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RESEARCH**

APPLICATION NUMBER:

761299Orig1s000

MULTI-DISCIPLINE REVIEW

Review Team/Cross-Discipline Team Leader/Division Summary Review

Date	02/23/2024
Clinical Divisions	Division of Rheumatology and Transplant Medicine (DRTM) Division of Dermatology and Dentistry (DDD) Division of Gastroenterology (DG) Division of Ophthalmology (DO)
Subject	Review Team/Cross-Discipline Team Leader/Division Summary Review
NDA/BLA # and Supplement#	BLA 761299
Applicant	Alvotect USA, Inc.
Date of Submission	August 24, 2023
BsuFA Goal Date	February 24, 2024
Proposed Proprietary (Non-Proprietary) Name	Simlandi (adalimumab-ryvk)
Applicant Proposed Indication(s)/Population(s)	Rheumatoid arthritis (RA) Juvenile idiopathic arthritis (JIA) (2 years of age and older) Psoriatic arthritis (PsA) Ankylosing spondylitis (AS) Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Ulcerative Colitis (UC) in adult patients Plaque Psoriasis (PsO) Hidradenitis Suppurativa (HS) in adult patients Uveitis (UV) in adult patients
Recommendation on Regulatory Action	Approval

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1. Introduction

Alvotech (also referred to as “Applicant” in this review) submitted an original biologics license application (BLA) 761299 under section 351(k) of the Public Health Service Act (PHS Act) for AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector as a proposed interchangeable to U.S.-licensed Humira (U.S.-Humira, adalimumab) injection, 40 mg/0.4 mL for subcutaneous use in a single-dose prefilled pen, on December 20, 2021. Prior to this, the Applicant also submitted an original BLA 761205 for the same product, AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector, as a proposed biosimilar to U.S.-Humira injection, 40 mg/0.4 mL for subcutaneous use in a single-dose prefilled pen on September 4, 2020.

For BLA 761205, the information submitted in BLA 761205 by the Applicant sufficiently demonstrated that AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector is biosimilar to U.S.-Humira injection, 40 mg/0.4 mL for subcutaneous use in a single-dose prefilled pen for the following indications for which U.S.-Humira has been previously approved and for which the Applicant is seeking licensure: RA, JIA in patients 2 years and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, and PsO. However, data submitted in BLA 761205 were not sufficient to support a conclusion that the manufacture of AVT02 was well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life (Refer to the Biosimilar Multi-Disciplinary Evaluation and Review (BMER) filed in DARRTS for BLA 761205 on August 15, 2022). Therefore, BLA 761205 received a Complete Response Letter on August 11, 2022. On October 13, 2022, the Applicant resubmitted BLA 761205 to address the deficiencies outlined in the August 11, 2022, Complete Response Letter. On April 12, 2023, BLA 761205 received another Complete Response Letter because the deficiencies had not been adequately addressed.

The review team for BLA 761299 concludes that the information submitted in BLA 761205 and also present in BLA 761299 sufficiently demonstrates that AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector is biosimilar to U.S.-Humira injection, 40 mg/0.4 mL for subcutaneous use in a single-dose prefilled pen for the following indications for which U.S.-Humira has been previously approved and for which the Applicant is seeking licensure under BLA 761299: RA, JIA in patients 2 years and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, and PsO. Refer to the BMER filed in DARRTS for BLA 761205 on August 15, 2022 and appended to this memorandum, and refer to

(b) (4)

(b) (4) AVT02 as biosimilar

to U.S.-Humira. The CDTL and the Signatory concur with the above conclusions regarding biosimilarity and confirm that they support licensure of AVT02 injection 40 mg/0.4mL for subcutaneous use in a single-dose autoinjector in BLA 761299.

For BLA 761299, the information submitted by the Applicant sufficiently demonstrated that AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector is interchangeable with U.S.-Humira injection, 40 mg/0.4 mL for subcutaneous use in a single-dose prefilled pen for the following indications for which U.S.-Humira has been previously approved and for which the Applicant is seeking licensure: RA, JIA in patients 2 years and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, and PsO (Refer to the BMER filed in DARRTS on December 20, 2022). However, data submitted in the initial BLA 761299 were not sufficient to support a conclusion that the manufacture of AVT02 was well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. Therefore, BLA 761299 received a Complete Response Letter on December 20, 2022.

On December 28, 2022, the Applicant submitted a response to the December 20, 2022 Complete Response Letter for BLA 761299. On June 28, 2023, BLA 761299 received another Complete Response Letter because the deficiencies had not been adequately addressed.

On August 24, 2023, the Applicant submitted a response to the June 28, 2023 Complete Response Letter for BLA 761299. In addition to the above proposed indications, the Applicant added Hidradenitis Suppurativa (HS) and Uveitis (UV) in adult patients as result of exclusivity expiration on 09/09/2022 and 06/30/2023, respectively.

Of note, the Applicant submitted the contents of BLA 761205 to BLA 761299, including information in all the modules (Modules 1-5 in BLA 761205). This is the review summary of this application, including regulatory consideration on biosimilarity as well as interchangeability designation for AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector for the proposed indications.

2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761299 for AVT02 (40 mg/0.4 mL, 100 mg/mL) manufactured by Alvotek hf, Reykjavik, Iceland. The data submitted in this application are adequate to support a conclusion that the manufacture of AVT02 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. OPQ recommends approval of the proposed AVT02 (40 mg/0.4 mL, 100 mg/mL) autoinjector presentation. Refer to the integrated quality assessment and related primary reviews for detailed information. The OPQ team determined that the data submitted for these proposed presentations in this application are adequate to support the following conclusions:

- The manufacture of AVT02 40 mg/0.4 mL, 100 mg/mL is well-controlled and leads to a product that is pure, potent, and safe.
- AVT02 40 mg/0.4 mL, 100 mg/mL is highly similar to U.S.-Humira (40 mg/0.4 mL, 100 mg/mL) notwithstanding minor differences in clinically inactive components
- The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using E.U.-Humira as the comparator for the assessment of biosimilarity.
- The strength of AVT02 40 mg/0.4 mL, 100 mg/mL in a single-dose autoinjector is the same as that of U.S.-Humira (40 mg/0.4 mL, 100 mg/mL).
- AVT02 40 mg/0.4 mL, 100 mg/mL also has the same dosage form and route of administration as that of U.S.-Humira (40 mg/0.4 mL, 100 mg/mL).

The CDTL and the signatory agree with this assessment and recommendations.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval.

4. Clinical Pharmacology

No new clinical pharmacology information is included in this resubmission. The clinical pharmacology were previously reviewed during the original review cycle for the current BLA to establish interchangeability and for BLA 761205 to establish biosimilarity. As discussed in section 1, the information submitted in BLA 761205 to support a demonstration of biosimilarity was also submitted in BLA 761299 and the review team, the CDTL, and the signatory conclude that the information submitted in BLA 761205 and also present in BLA 761299 and the review of that information in BLA 761205 (appended here) is relevant to and supports licensure of AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector in BLA 761299. There are no clinical pharmacology issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS

on December 20, 2022 and the Biosimilar Multi-Disciplinary Evaluation and Review filed for BLA 761205 on August, 15, 2022 (appended to this memorandum).

5. Statistical and Clinical Evaluation and Recommendations

No new clinical efficacy or safety information is included in this resubmission. The clinical efficacy and safety were previously reviewed during the original review cycle for the current BLA 761299 and for BLA 761205 to establish biosimilarity. As discussed in section 1, the information submitted in BLA 761205 to support a demonstration of biosimilarity was also submitted in BLA 761299 and the above-identified review team, the CDTL, and the signatory, conclude that the information submitted in BLA 761205 and also present in BLA 761299 and the review of that information in BLA 761205 (appended here) is relevant to and supports licensure of AVT02 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector in BLA 761299. There are no statistical issues or safety issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on December 20, 2022, and the Biosimilar Multi-Disciplinary Evaluation and Review filed for BLA 761205 on August, 15, 2022 (appended here).

6. Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant provided sufficient justification that AVT02 will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which U.S.-Humira has been previously approved. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

The Applicant provided sufficient scientific justification (based on the quality attributes, mechanism of action, PK, immunogenicity and toxicity profile), and sufficient data and information, including clinical conclusion that AVT02 “can be expected to produce the same clinical result as the reference product in any given patient” for each of the following indications for which U.S.-Humira has been previously licensed: RA, JIA, PsA, AS, PsO, CD, UC, HS, and UV.

Refer to Section 6.5 in the BMER for BLA 761299 and section 7 below for additional information.

7. Extrapolation

The Applicant is seeking licensure of AVT02 as an interchangeable for the following indications for which U.S.-Humira has been previously licensed: RA, PsA, AS, PsO, JIA in

patients 2 years of age and older, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, HS in adult patients, and UV in adult patients.

Refer to Section 1 of this memorandum regarding the review and conclusion that the Applicant has provided adequate data and information to support licensure of AVT02 as a biosimilar for the proposed indications: RA, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients and JIA 2 years of age and older. Refer to Section 6.5 and 6.6 in the BMER for BLA 761299 regarding the review and conclusion that the Applicant has provided adequate data and information to support licensure of AVT02 as an interchangeable for the proposed indications: RA, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients and JIA 2 years of age and older.

It is of note that the BMER 761205 (appended to this memorandum) did not cover the extrapolation justification for pediatric UC patients 5 years of age and older, UV, and HS, which were still under orphan exclusivity at that time. The following statements provide extrapolation justification for these three indications for AVT02 as a biosimilar to U.S.-Humira.

The rationale in support of extrapolation to the pediatric UC indication as biosimilar to U.S.-Humira is summarized below:

- The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults and in pediatric UC patients. Together with the demonstrated structural and functional similarity between AVT02 and U.S.-Humira, the mechanisms of action of AVT02 are not expected to be different from that of U.S.-Humira in pediatric UC, to the extent that the mechanisms are known or can be reasonably determined.
- Adalimumab concentrations are similar in adult and pediatric UC patients (Humira USPI, 2021). Together with the demonstrated 3-way PK similarity (AVT02 vs. U.S.-Humira and EU-Humira) in healthy volunteers, and between AVT02 vs. EU-Humira in patients with psoriasis, the PK following AVT02 are not expected to be different to that of U.S.-Humira in pediatric UC patients.
- Immunogenicity rates of U.S.-Humira were comparable between adult and pediatric UC patients (Humira USPI, 2021). Together with the comparable immunogenicity in healthy volunteers (AVT02 vs. U.S.-Humira vs. EU-Humira) and in patients with psoriasis (AVT02 vs. EU-Humira), the immunogenicity of AVT02 is not expected to be different from that of U.S.-Humira in pediatric UC patients.
- The safety profile of U.S.-Humira was comparable in adult vs. pediatric UC patients (Humira USPI, 2021). Together with the demonstrated comparable safety profile of AVT02 vs. EU-Humira in adult psoriasis patients, the 3-way PK similarity in healthy subjects, the safety of AVT02 is not expected to be different from that of U.S.-Humira in pediatric UC patients.

Similarly, scientific considerations to support for the biosimilarity extrapolation of data and information to support licensure for UV and HS are outlined below:

- Biosimilarity has been established between AVT02 and the reference product, U.S.-Humira based on extensive analytical characterization, comparative PK study, comparative clinical study, safety and immunogenicity data.
- Adequate scientific justification supporting extrapolation of scientific information and data (based on mechanism of action, PK and immunogenicity, safety and toxicities) as stated in BMER in BLA761205 (Section 7.6) (appended to this memorandum) to RA, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients and JIA 2 years of age and older.
- Similar extrapolation of scientific information and data from the original application applies to the indication that is subject of this supplement. Therefore, in patients with UV and HS:
 - a similar PK profile would be expected between AVT02 and U.S.-Humira
 - similar immunogenicity would be expected between AVT02 and U.S.-Humira
 - similar safety profile would be expected between AVT02 and U.S.-Humira
 - the Applicant addressed each of the known and potential mechanisms of action of U.S.-Humira and submitted data to support the conclusion that AVT02 and U.S.-Humira have the same mechanisms for UV and HS, to the extent that the mechanisms of action are known or can reasonably be determined.

In this submission, the Applicant also provided a scientific justification for extrapolating data and information to support licensure of AVT02 as interchangeable with U.S.-Humira for the indications of HS and UV in adult patients and for which U.S.-Humira has been previously approved. See Section 6.5 in BMER for BLA 761299. Note that while the Applicant has submitted acceptable extrapolation justification for pediatric UC patients 5 years of age to 17 years, FDA has determined that U.S.-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5-17 years. FDA therefore cannot license AVT02 for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

The scientific justification for extrapolation of data and information submitted in the application is adequate to support licensure of AVT02 as interchangeable with U.S.-Humira for the indications for which licensure is sought and for which U.S.-Humira has been previously approved. Therefore, we conclude that the Applicant has provided adequate data and information to support licensure of AVT02 injection, 40 mg/0.4 mL for subcutaneous use in a single-dose autoinjector as an interchangeable biosimilar product for the proposed indications: RA, PsA, AS, PsO, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, JIA in patients 2 years of age and older, HS in adult patients, and UV in adult patients.

8. Labeling Recommendations

Nonproprietary Name

The Applicant's proposed nonproprietary name, adalimumab-ryvk, was found to be conditionally accepted by the Agency. See Division of Medication Error and Prevention (DMEPA) reviews dated November 15, 2022, and March 31, 2023, for full details.

Proprietary Name

The proposed proprietary name for AVT02 is conditionally approved as Simlandi. This name has been reviewed by the DMEPA, who concluded the name was acceptable. See DMEPA reviews dated March 8, 2023, March 20, 2023, and October 31, 2023, for full details.

Other Labeling Recommendations

FDA determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The proposed prescribing information has incorporated relevant data and information from the U.S.-Humira prescribing information with appropriate modifications relevant to the indications.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this supplement. There were no findings in this program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

Not applicable.

12. REMS and Postmarketing Recommendations

None.

13. Recommended Comments to the Applicant

None.

14. Signatory Authority Comments

I concur with the team's assessment of the data and information submitted in BLA 761299.
The regulatory action is Approval.

15. Appendix

15.1 Signature Sheet

Discipline and Title or Role	Reviewer Name	Office/Division
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Clinical Pharmacology Reviewer	Tao Liu	OCP/DIIP
	Signature Tao Liu -S Digitally signed by Tao Liu -S Date: 2024.02.20 13:45:28 -05'00'	
Clinical Reviewer	Stefanie Freeman	OII/DRTM
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Clinical Reviewer	Felisa Lewis	OII/DDD
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Clinical Reviewer	Sandhya Apparaju	OII/DG
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Clinical Team Leader	Raj Nair	OII/DRTM
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Clinical Team Leader	Suna Seo	OII/DG
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Clinical Team Leader	Snezana Trajkovic	OII/DDD
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Deputy Division Director (Collaborative Review Division)	Juli Tomaino	OII/DG
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Deputy Division Director (Collaborative Review Division)	William M Boyd	OSM/DO
	Signature: William M. Boyd -S  Digitally signed by William M. Boyd -S Date: 2024.02.21 07:48:17 -05'00'	
Cross-Discipline Team Leader	Ping Ji	OCP/DIIP
	Signature: Ping Ji -S  Digitally signed by Ping Ji -S Date: 2024.02.20 13:30:23 -05'00'	
Designated Signatory Authority	Nikolay Nikolov	OII
	Signature: Nikolay P. Nikolov -S  Digitally signed by Nikolay P. Nikolov -S Date: 2024.02.22 09:19:02 -05'00'	

15.2 List of reviews attached to this memo

- BMER BLA 761205 8/15/2022
- BLA 761205 IQA-ASA ATL Memo 4June2021.pdf
- BLA 761205 IQA-CAA ATL Memo Addendum 15July2022.pdf
- BLA 761205 CDRH OPEQ Review ICC2000861 ICC2000863 final.pdf
- Nonproprietary name review BLA 761205 5/28/2021

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/

PING JI
02/22/2024 04:35:20 PM

NIKOLAY P NIKOLOV
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Cross-Discipline Team Leader/Division Summary Review

Date	6/23/2023
From	Nadia Habal (Clinical reviewer, OII/DRTM) Anil Rajpal (Clinical TL, OII/DRTM) Ping Ji (CDTL, OCP/DIIP) Nikolay Nikolov (Signatory, OII/DRTM)
Subject	Cross-Discipline Team Leader/Division Summary Review
NDA/BLA # and Supplement#	BLA 761299
Applicant	Alvotech USA, Inc.
Date of Submission	December 28, 2022
BsuFA Goal Date	June 28, 2023
Proposed Proprietary (Non-Proprietary) Name	Simlandi (Adalimumab-ryvk)
Applicant Proposed Indication(s)/Population(s)	Rheumatoid arthritis (RA) Juvenile idiopathic arthritis (JIA) (2 years of age and older) Psoriatic arthritis (PsA) Ankylosing spondylitis (AS) Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Ulcerative Colitis (UC) in adult patients Plaque Psoriasis (PsO)
Recommendation on Regulatory Action	Complete Response

1. Introduction

Alvotech (also referred to as “Applicant” in this review) submitted an original biologic license application (BLA 761299) under section 351(k) of the Public Health Service Act (PHS Act) for AVT02 40 mg/0.4 mL as a proposed interchangeable to US- licensed Humira (US-Humira, adalimumab) 40 mg/0.4 mL, on December 20, 2021. The information submitted by the Applicant sufficiently demonstrated that AVT02 40 mg/0.4 mL is interchangeable with U.S.-Humira 40 mg/0.4 mL for the following indications for which U.S.-Humira has been previously approved and for which the Applicant is seeking licensure: RA, JIA in patients 2 years and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, and PsO.

However, data submitted in the application was not sufficient to support a conclusion that the manufacture of AVT02 was well-controlled and would lead to a product that is pure and potent for the duration of the shelf-life. Therefore, the FDA review team recommended a Complete Response for the application on December 20, 2022. The Complete Response Letter outlined

the deficiencies and the information and data required to address the deficiencies. Also, refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on December 20, 2022.

On December 28, 2022, the Applicant resubmitted their biologic license application (BLA 761299) under section 351(k) of the Public Health Service Act (PHS Act) for AVT02 40 mg/0.4 mL as a proposed interchangeable to US-licensed Humira (US-Humira, adalimumab) 40 mg/0.4 mL. This is the review summary of this application.

2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761299 for AVT02 manufactured by Alvotek hf, Reykjavik, Iceland. The data submitted in this application are not sufficient to support a conclusion that the manufacture of AVT02 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to outline the deficiencies and the information and data that will be required to support approval. The CDTL and the Division Signatory agree with this assessment and recommendations.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval.

4. Clinical Pharmacology

No new clinical pharmacology information is included in this resubmission. There are no clinical pharmacology issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on December 20, 2022.

5. Clinical/Statistical- Efficacy

No new clinical/statistical efficacy information is included in this resubmission. There are no clinical/statistical efficacy issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS on December 20, 2022.

6. Safety

No new clinical safety information is included in this resubmission. There are no clinical safety issues that would preclude approval. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review filed in DARRTS in DARRTS on December 20, 2022.

7. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this supplement. There were no findings in this program that would warrant a discussion at an Advisory Committee meeting.

8. Pediatrics

Not applicable.

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

In view of the recommendation of a Complete Response, the labeling review was deferred until the next review cycle.

11. Postmarketing Recommendations

Because the recommended regulatory action for this application is Complete Response, no PMCs or PMRs are recommended at this time.

12. Recommended Comments to the Applicant

Data submitted in this application is not sufficient to support a conclusion that the manufacture of AVT02 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Satisfactory resolution of these deficiencies is required before this application may be approved. This reviewer recommends Complete Response of this application.

13. Division Director Comments

I concur with the team's assessment of the data and information submitted in this supplemental BLA and support Complete Response of this application.

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/

PING JI
06/23/2023 12:17:18 PM

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06/23/2023 12:18:45 PM

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BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	BLA 761299
Received Date	December 20, 2021
BsUFA Goal Date	December 20, 2022
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM) Division of Dermatology and Dentistry (DDD) Division of Gastroenterology (DG) Division of Ophthalmology (DO)
Review Completion Date	See DARRTS stamped date
Product Code Name	AVT02
Proposed Nonproprietary Name¹	Adalimumab-ryvk
Proposed Proprietary Name¹	Simlandi
Pharmacologic Class	Tumor necrosis factor (TNF) blocker
Applicant	Alvotech USA Inc.
Applicant Proposed Indication(s)	Rheumatoid arthritis (RA) Juvenile idiopathic arthritis (JIA) (2 years of age and older) Psoriatic arthritis (PsA) Ankylosing spondylitis (AS) Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Ulcerative Colitis (UC) in adult patients Plaque Psoriasis (PsO)
Recommendation on Regulatory Action	Complete Response

¹Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products

OPMA = Office of Pharmaceutical Manufacturing Assessment

OPDP = Office of Prescription Drug Promotion

OSIS = Office of Study Integrity and Surveillance

DMEPA = Division of Medication Error and Prevention Analysis

DRISK = Division of Risk Management

DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
AS	Ankylosing spondylitis
AUC	Area under the curve
AUC _{tau, wk26-28}	Area under the plasma concentration-time curve over the dosing interval of Week 26 to 28
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
C _{max}	Maximum concentration
C _{max, wk26-28}	Maximum observed plasma concentration during the dosing interval of Week 26 to 28
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EPR	Essential Performance Requirement
E.U.-Humira	E.U.-approved Humira
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio

ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
JIA	Juvenile idiopathic arthritis
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
Nab	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
PsA	Psoriatic arthritis
PsO	Plaque Psoriasis
RA	Rheumatoid arthritis
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
UC	Ulcerative Colitis
ULOQ	Upper Limit of Quantitation
U.S.-Humira	U.S.-licensed Humira

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1. Executive Summary

1.1. Product Introduction

Alvotech (hereafter referred to as the “Applicant”) submitted a biologics license application (BLA) (BLA 761299) under section 351(k) of the Public Health Service (PHS) Act for AVT02 (non-proprietary name: adalimumab-ryvk) as a proposed interchangeable to U.S.-Humira (adalimumab). The Applicant had previously also submitted a 351(k) BLA (BLA 761205) for the same product, AVT02 as a proposed biosimilar to U.S.-Humira.

AVT02 is a recombinant human IgG1 monoclonal antibody specific for human TNF-alpha. AVT02 is produced by recombinant DNA technology in a mammalian cell expression system. AVT02 is supplied with a 40 mg/0.4 mL single-dose prefilled pen. AVT02 is administered by subcutaneous injection.

The Applicant is seeking licensure of AVT02 as interchangeable with U.S.-Humira for the following indications for which U.S.-Humira has been previously approved:

- Rheumatoid arthritis (RA)
- Juvenile idiopathic arthritis (JIA) in patients 2 years of age and older
- Psoriatic arthritis (PsA)
- Ankylosing spondylitis (AS)
- Crohn’s disease (CD) in adults and pediatric patients 6 years of age and older
- Ulcerative colitis (UC) in adult patients
- Plaque psoriasis (PsO)

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

AVT02 has the same mechanism of action as that of U.S.-Humira.

AVT02 is proposed as 40 mg/0.4 mL in a single-dose prefilled pen for subcutaneous administration.

The proposed strength of 40 mg/0.4 mL for AVT02 in prefilled pen has the same dosage form

and route of administration as that of U.S. Humira.

Additionally, the conditions of use for which the Applicant is seeking licensure have been previously approved for U.S.-Humira.

1.4. Inspection of Manufacturing Facilities

Biosimilarity between AVT02 and U.S.-Humira was assessed in the BLA 761205, for which a Complete Response letter was issued to the Applicant outlining the identified inspection deficiencies from the standpoint of facilities assessment. The same inspection deficiencies are relevant to this BLA.

The CDTL and Division Signatory concur with these recommendations.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

E.U.-Humira (40 mg/0.4 mL) was used as the comparator product in the switching study (Study AVT02-GL-302) for the assessment of interchangeability. The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the switching study (Study AVT02-GL-302), which used E.U.-Humira (40 mg/0.4 mL) as the comparator for the assessment of interchangeability.

- In the 351(k) BLA761205 submission, the analytical portion of the scientific bridge was established based on results from the comparative analytical assessment of AVT02 (40 mg/0.4 mL), E.U.-Humira (40 mg/0.4 mL), and U.S.-Humira (40 mg/0.4 mL).
- In the 351(k) BLA761205 submission, the PK portion of the scientific bridge was established based on results of a 3-way PK similarity study (Study AVT02-GL-101) comparing AVT02 (40 mg/0.4 mL PFS), E.U.-Humira (40 mg/0.4 mL PFS), and U.S.-Humira (40 mg/0.4 mL PFS).

1.6. Interchangeability Assessment

Table 1: Summary and Assessment of Interchangeability

Biosimilarity Evidence	
Summary of Evidence	AVT02 was demonstrated to be a biosimilar to U.S.-Humira in patients with RA, JIA in patients 2 years and older, PsA, AS, PsO, CD in adults and pediatric patients 6 years and older, and UC in adults in the BLA 761205. The

	conclusion of biosimilarity between AVT02 and U.S.-Humira was based on: • AVT02 is highly similar to U.S.-Humira, notwithstanding minor differences in clinically inactive components. The proposed strength of AVT02 in prefilled pen (40 mg/0.4 mL) is the same as those of U.S.-Humira. The dosage form and route of administration are also the same as those of U.S.-Humira. • There are no clinically meaningful differences between AVT02 and U.S.-Humira based on PK, immunogenicity, safety, and efficacy assessment from the PK similarity study (Study AVT02-GL-101) in healthy subjects and the comparative clinical study in patients with moderate to severe chronic plaque PsO (Study AVT02-GL-301). • The PK portion of the scientific bridge was established based on results of a 3-way PK similarity study (Study AVT02-GL-101) comparing AVT02 (40 mg/0.4 mL PFS), E.U.-Humira (40 mg/0.4 mL PFS), or U.S.-Humira (40 mg/0.4 mL PFS) to support the relevance of the data generated using E.U.-Humira as the comparator in the comparative clinical study (Study AVT02-GL-301). • An adequate scientific justification for extrapolation of data and information to support licensure as a biosimilar for each of the additional indications for which the Applicant was seeking licensure and for which U.S.-Humira has been previously approved.
Assessment of Residual Uncertainties	• There were no residual uncertainties from regulatory perspective.
Switching Study	
Summary of Evidence	• A switching study (Study AVT02-GL-302) was conducted in patients with moderate to severe chronic plaque PsO. The study consisted of a single-arm run-in treatment period where all patients received E.U.-Humira (n=567) followed by a double-blind, 2-arm treatment period where patients were randomized to either the Switching Arm (to alternate AVT02 and E.U.-Humira treatments (n=277)) or Continuous Arm (to receive E.U.-Humira (n=273)). The Switching Arm incorporated two separate exposure periods for each

	product with the final switch from E.U.-Humira to AVT02. The study compared PK, efficacy, safety, and immunogenicity of the Switching and Continuous Arms. • The primary PK endpoints were met; the 90% confidence interval (refer to Section 5.3.1) for the least square mean ratios (Switching Arm/Continuous Arm) for area under the plasma concentration-time curve and maximum observed plasma concentration of the products during the dosing interval of Week 26 to 28 of AVT02/E.U.-Humira/AVT02 (in the Switching Arm) compared to E.U.-Humira (in the Continuous Arm) ($AUC_{\tau, \text{wk26-28}}$ and $C_{\max, \text{wk26-28}}$) were within the pre-specified acceptance criteria of 80% to 125%. The data establishes PK similarity between AVT02 and E.U.-Humira and supports the demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch. • The secondary efficacy endpoints were analyzed descriptively. The percentage of subjects achieving PASI75 was 95.4 and 95.8 for the Switching Arm and the Continuous Arm at Week 28, respectively. The percentage of subjects achieving sPGA was 92.0 and 91.7 for the Switching Arm and the Continuous Arm at Week 28, respectively. The efficacy data support the demonstration that the risk in terms of diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch. • The incidence of anti-drug antibody (ADA) formation at Week 28 was 78.3% and 76.4% in the Switching Arm and Continuous Arm, respectively. The incidence of neutralizing antibody (NAb) formation at Week 28 was 92.2% and 91.0% in the Switching Arm and Continuous Arm, respectively. Overall, the incidence of ADA and NAb formation was comparable between treatment arms in Study AVT02-GL-302, thus supporting the demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch.
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	In terms of clinical safety, the numbers of adverse events were small and are reasonably balanced between the study arms, and the safety experience is sufficiently similar to the historical safety experience with adalimumab to afford valid comparisons. None of the observed safety events impact the determination of interchangeability under review in this application. The clinical safety results from Study AVT02-GL-302 support a demonstration that the risk of in terms of safety of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch.
Assessment of Residual Uncertainties	There are no residual uncertainties from a clinical pharmacology and clinical perspective.
Any Given Patient Evaluation	
Summary of Evidence	The Applicant has provided adequate data and information in this BLA 761299 and in the BLA 761205, including the comparative analytical data and comparative pharmacokinetics, efficacy, safety, and immunogenicity data, to support a demonstration that AVT02 can be expected to produce the same clinical result of U.S.-Humira in any given patient.
Assessment of Residual Uncertainties	There are no residual uncertainties from a clinical perspective.
Extrapolation	
Summary of Evidence	- The information submitted in the BLA 761205 supports a demonstration that AVT02 and U.S.-Humira are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. - The information in this BLA supports a demonstration that AVT02 can be expected to produce the same clinical result as U.S.-Humira in any given patient. - The information in this BLA supports a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not

	greater than the use of U.S.- Humira without such alternation or switch in patients with PsO. • An adequate justification was provided to extrapolate data and information, including clinical data in the BLA 761205, to support a licensure of AVT02 as interchangeable with U.S.-Humira for the following indications for which the Applicant is seeking licensure and for which U.S.-Humira has been previously approved: RA, JIA in patients 2 years of age and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older and UC in adult patients. • The information submitted by the Applicant demonstrates that AVT02 is interchangeable with U.S.-Humira for the following indications for which the Applicant is seeking licensure and for which U.S.-Humira has been previously approved: RA, JIA in patients 2 years of age and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients and PsO.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical perspective.

1.7. Conclusions on Approvability

In BLA 761205, Alvotech sufficiently demonstrated that AVT02 is biosimilar to U.S.-Humira . The data and information provided by the Applicant in the current submission BLA 761299 are sufficient to demonstrate that AVT02 can be expected to produce the same clinical result as U.S.-Humira in any given patient. The risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the risk of using U.S.-Humira without such alternation or switch. Therefore, the information submitted by the Applicant demonstrates that AVT02 40 mg/0.4 mL is interchangeable with U.S.-Humira 40 mg/0.4 mL for the following indications for which U.S.-Humira has been previously approved and for which the Applicant is seeking licensure: RA, JIA in patients 2 years and older, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, and PsO. The CDTL and the Division Signatory agree with this assessment and recommendation.

However, data submitted in this application is not sufficient to support a conclusion that the manufacture of AVT02 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. Therefore, the FDA review team recommended a Complete Response for this application, and the CDTL and the Division Signatory agree with that

recommendation. The Complete Response Letter will outline the deficiencies and the information and data required to address the deficiencies.

Author:

Ping Ji, Ph.D., Clinical Pharmacology Team Lead/CDTL

2. Introduction and Regulatory Background

2.1. Important Safety Issues with Consideration to U.S.-Humira (adalimumab)

The reference product, U.S.-Humira (adalimumab), was originally approved by the FDA in December 2002 for reducing the signs and symptoms and inhibiting the progression of structural damage in adult patients with moderate to severe chronic plaque psoriasis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs. U.S.-Humira was subsequently approved for treatment of juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and uveitis.

Labeling for U.S.-Humira includes black box warnings for serious infections and malignancy. Regarding serious infections, the black box warning recommends to discontinue Humira if a patient develops a serious infection or sepsis during treatment, test for latent tuberculosis and start treatment for tuberculosis if positive prior to starting Humira, and monitor all patients for active tuberculosis even if the initial latent tuberculosis test is negative. Regarding malignancy, the black box warning notes that lymphoma and other malignancies have been reported in children and adolescent patients treated with TNF blockers including Humira.

Labeling for U.S.-Humira also includes warning and precautions for invasive fungal infections (for patients who develop a systemic illness on Humira, consider empiric antifungal therapy for patients who reside or travel to region where mycoses are endemic), anaphylaxis or serious hypersensitivity reactions, hepatitis B reactivation, demyelinating disease, cytopenias, heart failure (worsening or new onset), and development of a lupus-like syndrome.

2.2. Summary of Pre-submission Regulatory History Related to Submission

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP, now Division of Rheumatology and Transplant Medicine, DRTM) and Division of Dermatology and Dentistry (DDD) had several interactions with the Applicant during the development of AVT02.

Notable regulatory history for the development of AVT02 are as follows:

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|--------------------|------------------|--|
| BPD Type 2 meeting | October 30, 2018 | <ul style="list-style-type: none">• The overall development plan for AVT02 and analytical data needed to support the development of AVT02 as a proposed biosimilar to U.S.-Humira. This discussion included the use of U.S.-Humira 100 mg/mL to assess analytical similarity, a PK comparability study of PFS to |
|--------------------|------------------|--|

AI, and a human factors comprehensive use-related risk analysis of the AI.

BPD Type 2 meeting	September 4, 2019	The overall design and specific aspects of their proposed switching study to demonstrate interchangeability of AVT02 with U.S.- Humira were discussed. The FDA made recommendations regarding the design of the switching study (AVT02-GL-302) and recommended that the Applicant demonstrate PK similarity before proceeding with the conduct of the comparative clinical study and the switching.
BPD Type 2 meeting	December 18, 2019	The overall design and specific aspects of their proposed comparative clinical study and the overall approach of comparative analytical assessment of AVT02 with U.S.- Humira, including the scientific bridge between AVT02, U.S.-Humira, and E.U.-Humira were discussed. In addition, the criticality risk ranking of critical quality attributes of adalimumab, the statistical approach of comparison of the critical quality attributes, and the quality of AVT02 to support a future 351 (k) BLA submission were discussed.
BPD Type 4 meeting	July 16, 2020	The content and format of a complete application to support a 351(k) BLA submission demonstrating biosimilarity of AVT02 with U.S.-Humira were discussed. The most current version of the Initial Pediatric Study Plan (iPSP) is dated July 2020.
BLA 761205 submission	September 4, 2022	Biosimilarity submission. The submission received complete response because of inspection deficiencies from standpoint of facilities assessment.

2.3. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter under BLA 761205 for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2. Summary of Clinical Studies Supporting Demonstration of Interchangeability

Study Number	Study Title	Dose and Duration	Route	Number of Patients	Study Population
PK, Safety, and Immunogenicity Study					
AVT02-GL-302	“A multicenter, randomized, double-blind, parallel-group study to evaluate PK, efficacy, safety, and immunogenicity between subjects with moderate to severe chronic plaque psoriasis receiving Humira and subjects with moderate to severe chronic plaque psoriasis undergoing repeated switches between Humira and AVT02, followed by a safety extension phase of AVT02 (ALVOPAD-X)”	Lead in period: all patients treated with loading dose of 80 mg E.U.-Humira SC, followed by 40 mg SC q2 weeks starting 1 week after the initial loading dose. At Week 12, subjects with a clinical response (psoriasis area and severity index [PASI] ≥ 75 [PASI75] were randomly assigned in a 1:1 ratio to either of the following arms: Switching arm: AVT02 from Wk 12 until Wk 16, E.U.-Humira from Wk 16 until Wk 22, and AVT02 from Wk 22 to Wk 28 Non-switching arm: treatment with E.U.-Humira from Wk 12 to Wk 26	SC	277 in the switching arm 273 in the non-switching arm	Patients with moderate to severe chronic plaque psoriasis

Author:

Ping Ji, Ph.D., Clinical Pharmacology Team Lead/CDTL

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

Alvotech USA, Inc. previously submitted BLA 761205 to propose AVT02 as a biosimilar to U.S.-licensed Humira for the same indications as U.S.-Humira and which will follow the same administration and dosing regimen as approved for U.S.-Humira. This submission under BLA 761299 is to support an interchangeability designation for AVT02. The comparative analytical assessment of AVT02 and the manufacturing data to support the production of AVT02 were submitted and assessed under BLA 761205. Refer to the Office of Product Quality executive summary assessment memorandum and assessment memorandum addendum for BLA 761205 uploaded to Panorama June 4, 2021, and July 15, 2022 respectively for review of this information. Additional new chemistry, manufacturing, and controls data were submitted in BLA 761299 to address comments provided during the assessments of BLA 761205 and are assessed under this BLA. The newly submitted information was found to be acceptable. Refer to the OBP memorandum and the OPQ Executive summary uploaded to Panorama on July 21, 2022, and August 24, 2022 respectively for more details.

BLA 761205 received a complete response action letter due to deficiencies identified during the drug substance/drug product manufacturing facility inspection and a withhold determination for the facility. The deficiencies with the facility have not been resolved, and because they are relevant to this BLA, OPQ is recommending a complete response letter be issued to Alvotech USA, Inc. The CDTL and the Division Signatory agree with that recommendation.

Of note, the Applicant submitted information as an amendment dated November 29, 2022. Based on the review of that submission, the OPQ team has determined that the amendment cannot adequately address the outstanding deficiencies in the BLA. Thus, the review team did not consider this to be a major amendment to warrant extension of the review clock. The CDTL and the Division Signatory agree with that recommendation.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH reviewed the device interchangeability information, including the comparability analysis for the 40 mg/0.4 mL PFP to support the 351(k) application seeking interchangeability of AVT02 40 mg/0.4 mL PFP with U.S.-Humira 40 mg/0.4 mL. CDRH concluded that the device constituent of the combination product is approvable for the proposed indications and there are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies and there is no post-market commitments or requirements for this BLA.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA reviewed the comparative analyses, including the label and labeling, the Applicant

submitted to support their 351(k) application seeking interchangeability of AVT02 40 mg/0.4 mL PFP with corresponding U.S.-Humira dosage forms and strengths.

DMEPA determined that the Comparative Use Human Factor (CUHF) study results confirm that the differences in the user interface between the proposed Simlandi autoinjector (AI) and U.S.-licensed Humira Pen are acceptable, and the CUHF study demonstrates the proposed biosimilar interchangeable Simlandi is non-inferior to U.S.-licensed Humira Pen when used by adult patients. Refer to the review in DARRTS dated 12/20/2022.

The review team notes that the CUHF study conducted in support of the interchangeability of the AVT02 autoinjector was not optimally designed to provide comparative use data for all potential user populations, as it only included U.S.-Humira-experienced adult RA patients and not adolescents. However, as detailed in a separate memo (refer to memo in DARRTS dated 12/20/2022), the clinical review division considered the data and unique fact-pattern described in the memo and contextual information submitted in the application, together with clinical considerations, 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. As such, no additional CUHF data in pediatric patients are needed to support the demonstration of interchangeability of the AVT02 autoinjector with U.S.-Humira. DMEPA aligns in the decision to approve the product from CUHF perspective.

The CDTL and the Division Signatory agree with this assessment and conclusions.

3.3. Office of Study Integrity and Surveillance (OSIS)

Biopharmaceutical inspection was requested for the bioanalytical site for Study AVT02-GL-302. OSIS conducted a remote record review for immunogenicity assay at (b) (4) and concluded that the data from the immunogenicity analytical proportions of Study AVT02-GL-302 are reliable. The Division of New Drug Study Integrity within the OSIS determined that an inspection of (b) (4) for the PK bioanalytical proportions is not warranted at this time, since OSIS conducted a remote record review for the site in (b) (4) under BLA 761205, which falls within the surveillance interval.

3.4. Office of Scientific Investigations (OSI)

An OSI audit was not requested for the Study AVT02-GL-302.

Author:

Ping Ji, Ph.D., Clinical Pharmacology Team Lead/CDTL

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

Nonclinical Executive Summary and Recommendation

Not applicable. There was no nonclinical information required or included in this BLA.

Authors:

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Pharm Tox Reviewer

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Pharm Tox Team Leader

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Table 3. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	PK similarity between AVT02 (PFS, 40 mg/0.4 mL) (in the Switching Arm) and E.U.-Humira (PFS, 40 mg/0.4 mL) (in the Continuous Arm) was demonstrated in patients with moderate to severe chronic plaque psoriasis (Study AVT02-GL-302) and supports a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch.
Pharmacodynamics	Not applicable
Immunogenicity	The incidence of ADA and NAb formation in the Switching Arm was comparable to that of the Continuous Arm in patients with moderate to severe chronic plaque psoriasis (Study AVT02-GL-302) and supports a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch.

Under this 351(k) BLA submission, AVT02 is being proposed as an interchangeable biological product with U.S.-Humira. AVT02 (adalimumab-ryvk) was proposed as a biosimilar to U.S.-Humira; see BLA 761205 review in DARRTS dated 08/15/2022. The Applicant submitted a single clinical study in this BLA:

Study AVT02-GL-302: A multicenter, randomized, double-blind, parallel-group study to evaluate PK, efficacy, safety, and immunogenicity between subjects with moderate to severe chronic plaque psoriasis receiving E.U.-Humira and subjects with moderate to severe chronic plaque psoriasis undergoing repeated switches between E.U.-Humira and AVT02, followed by an Optional Extension Phase (open-label) for safety.

The results of the switching study (Study AVT02-GL-302) demonstrated PK similarity between AVT02 (in the Switching Arm) and E.U.-Humira (in the Continuous Arm) during the dosing interval of Week 26 to 28 using an analysis of covariance (ANCOVA) model with prespecified randomization stratification factors (Week 12 BMI and age). Although region is a stratification factor for randomization, it was not prespecified in the ANCOVA model. In this study, the 90% confidence interval for the arithmetic mean ratios (AMRs) (Switching Arm/Continuous Arm) for area under the plasma concentration-time curve (AUC) over the dosing interval of Week 26 to 28 ($AUC_{\text{tau}, \text{wk}26-28}$) and maximum observed plasma concentration during the dosing interval of Week 26 to 28 ($C_{\text{max}, \text{wk}26-28}$) constructed using the Fieller's theorem were contained within the pre-specified criteria of 80% to 125% (Table 4). Refer to Section 6 for additional discussion on the statistical method.

The immunogenicity of switching between E.U.-Humira and AVT02 (in the Switching Arm) was comparable to that of E.U.-Humira (in the Continuous Arm) after repeat dosing in patients with plaque psoriasis (Study AVT02-GL-302). The overall incidence of anti-drug antibody (ADA) formation at randomization baseline at Week 12 following repeat doses of E.U.-Humira in the lead-in period was 65.7% and 69.4% in patients who were randomized to the Switching Arm and Continuous Arm, respectively, and at Week 28 (primary PK assessment) was 78.3% and 76.4% in the Switching Arm and Continuous Arm, respectively. The overall incidence of neutralizing antibody (NAb) formation at randomization baseline at Week 12 following repeat doses of E.U.-Humira was 83.6% and 80.1% in ADA+ patients who were randomized to the Switching Arm and Continuous Arm, respectively, and at Week 28 was 92.2% and 91.0% in the Switching Arm and Continuous Arm, respectively.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was demonstrated between AVT02 (in the Switching Arm) and E.U.-Humira (in the Continuous Arm) in the switching study (Study AVT02-GL-302). Comparable incidence of immunogenicity was observed between the Switching Arm and the Continuous Arm in Study AVT02-GL-302. There were no clinical pharmacology residual uncertainties regarding the PK or immunogenicity assessment to support a demonstration that AVT02 40 mg/0.4 mL is interchangeable with U.S.-Humira 40 mg/0.4 mL.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

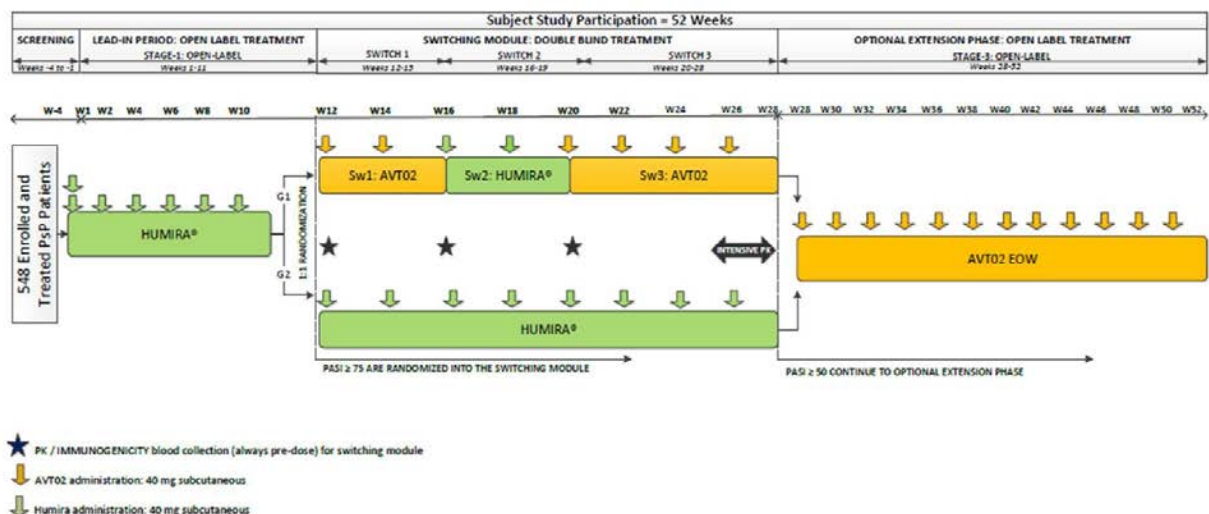
In the BLA 761205 submission, the PK portion of the scientific bridge was established based on the results of a 3-way PK similarity study (Study AVT02-GL-101) comparing AVT02 (40 mg/0.4 mL PFS), E.U.-Humira (40 mg/0.4 mL), or U.S.-Humira (40 mg/0.4 mL) to support the relevance of the data generated using E.U.-Humira as the comparator in the comparative clinical study (Study AVT02-GL-301). Refer to the Product Quality review for details regarding the analytical portion of the scientific bridge.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

5.3.1 Clinical Pharmacology Study Design Features

To demonstrate that “for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch,” the Applicant submitted a switching study, Study AVT02-GL-302.

The switching study was a multicenter, randomized, double-blind, parallel-group study to evaluate PK, efficacy, safety, and immunogenicity between subjects with moderate to severe chronic plaque psoriasis receiving Humira and subjects with moderate to severe chronic plaque psoriasis undergoing repeated switches between Humira and AVT02, followed by an Optional Extension Phase (open-label) for safety. (Study AVT02-GL-302, Figure 1). The 28-week treatment period was followed by 24 weeks of open label extension. During the lead-in period (Stage 1), all patients received E.U.-Humira (40 mg/0.4 mL prefilled syringe) at a dose of 40 mg every other week via subcutaneous (SC) injection from Day 1 to Week 10. At Week 12, responsive subjects (Psoriasis Area and Severity Index [PASI] $\geq$ 75 [PASI75]) were randomized (1:1) by body mass index (BMI) (< 30 kg/m² or ≥ 30 kg/m²), age (< 65 years or ≥ 65 years), and region (US or EU) to either the Switching Arm or Continuous Arm. The Switching Arm consisted of 3 switches. Patients in the Switching Arm received 40 mg of AVT02 (40 mg/0.4 mL PFS) at Weeks 12 and 14, 40 mg of E.U.-Humira (40 mg/0.4 mL PFS) at Weeks 16 and 18, and then 40 mg of AVT02 (40 mg/0.4 mL PFS) every other week from Week 20 to 26 via SC injection. Patients in the Continuous Arm received E.U.-Humira (40 mg/0.4 mL PFS) at a dose of 40 mg every other week from Week 12 to 26 via SC injection. A total of 550 patients received E.U.-Humira during the lead-in period and were randomized at Week 12 (n=277/Switching Arm, n=273/Continuous Arm).

Figure 1. Study AVT02-GL-302 Schematic

Abbreviations: EOW = every other week; G = group; mg = milligram; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; PsP = plaque psoriasis; Sw = switch; W = week

Source: Figure 9.1 of Clinical Study Report AVT02-GL-302-ALVOPAD-X

Clinical Pharmacology Study Endpoints

In Study AVT02-GL-302, the co-primary PK endpoints over the dosing interval of Week 26 to 28, $AUC_{\tau, \text{wk26-28}}$ and $C_{\max, \text{wk26-28}}$, were evaluated to compare the PK profiles of AVT02 and E.U.-Humira. The secondary endpoints of the study were PK ($T_{\max, \text{wk26-28}}$, $C_{\text{trough}, \text{wk26-28}}$, C_{trough} after each switch at Weeks 12, 16, and 20, Ratio of C_{trough} after the last administration of study drug at Week 26 to Week 12, C_{trough} after last administration of study drug at Week 26 in subjects who were PASI75 responders and ADA negative at Week 12), safety, and immunogenicity. The PK sampling duration was from baseline to Week 28, with patients undergoing intensive PK sampling between Weeks 26 and 28. The PK sampling schedule was as follows, baseline (pre-dose on Day 1), pre-dose at Weeks 12, 16, 20, and Week 26 pre-dose and at 12, 24, 48, 72, 96, 120, 144, 168, 216, 264, 336 (pre-dose at Week 28) hours post-dose. Refer to Section 6 for detailed information on the efficacy and safety endpoints for Study AVT02-GL-302.

Bioanalytical PK Method and Performance

The bioanalytical method used for quantitative detection of AVT02 and E.U.-Humira in human serum samples were sensitive, robust, and fully validated.

Method validation (N-A-IMM-19-152) and sample analysis supporting Study AVT02-GL-302 were in-line with the Agency's recommendations outlined in the guidance for industry Bioanalytical Method Validation (May 2018), and all acceptance criteria as specified in the guidance were met. See detailed information about the method validation in Appendix 14.4.

Statistical Analysis

In Study AVT02-GL-302, the statistical method used for analysis of the co-primary PK endpoints ($AUC_{\tau, \text{wk26-28}}$ and $C_{\text{max}, \text{wk26-28}}$) was analysis of covariance (ANCOVA) model in the original scale with terms for treatment and randomization stratification factors (BMI and age). The assessment for PK similarity between the Switching Arm and Continuous Arm was based on the 2-sided 90% confidence interval for the ratio of the least squares mean for the co-primary PK endpoints using a pre-specified acceptance criterion of 80% to 125%.

Reviewer's Comments:

- It is of note that the original analysis plan was based on the log-transformed data in the initial protocol. PK endpoints were assumed to be log-normally distributed which is recommended in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.
- Using the untransformed original scale for PK analysis is investigated by the reviewer's independent assessment (See Sections 6, 14, and 15).
- The original scale appears to better characterize the distribution of the primary PK endpoints (Figure 10 to Figure 15). On the original scale after adjustment for the prespecified randomization stratification factors (i.e., BMI and age), heteroscedasticity was less pronounced, unlike on the log-normal scale (Figure 9). The heteroscedasticity is likely due to the development of anti-drug antibodies which not only explain high variability but also the extreme low values in some patients.
- The development of anti-drug antibodies (ADA) not only led to high variability in exposure but also resulted in some extremely low concentrations in some patients. The variability of exposure in ADA/NAb positive patients is much higher than that in ADA/NAb negative patients. Moreover, in ADA positive patients, the higher the titer, the lower the exposure and a higher chance for below lower limit of quantitation (LLOQ) PK measurements. The particularly low exposure resulted in an apparent distribution with a "tail" of observations toward lower concentrations (i.e., to the left). This skewness (long tail toward lower values) is exacerbated by use of the log transformation.
- As such, we consider that the log-transformed approach would not be the appropriate method to demonstrate PK similarity due to significant impact of ADA on PK and the inflated variability for the log-transformed data. We agree that it is reasonable to analyze the primary endpoints, $AUC_{\tau, \text{wk26-28}}$ and $C_{\text{max}, \text{wk26-28}}$, on the untransformed original scale instead of on the logarithmic scale.

Subjects

Subjects disposition is summarized in Section 6. Among the per protocol set of 523 patients, 29 patients in the switching arm and 35 patients in the Continuous arm were excluded from the primary analysis due to: 1) Insufficient quantifiable data; all concentrations W26-28 <LLOQ; 2) Insufficient quantifiable data; <3 concentrations >LLOQ; 3) Insufficient quantifiable data; <3 consecutive concentrations >LLOQ; 4) Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ} ; Also, subject (b) (6) in the Continuous Arm was excluded from the analysis due to extremely high PK concentration (> 10 fold higher than other subjects).

Reviewer's Comments:

- Excluding subject (b) (6) in the Continuous Arm from analysis is reasonable because the extremely high PK concentration ($> (b) (4)$ -fold higher than other subjects) is physiologically unlikely.
- The Applicant excluded 14 subjects in the Switching Arm and 24 subjects in the Continuous Arm from the analysis because the terminal phase in these 38 subjects cannot be estimated, and the terminal phase is needed to estimate AUC_{τ} . However, as AUC_{last} is a reasonable approximate to these missing AUC_{τ} , the reviewer conducted an independent analysis for AUC_{last} , and the AMR and 90% confidence interval is similar to that estimated with AUC_{τ} (Table 55). As such, the missing values of AUC_{τ} due to the undeterminable terminal phase are not expected to change the overall conclusion for PK similarity.
- The Applicant also excluded 15 subjects in the Switching Arm and 11 subject in the Continuous Arm who had all or most of their PK samples below lower limit of quantification (LLOQ). The number of subjects with missing data due to the below LLOQ PK samples are balanced between the two arms and accounted for only $<5\%$ of the overall population. Therefore, these missing values due to below LLOQ PK samples are not expected to change the AMR (90% confidence interval) and the overall conclusion of PK similarity in this study. To further assess the LLOQ effect on PK similarity, the PK samples below LLOQ were imputed with $\frac{1}{2}$ LLOQ of 3.75 ng/mL to derive the AUC_{τ} and C_{max} . With the imputation of $\frac{1}{2}$ LLOQ, the AMRs (90% confidence intervals) remained similar to the results without imputation, and the overall conclusion of PK similarity did not change (Table 56).
- By including the imputation for both missing AUC_{τ} due to undeterminable terminal phase and missing AUC_{τ} and C_{max} due to below LLOQ PK samples as mentioned above, the AMRs and 90% confidence intervals remained similar to the results without imputation, and the overall conclusion of PK similarity did not change (Table 57).

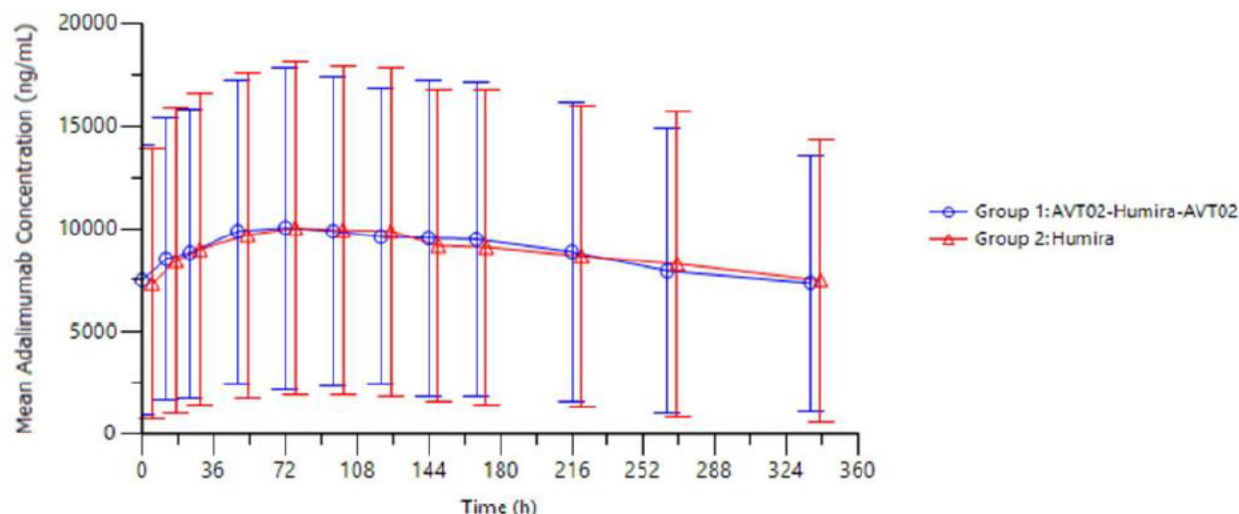
PK Similarity Assessment

The data from the switching study (Study AVT02-GL-302) established the PK similarity between AVT02 and E.U.-Humira (in the Switching Arm) and E.U.-Humira (in the Continuous Arm) during the Week 26 to 28 dosing interval. The mean serum concentration-time profiles during the Week 26 to 28 dosing interval as shown in Figure 2 were similar between the 2 treatment arms.

Statistical analysis showed that the 90% confidence intervals constructed using the Fieller's theorem for the AMR (Switching Arm/Continuous Arm) of $AUC_{\tau, wk26-28}$ and $C_{max, wk26-28}$ (co-primary PK endpoints) were within the pre-specified criteria of 80% to 125% (Table 4). The PK variability (CV%) for the co-primary PK endpoints in both treatment arms was 70.4% and 78.9% for $AUC_{\tau, wk26-28}$ and 65.6% and 70.7% for $C_{max, wk26-28}$ in the switching and Continuous Arms, respectively.

For additional assessment of primary endpoints, see Section 6 statistical review.

Figure 2. The mean (SD) serum concentration-time profiles during the Week 26 to 28 dosing interval (Study AVT02-GL-302, linear scale)



Note: Subject (b) (6) (E.U.-Humira Group) was considered an outlier during the Week 26-28 dosing interval; data for Subject (b) (6) were excluded from this figure.

Source: Figure 11.2 of Study AVT02-GL-302 CSR

Table 4. Summary of statistical analyses for comparison of PK parameters for Study AVT02-GL-302

PK Parameter	Arithmetic LSMean		AMR* (90%CI)
	Switching Arm (n=261)	Continuous Arm (n=262)	Switching Arm vs. Continuous Arm
AUC _{tau, wk26-28} (ng·hr/mL)	3154426.3	3102444.2	101.7 (91.4, 112.0)
C _{max, wk26-28} (ng/mL)	13986.7	12935.8	108.1 (98.3, 117.9)

*Presented as percent.

LS: Least squares

AMR: arithmetic mean ratio

n=number of patients contributing to the analysis

Results were obtained using ANCOVA model applied to data in the original scale, with terms for treatment and randomization stratification factor (BMI and age).

Pharmacokinetic parameters for primary PK endpoint were not estimated for some subjects in per protocol set.

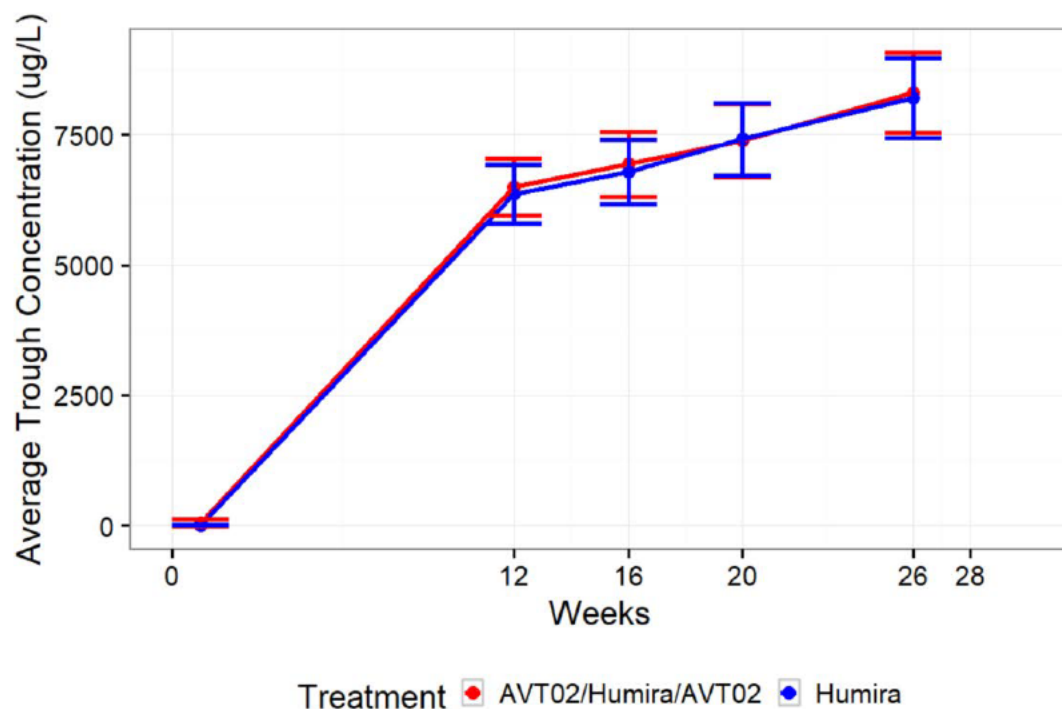
Source: Table 11.7 of Study AVT02-GL-302 CSR

The secondary PK endpoints are shown in Table 5 and Figure 3 and were comparable between the 2 treatment arms.

Table 5. Summary statistics of secondary PK endpoints for Study AVT02-GL-302

PK Parameter	Switching Arm		Continuous Arm	
	n	Mean (CV%)	n	Mean (CV%)
C _{trough, wk10-12} (ng/mL)	277	6498.6 (71.9%)	271	6346.6 (74.2%)
C _{trough, wk14-16} (ng/mL)	272	6528.3 (82.2%)	271	6250.5 (84.5%)
C _{trough, wk18-20} (ng/mL)	268	6739.6 (87.9%)	271	6834.1 (86.7%)
C _{trough, wk24-26} (ng/mL)	263	7459.6 (87.6%)	263	7364.8 (90.3%)
C _{trough, wk26-28} (ng/mL)	263	7294.7 (85.2%)	263	7408.1 (92.0%)

Source: Table 14.2.1.1.2a of Study AVT02-GL-302 CSR

Figure 3. Plot of trough serum concentrations (mean±SD) of AVT02 and E.U.-Humira by visit (Study AVT02-GL-302)

Source: FDA reviewer's analysis

5.4. Clinical Immunogenicity Studies

5.4.1. Design features of the clinical immunogenicity assessment

Immunogenicity was evaluated in patients with moderate to severe chronic plaque psoriasis in Study AVT02-GL-302. Patients were required to continue their methotrexate (MTX) background therapy throughout the study. During the lead-in period, all patients received E.U.-Humira from Day 1 to Week 10. Following randomization at Week 12, patients in the Switching Arm received AVT02, E.U.-Humira, and AVT02 (3 switches) and patients in the Continuous Arm received E.U.-Humira from Week 12 to 26. Refer to Section 5.3.1 for more details on the study design.

Immunogenicity endpoints

In Study AVT02-GL-302, the formation of, and titers for, ADA and NAb, were evaluated for immunogenicity assessment.

Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of AVT02 and E.U.-Humira. Refer to the OBP Immunogenicity review for more details.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

The sampling plan is adequate to capture the baseline, early onset, and dynamic profile of ADA and NAb formation. In Study AVT02-GL-302, blood samples were collected at baseline and pre-dose at Weeks 12, 16, 20, 26, and 28 for assessment of the ADA and NAb formation of AVT02 and E.U.-Humira.

Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

In Study AVT02-GL-302, the incidence of immunogenicity at baseline was comparable between the Switching Arm and Continuous Arm (Table 6). Following repeat doses of E.U.-Humira 40 mg every other week in all patients, at the randomization baseline at Week 12, 182/277 (13.2%) and 188/273 (15.5%) of patients assigned to the Switching Arm and Continuous Arm, respectively, had developed ADA (ADA+). At Week 28, following repeat doses of AVT02 and E.U.-Humira in the Switching Arm and repeat doses of E.U.-Humira in the Continuous Arm, 206/277 (78.3%) and 201/273 (76.4%) of patients were ADA+ in the Switching Arm and Continuous Arm, respectively. At Week 28, the timepoint for the assessment of the co-primary PK endpoints, the immunogenicity profile in patients who underwent 3 switches with AVT02 and E.U.-Humira were comparable to the patients who only received E.U.-Humira. In Study AVT02-GL-302, the ADA incidence was overall similar between the Switching Arm and Continuous Arm following repeat dosing in patients with plaque psoriasis.

Table 6. Immunogenicity results for binding ADA and NAb in Study AVT02-GL-302

Results	AVT02/Humira/AVT02 (N=277) n (%)	Humira (N=273) n (%)	Total (N=550) n (%)
Total Antibody Incidence ¹	m=277	m=273	m=550
Binding (ADA)	239 (86.3)	240 (87.9)	479 (87.1)
Neutralizing Antibodies*	217 (90.8)	220 (91.7)	437 (91.2)
Baseline (Pre-existing Antibody Incidence)	m=273	m=271	m=544
Binding (ADA)	36 (13.2)	42 (15.5)	78 (14.3)
Neutralizing Antibodies*	10 (27.8)	6 (14.3)	16 (20.1)
Week 12	m=277	m=271	m=548
Binding (ADA)	182 (65.7)	188 (69.4)	370 (67.5)
Neutralizing Antibodies*	152 (83.6)	152 (80.1)	304 (82.2)
Week 16	m=271	m=273	m=544
Binding (ADA)	205 (75.6)	202 (74.0)	407 (74.8)
Neutralizing Antibodies*	184 (89.8)	185 (91.6)	369 (90.1)
Week 20	m=269	m=271	m=540
Binding (ADA)	203 (75.5)	201 (74.2)	404 (74.8)
Neutralizing Antibodies*	189 (93.1)	192 (95.5)	381 (94.3)
Week 26	m=263	m=264	m=527
Binding (ADA)	201 (76.4)	206 (78.0)	407 (77.2)
Neutralizing Antibodies*	190 (94.5)	188 (91.3)	378 (92.9)
Week 28	m=263	m=263	m=526
Binding (ADA)	206 (78.3)	201 (76.4)	407 (77.4)
Neutralizing Antibodies*	190 (92.2)	183 (91.0)	373 (91.6)
Antibody Incidence Before Switching Module ²	m=277	m=273	m=550
Binding (ADA)	183 (66.1)	186 (68.1)	369 (67.1)
Neutralizing Antibodies	155 (84.7)	151 (81.2)	306 (82.9)
Treatment-emergent Antibody Incidence ³	m1=87	m1=77	m1=164
Binding (ADA)	50 (57.5)	44 (57.1)	94 (57.3)
Treatment-emergent Antibody Incidence ³	m2=78	m2=79	m2=157
Neutralizing Antibodies	62 (79.5)	65 (82.3)	127 (80.9)

¹ Positive result at any visit in Lead-In Period or Switching Module through Week 28.

² Positive result at any visit before Switching Module.

³ All results before Switching Module negative and at least 1 positive result in Switching Module.

Note: % = n/m, where m is the total number of subjects with ADA assessed at the specified time period.

% = n/m1, where m1 is the number of subjects with ADA assessed post-dose in Switching Module. Subjects with ADA positive before Switching Module are not included in m1.

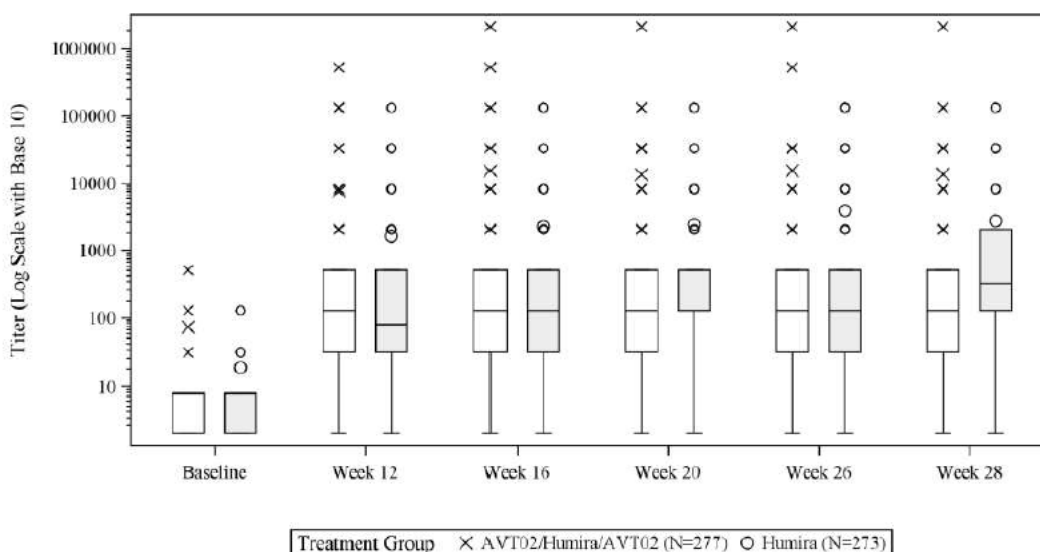
% = n/m2, where m2 is the number of subjects with ADA assessed post-dose in Switching Module. Subjects with NAb positive before Switching Module are not included in m2.

* The percentage of neutralizing antibodies is based on the number of subjects with ADA positive at the specified visit.

Abbreviations: ADA = anti-drug antibody; n = number of subjects in the sample; N = number of subjects;

NAb = neutralizing anti-drug antibody

Source: Data from Table 11.7 of Study AVT02-GL-302 CSR

Figure 4. Box plot for descriptive summary for ADA titers by visit in Study AVT02-GL-302

Source: Figure11.4 of Study AVT02-GL-302 CSR

Neutralizing antibodies

In Study AVT02-GL-302, 16 patient was positive for the presence of NAb (NAb+) at baseline in the lead-in period and 10 patients was randomized to the Switching Arm, 6 patients were randomized to the Continuous Arm at Week 12 (Table 6). At the randomization baseline at Week 12, following repeat doses of E.U.-Humira, 152/277 and 152/273 of patients assigned to the Switching Arm and Continuous Arm, respectively, were NAb+. At Week 28, following repeat doses of AVT02 and E.U.-Humira in the Switching Arm and repeat doses of E.U.-Humira in the Continuous Arm, 190/277 (68.6%) and 183/273 (67.0%) of patients were NAb+ in the Switching Arm and Continuous Arm, respectively. In Study AVT02-GL-302, the incidence of NAb+ was overall similar between the Switching Arm and Continuous Arm following repeat dosing in patients with rheumatoid arthritis.

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

Impact of ADA and NAb on PK

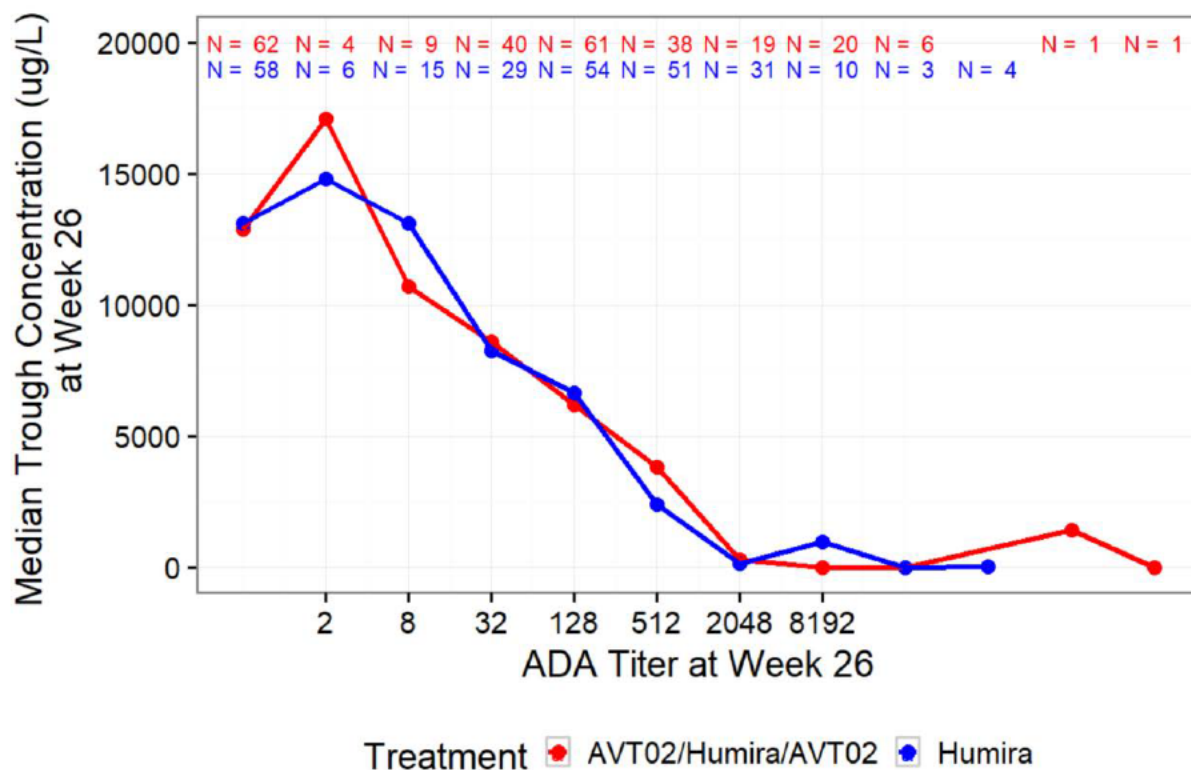
For Study AVT02-GL-302, the impact of ADA and NAb status on the primary PK endpoints at Week 26-28 in the Switching Arm and Continuous Arm is shown in Table 7. For the ADA subgroup analysis, in both the Switching and Continuous Arms, $AUC_{\tau, \text{wk26-28}}$ and $C_{\max, \text{wk26-28}}$ were observed to be lower in ADA+ patients compared to ADA- patients. A similar trend for $AUC_{\tau, \text{wk26-28}}$ and $C_{\max, \text{wk26-28}}$ was observed in NAb+ patients compared to NAb- patients in both treatment arms. The impact of ADA titer on the C_{trough} at Week 26 in the Switching Arm and Continuous Arm is shown in Figure 5 (ADA titer). Overall, the impact of ADA and NAb on the PK was comparable between the Switching and Continuous Arms.

Table 7. Primary PK endpoints in the Switching and Continuous Arms by ADA and NAb status in Study AVT02-GL-302

ADA/NAb Status	PK Parameter	Arithmetic LSMean	
		Switching Arm (n=261)	Continuous Arm (n=262)
ADA+	AUC _{tau, wk26-28} (ng·hr/mL)	2787611.4 (n=199)	2793769.0 (n=201)
	C _{max, wk26-28} (ng/mL)	12542.6 (n=211)	11836.0 (n=220)
ADA-	AUC _{tau, wk26-28} (ng·hr/mL)	5146222.5 (n=35)	5280406.5 (n=27)
	C _{max, wk26-28} (ng/mL)	21377.8 (n=36)	21178.1 (n=32)
NAb+	AUC _{tau, wk26-28} (ng·hr/mL)	2564441.8 (n=178)	2483210.1 (n=15)
	C _{max, wk26-28} (ng/mL)	11720.9 (n=21)	10848.4 (n=15)
NAb-	AUC _{tau, wk26-28} (ng·hr/mL)	4679239.3 (n=183)	5951117.4 (n=18)
	C _{max, wk26-28} (ng/mL)	19639.1 (n=201)	22284.2 (n=19)

n=Number of patients; Subject (b) (6) (Humira Group) was excluded

Source: Table 11.13 and Table 11.14 of Study AVT02-GL-302 CSR

Figure 5. Plot of Median C_{trough} by ADA titer at Week 26 in Study AVT02-GL-302

Source: FDA reviewer's analysis

Impact of ADA and NAb on efficacy

Both the mean absolute PASI value and the mean percent PASI improvement by ADA status from baseline to Week 12 were similar in AVT02/E.U.-Humira/AVT02 and E.U.-Humira group in the ADA positive subgroup (from 23.7 to 1.3 with 94.2% improvement and from 23.7 to 1.2 with 94.4% improvement, respectively) and in the ADA negative subgroup (from 23.4 to 1.1 with 95.4% improvement and from 20.7 to 0.9 with 95.7% improvement, respectively) (Table 8). This efficacy persisted and improved from baseline through Week 28 in the AVT02/ E.U.-Humira/AVT02 and E.U.-Humira group in the ADA positive subgroup (from 23.7 to 1.0 with 95.6% improvement and from 23.7 to 1.0 with 95.5% improvement, respectively) and in the ADA negative subgroup (from 23.4 to 0.2 with 98.9% improvement and 20.7 to 0.3 with 98.4% improvement, respectively).

Table 8. Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit by Anti-drug Antibody Status – Full Analysis Set – Switching Module (Weeks 12 - 28)

Time Point	Actual Value				Percent Improvement from Baseline			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
ADA Positive								
AVT02/Humira/AVT02 (N = 239)								
Baseline	239	23.7 (7.80)	21.9	13, 47				
Week 12	239	1.3 (1.76)	0.8	0, 11	239	94.2 (6.87)	96.6	75, 100
Week 28	227	1.0 (2.19)	0.0	0, 14	227	95.6 (8.88)	100.0	56, 100
Humira (N = 240)								
Baseline	240	23.7 (8.15)	22.2	12, 59				
Week 12	240	1.2 (1.72)	0.6	0, 10	240	94.4 (7.12)	97.0	75, 100
Week 28	232	1.0 (2.66)	0.0	0, 22	232	95.5 (10.32)	100.0	14, 100
ADA Negative								
AVT02/Humira/AVT02 (N = 38)								
Baseline	38	23.4 (10.17)	21.4	12, 55				
Week 12	38	1.1 (2.01)	0.0	0, 11	38	95.4 (6.90)	100.0	75, 100
Week 28	36	0.2 (0.48)	0.0	0, 2	36	98.9 (2.22)	100.0	91, 100
Humira (N = 33)								
Baseline	33	20.7 (6.27)	18.7	12, 41				
Week 12	33	0.9 (1.37)	0.2	0, 6	33	95.7 (6.08)	98.9	79, 100
Week 28	32	0.3 (0.53)	0.0	0, 2	32	98.4 (3.32)	100.0	88, 100

Notes: Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject received the first dose of study drug (Day 1) in Lead-In Period.

Percent improvement from Baseline = $-1 \times 100 \times (\text{post-Baseline} - \text{Baseline}) / \text{Baseline}$.

Missing percent improvement in PASI was not imputed.

Switching AVT02/ E.U.-Humira/AVT02: AVT02 at Weeks 12, 14; E.U.-Humira at Weeks 16, 18; AVT02 at Weeks 20, 22, 24, and 26.

Abbreviations: ADA = anti-drug antibody; ET = early termination; max = maximum; min = minimum; n = number of evaluable subjects; N = number of subjects in treatment group; PASI = Psoriasis Area and Severity Index; SD = standard deviation

Source: Table 11.6 of Study AVT02-GL-302 CSR

Impact of ADA and NAb on safety

For Study AVT02-GL-302, the incidence of relevant treatment-emergent adverse events (TEAEs) by ADA status and NAb status in the Switching and Continuous Arms is shown in Table 9 and Table 10. Overall, the incidence of TEAEs was comparable in patients with ADA+ status between the Switching Arm and Continuous Arm.

Table 9. Incidence of relevant treatment-emergent adverse events for the Switching Arm and Continuous Arm by ADA status in Study AVT02-GL-302

	AVT02/Humira/AVT02		Humira		Total	
	ADA Positive (N=239) n (%)	ADA Negative (N=38) n (%)	ADA Positive (N=240) n (%)	ADA Negative (N=33) n (%)	ADA Positive (N=479) n (%)	ADA Negative (N=71) n (%)
Any TEAE	73 (30.5)	13 (34.2)	79 (32.9)	11 (33.3)	152 (31.7)	24 (33.8)
Maximum severity of TEAEs						
Mild	46 (19.2)	8 (21.1)	53 (22.1)	11 (33.3)	99 (20.7)	19 (26.8)
Moderate	23 (9.6)	3 (7.9)	24 (10.0)	0	47 (9.8)	3 (4.2)
Severe	4 (1.7)	2 (5.3)	2 (0.8)	0	6 (1.3)	2 (2.8)
Treatment-related TEAEs	32 (13.4)	7 (18.4)	35 (14.6)	7 (21.2)	67 (14.0)	14 (19.7)
Serious TEAEs	4 (1.7)	1 (2.6)	1 (0.4)	0	5 (1.0)	1 (1.4)
Treatment-related serious TEAEs	0	0	0	0	0	0
TEAE leading to Early Study Withdrawal	6 (2.5)	2 (5.3)	2 (0.8)	0	8 (1.7)	2 (2.8)
TEAE leading to Study Drug Discontinuation	3 (1.3)	2 (5.3)	3 (1.3)	0	6 (1.3)	2 (2.8)
Treatment-related TEAE leading to Early Study Withdrawal	1 (0.4)	1 (2.6)	2 (0.8)	0	3 (0.6)	1 (1.4)
Serious TEAEs leading to Early Study Withdrawal	2 (0.8)	1 (2.6)	0	0	2 (0.4)	1 (1.4)
Treatment-related serious TEAEs leading to Early Study Withdrawal	0	0	0	0	0	0
TEAEs of special interest	21 (8.8)	4 (10.5)	23 (9.6)	5 (15.2)	44 (9.2)	9 (12.7)
Death	0	1 (2.6)	0	0	0	1 (1.4)

Notes: N = Number of subjects treated in the study phase for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug in Switching Module through Week 28 and before the day of first dose of study drug in Optional Extension Phase. Subjects were counted only once at the maximum severity in the following order: severe, moderate, and mild. Events with unknown severity were counted as severe. Subject was presented only once in the

respective subject count by highest relationship. Events with unknown relationship to study drug were counted as drug related.

Abbreviations: TEAE = treatment-emergent adverse event

Source: Table 12.21 of Study AVT02-GL-302 CSR

Table 10. Incidence of relevant treatment-emergent adverse events for the Switching Arm and the Continuous Arm by NAb status in Study AVT02-GL-302

	AVT02/Humira/AVT02		Humira		Total	
	NAb Positive (N=217) n (%)	NAb Negative (N=22) n (%)	NAb Positive (N=220) n (%)	NAb Negative (N=20) n (%)	NAb Positive (N=437) n (%)	NAb Negative (N=42) n (%)
Any TEAE	65 (30.0)	8 (36.4)	75 (34.1)	4 (20.0)	140 (32.0)	12 (28.6)
Maximum severity of TEAEs						
Mild	40 (18.4)	6 (27.3)	50 (22.7)	3 (15.0)	90 (20.6)	9 (21.4)
Moderate	21 (9.7)	2 (9.1)	24 (10.9)	0	45 (10.3)	2 (4.8)
Severe	4 (1.8)	0	1 (0.5)	1 (5.0)	5 (1.1)	1 (2.4)
Treatment-related TEAEs	29 (13.4)	3 (13.6)	32 (14.5)	3 (15.0)	61 (14.0)	6 (14.3)
Serious TEAEs	4 (1.8)	0	1 (0.5)	0	5 (1.1)	0
Treatment-related serious TEAEs	0	0	0	0	0	0
TEAE leading to Early Study Withdrawal	6 (2.8)	0	2 (0.9)	0	8 (1.8)	0
TEAE leading to Study Drug Discontinuation	3 (1.4)	0	3 (1.4)	0	6 (1.4)	0
Treatment-related TEAE leading to Early Study Withdrawal	1 (0.5)	0	2 (0.9)	0	3 (0.7)	0
Serious TEAEs leading to Early Study Withdrawal	2 (0.9)	0	0	0	2 (0.5)	0
Treatment-related Serious TEAEs leading to Early Study Withdrawal	0	0	0	0	0	0
TEAEs of special interest	17 (7.8)	4 (18.2)	20 (9.1)	3 (15.0)	37 (8.5)	7 (16.7)
Death	0	0	0	0	0	0

Notes: N = Number of subjects treated in the study phase for Safety Analysis Set is used as the denominator for percentage calculations. n (%) represents number and % of subjects with events starting on or after the day of first dose of study drug in Switching Module through Week 28 and before the day of first dose of study drug in Optional Extension Phase. Subjects were counted only once at the maximum severity in the following order: severe, moderate, and mild. Events with unknown severity were counted as severe. Subject was presented only once in the respective subject count by highest relationship. Events with unknown relationship to study drug were counted as drug related.

Abbreviations: NAb = neutralizing anti-drug antibody; TEAE = treatment-emergent adverse event

Source: Table 12.23 of Study AVT02-GL-302 CSR

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Study AVT02-GL-302 was a multicenter, randomized, double-blind, parallel-group study to evaluate pharmacokinetics, efficacy, safety, and immunogenicity in subjects with moderate to severe chronic plaque psoriasis with subjects receiving E.U.-Humira in one arm or undergoing repeated switches between E.U.-Humira and AVT02 in the other arm, followed by an Optional Extension Phase (open-label) for safety. Six hundred ninety-eight subjects were screened for the study; 131 subjects were screen failures. During the Lead-In Period (Weeks 1-12), all subjects (567) received Humira, 558 subjects completed the Lead-In Period. There were 550 subjects who progressed to the switching module (Weeks 12-28), 277 subjects were randomized to the AVT02/E.U.-Humira/AVT02 group, and 273 subjects were randomized to the E.U.-Humira group. The primary endpoints were the area under the concentration-time curve over the dosing interval from Week 26 to Week 28 ($AUC_{\tau, W26-28}$) and the maximum concentration over the dosing interval from Week 26 to Week 28 ($C_{\max, W26-28}$).

For the primary analyses, the original scale in lieu of log-transformed data was used in the final submission to support regulatory decision, although the pre-specified statistical analysis in the Statistical Analysis Plan (SAP) was based on the log-transformation data, as recommended in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product. The Applicant modified the SAP after unblinding to conduct the proposed analyses using the data on the original scale. The Applicant's justification for analyzing the data on the original scale, instead of using the log transformation, was based on the distribution of the primary endpoint data observed in histograms of the primary endpoints on the original scale and log scale, and the Shapiro-Wilks test for normality performed using the log-transformed primary endpoints. In this review we compared the original scale-based and log transformation-based analyses, and conducted simulations as an exploratory analysis comparing the two approaches. The large variability in geometric means is likely due to the high ADA incidence and titers (see discussion in Clinical Pharmacology section 5). The original scale-based analyses is acceptable considering (1) input received from Clinical Pharmacology reviewers that development of anti-drug antibodies may affect the data distribution and make the statistical assumption of log-transformation invalid or not feasible and (2) simulation studies indicating validity of the original scale-based analysis (Appendix 14.1.1).

The analysis excluded the outlier data from Subject (b) (6) and additional data from 64 or 26 subjects for AUC and $C_{\max}$ respectively. The Applicant justified exclusion due to: 1) Insufficient quantifiable data; all concentrations W26-28 <LLOQ; 2) Insufficient quantifiable data; <3 concentrations >LLOQ; 3) Insufficient quantifiable data; <3 consecutive concentrations >LLOQ; 4) Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ} (see Table 13

and Table 14). Sensitivity analyses by imputing the missing concentration data to $\frac{1}{2}$ LLOQ of 3.75 ng/mL were performed. It does not appear that the missing data due to insufficient quantifiable data will affect the final conclusion (Table 56 and Table 57). Please refer to Clinical Pharmacology review on further assessment of impact of missing data on PK endpoints (Section 5).

Based on the agency's overall assessment on the use of the original scale data and the exclusion of additional subjects, the 90% confidence interval for the least square mean ratios (Switching Arm/Continuous Arm) for area under the plasma concentration-time curve and maximum observed plasma concentration of the products during the dosing interval of Week 26 to 28 of AVT02/E.U.-Humira/AVT02 (in the Switching Arm) compared to E.U.-Humira (in the Continuous Arm) ($AUC_{\tau, \text{wk26-28}}$ and $C_{\max, \text{wk26-28}}$) were within the pre-specified acceptance criteria of 80% to 125%. The secondary efficacy endpoints were analyzed descriptively, and support the conclusion that there were no meaningful differences in the efficacy assessments between the Switching Arm and the Continuous Arm.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2 Review of Comparative Clinical Studies with Statistical Endpoints

6.1.2. Study AVT02-GL-302

Study AVT02-GL-302 was a phase 3, open-label, 2-arm, randomized, parallel group, comparative study assessing the switching between AVT02 and E.U.-Humira in combination with methotrexate in participants with moderately to severely active rheumatoid arthritis.

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Data Sources

The materials used for the statistical review are from the electronic submission dated December 20, 2021, and these materials are in the directories indicated below.

Clinical Study Report, Protocol, Statistical Analysis Plan (SAP), and Other Documents:

<\\CDSESUB1\evsprod\BLA761299\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\avt02-gl-302>

Datasets and Documentation:

<\\CDSESUB1\evsprod\BLA761299\0001\m5\datasets\avt02-gl-302>

Study Design and Endpoints

Study AVT02-GL-302 was a multicenter, randomized, double-blind, parallel-group study to evaluate pharmacokinetics, efficacy, safety, and immunogenicity between subjects with moderate to severe chronic plaque psoriasis receiving E.U.-Humira and subjects with moderate to severe chronic plaque psoriasis undergoing repeated switches between E.U.-Humira and AVT02, followed by an Optional Extension Phase (open-label) for safety. The identities of the study treatments were as follows (Table 9.1 of the Clinical Study Report):

Investigational Product

Name: AVT02

Formulation: solution for injection

Strength: 40 mg/0.4 mL

Route of administration: subcutaneous

Dose (unit):

- Switching Module
 - 40 mg every other week (EOW)
- Extension Phase
 - 40 mg every other week

Manufacturer: Alvotech Iceland

Batch Number(s): DP200002

Comparator Product

Name: E.U.-Humira

Formulation: solution for injection

Strength: 40 mg/0.4 mL

Route of administration: subcutaneous

Dose (unit):

- Lead-In Period
 - 80 mg (2 × 40 mg) initial dose
 - 40 mg EOW starting 1 week after the initial dose
- Switching Module
 - 40 mg EOW

Manufacturer: AbbVie Germany GmbH & Co. KG

Study AVT02-GL-302 was composed of the following 3 parts:

- Lead-In Period: Weeks 1-12 – open-label treatment
- Switching Module: Weeks 12-28 – double-blind treatment
- Optional Extension Phase: Weeks 28-52 – open-label treatment

Lead-In Period

After successfully completing Screening activities, subjects were enrolled in the Lead-In Period (open label).

During the Lead-In Period (open label), subjects received loading dose (initial dose of 80 mg E.U.-Humira [2×40 mg] administered subcutaneously [SC], followed by 40 mg SC given every other week (EOW) starting 1 week after the initial dose). At Week 12, subjects achieving treatment response, defined as Psoriasis Area and Severity Index [PASI] ≥ 75 [PASI75], were randomly assigned in a 1:1 ratio during the Double-Blind Switching Module to one of the following groups:

Switching Module

- Group 1: Subjects with the following repeated switches between AVT02 and E.U.-Humira from Week 12 until Week 26:
 - Switch 1 – E.U.-Humira to AVT02 (40 mg EOW) for 4 weeks (2 injections),
 - Switch 2 – AVT02 to E.U.-Humira (40 mg EOW) for 4 weeks (2 injections), and
 - Switch 3 – E.U.-Humira to AVT02 (40 mg EOW) for 8 weeks (4 injections).
- Group 2: Subjects continued to receive Humira 40 mg EOW from Week 12 until Week 26 (8 injections).

The last study treatment administration in the Double-Blind Switching Module was at Week 26. The last study assessment was at Week 28 for both groups. The end-of-study (EoS) Visit for the interchangeability (IC) part of the study (EoS IC Visit) was planned at Week 28 (i.e., 2 weeks after the last study treatment administration).

Optional Extension Phase

At Week 28, after the EoS IC Visit, subjects achieving partial response, defined as PASI ≥ 50 [PASI50], were offered to continue with the optional Open-Label Extension Phase (Weeks 28 to 52). AVT02 40 mg was administered EOW starting from Week 28 (after completing the EoS IC assessments), ending with the final study drug administration at Week 50. The EoS Visit was planned for Week 52.

The study schematic is presented in Figure 1 **Error! Reference source not found..**

Primary Endpoints

The primary endpoints were the area under the concentration-time curve over the dosing interval from Week 26 to Week 28 ($AUC_{\text{tau}, W26-28}$) and the maximum concentration over the dosing interval from Week 26 to Week 28 ($C_{\text{max}, W26-28}$).

Statistical Methods

Applicant's Statistical Methods

The Applicant's Statistical Analysis Plan (SAP) originally stated that analysis of the primary endpoints would be conducted on the log-transformed scale. However, post database lock and after the study was unblinded, the Applicant amended the SAP to include additional analyses based on the distribution of the primary endpoint data. The observed distributions are consistent with the recent understanding on ADA effect on increased uncertainty for geometric means. The additional analyses included analyzing the primary endpoints on the original scale and excluding data from Subject (b) (6), considered as an outlier, from analyses based on both the Per Protocol Set and the Full Analysis Set. Below we describe the Applicant's primary statistical analysis methods as described originally in the SAP and the updated primary analyses described in the amended SAP.

Statistical Analysis Methods Pre-Specified in the Statistical Analysis Plan

In the Statistical Analysis Plan (SAP) (Version 1.0 – dated July 14, 2021) the primary endpoint analysis is described as follows (Section 6.11.2 of the SAP).

The following statistical hypotheses will be tested to demonstrate the PK similarity of AVT02 and E.U.-Humira in terms of $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$.

The null hypotheses:

$$H_{01}: GM_{AVT02} / GM_{E.U.-Humira} \leq 80\%, \text{ or } H_{02}: GM_{AVT02} / GM_{E.U.-Humira} \geq 125\%$$

The alternative hypotheses:

$$H_{11}: GM_{AVT02} / GM_{E.U.-Humira} > 80\%, \text{ and } H_{12}: GM_{AVT02} / GM_{E.U.-Humira} < 125\%$$

where GM_{AVT02} and $GM_{E.U.-Humira}$ denote the Geometric Mean of PK parameter (i.e., $AUC_{\tau, W26-28}$ or $C_{\max, W26-28}$) in the AVT02 and E.U.-Humira group, respectively.

The statistical analysis will be performed using an analysis of covariance (ANCOVA) model on natural logarithms transformed $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$ (i.e., $\ln AUC_{\tau, W26-28}$ and $\ln C_{\max, W26-28}$) with the treatment group as fixed effect, with the age and BMI at Week 12 as the continuous covariate.

The analysis of the primary endpoints will involve calculating the 90% confidence intervals for the ratio of the geometric means between the 2 treatment groups. Geometric means for the least squares means from ANCOVA, and ratio of geometric mean and the 90% CI for the ratio of the geometric means across the 2 treatment groups will be presented after back transformation to the original scale. A conclusion of PK similarity will be made based on the 90% confidence intervals being within the range 80% to 125% for the Per-Protocol Set for both $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$.

Below is SAS example code for the ANCOVA:

```
PROC GLM DATA = <DATASET> ALPHA=0.10;  
CLASS TREAT ;  
MODEL lnAUCtau, W26-28 or lnCmax, W26-28 = TREAT Week12 _BMI AGE;  
LSMEANS TREAT / CL STDERR PDIF;   
ESTIMATE "1 2" TREAT 1 -1;  
ODS OUTPUT ESTIMATES = EST LSMEANS=LSM LSMEANDIFFCL=DIFF;  
RUN;
```

Where TREAT is treatment group.

The primary endpoint analysis will be repeated in the Full Analysis Set (FAS) as supportive analysis for both AUC_{tau, W26-28} and the C_{max, W26-28}.

Updated Statistical Analysis Methods in the Amended SAP

In the Post Database Lock Statistical Analysis Plan Addendum, the primary endpoint analysis is described as follows.

Analysis #1: Histograms for primary endpoints (AUC_{tau, W26-28} and C_{max, W26-28}) by treatment group in the original scale and log-transformed scale. Perform normality test (i.e., Shapiro-Wilks test) on the log-transformed PK parameters. The outlier (i.e., subject (b) (6)) will be excluded from the histograms.

Analysis #2: Analysis of primary endpoints (AUC_{tau, W26-28} and C_{max, W26-28}) on the original scale, i.e., calculate the arithmetic mean by treatment group and arithmetic mean ratio (AMR) between treatment group, and construct the 90% CI for the AMR using the Fieller's Theorem. The analysis will be performed based on Per-Protocol Set (PPS) and will be repeated in Full Analysis Set (FAS) as sensitivity analysis. The outlier (i.e., subject (b) (6)) will be excluded from both analyses.

Analysis #3: Repeat the analysis #2, the 90% CIs for the AMR between treatment group will be constructed using bootstrapping method. The analysis will be performed based on Per-Protocol Set (PPS) and Full Analysis Set (FAS). The outlier (i.e., subject (b) (6)) will be excluded from both analyses.

The Applicant also described additional analyses concerning secondary analyses.

Determination of Sample Size

The Applicant's sample size determination is described in Section 9.8.3 (page 62 of 174) of the Clinical Study Report as follows.

The primary endpoints for this study were AUC_{tau, W26-28} and C_{max, W26-28} calculated following the last administration of study drug at Week 26. Data for AUC_{tau} and C_{max} were based on population PK modelling for Humira as follows: median SD (lnAUC₂₆₋₂₈) = 0.641 and median

$SD(\ln C_{\max, 26-28}) = 0.504$. To demonstrate PK similarity for AUC_{τ} with margins of 80% to 125% for the ratio of the geometric means using 90% CIs, 160 subjects in each of the 2 treatment groups were required for 83% power, assuming a true ratio of 1.025. With this sample size, the corresponding power for $C_{\max}$ is 96.7%, and the joint power is 80.5%. Assuming an 18% non-evaluable rate among the PASI75 responders (due to dropouts and those not providing data at Week 26) and assuming that 71.5% of subjects initially recruited would be PASI75 responders at Week 12 (Abbott Study M04-716), approximately 548 subjects were planned to participate in the study at Week 1 (Baseline).

Reviewer's Comment:

The Applicant's sample size determination is based on analysis of log transformed $AUC_{\tau, W26-28}$ ($\log(AUC_{\tau, W26-28})$) and log transformed $C_{\max, W26-28}$ ($\log(C_{\max, W26-28})$) and assumes that $\log(AUC_{\tau, W26-28})$ and $\log(C_{\max, W26-28})$ are normally distributed. For sample size determination, the Applicant assumed that the difference of means between the two groups on the log-scale is $\log(1.025)$ (for both $\log(AUC_{\tau, W26-28})$ and $\log(C_{\max, W26-28})$) and the standard deviation is 0.641 for $\log(AUC_{\tau, W26-28})$ and 0.504 for $\log(C_{\max, W26-28})$. Using these assumptions, we found that with 160 subjects in each treatment group we were able to reproduce the Applicant's individual power calculations for $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$ using the power formula on page 52 of Chow, Shao, Wang, and Lokhnygina (2018). The Applicant has also provided the joint power, however, in the framework used here for power calculation, calculation of joint power generally requires an additional assumption pertaining to the correlation between endpoints $\log(AUC_{\tau, W26-28})$ and $\log(C_{\max, W26-28})$, but no assumption about the correlation was stated.

Subject Disposition

Applicant's Determinations

The Applicant defined the Enrolled Set, Full Analysis Set, Per-Protocol Set, and Safety Analysis Set in Section 11 of the Clinical Study Report (Page 75 of 174) as follows.

Enrolled Set: The Enrolled Set included all subjects who gave informed consent.

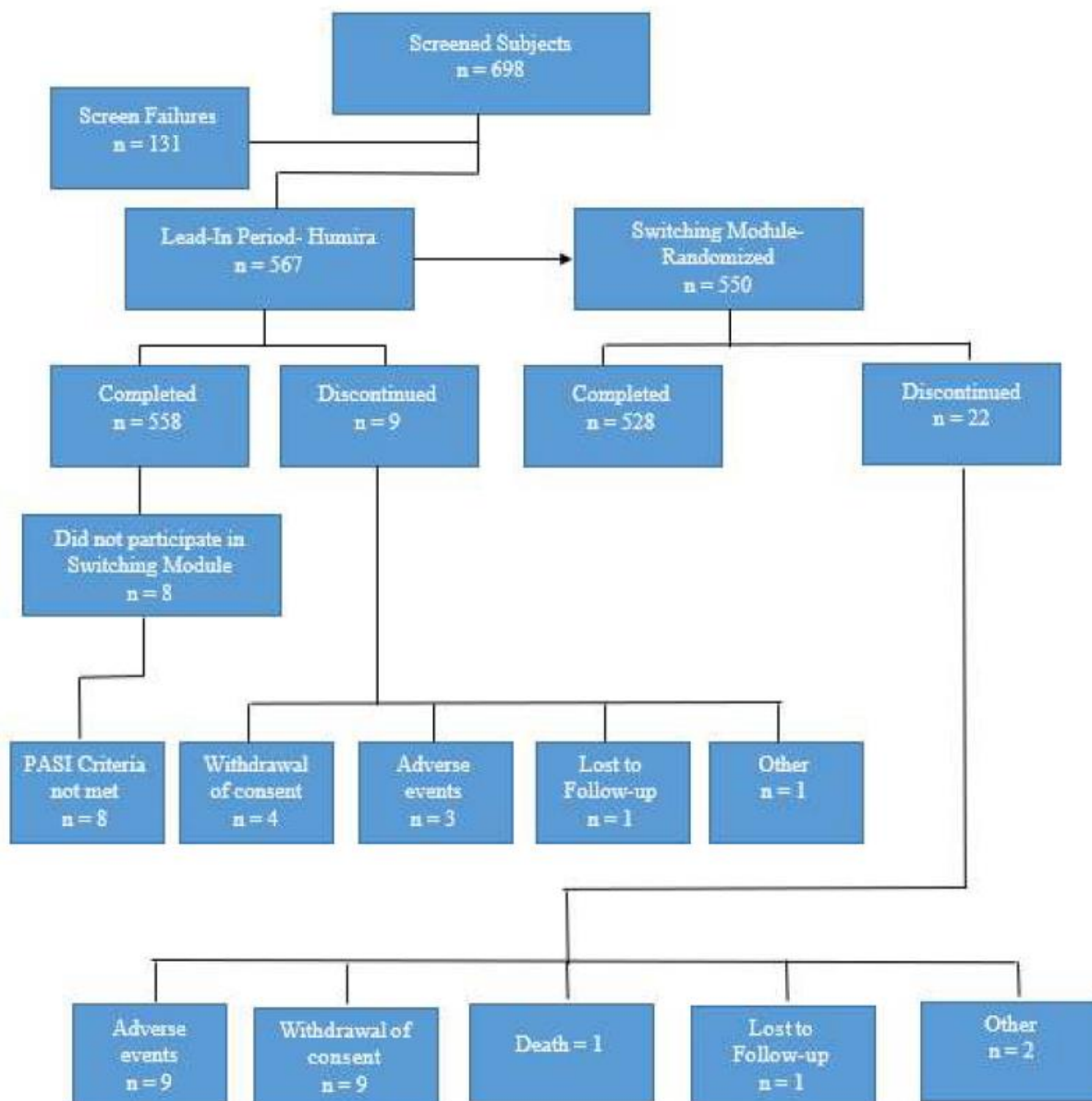
Full Analysis Set: The Full Analysis Set, consistent with the intention-to-treat principle, was defined as all subjects who received at least 1 dose of study drug.

Per-Protocol Set: The Per-Protocol Set was a subset of the Full Analysis Set that included subjects who had completed the treatment period (up to Week 28) without important protocol deviations and provided data on the primary endpoint between Week 26 and Week 28. Important protocol deviations were determined based on a blinded data review prior to database lock. The protocol deviations that impacted the primary endpoint assessment led to exclusion from the Per Protocol Set.

Safety Analysis Set: The Safety Analysis Set included all subjects who received at least 1 dose of study drug with treatment assignment based on actual treatment received.

The disposition of subjects as summarized by the Applicant is shown in Figure 6. The subject disposition in the Full Analysis Set as calculated by the Applicant is shown in Table 11, and the subject disposition in each analysis set and number of subjects excluded from the Per Protocol Set by reason for exclusion, as calculated by the Applicant, is shown in Table 12.

Figure 6. Disposition of study subjects



Abbreviations: PASI = Psoriasis Area and Severity Index; n = number of subjects in the sample

Source: Table 14.1.1.1

Source: Figure 10.1 of the Clinical Study Report

Table 11. Subject disposition in the full analysis set

	Lead-In Period (Weeks 1-12)	Switching Module (Weeks 12-28)			
	E.U.-Humira (N=567) n (%)	AVT02/E.U.-Humira/AVT02 (N=277) n (%)	E.U.-Humira (N=273) n (%)	Total (N=550) n (%)	Overall (N=567) n (%)
Full Analysis Set	567	277	273	550	567
Completed WK 1-12 open-label treatment	558 (98.4)	NA	NA	NA	558 (98.4)
Discontinued WK 1-12 open-label treatment	9 (1.6)	NA	NA	NA	9 (1.6)
Completed WK 1-12 but did not participate in WK 12-28 double-blind treatment	8 (1.4)	NA	NA	NA	8 (1.4)
PASI75 Responders at Week 12	550 (97.0)	NA	NA	NA	550 (97.0)
Reasons for subjects who completed WK 1-12 but did not participate further					
PASI75 Non-responders	8 (1.4)	NA	NA	NA	8 (1.4)
Completed in WK 12-28 double-blind treatment	NA	263 (94.9)	265 (97.1)	528 (96.0)	528 (93.1)
Discontinued WK 12-28 double-blind treatment	NA	14 (5.1)	8 (2.9)	22 (4.0)	22 (3.9)
Completed WK 12-28 but did not participate in WK 28-52 open-label treatment	NA	0	3 (1.1)	3 (0.5)	3 (0.5)
Primary Reason for Discontinuation					
Adverse Event	3 (0.5)	7 (2.5)	2 (0.7)	9 (1.6)	12 (2.1)
COVID-19 Related	0	1 (0.4)	0	1 (0.2)	1 (0.2)
Not COVID-19 Related	3 (0.5)	6 (2.2)	2 (0.7)	8 (1.5)	11 (1.9)
Death	0	1 (0.4)	0	1 (0.2)	1 (0.2)
Withdrawal of Consent	4 (0.7)	4 (1.4)	5 (1.8)	9 (1.6)	13 (2.3)
COVID-19 Related	0	0	1 (0.4)	1 (0.2)	1 (0.2)
Not COVID-19 Related	4 (0.7)	4 (1.4)	4 (1.5)	8 (1.5)	12 (2.1)
Lost to Follow-up	1 (0.2)	1 (0.4)	0	1 (0.2)	2 (0.4)
PASI Criteria Not Met	8 (1.4)	0	0	0	8 (1.4)
Non-Compliance	0	0	0	0	0
PI Decision	0	0	0	0	0
Other	1 (0.2)	1 (0.4)	1 (0.4)	2 (0.4)	3 (0.5)
PASI50 Responders at Week 28	NA	263 (94.9)	262 (96.0)	525 (95.5)	525 (92.6)

Note: At Week 12, responsive subjects PASI $\geq$ 75 were randomly assigned in to either of the following groups for participation in the double-blind switching module.

Switching AVT02/E.U.-Humira/AVT02: AVT02 at Weeks 12, 14; E.U.-Humira at Weeks 16, 18; AVT02 at Weeks 20, 22, 24 and 26.

Percentages are based on the number of subjects in the FAS by treatment group per each study phase.

Abbreviations: FAS = full analysis set; PASI = Psoriasis Area and Severity Index; PI = Principal Investigator; n = number of subjects in the sample; N = number of subjects; NA = not applicable; WK = week

Source: Table 10.2 (also Table 14.1.1.1) of the Clinical Study Report

Table 12. Subject disposition in each analysis set

	Lead-In Period (Week 1-12)	Switching Module (Week 12-28)			Overall
	E.U.-Humira (N=567) n (%)	AVT02/E.U.-Humira/AVT02 (N=277) n (%)	E.U.-Humira (N=273) n (%)	Total (N=550) n (%)	(N=567) n (%)
Enrolled Set	NA	NA	NA	NA	698
Safety Analysis Set	567 (100.0)	277 (100.0)	273 (100.0)	550 (100.0)	567 (100.0)
Full Analysis Set	567 (100.0)	277 (100.0)	273 (100.0)	550 (100.0)	567 (100.0)
Per Protocol Set	NA	261 (94.2)	262 (96.0)	523 (95.1)	523 (92.2)
Reasons for exclusion from the Per Protocol Set					
Subject with important protocol deviations that impacted the primary endpoint assessment	NA	2 (0.7)	3 (1.1)	5 (0.9)	5 (0.9)
Predose PK sample was not collected due to the study nurse omission	NA	1 (0.4)	0	1 (0.2)	—
Predose PK samples were not taken due to omission	NA	0	1 (0.4)	1 (0.2)	—
Subject Week 26 Visit / dated (b) (6) was missed (not conducted) due to the subject's personal reasons	NA	0	1 (0.4)	1 (0.2)	—
The subject participated in guselkumab/adalimumab (3:1) study till (b) (6) and there is no evidence that subject was not in adalimumab arm.	NA	0	1 (0.4)	1 (0.2)	—
Study procedures at site 9901 registered the Week 26 visit of subject (b) (6) for subject (b) (6) by mistake (b) (4) IP kit was assigned and administered to the subject (b) (6) instead of subject (b) (6).	NA	1 (0.4)	0	1 (0.2)	—
Subjects with ET before Week 28	NA	14 (5.1)	8 (2.9)	22 (4.0)	22 (4.0)

Abbreviations: ET = early termination; IP = investigational product; NA = not applicable; PK = pharmacokinetic.
Source: Table 11.1 (also Table 14.1.1.2 and Table 14.1.2.1) of the Clinical Study Report

Reviewer's Comments:

1. The Applicant presented the disposition of study subjects in the flow chart shown in Figure 6, and the Applicant presented the disposition of subject in the Full Analysis Set shown in Table 11. We used the Subject-Level Analysis Dataset (ADSL) to verify the subject disposition shown in Figure 6 and Table 11 and found the following discrepancy. According

to the data reported by the Applicant (shown in Figure 6 and Table 11), there are 8 subjects who completed Week 1-12 but did not participate in Week 12-28 because the PASI criteria was not met. However, according to the variable “CMP01FL” in the ADSL dataset, 2 of these 8 subjects did not complete Week 1-12. This discrepancy appears to be minor as it does not affect the analysis sets used for analysis of the primary endpoints.

2. The Applicant presented the subject disposition in each analysis set and number of subjects excluded from the Per Protocol Set by reason for exclusion in the table shown in Table 12. We used the ADSL dataset to verify the subject disposition shown in Table 12 and we were able to reproduce the numbers shown in the table (except in the cell in the last row and last column the percentage in parentheses should be 3.9 instead of 4.0 since it is based on N=567).
3. In the Applicant’s analysis of the primary endpoints, there are subjects who are in the Per Protocol Set but are excluded from the analysis of $AUC_{\tau, W26-28}$ and/or $C_{\max, W26-28}$, and for these excluded subjects the Applicant has not provided a value of $AUC_{\tau, W26-28}$ and/or $C_{\max, W26-28}$. The number of subjects in the Per Protocol Set who are excluded from analysis and reasons for exclusions (as provided in Appendix 16.2.9 of the Clinical Study Report) are shown in Table 60 for log transformation based analysis of $AUC_{\tau, W26-28}$, Table 61 for log transformation based analysis of $C_{\max, W26-28}$, Table 13 for original scale-based primary analysis of $AUC_{\tau, W26-28}$, and Table 14 for original scale-based primary analysis of $C_{\max, W26-28}$. For $AUC_{\tau, W26-28}$ note that if we compare Table 13 and Table 60 there is one additional subject excluded from the original scale-based analysis compared with the log-transformation based analysis, this is subject (b) (6) and the reason for exclusion is provided as “*Excluded from the analysis due to extremely high PK concentration*”. Similarly, for $C_{\max, W26-28}$ if we compare Table 14 and Table 61 there is one additional subject excluded from the original scale-based analysis compared with the log-transformation based analysis, this again is subject (b) (6) and the reason for exclusion is provided as “*Excluded from the analysis due to extremely high PK concentration*”. Table 62 shows a list of subjects who are in the Per Protocol Set but excluded from the Applicant’s analysis of the primary endpoints, and the reason for exclusion as provided in Appendix 16.2.9 of the Clinical Study Report.
4. The subjects listed in Table 62 were also included in the Full Analysis Set but excluded in analysis of the primary endpoint indicated in the table based on the Full Analysis Set. In addition to these exclusions there were 22 other subjects (Subjects (b) (6) who entered the switching module of the study and were in the Full Analysis Set, but not included in the primary endpoint analysis based on the Full Analysis Set because of early termination before Week 28. Furthermore, there was one additional subject (Subject (b) (4)) who entered the switching module of the study and was in the Full Analysis Set, but not included in the primary endpoint analysis based on the Full Analysis Set and it appears the reason is “*Subject Week 26 Visit / dated 27 Apr 21 was missed (not conducted) due to the subject's personal reasons*”.
5. Regarding the analysis set used for the primary analysis, Section 5.5 of the June 18, 2019 (Version 1.0), December 12, 2019 (Version 2.0), and August 3, 2020 (Version 3.0) versions

of the Protocol state that analysis of the primary endpoints will be performed using both the Full Analysis Set and the Per Protocol Set for the evaluation of PK similarity. However, in the May 11, 2021 (Version 4.0) version of the Protocol a change was made such that analysis of the primary endpoints would be performed based on the Per Protocol Analysis Set, and the primary endpoint analysis would be repeated in the Full Analysis Set as supportive analysis.

Table 13. Number of subjects in the Per-Protocol Set but excluded from Applicant's original scale-based primary analysis of AUC_{tau}, W26-28

Reason	AVT02-E.U.-Humira- AVT02	E.U.- Humira
Insufficient quantifiable data; all concentrations W26-28 <LLOQ	13	7
Insufficient quantifiable data; <3 concentrations >LLOQ	2	3
Insufficient quantifiable data; <3 consecutive concentrations >LLOQ	0	1
Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	14	24
Excluded from the analysis due to extremely high PK concentration	0	1
Total	29	36

Source: Appendix 16.2.9 of the Clinical Study Report and Reviewer's analysis

Table 14. Number of subjects in the Per-Protocol Set but excluded from Applicant's original scale-based primary analysis of C_{max}, W26-28

Reason	AVT02-E.U.-Humira- AVT02	E.U.- Humira
Insufficient quantifiable data; all concentrations W26-28 <LLOQ	13	7
Insufficient quantifiable data; <3 concentrations >LLOQ	2	3
Insufficient quantifiable data; <3 consecutive concentrations >LLOQ	0	1
Excluded from the analysis due to extremely high PK concentration	0	1
Total	15	12

Source: Appendix 16.2.9 of the Clinical Study Report and Reviewer's analysis

Demographics and Baseline Characteristics

The Applicant's demographics and baseline characteristics for the Full Analysis Set and Per Protocol Set are shown in Table 15 and Table 16.

Reviewer's Comment:

Using the ADSL dataset, we verified the Applicant's demographics and baseline characteristics shown in Table 15 and Table 16.

Table 15. Demographics and baseline characteristics in Full Analysis Set

	Lead-In Period	Switching Module			
	E.U.-Humira (N=567) n (%)	AVT02/E.U.-Humira/ AVT02 (N=277) n (%)	E.U.-Humira (N=273) n (%)	Total (N=550) n (%)	Overall (N=567) n (%)
Age (years) at Informed Consent					
n	567	277	273	550	567
Mean (SD)	41.7 (12.63)	41.2 (12.55)	41.8 (12.59)	41.5 (12.56)	41.7 (12.63)
Median	40.0	40.0	41.0	40.0	40.0
Min, Max	18, 73	18, 72	18, 73	18, 73	18, 73
Age group, n (%)					
<65 years	543 (95.8)	266 (96.0)	263 (96.3)	529 (96.2)	543 (95.8)
≥65 years	24 (4.2)	11 (4.0)	10 (3.7)	21 (3.8)	24 (4.2)
Gender, n (%)					
Male	364 (64.2)	189 (68.2)	165 (60.4)	354 (64.4)	364 (64.2)
Female	203 (35.8)	88 (31.8)	108 (39.6)	196 (35.6)	203 (35.8)
Ethnicity, n (%)					
Hispanic or Latino	5 (0.9)	3 (1.1)	2 (0.7)	5 (0.9)	5 (0.9)
Not Hispanic or Latino	562 (99.1)	274 (98.9)	271 (99.3)	545 (99.1)	562 (99.1)
Race, n (%)					
White	566 (99.8)	277 (100.0)	272 (99.6)	549 (99.8)	566 (99.8)
Black or African American	0	0	0	0	0
Asian	1 (0.2)	0	1 (0.4)	1 (0.2)	1 (0.2)
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Height (cm) at Screening					
n	567	277	273	550	567
Mean (SD)	173.42 (9.554)	174.08 (10.161)	172.85 (8.867)	173.47 (9.552)	173.42 (9.554)
Median	175.00	175.00	174.00	175.00	175.00
Min, Max	111.0, 197.0	111.0, 197.0	153.0, 196.0	111.0, 197.0	111.0, 197.0
Weight (kg) at Screening					
n	567	277	273	550	567
Mean (SD)	84.44 (18.512)	85.44 (18.429)	83.03 (18.421)	84.24 (18.448)	84.44 (18.512)
Median	83.80	85.00	81.50	83.50	83.80
Min, Max	45.0, 152.8	49.0, 149.6	45.0, 152.8	45.0, 152.8	45.0, 152.8
BMI (kg/m ²)					
n	567	277	273	550	567
Mean (SD)	28.03 (5.903)	28.22 (6.418)	27.69 (5.347)	27.96 (5.911)	28.03 (5.903)
Median	27.50	27.60	27.20	27.50	27.50
Min, Max	15.9, 90.1	16.8, 90.1	15.9, 47.7	15.9, 90.1	15.9, 90.1
BMI Category, n (%)					
<30 kg/m ²	380 (67.0)	187 (67.5)	184 (67.4)	371 (67.5)	380 (67.0)
≥30 kg/m ²	187 (33.0)	90 (32.5)	89 (32.6)	179 (32.5)	187 (33.0)
Psoriasis Area and Severity Index (PASI)					

n	567	277	273	550	567
Mean (SD)	23.36 (8.035)	23.62 (8.148)	23.31 (7.993)	23.47 (8.065)	23.36 (8.035)
Median	21.60	21.60	21.20	21.60	21.60
Min, Max	12.0, 58.8	12.0, 54.8	12.0, 58.8	12.0, 58.8	12.0, 58.8
Static Physicians Global Assessment (sPGA), n (%)					
Minimal	0	0	0	0	0
Mild	0	0	0	0	0
Moderate	329 (58.0)	156 (56.3)	160 (58.6)	316 (57.5)	329 (58.0)
Severe	170 (30.0)	85 (30.7)	81 (29.7)	166 (30.2)	170 (30.0)
Very Severe	68 (12.0)	36 (13.0)	32 (11.7)	68 (12.4)	68 (12.0)
Percentage of Body Surface Area (% BSA) Affected (%)					
n	567	277	273	550	567
Mean (SD)	29.45 (13.783)	29.73 (14.003)	29.18 (13.454)	29.46 (13.723)	29.45 (13.783)
Median	26.30	27.00	26.00	26.40	26.30
Min, Max	10.0, 90.0	10.0, 90.0	10.0, 75.0	10.0, 90.0	10.0, 90.0
Months from Diagnosis of Chronic Plaque Psoriasis to Informed Consent					
n	567	277	273	550	567
Mean (SD)	193.3 (140.73)	191.8 (136.78)	195.4 (144.62)	193.6 (140.61)	193.3 (140.73)
Median	162.0	162.0	162.0	162.0	162.0
Min, Max	3, 717	3, 717	9, 692	3, 717	3, 717

Source: Table 11.3, Table 14.1.3.1, and Table 14.1.4.1 of the Clinical Study Report

Table 16. Demographics and baseline characteristics in Per Protocol Set

	Lead-In Period	Switching Module			
	E.U.-Humira (N=523) n (%)	AVT02/E.U.- Humira/ AVT02 (N=261) n (%)	E.U.-Humira (N=262) n (%)	Total (N=523) n (%)	Overall (N=523) n (%)
Age (years) at Informed Consent					
n	523	261	262	523	523
Mean (SD)	41.5 (12.48)	41.2 (12.46)	41.7 (12.53)	41.5 (12.48)	41.5 (12.48)
Median	40.0	40.0	41.0	40.0	40.0
Min, Max	18, 73	18, 72	18, 73	18, 73	18, 73
Age group, n (%)					
<65 years	504 (96.4)	251 (96.2)	253 (96.6)	504 (96.4)	504 (96.4)
≥65 years	19 (3.6)	10 (3.8)	9 (3.4)	19 (3.6)	19 (3.6)
Gender, n (%)					
Male	341 (65.2)	180 (69.0)	161 (61.5)	341 (65.2)	341 (65.2)
Female	182 (34.8)	81 (31.0)	101 (38.5)	182 (34.8)	182 (34.8)
Ethnicity, n (%)					
Hispanic or Latino	5 (1.0)	3 (1.1)	2 (0.8)	5 (1.0)	5 (1.0)
Not Hispanic or Latino	518 (99.0)	258 (98.9)	260 (99.2)	518 (99.0)	518 (99.0)
Race, n (%)					
White	522 (99.8)	261 (100.0)	261 (99.6)	522 (99.8)	522 (99.8)
Black or African American	0	0	0	0	0
Asian	1 (0.2)	0	1 (0.4)	1 (0.2)	1 (0.2)
American Indian or Alaska Native	0	0	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Height (cm) at Screening					
n	523	261	262	523	523
Mean (SD)	173.57 (9.596)	174.18 (10.178)	172.97 (8.957)	173.57 (9.596)	173.57 (9.596)
Median	175.00	175.50	174.00	175.00	175.00
Min, Max	111.0, 197.0	111.0, 197.0	153.0, 196.0	111.0, 197.0	111.0, 197.0
Weight (kg) at Screening					
n	523	261	262	523	523
Mean (SD)	84.17 (18.367)	85.19 (18.178)	83.16 (18.531)	84.17 (18.367)	84.17 (18.367)
Median	83.50	84.50	81.50	83.50	83.50
Min, Max	45.0, 152.8	49.0, 149.6	45.0, 152.8	45.0, 152.8	45.0, 152.8
BMI (kg/m ²)					
n	523	261	262	523	523
Mean (SD)	27.90 (5.896)	28.12 (6.394)	27.69 (5.358)	27.90 (5.896)	27.90 (5.896)
Median	27.40	27.50	27.25	27.40	27.40
Min, Max	15.9, 90.1	16.8, 90.1	15.9, 47.7	15.9, 90.1	15.9, 90.1
BMI Category, n (%)					
<30 kg/m ²	355 (67.9)	178 (68.2)	177 (67.6)	355 (67.9)	355 (67.9)
≥30 kg/m ²	168 (32.1)	83 (31.8)	85 (32.4)	168 (32.1)	168 (32.1)
Psoriasis Area and Severity Index (PASI)					
n	523	261	262	523	523
Mean (SD)	23.58 (8.115)	23.92 (8.208)	23.24 (8.022)	23.58 (8.115)	23.58 (8.115)
Median	21.60	22.20	21.00	21.60	21.60
Min, Max	12.0, 58.8	12.0, 54.8	12.0, 58.8	12.0, 58.8	12.0, 58.8
Static Physicians Global Assessment (sPGA), n (%)					
Minimal	0	0	0	0	0
Mild	0	0	0	0	0
Moderate	301 (57.6)	146 (55.9)	155 (59.2)	301 (57.6)	301 (57.6)
Severe	158 (30.2)	81 (31.0)	77 (29.4)	158 (30.2)	158 (30.2)
Very Severe	64 (12.2)	34 (13.0)	30 (11.5)	64 (12.2)	64 (12.2)
Percentage of Body Surface Area (% BSA) Affected (%)					
n	523	261	262	523	523
Mean (SD)	29.63 (13.754)	30.25 (14.067)	29.01 (13.433)	29.63 (13.754)	29.63 (13.754)
Median	26.60	27.20	25.75	26.60	26.60
Min, Max	10.0, 90.0	10.0, 90.0	10.0, 75.0	10.0, 90.0	10.0, 90.0
Months from Diagnosis of Chronic Plaque Psoriasis to Informed Consent					
n	523	261	262	523	523
Mean (SD)	193.2 (139.23)	191.3 (135.53)	195.1 (143.05)	193.2 (139.23)	193.2 (139.23)
Median	163.0	164.0	162.5	163.0	163.0
Min, Max	3, 717	3, 717	9, 692	3, 717	3, 717

Source: Table 14.1.3.2 and Table 14.1.4.2

Applicant's Analysis Results

The Applicant's log transformation-based analysis results for $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$ using the Per Protocol Set are shown in Table 17, and the log transformation-based analysis results $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$ using the Full Analysis Set are shown in Table 18.

Table 17. Applicant's analysis results for primary endpoints based on log-transformed AUC_{tau, W26-28} or log-transformed C_{max, W26-28} using the Per Protocol Set

	AVT02/E.U.-Humira/AVT02 (N=261)	E.U.-Humira (N=262)
AUC _{tau, W26-28} (h*ng/mL)		
n	232	227
Geometric LSMean	1823058.1	1593941.6
Ratio of Geometric LSMean (%)	114.4	
90% CI for Ratio (%)	90.3, 144.8	
C _{max, W26-28} (ng/mL)		
n	246	251
Geometric LSMean	9527.8	8050.6
Ratio of Geometric LSMean (%)	118.3	
90% CI for Ratio (%)	98.3, 142.5	

Source: Table 14.2.1.2 of the Clinical Study Report

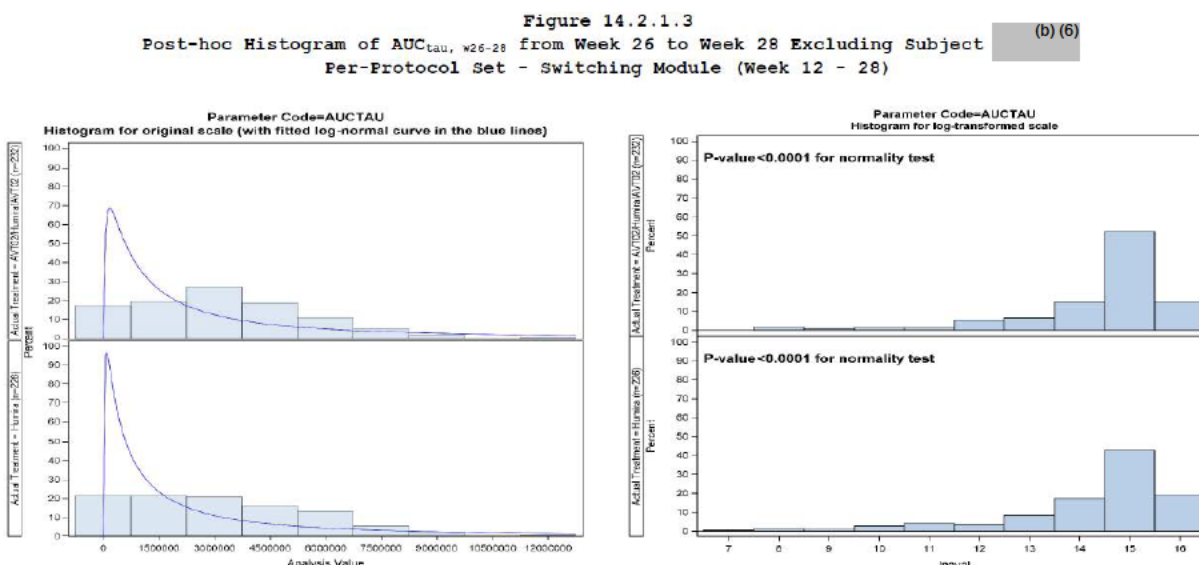
Table 18. Applicant's analysis results for primary endpoints based on log-transformed AUC_{tau, W26-28} or log-transformed C_{max, W26-28} using the Full Analysis Set

	AVT02/E.U.-Humira/AVT02 (N=277)	E.U.-Humira (N=273)
AUC _{tau, W26-28} (h*ng/mL)		
n	234	229
Geometric LSMean	1775649.4	1599403.8
Ratio of Geometric LSMean (%)	111.0	
90% CI for Ratio (%)	87.6, 140.7	
C _{max, W26-28} (ng/mL)		
n	248	253
Geometric LSMean	9347.6	8076.7
Ratio of Geometric LSMean (%)	115.7	
90% CI for Ratio (%)	96.1, 139.4	

Source: Table 14.2.1.3 of the Clinical Study Report

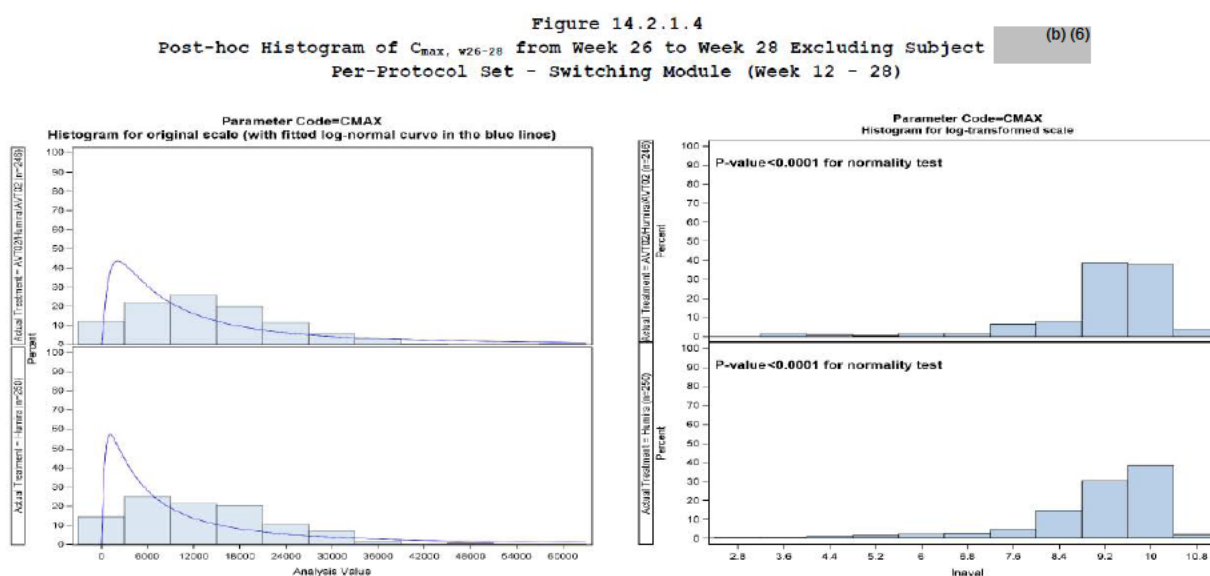
The Applicant's histograms for primary endpoints AUC_{tau, W26-28} and C_{max, W26-28} (on original scale and log-scale) and p-values for Shapiro-Wilks normality test on the log-transformed endpoints are shown in Figure 7 and Figure 8. These histograms and normality tests correspond to analysis #1 described in the post database lock statistical analysis plan addendum.

Figure 7. Histograms of $AUC_{\tau, W26-28}$ and $\log(AUC_{\tau, W26-28})$ in each treatment group based on the Per Protocol Set



Source: Figure 14.2.1.3 of the Clinical Study Report

Figure 8. Histograms of $C_{\max, W26-28}$ and $\log(C_{\max, W26-28})$ in each treatment group based on the Per Protocol Set



Source: Figure 14.2.1.4 of the Clinical Study Report

The Applicant's primary analysis results based on analysis on the original scale are shown in Table 19 for the Per Protocol Set and Table 20 for the Full Analysis Set.

Table 19. Applicant's updated analysis results for primary endpoints based on original scale analysis using the Per Protocol Set

	AVT02/E.U.-Humira/AVT02 (N=261)	E.U.-Humira (N=262)
AUC _{tau, W26-28} (h*ng/mL)		
n	232	226
Arithmetic LSMean	3154426.3	3102444.2
Ratio of Arithmetic LSMean (%)	101.7	
90% CI for Ratio (%) based on Fieller's Theorem	91.4, 112.0	
90% CI for Ratio (%) based on bootstrapping	91.7, 112.6	
C _{max, W26-28} (ng/mL)		
n	246	250
Arithmetic LSMean	13986.7	12935.8
Ratio of Arithmetic LSMean (%)	108.1	
90% CI for Ratio (%) based on Fieller's Theorem	98.3, 117.9	
90% CI for Ratio (%) based on bootstrapping	99.4, 117.8	

Subject (b) (6) is excluded from this analysis.

Source: Table 11.6 (also Table 14.2.1.2b and Table 14.2.1.2c) of the Clinical Study Report

Table 20. Applicant's updated analysis results for primary endpoints based on original scale analysis using the Full Analysis Set

	AVT02/E.U.-Humira/AVT02 (N=277)	E.U.-Humira (N=273)
AUC _{tau, W26-28} (h*ng/mL)		
n	234	228
Arithmetic LSMean	3131904.9	3096952.8
Ratio of Arithmetic LSMean (%)	101.1	
90% CI for Ratio (%) based on Fieller's Theorem	90.9, 111.4	
90% CI for Ratio (%) based on bootstrapping	90.7, 112.1	
C _{max, W26-28} (ng/mL)		
n	248	252
Arithmetic LSMean	13904.7	12944.0
Ratio of Arithmetic LSMean (%)	107.4	
90% CI for Ratio (%) based on Fieller's Theorem	97.7, 117.1	
90% CI for Ratio (%) based on bootstrapping	99.0, 116.8	

Subject (b) (6) is excluded from this analysis.

Source: Table 14.2.1.3a and Table 14.2.1.3b of the Clinical Study Report

Reviewer's Comments:

1. The Applicant's rationale for performing the statistical analysis on the original scale even though the log transformation-based analysis was prespecified in the Statistical Analysis Plan is described in the post database lock statistical analysis plan addendum as follows: *"Given the distribution of the primary endpoint data, a statistical analysis method based on a log-transformation scale is not appropriate and the data need to be analyzed on the original scale. As a result, arithmetic means and arithmetic mean ratio (AMR) instead of geometric mean and GMR are the correct metrics for the assessment of the primary endpoints $AUC_{tau, W26-28}$ and $C_{max, W26-28}$. Therefore 90% CIs for AMR will be constructed using Fieller's theorem as the primary analysis. Equivalence will be concluded if the 90% CIs for AMR for both primary endpoints are within the range of 80% to 125%. Subject (b) (6) has exceptionally high PK concentration during Week 26 and Week 28 (e.g., 100 times higher than the average PK concentration level), therefore this subject is considered as an outlier."* The updated analyses are consistent with the agency's analysis recommendations for this study design and patient population. See Reviewer's Comments in the Statistical Analysis subsection of Section 5.3.1.
2. We verified the analysis results shown in Table 17 and Table 18 using code we wrote to implement the analyses.
3. When verifying the analysis results shown in Table 19 and Table 20 using code we wrote to implement the analyses, we found the following discrepancy. In the results shown in Table 19 and Table 20 the Applicant stated that the confidence interval was computed based on Fieller's Theorem. However, we found a discrepancy here between our results and those of the Applicant. Upon inspecting the Applicant's code in the file "table_14_02_01_02ab.txt" we found that the confidence interval labeled in Table 19 and Table 20 as "90% CI for Ratio (%)" based on Fieller's Theorem" was computed using the following SAS code:



The SAS code shown above indicates that the confidence interval labeled in Table 19 and Table 20 as "90% CI for Ratio (%)" based on Fieller's Theorem" was actually computed using a statistical methodology based on the Taylor approximation (also known as the Delta-Method) which differs from the confidence interval computed using Fieller's Theorem (Franz 2007). This SAS code also indicates that the Applicant's implementation of the Taylor approximation-based confidence interval assumes that the covariance between estimators

corresponding to estimates referred to as “Arithmetic LSMean” of the AVT02/E.U.-Humira/AVT02 group and E.U.-Humira group equals zero. We wrote code to implement this Taylor approximation-based confidence interval assuming zero covariance, and using this code we were able to reproduce the confidence intervals in Table 19 and Table 20 labeled as “90% CI for Ratio (%) based on Fieller’s Theorem”. In the section titled In the section titled Reviewer’s Assessment below we present the confidence intervals obtained using Fieller’s theorem applied in the setting of the general linear model as described in Zerbe (1978).

4. Table 19 and Table 20 also present bootstrap confidence intervals. Our bootstrap results were similar to the Applicant’s but did not match exactly. Slight differences in these results are expected because of the nature of the bootstrap computations which utilize randomly generated samples from the empirical distribution based on the data.
5. In Table 17 and Table 18, for the analysis results of $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$, the results based on the Full Analysis Set include the following four additional subjects compared with the results based on the Per Protocol Set: Subjects (b) (6). Similarly, in Table 19 and Table 20, for the analysis results of $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$, the results based on the Full Analysis Set include the same four additional subjects compared with the results based on the Per Protocol Set. These four subjects were excluded from the Per Protocol Set for the following reasons.

Subject	(b) (6)	Predose PK sample was not collected due to the study nurse omission.
Subject	(b) (6)	Predose PK samples were not taken due to omission.
Subject	(b) (6)	The subject participated in guselkumab/adalimumab (3:1) study till (b) (6) and there is no evidence that subject was not in adalimumab arm.
Subject	(b) (6)	Study procedures at site 9901 registered the Week 26 visit of subject (b) (6) for subject (b) (6) by mistake (b) (4) IP kit was assigned and administered to the subject (b) (6) instead of subject (b) (6)

While the Per Protocol Set and Full Analysis Set contain 523 and 550 subjects, respectively, (during the switching module) because of the exclusions (see the Reviewer’s Comments in the section titled Subject Disposition), the analysis results in based on the Full Analysis Set (Table 18 and Table 20) use four additional subjects compared with the similar results based on the Per Protocol Set (Table 17 and Table 19).

6. In Table 17, Table 18, Table 19, Table 20 we observe that there are subjects in the analysis set (Per Protocol Set or Full Analysis Set) who entered the switching module of the study, but are excluded from the primary endpoint analysis. We provided details about these excluded subjects in the Reviewer’s Comments in the section titled Subject Disposition.
7. Regarding the treatment of missing data, Section 5.5.5 of the June 18, 2019 (Version 1.0), December 12, 2019 (Version 2.0), and August 3, 2020 (Version 3.0) versions of the Protocol describe the treatment of missing data as follows.

“Multiple Imputation (MI) will be used as the method for dealing with missing data for the analysis of the primary endpoint and several other PK endpoints in the FAS. Details regarding the methods for MI will be presented in the SAP before unblinding of the study.”

However, this section on the treatment of missing data that describes multiple imputation does not appear in the May 11, 2021 (Version 4.0) version of the Protocol. The Statistical Analysis Plan does not discuss a plan to use multiple imputation for handling missing data. We find that multiple imputation was not used, and subjects with missing values of $AUC_{\tau_{0.5}}$, W_{26-28} and/or $C_{\max, W_{26-28}}$ were excluded from the primary statistical analysis of the respective endpoint. These exclusions are described in the reviewer's comments in the Section titled Subject Disposition. For the Per Protocol Set, the reasons for exclusions are described in Table 62. For the Full Analysis Set, the reasons for exclusions include those described in Table 62, and additional subjects (see Reviewer's Comment #4 in the section titled Subject Disposition).

8. The confidence intervals shown in Table 17 and Table 18 obtained using the log transformation-based analysis are not contained in the PK similarity margin [80%, 125%]. The confidence intervals in Table 19 and Table 20 obtained using the original scale-based analysis are contained in the PK similarity margin [80%, 125%], and based on the results in Table 19 and Table 20 the Applicant concluded that comparable PK similarity between the AVT02/Humira/AVT02 and Humira groups was demonstrated.

Secondary Efficacy Evaluations

The Applicant states in Section 9.8.1.2.2 of the Clinical Study Report that the analyses of secondary efficacy endpoints were based on the observed data and utilized descriptive statistics on observed data for the Full Analysis Set only. There was no imputation of missing data. In Section 9.8.1.4 of the Clinical Study Report the Applicant states that all secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analyzed without any procedures to account for multiple comparisons.

The secondary efficacy endpoints included Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), Static Physicians Global Assessment (sPGA), and Percentage of Body Surface Area (%BSA) affected by psoriasis. Details on each of these secondary efficacy endpoints appear in Section 9.6.3.2 of the Clinical Study Report. Table 21, Table 22, Table 23 **Error! Reference source not found.**, and Table 24 display the Applicant's efficacy analysis results for PASI; **Error! Reference source not found.**, and **Error! Reference source not found.** display the Applicant's efficacy analysis results for DLQI; **Error! Reference source not found.** display the Applicant's efficacy analysis results for sPGA; and **Error! Reference source not found.** displays the Applicant's efficacy analysis results for %BSA affected by psoriasis. Additional descriptive analysis results related to these secondary efficacy endpoints appear in the Clinical Study Report.

As described in Section 11.6.11 of the Clinical Study Report, the Applicant concluded that there were no meaningful differences between the efficacy assessments in the AVT01/Humira/AVT02 group versus the Humira group in the Switching Module.

Reviewer's Comment:

As discussed above, these secondary efficacy endpoint analyses are intended to be interpreted as descriptive analyses. We verified the secondary efficacy endpoint analysis results shown in

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Table 21, Table 22, Table 23 **Error! Reference source not found.**, Table 24, Table 25, Table 26, Table 27, Table 28, and Table 29 using code we wrote to implement each of these analyses. To reproduce the Applicant's results shown in Table 24, we found it necessary to calculate the rounded (integer valued) percentage improvement in PASI for each subject (at the indicated time point) and to use this rounded percentage improvement in PASI for each subject to calculate the values referred to as "n" in this table.

Psoriasis Area and Severity Index (PASI)

Table 21. Percent improvement from baseline in Psoriasis Area and Severity Index (PASI) – Full Analysis Set – Switching Module (Weeks 12-28)

Time Point	Actual Value				Percent Improvement from Baseline			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02/Humira/AVT02 (N=277)								
Baseline	277	23.6 (8.15)	21.6	12, 55				
Week 12	277	1.3 (1.79)	0.6	0, 11	277	94.4 (6.88)	97.2	75, 100
Week 28	263	0.9 (2.05)	0.0	0, 14	263	96.0 (8.37)	100.0	56, 100
ET	5	2.8 (3.82)	2.2	0, 9	5	86.6 (18.88)	92.2	54, 100
Humira (N=273)								
Baseline	273	23.3 (7.99)	21.2	12, 59				
Week 12	273	1.2 (1.69)	0.6	0, 10	273	94.6 (7.00)	97.1	75, 100
Week 28	264	0.9 (2.51)	0.0	0, 22	264	95.8 (9.78)	100.0	14, 100
ET	4	14.5 (20.31)	6.9	0, 44	4	43.7 (61.62)	53.6	-32, 100

ET = Early Termination

Source: Table 14.2.2.1.2 and Table 11.9 of the Clinical Study Report.

Table 22. Percent improvement from Week 12 in Psoriasis Area and Severity Index (PASI) – Full Analysis Set – Switching Module (Weeks 12-28).

Time Point	Actual Value				Percent Improvement from Week 12			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02/Humira/AVT02 (N=277)								
Week 12	277	1.3 (1.79)	0.6	0, 11				
Week 28	263	0.9 (2.05)	0.0	0, 14	148 [#]	31.2 (123.48)	66.7	-1100, 100
ET	5	2.8 (3.82)	2.2	0, 9	5	5.8 (112.98)	25.0	-174, 100
Humira (N=273)								
Week 12	273	1.2 (1.69)	0.6	0, 10				
Week 28	264	0.9 (2.51)	0.0	0, 22	151 [#]	18.1 (130.61)	53.3	-882, 100
ET	4	14.5 (20.31)	6.9	0, 44	3	-364.6 (281.58)	-236.4	-688, -170

[#]After Week 12, subjects who had PASI response 0 were not taken under calculation.

ET = Early Termination

Source: Table 14.2.2.1.3 and Table 11.20 of the Clinical Study Report.

Table 23. Absolute improvement from baseline and Week 12 in Psoriasis Area and Severity Index (PASI) – Full Analysis Set – Switching Module (Weeks 12-28)

	Actual Value		Absolute Improvement from Baseline		Absolute Improvement from Week 12	
Time Point	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
AVT02/Humira/AVT02 (N=277)						
Baseline	277	23.62 (8.148)				
Week 12	277	1.27 (1.792)	277	22.35 (8.070)		
Week 28	263	0.89 (2.053)	263	22.96 (8.418)	263	0.37 (1.838)
Humira (N=273)						
Baseline	273	23.31 (7.993)				
Week 12	273	1.18 (1.688)	273	22.13 (8.058)		
Week 28	264	0.94 (2.512)	264	22.33 (8.187)	264	0.22 (2.259)
Difference between Treatment Groups at Week 28 (95% Confidence Interval)*			0.63 (-0.79, 2.05)		0.16 (-0.2, 0.51)	

*: Analysis was performed using analysis of variance (ANOVA) with treatment as fixed effect.

Source: Table 11.21 and Table 14.2.2.1.2a of the Clinical Study Report.

Table 24. Number and percentage of subjects achieving PASI 50, PASI 75, PASI 90, and PASI 100

	Lead-In Period			Switching Module						
	Humira				AVT02/Humira/AVT02			Humira		
	m	n	p		m	n	p	m	n	p
Week 12				Week 12						
PASI 50	556	551	99.1	PASI 50	277	277	100.0	273	273	100.0
PASI 75	556	550	98.9	PASI 75	277	277	100.0	273	273	100.0
PASI 90	556	436	78.4	PASI 90	277	216	78.0	273	220	80.6
PASI 100	556	235	42.3	PASI 100	277	119	43.0	273	116	42.5
				Week 28						
				PASI 50	263	263	100.0	264	262	99.2
				PASI 75	263	251	95.4	264	253	95.8
				PASI 90	263	228	86.7	264	235	89.0
				PASI 100	263	168	63.9	264	155	58.7

m = number of subjects in treatment group with assessment at both Baseline and the specified time point is used as the denominator for percentage calculations.

n = number of subjects achieving PASI 50, PASI 75, PASI 90 or PASI 100 at time point.

p = percentage of subjects achieving PASI 50, PASI 75, PASI 90 or PASI 100.

Source: Table 11.22, Table 14.2.2.2.1, Table 14.2.2.2.2 of the Clinical Study Report.

Dermatology Life Quality Index (DLQI)

Table 25. Change from baseline in Dermatology Life Quality Index (DLQI) – Full Analysis Set – Switching Module (Weeks 12-28)

	Actual Value				Change from Baseline			
Time Point	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02/Humira/AVT02 (N=277)								
Baseline	277	14.4 (6.87)	15.0	0, 30				
Week 12	277	2.0 (3.11)	1.0	0, 21	277	-12.4 (7.13)	-12.0	-30, 6

Week 28	263	1.6 (2.88)	0.0	0, 17	263	-12.9 (7.25)	-13.0	-30, 7
ET	5	2.4 (2.88)	2.0	0, 7	5	-13.8 (10.69)	-14.0	-28, -2
Humira (N=273)								
Baseline	273	14.5 (6.69)	15.0	0, 30				
Week 12	273	2.3 (3.47)	1.0	0, 25	273	-12.3 (7.15)	-12.0	-30, 8
Week 28	264	1.9 (3.36)	0.0	0, 22	264	-12.6 (7.46)	-13.0	-30, 6
ET	4	14.0 (10.55)	12.5	3, 28	4	-1.5 (10.25)	-3.0	-12, 12

ET = Early Termination.

Source: Table 14.2.3.2 of the Clinical Study Report.

Table 26. Change from Week 12 in Dermatology Life Quality Index (DLQI) – Full Analysis Set – Switching Module (Weeks 12-28)

Time Point	Actual Value				Change from Week 12			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02/Humira/AVT02 (N=277)								
Week 12	277	2.0 (3.11)	1.0	0, 21				
Week 28	263	1.6 (2.88)	0.0	0, 17	263	-0.4 (3.12)	0.0	-17, 16
ET	5	2.4 (2.88)	2.0	0, 7	5	1.0 (2.55)	0.0	-1, 5
Humira (N=273)								
Week 12	273	2.3 (3.47)	1.0	0, 25				
Week 28	264	1.9 (3.36)	0.0	0, 22	264	-0.4 (3.65)	0.0	-17, 14
ET	4	14.0 (10.55)	12.5	3, 28	4	9.3 (10.18)	5.5	2, 24

ET = Early Termination.

Source: Table 14.2.3.3 of the Clinical Study Report.

Static Physicians Global Assessment (sPGA)**Table 27. Percentage of patients achieving Static Physicians Global Assessment (sPGA) response of clear (0) or almost clear (1) over time – Full Analysis Set – Switching Module (Weeks 12-28)**

Visit	AVT02/Humira/AVT02 (N=277)			Humira (N=273)		
	m	n	p	m	n	p
Week 12 sPGA Response is Clear (0) or Almost Clear (1)	277	264	95.3	273	262	96.0
Week 28 sPGA Response is Clear (0) or Almost Clear (1)	263	242	92.0	264	242	91.7
ET sPGA Response is Clear (0) or Almost Clear (1)	5	4	80.0	4	1	25.0

ET = Early Termination.

m = number of patients in treatment group with assessment at both Baseline and the specified time point is used as the denominator for percentage calculations.

n = number of patients achieving sPGA Responses of clear (0) or almost clear (1) at time point.

p = percentage of patients achieving sPGA Responses of clear (0) or almost clear (1).

Source: Table 14.2.4.2 of the Clinical Study Report.

Table 28. Change from baseline in Static Physicians Global Assessment (sPGA) over time – Full Analysis Set – Switching Module (Weeks 12-28)

Treatment	Actual Value				Change from Baseline			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02/Humira/AVT02 (N=277)								
Baseline	277	3.6 (0.71)	3.0	3, 5				
Week 12	277	0.5 (0.61)	0.0	0, 3	277	-3.1 (0.98)	-3.0	-5, 0
Week 28	263	0.4 (0.72)	0.0	0, 3	263	-3.2 (0.95)	-3.0	-5, -1
ET	5	0.6 (0.89)	0.0	0, 2	5	-3.0 (1.58)	-3.0	-5, -1
Humira (N=273)								
Baseline	273	3.5 (0.70)	3.0	3, 5				
Week 12	273	0.5 (0.64)	0.0	0, 3	273	-3.0 (0.93)	-3.0	-5, 0
Week 28	264	0.4 (0.80)	0.0	0, 3	264	-3.1 (0.93)	-3.0	-5, 0
ET	4	2.3 (1.71)	2.5	0, 4	4	-1.3 (1.26)	-1.0	-3, 0

ET = Early Termination.

Source: Table 14.2.5.2 of the Clinical Study Report.

Percentage of Body Surface Area (%BSA)**Table 29. Change from baseline in Percentage of Body Surface Area (%BSA) affected by psoriasis evaluation – Full Analysis Set – Switching Module (Weeks 12-28)**

Treatment	Actual Value				Change from Baseline			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
AVT02/Humira/AVT02 (N=277)								
Baseline	277	29.7 (14.00)	27.0	10, 90				
Week 12	277	3.2 (4.84)	1.0	0, 32	277	-26.5 (13.73)	-23.5	-87, 0
Week 28	263	1.4 (2.95)	0.0	0, 17	263	-28.7 (14.58)	-26.0	-90, -1
ET	5	6.6 (9.04)	2.0	0, 21	5	-20.8 (15.83)	-17.0	-41, -3
Humira (N=273)								
Baseline	273	29.2 (13.45)	26.0	10, 75				
Week 12	273	3.1 (6.29)	1.4	0, 80	273	-26.1 (14.48)	-23.5	-75, 50
Week 28	264	1.7 (4.21)	0.0	0, 45	264	-27.4 (13.43)	-24.4	-75, -3
ET	4	13.7 (20.45)	5.5	0, 44	4	-21.4 (34.33)	-14.4	-68, 11

ET = Early Termination.

Source: Table 14.2.6.2 of the Clinical Study Report.

Reviewer's Assessments**Log Transformation-Based Analysis**

We implemented the log-transformation based statistical analysis using the same methodology as the Applicant using the Per Protocol Set and Full Analysis Set. We also excluded the same subjects from the analyses as the Applicant, values for the primary endpoints $AUC_{\tau, W26-28}$ or $C_{\max, W26-28}$ were not provided for the excluded subjects. Our results based on this analysis are shown in Table 30 and Table 31., and these results are the same as the Applicant's results shown in Table 17 and Table 18. To facilitate comparisons with the Applicant's results, throughout this section we label the rows in the tables using similar names as the Applicant used in their tables. The confidence intervals shown in Table 17 and Table 18 obtained using the log transformation-based analysis are not contained in the similarity margin [80%, 125%]. For the sake of completeness, Table 32. and Table 33. display the log-transformation based analysis results with Subject ^{(b) (6)} excluded.

Table 30. Reviewer's analysis results for primary endpoints based on log scale analysis using the Per Protocol Set. Subject ^{(b) (6)} is included in this analysis

	AVT02/E.U.-Humira/AVT02 (N=261)	E.U.-Humira (N=262)
$AUC_{\tau, W26-28}$ (h*ng/mL)		
n	232	227
Geometric LSMean	1823058.1	1593941.6
Ratio of Geometric LSMean (%)	114.4	
90% CI for Ratio (%)	(90.3, 144.8)	
$C_{\max, W26-28}$ (ng/mL)		

n	246	251
Geometric LSMean	9527.8	8050.6
Ratio of Geometric LSMean (%)	118.3	
90% CI for Ratio (%)	(98.3, 142.5)	

Source: FDA reviewer's analysis

Table 31. Reviewer's analysis results for primary endpoints based on log scale analysis using the Full Analysis Set. Subject (b) (6) is included in this analysis

	AVT02/E.U.-Humira/AVT02 (N=277)	E.U.-Humira (N=273)
AUC_{tau, W26-28} (h*ng/mL)		
n	234	229
Geometric LSMean	1775649.4	1599403.8
Ratio of Geometric LSMean (%)	111.0	
90% CI for Ratio (%)	(87.6, 140.7)	
C_{max, W26-28} (ng/mL)		
n	248	253
Geometric LSMean	9347.6	8076.7
Ratio of Geometric LSMean (%)	115.7	
90% CI for Ratio (%)	(96.1, 139.4)	

Source: FDA reviewer's analysis

Table 32. Reviewer's analysis results for primary endpoints based on log scale analysis using the Per Protocol Set. Subject (b) (6) is excluded from this analysis

	AVT02/E.U.-Humira/AVT02 (N=261)	E.U.-Humira (N=262)
AUC_{tau, W26-28} (h*ng/mL)		
n	232	226
Geometric LSMean	1825621.0	1559720.9
Ratio of Geometric LSMean (%)	117.0	
90% CI for Ratio (%)	(92.7, 147.8)	
C_{max, W26-28} (ng/mL)		
n	246	250
Geometric LSMean	9544.1	7880.6
Ratio of Geometric LSMean (%)	121.1	
90% CI for Ratio (%)	(100.9, 145.3)	

Source: FDA reviewer's analysis

Table 33. Reviewer's analysis results for primary endpoints based on log scale analysis using the Full Analysis Set. Subject (b) (6) is excluded from this analysis

	AVT02/E.U.-Humira/AVT02 (N=277)	E.U.-Humira (N=273)
AUC_{tau, W26-28} (h*ng/mL)		
n	234	228
Geometric LSMean	1777924.5	1565567.9

Ratio of Geometric LSMean (%)	113.6	
90% CI for Ratio (%)	(89.9, 143.5)	
C _{max} , W26-28 (ng/mL)		
n	248	252
Geometric LSMean	9362.5	7908.3
Ratio of Geometric LSMean (%)	118.4	
90% CI for Ratio (%)	(98.6, 142.2)	

Source: FDA reviewer's analysis

Original Scale-Based Analysis

We implemented the original scale-based statistical analysis using the same methodology as the Applicant using the Per Protocol Set and Full Analysis Set. We also excluded the same subjects from the analyses as the Applicant, values for the primary endpoints $AUC_{\tau, W26-28}$ or $C_{\max, W26-28}$ were not provided for the excluded subjects except for Subject (b) (6). Our results based on this analysis are shown in Table 34. for the Per Protocol Set and in Table 35 for the Full Analysis Set. In Table 34. and Table 35 the confidence interval labeled “90% CI for Ratio (%) based on Fieller’s Theorem” differs from the Applicant’s confidence intervals with the same label in Table 19 and Table 20 because the Applicant’s confidence interval was calculated using the Taylor approximation method and we used Fieller’s theorem as presented by Zerbe (1978). This issue is discussed in the Reviewer’s Comments in the section titled Applicant’s Analysis Results of this statistical review. Also in Table 34. and Table 35, the confidence interval labeled “90% CI for Ratio (%) based on bootstrapping” differs slightly from the Applicant’s confidence intervals with the same label in Table 19 and Table 20 and such a difference is expected because of the nature of the bootstrap computations which utilize randomly generated samples from the empirical distribution based on the data.

Subject (b) (6) was excluded from the Applicant’s original scale-based analysis and the Applicant provided the following reason for this exclusion: “*Excluded from the analysis due to extremely high PK concentration*” (see Table 62). As an exploratory analysis, we performed the original scale-based analysis with the outlier Subject (b) (6) included in the analysis. These results are shown in Table 36. for the Per Protocol Set, and in Table 37. for the Full Analysis Set. We observe in both Table 36. and Table 37., that for both the Per Protocol Set and the Full Analysis Set, when Subject (b) (6) is included in the analyses the 90% confidence intervals obtained under both $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$ are not within the similarity margin [80%, 125%].

Table 34. Reviewer’s analysis results for primary endpoints based on original scale analysis using the Per Protocol Set. Subject (b) (6) is excluded from this analysis

	AVT02/E.U.-Humira/AVT02 (N=261)	E.U.-Humira (N=262)
$AUC_{\tau, W26-28}$ (h*ng/mL)		
n	232	226
Arithmetic LSMean	3154426.3	3102444.2
Ratio of Arithmetic LSMean (%)	101.7	

90% CI for Ratio (%) based on Fieller's Theorem	(91.9, 112.6)	
90% CI for Ratio (%) based on bootstrapping	(91.8, 112.5)	
C _{max} , W26-28 (ng/mL)		
n	246	250
Arithmetic LSMean	13986.7	12935.8
Ratio of Arithmetic LSMean (%)	108.1	
90% CI for Ratio (%) based on Fieller's Theorem	(98.8, 118.4)	
90% CI for Ratio (%) based on bootstrapping	(99.1, 118.5)	

Source: FDA reviewer's analysis

Table 35. Reviewer's analysis results for primary endpoints based on original scale analysis using the Full Analysis Set. Subject (b) (6) is excluded from this analysis

	AVT02/E.U.-Humira/AVT02 (N=277)	E.U.-Humira (N=273)
AUC _{tau, W26-28} (h*ng/mL)		
n	234	228
Arithmetic LSMean	3131904.9	3096952.8
Ratio of Arithmetic LSMean (%)	101.1	
90% CI for Ratio (%) based on Fieller's Theorem	(91.4, 112.0)	
90% CI for Ratio (%) based on bootstrapping	(91.0, 111.6)	
C _{max, W26-28} (ng/mL)		
n	248	252
Arithmetic LSMean	13904.7	12944.0
Ratio of Arithmetic LSMean (%)	107.4	
90% CI for Ratio (%) based on Fieller's Theorem	(98.1, 117.6)	
90% CI for Ratio (%) based on bootstrapping	(98.1, 117.4)	

Source: FDA reviewer's analysis

Table 36. Reviewer's analysis results for primary endpoints based on original scale analysis using the Per Protocol Set. Subject (b) (6) is included in this analysis

	AVT02/E.U.-Humira/AVT02 (N=261)	E.U.-Humira (N=262)
$AUC_{tau, W26-28}$ (h*ng/mL)		
n	232	227
Arithmetic LSMean	3155771.0	3771419.0
Ratio of Arithmetic LSMean (%)	83.7	
90% CI for Ratio (%) based on Fieller's Theorem	(58.8, 116.7)	

90% CI for Ratio (%) based on bootstrapping	(62.2, 108.6)	
C _{max} , W26-28 (ng/mL)		
n	246	251
Arithmetic LSMean	13858.3	17392.5
Ratio of Arithmetic LSMean (%)	79.7	
90% CI for Ratio (%) based on Fieller's Theorem	(46.7, 128.1)	
90% CI for Ratio (%) based on bootstrapping	(52.2, 115.7)	

Source: FDA reviewer's analysis

Table 37. Reviewer's analysis results for primary endpoints based on original scale analysis using the Full Analysis Set. Subject (b) (6) is included in this analysis

	AVT02/E.U.-Humira/AVT02 (N=277)	E.U.-Humira (N=273)
AUC _{tau, W26-28} (h*ng/mL)		
n	234	229
Arithmetic LSMean	3135630.7	3757664.2
Ratio of Arithmetic LSMean (%)	83.4	
90% CI for Ratio (%) based on Fieller's Theorem	(58.7, 116.3)	
90% CI for Ratio (%) based on bootstrapping	(62.5, 108.4)	
C _{max, W26-28} (ng/mL)		
n	248	253
Arithmetic LSMean	13793.0	17350.2
Ratio of Arithmetic LSMean (%)	79.5	
90% CI for Ratio (%) based on Fieller's Theorem	(46.7, 127.5)	
90% CI for Ratio (%) based on bootstrapping	(52.4, 114.3)	

Source: FDA reviewer's analysis

Comments on Log Transformation-Based and Original Scale-Based Analysis

We note that the FDA Guidance on Considerations in Demonstrating Interchangeability With a Reference Product, May 2019 recommends analyzing the endpoints AUC_{τ} and $C_{\max}$ using the log transformation.

Because the original scale-based analysis here is based on amendments to the Statistical Analysis Plan that were made post database lock and after the study was unblinded, there are concerns about the nature of this original scale-based analysis. We conducted simulation studies to examine the statistical properties of the log transformation-based and original scale-based analyses. The simulation studies are described in the appendix where we used data from the Per Protocol Set, excluding the outlier Subject (b) (6) to construct populations which were used to

draw repeated simulated sample data. The simulation results give some indication that if the target estimand for conducting the statistical equivalence test is the ratio of means $\theta_1 = E(Y_1)/E(Y_2)$ (as defined in the appendix), then the original scale-based analysis may be appropriate. In this case PK similarity is evaluated by testing the hypotheses

$$H_0: \theta_1 \leq 0.80 \text{ or } \theta_1 \geq 1.25 \text{ versus } H_1: 0.80 < \theta_1 < 1.25.$$

and rejection of the null hypothesis provides support for the conclusion that PK similarity holds with respect to the appropriate pharmacokinetic parameter. As is generally the case, the findings of the simulation studies are driven by the models and methods used to construct the simulation scenarios. Additional research may be useful to study and compare log transformation-based and original scale-based analysis in a situation such as the present one.

Summary and Conclusions

Side By Side Tables

Table 38. (Per Protocol Set) and Table 39 (Full Analysis Set) summarize the Applicant's statistical analysis results side by side with our statistical analysis results. Note that our original scale analysis results do not match the Applicant's because our confidence intervals were computed using Fieller's theorem as presented by Zerbe (1978) while the Applicant used a statistical methodology based on Taylor approximation (this issue is discussed in the reviewer's comments in the section titled Applicant's Analysis Results). Also, note that while the Per Protocol Set and Full Analysis Set contain 523 and 550 subjects, respectively, (during the switching module) because of the exclusions, the results based on the Full Analysis Set use four additional subjects compared with the results based on the Per Protocol Set, see the Reviewer's Comments in the section titled Applicant's Analysis Results for details. Because the 90% confidence intervals based on the original scale analysis excluding Subject (b) (6) (and excluding additional subjects as shown in Table 62, and described in the section titled Subject Disposition) are within the margin [80%, 125%], the Applicant concluded that the AVT02/E.U.-Humira/AVT02 and E.U.-Humira groups demonstrated comparable PK similarity.

Table 38. 90% confidence intervals (%) for PK similarity analysis using Per Protocol Set

Analysis Method	Applicant's Results*	Reviewer's Results**
AUC_{tau, W26-28} (h*ng/mL)		
Original Scale, Exclude Subject (b) (6)	(91.4, 112.0)	(91.9, 112.6)
Original Scale, Include Subject (b) (6)	(55.7, 111.7)	(58.8, 116.7)
Log Scale, Exclude Subject (b) (6)	Not Available	(92.7, 147.8)
Log Scale, Include Subject (b) (6)	(90.3, 144.8)	(90.3, 144.8)
C_{max, W26-28} (ng/mL)		
Original Scale, Exclude Subject (b) (6)	(98.3, 117.9)	(98.8, 118.4)
Original Scale, Include Subject (b) (6)	(41.5, 117.9)	(46.7, 128.1)
Log Scale, Exclude Subject (b) (6)	Not Available	(100.9, 145.3)
Log Scale, Include Subject (b) (6)	(98.3, 142.5)	(98.3, 142.5)

*Source: Table 14.2.1.2 (log scale-based analysis including Subject (b) (6)), Table 11.6 and Table 14.2.1.2b (both tables present original scale-based analysis excluding Subject (b) (6)), Table 14.2.1.2a (original scale-based analysis including Subject (b) (6)) of the Clinical Study Report.

**Source: Reviewer's analysis

Table 39. 90% confidence intervals (%) for PK similarity analysis using Full Analysis Set

Analysis Method	Applicant's Results*	Reviewer's Results**
AUC_{tau, W26-28} (h*ng/mL)		
Original Scale, Exclude Subject (b) (6)	(90.9, 111.4)	(91.4, 112.0)
Original Scale, Include Subject (b) (6)	Not Available	(58.7, 116.3)
Log Scale, Exclude Subject (b) (6)	Not Available	(89.9, 143.5)
Log Scale, Include Subject (b) (6)	(87.6, 140.7)	(87.6, 140.7)
C_{max, W26-28} (ng/mL)		
Original Scale, Exclude Subject (b) (6)	(97.7, 117.1)	(98.1, 117.6)
Original Scale, Include Subject (b) (6)	Not Available	(46.7, 127.5)
Log Scale, Exclude Subject (b) (6)	Not Available	(98.6, 142.2)
Log Scale, Include Subject (b) (6)	(96.1, 139.4)	(96.1, 139.4)

*Source: Table 14.2.1.3 (log scale-based analysis including Subject (b) (6)), Table 14.2.1.3a (original scale-based analysis excluding Subject (b) (6)) of the Clinical Study Report

**Source: Reviewer's analysis

Reviewer's Comments:

1. The Statistical Analysis Plan originally stated that the primary endpoints AUC_{tau, W26-28} and C_{max, W26-28} would be analyzed using the log-transformation. Amendments to the Statistical Analysis Plan were made post database lock and after the study was unblinded to analyze these primary endpoints on the original scale instead of using the log transformation (and to exclude the outlier Subject (b) (6) from the original scale-based analysis). The confidence intervals obtained using the log transformation-based analysis (Table 17 and Table 18) do not fall within the PK similarity margin [80%, 125%], while the confidence intervals obtained using the original scale-based analysis with Subject (b) (6) excluded (Table 19, Table 20, Table 34., Table 35) do fall within the PK similarity margin [80%, 125%]. We performed some simulation studies, and the simulation results give some indication that if the target estimand for conducting the statistical equivalence test is the ratio of means $\theta_1 = E(Y_1)/E(Y_2)$ (as defined in the appendix), then the original scale-based analysis may be appropriate. This issue is discussed in the section titled Reviewer's Assessment and the simulation results are presented in the appendix.
2. Subject (b) (6) (in Humira group during the switching module) was excluded from the Applicant's original scale-based analysis for the following reason: "Excluded from the analysis due to extremely high PK concentration" (see Table 62). The FDA Guidance on Statistical Approaches to Establishing Bioequivalence, January 2001 discusses outlier considerations. This guidance discusses the possibility that the existence of a subject outlier with no protocol violations could indicate product failure or subject-by-formulation interaction. This guidance mentions that the deletion of outliers is generally discouraged, particularly for nonreplicated designs. We note that the present study uses a parallel design, and therefore in this situation we cannot obtain the within subject comparison for Subject

(b) (6) between the two treatment groups. We observe in both Table 36. and Table 37., that for both the Per Protocol Set and the Full Analysis Set, when Subject (b) (6) is included in the analyses the 90% confidence intervals obtained under both $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$ are not within the PK similarity margin [80%, 125%].

To explore the magnitude of the outlier data for Subject (b) (6) relative to other large observed values, Table 40. and Table 41. display the five largest values of $AUC_{\tau, W26-28}$ and $C_{\max, W26-28}$, respectively, by treatment group in the Per Protocol Set.

Table 40. Five largest observed values of $AUC_{\tau, W26-28}$ by treatment group in the Per Protocol Set

AVT02/E.U.-Humira/AVT02		E.U.-Humira	
12,594,045.28	(Subject (b) (6))	155,271,679.1	(Subject (b) (6))
9,215,028.246	(Subject (b) (6))	12,249,079.07	(Subject (b) (6))
8,810,382.867	(Subject (b) (6))	9,247,602.785	(Subject (b) (6))
8,469,755.071	(Subject (b) (6))	8,873,380.576	(Subject (b) (6))
8,294,889.237	(Subject (b) (6))	8,782,125.938	(Subject (b) (6))

The values shown in this table are also the five largest observed values of $AUC_{\tau, W26-28}$ by treatment group in the Full Analysis Set.

Source: Reviewer's analysis

Table 41. Five largest observed values of $C_{\max, W26-28}$ by treatment group in the Per Protocol Set

AVT02/E.U.-Humira/AVT02		E.U.-Humira	
60,800	(Subject (b) (6))	1,100,000	(Subject (b) (6))
39,000	(Subject (b) (6))	46,300	(Subject (b) (6))
35,900	(Subject (b) (6))	35,700	(Subject (b) (6))
35,600	(Subject (b) (6))	33,700	(Subject (b) (6))
35,100	(Subjects (b) (6))	33,400	(Subject (b) (6))

The values shown in this table are also the five largest observed values of $C_{\max, W26-28}$ by treatment group in the Full Analysis Set.

Source: Reviewer's analysis

3. (a) Beside the exclusion of Subject (b) (6) as discussed directly above, in the Applicant's analysis of the primary endpoints, there are several other subjects who are in the Per Protocol Set but are excluded from the analysis based on the Per Protocol Set because $AUC_{\tau, W26-28}$ or $C_{\max, W26-28}$ were not calculated for these subjects. These subjects were excluded for one of the following reasons:

- Insufficient quantifiable data; all concentrations $W26-28 < LLOQ$
- Insufficient quantifiable data; < 3 concentrations $> LLOQ$
- Insufficient quantifiable data; < 3 consecutive concentrations $> LLOQ$
- Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}

These subjects were also excluded from the analysis based on the Full Analysis Set, and for the Full Analysis Set there are some additional exclusions because of subjects having early termination before Week 28 and one subject missing the Week 26 visit. This issue is discussed in the Reviewer's Comments in the sections titled Subject Disposition and Applicant's Analysis Results. Table 62 provides the list of subjects in the Per Protocol Set who are excluded from the analysis of the primary endpoints, and the Applicant's reasons for exclusion.

(b) Regarding the treatment of missing data, Section 5.5.5 of the June 18, 2019 (Version 1.0), December 12, 2019 (Version 2.0), and August 3, 2020 (Version 3.0) versions of the Protocol describe the treatment of missing data as follows.

“Multiple Imputation (MI) will be used as the method for dealing with missing data for the analysis of the primary endpoint and several other PK endpoints in the FAS. Details regarding the methods for MI will be presented in the SAP before unblinding of the study.”

However, this section on the treatment of missing data that describes multiple imputation does not appear in the May 11, 2021 (Version 4.0) version of the Protocol. The Statistical Analysis Plan does not discuss a plan to use multiple imputation for handling missing data. We find that multiple imputation was not used, and subjects with missing values of AUC_{τ} , W_{26-28} and/or $C_{\max, W_{26-28}}$ were excluded from the primary statistical analysis of the respective endpoint (part (a) above describes the reasons for exclusions from primary endpoint analyses).

4. We found that the Applicant's confidence intervals labeled in Table 19 and Table 20 as “90% CI for Ratio (%) based on Fieller's Theorem” were computed using a statistical methodology based on the Taylor approximation (also known as the Delta-Method) which differs from the confidence interval computed using Fieller's Theorem (Franz 2007). In Table 34. and Table 35 we present results analogous to those in Table 19 and Table 20, respectively where the confidence intervals are obtained using Fieller's theorem applied in the setting of the general linear model as described by Zerbe (1978). When comparing Table 19 and Table 20 with Table 34. And Table 35 we find that using Fieller's theorem as described by Zerbe (1978) instead of Taylor approximation does not affect the conclusions drawn from these sets of results.
5. The Clinical Reviewer discovered a discrepancy where according to the data tables, Subjects (b) (6) were in the E.U.-Humira group during the switching period of the study, but according to the adverse event narratives these three subjects were in the AVT02/E.U.-Humira/AVT02 group. According to the ADSL and ADPP datasets used for this review, these subjects were in the E.U.-Humira arm during the switching period of the study. In the information request response received on 06/07/2022 the Applicant stated that these three subjects were in the E.U.-Humira arm during the switching period, which are the treatment assignments used for the analysis results presented in this review.

Authors:

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6.3. Review of Safety Data**6.3.1. Methods****Clinical Studies Used to Evaluate Safety**

Under the current submission for the BLA 761299 for interchangeability, the Applicant has submitted results of a single switching Study AVT02-GL-302 entitled "Multicenter, Double-blind, Randomized, Parallel-group, Study Evaluating Pharmacokinetic, Efficacy, Safety, and Immunogenicity Between Patients with Moderate to Severe Chronic Plaque Psoriasis Receiving United States-licensed Humira and Patients with Moderate to Severe Chronic Plaque Psoriasis Undergoing Repeated Switches Between United States-licensed Humira and AVT02 Followed by a Safety Extension Phase of AVT02 (ALVOPAD-X)" to demonstrate that AVT02 is interchangeable with U.S.-licensed Humira, including comparable safety profiles between the Switching Arm and the Continuous Arm in the post-randomization period for subjects with moderate to severe plaque psoriasis.

The study population for Study AVT02-GL-302 included adult subjects with a diagnosis of moderate to severe chronic plaque psoriasis (baseline PASI $\geq$ 12, sPGA $\geq$ 3, and a body surface area (BSA) $\geq$ 10% and no exacerbations/flare $\geq$ 2 months prior to randomization) who were candidates for systemic therapy or phototherapy and had no history of prior treatment with biologic therapy.

Safety assessments as secondary endpoints were the incidence, type, and severity of adverse events (AEs) including adverse drug reactions (ADRs); and incidence and severity of injection site reactions (ISRs).

Population Demographics**Table 42. Safety Population Demographics**

	AVT02/E.U.- Humira/AVT02 N = 277	E.U.- Humira N = 273
Age		
18-65	270 (97.5)	263 (96.3)
66+	7 (2.5)	10 (3.7)

Sex		
M	189 (68.2)	165 (60.4)
F	88 (31.8)	108 (39.6)
Race		
White	277 (100)	272 (99.6)
Asian	0 (0)	1 (0.4)
Ethnicity		
Hispanic	3 (1.1)	2 (0.7)
Non-Hispanic	274 (98.9)	271 (99.3)

Source: FDA Reviewer

The safety population was primarily between ages 18-65 (96.3-97.5%), white (99.6-100%) and non-Hispanic (98.9-99.3%). The ratio of males to females was approximately 2:1.

Categorization of Adverse Events

Safety assessments included Adverse Events (AE), physical examination, vital signs (BP, P, T), 12-lead electrocardiograms, safety laboratory measurements (chemistry, hematology, urinalysis, and pregnancy tests), and injection site reactions.

The clinical study protocol defined an AE as “any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.” This reviewer found this description satisfactory.

Treatment Emergent Adverse Events (TEAE) were defined as AEs that started or worsened on or after the first dose of study post-randomization medication, and prior to the last dose of study post-randomization medication of the Switching Period, including any additional data submitted by the Applicant for the Extension Period.

Serious adverse events (SAE) were defined as any untoward medical occurrence which:

- Results in death.
- Is life-threatening (an event in which the patient was at risk of death at the time of the event).
- Requires inpatient hospitalization or prolongs existing hospitalization, or
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor]).

Adverse events of special interest (AESIs) were defined in the protocol as potential AEs (based on safety knowledge from other compounds in the same class) for prospective safety monitoring and included:

- a. Autoimmune disorders
- b. Demyelinating disorders
- c. Serious infections
- d. Malignancies and lymphoproliferative disorders
- e. Hypersensitivity reactions
- f. Hematological reactions
- g. Heart failure
- h. Liver enzyme elevations
- i. ISRs

AEs were categorized by the Applicant by intensity (mild/moderate/severe) and causal relationship to the study drug and coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1.

Safety Analyses

Safety analyses were performed on the results of a single study, Study AVT02-GL-302 (Alvopad-X). The Applicant submitted a complete dataset for all subjects through Week 28. The primary safety analysis for this BLA was based on a comparison of data between subjects in the Switching Arm (AVT02/E.U.-Humira/AVT02) and the non-switching (E.U.-Humira) Arm between Weeks 12 and 28 (the Switching Phase). Additional data for the Extension Phase (Weeks 28-52) was incomplete for the majority of subjects, thus the tables presented for the Extension Phase below are based solely on the Applicant's 120-day Safety Update Report. The 120-day Safety Update Report consisted of descriptive summaries and safety narratives on any deaths, other serious treatment-emergent adverse events (serious TEAEs), treatment-emergent adverse events of special interest (TEAESIs) with exclusion of injection site reactions (ISRs) and premature study discontinuation for safety grounds (TEAEDCs) that occurred in Study AVT02-GL-302 in Extension Phase (Weeks 28 to 52).

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Refer to Table 19, Demographics and Baseline Characteristics of the Per-Protocol Population.

Deaths

One death was reported during the Switching Phase and no deaths were reported during the Extension Phase. The subject was a 19 yo male in the Switching Arm (AVT02/E.U.-Humira/AVT02) who died due to accidental carbon monoxide poisoning experienced while in a closed car after an accident on Day 94. His last dose of study treatment was AVT02 40mg SC two days prior to the accident.

The investigator and the Applicant assessed the events of carbon monoxide poisoning and the resulting death as not related to the study drug.

Reviewer's comment:

I agree that carbon monoxide poisoning is not likely related to the study drug.

Serious Adverse Events

Table 43. SAEs during the Switching Phase (Weeks 12-28)

	AVT02/E.U.- Humira/AVT02 N = 277	E.U.- Humira N = 273
Total, n (%)	5 (1.8)	1 (0.4)
Carbon monoxide poisoning	1 (0.4)	0 (0)
Pancreatic carcinoma metastatic	1 (0.4)	0 (0)
Extrapulmonary tuberculosis	1 (0.4)	0 (0)
Skin ulcer	1 (0.4)	0 (0)
COVID-19 pneumonia	1 (0.4)	0 (0)
COVID-19	0 (0)	1 (0.4)

Source: FDA Reviewer

During the Switching Module, there were 5 (1.8%) SAEs in the switching arm and one SAE in the E.U.-Humira arm (0.4%). See Table 44. During the Extension Phase, the Applicant reported three additional SAEs of prostate cancer, erysipelas, and abnormal liver function test.

Dropouts and/or Discontinuations**Table 44. Discontinuations in the Safety Population during Switching Phase (Weeks 12-28)**

	AVT02/E.U.- Humira/AVT02 N = 277	E.U.- Humira N = 273
Total Discontinuations, n (%)	15 (5)	11 (4.1)
Death	1 (0.4)	0 (0)
Adverse Event	7 (2.5)	4 (1.5)
Withdrawal of consent	5 (1.8)	3 (1.1)
Lost to follow-up	1 (0.4)	0 (0)
PASI criteria not met	0 (0)	3 (1.1)
Other	1 (0.4)	1 (0.4)

Source: FDA Reviewer

There were few discontinuations during the Switching Phase, 15 (5%) in the Switching Arm and 11 (4.1%) in the Continuous Arm (see Table 5). The Switching Arm discontinuations included one death (carbon monoxide poisoning, described above) and 7 (2.5%) due to AEs, 4 of which were also SAEs.

Table 45. TEAEs that led to Study Discontinuation, Switching Phase (Weeks 12-28)

	AVT02/E.U.- Humira/AVT02 N = 277	E.U.- Humira N = 273
Total, n (%)	8 (2.9)	4 (1.5)
Hepatic enzyme increased	2 (0.7)	0 (0)
Skin ulcer	1 (0.4)	0 (0)
Urinary tract infection/extrapulmonary TB	1 (0.4)	0 (0)
Pancreatic carcinoma metastatic	1 (0.4)	0 (0)
Carbon monoxide poisoning	1 (0.4)	0 (0)
COVID-19 pneumonia	1 (0.4)	0 (0)
Blood disorder	1 (0.4)	0 (0)
Urticaria	0 (0)	2 (0.7)
COVID-19	0 (0)	1 (0.4)
Psoriasis	0 (0)	1 (0.4)

Source: FDA Reviewer

The additional AEs leading to study discontinuation were due to hepatic enzyme increases and blood disorder.

- Subject (b) (6) was a 42 yo white female with chronic plaque psoriasis who was randomized to the Switching Arm on (b) (6). On (b) (6) (SD 133), the subject's WBC count was 1.1g/L (ref range 3.5-10g/L), coded as "blood disorder". The study drug was withdrawn and the investigator assessed the AE as related to the study

drug. The subject discontinued the study on (b) (6) due to the AE. Although the WBC had improved to 3.5g/L, the subject was treated with oral methyluracil 500mg TID and oral ribonucleic acid 250mg BID for the decreased WBC.

- Subject (b) (6) was a 46 yo white female with chronic plaque psoriasis that had elevated hepatic enzymes at screening. The subject's hepatic enzymes returned to the reference range with treatment of phospholipids, oral timonacic, and oral liver therapy before starting the Lead-In Phase. With maintenance of oral timonacic and oral liver therapy, the hepatic enzymes were in the reference range during the Lead-In Phase. She was randomized to the Switching Arm on (b) (6). On the day of the first AVT02 dose, the subject's ALT was 175 IU/L (ref range 6.6-22.9), AST 236 (ref 11.8-25.7) and GGT 176 (ref 3.9-23.6). On (b) (6) her hepatic enzymes had decreased but were still elevated, and the study drug was withdrawn. The investigator assessed the AE as not related to the study drug.
- Subject (b) (6) was a 55 yo white male with chronic plaque psoriasis who was randomized to the Switching Arm on (b) (6). On (b) (6) (SD 79), the subject's ALT was 139 and the GGT was elevated to 1146 (and 1267 (b) (6)). The study drug was withdrawn and the subject discontinued the study on (b) (6) due to the AE. At discontinuation, the GGT was 120.

Table 46. Discontinuations in the Safety Population during the Extension Phase

	Total N=525
Total Discontinuations, n (%)	11 (2.1)
Adverse Event	6 (1.1)
Withdrawal of consent	4 (0.8)
Other	1 (0.2)

Source: Applicant, Safety Update from AVT02-GL-302

Table 47. TEAEs in the Safety Population Leading to Study Discontinuation, Extension Phase

	Total N=525
TEAEs, n (%)	6 (1.1)
<i>M. tuberculosis</i> complex test, positive	2 (0.4)
Psoriasis exacerbation	2 (0.4)
Post-acute COVID-19 syndrome	1 (0.2)
Prostate cancer	1 (0.2)

Source: Applicant, Safety Update from AVT02-GL-302

During the Extension Phase, the Applicant reported 11 discontinuations (2.1%), 6 of which were due to AEs. The narratives for the AEs of positive *M. tuberculosis* tests and prostate cancer are described in Section 7.1.3.

Treatment Emergent Adverse Events

During the Switching Phase, TEAEs reported were consistent with the known safety profile of U.S.-Humira. No new safety signals were identified, which supports the review conclusion that there is no demonstrated greater risk in terms of safety between the Switching Arm and the Continuous Arm of Study AVT02-GL-302 for subjects with moderate to severe plaque psoriasis.

Table 48. TEAEs >1% and AESIs in the Safety Population during the Switching Phase

Preferred Term, n (%)	AVT02/E.U.- Humira/AVT02 N = 277	E.U.-Humira N = 273
Hepatic enzyme increased ^a	25 (9)	16 (5.9)
Hematology test abnormal ^b	17 (6.1)	19 (7)
COVID-19 ^c	11 (4.3)	12 (4.4)
Nasopharyngitis ^d	11 (4)	7 (2.6)
Blood creatine phosphokinase increased	11 (4)	3 (1.1)
Hypercholesterolemia ^e	10 (3.6)	10 (3.7)
Injection site reaction	7 (2.5)	15 (5.5)
Serious infection ^f	6 (2.2)	3 (1.1)
Urinary tract infection	5 (1.8)	1 (0.4)

Source: FDA reviewer analysis

^a Hepatic enzyme increased includes ALT increased, GGT increased, AST increased, hepatic enzyme increased, LFT increased, drug-induced liver injury, and hypertransaminemia

^b Hematology test abnormal includes anemia, blood disorder, eosinophil count increased, hematology test abnormal, leukocytosis, leukopenia, lymphocyte count increased, lymphopenia, monocyte count increased, neutropenia, neutrophil count decreased, RBC decreased, thrombocytopenia, WBC decreased, and WBC increased

^c COVID-19 includes COVID-19, SARS-COV2 test positive, and post-acute COVID syndrome

^d Nasopharyngitis includes nasopharyngitis, oropharyngeal pain, pharyngitis, rhinorrhea, upper respiratory tract infection, and sinusitis

^e Hypercholesterolemia includes blood cholesterol increased, blood triglycerides increased, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, lipid metabolism disorder, and type V hyperlipidemia

^f Serious infection includes COVID pneumonia, extrapulmonary tuberculosis, *Haemophilis influenza*, influenza-like illness, and pneumonia

TEAEs by PT

In general, the frequencies of reported TEAEs for most PTs were balanced in each arm. In the Switching Arm compared to the Continuous Arm, TEAEs were reported more frequently for hepatic enzyme increased (9% vs 5.9%), nasopharyngitis (4% vs 2.6%), blood creatinine phosphokinase increased (4% vs 1.1%), serious infections (2.2% vs 1.1%), and urinary tract infection (1.8% vs 0.4%).

6.3.3. Additional Safety Evaluations

During the Switching Phase, no clinically meaningful changes were reported for clinical laboratory, vital signs, weights, physical examinations, ECG, pregnancy, and tuberculosis tests, in

any treatment arms; and no patterns were identified to suggest a new safety signal or an unexpected safety finding.

Clinical laboratory evaluations

Clinical laboratory measurements were generally stable from baseline measurements at randomization for the duration of the study, and similar between the Switching and Continuous Arms.

Vital signs and weight.

Systolic and diastolic blood pressure, pulse rate, temperature, and body weight group mean and median measurements were similar between treatment arms and stable for the duration of the study. No clinically meaningful changes from baseline were reported for any treatment arm.

Physical Examination

The physical examination findings were similar between treatment arms and stable for the duration of the study. No clinically meaningful changes from baseline were reported any treatment arm.

Electrocardiogram (ECG)

Abnormal, clinically significant ECG evaluations were infrequent and balanced between the study arms. The Applicant reported no subjects with an abnormal ECG, with most assessments remaining as they were assessed at baseline through the study with minimal changes.

Pregnancy

Pregnancy was an exclusion criterion for the study. No pregnancies were reported during Study AVT02-GL-302.

Tuberculosis

During the Switching Phase, there was one case of extrapulmonary tuberculosis (ovaries, omentum) reported by the Applicant.

- Subject (b) (6) was a 34 yo white female with chronic plaque psoriasis was randomized to the Switching Arm on (b) (6) (SD 77). On (b) (6) (SD 168), she was diagnosed with a urinary tract infection of moderate severity. The study drug was subsequently withdrawn, and the subject discontinued the study on (b) (6). Concurrently, the subject was suspected to have ovarian cancer. A CT with contrast of the pelvic organs, thorax, and abdominal cavity was performed on (b) (6) as well as a pleural puncture and laparoscopic biopsy. Over the course of (b) (6), the diagnosis was confirmed to be extrapulmonary tuberculosis. The subject confirmed that she was taking anti-tuberculosis therapy (non-specified) in a follow-up phone call. The AE of extrapulmonary TB was considered by the Applicant to be expected and possibly related to adalimumab.

During the Extension Phase, there were two cases of *Mycobacterium tuberculosis* complex test positive reported by the Applicant.

- Subject (b) (6) was a 64 yo male with chronic plaque psoriasis was randomized to the Switching Arm on SD 78. She then started the Extension Phase with AVT02 40mg SC every other week on SD 189. On (b) (6) (SD 190), the subject had a positive

Mycobacterium tuberculosis complex test. The intensity of the event was reported as mild and not requiring any additional treatment. Although the event assessed as not related to the study drug, the subject discontinued the study on (b) (6) (SD198). A follow-up chest x-ray performed on (b) (6) was negative for TB.

- Subject (b) (6) was a female in her twenties with chronic plaque psoriasis was randomized to the Switching Arm on SD 78. She then started the Extension Phase with AVT02 40mg SC every other week starting from Week 28 (~SD 190). On (b) (6) (SD 190), the subject had a positive *Mycobacterium tuberculosis* complex test. A follow-up chest x-ray performed on (b) (6) was negative for TB. The intensity of the event was reported as mild and not requiring any additional treatment. Although the event was assessed as not related to the study drug, the study drug was withdrawn.

Malignancy

There were two malignancies reported during AVT02-GL-302, one during the Switching Phase and one during the Extension Phase.

- Subject (b) (6) was a 68 yo female with chronic plaque psoriasis who was randomized to the Switching Arm for the Switching Phase. She was diagnosed on (b) (6) (SD 164) with metastatic pancreatic carcinoma and the study drug was withdrawn. The subject withdrew from the study on (b) (6) due to the metastatic carcinoma and was awaiting an oncology consult. The Applicant assessed the AE as not related to the study drug due to the latency period of about 10 years between the start of pancreatic carcinogenesis and symptomatic disease.
- Subject (b) (6) was a 64 yo male with chronic plaque psoriasis who was randomized to the Switching Arm for the Switching Phase. He was enrolled in the Extension Phase on SD 189. On (b) (6) (SD 301), an SAE of prostate cancer was reported and considered serious. The Applicant assessed the AE as not related to the study drug. The subject started leuporelin acetate 7.5mg QD on SD 306. The study drug was withdrawn and the subject discontinued the study on SD 362 (b) (6). The AE was ongoing at the time of study discontinuation.

Overall Safety Conclusions

The size of the safety database and the duration of Study AVT02-GL-302 appear adequate to support the Applicant's assertion that the study results demonstrated "no clinically meaningful differences" in the safety profiles between the Continuous Arm and the Switching Arm during the post-randomization Switching Phase (through 28 weeks). During the Switching Phase, the numbers of events were small and are reasonably balanced between the study arms, and the safety experience was sufficiently similar to the historical safety experience with U.S.-Humira to afford valid comparisons. None of the safety events observed impact the determination of interchangeability under review in this application. We conclude that the safety results from AVT02-GL-302 support a demonstration that the risk in terms of safety of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such alternation or switch.

6.4. Clinical Conclusions on Immunogenicity

This clinical reviewer agrees with the Clinical Pharmacology reviewer's assessment of immunogenicity as described in Section 5.4.1.

Based on the ADA status and NAb status of subjects at Week 12 (pre-randomization) in the Switching and Continuous Arms of Study AVT02-GL-302, the incidence of the following TEAEs (hypersensitivity reaction, anaphylactic reaction, serious infection, DILI, injection site reaction) appear to be comparable in subjects with ADA+ status between the Switching Arm and Continuous Arm. Similarly, the incidence of the above TEAEs appears comparable in subjects with NAb status between the Switching Arm and Continuous Arm.

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6.5. Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant provided sufficient justification that AVT02 will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which U.S.-Humira has been previously approved. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

Quality attributes

The data and information included in BLA 761205 supported a demonstration that AVT02 is highly similar to U.S.-Humira notwithstanding minor differences in the clinically inactive components. Minor differences in certain critical quality attributes evaluated in the comparative analytical assessment (e.g., N-linked oligosaccharides (high mannose, glycation, afucosylation and sialylation) and charge variants (CEX assay)) were considered insignificant for the mode of action and biological function, and they were not considered as likely having an effect on safety, efficacy, or immunogenicity, based on the existing knowledge of the clinical relevance of these differences in attributes. As such, these identified minor analytical differences should not preclude the conclusion of establishing interchangeability between AVT02 and U.S.-Humira for any given patient.

Mechanism of action

AVT02 was shown in BLA 761205 to utilize the same mechanism or mechanisms of action, to the extent such mechanism or mechanisms of action are known, for U.S.-Humira in each condition of use for which AVT02 was seeking licensure as biosimilar to U.S.-Humira: RA, JIA, AS, PsA, PsO, UC, and CD.

For these conditions of use, the primary mechanism of action of adalimumab is direct binding of TNF- α , resulting in blockade of TNF- α receptor-mediated activities. Adalimumab blocks both TNFR1 and TNFR2 receptors by binding both soluble(s) and transmembrane(tm) TNF- α . This mechanism involves the Fab (antigen binding) region and is known as the mechanism for the treatment of RA, JIA, AS, PsA, PsO.

For IBD indications such as UC and CD, in addition to Fab (antigen binding) region which directly relates the binding of TNF- α , Fc (constant) region is also likely involved in the mechanism of action. TNF- α plays a central role in the pathology of IBD. TNF- α inhibition plays an important role in treating these diseases as evidenced by the efficacy of the TNF- α inhibitor class of medications in treating IBD. In addition, adalimumab has mechanisms of action involving the Fc region of the antibody which are thought to be plausible mechanisms involved in the efficacy of adalimumab for the treatment of IBD.

Pediatric UC in patients 5 years and older, Hidradenitis Suppurativa (HS) and Uveitis (UV) are still protected by orphan drug exclusivity. From the mechanism of action perspective, in comparison to adult IBD (CD and UC), the pharmacodynamic effects are unlikely to be uniquely active in the pediatric IBD indications. Adalimumab specifically targets and blocks TNF- α which contributes to the inflammation that causes the abscesses, inflammatory nodules, and draining fistulas in HS. TNF- α is also known to drive chronic inflammation of uveitis and it is overexpressed in the serum and ocular fluid in patients with uveitis. Blockage of TNF- α is associated with a reduction in the re-activation of inflammatory ocular disease.

As such, soluble and transmembrane TNF- α binding, blocking of TNFR1 and TNFR2 activity, and the potential Fc region mediated mechanisms of action are similar between AVT02 and U.S.-Humira.

The mechanisms of action of adalimumab for establishing biosimilarity are also relevant to establish interchangeability in any given patient.

Pharmacokinetics (PK)

As described in this Section above under “Quality Attributes”, in the BLA 761205, AVT02 was demonstrated to be highly similar to U.S.-Humira notwithstanding minor differences in the clinically inactive components. Importantly, there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between AVT02 and U.S.-Humira in any given patient. PK similarity was concluded between AVT02 and U.S.-Humira as demonstrated in the BLA 761205.

Immunogenicity

The quality attributes expected to impact immunogenicity are similar between AVT02 and U.S.-Humira. AVT02 has an identical primary amino acid sequence compared with U.S.-Humira. Other CQAs which define secondary and tertiary 3-dimensional structures like glycosylation are highly similar. The data from the 3-way PK similarity study AVT02-GL-101 in healthy volunteers and the comparative clinical study AVT02-GL-301 and switching study AVT02-GL-302 showed that the immunogenicity profiles, time course of ADA development, the percentage of patients with positive ADA response, the titer of ADA responses, and the percentage of patients with NAb response were comparable for AVT02 and U.S.-Humira. These data show that AVT02 and U.S.-Humira do not differ with respect to immunodominant epitopes, indicating that it is not likely to have differential immunogenicity response in any given patient.

Toxicity profile

The primary assessment of adverse events was completed in the review of BLA 761205. In controlled clinical studies of U.S.-Humira, as described in the approved labeling, the types of adverse events and their rates were similar across indications. Given the similar product quality attributes, PK, and immunogenicity as demonstrated in the BLA 761205 review, there is no reason to expect that the safety profile of AVT02 in any given patient would be different from that observed in U.S.-Humira.

The Applicant provided sufficient scientific justification (based on the quality attributes, mechanism of action, PK, immunogenicity and toxicity profile), and sufficient data and information, including clinical conclusion that AVT02 “can be expected to produce the same clinical result as the reference product in any given patient” for each of the following indications for which U.S.-Humira has been previously licensed: RA, JIA, PsA, AS, PsO, CD, UC, HS, and UV.

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6.6. Extrapolation

The Applicant is seeking licensure of AVT02 as an interchangeable for the following indications for which U.S.-Humira has been previously licensed: RA, PsA, AS, PsO, JIA in patients 2 years

of age and older, CD in adults and pediatric patients 6 years of age and older, and UC in adult patients.

The Applicant submitted data and information in BLA 761205 demonstrating that AVT02 is highly similar to U.S.-Humira notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between AVT02 and U.S.-Humira in patients with PsO. In the review of BLA 761205, it was concluded that the totality of the data supported a demonstration of biosimilarity between AVT02 and U.S.-Humira for PsO as well as for the non-studied indications including PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients, JIA in patients 2 years of age and older, and RA.

The Applicant submitted data and information in this BLA demonstrating that AVT02 can be expected to produce the same clinical result as U.S.-Humira in any given patient (see Section 6.5), and that the risk in terms of safety or diminished efficacy of alternating or switching between use of AVT02 and U.S.-Humira is not greater than the use of U.S.-Humira without such switch or alternation in patients with moderate to severe chronic plaque psoriasis (see Sections 5 and 6).

The Applicant is seeking licensure of AVT02 as an interchangeable for the following indications for which U.S.-Humira has been previously licensed: RA, PsA, AS, PsO, JIA in patients 2 years of age and older, CD in adults and pediatric patients 6 years of age and older, and UC in adult patients. Note that while the Applicant has also submitted acceptable extrapolation justification for pediatric UC patients 5 years of age and older, UV, and HS, FDA has determined that U.S.-Humira is eligible for orphan drug exclusivity for UC in pediatric patients 5 years of age and older, UV, and HS. FDA therefore cannot license AVT02 for these three indications prior to the expiration of the orphan drug exclusivity(ies).

The Applicant provided a scientific justification for extrapolating data and information to support licensure of AVT02 as an interchangeable for each indication for which licensure is sought and for which U.S.-Humira has been previously approved. See Section 6.5. The scientific justification for extrapolation of data and information submitted in the application is adequate to support licensure of AVT02 as an interchangeable for the indications for which licensure is sought and for which U.S.-Humira has been previously approved. Therefore, we conclude that the Applicant has provided adequate data and information to support licensure of AVT02 as an interchangeable for the proposed indications: RA, PsA, AS, CD in adults and pediatric patients 6 years of age and older, UC in adult patients and JIA 2 years of age and older.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's nonproprietary name, adalimumab-ryvk was found to be conditionally accepted by the Agency (DMEPA review dated May 25, 2021).

7.2. Proprietary Name

The Applicant's proposed proprietary name for AVT02, Simlandi, has been conditionally approved. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded that the name is acceptable (DMEPA review dated December 2, 2020).

7.3. Other Labeling Recommendations

In view of the recommendation for a Complete Response, the labeling review was deferred until the next review cycle.

Authors:

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8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant has adequately disclosed financial interests and arrangements with the investigators and sub investigators who participated in covered clinical studies for AVT02.

Form 3454 is noted (Module 1.3.4, SDN 104) and verifies that no compensation is linked to study outcome. The Principal Investigators and sub investigators did not disclose any proprietary interest to the Applicant.

The covered clinical studies as defined in 21 CFR 54.2 (e) was Study AVT02-GL-302. Refer to Sec. 14.2 of this review [Financial disclosure].

Author:

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Clinical Pharmacology Team Leader/CDTL

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this application, as it was determined that there were no issues where the Agency needed input from the Committee.

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10. Pediatrics

In view of the recommendation for a Complete Response, any recommendations for PREA post-marketing requirement(s) were deferred until the next review cycle.

Authors:

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

Not applicable.

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12. Comments to Applicant

The regulatory action for this BLA is Complete Response for the following deficiency.

DEFICIENCY

Facility Inspection:

Following inspection of the Alvotek hf, Reykjavik, Iceland (FEI: 3013702557) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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Clinical Pharmacology Team Leader/CDTL

Nikolay Nikolov, M.D.

Division Director, Division of Rheumatology and Transplant Medicine

13. Appendices

14.1. References

Shein-Chung Chow, Jun Shao, Hansheng Wang, Yuliya Lokhnygina (2018). Sample Size Calculations in Clinical Research. Third Edition. CRC Press.

FDA Guidance on Considerations in Demonstrating Interchangeability With a Reference Product, May 2019. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry>

Volker H. Franz (2007). Ratios: A Short Guide to Confidence Limits and Proper Use. <https://doi.org/10.48550/arXiv.0710.2024>

Gary O. Zerbe (1978). On Fieller's Theorem and the General Linear Model. The American Statistician, Vol. 32, No. 5, pages 103-105.

14.2. Financial Disclosure

Table 49. Financial Disclosure of Covered Clinical Study AVT02-GL-302

Was a list of clinical investigators provided:	Yes x	No ☐ (Request list from Applicant)
Total number of investigators identified: 88		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): n/a Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

14.3. Clinical Pharmacology Appendices

14.3.1. Summary of Bioanalytical Method Validation and Performance Pharmacokinetics

For the switching study (Study AVT02-GL-302), AVT02 and E.U.-Humira concentrations in human serum measured using a validated enzyme linked immunosorbent assay (ELISA) were suitable for assessment of PK similarity. The ELISA method (N-A-IMM-19-212) was validated (b) (4). The summary of the bioanalytical method is given in Table 50.

Table 50. Summary of the bioanalytical method validation update for measurement of AVT02 and E.U.-Humira in human serum

Bioanalytical method validation report name, amendments, and hyperlinks	Report N-A-IMM-19-152		
	Report Amendment 01 of N-A-IMM-19-152		
Method description	A validated sandwich format on 96 well plates using commercial anti-adalimumab Fab fragment as capture and anti-adalimumab IgG coupled to ECL-Sulfo-Tag as detection.		
Materials used for standard calibration curve and concentration	AVT02, lot# AEG-R19036, expiration date 05 May 2021		
Validated assay range	7.5 – 360 ng/mL (at MRD: 1.875 - 90.0 ng/mL)		
Material used for quality controls (QCs) and concentration	AVT02, lot# AEG-R19036, expiration date 05 May 2021 EU-Humira, lot# 93453XH05, expiration date 31 Aug 2020 US-Humira, lot# 1104991, expiration date 30 April 2020		
Minimum required dilutions (MRDs)	1:4 (25% matrix concentration)		
Source and lot of reagents	See validation report		
Regression model and weighting	4-PL regression 1/y2		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Table 9 of report N-A-IMM-19-152
	Cumulative accuracy (%bias) from LLOQ to ULOQ AVT02	-4.9 to 9.9%	Table 39 of report N-A-IMM-19-152
	Cumulative precision (%CV) from LLOQ to ULOQ AVT02	≤ 3.2%	Table 39 of report N-A-IMM-19-152
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs		Table 1 of report N-A-IMM-19-152
	QCs for product AVT02 (360, 270, 80, 20, 7.5 ng/mL)	-15.3 to -5.0%	
	QCs for product EU-Humira (360, 270, 80, 20, 7.5 ng/mL)	-12.5 to 15%	
	QCs for product US-Humira (360, 270, 80, 20, 7.5 ng/mL)	-16.5 to -1.3%	Table 1 of report N-A-IMM-19-152
	Inter-batch %CV		
	QCs for product AVT02 (360, 270, 80, 20, 7.5 ng/mL)	≤ 7.7%	
	QCs for product EU-Humira (360, 270, 80, 20, 7.5 ng/mL)	≤ 12.1%	
	QCs for product US-Humira (360, 270, 80, 20, 7.5 ng/mL)	≤ 11.2%	

	<u>Total Error (TE)</u> QCs for product AVT02 (360, 270, 80, 20, 7.5 ng/mL) $\leq 19.2\%$ QCs for product EU-Humira (360, 270, 80, 20, 7.5 ng/mL) $\leq 20.8\%$ QCs for product US-Humira (360, 270, 80, 20, 7.5 ng/mL) $\leq 27.8\%$	Table 1 of report N-A-IMM-19-152
Selectivity & matrix effect	For AVT02: 10 lots tested, 90% of analyzed samples were acceptable For EU-Humira: 10 lots tested, 100% of analyzed samples were acceptable For US-Humira: 10 lots tested, 100% of analyzed samples were acceptable	Table 1 of report N-A-IMM-19-152
Interference & specificity	Impact of anti-AVT02 antibodies (ADA) on PK assay performance tested For AVT02: two concentrations tested (360, 7.5 ng/mL): At 360 ng/mL: no interference with 2.5, 25 and 250 ng/mL anti-AVT02 ab At 7.5 ng/mL: no interference with 2.5 and 25 ng/mL anti-AVT02 ab, interference with 250 ng/mL anti-AVT02 ab For EU-Humira: two concentrations tested (360, 7.5 ng/mL): At 360 ng/mL: no interference with 2.5, 25 and 250 ng/mL anti-AVT02 ab At 7.5 ng/mL: no interference with 2.5 and 25 ng/mL anti-AVT02 ab, interference with 250 ng/mL anti-AVT02 ab For US-Humira: two concentrations tested (360, 7.5 ng/mL): At 360 ng/mL: no interference with 2.5, 25 and 250 ng/mL anti-AVT02 ab At 7.5 ng/mL: no interference with 2.5 and 25 ng/mL anti-AVT02 ab, interference with 250 ng/mL anti-AVT02 ab	Table 1 of report N-A-IMM-19-152
Hemolysis effect	For AVT02: 2 lots tested, both tested samples $\leq 20\%$ accuracy For EU-Humira: 2 lots tested, both tested samples $\leq 20\%$ accuracy For US-Humira: 2 lots tested, both tested samples $\leq 20\%$ accuracy	Table 1 of report N-A-IMM-19-152
Lipemic effect	For AVT02: 2 lots tested, both tested samples $\leq 20\%$ accuracy For EU-Humira: 2 lots tested, both tested samples $\leq 20\%$ accuracy For US-Humira: 2 lots tested, both tested samples $\leq 20\%$ accuracy	Table 1 of report N-A-IMM-19-152
Dilution linearity & hook effect	Start concentration: 40000 ng/mL; 4 dilutions tested (1:4, 1:600, 1:2000; 1:8000); 5 sets measured per dilution For AVT02: bias between -16.9 and 14.6% (1 of 5 tested sets was out of range (bias at 22.0%); no deviation) For EU-Humira: bias between -4.7 and 17.2% (2 of 5 tested sets were out of range (at DF600: bias 24.0% and 31.9%); no deviation)	Table 1 of report N-A-IMM-19-152

	For US-Humira: bias between -8.6 and 19.5% (2 of 5 tested sets were out of range (1 set at DF600 and 1 set at DF2000: bias 21.0% and 22.9%); no deviation)	
Bench-top/process stability	Not validated in this partial validation; stability already validated in N-A-IMM-19-136	NA
Freeze-Thaw stability	Not validated in this partial validation; stability already validated in N-A-IMM-19-136	NA
Long-term storage	Not validated in this partial validation; stability already validated in N-A-IMM-19-136	NA
Parallelism	Performed in clinical Study AVT02-GL-301; 2 samples analyzed; mean CV% 3.4 and 8.0; parallelism passed	Table 19 of report N-A-IMM-19-153
Carry over	NA	NA
Method performance in Study AVT02-GL-301 (Bioanalytical Report N-A-IMM-19-153)		
Assay passing rate	145 runs met all applicable acceptance criteria. 6 runs failed due to unacceptable Cal and QC performance. Within the qualifying runs 3 out of 8 did not fulfill acceptance criteria due to unacceptable QC performance. 94% of the assays passed.	Table 14 of report N-A-IMM-19-153
Standard curve performance	Cumulative bias range: -5.3 to 7.7% Cumulative precision: $\leq 7.0\%$ CV	Table 20 of report N-A-IMM-19-153
QC performance	Cumulative bias range: -8.0 to 0.4% Cumulative precision: $\leq 11.6\%$ CV TE: $\leq 17.2\%$	Table 21 of report N-A-IMM-19-153
Method reproducibility	A total of 207 samples were selected for ISR. 169 (81.6%) of the 207 selected samples were within $\pm 30.0\%$ deviation.	Table 18 of report N-A-IMM-19-153
Study sample analysis/ stability	All samples were stored at $-75^{\circ}\text{C} \pm 15^{\circ}\text{C}$ upon arrival and analyzed within one year after sample collection (less than 5 backup samples were stored up to 454 days). The documented stability data for this analyte is 24 months (752 days) at $-75^{\circ}\text{C} \pm 15^{\circ}\text{C}$ (long-term stability was reported in N-A-IMM-19-136 Amendment 01, 02 and 03).	Executive summary of report N-A-IMM-19-153
Method performance in Study AVT02-GL-302 (Bioanalytical Intermediate Report N-A-IMM-20-149)		
Assay passing rate	353 runs met all applicable acceptance criteria. 49 runs failed due to unacceptable Cal and QC performance. Within the qualifying runs 4 out of 15 did not fulfill acceptance criteria due to unacceptable QC performance. 87.8% of the assays passed.	Table 14 of report N-A-IMM-20-149
Standard curve performance	Cumulative bias range: -4.0 to 5.7% Cumulative precision: $\leq 7.1\%$ CV	Table 18 of report N-A-IMM-20-149
QC performance	Cumulative bias range: -8.3 to -0.7% Cumulative precision: $\leq 11.8\%$ CV TE: $\leq 17.9\%$	Table 19 of report N-A-IMM-20-149
Method reproducibility	No ISR performed.	NA

Study sample analysis/ stability	All samples were stored at -75°C±15°C upon arrival and analyzed within one year after sample collection. The documented stability data for this analyte is 24 months (752 days) at -75°C±15°C (long-term stability was reported in N-A-IMM-19-136 Amendment 01, 02 and 03).	Executive summary of report N-A-IMM-20-149
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Source: Report [N-A-IMM-19-152](#), Report [Amendment 01 of N-A-IMM-19-152](#)

ab = antibody; ADA = antidrug antibody; CV = coefficient of variation; ECL = electrochemiluminescence; Fab = antigen binding fragment; IgG = immunoglobulin G; ISR = incurred sample re-analysis; LLOQ = lower limit of quantitation; MRD = minimum required dilution; NA = not applicable; PK = pharmacokinetics; PsO = plaque psoriasis; QC = quality control; TE = total error; ULOQ = upper limit of quantitation

Source: Table 10 of 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

12.3.2. Pharmacometric Sensitivity Assessment

Per the Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry (May 2019), for subcutaneous (SC) studies, C_{max} and AUC_{tau} will be considered as co-primary study endpoints. The log-transformed AUC_{tau} and C_{max} data should be statistically analyzed using an average equivalence statistical approach. The 90% confidence interval for the geometric mean ratio (GMR) of AUC_{tau} and C_{max} between the proposed interchangeable product and the reference product should be within 80% to 125%.

However, in some cases, the actual distribution of the primary endpoint data is NOT a log-normal distribution due to the anti-drug antibody (ADA) effect. Therefore, a statistical analysis method based on a Fieller's theory was proposed, in which arithmetic mean and arithmetic mean ratio (AMR) instead of geometric mean and GMR were used for the assessment of the primary endpoints AUC_{tau} and C_{max} . The analysis of the primary endpoints involved calculating the 90% confidence intervals (CIs) for the AMRs. A conclusion of PK similarity was made based on the 90% CIs being within the range 80% to 125% for AUC_{tau} and C_{max} .

Meanwhile, covariates in ANCOVA models also play an important role in the PK similarity assessment. Therefore, sensitivity analyses were further performed for AMR, GMR methods and covariate inclusion in ANCOVA models.

Sensitivity assessment of GMR and AMR methods

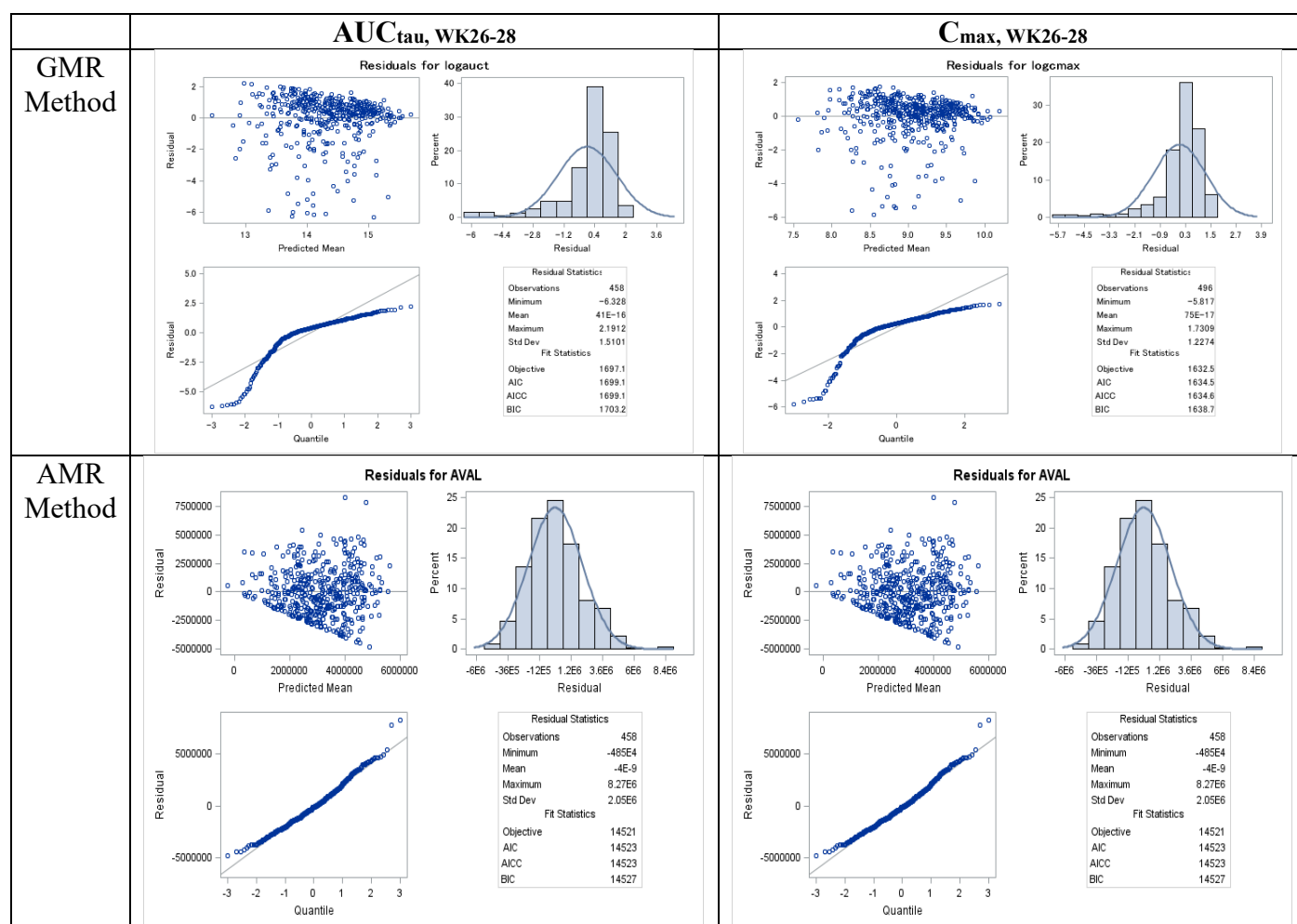
ANCOVA models were assessed with GMR and AMR methods with prespecified randomization stratification factor (Week 12 BMI and age). The ANCOVA model of an GMR method is $\log(AUC_{tau, WK26-28} \text{ or } C_{max, WK26-28}) \sim \text{trt} + \text{BMI} + \text{age}$, and the ANCOVA model of an AMR method is $AUC_{tau, WK26-28} \text{ or } C_{max, WK26-28} \sim \text{trt} + \text{BMI} + \text{age}$. The assessment results showed that the AMR method can pass PK similarity assessment while the GMR method can NOT pass the PK similarity assessment, shown in Table 51. It is consistent with residuals quantile plots of exposures shown in

Figure 9, in which the residual-quantile plots showed that the AMR method describes the data better than the GMR method.

Table 51. ANCOVA assessment of GMR and AMR methods

PK parameters	Assessment			
	Geometric mean Power (26.5)		Arithmetic mean Power (92.7)	
	Ratio %	CI	Ratio %	CI
AUC _{tau} , WK26-28	117.1	92.7 – 147.8	101.7	91.4 - 112
C _{max} , WK26-28	121.1	100.9 – 145.3	108.1	98.3 - 117.9

Source: FDA reviewer analysis

Figure 9. Diagnostic plots of AUC_{tau}, WK26-28 and C_{max}, WK26-28 by GMR and AMR methods

Source: FDA reviewer analysis

Sensitivity assessment of covariates

Proper inclusion of covariates in ANCOVA models is important for the PK similarity assessment in ANCOVA models. Therefore, logWT (log(body weight)), logTITER (log(titer)), C_{trough} (trough concentration), age, BMI (body mass index), logALB (log(albumin)) were selected based on the correlation indexes between exposures and covariates. The full model was evaluated by backward elimination methods shown in Table 52, in which a covariate will be deleted if its P value is the largest and over 0.05. C_{trough}, logWT, logTITER and age were identified to be statistically significant covariates² in the final model, by which PK similarity was assessed, shown in Table 53. The PK similarity evaluation is consistent with Applicant's result. Therefore, the decision will not change based on the sensitivity analysis.

Table 52. Model selection of AMR method

Model	Covariates	P value (AUC _{tau, WK26-28})	P value (C _{max, WK26-28})
Full model AUC _{tau, WK26-28} or C _{max, WK26-28} ~ trt + BMI + age + logWT + logTITER + C _{trough} + ADA +logALB	logTITER	0.01	0.013
	logWT	0.007	0.0036
	C _{trough}	<0.001	<0.001
	ADA	0.073	0.44
	BMI	0.96	0.678
	logALB	0.056	0.13
	age	0.0002	<0.001
Model without BMI AUC _{tau, WK26-28} or C _{max, WK26-28} ~ trt + age + logWT + logTITER + C _{trough} + ADA +logALB	logTITER	0.0099	0.013
	logWT	<0.001	<0.001
	C _{trough}	<0.001	<0.001
	ADA	0.073	0.44
	logALB	0.054	0.108
	age	0.0001	<0.001
Model without BMI, ADA AUC _{tau, WK26-28} or C _{max, WK26-28} ~ trt + logWT + logTITER + C _{trough} + age + logALB	logTITER	<.0001	<.0001
	logWT	<0.001	<0.001
	C _{trough}	<0.001	<0.001
	logALB	0.0578	0.11
	age	<.0001	<.0001
Final model AUC _{tau, WK26-28} or C _{max, WK26-28} ~ trt + logWT + logTITER + C _{trough} + age	logTITER	<.0001	<.0001
	logWT	<0.001	<0.001
	C _{trough}	<0.001	<0.001
	age	0.0003	<0.001

Source: FDA reviewer analysis

Table 53. Final model assessment

PK parameters	Assessment
---------------	------------

² All the covariates' values were obtained before randomization.

	Arithmetic mean	
	Ratio %	90% CI
AUC _{tau, WK26-28}	96.7	89.9 – 104.0
C _{max, WK26-28}	103.4	96.4 – 111.0

Source: FDA reviewer analysis

Sensitivity tests for covariate inclusion on study power were further performed based on the bootstrapping of the control arm shown in Table 54. When covariates are BMI and age, the power of the AMR method is 93, and if more statistically significant covariates were added, the power will become larger. The trend is consistent for GMR methods, despite the much lower powers.

Table 54. Covariates evaluation by power^a

Data	Covariates	Power (AUC _{tau, WK26-28} or C _{max, WK26-28})
AMR	BMI AGE	93 (94.3, 98.5)
AMR	logWT logTITER C _{trough} age	99.9 (99.9, 100)
GMR	BMI AGE	0.2 (1, 23.6)
GMR	logWT logTITER logC _{trough} age	17.3 (29.7, 56.8)

a: The power method is to generate 1000 datasets from **unswitched** arm, by which ratio and 90% CI of normal or log scale is assessed. If 90% CI is in [80.00, 125.00], it was set to be 1, otherwise it is set to be 0. Power is counted as the percentage of events of 90% CI in [80.00, 125.00].

Source: FDA reviewer analysis

Sensitivity assessment of missing data and imputation strategy

As listed in section 6, the Applicant excluded 38 subjects in the primary PK analysis due to the undeterminable terminal phase. While AUC_{tau} was not calculable in these subjects, AUC_{last} could be a good proximate for these missing AUC_{tau}. Therefore, the reviewer conducted an independent analysis for AUC_{tau} and AUC_{last} using Fieller's method with AMR to evaluate the impact of missing data on the overall conclusion of PK similarity. The AMRs and 90% CIs of AUC_{tau} and AUC_{last} are given in Table 55 below. The conclusion of PK similarity remained unchanged based on the AMR and 90%CI, therefore, without imputing the missing AUC_{tau}, the Applicant's approach is not expected to change the overall conclusion for PK similarity.

Table 55. Comparison of AMR and 90% CI between AUC_{tau} and AUC_{last}

PK Parameter	Arithmetic LSMean		AMR* (90%CI)
	Switching Arm	Continuous Arm	Switching Arm vs. Continuous Arm

AUC _{tau, wk26-28} (ng·hr/mL)	3154426.3 (n=232)	3102444.2 (n=226)	101.7 (91.4, 112.0)
AUC _{last, wk26-28} (ng·hr/mL)	3163662 (n=246)	3101803 (n=250)	103.2 (93.6, 112.7)

*Presented as percent.

LS: Least squares

AMR: arithmetic mean ratio

n=number of patients contributing to the analysis

Results were obtained using ANCOVA model applied to data in the original scale, with terms for treatment and randomization stratification factor (BMI and age).

Source: Reviewer's analysis

Similarly, the Applicant excluded 26 subjects in the primary PK analysis due to lack of PK samples above LLOQ. The reviewer imputed the below LLOQ PK samples for these excluded subjects with ½ LLOQ of 3.75 ng/mL and derived the AUC_{tau} and C_{max} at Week 26 to 28. The reviewer's analysis results are given in Table 56 below. With the imputation for LLOQ PK samples, the AMR and 90%CI remained similar to the Applicant's analysis without any imputation. Therefore, the exclusion of missing data due to the LLOQ is acceptable and should not change the overall conclusion for PK similarity in this study.

Table 56. Comparison of AMR and 90% CI with or without the imputation of missing AUC_{tau} and C_{max} with ½ LLOQ

Imputation with ½ LLOQ	PK Parameter	Arithmetic LSMean		AMR* (90%CI)
		Switching Arm	Continuous Arm	Switching Arm vs. Continuous Arm
No	AUC _{tau, wk26-28} (ng·hr/mL)	3154426.3 (n=232)	3102444.2 (n=226)	101.7 (91.4, 112.0)
Yes	AUC _{tau, wk26-28} (ng·hr/mL)	2972416 (n=247)	2948630 (n=237)	99.7 (89.6, 109.8)
No	C _{max, wk26-28} (ng/mL)	13986.7 (n=246)	12935.8 (n=250)	108.1 (98.3, 117.9)
Yes	C _{max, wk26-28} (ng/mL)	13114 (n=261)	12460 (n=261)	105.7 (96.0, 115.4)

*Presented as percent.

LS: Least squares

AMR: arithmetic mean ratio

n=number of patients contributing to the analysis

Results were obtained using ANCOVA model applied to data in the original scale, with terms for treatment and randomization stratification factor (BMI and age).

Pharmacokinetic parameters for primary PK endpoint were not estimated for some subjects in per protocol set.

Source: Reviewer's analysis

With the imputation of AUC_{tau} and C_{max} for all the missing data except for Subject (b) (6) as mentioned above, the AMR and 90% CI are given in Table 57 below. The overall conclusion for PK similarity did not change.

Table 57. AMR and 90% CI with the imputation of all the missing data except for Subject (b) (6)

PK Parameter	Arithmetic LSMean		AMR* (90%CI)
	Switching Arm	Continuous Arm	Switching Arm vs. Continuous Arm
AUC _{tau, wk26-28} (ng·hr/mL)	2978842 (n=261)	2980308 (n=261)	100.8 (91.1, 110.5)
C _{max, wk26-28} (ng/mL)	13114 (n=261)	12460 (n=261)	105.7 (96.0, 115.4)

*Presented as percent.

LS: Least squares

AMR: arithmetic mean ratio

n=number of patients contributing to the analysis

Results were obtained using ANCOVA model applied to data in the original scale, with terms for treatment and randomization stratification factor (BMI and age).

Pharmacokinetic parameters for primary PK endpoint were not estimated for some subjects in per protocol set.

Source: Reviewer's analysis

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(Pharmacometrics)**14. Statistical Appendices****14.1.1. Simulation Studies Exploring Original Scale and Log Transformation Based Analyses**

Suppose we have the following.

- $(Y_{11}, X_{11}), \dots, (Y_{1n_1}, X_{1n_1}) \sim iid \sim (Y_1, X_1)$
- $(Y_{21}, X_{21}), \dots, (Y_{2n_2}, X_{2n_2}) \sim iid \sim (Y_2, X_2)$
- $(Y_{11}, X_{11}), \dots, (Y_{1n_1}, X_{1n_1}), (Y_{21}, X_{21}), \dots, (Y_{2n_2}, X_{2n_2})$ are independently distributed
- Y_1 and Y_2 are positive random variables.
- X_1 and X_2 are identically distributed $p \times 1$ dimensional random vectors.
- Assume all moments and quantities described below exist and are finite.

In this setup, Y_{ij} is the primary outcome variable (AUC_{tau, w26-28} or C_{max, w26-28}) for subject j in treatment group i (AVT02/Humira/AVT02 group or E.U.-Humira group during switching module)

and $\mathbf{X}_{ij}$ is a vector of baseline covariates (BMI before randomization and age) for subject j in treatment group i , $i = 1, 2, j = 1, \dots, n_i$. Define:

$$\theta_1 = \frac{E(Y_1)}{E(Y_2)}$$

$$\theta_2 = \frac{\exp[E(\log(Y_1))]}{\exp[E(\log(Y_2))]}$$

If $\log(Y_1) \sim N(\mu_1, \sigma^2)$ and $\log(Y_2) \sim N(\mu_2, \sigma^2)$ then

$$\theta_1 = \frac{E(Y_1)}{E(Y_2)} = \frac{\exp[\mu_1 + \sigma^2/2]}{\exp[\mu_2 + \sigma^2/2]} = \frac{\exp[\mu_1]}{\exp[\mu_2]} \frac{\exp[\sigma^2/2]}{\exp[\sigma^2/2]} = \frac{\exp[\mu_1]}{\exp[\mu_2]} = \frac{\exp[E(\log(Y_1))]}{\exp[E(\log(Y_2))]} = \theta_2$$

However, in general, θ_1 and θ_2 can be unequal.

To conduct the simulation studies, we generated 10^5 simulated samples from the empirical distribution within each treatment group based on the Per Protocol Set and excluding Subject (b) (6) and all other subjects in the Per Protocol Set excluded by the Applicant (see Table 62). When generating simulated samples, we used the same sample sizes as in the actual analyses. For $AUC_{\tau, W26-28}$ the sample sizes were 232 and 226 for the AVT02/E.U.-Humira/AVT02 group and E.U.-Humira group, respectively, and for $C_{\max, W26-28}$, the sample sizes were 246 and 250 for the AVT02/E.U.-Humira/AVT02 group and Humira group, respectively (see Table 19).

In the simulation studies we considered two cases: (1) the target estimand is θ_1 , and (2) the target estimand is θ_2 . In each case, the simulation results show Monte Carlo estimates of the confidence interval coverage, average confidence interval length, and power of the test for PK similarity implemented using the confidence interval (note in the simulation settings, both θ_1 and θ_2 fall within the PK similarity margin [0.80, 1.25]). The results are shown both with and without using covariate adjustment in the analysis.

The simulation results based on populations constructed using $C_{\max, W26-28}$ data are in Table 58, and the simulation results for population constructed based on $AUC_{\tau, W26-28}$ data are shown in Table 59. In the simulation results, we observe that if the target estimand is θ_1 , then the confidence intervals under the original scale-based analyses have estimated coverage probability approximately equal to the nominal value 0.9, while the confidence interval under the log transformation-based analyses have estimated coverage less than 0.9. In the simulation results, we also observe that if the target estimand is θ_2 , then the confidence intervals under the original scale-based analyses have estimated coverage probability less than the nominal value 0.9, while the confidence intervals under the log transformation-based analyses have estimated coverage probability approximately equal to 0.9. These simulation results give some indication that in the present scenario, if the target estimand is θ_1 , then the original scale-based analysis is appropriate, and if the target estimand is θ_2 , then the log transformation-based analysis is appropriate. While the empirical distribution of the outcome variables does not appear to be normally distributed on the original scale nor on the log scale (see Figure 10, Figure 11, Figure 12, Figure 13 and the

discussion in the section titled Reviewer's Assessment, the sample sizes may be large enough so that the statistical procedures used under either original scale-based or log transformation-based analyses can be justified via large sample theory, as long as the analysis method is used for the proper estimand.

Based on the Monte Carlo estimates of power in Table 58 and Table 59 we observe that for this simulation scenario, under the log transformation-based analysis, the power appears quite low, while the power appears to be much higher under the original scale-based analysis. Based on the Monte Carlo estimates of mean confidence interval length in Table 58 and Table 59 we also observe that for this simulation scenario the mean confidence interval length under the log transformation based analysis appears to be greater than the mean confidence interval length under the original scale-based analysis. As noted above, the confidence interval under the log transformation-based analysis appears to be appropriate for estimating θ_2 while the confidence interval under the original scale-based analysis appears to be appropriate for estimating θ_1 . As is generally the case, the findings of the simulation studies are driven by the models and methods used to construct the simulation scenarios. Additional research may be useful to study and compare log transformation-based and original scale-based analysis under population distributions that may be plausible for the sample data observed in this clinical trial. These simulation studies were conducted only as an exploratory analysis that may help provide some insight into issues pertaining to log transformation and original scale-based analyses.

Table 58. Simulation results using populations constructed from $C_{\max}$, W26-28 data from Per Protocol Set excluding Subject (b) (6) and all other subjects in the Per Protocol Set excluded by the Applicant (see Table 62) in the original scale-based primary analysis

Estimand	Analysis Method	Covariate Adjustment?	MC Estimate of CI Coverage*
$\theta_1 \approx 1.07$	Original Scale-Based	No	0.9000
	Original Scale-Based	Yes	0.8950
	Log Transformation-Based	No	0.7641
	Log Transformation-Based	Yes	0.6963
$\theta_2 \approx 1.19$	Original Scale-Based	No	0.4616
	Original Scale-Based	Yes	0.4591
	Log Transformation-Based	No	0.8995
	Log Transformation-Based	Yes	0.8941
Analysis Method		Covariate Adjustment?	MC Estimate of Power of PK similarity Test Using CI
Original Scale-Based		No	0.2171
Original Scale-Based		Yes	0.1967
Log Transformation-Based		No	0.4662
Log Transformation-Based		Yes	0.4451

*Nominal confidence interval coverage is 0.90.

CI = Confidence Interval, MC = Monte Carlo

Source: Reviewer's analysis

Table 59. Simulation results using populations constructed from $AUC_{\tau, W26-28}$ data from Per Protocol Set excluding Subject (b) (6) and all other subjects in the Per Protocol Set excluded by the Applicant (see Table 62) in the original scale-based primary analysis

Estimand	Analysis Method	Covariate Adjustment?	MC Estimate of CI Coverage*
$\theta_1 \approx 1.02$	Original Scale-Based	No	0.8984
	Original Scale-Based	Yes	0.8966
	Log Transformation-Based	No	0.7478
	Log Transformation-Based	Yes	0.7491
$\theta_2 \approx 1.18$	Original Scale-Based	No	0.3390
	Original Scale-Based	Yes	0.2128
	Log Transformation-Based	No	0.9001
	Log Transformation-Based	Yes	0.9008
Analysis Method		Covariate Adjustment?	MC Estimate of Power of PK similarity Test Using CI
Original Scale-Based		No	0.2373
Original Scale-Based		Yes	0.2076
Log Transformation-Based		No	0.6008
Log Transformation-Based		Yes	0.5548

*Nominal confidence interval coverage is 0.90.

CI = Confidence Interval, MC = Monte Carlo

Source: Reviewer's analysis

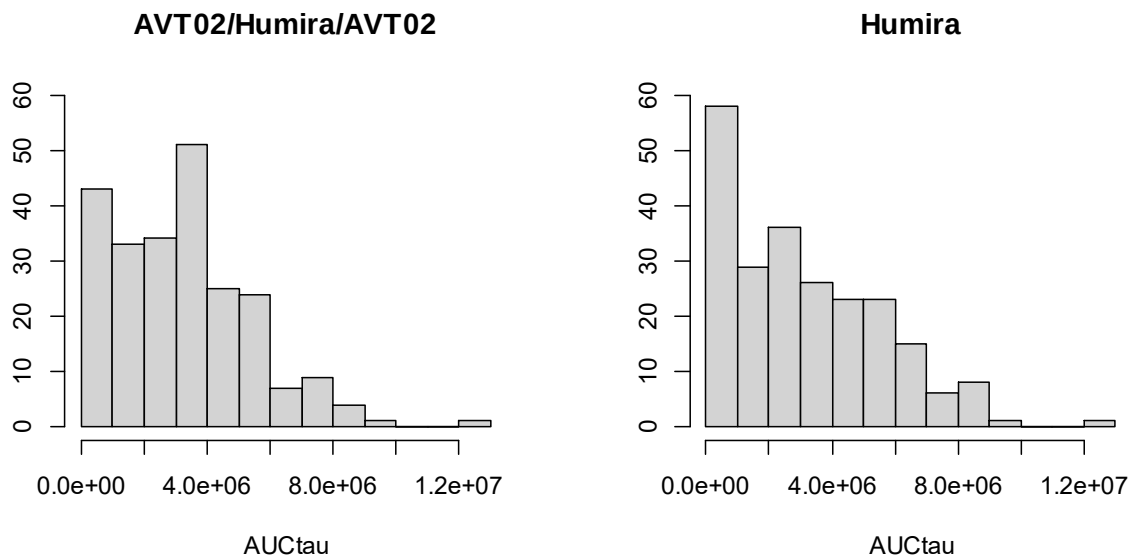
14.1.2. Histograms Showing Distribution of Primary Endpoints and Residuals

The Applicant's justification for changing from the log transformation-based analysis to the original scale-based analysis was that the distributions of the log transformed primary endpoints did not appear to satisfy the normality assumptions as indicated in the Applicant's histograms shown in Figure 7 and Figure 8. We also constructed similar histograms. Our histograms showing the distributions of $AUC_{\tau, W26-28}$ and log of $AUC_{\tau, W26-28}$ are shown in Figure 10 and Figure 11 for subjects in the Per Protocol Set (Subject (b) (6) is excluded from the histograms). Similar histograms for $C_{\max, W26-28}$ and log of $C_{\max, W26-28}$ are shown in Figure 12 and Figure 13. Note that the binning used in our histograms differs from the binning used in the Applicant's histograms shown in Figure 7 and Figure 8. For each of the histograms shown in Figure 10, Figure 11, Figure 12, and Figure 13 we observe that the data do not appear to be normally distributed (neither on the original scale nor log scale), and as an additional exploratory analysis we ran the Shapiro-Wilk Test for normality on the underlying data for each of these histograms and obtained $P\text{-value} < 0.0001$ in all eight cases, providing some evidence that normality does not hold (on neither the log scale nor original scale).

Because the Applicant's statistical analyses shown in Table 17, Table 18, Table 19, and Table 20 use ANCOVA models (including treatment group as a fixed effect, and with age and BMI at Week 12 as covariates), we have plotted histograms of the residuals under each of the ANCOVA models. These histograms of residuals appear in Figure 14 for the models using original scale $AUC_{\tau, W26-28}$ and log-scale $AUC_{\tau, W26-28}$, and the histograms appear in Figure 15 for the

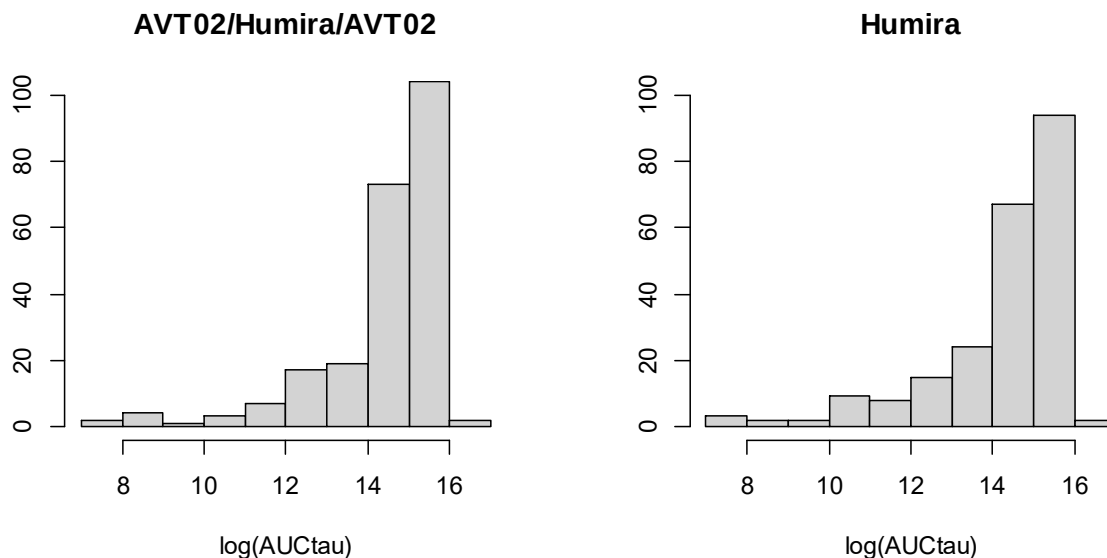
models using original scale $C_{\max, W26-28}$ and log-scale $C_{\max, W26-28}$. The Applicant included Subject (b) (6) in the log transformation-based analysis, and excluded this subject from the original scale-based analysis; and therefore in Figure 14 and Figure 15 Subject (b) (6) was included in the log transformation-based analysis and excluded from the original scale-based analysis. As an additional exploratory analysis we ran the Shapiro-Wilk Test for normality on the underlying data for each of the histograms in Figure 14 and Figure 15 and obtained a P-value<0.0001 in all four cases, providing some evidence that normality does not hold.

Figure 10. Histograms of original scale $AUC_{\tau, W26-28}$ in each treatment group based on the Per Protocol Set. Subject ^{(b) (6)} (in the E.U.-Humira group having $AUC_{\tau, W26-28}$ value 155271679.1) is excluded from the histograms



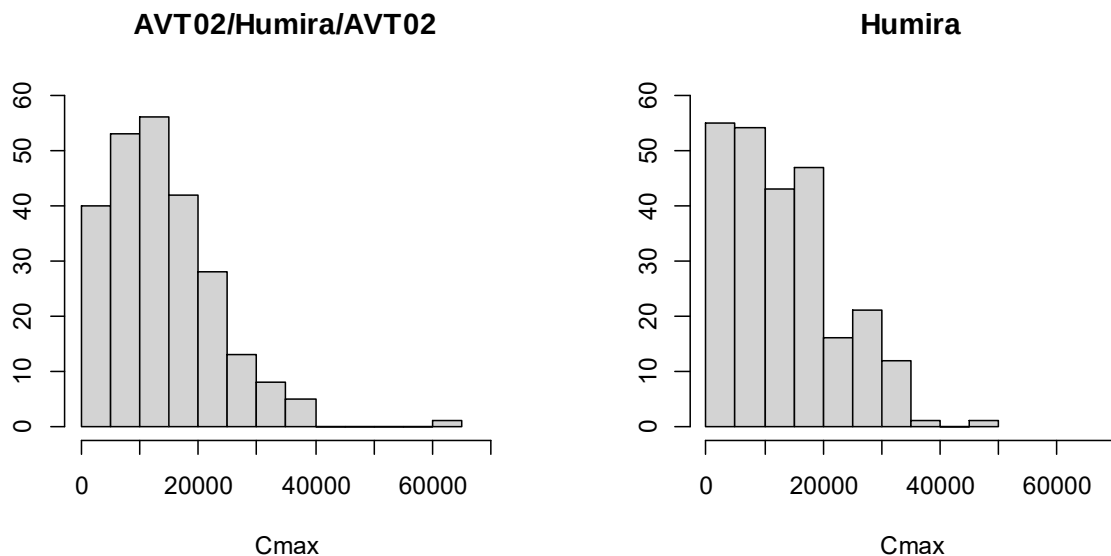
Source: Reviewer's analysis

Figure 11. Histograms of log scale $AUC_{\tau, W26-28}$ in each treatment group based on the Per Protocol Set. Subject ^{(b) (6)} (in the E.U.-Humira group having $\log(AUC_{\tau, W26-28})$ value ≈ 18.86) is excluded from the histograms



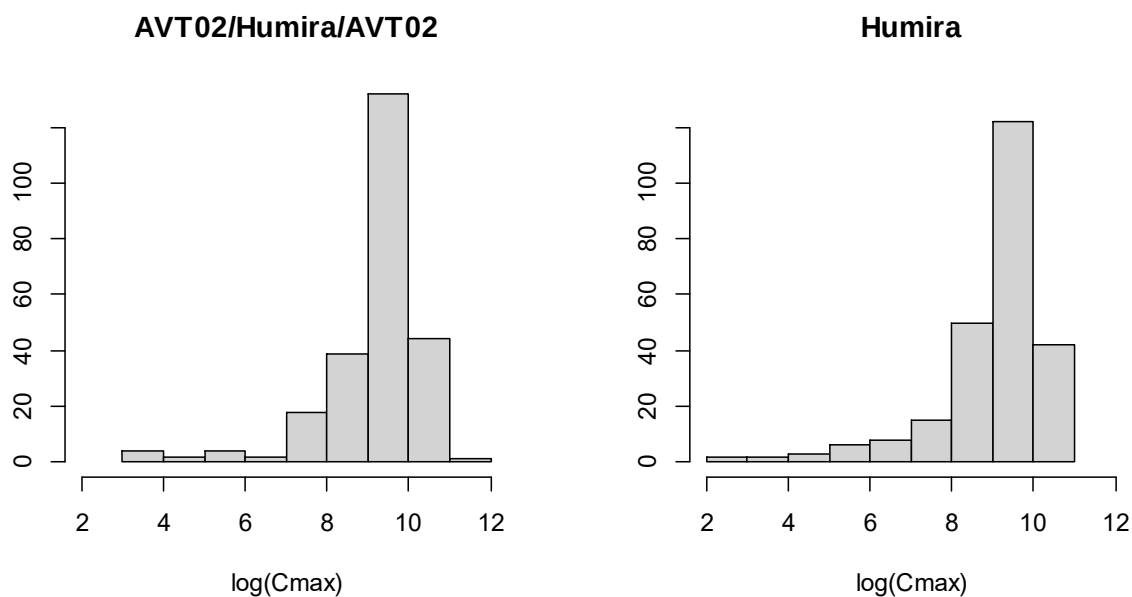
Source: Reviewer's analysis

Figure 12. Histograms of original scale $C_{\max, W26-28}$ in each treatment group based on the Per Protocol Set. Subject ^{(b) (6)} (in the E.U.-Humira group having $C_{\max, W26-28}$ value 1100000) is excluded from the histograms



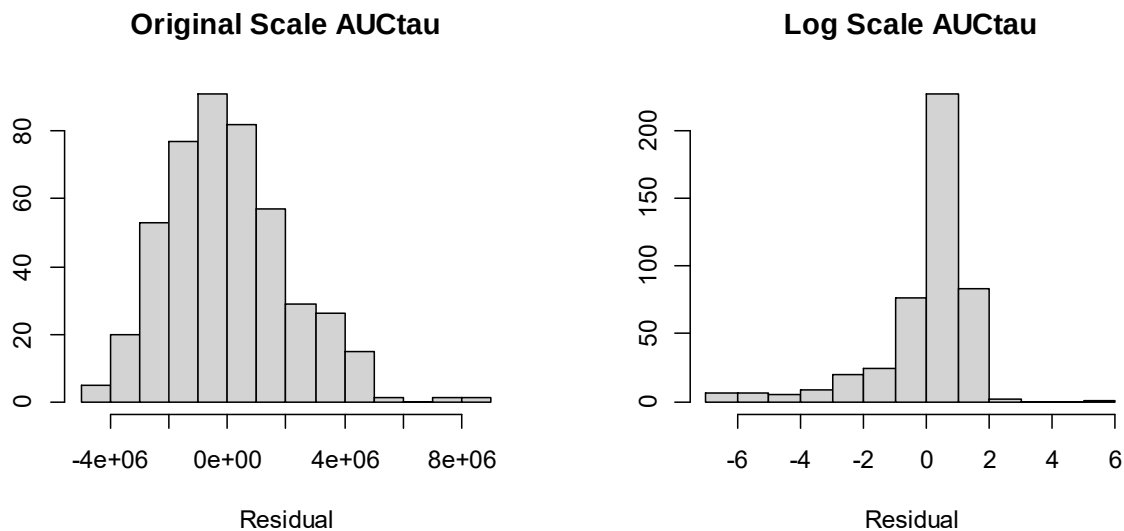
Source: Reviewer's analysis

Figure 13. Histograms of log scale $C_{\max, W26-28}$ in each treatment group based on the Per Protocol Set. Subject ^{(b) (6)} (in the E.U.-Humira group having $\log(C_{\max, W26-28})$ value ≈ 13.91) is excluded from the histograms



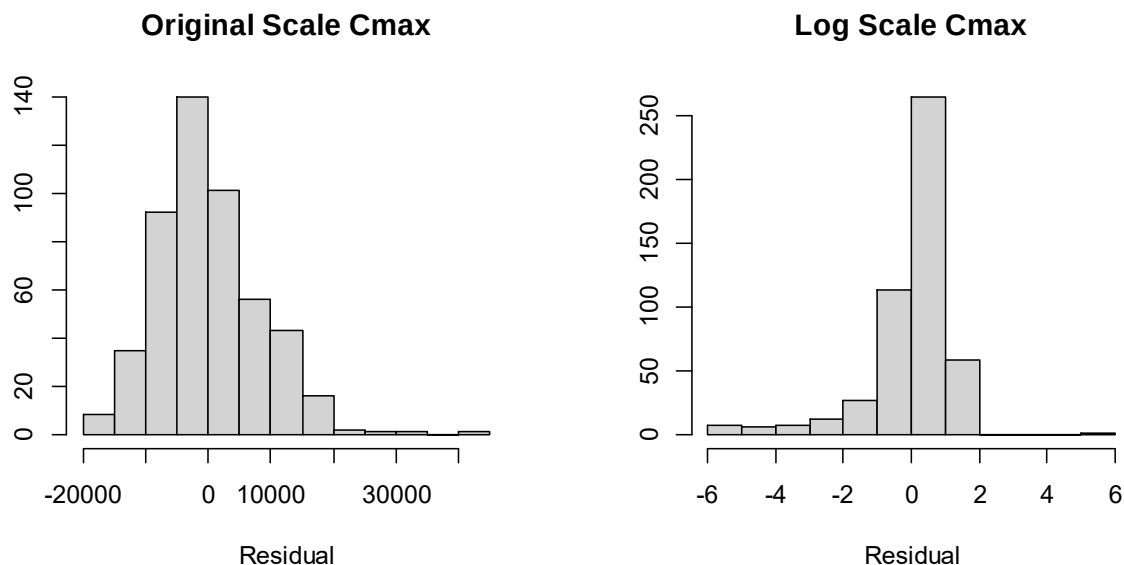
Source: Reviewer's analysis

Figure 14. Histograms of residuals under the ANCOVA model used for analysis. Subject (b) (6) was included in the log transformation-based analysis and excluded from the original scale-based analysis in correspondence with the Applicant's analysis results



Source: Reviewer's analysis

Figure 15. Histograms of residuals under the ANCOVA model used for analysis. Subject (b) (6) was included in the log transformation-based analysis and excluded from the original scale-based in correspondence with the Applicant's analysis results



Source: Reviewer's analysis

14.1.3. Additional tables on subjects excluded from Applicant's analysis

Table 60. Number of subjects in the Per-Protocol Set but excluded from Applicant's log transformation-based primary analysis of AUC_{τ} , W26-28

Reason	AVT02-E.U.-Humira- AVT02	E.U.- Humira
Insufficient quantifiable data; all concentrations W26-28 <LLOQ	13	7
Insufficient quantifiable data; <3 concentrations >LLOQ	2	3
Insufficient quantifiable data; <3 consecutive concentrations >LLOQ	0	1
Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	14	24
Total	29	35

Source: Appendix 16.2.9 of the Clinical Study Report and Reviewer's analysis

Table 61. Number of subjects in the Per-Protocol Set but excluded from Applicant's log transformation-based primary analysis of $C_{\max}$, W26-28

Reason	AVT02-E.U.-Humira- AVT02	E.U.- Humira
Insufficient quantifiable data; all concentrations W26-28 <LLOQ	13	7
Insufficient quantifiable data; <3 concentrations >LLOQ	2	3
Insufficient quantifiable data; <3 consecutive concentrations >LLOQ	0	1
Total	15	11

Source: Appendix 16.2.9 of the Clinical Study Report and Reviewer's analysis

Table 62. Subjects in Per Protocol Set but excluded from Applicant's analysis of primary endpoints

Subject	Applicant's Reason for Exclusion	Missing Primary Endpoints
Treatment Description in Switching Module: AVT02/Humira/AVT02		
(b) (6)	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	AUC_{τ}
	Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	AUC_{τ}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	AUC_{τ}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	AUC_{τ}
	Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	AUC_{τ}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; <3 concentrations >LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC_{τ} and $C_{\max}$
	Could not be estimated; no apparent terminal phase for extrapolating AUC_{τ}	AUC_{τ}

(b) (6)	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; <3 concentrations >LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
Treatment Description in Switching Module: Humira		
(b) (6)	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; <3 concentrations >LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Insufficient quantifiable data; <3 concentrations >LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; <3 concentrations >LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Could not be estimated; no apparent terminal phase for extrapolating AUC _{tau}	AUC _{tau}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Insufficient quantifiable data; all concentrations W26-28 <LLOQ	AUC _{tau} and C _{max}
	Insufficient quantifiable data; <3 consecutive concentrations >LLOQ	AUC _{tau} and C _{max}
	Excluded from the analysis due to extremely high PK concentration	AUC _{tau} and C _{max}

*Subject (b) (6) was excluded from the Applicant's original scale-based analysis of AUC_{tau, W26-28} and C_{max, W26-28} but included in the Applicant's log-transformation-based analysis of these endpoints.

Note: In this table AUC_{tau, W26-28} and C_{max, W26-28} are abbreviated as AUC_{tau} and C_{max}, respectively.

Source: Appendix 16.2.9 of the Clinical Study Report and Reviewer's analysis

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