CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761299Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	January 11, 2024
To:	Saharat Patanavanich Regulatory Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD 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 (MG) and Instructions for Use (IFU)
Drug Name (established name):	SIMLANDI (adalimumab-ryvk)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761299
Applicant:	Alvotech USA, Inc.

1 INTRODUCTION

On August 24, 2023, Alvotech USA, Inc., submitted for the Agency's review, a resubmission of Biologics License Application (BLA) #761299 for SIMLANDI (adalimumab-ryvk)**,** injection, a proposed biosimilar product to US-licensed HUMIRA (adalimumab).

Alvotech USA, Inc., is seeking approval of SIMLANDI (adalimumab-ryvk), injection for the following indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (PsO).

Alvotech USA, Inc. is seeking approval for the (b) (4) single-dose autoinjector SIMLANDI presentation.

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 Rheumatology and Transplant Medicine (DRTM) on December 1, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SIMLANDI (adalimumab-ryvk) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft SIMLANDI (adalimumab-ryvk) MG and IFU received on August 24, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 5, 2024.
- Draft SIMLANDI (adalimumab-ryvk) Prescribing Information (PI) received on August 24, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 5, 2024.
- Approved HUMIRA comparator dated November 3, 2023.

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 MG and 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 comparator 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 and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
01/11/2024 08:28:12 AM
DMPP review of SIMLANDI (adalimumab-ryvk) BLA 761299 MG and IFU

KYLE SNYDER
01/11/2024 08:30:49 AM

MARCIA B WILLIAMS
01/11/2024 08:42:31 AM

LASHAWN M GRIFFITHS
01/11/2024 09:09:51 AM

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

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

Memorandum

Date: January 8, 2024

To: Saharat Patanavanich, Senior Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

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

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for SIMLANDI® (adalimumab-ryvk) injection, for subcutaneous use

BLA: 761299

Background:
In response to DRTM's consult request dated December 1, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for SIMLANDI® (adalimumab-ryvk) injection, for subcutaneous use.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 5, 2024, and we do not have any comments at this time.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on January 5, 2024, and we do not have any comments at this time.

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

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/s/

KYLE SNYDER
01/08/2024 05:04:30 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	12/1/2023		
To:	Kakon Nowrin, CDER/OPQ/OPRO/DRBPMI/RBPMB2		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Division): ***optional**	Shruti Mistry, Acting Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: Engineering: ICCR 00942346 ICCR #00942346 Facilities: ICCR 00942360 ICCR #00942360		
Recommendation:	• CDRH recommends approval of the device constituents of the combination product. • Please see the attached memo from the original review for Facilities Inspection and related information.		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**
Florencia T. Wilson -S Digitally signed by Florencia T. Wilson -S Date: 2023.12.01 14:14:51 -05'00'	Shruti N. Mistry -S	Digitally signed by Shruti N. Mistry -S Date: 2023.12.05 17:23:05 -05'00'

1. SUBMISSION OVERVIEW

Table 1. Submission Information		
Consult Identification #	ICCR 00942346 (Engineering)	Case 00942346
	ICCR 00942360 (Facilities)	Case 00942360
Consult Request Link	See above	
ICC tracking #	ICC2300797	ICCR 00942346 (Engineering)
	ICC2300798	ICCR 00942360 (Facilities)
Submission Number	BLA 761299	
Sponsor	Alvotech USA Inc.	
Drug/Biologic	adalimumab-ryvk	
Indications for Use	Rheumatoid Arthritis (RA)	
Device Constituent	Auto Injector	
Related Files	BLA 761299, adalimumab-ryvk ICC2300035, Case 00891578 and ICC2300036, Case 00891581 ICC2200096, Case 00821318 ICC2000861, Case 00030275 and ICC2000863, Case 00030274	

	ICC2000400

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, Other:	**Engineering** ICCR 00942346 ICCR #00942346: OPQ requests CDRH review for this because this BLA original application resubmission because the application has information about pre-filled syringe (PFS) enclosed in an autoinjector (AVT02-AI). Therefore, we need CDRH consult for their evaluation on the device part. The assigned CDRH assessor will be invited to the CMC team meetings and to the OND Team meetings. Additional information will be provided via email communications.
	Facilities ICCR 00942360 ICCR #00942360: OPQ requests CDRH review for this because this BLA original application resubmission because the application has information about pre-filled syringe (PFS) enclosed in an autoinjector (AVT02-AI). Therefore, we need CDRH consult for their evaluation on the device part. The assigned CDRH assessor will be invited to the CMC team meetings and to the OND Team meetings. Additional information will be provided via email communications.
Device Presentation(s) being evaluated:	Auto Injector
Objective of this Memo:	The object of this memo is to determine if there are device constituent information to be reviewed.
Review **Comments**:	This current Complete Letter response (resubmission) is to address the deficiencies related to the Alvotech hf Iceland manufacturing facility inspection findings. There are no outstanding device constituent deficiencies. Therefore as stated in the previous ICCRs (ICC2300035/Case 00891578 and ICC2300036/Case 00891581), "As provided in the original review under ICC2200096, Case 00821318 CDRH recommends approval of the device constituents of the combination product."
Review **Recommendation**:	As provided in the original review under ICC2200096, Case 00821318 CDRH recommends approval of the device constituents of the combination product.

Related review memo:

BLA 761299.CDRH-OPEQ F

---END OF REVIEW---

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/s/

NOWRIN S KAKON
12/05/2023 06:45:57 PM
CDRH review is uploaded on behalf of CDRH assessors.

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:	December 14, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761299
Product Name, Dosage Form, and Strength:	Simlandi (adalimumab-ryvk) injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Alvotech USA Inc.
TTT ID #:	2023-3233-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader (Acting):	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 13, 2023 for Simlandi. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Simlandi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Vee, S. Label and Labeling Review for Simlandi (BLA 761299). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV 27. TTT ID No.: 2023-3233.

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/s/

SARAH K VEE
12/14/2023 12:05:44 PM

DAMON A BIRKEMEIER
12/14/2023 12:10:41 PM

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

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

Date of This Review:	November 27, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761299
Product Name, Dosage Form, and Strength:	Simlandi (adalimumab-ryvk) injection, 40 mg/0.4 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant:	Alvotech USA Inc.
FDA Received Date:	August 24, 2023 and November 23, 2023
TTT ID #:	2023-3233
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Simlandi (adalimumab-ryvk) injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Simlandi prescribing information, instructions for use, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On December 20, 2021, Alvotech submitted an original Biologics License Application (BLA) for Simlandi as a proposed interchangeable biosimilar to US-licensed Humira. However, the application received a Complete Response (CR) on December 20, 2022 and June 28, 2023 due to manufacturing facility deficiency. On August 24, 2023, the Applicant submitted a response to the CR.

We note that review of prescribing information, instructions for use, container label and carton labeling for Simlandi was conducted under BLA 761205 (see Appendix B) and crossed referenced in this review. BLA 761205 was submitted as a proposed biosimilar to US-licensed Humira. However, BLA 761205 received a CR on August 11, 2022. BLA 761205 is not being resubmitted at this time, nor has it been approved.

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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed prescribing information, instructions for use, and container label are acceptable from a medication error perspective did not identify areas of vulnerability that may lead to medication errors. However, our review identified areas for improvement for the carton labeling.

5 CONCLUSION & RECOMMENDATIONS

The proposed carton labeling is not acceptable from a medication error perspective, and we have provided recommendations for Alvotech in Section 5.1.

5.1 RECOMMENDATIONS FOR ALVOTECH USA INC.

We recommend the following be implemented prior to approval of this BLA:

A. Carton Labeling

1. The back panel contains redundant information that may be deleted to reduce clutter and increase readability. We recommend deleting the following statements: (b) (4) (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Simlandi received on August 24, 2023 from Alvotech USA Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Simlandi and the Listed Drug		
Product Name	Simlandi	Humira[a]
Initial Approval Date	N/A	12/31/2002
Nonproprietary Name	adalimumab-ryvk	adalimumab
Route of Administration	Subcutaneous injection	Subcutaneous injection
Dosage Form	injection	injection
Strength	Prefilled Pen: 40 mg/0.4 mL	Prefilled pen: 80 mg/0.8 mL, 40 mg/0.8 mL, and 40 mg/0.4 mL Prefilled syringe: 80 mg/0.8 mL, 40 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.4 mL, 20 mg/0.2 mL, 10 mg/0.2 mL, 10 mg/0.1 mL Single-dose glass vial for institutional use only: 40 mg/0.8 mL

[a] Humira [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Feb/2021. [cited 2023 OCT 13]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf.

Table 2. Relevant Product Information for Simlandi and the Listed Drug

Product Name

Simlandi

Humira[a]

Dose and Frequency

Simlandi

- Administer by subcutaneous injection.

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis:

- *Adults:* 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week.

Juvenile Idiopathic Arthritis:

Pediatric Weight 2 Years of Age and older	Recommended Dosage
30 kg (66 lbs) and greater	40 mg every other week

Crohn's Disease:

- *Adults:* 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15, and 40 mg every other week starting on Day 29.
- *Pediatric Patients 6 Years of Age and Older:*

Pediatric Weight	Recommended Dosage	
	Days 1 and 15	Starting on Day 29
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

Ulcerative Colitis:

- *Adults:* 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15, and 40 mg every other week starting on Day 29.
  Discontinue in patients without evidence of clinical remission by eight weeks (Day 57).

Plaque Psoriasis or Adult Uveitis:

- *Adults:* 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

Hidradenitis Suppurativa:

- *Adults*:
  - Day 1: 160 mg (given in one day or split over two consecutive days)
  - Day 15: 80 mg

Humira[a]

- Administer by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):

- *Adults:* 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week.

Juvenile Idiopathic Arthritis or Pediatric Uveitis (2.2):

Pediatric Weight 2 Years of Age and Older	Recommended Dosage
10 kg (22 lbs) to less than 15 kg (33 lbs)	10 mg every other week
15 kg (33 lbs) to less than 30 kg (66 lbs)	20 mg every other week
30 kg (66 lbs) and greater	40 mg every other week

Crohn's Disease (2.3):

- *Adults:* 160 mg on Day 1 (given in one day or split over two consecutive days); 80 mg on Day 15; and 40 mg every other week starting on Day 29.
- *Pediatric Patients 6 Years of Age and Older*:

Pediatric Weight	Recommended Dosage	
	Days 1 and 15	Starting on Day 29
17 kg (37 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 15: 40 mg	20 mg every other week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week

Ulcerative Colitis (2.4):

- *Adults:* 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15 and 40 mg every other week starting on Day 29. Discontinue in patients without evidence of clinical remission by eight weeks (Day 57).
- *Pediatric Patients 5 Years of Age and Older*:

Pediatric Weight	Recommended Dosage	
	Days 1 through 15	Starting on Day 29*
20 kg (44 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 8: 40 mg Day 15: 40 mg	40 mg every other week or 20 mg every week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 8: 80 mg Day 15: 80 mg	80 mg every other week or 40 mg every week

*Continue the recommended pediatric dosage in patients who turn 18 years of age and who are well-controlled on their HUMIRA regimen.

Plaque Psoriasis or Adult Uveitis (2.5):

- *Adults*: 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

Hidradenitis Suppurativa (2.6):

- *Adults:*
  - Day 1: 160 mg (given in one day or split over two consecutive days)
  - Day 15: 80 mg
  - Day 29 and subsequent doses: 40 mg every week or 80 mg every other week
- *Adolescents 12 years of age and older:*

Adolescent Weight	Recommended Dosage
30 kg (66 lbs) to less than 60 kg (132 lbs)	Day 1: 80 mg Day 8 and subsequent doses: 40 mg every other week
60 kg (132 lbs) and greater	Day 1: 160 mg (given in one day or split over two consecutive days) Day 15: 80 mg Day 29 and subsequent doses: 40 mg every week or 80 mg every other week

Table 2. Relevant Product Information for Simlandi and the Listed Drug		
Product Name	Simlandi	Humira[a]
	Day 29 and subsequent doses: 40 mg every week or 80 mg every other week	

Table 2. Relevant Product Information for Simlandi and the Listed Drug		
Product Name	Simlandi	Humira[a]
How Supplied	• SIMLANDI Pen Carton - 40 mg/0.4 mL (One Count) • SIMLANDI Pen Carton - 40 mg/0.4 mL (Two Count)	•HUMIRA Pen Carton -40 mg/0.8 mL •HUMIRA Pen Carton -40 mg/0.4 mL •HUMIRA Pen Carton – 80 mg/0.8 mL • HUMIRA Pen 40 mg/0.8 mL -Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa HUMIRA is supplied in a carton containing 6 alcohol preps and 6 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). • HUMIRA Pen 40 mg/0.4 mL -Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa HUMIRA is supplied in a carton containing 6 alcohol preps and 6 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). • HUMIRA Pen 80 mg/0.8 mL -Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa HUMIRA is supplied in a carton containing 4 alcohol preps and 3 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). • HUMIRA Pen 40 mg/0.8 mL -Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package HUMIRA is supplied in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package). • HUMIRA Pen 40 mg/0.4 mL -Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package HUMIRA is supplied in a carton • HUMIRA Pen 80 mg/0.8 mL and 40 mg/0.4 mL -Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package HUMIRA is supplied in a carton containing 4 alcohol preps and 3 dose trays (Psoriasis, Uveitis or Adolescent Hidradenitis Suppurativa Starter Package). •HUMIRA Pen 80 mg/0.8 mL – Starter Package for Pediatric Ulcerative Colitis (4 count) HUMIRA is supplied in a carton containing 4 alcohol preps and 4 dose trays (Starter Package for Pediatric Ulcerative Colitis). •Prefilled Syringe Carton -40 mg/0.8 mL HUMIRA is supplied in a carton containing two alcohol preps and two dose trays.

Table 2. Relevant Product Information for Simlandi and the Listed Drug		
Product Name	Simlandi	Humira[a]
		•Prefilled Syringe Carton -40 mg/0.4 mL HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. •Prefilled Syringe Carton -20 mg/0.4 mL HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. •Prefilled Syringe Carton -20 mg/0.2 mL HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. •Prefilled Syringe Carton -10 mg/0.2 mL HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. •Prefilled Syringe Carton -10 mg/0.1 mL • HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (6 count) HUMIRA is supplied in a carton containing 6 alcohol preps and 6 dose trays (Pediatric Starter Package). • HUMIRA Prefilled Syringe 80 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (3 count) HUMIRA is supplied in a carton containing 4 alcohol preps and 3 dose trays (Pediatric Starter Package).. • HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (3 count) • HUMIRA Prefilled Syringe 80 mg/0.8 mL and 40 mg/0.4 mL -Pediatric Crohn's Disease Starter Package (2 count) HUMIRA is supplied in a carton containing 2 alcohol preps and 2 dose trays (Pediatric Starter Package). • Single-Dose Institutional Use Vial Carton -40 mg/0.8 mL

Table 2. Relevant Product Information for Simlandi and the Listed Drug		
Product Name	Simlandi	Humira[a]
Storage	Do not use beyond the expiration date on the container. SIMLANDI must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, SIMLANDI may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. SIMLANDI should be discarded if not used within the 14-day period. Record the date when SIMLANDI is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store SIMLANDI in extreme heat or cold.	Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store HUMIRA in extreme heat or cold.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 26, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "Simlandi" and "AVT02". Our search identified two previous reviews[b,c] and we confirmed that our previous recommendations were implemented.

[b] Patel, M. Label and Labeling Review for Simlandi (BLA 761205). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 22. TTT ID No.: 2022-2360.

[c] Barlow, M. Human Factors Study Results & Label and Labeling Review for Simlandi (BLA 761205). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 15. RCM No.: 2020-1887 and 2020-1888.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Simlandi labels and labeling submitted by Alvotech USA Inc..

- Container label received on November 23, 2023
- Carton labeling received on November 23, 2023
- Instructions for Use (Image not shown) received on March 24, 2023, available from \\CDSESUB1\evsprod\BLA761205\0068\m1\us\114-labeling\114a-draft-label
- Prescribing Information (Image not shown) received on August 24, 2023, available from \\CDSESUB1\evsprod\BLA761299\0025\m1\us\114-labeling\114a-draft-label
- Medication Guide received on August 24, 2023, available from \\CDSESUB1\evsprod\BLA761299\0025\m1\us\114-labeling\114a-draft-label

F.2 Label and Labeling Images

Container label

Blister Label

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

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/s/

SARAH K VEE
11/27/2023 03:21:39 PM

MISHALE P MISTRY on behalf of IDALIA E RYCHLIK
11/28/2023 08:40:31 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	4/6/2023		
To:	Kakon Nowrin, CDER/OPQ/OPRO/DRBPMI/RBPMB2		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Division): *optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: **Engineering**: ICC2300035 ICCR #00891578 **Facilities**: ICC2300036 ICCR #00891581		
Recommendation:	• CDRH recommends approval of the device constituents of the combination product. • Please see the attached memo from the original review for Facilities Inspection and related information.		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**
Florencia T. Wilson -S Digitally signed by Florencia T. Wilson -S Date: 2023.04.07 14:42:34 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2023.04.07 15:09:21 -04'00'	

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR# **Engineering**: ICC2300035 ICCR #00891578 **Facilities**: ICC2300036 ICCR #00891581
Consult Request Link	Engineering Facilities
ICC tracking #	See Consult Identification above
Submission Number	BLA 761299
Sponsor	Alvotech USA Inc.
Drug/Biologic	adalimumab-ryvk
Indications for Use	Rheumatoid Arthritis (RA)
Device Constituent	Auto Injector
Related Files	BLA 761299, adalimumab-ryvk ICC2200096, Case 00821318 ICC2000861, Case 00030275 and ICC2000863, Case 00030274 ICC2000400

2. CDRH REVIEW

<table>
<tr><td>ICC Review Request from CDER/OPQ, Other:</td><td>Engineering:
OPQ requests CDRH review for this because this BLA has information about pre-filled syringe (PFS) enclosed in an autoinjector (AVT02-AI). Therefore, we need CDRH consult for their evaluation on the device part. The assigned CDRH assessor will be invited to the CMC team meetings and to the OND Team meetings. Additional information will be provided via email communication.

Facilities:
Request consult for device facility --this is a biologic-device combination product (pre-filled syringe (PFS) enclosed in an autoinjector (AVT02-AI). The assigned CDRH assessor will be invited to the CMC team meetings and to the OND Team meetings. Additional communications will be shared via email.</td></tr>
<tr><td>Device Presentation(s) being evaluated:</td><td>Auto Injector</td></tr>
<tr><td>Objective of this Memo:</td><td>Background information
This BLA (BLA 761299) is related to BLA 761205. BLA 761205 application is for Biosimilar to the licensed Humira and BLA 761299 is proposed to be interchangeable biosimilar (which was submitted subsequently with BLA 299205).
Both applications have the exact same drug product and device constituent. The following are background information for the 2 BLAs:
<table>
<tr><td>BLA 761205
ICC 2000861 and 2000863
Case 00030275 and 00030274</td><td>BLA761299
ICC2200096
Case 00821318</td></tr>
<tr><td>(b) (4)</td><td>During the initial review of this proposed biosimilar interchangeable, this reviewer inquired with CDER if we can asked for the response to the 2 additional comments provided in BLA 761205 (because at that time, this application was on CR hold) and the team agreed. The Sponsor provided the response to the additional comments and this reviewer found it to be adequate.
It is also noted that PAI was recommended for both applications.
The update on this BLA is that the Sponsor removed (b) (4) (b) (4) from its facilities.
It is noted that the facilities inspection from BLA 761205 received a VAI and CDER requested CDRH to review or provide comments to the 2nd observation in the EIR. The 2nd observation was about the</td></tr>
</table></td></tr>
</table>

	Validation/Qualifications (b) (4) [redacted] Based on the provided response to Observation #2 of the FDA Form 483, (b) (4) [redacted] addressed Observation #2 and effectiveness check were performed and no elevated rejects observed. CDRH does not have further issues with the Observation related to the device. In conclusion to the review of BLA 761299, CDRH recommended approval of the device constituents of the combination product.
CR'd on 8/11/2022 Facilities inspection in which deficiencies where conveyed to the representative of facilities (note that there was a delay in inspection for this BLA due to COVID-19 pandemic and eventually inspection was performed on March 10-18, 2022 which applies to both BLAs). It is noted that the inspection received VAI – this was reviewed in BLA 761299.	CR'd on 12/20/2022 Since this BLA is related to BLA 761205, it was also CR'd because of the recommendations from the facilities inspection and at this time, the Sponsor has not responded to the deficiencies from BLA 761205. CDRH did not have any outstanding issues in the CR letter.
Resubmitted on 10/13/2022	Resubmitted on 12/28/2022
	CDRH was consulted for this resubmission for Engineering and facilities.

Although CDRH did not have any CR deficiencies or Additional comments, we were consulted because the BLA 761299 resubmission has information about the device constituents of the combination product.
The objective of this review is to look at the reviewer's guide and address any pertinent comments related to CDRH related documents. The reviewer's guide is located in Seq 0021, 1.2, Reviewer's Guide – Resubmission 28Dec2022, Section 5. This reviewer looked at Module 3CMC section and documents were compared from Seq 0019 to applicable sequence that is in the purview of CDRH.
The following are the modules that this reviewer looked at.

3.2.P.3.5.1 Transport Validation	Process Validation and/or Evaluation	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However, reverting to its earlier sequence (0009), as these amendments will now be submitted as CMC Supplements after the BLA approval.

Table 8 Functional Testing Results for AVT02-AI

			Results			
	Product		AVT02-AI40			
	Batch n°		IL200001		IL200002	
	ASTM Simulation		D4169-16 (pallet)	D7386-16 (single shipper)	D4169-16 (pallet)	D7386-16 (single shipper)
Quality attribute	Acceptance criteria	Parameter				
Delivery time	(b) (4)	Mean (s)	5.1	5.5	3.7	3.9
		Minimum (s)	4.4	4.6	3.2	3.6
		Maximum (s)	5.9	7.2	4.4	4.6
		Standard deviation	0.4	0.6	0.3	0.2
Delivered dose		Mean (mL)	0.4176	0.4167	0.4090	0.4088
		Minimum (mL)	0.4126	0.4132	0.4008	0.4038
		Maximum (mL)	0.4201	0.4207	0.4135	0.4142
		Standard deviation	0.0019	0.0021	0.0033	0.0022
Needle extension		Mean (mm)	5.46	5.39	5.35	5.20
		Minimum (mm)	5.10	4.97	4.88	4.69
		Maximum (mm)	5.79	5.74	5.73	5.93
		Standard deviation	0.194	0.205	0.215	0.282
Actuation force		Mean (N)	6.450	6.437	6.445	6.376
		Minimum (N)	5.998	6.017	5.976	5.914
		Maximum (N)	7.089	7.485	6.986	7.409
		Standard deviation	0.319	0.394	0.246	0.364
Nondestructive visual inspection	Visually intact	PASS/FAIL	PASS	PASS	PASS	PASS
Lock Out Force		PASS/FAIL	PASS	NT	PASS	NT

NT = Not tested

Data was reviewed and it is similar on both sequence. Adequate

3.2.P.2.3.2	Manufacturing Process Development – AVT02-AI	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However, reverting to its earlier sequence (0014), as this amendment will now be submitted as CMC Supplement after the BLA approval.

The content of 3.2.P.2.3.2 was reviewed and found no changes in the same document in Sequence 0019 and 0014. Adequate

3.2.P.2.4.2	Container closure system	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However,
		reverting to its earlier sequence (0001), as this amendment will now be submitted as CMC Supplement after the BLA approval.

The content of 3.2.P.2.4.2 was reviewed and found no changes in the same document in Sequence 0019 and 0001. Adequate

3.2.P.3.3.2	Description of manufactuirng process and process controls	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However, reverting to its earlier sequence (0001), as this amendment will now be submitted as CMC Supplement after the BLA approval.

The content of 3.2.P.2.3.2 was reviewed and found no changes in the same document in Sequence 0019 and 0001. Adequate

3.2.P.3.4.2	Controls of critical steps and intermediates	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However, reverting to its earlier sequence (0001), as this amendment will now be submitted as CMC Supplement after the BLA approval.

The content of 3.2.P.3.4.2 was reviewed and found no changes in the same document in Sequence 0019 and 0001. Adequate

3.2.P.3.5.2	Process validation and/or evaluation	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However, reverting to its earlier sequence (0001), as this amendment will now be submitted as CMC Supplement after the BLA approval.

The content of 3.2.P.3.5.2 was reviewed and found no changes in the same document in Sequence 0019 and 0001. Adequate

3.2.P.7.2	Container closure system	This section was updated in sequence 0019, during the CMC Amendment submission with information outside the inspection related issues, dated November 29, 2022. However, reverting to its earlier sequence (0001), as this amendment will now be submitted as CMC Supplement after the BLA approval.

The content of 3.2.P.7.2 was reviewed and found no changes in the same document in Sequence 0019 and 0001. Adequate

Review **Comments**:	After review of the reviewer's guide the following subsections above are reviewed and I didn't find any discrepancies.
Review **Recommendation**:	As provided in the original review under ICC2200096, Case 00821318 CDRH recommends approval of the device constituents of the combination product.

Facilities Information

The following are taken from ICC2200096, Case 00821318 (Please see Salesforce for the full memo -ICCR 00821318):

Firm Name:	Alvotech hf
Address:	Sæmundargata 15-19, Reykjavik, 101, Iceland
FEI:	3013702557
Responsibilities:	Manufacturing of AVT02-DP PFS, release testing and stability testing. Container closure integrity testing for AVT02-DP PFS release and stability. AVT02-AI identity release testing. AVT02-AI release testing and stability testing (device functional testing). AVT02-AI batch release.

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 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:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Container closure integrity testing for AVT02-DP PFS stability

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

Firm Name:	(b) (4)
Address:	(b) (4)

FEI:	(b) (4)
Responsibilities:	Assembly of AVT02-AI, secondary packaging, labelling, batch release

***Note from review of BLA 761205**

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Assembly of AVT02-AI, Secondary packaging, Labeling. Update at the midcyle meeting in Feb 2021 – release testing moved (b) (4) to Alvotech, (b) (4) will no longer do release testing.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4) The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

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

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4) The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

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

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Reviewer Comment

Alvotech hf:
It is noted that under BLA 761205 (Biosimilar application - approval pending due to delay in facility inspection), the CDRH reviewer recommended PAI because the firm is responsible for major activities related to the manufacturing. It is also noted from CDER (Madushini Dharmasena, CDER/OPQ/OPMA/DBM/BMB2) that there is a scheduled inspection on March 10-18, 2022. An inspector with device specialty will also be accompanying Ms. Dharmasena).

(b) (4)

This manufacturer is added to BLA 761299, however, the major responsibility of this firm is Container closure integrity testing for AVT02-DP PFS stability

Alvotech commits to provide additional data for 3 batches of AVT02-DP-PFS, 3batches AVT02-AI and 3 batches of assembled AVT02-AI post transport validation(real world and simulated shipping) using the validated spectrophotometric dye ingress method in May 2021.CCIT testing is always performed after shipping due to the different locations of the AVT02 manufacturing and assembly facilities and the CCIT testing facility. The shipping flow for the AVT02 AI is as follows. (b) (4)

(b) (4)

Under BLA 761205, a PAI is recommended, but delayed.

(b) (4)

Removed per the application and CDER

From Mid-Cycle meeting:

- **Alvotech hf (Iceland,** FEI: 3013702557): Manufacture of DS/PFS DP, AVT02-AI assembly, secondary packaging, labeling, in-process testing, release testing, and stability testing
  - Pre-license inspection (PLI) to support BLA 761205 and BLA 761299 facilities conducted March 10-17, 2022. The inspection concluded with a 13-item Form 483. Initial recommendation is withhold.
  - The final recommendation will be determined by the compliance reviewer after reviewing responses to the 483.
- (b) (4) AVT02-AI assembly, secondary packaging, labeling, and batch release.
  - Inspection is Scheduled (b) (4)
  - Based on a conversation with CDER, the inspection received a VAI

EIR/FORM 483:

CDRH recommended a PAI for the device constituents of the combination product (autoinjector) which resulted in a VAI recommendation. Per the FDA Form 483, there were three observations. The 2nd on observation which is related to Validation/Qualifications (b) (4) lack the following:

(b) (4)

(b) (4)

Based on the provided response to Observation #2 of the FDA Form 483, (b) (4) addressed Observation #2 and effectiveness check were performed and no elevated rejects observed. CDRH does not have further issues with the Observation related to the device.

Related review memo:

BLA 761299.CDRH-OPEQ

BLA 761205 CDRH OPEQ Review ICC200

---END OF REVIEW---

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/s/

NOWRIN S KAKON
04/07/2023 03:31:37 PM
CDRH review is uploaded on behalf of CDRH assessors.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date :	12/21/2022
From:	Division of Pediatrics and Maternal Health (DPMH)
To:	DMEPA and DRTM
BLA Number:	761299
Drug Product:	AVT-02 (adalimumab-ryvk)
Applicant:	Alvotech USA Inc.

DMEPA submitted a consult request to DPMH on August 25, 2022, to attend consult meetings and provide input on the discussion for the CUHF study and the need for a pediatric user group.

DPMH participated in multiple internal team meetings (September 9 and September 30, 2022) with the review team to discuss the review issues with the application. In addition, DPMH participated in the Late cycle meeting on November 11, 2022. During these meetings, it was communicated and confirmed that the plan for the current application was a Complete Response Action for both biosimilar and interchangeable BLAs.

DPMH has no further comments at this time, thus, this memorandum will close out the consult request. If additional input is needed upon resubmission, DPMH may be re-consulted.

DPMH Pediatric MO Reviewer – Karen Fratantoni
DPMH Pediatric Team Leader – Shetarra Walker
DPMH RPM – Jacquline Yancy
DPMH CPMS- George Greeley

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/s/

JACQULINE A YANCY
03/03/2023 01:25:40 PM

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

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

Memorandum

Date: December 27, 2022

To: Susan Rhee, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

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

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for Simlandi (adalimumab-ryvk) injection, for subcutaneous use

BLA: 761299

This memo is in response to DRTM's labeling consult request dated March 7, 2022. OPDP defers comment on the proposed labeling at this time, and requests that DRTM submit a new consult request during the subsequent review cycle. If you have any questions, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
12/27/2022 04:49:37 PM

DATE: December 20, 2022

FROM: Division of Rheumatology and Transplant Medicine,
Office of Immunology and Inflammation,
Office of New Drugs, CDER

SUBJECT: BLA 761299, submitted by Alvotech USA Inc.

TO: BLA 761299, submitted by Alvotech USA Inc.

This memorandum is to document Division of Rheumatology and Transplant Medicine's rationale for the determination that the information provided in support of the AVT02 autoinjector is sufficient to support its approval as an interchangeable biosimilar to the Humira Pen.

I. Device Similarities and Differences Between Humira Pen and AVT02 Autoinjector

A. Humira Pen and AVT02 Autoinjector Devices Physical Comparison

Both the Humira Pen and the AVT02 autoinjector are prefilled, single-use devices that are designed to deliver a subcutaneous injection of adalimumab in the abdomen or thigh. Both the injectors deliver a 40 mg/0.4 mL dose.

The two other differences between them are:

1) [Fig 1 below] Humira Pen has two caps (gray and plum)—one covers the needle end and the other covers the end of the pen with the injection button. In contrast, AVT02 autoinjector has one clear, colorless cap over the needle end.
2) [Fig 2 below] Underneath Cap 2 of the Humira Pen, there is a plum injection button which users must press to initiate the injection; whereas for AVT02, users need only to press the pen down onto the injection site to initiate the injection. Therefore, AVT02 does not have an injection button, and no second cap exists.

An assessment of these two major differences will be discussed further in the context of the comparative use human factor study results below.

Humira Autoinjector (Reference Product)	AVT02 Autoinjector (Proposed Interchangeable Biosimilar Combination Product)
	(b) (4)

Similarities: Both autoinjectors have a cap that protects the needle.

Differences: The Humira autoinjector has two caps (one on each end) that must be removed before the user can inject their dose. The AVT02 autoinjector only has a single cap that must be removed before injection. The shape of the cap that protects the needle also differs. The AVT02 cap includes an extra plastic lip at the base of the cap to support users with limited hand dexterity and strength in removing the cap.

Figure 1: Source: AVT02 Autoinjector Threshold Analysis Report, 3.2b Cap Design, BLA 761299, Orig Sub, Section 5.3.5.4, submitted 12/20/21

Humira Autoinjector (Reference Product)	AVT02 Autoinjector (Proposed Interchangeable Biosimilar Combination Product)
	(b) (4)

Similarities: None.

Differences: The AVT02 autoinjector does not have a button. This difference was intentionally included in the design to eliminate the requirement to push a button to initiate the injection. This enabled removal of two active tasks (removal of a second cap and the requirment to push the button) that now cannot be done in error.

Figure 2: Source: AVT02 Autoinjector Threshold Analysis Report, 3.2f Injection Button, BLA 761299, Orig Sub, Section 5.3.5.4, submitted 12/20/21

Humira Autoinjector (Reference Product)	AVT02 Autoinjector (Proposed Interchangeable Biosimilar Combination Product)
	(b) (4)
Similarities: Both autoinjectors include a colored plunger rod to give the user feedback while the device is injecting. In addition, for both autoinjectors the plunger stops moving and is visible inside the viewing window when the injection is complete. **Differences:** The Humira Pen has an arrow indicating the direction of the needle end. The elimination of the second cap and button have obviated the need for the arrow on the AVT02 injector.	

Figure 3: Source: AVT02 Autoinjector Threshold Analysis Report, 3.2d Plunger Rod, BLA 761299, Orig Sub, Section 5.3.5.4, submitted 12/20/21

With respect to other aspects of the devices pertaining to the injection, there are parallels with each device. As shown in Fig 3 above, both devices have colored plunger rods that move down into the viewing window as the injection completes (yellow for Humira and orange for AVT02), injection hold times are instructed to be 10 secs for both (although injection duration is less than half that time—see performance characteristics below) and both have needle sleeves that descend and lock over the needle as the injectors are lifted from the skin.

B. Humira Pen and AVT02 Autoinjector Performance Characteristics

Generally, the performance characteristics of the Humira Pen and AVT02 Autoinjector are overlapping. However, two performance characteristics are not overlapping (Table 1, in yellow):

Table 1: Summary of Performance Characteristics

Performance Characteristic	Humira Pen (mean ± SD)	AVT02 Autoinjector (mean ± SD)
Force to push pen down (N)	16.31 ± 1.40	6.65 ± 0.47
Force to hold pen down, complete injection (N)	7.15 ± 0.68	5.10 ± 0.15
Injection Duration (s)	3.53 ± 0.16	4.48 ± 0.41
Needle extension (mm)	7.07, 7.27	6.01 ± 0.11
Needle cap removal force (N)	8.93 ± 1.00	18.26 ± 2.98
Injection button cap removal force (N)	11.11 ± 0.90	n/a

Source: AVT02 Autoinjector Threshold Analysis Report, 3.2g Performance Characteristics, BLA 761299, Orig Sub, Section 5.3.5.4, submitted 12/20/21

- The force needed to push the needle guard down, in preparation for an injection, is higher with Humira Pen than for the AVT02 autoinjector ((b) (4) N). However, the main difference here is that pushing down on the pen will activate the AVT02 autoinjector to initiate injection, whereas for the Humira Pen, the injector button must be pushed to initiate an injection.
    - One would anticipate that users who are Humira-experienced may be surprised by the initiation of the injection with pushing the AVT02 autoinjector down, and this may cause a startle reflex that results in pulling the injector up before the injection has completed.
    - Premature removal of the autoinjector from the skin was a use error observed in the human factors validation study HFVP-AI (refer to Task 19 in Table 3 below) for which participants showed learning over subsequent use attempts. We note that while there appeared to be a learning effect over multiple injections in the HF Validation Study, it is difficult to interpret how well this learning effect would translate to actual use of the product because in actual use, it would not be typical for a user to perform multiple injections.
- The force needed to remove the needle cap, is higher with the AVT02 injector than with Humira Pen (18.26 vs 8.93 N).
    - This higher force is also within the known feasible hand grip forces generated by adults with arthritis ((b) (4) N)[1] and children as young as 8 to 12 years ((b) (4) N)[2]. It is also likely that the younger and weaker children would have an adult caregiver available to assist with cap removal, if needed.
    - In the human factors validation study HFVP-AI, more adults than juvenile idiopathic arthritis (JIA) patients had difficulty with cap removal (refer to Task 14 in Table 3 below). All user groups improved their performance of this task over subsequent use attempts.

C. Humira Pen and AVT02 Autoinjector Task Comparison

The key tasks that might be impacted by design differences between the AVT02 autoinjector and the Humira pen are highlighted in yellow in Table 2 below. The many steps involved in storage and handling and pre-/post- injection activities are identical. The key questions are: 1) whether one vs. two caps prevents successful injection or disorients the user as to which end of the injector to point to the injection site; and 2) whether the lack of having to press a button to initiate injection prevents successful injection—either by a user not knowing how to initiate injection or being surprised by the initiation of injection without pressing the button and prematurely lifting the injector off the skin. These questions were evaluated in the human factors validation study HFVP-AI and the comparative use human factor (CUHF) study, to be discussed in further detail below.

Table 2: Task Comparison

Humira Pen	AVT02 Autoinjector
Take out of refrigerator	Identical
Leave at Room Temperature for 15 to 30 minutes	Identical
Check expiration date on Pen label	Identical

[1] Source: Sferra da Silva, G., de Almeida Lourenço, M. & de Assis, M.R. Hand strength in patients with RA correlates strongly with function but not with activity of disease. Adv Rheumatol 58, 20 (2018). https://doi.org/10.1186/s42358-018-0020-1

[2] Source: Barbir et al., Designing auto-injectors for children: Effect of form factor on the human factors of efficient drug delivery. J Allergy and Clin Immunol February 2015, 135(2): Supplement AB210. Abstract 678.

Gather/place supplies	Identical
Wash and dry your hands	Identical
Choose an injection site	Identical
Prepare injection site	Identical
Inspect the Drug	Identical
Remove and Dispose of Gray and Plum Caps	Remove and dispose of single clear cap
Orient pen so needle end points toward injection site	Identical
Check device for medication damage and exp. date	Identical
Pinch skin	Identical
Position autoinjector straight (90°) against injection site	Identical
Press down to collapse needle guard against skin	Identical
Press button to activate dose—initial audible click	Dose is activated in pressing injector down against skin—initial audible click is same
Maintain pen position during injection—count for 10 seconds and observe dose window indicator color chg.	Maintain pen position during injection, also for 10 secs; observe dose window indicator color chg. or wait for audible second click
Lift autoinjector from skin when injection complete	Identical
Treat injection site	Identical
Dispose into sharps container	Identical
Store in refrigerator or at room temp for up to 14 days	Identical

Adapted from Section 3.1a of AVT02 Threshold Analysis Report

II. Results of AVT02 Human Factors Validation Study hfvp-ai[3]

The human factors (HF) validation study protocol for the proposed prefilled pen (PFP) presentation was submitted and designed in early 2019 in conjunction with review and advice provided by FDA. The study was conducted by a contract research organization (b) (4) at 3 different sites in the US (Chicago, Los Angeles, and San Francisco). A total of 60 participants were enrolled: 15 Rheumatoid Arthritis (RA) patients (6 Humira-experienced, 9 Humira-naïve); 15 adolescent juvenile idiopathic arthritis (JIA) patients ages 12 to 17 years (5 Humira-experienced, 10 Humira-naïve); 15 lay caregivers; and 15 healthcare providers (HCP).

All pts were untrained. Each participant attended one test session which included three simulated use scenarios and a knowledge task scenario:

- Use scenario 1: Administer a 40 mg dose. Participants were required to simulate all tasks related to preparation and administration of the proposed product. If a participant was unsuccessful in delivering a full dose (trial 1), they were asked to complete another trial (trial 2) without being informed they had committed any use issues. If they were still unsuccessful, they were asked to complete a "probing trial" (trial 3) using the instructions as a guide without the moderator indicating whether the behavior was correct or incorrect. The probing trial was completed after all simulated use scenarios were complete, to avoid biasing participant performance.
- Use scenario 2: 80 mg dose. This simulated scenario only evaluated knowledge of the tasks, i.e., identifying correct injection sites and correct number of AI needed to achieve the respective dose.

[3] BLA 761205, Orig Sub, Section 5.3.5.4, Submitted 09/04/2020; also in BLA 761299, Section 5.3.5.4, submitted 12/20/21; DMEPA review archived under BLA 761205, dated 9/15/21

- Use scenario 3: 160 mg dose. This simulated scenario also only evaluated knowledge of the tasks, i.e., identifying correct injection sites and the correct number of AI needed to achieve the respective dose.
- Knowledge Based Tasks
    - This included a series of questions evaluating participants' ability to detect and comprehend critical information provided in the product labeling.

A compilation summary of use task results from the HF validation study HFVP-AI, by user group, may be found in Table 3 below. Critical tasks directly related to successful administration of a dose using the device are highlighted in yellow. For the critical tasks needed to use the device, i.e., identifying allowable injection sites, removing the needle cap, orienting the injector correctly, pushing the autoinjector down (including sufficient hold time), JIA patients performed similarly to adult RA patients and caregivers. Similar to adult RA patients and caregivers, learning for a given task occurred across three trials for JIA patients.

Table 3: Summary of use task results from HF Validation Study HFVP-AI

Use Task Descriptions	RA	JIA	Caregivers	HCPs
Participant Demographics				
○ Age (yrs)	○ 53 (30, 68)	○ 14 (12, 17)	○ 50 (34, 63)	○ 37 (23, 61)
○ Gender	○ M=12; F=3	○ M=4; F=11	○ M=4; F=11	○ M=1; F=14
○ Handedness	○ R=14; L=1	○ R=14; L=1	○ R=13; L=2	○ R=15; L=0
○ Injection Experience	○ Yes=6; No=9	○ Yes=5; No=10	○ Yes=8; No=7	○ 12 yrs (0.75-35)
Summary results of all tasks for 40 mg injection:				
Overall administration success: By Trial 1: 53/60 (88%); By Trial 2: 57/60 (95%); By Trial 3: 60/60 (100%)				
Trial 1	33 UE, 8 UD	36 UE, 5 UD	33 UE, 1 UD	12 UE, 1 UD
Trial 2	5 UE, 1 UD	14 UE, 2 UD	6 UE,	0
Trial 3	1 UE, 1 UD	5 UE	3 UE	0
Results for individual tasks, by trial 1/trial 2/trial 3, as applicable				
1. Storage	3/1/0 UE 1/0/0 UD	2/0/0 UE	0/0/0	0/0/0
2. Open packaging and remove device from packaging	0/0/0	1/1/0 UD	0/0/0	0/0/0
3. Take device out of refrigerator				
4. Record date of removal from refrigerator				
5. Confirm correct product				
6. Inspect product				
7. Inspect expiration date				
8. Warm drug	4/0/0 UE 1/0/0 UD	2/0/0 UE	3/0/0 UE	2/0/0 UE
9. Gather injection supplies	0/0/0	0/0/0	0/0/0	0/0/0
10. Wash hands	2/0/0 UE	5/2/1 UE	4/0/0 UE	0/0/0
11. Identify allowable injection sites	1/0/0 UE	2/0/0 UE	2/0/0 UE	0/0/0
12. Clean injection site	1/0/0 UE	3/2/1 UE	3/0/0 UE	0/0/0
13. Inspect drug				
14. Remove needle cap	11/1/0 UE 2/0/0 UD	3/2/1 UE 3/1/0 UD	5/2/1 UE	3/0/0 UE 1/0/0 UD
15. Dispose of needle cap	0/0/0	0/0/0	0/0/0	0/0/0
16. Point needle sleeve toward injection site	0/0/0	0/0/0	0/0/0	0/0/0
17. Pinch skin	2/1/0 UE	5/2/1 UE	9/2/11 UE	3/0/0 UE

18. Place needle sleeve against injection site	0/0/0	0/0/0	0/0/0	0/0/0
19. Push autoinjector down against injection site	2/0/0 UE 4/1/1 UD	3/2/0 UE 1/0/0 UD	4/1/0 UE 1/0/0 UD	0/0/0
20. Pull autoinjector from skin	0/0/0	0/0/0	0/0/0	0/0/0
21. Check injection site for liquid	0/0/0	0/0/0	0/0/0	0/0/0
22. Treat injection site	6/2/1 UE	9/2/1 UE	2/1/1 UE	4/0/0 UE
23. Dispose of device	1/0/0 UE	2/2/0 UE	1/0/0 UE	0/0/0
24. Dispose of injection supplies	0/0/0	0/0/0	0/0/0	0/0/0
1. Use 2 autoinjectors for 80 mg dose	0	2 UE, 1 UD	0	0
2. Choose injection sites for 80 mg dose	1 UE	1 UE	0	0
1. Use 4 autoinjectors for 160 mg dose	0	2 UE	1 UE	1 UE
2. Choose injection sites for 160 mg dose	2 UE, 2 UD	3 UE	1 UE	2 UE, 1 UD

UE=Use Error; UD=Use Difficulty; slashes separate trials, i.e., Trial 1/Trial 2/Trial 3, as applicable

For certain tasks not specific to the operation of the device and knowledge-heavy tasks (e.g. scenario 2 and 3, highlighted in orange in Table 3 above, and the knowledge based questions below in Table 4) JIA patients appeared to have more difficulty finding and understanding the information. However, this does not raise a concern regarding the AVT02 pen that would need to be further assessed in a CUHF study in adolescents to support an interchangeability determination because the 80 mg and 160 mg doses are mainly loading doses, given on initiation of therapy, when switching between products is not likely to occur. The 80 mg dose may also be an alternative maintenance regimen for larger (likely older) adolescents with ulcerative colitis. Finally, other knowledge-heavy tasks related to the general storage and handling of the medicine are likely to be in the purview of the heads of the household (adult guardians or parents) unless intentionally deferred to a responsible adolescent.

Table 4: AVT02 HF Validation Study Knowledge Task Results

Knowledge-based questions	RA results	JIA results	Caregivers	HCPs
Summary of results	Understanding: 2 I, 1 DU; Locating: 14 UE 6 UD	Understanding: 1 I, 2 DU; Locating: 22 UE, 0 UD	Understanding: 2 I, 4 DU; Locating: 11 UE, 3 UD	Understanding: 1 I, 1 DU; Locating: 7 UE, 1 UD
What is the name of the drug in this autoinjector?	0/0	0/0	0/0	0/0
What is the expiration date of this autoinjector?	0/0	0/0	0/0	0/0
How should you protect the autoinjector from light exposure?	Understanding: 0; Locating 1 UD, 5 UE	Understanding 0; Locating 6 UE	Understanding: 1I; Locating 1 UD, 5 UE	Understanding: 1 DU; Locating: 1 UD, 2 UE
Where should the autoinjector be stored at home?	0/0	0/0	0/0	0/0
Should you ever freeze your autoinjector?	0/0	0/0	0/0	0/0
Let's imagine that you left your autoinjector in the car all day on a 100F day. Should you use it?	0/0	Understanding 0; Locating 2 UE	Understanding 1 DU; Locating 1 UE	0/0
Let's imagine that you left your autoinjector in your car all day when it is 0F outside. Should you use it? What about if you thawed it first?	0/0	Understanding 0; Locating 2 UE	Understanding 1I; Locating 2 UE	0/0

Should you use the autoinjector if it has been left in direct sunlight?	Understanding: 0; Locating 1 UD, 4 UE	Understanding 0; Locating 7 UE	Understanding 2 DU; Locating 2 UE	Understanding: 0; Locating: 4 UE
After removing the autoinjector from the refrigerator, how should you warm it?	Understanding: 0; Locating 1 UE	0/0	0/0	Understanding 1 I; Locating 1 UE
How long can you leave the autoinjector out at room temp?	Understanding 0; Locating 1 UD	Understanding 1 DU; Locating 1 UE	Understanding 1 DU; Locating 1 UD, 1 UE	0/0
After the injection how should you dispose of the device?	Understanding 1I; Locating 0	Understanding 1 DU; Locating 0	0/0	0/0
How do you know if the autoinjector is good to use?	Understanding: 1 DU; Locating 1 UD, 1 UE	Understanding 1I; Locating 3 UE	0/0	0/0
What should you do if the autoinjector has been dropped or damaged?	Understanding 1 I; Locating 2 UE	0/0	Understanding 0; Locating 1 UD	0/0
According to the instructions, should you inject through clothing?	Understanding: 0; Locating: 2 UD	0/0	0/0	0/0
According to the instructions what types of skin should you avoid injecting in?	Understanding 0; Locating 1 UE	Understanding 0, Locating 1 UE	0/0	0/0

*Definitions of Knowledge Task Performance outcomes: For Understanding Critical Information: DU = Difficulty Understanding; I = Incorrect Answer. For Locating critical information: UD = Use Difficulty (i.e. found the information in the instructions for use (IFU), but with difficulty); UE = Use Error (i.e., could not find the information in the IFU).

While this human factor validation study is not comparative in nature, these data provide evidence that JIA patients would be able to navigate the critical tasks to use the AVT02 pen and learn from their errors in a similar fashion to adults.

III. Results of AVT02 Comparative Use Human Factors Study[4]

AVT02 CUHF Study was conducted by the same CRO, (b) (4) at 12 locations in the U.S., over the dates of July 26th – August 19th, 2021. A total of 73 RA patients, experienced with the Humira pen, participated in the study. Each individual participated in a 60-minute one-on-one session, including use of both the AVT02 autoinjector and the Humira pen in randomized sequence. Of the 73 participants, 6 were withdrawn according to pre-specified withdrawal criteria or one participant (the first one), who was removed because the simulated injection pad was not prepared appropriately before testing. This resulted in a per protocol population of 67 which was accounted for within the statistical analysis plan. A non-inferiority margin of 12.5% was chosen for the study based on the nature of the drug being chronically administered, not being an emergency-use drug, and due to evidence of self-correction in the human factors validation studies. The overall use success rates were assumed to be 88% for the test product (S_{AVT02}) and 90% for the reference products (S_{RP}) (i.e., $S_{RP} - S_{AVT02} = 2\%$). Sixty-five participants provide at least 90% power to demonstrate non-inferiority using a non-inferiority limit (d) of 12.5%, a within-subject correlation of 0.8 in overall use SRs, and a type I error rate of 5%. Considering a 10% of non-evaluable participants for the Per Protocol Population, 73 subjects were randomized.

[4] BLA 761299 orig sub, Section 5.3.5.4, AVT02 CUHF Report Body, submitted 12/20/21

One user group (Humira-pen experienced RA patients) was recruited for the study, which the sponsor chose to do based on risk analysis related to the design differences (i.e., hand dexterity or strength limitations, and not having the benefit of a caregiver present). Participants were >18 yrs of age and currently using (or had used within the last 6 months) the Humira pen, with a minimum of 2 months of self-injection experience. Individuals with debilitating symptoms related to vision, hearing, grip, or RA were excluded, as were individuals who had participated in the AVT02 HF validation study, or any other market research studies within the last 6 months.

The tasks that involved design differences in this protocol are the following:

i. removal of cap 1 (needle cap)
ii. removal of cap 2 (Humira pen only)
iii. push autoinjector down at site
iv. push injection button (Humira pen only)
v. hold in place for 10 seconds (or until second click for AVT02 injector)

Each participant completed tasks using both the AVT02 injector and the Humira Pen to perform a simulated injection, in a randomized order. No participants received training during the study.

The use of AVT02 autoinjector (Scenario A) or Humira Pen (Scenario B) first was randomized among participants, and after completing the first simulated use scenario, the participant immediately moved on to the simulated use scenario of the other injector.

- Scenario A: Administer 40 mg dose (using an injection pad) with AVT02 Autoinjector
  - Moderator introduces the AVT02 autoinjector as a "new generic version" of the Humira pen and hands the AVT02 autoinjector to the participant in its full packaging. Moderator asks the participant if they would do anything prior to using the device for the first time and allows the participant to prepare as they independently would for use.
  - Moderator assigns the participant to strap the injection pad to either the thigh or the abdomen (counterbalanced between participants).
- Scenario B: Administer 40 mg dose (using an injection pad) with Humira Pen
  - Moderator introduces the Humira pen as the current on-the-market product that participants were currently using.
  - Moderator assigns the participant to strap the injection pad to either the thigh or the abdomen (counterbalanced between participants).

The demographic characteristics of the study population, shown in Table 5 below, is consistent with and reflective of the overall RA population demographics.

Table 5 Participant Demographic Characteristics in the AVT02 CUHF Study

Demographic Characteristic	Total (N=73)
Age in yrs (mean), min, max	51 (22, 74)
Gender (n, %)	Female 54 (76.7); Male 17 (23.3)
Race (n, %)	
Asian	2 (2.7)
Black/African-American	17 (23.3)
Multiple	1 (1.4)

Other	1 (1.4)
White	52 (71.2

Source: Table 14.1.2. AVT02 CUHF Study Report

The primary analysis results for AVT02 CUHF Study is shown in Table 5 below. Use of AVT02 autoinjector was demonstrated to be non-inferior to use of the Humira Pen with respect to overall use success rate, 91% with the AVT02 autoinjector and 71.6% with the Humira Pen.[5] Focusing on the specific use errors by task, removing the AVT02 needle cap was associated with fewer use errors than removing the Humira Pen caps, and pushing and holding the AVT02 injector down was associated with fewer use errors than the corresponding process for Humira Pen.

However, as noted in Table 6 below, the apparent difference in overall use success rates with AVT02 autoinjector and Humira Pen is derived from removing the two Humira caps in the order instructed in the Humira Pen IFU (i.e, cap #1 first, cap #2 second). When the order of cap removal is not taken into account, the remaining difference in success rates appears to be due to the step of holding the pen down for approximately 10 seconds, which can be indicated by the colored indicator stopping moving within the viewing window, or a second click with AVT02 autoinjector. Participants had more success using the AVT02 autoinjector in this task (4 use errors vs 8 use errors).

In both the primary analysis and the sensitivity analysis, the point estimate for success rates for use of the AVT02 autoinjector were higher than the success rates for use of the Humira Pen, which indicates the conclusion of non-inferiority is secure, irrespective of the specific margin chosen.

[5] See also DBVIII review dated November 8, 2022, where a re-analysis using a delta of 10% still demonstrated non-inferiority (https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80697239)

Table 6: Primary Analysis Results from the AVT02 CUHF Study

Table 14.2.1. Comparative Use Human Factor Results: Non-Inferiority Analysis - Per Protocol Population

	AVT02 Autoinjector (N=67) n (%)	Humira Pen (N=67) n (%)
Critical Tasks: Successes / Use Errors		
Remove Needle Cap or Remove Gray Cap (cap #1)	65 (97.0) / 2 (3.0)	54 (80.6) / 13 (19.4)
Pull off Plum Cap (cap #2)	-	56 (83.6) / 11[1] (16.4)
Push Autoinjector down against the site	67 (100) / 0	65 (97.0) / 2 (3.0)
Press the plum activator button to inject	-	66 (98.5) / 1 (1.5)
Hold Until Second Click or Count for 10 Seconds	63 (94.0) / 4 (6.0)	59 (88.1) / 8 (11.9)
Overall Use Success	61	48
Overall use Success rate (%)	91.0	71.6
Non-Inferiority Margin (%)	12.5	
Difference in Overall Use Success Rate (%)	-19.4	
95% one-sided CI (%) *	-8.7	

*Calculated using the Tango method, a statistical test appropriate for paired binary data.
Overall use success: participants not failing any critical tasks related to external design differences.
Overall use success rate: number of participants not failing any critical tasks related to external design differences divided by total number of participants in the Per-Protocol Population.
Note: If the upper bound of the one-sided 95% Confidence Interval (CI) of the difference in overall use success rate (i.e., Success rate of Humira pen - Success rate of AVT02 Autoinjector) is less than the acceptable non-inferiority margin of 12.5%, then the AVT02 Autoinjector can be concluded Non-Inferior to the Humira pen in terms of overall use success.

[1] One use error was originally recorded (in locked database) for participant 1105 for the Humira task of "Pull off plum cap." Participant 1105 was marked as having a use error for this, but upon further investigation it was not (participant did not initially move plum cap, but did immediately before starting the injection). The use error was removed from Section 4. CUHF Study Results, but was included in this table since the discovery occurred after database lock. The correct number should be "10." Because participant 1105 committed other errors (did not hold down long enough), the oversight did not impact the overall use success rate.

Table 7: Sensitivity Analysis Not Counting Order of Cap Removal for Humira Pen as a Use Error

Table 14.2.3. Comparative Use Human Factor Results: Sensitivity Analysis (not considering order of caps removal) - Per Protocol Population

	AVT02 Autoinjector (N=67) n (%)	Humira Pen (N=67) n (%)
Critical Tasks: Successes / Use Errors		
Remove Needle Cap or Remove Gray Cap (cap #1)	65 (97.0) / 2 (3.0)	63 (94.0) / 4 (6.0)
Pull off Plum Cap (cap #2)	-	65 (97.0) / 2[2] (3.0)
Push Autoinjector down against the site	67 (100) / 0	65 (97.0) / 2 (3.0)
Press the plum activator button to inject	-	66 (98.5) / 1 (1.5)
Hold Until Second Click or Count for 10 Seconds	63 (94.0) / 4 (6.0)	59 (88.1) / 8 (11.9)
Overall Use Success	61	57
Overall use Success rate (%)	91.0	85.1
Non-Inferiority Margin (%)	12.5	
Difference in Overall Use Success Rate (%)	-5.9	
95% one-sided CI (%) *	2.8	

*Calculated using the Tango method, a statistical test appropriate for paired binary data.
Note: In this analysis, the critical tasks pull of Gray Cap and Pull off Plum Cap for the Humira Pen can be performed in any order. Therefore, when the participant removes the Plum Cap first it will not be seen as a Use Error, however in case the subject doesn't remove the caps at all it is still classified as a Use Error.
Overall use success: participants not failing any critical tasks listed in the table.
Overall use success rate: number of participants not failing any critical tasks listed in the table divided by total number of participants in the Per-Protocol Population.

IV. Conclusions Regarding the Applicability of Results Across User Populations

The CUHF study conducted in support of the AVT02 autoinjector was not optimally designed to provide comparative use data for all potential user populations, as it only included Humira-experienced adult RA patients. An additional user population for AVT02 autoinjector is adolescents.[6] While we note that some CUHF data from an adolescent population would be ideal, the Applicant identified there would be significant challenges in recruiting adolescent Humira users, specifically stating, "Upon consulting with specialized recruiters about fulfilling the participant numbers of the study, three out of four firms immediately declined to participate citing inability to find the required participants." In this particular case, the Division of Rheumatology and Transplant Medicine (DRTM) concludes that there is sufficient information available to determine that differences between the AVT02 autoinjector and the Humira Pen do not preclude a determination of interchangeability and that the statutory standard for interchangeability has been met. The following reasons:

A. The use tasks needed to administer the AVT02 autoinjector were observed to have low numbers of use errors, and do not appear to be more error-prone for particular user groups, including adolescents
    1. Results for the human factors validation Study HFVP-AI demonstrate that both adult and adolescent user groups, regardless of prior Humira experience, experienced few use errors with the AVT02 autoinjector. The pattern of use errors was consistent across all user groups tested, including adolescent JIA patients. Importantly, JIA patients were not more prone to use error than adults when using the device, although they were not as good at finding information or answering questions about use.
    2. Further, the types of use errors seen with adults in the CUHF study did not appear to differ from the types of use errors seen in the HF validation study with adult and adolescent Humira experienced users.
    3. The available human factors validation Study HFVP-AI data, demonstrating few use errors consistent across all user groups tested, including adolescents, together with the similar types of errors seen in the CUHF study in adults, support a scientific rationale to leverage this unique fact pattern to support the conclusion that adolescents are likely to handle the switching between these two specific devices similarly to adults and that a dedicated adolescents CUHF study is not likely to provide additional information in this case.

B. The key differences in use tasks needed to administer the AVT02 autoinjector and the Humira Pen do not appear to be difficult for adult or pediatric users to accommodate without training
    1. Both Study HFVP-AI and the AVT02 CUHF study were conducted without training. Therefore, the use errors observed in Study HFVP-AI, and the success rates observed in the CUHF study were representative of a "higher-risk" home-use scenario.

[6] We note that some of the indications being sought include pediatric patients as young as 2 years of age. However, the pediatric user group expected to self-administer is primarily adolescents, as detailed in the DMEPA review. Therefore, the interchangeability determination for the AVT02 autoinjector is supported, in part, by the adult CUHF data that is relevant to adult caregivers who may administer to pediatric population, including those who are too young to self-administer. Further, there is no dosage form for AVT02 that allows weight-based dosing for pediatric patients below 40 kg.

C. Based on the type of product (for example, that has long half-life and prolonged pharmacodynamic and carryover effect in its chronic uses), the risk of harm or negative clinical impact with switching by pediatric patients for this particular product is not greater than the risk of using the reference product without such alternation or switch.

Based on the overall information and unique fact-pattern described above, we conclude that the absence of pediatric CUHF data does not preclude a conclusion of interchangeability for this product, and that there is sufficient data and information here, together with a scientific justification to conclude that —the standard of being able to produce the same clinical result as the reference product in any given patient and with respect to the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product not being greater than the risk of using the reference product without such alternation or switch.

The scientific, regulatory, and policy considerations regarding the need for adolescent CUHF data for the proposed interchangeability of AVT02 autoinjector with US-Humira Pen were discussed in detail at the FDA Biosimilar Review Committee (BRC), including senior leadership from OND, OSE, and CDER on October 13, 2022. The Committee discussed that in this specific case, the data submitted by the Applicant was adequate to support the licensure of the AVT02 as interchangeable with the US-Humira Pen.

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/

SUSAN RHEE
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COMPARATIVE USE HUMAN FACTORS STUDY RESULTS 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:	December 20, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761299
Product Name, Dosage Form, and Strength:	Simlandi (adalimumab-ryvk) injection, 40 mg/0.4 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alvotech
FDA Received Date:	December 20, 2021
TTT ID #:	2022-1858
DMEPA 1 Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director of Human Factors:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

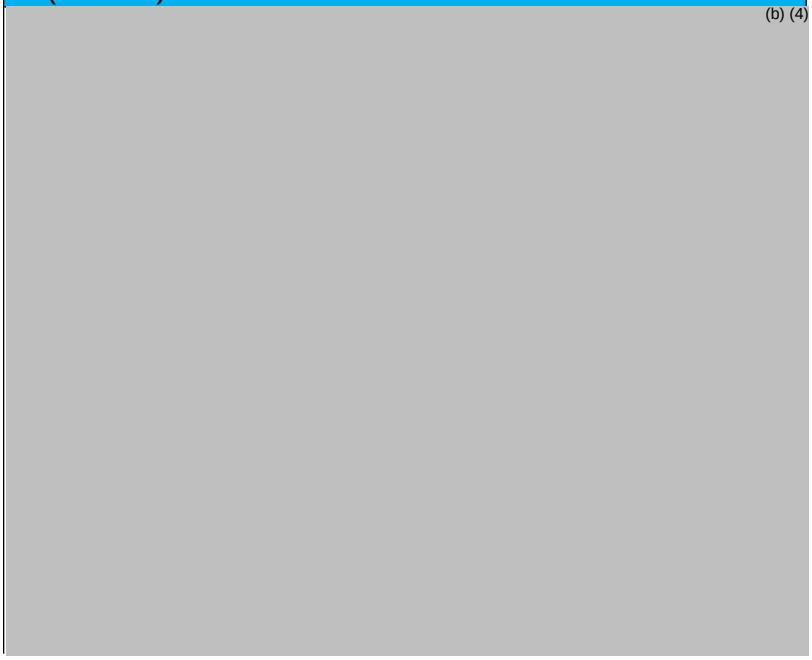
On December 20, 2021, Alvotech submitted an original Biologics License Application (BLA) for Simlandi as a proposed interchangeable biosimilar to US-licensed Humira for the treatment of Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (PsO).

This review evaluates the comparative use human factors (CUHF) study results report submitted under BLA 761299 for Simlandi (adalimumab-ryvk) injection.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed autoinjector (AI) device constituent part that is intended for the aforementioned indications. The proposed autoinjector delivers a subcutaneous injection of 40 mg/0.4 mL of drug, when pushed against the injection site. The reference drug is US-licensed Humira, BLA 125057 (see Figure 1 below). For additional product information, see Table 4 in Appendix A.

Figure 1. US-licensed Humira (Top) and proposed Simlandi AI(Bottom)



1.2 REGULATORY HISTORY

We provided guidance and recommendations regarding the Sponsor's HF development program, specifically regarding their proposed HF validation and comparative analyses

approach for biosimilarity and interchangeability in previous communications[a,b]. Additionally, we reviewed the HF validation study protocol for their proposed AI presentations and provided recommendations on April 16, 2019[c].

On September 4, 2020, the Sponsor submitted a biologics license application (BLA) as a proposed biosimilar for the AI presentation, which included HF validation study results. We reviewed the HF validation study data and provided recommendations on September 15, 2021[d].

On March 15, 2021, the Sponsor submitted their comparative analyses for interchangeability for the PFS and AI presentations. We completed our review of the comparative analyses and provided our conclusion and recommendation on March 28, 2022.

On May 4, 2021, the Sponsor submitted their proposed CUHF study protocol for the AI presentation; however, the Sponsor conducted the study prior to receiving Agency feedback[e].

2 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
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Sponsor Responses to Agency's IRs	F

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

[a] Nabavian, S. BPD Type 2 Meeting Minutes for AVT02. Silver Spring (MD): FDA, CDER, OND, DPARP (US); 2019 JAN 10. IND 136459.
[b] Nabavian, S. BPD Type 4 Meeting Minutes for AVT02. Silver Spring (MD): FDA, CDER, OND, DPARP (US); 2020 SEPT 18. IND 136459.
[c] Barlow, M. Human Factors Validation Study Protocol Review for AVT02 (IND 136459). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 16. RCM No.: 2019-416.
[d] Barlow, M. Human Factors Validation Study Results & Labels and Labeling Review for AVT02 (BLA 761205). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEPT 15. RCM No.: 2020-1887 and 2020-1888.
[e] Nabavian, S. BPD Type 4 Meeting Minutes for AVT02. Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2021 NOV 22. IND 136459.

The sections below provide a summary of the study design, CUHF study results, and our analysis to determine if the results demonstrate that the proposed Simlandi product user interface design is non-inferior to that of US-licensed Humira, when used by patients in representative use scenarios and use environments.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the CUHF study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for CUHF Study	
Study Design Elements	Details Submitted by Applicant
Purpose	The objective for conducting the CUHF study was to confirm that the overall rate of success of injection by the AVT02 Autoinjector, was not inferior to the overall rate of success of injection by the Humira Pen. This was determined by evaluating use errors observed during performance of critical tasks related to external design differences, when used by RA patients experienced with the use of the Humira Pen.
Participants	Adult RA patient user group with Humira pen-experienced (n=73)
Training	No training was given to the participants
Test Environment	The CUHF study was conducted in usability labs in a simulated home environment. For patients and caregivers, the study room was set up with a table and chairs similar to a home environment where the AVT02 Autoinjector would be used. The study room had ambient noise that would be expected in the actual use environment. The study room was illuminated by overhead fluorescent lighting such that the lighting level is comparable to that in a home environment.

	(b) (4)
Sequence of Study	• Participant Enrollment • Introduction and Background Interview • Scenario Introduction and Simulated Use Scenarios o Use of Simlandi AI or Humira Pen first was randomized among participants. After completing the first simulated use scenario, the participant immediately moved on to the simulated use scenario of the other product. • Simulated Use Deviation Probing • Post Study Interview • Wrap up and Compensation

3.2 DISCUSSION OF METHODOLOGY CONCERN

Our review of the CUHF study methodology identified one flaw. Specifically, the Sponsor did not include a pediatric user group in the CUHF study. In the CUHF study result report, the Sponsor provided the following rationale:

"JIA patients are children or adolescents who would need, in most cases, the assistance of an adult caregiver in order to obtain the prescription from a doctor and procure the drug from a pharmacy. As the caregiver is likely aware of both the occurrence of the doctor's appointment and the procurement of the drug, it is also reasonable that the caregiver would be aware that an interchangeable biosimilar has been dispensed in place of the reference product. JIA patients are therefore likely expected to have caregiver supervision during the first injection as well. Lastly, the minimum patient weight to accurately use the Humira pen (40 mg/0.4 ml) is 66 pounds and above; in the US, 66 pounds (50th percentile in weight) corresponds to a 9.5 year

old child. It is unlikely that a patient of this age is performing self-injections, and even if they were it is unlikely they would be self-injecting in an unsupervised setting. Therefore, the use pattern leading into receiving a new interchangeable biosimilar is, at a minimum, a supervised setting which increases the likelihood that the first use of an interchangeable biosimilar would be overseen, if not performed by the caregiver. This leaves the subset of older JIA patients, who can be adequately represented by adult RA patients for the purpose of this study."

We do not find this justification adequate because the Sponsor did not provide any additional data supporting their assertions. First, with real world use there is no guarantee that caregivers would be present during administration. Additionally, potential pediatric groups are not necessarily represented by the adult patient population as we expect there would be cognitive and behavioral differences between the two populations. Furthermore, we are aware of scientific literature that supports the idea that pediatric patients, particularly those managing chronic disease, self-administer as young as 10 years of age[f].

On March 24, 2022 we sent an information request (IR) notifying the Sponsor we disagreed with their justification to not include a pediatric user group and requested additional information and/or data to support not including a distinct pediatric user group in the CUHF study. On March 31, 2022, the Sponsor responded to our IR (See Appendix F for further details).

On May 20, 2022, we sent an IR communicating that we did not agree with the Sponsor's determination that no pediatric CUHF data was needed to support a finding of interchangeability in pediatric users. Additionally, in this IR, we requested they conduct a CUHF study with pediatric user group representative of intended users (i.e., pediatric Crohn's patients, JIA patients, etc.). On June 3, 2022, the Sponsor responded with further clarifying questions regarding our determination for the need of a CUHF study with pediatric users (See Appendix F for further details).

On July 8, 2022, we completed our review of the Sponsor's clarifying questions and provided responses[g].

On August 11, 2022, the Sponsor submitted additional questions/discussion topics related to this issue. Additionally, the Sponsor submitted a BPD Type 1 meeting package on August 25, 2022 with additional questions and related information. On September 20, 2022, a teleconference was held to provide responses to the Sponsor's questions[h].

3.3 DISCUSSION OF RESULTS AND ANALYSES

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[f] Hollan-Hall, C., & Burstein, G. (2016). Adolescent Development. In R. Kliegman, B. Stanton, J. Geme, & N. Schor, Nelson Textbook of Pediatrics 20th edition (pp. 926-936). Elsevier.

[g] Barlow, M. Review of Response to HF Advice for Simlandi (BLA 761299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JUL 08.

[h] Rhee, S. BPD Type 1 Meeting Minutes for Simlandi. Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2022 OCT 20. BLA 761299.

The CUHF results identified 4 use errors with the proposed Simlandi product and 8 use errors with the US-licensed Humira product for the following critical task related to the "other" difference identified between Simlandi and US-licensed Humira: "Hold for 10 seconds". We discuss the use issues in Table 3 below. Furthermore, the adult patient data, under the CUHF framework, correlates to adult caregivers that may administer the product to pediatric patients too young to self-administer.

Table 3. Select CUHF Study Results

CUHF Study Results & Applicant's Analysis	DMEPA's Analysis
Simlandi Task: Hold until second click (or 10 seconds, or orange indicator stops moving) Failure Criteria: Lifting early before full dose is administered • 4 participants lifted up the Simlandi AI early, before the full dose was administered. o Participant 123 lifted up shortly after activating, then tried to press back down again and said "oops" when the shield was locked out. The participant noted some medication was not injected into the pad, and they attributed this to not being quite ready for the injection to go off. They felt it was easier than expected. o Participant 802 held the device down on the injection pad for half of a second and then lifted, spraying medication. The participant was aware a full dose was not delivered. They were attempting to use the instructions on the device, but their hand positioning blocked the label. The participant was able to find the correct hold time information on their own after the injection without assistance. o Participant 1001 pressed the device down and it popped up, leaking out medication. This	The provided data does not indicate that most of these use errors are related to design differences between the proposed AI and US-licensed Humira. We did note one participant expecting to have to press a button to activate the injection; however, this participant was aware a full dose was not administered and without assistance or prompting referred to the instructions and comprehended the need to hold down the proposed AI down firmly from the beginning.

participant did not use any labeling. They felt it pushed and activated easier than expected, and they initially were expecting to have to press a button. The participant was aware a full dose was not given and confirmed they knew now to hold it down firmly from the beginning. Additionally, they did comprehend the instructions once reading them. o Participant 1105 held the device down in the injection pad for a few seconds and lifted early, locking the needle. This participant usually counts to 3 when using their Humira pen and did the same thing for the Simlandi AI. US-licensed Humira Task: Count/Hold for 10 seconds Failure Criteria: Lifting early before full dose is administered • 8 participants lifted the US-licensed Humira pen early before full dose was administered. o Participant 104 only held the pen down to inject for about 3-4 seconds, they did report feeling liquid after the injection. They relied on the window and did not count, but per the report this participant lifted early before the yellow plunger filled the window. o Participant 108 held the pend down to inject for about 5 seconds, stopping when she heard a "squishy sound." o Participant 109 held the pen down to inject for about 5 seconds, no liquid was on the pad. They relied	

on a “noise that meant the medicine was out of the pen.” o Participant 113 held the pen down for about 3 seconds, and a significant amount of medication remained on the pad afterward. They attributed this to the current Humira pens not being consistent with injection times and not fully paying attention to the count. o Participant 122 held the pen down for about 6 seconds, but they thought they held it down for 10 seconds. o Participant 406 held the pen down for a few seconds with the gray cap still in place. They were aware to call the pharmacy/company to see if a full dose was given. o Participant 503 did not inject because the gray cap was still in place. After lifting the pen, the participant removed the cap causing medication to shoot across the table. o Participant 1105 stopped the injection halfway to flip the pen over.	

3.4 DBVIII STATISTICS REVIEW

According to the DBVIII review, the CUHF study results demonstrated, that in terms of use success, the proposed Simlandi AI met the non-inferiority margin and is non-inferior to US-licensed Humira when used by adult patients[i].

4 CONCLUSION & RECOMMENDATIONS

Based on the totality of evidence considered, we determine that the CUHF study results confirm that the differences in the user interface between the proposed Simlandi AI and US-licensed Humira are acceptable, and the CUHF study demonstrates the proposed biosimilar

[i] Wang, Y. Statistical Review and Evaluation (Consult) for Simlandi BLA 761299. Silver Spring (MD): FDA, CDER, OTS, OB, DBVIII (US); 2022 NOV 08.

interchangeable Simlandi is non-inferior to US-licensed Humira when used by adult patients. However, based on the submitted CUHF study, we are unable to determine whether the proposed Simlandi AI is non-inferior to US-licensed Humira when used by adolescent patients.

4.1 BIOSIMILAR REVIEW COMMITTEE MEETING DISCUSSION

On October 13, 2022, a Biosimilar Review Committee (BRC) meeting was held to discuss the lack of pediatric CUHF data. The BRC discussed that, in this specific instance, CUHF data on adolescents is not necessary in light of the other data and information submitted, together with clinical considerations, to support the approval of the proposed interchangeable. We note that the Division of Rheumatology and Transplant Medicine (DRTM) has drafted a memorandum detailing their scientific thinking. While DMEPA cannot make an affirmative conclusion of non-inferiority regarding adolescent patients in the absence of CUHF data in adolescents, DMEPA believes it is reasonable for the Division in its role to exercise its scientific judgement here based on the data and information submitted in the application, together with clinical considerations, in the absence of such data for this product. DMEPA defers to DTRM's scientific judgment and decision regarding the determination of interchangeability for this product and DMEPA aligns in the decision to approve the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Simlandi received on December 20, 2021, from Alvotech, and US-licensed Humira.

Table 4. Relevant Product Information for Simlandi and US-licensed Humira		
Product Name	Simlandi	US-licensed Humira[j]
Initial Approval Date	N/A	December 31, 2002
Nonproprietary Name	adalimumab-ryvk	adalimumab
Indication	a tumor necrosis factor (TNF) blocker indicated for treatment of: • Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older. • Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.	a tumor necrosis factor (TNF) blocker indicated for treatment of: • Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older. • Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

[j] Humira [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 May 3. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf.

	• Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS. • Crohn's Disease (CD): treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older. • Ulcerative Colitis (UC): Treatment of moderately to severely active ulcerative colitis in adult patients. Limitations of Use: Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.	• Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS. • Crohn's Disease (CD): treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older. • Ulcerative Colitis (UC): treatment of moderately to severely active ulcerative colitis in adults and pediatric patients 5 years of age and older. • Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. • Hidradenitis Suppurativa (HS): The treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older. • Uveitis (UV): treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	injection	injection
Strength	40 mg/0.4 mL	10 mg/0.1 mL; 10 mg/0.2 mL; 20 mg/0.2 mL; 20 mg/0.4 mL;

		40 mg/0.4 mL; 40 mg/0.8 mL; 80 mg/0.8 mL
Dose and Frequency	• Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: o 40 mg every other week. o Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week or 80 mg every other week. • Juvenile Idiopathic Arthritis: o ≥ 30 kg (66 lbs): 40 mg every other week • Adult Crohn's Disease and Ulcerative Colitis: o Initial dose (Day 1): 160 mg o Second dose two weeks later (Day 15): 80 mg o Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. • Pediatric Crohn's disease ≥ 40 kg: Day 1: 160 mg Day 15: 80 mg Day 29: start dosage of 40 mg every other week • Plaque Psoriasis: o 80 mg initial dose, followed by 40 mg every other week	• Adult RA, PsA, and AS: 40 mg every other week. Some RA patients may benefit from 40 mg every week or 80 mg every other week • JIA and Pediatric UV 10 kg to < 15 kg: 10 mg every other week 15 kg to < 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week • Adult Crohn's disease and Adult Ulcerative Colitis Day 1: 160 mg Day 15: 80 mg Day 29: begin dosage of 40 mg every other week • Pediatric Crohn's disease 17 kg to < 40 kg: Day 1: 80 mg Day 15: 40 mg Day 29: start dosage of 20 mg every other week ≥ 40 kg: Day 1: 160 mg Day 15: 80 mg Day 29: start dosage of 40 mg every other week • Pediatric Ulcerative Colitis 20 kg to <40 kg: Day 1: 80 mg Day 8: 40 mg Day 15: 40 mg Starting on Day 29: 40 mg every other week or 20 mg every week ≥ 40 kg: Day 1: 160 mg Day 8: 80 mg

	starting one week after initial dose.	Day 15: 80 mg Starting on Day 29: 80 mg every other week or 40 mg every week. • Adult Ps or Adult Uveitis Initial dose: 80 mg Followed by: 40 mg every other week starting one week after initial dose • Adult HS Day 1: 160 mg Day 15: 80 mg Day 29: begin 40 mg every week or 80 mg every other week • Pediatric HS (12 and older) 30 kg to <60 kg: Day 1: 80 mg Day 8 and subsequent dose: 40 mg every other week >60 kg: Day 1: 160 mg Day 15: 80 mg Day 29 and subsequent doses: 40 mg every week or 80 mg every other week
How Supplied	40 mg/0.4 mL AI	80 mg/0.8 mL Humira Pen 40 mg/0.8 mL Humira Pen 40 mg/0.4 mL Humira Pen 80 mg/0.8 mL PFS 40 mg/0.8 mL PFS 40 mg/0.4 mL PFS 20 mg/0.4 mL PFS 20 mg/0.2 mL PFS 10 mg/0.2 mL PFS 10 mg/0.1 mL PFS 40 mg/0.8 mL vial for institutional use only

Storage	Do not use beyond the expiration date on the container. TRADENAME must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, TRADENAME may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. TRADENAME should be discarded if not used within the 14-day period. Record the date when TRADENAME is first removed from the refrigerator in the spaces provided on the carton and dose pack. Do not store TRADENAME in extreme heat or cold.	Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store HUMIRA in extreme heat or cold.
Container Closure	AI	AI; PFS; Vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 11, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 136459, 761205, and 761299. Our search identified 6 previous reviews[k,l,m,n,o,p,q], and we confirmed that our previous recommendations were implemented or considered.

[k] Nabavian, S. BPD Type 2 Meeting Minutes for AVT02. Silver Spring (MD): FDA, CDER, OND, DPARP (US); 2019 JAN 10. IND 136459.

[l] Barlow, M. Human Factors Validation Study Protocol Review for AVT02 (IND 136459). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 16. RCM No.: 2019-416.

[m] Nabavian, S. BPD Type 4 Meeting Minutes for AVT02. Silver Spring (MD): FDA, CDER, OND, DPARP (US); 2020 SEPT 18. IND 136459.

[n] Barlow, M. HF Validation Study Results and Label and Labeling Review for AVT02 (BLA 761205). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEPT 16.

[o] Nabavian, S. BPD Type 4 Meeting Minutes for AVT02. Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2021 NOV 22. IND 136459.

[p] Barlow, M. Comparative Analyses and URRA Review for Simlandi (IND 136459). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAR 28.

[q] Barlow, M. Response to HF Advice for Simlandi (BLA 761299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JUL 08.

APPENDIX C. COMPARATIVE USE HUMAN FACTORS STUDY

- The CUHF study results report can be accessible via: \\CDSESUB1\EVSPROD\bla761299\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\cuhf\cuhf-report-body.pdf

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F. SPONSOR RESPONSES TO AGENCY IRS

- Sponsor's March 31, 2022 Response to the Agency's March 24, 2022 IR can be accessible via: \\CDSESUB1\EVSPROD\bla761299\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\response\response-document.pdf
- Sponsor's June 3, 2022 Response to the Agency's May 25, 2022 IR can be accessible via: \\CDSESUB1\EVSPROD\bla761299\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\response\5354-response.pdf
- Sponsor's August 11, 2022 Response to the Agency's July 8, 2022 Review of Response to HF Advice can be accessible via: \\CDSESUB1\EVSPROD\bla761299\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\response\5-3-5-4-response.pdf

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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/

MATTHEW J BARLOW
12/20/2022 10:31:37 AM

JASON A FLINT
12/20/2022 10:39:19 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	10/27/2022		
To:	Teshara Bouie, CDER/OPQ/OPRO/DRBPMI/RBPMB2		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Division): ***optional**	Courtney Evans, Team Lead OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: BLA 761299, adalimumab-ryvk ICC2200096 Case 00821318		
Recommendation:	• CDRH recommends approval of the device constituents of the combination product. • Please see Section 3 for Facilities Inspection and related information		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division o tional)**
Digitally signed by Florencia T. Wilson -S Date: 2022.10.27 17:29:10 -04'00'		Alan M. Stevens -S3

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR# Case 00821318
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/500t000000wafDfAAI/view
ICC tracking #	ICC2200096
Submission Number	BLA 761299
Sponsor	Alvotech
Drug/Biologic	adalimumab-ryvk
Indications for Use	Rheumatoid Arthritis (RA)
Device Constituent	Auto-Injector
Related Files	ICC2000861 and ICC2000863 Case 00030275 and Case 00030274 ICC2000400

2. CDRH REVIEW

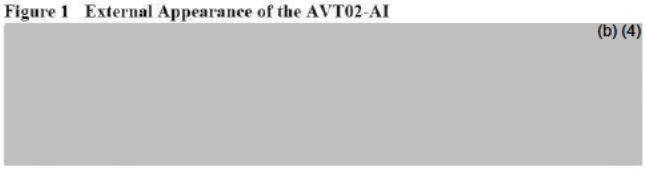
ICC Review Request from Choose an item., Choose an item.:	The AVT02 finished product is supplied as a sterile, preservative-free solution for s.c. injection containing 100 mg/mL AVT02 drug substance at 40 mg / 0.4 mL strength filled into a syringe with a stopper, that also includes the needle and needle cap and referred to as AVT02-DP PFS (see Section 3.2.P.1 and Section 3.2.P.7.1). AVT02-DP PFS is then assembled into an autoinjector (AI) presentation consisting of functional components including a plunger rod that drives AVT02 delivery, together with two housing covers, and a cap remover sleeve that encloses the AVT02-DP-PFS (for finished product description see Module 3.2.P.7.2). The drug product presentation for BLA 761299 is the same as the one proposed in pending BLA 761205. CDRH was consulted for BLA 761205. The intercenter consult numbers for BLA 761205 are 2000861 and 2000863. The assigned CDRH reviewers are Suzanne Hudak and Rumi Young from OPEQ/OHT2/DHT3C. Because of the experience with this product in BLA 761205, we request the same CDRH team for this BLA 761299 consult. In addition, please note, (b) (4) (FEI: (b) (4)), which was included in BLA 761205 as a release and stability testing (device functional testing) site for AVT02-AI, is no longer listed in BLA 761299. Instead, AVT02-AI release and stability testing (device functional testing) is performed at Alvotech hf (FEI: 3013702557).
Device Presentation(s) being evaluated:	The following are taken from 3.2.P.7 **Figure 1 Photograph of the AVT02-DP PFS** (b) (4)  **Figure 1 External Appearance of the AVT02-AI** (b) (4) 

	Figure 2 Customized Alvotech Device in its Final Assembled State (b) (4) (b) (4) is single use, intended for single fixed dose between (b) (4) mL into the subcutaneous tissue. The housing is customized for added ergonomics. The AVT02-AI is intended to enable the subcutaneous injection of a single, fixed 0.4 mL dose of AVT02 by healthcare professionals and trained lay users (e.g. caregivers, patients) in the clinic or home environments according to the prescribed dosing frequency. Using the device: -Remove Protective Cap -Push the AI onto the skin to deliver drug. There is no button. The first click indicates start of injection. The second click indicates completion of administration. Once the AI is removed from the injection site, the cover sleeve spring pushes the cover sleeve automatically back into initial position, where it locks permanently.
Objective of this Memo:	It is noted that the combination product is exactly the same as the one in BLA 761205. The only difference is the Indications for Use. It is noted that there are two pending Post-Market commitment/requirement with BLA 761205. In addition, there was a PAI recommendation for device for BLA 761205, which also applies to this BLA. The device constituents for BLA 761205 has a recommendation of approval. Therefore, the objective of this review is to request and review the Post-Market commitment/requirement and if needed look at the result of the device inspection requested that is applicable for both BLAs (761205 and 761299). Please see Section 3 for the Facility information.
Review Comments:	In the review of BLA 761205, the recommendation is "Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments" **Post-Market Commitment or Requirement:** (b) (4) During the mid-cycle meeting, CDRH proposed to send IRs related to the PMC/PMR which was cleared by the review team at CDER.

IR sent related to the BLA 761205 PMC on 5/24/2022 with a 4 week deadline, if extension is needed we can grant.

(b) (4)

Reviewer Comment
The provided response to the IR is acceptable. **Resolved**

(b) (4)

Sponsor's Response:

	(b) (4)
	Sponsor's response (September 2022)
	(b) (4)

	(b) (4) **Reviewer Comment** (b) (4) I do not have further issues with this below the line deficiency. **Resolved** After review of the provided information, the Sponsor has provided adequate response to the PMC/PMR.
Review **Recommendation**:	CDRH recommends approval of the device constituents of the combination product.

3. Facilities Information

3.2.P.3.1.1 Manufacturer(s) - AVT02-AI

Manufacturing and test facilities for AVT02-AI are listed below.

Table 1 AVT02-AI Manufacturer and Test Facilities

Name and Address of Manufacturer	Function	Regulatory Status
Alvotech hf Sæmundargata 15-19, Reykjavik, 101, Iceland Contact: Tanya Zharov Phone number: +354-5222900 Email: Tanya.Zharov@alvotech.com DUNS: 500791692 FEI: 3013702557	Manufacturing of AVT02-DP PFS, release testing and stability testing. Container closure integrity testing for AVT02-DP PFS release and stability. AVT02-AI identity release testing. AVT02-AI release testing and stability testing (device functional testing). AVT02-AI batch release.	cGMP 21 CFR Parts 210, 211, 600 and overlay of relevant QSRs in Part 820
(b) (4)	Sterility testing for AVT02-DP PFS release and stability	cGMP

Name and Address of Manufacturer	Function	Regulatory Status
(b) (4)	Container closure integrity testing for AVT02-DP PFS stability	cGMP
	Assembly of AVT02-AI, secondary packaging, labelling, batch release	cGMP
	Manufacturer of the empty syringes (device only)	DIN EN ISO 15378:2016 and ISO 15378:2015 ISO 9001:2015 ISO 14001:2015 and ISO 50001:2011

Name and Address of Manufacturer	Function	Regulatory Status
(b) (4)	Manufacturer of the plunger stoppers (device only)	ISO 9001:2015 ISO 15378:2017
	Manufacturer of the plunger stoppers (device only)	ISO 9001:2015 ISO 15378:2017
	Manufacturer of the autoinjector device components (device only)	ISO 13485:2016

FEI:	3013702557
Responsibilities:	Manufacturing of AVT02-DP PFS, release testing and stability testing. Container closure integrity testing for AVT02-DP PFS release and stability. AVT02-AI identity release testing. AVT02-AI release testing and stability testing (device functional testing). AVT02-AI batch release.

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 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:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Container closure integrity testing for AVT02-DP PFS stability

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

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)

ICC# (b) (4)
BLA (b) (4)
(b) (4)

Responsibilities:	Assembly of AVT02-AI, secondary packaging, labelling, batch release

***Note from review of BLA 761205**

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Assembly of AVT02-AI, Secondary packaging, Labeling. Update at the midcyle meeting in Feb 2021 – release testing moved (b) (4) to Alvotech, (b) (4) will no longer do release testing.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4) The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

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

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4) The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

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

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Reviewer Comment

Alvotech hf:
It is noted that under BLA 761205 (Biosimilar application - approval pending due to delay in facility inspection), the CDRH reviewer recommended PAI because the firm is responsible for major activities related to the manufacturing. It is also noted from CDER (Madushini Dharmasena, CDER/OPQ/OPMA/DBM/BMB2) that there is a scheduled inspection on March 10-18, 2022. An inspector with device specialty will also be accompanying Ms. Dharmasena).

(b) (4)

This manufacturer is added to BLA 761299, however, the major responsibility of this firm is Container closure integrity testing for AVT02-DP PFS stability

Alvotech commits to provide additional data for 3 batches of AVT02-DP-PFS, 3batches AVT02-AI and 3 batches of assembled AVT02-AI post transport validation(real world and simulated shipping) using the validated spectrophotometric dye ingress method in May 2021.CCIT testing is always performed after shipping due to the different locations of the AVT02 manufacturing and assembly facilities and the CCIT testing facility. The shipping flow for the AVT02 AI is as follows. (b) (4)

(b) (4)

(b) (4)

Under BLA 761205, a PAI is recommended, but delayed.

(b) (4)

Removed per the application and CDER

From Mid-Cycle meeting:

- **Alvotech hf (Iceland,** FEI: 3013702557): Manufacture of DS/PFS DP, AVT02-AI assembly, secondary packaging, labeling, in-process testing, release testing, and stability testing
  - Pre-license inspection (PLI) to support BLA 761205 and BLA 761299 facilities conducted March 10-17, 2022. The inspection concluded with a 13-item Form 483. Initial recommendation is withhold.
  - The final recommendation will be determined by the compliance reviewer after reviewing responses to the 483.
- (b) (4) AVT02-AI assembly, secondary packaging, labeling, and batch release.
  - Inspection is Scheduled (b) (4)
  - Based on a conversation with CDER, the inspection received a VAI

EIR/FORM 483:

CDRH recommended a PAI for the device constituents of the combination product (autoinjector) which resulted in a VAI recommendation. Per the FDA Form 483, there were three observations. The 2nd on observation which is related to Validation/Qualifications (b) (4) lack the following:

(b) (4)

(b) (4)

Based on the provided response to Observation #2 of the FDA Form 483, (b) (4) addressed Observation #2 and effectiveness check were performed and no elevated rejects observed. CDRH does not have further issues with the Observation related to the device.

---END OF REVIEW---

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

/s/

SUSAN RHEE
12/15/2022 11:08:45 PM
Completed in ICCR

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CONSULT REVIEW

Consult Requester	Matt Barlow, CDER/OSE/OMEPRM/DMEPAI
Type of Consult	Comparative Use Human Factors (CUHF) study results
BLA Number	BLA 761299
Drug Name	AVT02 Autoinjector
Applicant	Alvotech USA Inc.
Reference Listed Drug	Humira 40mg/0.4mL pen
Indication	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Plaque Psoriasis (Ps), pediatric and adult Crohn's Disease (CD), Ankylosing Spondylitis (AS), and Ulcerative Colitis (UC)
Dates	FDA Received Date: 12/20/2021 Review Assignment Date: 2/16/2022 Review Completion Date: 11/8/2022
Biometrics Division **Primary Statistical Reviewer** **Secondary Statistical Reviewer**	 Yifan (Katie) Wang, Ph.D., CDER/OTS/OB/DBVIII Somesh Chattopadhyay, Ph.D., CDER/OTS/OB/DBVIII
Keywords	Humira biosimilar, autoinjector, Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), comparative use human factors (CUHF) study, critical task, overall use success, sample size calculation, non-inferiority (NI), NI margin, experienced reference product users

1. Background Information

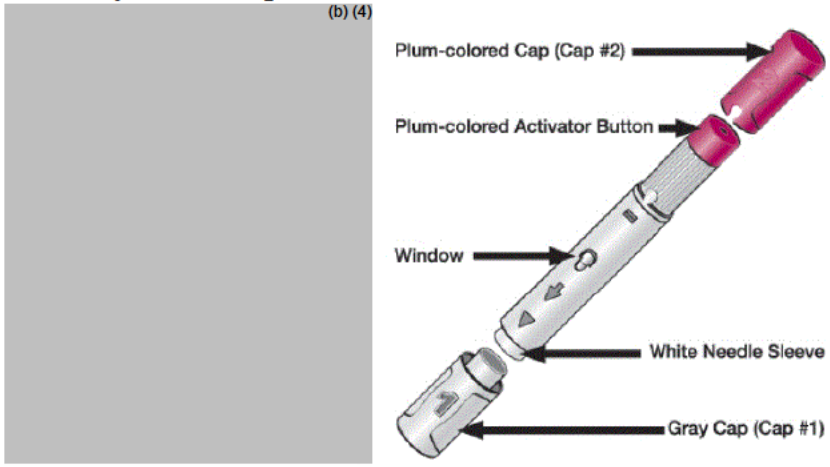
The purpose of this consult review is to provide the Division of Biometrics VIII (DBVIII)'s statistical evaluations of the Comparative Use Human Factors (CUHF) study report for BLA 761299 submitted by Alvotech USA Inc. on 12/20/2021 for Humira Biosimilar, in response to the consult request from the Division of Medication Error Prevention and Analysis (DMEPA).

1.1 Overview

Alvotech USA Inc. conducted a CUHF study of the AVT02 Autoinjector as compared to the reference product Humira 40mg/0.4mL pen. The AVT02 Autoinjector is a single-use and disposable device, delivering a subcutaneous injection of 40mg per 0.4mL of drug when pushed against the injection site. This is an interchangeable biosimilar product that the AVT02 Autoinjector will be substituted for the Humira pen to a patient without the intervention of health care providers.

The objective of this CUHF study is to confirm that the overall rate of success of injection by the AVT02 Autoinjector is not inferior to that by the Humira Pen, by evaluating use errors (UEs) observed during the performance of critical tasks related to external design differences, when used by RA patients who were experienced Humira pen users. Figure 1 presents the Test and Reference pen parts.

Figure 1: Physical Comparison of Pen Devices Between Test and Reference



Note: the device on the left is the Test pen, the device on the right is the Humira pen.
Source: Applicant's CUHF study report Figure 1 (Page 13 of 241) and https://www.rxlist.com/humira-drug.htm.

A total of 73 Humira-experienced RA patients from 12 sites participated in this study. Each individual participated in a 60 minute one-on-one session, including use of both the AVT02 autoinjector and the Humira pen in randomized sequence. Of the 73 participants, 6 were withdrawn according to established criteria or due to unforeseen artifact, resulting in a per-protocol population (PPP) of 67 partieticipents.

1.2 Consult Request

DMEPA is consulting DBVIII regarding the CUHF study results with the following notes.

- The applicant did not include a JIA user group.
- The applicant chose a delta of 12.5%. We normally see a delta of 10%. Is the Applicant's delta and justification acceptable?
- The Agency did not provide feedback/recommendations on the CUHF study protocol prior to the Applicant conducting the CUHF study.

This consult review provides a summary of and DBVIII's comments to the CUHF study report.

2. SUMMARY OF CUHF STUDY REPORT

This section summarizes Alvotech USA Inc.'s CUHF study report submitted on 12/20/2021.

2.1 Study Design

This study was conducted in one-on-one, 60 minutes in-person interview sessions, including a total of 73 Humira-experienced RA patients. All participants used both the AVT02 Autoinjector and Humira pen to perform simulated injections in randomized order. No participants received training during the study.

2.2 Randomization

The Applicant stated that the usability evaluation session included two randomized scenarios:

- Scenario A: Administer 40mg dose (using an injection pad) with AVT02 Autoinjector
- Scenario B: Administer 40mg dose (using an injection pad) with Humira pen

Each participant was assigned an alphanumerical participant ID upon enrollment, for example 101, 102, 201, 202, etc., where the last two digits corresponded to the order of enrolment at that site, and the remaining first one digit (or two digits) corresponded to the participant's testing site.

Reviewer's Comments:

The randomization schedule that the Applicant claimed in the study report cannot be located. However, the randomization sequence information shown in Appendix B: Overview of Trials appears to be randomized sequences.

2.3 Critical Tasks

Critical tasks are defined as tasks which, if performed incorrectly or not performed at all, would or could cause harm to the subject or user, where harm is defined to include compromised medical care. The Applicant stated that the critical tasks that involved design differences in this study are the following: removal of cap 1, removal of cap 2 (Humira pen only), pushing autoinjector down

against injection site, pressing an activator button (Humira pen only), and holding down the pen for long enough to administer complete dose. Table 3 presents the critical tasks that were assessed in this study. Please note that the numbers of critical tasks are different between the Test and Reference products.

Table 1: Critical Tasks Relates to Design Differences

Task (AVT02 Autoinjector)	Task (Humira pen)	Success criteria[17]	Task relates to design differences?
Remove device from packaging* (Non-evaluated)	Remove device from packaging* (Non-evaluated)	n/a	n/a
Remove needle cap **(Critical task related to design difference)**	Remove needle cap (gray cap, cap #1) **(Critical task related to design difference)**	User removes needle cap	**Yes**
n/a	Pull off plum cap (cap #2) next **(Critical task related to design difference)**	User removes plum needle cap	**Yes**
Push autoinjector down against injection site **(Critical task related to design difference)**	Push autoinjector down against injection site **(Critical task related to design difference)**	User presses autoinjector against injection site	**Yes**
n/a	Press the plum activator button to inject **(Critical task related to design difference)**	User pushes down on the plum activator button to start the injection	**Yes**
Hold until second click (or 10 seconds, or orange indicator stops moving) **(Critical task related to design difference)**	Count for 10 seconds (or yellow marker fully appears in the window view and stops moving) **(Critical task related to design difference)**	User keeps autoinjector pressed against injection site for 10 seconds	**Yes**

Source: Applicant's CUHF Study Report Table 8, Page 33-34 of 241.

2.4 Primary Endpoint

According to the Applicant, the primary endpoint for this CUHF study was the overall use success rate observed for both the test and reference products. The overall use success for each pen is defined as participants performing a successful injection with no use errors in any critical tasks related to external design differences.

2.5 Non-inferiority (NI) Margin

According to the Applicant, the NI margin of 12.5% was used in this CUHF study mainly because of the nature of the drug, which is chronically administered, not life-sustaining or life-supporting and due to evidence of self-correction in the summative studies.

Reviewer's Comments:

The justification for using 12.5% as the NI margin is not adequate. We usually recommend that the Applicant provide justification from literature or past reference studies for choosing the NI margin.

2.6 Sample Size Calculation

According to the Applicant, the overall use success rates were assumed to be 88% for the Test product (S_{AVT02}) and 90% for the Reference products (S_{RP}) (i.e., S_{RP} - S_{AVT02} = 2%). A total of 65 participants would provide at least 90% power to demonstrate NI using a NI limit of 12.5%, a within-subject correlation of 0.8 in overall use success rates, and a type I error rate of 5%. Considering a 10% of non-evaluable participants for the PPP, 73 subjects were randomized.

Reviewer's Comments:

The current sample size of 65 could attain power above 90% with a Test success rate 88%, a Reference success rate 90%, a within-subject correlation 0.8, and a NI margin 12.5%, using the Tango method. However, the justification that the Applicant provided for using a 12.5% NI margin is not adequate.

Assuming equal success rates of 80%, 85% or 90% for the Test and Reference products, with a within-subject correlation 0.8 and a smaller NI margin of 10%, the sample size of 65 would obtain power above 80%.

Table 2: Reviewer's Calculation of Power for Different NI Margins and Sample Sizes

Sample Size	Success Rate of Test	Success rate of Reference	Correlation	Margin	Power
65	0.88	0.9	0.8	0.125	90.9%
65	0.88	0.9	0.8	0.1	78.2%
70	0.88	0.9	0.8	0.1	75.7%
75	0.88	0.9	0.8	0.1	83.2%
65	0.9	0.9	0.8	0.1	93.8%
65	0.85	0.85	0.8	0.1	88.6%
65	0.8	0.8	0.8	0.1	82.8%

Source: Reviewer's analysis.

2.7 Study Participants

According to the Applicant, this study focused on the Humira-experienced users who might be negatively impacted by an automatic substitution. A total of 73 individuals from one user group (RA patients) participated in this CUHF study.

The Applicant stated that RA patients were determined to be the group most at risk in an automatic substitution scenario, since they are most likely to have hand dexterity or strength limitations and would not have the benefit of a caregiver present (as in the JIA group). Hence, this study focused on this highest-risk user group.

The Applicant also stated that JIA patients were children or adolescents who would need the assistance of an adult caregiver to obtain the prescription from a doctor and procure the drug from a pharmacy. JIA patients were likely expected to have caregiver supervision during the first injection. The Applicant claimed that the minimum patient weight to accurately use the Humira pen (40 mg/0.4 ml) was 66 pounds and above; in the US, 66 pounds (50th percentile in weight) corresponds to a 9.5-year-old child. It was unlikely that a patient of this age was performing self-injections, and even if they were, it was unlikely they would be self-injecting in an unsupervised setting. Therefore, the use pattern leading into receiving a new interchangeable biosimilar was a supervised setting which increased the likelihood that the first use of an interchangeable biosimilar would be overseen, if not performed by the caregiver. This left the subset of older JIA patients, who could be represented by adult RA patients for the purpose of this study.

Reviewer's Comments:

The Applicant may need to include a sufficient number of juvenile participants for a meaningful NI comparison, if the juvenile and adult groups are considered as separate and distinct user groups. The current sample size of 73 participants does not include any juveniles. We defer the determination of adequacy of the user group to DMEPA.

Assuming equal success rates of 50%, 60%, or 70% for the Test and Reference products, with a within-subject correlation 0.8 and a NI margin of 10%, the following table presents the simulation results for sample size needed that would obtain power above 80%.

Table 3: Reviewer's Calculation of Power for Different Success Rates and Sample Sizes

Sample Size	Success Rate of Test	Success rate of Reference	Correlation	Margin	Power
70	0.5	0.5	0.8	0.1	77.7%
75	**0.5**	**0.5**	**0.8**	**0.1**	**81.0%**
65	0.6	0.6	0.8	0.1	78.1%
70	**0.6**	**0.6**	**0.8**	**0.1**	**80.2%**
60	0.7	0.7	0.8	0.1	75.3%
65	**0.7**	**0.7**	**0.8**	**0.1**	**80.3%**

Source: Reviewer's analysis.

2.8 Statistical Methods

The evaluation of NI was conducted in the PPP. The primary endpoint related to this study was whether the Test product was non-inferior to the Reference product in terms of overall use success. The hypotheses for evaluating NI were defined as:

$$H_0: S_{RP} - S_{AVT02} \geqslant d \text{ (not non-inferior)}$$

$$H_1: S_{RP} - S_{AVT02} < d \text{ (non-inferior)}$$

The point estimate of the difference in overall use success rate ($S_{RP} - S_{AVT02}$) and the corresponding upper bound of the 95% one-sided confidence interval (CI) (equivalent to upper limit of the 90% two-sided CI) were calculated using the Tango Method for paired binary data.

If the upper bound of the one-sided 95% CI for $S_{RP} - S_{AVT02}$ was less than the acceptable NI margin of 12.5%, the Test product could be concluded as non-inferior to the Reference product in terms of overall use success.

2.9 Analysis Results

Tables below present the Applicant's primary endpoint analysis and sensitivity analysis results. Table 4 shows the NI analysis using the PPP of 67 subjects. Table 5 presents a sensitivity analysis for the full randomized population of 73 subjects, excluding order of cap removal use errors for the Humira pen. In both cases, the Test product was determined to be non-inferior to the Reference product in terms of overall use success.

Table 4: Applicant's Non-inferiority Analysis Results (PP Population)

	AVT02 Autoinjector (N=67) n (%)	Humira Pen (N=67) n (%)
Critical Tasks: Successes / Use Errors		
Remove Needle Cap or Remove Gray Cap (cap #1)	65 (97.0) / 2 (3.0)	54 (80.6) / 13 (19.4)
Pull off Plum Cap (cap #2)	-	56 (83.6) / 11[18] (16.4)
Push Autoinjector down against the site	67 (100) / 0	65 (97.0) / 2 (3.0)
Press the plum activator button to inject	-	66 (98.5) / 1 (1.5)
Hold Until Second Click or Count for 10 Seconds	63 (94.0) / 4 (6.0)	59 (88.1) / 8 (11.9)
Overall Use Success	61	48
Overall use Success rate (%)	91.0	71.6
Non-Inferiority Margin (%)	12.5	
Difference in Overall Use Success Rate (%)	-19.4	
95% one-sided CI (%) *	-8.7	

*Calculated using the Tango method, a statistical test appropriate for paired binary data.
Overall use success: participants not failing any critical tasks related to external design differences.
Overall use success rate: number of participants not failing any critical tasks related to external design differences divided by total number of participants in the Per-Protocol Population.
Note: If the upper bound of the one-sided 95% Confidence Interval (CI) of the difference in overall use success rate (i.e., Success rate of Humira pen - Success rate of AVT02 Autoinjector) is less than the acceptable non-inferiority margin of 12.5%, then the AVT02 Autoinjector can be concluded Non-Inferior to the Humira pen in terms of overall use success.

Source: Applicant's CUHF Study Report Table 10, Page 39 of 241.

Table 5: Applicant's Sensitivity Analysis Results (Randomized Population)

	AVT02 Autoinjector (N=73) n (%)	Humira Pen (N=73) n (%)
Critical Tasks: Successes / Use Errors		
Remove Needle Cap or Remove Gray Cap (cap #1)	70 (95.9) / 2 (2.7)	57 (78.1) / 16 (21.9)
Pull off Plum Cap (cap #2)	-	59 (80.8) / 14 (19.2)
Push Autoinjector down against the site	72 (98.6) / 0	68 (93.2) / 5 (6.8)
Press the plum activator button to inject	-	70 (95.9) / 3 (4.1)
Hold Until Second Click or Count for 10 Seconds	67 (91.8) / 5 (6.8)	62 (84.9) / 11 (15.1)
Overall Use Success	65	50
Overall use Success rate (%)	89.0	68.5
Non-Inferiority Margin (%)	12.5	
Difference in Overall Use Success Rate (%)	-20.5	
95% one-sided CI (%) *	-10.4	

*Calculated using the Tango method, a statistical test appropriate for paired binary data.
Overall use success: participants not failing any critical tasks related to external design differences.
Overall use success rate: number of participants not failing any critical tasks related to external design differences divided by total number of participants in the Randomized Population.

Source: Applicant's CUHF Study Report Table 10, Page 40 of 241.

3. REVIEWER'S RESPONSE TO THE CONSULT

3.1 Comments for Internal Use (FDA)

We have the following comments regarding the Applicant's CUHF Study Report for AVT02 Autoinjector for Humira Biosimilar submitted in the BLA 761299 on 12/20/2021.

1) The randomization schedule that the Applicant claimed in the study report cannot be located. However, the randomization sequence information shown in Appendix B: Overview of Trials appears to be randomized sequences.

2) The justification for using 12.5% as the NI margin appears to be not adequate. We usually recommend that the Applicant provide justification from literature or past reference studies for choosing the NI margin.

3) The current sample size of 65 could attain power above 90% with a Test success rate 88%, a Reference success rate 90%, a within-subject correlation 0.8, and a NI margin 12.5%, using the Tango method.

4) Assuming equal success rates of 80%, 85% or 90% for the Test and Reference products, with a within-subject correlation 0.8 and a smaller NI margin of 10%, the sample size of 65 would obtain power above 80%.

5) The Applicant may need to include a sufficient number of juvenile participants for a meaningful NI comparison, if the juvenile and adult groups are considered as separate and distinct user groups. The current sample size of 73 participants does not include any juveniles. We defer the determination of adequacy of the user group to DMEPA.

6) The primary endpoint and statistical methods for testing the NI between the use of Test and Reference products appear to be appropriate.

7) Based on the submitted data and a 10% non-inferiority margin, the completed CUHF study shows that the test device is non-inferior to the reference device with respect to overall use success rate in adult subjects.

4. REFERENCES

Draft Guidance for Industry (January 2017). Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.

Draft Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness (November 2016)

Tango, T. (1998). Equivalence Test and Confidence Interval for the Difference in Proportions for the Paired-Sample Design. Statistics in Medicine, Vol 17: 891-908

APPENDIX A: ORIGINAL CONSULT REQUEST

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		**REQUEST FOR CONSULTATION**		
TO *(Office/Division)*: OTS/DBVIII			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Matt Barlow, OMEPRM/DMEPA 240-402-4576	
DATE 01/03/2022	IND NO. N/A	BLA NO. 761299	TYPE OF DOCUMENT Comparative Use Human Factors Study Results	DATE OF DOCUMENT December 20, 2021
NAME OF DRUG AVT-02 (adalimumab-ryvk)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG TNF blocker	DESIRED COMPLETION DATE February 21, 2021
NAME OF FIRM: Alvotech USA Inc.				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ CONTROL SUPPLEMENT	☒ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☒ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please review the CUHF study results.

In addition to your review of the CUHF study results, please note the following:

- The applicant did not include a JIA user group.
- The applicant chose a delta of 12.5%. We normally see a delta of 10%. Is the Applicant's delta and justification acceptable?
- The Agency did not provide feedback/recommendations on the CUHF study protocol prior to the Applicant conducting the CUHF study.

The study report is available via:
\\CDSESUB1\evsprod\bla761299\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\all\5354-other-stud-rep\cuhf\cuhf-report-body.pdf

Reference ID: 4922665

SIGNATURE OF REQUESTOR and DMEPA Point of Contact Matt Barlow	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/

YIFAN WANG
11/08/2022 02:59:41 PM

SOMESH CHATTOPADHYAY
11/08/2022 03:00:52 PM

M E M O R A N D U M

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

DATE: September 30, 2022

TO: Nikolay Nikolov, M.D.
Director
Division of Rheumatology and Transplant Medicine
Office of New Drugs

FROM: Melkamu Kebtie Getie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Monica Javidnia, Ph.D.
DGDSI
OSIS

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
DGDSI
OSIS

SUBJECT: Remote regulatory assessment (RRA) (b) (4) (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion (immunogenicity assays) of Study AVT02-GL-302 (BLA 761299, AVT02 [a proposed biosimilar to adalimumab/Humira®]) conducted at (b) (4)

We observed the following objectionable condition during the RRA:

Discrepancies were noted in summary tables of the 28-week interim immunogenicity (ADA and NAb) bioanalytical reports.

Based on the evaluation of the observation and the firm's response, the objectionable condition relates to minor reporting errors and had no impact on the integrity of the data. Therefore, we conclude that the ADA and NAb assays data from the audited study are reliable. However, we recommend that the review division requests the applicant to submit final 52-week sample analysis reports for projects (b) (4) 20-531-079 (ADA

report) and [redacted]20-531-080 (NAb report) containing the corrected summary tables.

2. Reviewed Studies

AVT02-GL-302 (BLA 761299)
"Multicenter, Double-Blind, Randomized, Parallel-Group, Study Evaluating Pharmacokinetic, Efficacy, Safety, and Immunogenicity Between Patients with Moderate to Severe Chronic Plaque Psoriasis Receiving Humira® and Patients with Moderate to Severe Chronic Plaque Psoriasis Undergoing Repeated Switches Between Humira® and AVT02 Followed by a Safety Extension Phase of AVT02 (ALVOPAD-X)"

Sample Analysis Period:
ADA assay: [redacted] Project Number: [redacted]20-531-079

NAb assay: [redacted] Project Number: [redacted]20-531-080

3. Scope of RRA

OSIS scientists Melkamu Getie-Kebtie, Ph.D., R.Ph., and Monica Javidnia, Ph.D., reviewed the analytical portion of the above [redacted]

The RRA included an examination of records and processes for ADA and NAb method validation, and study sample analysis. The RRA also included interviews with the firm's management and staff.

4. RRA Observation

At the conclusion of the RRA, we observed an objectionable condition, which was discussed with the firm's management during the RRA close-out meeting.

Our evaluation of the observation and the firm's response dated 09/21/2022 (**Attachment 1**) are presented below.

4.1. Observation discussed at the close-out of RRA

Discrepancies were noted between the 28-week interim bioanalytical reports and source documents for immunogenicity assessment of AVT02 (adalimumab). Specifically, [redacted]

(b) (4)
(b) (4) **were not consistent with information recorded in source documents.**

Firm's Response: In their written response, the firm (b) (4)
(b) (4)

(b) (4)

As corrective actions, the firm stated the following.

(b) (4)

(b) (4)

OSIS Evaluation: The firm's corrective actions are acceptable to prevent future occurrence of such errors. The (b) (4)
(b) (4)
(b) (4) are minor reporting errors that do not impact the reliability of the ADA and NAb data from subjects in study AVT02-GL-302.

Note that the inaccurate information in the summary tables were initially identified from the 28-week interim bioanalytical reports. During the RRA, the firm informed us that a 52-week final sample analysis report was recently finalized. The firm conducted a QC check of the information in the summary tables of the final reports for projects (b) (4)20-531-079 and (b) (4)20-531-080 and provided excel copy of the summary tables with information about corrections (**Attachments 2 and 3**). We recommend that the review division requests the applicant to submit these final reports with the corrected summary tables.

Draft: MG 9/29/22, 9/30/22
Edit: MJ 9/29/22; SA 9/29/22, 9/30/22 KAB 09/30/2022

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ (b) (4)
(b) (4)
OSIS File #: (b) (4)

Attachments

1. Firm response to observation
2. Corrected summary table for (b) (4)20-531-079 report
3. Corrected summary table for 20-531-080 report

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/s/

MELKAMU GETIE KEBTIE
09/30/2022 05:08:47 PM

MONICA JAVIDNIA
09/30/2022 05:10:58 PM

STANLEY AU
09/30/2022 05:21:06 PM
Team Lead

KIMBERLY A BENSON
10/03/2022 01:54:44 PM

M E M O R A N D U M

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

DATE: 4/25/2022

TO: Division of Rheumatology and Transplant Medicine (DRTM)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

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

RE: BLA 761299

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Record Review (RRR) for the site in (b) (4) which falls within the surveillance interval. The RRR was conducted under the following submission: BLA 761205.

OSIS observed the following objectionable conditions:

(b) (4)

After receiving a written response from the site, OSIS concluded that data from the reviewed study was reliable. (OSIS Final Review – (b) (4) RRR)

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

WENDY NG
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