HDPE, (+) Latex; 37C for 24 hours; triplicates Test method acceptable	No reactivity for test article or negative control Positive control had moderate reactivity
Sensitization – ISO 10993-10	ISO Guinea Pig Maximization Sensitization Test	Extraction: SC, SO; 50C for 72 hours 10 test, 5 control Assessed at 24 & 48 hours Positive control study (DNCB) Test method acceptable	No dermal reactions
Irritation – ISO 10993-10	ISO Intracutaneous Irritation Test	Extraction: SC, SO; 50C for 72 hours 3 rabbits Tested at 1, 24, 48, & 72 hours Test method acceptable	Primary Irritation Index: 0.2 There was one animal death due to gastroenteritis and was unrelated to the test article administration
Fluid Path Assembly			
Cytotoxicity – ISO 10993-5	ISO MEM elution using L-919 Mouse Fibroblast Cells	Extraction: MEM with (-) HDPE, (+) Latex; 37C for 24 hours; triplicates Test method acceptable	No reactivity for test article or negative control Positive control had severe reactivity
Sensitization – ISO 10993-10	ISO Guinea Pig Maximization Sensitization Test	Extraction: SC, SO; 50C for 72 hours 10 test, 5 control Assessed at 24 & 48 hours	No dermal reactions

		Positive control study (DNCB) Test method acceptable	
Irritation – ISO 10993-10	ISO Intracutaneous Irritation Test	Extraction: SC, SO; 50C for 72 hours 3 rabbits Tested at 1, 24, 48, & 72 hours Test method acceptable	SC: 0.0 (negligible) SO: 0.0 (negligible)
Acute Systemic Toxicity – ISO 10993-11	ISO Acute Systemic Injection Test	Extraction: SC, SO; 50C for 72 hours 20 mice, 50 mL/kg injection, SC-IV, SO-IP Assessment at 4, 24, 48, and 72 hours Test method acceptable	SC: 0/5 test animals for fatalities, all appeared normal at timepoints, and slight weight gain SO: 0/5 test animals for fatalities, all appeared normal at timepoints, and slight weight gain
Hemocompatibility – ASTM F756	ASTM Hemolysis Assay – Extract Method	(-) control HDPE (+) SWFI Vehicle: CMF-PBS; 50C for 72 hours Appearance of extract: clear Blood: anticoagulated whole rabbit blood, pooled, diluted 3 rabbits	Hemolytic Index: 0.0% (test article in direct contact with blood) Hemolytic Index: 1.3% (test article extract)
Pyrogenicity – ISO 10993-11	ISO Material Mediated Rabbit Pyrogen	Extraction: SC; 50C for 72 hours 8 rabbits Test method acceptable	Maximum temperature rise for test rabbits: 1.3C (original) Maximum temperature rise for test rabbits: 1.9C (continuation)

9.1.7. Sterilization & Packaging Validation

1. Sterilant: Ethylene Oxide	
a. **Sterilization method** description (e.g., Steam (moist heat), EO, Radiation):	EO
b. A description of the **sterilization chamber** if not rigid:	Not applicable
c. Information regarding Established B methods	Not applicable
d. **Sterilization site**:	(b) (4)
e. For chemical sterilants (e.g., EO, H2O2), the maximum levels of **sterilant residuals** that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.	(b) (4)
2. A description of the Validation Method for the sterilization cycle (not data): (Full citation of an FDA recognized standard is recommended including date (e.g., ANSI/AAMI/ISO 11135:2007)),	(b) (4)
3. Sterility assurance level (SAL): (e.g., 10^{-6} for all devices (except 10^{-3} for devices that contact intact skin))	10^{-6}
5. Packaging a. A description of the packaging (not including package integrity test data):	Two compartment bluster with a cover and sealed (b) (4) lid that forms the sterile barrier
b. Description of the package test methods	ASTM D4169-16 ASTM F1929 ASTM F1886 ASTM F88 ASTM F2096

9.1.8. EMC

EMC & RF – AbbVie

AbbVie provided a summary of EMC testing within the Design Verification documentation. The following standards were utilized in this testing:

- IEC 60601-1-2:2014 Edition 4.0 *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance*
- ISO 11608-1: 2014 *Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems*
- ISO 11608-4:2006 *Pen-injectors for medical use – Part 4: Requirements and test methods for electronic and electromechanical pen-injectors*

Tests were performed on both configurations. The configurations differ from the final commercial configurations due to the battery change and (b) (4) revision caused by the (b) (4). The tested configurations were built with (b) (4) batteries instead of Murata batteries used in the final finished combination product. The sponsor states since the EMI is great and the impedance is lower the EMI would affect the circuit rather than the batteries. Thus, replacing the batteries has no impact on EMI.

EMC & RF – (b) (4)
The EMC testing provided by (b) (4) in the DMF include the following tests:

(b) (4)

All samples for both configurations were indicated as “Pass”.

Reviewer Comment
AbbVie and (b) (4) provided documentation on EMC testing for the OBDS. The documentation in the BLA and DMF had missing information. It is unclear which test report was intended to be the document reviewed. See Mid-Cycle Deficiency 3 – Resolved.

Sponsor Response – Reviewer Comments
The EMC test reports specified for reference were performed by (b) (4) located in the DMF. The report located in the DMF contains the EMC and Electrical Safety testing for the 1.2mL and 2.4mL configurations of the OBDS.

9.1.9. Needle Safety

(b) (4) performed testing on the needle safety mechanism according to ISO 29308:2011 *Sharps injury protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling*. Some tests performed were guided by ISO 11608-5:2012 *Needle-based injection systems for medical use – Requirements and test methods – Part 5: Automated*. This feature was tested after shelf-life testing.

Test Description	Product Requirements Document (PRD)	Confidence/ Reliability	Sample Size Test Type Criteria	Data Range	Test Results
Needle shielding	PRD 3.10.a Safety latch in open position shields needle	95%/97.5%	N=119 Attribute Accept:0 Failures	Not numerical data	Pass
Safety latch overriding force	PRD 3.10.b Safety Latch shall resist (b) (4) forces in closing, opening and side orientation.	Closing Orientation: 95%/99%	N=299 Attribute Accept:0 Failures	Not numerical data	Pass
		Opening Orientation: 95%/97.5%	N=119 Attribute Accept:0 Failures	Not numerical data	
		Side Orientation: 95%/97.5%	N=119 Attribute Accept (b) Failures	Not numerical data	
Safety latch opening force	PRD 8.1.a The force generated by safety latch spring at closed position shall be ≥ (b) gf.	95.0%/97.5%	N=40 (minimum required N=30) One-sided variable: (b) (4) gf	Force (gf) Mean:17 Std: 0.4 Max: (b) (4) Min:	Pass
Safety latch deployment time	PRD 8.2.a Safety latch deployment time shall be ≤ (b) sec	95.0%/97.5%	N=119 Attribute Accept: 0 Failure	Time (s) Max: (b) (4) Min:	Pass
Safety latch closing force	PRD 3.12.b Safety Latch closing force shall be (b) kg	95.0%/95.0%	N=40 (minimum required N=30) One-sided variable: (b) (4) kgf	Force (kg) Mean: 0.01 Std: 0.0004 Max: (b) (4) Min:	Pass
Needle pre-injection position	PRD 5.3.a Needle pre-injection shall be recessed ≥ (b) mm	95.0%/95.0%	N=35 (minimum required N=30) One-sided variable (b) (4) mm	(mm) Mean: 0.7 Std: 0.08 Max: (b) (4) Min:	Pass

9.1.10. Software

Software-Related Documentation	Present/Absent	Comments
Software/Firmware Version	Present	(b) (4) 1.2mL: 2.4mL:
Level of Concern	Present	(b) (4)

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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 review issues identified with the performance testing have been resolved.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
	12/28/2021	**1/10/2022**

(b) (4)

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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
This information was obtained from the following **documents**:

- Tabular Listing of Clinical Studies – CD
- M19128-synopsis
- M19128-body

Study Name	A Phase 1, Pharmacokinetic Comparability Study of Intravenous and Subcutaneous Administration of Risankizumab in Healthy Subjects
Study Type	BE
Objectives/Endpoints	Substudy 1: To assess the relative bioavailability of Risankizumab in the to-be-marketed 360 mg on-body delivery system (OBDS) versus the 90 mg prefilled syringe (PFS) used in the Phase 3 studies following a single subcutaneous (SC) administration at the dose of 360 mg. Additionally, this study was to assess the pharmacokinetics of Risankizumab in a 180 mg OBDS following a single SC administration at the dose of 180 mg. Substudy 2: To assess the relative bioavailability of Risankizumab in the to-be-marketed 600 mg liquid vial versus the 300 mg liquid vial used in the Phase 3 studies following a single intravenous (IV) administration of 1800 mg.
Drug/Device Studied	Risankizumab – OBDS, PFS, IV
Number and Type of Subjects	Substudy 1: Planned – 282, Enrolled – 287, Completed – 269, Evaluated for Safety – 286, Evaluated for Pharmacokinetics – 258 Substudy 2: Planned – 106, Enrolled – 107, Completed – 95, Evaluated for Safety – 107, Evaluated for Pharmacokinetics – 98 Healthy male and females aged 18 to 60 years old inclusive. In Substudy 1, Groups 1 and 2 enrolled 8 Japanese subjects in each group
Brief description of protocol	Substudy 1 • Group 1: Risankizumab 360 mg SC injection (4 x 90 mg PFS) (reference, N = 127, including N = 8 Japanese) • Group 2: Risankizumab 360 mg OBDS x 1 SC injection (2.4 ML of 150 mg/mL) (test, N = 127, including N = 8 Japanese) • Group 3: Risankizumab 180 mg OBDS x 1 SC injection (1.2 ML of 150 mg/mL) (N = 30) Substudy 2 • Group 4: Risankizumab 1800 mg IV infusion – 6 x 300 mg liquid vials (90 mg/mL) (reference, N = 53) • Group 5: Risankizumab 1800 mg IV infusion – 3 x 600 mg liquid vials (60 mg/mL) (test, N = 54) Serial blood samples for pharmacokinetic, anti-drug antibody (ADA), and neutralizing antibody (Nab) were controlled over a period of 113 days.
Results	Substudy 1: The point estimates and 90% CI for the bioavailability of the Risankizumab 360 mg OBDS relative to the 90 mg PFS and Risankizumab 180 mg OBDS relative to the

	360 mg OBDS are presented for Groups 1 – 3. 28 subjects from Substudy 1 are excluded from analysis – 11 for OBDS-dosing failures or related issue, 8 subjects for incomplete PK profiles without terminal phase, 8 subjects for violating eligibility criterion #23 from the protocol by enrolling in both studies, 1 subject for violating eligibility criterion #23 from the protocol by enrolling in two treatment groups of Substudy 1. Substudy 2: The point estimated and 90% CI for the relative bioavailability of the Risankizumab 600 mg vial (Group 5) compared to the Risankizumab 300 mg vial (Group 4) are presented. 9 subjects from Substudy 2 are excluded – 1 subject prematurely discontinued from the study at Day 2, 8 subjects for violating eligibility criterion #23 from the protocol by enrolling in both studies. The overall frequency of AEs was higher in the 360 mg OBDS group (49.6% versus 30.7% in the reference 90 mg/mL PFS group) due to the higher incidence of ISRs (34.9% versus 8.7% in the 90 mg/mL PFS group). Majority of injection site AEs were related to induration, erythema and smelling, events not unexpected with a higher volume of drug injected per site. All ISRs and device-related AEs were Grade 1 and mild in severity and a majority (80%) resolved in one day. The AW of injection-site pain was comparable across the difference SC treatment groups. There was no notable difference in the frequency or severity of patient reported outcome (PRO) of pressure/soreness between the PFS and OBDS 360 mg arms.
Device Related Comments	According to the Clinical Study Report provided, 11 subjects were excluded from analysis due to OBDS dosing failures or related issue. Further, there was a higher amount of AEs and ISRs for the OBDS.
Reviewer Comments	The amount of exclusions based on dosing failures from the OBDS is higher than anticipated for a study. The dosing failures were not explained, and it was not clear if the sponsor had investigated to find the root cause of the failures. The higher incidence of AEs and ISRs for the OBDS is expected as the OBDS is adhered onto the skin. Though the OBDS is adhered to the skin for approximately 5 minutes.
Reviewer Conclusion	The BE study provided utilizing the OBDS demonstrates the bioequivalence of the drug substance but does raise questions of safety and effectiveness relating to the dosing failures of the device. The sponsor should provide a detailed discussion of these dosing failures including the root cause.

Reviewer Comment
The OBDS device was not used in the Phase 3 clinical study; however, the sponsor performed a BE study. The BE study states there were 14 total device failures. The documentation provided indicate the causes were use errors, fluid path obstruction, and manufacturing. The sponsor should provide a discussion on any investigations performed to find the root cause of these failures and if these dosing failures were implemented into their risk analysis documentation/HF validation protocol. See Mid-Cycle Deficiency 4 – Resolved.

Additionally, there was a high rate of ISRs due to pain, itching, erythema, pruritus, swelling, induration, edema, discomfort, bruising, and irritation. One participant did report ecchymosis at the injection site. One participant reported a topical adhesive allergy. These will be reviewed in depth by clinical review team(s).

In response to the deficiency sent to determine the extent of investigation into root causes for the device failures, the sponsor indicated that investigative sites complete product compliance forms and product samples were retrieved from the sites for further investigation. The batch production records, device logs, visual inspection, functional evaluations, and examination of CT scans if needed were completed on the failed devices. The sponsor states that is likely a patient

would be aware of a missed dose situation via audible and visual notifications. The residual risks were evaluated as acceptable "as the harm severity and clinical impact to patients is considered minimal".

An inter-center IR was sent to determine the functions of the device compared to approved versions (OBDS platform) and further information on the functionality of the activation button. We requested the sponsor provide an overview of the sequence of events the device performs prior to initiation of injection, the depth the activation button has to travel to initiate injection compared to the depth needed for needle lockout, and how the injection can be initiated without the needle locked out. In response, the sponsor provided a comparison of the proposed OBDS with the platform configuration and currently approved Repatha. (b) (4) The sponsor provided an overview of the sequence of events for the device during the activation stage and the four scenarios that may occur if the activation button is not fully locked out. However, the probability of occurrence of an impartial activation button press and how the activation button may remain partially pressed and initiate/continue injection were unclear. The aforementioned issues were relayed in a second inter-center IR. The sponsor provided a response detailing the risk activities and scenario in which the button has been pressed enough that the snap fit edges maintain a partial press which may lead to initiation of injection without the needle being locked out.

CDER requested OSE to perform a review of the FAERS reports for Repatha OBDS to determine the amount of cases reported for device leakage and reports resulting in a root cause of "activation button not fully pressed". There was a total of 1,254 cases reported for device-related issues. Of these reports, 59 were related to device leakage. Of these 59 reports, 6 had a root cause of "activation button not fully pressed". Respectively, these amount to 4.7% and < 1% of cases reported for the Repatha OBDS.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION 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 sufficient information on the dosing failures observed in the BE study.		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: **12/28/2021**	**Date/Sequence Received:** **1/10/2022**
Mid-Cycle Deficiency #4	You have identified 11 dosing errors within the BE study conducted. According to your documentation, root causes behind the dosing errors were use errors, fluid path obstructions, and manufacturing. However, your description of the dosing failures are not sufficient. An understanding of the root causes for dosing failures seen in the study are needed to ensure the device functions as intended and correlates with the performance testing provided. Please provide a discussion of the user errors resulting in dosage errors and any documentation collected during the study providing investigational details into each dosing failure. For each failure mode, describe any additional mitigations implemented and provide evidence these mitigations are likely to be effective.	
Sponsor Response	*For all dosing errors that occurred during the M19-128 BE study, the investigative sites completed the AbbVie product compliance forms reporting all details on the device complains. In addition, product samples were retrieved from the sites and investigations were conducted to determine the root cause. The following assessments, as applicable, were conducted:* • *Review of batch production records for the subject device lot number* • *Review of device log (cradle reading)*	

- *Visual inspection*
- *Functional evaluation*
- *Examination of CT scans (if root cause could not be determined using methods above)*

For each complaint received, a detailed description of the issue observed during use, the complaint investigation results, the root cause conclusions, and actions taken to mitigate are summarized in Table 11. Complaint investigation reports have been provided with this submission in Section 3.2.R. Note: Some complaints have been grouped together in Table 11 based on the similarities in root causes.

In summary, root causes associated with manufacturing, fluid path obstructions or use errors were mitigated as follows:

- *Manufacturing: Changes to the* (b) (4) *address the manufacturing event.*
- *Use errors and fluid path obstructions: The IFU has been revised to address the aforementioned dosing errors and fluid path obstructions.*

AbbVie used the experiences from M19-128 BE study along with learnings from multiple Human Factors (HF) studies to make the changes to the IFU, including those described above, to improve usability as part of the HF program for the OBI system. Regarding residual risk if these dosing errors were to occur, it is likely that a patient would be aware of a missed dose situation, since the OBDS is designed with a medicine window and provides audible and visual notifications to confirm dose delivery. In addition, it provides audible and visual notifications in the event of a delivery error (as seen in complaints from M19-128). Users are instructed via the IFU to contact patient support if this occurs. The user is expected to receive the replacement product within (b) (4) *days, but even a 30 day delay to re-dose would be acceptable and is unlikely to impact the efficacy given risankizumab's long half-life, sustained duration of exposure, and plateaued exposure-efficacy relationship at the dose of 360 mg. Therefore, residual risks from these errors are acceptable as the harm severity and clinical impact to patients is considered minimal. No additional changes are considered necessary to further reduce the risks of these use errors.*

Reviewer Comments

The table contains columns for Complaint ID, Event Description, Investigation Results, Root Cause, and Mitigations. The combinations of Complaint, Root Cause, and Mitigations are summarized below.

Complaint	Root Cause	Mitigations
Device did not activate upon removal of green adhesive liner tab	Glue blooming residue on battery interrupted power supply	(b) (4)
Device stopped upon applying device to skin (error alarm)	Use error (device applied to site more than 30 minutes after activation – "Time Out" alarm)	Changes to Step 3C in IFU
Device stopped after pressing start button (error alarm)	Use error (safety latch open, device not properly applied to the skin)	Changes to Steps 3C and 3D in IFU

Device stopped approximately 1 minute into injection (error alarm)	Use error (safety latch open, device not properly applied to the skin)	Changes to Steps 3C and 3D in IFU
Device stopped immediately after pressing start button (error alarm)	Use error (start button not fully pressed)	Changes to Step 4A in IFU
Leakage observed coming from right side of OBDS during injection	Use error (start button not fully pressed)	Changes to Step 4A in IFU
Continuous leakage from injection site approximately 2-3 minutes into injection (error alarm)	Use error (start button not fully pressed)	Changes to Step 4A in IFU
Error alarm after 5 minutes, 80% drug injected, white plunger was not fully advanced, intermittent stopping and restarting of pumping sounds	Use error (start button not fully pressed)	Changes to Step 4A in IFU
Error alarm near completion	Use error (insertion of PCA not per IFU)	Changes to step 2D in IFU
Alarm immediately after injection completion	Unable to confirm root cause – likely a fluid path obstruction	Changes to step 2D in IFU

AbbVie provided an overview of the complaints within their response to the deficiency. They also submitted (b) (4) complaint investigation documents with details of the tests performed for each complaint.

The change from (b) (4) for the OBDS appears reasonable. In addition to this complaint, there were two complaints in which the PFC was not entered correctly, and the device was activated after 30 minutes after removing the pull tabs. These both resulted in errors for which the root cause is clear.

Two complaints noted were for alarms post-injection whose root causes could not be confirmed. It is thought by (b) (4) that the errors were due to a fluid path obstruction within the cartridge causing the plunger to be unable to advance and deliver the remaining amount of drug. The device operated as intended by alerting the user that the device was unable to complete injection.

The remaining complaints (9) were designated as use errors due to the patient either not adhering the device properly or the start button not being fully pressed. When the device was not adhered properly, the safety latch would open and create an alarm. When the activation button was not fully pressed, injection would stop at the initiation or during injection. There were signs of leakage in some cases. In some cases, the device post-operation logs indicate the activation button had been pressed but upon investigation it was determined that the button was not locked.

For complaint 1744396, it was unknown whether the activation button was locked into position post-injection during shipping and handling of the device.

Response Adequate:	☐ Yes ☑ No, See IR #1 Sent on 1/14/2022

Follow-On Deficiency	Date Sent: 1/14/2022	Date/Sequence Received: 1/21/2022
(b) (4)		

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	(b) (4)
Reviewer Comments	In addition to the IR response from the sponsor, CDER requested OSE perform a review of the Repatha FAERS reports. The FAERS search yielded 1,254 reports which may include duplicate reports for the same patient from multiple reporters, miscoded reports, or reports unrelated to Pushtronex devices. The reviewer used MedDRA Preferred Terms (PTs) for the reports to identify reports related to device leakage or similarity of auditory alarms. The following table outlines the number of FAERS reports for device-related PTs.

Table 2. Device-Related Issues MedDRA PTs With Repatha Received by FDA Through February 15, 2022, Sorted by Decreasing Number of FAERS Reports per PT

	MedDRA PT	Number of FAERS Reports*
1	**Incorrect dose administered by device**	481
2	**Device issue**	398
3	Wrong technique in product usage process	348
4	Drug dose omission by device	244
5	**Device malfunction**	164
6	Device use error	62
7	Device delivery system issue	61
8	**Device failure**	42
9	**Device leakage**	27
10	Device defective	26
11	Device difficult to use	22
12	Wrong technique in device usage process	17
13	Needle issue	10
14	Drug delivery system malfunction	9
15	Device adhesion issue	7

Table 2. Device-Related Issues MedDRA PTs With Repatha Received by FDA Through February 15, 2022, Sorted by Decreasing Number of FAERS Reports per PT

	MedDRA PT	Number of FAERS Reports*
16	Device power source issue	6
17	**Drug delivery system issue**	5
18	Device physical property issue	4
19	Injury associated with device	4
20	Incorrect dose administered	3
21	Product preparation error	3
22	**Device alarm issue**	2
23	Device operational issue	2
24	Incorrect route of product administration	2
25	Liquid product physical issue	2
26	Device breakage	1
27	Device deployment issue	1
28	Device occlusion	1
29	Incorrect dose administered by product	1
30	Incorrect product administration duration	1
31	Product communication issue	1
32	Product dispensing error	1
33	Product physical issue	1
34	Product quality issue	1
35	Unintentional medical device removal	1

* A report can contain more than one MedDRA PT

Reports coded with the PT "device leakage" returned 177 reports. 118 reports were excluded due to leakage occurring during the loading process, no leakage reported, leakage occurring during/after the removal process, unspecified leakage, cartridge leakage, and duplicate reports. This resulted in a total of 59 cases related to leakage in the OBDS injection.

The report contained the following table for descriptive characteristics of cases concerning leakage.

Table 3. Descriptive Characteristics of Cases Describing Leakage During Repatha (Evolocumab) Pushtronex Injection in This FAERS Case Series, Received by FDA From All Dates through February 15, 2022 (N=59)	
Country	
USA	59
Report type	
Expedited	2
Non-expedited	57
Initial FDA received year	
2018	11
2019	21
2020	13
2021	13
2022	1
Reporter qualifications	
Consumer	37
Healthcare professional	22
Serious outcome(s)* (n=2)	
Other	2
Red light present	
Yes	14
No	26
Not reported	19
Time to leakage (from start of injection)	
<1 min	4
1-2 min	5
3-4 min	6
5-9 min	4
Not reported	40
Needle punctured/puncture marks†	
Yes	11
No	27
Not reported	21
Patient received the full dose	
Yes	0
No	29
Not reported	30
Empty cartridge at the end of infusion	
Yes	8
No	6
Not reported	45

Table 3. Descriptive Characteristics of Cases Describing Leakage During Repatha (Evolocumab) Pushtronex Injection in This FAERS Case Series, Received by FDA From All Dates through February 15, 2022

(N=59)

Result of root cause analysis‡	
Activation button not fully pressed	6
Activated out of specified temperature range	2
Door closed during transport	2
No indication of device malfunction/unconfirmed error	2
Activation button pressed prior to placement on skin	1
Cartridge not inserted	1
Could not be determined	1
Door not fully closed	1
Unit removed before delivery was complete	1
Not reported	42

* For the purposes of this review, the following outcomes qualify as serious: other serious important medical events.
† Includes reports stating that the patient did not feel the needle puncture
‡ This information was contained in the case narratives but did not always explicitly mention that the device was investigated.

FAERS 17685998: The user experienced leakage on the seventh injection approximately 3-4 minutes after initiation. The device did not error out and completed the injection. The user states they did not feel the needle insert/observe a puncture. They did not think they received a dose as they did not feel a stinging sensation as the device was injecting. The investigation conclusion was that the activation button was not fully pressed. To mitigate this issue, there were proposed changes to the IFU.

FEARS 19153067: The patient had the OBDS administered by a nurse due to their inability to administer it themselves. The nurse observed the device operated as intended until approximately 3 minutes into the injection. The device did not error out. A puncture mark was noticed once the device was removed. The patient received half of the medication due to leakage. The root cause was not provided.

FEARS 116839804: The patient pressed the activation button several time to initiate injection. The device did not error out and the needle did pierce the skin. Approximately 1 minute into injection, the patient observed leakage. The patient removed the device. The root cause was not provided.

Appendix D contains a list of the leakage reports. The ages of the users ranged from 33 – 89.

In total, the 59 cases of leakage account for 4.7% of total device issues. The 6 cases of root causes identified as “activation button not fully pressed” account for < 1% of total device issues. Other scenarios of leakage reported contained root causes such as device activated before being brought to room temperature, door assembly not fully closed during operation, and unit removed before delivery complete.

The occurrence of “activation button not fully pressed” accounts for 2.5% of devices used in the BE study. According to the data and information obtained by AbbVie/ (b) (4) based on their SRA, the occurrence rating would be approximately

	0.019%. The increase in the cases observed in the BE study is concerning. However, there have been no incidences of "activation button not fully pressed" in the RLHS to date.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

11.HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA Review Instructions	☑

Reviewer Comment
Matthew Barlow, DMEPA reviewer, noted that some participants (n=3) were able to rip the entire backing off of the OBDS, few participants (n=3) pressed the activation button prematurely which led to device error alarm when the injector was activated, and there was one participant that pressed the activation button prematurely, yet the device successfully delivered the injection.

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:	
Address & FEI:	
Responsibilities:	
Site Inspection Recommendation:	Choose an item..

Reviewer Comments
A recommendation for inspection was provided at the beginning of the review process. The inspection has not been conducted and the dates for inspection have not been provided at this time.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☐ No

12.2. Quality Systems Documentation Review

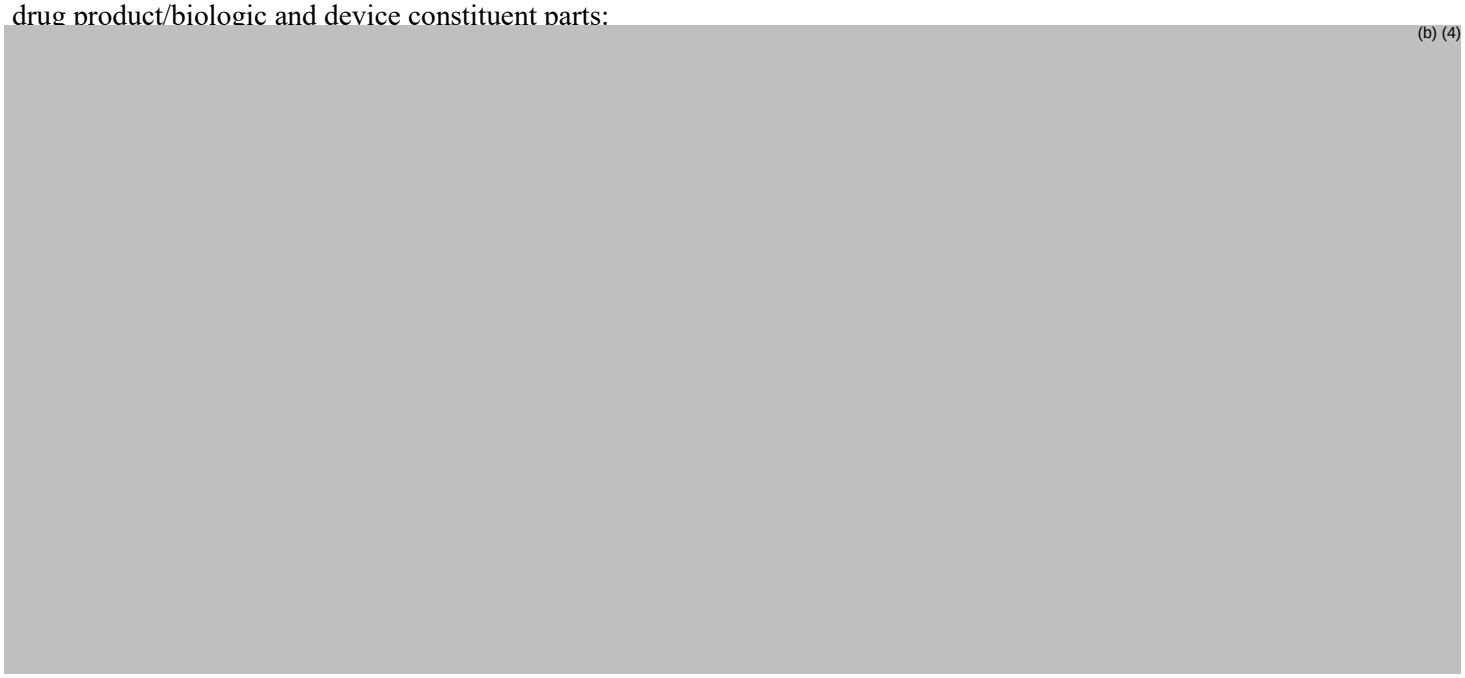
CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)



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	(b) (4)
Response Adequate:	☐ **Yes** ☑ **No, See IR #1 Sent on 1/14/2022**

Follow-On Deficiency	**Date Sent:** 1/14/2022	**Date/Sequence Received:** 1/21/2022
Information Request #1	(b) (4)	
Sponsor Response		
Reviewer Comments		
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

<<END OF REVIEW>>

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/s/

JAY R FAJICULAY
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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:	June 15, 2022
To:	Jay Fajiculay, Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide and Instructions for Use (IFU)
Drug Name (established name), dosage form and route, application type/number, supplemental number:	SKYRIZI (risankizumab-rzaa) injection, for intravenous use BLA 761262 SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use BLA 761105/S-016
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On September 16, 2021, AbbVie, Inc., submitted for the Agency's review:

- Biologics License Application (BLA) #761262 SKYRIZI (risankizumab-rzaa) injection, for intravenous use.
- a prior approval efficacy supplement for their approved Biologics License Application (BLA) #761105/S-016 for SKYRIZI (risankizumab-rzaa) injection, for subcutaneous use.

With these submissions, the Applicant proposes a new indication for the treatment of moderately to severely active Crohn's disease in adults. BLA #761261 proposes an intravenous induction dosing regimen for Crohn's disease and BLA #761105/S-016 proposes a new On-Body Injector (OBI) with prefilled cartridge (PFC) presentation for subcutaneous maintenance dosing regimen for Crohn's disease.

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 Gastroenterology (DG) on September 16, 2021, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for SKYRIZI (risankizumab-rzaa) injection, for intravenous or subcutaneous use.

2 MATERIAL REVIEWED

- Draft SKYRIZI (risankizumab-rzaa) MG and IFU received on September 16, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 1, 2022.
- Draft SKYRIZI (risankizumab-rzaa) Prescribing Information (PI) received on September 16, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 1, 2022.
- Approved SKYRIZI (risankizumab-rzaa) labeling dated January 21, 2022.
- Approved STELARA (ustekinumab) labeling dated December 11, 2020.

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%.

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 IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG 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 MG 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 MG or IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of SKYRIZI BLA761105 S-016 and BLA 761262 MG and IFU

KYLE SNYDER
06/15/2022 01:38:41 PM

SHARON W WILLIAMS
06/15/2022 02:26:40 PM

LASHAWN M GRIFFITHS
06/15/2022 02:29:52 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum

Date:	June 14, 2022
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD MS Division of Epidemiology I
Division Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum
Drug Name:	SKYRIZI (risankizumab-rzaa)
Application Type/Number:	BLAs 761262 & 761105 (S-016)
Submission Number:	eCTD 0712
Applicant/sponsor:	AbbVie
OSE RCM #:	2022-838

EXECUTIVE SUMMARY

Memorandum type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Risankizumab (first approved in April 2019 for plaque psoriasis and in January 2022 for psoriatic arthritis) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (with 28-day half-life) that selectively binds the p19 subunit of human interleukin-23 (IL-23). BLAs 761262 & 761105 (S-016) seek FDA approval for risankizumab as a treatment for moderately to severely active Crohn's disease (CD) in patients aged 16 years and older.

For psoriasis and psoriatic arthritis, U.S. Prescribing Information (USPI) for risankizumab recommends dosing at 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.[a] Phase 3 trials for CD assessed the safety and efficacy of treatment with higher doses of risankizumab, (1) for induction of response (Studies M15-991 and M16-006), 600 mg or 1200 mg administered by intravenous infusion at Week 0, Week 4, and Week 8 and (2) maintenance of response (Study M16-000), 180 mg or 360 mg administered by subcutaneous injection at Week 12 and every 8 weeks thereafter.

1.2. Describe the Safety Concern

The Division of Gastroenterology (DG) presents the safety concern as Hepatotoxicity in Treatment of Crohn's Disease. Data suggesting potential for hepatotoxicity emerged from a 12-week induction study (M16-006), which showed higher frequencies of liver-related laboratory test abnormality in risankizumab- than placebo-treated patients (Table 1).

[a] U.S. Prescribing Information for SKYRIZI® (risankizumab-rzaa) injection for subcutaneous use, accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761105s014lbl.pdf on May 19, 2022.

Table 1: Number and percentage of subjects meeting criteria for liver-related elevations during the 12-week induction period (Study M16-006).

Criterion		Placebo (N=186)		Risankizumab (N=745)	
		n	%	n	%
ALT	≥3 ULN	1	0.5	11	1.5
AST	≥3 ULN	1	0.5	7	0.9
TBL	≥2 ULN	1	0.5	7	0.9
ALP	≥1.5 ULN	3	1.6	16	2.1

SOURCE: Study M16-006 CSR, Table 56, p 221
ABBREVIATIONS: ALT – alanine aminotransferase; AST – aspartate aminotransferase; TBL – total bilirubin; ALP – alkaline phosphatase; ULN – upper limit of normal

At DG's request, the Drug-Induced Liver Injury (DILI) Team in the Division of Hepatology and Nutrition (DHN) assessed risankizumab for hepatotoxicity.[b] The DILI Team completed a case-level analysis of BLA subjects with treatment-emergent elevations in liver biochemistry to find five patients with at least probable risankizumab-induced liver injury (35-81-day latency from drug start). One of five subjects satisfied Hy's law (peak ALT or AST ≥3 x ULN and bilirubin ≥2 x ULN within 30 days of ALT/AST elevation).[c]

The DILI Team concluded that risankizumab for CD "appears to carry a small but significant DILI risk" (estimated at one Hy's law case per 1100 patients). The DILI Team attributed a possibly CD-specific DILI risk to the higher intravenous risankizumab dosing for induction or a lowered threshold for immune-mediated liver injury.

The Integrated Review (Section 7.7.1) for BLAs 761262 & 761105 (S-016) recommends three measures to mitigate possible DILI risk: (1) presentation of Hepatotoxicity in Treatment of Crohn's Disease in USPI Section 5 (WARNINGS AND PRECAUTIONS), (2) accelerated spontaneous-adverse-event reporting (enhanced pharmacovigilance), and (3) a necessary post-approval observational study with DILI included "as a prespecified endpoint."

1.3. Regulatory Purpose

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[b] Lan L, PH Hayashi, M Avigan, and J Toerner, Division of Hepatology and Nutrition Consultation, filed under BLA 761105 on March 21, 2022 (DARRTS Reference ID: 4955718).

[c] ALT – alanine aminotransferase; AST – aspartate aminotransferase; TBL – total bilirubin; ULN – upper limit of normal

1.4. Regulatory Objectives

To identify an unexpected risk for serious liver injury from risankizumab when used in the post-market setting to treat adults with CD.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Decisions about sample size should assess DILI as an infrequent event, expected to occur in no more than two patients for every 1000 patients exposed.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

We defined the desired surveillance population as patients with CD.

2.2 Is ARIA sufficient to assess the intended population?

Yes. We determined that the Sentinel Distributed Database (SDD) permits identification of patients with a medical care encounter linked to a CD diagnosis (ICD-10-CM K50).

3 EXPOSURES

3.1 Treatment Exposure

We defined the exposure of interest as an episode of treatment with risankizumab.

National Drug Codes (Table 2) in SDD permit the identification of pharmacy dispensings for risankizumab.

Table 2: National Drug Codes (NDCs) for SKYRIZI@ (risankizumab-rzaa) injection.

NDC	Description	Route
0074-2100	150 mg/mL single-dose pen	SQ
0074-1050	150 mg/mL single-dose prefilled syringe	SQ
0074-2042	75 mg/0.83 mL single-dose prefilled syringe	SQ
0074-1070	360 mg/2.4 mL (150 mg/mL) single-dose prefilled cartridge with on-body injector	SQ
0074-5015	600 mg/10 mL (60 mg/mL) single-dose vial	IV

ABBREVIATIONS: SQ – subcutaneous; IV – intravenous

Procedure codes (Table 3) in SDD permit the non-specific identification of a risankizumab administration by a medical provider.

Table 3: Healthcare Common Procedure Coding System (HCPCS) codes applicable to the administration of risankizumab by a medical provider.

HCPCS	Description
J3590	UNCLASSIFIED BIOLOGICS
C9399	UNCLASSIFIED DRUGS OR BIOLOGICALS

3.2 Comparator Exposure

For comparator population, we assessed adult CD patients started on an injectable therapeutic regarded as appropriate only for patients with moderately to severely active disease. Examples include inhibitors of tumor necrosis factor (TNF)-α (adalimumab, certolizumab pegol, and infliximab) and an anti-integrin (vedolizumab).

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. We determined that elements in the SDD dispensing table (i.e., RxDate, Rx, Rx_CodeType, RxSup, and RxAmt) and procedure table (i.e., ADATE, PX, and PX_CodeType) permit (within limits) the identification of patients with a treatment exposure to risankizumab or comparator therapeutic.

Induction therapy with risankizumab for CD entails a sequence of intravenous administrations. As noted previously, HCPCS does not currently offer a procedure code specific to risankizumab. Therefore, ARIA algorithms that combine information in SDD procedure and dispensing tables might (1) incorrectly identify some patients as risankizumab exposed, (2) not identify some risankizumab-exposed patients, or (3) incorrectly specify for some patients the start date for induction therapy. Because of inconsistent coding by medical facilities, ARIA might not ascertain risankizumab administrations that occur during a hospital stay.

4 OUTCOMES

4.1 Outcomes of Interest

We defined the outcome of interest as risankizumab-induced liver disease.

4.2 Code Algorithms for Drug-Induced Liver Injury (DILI)

For pre-market assessment, FDA Guidance for Industry describes certain laboratory test results (aminotransferase elevation accompanied by increased serum total bilirubin) as the "single clearest (most specific) predictor" for a drug's potential for severe hepatotoxicity.[d] For reasons summarized below, ARIA effectively excludes laboratory data as a source of information for post-market assessment of DILI risk. As a possible alternative, we assessed algorithmic approaches that use diagnosis codes alone to identify DILI.

Referencing a Mini-Sentinel project completed during an era of coding under ICD-9-CM, a Working Group convened by the Council for International Organizations of Medical Sciences (CIOMS) determined in 2020 that "there are no algorithms that have been validated to interrogate DILI signals in Sentinel."[e]

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[d] Food and Drug Administration Guidance for Industry, July 2009, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, accessed at https://www.fda.gov/media/116737/download on May 11, 2022, p 4.

[e] Lo Re V, 3rd, Haynes K, Goldberg D, et al., December 6, 2012, Validity of Diagnostic Codes to Identify Cases of Severe Acute Liver Injury in the Mini-Sentinel Distributed Database, accessed at https://www.sentinelinitiative.org/sites/default/files/surveillance-tools/validations-literature/Mini-Sentinel_Validation-of-Severe-Acute-Liver-Injury-Cases.pdf on May 11, 2022.

Lo Re V, 3rd, Haynes K, Goldberg D, et al. Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database. Pharmacoepidemiol Drug Saf. 2013;22(8):861-872 (https://doi.org/10.1002/pds.3470).

Council for International Organizations of Medical Sciences (CIOMS), 2020, Drug-Induced Liver Injury (DILI):

A rebuttal submitted by the Applicant references a study of liver-related ICD-9-CM and CPT codes.[f,g] The referenced study reported that one highly insensitive but moderately specific code set correctly classified 312 (74%) of 420 possible events (identified by codes alone) as acute liver injury (ALI).[h] The study authors portrayed algorithms using this restricted code set as a possible option in certain situations "where [chart] validation is not possible."

The ICD-10-CM era introduced K71 (Toxic liver disease), a code set with possibly greater specificity for DILI. Recent work suggests that certain K71 codes, if listed as the principal reason for hospitalization, might suitably and consistently identify occurrences of drug-associated ALI in patients without certain pre-existing conditions (e.g., chronic liver, alcohol-related, biliary, or pancreatic disease).[i,j]

As summarized above, the available evidence characterizes the sensitivity and specificity of DILI code algorithms as questionable for any application, including signal detection. We determined, however, that an acceptable observational study might combine a broad (sensitive) code algorithm for initial screening and some element of chart review for confirmation.

4.3 Is ARIA sufficient to assess the outcomes of interest?

No. We identified access to laboratory data (either directly or indirectly through chart review) as a necessary condition for sufficient assessment of DILI risk. (For rationale, see Section 4.2, above.)

ARIA's Sentinel Common Data Model (SCDM) captures laboratory data in a Laboratory Result data table.[k] Minimum requirements for initial screening include complete outpatient laboratory values for alanine transferase (ALT) and alkaline phosphatase (ALP),[l] both of which

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Current Status and Future Directions for Drug Development and the Post-Market Setting, accessed at https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf on May 11, 2022, p 71.

[f] AbbVie, Follow-up Response to May 16, 2022, Post-marketing Requirement Comments, submitted to BLA 761105 (eCTD 0220) on June 2, 2022.

[g] Bui CL, Kaye JA, Castellsague J, et al. Validation of acute liver injury cases in a population-based cohort study of oral antimicrobial users. Curr Drug Saf. 2014;9(1):23-28.

[h] Code set: ICD-9-CM 570.xx, 572.2x, or 573.3x in any position of an insurance claim for a hospital or emergency department encounter. Validation criterion: ALT >2 x ULN, TBL >2 x ULN, or any increase in AST, ALP, and TBL with at least one (AST, ALP, or TBL) >2 x ULN.

[i] Forns J, Cainzos-Achirica M, Hellfritzsch M, et al. Validity of ICD-9 and ICD-10 codes used to identify acute liver injury: A study in three European data sources. Pharmacoepidemiol Drug Saf. 2019;28(7):965-975.

Timmer A, de Sordi D, Kappen S, et al. Validity of hospital ICD-10-GM codes to identify acute liver injury in Germany. Pharmacoepidemiol Drug Saf. 2019;28(10):1344-1352.

[j] Might suitably identify – as indicated by positive predictive value >60%.

[k] See, Sentinel, SCDM: Laboratory Result Table Structure, accessed at https://dev.sentinelsystem.org/projects/SCDM/repos/sentinel_common_data_model/browse/files/800_11file02610_clinical_lab_result.md?at=refs%2Fheads%2FSCDM8.1.0 on May 11, 2022.

[l] Cheetham TC, Lee J, Hunt CM, et al. An automated causality assessment algorithm to detect drug-induced liver injury in electronic medical record data. Pharmacoepidemiol Drug Saf. 2014;23(6):601-608.

are included in the SCDM. However, Sentinel Data Partners populate the Laboratory Result data table for a subset of individuals, and completeness of laboratory data for these individuals is unknown.

Sentinel offers access to data sources (e.g., TriNetX and PCORnet®) with access to laboratory data in electronic health records (EHRs). However, these EHR data sources are not currently considered part of the ARIA system.

Sentinel permits access to medical charts for retrieval of missing patient information (e.g., laboratory data). However, medical chart review is not considered part of the ARIA system.

5 COVARIATES

5.1 Baseline Covariates of Interest

Important baseline covariates include age, sex, medical history (particularly pre-existing liver diseases such as viral and alcoholic hepatitis), and drug-treatments (particularly drugs with DILI potential).[m]

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes. Satisfactory analysis using ARIA might estimate DILI risk in (1) patient groups defined by age and sex and (2) a patient group without pre-existing liver disease or recent exposure to a non-risankizumab drug with DILI potential. With this purpose in mind, we assessed variables derived from elements in the:

- SDD demographic table (i.e., Birth_Date and Sex) as reliable and accurate indicators of patient age and sex.
- SDD diagnosis table (i.e., ADate, DX, Dx_Codetype, and PDX) as sufficient indicators for the medical history covariates of interest.
- SDD dispensing table (i.e., RxDate and Rx_CodeType) and procedure table (i.e., ADate, PX, and PX_CodeType) as sufficient indicators for the drug treatment covariates of interest.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

We assessed ARIA tools for signal detection.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA Level 2 tools (Covariate Stratification or Propensity Score Analysis) are sufficient for estimating relative risks for the outcome of interest (DILI) during defined periods of time after the initiation of treatment with risankizumab (drug of interest) or comparator therapeutic.

[m] For a list of drugs most concerning for DILI, see, Food and Drug Administration, Drug Induced Liver Injury Rank (DILIrank) Dataset, accessed at https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset on May 10, 2022.

7 NEXT STEPS

The BLA review team discussed post-marketing requirements (PMRs) and commitments (PMCs) on May 6, 2022. DG and the Division of Epidemiology I (DEPI) subsequently agreed on content for a PMR/506B PMC DEVELOPMENT TEMPLATE, which included the PMR/PMC Rationale for a prospective registry-based study to determine the incidence of DILI after the initiation of treatment with risankizumab in adults with CD.[n]

On May 17, 2022, OSE concluded a Signal Assessment Meeting by email (virtual SAM) with scientific representatives from the OSE Sentinel Core Team, OSE DEPI, OSE Division of Pharmacovigilance I, and OND DG. When polled, representatives from these entities concurred with a determination of ARIA Not Sufficient for assessing risankizumab-induced liver injury in adults with CD.[o]

In addition to appropriate labeling and enhanced pharmacovigilance, the review team for BLAs 761262 & 761105 (S-016) recommended a 505(o)(3) PMR fitting the description shown below.

Conduct a prospective registry-based study to determine the incidence of drug-induced liver injury (DILI) after the initiation of treatment with SKYRIZI (risankizumab) in adults with moderate to severely active Crohn's disease. Follow each enrolled patient for at least 18 months (if continued on treatment) or at least three months after discontinuation of treatment (if discontinued before 18 months). Enroll enough patients to exclude DILI risk greater that 2 per 1000 patients.

DG proposed the PMR described above to AbbVie.[p] AbbVie rebutted DG's proposal with a counter proposal for an observational study that might be conducted in "a large database of administrative claims from multiple health insurance providers, with targeted collection of medical charts to validate claims-based definitions for the outcomes of interest."[q] AbbVie proposed a PMR fitting the description shown below.

Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active Crohn's disease who are exposed to risankizumab, relative to other therapies used to treat Crohn's disease. Compare rates (per person-time) or risks (proportion of patients with a minimum amount of follow-up). Describe and justify the choice of appropriate comparator population(s). Specify concise case definition for severe liver injury and validation of algorithm(s) to identify severe liver injury in the proposed data source. For the risankizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any

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[n] Email communications, filed in RM Client as [BLA761262_761105-S016 Skyrizi PMR - Longterm Safety & DILI.pdf] on May 11, 2022 (Object ID: 090026fc80479d33).

PMR/506B PMC DEVELOPMENT TEMPLATE, filed in RM Client as [BLA 761272 sBLA 761105 PMR DILI registry.pdf] on May 11, 2022 (Object ID: 090026fc80479d32).

[o] Virtual SAM, filed in RM Client as [Re_ Virtual Signal Assessment Meeting (SAM) for risankizumab BLAs 761262 & 761105 (S-016).pdf] on May 17, 2022 (Object ID: 090026fc8047c1d5.

[p] Labeling PMR/PMC Discussion Comments, filed under BLA 761105 on May 16, 2022 (DARRTS Reference ID: 4984693).

[q] AbbVie, *op. cit.*, p 4.

exclusion and inclusion criteria. Ensure that the data source allows for average follow-up for at least 1 year. Specify a minimum sample size and justify the precision of the estimate achievable with the proposed study.

Assessing AbbVie's rationale as reasonable, DG (1) changed the PMR study objective from signal refinement to signal detection and (2) decided to accept AbbVie's counter proposal.[r]

[r] Email communication from S. Seo to J. Weissfeld, June 9, 2022, filed in RM Client as [BLA761262 _ 761105 Skyrizi PMR #4 DILI Registry vs. Obs Study.pdf] on June 9, 2022 (Object ID: 090026fc804a82d7).

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/

JOEL L WEISSFELD
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ROBERT BALL
06/14/2022 12:16:14 PM

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

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

Memorandum

Date: June 8, 2022

To: Jay Fajiculay, Regulatory Project Manager
Division of Gastroenterology (DG)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for SKYRIZI® (risankizumab-rzaa) injection, for subcutaneous use (Skyrizi)

BLA: 761262 and 761105/S-016

In response to DG's consult request dated September 24, 2021, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the BLA submissions for Skyrizi. These submissions provide for a new indication and updates to the dosage form and presentations.

Labeling: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DG on June 1, 2022, and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DG on June 8, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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

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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/

KYLE SNYDER
06/08/2022 02:50:50 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memorandum

Date:	May 17, 2022
Reviewer:	Lisa Wolf, PharmD, BCCCP, Team Leader Division of Pharmacovigilance I (DPV-I)
Deputy Division Director:	CDR Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name(s):	Skyrizi (risankizumab-rzaa)
Subject:	Venous thromboembolism
Application Type/Number:	BLA 761105
Applicant/Sponsor:	Abbvie Inc
OSE RCM #:	2022-896

1 INTRODUCTION

The purpose of this memorandum is for the Division of Pharmacovigilance I (DPV-I) to provide the Division of Gastroenterology (DG) an assessment of postmarketing cases of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), with Skyrizi (risankizumab-rzaa[a]) reported to the FDA Adverse Event Reporting System (FAERS) database. The results of this analysis will assist DG in their review of a prior approval efficacy supplement and new Biologics License Application for risankizumab for the treatment of moderately to severely active Crohn's disease (CD) in patients aged 16 years and older submitted by the applicant, AbbVie Inc., to FDA on September 16, 2021.

Risankizumab, an interleukin-23 (IL-23) antagonist, was originally approved by FDA on April 23, 2019, for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. On January 21, 2022, the indications were expanded to include treatment of active psoriatic arthritis (PsA) in adults. The recommended dose of risankizumab for both indications is 150 mg administered subcutaneously (SC) at Week 0, Week 4, and every 12 weeks thereafter. A VTE signal was not identified in the psoriasis or PsA clinical development programs, and VTE is currently not included in risankizumab product labeling.[1] Of note, the proposed dosing for the CD indication is 600 mg intravenous (IV) at Weeks 0, 4, and 8, and 180 mg or 360 mg SC at Week 12 and every 8 weeks thereafter.

(b) (4)

2 METHODS AND MATERIALS

DPV-I searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	May 5, 2022
Time period of search	All reports through May 4, 2022

[a] Risankizumab will be used throughout the remainder of the memo.

(b) (4)

Table 1. FAERS Search Strategy*	
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: Risankizumab, risankizumab-rzaa
MedDRA search terms (Version 25.0)	Embolic and thrombotic events, venous (SMQ) (SMQ Broad), Thrombosis (PT)
* See **Appendix A** for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, PT=Preferred Term	

3 RESULTS

The FAERS search retrieved 112 reports[c], of which 24 were excluded because they did not describe an VTE[d] event of interest[e,f] temporal to risankizumab therapy (n=22) or were duplicates (n=2). The remaining 88 cases are summarized below.

Table 2 contains the descriptive characteristics of the remaining 88 cases. **Appendix B** contains a line listing of the 88 FAERS cases included in this case series.

Table 2. Descriptive Characteristics of Cases of VTE with Risankizumab in this FAERS Case Series, Received by FDA through May 4, 2022, Stratified by Confirmation* of VTE Diagnosis			
	Total (N=88)	**Confirmed (n=31)**	**Unconfirmed (n=57)**
Age, years, median (range)†	60 (29-87)	57 (34-78)	61 (29-87)
Age 29 to 39 years	4	2	2
Age 40 to 49 years	11	7	4
Age 50 to 59 years	26	7	19
Age 60 to 69 years	26	8	18
Age 70 to 79 years	16	6	10
Age 80 to 89 years	2	0	2
Not reported, n	3	1	2
Sex, n			
Male	41	16	25
Female	45	15	30
Not reported	2	0	2

[c] For context, a search of the FAERS database for all reports with risankizumab through May 4, 2022 (i.e., same timeframe as search in **Table 1**), retrieved 7,882 reports.

[d] Adverse events of interest are DVT and PE. For completeness, we also included events described as thrombosis and blood clot (in the extremities or not otherwise specified), however, it is possible that these events are not actually a DVT.

[e] Other reported adverse events included stroke, myocardial infarction or possible myocardial infarction, clot at site of groin procedure, renal artery thrombosis, partial occlusion of neck vein, anal venous thrombosis, eye blood clot, blood clotting disorder, hypoechoic mass, internal jugular vein thrombosis, and stent blood clot.

[f] One fatal case (FAERS case #17574347) was excluded. This case describes a 58-year-old male who "died in his chair two weeks following Skyrizi injection. Patient only received initial dose of SKYRIZI (150mg). Primary reporter did not have a date or known cause of death. The Physician reported that cause of death could possibly be due to pulmonary embolism or a heart attack, however this was not confirmed."

Table 2. Descriptive Characteristics of Cases of VTE with Risankizumab in this FAERS Case Series, Received by FDA through May 4, 2022, Stratified by Confirmation[*] of VTE Diagnosis			
	Total (N=88)	**Confirmed (n=31)**	**Unconfirmed (n=57)**
Adverse event reported, n			
DVT/vein thrombosis/blood clot	38	12	26
Lower extremity	18	5	13
Upper extremity	3	1	2
NOS	17	6	11
PE	40	15	25
PE and lower extremity DVT	10	4	6
Time to onset, days, median (range)	184 (7-1,050)	184 (16-1,050)	190 (7-912)
Not reported, n	54	12	42
Risankizumab dose, n[‡]			
75 mg	3	1	2
150 mg	43	21	22
Not reported	42	9	33
Risankizumab reason for use, n			
Psoriasis/PsA	81	31	50
Not reported	5	0	5
CD/UC	2	0	2
Risk factors present, n[§]			
0[‖]	8	4	4
1	32	9	23
2	36	12	24
3	5	2	3
4	6	3	3
5	1	1	0
Most commonly reported risk factors, n			
Age ≥ 40 years	81	28	53
Recent infection	24	8	16
COVID-19	10	3	7
Other[¶]	19	7	12
Obesity	9	7	2
Cancer or clotting disorder	8	3	5
Smoker	7	4	3
Recent surgical procedure	5	2	3
Reporter, n			
Physician	8	3	5
Other healthcare professional	4	2	2
Consumer	76	26	50
Serious outcomes, n[**]	86	30	56
Death[††]	6	0	6
Hospitalization	53	20	33
Life-threatening	1	0	1
Other	48	20	28
Report type, n			
Expedited	86	30	56
Direct	2	1	1

Table 2. Descriptive Characteristics of Cases of VTE with Risankizumab in this FAERS Case Series, Received by FDA through May 4, 2022, Stratified by Confirmation* of VTE Diagnosis

	Total (N=88)	Confirmed (n=31)	Unconfirmed (n=57)
Year received by FDA, n			
2019	4	1	3
2020	19	8	11
2021	44	18	26
2022	21	4	17
Country			
United States	65	21	44
Foreign	23	10	13
Report source			
Solicited	82	28	54
Spontaneous	6	3	3

* Confirmed VTE: Reporting VTE, thrombosis, or blood clot AND reporting objective data such as ultrasound, computed tomography, or magnetic resonance imaging OR initiation of anticoagulation or thombolytic therapy for treatment; Unconfirmed VTE: Reporting of VTE, thrombosis, or blood clot with no supportive diagnostic imaging findings and no report of initiation of anticoagulation or thrombolytic therapy.

† The risk of VTE changes with increasing age, with 40 years of age being considered the breakpoint at which patients are at increased risk. Risk increases with each subsequent increase in decade.[4]

‡ Frequency of risankizumab administration was not reported in most cases. One case (FAERS case #18842790) describes a 60-year-old female who developed a PE shortly after her risankizumab dosage was changed to 150 mg every 6 weeks.

§ The underlying indication for use of risankizumab was not included in the number of risk factors present, but may contribute to increased risk of VTE.

|| Three of four cases involving patients less than 40 years of age had zero additional risk factors; one endorsed the 24-year-old female patient was "perfectly healthy", but the other two cases (29-year-old female, 37-year-old male) did not report past medical, medication, or social history to assess risk factors. The remaining case (39-year-old female) had two risk factors present (COVID-19/sepsis, obesity).

¶ Other risk factors include: chronic medical conditions (irritable bowel syndrome, diabetes mellitus, chronic kidney disease), prior history of blood clots, trauma/injury to affected area, hospitalization and critical illness prior to event, extended period of inactivity.

** For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.

†† Of the 6 fatal cases, 3 described patients with psoriasis ages 54, 58, and 64 years who experienced unconfirmed PEs approximately 133, 48, and 356 days after starting risankizumab, respectively; it was unknown if autopsies were performed and only the case in the 58-year-old reported an additional risk factor for the event (obesity with body mass index of 41 kg/m^2). The remaining three cases described patients who experienced a VTE while critically ill with multiple complex medical conditions (e.g., cancer, sepsis, recent surgery, heart attack, kidney failure, pneumonia).

Abbreviations: VTE=venous thromboembolism, DVT=deep vein thrombosis, NOS=not otherwise specified, PE=pulmonary embolism, mg=milligrams, PsA=psoriatic arthritis, CD=Crohn's disease, UC=ulcerative colitis, COVID-19=Coronavirus disease 2019, kg=kilogram, m=meter

Four representative cases occurring in younger patients with close temporal relationship between the events and risankizumab initiation are highlighted below.

FAERS case #17898978, Hospitalization, USA, 2020:
A solicited report from a consumer describes a 44-year-old female (height 163 centimeters (cm); weight 91.25 kilograms (kg)) receiving risankizumab for approximately 1 month for psoriasis and methotrexate (indication and duration of use not reported) who was hospitalized after developing stabbing pain in her legs and lungs, later diagnosed as bilateral PE and blood clot in legs. She was treated with heparin and apixaban. Medical history was significant for

gastroesophageal reflux disease, psoriatic arthropathy, migraine, and hypertension. Social history was negative for tobacco.

Reviewer comment: This case is notable because it describes a younger patient who experienced a DVT and PE after approximately a month of starting risankizumab and contains more clinical detail than most cases in the case series. The patient had possible contributory factors for the events (underlying indication for use of risankizumab[g], obesity with body mass index of 34.3 kg/m^2).[h,5] Based on the information provided, we cannot exclude the role of risankizumab.

FAERS case #17393758, Hospitalization/other important medical event, CAN, 2020:
A solicited report from a consumer describes a 34-year-old female non-smoker (weight 58 kg) who experienced a right lower leg DVT 73 days after starting risankizumab 150 mg (frequency not reported) for the treatment of psoriasis. The deep vein thrombosis "… was not pre existing prior to the first dose of SKYRIZI. She did not saw [sic] any reason to have something like this happen as she was perfectly healthy. She had tingling sensation all over her body so she went to the hospital…" An ultrasound was positive for DVT of the right lower leg, and she was treated with apixaban.

Reviewer comment: This case is notable because it describes a younger patient who experienced a DVT approximately 2 months after starting risankizumab and contains more clinical detail than most cases in the case series. The case notes the patient as "perfectly healthy" and did not describe any additional risk factors, other than the underlying indication for use of risankizumab, for the DVT event. Based on the information provided, we cannot exclude the role of risankizumab in this case.

FAERS case #17834930, Other important medical event, CAN, 2020:
A solicited report from a consumer describes a 41-year-old male who developed leg pain approximately 2 weeks after his most recent risankizumab 150 mg injection for psoriasis (treatment duration 42 days). He was diagnosed with a DVT on ultrasound. He was treated with rivaroxaban which was switched to enoxaparin. No additional information was reported.

Reviewer comment: This case is notable because it describes a younger patient who experienced a DVT with a close temporal relationship to risankizumab initiation (approximately 6 weeks). Other than psoriasis, the case does not contain any other VTE risk factors, however, risk factor information is not reported. Based on the information provided, we cannot exclude the role of risankizumab in this case.

FAERS case #18721645, Hospitalization, USA, 2021:
A solicited report from a consumer describes a 44-year-old female who experienced "blood clots in her heart and lungs", fatigue, and weakness 109 days after starting risankizumab for psoriasis. She was hospitalized and given blood thinners. She was discharged 3 days later on oxygen. She did not take concomitant drugs and was reported to have no relevant medical history.

[g] Indication structured coded field states "psoriasis", but medical history positive for psoriatic arthropathy.
[h] The World Health Organization defines obesity as a body mass index of at least 30 kg/m^2.

Reviewer comment: This case is notable because it reports a close temporal relationship between the events and risankizumab initiation and reports the patient did not take concomitant drugs or have past medical conditions that may be risk factors for the events. We cannot exclude the role of risankizumab in this case.

4 REVIEWER COMMENTS

(b) (4)

the ability to establish a causal relationship between an adverse event and a drug or therapeutic biologic from postmarketing case reports is greatest for adverse events that are rare, that are generally the result of drug treatment, and that do not have a high background rate among the population in question. Therefore, it is unlikely that postmarketing case reports would be sufficient alone to determine if a true safety concern exists.[6]

VTE has a high baseline incidence in the general population, occurring in approximately 1 to 2 individuals per 1,000 each year, corresponding to approximately 300,000 to 600,000 events in the United States annually.[7] Other factors identified within our case series may make this cohort at further increased risk for VTE events. The median age of the cohort was 60 years; this is important because the increase in risk for VTE starts in the 40's and dramatically increases at 60 years of age.[4,8] Risk factors for VTEs are numerous and variable, including but not limited to active infections, trauma, recent surgeries, and malignancies, all of which were identified within our FAERS case series. Overall, 91 percent (80/88) of cases in the case series contained 1 or more VTE risk factors and over 50 percent (48/88) contained 2 or more VTE risk factors. Chronic inflammatory conditions, including all of those for which risankizumab is indicated (i.e., psoriasis, PsA), may also increase the risk for VTE.[9,10] However, we did not include indication for use into our risk factor assessment because it is not entirely clear if the disease itself; disease control, which could not be assessed from FAERS cases; and/or potential risk factors that are more common among these patients puts this population at increased risk.[11] It is difficult to determine how the interaction between the various combinations of risk factors reported among the cases contributes to an individual's overall increased risk for VTE.

Information helpful to determine whether there is a reasonable possibility that risankizumab is associated with the VTE events was missing in many cases. For example, 61 percent of cases (54/88) did not report the time between risankizumab initiation and event occurrence. Many cases with zero or one additional risk factor[i] for the events omitted risk factor information altogether; therefore, it is possible other risk factors were present in the cases that we cannot account for in our assessment.

Nevertheless, we did identify a small subset of cases, which are described above, that occurred in younger patients (i.e., under 45 years of age) who seemingly did not have major VTE risk factors and experienced VTE events temporal to risankizumab initiation. Of note, these cases did not report detailed family history related to VTE events; generally, younger patients less than 45 years of age who experience unprovoked VTEs, especially who have pertinent family history, should be tested for inherited thrombophilia and antiphospholipid syndrome.[8] Although these

[i] Other than age, risk factor information was omitted.

cases are noteworthy, they are insufficient to determine whether a true signal of VTE exists for risankizumab and should be interpreted in the context of the totality of data (e.g., clinical trial data with risankizumab). It may be prudent to ask the applicant for risankizumab to complete a full assessment of all available data sources to inform the ongoing review of this possible signal.

5 APPENDICES

5.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

5.2 APPENDIX B. FAERS LINE LISTING OF VTE WITH RISANKIZUMAB CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	03-JUL-2019	16526370	4	CA-ABBVIE-19K-028-2838633-00	Expedited (15-Day)	87	FEMALE	CAN	Hospitalization, Other
2	09-OCT-2019	16900585	1	US-ABBVIE-19P-163-2956171-00	Expedited (15-Day)	52	MALE	USA	Other
3	25-OCT-2019	16959322	1	US-ABBVIE-19P-163-2977720-00	Expedited (15-Day)	55	FEMALE	USA	Hospitalization
4	07-NOV-2019	17004977	2	US-ABBVIE-19P-163-2992092-00	Expedited (15-Day)	56	FEMALE	USA	Hospitalization
5	04-FEB-2020	17365285	1	US-ABBVIE-20K-163-3247806-00	Expedited (15-Day)	60	MALE	USA	Hospitalization
6	09-FEB-2020	17393758	4	CA-ABBVIE-20K-028-3264084-00	Expedited (15-Day)	34	FEMALE	CAN	Hospitalization, Other
7	11-FEB-2020	17399771	1	US-ABBVIE-20K-163-3267119-00	Expedited (15-Day)	62	MALE	USA	Other
8	17-FEB-2020	17424311	2	US-ABBVIE-20K-163-3275706-00	Expedited (15-Day)	54	MALE	USA	Hospitalization
9	19-MAR-2020	17563707	1	US-ABBVIE-20K-163-3325372-00	Expedited (15-Day)	53	FEMALE	USA	Hospitalization
10	24-MAR-2020	17578996	1	US-ABBVIE-20K-163-3297715-00	Expedited (15-Day)	61	FEMALE	USA	Hospitalization
11	18-MAY-2020	17799406	1	US-ABBVIE-20K-163-3407751-00	Expedited (15-Day)	NR	MALE	USA	Life Threatening
12	25-MAY-2020	17819959	1	US-ABBVIE-20K-163-3416989-00	Expedited (15-Day)	53	MALE	USA	Hospitalization
13	28-MAY-2020	17834930	2	CA-ABBVIE-20K-028-3420489-00	Expedited (15-Day)	41	MALE	CAN	Other
14	10-JUN-2020	17878807	1	US-ABBVIE-20K-163-3438257-00	Expedited (15-Day)	61	FEMALE	USA	Other
15	16-JUN-2020	17898978	2	US-ABBVIE-20K-163-3446580-00	Expedited (15-Day)	44	FEMALE	USA	Hospitalization
16	11-AUG-2020	18137758	2	US-ABBVIE-20K-163-3515881-00	Expedited (15-Day)	67	MALE	USA	Hospitalization, Other
17	07-SEP-2020	18236345	2	US-ABBVIE-20K-163-3553759-00	Expedited (15-Day)	57	FEMALE	USA	Other
18	23-SEP-2020	18297311	2	US-ABBVIE-20K-163-3533063-00	Expedited (15-Day)	59	MALE	USA	Other
19	09-OCT-2020	18368417	1	US-ABBVIE-20K-163-3593725-00	Expedited (15-Day)	37	MALE	USA	Other

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
20	16-OCT-2020	18389350	1	BG-ABBVIE-20K-022-3611179-00	Expedited (15-Day)	54	NR	BGR	Death, Other
21	04-DEC-2020	18581513	1	DE-ABBVIE-20K-062-3678950-00	Expedited (15-Day)	58	MALE	DEU	Death
22	08-DEC-2020	18588807	1	CA-ABBVIE-20K-028-3627183-00	Expedited (15-Day)	68	MALE	CAN	Hospitalization
23	29-DEC-2020	18671959	6	US-ABBVIE-20K-163-3706393-00	Expedited (15-Day)	57	MALE	USA	Hospitalization, Other
24	04-JAN-2021	18693654	3	US-ABBVIE-21K-163-3714434-00	Expedited (15-Day)	54	MALE	USA	Hospitalization, Other
25	10-JAN-2021	18721645	1	US-ABBVIE-21K-163-3718877-00	Expedited (15-Day)	44	FEMALE	USA	Hospitalization
26	18-JAN-2021	18753651	2	US-ABBVIE-20K-163-3693877-00	Expedited (15-Day)	64	MALE	USA	Hospitalization, Other
27	02-FEB-2021	18826655	4	US-ABBVIE-20K-163-3605908-00	Expedited (15-Day)	68	MALE	USA	Hospitalization, Other
28	04-FEB-2021	18842790	1	CA-ABBVIE-21K-028-3759413-00	Expedited (15-Day)	60	FEMALE	CAN	Hospitalization
29	08-FEB-2021	18866555	2	US-ABBVIE-21K-163-3762487-00	Expedited (15-Day)	62	FEMALE	USA	Hospitalization
30	10-FEB-2021	18872975	1	US-ABBVIE-21K-163-3764531-00	Expedited (15-Day)	68	FEMALE	USA	Other
31	11-FEB-2021	18875709	3	US-ABBVIE-21K-163-3766787-00	Expedited (15-Day)	61	FEMALE	USA	Hospitalization, Other
32	22-FEB-2021	18925716	1	CA-ABBVIE-21K-028-3781173-00	Expedited (15-Day)	65	MALE	CAN	Hospitalization
33	04-MAR-2021	18966606	1	US-ABBVIE-21K-163-3797754-00	Expedited (15-Day)	62	MALE	USA	Hospitalization
34	07-MAR-2021	18978426	1	US-ABBVIE-21K-163-3800379-00	Expedited (15-Day)	29	FEMALE	USA	Hospitalization
35	05-APR-2021	19095081	4	CA-ABBVIE-21K-028-3842454-00	Expedited (15-Day)	78	MALE	CAN	Hospitalization
36	07-APR-2021	19105229	1	US-ABBVIE-21K-163-3846867-00	Expedited (15-Day)	NR	NR	USA	Hospitalization
37	21-APR-2021	19166909	1	US-ABBVIE-21K-163-3867280-00	Expedited (15-Day)	52	FEMALE	USA	Hospitalization
38	22-APR-2021	19171069	1	GB-ABBVIE-21K-167-3866425-00	Expedited (15-Day)	47	FEMALE	GBR	Hospitalization
39	23-APR-2021	19172047	1	US-ABBVIE-21K-163-3866532-00	Expedited (15-Day)	56	MALE	USA	Other
40	27-MAY-2021	19317199	1	US-ABBVIE-21K-163-3923971-00	Expedited (15-Day)	75	MALE	USA	Hospitalization

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
41	31-MAY-2021	19351258	2	US-ABBVIE-21K-163-3925529-00	Expedited (15-Day)	77	MALE	USA	Hospitalization
42	31-MAY-2021	19354136	1	US-ABBVIE-21K-163-3925342-00	Expedited (15-Day)	64	MALE	USA	Hospitalization
43	21-JUN-2021	19440683	1	CA-ABBVIE-21K-028-3954900-00	Expedited (15-Day)	71	FEMALE	CAN	Other
44	23-JUN-2021	19455365	3	BR-ABBVIE-21K-020-3956450-00	Expedited (15-Day)	67	FEMALE	BRA	Death, Hospitalization, Other
45	12-JUL-2021	19517428	2	US-ABBVIE-21K-163-3981807-00	Expedited (15-Day)	44	FEMALE	USA	Hospitalization, Other
46	13-JUL-2021	19541533	2	US-ABBVIE-21K-163-3988070-00	Expedited (15-Day)	70	MALE	USA	Hospitalization
47	15-JUL-2021	19548724	1	DE-ABBVIE-21K-062-3988939-00	Expedited (15-Day)	58	MALE	DEU	Other
48	15-JUL-2021	19551817	3	US-ABBVIE-21K-163-3982950-00	Expedited (15-Day)	71	FEMALE	USA	Hospitalization, Other
49	03-AUG-2021	19648988	1	US-ABBVIE-21K-163-4019437-00	Expedited (15-Day)	55	FEMALE	USA	Hospitalization
50	03-AUG-2021	19655181	1	US-ABBVIE-21K-163-4017440-00	Expedited (15-Day)	70	FEMALE	USA	Other
51	11-AUG-2021	19689770	3	US-ABBVIE-21K-163-4032044-00	Expedited (15-Day)	77	MALE	USA	Hospitalization, Other
52	31-AUG-2021	19767810	1	US-ABBVIE-21K-163-4059327-00	Expedited (15-Day)	50	MALE	USA	Hospitalization
53	02-SEP-2021	19783490	1	US-ABBVIE-21K-163-4063407-00	Expedited (15-Day)	66	FEMALE	USA	Other
54	02-SEP-2021	19783492	2	GB-ABBVIE-21K-167-4063465-00	Expedited (15-Day)	83	FEMALE	GBR	Hospitalization, Other
55	07-SEP-2021	19800043	2	US-ABBVIE-21K-163-4068251-00	Expedited (15-Day)	39	FEMALE	USA	Hospitalization, Other
56	08-SEP-2021	19800779	3	US-ABBVIE-21K-163-4069020-00	Expedited (15-Day)	64	MALE	USA	Other
57	23-SEP-2021	19870944	2	US-ABBVIE-21K-163-4090384-00	Expedited (15-Day)	56	FEMALE	USA	Hospitalization, Other
58	29-SEP-2021	19893830	1	GB-ABBVIE-21K-405-4097532-00	Expedited (15-Day)	42	MALE	GBR	Other
59	29-SEP-2021	19895548	2	CA-ABBVIE-21K-028-4097050-00	Expedited (15-Day)	71	FEMALE	CAN	Hospitalization, Other
60	29-SEP-2021	19901868	8	CA-ABBVIE-21K-028-4096625-00	Expedited (15-Day)	74	MALE	CAN	Death, Hospitalization, Other

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
61	13-OCT-2021	19951197	4	US-ABBVIE-21K-163-4115304-00	Expedited (15-Day)	51	FEMALE	USA	Hospitalization
62	22-OCT-2021	19981097	1	AR-ABBVIE-21K-007-4131274-00	Expedited (15-Day)	49	MALE	ARG	Other
63	25-OCT-2021	19992631	1	US-ABBVIE-21K-163-4132669-00	Expedited (15-Day)	77	MALE	USA	Other
64	28-OCT-2021	20005835	1	US-ABBVIE-21K-163-4131101-00	Expedited (15-Day)	49	FEMALE	USA	Other
65	04-NOV-2021	20032727	1	US-ABBVIE-21K-163-4144369-00	Expedited (15-Day)	55	FEMALE	USA	Other
66	09-NOV-2021	20046474	1	US-ABBVIE-21K-163-4074304-00	Expedited (15-Day)	48	FEMALE	USA	Hospitalization
67	26-NOV-2021	20115509	2	US-ABBVIE-21K-163-4174371-00	Expedited (15-Day)	72	FEMALE	USA	Other
68	03-JAN-2022	20278358	2	US-ABBVIE-21K-163-4217349-00	Expedited (15-Day)	66	MALE	USA	Hospitalization, Other
69	13-JAN-2022	20334162	1	US-ABBVIE-22K-163-4231111-00	Expedited (15-Day)	56	MALE	USA	Other
70	17-JAN-2022	20339061	1	AR-ABBVIE-22K-007-4236340-00	Expedited (15-Day)	NR	MALE	ARG	Other
71	26-JAN-2022	20377339	1	US-ABBVIE-22K-163-4244350-00	Expedited (15-Day)	61	MALE	USA	Other
72	26-JAN-2022	20380075	1	US-ABBVIE-22K-163-4243763-00	Expedited (15-Day)	61	MALE	USA	Other
73	03-FEB-2022	20422370	1	US-ABBVIE-22K-163-4261178-00	Expedited (15-Day)	58	FEMALE	USA	Hospitalization
74	07-FEB-2022	20440619	1	US-ABBVIE-22K-163-4265528-00	Expedited (15-Day)	43	FEMALE	USA	Hospitalization
75	15-FEB-2022	20477244	1	US-ABBVIE-22K-163-4278210-00	Expedited (15-Day)	68	FEMALE	USA	Hospitalization
76	16-FEB-2022	20482226	2	ES-ABBVIE-22K-144-4279856-00	Expedited (15-Day)	47	MALE	ESP	Hospitalization
77	18-FEB-2022	20487474	1	DE-ABBVIE-22K-062-4283631-00	Expedited (15-Day)	64	FEMALE	DEU	Death
78	17-FEB-2022	20489608	1	FDA-CDER-CTU-2022-13694	Direct	63	MALE	USA	
79	02-MAR-2022	20542070	1	FDA-CDER-CTU-2022-17187	Direct	68	MALE	USA	
80	07-MAR-2022	20563017	1	US-ABBVIE-22K-163-4300214-00	Expedited (15-Day)	74	FEMALE	USA	Hospitalization
81	11-MAR-2022	20583248	1	US-ABBVIE-22K-163-4311198-00	Expedited (15-Day)	73	FEMALE	USA	Other

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
82	25-MAR-2022	20638925	1	CA-ABBVIE-22K-028-4328658-00	Expedited (15-Day)	73	FEMALE	CAN	Other
83	02-APR-2022	20665377	1	US-ABBVIE-22K-163-4341352-00	Expedited (15-Day)	55	FEMALE	USA	Other
84	07-APR-2022	20687207	1	US-ABBVIE-22K-163-4349590-00	Expedited (15-Day)	73	FEMALE	USA	Hospitalization
85	09-APR-2022	20692501	1	US-ABBVIE-22K-163-4348038-00	Expedited (15-Day)	63	FEMALE	USA	Hospitalization
86	29-APR-2022	20770344	1	US-ABBVIE-22K-163-4374852-00	Expedited (15-Day)	56	MALE	USA	Other
87	04-MAY-2022	20780551	1	CA-ABBVIE-22K-028-4378688-00	Expedited (15-Day)	59	FEMALE	CAN	Death, Other
88	05-MAY-2022	20787697	1	US-ABBVIE-22K-163-4378808-00	Expedited (15-Day)	51	FEMALE	USA	Hospitalization

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: NR=not reported

6 REFERENCES

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(b) (4)

(b) (4)

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11. Hillary T, Clijmans J, Vermeire S, et al. Venous thrombotic events in psoriasis patients: a systematic review with meta-analysis. *Ann Med* 2021;53:1074-1081.

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/s/

LISA M WOLF
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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021410
BLA# (ref IND):	761262 (reference IND 118701)
Sponsor:	AbbVie
Established Name/Trade Name:	SKYRIZI® (risankizumab-rzaa) injection
Indication:	Treatment of moderately to severely active Crohn's disease in patients aged 16 years and older. ☒Rare Disease/**Orphan Designation** ☐Pediatrics
Meeting Type:	BLA Review
Review Division:	Division of Gastroenterology
Clinical Reviewer	Suruchi Batra
Clinical Team Leader (TL)	Suna Seo
Regulatory Project Manager:	Jay Fajiculay
COA Reviewer:	Susan Pretko, PharmD, MPH
COA TL:	David Reasner, PhD
COA Director:	David Reasner, PhD
Date Consult Request Received:	October 1, 2021
Date COA Briefing Package/Submission Received:	September 16, 2021
Instruments reviewed:	☒ Patient-reported outcome • Functional Assessment of Chronic Illness Therapy – Fatigue • Self-Injection Assessment Questionnaire • Patient Global Impression of Change • Patient Global Impression of Severity

1 EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to BLA 761262 and sBLA 761105/S016 for risankizumab-rzaa injection to treat moderately to severely active Crohn's disease (CD) in patients aged 18-(b) (4) years, inclusive. BLA 761262 is indicated for intravenous (IV) induction dosing of risankizumab-rzaa and sBLA 761105/S016 is indicated for sub-cutaneous (SC) maintenance dosing of risankizumab-rzaa.

Based on discussion with the clinical review division[1] this COA review is limited to the following COA measures:

- The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), a patient-reported outcome (PRO) measure assessing symptoms and impacts of fatigue (ranked secondary endpoint in the randomized, placebo-controlled, phase 3 clinical trials). Additional information on the FACIT-F is in Appendix 1.

1 The CSS is not addressed given that it was positioned to support an exploratory endpoint in the phase 3 studies. Interpretation of CDAI AP and BM scores is not addressed given that qualitative evidence was not submitted to support meaningful change in AP and SF scores as assessed by the CDAI. Refer to the previous COA review (C2017190) for more detail.

- The Self-Injection Assessment Questionnaire (SIAQ), a PRO measure assessing overall patient experience with SC self-injection. SIAQ data was used to support inclusion of the on-body injector (OBI) in the marketing application.

BLA 761262 and sBLA 761105/S016 reference the COA evidence dossiers submitted to sBLA 761105/S016 including the FACIT-F Evidence Dossier.

The review concludes the following:

- The evidence submitted by the applicant is sufficient to demonstrate that:
  - the FACIT-F measure is fit-for-purpose[2] to measure fatigue symptoms and impacts for the context of use of this drug development program.
  - the threshold range of 7-10 points appears appropriate to interpret clinically meaningful within-patient change in FACIT-F total score from Baseline to Week 12 in CD induction therapy with risankizumab.
  - the SIAQ appears appropriate to support acceptability of the OBI.

2 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- Under the reference IND, the Agency advised the sponsor to submit both the intravenous (IV) induction dosing regimen and the sub-cutaneous (SC) maintenance dosing regimen as efficacy supplements to existing BLA 761105; however, if the sponsor submits a separate BLA for the IV induction dosing regimen, then all of the necessary data and information on both formulations should be included in a single submission.[3] Thus, BLA 761105 is related to the IV induction dosing regimen whereas sBLA 761105-06 is related to the SC maintenance dosing. Clinical trial data to support efficacy of both formulations were submitted to sBLA 761105-05.[4]
- The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is described in FDA-approved labeling.
- The Self-Injection Assessment Questionnaire (SIAQ) has previously been included in regulatory submissions, including the submission leading to the 2021 FDA approval of the risankizumab 150 mg/mL autoinjector (sBLA 761105-S09).
- Skyrizi® (risankizumab-rzaa) was approved on April 23, 2019 (BLA 761105) for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Previous Clinical Outcome Assessment (COA) Reviews:

The Division of COA (DCOA) has previously provided reviews for the reference IND 118701. However, these reviews addressed other patient-reported outcome (PRO) measures that were not used to support an alpha-controlled secondary endpoint in the Skyrizi® clinical trials.

[2] 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/)
[3] Type B Pre-BLA Meeting Minutes (DARRTS Reference ID: 4798641)
[4] sBLA 761105-s016 SN 0136 received September 16, 2021.

Refer to the previous COA review for comment on evidence needed to support remission defined by abdominal pain (AP) and stool frequency (SF).[5]

Disease Background:

Crohn's disease (CD) is a chronic disease that causes inflammation in any part of the gastrointestinal tract. Symptoms of CD can vary depending on the location and severity of the inflammation. There is no cure for CD, but treatments can decrease inflammation, relieving symptoms and preventing complications. Treatments include medicines, bowel rest, and surgery.[6]

Investigational Product:

Risankizumab is a fully humanized monoclonal antibody that inhibits interleukin (IL)-23, an inflammatory cytokine. Inhibition of IL-23 is proposed to alleviate signs and symptoms of active CD and reduce mucosal inflammation.

Other materials reviewed:

- FDA Draft Guidance for Industry, "Crohn's Disease: Developing Drugs for Treatment". April 2022. Available at: https://www.fda.gov/media/158001/download

3 COA REVIEW

The risankizumab for CD development program consisted of a phase 2 induction study (Study M15-993[7]), two phase 3 induction studies (Study M15-991 and Study M16-006), and a phase 3 maintenance study (Study M16-000). This review focuses on the phase 3 studies.

3.1 Clinical Trial Population

Select inclusion criteria and details on the clinical trial population randomized into the induction and maintenance clinical trials are in Table 1. A complete list of the inclusion and exclusion criteria is summarized in the Clinical Study Reports.

Table 1. Select inclusion criteria and population demographics in the induction[8] and maintenance clinical trials

Study	Inclusion Criteria at Baseline	Study Population Demographics
Study M16-006 (phase 3 induction study)	• Male or female aged ≥ 18 to ≤ 80 years • Moderate-severely active CD[9] • Endoscopic evidence of mucosal inflammation[10] • Average daily SF ≥ 4 and/or average daily AP score ≥ 2	The mean age for all subjects in the ITT1A population (n=850) was 37.5 years (standard deviation (SD): 13.28 years), ranging from 16-79 years. The majority of subjects were male (n=460, 54.1%) and white (n=639, 75.2%). The largest proportion of subjects were located in Western Europe (n=272, 32.0%) followed by North America (n=192, 22.6%).

[5] C2017190_IND 121783_Kovacs (DARRTS Reference ID: 4288671)
[6] Health Topics, 2022. Crohn's Disease | MedlinePlus. [online] Medlineplus.gov. Available at: <https://medlineplus.gov/crohnsdisease.html> [Accessed 25 January 2022].
[7] Study M15-993 was a 12-week, phase 2 induction study to evaluate efficacy of risankizumab in inducing clinical remission.
[8] This review is limited to the 1st 12-Week Induction Period (ITT1A Population) as the COA quantitative analyses were performed using only data from this part of the induction clinical trials.
[9] Defined by Crohn's disease activity index (CDAI) score of 220-450
[10] Defined by Simple Endoscopic Score for Crohn's disease (SES-CD) score ≥ 3

Study M15-991 (phase 3 induction study)	Same as study M16-006	The mean age for all subjects in the ITT1A population (n=569) was 39.6 years (SD: 13.31 years), ranging from 16-80 years. The majority of subjects were male (n=296, 51.5%) and white (n=506, 88.9%). The largest proportion of subjects were in North America (n=198, 34.8%) followed by Western Europe (n=188, 33.0%).
Study M16-000 (phase 3 maintenance study)	Eligible subjects must have completed Study M16-006, Study M15-991, Study M15-993, or another AbbVie risankizumab CD study and achieved clinical response[11].	The mean age for all subjects (n=462) was 38.1 years (SD: 13.55 years), ranging from 16-76 years. The majority of subjects were male (n=238, 51.5%) and White (n=364, 78.8%). Approximately 27.5% (n=127) of subjects were located in North America.

3.2 Clinical Trial Design

3.2.1 Study M16-006 and Study M15-991 (Phase 3 induction studies)

The design of studies M16-006 and M15-991 were identical: both studies were multicenter, multinational, randomized, double-blind, placebo-controlled, 24-week phase 3 studies designed to evaluate the efficacy and safety of risankizumab as induction treatment in subjects with moderately to severely active CD[12].

The studies were comprised of 2, 12-week induction periods. At the Week 12 visit, all subjects were evaluated for a clinical response[13]. Subjects that achieved a clinical response were considered to enter Study M16-000. Subjects that did not achieve clinical response at Week 12 were randomized into Induction Period 2, a double-blind, double-dummy 12-week treatment period. At week 24, achievement of clinical response was re-assessed.

PRO data was collected at Baseline, and Weeks 4, 12, and 24 using an electronic format (Tablet device). Subjects received and were trained on the electronic diary and received a patient information card[14] at the Screening visit. The diary was reviewed by site personnel with the subject at each visit prior to performing any clinic assessments.

3.2.2 Study M16-000 (Phase 3 maintenance study)

Study M16-000 was a phase 3 study designed to evaluate the efficacy and safety of risankizumab as maintenance therapy in subjects with moderately to severely active CD. The study was comprised of 4 studies:

- Sub-study (SS) 1: a 52-week randomized, double-blind, placebo-controlled maintenance study
- SS2: a 52-week randomized, exploratory maintenance study of 2 different dosing regimens (therapeutic drug monitoring vs. clinical assessment for dose escalation)

[11] Clinical response was defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score, and both not worse than Baseline of the induction study

[12] Moderately to severely active CD was defined based on 3 criteria: (1) average daily liquid or very soft SF ≥ 4 and/or average daily AP score ≥ 2; (2) CDAI 220-450; (3) SES-CD ≥ 6 (or ≥ 4 for isolated ileal disease).

[13] Clinical response defined as ≥ 30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline).

[14] A patient information card with information of the symptoms and signs of hypersensitivity reactions, infusion-related reactions as well as late stage reactions was provided so that any such events once occurred will be reported immediately by the patients to the investigator.

- SS3: a 220-week open-label (OL) long-term extension (LTE) study
- SS4: a 220-week OL LTE study subjects from SS3 willing to comply with the requirements of SS 4, including self-administration of SC injections using the On-Body Injector (OBI). SS4 was a Real-Life Handling Study (RLHS) to confirm a subject's ability to self-administer risankizumab via the OBI with pre-filled cartridge (PFC) in a safe and effective manner and to understand its generalizability to real-world performance.

PRO data was collected using an electronic format. In SS1 and SS2, FACIT-F data was collected at Week 0[15] and at week 52/Premature Discontinuation.

In SS4, SIAQ data for the PRE-dose module was collected at Week 0 and SIAQ data for the POST-dose module was collected at Weeks 0, 8, and 16. The SIAQ PRE-dose module was completed by subjects immediately before the first OBI self-injection at baseline. The SIAQ POST-dose module was completed by subjects 20-40 minutes following injections.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 2 describes the intended placement of the PRO measures in the endpoint hierarchy, including the endpoint definition and assessment schedule for the phase 3 induction studies. Corresponding information for the phase 3 maintenance study is in Table 3.

Table 2. Endpoint Position, Definition, and Assessment Schedule for Induction Studies M16-006 (US Protocol) and M15-991

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Co-Primary	1. CDAI clinical remission[1] 2. SES-CD	1. The proportion of subjects with CDAI clinical remission at Week 12 2. The proportion of subjects with endoscopic response at Week 12	☒ Assessment within 140 days of early discontinuation 1. CDAI ☒ Monthly: Baseline and Weeks 4, 8, 12, 16, 20, and 24[2] 2. SES-CD ☒Other: Screening, Week 12, Week 24
Secondary COA ☒ Multiplicity adjusted	4th ranked secondary endpoint: FACIT-F (PRO)	Change from baseline of FACIT-F total score at Week 12	4. FACIT-F ☒Other: Baseline and Weeks 4, 12, and 24

Abbreviations: CDAI: Crohn's disease activity index; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; PRO: Patient-reported outcome; SES-CD: Simple Endoscopic Score for Crohn's disease.
[1] CDAI clinical remission defined as a CDAI score < 150
[2] Baseline, Week 4, Week 8, and Week 12 are part of Induction Period 1. Weeks 16, 20, and 24 are part of Induction Period 2.

[15] The final visit of Study M16-006 or Study M15-991 (Week 12 or Week 24) was considered as the Week 0 visit for Study M16-000.

Table 3. Endpoint Position, Definition, and Assessment Schedule for Maintenance Study M16-000

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Co-Primary	1. CDAI clinical remission[1] 2. SES-CD	1. The proportion of subjects with CDAI clinical remission at Week 52 2. The proportion of subjects with endoscopic response at Week 12	☒ Assessment within 140 days of early discontinuation 1. CDAI ☒ Monthly: Baseline and Weeks 4, 8, 12, 16, 20 2. SES-CD ☒Other: Screening, Week 12, Week 24
Secondary COA ☒ Multiplicity adjusted	5th ranked secondary endpoint: FACIT-F	Change from Baseline of induction study in FACIT-F Total Score	☒ Assessment within 140 days of early discontinuation ☒Other: Induction Basline and Maintenance Week 0 and Week 52

Abbreviations: CDAI: Crohn's disease activity index; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; PRO: Patient-reported outcome; SES-CD: Simple Endoscopic Score for Crohn's disease.
[1] CDAI clinical remission defined as a CDAI score < 150

***[Reviewer's Comment(s)**: A more appropriate endpoint for the FACIT-F in the maintenance study would be the change from maintenance baseline to Week 52.]*

3.4 Targeted COA-Related Labeling Claim(s)

The applicant proposes the following COA-related labeling claims:

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The clinical trial results are in Appendix 5.

SIAQ results have not been included in product labeling, nor were SIAQ labeling claims proposed for BLA 761262/sBLA 761105-S016.

[Reviewer's Comment(s):
Refer to the Integrated Review for BLA 761262/sBLA 761105-S016 for discussion on secondary endpoints proposed for labeling.]

3.5 Clinical Outcome Assessment(s)

3.5.1 Clinical Outcome Assessment Description(s)

FACIT-F

The FACIT-F is a 13-item PRO measure assessing fatigue symptoms and fatigue impacts (i.e., severity, impacts to daily activities, emotional impacts).

Patient Global Impression of Change (PGIC)

The PGIS is a single item PRO measure asking subjects to rate the change in overall symptoms due to CD compared to before treatment began. The PGIC is in Appendix 2.1.

Patient Global Impression of Severity (PGIS)

The PGIS is a single item PRO measure asking subjects to rate the severity of their CD symptoms for the past week. The PGIS is in Appendix 2.2

SIAQ

The SIAQ is a PRO measure assessing overall patient experience with SC self-injection [16]. It was developed as a generic questionnaire based on qualitative input from 6 patients with rheumatoid arthritis (RA) and 6 patients with CD and was quantitatively assessed in a population of RA subjects. The SIAQ contains 2 modules:

1. PRE module: The PRE module consists of 7 items grouped into 3 domains:
    a. Feelings about injections (FL)
    b. Self-confidence (CO)
    c. Satisfaction with current mode of administration (SA)

2. POST module: The POST module consists of 21 items (two of which are subdivided into eight sub-items) grouped into 6 domains:
    a. 5 causal domains: FL (3 items), Self-image (IM, 1 item), CO (3 items), Injection-site reactions (RE, 2 items), and Ease of use (EU, 5 items)
    b. SA domain (7 items)

The Applicant states that the SIAQ was included in the submission leading to the 2021 FDA approval of the risankizumab 150mg/mL autoinjector.

***[Reviewer's Comment(s)**:*
Based on references provided by the Applicant, the SIAQ v1.0 was developed in English then evaluated through cognitive interviews in a new group of 5 patients with RA and 5 patients with CD. The $SIAQ_{v1.0}$ was revised to the $SIAQ_{v1.1}$ based on the results from an exploratory factor analysis, and the $SIAQ_{v1.1}$ was revised to the $SIAQ_{v2.0}$ based on the results of confirmatory factor analysis and assessments of reliability and validity using data from the RAPID-2 clinical trial[17]. The original US English language version of the SIAQ v1.0 was translated into Czech and Polish and linguistic adaptation was performed using a 5-step process[18].

The SIAQ is not described in FDA-approved labeling. However, the SIAQ appears appropriate to evaluate subject experience and rating of acceptability with the OBI.]

[16] Keininger D, Coteur G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes. 2011;9:2.
[17] The RAPID-2 study was a multicenter, open-label, single-arm extension study assessing safety and efficacy of certolizumab pegol in the treatment of active RA.
[18] Acquadro C, Conway K, Giroudet C, Mear I: Linguistic validation manual for patient-reported outcomes instruments. Lyon: Mapi Research Institute; 2004.

3.5.2 Conceptual Framework(s)

FACIT-F Conceptual Framework

The FACIT-F conceptual framework is in Table 6 of the FACIT-F evidence dossier and is shown below.

Table 6. Conceptual Framework for the Functional Assessment of Chronic Illness Therapy – Fatigue Assessment (FACIT-Fatigue)[22]

Item		Concept		Domain		General Concept
Item 1 (HI7). I feel fatigued	→	Fatigue	→	Fatigue experience	→	Fatigue
Item 2 (HI12). I feel weak all over	→	Weakness				
Item 3 (An1). I feel listless ("washed out")	→	Listless				
Item 4 (An2). I feel tired	→	Tired				
Item 5 (An5). I have energy	→	Energy				
Item 6 (An3). I have trouble starting things because I am tired	→	Initiating activities	→	Fatigue impact		
Item 7 (An4). I have trouble finishing things because I am tired	→	Finishing activities				
Item 8 (An7). I am able to do my usual activities	→	Usual activities				
Item 9 (An8). I need to sleep during the day	→	Daytime sleep				
Item 10 (An12). I am too tired to eat	→	Too tired to eat				
Item 11 (An14). I need help doing my usual activities	→	Support with usual activities				
Item 12 (An15). I am frustrated by being too tired to do the things I want to do	→	Frustration				
Item 13 (An16). I have to limit my social activity because I am tired	→	Social activity limit				

SIAQ Conceptual Framework[19]

The conceptual framework for the SIAQ measure is shown in Tables 4-5.

Table 4. SIAQ Pre- Module

Domain	Item	Answer category
Feeling about injections	1. In general, how afraid are you of needles? 2. In general, how afraid are you of having an injection? 3. How anxious do you feel about giving yourself an injection?	• Extremely • Very • Moderately • A little • Not at all
Self-confidence	1. How confident are you about giving yourself an injection in the right way? 2. How confident are you about giving yourself an injection in a clean and sterile way? 3. How confident are you about giving yourself an injection safely?	
Satisfaction with self-injection	1. Overall, how satisfied are you with your current way of taking your medication?	• Very satisfied • Satisfied • Neither satisfied nor dissatisfied • Dissatisfied • Very dissatisfied

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Table 5. SIAQ Post-Module

Domain	Item	Answer category
Self-image	How embarrassed would you feel if someone saw you with the self-injection device?	• Extremely • Very • Moderately • A little • Not at all
Pain and reaction during or after the injection	Pain • Pain? • Burning sensation? • Cold sensation? Reaction • Itching at the injection site? • Redness at the injection site? • Swelling at the injection site? • Bruising at the injection site? • Hardening at the injection site?	
Ease of use of the self-injection device	• Remove the cap? • Depress the device? • Administer injection without any help? • Use the self-injection device?	• Very difficult • Difficult • Somewhat difficult • Somewhat easy • Easy • Very easy
	• How does the device fit in your hand?	• Very comfortably • Comfortably • Somewhat comfortably • Somewhat uncomfortably • Uncomfortably • Very uncomfortably

Domain	Item	Answer category
Satisfaction with self-injection	• How easy was it to give yourself an injection?	• Extremely • Very • Moderately • A little • Not at all
	• How satisfied are you with how often you give yourself an injection? • How satisfied are you with the time it takes to inject the medication?	• Very satisfied • Satisfied • Neither satisfied nor dissatisfied • Dissatisfied • Very dissatisfied
	• Overall, how convenient is the self-injection device?	• Very convenient • Convenient • Neither convenient nor inconvenient • Inconvenient • Very inconvenient
	• After this study, would you choose to continue self-injecting your medication?	• Yes, definitely • Yes, probably • I don't know • Probably not • No
	• After this study, how confident would you be to give yourself injections at home?	• Extremely • Very • Moderately • A little • Not at all

3.5.3 FACIT-F Scoring Algorithm

Responses to FACIT-F items are scored from 0 ("Not at all") to 4 ("Very Much"). Items 7 ("I have energy") and 8 ("I am able to do my usual activities") express a positive connotation, whereas all other FACIT-F items express a negative connotation. For all FACIT-F items except items 7 and 8, the item score is calculated by subtracting the item response score from 4, such that lower scores reflect greater fatigue. Items 7 and 8 are reverse scored by adding the score assigned to the item response to 0 so that directionality for interpreting all of the items is the same. The FACIT-F total score is calculated as: (sum of item scores × 13) / number of items answered. The potential FACIT-F total score ranges from 0 to 52, with higher scores reflecting less fatigue. The FACIT-F scoring algorithm is illustrated below.

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered:

_____=**Fatigue Subscale score**

3.5.4 Content Validity of the FACIT-F

The following section describes the evidence submitted by the applicant to support content validity of the FACIT-F in the context of use for the Skyrizi® CD development program.

Literature Review

The applicant performed a literature review demonstrating fatigue is highly prevalent, relevant, and important to individuals with CD.

The FACIT-F was originally developed to assess fatigue and its impacts on daily function among cancer patients with anemia. Since its development, the applicability of the FACIT-F has expanded to other chronic diseases.

Patient interviews

To support content validity for the FACIT-F measure in the context of the risankizumab drug development program, the applicant conducted a non-interventional cross-sectional qualitative patient interview study in the U.S. (Study VR8417A) consisting of concept elicitation (CE) interviews to explore CD-related fatigue experiences and impacts and cognitive interviews to assess the readability, relevance, and comprehensiveness of the FACIT-F measure. The study included semi-structured one-on-one interviews with adult participants aged ≥ 18 years and adolescent participants aged 15-17 years (inclusive). Participants were recruited by clinician referral and were considered eligible if they had a physician-confirmed diagnosis of moderately to severely active CD[20].

A total of 10 adolescents (ages 15–17 years) and 20 adults (≥ 18 years) with a physician-confirmed diagnosis of moderately to severely active CD were interviewed. Participants were recruited from 4 US clinical sites located in Chicago, Illinois (n=14); St. Louis, Missouri (n=2); New Orleans, Louisiana (n=5); and Los Angeles, California (n=9). The mean age of participants was 36.6 years (SD: 19.2; Range: 15.1-75.4) and the majority of participants were female (n=16, 53.3%), White (n=22, 73.3%), and had moderate CD (n=15, 50.0% as reported by patients; n=19, 63.3% as reported by clinicians)[21]. The largest proportion of adult subjects had completed some college or associate degree (n=8, 40%) and the majority of adolescent subjects were in 12th grade (n=5, 50%).

All of the subjects interviewed reported they experienced CD-related fatigue. Participant descriptions of fatigue and its most salient dimensions are summarized in Appendix 1.2. The most frequently reported experiences of fatigue were physical fatigue (n=23, 76.7%) and sleepiness (n=18, 60.0%). The majority of participants reported experiencing cognitive (n=20, 66.7%), physical (n=18, 60.0%), and social (n=17, 56.7%) fatigue. The majority of subjects reported that CD-related fatigue impacted activities of daily living (n=15, 50%). Based on a 0-10 numeric rating scale where 0=Not at all bothersome and 10=Most bothersome, the mean fatigue bothersomeness rating was 6.8 (n=29, SD=2.3). Approximately, 66% of participants (reported a bothersomeness rating ≥ 7 (n=19/29).

The results from the cognitive interviews for the FACIT-F instrument are in Appendices 1.3.

***[Reviewer's Comment(s)**:*

The qualitative research conducted by the applicant were appropriately developed and conducted to inform content validity of the FACIT-F measure within the context of this drug development program. Content validity is supported based on the following results:

- *The item concepts are relevant/important to the target patient population and appropriate to the study design and objectives*
- *The instrument is comprehensive with respect to the concept (i.e., does not omit important content)*

[20] Study participants were categorized as having moderately-to-severely active UC if he/she was prescribed, immunomodulators (azathioprine or 6-mercaptopurine), 5-aminosalicylic acid (5-ASA [e.g., mesalamine or sulfasalazine]), or advanced therapy, including biologics (e.g., anti-TNF agents).

[21] Patient and clinical demographics not mutually exclusive.

- *Studied sample for qualitative research adequately represents the target patient population*
- *Instructions, item stems, recall period, and response options were well understood and appropriate for the study design and objectives*
- *Response options are appropriate for the item stems (measure the same dimensions, such as frequency or intensity)*
- *The FACIT-F is culturally adapted and adequately translated*
- *Descriptive statistics for the analysis of qualitative data support content relevance*

This reviewer notes that the FACIT-F measure does not ask about cognitive fatigue, which the majority of participants in the qualitative interviews reported as part of their experience with CD.]

3.5.5 Other Measurement Properties

To support evaluation of other measurement properties for the FACIT-F measure, the applicant submitted the full quantitative analysis plan and a quantitative summary report describing evidence to support reliability, construct validity, ability to detect change and scoring. The quantitative assessments used data from the Baseline, Week 4, and Week 12 visits of the phase 3 induction studies and at Week 0 and Week 52 for the maintenance study. Details on the methods and results of the quantitative assessment for the FACIT-F measure are in Appendix 1.4.

[Reviewer's Comment(s):
The quantitative analyses and interpretation appear appropriate. In combination with the evidence to support content validity of the FACIT-F measure in the proposed context of use, the COA review concludes that the FACIT-F is fit for purpose to support the Skyrizi® CD drug development program.

The assessments used to support convergent validity of the FACIT-F total score with other COA measures are not ideal as they measure different concepts than the FACIT-F measure. However, this limitation is unlikely to bias the quantitative analyses for the FACIT-F total score.]

3.5.6 Interpretation of Meaningful Within-Patient Score Changes

Interpretation of clinically meaningful within-patient score change in the FACIT-F total score was evaluated using anchor- and distribution-based methods. Based on the results of these analyses, the sponsor proposes that meaningful within-patient change in the FACIT-F total score is between 7-10 points.

The methods and results of the anchor- and distribution-based analyses are described in Table 4.

Table 4. Results of anchor- and distribution-based methods supporting meaningful change interpretation of the FACIT-F Total Score

Anchor-based Methods	
Analysis	Results
Mean Change from Baseline to Week 12 in the FACIT-F Total Score according to a 1-2-point improvement on the 7-category PGIS in the phase 3 induction studies	Study M16-006 A 1-2 point improvement on the PGIS corresponded with a mean FACIT-F total score change of 6.17-10.03 points (Figure 2 and Table 29 of Appendix 1.5)

	Study M15-991 A 1-2 point improvement on the PGIS corresponded with a mean FACIT-F total score change of 6.72-11.47 points (Figure 3.1.1.1 and Table 31 of Appendix 1.5)
Mean Change from Baseline to Week 12 in the FACIT-F Total Score according to a response of "minimally improved" and "much improved" On the PGIC in the phase 3 induction studies	Study M16-006 Responses of "minimally improved" or "much improved" on the PGIC corresponded with a mean FACIT-F total score change of 6.83-13.63 points (Figure 3 and Table 30 of Appendix 1.5) Study M15-991 Responses of "minimally improved" or "much improved" on the PGIC corresponded with a mean FACIT-F total score change of 7.31-13.88 points (Figure 3.1.1.4 and Table 32 of Appendix 1.5)
Median change from Baseline to Week 12 in the FACIT-F Total Score according to a 1-2-point improvement on the 7-category PGIS in study M16-006	Study M16-006 The median for change in FACIT-F total score that corresponded to a 1-2-point improvement on the PGIS was 5-10 points (Table 36 of Appendix 1.5)
Median Change from Baseline to Week 12 in the FACIT-F Total Score according to a response of "minimally improved" and "much improved" on the PGIC in study M16-006	Study M16-006 The median for change in FACIT-F total score that corresponded to a 1-2-point improvement on the PGIC was 5-13 points (Table 37 of Appendix 1.5)
Distribution-based Methods	
Analysis	Results
Clinically Important Responder Estimates by Received Operating Characteristic Analysis for the FACIT-Fatigue Change in Total Score from Baseline to Week 12 in the phase 3 induction studies	Results based on the PGIS support an improvement/increase in FACIT-F Total Score of 7-points Results based on the PGIC support an improvement/increase in FACIT-F Total Score of 7-8-points
Estimates of MCID for the FACIT-F Total Score at Baseline in Study M16-006	MCID1[a] = 5.64 MCID2[b] = 3 or more points (reliability = 0.93)

[a] Calculated as 0.5 of the SD of the FACIT-F Total Score at Baseline
[b] Assessed using Cronbach's alpha at Baseline for the FACIT-F total scores

[Reviewer's Comment(s):
Literature describes that a normal FACIT-F total score in the general healthy population is ≥ 40. The proposed threshold range for interpretation of clinically meaningful within-patient change based on triangulation of the results using anchor- and distribution-based methods appears appropriate.]

Meaningful change on PGIS and PGIC anchor scales

The applicant conducted semi-structured 1:1 cognitive interviews with adults (aged ≥ 18 years) and adolescents (aged 15-17 years, inclusive) with the following goals: 1) to evaluate individuals' ability to read and understand the items of the PGIS and PGIC; 2) to evaluate individuals' ability to distinguish between response options on the PGIS and PGIC and select a response on the PGIS representative of their health status; 3) to identify the level of change of the PGIS and PGIC ratings that would constitute (i) noticeable and (ii) meaningful improvement or worsening for individuals with CD; and 4) to identify the response option level of the PGIS that would be meaningful to individuals with CD at the end of a clinical trial.

A total of 36 participants (n=10 adolescents; n=26 adults) were interviewed. The mean age of participants was 41.3 years (SD=20.7; range: 15.1-80.8 years) and the majority of participants were male (n=20/36, 83.3%), identified as white (n=28/36, 77.8%), and had moderate CD as reported by clinicians (n=25/36, 69.4%). Of the adult patients, the majority had less than a college or university degree (n=13/26, 50%), and the largest proportion of adults reported having severe (n=5), moderately severe (n=6), or mild (n=5) CD on the PGIS. A total of 5 participants did not report experiencing CD symptoms within the recall period or had his/her response excluded from the analysis of response selected due to an interpretation issue but all had experienced CD symptoms in the past. Of all participants, 44% (n=16/36; n=12 adults and 4 adolescents) mentioned fatigue when describing their interpretation of the item and/or response options.

The average change on the PGIS reported by participants that would constitute meaningful change was 1.25 (SD =0.51) points for improvement and -1.23 (SD=0.49) points for worsening. The majority of adult participants asked (n=18/25, 72%) reported a 1-point category change would be meaningful. The majority of adult participants asked (n=20/26, 76.9%) reported "minimally improved" on the PGIC would be meaningful.

[Reviewer's Comment(s)]:
Participants reported a 1-category change on the PGIS would be meaningful across all levels of category change except very severe to severe (no patients reported having very severe symptoms). The PGIS and PGIC are not ideal anchor scales to interpret FACIT-F scores as they ask subjects to rate overall symptoms due to CD rather than specifically asking about CD-related fatigue. No participants mentioned fatigue when considering meaningful change based on PGIS response categories; however, 4 participants mentioned fatigue when considering meaningful change based on PGIC response categories. Thus, while the use of the PGIS and PGIC scales appear sufficient for anchor-based methods to interpret FACIT-F total scores, interpretation of these analyses is limited.]

6. APPENDICES

Appendix 1: FACIT-F: Additional Information

Appendix 1.1. Copy of the FACIT-F Instrument

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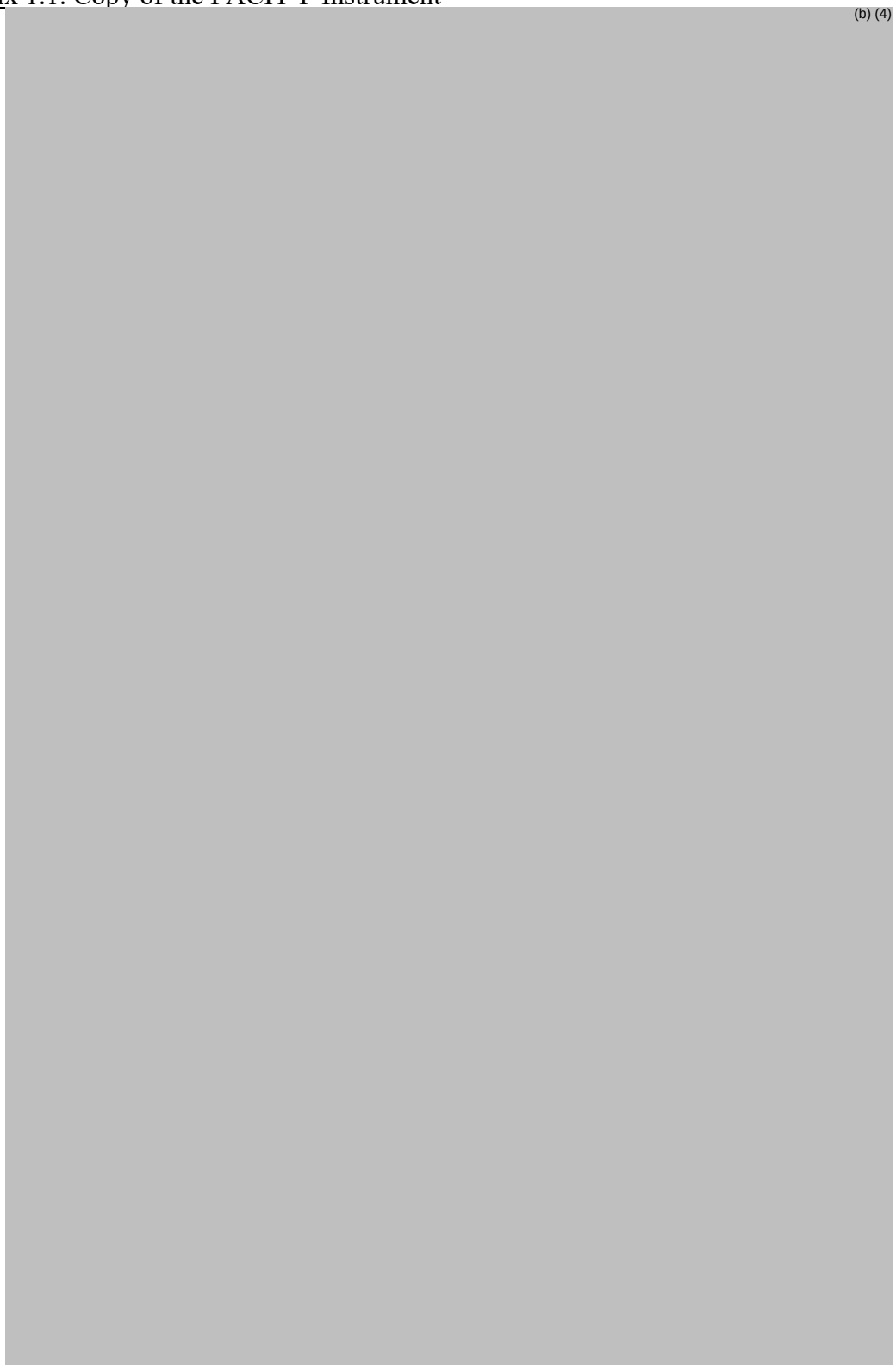

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Appendix 1.2. Participant description of their CD-related fatigue experience

Table 4. Concept Description and Clarification of Crohn's Disease-related Fatigue

Concept aspect	Description based on patient quotes	Frequency of participant reports; N=30 n (%)
Description	A feeling of physical or mental tiredness that comes in waves; exhaustion, weakness, total discomfort, lethargy, lack of motivation, lack of energy, and/or wanting to go to bed	30 (100%)
Severity	Most severe form of fatigue resulted in wanting to lay down and sleep (n=10, 34.5%), not being able to move easily (n=7, 24.1%), severe stomach pain (n=2, 6.9%), and having no appetite (n=1, 3.4%)	30 (100%)
Frequency	Most frequently reported as occurring intermittently, at least once per week (n=23, 79.3%); however, some participants reported it being a constant/daily symptom (n=3, 10.3%), and others reported experiencing fatigue only during flares (n=2, 6.9%)	29 (96.7%)
Duration	Most frequently reported as lasting between a couple and several hours in a given day (n=14, 48.3%); however, some participants reported it lasting all day long (n=8, 34.8%), others reported it lasting several days (n=9, 31.0%), and others reported it lasting about an hour or less (n=4, 13.7%)	29 (96.7%)
Location	Fatigue was reported as being experienced in many different areas of the body, including throughout the whole body (n=11, 39.3%), the head (n=4, 14.3%), the limbs (n=4, 14.3%), the muscles and joints (n=4, 14.3%), and the stomach area (n=3, 10.7%)	28 (93.3%)
Occurrence	Most frequently reported as occurring during flare-ups and worsening of bowel symptoms (n=5, 35.7%), after meals or when eating certain foods (n=2, 14.3%), in the morning (n=2, 14.3%), and when stressed (n=2, 14.3%)	14 (46.7%)

Table 5. Symptom-Concept Description Table for Crohn's Disease-related Fatigue Experiences as Reported by Participants

Concept	Description	Frequency of participant reports; N=30 n (%)
Physical fatigue	A general physical tiredness experienced throughout different parts of the body such as the arms, legs, neck, and chest	23 (76.7%)
Sleepiness	Feeling drowsy, wanting to lay down and rest, and having a desire to quickly fall asleep	18 (60.0%)
Lack of energy	Feeling lethargic and having no energy	11 (36.7%)
Exhausted	Feeling drained, depleted, wiped out, and incapacitated	10 (33.3%)
Mental fatigue	General mental tiredness, a mental "shutdown," feeling stressed, and being not motivated to keep moving	10 (33.3%)
Brain fog	An inability to think or speak clearly, having a foggy or fuzzy feeling in the brain, and not being able to focus	7 (23.3%)
Sluggish/slow	Feeling "draggy," moving slowly, and thinking slowly	7 (23.3%)
Weakness	A lack of physical strength often resulting in difficulty moving or lifting things	5 (16.7%)
Aches	Having joint pain or feeling sore all over the body	3 (10.0%)

Appendix 1.3. Cognitive interview results for the FACIT-F instrument

Instructions

Participant interpreted the instructions as intended	Participant interpreted the recall period as intended	Participant experienced CD-related fatigue over the past 7 days
30/30 (100.0%)	28/30 (93.3%)	29/30 (96.7%)

Items

	Participant interpreted the item as intended	Participant experienced item concept within the recall period	Participant reported never experiencing the item concept	Participant provided a suggestion for revising the item
Item 1: I feel fatigued	22/30 (73.3%)	22/24 (91.7%)	0	0
Item 2: I feel weak all over	24/28 (85.7%)	19/24 (79.2%)	3/24 (12.5%)	0
Item 3: I feel listless ("washed out")	21/30 (70.0%)	21/30 (70.0%)	2/29, 6.9%	3/30 (10.0%)
Item 4: I feel tired	27/30 (90.0%)	26/27 (96.3%)	0	1/30 (3.3%)
Item 5: I have trouble starting things because I am tired	26/30 (86.7%)	23/27 (85.2%)	3/29, 10.5%	0
Item 6: I have trouble finishing things because I am tired	25/30 (83.3%)	21/25 (84.0%)	3/27, 11.1%	0
Item 7: I have energy	27/30 (90.0%)	27/27 (100.0%)		0
Item 8: I am able to do my usual activities	27/30 (90.0%)	20/27 (74.1%)	4/29, 13.8%	0
Item 9: I need to sleep during the day	27/30 (90.0%)	24/27 (88.9%)	2/29, 6.9%	0
Item 10: I am too tired to eat	27/30 (90.0%)	17/28 (60.7%)	8/30, 26.7%	0
Item 11: I need help doing my usual activities	26/30 (86.7%)	12/26 (46.2%)	6/27, 22.2%	0
Item 12: I am frustrated by being too tired to do the things I want to do	27/30 (90.0%)	23/27 (85.2%)	2/29, 6.9%	0
Item 13: I have to limit my social activity because I am tired	28/30 (93.3%)	23/28 (82.1%)	2/30, 6.7%	0

Response options

	N (%)
Items 1-6 and items 9-13 (Not at all – Very Much)	
Participant interpreted the response option "very much" as intended	30/30 (100.0%)
Participant interpreted the response option "quite a bit" as intended	29/30 (96.7%)
Participant interpreted the response option "somewhat" as intended	27/30 (90.0%)
Participant interpreted the response option "a little bit" as intended	28/30 (93.3%)
Participant interpreted the response option "not at all" as intended	29/30 (96.7%)
Participant reported that the response options (not at all – very much) were distinguishable and no response options were the same	26/30 (86.7%)
Participant provided a suggestion for revising the response scale (not at all – very much)	4/30 (13.3%)
Items 7-8 (Reversed response options)	
Participant interpreted the reversed response scale as intended	29/30 (96.7%)

Overall

Cognitive Interview Concept	**n (%)**
Participant reported the questionnaire was easy to complete	30/30 (100.0%))
Participant reported that all items were relevant to ask about	30/30 (100.0%)
Most important item to ask about	Item 1: 11/30 (36.7%) Item 5: 11/30 (36.7%) Item 6: 11/30 (36.7%)
Participant reported that none of the items were repetitive	17/29 (58.6%)
Participant reported that feeling fatigued (Item 1) and feeling tired (Item 4) were repetitive	11/29, 37.9%
Participant reported no concepts are missing from the questionnaire	22/30 (73.3%)
Participant did not provide any suggestions for revising the questionnaire	15/30 (50.0%)

Appendix 1.4. Quantitative Assessment of the FACIT-F measure

Table 5. Summary of Quantitative Assessments of the FACIT-F measure

Assessment	Methods	Results
Item characteristics	Methods The quality of completion of the FACIT-F items was summarized at Baseline, Week 4, and Week 12 for the induction studies (M15-991 and M16-006) and at Induction Baseline, Maintenance Week 0, and Week 52 for the maintenance study (M16-000 sub-study 1). The distribution of responses for each FACIT-F item was assessed at Baseline, Week 4, and Week 12 in Studies M15-991 and M16-006, and at Week 0 and Week 52 for Study M16-000. The presence of floor and ceiling effects was determined based on the following definitions: • A floor or ceiling effect was defined as > 15% of participants endorsing the lowest or highest response option • An extreme floor or ceiling effect was defined as > 40% of participants endorsing the lowest or highest response option.	*Study M15-991 (phase 3 induction study)* At Baseline (n=568), Week 4 (n=561) and Week 12 (n=537), the proportion of subjects with missing FACIT-F total scores was 3.5%, 0.7%, and 5.2%, respectively. At Baseline, there were no extreme floor nor ceiling effects. *Study M16-006 (phase 3 induction study)* At Baseline (n=850), Week 4 (n=841) and Week 12 (n=819), the proportion of subjects with missing FACIT-F total scores was 1.6%, 1.9%, and 5.0%, respectively. At Baseline, there were no extreme ceiling effects. There was an extreme floor effect for: • Item 10: "I am too tired to eat" (n=349, 41.1% of subjects responded "Not at all") • Item 11: "I need help doing my usual activities" (n=392, 46.1% of subjects responded "Not at all") *Study M16-000 (phase 3 maintenance study)* At Induction Baseline (n=462), Maintenance Week 0 (n=462), and Week 52 (n=449), the proportion of subjects with missing FACIT-F total scores was 1.1%, 0.6%, and 3.1%, respectively. At Induction Baseline, there were no extreme ceiling effects. There was an extreme floor effect for: • Item 11: "I need help doing my usual activities" (n=198, 42.9% of subjects responded "Not at all")

Inter-item correlation[a]	Pearson and Spearman correlation coefficients were calculated to reflect the relationships between each of the FACIT-F items using data generated at Induction Baseline and Weeks 4 and 12 for M15-991 and M16-006. The following guidelines were used for the interpretation of correlation coefficients: • Weak relationship: $0.00 \leq \|r\| \leq 0.30$ • Moderate relationship: $0.30 \leq \|r\| \leq 0.70$ • Strong relationship: $0.70 \leq \|r\| \leq 0.90$ • Very strong relationship: $0.90 \leq \|r\| \leq 1.00$ The acceptable range of pairwise inter-item correlation was defined as 0.03-0.90.	<u>Study M15-991</u> • At Baseline, the Pearson and Spearman Correlation Coefficients demonstrated moderate to strong relationships between each of the items except for the following pairs, where a weak relationship was observed: o Item 7 "I have energy" and Item 9 "I need to sleep during the day" (Pearson correlation coefficient=0.28) o Item 7 and Item 10 "I am too tired to eat" (Pearson correlation coefficient =0.16; Spearman correlation coefficient=0.19) o Item 7 and Item 11 "I need help doing my usual activities" (Pearson correlation coefficient =0.21; Spearman correlation coefficient=0.23) o Item 8 "I am able to do my usual Activities" and Item 10 (Pearson correlation coefficient =0.25; Spearman correlation coefficient=0.24) • At Week 4, the Pearson and Spearman Correlation Coefficients demonstrated moderate to strong relationships between each item pair. • At Week 12, the Pearson and Spearman Correlation Coefficients demonstrated moderate to strong relationships between each item pair except for the following pairs, where a weak or very strong relationship was observed: o Item 7 and Item 10 (Pearson correlation coefficient=0.23; Spearman correlation coefficient=0.27) o Item 8 and Item 9 (Pearson correlation coefficient=0.27; Spearman correlation coefficient=0.29) o Item 8 and Item 10 (Pearson correlation coefficient=0.25) o Item 5 "I have trouble starting things because I am tired" and Item 6 "I have trouble finishing things because I am tired (Pearson correlation coefficient=0.91) <u>Study M16-006</u> • At Baseline, the Pearson and Spearman Correlation Coefficients demonstrated moderate to strong relationships between each of the item pairs except for the following pairs, where a weak relationship was observed: o Item 7 and Item 10 (Pearson correlation coefficient =0.27; Spearman correlation coefficient=0.29) o Item 8 and Item 9 (Pearson correlation coefficient =0.28; Spearman correlation coefficient=0.29) • At Week 4, the Pearson and Spearman Correlation Coefficients demonstrated moderate to strong relationships between each of the items except for the following pairs, where a weak relationship was observed: o Item 8 and Item 9 (Pearson correlation coefficient =0.26; Spearman correlation coefficient=0.26)

Assessment	Methods	Results
		○ Item 8 and Item 10 (Pearson correlation coefficient =0.27; Spearman correlation coefficient=0.28) • At Week 12, the Pearson and Spearman Correlation Coefficients demonstrated moderate to strong relationships between each of the item pairs.
Item-total correlation[b]	Polyserial correlation and Spearman correlation coefficients were calculated to reflect the relationship between each FACIT-F item and the FACIT-F Total score at Baseline, and Weeks 4 and 12 in studies M15-991 and M16-006. A correlation ≥ 0.3 was defined as an acceptable item-total correlation.	Study M15-991 • The magnitude of the polyserial correlation coefficients between each item in the FACIT-F instrument and the FACIT-F total score at Baseline, Week 4, and Week 12 ranged between 0.57 to 0.87, 0.65 to 0.91, and 0.58 to 0.93, respectively. • The magnitude of the Spearman correlation coefficients between each item in the FACIT-F instrument and the FACIT-F total score at Baseline, Week 4, and Week 12 ranged between 0.54 to 0.84, 0.64 to 0.89, and 0.60 to 0.91, respectively. Study M16-006 • The magnitude of the polyserial correlation coefficients between each item in the FACIT-F instrument and the FACIT-F total score at Baseline, Week 4, and Week 12 ranged between 0.59 to 0.90, 0.57 to 0.91, and 0.61 to 0.92, respectively. • The magnitude of the Spearman correlation coefficients between each item in the FACIT-F instrument and the FACIT-F total score at Baseline, Week 4, and Week 12 ranged between 0.55 to 0.88, 0.55 to 0.89, and 0.61 to 0.89, respectively.
Internal consistency reliability	• Cronbach's alpha coefficients between individual items and the FACIT-F total score were calculated at BL, Weeks 4, and week 12.[c] • Cronbach's alpha coefficients were calculated upon removal of each item to assess the impact of an item removal on internal consistency reliability.[d]	Study M15-991 • The magnitude of the Cronbach's alpha coefficient for item scores and the FACIT-F total score at Baseline, Week 4, and Week 12 ranged from 0.83 to 0.89. 0.86 to 0.92, and 0.86 to 0.92, respectively. Study M16-006 • The magnitude of the Cronbach's alpha coefficient for item scores and the FACIT-F total score at Baseline, Week 4, and Week 12 ranged from 0.83 to 0.90. 0.85 to 0.91, and 0.84 to 0.91, respectively.

Assessment	Methods	Results
Test-retest reliability	Test-retest reliability was analyzed using the intra-class correlation coefficient (ICC)[c] using the following definitions of stable patients: i. Subjects who selected the same responses on the PGIS at induction Baseline, Week 4, and Week 12 (M15-991, M16-006) ii. Subjects who selected the same responses on the PGIS at Week 4 and Week 12 (M15-991, M16-006) iii. Subjects who selected no change on the PGIC at Week 4 (M15-991, M16-006)	Study M15-991 i. PGIS Stable (Baseline and Week 4): ICC (n=257) = 0.578 (95% CI: 0.383, 0.705) ii. PGIS Stable (Week 4 and Week 12): ICC (n=257) = 0.712 (95% CI: 0.626, 0.778) iii. PGIC Stable (Week 4 and Week 12): ICC (n=148) = 0.787 (95% CI: 0.681, 0.855) Study M16-006 i. PGIS Stable (Baseline and Week 4): ICC (n=388) = 0.642 (95% CI: 0.474, 0.748) ii. PGIS Stable (Week 4 and Week 12): ICC (n=388) = 0.726 (95% CI: 0.643, 0.787) iii. PGIC Stable (Week 4 and Week 12): ICC (n=213) = 0.626 (95% CI: 0.495, 0.722)
Convergent and Discriminant validity:	Spearman correlation coefficients[a] were calculated to assess whether the association of fatigue as measured by the FACIT-F and concepts measured by other instruments (CDAI, PGIS, Inflammatory Bowel Disease Questionnaire (IBDQ), 36-Item Short-Form Survey, version 2 (SF-36v2®), five-level European Quality of Life 5 Dimensions (EQ-5D-5L), and Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI:CD) were as expected. Analyses were conducted at Baseline, Week 4, and Week 12 for the induction studies (M15-991 and M16-006) and at Induction Baseline, Maintenance Week 0, and Week 52 for the maintenance study (M16-000 sub-study 1).	For Study M15-991, Study M16-006, and Study M16-000, the correlations between the FACIT-F total score and scores on all concurrent measures were either as strong or stronger than expected in the correct directions.

Assessment	Methods	Results
Known groups validity	The known-groups analysis for the FACIT-F total scores was evaluated using remission vs. non-remission scores based on the CDAI and IBDQ, and PGIS response categories. The analysis used the cross-sectional analysis population at Week 4 and Week 12 for studies M15-991 and M16-006 and at Maintenance Week 0 and Week 52 for study M16-000 SS1. The following group definitions were used: • Remission: o CDAI <150 o IBDQ total score ≥170 • Non-remission: o CDAI ≥150 o IBDQ total score < 170	For Study M15-991, Study M16-006, and Study M16-000, the FACIT-F total score demonstrated the ability to differentiate between remission and non-remission groups based on the CDAI and IBDQ total score (p-value < 0.001)
Sensitivity to change	Sensitivity to change was assessed by correlating change scores of the FACIT-F to the change scores of PGIS, EQ-5D-5L, SF-36v2®, WPAI, and CDAI from Baseline to Week 12 for studies M15-991 and M16-006 and from Induction Baseline to Week 52 for study M16-000 SS1, as well as PGIC scores at Week 12 for studies M15-991 and M16-006 and at Week 52 for study M16-000 SS1.	For both induction studies, moderate to strong Spearman correlations (r between 0.43 and 0.62 across most measures) were observed between the FACIT-F change score and change scores on all concurrent measures except for the EQ-5D-5L mobility domain, EQ-5D-5L selfcare domain, and WPAI:CD work time missed domain, which weakly correlated with the FACIT-F change score (r=0.287, r=0.236, and r=0.269, respectively, for study M16-006). Results were similar for both study M15-991 and study M16-000 SS1.

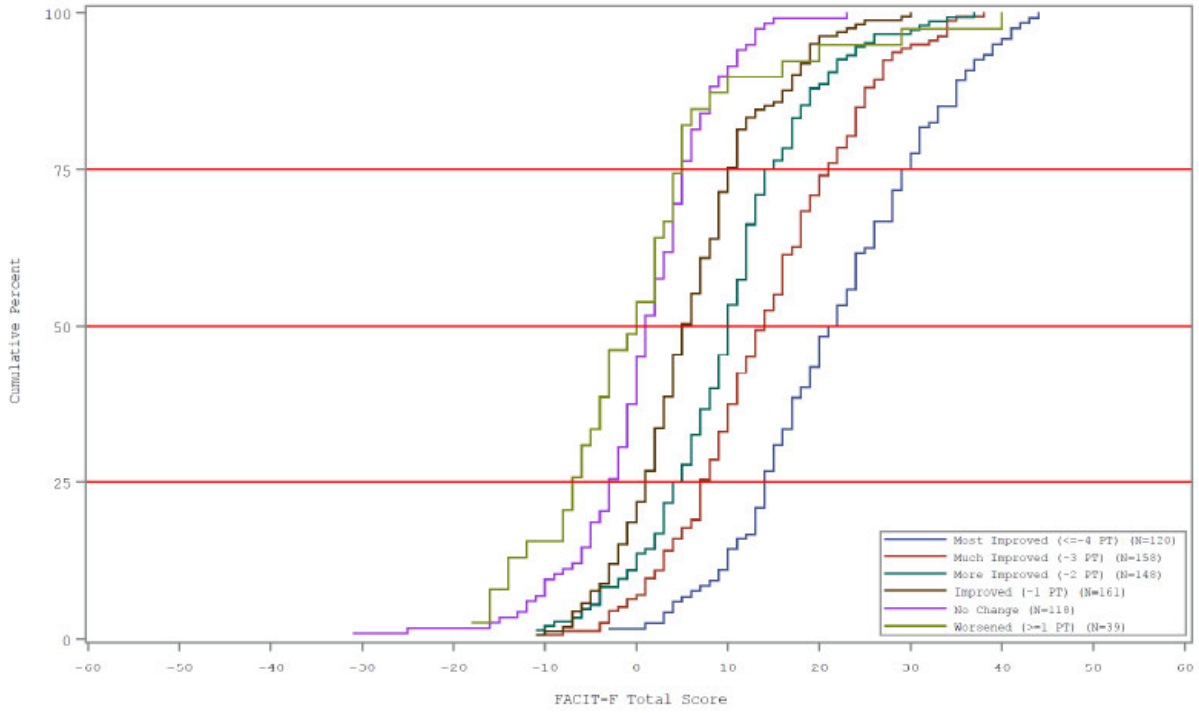
[a] To facilitate interpretation of the analyses for inter-item correlation, the following guidelines were used: Weak relationship: $0.00 \leq |r| \leq 0.30$; Moderate relationship: $0.30 < |r| \leq 0.70$; Strong relationship: $0.70 < |r| \leq 0.90$; and Very strong relationship: $0.90 < |r| \leq 1.0024$
[b] A correlation ≥0.3 was considered acceptable
[c] A correlation coefficient > 0.7 was considered acceptable
[d] If the removal of an item causes the alpha to increase, then that item may not be fitting well with its scale.

Appendix 1.5. Results of Anchor-Based Methods to Interpret Meaningful Change in the FACIT-F Total Score

Study M16-006

Analyses based on the PGIS anchor scale

Figure 2. Empirical Cumulative Distribution Function (eCDF) for Change in FACIT-Fatigue Total Score by Patient Global Impression of Severity (PGIS) Change Response Groups from Baseline to Week 12 for M16-006 (N=819)



Source: Appendix I, Figure 3.2.1.1.

Table 29. Anchor-based Estimates FACIT-Fatigue Score by Patient Global Impression of Severity (PGIS) Stratified Anchor Categories from Baseline to Week 12 (M16-006)

Score	Change in PGIS (Baseline to Week 12)	N	Baseline Mean (SD)	Week 12 Mean (SD)	Mean Change (SD)	Within-group p-value*	Between-group p-value†
FACIT-Fatigue total score	Most improved (4-point or greater improvement)	120	20.09 (10.44)	41.90 (8.95)	21.81 (10.54)	<0.001	<0.001
	Much improved (3-point improvement)	158	25.62 (10.55)	39.82 (8.74)	14.20 (9.61)	<0.001	
	More improved (2-point improvement)	**148**	**25.87 (10.61)**	**35.90 (10.45)**	**10.03 (8.88)**	**<0.001**	
	Improved (1-point improvement)	**161**	**26.14 (11.23)**	**32.30 (11.26)**	**6.17 (7.74)**	**<0.001**	
	No change	118	26.64 (12.18)	27.54 (12.85)	0.90 (7.64)	0.042	
	Worsened (1-point or greater deterioration)	39	25.08 (11.99)	25.38 (10.89)	0.31 (11.69)	0.630	

*The within group p-value is from a Wilcoxon Signed Rank test on change scores at each level of PGIS (7-Level) response.
†The between group p-value is from a Kruskal-Wallis testing distributional shift in change scores between PGIS (7-Level) response groups.
Source: Appendix I, Tables 14.2.1.1

Table 34. FACIT-Fatigue Change Score Percentiles for Patients Who Reported a One-point Improvement Between Baseline and Week 12 on the PGIS for Study M16-006

Change in FACIT-Fatigue Total Score	Baseline (to Week 12) PGIS Anchor Category						
	Minimal (to Absent)	Mild (to Minimal)	Moderate (to Mild)	Moderately Severe (to Moderate)	Severe (to Moderately Severe)	Very Severe (to Severe)	Total (All)
N	3	13	23	50	55	17	161
Mean (SD)	4.00 (6.56)	5.31 (6.73)	6.52 (8.32)	5.90 (7.20)	7.20 (7.27)	4.18 (10.85)	6.17 (7.74)
10th percentile	-2.00	-1.00	-5.00	-1.50	-1.00	-7.00	-3.00
25th percentile	-2.00	1.00	-2.00	1.00	2.00	-4.00	1.00
Median (50th percentile)	3.00	4.00	9.00	5.50	5.00	3.00	5.00
75th percentile	11.00	7.00	12.00	9.00	11.00	9.00	10.00
90th percentile	11.00	18.00	17.00	17.00	18.00	25.00	17.00

Source: Appendix I, Tables 14.3.2.1

Table 35. FACIT-Fatigue Change Score Percentiles for Patients Who Reported a Two-point Improvement Between Baseline and Week 12 on the PGIS for Study M16-006

Change in FACIT-Fatigue Total Score	Baseline (to Week 12) PGIS Anchor Category					
	Mild (to Absent)	Moderate (to Minimal)	Moderate Severe (to Mild)	Severe (to Moderate)	Very Severe (to Moderately Severe)	Total (All)
N	7	30	59	37	15	148
Mean (SD)	5.86 (7.31)	11.57 (7.51)	7.53 (8.48)	12.81 (9.34)	11.87 (10.09)	10.03 (8.88)
10th percentile	-10.00	3.50	-4.00	-1.00	2.00	-1.00
25th percentile	6.00	6.00	1.00	7.00	4.00	4.50
Median (50th percentile)	8.00	10.00	9.00	12.00	12.00	10.00
75th percentile	10.00	14.00	14.00	19.00	14.00	14.50
90th percentile	12.00	21.00	18.00	25.00	26.00	21.00

Source: Appendix I, Tables 14.3.2.2

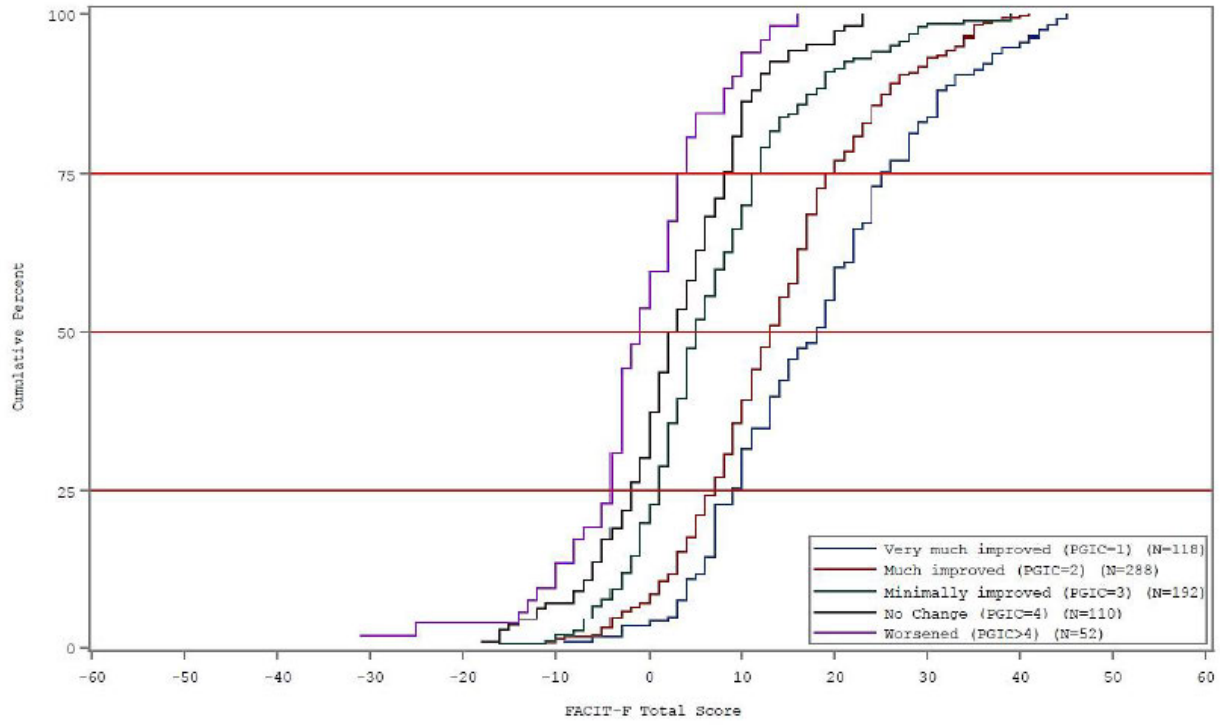
Table 36. Percentile Change in FACIT-Fatigue Total Scores from Baseline to Week 12 by PGIS Response Groups per Empirical Cumulative Distribution Function (eCDF) Curve (M16-006)

	Baseline to Week 12 PGIS (7-level) Anchor Category							
Change in FACIT-Fatigue Total Score	≥3-point Improvement	2-point Improvement	1-point Improvement	No Change	1-point Deterioration	2-point Deterioration	≥3-point Deterioration	Total
N	278	148	161	118	33	5	1	744
Mean (SD)*	17.49 (10.69)	10.03 (8.88)	6.17 (7.74)	0.90 (7.64)	0.94 (10.85)	-0.60 (16.92)	-16.00 (N.A.)	10.02 (11.38)
10th percentile†	4.00	-1.00	-3.00	-9.00	-12.00	-14.00	-16.00	-3.00
25th percentile†	10.00	4.50	1.00	-3.00	-4.00	-7.00	-16.00	2.00
Median (50th percentile)†	17.00	10.00	5.00	1.00	2.00	-6.00	-16.00	9.00
75th percentile†	25.00	14.50	10.00	5.00	5.00	-5.00	-16.00	17.00
90th percentile†	33.00	21.00	17.00	10.00	10.00	29.00	-16.00	26.00

*Mean (SD) for the change score on the FACIT-Fatigue between Baseline and Week 12 for each anchor category
†Change score for FACIT-Fatigue is presented associated with each percentile group.
Source: Appendix I, Table 15.2.1.1

Analyses based on the PGIC anchor scale

Figure 3. eCDF for Change in FACIT-Fatigue Total Score by Patient Global Impression of Change (PGIC) Response



Source: Appendix I, Figure 3.2.1.4.

Table 30. Anchor-based Estimates FACIT-Fatigue Score by Patient Global Impression of Change (PGIC) Stratified Anchor Categories from Baseline to Week 12 (M16-006)

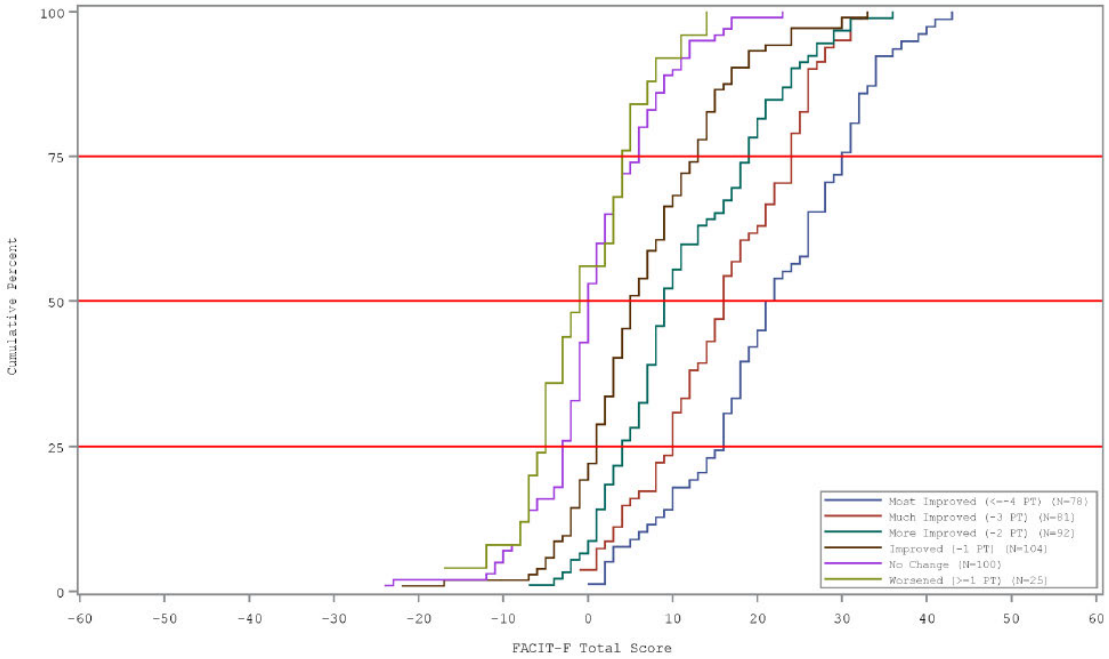
Score	PGIC at Week 12	N	Baseline Mean (SD)	Week 12 Mean (SD)	Mean Change (SD)	Within-group p-value*	Between-group p-value†
FACIT-Fatigue total score	Very much improved (PGIC=1)	118	26.41 (11.90)	44.44 (7.50)	18.03 (11.54)	<0.001	<0.001
	Much improved (PGIC=2)	**288**	**24.77 (10.76)**	**38.40 (9.58)**	**13.63 (10.20)**	**<0.001**	
	Minimally improved (PGIC=3)	**192**	**25.33 (11.28)**	**32.17 (10.34)**	**6.83 (9.34)**	**<0.001**	
	No change (PGIC=4)	110	24.75 (11.96)	27.60 (12.31)	2.85 (8.23)	<0.001	
	Worsened (PGIC >4)	52	23.44 (11.80)	22.21 (11.23)	-1.23 (8.53)	0.451	

*The within group p-value is from a Wilcoxon Signed Rank test on change scores at each level of PGIC (7-Level) response.
†The between group p-value is from a Kruskal-Wallis testing distributional shift in change scores between PGIC (7-Level) response groups.
Source: Appendix I, Tables 14.2.1.4

Study M15-991

Analyses based on the PGIS anchor scale

Figure 3.1.1.1: Empirical Cumulative Distribution Function (eCDF) for Change in FACIT-F Total Score by Patient Global Impression of Symptom Severity (PGIS) Change Response Groups from Baseline to Week 12 (M15-991 CS-AP) (N=537)



NOTE: CS-AP population is all ITT1A subjects who have completed at least one item on CSS or FACIT-Fatigue at any of the following timepoints: M15-991 induction baseline and weeks 4 and 12, M16-006 induction baseline and weeks 4 and 12, and M16-000 maintenance baseline and week 52.
NOTE: The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) total score ranges from 0-52 with higher scores indicating lower fatigue severity (better QOL).
NOTE: Response groups based on PGIS Change Response Groups between Baseline and Week 12.

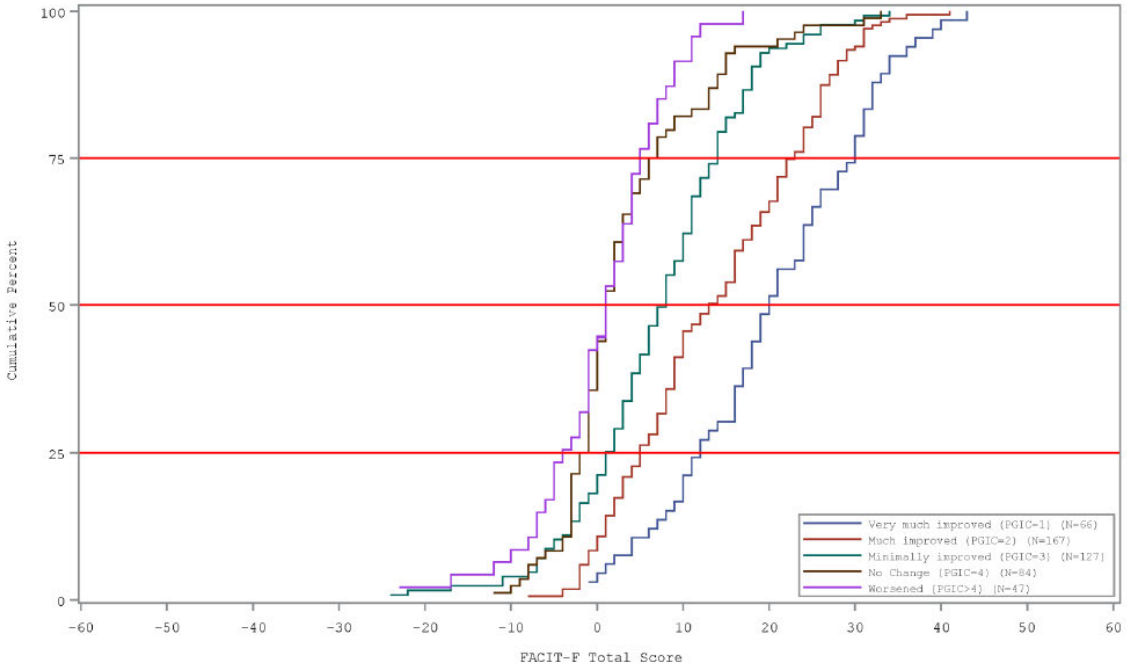
Table 31. Anchor-based Estimates FACIT-Fatigue Score by PGIS Stratified Anchor Categories from Baseline to Week 12 (M15-991)

Score	Change in PGIS (Baseline to Week 12)	N	Baseline Mean (SD)	Week 12 Mean (SD)	Mean Change (SD)	Within-group p-value*	Between-group p-value†
FACIT-Fatigue total score	Most improved (4-point or greater improvement)	78	19.64 (9.97)	41.35 (9.72)	21.71 (10.45)	<0.001	<0.001
	Much improved (3-point improvement)	81	23.25 (9.52)	39.19 (8.28)	15.94 (8.97)	<0.001	
	More improved (2-point improvement)	**92**	**24.86 (10.55)**	**36.33 (10.69)**	**11.47 (9.36)**	**<0.001**	
	Improved (1-point improvement)	**104**	**22.37 (10.93)**	**29.09 (11.43)**	**6.72 (9.02)**	**<0.001**	
	No change	100	24.00 (11.62)	24.92 (11.71)	0.92 (7.51)	0.214	
	Worsened (1-point or greater deterioration)	25	23.56 (8.95)	22.92 (10.70)	-0.64 (7.23)	0.666	

*The within group p-value is from a Wilcoxon Signed Rank test on change scores at each level of PGIS (7-Level) response.
†The between group p-value is from a Kruskal-Wallis testing distributional shift in change scores between PGIS (7-Level) response groups.
Source: Appendix I, Tables 14.1.1.1

Analyses based on the PGIC anchor scale

Figure 3.1.1.4: Empirical Cumulative Distribution Function (eCDF) for Change in FACIT-F Total Score by Patient Global Impression of Change (PGIC) Response Groups from Baseline to Week 12 (M15-991 CS-AP) (N=537)



NOTE: CS-AP population is all ITT1A subjects who have completed at least one item on CSS or FACIT-Fatigue at any of the following timepoints: M15-991 induction baseline and weeks 4 and 12, M16-006 induction baseline and weeks 4 and 12, and M16-000 maintenance baseline and week 52.
NOTE: The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) total score ranges from 0-52 with higher scores indicating lower fatigue severity (better QOL).
NOTE: Response groups based on PGIC response groups at Week 12.

Table 32. Anchor-based Estimates FACIT-Fatigue Score by PGIC Stratified Anchor Categories from Baseline to Week 12 (M15-991)

Score	PGIC at Week 12	N	Baseline Mean (SD)	Week 12 Mean (SD)	Mean Change (SD)	Within-group p-value*	Between-group p-value†
FACIT-Fatigue total score	Very much improved (PGIC=1)	66	22.36 (9.79)	42.59 (9.28)	20.23 (10.94)	<0.001	<0.001
	Much improved (PGIC=2)	**167**	**23.55 (10.78)**	**37.43 (9.45)**	**13.88 (10.54)**	**<0.001**	
	Minimally improved (PGIC=3)	**127**	**24.49 (10.67)**	**31.80 (11.02)**	**7.31 (9.80)**	**<0.001**	
	No change (PGIC=4)	84	22.69 (11.01)	26.04 (12.08)	3.35 (8.45)	0.002	
	Worsened (PGIC >4)	47	19.30 (10.23)	19.83 (9.57)	0.53 (7.49)	0.384	

*The within group p-value is from a Wilcoxon Signed Rank test on change scores at each level of PGIC (7-Level) response.
†The between group p-value is from a Kruskal-Wallis testing distributional shift in change scores between PGIC (7-Level) response groups.
Source: Appendix I, Tables 14.1.1.4

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Appendix 3.3. SIAQ Scoring Algorithm

Subjects rate the 7 item of the PRE SIAQv2 and items 1-9 and 15-21 of the POST SIAQv2 on a 5-point verbal rating scale (VRS) (scored 1-5). Items 10-14 of the POST SIAQv2 are rated on a 6-point VRS (scored 1-6). The rating for each item is transformed to an item score ranging from 0 (worst experience) to 10 (best experience). A domain score can be derived by averaging the transformed item scores contributing to a domain. The scoring algorithm is illustrated in Table 1.

Table 1: Scoring of domains from raw item scores

	Items	Transformed item score	Domain score calculation	Domain score range
PRE module domain				
FL	1-3	((raw score)-1)*2.5	Average of transformed item scores	0-10
CO	4-6	((raw score)-1)*2.5		
SA	7	((raw score)-1)*2.5		
POST module domain				
FL	1-3	((raw score)-1)*2.5	Average of transformed item scores	0-10
IM	4	((raw score)-1)*2.5		
CO	5-7	((raw score)-1)*2.5		
RE	8-9	((raw score)-1)*2.5[NOTE1]		
EU	10-14	**((raw score)-1)*2**		
SA	15-21	((raw score)-1)*2.5		

Domain scores are calculated only if 50% or more items of the domain are completed.

NOTE1:
For items 8 and 9: The raw item sub-scores (e.g., 8a, 8b, 8c) should be first averaged (only if 50% of items or more are completed) and then transformed to 0-10 using the formulas in the manual. From the averaged and transformed 8 and 9 items the domain score can be calculated.

SIAQ domain scores range from 0-10 where higher scores reflect a better experience with the injection. The threshold for clinically meaningful within patient change in SIAQ scores has not been evaluated.

Appendix 4. Description of Crohn's Disease-related Fatigue

Table 4. Concept Description and Clarification of Crohn's Disease-related Fatigue

Concept aspect	Description based on patient quotes	Frequency of participant reports; N=30 n (%)
Description	A feeling of physical or mental tiredness that comes in waves; exhaustion, weakness, total discomfort, lethargy, lack of motivation, lack of energy, and/or wanting to go to bed	30 (100%)
Severity	Most severe form of fatigue resulted in wanting to lay down and sleep (n=10, 34.5%), not being able to move easily (n=7, 24.1%), severe stomach pain (n=2, 6.9%), and having no appetite (n=1, 3.4%)	30 (100%)
Frequency	Most frequently reported as occurring intermittently, at least once per week (n=23, 79.3%); however, some participants reported it being a constant/daily symptom (n=3, 10.3%), and others reported experiencing fatigue only during flares (n=2, 6.9%)	29 (96.7%)
Duration	Most frequently reported as lasting between a couple and several hours in a given day (n=14, 48.3%); however, some participants reported it lasting all day long (n=8, 34.8%), others reported it lasting several days (n=9, 31.0%), and others reported it lasting about an hour or less (n=4, 13.7%)	29 (96.7%)
Location	Fatigue was reported as being experienced in many different areas of the body, including throughout the whole body (n=11, 39.3%), the head (n=4, 14.3%), the limbs (n=4, 14.3%), the muscles and joints (n=4, 14.3%), and the stomach area (n=3, 10.7%)	28 (93.3%)
Occurrence	Most frequently reported as occurring during flare-ups and worsening of bowel symptoms (n=5, 35.7%), after meals or when eating certain foods (n=2, 14.3%), in the morning (n=2, 14.3%), and when stressed (n=2, 14.3%)	14 (46.7%)

Appendix 5. Clinical Trial Efficacy Results for the Secondary FACIT-F Endpoint

Appendix 5.1. Study M15-991

Change from Baseline in FACIT Fatigue at Week 12

TABLE 14.2 1.3.3

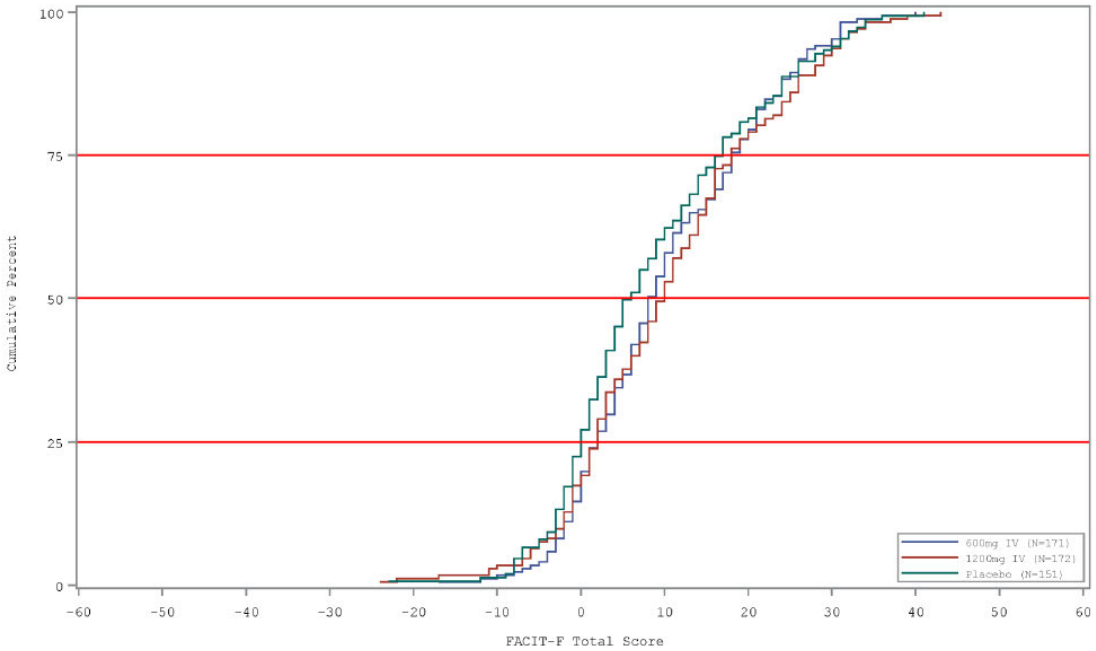
Change from Baseline in FACIT Fatigue at Week 12 (MMRM, PMM)
(ITT1A Population)

Analysis Method / Treatment	N	Missing Due to COVID-19 n	Baseline Mean	Visit Mean	Within Group Change from Baseline LS Mean	[95% CI]	SE	Between Group Difference Compared to Placebo LS Mean	[95% CI]	SE	P-value
MMRM [A]											
Placebo IV	144	3	22.2	31.0	7.7	[6.0, 9.4]	0.87				
Risankizumab 600 mg IV	168	1	23.4	33.8	10.5	[8.9, 12.1]	0.81	2.8	[0.4, 5.1]	1.18	0.020*
Risankizumab 1200 mg IV	172	1	23.6	34.2	10.8	[9.2, 12.4]	0.81	3.0	[0.7, 5.3]	1.17	0.010**
PMM [B]											
Placebo IV	144	3	22.2	31.0	7.3	[5.6, 9.0]	0.88				
Risankizumab 600 mg IV	168	1	23.4	33.8	10.6	[9.0, 12.2]	0.82	3.3	[1.0, 5.6]	1.19	0.006**
Risankizumab 1200 mg IV	172	1	23.6	34.2	10.8	[9.2, 12.4]	0.81	3.5	[1.2, 5.9]	1.18	0.003**

Note: ITT1A Population includes randomized subjects who received at least one dose of study drug during the 12-Week Induction Period, and had baseline eligible SES-CD of >= 6 (>= 4 for isolated ileal disease).
[A]: MMRM is the Mixed-Effect Model Repeat Measurement with baseline FACIT-F, stratification factors (Number of Prior Biologics Failed (<= 1, > 1) and Baseline Steroid Use (Yes, No)), treatment, visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix is used.
[B]: PMM (Pattern Mixture Model) is based on Hedeker & Gibbons 1997.
Baseline FACIT-F, stratification factors (Number of Prior Biologics Failed (<= 1, > 1) and Baseline Steroid Use (Yes, No)), treatment, visit, missing pattern, treatment-by-visit interaction and treatment-by-missing pattern interaction are included in the model.
The following missing pattern are considered in the model:
(1) Subjects with data available at all visits; (2) Subjects with missing data at Week 4, or Week 12.
* P-value <= 0.05; ** P-value <= 0.01; *** P-value < 0.001.

eCDF for Change in FACIT-F Total Score by Treatment Groups from Baseline to Week 12

Figure 3.1.1.16: Empirical Cumulative Distribution Function (eCDF) for Change in FACIT-F Total Score by Treatment Groups from Baseline to Week 12 (M15-991 CS-AP) (N=537)



NOTE: CS-AP population is all ITT1A subjects who have completed at least one item on CSS or FACIT-Fatigue at any of the following timepoints: M15-991 induction baseline and weeks 4 and 12, M16-006 induction baseline and weeks 4 and 12, and M16-000 maintenance baseline and week 52.
NOTE: The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) total score ranges from 0-52 with higher scores indicating lower fatigue severity (better QOL).

Appendix 5.2. Study M16-006

Change from Baseline in FACIT-F Total Score at Week 12

TABLE 14.2__1.3.3

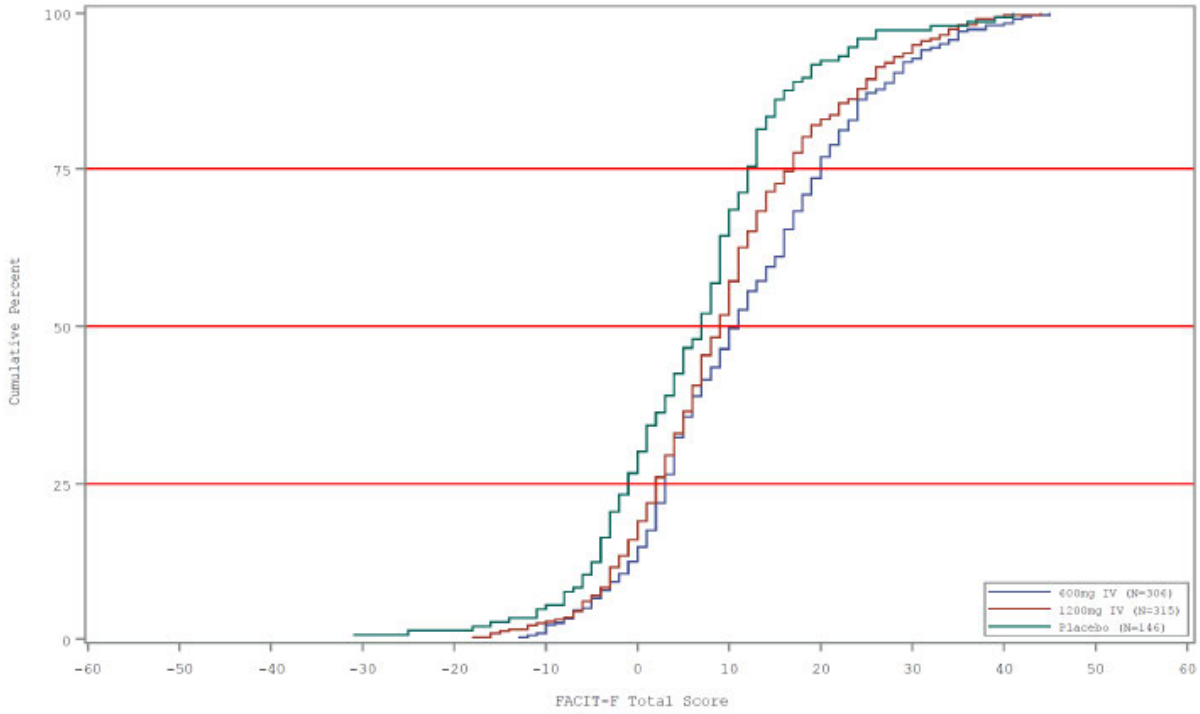
Change from Baseline in FACIT Fatigue at Week 12 (MMRM, PMM)
(ITT1A Population)

Analysis Method / Treatment	N	Missing Due to COVID-19 n	Baseline Mean	Visit Mean	Within Group: Change from Baseline: LS Mean	[95% CI]	SE	Between Group Difference: Compared to Placebo: LS Mean	[95% CI]	SE	P-value
MMRM [A]											
Placebo IV	134	2	25.3	32.2	6.0	[4.4, 7.7]	0.86				
Risankizumab 600 mg IV	302	2	24.0	36.0	11.2	[10.1, 12.4]	0.59	5.2	[3.2, 7.2]	1.02	<0.001***
Risankizumab 1200 mg IV	310	3	25.7	35.7	10.1	[9.0, 11.3]	0.58	4.1	[2.1, 6.1]	1.02	<0.001***
PMM [B]											
Placebo IV	134	2	25.3	32.2	5.7	[4.0, 7.4]	0.87				
Risankizumab 600 mg IV	302	2	24.0	36.0	11.1	[10.0, 12.3]	0.59	5.5	[3.5, 7.5]	1.03	<0.001***
Risankizumab 1200 mg IV	310	3	25.7	35.7	10.1	[9.0, 11.3]	0.59	4.4	[2.4, 6.5]	1.03	<0.001***

Note: ITT1A Population includes randomized subjects who received at least one dose of study drug during the 12-Week Induction Period, and had baseline eligible SES-CD of >= 6 (>= 4 for isolated ileal disease).
[A]: MMRM is the Mixed-Effect Model Repeat Measurement with baseline FACIT-F, stratification factors (Number of prior biologics failed (0, 1, >1) and baseline steroid use (Yes, No)), treatment, visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix is used.
[B]: PMM (Pattern Mixture Model) is based on Hedeker & Gibbons 1997. Baseline FACIT-F, stratification factors (Number of prior biologics failed (0, 1, >1) and baseline steroid use (Yes, No)), treatment, visit, missing pattern, treatment-by-visit interaction and treatment-by-missing pattern interaction are included in the model.
The following missing pattern are considered in the model: (1) Subjects with data available at all visits; (2) Subjects with missing data at Week 4, or Week 12.

eCDF for Change in FACIT-Fatigue Total Score by Treatment Groups from Baseline to Week 12

Figure 4. eCDF for Change in FACIT-Fatigue Total Score by Treatment Groups from Baseline to Week 12 for M16-006 (N=819)



Source: Appendix I, Figure 3.2.1.16.

Appendix 5.3. Study M16-000

SS1: Change from Induction Baseline at Week 52

TABLE 14.2__3.5.1

Change from Baseline of the Induction Study in FACIT Fatigue at Week 52 (ANCOVA)
(ITT1A Population)

				Within Group: Change from Baseline			Between Group Difference: Compared to Placebo			
Treatment	N	Baseline Mean	Visit Mean	LS Mean	[95% CI][A]	SE	LS Mean	[95% CI][A]	SE	P-value[A]
Placebo SC	93	23.3	39.2	15.0	[13.3, 16.6]	0.85				
Risankizumab 180 mg SC	117	23.8	40.4	15.5	[13.9, 17.0]	0.76	0.5	[-1.7, 2.7]	1.13	0.663
Risankizumab 360 mg SC	104	27.0	40.8	15.4	[13.8, 17.0]	0.80	0.4	[-1.9, 2.7]	1.17	0.703

Note: ITT1A Population includes the randomized subjects in the intent-to-treat population who received IV risankizumab for only one period of 12 weeks in the induction study M16-006 or M15-991 and at least one dose of study drug in the sub-study 1, and had eligible SES-CD of >= 6 (>= 4 for isolated ileal disease) at baseline of induction study.
[A]: 95% CI for within group LS Mean and 95% CI for LS Mean in treatment difference and p-value are calculated according to the ANCOVA with strata (endoscopic response at Week 0 (yes or no), clinical remission status at Week 0 (yes or no) and last IV dose during risankizumab induction periods (1200 mg or 600 mg)) and induction baseline FACIT fatigue and Week 0 FACIT fatigue as covariates for the comparison of two treatment groups.
* P-value <= 0.05; ** P-value <= 0.01; *** P-value < 0.001.

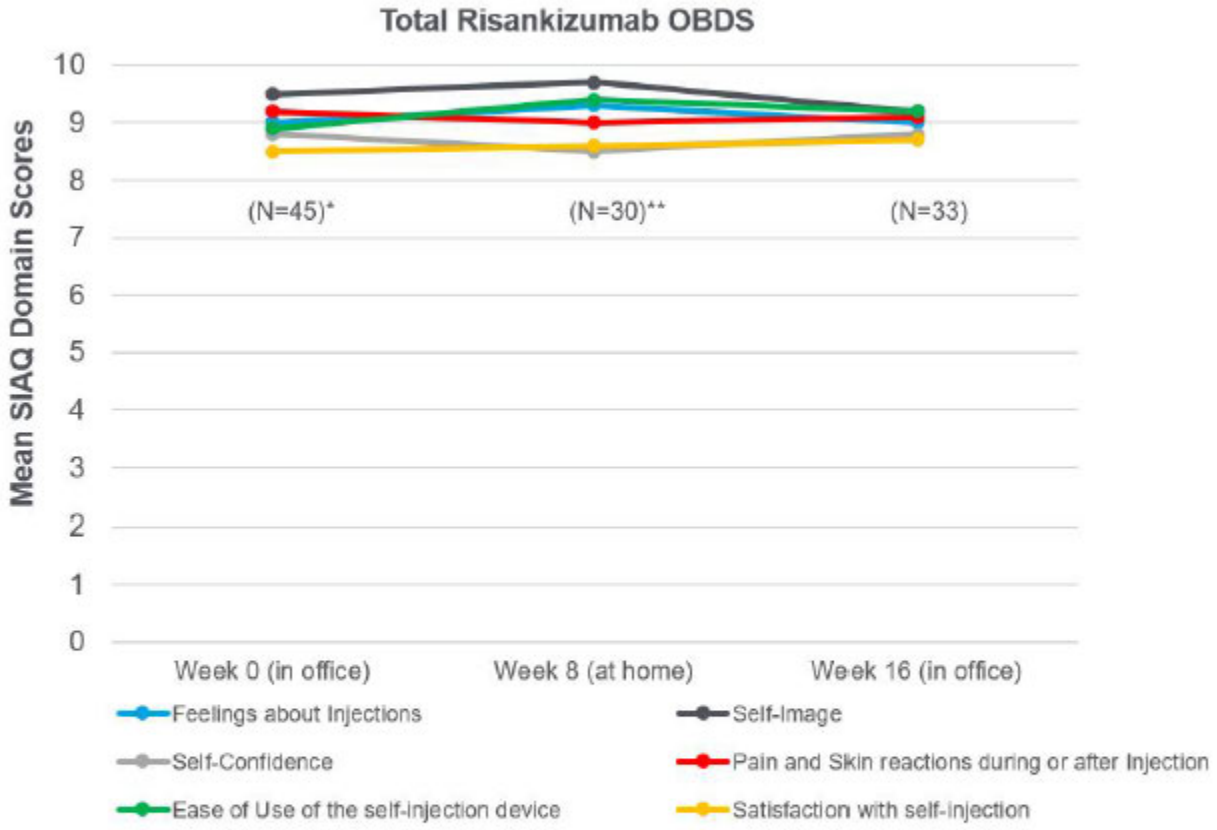
Program Source Code: (b) (4)

SS4: Subject rating of OBI acceptability

The mean PRE-dose SIAQ domain scores for the Feelings about injections (FL), Self-confidence (CO), and Satisfaction with current mode of administration (SA) domains were all ≥ 8.4 for the pooled risankizumab 180mg OBI (n=31) and risankizumab 360mg OBI (n=15) treatment arms prior to the initial OBDS injection (Week 0).

The POST-dose SIAQ domain scores for the FL, CO, SA, Self-image (IM), Injection-site reactions (RE) and Ease of Use (EU) domains were all ≥ 8.5 for the pooled treatment arms after the OBDS injection at Weeks 0, 8, and 16, as shown in Figure 3.22

Figure 3. Post Module Mean SIAQ Domain Scores Over Time



ITT4 population includes all subjects who have at least 1 dose of study drug in SS4.
Data are as observed. Appendix K Table 14.2_11.
Scores range from 0 (worst experience) to 10 (best experience).
*N=46 for feelings about injections, self-image, and self-confidence domains.
**N=29 for self-image domain.

[22] sBLA 761105-s016 SN 0199(1084) received February 22, 2022.

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SUSAN M PRETKO
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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

BLA	761262 and 761105 (S-016)
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Risankizumab
Indication	Crohn's Disease
Applicant	AbbVie
Requesting Division	Division of Gastroenterology (DG)
Primary Reviewer	Ling Lan, MD, PhD Clinical Analyst, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Mar 19, 2022

Context: Risankizumab (RZB) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds interleukin 23 (IL-23). IL-23 enhances T-helper 17 (TH-17) lymphocyte development, and TH-17 cells are thought to have a key role in inflammatory diseases such as psoriasis (PsO) and psoriatic arthritis (PsA). The FDA approved RZB for adult plaque PsO on April 23, 2019, and for adult PsA on January 21, 2022. In this combined BLA of intravenous induction therapy and supplement subcutaneous maintenance therapy, it is indicated for Crohn's disease (CD). The sponsor proposed label on CD did not include information regarding hepatic events. Division of Gastroenterology (DG) noted elevations in liver function tests (LFTs) in the initial 12-week IV induction treatment period. They requested DHN's DILI Team comments on this potential hepatotoxicity signal and the related labeling issues.

Executive Summary: Risankizumab (RZB) for Crohn's disease (CD) appears to carry a small but significant DILI risk. The Hy's Law case arising from about 1100 exposed CD subjects and increased ALT elevation in the 600 mg treatment arm are concerning. However, risk mitigation through labeling and post-market requirements may forge a path for approval, if efficacy and need are high. The liver injury signal in CD subjects is likely due to the higher dose used compared to the approved dose for psoriasis. While we recognize CD may need higher drug exposure, we did not find data to support the dosing chosen for the phase 3 trials. Nevertheless, limiting RZB induction to three doses over 8 weeks with liver test monitoring should lower the risk to an acceptable level. The presenting rash in the Hy's Law case, narrow latency, and likely immune mediated DILI that is steroid responsive may also aid DILI detection and treatment. We have specific recommendations for labeling and post-market requirements should RZB be approved for CD.

Full Consultation Sections:

Section 1.0 – Disease and Rationale
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.

Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
Bio-IR: inadequate response or intolerance to use of one or more of the approved CD biologic agents.
CD: Crohn's disease
DB: double blind
DDI: drug-drug interaction
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
IL-23: interleukin 23
OLE: open-label extension
PsA: psoriatic arthritis
PsO: plaque psoriasis
RZB: risankizumab
SC: subcutaneous
SSZ: sulfasalazine
TB: total bilirubin
TH-17: T-helper 17 lymphocyte
ULN: upper limit normal

1.0 Disease and Rationale:

1.3 Disease: Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract from the mouth to the anus. CD affects all ages and onset is most common in the 20-30s. Female individuals are affected slightly more than males, and the risk for disease is higher in some ethnic groups[1,2]. The CD incidence is highest in North America and Europe, with estimates of 23.8 and 15.4 per 100,000 person-years,

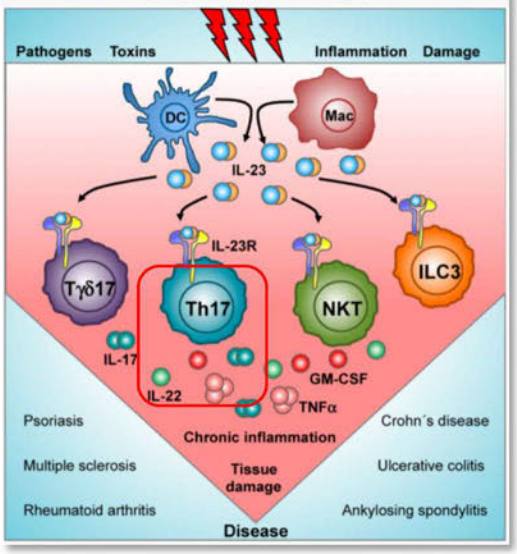
[1] Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-17.
[2] Probert CS, Jayanthi V, Rampton DS, et al. Epidemiology of inflammatory bowel disease in different ethnic and religious groups: limitations and aetiological clues.Int J Colorectal Dis. 1996;11(1):25-8.

respectively[3]. Estimated prevalence is also highest in Europe (322 per 100,000 persons) and North America (319 per 100,000 persons)[3].

Treatment of CD[4] include induction medications for initial remission, followed by maintenance medications that prevent relapse. The medications for CD include aminosalicylates, corticosteroids (e.g., budesonide, beclomethasone, prednisone), immunosuppressive agents (e.g., azathioprine, methotrexate, and tacrolimus), mono-clonal antibodies, and antibiotics. FDA approved biologic therapies for CD include TNFα-inhibitors (adalimumab, certolizumab, infliximab), an IL-12/23 inhibitor (ustekinumab), and anti-integrin agents (natalizumab and vedolizumab).

1.4 Rationale (Drug mechanism of action): RZB is a humanized IgG1 monoclonal antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23). This binding blocks interaction with its cell surface receptor and inhibits IL-23 mediated intracellular signaling and release of proinflammatory cytokines (such as IL-17) and chemokines (Figure 1). IL-23 plays a role in the differentiation and function of T-helper (Th) 17 cells. Th-17 cells have emerged as an important T-cell subpopulation in the pathogenesis of immune mediated disorders such as PsA and CD. RZB is already approved to treat PsO (Apr 23, 2019) and PsA (Jan 21, 22).

Figure 1. Role of interleukin 23 (IL-23) in chronic inflammatory diseases. IL-23 is produced by dendritic cells (DCs) and activated macrophages, and its actions are mainly mediated by the CD4 T helper subset Th17, a distinct subpopulation of gamma/delta T cells (Tγδ17 cells), subsets of natural killer T (NKT) cells, and type 3 innate lymphoid cells (ILC3s). IL-23 signaling promotes the production of pro-inflammatory mediators (IL-17, IL-22, granulocyte-macrophage colony-stimulating (GM-CSF), or the tumor necrosis factor (TNFα)) by target populations. These pathogenic mediators promote the recruitment and activation of granulocytes and macrophages, causing the tissue damage that induce chronic inflammation and, finally, the development of clinical symptoms.



5

[3] Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769-78.

[4] Medical Management of Crohn's Disease https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7325380/ Accessed on Feb 3, 2022

[5] Pastor-Fernandez G, et al. Cells 2020

2.0 ADME pertinent to DILI: The proposed dose of RZB for CD is 600 mg intravenous (IV) at Week 0, Week 4, and Week 8, followed by 360 mg subcutaneous (SC) at Week 12, and every 8 weeks thereafter. The ADME data below help with estimating drug exposure, metabolism, and elimination, but the target binding affinity and turnover of drug and target have broad implications for pharmacokinetics, pharmacodynamics, safety and efficacy that may not be accountable in typical ADME studies. Moreover, CD activity may affect binding and turnover.

2.1 Absorption: GI absorption is not pertinent to this parenteral drug. In subjects with plaque psoriasis 150 mg subcutaneously at Weeks 0, 4, and every 12 weeks thereafter, steady-state concentrations were achieved by Week 16. The estimated steady-state peak (C_{max}) and trough concentrations (C_{trough}) were 12 mcg/mL and 2 mcg/mL, respectively. In CD subjects, 600 mg IV at Weeks 0, 4, and 8 followed by 360 mg SC at Week 12 and every 8 weeks thereafter, yielded median peak (C_{max}) and trough concentrations (C_{trough}) of 156 mcg/mL and 38.8 mcg/mL, respectively, during the induction period (Weeks 8-12); the steady-state median peak (C_{max}) and trough concentrations (C_{trough}) were 28.0 mcg/mL and 8.13 mcg/mL, respectively, during maintenance (Weeks 40-48).

2.2 Distribution: The estimated steady-state volume of distribution (inter-subject CV%) was 7.68 L (64%) in subjects with CD.

2.3 Metabolism: The metabolic pathway of RZB has not been characterized. As a humanized IgG1 monoclonal antibody, RZB is expected to be degraded peripherally into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG. Liver metabolism and metabolites are predicted to be insignificant, though the possibility for small peptides forming neoantigens leading to DILI remains.

2.4 Excretion: The estimated systemic clearance (inter-subject CV%) was 0.30 L/day (34%) and terminal elimination half-life was approximately 21 days in subjects with CD.

3.0 Non-clinical data related to DILI:

3.1 In vitro studies: Traditional in vitro studies (e.g., microsome, glutathione trapping, transporter inhibition) are not reported and not pertinent to this monoclonal antibody metabolism and toxicity.

3.2 Animal studies: The sponsor did not conduct animal studies specific for CD applications. For PsA, the sponsor submitted 4-week and 26-week exposure studies in cynomolgus monkeys. The longer exposure study included 32 monkeys (16 males & 16 females) given 0, 5, 20 or 50 mg/kg/week with an 8-week recovery. Systemic exposure to RZB increased "proportionately with dose on Day 1, Weeks 4 and 26 with some degree of accumulation." Anti-drug antibody (ADA) formation occurred but was not associated with change in RZB levels or liver toxicity. All monkeys survived to necropsy. All 32 livers were examined and there was no increase in organ weight or histopathology found. NOAEL was 20 mg/kg/wk for SC delivery with an AUC (0-168 hours) of 27 mg*hr/mL at week 4.

4 Clinical data

4.1 In class or near class DILI data: There is little evidence to suggest that binding IL23 by monoclonal antibodies leads to clinically significant liver injury. Monoclonal antibodies and immunoglobulins are generally taken up and metabolized intracellularly to short peptides and amino acids so metabolism by hepatocytes is expected to be nil. Neoantigen formation from the drug breakdown and anti-drug antibodies are theoretical risk for liver injury. Mild-to-moderate transient serum aminotransferase elevations were seen in up to 1.4% of CD patients treated with ustekinumab, an anti-IL12/IL23.[6] Ustekinumab is approved for the treatment of CD (Sep 2016). A PubMed search for ustekinumab DILI yielded just one report of severe transaminase elevation (AST 756, ALT 1212 U/L) after one dose given to a PsO patient.[7] Liver biopsy showed only modest portal inflammation and piecemeal necrosis. The patient had no jaundice and recovered rapidly.

LiverTox® reports mild-to-moderate transient serum aminotransferase elevations in up to 10% of PsO patients treated with RZB.[8] The mechanism for enzyme elevations associated with RZB are unclear. The RZB label for PsO mentions two subjects who discontinued RZB due to isoniazid liver injury, with no other mention of hepatic adverse events in the label. There are no RZB DILI cases reported in the post marketing literature (PubMed search) or safety surveillance. FDA approval for PsO was in 2019.

FDA approved RZB for PsA in January 2022. Hence, there was no LiverTox® reports, post marketing literature or safety surveillance data on RZB in PsA. The RZB label for PsA mentions a higher incidence of hepatic events (5.4%, 16.7 events per 100 patient years) compared to placebo (3.9%, 12.6 events per 100 patient years) in phase 3 clinical trials. The phase 3 studies also report mild-to-moderate transient aminotransferase elevations arise in up to 3.3% treated with RZB.

4.2 Summary of Studies:

The CD program includes one phase 2 dose ranging study (M15-993), two pivotal phase 3 induction studies (M15-991 and M16-006) and one pivotal phase 3 maintenance study (M16-000 sub-study 1) (Table 1). Study M16-000 sub-study 1 re-randomized clinical responders from the two inductions studies to the 52-week withdrawal maintenance phase. The safety evaluation of RZB included safety analysis sets described in Table 2. Figures 2, 3 and 4 show study schematics for the phase 2 study and 3 studies.

Table 1 Clinical Studies in CD Patients

[6] LiverTox: https://www.ncbi.nlm.nih.gov/books/NBK548014/

[7] Lovero R, et al. Current Drug Safety 2018

[8] LiverTox: https://www.ncbi.nlm.nih.gov/books/NBK571856/

Study	Phase	Design and Duration	Participants and Number	Placebo
M15-993	2	Period 1: 12-wk, R (1:1:1), DB, PBO, 2 doses Period 2: 14-wk OL Period 3: 26-wk 180 mg SC OL Responders rolled over to M15-989 (206-wk OLE)	121	Yes
M15-991	3	49-wk induction study: Period 1: 12-wk, R (1:1:1), DB, PBO, 2 doses Period 2: another 12-wk R, DB, 3 doses re-introduction in Period 1 RZB non-responders Period 3: 20-wk OLE	618 IR on detailed narratives for temple's corollary subjects	Yes
M16-006	3	Same as M15-991 except R (2:2:1)	931 same IR as for M15-991	Yes
M16-000	3	220-wk maintenance study: Period 1: SS2 starts after SS1 enrollment complete. a. SS1: 52-wk R (1:1:1), DB, PBO 2 doses in the first 542 12-wk responders from M15-991 and M16-006. b. SS2: 52-wk R, OL (after blinded 1st dose), in 24-wk responders and the remaining 12-week responders from M15-991 and M16-006. Period 2: OLE (SS3)	542 Re-randomized 12-wk RZB responders from two induction studies.	Yes

DB = double blind; SOC = standard of care; IR = inadequate response; OLE = open label extension; PBO = placebo; R = randomized; SS=Sub-study.
Source: DILI team

Table 2 Integrated Safety Analysis Sets

Analysis Set	N	Integration Status / Studies / Treatment Periods or Sub-Studies	Study Population	Treatment Groups	Key Analyses or Purpose
Placebo-Controlled 12-Week Induction Period Safety Analysis Set (ISS1)	1629	Integrated M15-991 / M16-006 12-Week Induction Period; M15-993 Period 1[b]	All subjects who received at least 1 dose of study drug during the studies and treatment periods indicated	RZB 1200 mg IV RZB 600 mg IV PBO IV	Safety of risankizumab as induction treatment[a]
Placebo-Controlled 52-Week Maintenance Period Safety Analysis Set	542	Not integrated M16-000 Sub-Study 1	All randomized subjects who received at least 1 dose of study drug in M16-000 SS1 and who had received IV risankizumab induction	RZB 360 mg SC RZB 180 mg SC Withdrawal (PBO) SC	Safety of risankizumab as maintenance treatment in subjects with clinical response to IV risankizumab induction
All Treated Safety Analysis Set (ISS4) OLE for M15-993	1670	Integrated M15-993 Period 1, 2, and 3; M15-989; M15-991 / M16-006 12-Week Induction Period, Induction Period 2; M16-000 Sub-Study 1, Sub-Study 2, Sub-Study 3	All subjects who received at least 1 dose of study drug from all Phase 2 and 3 CD studies	RZB 1200 mg IV RZB 600 mg IV RZB 360 mg SC RZB 180 mg SC Any RZB IV Any RZB SC Any RZB PBO IV/SC (RZB naïve)	Comprehensive overview of safety and exposure to RZB and PBO in all Phase 2 and 3 Studies PBO subjects were included to capture all events and exposure time attributed to PBO IV and SC therapy, up until their first dose of RZB (RZB naïve)

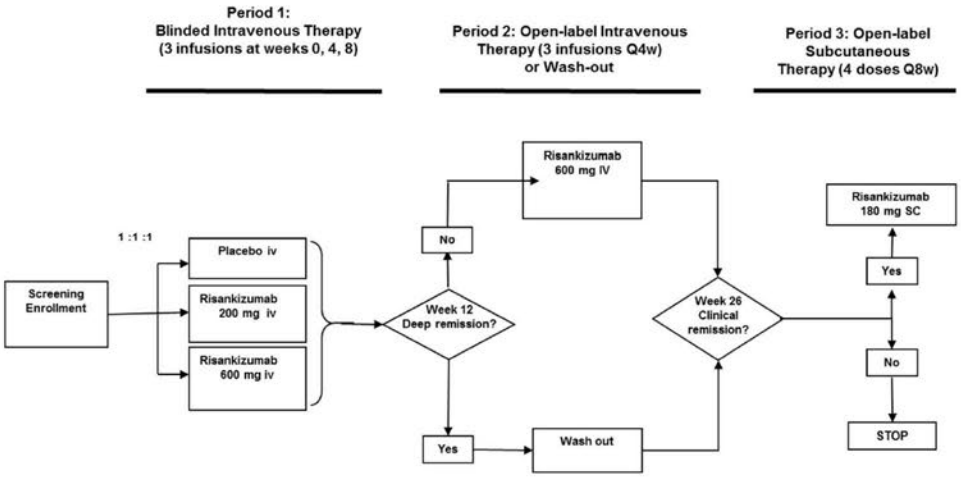
IV = intravenous; PBO = placebo; RZB = risankizumab; SC = subcutaneous; SS1 = Sub-Study 1

a. Selected analyses will be performed overall, as well as presented for selected outputs by subjects having Baseline eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease), for the Placebo-controlled 12-week Induction Period Safety Analysis Set.

b. Only the risankizumab 600 mg IV and Placebo IV groups are included for Study M15-993 Period 1 in the Placebo-Controlled 12-Week Induction Period analysis.

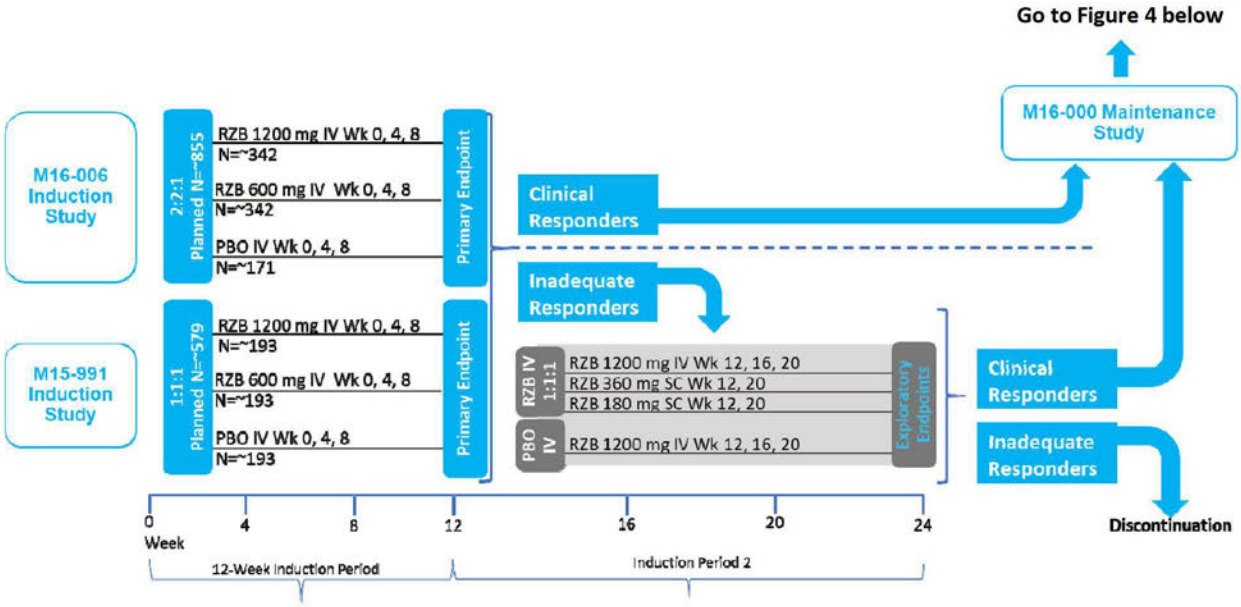
Source: Integrated summary of Safety (ISS) page 32

Figure 2: Study M15-993 (Phase 2) Design (n = 121)

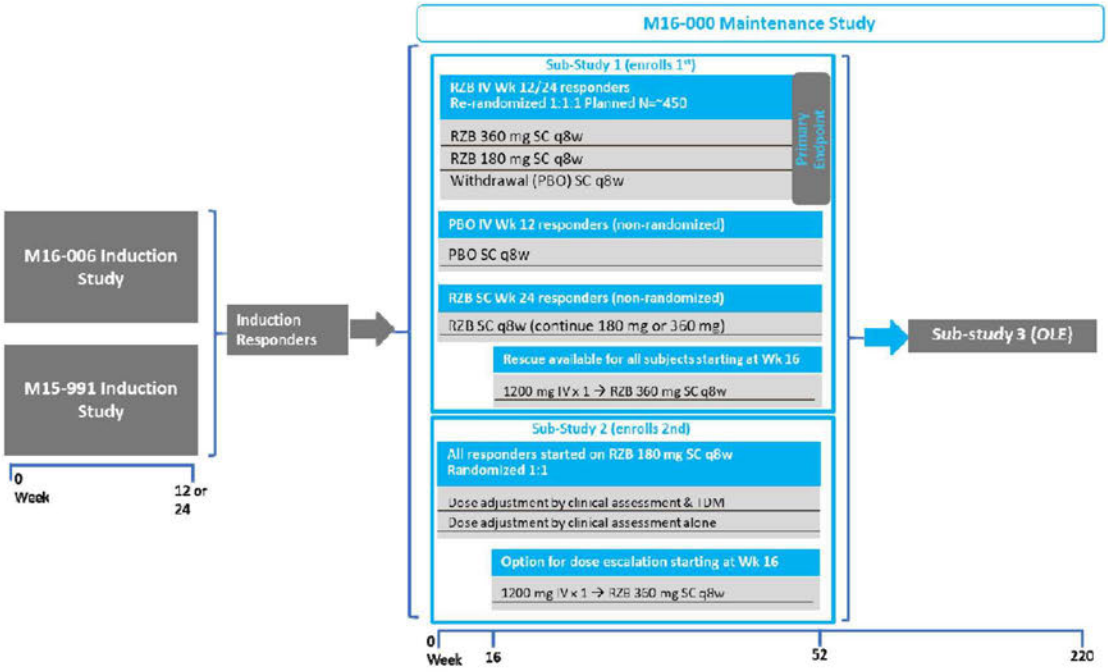


Source: Study M15-993 clinical study report (CSR) page 75

Figure 3: Studies M16-006 and M15-991 (Phase 3 induction) Design (n= 931 and 618)



IV = intravenous; PBO = placebo; RZB = risankizumab; SC = subcutaneous; wk = week



IV = intravenous; PBO = placebo; q8w = every 8 weeks; RZB = risankizumab; SC = subcutaneous; TDM = therapeutic drug monitoring; Wk = Week

In study M16-000, open-label 1200 mg IV RZB x 1 followed by 360 mg SC could be given as rescue therapy for inadequate response.

4.3 Phase 3 studies design features related to DILI evaluation:

Study population: Study M15-993 enrolled 94.2% CD subjects who received prior anti-TNF therapy. All subjects in Study M15-991 had a documented inadequate response or intolerance to use of a biologic agent for CD (Bio-IR) of which 20% received ustekinumab. Study M16-006 enrolled 58% subjects who were Bio-IR (including 14% who had prior ustekinumab); thus 42% were Non-Bio-IR. Percentages are based on safety populations.

Study periods: Each phase 3 induction study had three periods. Period 1 was the DB treatment period from baseline to Week 12 (induction period 1). At the end of Period 1, the RZB responders were re-randomized to the withdrawal maintenance sub-study 1 (Study M16-000) to receive 52-week DB maintenance treatment. Period 2 was the second induction period at Weeks 12-24 in for 12-week RZB non-responders only. Period 3 was the 20-week OLE phase from the last dose of study drug.

Inclusion Criteria: Baseline serum ALT and AST < 2 x ULN; TB ≤ 2 mg/dl except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome.

Exclusion criteria: The studies excluded persons actively infected with Hepatitis B virus (HBV) or hepatitis C virus (HCV), human immunodeficiency virus (HIV), or M. tuberculosis. Subjects positive for HBsAg and/or HBV DNA are excluded, but those with anti-HBc and/or anti-HBs are not. Subjects with antibody to hepatitis C but no HCV RNA were allowed. Subjects with anti-HIV antibody are excluded regardless of HIV control or therapy. Subjects with latent tuberculosis are not excluded but must receive prophylactic therapy prior to or during the study.

Concomitant medication:

1) Induction period: Subjects on corticosteroids at baseline must continue at the same dose during the 12-week induction period. Initiation or increasing doses of corticosteroids was prohibited. Decreasing doses of corticosteroids is also prohibited except in the event of moderate-to-severe treatment related toxicities and upon sponsor approval.
2) Maintenance period: Increasing doses of or starting aminosalicylates, immunomodulators, and/or CD-related antibiotics is prohibited.
    a. Antibiotics may be discontinued starting at the Week 0 visit of Study M16-000 at the discretion of the investigator.
    b. Aminosalicylates and/or immunomodulators were to stay at stable doses at Week 0 through end of the study. Doses may be decreased in the event of moderate-to-severe treatment related toxicities upon the sponsor approval.
    c. Systemic corticosteroids were tapered based on study protocol at Week 0. After tapering dosage, in the event of a loss of satisfactory clinical response per the Investigator's judgment, dosage could be increased back to the dose at the induction study baseline.

4.4 Study Level Findings relevant to DILI

4.4.1 Phase 2 study (M15-993, n = 121): No subject met the Hy's law criteria in this study. There was no jaundice case or case with ALT > 3 x ULN. This is reasonable given the limited sample size. The sponsor reported the total number of TEAEs associated with DILI or hepatic disorders during DB period 1 in Table 3. The proportion of subjects with TEAEs associated with DILI was similar between the placebo group and RZB 200 + 600 mg IV group (2.6% vs 2.4%, respectively).

Table 3 Study M15-993: Subjects with Treatment-Emergent DILI AEs or Hepatic disorders by MedDRA PT (DB IV Period 1; Safety Population)

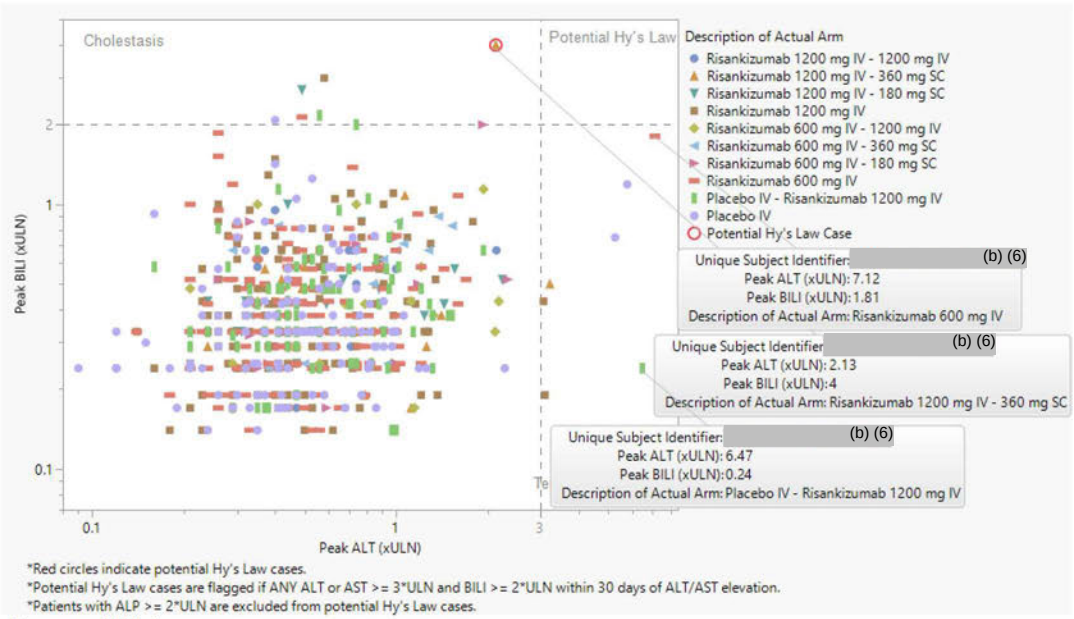
		Risankizumab		
	Placebo N = 39	200 mg IV N = 41	600 mg IV N = 41	Total (200 + 600 mg IV) N = 82
MedDRA 19.1 PT		**n (%)**		
Any AE associated with DILI	1 (2.6)	2 (4.9)	0	2 (2.4)
Gamma-glutamyltransferase (GGT) increased	1 (2.6)	1 (2.4)	0	1 (1.2)
Hepatic enzyme increased	0	1 (2.4)	0	1 (1.2)

Note: The sum of the total number of subjects observed to have each of the PTs should be greater than or equal to the SOC total. A subject who has 2 or more different PTs that are in the same SOC is counted only once in the SOC total. TEAEs during DB IV period are defined as events that began or worsened during this period, and within 105 days after the last dose of the study drug if subject discontinued treatment in this period.

Source: Study M15-993 CSR Page 163

4.4.2 Phase 3 induction study (M15-991, n=618): The sponsor reported exposure adjusted event rate for treatment emergent hepatic events of 3.5, 1.9 and 3.9 per 100 patient-years for placebo, 600 mg RZB IV and 1200 mg RZB IV arm respectively. The CSR included no clinically relevant LFTs during the DB period and did not include a table for LFT in terms of ULN.

The eDISH plot (Figure 5) shows no subjects in Hy's Law quadrant. There were several jaundice cases in the cholestasis quadrant. Temple's corollary quadrant included 7 subjects with ALT > 3x ULN. Three of the 7 cases were from placebo arm who had prior biologics. This is reasonable since moderate to severe CD patients were known to have accompanying liver injury. Note that one case with ID (b) (6) had ustekinumab prior to baseline. The other one of the 3 placebo cases had ALT elevation on Day 154, past the 12-week period.



Source: DILI team

4.4.3 Phase 3 induction study (M16-006, n = 931) is the focus of this review because a liver injury signal is apparent. Its results drove the overall hepatic injuries during induction periods in this RZB submission. The sponsor reported the hepatic AEs in Table 4. The CSR concluded the incidence of these mild to moderate hepatic events were similar across treatment arms. However, the summary of LFT elevations (Table 5) from the CSR, say Grade 3 elevations, were not consistent with those in Table 4. Table 5 shows the proposed dose arm 600 mg RZB IV had higher percentage of subjects experienced LFT elevations. The highest dose 1200 mg RZB IV arm also had more LFT elevations than that in the placebo arm. However, there appears no clear dose response relationship between the 600 mg and 1200 mg arms. It is not clear whether the 600 mg induction does used in CD may represent a threshold at or above which LFT abnormalities appear. The experiences of those re-induction subjects confirmed that the abnormalities remained in those received 1200 mg RZB IV only.

The eDISH plot demonstrated a clear imbalance between placebo arm (1/186) and the 600 RZB arm (8/383) for those had ALT > 3 x ULN. More details are provided in case level analysis (Section 4.6).

MedDRA 23.1 Preferred Term	Placebo IV (N = 186) n (%)	Risankizumab 600 mg IV (N = 373) n (%)	Risankizumab 1200 mg IV (N = 372) n (%)	Risankizumab Total (N = 745) n (%)
Any AE	4 (2.2)	9 (2.4)	6 (1.6)	15 (2.0)
Alanine aminotransferase increased	1 (0.5)	0	2 (0.5)	2 (0.3)
Aspartate aminotransferase increased	0	1 (0.3)	1 (0.3)	2 (0.3)
Blood alkaline phosphatase increased	0	2 (0.5)	0	2 (0.3)
Drug-induced liver injury	0	2 (0.5)	0	2 (0.3)
Gamma-glutamyltransferase increased	0	3 (0.8)	0	3 (0.4)
Hepatic enzyme increased	1 (0.5)	0	0	0
Hepatic function abnormal	1 (0.5)	3 (0.8)	1 (0.3)	4 (0.5)
Hepatosplenomegaly	0	1 (0.3)	0	1 (0.1)
Hepatotoxicity	0	0	1 (0.3)	1 (0.1)
Hypoalbuminaemia	1 (0.5)	0	0	0
Liver disorder	0	0	1 (0.3)	1 (0.1)
Liver function test abnormal	0	1 (0.3)	0	1 (0.1)
Transaminases increased	0	0	1 (0.3)	1 (0.1)

AE = adverse event; IV = intravenous; MedDRA = Medical dictionary for regulatory activities; SA = safety population
For n (%), subjects are counted once in each row, regardless of the number of events they may have had.

Source: Study M16-006 CSR page 184

Table 5 Study M16-006 LFT Elevations During the First 12-week Induction Period 1

Criteria	Placebo IV (N = 186) n/N_OBS (%)	Risankizumab 600 mg IV (N = 373) n/N_OBS (%)	Risankizumab 1200 mg IV (N = 372) n/N_OBS (%)	Risankizumab Total (N = 745) n/N_OBS (%)
ALT				
ALT ≥ 3 × ULN	1/184 (0.5)	8/370 (2.2)	3/370 (0.8)	11/740 (1.5)
ALT ≥ 5 × ULN	0/184	2/370 (0.5)	2/370 (0.5)	4/740 (0.5)
AST				
AST ≥ 3 × ULN	1/184 (0.5)	4/369 (1.1)	3/370 (0.8)	7/739 (0.9)
AST ≥ 5 × ULN	0/184	2/369 (0.5)	0/370	2/739 (0.3)
TBL				
TBL ≥ 2 × ULN	1/184 (0.5)	6/372 (1.6)	1/370 (0.3)	7/742 (0.9)
Alkaline phosphatase				
Alkaline phosphatase ≥ 1.5 × ULN	3/184 (1.6)	10/372 (2.7)	6/370 (1.6)	16/742 (2.2)
ALT and/or AST and TBL				
ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN	0/184	3/370 (0.8)	0/370	3/740 (0.4)
ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	0/184	2/370 (0.5)[a]	0/370	2/740 (0.3)

Source: Study M16-006 CSR page 221 (DILI team adapted version)

Table 6 Study M16-006 Distribution of Subjects with Treatment-Emergent Hepatic Event by Preferred Term During Induction Period 2 Weeks 12-24

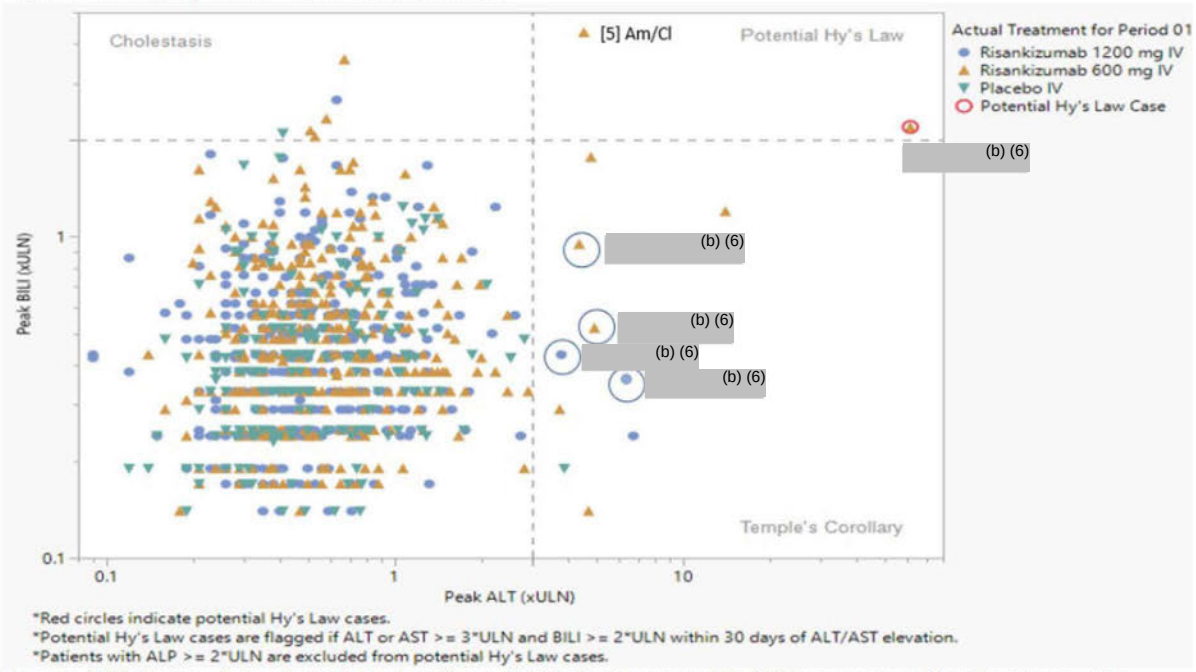
MedDRA 23.1 Preferred Term	Randomized Treatment Groups: Risankizumab 180 mg SC (N = 67) n (%)	Risankizumab 360 mg SC (N = 68) n (%)	Risankizumab 1200 mg IV (N = 67) n (%)	Placebo IV/ Risankizumab 1200 mg IV (N = 76) n (%)	Total (N = 278) n (%)
Any AE	0	0	4 (6.0)	1 (1.3)	5 (1.8)
Alanine aminotransferase increased	0	0	2 (3.0)	0	2 (0.7)
Aspartate aminotransferase increased	0	0	1 (1.5)	0	1 (0.4)
Blood alkaline phosphatase increased	0	0	1 (1.5)	0	1 (0.4)
Gamma-glutamyltransferase increased	0	0	2 (3.0)	0	2 (0.7)
Hepatic enzyme increased	0	0	0	1 (1.3)	1 (0.4)

AE = adverse event; IV = intravenous; MedDRA = Medical dictionary for regulatory activities; SA = safety population; SC = subcutaneous

For n (%), subjects are counted once in each row, regardless of the number of events they may have had.

Source: Study M16-006 CSR page 185

Figure 6 Study M16-006 eDISH Plot



Source: DILI Team. A bracketed number three ([3]) indicates probable DILI assessment by the Team. The bracketed five followed by AM/Cl indicates unlikely DILI due to RZB but rather DILI due to amoxicillin-clavulanic acid. Those subjects without bracketed numbers in Temple's Corollary were either unlikely or possible DILI only.

4.4.4 Phase 3 maintenance study (M16-000, n = 542): Overall, there was no Hy's law case in this 52-week maintenance study. The sponsor concluded minimal and balanced changes across treatment arms. Table 7 from the CSR shows that as RZB dose increases the percentage of subjects experienced treatment emergent hepatic

events increases (2.2%, 2.8% and 3.9% for placebo, 180 mg SC and 360 mg SC arm, respectively). The LFT elevation exhibits a similar dose-response pattern across treatment arms. Note that analogous to Study M16-006, Study M16-000 had inconsistency between hepatic AEs table and the LFT elevation table.

The eDISH plot illustrates the higher number of RZB subjects than placebo subjects in the Temple's corollary and cholestasis quadrants. An exploratory analysis by rescue medication usage did not reveal clear association with LFT elevation imbalance between RZB and placebo arms.

Table 7 Study M16-000 Distribution of Subjects with Treatment-Emergent Hepatic Event by Preferred Term During the 52-Week Maintenance Period

		Risankizumab			
MedDRA 23.1 Preferred Term	Placebo SC (N=184) n (%)	180 mg SC (N=179) n (%)	360 mg SC (N=179) n (%)	Total (N=358) n (%)	Risankizumab Rescue Therapy* (N=150) n (%)
Any adverse event (Hepatic Related)	4 (2.2)	5 (2.8)	7 (3.9)	12 (3.4)	4 (2.7)
Alanine aminotransferase increased	1 (0.5)	2 (1.1)	0	2 (0.6)	3 (2.0)
Aspartate aminotransferase increased	0	0	0	0	1 (0.7)
Blood alkaline phosphatase increased	0	0	1 (0.6)	1 (0.3)	0
Blood bilirubin increased	0	1 (0.6)	0	1 (0.3)	0
Gamma-glutamyltransferase increased	0	0	0	0	1 (0.7)
Hepatic function abnormal	0	1 (0.6)	0	1 (0.3)	0
Hepatic steatosis	0	2 (1.1)	2 (1.1)	4 (1.1)	1 (0.7)
Hepatomegaly	0	0	1 (0.6)	1 (0.3)	0
Hyperbilirubinaemia	1 (0.5)	0	2 (1.1)	2 (0.6)	0
Hypoalbuminaemia	0	0	1 (0.6)	1 (0.3)	0
Liver function test abnormal	1 (0.5)	0	0	0	0
Liver function test increased	1 (0.5)	0	1 (0.6)	1 (0.3)	0
Urine bilirubin increased	0	0	1 (0.6)	1 (0.3)	0

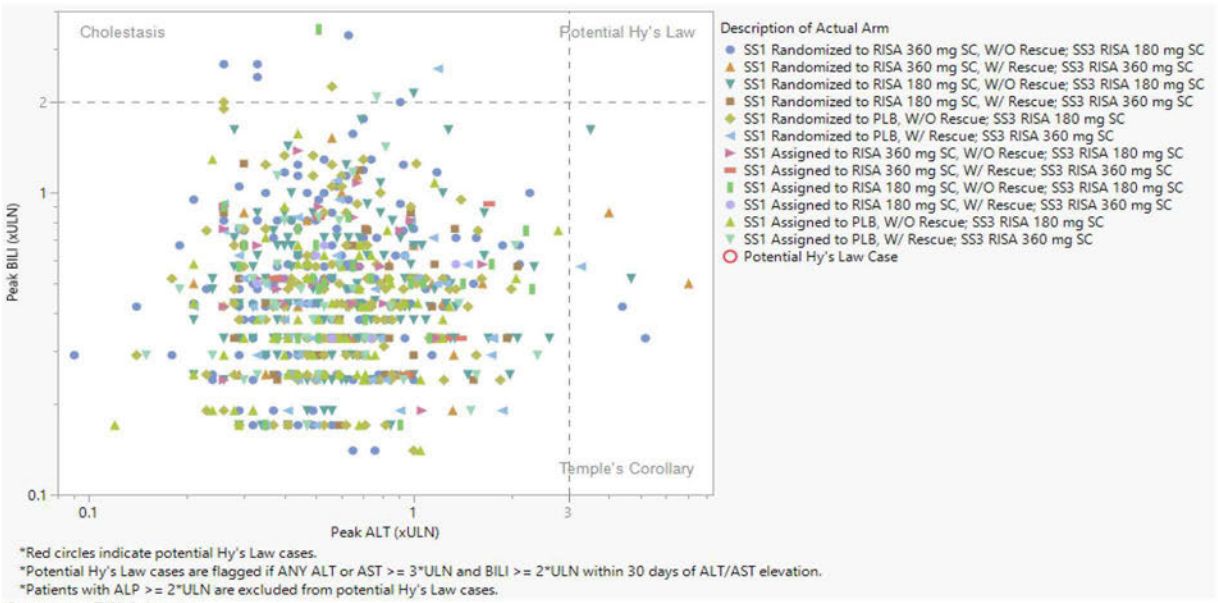
Source: Study M16-000 CSR page 1906

Table 8 Study M16-000 LFT Elevations During the Maintenance Period

	Randomized Double-Blind Treatment Arms				RZB
Criteria	Withdrawal (PBO SC)[a] (N = 184) n/N_OBS (%)	RZB 180 mg SC (N = 179) n/N_OBS (%)	RZB 360 mg SC (N = 179) n/N_OBS (%)	RZB Total (N = 358) n/N_OBS (%)	Rescue Therapy (N = 150) n/N_OBS (%)
ALT ≥ 3 × ULN	1/175 (0.6)	1/172 (0.6)	3/173 (1.7)	4/345 (1.2)	1/134 (0.7)
ALT ≥ 5 × ULN	0/175	0/172	2/173 (1.2)	2/345 (0.6)	0/134
AST ≥ 3 × ULN	2/175 (1.1)	0/171	2/173 (1.2)	2/344 (0.6)	1/133 (0.8)
AST ≥ 5 × ULN	1/175 (0.6)	0/171	1/173 (0.6)	1/344 (0.3)	0/133
TBL ≥ 2 × ULN	3/176 (1.7)	1/172 (0.6)	5/173 (2.9)	6/345 (1.7)	1/134 (0.7)
Alkaline phosphatase ≥ 1.5 × ULN	4/176 (2.3)	1/172 (0.6)	0/173	1/345 (0.3)	1/134 (0.7)
ALT and/or AST and TBL					
ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN	0/175	1/172 (0.6)	0/173	1/345 (0.3)	0/133
ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	0/175	0/172	0/173	0/345	0/133

Source: Study M16-000 CSR page 230 (DILI team adapted version)

Figure 8 Study M16-000 eDISH Plot



Source: DILI team

4.5 Integrated Safety Summary

4.5.1 All treated safety analysis set (SS4): The summary of clinical safety (SCS) reported two serious hepatic events that occurred in subjects [redacted] (b) (6) on RZB IV doses in Study M16-006. Refer to Section 4.6 on details for these two cases. SCS stated there were no confirmed Hy's law cases. The rate of hepatic TEAE by MedDRA 23.1 preferred term showed a potential dose-dependent pattern where any RZB IV group had a rate of 6.5 E/PY as compared to 2.5 events/person-year in subjects on any RZB SC.

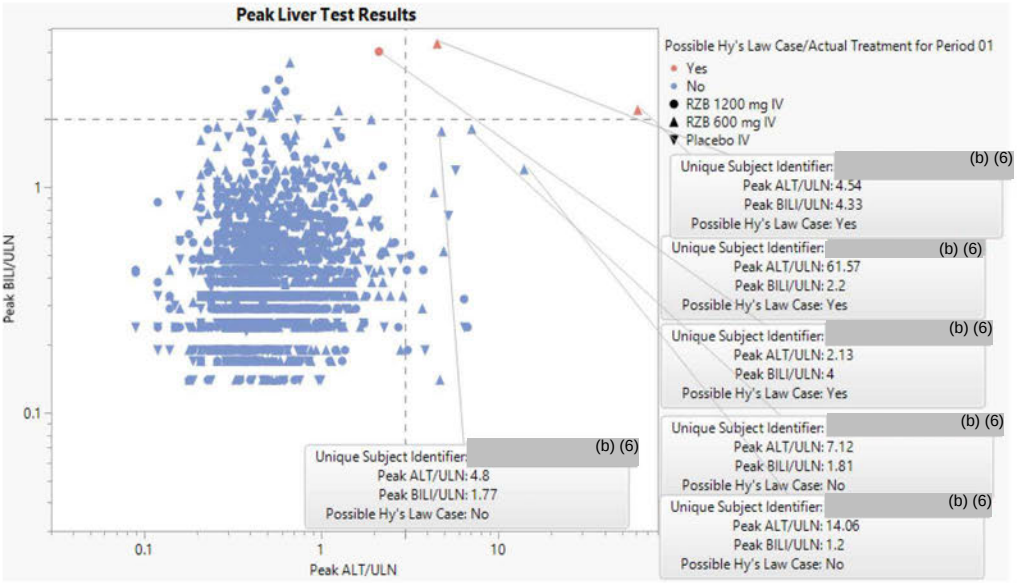
Table 9 Treatment-Emergent Hepatic Events in Exposure-Adjusted Incidence Rate Per 100 Patient Years by Primary MedDRA System Organ Class and Preferred Term (All Treated Safety Analysis Set)

System Organ Class MedDRA 23.1 Preferred Term	Placebo IV/SC (RZB naive) (N = 432) n/PYs (n/100 PYs)	RZB 180 mg SC (N = 1096) n/PYs (n/100 PYs)	RZB 360 mg SC (N = 533) n/PYs (n/100 PYs)	RZB 600 mg IV (N = 688) n/PYs (n/100 PYs)
Any adverse event (Hepatic Related)	8/196.4 (4.1)	25/1071.6 (2.3)	13/433.3 (3.0)	15/197.0 (7.6)
Hepatobiliary disorders	1/199.0 (0.5)	11/1092.5 (1.0)	7/438.6 (1.6)	8/198.6 (4.0)
Autoimmune hepatitis	0/199.4	1/1104.1 (<0.1)	0/442.6	0/200.8
Drug-induced liver injury	0/199.4	1/1104.1 (<0.1)	1/442.3 (0.2)	2/200.5 (1.0)
Investigations	6/197.2 (3.0)	16/1077.8 (1.5)	7/437.5 (1.6)	8/199.1 (4.0)
Alanine aminotransferase increased	1/199.3 (0.5)	8/1093.0 (0.7)	2/440.6 (0.5)	1/200.6 (0.5)
Aspartate aminotransferase increased	0/199.4	4/1097.3 (0.4)	1/442.3 (0.2)	2/200.2 (1.0)
Blood alkaline phosphatase increased	0/199.4	3/1101.6 (0.3)	1/442.1 (0.2)	2/200.4 (1.0)
Blood bilirubin increased	0/199.4	1/1104.0 (<0.1)	0/442.6	1/200.6 (0.5)

System Organ Class MedDRA 23.1 Preferred Term	RZB 1200 mg IV (N = 1023) n/PYs (n/100 PYs)	Any RZB SC (N = 1318) n/PYs (n/100 PYs)	Any RZB IV (N = 1536) n/PYs (n/100 PYs)	Any RZB (N = 1574) n/PYs (n/100 PYs)
Any adverse event	16/295.5 (5.4)	37/1494.2 (2.5)	32/502.5 (6.4)	68/1953.1 (3.5)
Hepatobiliary disorders	5/298.8 (1.7)	18/1524.0 (1.2)	13/509.0 (2.6)	31/2019.6 (1.5)
Autoimmune hepatitis	0/299.3	1/1546.7 (<0.1)	0/512.2	1/2058.4 (<0.1)
Drug-induced liver injury	0/299.3	2/1542.1 (0.1)	2/511.4 (0.4)	4/2052.1 (0.2)
Investigations	11/296.0 (3.7)	22/1510.1 (1.5)	20/505.1 (4.0)	42/1982.7 (2.1)
Alanine aminotransferase increased	5/297.9 (1.7)	10/1533.6 (0.7)	6/510.1 (1.2)	16/2031.5 (0.8)
Aspartate aminotransferase increased	2/298.6 (0.7)	5/1538.5 (0.3)	4/510.7 (0.8)	9/2040.4 (0.4)
Blood alkaline phosphatase increased	1/298.8 (0.3)	4/1542.3 (0.3)	3/510.5 (0.6)	7/2051.5 (0.3)
Blood bilirubin increased	1/299.3 (0.3)	1/1546.7 (<0.1)	2/512.0 (0.4)	3/2057.2 (0.1)

Source: SCS TABLE 2.4__1.5.4.1.26 (DILI team adapted version)

4.5.2 TEAEs in Placebo-Controlled 12-week Induction Period Safety Analysis Set (SS1): As mentioned in Section 4.5.1, the same two serious hepatic events were reported in SS1. The eDISH plot (Figure 9) were consistent with the TEAE findings in SS1. It appears that Study M16-006 LFT elevations had driven the SS1 results. Note that SS1 had similar inconsistency between the TEAE table and LFT table as that for Study M16-006 and M15-991.



Source: DILI team

System Organ Class MedDRA 23.1 Preferred Term	Placebo IV (N = 432) n (%) [SSA%]	Risankizumab 600 mg IV (N = 620) n (%) [SSA%]	Risankizumab 1200 mg IV (N = 577) n (%) [SSA%]	Risankizumab Total (N = 1197) n (%) [SSA%]
Any adverse event	**7 (1.6) [1.7]**	**10 (1.6) [1.6]**	**8 (1.4) [1.4]**	**18 (1.5) [1.4]**
Hepatobiliary disorders	**1 (0.2) [0.3]**	**6 (1.0) [0.9]**	**3 (0.5) [0.5]**	**9 (0.8) [0.7]**
Drug-induced liver injury	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Hepatic function abnormal	1 (0.2) [0.3]	3 (0.5) [0.5]	1 (0.2) [0.2]	4 (0.3) [0.3]
Hepatosplenomegaly	0	1 (0.2) [0.2]	0	1 (< 0.1) [< 0.1]
Hepatotoxicity	0	0	1 (0.2) [0.2]	1 (< 0.1) [< 0.1]
Liver disorder	0	0	1 (0.2) [0.2]	1 (< 0.1) [< 0.1]
Investigations	**5 (1.2) [1.1]**	**5 (0.8) [0.8]**	**5 (0.9) [0.9]**	**10 (0.8) [0.8]**
Alanine aminotransferase increased	1 (0.2) [0.3]	0	2 (0.3) [0.3]	2 (0.2) [0.2]
Aspartate aminotransferase increased	0	1 (0.2) [0.2]	1 (0.2) [0.2]	2 (0.2) [0.2]
Blood alkaline phosphatase increased	0	2 (0.3) [0.3]	0	2 (0.2) [0.2]
Blood bilirubin increased	0	1 (0.2) [0.2]	0	1 (< 0.1) [< 0.1]
Gamma-glutamyltransferase increased	1 (0.2) [0.1]	3 (0.5) [0.5]	1 (0.2) [0.2]	4 (0.3) [0.3]
Hepatic enzyme abnormal	1 (0.2) [0.2]	0	0	0
Hepatic enzyme increased	1 (0.2) [0.3]	0	1 (0.2) [0.2]	1 (< 0.1) [< 0.1]
Liver function test abnormal	1 (0.2) [0.2]	1 (0.2) [0.2]	0	1 (< 0.1) [< 0.1]
Transaminases increased	0	0	1 (0.2) [0.2]	1 (< 0.1) [< 0.1]

Source: SCS Page 148 (DILI team adapted version)

Criteria	Placebo IV (N = 432) n/N_OBS (%) [SSA%]	Risankizumab 600 mg IV (N = 620) n/N_OBS (%) [SSA%]	Risankizumab 1200 mg IV (N = 577) n/N_OBS (%) [SSA%]	Risankizumab Total (N = 1197) n/N_OBS (%) [SSA%]	Treatment Comparison (95% CI)[a] 600 mg IV - Placebo	Treatment Comparison (95% CI)[a] 1200 mg IV - Placebo
ALT ≥ 3 × ULN	4/422 (0.9) [0.9]	9/616 (1.5) [1.4]	5/573 (0.9) [0.9]	14/1189 (1.2) [1.1]	0.5 [-0.7, 1.8]	-0.0 [-1.2, 1.2]
ALT ≥ 5 × ULN	3/422 (0.7) [0.6]	3/616 (0.5) [0.5]	2/573 (0.3) [0.3]	5/1189 (0.4) [0.4]	-0.1 [-0.9, 0.8]	-0.3 [-1.1, 0.5]
AST ≥ 3 × ULN	3/423 (0.7) [0.7]	6/615 (1.0) [1.0]	4/573 (0.7) [0.7]	10/1188 (0.8) [0.8]	0.3 [-0.8, 1.4]	-0.0 [-1.1, 1.0]
AST ≥ 5 × ULN	1/423 (0.2) [0.2]	3/615 (0.5) [0.5]	0/573	3/1188 (0.3) [0.2]	0.3 [-0.4, 1.0]	-0.2 [-0.6, 0.2]
TBL ≥ 2 × ULN	2/424 (0.5) [0.5]	9/619 (1.5) [1.3]	4/572 (0.7) [0.8]	13/1191 (1.1) [1.1]	0.8 [-0.3, 2.0]	0.2 [-0.8, 1.3]
ALP ≥ 1.5 × ULN	10/424 (2.4) [2.1]	14/619 (2.3) [2.2]	9/572 (1.6) [1.6]	23/1191 (1.9) [1.9]	0.1 [-1.7, 1.9]	-0.4 [-2.1, 1.3]
ALT and/or AST ≥ 3 × ULN and TBL ≥ 1.5 × ULN	0/423	4/616 (0.6) [0.6]	1/572 (0.2) [0.2]	5/1188 (0.4) [0.4]	0.6 [0.0, 1.3]	0.2 [-0.2, 0.6]
ALT and/or AST ≥ 3 × ULN and TBL ≥ 2 × ULN	0/423	2/616 (0.3) [0.3]	1/572 (0.2) [0.2]	3/1188 (0.3) [0.2]	0.3 [-0.1, 0.7]	0.2 [-0.2, 0.6]

Source: SCS Page 140 (DILI team adapted version

4.6 Case level analysis: Thirty-seven subjects exposed to RZB were analyzed for potential DILI based on treatment emergent elevation in liver biochemistries and appearance in Hy's Law, Temple's Corollary or cholestasis quadrants. Of the 37, 32 were unlikely (29) or possible (3) DILI due to RZB. Twelve subjects had isolated indirect bilirubin elevation without significant liver enzyme elevation suggesting non-liver related source. The next most common alternative causes were unknown (7), infection (3) and fatty liver (3), both alcohol and non-alcohol related. There were two subjects with gallstone or biliary related alternative causes.

The remaining five subjects were considered probable DILI due to RZB, with one meeting Hy's Law criteria (ID: (b) (6)). All five were in study M16-006 (Table 12). Latency from drug start had a median of 57 days (range 35-81). Latencies from RZB stop were negative values for four subjects because they continued to the maintenance phase of much lower dosing suggesting tolerance with dose decrease and/or dose threshold for injury. Injury pattern tended to be hepatocellular with median and mean R-values of 4.9 and 9.2, based on peak ALT. These five cases are discussed in detail in 4.6.1 with line graphs of liver biochemistries by study day.

Table 12: Cases assessed as at least probable DILI due to RZB.

ID	Study	Causality Score*	Age	Sex	Race	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)
(b) (6)	M16-006	3	30	M	Asian	Yes	Yes	81	27	1198	2155	115	2.67	31.9	57.3
	M16-006	3	36	F	White	No	No	60	-80	129	100	233	0.41	1.7	1.3
	M16-006	3	58	F	White	No	No	35	-114	168	89	104	0.64	4.9	2.6
	M16-006	3	53	F	White	Yes	No	56	-599	219	163	333	0.23	2.0	1.5
	M16-006	3	29	M	Asian	No	No	54	-398	188	196	104	1.32	5.5	5.8
	Mean	*41*						*57*	*-233*	*380*	*541*	*178*	*1.05*	*9.2*	*13.7*
	Std Dev	*12*						*15*	*231*	*410*	*808*	*92*	*0.89*	*11.4*	*21.9*
	Median	*36*						*56*	*-114*	*188*	*163*	*115*	*0.64*	*4.9*	*2.6*
	Mean	*29*						*35*	*-599*	*129*	*89*	*104*	*0.23*	*1.7*	*1.3*
	Max	*58*						*81*	*27*	*1198*	*2155*	*333*	*2.67*	*31.9*	*57.3*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

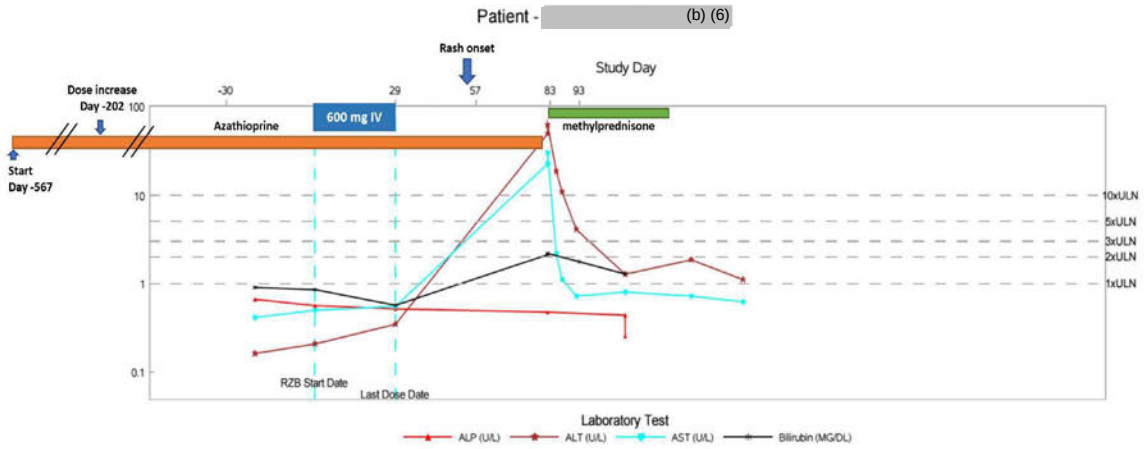
4.6.1 Subject (b) (6) This subject was the only one who met Hy's Law criteria, so this case is described and discussed in detail.

Summary: Subject was a 30-year-old Asian man who developed elevated transaminases and jaundice that was detected 11-12 weeks after starting RZB at 600 mg IV q 4 weeks.

His BMI was 18.8 kg/m^2. He had no history of alcohol use but did have "hepatic steatosis". Baseline liver tests were normal. He was on azathioprine since Day -567 with a dose increase at Day -202.

He started RZB on Apr 20, 2020 (Day 0). On (b) (4) (Day 55), he had a rash, and RZB was held. Therefore, he only received two doses. No labs were drawn at that time. The rash resolved but then recurred (b) (4) (Day 80). He was admitted for this rash that spread over his chest and back. On (b) (4) (Day 81), his ALT was 1198 U/L, AST 2155 U/L, AP 115 U/L and TB 2.67 mg/dL. He had no liver specific symptoms but had mild scleral icterus. The patient was given methylprednisolone, 40 mg/d IV x 5 followed by 20 mg/d PO x 3 weeks, then 12 mg/d PO x 2-3 weeks. Enzymes and bilirubin fell rapidly. HAV, HBV, HCV and HEV serologies were all negative. ANA, ASMA, and IgG were not done. No biopsy or imaging done.

Subject (b) (6) (Liver tests by Study Day):



Assessment: We assessed this case as probable DILI due to the latency, rash and washout. We suspect liver biochemistries were already elevated at rash onset. Azathioprine competes poorly due to long latency (200-567 days) and marked hepatocellular injury pattern. Azathioprine injury is typically more mixed or cholestatic.

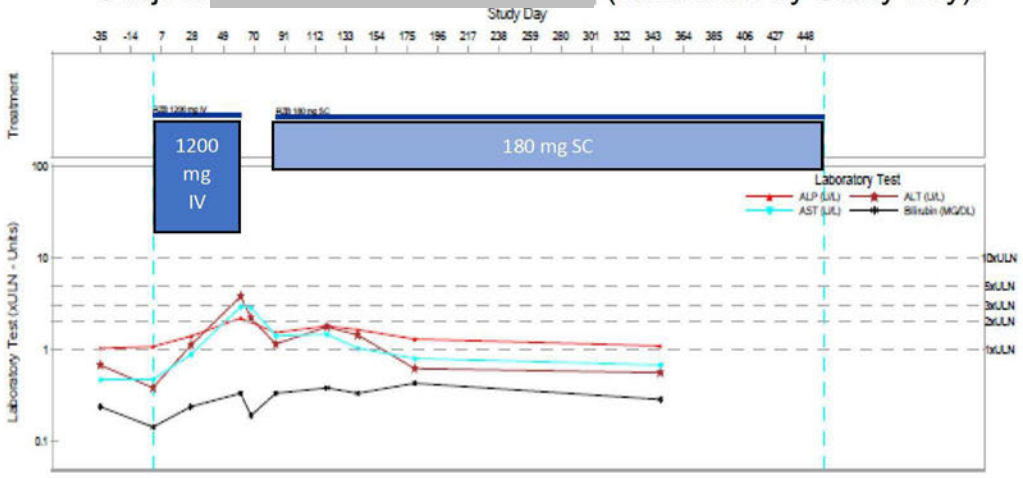
Autoimmune hepatitis (AIH) competes, but rash is not a common presenting sign with AIH. The apparent rapid response to steroids may also occur with immune mediated DILI. Alternatively, the enzymes were already on the decline having peaked at or shortly after rash onset. No labs were drawn at rash onset. The first TB checked was already >2x ULN suggesting a significant injury was already ongoing or had peaked.

4.6.2 Subjects (b) (6): These four had less severe enzyme elevations without jaundice (TB < 2x ULN). All had enzymes elevation toward the end of induction that declined shortly after or as they transitioned to the lower dose maintenance phase. There were no other obvious causes, but evaluation testing was limited or not done due to resolving injuries.

Subject (b) (6): Subject was a 36-year-old white woman who had moderate ALT and AST elevation 60 days after starting RZB 1200 mg IV q4weeks. At baseline, she had a diagnosis of NAFLD, hypothyroidism, and insulin resistance. BMI was 26.1 kg/m^2; she did not drink alcohol. Liver biochemistries were normal at baseline except a mildly elevated AP. Medications were mesalamine and thyroid hormone replacment. She started RZB on Nov 7, 2019. By week 4, her ALT and AST had more than doubled from her baseline of 13 and 16. At week 8, ALT was up to 129, AST 100 and AP 233. TB remained normal. She had no symptoms. No evaluation testing done. She transitioned to 180 mg SC q8w at

week 12. Liver enzymes fell quickly at first, but there was second mild rise in ALT and AST coincident with starting maintenance before falling to normal.

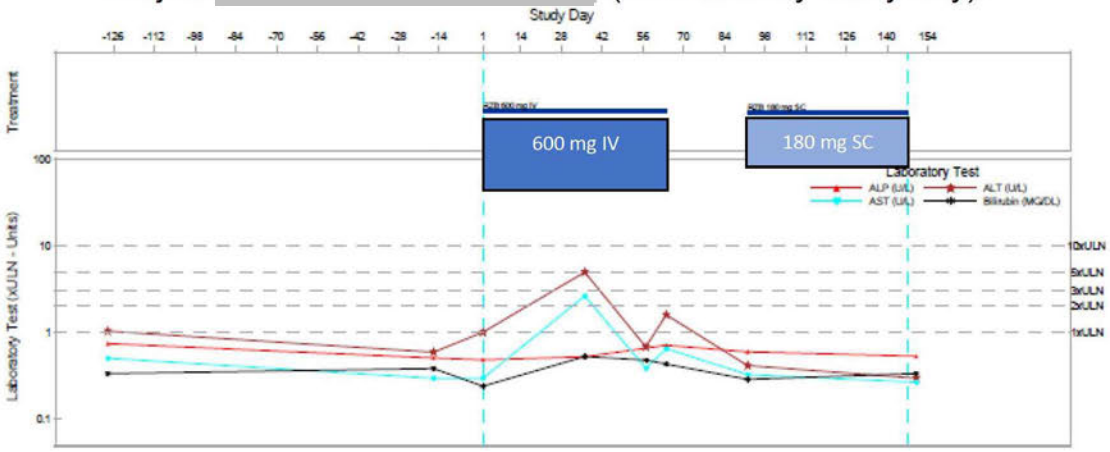
Subject [redacted] (b) (6) (Liver tests by Study Day):



Subject [redacted] (b) (6) Subject is a 58-year-old white woman who developed moderate ALT and AST elevation 35 days after starting RZB 600 mg IV q4 weeks. At baseline, she had hypertension and latent tuberculosis. No history of alcohol use. BMI was 25.9 kg/m^2. Liver tests were normal at baseline. She was on mesalazine, 6-mercaptopurine, and methylprednisone. She started RZB on Jun 19, 2019. At week 4, her ALT rose to 168 and AST to 89 without symptoms, AP elevation or jaundice. They all fell to normal within 3 weeks, but rose again slightly, and finally fell to normal. No evaluation testing done. RZB dose fell to 180 mg q8 weeks per protocol and enzyme fell to normal.

Subject [redacted] (b) (6) (Liver tests by Study Day):

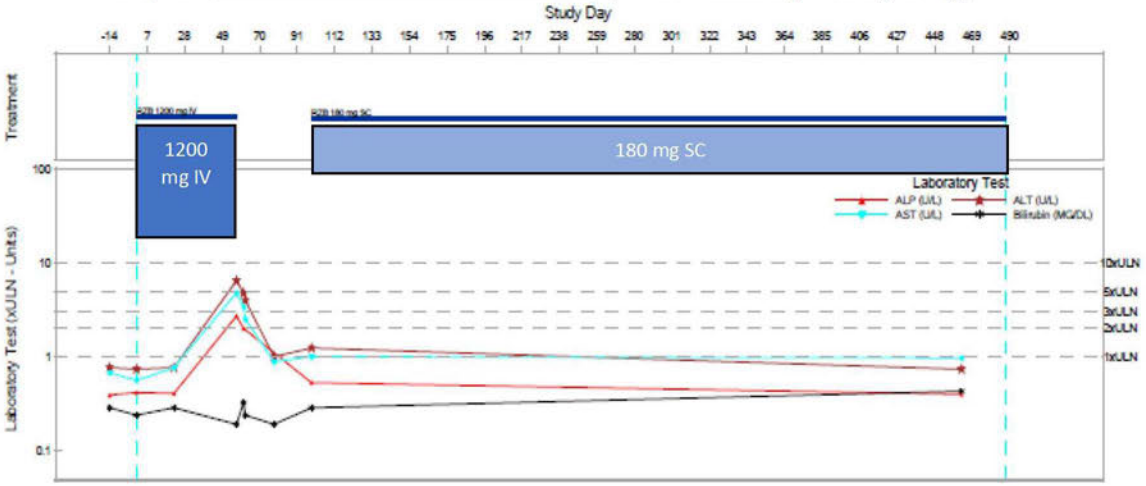
APPEARS THIS WAY ON ORIGINAL



Subject [redacted] (b) (6): The subject was a 53-year-old white woman who developed elevated ALT, AST and AP 56 days after starting

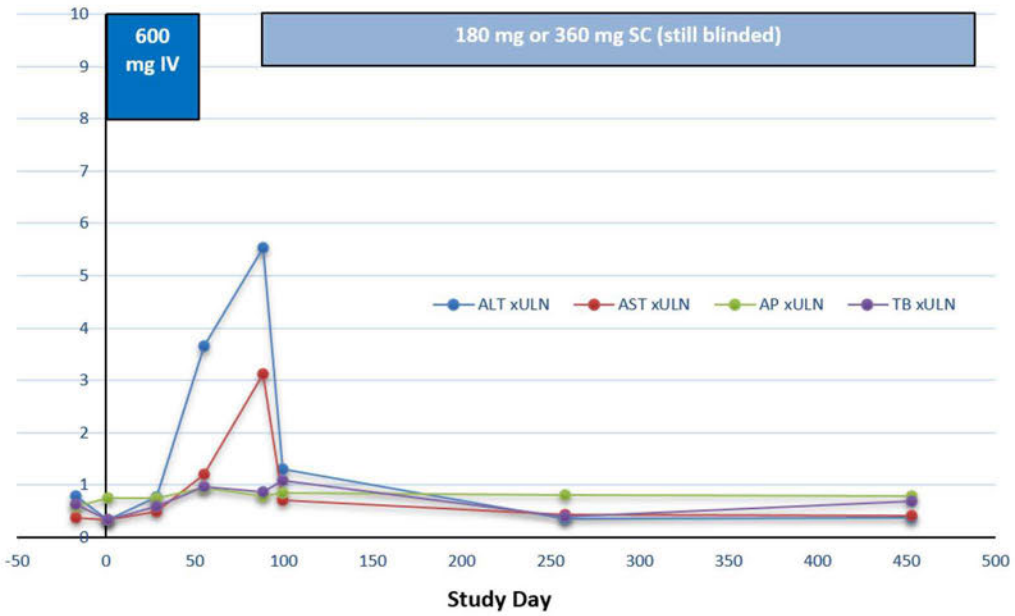
RZB 1200 mg IV q 4 weeks. At baseline, she had hypertension and ankylosing spondylitis. She was on prednisone and azathioprine (azathioprine exposure: Days -182 to 3). She did not drink alcohol, and BMI was 27 kg/m^2. Liver tests were normal at baseline. She started RZB on 28-Nov-2019 (Day 0). On Jan 23, 2020 (Day 57), her ALT was 219, AST 163, and AP 333. TB remained normal. She was fatigued. RZB was held. Evaluation included "CPK, EBV, hepatitis A and hepatitis B serologies." No results were provided. US showed "steatosis". Liver tests gradually improved, as she entered maintenance phase of 180 mg SC dosing.

Subject [redacted] (b) (6) (Liver tests by Study Day):



Subject [redacted] (b) (6) Subject was a 29-year-old Asian man who had elevation in ALT and AST 54 days after starting RZB 600 mg IV q 4 weeks. At baseline, he had no relevant medical history except his CD. His BMI was 16.5 kg/m^2. He did not drink alcohol. His liver tests were normal at baseline. He took an herbal supplement for a cold at Day 10 for one day. Otherwise, he took no medications relevant to DILI. He started RZB on Jul 17, 2020 (Day 0). On Sep 9, 2020 (Day 54), he had asymptomatic liver enzyme elevation without jaundice. ALT was 124, AST 41, AP normal, and TB normal. As he transitioned, to Sub-study 1 (M16-000) his ALT and AST rose a bit further (ALT 188, AST 196), only to fall thereafter. No evaluation testing done. Subject remains blinded but received either 180 mg or 360 mg SC in M16-000.

Subject [redacted] (b) (6) (Liver tests by Study Day):



5 Assessment & Recommendations

5.1 Assessment: Risankizumab (RZB) is a humanized IgG1 monoclonal antibody that binds interleukin 23 (IL-23). It is delivered intravenously (IV) for induction and subcutaneously (SC) for maintenance for Crohn's disease (CD). Binding IL-23 inhibits IL-23 mediated intracellular signaling and release of proinflammatory cytokines (e.g., IL-17) and chemokines felt key to the pathophysiology of several immune mediated diseases including CD.

Non-clinical data do not suggest a DILI risk. The FDA approved RZB for psoriasis (PsO) in 2019 without DILI concerns, and post-market data do not suggest a DILI risk either. However, the higher dose for CD, delivered IV likely led to a liver injury signal in this BLA: 600-1200 mg IV every 4 weeks x 3 for CD induction versus 150 mg SC every 4 weeks x 2 for PsO. In addition, CD patients may have a lower threshold for immune mediated DILI because their livers receive more endotoxins and pathogen associated molecular patterns, or PAMPS, thus altering immune tolerance to drugs.

M15-993 (phase 2) and M15-991 (phase 3) studies did not show obvious liver injury risk. Total subjects exposed to ≥ 600 mg dosing was about 441 in these two studies. However, the larger M16-006 (phase 3) study showed a liver injury signal and is the subject of much of our analysis. M16-006 included 745 exposed to ≥600 mg. A higher proportion of subjects receiving 600 mg in the 12-week Period 1 had elevations in ALT >3x ULN compared to placebo (2.2% vs. 0.5%). This imbalance did not persist in the 1200 mg arm (0.8% versus 0.5%) but did appear in Period 2, the 12–24-week re-induction for inadequate responders (3% for 600-1200 to 1200 mg vs 0% for placebo to 1200 mg). In the all-treated analysis set, there was a higher proportion of hepatic TEAEs for the 600 and 1200 mg dosing compared to placebo (7.6 vs. 5.4 vs. 2.5 per 100-patient-years, respectively)

Thus, there was no clear dose dependent relationship, but perhaps a risk threshold at 600 mg based on this BLA data and no significant risk for the lower 150 mg used in PsO. It is unclear why the injury signal was not seen in the smaller M15-991 study, but lack of power and higher proportion of biologic experienced subjects (Bio-IR) may be explanatory. All subjects in M15-991 had Bio-IR compared to 58% in M16-006, the larger phase 3 study that picked up a liver injury signal. Subjects who had liver toxicity with prior biologics may be less apt to enroll in another biologic study limiting enrollment of higher risk subjects in M15-991. Four of the five probable DILI subjects in M16-006 were biologic naïve. However, DILI occurring across biologics is not well established, so this hypothesis is speculative.

The five probable DILI subjects were all from M16-006. One met Hy's Law, presenting with rash after two doses of RZB (600 mg). ALT was >1000 but jaundice was modest (2.7 mg/dL). He recovered quickly with holding RZB and receiving high dose steroid therapy. The other four (2 on 600 mg and 2 on 1200 mg induction) had less severe injury, possibly due to trial design that moved them to lower SC dose below the threshold for further injury. Overall, median latency from RZB start was 56 days (range 35-81) and tended to be hepatocellular for these five subjects.

RZB for CD appears to carry a small but significant DILI risk. The Hy's Law case arising from about 1100 exposed subjects and increased ALT elevation in the 600 mg treatment arm are concerning. The liver injury signal is likely due to a dose threshold that was reached for the CD indication. While we recognize CD may need higher drug exposure, we did not find non-clinical or early phase study data to support the dosing chosen for the registry trials. Nevertheless, risk mitigation through labeling and post-market studies can forge a path to approval, if efficacy and need are high. Limiting RZB induction to 600 mg IV x 3 over 8 weeks with liver test monitoring should lower the risk to an acceptable level. The presenting rash in the Hy's Law case, narrow latency, and immune mediated DILI that is steroid responsive help with DILI detection and treatment.

5.2 Recommendations for labeling and post-market requirements should this BLA be approved.

The DILI risk and mitigation pertaining to this indication and its dosing should be conveyed in labeling, at a minimum Section 5.0, and potentially in other sections as well.

1) Baseline liver tests should meet the following criteria:
    a. ALT and AST less than twice upper limit of normal (ULN).

b. Total bilirubin less than twice ULN unless predominantly indirect or unconjugated without other liver enzyme elevations (e.g., Gilbert's).
c. ALP less than twice ULN unless known to be from a non-liver source, or from a stable or well-controlled liver disorder (e.g., stable primary sclerosing cholangitis or primary biliary cholangitis)

2) Liver enzymes and bilirubin should be monitored monthly x 3, before each 600 mg dosing, and one month after last induction dose.
3) Criteria for increased monitoring of liver enzymes and bilirubin (e.g., recheck in 3-5 days) should be labeled. Suggested criteria are below:
    a. ALT or AST rise to > 3x ULN (or > 3x baseline) without symptoms

    Evaluation testing should ensue if criteria continue to be met without explanation.
4) Criteria for stopping RZB should be labeled (e.g., in Section 2, Dosing and Administration) and be similar to FDA Guidance for Industry on DILI (2009):
    a. ALT or AST > 8 x ULN
    b. ALT or AST > 5 x ULN persisting for $\geq$ 2 weeks
    c. ALT or AST > 3 x ULN with TB > 2 x ULN and/or INR > 1.5
    d. ALT or AST > 3 x ULN with appearance of symptoms below:
        i. fatigue, rash, vomiting, nausea, new abdominal pain, fever, eosinophilia.
5) Any new on treatment symptoms listed in 4.d.i above should prompt a check of liver biochemistries.
6) Patients with decompensated cirrhosis, uncontrolled chronic liver disease or acute liver disease should not receive RZB (e.g., conveyed in "Hepatic Impairment" Section 8 or elsewhere in labeling). Examples of uncontrolled chronic liver diseases include the following:
    a. Untreated chronic hepatitis C, B and D.
    b. Primary sclerosing cholangitis with acute cholangitis episodes within 90 days prior to RZB start unless definitive treatment of a dominant stricture was done.
    c. Autoimmune hepatitis patients who do not meet enrollment liver enzyme and bilirubin criteria.
7) Post-Market Requirement safety surveillance studies (e.g., 5-year observational study for safety evaluation) designed and pre-specified to detect significant DILI and other safety events of concern with the approved dose.
8) Enhanced pharmacovigilance for FAERS reporting that would provide 15-day reports of all serious liver injuries with available case-level information on Risankizumab induction and maintenance dose levels, time to onset, disease background information, concomitant drugs, clinical & biochemical course and diagnostic evaluation to exclude alternative causes of liver injury.

Ling Lan -S

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Joseph G. Toerner -S

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Joseph Toerner, MD, MPH
Director, Division of Hepatology and Nutrition
CDER/OND

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/

PAUL H HAYASHI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memo

Date:	March 16, 2022
Reviewer:	Suprat Saely, PharmD, BCPS, FCCM Division of Pharmacovigilance I (DPV-I)
Team Leader:	Lisa Wolf, PharmD, BCCCP DPV-I
Deputy Division Director:	CDR Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Repatha (evolocumab) Skyrizi (risankizumab-rzaa)
Subject:	Repatha Pushtronex device issues (i.e., wet injection and alarm error events)
Application Type/Number:	BLA 125522 (Repatha) BLAs 761262/761105 (Skyrizi)
Applicant/Sponsor:	Amgen, Inc (Repatha) AbbVie, Inc (Skyrizi)
OSE RCM #:	2022-404

1 INTRODUCTION

This review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an evaluation of the FDA Adverse Event Reporting System (FAERS) database for cases of select device issues with Repatha (evolocumab) Pushtronex system (on-body infusor with prefilled cartridge). This data will be used to inform DG as they review a new Biologics License Application (BLA) and a prior approval efficacy supplement for Skyrizi (risankizumab-rzaa) in the treatment of moderately to severely active Crohn's disease in patients aged 16 years and older that was submitted by the applicant, AbbVie Inc., to the FDA on September 16, 2021. The Applicant proposed the use of (b) (4) on-body drug-device combination with risankizumab-rzaa (b) (4) DG requested this review to determine if there are safety issues associated with the current marketed Repatha Pushtronex system to determine approvability of the proposed risankizumab-rzaa drug-device combination (b) (4)

1.1 BACKGROUND AND REGULATORY HISTORY

1.1.1 Skyrizi (Risankizumab)

Risankizumab-rzaa is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor, inhibiting the release of pro-inflammatory cytokines and chemokines. The FDA first approved risankizumab-rzaa on April 23, 2019, for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[1] On January 21, 2022, the FDA approved a prior approval efficacy supplement (S-014) for the use of risankizumab-rzaa (BLA 761105) in the treatment of active psoriatic arthritis (PsA) in adults.[2] The recommended dose of risankizumab-rzaa is 150 mg (two 75 mg injections) administered subcutaneously (SC) at Week 0, Week 4, and every 12 weeks thereafter. Risankizumab-rzaa is currently available in a 150 mg/ml single-dose prefilled pen, or 75 mg and 150 mg prefilled syringes for SC injections.[3]

On September 16, 2021, the Applicant submitted a new BLA 761262 and prior approval efficacy supplement 761105/S-16 seeking FDA approval of risankizumab-rzaa for the treatment of moderately to severely active Crohn's disease in patients 16 years or older. The proposed dose of risankizumab-rzaa is 600 mg administered by intravenous (IV) infusion at Week 0, 4, and 8, followed by 360 mg administered by SC injection at Week 12, and every 8 weeks thereafter. The new BLA (761262) is for the IV induction therapy and the prior approval efficacy supplement (BLA 761105) is for the SC maintenance regimen. The Applicant is proposing a single-use, drug-device combination using an on-body delivery system (OBDS) (b) (4) (b) (4) for the SC maintenance dosing.[4] The proposed OBDS consists of the on-body injector device and the prefilled cartridge containing 360 mg of risankizumab-rzaa to be administered via SC injection of up to 5 minutes.[5] Of note, (b) (4) OBDS drug-device combination is currently approved for Repatha (evolocumab) as a single-dose Pushtronex system (on-body infusor with prefilled cartridge).

During the risankizumab-rzaa submission review, dosing errors were identified within the bioequivalence (BE) study. According to Applicant documentation, the root causes behind the dosing errors were use errors, fluid path obstruction, and manufacturing issues. FDA issued an information request (IR) to the Applicant on December 28, 2021, to provide 1) a discussion of the use errors resulting in dosage errors, 2) any documentation collected during the study providing investigational details into each dosing failure, and 3) to describe any additional mitigations implemented for each failure mode.

The Applicant responded to the IR on January 11, 2022.[6] Within the response, the Applicant summarized two complaints in which leakage was observed from the device at some time after initiating the injection.[a] The Applicant determined the root cause to be user error in which the start button was not fully pressed to lock the needle into the activated position during injection. The Applicant proposed a change to Step 4A in the risankizumab-rzaa Instructions for Use (IFU) to mitigate the issue (see image below); the proposed changes included reorganization of the existing information and addition of the word, "click," to the image. (b) (4)

(b) (4)

In addition, during submission review, the FDA human factors reviewer raised concerns related to the similarity between the auditory alarms indicating the "on-body injector is not working properly" and "complete" injection. Theoretically, a patient could interpret the auditory alarm of "not working properly" as injection complete and prematurely remove the device; this potential issue was not addressed by the applicant in the IR response.

[a] Complaint ID 1744369: Leakage observed coming from the right side of the OBDS during injection. Complaint ID 1766065: Continuous leaking from injection site observed, starting approximately 2-3 minutes into injection. Error alarm experienced at end of injection.

On February 24, 2022, DG consulted DPV-I to conduct a FAERS search of select device issues related to Repatha Pushtronex drug-device system, with a focus on 1) issues involving leakage during injection, and 2) similarity between auditory alarms indicating the "on-body injector is not working properly" and "complete" injection.

1.1.2 (b) (4)

(b) (4)

1.2 RELEVANT PRODUCT LABELING

Portions of the Repatha Pushtronex system IFU relevant to the review are summarize below.

- After loading the cartridge into the on-body infusor and closing the door of the device, peel away the two green tabs to show the adhesive. **The on-body infusor is on when the blue status light flashes (beep-beep-beep)**.
- When the blue light flashes, the on-body infusor is ready. Keep the stretch (stomach area method only). Hold the loaded on-body infusor with the blue light visible, and place it on your skin. You may hear beeps.

- Firmly press and release the start button. **A flashing green light and a click signals the injection has started (beep-beep-beep)**.
- The injection takes about 5 minutes to finish. **The status light turns solid green, and the device beeps, when done. Injection is finished when: the status light changes to solid green, you hear several beeps, and the plunger fills medicine window all the way**. It is okay to hear a pumping sound start and stop during injection.
- When the injection is done, grab the skin adhesive to carefully peel the on-body infusor off skin. After removal, check the medicine window. **The green light should now be off**. **The used on-body infusor will beep when removed from your skin**.

Troubleshooting:

- **What do I do if the loaded on-body infusor status light continuously flashes red and I hear beeps?**
- Stop using the loaded on-body infusor. If the on-body infusor is attached to your body, carefully remove it. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	February 16, 2022
Time period of search	All dates through February 15, 2022
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product active ingredient: evolocumab
MedDRA search terms (Version 24.1)	HLT: *Device information output issues, Device issues NEC, Device malfunction events NEC, Device operational issues NEC*†
Key word text filters‡	Narrative: *Pushtronex, on-body, on body, infusor, adhesive, cartridge* Product 1 dose: *420 mg* Product 2 dose: *420 mg*
* See Appendix B for a description of the FAERS database. † See Appendix C for a list of MedDRA Preferred Terms (PTs) ‡ These terms are used to identify reports associated with Pushtronex system. Repatha has three marketed formulations: 1) prefilled syringe, 2) pre-filled SureClick, and 3) Pushtronex system. The Pushtronex system is an on-body infusor drug-device combination that is given as a single 420 mg dose. The other two formulations are given as a 140-mg dose and are not the focus of this review. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, HLT=High Level Term	

2.2 PERIODIC SAFETY REPORTS

DPV screened the following periodic safety reports for the Applicant's assessment of automated mini-doser (AMD) device (also known as Pushtronex system in the United States) safety update with Repatha use:

- Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) No. 12 (July 18, 2020 to July 17, 2021)[9]

3 RESULTS

3.1 FAERS CASE SELECTION

3.1.1 High-Level Overview of FAERS Cases

The FAERS search on February 16, 2022, yielded 1,254 reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or reports unrelated to Pushtronex devices.

We reviewed the device-related issues MedDRA Preferred Terms (PTs) for these reports to identify potential PTs related to device leakage or similarity of auditory alarms for hands-on review. **Table 2** lists the device-related issues MedDRA PTs with Repatha, and corresponding report counts from the FAERS search; identified PTs of interest are bolded below.

Table 2. Device-Related Issues MedDRA PTs With Repatha Received by FDA Through February 15, 2022, Sorted by Decreasing Number of FAERS Reports per PT

	MedDRA PT	Number of FAERS Reports*
1	**Incorrect dose administered by device**	481
2	**Device issue**	398
3	Wrong technique in product usage process	348
4	Drug dose omission by device	244
5	**Device malfunction**	164
6	Device use error	62
7	Device delivery system issue	61
8	**Device failure**	42
9	**Device leakage**	27
10	Device defective	26
11	Device difficult to use	22
12	Wrong technique in device usage process	17
13	Needle issue	10
14	Drug delivery system malfunction	9
15	Device adhesion issue	7

Table 2. Device-Related Issues MedDRA PTs With Repatha Received by FDA Through February 15, 2022, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT		**Number of FAERS Reports***
16	Device power source issue	6
17	**Drug delivery system issue**	5
18	Device physical property issue	4
19	Injury associated with device	4
20	Incorrect dose administered	3
21	Product preparation error	3
22	**Device alarm issue**	2
23	Device operational issue	2
24	Incorrect route of product administration	2
25	Liquid product physical issue	2
26	Device breakage	1
27	Device deployment issue	1
28	Device occlusion	1
29	Incorrect dose administered by product	1
30	Incorrect product administration duration	1
31	Product communication issue	1
32	Product dispensing error	1
33	Product physical issue	1
34	Product quality issue	1
35	Unintentional medical device removal	1
* A report can contain more than one MedDRA PT		

3.1.2 Leakage During Infusion

To identify potential cases of leakage during Repatha Pushtronex injection, we reviewed all reports coded with the PT *Device leakage* and searched the remaining report narratives (retrieved by the search in **Table 1**) for the term, "leak," and identified 177 reports for hands-on review. After reviewing all reports, 118 were excluded for the following reasons: leakage occurred during the loading process (n=54), no leakage reported (n=30), leakage occurred during/after the removal process (n=22), unspecified leakage (n=7), cartridge leakage (n=3), and duplicate report (n=2). We deemed 59 cases to be related to leakage during Repatha Pushtronex injection.

Table 3 lists the descriptive characteristics of the 59 cases reporting leakage during Repatha Pushtronex injection. **Appendix D** contains a line listing of the 59 cases in this case series.

Table 3. Descriptive Characteristics of Cases Describing Leakage During Repatha (Evolocumab) Pushtronex Injection in This FAERS Case Series, Received by FDA From All Dates through February 15, 2022 **(N=59)**	
Country	
USA	59
Report type	
Expedited	2
Non-expedited	57
Initial FDA received year	
2018	11
2019	21
2020	13
2021	13
2022	1
Reporter qualifications	
Consumer	37
Healthcare professional	22
Serious outcome(s)* (n=2)	
Other	2
Red light present	
Yes	14
No	26
Not reported	19
Time to leakage (from start of injection)	
<1 min	4
1-2 min	5
3-4 min	6
5-9 min	4
Not reported	40
Needle punctured/puncture marks†	
Yes	11
No	27
Not reported	21
Patient received the full dose	
Yes	0
No	29
Not reported	30
Empty cartridge at the end of infusion	
Yes	8
No	6
Not reported	45

Table 3. Descriptive Characteristics of Cases Describing Leakage During Repatha (Evolocumab) Pushtronex Injection in This FAERS Case Series, Received by FDA From All Dates through February 15, 2022	
(N=59)	
Result of root cause analysis‡	
Activation button not fully pressed	6
Activated out of specified temperature range	2
Door closed during transport	2
No indication of device malfunction/unconfirmed error	2
Activation button pressed prior to placement on skin	1
Cartridge not inserted	1
Could not be determined	1
Door not fully closed	1
Unit removed before delivery was complete	1
Not reported	42

* For the purposes of this review, the following outcomes qualify as serious: other serious important medical events.
† Includes reports stating that the patient did not feel the needle puncture
‡ This information was contained in the case narratives but did not always explicitly mention that the device was investigated.

Reviewer's comment: A small subset of cases contained documentation of the root cause of the events. Six cases were deemed to have a root cause of the activation button not fully being pressed, causing the exposure of the patient needle and leakage from this location. This is the same leakage issue identified in the BE study with risankizumab-rzaa.

The majority of cases did not contain a documented root cause for the events. We are unable to determine if the events are a result of user error, device malfunction, or both because of limited information in the cases and lack of physical device evaluation documented by the Applicant.

Example Cases of Leakage During Injection

FAERS 17685998, MCN: US-AMGEN-USASP2020060881, USA: This case reported a 71-year-old female who has been using Repatha for "seven to nine" months. On the seventh injection, the patient prepared the site by cleaning with alcohol and cotton. She applied the device to her abdomen and removed the tabs. The light turned blue as normal, and it beeped. The device started pumping as usual when the blue start button was pushed. Then after 3 to 4 minutes, the patient noticed the medication was "dripping down her leg and the medication started leaking out everywhere." The device kept pumping for the entire 9 minutes. The patient did not feel the needle pierce her skin, but she did not always feel the needle during her injections. The patient did not see "a puncture hole" and no blood was observed. She did not think she received any dose as she normally feels a stinging sensation as the device is injecting.

"Investigation Conclusion: For 20-0095050-PC-01: The root cause is the Activation Button was not fully pressed, causing the exposure of the Patient Needle and leakage from this location."

Reviewer's comment: The root cause, activation button not being fully pressed, is the same issue identified in the BE study for risankizumab. The Applicant proposed some minor changes to the IFU for risankizumab-rzaa to mitigate this issue; the Repatha IFU currently contains similar information regarding activating the device and what the patient/caregiver should expect (e.g., click signals the injection has started, may feel a pinch, and status flight changes).

FAERS 19153067, MCN: US-AMGEN-USASP2021056466, USA: This case reported an 83-year-old female who received Repatha Pushtronex by a nurse in "the office" because of concerns that the patient would be unable to administer the injections herself due to dementia. Medical history included coronary artery disease, hyperlipidemia, and aortic valve disease. The patient picked up the Repatha Pushtronex device from the pharmacy and brought it to the office. The nurse read the IFU, watched the Repatha instruction video, and had access to a demo device. The nurse followed instructions and "the green and blue lights went off perfectly" and she did not have any issues opening the blue door, inserting the cartridge, or closing the blue door. Both adhesive tabs were removed, and no defects were noted. The nurse cleaned the abdomen with the alcohol pad and placed the device on the patient's upper quadrant of the stomach. The patient remained stationary for the administration. The nurse "heard all the pumping noises and everything worked well." However, after approximately three minutes, the nurse noted a drop of medication leaking so she placed a piece of gauze near the adhesive. There were no red light errors. The device was removed, and the nurse noted a puncture mark where the needle had pierced the skin. The patient only received half of the medication and the rest leaked onto the gauze.

Reviewer's comment: This case suggests the nurse followed the Repatha Pushtronex IFU correctly as the appropriate lighting sequence indicated the device was ready for use, and the status light did not flash red at any point during the injection. The device administered the medication for approximately 3 minutes before leakage was noted. Although there is similarity between this case and the leakage cases observed in the BE study, we cannot determine the root cause of the event.

FAERS 116839804, MCN: US-AMGEN-USASP2019153114, USA: This case involves a 35-year-old female using Repatha Pushtronex device. The patient's husband applied the device on the patient's abdomen. The patient "pressed the blue button several times" and thought she might have broken something inside. The patient never saw red lights, but noted the green light was flashing after she pressed the button. The needle pierced her skin. About a minute after pressing the blue start button, the medication leaked out of the Pushtronex onto the patient's skin. The patient removed the device from the skin and the lights turned off, but the pumping noises were still present. The patient was unsure how much of the medication was left in the window, but "quite a bit of liquid leaked onto her skin."

Reviewer's comment: This case reported the user pressing the Start button several times, which may have led to leakage during injection. The patient felt the needle pierce her skin and the flashing green status light indicated the injection had started. Although we cannot determine the root cause of the leakage issue, there is similarity between this case and the leakage cases observed in the BE study with risankizumab-rzaa.

3.1.3 Similarity Between the Auditory Alarms of Complete and Incomplete Injection

To identify potential cases, we performed a narrative text word search using the terms, "beep" and "alarm," of reports coded with the following PTs: *Device alarm issue, Incorrect dose administered by device, Device issue, Device malfunction, Device failure,* and *Device delivery system issue*. We performed a hands-on review of the 238 reports retrieved from this search. However, we did not identify any cases describing patients misinterpreting the auditory alarm signifying "the on-body injector was not working properly" for "injection complete" and prematurely removing the device. Of note, many reports described proper interpretation of the status light (blue, green, and red lights) in conjunction with the beeping alarm to determine the device status.

3.2 PERIODIC SAFETY REPORTS

The Applicant provided a Pushtronex device safety update associated with Repatha use (b) (4) . During the reporting period (July 18, 2020 to July 17, 2021), there were 8,797 adverse events (4565 cases) with Pushtronex dose administration of Repatha. The most frequently reported postmarket events were wrong technique in product usage process (1184; 13.5%), accidental exposure to product (699; 8.0), injection site pain (580, 6.6%), incorrect dose administered by device (324; 3.7%), injection site swelling (317; 3.6%), injection site hemorrhage (222, 2.5%), injection site erythema (184; 2.1%), injection site mass (176; 2.0%), device defective (164; 1.9%), and drug dose omission by device (162; 1.9%). The Applicant did not provide further details on device-related issues associated with Repatha Pushtronex device.

The estimated number of patient-years of exposure to evolocumab in the United States during the reporting period and cumulatively since launch was (b) (4) and (b) (4) respectively. The estimated number of patients exposed to evolocumab in the United States during the reporting period and cumulatively since launch was (b) (4) and (b) (4) respectively. The Applicant did not provide exposure estimates by Repatha injection dosage form (i.e., prefilled syringe vs. prefilled SureClick autoinjector vs. Pushtronex system).

4 DISCUSSION

Our search of the FAERS database for all reports of potential device-related issues associated with Repatha Pushtronex system retrieved 1,254 reports. We performed a targeted review of these reports to identify cases of device leakage during injection or audio alarm misinterpretation leading to incomplete injection with the Pushtronex system to inform DG in their current assessment of the risankizumab-rzaa (b) (4) application, (b) (4)

Through our hands-on review, we identified 59 cases reporting device leakage during Repatha Pushtronex injection, representing about 5% of the total retrieved device issue reports from our search. Notably, only 14 cases described the status light turning red during the injection, signaling the on-body injector was not working properly, and 26 cases confirmed the status light did not turn red at any point despite experiencing device leakage. The time the leakage occurred

from the start of the injection varied between less than 1 minute (n=4), 1-2 minutes (n=5), 3-4 minutes (n=6), and 5-9 minutes (n=4); however, this information was not reported in most cases (n=40).

Importantly, the root cause of the device leakage was documented, presumably by the Applicant, in 17 cases. Although most cases did not explicitly contain mention of whether the physical device was received by the Applicant and evaluated, it was suggested by the documentation provided in the case. Six cases, representing <1% of the total retrieved device issue reports from our search, described the root cause of the leakage to be user error in which the activation button was not fully being pressed, causing the exposure of the patient needle and leakage from this location. This is the same root cause of the two leakage complaints identified in the BE study with risankizumab-rzaa. The Applicant proposed modifications to the risankizumab-rzaa OBDS IFU to mitigate this use error; however, similar information is already in the Repatha Pushtronex IFU.

Other cases of leakage during Repatha Pushtronex injection identified in the FAERS database contained root causes such as device activated before being brought to room temperature, door assembly was not fully closed during operation, and unit removed before delivery was complete. Many additional cases did not contain a root cause for the device leakage.

We did not identify any cases describing patients misinterpreting the auditory alarm signifying the “on-body injector was not working properly” for “injection complete” and prematurely removing the device. This finding is reassuring, especially since this issue of alarm misinterpretation was a theoretical concern. However, it is important to note that the absence of cases in the FAERS database cannot fully confirm absence of a device issue because we do not receive all reports with a specific product.

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6.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.3 APPENDIX C. MEDDRA PREFERRED TERMS (PTS) FOR HLT DEVICE INFORMATION OUTPUT ISSUES, DEVICE ISSUES NEC, DEVICE MALFUNCTION EVENTS NEC, DEVICE OPERATIONAL ISSUES NEC

HLT: Device issues NEC

Absorbable device issue
Device adhesion issue
Device catching fire
Device connection issue
Device cybersecurity issue
Device data issue
Device delivery system issue
Device dislocation
Device effect decreased
Device effect delayed
Device effect incomplete
Device effect increased
Device effect variable
Device end of service
Device expulsion
Device extrusion
Device failure
Device ineffective
Device inversion
Device issue
Device lead issue
Device leakage
Device loosening
Device safety feature issue
Device temperature issue
Device user interface issue
Device wireless communication issue
Embedded device
Implant subsidence
Internal device exposed
Lead dislodgement
Mobile medical application issue
Prosthetic cardiac valve failure
Unevaluable device issue

HLT: Device information output issues

Device alarm issue
Device information output issue
Device telemetry issue

HLT: Device malfunction events NEC

Device audio issue
Device capturing issue
Device deployment issue
Device inappropriate shock delivery
Device ineffective shock delivery
Device infusion issue
Device malfunction
Device occlusion
Device optical issue
Device pacing issue
Device power source issue
Device signal detection issue
Device signal transmission issue
Device stimulation issue
Medical device entrapment
No device malfunction
Oversensing
Prosthetic cardiac valve malfunction
Stent malfunction
Thrombosis in device
Undersensing

HLT: Device operational issues NEC

Device operational issue

6.4 APPENDIX D. FAERS LINE LISTING OF LEAKAGE DURING INJECTION AND REPATHA (EVOLOCUMAB) CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	06/02/2021	19354787	1	US-AMGEN-USASP2021082068	NON-EXPEDITED	89	Male	USA	
2	04/02/2021	19087040	2	US-AMGEN-USASP2021047800	NON-EXPEDITED	87	Female	USA	
3	08/01/2019	16658046	1	US-AMGEN-USASP2019119295	NON-EXPEDITED	84	Female	USA	
4	04/19/2021	19153067	2	US-AMGEN-USASP2021056466	NON-EXPEDITED	83	Female	USA	
5	04/03/2019	16155331	2	US-AMGEN-USASP2019046091	NON-EXPEDITED	79	Female	USA	
6	12/03/2018	15679502	1	US-AMGEN-USASP2018170268	NON-EXPEDITED	78	Male	USA	
7	05/28/2021	19328677	2	US-AMGEN-USASP2021079551	NON-EXPEDITED	81	Female	USA	
8	06/07/2021	19388893	1	US-AMGEN-USASP2021086681	NON-EXPEDITED	79	Female	USA	
9	01/05/2022	20297279	2	US-AMGEN-USASP2021205966	NON-EXPEDITED	78	Male	USA	
10	03/17/2020	17548150	1	US-AMGEN-USASP2020041130	NON-EXPEDITED	76	Female	USA	
11	06/09/2021	19391261	1	US-AMGEN-USASP2021085762	NON-EXPEDITED	77	Female	USA	
12	10/17/2018	15521892	1	US-AMGEN-USASL2018120255	NON-EXPEDITED	74	Female	USA	
13	07/16/2019	16575691	3	US-AMGEN-USASP2019109604	NON-EXPEDITED	75	Male	USA	
14	07/20/2018	15174379	1	US-AMGEN-USASL2018059475	NON-EXPEDITED	73	Female	USA	
15	11/26/2018	15654587	2	US-AMGEN-USASP2018166327	NON-EXPEDITED	73	Male	USA	
16	02/04/2019	15904018	3	US-AMGEN-USASP2019014843	EXPEDITED	73	Male	USA	OT
17	05/03/2019	16267658	1	US-AMGEN-USASP2019067841	NON-EXPEDITED	73	Female	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
18	07/20/2018	15177848	2	US-AMGEN-USASL2018083883	NON-EXPEDITED	71	Female	USA	
19	04/22/2020	17691719	3	US-AMGEN-USASP2020063435	NON-EXPEDITED	73	Male	USA	
20	10/17/2018	15520088	1	US-AMGEN-USASL2018100479	NON-EXPEDITED	70	Female	USA	
21	11/10/2021	20054816	2	US-AMGEN-USASP2021169833	NON-EXPEDITED	73	Male	USA	
22	04/16/2020	17676414	4	US-AMGEN-USASP2020060129	NON-EXPEDITED	71	Female	USA	
23	04/20/2020	17685998	4	US-AMGEN-USASP2020060881	NON-EXPEDITED	71	Female	USA	
24	01/17/2019	15835536	1	US-AMGEN-USASP2019004771	NON-EXPEDITED	70	Male	USA	
25	12/12/2021	20173518	1	US-AMGEN-USASP2021191793	NON-EXPEDITED	71	Female	USA	
26	06/11/2019	16414220	3	US-AMGEN-USASP2019089207	NON-EXPEDITED	69	Male	USA	
27	03/28/2020	17595107	3	US-AMGEN-USASP2020048670	NON-EXPEDITED	69	Male	USA	
28	04/08/2021	19107021	2	US-AMGEN-USASP2021052155	NON-EXPEDITED	71	Male	USA	
29	07/04/2020	17980638	1	US-AMGEN-USASP2020105255	NON-EXPEDITED	69	Female	USA	
30	03/15/2019	16075324	2	US-AMGEN-USASP2019035364	NON-EXPEDITED	67	Female	USA	
31	04/02/2019	16145139	2	US-AMGEN-USASL2018170183	NON-EXPEDITED	67	Female	USA	
32	07/23/2018	15184186	1	US-AMGEN-USASP2018069242	NON-EXPEDITED	65	Male	USA	
33	08/05/2019	16667450	2	US-AMGEN-USASP2019118881	NON-EXPEDITED	66	Female	USA	
34	01/25/2020	17319744	1	US-AMGEN-USASP2020007952	NON-EXPEDITED	65	Female	USA	
35	07/23/2018	15182628	2	US-AMGEN-USASL2018094235	NON-EXPEDITED	63	Male	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
36	04/09/2020	17653891	1	US-AMGEN-USASP2020057492	NON-EXPEDITED	64	Male	USA	
37	04/26/2019	16243374	4	US-AMGEN-USASP2019063931	NON-EXPEDITED	63	Female	USA	
38	04/23/2019	16227128	2	US-AMGEN-USASP2019061473	NON-EXPEDITED	62	Male	USA	
39	03/19/2019	16087124	1	US-AMGEN-USASP2019039584	NON-EXPEDITED	61	Female	USA	
40	01/21/2019	15850728	1	US-AMGEN-USASP2019006691	NON-EXPEDITED	61	Male	USA	
41	09/08/2020	18241499	2	US-AMGEN-USASP2020132657	NON-EXPEDITED	62	Female	USA	
42	10/18/2018	15529820	1	US-AMGEN-USASP2018124491	NON-EXPEDITED	60	Male	USA	
43	05/26/2020	17822414	2	US-AMGEN-USASP2020083241	NON-EXPEDITED	62	Female	USA	
44	08/12/2019	16694635	2	US-AMGEN-USASP2019125930	NON-EXPEDITED	60	Male	USA	
45	12/30/2019	17211749	2	US-AMGEN-USASP2019214636	NON-EXPEDITED	60	Female	USA	
46	02/11/2020	17403926	3	US-AMGEN-USASP2020019396	NON-EXPEDITED	57	Female	USA	
47	03/20/2020	17567542	2	US-AMGEN-USASP2020045151	NON-EXPEDITED	56	Female	USA	
48	12/18/2018	15732959	1	US-AMGEN-USASP2018178246	NON-EXPEDITED	55	Female	USA	
49	05/07/2019	16279888	2	US-AMGEN-USASP2019069807	EXPEDITED	55	Female	USA	OT
50	08/11/2020	18132734	2	US-AMGEN-USASP2020124643	NON-EXPEDITED	54	Female	USA	
51	04/13/2021	19126638	2	US-AMGEN-USASP2021052392	NON-EXPEDITED	55	Male	USA	
52	02/22/2019	15993267	3	US-AMGEN-USASP2019023935	NON-EXPEDITED	53	Female	USA	
53	07/20/2018	15177804	2	US-AMGEN-USASL2018082260	NON-EXPEDITED	50	Female	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
54	06/02/2021	19364415	2	US-AMGEN-USASP2021080400	NON-EXPEDITED	53	Female	USA	
55	09/23/2019	16839804	2	US-AMGEN-USASP2019153114	NON-EXPEDITED	35	Female	USA	
56	09/08/2021	19800126	2	US-AMGEN-USASP2021135557	NON-EXPEDITED	33	Female	USA	
57	09/23/2019	16840986	1	US-AMGEN-USASP2019153186	NON-EXPEDITED		Male	USA	
58	04/08/2019	16169172	1	US-AMGEN-USASP2019051975	NON-EXPEDITED		Male	USA	
59	08/10/2021	19677988	2	US-AMGEN-USASP2021119233	NON-EXPEDITED		Male	USA	

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: OT=other medically significant

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/

SUPRAT N SAELY
03/16/2022 03:56:51 PM

LISA M WOLF
03/16/2022 03:58:03 PM

MONICA MUNOZ
03/16/2022 04:10:49 PM

Clinical Inspection Summary

Date	11 Feb 2022
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jay Fajiculay, PharmD, RPM Suruchi Batra, MD, Medical Reviewer Suna Seo, MD, Medical Team Leader Division of Gastroenterology (DG)
BLA #	761105-S016 and 761262
Applicant	AbbVie, Inc.
Drug	Skyrizi (risankizumab-rzaa) solution for injection (b) (4) mg/mL)
NME	No
Proposed Indication	For the treatment of moderately or severely active Crohn's disease (CD) in patients 16 years of age and older
Consultation Request Date	2 Nov 2021
Summary Goal Date	15 Feb 2022
Action Goal Date	16 Mar 2022
PDUFA Date	16 Mar 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Chapman, DuVall, Hellstern, Sedghi and the sponsor, AbbVie, Inc, were inspected in support of BLAs 761105-S016 and 761262, covering three clinical studies: M15-991, M16-000, and M16-006.

During the clinical investigator and sponsor inspections, source records related to the co-primary and key secondary efficacy endpoints of Crohn's Disease Activity Index (CDAI) clinical remission and response and endoscopic response (at Baseline and Week 12 for Protocols M15-991 and M16-006 and at Week 52 for Protocol M16-000) were verified against the sponsor's data line listings for all subjects randomized (n=88) at the 4 sites inspected. Review and verification of the source records related to total CDAI score and CDAI subcomponent scores included patient-reported daily stool frequency, daily abdominal pain, and general well-being scores; hematocrit (HCT) levels; standard and actual subject weight; anti-diarrhea drug use; and presence of abdominal mass and other extraintestinal findings and complications. Review and verification of source records related to endoscopic response included the central reviewer's endoscopy sub-scores by segment and the Simple Endoscopy Score – Crohn's Disease (SES-CD).

Minor discrepancies in the CDAI sub-components of patient-reported stool frequency,

abdominal pain, and well-being scores were noted at 1 of the 4 clinical investigator sites (Dr. Chapman). These minor discrepancies had no impact on the primary or secondary efficacy endpoint assessments because they either resulted in no change in the total CDAI score for that visit or the discrepancy occurred at a timepoint that was not used in the primary or secondary efficacy endpoints. No discrepancies or issues were noted in the central reviewer's endoscopy sub-scores by segment and the SES-CD documenting endoscopy response. All discrepancies are described in more detail in Section III of this Clinical Inspection Summary (CIS).

During the sponsor inspection, data reliability concerns were identified related to data collection of CDAI sub-component and total CDAI scores. In Section 9.6.3 of the Clinical Study Reports (CSR) and in Section 16.1_9.2 of the Statistical Analysis Plans (SAP) for Protocols M15-991 and M16-006, the applicant noted that errors were detected, specifically in the CDAI sub-component and total scores after the interim database lock in December 2020 (i.e., after all subjects had completed their Week 12 visit). In a 9 November 2021 response to an IR, the sponsor provided a listing of all CDAI sub-component and total CDAI score errors that were detected and changes made to this data after the interim database lock. Per this listing, these errors appear to have been widespread, occurring across multiple sites and in many subjects. The errors occurred in at least 104 subjects at 74 sites in Study M15-991 and in at least 207 subjects at 123 sites in Study M16-006.

The causes of this systemic and widespread data collection issue appear to be multifactorial and are related to the following:

- Inadequate clinical investigator, site staff, and monitor training on CDAI data entry and CDAI source data verification
- Inadequate monitoring, including an inadequate monitoring plan
- Inadequate sponsor processes and procedures for query resolution, including communication issues between the monitors themselves and between the monitors and the sponsor staff
- Electronic case report form (eCRF) design and system programming issues (that contributed to the CDAI score calculation errors) and a lack of implemented eCRF edit checks to highlight out of range and/or incorrect values at the point of entry

Of particular interest, our review of the listing of CDAI score errors noted that the changes made to the Week 12 total CDAI score after the interim database lock in December 2020 resulted in a change in the patient's co-primary efficacy outcome (e.g., change from non-responder to responder) in at least 6 subjects. In addition, changes made to the Baseline total CDAI scores impacted subject eligibility in at least 6 subjects. Specifically, the following was noted:

- For Subjects (b) (6): the Week 12 total CDAI scores changed from >150 to <150
- For Subject (b) (6) The Week 12 total CDAI score changed from <150 to >150
- For Subjects (b) (6): the Baseline total CDAI scores were noted to have changed such that these subjects did not meet the protocol's eligibility criteria (i.e., inclusion criteria #3 states that subjects must have a total CDAI score of 220 to 450 at baseline to be eligible for inclusion in the study).

The applicant stated in the CSR and SAP that the primary analysis was rerun on the final version of the database, which included the corrected and updated CDAI data and that these data changes did not impact the primary efficacy conclusion. We recommend that FDA's statistical team confirm this conclusion.

Notwithstanding the data collection issues (e.g., CDAI sub-component and total score discrepancies and errors, inadequate protocol training, inadequate monitoring, and issues related to eCRF design and validation) noted during the inspections and in the review, the data otherwise generated by the 4 clinical investigator sites inspected appear acceptable in support of the respective indication.

II. BACKGROUND

Supplemental BLA 761105-S016 and BLA 761262 were submitted in support of the use of Skyrizi (risankizumab-rzaa) for the treatment of moderately or severely active Crohn's disease (CD) in patients 16 years of age and older. The key studies supporting the application were the following:

- Protocol M15-991, "A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment."
- Protocol M16-006, "A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease."
- Protocol M16-000, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease."

Protocols M15-991 and M16-006 were similar in design. Both studies were phase 3, multicenter, randomized, double-blind, placebo-controlled studies designed to evaluate the efficacy and safety of risankizumab as induction treatment in subjects with moderate to severe active CD.

- The objective of M15-991 was to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD who had failed a prior biologic.
- The objective of Study M16-006 was to evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in subjects with moderately to severely active CD.

Protocols M15-991 and M16-006 enrolled subjects with a confirmed diagnosis of CD. Subjects in M15-991 also had to have a documented inadequate response or intolerance to one or more of the approved biologic agents (i.e., the study only enrolled subjects who had inadequate response or intolerance to prior biologic therapy). Subjects in M16-006 could have either had or not had an inadequate response to prior biologic therapy.

For both studies, M15-991 and M16-006, the study duration was up to 49 weeks and included the following:

- Screening period of up to 35 days
- 12-week Induction Period 1
- 12-week Induction Period 2 for those subjects who did not achieve Stool Frequency/ Abdominal Pain Score clinical response at Week 12
- 140-day follow up period from the last dose of study drug

Screening Period: Within 35 days prior to the Baseline visit, subjects provided written informed consent and underwent the screening procedures. The Screening Period (35 days ± 7 days) allowed for enough time for the return of endoscopy central reading and lab results. All subjects must have had their average daily stool frequency, average daily abdominal pain score, and CDAI calculated and meet certain eligibility criteria before randomization at Baseline.

During screening, subjects were dispensed an electronic diary (eDiary), and site staff trained the subjects on how to count the number of soft and liquid stools and complete the diary. All subjects were required to complete their eDiary on a daily basis throughout the entire study. Site personnel were required to review the diary with the subject at each visit and collect the eDiary at the Final/Premature Discontinuation visit, unless the subject continued into Study M16-000 (i.e., the maintenance study).

12-Week Induction Period 1: Eligible subjects were stratified by number of prior biologics failed (1 or >1), steroid use at Baseline (yes/no), and Baseline SES-CD (original or alternative) and then randomized via an Interactive Response Technology (IRT) system (for M15-991 in a 1:1:1 ratio and for M16-006 in a 2:2:1 ratio) to receive one of the following blinded treatment regimens:

- Risankizumab 1200 mg intravenous (IV) Weeks 0, 4, 8
- Risankizumab 600 mg IV Weeks 0, 4, 8
- Placebo IV Weeks 0, 4, 8

Induction Period 2: Subjects in the risankizumab treatment arms who did not achieve Stool Frequency/Abdominal Pain Score clinical response at Week 12 were offered blinded induction therapy with risankizumab and randomized via an IRT system in a 1:1:1 ratio to receive one of the following blinded treatment groups:

- Group 1: Risankizumab 1200 mg IV and matching SC placebo at Weeks 12, 16, 20
- Group 2: Risankizumab 360 mg subcutaneous (SC) and matching IV placebo at Weeks 12, 20
- Group 3: Risankizumab 180 mg SC and matching IV placebo Weeks 12, 20

Subjects randomized to the placebo arm in Induction Period 1 who did not achieve stool frequency/ abdominal pain score clinical response at Week 12 received Risankizumab 1200 mg IV in Induction Period 2 at Weeks 12, 16, and 20.

Visits for clinical evaluation occurred at Baseline, and Weeks 4, 8, and 12 or premature discontinuation. For subjects who underwent a second blinded induction in Induction Period 2

were further evaluated at Weeks 12, 16, and 20 and evaluation for Stool Frequency/Abdominal Pain Score clinical response at Week 24.

Follow-up Period: Subjects who discontinued the study or subjects who completed the Week 12/Week 24 visit and who did not roll-over into Study M16-000 should have had a follow-up call 140 days from the last dose of study drug to obtain information on any new or ongoing adverse events.

Protocol M16-000 was a Phase 3, multicenter study that enrolled subjects who achieved clinical response at the last visit of induction Studies M16-006 or M15-991. Study M16-000 consisted of 3 sub-studies:

- Sub-Study 1 was a 52-week randomized, double-blind, placebo-controlled maintenance study.
- Sub-Study 2 is a 52-week randomized, exploratory maintenance study of 2 different dosing regimens (therapeutic drug monitoring vs. clinical assessment for dose escalation).
- Sub-Study 3 is an open-label long-term extension.

The objective of M16-000 Sub-Study 1 was to evaluate the efficacy and safety of continuing risankizumab as maintenance therapy versus withdrawing risankizumab treatment in subjects with moderately to severely active CD who responded to IV risankizumab induction treatment in Study M16-006 or Study M15-991 and had a Baseline of induction eligibility SES-CD of ≥ 6 (≥4 for isolated ileal disease). For subjects who had been enrolled in M16-000 Sub-Study 1, Baseline was defined as the Baseline visit of the induction Studies, M15-991 or M16-006.

The duration of M16-000 Sub-Study 1 was up to approximately 68 weeks and included the following:

- 52-week maintenance period
- 140-day follow-up period (except for subjects who continued in Sub-Study 3) from last dose administration of study drug

Subjects who achieved a stool frequency/abdominal pain score clinical response to IV risankizumab induction at Week 12 of Induction Period 1 or Week 24 of Induction Period 2 in the induction studies (i.e., M15-991 and M16-006) and a Baseline induction eligibility SES-CD of ≥ 6 (≥ 4 for isolated ileal disease) were stratified based on (1) endoscopic response (per local read); (2) stool frequency/abdominal pain score clinical remission status at Week 0; and (3) last risankizumab induction IV dose received, and then re-randomized via an IRT system in a 1:1:1 ratio to receive one of the following:

- Risankizumab 180 mg SC dosing q8w (Weeks 0, 8, 16, 24, 40, and 48)
- Risankizumab 360 mg SC q8w (Weeks 0, 8, 16, 24, 40, and 48)
- Placebo SC q8w (Weeks 0, 8, 16, 24, 40, and 48) (to have risankizumab treatment withdrawn)

Subjects who achieved a stool frequency/abdominal pain score clinical response to IV placebo induction treatment or to SC risankizumab at Week 24 were assigned by the IRT system to

continue to receive the same blinded study drug, either placebo SC or risankizumab SC, and were excluded from the primary population for efficacy analysis.

Subjects who demonstrated inadequate response during M16-000 Sub-Study 1 received open-label risankizumab rescue therapy starting at the Week 16 visit based upon increased symptom activity and confirmation with objective markers of inflammation. Clinical and laboratory assessments of disease activity were performed during Sub-Study 1 at Weeks 0, 8, 16, 24, 32, 40, 48, and 52/premature discontinuation.

The ***co-primary efficacy endpoint*** for Protocols M15-991, M16-006, and M16-000 were as follows:

- Proportion of subjects with CDAI clinical remission at Week 12 (for M15-991 and M16-006) and at Week 52 (for M16-000). CDAI clinical remission was defined as a CDAI score <150.
- Proportion of subjects with endoscopic response at Week 12 (for M15-991 and M16-006) and at Week 52 (for M16-000). Endoscopic response was defined as a decrease in SES-CD >50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline), as scored by central reviewer.

Key secondary efficacy endpoints for Protocols M15-991, M16-006, and M16-000 conducted in the U.S. were as follows:

- Proportion of subjects with clinical remission at Week 12 (for M15-991 and M16-006) and at Week 52 (for M16-000). Clinical remission was defined as average daily stool frequency ≤ 2.8 and not worse than Baseline AND average daily abdominal pain score ≤ 1 and not worse than baseline.
- Proportion of subjects with CDAI clinical response at Week 12 (for M15-991 and M16-006) and at Week 52 (for M16-000). Clinical response was defined as ≥30% decrease in average daily stool frequency and/or ≥ 30% decrease in average daily abdominal pain score and both not worse than Baseline

Efficacy Endpoint Data Collection and Handling for All Three Protocols

The following central laboratories and vendors were contracted to process/manage the primary efficacy and key secondary endpoints:

- (b) (4) ePRO vendor who supplied devices and managed ePRO system (i.e., Trialmax) and ePRO data (e.g., CDAI scores)
- (b) (4) Central Endoscopy Reviewer
- (b) (4) Central Laboratory (e.g., HCT values)

Total Crohn's Disease Activity Index (CDAI) score: The total CDAI score is made up of the following:

- Electronic patient-reported outcome data (ePRO) (e.g., number of liquid stools, abdominal pain, and general well-being)
- Data from the central laboratory (i.e., hematocrit (HCT) values)
- Data collected by the site staff (e.g., weight, concomitant antidiarrheals, etc.)

The site staff transcribed data from the ePRO database (i.e., TrialMax), the central lab, and other source records into the eCRFs (Medidata Rave) to calculate the total CDAI score.

Endoscopies: The same endoscopist, where possible, should have performed all endoscopies. All endoscopies were read locally and also reviewed and read by a blinded central reviewer. Endoscopies were performed on the following visits:

- During Screening
- Induction Period 1, Week 12/Premature Discontinuation
- Induction Period 2, Week 24
- Week 52/premature discontinuation (for M16-000, Sub-Study 1)

The endoscopies performed at these time points were used to provide the endoscopy sub-scores to calculate the Simple Endoscopy Score – Crohn's Disease (SES-CD). The endoscopy sub-scores by segment were read locally by the endoscopist and centrally by a central reviewer. The central reviewer's endoscopy sub-scores were used for the efficacy analyses.

The sponsor contracted with (b) (4) to handle manage the central reviewer's endoscopy data. Per the protocol, the central reviewer's assessments and data were not provided to clinical investigator sites for visits after screening per study design. For the first 3 months, the central reviewers recorded their endoscopy scores on a paper case report form (CRF). The original paper CRF was sent to (b) (4) for data entry. As of April 2018, the central reviewers entered their scores directly in an EDC system (i.e., IBM Clinical Development).

Protocol M15-991:

- ***Subjects:***
  - A total of 988 subjects were screened and 618 subjects were randomized into Induction Period 1 (i.e., 207 subjects were randomized to placebo, 206 subjects were randomized to risankizumab 600 mg, and 205 subjects were randomized to risankizumab 1200 mg)
  - 587 subjects completed the 12-week Induction Period 1 (i.e., 186 subjects randomized to placebo, 202 subjects randomized to risankizumab 600 mg, and 199 subjects randomized to risankizumab 1200 mg)
  - 211 subjects entered Induction Period 2 (i.e., 41 subjects received risankizumab 180 mg, 42 subjects received risankizumab 360 mg, 42 subjects received risankizumab 1200 mg; and 86 subjects who received placebo in Induction Period 1 received risankizumab 1200 mg in Induction Period 2)
  - 192 subjects completed the Induction Period 2 (i.e., 39 subjects who received risankizumab 180 mg, 39 subjects who received risankizumab 360 mg, 38 subjects who received risankizumab 1200 mg, and 76 subjects who had received placebo in Induction Period 1 and who subsequently received risankizumab 1200 mg in Induction Period 2)

- ***Sites:*** The study was conducted at 214 sites (in Argentina, Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czechia, Denmark, Egypt, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Lithuania, Netherlands, New Zealand, Poland, Portugal, Romania, Russian Federation,

Serbia, Singapore, Slovakia, South Africa, South Korea, Spain, Switzerland, Taiwan, United Kingdom, and United States)

- ***Study Initiation and Completion Dates:*** 18 Dec 2017 (First Subject First Visit) to 19 May 2021 (Last Subject Last Visit)

- ***Interim Database Lock:*** 17 Dec 2020; ***Final Database Lock:*** 20 May 2021

- ***Study Unblinding Date:*** 17 Dec 2020

Protocol M16-006:

- ***Subjects:***
  - A total of 1578 subjects were screened and 931 subjects were randomized into Induction Period 1 (i.e., 186 subjects were randomized to placebo, 373 subjects were randomized to risankizumab 600 mg, and 372 subjects were randomized to risankizumab 1200 mg)
  - 894 subjects completed the 12-week Induction Period 1 (i.e., 163 subjects randomized to placebo, 364 subjects randomized to risankizumab 600 mg, and 366 subjects randomized to risankizumab 1200 mg)
  - 278 subjects entered Induction Period 2 (i.e., 62 subjects received risankizumab 180 mg, 68 subjects received risankizumab 360 mg, 67 subjects received risankizumab 1200 mg; and the 76 subjects who had received placebo in Induction Period 1 received risankizumab 1200 mg in Induction Period 2)
  - 265 subjects completed the Induction Period 2 (i.e., 62 subjects who received risankizumab 180 mg, 65 subjects who received risankizumab 360 mg, 64 subjects who received risankizumab 1200 mg, and 74 subjects who had received placebo in Induction Period 1 and who subsequently received risankizumab 1200 mg in Induction Period 2)

- ***Sites:*** The study was conducted at 297 sites (in Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Estonia, Germany, Greece, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Ukraine, United Kingdom, and United States)

- ***Study Initiation and Completion Dates:*** 10 May 2017 (First Subject First Visit) to 14 April 2021 (Last Subject Last Visit)

- ***Interim Database Lock:*** 13 Dec 2020; ***Final Database Lock:*** 18 May 2021

- ***Study Unblinding Date:*** 13 Dec 2021

Protocol M16-000:

- **Subjects:**
  - A total of 712 subjects were enrolled in Sub-Study 1

- 542 subjects were in the randomized portion (subjects who had received IV risankizumab induction) and 170 subjects were in the non-randomized portion (subjects who had received either IV placebo only or SC Risankizumab during the induction studies)
- 184 subjects were randomized to placebo, 179 subjects were randomized to risankizumab 180 mg, and 179 subjects were randomized to risankizumab 360 mg
- 384 subjects completed the randomized portion of Sub-Study 1: 160 subjects receiving placebo, 164 subjects receiving Risankizumab 180 mg, and 160 subjects receiving risankizumab 360 mg

- ***Sites:*** The study was conducted at 273 sites (in Argentina, Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Chile, China, Columbia, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Ukraine, United Kingdom, and United States)

- ***Study Initiation and Completion Dates:*** 9 Apr 2018 (First Subject First Visit) to 15 May 2021 (Data Cutoff for Sub-Study 1)

- ***Interim Database Lock:*** 13 May 2021

Rationale for Site Selection

The clinical sites were chosen using a risk-based approach, primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history. In addition, the sponsor, AbbVie, Inc. was selected for inspection.

III. RESULTS (by site):

1. **Jonathan Chapman, MD**
   Site # 120610
   9103 Jefferson Highway
   Baton Rouge, LA 70809
   PDUFA Inspection Dates: 6 to 10 Dec 2021

At this site for Protocol M15-991, 8 subjects were screened, 5 were randomized, and 4 subjects completed the study. Subject (b) (6) (randomized to placebo) terminated early due to worsening disease. For Protocol M16-006, 11 subjects were screened, 6 were randomized, and 6 subjects completed the study. For M16-000, Sub-Study 1, four subjects were enrolled in the randomized portion of Sub-Study 1. Subject (b) (6) (randomized to placebo) terminated early due to worsening disease. M16-000 is still open to enrollment.

A full audit of the study records for all 15 randomized subjects in the 3 studies was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Institutional Review Board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); co-primary and key secondary efficacy endpoint data related to CDAI clinical remission and clinical response scores; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters. Of note, part of the co-primary efficacy endpoint of endoscopy response was not verified during the inspection because the central reviewer's endoscopy sub-scores by segment and the SES-CD were not provided to clinical investigator sites for visits after screening per study design. This data was verified during inspection of the sponsor. See inspection of AbbVie in Section III.5 below.

There was no evidence of under-reporting of adverse events. The source records documenting CDAI clinical remission and clinical response scores (i.e., total CDAI score: patient-reported daily stool frequency, daily abdominal pain, general well-being scores; hematocrit levels; standard and actual subject weight; anti-diarrhea drug use; and presence of abdominal mass and other extraintestinal findings and complications) at Baseline and Week 12 (for Protocols M15-991 and M16-006) and at Week 52 (for Protocol M16-000) were reviewed and verified against the sponsor's data line listings for 14 of the 15 randomized subjects. CDAI scores for Subject (b) (6) could not be verified during the inspection because this subject was transferred to another site (Site 116413, Dr. Siddiqui) after Week 12, and the site staff no longer had access to the ePRO source data for this subject. Minor discrepancies were noted in the daily patient-reported scores for stool frequency, abdominal pain, and general well-being in 7 of the 14 randomized subjects whose data were verified.

Reviewer's comments: *Only one discrepancy that occurred in Subject (b) (6) (randomized to Placebo SC in Protocol M16-000) on Day 6 of the Week 24 Visit resulted in a minor change in the total CDAI score (Week 24 total CDAI score of 85 instead of 84). This total CDAI score discrepancy was very minor and does not have an impact on the primary or secondary efficacy endpoint assessments because it occurred at a timepoint that was not used in the primary or secondary efficacy endpoints.*

The remaining discrepancies in the other 6 subjects were due to transcription errors by site personnel who entered the patient-reported 7-day stool frequency, abdominal pain, and well-being scores in reverse order (i.e., Day 7 scores were entered as Day 1 scores, Day 6 scores were entered as Day 2 scores, etc.). These discrepancies affect the accuracy of reporting of the patient-reported daily scores, but none of these discrepancies resulted in a change in the total CDAI scores for the subjects' respective Study Visits.

2. George Aaron DuVall, MD
Site #134989
1720 S Beckham Ave
Tyler, TX 75701-4464
PDUFA Inspection Dates: 6 to 9 Dec 2021

At this site for Protocol M15-991, 13 subjects were screened, 12 were randomized, and 11 subjects completed the study. Subject (b) (6) (randomized to Placebo IV) discontinued early due to unblinding secondary to an adverse event (i.e., viral myocarditis). For Protocol M16-006, 14 subjects were screened, 12 were randomized, and 12 subjects completed the study. For M16-000, Sub-Study 1, seven subjects were enrolled in the randomized portion of Sub-Study 1. Subject (b) (6) (randomized to 180 mg SC) was lost to follow-up. M16-000 is still open to enrollment.

A full audit of the study records for all 31 randomized subjects in the 3 studies was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); co-primary and key secondary efficacy endpoint data related to CDAI clinical remission and clinical response scores; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters. Of note, part of the co-primary efficacy endpoint of endoscopy response was not verified during the inspection because the central reviewer's endoscopy sub-scores by segment and the SES-CD were not provided to clinical investigator sites for visits after screening per study design. This data was verified during inspection of the sponsor. See inspection of AbbVie in Section III.5 below.

There was no evidence of under-reporting of adverse events. The source records documenting CDAI clinical remission and clinical response scores (i.e., total CDAI score: patient-reported daily stool frequency, daily abdominal pain, general well-being scores; hematocrit levels; standard and actual subject weight; anti-diarrhea drug use; and presence of abdominal mass and other extraintestinal findings and complications) at Baseline and Week 12 (for Protocols M15-991 and M16-006) and at Week 52 (for Protocol M16-000) were reviewed and verified against the sponsor's data line listings for the 31 randomized subjects. No discrepancies were noted.

3. Paul A. Hellstern, Jr, MD
Site #87887
Nature Coast Clinical Research
411 West Highland Blvd.
Inverness, Florida 34452
*PDUFA Inspection Dates:*16 to 27 Dec 2021

At this site for Protocol M16-006, 20 subjects were screened, 8 were randomized, and 8 subjects completed the study. For M16-000, Sub-Study 1, 4 subjects were enrolled in the

randomized portion of Sub-Study 1, and 4 subjects completed the study. M16-000 is still open to enrollment.

A full audit of the study records for all 12 randomized subjects in the 2 studies was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); co-primary and key secondary efficacy endpoint data related to CDAI clinical remission and clinical response scores; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters. Of note, part of the co-primary efficacy endpoint of endoscopy response was not verified during the inspection because the central reviewer's endoscopy sub-scores by segment and the SES-CD were not provided to clinical investigator sites for visits after screening per study design. This data was verified during inspection of the sponsor. See inspection of AbbVie in Section III.5 below.

There was no evidence of under-reporting of adverse events. The source records documenting CDAI clinical remission and clinical response scores (i.e., total CDAI score: patient-reported daily stool frequency, daily abdominal pain, general well-being scores; hematocrit levels; standard and actual subject weight; anti-diarrhea drug use; and presence of abdominal mass and other extraintestinal findings and complications) at Baseline and Week 12 (for Protocol M16-006) and at Week 52 (for Protocol M16-000) were reviewed and verified against the sponsor's data line listings for the 12 randomized subjects. No discrepancies were noted.

4. Shahriar Sedghi, MD
Site #33899
610 Third Street, Suite 204
Macon, GA 31201
PDUFA Inspection Dates: 29 Nov to 10 Dec 2021

At this site for Protocol M15-991, 21 subjects were screened, 12 were randomized, and 11 subjects completed the study. Subject (b) (6) (randomized to Placebo IV) was lost to follow-up at week 4 of the study. For Protocol M16-006, 13 subjects were screened, 9 were randomized, and 9 subjects completed the study. For M16-000, Sub-Study 1, 9 subjects were enrolled in the randomized portion of Sub-study 1, and 9 completed the study.

A full audit of the study records for all 30 randomized subjects in the 3 studies was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records and other regulatory documentation (e.g., Form FDA 1572s); co-primary and key secondary efficacy endpoint data related to CDAI clinical remission and clinical response scores; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters. Of note, part of the co-primary efficacy endpoint of endoscopy response was not verified during the inspection because the central reviewer's endoscopy sub-scores by

segment and the SES-CD were not provided to clinical investigator sites for visits after screening per study design. This data was verified during inspection of the sponsor. See inspection of AbbVie in Section III.5 below.

There was no evidence of under-reporting of adverse events. The source records documenting CDAI clinical remission and clinical response scores (i.e., total CDAI score: patient-reported daily stool frequency, daily abdominal pain, general well-being scores; hematocrit levels; standard and actual subject weight; anti-diarrhea drug use; and presence of abdominal mass and other extraintestinal findings and complications) at Baseline and Week 12 (for Protocols M15-991 and M16-006) and at Week 52 (for Protocol M16-000) were reviewed and verified against the sponsor's data line listings for the 30 randomized subjects. No discrepancies were noted.

5. AbbVie Inc
1 North Waukegan Road
North Chicago, IL 60064
PDUFA Inspection Dates: 8 to 15 Dec 2021

The inspection of the sponsor, AbbVie, Inc, focused on the control, oversight, and management of Protocols M15-991, M16-006, and M16-000; verification of part of the co-primary efficacy endpoint of endoscopy response (i.e., the central reviewer's endoscopy sub-scores by segment and the SES-CD); and review of processes and procedures related to the collection, handling and management of the CDAI sub-component scores, total scores, central reviewers' endoscopy scores, and locking of the study database.

Study records reviewed included records related to the roles and responsibilities of sponsor and their service providers; the organization and its personnel; selection and monitoring of clinical investigators; quality control and assurance activities, including selection of monitors, monitoring procedures and activities, and sponsor audits; safety and adverse event reporting; data collection and handling; record retention, financial disclosure, electronic records and signature compliance; test article accountability; relevant communication and correspondence; and registration of studies on clinicaltrials.gov.

Verification of endoscopy sub-scores by segment and SES-CD

The sponsor contracted with (b) (4) to collect and manage the central reviewer endoscopy data. The central reviewers entered their endoscopy data directly in (b) (4) database (i.e., IBM Clinical Development). During the sponsor inspection, the electronic source records containing the central reviewer's endoscopy sub-scores by segment and the SES-CD documenting endoscopy response at baseline and Week 12 (for Protocols M15-991 and M16-006) and at Week 52 (for Protocol M16-000) were reviewed and verified against the sponsor's data line listings for the 88 randomized subjects at the 4 clinical investigator sites selected for inspection (i.e., Drs. Chapman, DuVall, Hellstern, and Sedghi). No discrepancies were noted.

In addition, in a 9 November 2021 response to an IR, the sponsor noted that the central

reviewers made changes to their endoscopy data during the trial after initial entry. According to the sponsor, these changes were made as a result of data entry errors, central reviewers' re-review of endoscopy videos, and a protocol amendment which changed eligibility criteria. During the inspection, audit trails of the endoscopy data changes were reviewed in order to verify the sponsor listing of endoscopy data changes submitted to the NDA. No discrepancies were noted.

CDAI sub-component data entry and score calculation errors and data corrections

In Section 9.6.3 of the Clinical Study Reports and in Section 16.1_9.2 of the Statistical Analysis Plans for Protocols M15-991 and M16-006, the sponsor noted that errors were detected, specifically in the CDAI sub-components, after the interim database lock in December 2020 (i.e., after all subjects had completed their Week 12 visit). In a 9 November 2021 response to an IR, the sponsor provided a listing of all CDAI sub-component errors that were detected, including the changes made to this data after the interim database lock. CDAI sub-component and total score errors included the following:

- Hematocrit (HCT) values entered as fractionated hematocrit or hemoglobin values instead of percent hematocrit
- HCT entered from a previous visit when HCT was available for the current visit
- Standard weights entered in pounds instead of kilograms
- Stool frequency, abdominal pain, and well-being scores incorrectly included days that subjects received bowel preparation medication, days when the subjects underwent endoscopy, and the 2 days following the endoscopy
- Anti-diarrhea drug use entered incorrectly
- Information related to the presence of abdominal mass and other extraintestinal findings and complications entered incorrectly

The CDAI data entry and score calculation error issue was reviewed and further discussed with the sponsor during the inspection. The sponsor acknowledged this widespread and systemic data collection issue and noted that site staff and monitors were subsequently retrained on CDAI data entry and source data verification, respectively. Of note, source records for the CDAI sub-component scores were reviewed and verified against the data line listings during the four clinical investigator inspections and minor discrepancies were found. See clinical investigator inspection summaries above.

Reviewer's comment: *It should be noted that the sponsor's corrective plan of solely retraining sites on data entry was insufficient because the cause of this systemic data collection issue appears to be multifactorial and not just an issue of inadequate site and monitor training. Based on the inspection findings and review of all exhibits, the cause includes not only the inadequate training but also problems related to the following:*

- *Inadequate monitoring and source data verification of critical source data during the conduct of the trial (e.g., CDAI subcomponent scores, total CDAI scores, and endoscopy scores)*

- *Use of a universal monitoring plan template (i.e., one-size fits all) that was not tailored to*

the complexity of and risks associated with Protocols M15-991, M16-000, and M16-006. Specifically, the plan describes AbbVie's monitoring approach as risk-proportionate. However, it does not describe the critical to quality factors specific to the complex protocols, nor does it provide details about how that risk-proportionate approach should be implemented and executed by onsite, remote, and central monitors. For example, the monitoring plan does not emphasize study processes and procedures and source data verification that are critical to subject safety and data reliability and how these processes and source data should be reviewed, verified and monitored. Overall, this may point to deficiencies in the sponsor's quality management system for managing risks to those factors that are critical to data reliability and subject safety.

- *Inadequate sponsor processes and procedures for query resolution that included communication issues between the monitors themselves and between the monitors and the sponsor staff (e.g., data scientists). For example, per exhibits in the inspection report, the sponsor states that one group of monitors would identify a discrepancy and another group would close the query before the site had taken action. The sponsor further noted in the collected exhibits that this communication issue was not discovered by any group until after the interim database lock.*

- *EDC system design, validation, and user acceptance testing which contributed to the CDAI score calculation and data entry errors. For example, there were EDC programming errors that resulted in CDAI score calculation errors and there was a lack of EDC system edit checks implemented to highlight out of range/incorrect values at the point of entry. The sponsor stated during inspection that the EDC system design and validation was the responsibility of the service provider. However, the sponsor has an overarching responsibility to ensure that the investigation is conducted in accordance with the general investigational plan and protocol, and this includes ensuring that the eCRFs are designed per the data collection needs as outlined in the protocol and validated to ensure that the system is fit for its intended purpose.*

A closer review of the listing of CDAI data changes made after the interim database lock provided by the sponsor in their 9 Nov 2021 response revealed that these errors occurred in 104 subjects at 74 sites in Study M15-991 and 207 subjects at 123 sites in Study M16-006.

Of particular interest, our review of the listing of CDAI score errors found that the changes made to the Week 12 total CDAI score after the interim database lock in December 2020 resulted in a change in the patient's co-primary efficacy outcome (e.g., change from non-responder to responder) in at least 6 subjects. In addition, changes made to the Baseline total CDAI scores impacted subject eligibility in at least 6 subjects. Specifically, the following was noted:

- *For Subjects* (b) (6)*: The Week 12 total CDAI scores changed from >150 to <150*
- *For Subject* (b) (6) *The Week 12 total CDAI scores changed from <150 to >150*
- *For Subjects* (b) (6)*: Baseline total CDAI scores were noted to have changed such that these subjects did not meet the*

protocol's eligibility criteria (i.e., inclusion criteria #3 states that subjects must have a total CDAI score of 220 to 450 at baseline to be eligible for inclusion in the study).

The applicant stated in the CSR and SAP that the primary analysis was rerun on the final version of the database, which included the corrected and updated CDAI data and that these data changes did not impact the primary efficacy conclusion. We recommend that FDA's statistical team confirm this conclusion.

{See appended electronic signature page}

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cc:
Central Doc. Rm. BLAs 761105-S016 and 761262
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DG/Medical Reviewer/Suruchi Batra
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OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From:	Mona Khurana, M.D. Division of Pediatrics and Maternal Health (DPMH) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs Office of New Drugs (OND)
Through:	John J. Alexander, MD, MPH, Deputy Director DPMH, ORPURM, OND
To:	Division of Gastroenterology (DG)
Subject:	Pediatric Labeling Review
Applicant:	AbbVie, Inc.
Applications:	Intravenous (IV) dosage form: BLA 761262 Subcutaneous (SC) dosage form: BLA 761105/S-016
Drug:	Skyrizi (risankizumab)
Dosage Forms:	IV: 600 mg/10 mL in each single-dose vial (60 mg/mL) SC: 360 mg/2.4 mL in each single-dose prefilled cartridge (150 mg/mL)
Proposed Indication:	Treatment of moderately to severely active Crohn's disease (CD) in patients 16 years of age and older

Proposed Dosing Regimen: Induction: 600 mg IV at Weeks 0, 4, and 8

Maintenance: 360 mg SC at Week 12 then every 8 weeks thereafter

Consult Request

DG initially consulted DPMH to review the adequacy of the pediatric use information in labeling and subsequently asked DPMH to also opine on options for regulatory action for the adolescent population given the limited number of adolescents enrolled in the pivotal adult phase 3 trials.

Brief Regulatory History of this Application

Skyrizi (risankizumab) is an interleukin 23 antagonist that was initially FDA approved in April 2019 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The Agency granted a partial waiver of study requirements under the Pediatric Research Equity Act (PREA) in patients less than 6 years of age and issued the following PREA PMR in patients 6 to less than 17 years of age with this initial US approval:

PMR 3594-1: Conduct a pharmacokinetic (PK), safety, and efficacy study in pediatric subjects 6 to < 18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to Risankizumab of at least one year).

Final Protocol Submission:	June 2020
Trial Completion:	September 2025
Final Report Submission:	March 2026

The current applications are seeking approval for the treatment of patients 16 years of age and older with moderately to severely active CD. The Applicant submitted BLA 761262 for an IV dosage form intended only for the induction indication and BLA 761105/S-016 for a SC dosage form intended only for the maintenance indication. The Applicant received orphan drug designation for this product for treatment of pediatric CD. Therefore, both BLAs are exempt from PREA pediatric study requirements for the CD indication.

Adult Clinical Program

The clinical developmental program to support the CD indication consisted of the following three pivotal trials:

- Study M15-991: a 12-week IV induction trial in patients with a documented inadequate response or intolerance to at least 1 approved biologic
- Study M16-006: a 12-week IV induction trial in patients with or without a documented inadequate response or intolerance to at least 1 approved biologic

- Study M16-000: a 52-week SC maintenance trial of those enrolled in either induction trial who met the pre-specified definition of clinical responder

All three trials were randomized, double-blind, and placebo-controlled in design that relied on the CD activity index and endoscopic remission as the primary efficacy endpoints.

In the adult clinical program, the Applicant targeted enrollment of pediatric patients between the ages of 16 to 18 years with Tanner Stage 5 pubertal development. The protocols did not specify a minimum number of adolescents to be enrolled. Overall, a total of 14 adolescent patients with Tanner V development and weight greater than 40 kg were enrolled in the two induction trials, 3 of whom were subsequently enrolled in the maintenance trial. See Table 1 and 2. A single male patient between 16-18 years of age received the to be marketed initiation (600 mg IV) and maintenance (360 mg SC) dose.

Table 1. Demographic Characteristics of Enrolled Patients in Both Induction Trials

Characteristic	RZB 600 mg IV N=620	RZB 1200 mg IV N=577	Placebo IV N=432
Sex, n (%)			
Female	299 (48.2)	272 (47.1)	220 (50.9)
Male	321 (51.8)	305 (52.9)	212 (49.1)
Age, years			
Mean (SD)	39.2 (13.3)	38.3 (13.3)	38.2 (13.5)
Median (min, max)	37 (16, 79)	36 (16, 74)	35.5 (16, 80)
Age group, years, n (%)			
<18 years (n=14)	4 (0.6)	5 (0.9)	5 (1.2)

Source: Slide 31 January 6, 2022 Joint Assessment Meeting

Table 2. Demographic Characteristics of Enrolled Patients in the Maintenance Trial

Characteristic	RZB 180 mg SC Q8W N=179	RZB 360 mg SC Q8W N=179	Placebo SC Q8W N=184
Sex, n (%)			
Female	101 (56.4)	77 (43.0)	86 (46.7)
Male	78 (43.6)	102 (57.0)	98 (53.3)
Age, years			
Mean (SD)	39.4 (14.5)	37.9 (13)	38.3 (13.5)
Median (min, max)	37 (16, 75)	35 (16, 71)	37 (17, 76)
Age group, years, n (%)			
<18 (n=5)	1 (0.5)	2 (1.1)	1 (0.5)

Source: Source: Slide 31 January 6, 2022 Joint Assessment Meeting

There were no pediatric deaths in the three trials, and the treatment emergent adverse events (TEAEs) were similar between adolescent patients and adults enrolled in all three trials. Many reported TEAEs such as headache, nasopharyngitis, and influenza-like illness are already included in risankizumab drug labeling, and others such as arthralgia, arthropathy, and emesis were attributed by the review team to the underlying disease or intercurrent event.

The review team considered the approvability of the products in the adolescent population given the limited number of adolescent patients relative to adults enrolled in the clinical program. See Table 3.

Table 3. Demographic Characteristics of Pooled Safety Population

Characteristic	RZB 600 mg IV N=620	RZB 1200 mg IV N=577	Placebo IV N=432
Sex, n (%)			
Female	299 (48.2)	272 (47.1)	220 (50.9)
Male	321 (51.8)	305 (52.9)	212 (49.1)
Age, years			
Mean (SD)	39.2 (13.3)	38.3 (13.3)	38.2 (13.5)
Median (min, max)	37 (16, 79)	36 (16, 74)	35.5 (16, 80)
Age group, years, n (%)			
<18 years	4 (0.6)	5 (0.9)	5 (1.2)
≥18 years to <40 years	341 (55.0)	329 (57.0)	255 (59.0)
≥40 years to <65 years	244 (39.4)	219 (38.0)	150 (34.7)
≥65 years	31 (5.0)	24 (4.2)	22 (5.1)

Source: Slide 31 from December 14, 2021 Mid-Cycle Meeting

The population PK analysis showed no difference in PK between adolescent patients (n=5; ≥ 40 kg) and adults. The team discussed the generalizability of the safety data collected in adults down to 16 years of age given the similarity of observed AEs between the adults and adolescent patients included in the pooled safety analyses. However, the review team noted that approving the IV and SC products based on the limited adolescent data and reliance predominantly on data collected in adults would be inconsistent with the Division's requirement to enroll higher number of adolescent patients to support pediatric use of other products in development for the CD indication. FDA approved adalimumab and infliximab for pediatric CD in patients six years and older after initial approval in adults. The safety population comprising the adalimumab[1] pediatric program included 40 patients 16 to 17 years of age in the open-label induction phase and 32 patients in the placebo-controlled maintenance phase.[2] The pediatric infliximab[3] program

[1] BLA 125057

[2] Slide 40 January 6, 2022 Joint Assessment Meeting

[3] BLA 103772

enrolled approximately 15 patients 15 to 18 years of age, 7 of whom received the final to be marketed dose of infliximab. DPMH notes that adolescent approval of both adalimumab and infliximab for the CD indication was based on adolescent data collected after adult approval from pediatric trials that enrolled patients 6 to 17 years of age. Thus, PK, safety, and efficacy data collected in both adults and younger pediatric patients were likely leveraged to support adolescent approval of those products. (b) (4)

(b) (4)

Given the small sample size relative to other CD pediatric programs, the Division plans to limit approval of both the IV and SC dosage forms of Skyrizi to adults with CD with the plan to issue a pediatric post-marketing commitment (PMC) for the Applicant to conduct a randomized, blinded, controlled, dose-ranging trial to evaluate the safety and efficacy of Skyrizi in pediatric patients 2 to 17 years of age with CD. This approach is consistent with the Division's approach to other drugs and biologics in development for CD that have received orphan drug designation from FDA for this indication and are, therefore, exempt from PREA study requirements. Because the Applicant is not required to conduct a PMC, DPMH discussed other options with the Division to obtain the data needed to inform pediatric use of this product in CD. DPMH suggested the Division could encourage the Applicant to submit a Proposed Pediatric Study Request (PPSR) during PMC negotiations. Alternatively, DPMH stated that the Division could initiate issuance of a Written Request without a PPSR.

Because the Division plans to approve the IV and SC products in adults only, DPMH participation in labeling meetings focused on how to include a description of the limited adolescent data in product labeling. Because the review team had pooled the adolescent efficacy and safety data with the adult data, DPMH and the Division agreed that language and sample sizes described in Sections 6 and 14 of product labeling would include the adolescent cohort and added disclaimer language in these sections reiterating to prescribers that the product is not approved in patients less than 18 years of age. Based on the planned adult only approval, DPMH agrees that subsection 8.4 should state that the safety and effectiveness of Skyrizi have not been established in pediatric patients.

[4] (b) (4)

[5] (b) (4)

APPEARS THIS WAY ON ORIGINAL

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: January 28, 2022 **Date consulted:** September 24, 2021

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health, DPMH, ORPURM, OND

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

To: Division of Gastroenterology (DGE)

Drug: SKYRIZI (risankizumab-rzaa) injection (subcutaneous and intravenous)

BLA: 761262 (IND 118701)

- Non-NME original BLA for the intravenous (IV) induction dosing regiment for Crohn's Disease (CD)

761105 (IND 113306)

- Efficacy supplement sBLA for the subcutaneous (SC) maintenance dosing regiment for CD administrated via an On-Body Injector (OBI) with pre-filled cartridge (PFC)

Applicant: AbbVie

Subject: Pregnancy and Lactation Labeling Recommendations and Formatting

Approved Indication: For the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (approved under BLA 761105)

Proposed Indication: For the treatment of moderately to severely active Crohn's disease (CD) in patients aged 16 or older (BLA 761262 and BLA 761105)

Materials Reviewed:

- December 10, 2021, Amendment to BLA 761262 and 761105 to provide response to FDA's information request dated November 16, 2021
- September 24, 2021, DGE consult to DPMH for BLA 761105 and BLA 761262, PLLR, DARRTS Reference IDs 486277 and 4862754
- September 16, 2021, BLA 761262, Non-NME original BLA for the intravenous (IV) induction dosing regiment for CD
- September 16, 2021, BLA 761105, Efficacy supplement sBLA for the subcutaneous (SC) maintenance dosing regiment for CD administrated via an On-Body Injector (OBI) with pre-filled cartridge (PFC)
- April 27, 2020, DPMH-Biometrics-Epidemiology collaborative review of retrospective pregnancy cohort study protocol, DARRTS Reference ID 4595726
- January 31, 2020, DPMH-Biometrics-Epidemiology collaborative review of pregnancy registry protocol, DARRTS Reference ID 4554265

Consult Question: "DG kindly asks for a Maternal Health Team (MHT) review of the submitted PI to ensure appropriate compliance with the PLLR. DG asks that the assigned MHT reviewer initially confirm whether the Applicant included the necessary PLLR data."

INTRODUCTION

On September 16, 2021, AbbVie submitted BLA 761262, for SKYRIZI (risankizumab-rzaa) injection, a non-NME original BLA for the intravenous (IV) induction dosing regiment for CD, and BLA 761105, for SKYRIZI (risankizumab-rzaa) injection, an efficacy supplement, sBLA for the subcutaneous (SC) maintenance dosing regiment for CD administrated via an On-Body Injector (OBI) with pre-filled cartridge (PFC). The Division of Gastroenterology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on September 24, 2021, to assist with the Pregnancy and Lactation subsections of the SKYRIZI labeling.

BACKGROUND

Relevant Regulatory History

SKYRIZI (risankizumab-rzaa) injection was originally approved on April 23, 2019, as a subcutaneous injection for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy under BLA 761105.

Drug Characteristics

Table 1 – Risankizumab product characteristics

Drug class and mechanism[1]	Immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with IL-23 receptor. IL-23 is naturally occurring and involved in inflammation and immune responses.
Molecular Weight[1]	146,000 Daltons
Half-life[1]	28 days
Bioavailability[1]	89% following subcutaneous injection
Dosing regimen for plaque psoriasis[1]	150 mg
Dosing regimen for CD[2]	600 mg administered by IV infusion at week 1, week 4 and week 8 followed by 360 mg administered by subcutaneous injection at week 12 and every 8 weeks thereafter

Current State of the Labeling[1]

The risankizumab labeling was formatted into the PLR/PLLR format upon approval on April 23, 2019. DPMH was not involved in the original PLLR review. However, DPMH was involved in two protocol reviews for risankizumab for a prospective pregnancy registry and a retrospective cohort study both which are postmarketing requirements (PMRs) issued upon initial product approval.

- There is not a boxed warning on embryofetotoxicity
- There are no existing contraindications for pregnancy or lactation
- Serious adverse reactions: increased risk of infections
- Common adverse reactions include upper respiratory infections, headache, fatigue, injection site reaction and tinea infections
- Pregnancy: Limited available data with SKYRIZI use in pregnant women are insufficient to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. In animal reproduction studies in pregnant monkeys administered subcutaneous risankizumab-rzaa at 20 times the maximum recommended dose (2.5 mg/kg based on administration of a 150 mg dose to 60 kg individuals), increased fetal loss was noted. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. Maternal toxicity was not observed.
- Lactation: There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk.
- There are no existing pregnancy testing/contraception recommendation
- There are no known drug-drug interactions with hormonal contraceptives

[1] BLA 761105. April 26, 2021, FDA approved labeling.
[2] Current proposed dosing and administration not yet approved.

REVIEW

PREGNANCY

Crohn's disease (CD) and Pregnancy

- Crohn's disease (CD) is an inflammatory bowel disease (IBD) which is an autoimmune condition that often occurs in women of reproductive potential. During pregnancy it is important to optimize disease management and pregnancy outcomes by the continuation of treatment.[3] IBD includes Crohn's disease (CD) and ulcerative colitis (UC). Approximately 0.5% of the United States population (1.6 million people) have IBD and approximately half of those are females.[4]
- The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine make the following recommendations:
    - "Many commonly prescribed drugs can be used safely during pregnancy without risk of teratogenicity or pregnancy complications, whereas a few are strictly contraindicated."[3]
    - "Decision making regarding patient plans should be individualized and shared and should include consideration of pregnancy and maternal risks associated with untreated disease."[3]
    - "In general, immunomodulating drugs that are not contraindicated in pregnancy are compatible with breastfeeding. Health care providers are encouraged to use LactMed to find the most up-to-date information for counseling."[3]
- Concerns related to IBD during pregnancy include impact on maternal and fetal outcomes. One of these concerns includes disease flareup which complicates 30 to35% of pregnancies. According to the *American Gastroenterological Association IBD Parenthood Project Working Group,* a meta-analysis of 14 studies found a higher risk of active disease during pregnancy in patients who had active disease during conception compared to those in remission at conception.[4,5] These results are consistent with a multicenter European cohort study demonstrating that 14% of patients in remission at conception relapsed during pregnancy; however, 26% of patients with active disease at conception remained with active disease until delivery.[6] Increased rates of preterm birth as associated with active disease. Likewise, in a Danish cohort study on the impact of CD on birth outcomes, preterm birth risk was 2-times

[3] The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine. ACOG Committee Opinion. Number 776. Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Immune Modulating Therapies in Pregnancy and Lactation. Vol. 133, No. 4, April 2019.

[4] Mahadevan U, C Robinson, N Bernasko et al. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group. Gastroenterology 2019; 156:1508-1524.

[5] Abhyankar A, Ham M, Moss AC. Meta-analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:460– 466.

[6] Bortoli A, Pedersen N, Duricova D, et al, Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003– 2006. Aliment Pharmacol Ther 2011;34:724–734.

higher in women with low to moderate-high disease activity during pregnancy compared to those without active disease.[7]
    - In addition, active perianal disease, which presents as anorectal fistula/abscess, rectovaginal fistula, anal fissure or anal stenosis, holds a 10-fold increased risk of 4th degree laceration when active disease is present in pregnant patients with CD.[8]
- Treatment guidelines for IBD during pregnancy and lactation from the American Gastroenterological Association IBD Parenthood Project 2019 Working Group can be viewed in Appendix A (Table A-1).[4]

Nonclinical Experience

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition, and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. [9]

DPMH discussed the relevance of the animal reproduction study findings in monkeys with the DG Pharmacology/Toxicology Team. The Pharmacology/Toxicology Team noted that although risankizumab is an anti-human IL-23 monoclonal antibody, the binding affinity of risankizumab to cynomolgus monkey is similar or slightly higher than that observed in humans. Adverse findings in the monkey pre- and post-natal development study are considered related to treatment with the product and are most likely relevant to humans.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of available published literature regarding Skyrizi use during pregnancy. Refer to applicant's submission for search parameters.[10] The applicant identified five articles described in Appendix B (Table B-1). Only one of the five articles includes risankizumab use and pregnancy. The article describes risankizumab use in healthy subjects in a pharmacokinetic comparability, immunogenicity and tolerability study in which one female subject reported a first trimester spontaneous abortion on day 112 after risankizumab 90 mg subcutaneous administration at approximately 9 weeks gestation.[10,11] The subject was currently using an intrauterine device during conception and no other medications were reported.[11,11] The subject had a reported history of caesarean

[7] Norgard B, Hundborg HH, Jacobsen BA, et al. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol 2007;102:1947–1954.
[8] Hatch Q, Champagne BJ, Maykel JA, et al. Crohn's disease and pregnancy: the impact of perianal disease on delivery methods and complications. Dis Colon Rectum 2014;57:174–178.
[9] BLA 761105 Multi-disciplinary Review and Evaluation, April 23, 2019, DARRTS Reference ID 4422774.
[10] December 10, 2021, Amendment to BLA 761262 and 761105 to provide response to FDA's information request dated November 16, 2021.
[11] Lon HK, Cheng L, Nudurupati S, et al. Pharmacokinetic comparability of risankizumab formulations in prefilled syringe and auto-injector for subcutaneous injection. Clin Ther. 2021;43(3):629-36.

section, live-birth, mammoplasty and premature delivery.[11,11] No further details were provided. This case is also included in the pharmacovigilance/clinical trial data described below.

DPMH's Review of Literature
DPMH conducted a search of published literature using PubMed and Embase regarding risankizumab exposure during pregnancy using the following search terms, "risankizumab and fetal malformations," "risankizumab and spontaneous abortion and miscarriage," "risankizumab and embryo-fetotoxicity." No additional data were found.

There are no additional data for review in Micromedex[12] or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.[13]

Review of Pharmacovigilance Database
The applicant provided a summary of pregnancy outcomes from the AbbVie Pharmacovigilance Database which includes cases from clinical trials and also post-marketing reports summarized below.

Clinical Trial Reports of Pregnancy Outcomes
Sixty reports of pregnancy were recorded from risankizumab clinical trials. Refer to summary table below and specific case summaries in Appendix C.

Table 2. Summary of Pregnancy Outcomes from Clinical Trial Reports
(copied from Table 3, page 9, applicant's submission)[10]

Maternal Exposure Outcomes	Psoriasis	Crohn's Disease	Other Indications (HS, AS)	Healthy Volunteers	Total
Live birth without congenital anomaly (Table 6)	12	6	0	0	18
Spontaneous abortion (Table 5)	5	5	0	1	11
Elective termination (fetal defects) (Table 4)	1	1	0	0	2
Elective termination with no fetal defects	5	5	2	0	12
Ongoing pregnancy	1	6	1	1	9
Subject lost to follow up	5	3	0	0	8
Total	**29**	**26**	**3**	**2**	**60**

AS = ankylosing spondylitis; HS = hidradenitis suppurativa.

No maternal exposure pregnancies occurred in the psoriatic arthritis clinical studies.

[12] Risankizumab. Truven Health Analytics LLC. Micromedex.
[13] Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi.

Post-marketing Reports
Refer to Appendix D for case specifics

- 188 post-marketing reports of maternal pregnancy through November 19, 2021
  - n=159 psoriasis indication
  - n=29 no indication reported
- 14 spontaneous abortions
- 80 pregnancies ongoing at time of report
- 74 pregnancies just past their due date and follow-up not yet completed
- 5 elective terminations with no fetal defects (no reasons given)
- 15 reports of live-birth without congenital anomaly

In summary, there are currently 33 reports of live-births (18 from clinical trials and 15 from post-marketing reports) with risankizumab exposure within five half-lives of the last menstrual period through 8 weeks gestation. There are no reports of congenital anomalies in the live-births.

Drug Utilization Rates Amongst Females of Reproductive Potential
The applicant provided an estimation of risankizumab use amongst females of reproductive age 15-44 years using *The Symphony Health Solutions IDV (Integrated Dataverse)*. From April 1, 2019, through September 30, 2021, a total of 39,503 risankizumab users were identified, 36.6% females between 15-44 years. See table below provided by applicant.

Table 3. Risankizumab Drug Utilization Rates Amongst Females of Reproductive Potential
(copied from Table 12, page 41, applicant's submission)[10]

	Females		Males		Total	
Age (Years)	Number of Patients	%	Number of Patients	%	Number of Patients	%
0 – 14	-	-	3	0.01	3	0.01
15 – 44	**7082**	36.59	7977	39.60	15,059	38.12
45 – 64	9463	48.89	9722	48.26	19,185	48.57
65 – 74	2176	11.24	1952	9.69	4,128	10.45
75 +	636	3.29	492	2.44	1,128	2.86
Total	**19,357**	**49.00**	**20,146**	**51.00**	**39,503**	**100**

* Symphony Health Solutions is representative of > 90% of the patient exposure in the US.

Reviewer comment:
The applicant's PLLR submission is adequate for review. See Discussion and Conclusions section for DPMH's recommendations regarding the data.

LACTATION
Nonclinical Experience
There are no available non-clinical lactation data with regard to risankizumab exposure during breastfeeding.

Review of Literature

The applicant as well as DPMH conducted a review of published literature with regard to risankizumab and lactation, and no data were found. In addition, there are no additional data for review in *Drugs in Pregnancy and Lactation* by Briggs and Freeman,[13] *Medication and Mothers Milk*,[14] or LactMed.[15]

Review of Pharmacovigilance Database

The applicant provided summaries of five case reports from their global safety database that were reported as risankizumab exposure and breast milk. See table below. No serious adverse events related to breastfeeding were reported.

Table 4. Report of Exposure During Breastfeeding from Pharmacovigilance Database
Copied from Table 9, page 37, applicant's submission)[10]

AER/Source	Age/Gender	Preferred Terms	Comment
3400632 PM Solicited	NR/NR	Exposure via breast milk	The report contains limited information on maternal risankizumab therapy dates and its temporality with breastfeeding duration. No adverse event related to breastfeeding is reported.
4036658 PM Solicited	NR/NR	Exposure via breast milk, Foetal exposure during pregnancy, Ear infection	The report contains limited information on maternal risankizumab therapy dates and its temporality with breastfeeding duration. The infant had a non-serious event of ear infection on an unknown date; ear infection events are common in infants.
3802453 PM Solicited	7 months/NR	Exposure via breast milk	The report contains limited information on maternal risankizumab therapy dates and its temporality with breastfeeding duration. No adverse event related to breastfeeding is reported.
3813044 PM Solicited	NR/NR	Diarrhoea, Exposure via breast milk	The report contains limited information on maternal risankizumab therapy dates and its temporality with breastfeeding duration. The infant experienced a non-serious event of diarrhea, a non-specific event, common in neonates, on an unknown date.
4125355 PM Solicited	NR/NR	Exposure via breast milk	Maternal use of risankizumab was ongoing at the time of breastfeeding; however, exact therapy dates as well as breastfeeding duration are unknown. No adverse event related to breastfeeding is reported.

AER = adverse event report; PM = post-marketing; NR = not reported.

Reviewer comment:
The applicant's PLLR submission is adequate for review. The reader is referred to the Discussion and Conclusions section for DPMH's recommendations.

[14] Medication and Mothers Milk. Hale, Thomas. www.halesmeds.com, accessed December 30, 2021.
[15] http://toxnet.nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No effects on male fertility parameters were observed in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab once weekly for 26 weeks. There were no adverse findings in female cynomolgus monkeys.[9]

Review of Literature

The applicant as well as DPMH conducted a review of available published literature with regard to risankizumab and females of reproductive potential, and no data were found.

Review of Pharmacovigilance Database

The applicant conducted a search of their global safety database through November 19, 2021, with regard to risankizumab exposure and fertility. See summary below:

Reports of Male Related Fertility Disorders

1. Haematospermia
    a. 37-year-old male with psoriasis reported blood in semen; no medical history reported; details and timing of exposure not reported
2. Infertility
    a. Unknown age; psoriasis indication; no medical history reported; patient and wife reported trying to conceived second child and unsuccessful; details and timing of exposure not reported

Reports of Female Related Fertility Disorders

The applicant located 45 reports in their database classified as fertility related disorders; however, upon review there is no indication that any of the reported issues are related to risankizumab exposure. See summary below:

- 17 irregular menstruation
- 14 amenorrhea
- 5 menstruation delayed
- 3 oligomenorrhea
- 2 hypomenorrhea
- 2 polycystic ovaries
- 1 uterine bleeding
- 1 fallopian tube obstruction
- 1 female infertility
- 1 uterine adhesions

Overall, there is not enough data to assess for risankizumab causation and fertility disorders.

Reviewer comment:
The applicant's PLLR submission is adequate for review. The reader is referred to the Discussion and Conclusions section for DPMH's recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Risankizumab injection was originally approved on April 23, 2019, as a subcutaneous injection for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Risankizumab is currently under review for intravenous (IV) induction therapy for the treatment of Crohn's disease and subcutaneous maintenance therapy for Crohn's disease. In animal reproduction studies in cynomolgus monkeys, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. Based on input from the DG Pharmacology/Toxicology Team, the binding affinity of risankizumab to cynomolgus monkey is similar or slightly higher than that observed in humans. Therefore, adverse findings in the monkey pre- and post-natal development study are considered related to treatment with the product and are most likely relevant to humans.

Review of available human data of risankizumab exposure during pregnancy from clinical trials and the applicant's pharmacovigilance database are insufficient to establish a risk of spontaneous abortion, congenital anomaly or maternal or fetal adverse reactions. Risankizumab is a typical IgG1 monoclonal antibody. In discussion with FDA Clinical Pharmacologist, Yow-Ming Wang, DPMH agrees that risankizumab should behave similarly to endogenous IgG1. Therefore, similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under 8.1 Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the in-utero exposed infant and the risks and benefits that should be considered prior to administration of live vaccines. In discussion with the DG Clinical Pharmacology Team, DPMH agrees that live vaccines should be delayed for a minimum five months (half-life of 28 days x5) after birth.

Upon initial approval, the applicant was issued two postmarketing requirements (PMRs) for pregnancy related studies with risankizumab. One study is a pregnancy registry (PMR 3494-2) and the other a database study. The first interim annual report for both studies is expected in June 2022. The applicant is also proposing to conduct an additional pregnancy registry study in women with Crohn's disease treated with risankizumab. DPMH recommends that DGE issue two new pregnancy study PMRs to identify an unexpected serious risk for adverse pregnancy, fetal, or infant outcomes from the use of risankizumab during pregnancy in females regardless of indication. The first PMR requires a registry for prospective collection of detailed clinical information about pregnancy exposures and outcomes. The second PMR requires a complementary retrospective cohort study in an appropriate database in order to offset the typically slow accrual to pregnancy registries. The reader is referred to specific PMR language below.

Lactation

There are no available animal data with regards to risankizumab-rzaa exposure and breastfeeding. There were cases reported to the applicant's pharmacovigilance database of drug exposure during breastfeeding; however, upon review there are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production among the reports. The molecular weight for risankizumab is 146,000 Daltons, and according to breastfeeding experts, the amount in human milk, if any, is expected to be very low. Risankizumab is a typical IgG1 monoclonal

antibody. In discussion with FDA Clinical Pharmacologist, Yow-Ming Wang, DPMH agrees that risankizumab should behave similarly to endogenous IgG1. Therefore, similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under 8.2 that notes: "Maternal IgG and monoclonal antibodies are known to be present in human milk."

DPMH recommends the issuance of a postmarketing requirement (PMR) for a clinical lactation study with risankizumab to inform labeling. Risankizumab is used in females of reproductive age, and there are no current data available to inform women of risankizumab use during breastfeeding. Refer to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 9, 2019. https://www.fda.gov/media/124749/download.

Females and Males of Reproductive Potential

No effects were seen on male fertility parameters in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab. There were no adverse findings in female cynomolgus monkeys. Although there are cases reported to the applicant's pharmacovigilance database that are coded as fertility-related, it does not appear that any of the outcomes are directly related to risankizumab exposure.

POSTMARKETING REQUIREMENT (PMR)

1. A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumb-containing products regardless of indication during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.
2. An additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to risankizumb- containing products regardless of indication during pregnancy compared to an unexposed control population.
3. Perform a lactation study (milk only) in lactating women who have received risankizumab to assess concentrations of risankizumab in breast milk using a validated assay and to assess the effects on the breastfed infant.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (6)

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

APPENDICES
APPENDIX A – IBD treatment in pregnancy guidelines
APPENDIX B – Applicant's Literature Search Results
APPENDIX C – Clinical Trial Reports of Pregnancy Outcomes
APPENDIX D – Pharmacovigilance Reports

APPENDIX A – IBD treatment in pregnancy guidelines from the 2019 American Gastroenterological Association IBD Parenthood Project Working Group

Table A-1. IBD maintenance therapy recommendations during pregnancy and lactation
(copied from Table 2. Page 8, Mahadevan U, C Robinson, N Bernasko et al 2019)[4]

APPEARS THIS WAY ON ORIGINAL

Medication	Maintenance dosing recommendation	Breastfeeding considerations
Aminosalicylates	Maintain prepregnancy dosing	
Mesalamine	All preparations are now phthalate-free	Compatible with breastfeeding No preparation preference Monitor infant for diarrhea
Sulfasalazine	Consider 2-mg folate supplement in pregnancy Azulfidine EN contains phthalate	Compatible with breastfeeding Mesalamine preferred
Immunomodulators	Dosing may be altered due to increased renal clearance with pregnancy. Therapeutic drug monitoring recommended	Routine infant monitoring not necessary
Cyclosporine (calcineurin inhibitor)	Limited data in pregnancy suggest associations with hypertension, gestational diabetes, preterm birth, low birthweight/SGA. Used as a salvage therapy.	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Methotrexate	Contraindicated in pregnancy. Stop 3 months before conception.	Limited human data. Not advised.
Thiopurines (azathioprine, 6-mercaptopurine)	Continue as monotherapy In appropriate patients, consider cessation of thiopurine as combination therapy, given possible association with increased infant infections. Use with caution in combination with allopurinol, which carries potential embryo toxic effects	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Small molecules		
Tofacitinib	Limited human data. Consider other options, particularly in first trimester	Limited human data. Not advised.
Biologics	Maintain prepregnancy dosing Continue dosing throughout all 3 trimesters If possible, plan final dose according to drug half-life to minimize transfer	Compatible with breastfeeding Encourage participation in pregnancy registries if not already done during pregnancy.
Adalimumab	Plan final pregnancy injection 2–3 wk before EDC and resume postpartum[a] (1–2 wk if weekly dosing)	
Certolizumab pegol	May continue scheduled dosing throughout pregnancy.	
Golimumab	Plan final pregnancy injection 4–6 wk before EDC and resume postpartum[a]	
Infliximab	Plan final pregnancy infusion 6–10 wk before EDC and resume postpartum[a] (If every-4-wk dosing, then 4–5 wk before EDC) Base dosing on prepregnancy weight during pregnancy and immediate postpartum	
Natalizumab	Plan final pregnancy infusion 4–6 wk before EDC and resume postpartum[a]	
Ustekinumab[b]/ Vedolizumab[b]	Plan final pregnancy dose 6–10 wk before EDC and resume postpartum[a] (If every-4-week dosing, then 4–5 wk before EDC)	
Corticosteroids	Reserved for active flares in pregnancy. Not recommended for planned maintenance therapy during pregnancy.	Compatible with breastfeeding Subtherapeutic infant exposure expected, even with flare dosing Avoiding feeding 1–2 h post-dose (non-enteric coated forms) can further minimize exposure but is not necessary
Antibiotics	Reserved for perianal disease and pouchitis and not recommended for planned maintenance therapy (amoxicillin/metronidazole preferred over ciprofloxacin)	Amoxicillin/clavulanic acid compatible with breastfeeding Ciprofloxacin preferred over metronidazole

EDC, estimated date of confinement; SGA, small for gestational age.
[a]48 hours post-delivery
[b]Limited pregnancy data

APPENDIX B – Applicant's Literature Search Results

Table B-1. Summary of Literature (copied from applicant' submission Table 2, pages 5-7)[10]

Publication Date/ Authors	Article Title	Type of study/ article	Number of patients exposed/ unexposed	Objective/End Points	Comment/ Outcomes
May-June 2021 Russo, R.; Gasparini, G.; Cozzani, E.; Burlando, M.; Parodi, A.[1]	Considerations on inhibition of IL-23 in psoriatic women of childbearing potential	Review article	N/A for risankizumab	To review use of anti-IL-23 drugs in treatment of psoriasis in women of childbearing age	This review article highlights the lack of safety data to provide guidance on the use of IL-23 inhibitors for the treatment of psoriasis during pregnancy. Post hoc analyses of pregnant women from tildrakizumab and guselkumab psoriasis clinical trials had similar rates of spontaneous abortions compared to the general population.[2,3] There was no data on pregnant patients retrieved from clinical trials for risankizumab in psoriasis (IMMvent, UltIMMa-1 and -2, IMMhance). Based on the limited sample sizes mentioned for tildrakizumab (n = 14), guselkumab (n = 2) and risankizumab (n = 0) the authors recommend terminating IL-23 therapy during pregnancy.
March 2021 Kimball, A. B.; Guenther, L.; Kalia, S.; De Jong, E. M. G. J.; Lafferty, K. P.; Chen, D. Y.; Langholff, W.; Shear, N. H.[4]	Pregnancy Outcomes in Women with Moderate-to-Severe Psoriasis from the Psoriasis Longitudinal Assessment and Registry (PSOLAR)	Cohort study	N/A for risankizumab	To report pregnancy outcomes observed in the Psoriasis Longitudinal Assessment and Registry (PSOLAR)	The objective of the article is to report pregnancy outcomes observed in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) for treatments manufactured by the study sponsor (Janssen) including ustekinumab, infliximab, and golimumab. Therefore, exposure to biologic therapy was collected specifically for these drugs, while other biologics used to treat psoriasis were combined and reported as 'other biologic' treatment arm. No specific data on risankizumab was included in the publication. The authors concluded that pregnancy outcomes among women with moderate-to-severe psoriasis are consistent with previously reported data and the general population.

Publication Date/ Authors	Article Title	Type of study/ article	Number of patients exposed/ unexposed	Objective/End Points	Comment/ Outcomes
January 2021 Lon, H K; Cheng, L; Nudurupati, S; Loebbert, R; Duan, R; Kalabic, J; Pang, Y N[5]	Pharmacokinetic Comparability of Risankizumab Formulations in Prefilled Syringe and Auto-injector for Subcutaneous Injection	Bioequivalence pharmacokinetic study (Single dose)	226	To evaluate the pharmacokinetic comparability, immunogenicity, and tolerability of the risankizumab 90 mg/mL prefilled syringe (PFS) and the risankizumab 150 mg/mL PFS and auto-injector (AI) in healthy subjects	There was 1 adverse event of spontaneous abortion reported in a pregnant subject on Day 112 after risankizumab 90 mg/mL PFS, 150 mg (75 mg x2) subcutaneous administration. Note: The study was sponsored by AbbVie. This subject is described in Table 5 (AER 2912345; M15-990 Subject (b) (6))
May 2018 Rawla, P.; Sunkara, T.; Raj, J. P.[6]	Role of biologics and biosimilars in inflammatory bowel disease: Current trends and future perspectives	Review article	N/A for risankizumab	To summarize clinical pharmacology, indications for inflammatory bowel disease, usage in pregnancy and lactation, and adverse events of current biologics (tumor necrosis factor-alpha, integrins, and IL-12 and/or IL/23 inhibitors.	Risankizumab is mentioned as a pipeline biologic in this article with no further discussion on pregnancy or lactation
March 2018 Carrascosa, J.M.; Del-Alcazar, E.[7]	New therapies versus first-generation biologic drugs in psoriasis: a review of adverse events and their management	Review article	N/A for risankizumab	To review adverse events associated with the biologic agents currently available for the treatment of psoriasis and the new inhibitors targeting the p19 subunit of the IL-23 and IL-17A receptor. The review covers injection site reactions, infections, cardiovascular events, demyelinating disorders, tumours, class effects secondary adverse events, immunogenicity, safety in pregnancy and vaccines efficacy.	This review includes a brief summary of the safety in pregnancy of biologic agents approved for the treatment of psoriasis. While this article highlights the sparse data in pregnant females using etanercept, infliximab, adalimumab, certolizumab, ustekinumab, secukinumab and ixekinumab, it did not mention the role of risankizumab in pregnancy. Risankizumab is discussed briefly in another adverse event section, unrelated to pregnancy.

AI = autoinjector; IL = interleukin; N/A = not applicable; PFS = pre-filled syringe.

APPENDIX C – Clinical Trial Reports of Pregnancy Outcomes

Table C-1. Clinical Trial Reports of Elective Termination with Fetal Defects
(copied from Table 4, page 10-12, applicant's submission)[10]

AER Protocol/Patient No. Country	Age (years) Indication	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Comment
1666976 1311.2/ (b) (6) USA	39 PsO	2 miscarriages (pregnancy from in vitro fertilization (IVF) treatment)	RZB 18 mg: (b) (6) First trimester	(b) (6)	19	Subject underwent IVF due to infertility. Two IVF treatments resulted in pregnancy followed by early miscarriage. For the third IVF pregnancy, an anatomic abnormality suggestive of a **chromosome 21 defect** was identified on ultrasound at Week 19. No genetic test results were reported. Subject decided to undergo induced abortion due to high risk of genetic abnormalities given the advanced maternal age. The investigator and the sponsor assessed this event as having no reasonable possibility of being related to risankizumab. Risk factors: Advanced maternal age may increase the risk for chromosomal defects. Based on the biophysical nature of monoclonal antibodies and the mode of action of risankizumab, it is not expected that these substances would cause genotoxicity, as outlined in ICH guideline S6 (R1).

Table C-1 continuation

AER Protocol/Patient No. Country	Age (years) Indication	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Comment
2104977 1311.2 (M15-989)/ (b) (6) UK	24 CD	N/A	RZB 180 mg SC: (b) (6) First Trimester	(b) (6)	14	Subject's concomitant medications included nortriptyline (indication not reported) and desogestrel. At 12 weeks gestation screening test, an ultrasound revealed a nuchal translucency measuring 8.7 mm, a cystic hygroma and early hydrops with the fluid extending down the fetal back. Chromosomal analysis from chorionic villus sampling was normal, and human parvovirus testing was not suggestive of an acute infection. Subject underwent elective termination at 14 weeks of gestation.

Table C-1 continued. Case below continuation from above case patient M115-989

AER Protocol/Patient No. Country	Age (years) Indication	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Comment
						The event was assessed by the investigator with reasonable possibility of relationship to study drug. The sponsor assessed this event with no reasonable possibility of being related to risankizumab based on published data that IgG antibody is actively transported from mother to fetus via Fc receptors on the syncytiotrophoblast that appear after Week 14 of gestation and the active transportation of IgG antibodies starts in the second trimester, increasing throughout the third trimester. The absence of Fc-receptors in the first trimester indicates that the fetus in this period is not exposed to IgG class monoclonal antibodies during the period of organogenesis (between Weeks 3 and 8) and therefore the risk of mutagenic and teratogenic effects from maternal exposure to an IgG class antibody is negligible.[8-10] After discontinuation from Study M15-989, this subject experienced spontaneous abortion from a subsequent pregnancy almost 5 months after last elective termination, which was well beyond the risankizumab five half-lives, suggesting a maternal profile at a higher risk of adverse pregnancy outcomes.

AER = adverse event report; CD = Crohn's disease; PsO = psoriasis, EDC = estimated due date; IgG = immunoglobulin; IVF = in vitro fertilization; LMP = last menstrual period; RZB = risankizumab; SC = subcutaneous.

Table C-2. Clinical Trial Reports of Spontaneous Abortion
(copied from Table 5, page 13-17, applicant's submission)[10]

AER Protocol/Patient No. Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Risk Factors
Crohn's Disease						
3964906 M16-000/ (b) (6) Japan	36	N/A	RZB 360 mg SC: (b) (6) Preconception (14 weeks after last dose)	(b) (6)	6	Advanced maternal age, active Crohn's disease
3253414 M16-000 (b) (6) Belgium	32	Anaemia, Cervical conisation, Cervical dysplasia, Ex-tobacco user (1 cig/day for 2 years; stopped 2010), Haemoglobin decreased, Term baby	RZB 180 mg SC: (b) (6) Preconception	NR NR (b) (6)	NR	Prior history of conization and anemia

Table C-2. continued

AER Protocol/Patient No. Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Risk Factors
Crohn's Disease						
3979446 M16-000 (b) (6) USA	33	Premenstrual dysphoric disorder	RZB 360 mg SC: (b) (6) RZB 1200 mg IV and RZB 360 mg SC: (b) (6) First trimester	(b) (6)	8	N/A
2495052 M15-989 (b) (6) UK **Note: this is the same subject described in Table 4 of elective termination with fetal defects*	24	N/A	RZB 180 mg SC: (b) (6) Preconception	NR (for all dates)	NR	N/A

Table C-2. continued

AER Protocol/Patient No. Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Risk Factors
Crohn's Disease						
2589313 M15-991 (b) (6) USA	39	Abortion spontaneous, Caesarean section, Depression, Dysmenorrhoea, Iron deficiency anaemia, Mammoplasty, Oophorectomy, Pelvic adhesions, Uterine dilation and curettage	RZB 600 mg IV: (b) (6) RZB 360 mg SC: (b) (6) First trimester	(b) (6)	4	Advanced maternal age, pelvic adhesions, prior history of spontaneous abortion and oophorectomy
Psoriasis						
3431742 M15-997/ (b) (6) USA	26	Thalassaemia	RZB 150 mg SC: (b) (6) Preconception (8 weeks since last dose)	(b) (6)	9	Medical history of thalassaemia

Table C-2. continued

AER Protocol/Patient No. Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Risk Factors
Psoriasis						
2322800 M15-997 (b) (6) USA	36	Anaemia, Hypertension	RZB 150 mg SC:12- (b) (6) First trimester	NR NR (b) (6)	NR	Advanced maternal age and medical history of hypertension, and anemia
1998385 1311.3 (b) (6) USA	30	Spontaneous abortion	RZB 150 mg SC: (b) (6) Preconception (9 weeks since last dose)	(b) (6)	4	Prior history of spontaneous abortion
2440567 M15-997 (b) (6) Germany	31	Spontaneous abortion, Ex-tobacco user (8 cigs/day for 13 years; stopped 2016)	RZB 150 mg SC: (b) (6) First trimester	(b) (6)	11	Prior history of spontaneous abortion, and tobacco use

Table C-2. continued

AER Protocol/Patient No. Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date/ EDC Date/ End of Pregnancy Date	Gestational Age (weeks)	Risk Factors
Psoriasis						
1691187 1311.3 (b) (6) Australia	35	Fallopian tube disorder, Current tobacco user (quantity NR)	RZB 150 mg SC: (b) (6) First trimester	(b) (6)	8	Medical history of fallopian tube disorder and tobacco use
Healthy Volunteer						
2912345 M15-990 (b) (6) USA	30	Caesarean section, Live birth, intrauterine device (type and name not reported), Mammoplasty, Premature baby	RZB 90 mg SC: (b) (6) Preconception (9 weeks since last dose)	(b) (6)	9	Pregnancy in the context of an intrauterine device which can be a risk factor for spontaneous abortion.

AER = adverse event report; EDC = estimated due date; IV = intravenous; LMP = last menstrual period; NR = not reported; N/A = not applicable; RZB = risankizumab; SC = subcutaneous.

APPENDIX D – Pharmacovigilance Reports

Table D-1. Post-marketing Reports of Spontaneous Abortion
(copied from Table 7, page 27-30, applicant's submission)[10]

AER Source Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date EDC Date End of Pregnancy Date/	Gestational age (weeks)	Risk Factor
3504915 PM Solicited Canada	30	NR	RZB 150 mg SC: (b) (6) NR	NR NR (b) (6)	NR	Medical history not reported
3757826 PM Solicited USA	NR	NR	NR NR	NR (for all dates)	NR	Maternal age and medical history not reported
3534136 PM Solicited Canada	26	NR	RZB 150 mg SC: (b) (6) (b) (6) First trimester	NR NR (b) (6)	NR	Medical history not reported
3424628 PM Solicited USA	NR	Abstains from alcohol, Non-tobacco user	RZB unk dose: NR to (b) (6) Unk	NR (for all dates)	NR	Maternal age and medical history not reported

Table D-1 continued

AER Source Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date EDC Date End of Pregnancy Date/	Gestational age (weeks)	Risk Factor
3615165 PM Solicited USA	36	NR	RZB unk dose: (b) (6) NR	NR NR (b) (6)	NR	Advanced maternal age
3843395 PM Solicited USA	NR	NR	(b) (6) NR	NR (for all dates)	NR	Maternal age and medical history not reported
3600987 PM Spontaneous Germany	34	Previous pregnancy (outcome NR)	RZB 150 mg SC: (b) (6) First trimester	NR (for all dates)	8	Medical history not reported
3860162 PM Solicited USA	NR	NR	RZB 150 mg SC: NR to (b) (6) Unk	NR (for all dates)	NR	Maternal age and medical history not reported

Table D-1 continued

AER Source Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date EDC Date End of Pregnancy Date/	Gestational age (weeks)	Risk Factor
3793243 PM Spontaneous Brazil	29	Abortion, Ascites, Hepatic cirrhosis, Hospitalisation	NR NR	NR NR (b) (6)	NR	Prior history of abortion
3922996 PM Solicited Canada	32	NR	RZB 150 mg SC: (b) (6) First trimester	NR (for all dates)	11	Maternal age and medical history not reported
3002018 PM Solicited Canada	30	NR	RZB 150 mg SC: (b) (6) Preconception (6 weeks after last dose)	(b) (6)	11	Medical history not reported
3318825 PM Solicited USA	35	Spontaneous abortion, Ectopic pregnancy, Gestational diabetes, Ex-obacco user (1-2 cigs/day for 13 years; stopped 2017)	RZB 150 mg SC: (b) (6) NR	NR (for all dates)	NR	Elderly gravida (history of 3 previous miscarriages. Two of these pregnancies considered high risk with gestational diabetes). Medical history of tobacco use

Table D-1 continued

AER Source Country	Age (years)	Relevant Medical History	Therapy Dates Time to Exposure	LMP Date EDC Date End of Pregnancy Date/	Gestational age (weeks)	Risk Factor
2895118 PM Solicited USA	NR	NR	NR NR	NR (for all dates)	NR	Maternal age and medical history not reported
3788823 PM Solicited USA	NR	NR	NR NR	NR (for all dates)	NR	Maternal age and medical history not reported

AER = adverse event report; EDC = estimated due date; LMP = last menstrual period; NR = not reported; PM = post-marketing; Unk = unknown; RZB = risankizumab; SC = subcutaneous.

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/s/

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01/28/2022 04:12:29 PM

LYNNE P YAO
01/31/2022 09:04:08 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)

Date of This Memorandum:	January 14, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761262; BLA 761105/S-016
Product Name and Strength:	Skyrizi (Risankizumab-rzaa) injection, 600 mg/10 mL (60 mg/mL) Skyrizi (Risankizumab-rzaa) Injection, 360 mg/2.4 mL (150 mg/mL)
Applicant/Sponsor Name:	Abbvie Inc
OSE RCM #:	2021-1835-1; 2021-1864-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 11, 2022 for Skyrizi. Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Skyrizi (Appendix A) to determine if it is 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

[a] Vee, S. Label and Labeling Review for Skyrizi (BLA 761262; BLA 761105/S-016). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 06. RCM No.: 2021-1835; 2021-1864.

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

SARAH K VEE
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IDALIA E RYCHLIK
01/14/2022 12:13:10 PM

LABLE 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:	January 6, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761262; BLA 761105/S-016
Product Name, Dosage Form, and Strength:	Skyrizi (Risankizumab-rzaa) injection, 600 mg/10 mL (60 mg/mL) Skyrizi (Rizankizumab-rzaa) Injection, 360 mg/2.4 mL (150 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Abbvie Inc
FDA Received Date:	September 16, 2021
OSE RCM #:	2021-1835; 2021-1864
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

Abbvie Inc submitted a non-NME BLA (BLA 761262) for Skyrizi (Risankizumab-rzaa) injection for the proposed indication for the treatment of moderate to severely active Crohn's disease in patients aged 16 years and older for the intravenous induction dosing regimen. In addition, Abbvie submitted an efficacy supplement for BLA 761105 for the same indication for the subcutaneous maintenance dosing regimen. Subsequently, the Division of Gastroenterology (DG) requested that we review the proposed Skyrizi prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Skyrizi (BLA 761105) was approved on April 23, 2019 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The initial approval was for the 75 mg/0.83 mL single-dose prefilled syringe (PFS). Subsequently, 150 mg/mL PFS and autoinjector were approved on April 26, 2021.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

For BLA 761262, the induction dosing regimen for CD includes the intravenous route of administration using the new presentation of a single dose vial (600 mg/10 mL). The vial presentation should be prepared and administered by a healthcare provider. For the efficacy supplement BLA 761105/S-016, the new presentation of an On-Body Injector (OBI) with the pre-filled cartridge (PFC) may be injected by the patient after training on the proper use of the device. The Applicant proposes one PI for the addition of the new indication and the proposed

new device presentations. It is an accepted practice to have one PI for multiple indications and dosage forms and for this instance we do not have concerns from a medication error perspective.

We reviewed the proposed PI, container labels, and carton labeling submitted for the indication of Crohn's disease (CD). Our evaluation of the proposed label and labeling identified areas that may lead to medication errors. We provide recommendations in Section 5.1 for the Division and 5.2 for the Applicant.

5 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Skyrizi prescribing information, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 5.1 for the Division of Gastroenterology and Section 5.2 for the Applicant. We ask that the Division convey Section 5.2 in its entirety to Abbvie so that recommendations are implemented prior to approval of this BLA and BLA supplement.

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

5.1 RECOMMENDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

    a. How supplied table contains trailing zeroes. Remove the trailing zeroes (600 mg/10.0 mL single-dose vial).

5.2 RECOMMENDATIONS FOR ABBVIE INC

We recommend the following be implemented prior to approval of this BLA and BLA Supplement:

A. General Comments (Container labels & Carton Labeling)

1. Note that DMEPA 1 is evaluating the human factors validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.
2. We note the vial container labels and carton labeling contain placeholders for the expiration date, but do not define the proposed format for the expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters

are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

B. Container Label (600 mg/10 mL vial)

1. Decrease the prominence of the statements "Rx Only", "Single-dose vial", and net quantity (1 x 10 mL vial) as these information appear more prominent than other important information (e.g., established name, route of administration) on the principal display panel.
2. Decrease the prominence of the statement, "Not for sale" as it distracts from other important information on the principal display panel. Consider using the term "Sample" instead of "Not for sale".
3. Increase the prominence of the route of administration and the statement "must be diluted prior to use" (e.g., bolding or boxing).
4. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual vial as required per 21CFR 201.25(c)(2).
5. Delete or define the undefined numerals (e.g., "20069459").
6. The proposed package type for your product is "single-dose vial". If the vial contains more drug than needed to provide the dose listed in the Dosage and Administration section of the prescribing information, include the statement, "Discard Unused Portion" after the "single-dose vial" statement.

C. Carton Labeling (600 mg/10 mL Vial)

1. Revise the statement "(b) (4) (b) (4)" to read "Recommended Dosage: See package insert for full prescribing information" per 21 CFR 201.55.
2. Increase the prominence of the route of administration and the statement "must be diluted prior to use" (e.g., bolding or boxing).
3. Carton labeling contains the statements, "Discard unused portion" after the package type, "single-dose vial" and is not consistent with the container label, which only contains the statement "single-dose vial" (see Comment B.5). Ensure that the container label and carton labeling are consistent.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Skyrizi received on September 16, 2021 from Abbvie Inc.

Table 1. Relevant Product Information for Skyrizi		
Product Name	Skyrizi (BLA 761262)	Skyrizi (BLA 761105/S-016)
Intended Pronunciation	sky-RIZZ-ee	
Initial Approval Date	N/A	April 23, 2019
Active Ingredient	Risankizumab-rzaa	
Indication	for the treatment of moderately to severely active Crohn's disease in patients 16 years of age and older.	
Route of Administration	Intravenous injection	Subcutaneous injection
Dosage Form	injection	
Strength	600 mg/10 mL (60 mg/mL)	360 mg/2.4 mL (150 mg/mL)
Dose and Frequency	CROHN'S DISEASE The recommended dose is 600 mg administered by intravenous infusion at Week 0, Week 4, and Week 8, followed by 360 mg administered by subcutaneous injection at Week 12, and every 8 weeks thereafter.	
How Supplied	Carton of 1 600 mg/10 mL single-dose vial	360 mg/2.4 mL: Kit of single-dose prefilled cartridge with on-body injector
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46° F). Do not freeze. Do not shake. Keep in the original cartons to protect from light.	

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Skyrizi labels and labeling submitted by Abbvie Inc.

- Container label received on September 16, 2021
- Carton labeling received on September 16, 2021
- Prescribing Information (Image not shown) received on September 16, 2021, available from \\CDSESUB1\evsprod\BLA761105\0136\m1\us\114-labeling\draft\labeling
- Medication Guide received on September 16, 2021, available from \\CDSESUB1\evsprod\BLA761105\0136\m1\us\114-labeling\draft\labeling

G.2 Label and Labeling Images

BLA 761262

(b) (6)

[redacted]

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	November 19, 2021
Reviewer:	Tiffany Kim, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance I
Team Leader:	Lisa Wolf, PharmD, BCCCP DPV-I
Deputy Division Director:	CDR Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Skyrizi (risankizumab-rzaa) injection, for subcutaneous and intravenous use
Subject:	Postmarketing Safety
Application Type/Number:	BLA 761105/ BLA 761262
Applicant:	AbbVie Inc.
OSE RCM #:	2021-1900, 2021-1902, 2021-2186

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an analysis of all adverse events associated with risankizumab-rzaa in the FDA Adverse Event Reporting System (FAERS) database and the medical literature. This review will inform DG as they conduct a review of a prior approval efficacy supplement and new Biologics License Applications (BLA) for risankizumab-rzaa treatment of moderately to severely active Crohn's disease in patients aged 16 years and older submitted by the applicant, AbbVie Inc., to FDA on September 16, 2021.

The FDA approved risankizumab-rzaa on April 23, 2019, for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The recommended dose of risankizumab-rzaa is 150 mg (two 75 mg injections) administered subcutaneously (SC) at Week 0, Week 4, and every 12 weeks thereafter.

On March 23, 2021, AbbVie Inc. submitted a prior approval efficacy supplement to Division of Rheumatology and Transplant Medicine (DRTM) for risankizumab-rzaa for the treatment of active psoriatic arthritis in adults. DRTM consulted DPV-I on November 15, 2021, to evaluate hepatic adverse events and hypersensitivity reactions in association with risankizumab-rzaa.

On June 24, 2020, DPV-I completed a Postmarket Drug Safety Surveillance Summary to identify safety signals for risankizumab-rzaa. DPV-I did not identify any Newly Identified Safety Signals (NISSs) at that time, and continued routine pharmacovigilance monitoring, especially for serious hypersensitivity reactions. To date, there are no opened NISSs for risankizumab-rzaa.

The FAERS search on September 29, 2021, yielded 4,206 reports. For the purposes of this review, a case-level analysis was not performed on all reports. We reviewed all PTs and reported Designated Medical Events for new potential safety signals. We did not identify medical literature publications with relevant new safety findings in our literature search from the safety surveillance summary data lock date, April 28, 2020, to October 19, 2021.

We reviewed unlabeled adverse events with the potential for serious outcomes labeled adverse events with unexpected characteristics, such as an increase in severity. We find an association between risankizumab-rzaa and anaphylaxis. There does not appear to be a postmarket safety signal for other adverse events associated with risankizumab-rzaa at this time.

Based on this review, DPV-I recommends adding anaphylaxis and angioedema to the WARNINGS AND PRECAUTIONS section of the labeling.

1 INTRODUCTION

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an analysis of all adverse events associated with risankizumab-rzaa in the FDA Adverse Event Reporting System (FAERS) database and the medical literature. This review will inform DG as they conduct a review of a prior approval efficacy supplement and new Biologics License Applications (BLA) for risankizumab-rzaa treatment of moderately to severely active Crohn's disease in patients aged 16 years and older submitted by the applicant, AbbVie Inc., to FDA on September 16, 2021.

1.1 BACKGROUND AND REGULATORY HISTORY

Risankizumab-rzaa is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor, inhibiting the release of pro-inflammatory cytokines and chemokines. The FDA approved risankizumab-rzaa on April 23, 2019, for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The recommended dose of risankizumab-rzaa is 150 mg (two 75 mg injections) administered subcutaneously (SC) at Week 0, Week 4, and every 12 weeks thereafter.[1]

At the time of initial approval, postmarketing requirement 3594-4 (PMR 3594-4) determined that an observational study would be conducted to assess the long-term safety of risankizumab-rzaa compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis. The study's primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal (GI) and hematologic adverse events. Data accrual for both studies is ongoing. The first data extraction for PMR 3594-4 will take place in December 2021, with the first annual report to be submitted to the FDA in second quarter of 2022.[2]

On September 16, 2021, DG consulted DPV-I to evaluate postmarketing adverse event reports in the FAERS database and medical literature for risankizumab-rzaa to inform DG as they review prior approval efficacy supplement and new BLA for risankizumab-rzaa for the treatment of moderately to severely active Crohn's disease in patients aged 16 years and older.

- BLA 761262: Induction therapy: 600 mg intravenous (IV) at Weeks 0, 4 and 8
- sBLA 761105/S-016: Maintenance therapy: 360 mg SC every (b) (4) weeks thereafter

On March 23, 2021, AbbVie Inc. submitted a prior approval efficacy supplement to Division of Rheumatology and Transplant Medicine (DRTM) for risankizumab-rzaa for the treatment of active psoriatic arthritis in adults. DRTM consulted DPV-I on November 15, 2021, to evaluate hepatic adverse events and hypersensitivity reactions in association with risankizumab-rzaa.

Of note, postmarketing exposure to risankizumab-rzaa from March 26, 2019, to March 25, 2021, is (b) (4) patient treatment years cumulatively estimated from AbbVie sales and distribution data.[3]

1.2 RISANKIZUMAB-RZAA SAFETY SURVEILLANCE SUMMARY

On June 24, 2020, DPV-I completed a Postmarket Drug Safety Surveillance Summary to identify safety signals for risankizumab-rzaa. The following data sources were reviewed: 1) FAERS reports received by FDA from the date of product approval, April 23, 2019, through April 28, 2020, 2) the medical literature, and 3) the Applicant's periodic safety reports. DPV-I did not identify any Newly Identified Safety Signals (NISSs) at that time, and continued routine pharmacovigilance monitoring, especially for serious hypersensitivity reactions.

To date, there are no opened NISSs for risankizumab-rzaa.

1.3 RELEVANT PRODUCT LABELING

The applicant's proposed product label for IV and SC risankizumab-rzaa contains the same information as the current label as described below. No new safety information is proposed for the POSTMARKETING EXPERIENCE section.

(b) (4)

2 METHODS AND MATERIALS

DPV-I reviewed information from FAERS and searched the medical literature to identify adverse events to further review.

2.1 CAUSALITY CRITERIA

We performed a high-level analysis of the top 50 Preferred Terms (PTs) with risankizumab-rzaa. We subsequently performed a hands-on analysis of all reports with PTs related to unlabeled events for risankizumab-rzaa or adverse events of interest. Potential signals resulting from these analyses are discussed further in Section 4. When applicable, reports were assessed for a causal relationship between the adverse events and reported product using a modified version of the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment tool (see Table 1).

Table 1. Causality Classification and Criteria based on the WHO-UMC System[4]

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.2 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	September 30, 2021
Time period of search	April 29, 2020† through September 29, 2021
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Risankizumab, Risankizumab-rzaa (Product active ingredient)
MedDRA version 24.0	All adverse events

Table 2. FAERS Search Strategy*
* See Appendix A for a description of the FAERS database. † Data lock date for Postmarket Drug Safety Surveillance Summary Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

2.3 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Date of search	October 20, 2021
Database	Embase, PubMed@FDA
Search terms	Pubmed: ("risankizumab"[Supplementary Concept] OR "risankizumab"[All Fields]) AND ("adverse"[All Fields] OR "adversely"[All Fields] OR "adverses"[All Fields]) AND ("event"[All Fields] OR "event s"[All Fields] OR "events"[All Fields])

Search terms	Embase: ('risankizumab'/exp/'adverse drug reaction','drug toxicity','drug interaction' OR 'risankizumab-induced':de,ab,ti OR (('risankizumab':de OR 'risankizumab':tn,ti,ab OR 'risankizumab rzaa':tn,ti,ab OR 'risankizumab-rzaa':tn,ti,ab OR 'skyrizi':tn,ti,ab) AND ('adverse drug reaction'/exp OR 'adverse drug reaction':lnk OR adverse:de,ab,ti OR (((side OR undesirable OR unwanted) NEXT/2 (effect* OR reaction* OR event* OR outcome*)):de,ab,ti) OR 'side effect'/lnk OR 'side effect'/exp OR 'complication'/lnk OR 'complication'/exp OR complication*:de,ab,ti OR 'worsening':de,ab,ti OR 'case report*':de,ab,ti OR 'pharmacovigilance':de,ab,ti OR 'postmarketing surveillance'/exp OR 'drug interaction':lnk OR 'drug interaction'/exp OR 'toxicity'/exp OR 'drug toxicity':lnk OR toxic*:de,ab,ti OR intox*:de,ab,ti OR 'safety':de,ab,ti OR poison*:de,ab,ti OR pharmacotox*:de,ab,ti OR neurotox*:de,ab,ti OR cardiotox*:de,ab,ti OR nephrotox*:de,ab,ti OR hepatotox*:de,ab,ti OR immunotox*:de,ab,ti OR immunocytotox*:de,ab,ti OR cytotox*:de,ab,ti OR carcinogen*:de,ab,ti OR cancerogen*:de,ab,ti OR mutagen*:de,ab,ti OR terato*:de,ab,ti OR 'fatal outcome'/exp OR 'death'/exp OR death*:de,ab,ti OR 'suicide'/exp OR suicid*:de,ab,ti OR mortal*:de,ab,ti OR fatal*:de,ab,ti OR 'risk'/exp OR nocebo:de,ab,ti OR 'lethal concentration'/exp OR 'iatrogenic disease'/exp OR 'fertility'/exp OR 'substance-related disorders'/exp OR 'chemically induced':de,ab,ti OR 'morbidity':de,ab,ti OR 'congenital disorder':de,ab,ti OR 'infertility'/exp OR 'injury'/exp OR 'pregnancy'/exp OR pregnant*:de,ab,ti OR pregnanc*:de,ab,ti OR 'pregnancy complication'/exp OR 'pregnancy disorder'/exp OR 'abortion'/exp OR 'abortion':de,ab,ti OR 'lactation'/exp OR 'breast feeding':de,ab,ti OR 'breastfeeding':de,ab,ti OR 'breast milk':de,ab,ti OR 'reproduction'/de OR 'fetus'/de OR 'embryo'/de OR 'prenatal':de,ab,ti OR 'perinatal':de,ab,ti OR 'newborn':de,ab,ti OR 'parameters concerning the fetus, newborn and pregnancy'/exp OR 'aged'/exp OR elderly:de,ti,ab OR geriatric*:ti,ab OR (((environmental OR occupational) NEXT/1 exposure*):de,ab,ti) OR 'compassionate use':de,ab,ti OR ((named NEXT/1 (use OR patient*)):ab,ti) OR 'inappropriate prescri*':de,ab,ti OR 'drug metabolism'/exp OR 'organ dysfunction':de,ab,ti OR 'organ failure':de,ab,ti OR 'hypersensitivit*':de,ab,ti OR allerg*:de,ab,ti OR counterfeit:de,ab,ti OR 'falsified drug':de,ab,ti OR (('unavailab*' NEAR/2 drug):de,ab,ti) OR 'drug resistance'/exp OR 'drug resistance':de,ab,ti OR 'withdrawal syndrome'/de OR ((drug* NEAR/3 (withdrawal OR toleran* OR interact* OR exposure* OR induc* OR resist* OR ineff* OR nonrespon* OR unrespon*)):de,ab,ti) OR 'drug tolerance'/exp OR (((drug* OR treatment) NEXT/1 (failure* OR contraindication*)):de,ab,ti) OR 'medication error'/exp OR ((near NEXT/1 miss*):ab,ti) OR ineff*:ti

Table 3. Literature Search Strategy	
	OR nonrespon*:ti OR unrespon*:ti OR (((lack OR no OR non OR 'not') NEXT/2 (eff* OR respon*)):ab,ti) OR 'device failure':de,ab,ti OR (manufacturing NEAR/3 (error OR fault OR mistake OR failure OR contamination OR impurity)) OR 'patient compliance'/exp OR overdos*:de,ab,ti OR 'drug abuse'/exp OR abus*:de,ab,ti OR misus*:de,ab,ti OR 'off label':de,ab,ti OR unlicensed:de,ab,ti))) AND ('human'/exp OR human OR m?n OR wom?n OR child OR boy OR girl)
Years included in search	2020, 2021

3 RESULTS

3.1 FAERS

The FAERS search on September 29, 2021, yielded 4,206 reports. For the purposes of this review, a case-level analysis was not performed on all reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes; causality and the role of the product in the coded outcome have not been determined for all reports (see Appendix A for FAERS limitations).

Table 4 provides the descriptive characteristics of the FAERS reports retrieved by the search strategy described in Table 2.

Table 4. Descriptive Characteristics of FAERS Reports With Risankizumab-rzaa, Received by FDA From April 29, 2020, through September 29, 2021 N=4,206*		
Sex	Male	1902
	Female	2100
	Unknown	204
Age	<1 year	1†
	17 to <65 years	2,305
	≥ 65 years	1,370
	Null	530
Country	United States	3,294
	Foreign	912
Report type	Expedited	3,553
	Direct	12
	Periodic	641
Top 5 reported reasons for use‡	Psoriasis-related	3936
	Not reported/unknown	910
	Rheumatoid arthritis	11

Table 4. Descriptive Characteristics of FAERS Reports With Risankizumab-rzaa, Received by FDA From April 29, 2020, through September 29, 2021 N=4,206*		
	Crohn's disease	8
	Eczema	6
Serious outcomes§ (n=3,515)	Death	255
	Life-threatening	25
	Hospitalization	1,389
	Disability	38
	Congenital anomaly	10
	Other serious	2,250

* May include duplicates.
† Indicates neonatal exposure.
‡ A report can have one or more reported reasons for use.
§ For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A report can have one or more outcome.

Table 5 lists the most frequently reported MedDRA PTs and the labeling status of each PT. Although only PTs with a frequency ≥30 are listed in the table, we reviewed all PTs for new potential safety signals.

Table 5. Most Frequently Reported MedDRA PTs With N ≥ 30 With Risankizumab-rzaa, Received by FDA From April 29, 2020 through September 29, 2021, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location† or Other Category
Psoriasis	423	No; IR
COVID-19	233	No; see section 4.2.1
Death	174	No; see section 4.1.1
Drug ineffective	167	No; U
Fatigue	144	Yes; AR
Fall	136	No; U or reported risk factors (accidents, sports, or occupational injuries)
Pain	134	Yes; AR
Pneumonia	130	Yes; W/P (infections)
Arthralgia	111	No; some cases DR
Surgery	98	No; U
Cerebrovascular accident	93	No; see section 4.1.2
Dyspnoea	90	Yes; W/P (upper respiratory infections)
Headache	90	Yes; AR
Myocardial infarction	89	No; see section 4.1.2
Pruritus	89	Yes; AR

Table 5. Most Frequently Reported MedDRA PTs With N ≥ 30 With Risankizumab-rzaa, Received by FDA From April 29, 2020 through September 29, 2021, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT	**Number of FAERS Reports***	**Labeled (Yes/No), Location† or Other Category**
Pain in extremity	79	Yes; AR
Asthenia	78	Yes; AR
Cataract	75	No; U
Skin cancer	74	No; see section 4.1.3
Rash	68	No; DR
Weight decreased	63	Yes; (b) (4)
Malaise	61	No; U
Urinary tract infection	60	Yes; W/P (infections)
Neoplasm malignant	59	No; U
Pyrexia	59	Yes; W/P (infections)
Diarrhoea	58	Yes; (b) (4)
Unevaluable event	58	No; U
Erythema	55	Yes; AR
Dizziness	53	No; U
Therapeutic response shortened	52	No; U
Back pain	51	Yes; AR
Hypertension	50	No; no possible or probable cases identified
Cough	49	Yes; (b) (4)
Knee arthroplasty	49	No; U
Nausea	48	No; U
Skin disorder	47	No; DR
Atrial fibrillation	46	No; no possible or probable cases identified
Off label use	46	No; U
Basal cell carcinoma	44	No; see section 4.1.3
Peripheral swelling	44	No; U
Stress	43	No; U
SARS-CoV-2 test positive	42	No; see section 4.2.1
Illness	40	No; U
Therapeutic product effect incomplete	39	No; U
Spinal operation	38	No; U
Gait disturbance	37	No; U
Loss of consciousness	37	No; U
Osteoarthritis	37	No; U
Alopecia	36	No; U
Coronary artery occlusion	36	No; see section 4.1.2
Psoriatic arthropathy	36	No; DR

Table 5. Most Frequently Reported MedDRA PTs With N ≥ 30 With Risankizumab-rzaa, Received by FDA From April 29, 2020 through September 29, 2021, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT	**Number of FAERS Reports***	**Labeled (Yes/No), Location† or Other Category**
Abdominal pain	35	Yes; AR
Arthritis	35	No; DR
Hypoaesthesia	35	No; U
Skin plaque	35	No; DR
Breast cancer female	34	No; U
Skin exfoliation	34	No; DR
Drug hypersensitivity	33	No; see section 4.1.5
Hip arthroplasty	33	No; U
Hospitalisation	33	No; U
Myalgia	33	No; U
Therapeutic product effect decreased	33	No; U
Urticaria	33	Yes; AR
Maternal exposure during pregnancy	32	No; no possible or probable cases identified
Vomiting	32	No; U
Cardiac failure congestive	31	No; no possible or probable cases identified
Mobility decreased	31	No; U
Knee operation	30	No; U
Localised infection	30	Yes; AR
Post procedural complication	30	No; U

* A report can contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, W/P = Warnings/Precautions, AR = Adverse Reactions, DR = Disease-related, IR = Indication-related, U = Uninformative

Designated Medical Events (DMEs) are adverse events that are considered serious and, from a pharmacovigilance perspective, may often be caused by exposure to drugs from many pharmacological or therapeutic classes. Identification of these events is a priority, even when the number of cases is small, and before there is evidence of disproportional reporting. DMEs are not intended to include events with a high prevalence in the general population. See Appendix B for a list of the Office of Surveillance and Epidemiology's (OSE) DMEs.

Table 6 lists the most frequently reported DMEs and the labeling status of each. Although only PTs with a frequency ≥ 5 are listed in the table, we reviewed all reported DMEs for new safety signals.

Table 6. Most Frequently Reported DMEs With N ≥ 5 With Risankizumab-rzaa, Received by FDA From April 29, 2020, through September 29, 2021, Sorted by Decreasing Number of FAERS Reports per PT		
DME MedDRA PT	**Number of FAERS Reports***	**Labeled (Yes/No), Location† or Other Category**
Seizure	22	No; see section 4.1.4
Deafness	14	No; Unassessable or unlikely
Anaphylactic reaction	11	No; see section 4.1.5
Blindness	11	No; Unassessable or unlikely
Hepatic failure	6	No; see section 4.1.6
Acute kidney injury	5	No; see section 4.1.7
Blindness unilateral	5	No; Unassessable or unlikely
* A report can contain more than one MedDRA PT. † If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: DME = Designated Medical Event, MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term		

3.2 MEDICAL LITERATURE

We did not identify medical literature publications with relevant new safety findings in our literature search from the safety surveillance summary data lock date, April 28, 2020, to October 19, 2021.

4 REVIEWER COMMENTS

Eight reports described the use of risankizumab-rzaa for the indication of Crohn's disease. We did not identify any additional safety concerns during the review of the eight reports.

A summary of our analysis of 1) unlabeled adverse events with the potential for serious outcomes, 2) labeled adverse events with unexpected characteristics, such as an increase in severity is provided below:

4.1 UNLABELED ADVERSE EVENTS WITH POTENTIAL FOR SERIOUS OUTCOMES

4.1.1 Deaths

The safety surveillance summary completed in 2020 described 36 FAERS reports with an outcome of death. Nineteen cases provided no cause of death or recent events preceding the death and provided limited information to assess the role of risankizumab-rzaa. In the remaining 17 reports, death was attributed to or reported with the following cause: infections (5), pulmonary events (5), cardiovascular events (4), GI events (2), and motor vehicle accident (1).

We identified and reviewed 255 reports which described an outcome of death. Outcome of death was reported in patients with age ranging from 29 to 92-years-old. Of the 255 reports, 175 reported an unknown cause of death. The remaining 80 reports described death from Coronavirus disease-2019 (COVID-19; 22), malignancy (16), myocardial infarction (MI;

8), infections (7), cardiac reasons (6), liver failure (6), cerebrovascular accident (4), pulmonary embolism (3), acute renal failure (2), anaphylaxis to other drugs (1), aneurysm (1), aortic occlusion (1), pulmonary fibrosis (1), volvulus (1), and fall (1).

Most reports were deemed unassessable because they contained insufficient information including time to onset and details preceding the death. Two cases reported MI resulting in deaths on the same day and three days after risankizumab-rzaa administration, respectively. One case of MI is described in Section 4.1.2. Major Adverse Cardiovascular Events.

4.1.2 Major Adverse Cardiovascular Events and Dyslipidemia

The safety surveillance summary completed in 2020 identified 48 FAERS reports with one or more of the following: MI (23), stroke (23), or transient ischemic attack (4). No cases reported unstable angina. The majority of reports contained one or more cardiovascular risk factors; other reports did not provide information, such as medical history or concomitant medications, to assess for risk factors.

The reviewers noted that there appeared to be an imbalance in serious cardiac adverse events in controlled trials of risankizumab-rzaa compared to ustekinumab primarily from congestive heart failure or supraventricular arrhythmia. Based on the high background rate of MI and stroke in the treatment population and the limitations of the information provided in the FAERS reports, the reviewers could not evaluate the association between MACE and risankizumab-rzaa use. A postmarketing requirement (PMR 3594-4) for an observational study to assess the long-term safety of risankizumab-rzaa compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis was issued at product approval and includes cardiovascular adverse events as a secondary outcome.

We identified and reviewed 267 FAERS reports coded with PTs in the Standardised MedDRA Queries (SMQs), *Ischemic heart disease* (narrow) or *Central nervous system vascular disorders* (narrow), or coded with the PTs *Sudden cardiac death*, *Cardiac death*, or *Sudden death.*

Some of the most commonly reported major adverse cardiovascular event PTs associated with the 267 reports included: *Cerebrovascular accident* (93), *Myocardial infarction* (89), *Coronary artery occlusion* (36), *Transient ischaemic attack* (17), *Coronary artery disease* (12), and *Coronary arterial stent insertion* (10). The complete list of PTs is in Appendix C.

We identified 31 cases of MI (23) or stroke (8) with possible causal association to risankizumab-rzaa; the remaining reports were unlikely or did not contain sufficient information to assess causality. Age ranged from 41 to 81-years-old. Out of 31 cases, 11 cases reported cardiovascular risk factors including a history of hypertension, coronary artery disease, hyperlipidemia, and tobacco use. Thirteen cases did not report a medical history and 7 cases reported no relevant medical history. Time to onset ranged from 1 day to 23 months. Two cases which described MI with a possible causal association to risankizumab-rzaa with a plausible temporal association are described below:

FAERS# 18110505, MCN: SK-ABBVIE-20K-260-3503957-00, Slovenia, 2020
This case describes a 69-year-old female who experienced a MI 1 day following the initiation of risankizumab-rzaa for plaque psoriasis. Her past medical history included hyperlipidemia, hypertension, and diabetes mellitus. After the first dose of risankizumab-rzaa, she experienced a non-ST segment elevation MI. She received percutaneous coronary intervention and one drug eluting stent. Follow up was not reported.

FAERS# 18742597, MCN: IT-ABBVIE-21K-083-3731022-00, Italy, 2021
This case describes a male with unknown age who experienced a fatal MI on the same day following the initiation of risankizumab-rzaa for unknown indication. His past medical history included metabolic syndrome with endovascular prosthesis, hyperlipidemia, congestive heart failure, atrial fibrillation, diabetes mellitus, and subrenal aortic aneurysm. He died from the heart attack.

Reviewer's comments:
Both cases were assessed as having a possible causal association between MI and risankizumab-rzaa because of a plausible temporal relationship between risankizumab-rzaa initiation and event onset. Medical history of cardiovascular risk factors (i.e., hyperlipidemia and diabetes mellitus) is considered to have a causal contributory role.

Patients who develop psoriasis at a younger age or with severe psoriasis are at higher risk for cardiometabolic comorbidities than the general population, and psoriasis is associated with vascular inflammation and high-risk atherosclerotic plaques.[5] *Given the high background rate of major adverse cardiovascular events in the general adult population and cardiovascular risk factors present, all cases were assessed to have a possible causal association between major adverse cardiovascular event and risankizumab-rzaa. However, the role of risankizumab-rzaa in the development of major adverse cardiovascular event could not be ruled out.*

We identified and reviewed 24 reports coded with PTs in *Dyslipidemia* SMQ (narrow). All reports did not contain sufficient laboratory evaluation to assess for causality.

4.1.3 Cutaneous malignancies

The safety surveillance summary completed in 2020 identified 11 reports of non-melanoma skin cancer coded with PTs related to basal cell carcinoma (BCC) or squamous cell carcinoma (SCC); 9 reports described BCC, of which two also reported SCC. No reports of basosquamous carcinoma or Bowen's disease were identified. Three reports were coded with the PT *Skin cancer but* did not specify the type of skin cancer. The reviewers noted that based on prior histories of NMSC and presence of other risk factors in the reports, the role of Risankizumab-rzaa appeared limited.

Of note, PMR 3594-4, an observational study to assess the long-term safety of risankizumab-rzaa compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis has a primary outcome of long-term malignancy.

We identified and reviewed 163 reports coded with one or more of the following PTs in *Skin malignant tumours* SMQ (narrow): *Skin cancer* (74), *Basal cell carcinoma* (44), *Malignant melanoma* (22), *Cutaneous T-cell lymphoma* (12), and *Squamous cell carcinoma of skin* (10). One report was coded with the PT *Bowen's disease*. The complete list of PTs is in Appendix C.

We identified 11 cases with cutaneous malignancy with possible association to risankizumab-rzaa including BCC (5), malignant melanoma (5), and SCC (1); the remaining reports were unlikely or did not contain sufficient information to assess causality. Time to onset ranged from 2 to 12 months. Two representative cases are described below:

FAERS # 19416869, MCN: JP-ABBVIE-21K-087-3943653-00, Japan, 2021:
This case describes a 74-year-old male who experienced malignant melanoma 2 months following the initiation of risankizumab-rzaa for psoriasis. Past medical history included spinal stenosis, stasis panniculitis, skin pigmentation of left cheek, psoriasis, hypertension, type 2 diabetes mellitus, and diarrhea. Concomitant medications were not reported. Patient has a history of unspecified sun exposure. Prior to therapy initiation, patient noticed a skin pigmentation on his left cheek. Two months following the initiation of risankizumab-rzaa, he noticed raising of the skin pigmentation and biopsy diagnosed him with malignant melanoma. Patient recovered.

FAERS # 19413821, MCN: US-ABBVIE-21K-163-3948095-00, USA, 2021:
This case describes a 56-year-old female who experienced BCC on her leg 7 months following the initiation of risankizumab-rzaa for unknown indication; the lesion was removed. Past medical history included a removal of cancerous lesion on the back 6 months prior. Concomitant medications were not reported. Patient had a history of unspecified sun exposure. Follow up was not reported.

Reviewer's comments: Given the high background rate of cutaneous malignancies in the general adult population, all cases were assessed to have a possible causal association between cutaneous malignancies and risankizumab-rzaa based on a plausible temporal sequence between risankizumab-rzaa exposure and event onset. Overall, the cases lacked sufficient information, such as concomitant medications and past medical history, to rule out contributory factors; this is important because of the long time-to-onset in some cases.

We cannot rule out an association between cutaneous malignancies including BCC, SCC, and malignant melanoma. Many immune modulators are associated with an increased risk of cutaneous malignancies. [6]

4.1.4 Seizure

The safety surveillance summary completed in 2020 identified nine reports coded with the PTs *Seizures* and *Generalised tonic-clonic seizure.* All reports were deemed unlikely or did not contain sufficient information to assess causality.

We identified and reviewed 32 reports that were coded with PTs in the *Convulsion* SMQ (narrow). The complete list of PTs is in Appendix C.

We identified four cases that described seizures (tonic-clonic (2), right temporal lobe epilepsy (1), partial seizures (1)) with possible association to risankizumab-rzaa; the remaining reports were unlikely or did not contain sufficient information to assess causality. Time-to-onsets were reported as 5 minutes, 1 hour, 2 days, and one case reported an unspecified time 'after' risankizumab-rzaa dose. Three cases reported a past medical history of seizures without description of seizure control and one case did not report a past medical history which is described below.

FAERS # 19841744, MCN: AU-ABBVIE-21K-008-4078609-00, Australia, 2021
This case describes a 68-year-old female who experienced tonic-clonic seizure 2 days following the initiation of risankizumab-rzaa for an unknown indication. Past medical history was not reported. Two days following the first dose of risankizumab-rzaa, she had a grand mal seizure and was admitted to the hospital. She presented with a right-sided facial droop and magnetic resonance imaging revealed chronic hydrocephalus. She had another onset of tonic-clonic seizure witnessed by her husband. Follow up was not reported.

Reviewer's comments: This case is assessed as having a possible causal association between seizure and risankizumab-rzaa because of a plausible temporal relationship between risankizumab-rzaa initiation and event onset. Hydrocephalus is not commonly recognized as a cause of seizure in general.[7] The underlying hydrocephalus may result in chronic lesions which may result in epilepsy or seizures when the seizure threshold is temporarily lowered. The unknown past medical history and concomitant medications limit our ability to fully evaluate this case for causality.

One population-based study reported that the odds of epilepsy is 1.9 fold higher among people with psoriasis compared to controls.[8] The role of risankizumab-rzaa in the development of seizures could not be ruled out considering the plausible temporal relationship.

4.1.5 Hypersensitivity and Anaphylactic Reaction

The safety surveillance summary completed in 2020 identified 80 FAERS reports coded with PTs in these SMQs: *Anaphylactic reactions*, *Angioedema*, *Hypersensitivity*, and *Severe cutaneous adverse reactions*. Of the 80 reports, 8 did not appear related to hypersensitivity events. The remaining 71 cases reported one or more of the following adverse events: rash (34), urticaria (9), eczema or atopic dermatitis (8), hypersensitivity reactions not otherwise specified (5), skin reactions, other or unspecified (5), anaphylaxis (4), erythroderma or erythrodermic psoriasis (4), pharyngeal edema or throat tightness (3),

angioedema (1), bronchospasm (1), erythema multiforme (1), giant papillary conjunctivitis (1), and leukocytoclastic vasculitis (1). None of the four cases reporting anaphylaxis reported treatment with epinephrine, and only one case described symptoms that potentially met the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for anaphylaxis.[9]

We identified and reviewed 244 reports with PTs in these SMQs: *Anaphylactic reactions, Angioedema, Hypersensitivity,* and *Severe cutaneous adverse reactions*. The complete list of PTs is in Appendix C.

Three cases described adverse events reported as angioedema (1) and anaphylaxis (2) with possible association to risankizumab-rzaa; the remaining reports were unlikely or did not contain sufficient information to assess causality. One case described symptoms that met the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for anaphylaxis.[8] The three representative cases are described below:

FAERS# 19609001, MCN: GB-ABBVIE-21K-167-4010417-00, Great Britain, 2021
This case describes a 62-year-old female who experienced anaphylaxis 15 minutes after her first dose of risankizumab-rzaa for psoriasis. Past medical history and concomitant medications were not reported. Fifteen minutes after injection, she experienced shortness of breath, tightness of chest, wheezing, swollen lips, developed a stridor, and went to the hospital. Patient received epinephrine, chlorpheniramine, hydrocortisone, and oxygen. Follow up was not reported.

FAERS 19015753, MCN: US-ABBVIE-21K-163-3818084-00, USA, 2020
This case describes a 52-year-old female who experienced anaphylaxis after her last two injections of risankizumab-rzaa for psoriasis. Her past medical history was not reported. No concomitant medications were taken. She was hospitalized in the intensive care unit after her last injection. She reported discontinuing treatment with risankizumab-rzaa. Follow up was not reported.

FAERS# 18583476, MCN: US-ABBVIE-20K-163-3671262-00, USA, 2020
This case describes a 43-year-old male who experienced angioedema 7 days following initiation of risankizumab-rzaa for psoriasis. His past medical history was not reported. No concomitant medications were taken. Seven days following initiation of risankizumab-rzaa, he presented with tongue swelling and swelling in his hands. He reported to the emergency room and was admitted and intubated for 7 days. Follow up was not reported.

Reviewer's comments: These three cases are assessed as having a possible causal association between anaphylaxis and angioedema and risankizumab-rzaa because of a plausible temporal relationship between risankizumab-rzaa initiation and event onset.

Biologic plausibility of the association with anaphylaxis with risankizumab-rzaa is further supported by the association of hypersensitivity and anaphylaxis with

guselkumab. Guselkumab is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. On February 4, 2020, the Applicant of guselkumab submitted a prior approval supplement for the addition of anaphylaxis to Sections 5.3 and 6.3 of the guselkumab labeling, which was approved on June 1, 2020. The approval was based on one well-documented case of anaphylaxis reported with guselkumab use and based on the potential for serious outcomes.

Recently, one case of anaphylaxis was identified during the phase 2 development program for risankizumab-rzaa for psoriatic arthritis dosed at 150 mg every 4 weeks. The Division of Dermatology and Dentistry is reviewing this safety signal currently.

The seriousness and clinical severity of anaphylaxis and angioedema, the reasonable evidence for a causal association between anaphylaxis and risankizumab-rzaa based on temporal relationship and biologic plausibility derived from the guselkumab experience, and the implications for prescribing decisions and patient management, all suggests a new potentially serious and clinically significant risk and warrants safety labeling change in the WARNINGS AND PRECAUTIONS section of the risankizumab-rzaa prescribing information.

4.1.6 Hepatic Adverse Events

The safety surveillance summary completed in 2020 identified 23 FAERS reports coded with PTs in the *Drug related hepatic disorders – comprehensive search* SMQ (narrow), the *Hepatic and hepatobiliary disorders NEC* High Level Term (HLT), and the *Hepatobiliary investigations* High Level Group Term (HLGT). Of the 23 reports, 7 described increased liver enzymes with limited information; 6 described increased liver enzymes occurring with symptoms or other adverse events (sepsis (2), mononucleosis (1), stroke or MI (1), increased neutrophil count and rash (1), and hepatic pain (1)); three reported liver failure without diagnostic information occurring in the presence of other comorbidities that likely contributed to the events; and the remaining cases were uninformative and/or reported other potential risk factors (e.g., gallstones) for the events. Based on the presence of other reported risk factors or missing information on medical history or concomitant medication use, the reviewers did not identify any serious cases of hepatic adverse events that appeared to be related to risankizumab-rzaa.

We identified and reviewed 106 FAERS reports coded with PTs in the *Drug related hepatic disorders –comprehensive search* SMQ (narrow), *the Hepatic and hepatobiliary disorders NEC* HLT, and the *Hepatobiliary investigations* HLGT. Of the 106 reports, 34 were excluded from further review because they described malignancies of the liver (17), described an unspecified liver disorder with no additional information (10), or were duplicates (7).

The remaining 72 reports described hepatic adverse events categorized as elevated or abnormal liver enzymes (32), cirrhosis (27), fatty liver disease (9), or hepatic failure (4). Of these reports, 9 contained alternative causes for the events. The remaining reports were

mostly solicited and contained limited information to assess the adverse event itself and assess the event's association with risankizumab-rzaa use (e.g., missing time-to-onset, diagnostic criteria, laboratory evaluations, medical history, concomitant medications).

Four cases are summarized below to illustrate the scarcity of data provided in the reports.

FAERS # 18646095 MCN: US-ABBVIE-20K-163-3694777-00, USA, 2020
This solicited case describes a 35-year-old female who experienced elevations of liver enzymes 7 months following risankizumab-rzaa initiation for unknown indication. Concomitant medications and past medical history were not reported. Reported past medication use history included use of adalimumab. Follow up was not reported.

FAERS # 19488952 MCN: BR-ABBVIE-21K-020-3975763-00, Brazil, 2021
This case describes a 37-year-old male who experienced fatal cirrhosis 5 months following initiation of risankizumab-rzaa for unknown indication. Reported past medical history included diabetes and concomitant medications included insulin. Cause of death were identified as cirrhosis, hemorrhage, and anemia. No other biopsy information was reported.

FAERS # 19034682 MCN: US-ABBVIE-21K-163-3819538-00, USA, 2021
This solicited case describes a 35-year-old male who experienced fatal liver failure unknown time following initiation of risankizumab-rzaa for unknown indication. Concomitant medications and past medical history were not reported. Follow-up and autopsy were not provided.

FAERS # 17997368 MCN: AU-ABBVIE-20K-008-3474614-00, Australia, 2020
This case describes a 63-year-old female who experienced fatty liver disease 10 months following initiation of risankizumab-rzaa for unknown indication. Concomitant medications and past medical history were not reported. Ten months following initiation of risankizumab-rzaa, she presented with abdominal pain and chest pain and was hospitalized. computerized tomography (CT) scan showed fat on the liver. Follow-up was not provided.

4.1.7 Acute Kidney Injury

The safety surveillance summary completed in 2020 described two reports coded with *acute kidney injury* which were unlikely or did not contain sufficient information to assess causality.

We identified and reviewed 47 FAERS reports coded with PTs in the *Acute renal failure* SMQ (narrow). The complete list of PTs is in Appendix C. One case described acute renal failure with possible association to risankizumab-rzaa use, which is described below; all other reports were unlikely or did not contain sufficient information to assess causality.

FAERS # 19064602, MCN: AU-ABBVIE-21K-008-3831559-00, 2021, Australia:

This case describes a female with unknown age who experienced acute renal failure following initiation of risankizumab-rzaa for palmoplantar psoriasis. She developed acute tubular necrosis an unknown period of time after initiation of risankizumab-rzaa. Nephrologist believed the adverse event was attributable to the drug. Condition improved with dechallenge and worsened when rechallenged with risankizumab-rzaa. Treatment was discontinued. Follow up was not reported.

Reviewer's comments: This case describes a possible causal association of acute renal failure sometime following initiation of risankizumab-rzaa. The case describes positive dechallenge followed by positive rechallenge, however, the case contains very limited to detail to confirm the events. Although the case does not report laboratory evaluations and time to onset, we included this case because of positive rechallenge and the nephrologist's opinion of drug attributability.

We recommend continuing routine pharmacovigilance because of the lack of well-documented cases.

4.1.8 Incorrect route of administration

We identified and reviewed 95 FAERS reports coded with PTs in the *Medication errors* SMQ (narrow). Two reports were coded with PT *Incorrect route of product administration* and described accidental intramuscular administration instead of SC administration. We did not identify any reports describing accidental IV route of administration.

4.2 LABELED ADVERSE EVENTS WITH UNEXPECTED CHARACTERISTICS

4.2.1 Infections

The safety surveillance summary completed in 2020 identified 38 cases coded with the PT *Pneumonia* or other pneumonia-related PTs (for example *Pneumonia bacterial* or *Pneumonia mycoplasmal*), of which 7 cases provided information on causative organisms. These included: *Aspergillus* and *Staphylococcus aureus* (1; case discussed below), bacteria not otherwise specified (1), COVID-19 (1), *Haemophilus influenzae* (1), *Mycobacterium tuberculosis* (1; case discussed below), *Mycoplasma* (1), and respiratory syncytial virus (1). Twenty-four of the 38 cases reported one or more risk factors for pneumonia, including age >65 years, smoking, COPD, concomitant immunosuppressant use, or a prior history of pneumonia.

We identified and reviewed 27 reports with PTs in the *Opportunistic infections* SMQ (narrow). The complete list of PTs is in Appendix C.

One case described *Pneumocystis jirovecii* pneumonia in association with risankizumab-rzaa resulting in death. However, the case was confounded by adalimumab and corticosteroids. One case described (b) (4) herpes zoster in association with risankizumab-rzaa, which is a labeled event.

DPV-I did not identify any additional cases describing opportunistic infections in association with risankizumab-rzaa; all reports were unlikely or did not contain sufficient information to assess causality.

We identified 258 reports coded with the PTs *COVID-19* (233), *COVID-19 pneumonia* (14), *Suspected COVID-19* (11), and *Asymptomatic COVID-19* (2). Reports with the PTs *COVID-19 pneumonia* or *SARS-COV-2 test positive* reflect diagnosis of COVID-19 during the 2020 – 2021 pandemic while receiving risankizumab-rzaa.

5 CONCLUSION

In conclusion, we find an association between risankizumab-rzaa and anaphylaxis. No additional safety signals were identified from our review of postmarketing reports associated with risankizumab-rzaa at this time.

6 RECOMMENDATIONS

Based on this review, DPV-I recommends adding anaphylaxis and angioedema to the WARNINGS AND PRECAUTIONS section of the labeling.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA version 24.1)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Pancytopenia
	Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye disorders	Blindness
	Blindness transient
	Blindness unilateral
	Optic ischaemic neuropathy
	Sudden visual loss
	Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant
Immune system disorders	Anaphylactic reaction
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock
Infections and infestations	Progressive multifocal leukoencephalopathy

System Organ Class	Preferred Terms (MedDRA version 24.1)
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	Seizure
	Serotonin syndrome
	Status epilepticus
Product issues	Product compounding quality issue
	Product contamination
	Product contamination chemical
	Product contamination microbial
	Product contamination physical
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms
	Generalised bullous fixed drug eruption
	SJS-TEN overlap
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

8.3 APPENDIX C. COMPLETE LIST OF PTS

Table 1. Major Adverse Cardiovascular Events

Preferred Terms	**Total Cases**
Cerebrovascular accident	93
Myocardial infarction	89
Coronary artery occlusion	36
Transient ischaemic attack	17
Coronary artery disease	12
Coronary arterial stent insertion	10
Coronary artery bypass	9
Cerebral haemorrhage	7
Hemiplegia	4
Angina pectoris	3
Carotid artery occlusion	3
Hemiparesis	3
Intracranial aneurysm	3
Acute myocardial infarction	2
Arteriosclerosis coronary artery	2
Carotid arteriosclerosis	2
Cerebral artery occlusion	2
Cerebral thrombosis	2
Myocardial ischaemia	2
Acute coronary syndrome	1
Angina unstable	1
Blood creatine phosphokinase MB increased	1
Brain stem infarction	1
Cardiac death	1
Carotid artery disease	1
Carotid artery dissection	1
Cerebellar infarction	1
Cerebral artery stenosis	1
Cerebral haematoma	1
Cerebral infarction	1
Coronary artery dissection	1
Embolic cerebellar infarction	1
Haemorrhagic stroke	1
Stress cardiomyopathy	1
Subarachnoid haemorrhage	1

Thalamus haemorrhage	1
Troponin increased	1
Vascular stent occlusion	1
Vascular stent stenosis	1

Table 2. Cutaneous malignancies

Preferred Terms	**Total Cases**
Skin cancer	74
Basal cell carcinoma	44
Malignant melanoma	22
Cutaneous T-cell lymphoma	12
Squamous cell carcinoma of skin	10
Bowen's disease	1
Carcinoma in situ of skin	1
Cutaneous T-cell lymphoma stage III	1
Extramammary Paget's disease	1
Lentigo maligna	1
Malignant melanoma in situ	1
Skin squamous cell carcinoma recurrent	1

Table 3. Seizure

Preferred Terms	**Total Cases**
Seizure	22
Epilepsy	6
Generalised tonic-clonic seizure	3
Partial seizures	1
Postictal state	1
Simple partial seizures	1
Temporal lobe epilepsy	1

Table 4. Hypersensitivity and Anaphylactic Reaction

Preferred Terms	**Total Cases**
Rash	68
Urticaria	34
Drug hypersensitivity	33
Dermatitis exfoliative generalised	24

Hypersensitivity	14
Eczema	13
Rash macular	13
Face oedema	12
Anaphylactic reaction	11
Swelling face	9
Rash pruritic	7
Dermatitis	6
Swollen tongue	6
Lip swelling	5
Dermatitis allergic	4
Dermatitis contact	4
Pharyngeal swelling	4
Rash erythematous	4
Angioedema	3
Eye swelling	3
Allergy to vaccine	2
Anaphylactic shock	2
Dermatitis psoriasiform	2
Drug eruption	2
Injection site hypersensitivity	2
Allergic cough	1
Allergic oedema	1
Allergic sinusitis	1
Allergy to surgical sutures	1
Circulatory collapse	1
Contrast media allergy	1
Contrast media reaction	1
Cutaneous vasculitis	1
Dermatitis atopic	1
Device allergy	1
Erythema multiforme	1
Eye oedema	1
Henoch-Schonlein purpura	1
Injection site rash	1
Periorbital oedema	1
Pruritus allergic	1
Rash maculo-papular	1
Rash pustular	1
Rash vesicular	1
Scrotal dermatitis	1

Shock	1
Swelling of eyelid	1
Symmetrical drug-related intertriginous and flexural exanthema	1

Table 5. Hepatic Adverse Events

Preferred Terms	**Total Cases**
Hepatic cirrhosis	25
Hepatic enzyme increased	15
Liver disorder	14
Hepatic steatosis	12
Alanine aminotransferase increased	9
Aspartate aminotransferase increased	7
Liver function test increased	7
Hepatic failure	6
Hepatic cancer	5
Ascites	3
Hepatocellular carcinoma	3
Jaundice	3
Ammonia increased	2
Gamma-glutamyltransferase increased	2
Hepatic enzyme abnormal	2
Hepatic function abnormal	2
Hepatic lesion	2
Hepatic neoplasm	2
Hepatitis	2
Hepatomegaly	2
Portal hypertension	2
Aspartate aminotransferase	1
Aspartate aminotransferase abnormal	1
Bilirubin urine present	1
Biopsy liver	1
Blood bilirubin increased	1
Blood fibrinogen decreased	1
Cholestasis	1
Drug-induced liver injury	1
Gastric varices haemorrhage	1
Hepatic cancer metastatic	1

Hepatic cyst	1
Hepatic mass	1
Hepatobiliary procedural complication	1
Hepatobiliary scan abnormal	1
Hepatosplenomegaly	1
Hepatotoxicity	1
International normalised ratio increased	1
Liver function test abnormal	1
Liver injury	1
Ocular icterus	1
Prothrombin time prolonged	1
Varices oesophageal	1

Table 6. Acute Kidney Injury

Preferred Terms	**Total Cases**
Renal failure	18
Renal impairment	14
Dialysis	10
Acute kidney injury	5
Peritoneal dialysis	1
Prerenal failure	1

Table 7. Infections

Preferred Terms	**Total Cases**
COVID-19	234
Pneumonia	131
Urinary tract infection	61
Localised infection	30
Nasopharyngitis	28
Infection	27
Cellulitis	25
Sepsis	25
Staphylococcal infection	18
Appendicitis	16
Tuberculosis	16
COVID-19 pneumonia	15
Diverticulitis	15
Post procedural infection	14
Sinusitis	13

Bronchitis	12
Kidney infection	12
Suspected COVID-19	11
Influenza	10
Wound infection	10
Abscess	9
Latent tuberculosis	9
Gastrointestinal infection	8
Skin infection	8
Bacterial infection	7
Botryomycosis	7
Food poisoning	7
Genital herpes	7
Herpes zoster	7
Wound infection staphylococcal	7
Abscess limb	6
Clostridium difficile infection	6
Ear infection	6
Fungal infection	6
Fungal skin infection	6
Purulent discharge	6
Upper respiratory tract infection	6
Coronavirus infection	5
Device related infection	5
Escherichia infection	5
Furuncle	5
Hepatitis C	5
Pneumonia bacterial	5
Pustule	5
Pyelonephritis	5
Septic shock	5
Staphylococcal sepsis	5
Appendicitis perforated	4
Bacteraemia	4
Candida infection	4
Cystitis	4
Laryngitis	4
Postoperative wound infection	4
Skin papilloma	4

Urosepsis	4
Viral infection	4
Abscess intestinal	3
Blister infected	3
Gastroenteritis	3
Infected skin ulcer	3
Infectious mononucleosis	3
Meningitis viral	3
Necrotising fasciitis	3
Osteomyelitis	3
Papilloma viral infection	3
Pharyngitis	3
Streptococcal infection	3
T-cell lymphoma	3
Tinea pedis	3
Tonsillitis	3
Abdominal abscess	2
Acarodermatitis	2
Arthritis infective	2
Asymptomatic COVID-19	2
Cardiac infection	2
Conjunctivitis	2
Epiglottitis	2
Eye infection	2
Gastroenteritis viral	2
Gingivitis	2
Groin abscess	2
Herpes ophthalmic	2
Herpes virus infection	2
Infected neoplasm	2
Joint abscess	2
Klebsiella infection	2
Lower respiratory tract infection	2
Medical device site abscess	2
Nail infection	2
Parotitis	2
Pneumonia viral	2
Purulence	2
Renal abscess	2
Respiratory tract infection	2

Rhinovirus infection	2
Staphylococcal bacteraemia	2
Tooth abscess	2
Acne pustular	1
Administration site cellulitis	1
Anal abscess	1
Arthritis bacterial	1
Atypical pneumonia	1
Bacterial vaginosis	1
Breast abscess	1
Bursitis infective	1
Cellulitis staphylococcal	1
Chikungunya virus infection	1
Chronic sinusitis	1
Cutaneous tuberculosis	1
Dengue fever	1
Diverticulitis intestinal perforated	1
Ebola disease	1
Encephalitis	1
Erysipelas	1
Escherichia sepsis	1
Escherichia urinary tract infection	1
Gallbladder empyema	1
Gastroenteritis bacterial	1
Gastrointestinal bacterial overgrowth	1
Guillain-Barre syndrome	1
HIV infection	1
Helicobacter infection	1
Hepatic infection	1
Hepatitis B	1
Hepatitis E	1
Herpes simplex	1
Hordeolum	1
Impetigo	1
Implant site infection	1
Infected cyst	1
Infection susceptibility increased	1
Infective thrombosis	1
Injection site abscess	1

Injection site cellulitis	1
Intestinal sepsis	1
Labyrinthitis	1
Liver abscess	1
Medical device site infection	1
Mycobacterium avium complex infection	1
Myiasis	1
Neurosyphilis	1
Norovirus infection	1
Oesophageal candidiasis	1
Onychomycosis	1
Ophthalmic herpes zoster	1
Opportunistic infection	1
Oral fungal infection	1
Oral herpes	1
Oral infection	1
Oropharyngeal candidiasis	1
Otitis media	1
Overgrowth bacterial	1
Paronychia	1
Pharyngitis streptococcal	1
Pilonidal cyst	1
Pneumocystis jirovecii pneumonia	1
Pneumonia fungal	1
Pneumonia mycoplasmal	1
Post procedural cellulitis	1
Post procedural pneumonia	1
Rash pustular	1
Rectal abscess	1
Respiratory tract infection bacterial	1
Respiratory tract infection fungal	1
Rhinitis	1
Scarlet fever	1
Shewanella algae bacteraemia	1
Skin bacterial infection	1
Spinal cord abscess	1
Spinal cord infection	1
Staphylococcal skin infection	1
Subcutaneous abscess	1

Syphilis	1
Testicular abscess	1
Tinea capitis	1
Tinea infection	1
Tonsillitis streptococcal	1
Tooth infection	1
Urethritis	1
Vibrio vulnificus infection	1
Vulvovaginal mycotic infection	1
Wound sepsis	1
Zika virus infection	1

Table 8. Opportunistic Infections

Preferred Terms	**Total Cases**
Tuberculosis	16
Herpes ophthalmic	2
Cutaneous tuberculosis	1
Infection susceptibility increased	1
Mycobacterium avium complex infection	1
Oesophageal candidiasis	1
Ophthalmic herpes zoster	1
Opportunistic infection	1
Pneumocystis jirovecii pneumonia	1
Pneumonia fungal	1
Respiratory tract infection fungal	1

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