BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA
Application Number	761343
Received Date	October 11, 2022
BsUFA Goal Date	October 11, 2023
Division/Office	Division of Dermatology and Dentistry (DDD)/Office of Immunology and Inflammation (OII)
Review Completion Date	See DARRTS stamped date
Product Code Name	AVT04
Proposed Nonproprietary Name[1]	Ustekinumab-aekn
Proposed Proprietary Name[1]	Selarsdi
Pharmacologic Class	Interleukin-12 and -23 antagonist
Applicant	Alvotech USA Inc.
Applicant Proposed Indication(s)	• Patients 6 years and older with plaque psoriasis (PsO) • Patients 6 years and older with psoriatic arthritis (PsA)
Recommendation on Regulatory Action	Complete Response

[1]Section 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.

Table of Contents

Table of Tables

Table of Figures

Reviewers of Biosimilar Multidisciplinary Evaluation and Review

Regulatory Project Manager	Sascha Randolph
Nonclinical Pharmacology/Toxicology Reviewer(s)	Jianyong (Jerry) Wang
Nonclinical Pharmacology/Toxicology Supervisor	Barbara Hill
Clinical Pharmacology Reviewer(s)	Anand Balakrishnan
Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer(s)	Sangeeta Jain
Clinical Team Leader(s)	Snezana Trajkovic
Clinical Statistics Reviewer(s)	Carin Kim
Clinical Statistics Team Leader(s)	Somesh Chattopadhyay
Cross-Discipline Team Leader(s) (CDTL(s))	Snezana Trajkovic
Designated Signatory Authority	Shari Targum

Additional Reviewers of Application

OBP	Patrick Lynch, OBP Review Chief Shadia Zaman, OBP Team Leader (Application Technical Lead - ATL) Lei Zhang, OBP Reviewer Scott Dallas, OBP Labeling Reviewer
OPMA	Madu Dharmasena
OPDP	David Foss
OSI	Stephanie Coquia
OSE/DEPI	
OSE/DMEPA	
OSE/DRISK	
DPMH	
OPMA Facility/Micro Branch Chief	Candace Gomez-Broughton
OPMA Primary Drug Substance Micro and Facility Reviewer	Richard Ledwidge
OPMA Primary Drug Product Micro and Facility Reviewer	Richard Ledwidge
DRTM	Suzette Peng

OBP = Office of Biotechnology Products

OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
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
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
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
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
EU-Stelara	EU-approved Stelara
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
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
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
ULOQ	Upper Limit of Quantitation
US-Stelara	U.S.-licensed Stelara

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Nonclinical Reviewer	Jianyong (Jerry) Wang		4, 14.3
	Signature: Jianyong Wang -S Digitally signed by Jianyong Wang -S Date: 2023.10.06 17:25:05 -04'00'		
Nonclinical Supervisor	Barbara Hill		4, 14.3
	Signature: Barbara A. Hill -S Digitally signed by Barbara A. Hill -S Date: 2023.10.10 07:11:10 -04'00'		
Clinical Pharmacology Reviewer	Anand Balakrishnan		5, 14.4
	Signature: Anand Balakrishnan -S Digitally signed by Anand Balakrishnan -S Date: 2023.10.10 09:03:51 -04'00'		
Clinical Pharmacology Team Leader	Amer Al- Khouja on behalf of Chinmay Shukla		5, 14.4
	Signature: Amer Al-khouja -S Digitally signed by Amer Al-khouja -S Date: 2023.10.10 09:51:48 -04'00'		
Clinical Reviewer	Snezana Trajkovic on behalf of Sangeeta Jain		2, 6.3, 6.4, 7, 8, 10, 11, 14.2, 14.5
	Signature: Snezana Trajkovic -S Digitally signed by Snezana Trajkovic -S Date: 2023.10.10 10:19:30 -04'00'		
Clinical Team Leader	Snezana Trajkovic		2, 6.3, 6.4, 7, 8, 10, 11, 14.2, 14.5
	Signature: Snezana Trajkovic -S Digitally signed by Snezana Trajkovic -S Date: 2023.10.10 10:20:34 -04'00'		

Clinical Reviewer (Optional, Collaborative Review Division)	Suzette Peng		6.5.1
	Signature: Suzette W. Peng -S Digitally signed by Suzette W. Peng -S Date: 2023.10.10 11:42:53 -04'00'		
Clinical Team Leader (Optional, Collaborative Review Division)	Raj Nair		6.5.1
	Signature: Raj G. Nair -S Digitally signed by Raj G. Nair -S Date: 2023.10.10 11:46:15 -04'00'		
Clinical Statistics Reviewer	Carin Kim		6.1, 6.2
	Signature: Carin Kim -S Digitally signed by Carin Kim -S Date: 2023.10.10 12:09:48 -04'00'		
Clinical Statistics Team Leader	Somesh Chattopadhyay		6.1, 6.2
	Signature: Somesh Chattopadhyay -S Digitally signed by Somesh Chattopadhyay -S Date: 2023.10.10 13:25:29 -04'00'		
Associate Director for Labeling (Optional)			
	Signature:		
Cross-Discipline Team Leader	Snezana Trajkovic		1, 3, 6.5, 9
	Signature: Snezana Trajkovic -S Digitally signed by Snezana Trajkovic -S Date: 2023.10.10 13:57:27 -04'00'		
Designated Signatory Authority	Shari Targum		N/A

	Signature: Shari L. Targum -S Digitally signed by Shari L. Targum -S Date: 2023.10.10 14:04:19 -04'00'

1. Executive Summary

1.1. Product Introduction

Alvotech (also referred to as "Applicant" in this review) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for AVT04 (ustekinumab-aekn, Selarsdi) 45 mg/0.5 mL and 90 mg/1.0 mL solutions in single-dose prefilled syringes, developed as a proposed biosimilar to US-licensedStelara (US-Stelara).

AVT04 is a recombinant, fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody (mAb) that binds to the p40 subunit of interleukin (IL)-12 and IL-23. Binding of the antigen binding fragment (Fab) domain to the p40 protein subunit of both IL-12 and IL-23 inhibits the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signaling pathways.

Alvotech is seeking licensure for AVT04 for the same indications approved for US-Stelara, noting that some indications will not be sought at this time (i.e., Crohn's disease (CD) and ulcerative colitis (UC)):

Patients 6 years and older with:

- moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy (PsO).
- active psoriatic arthritis (PsA)

The routes of administration and dosing regimens of AVT04 are the same as those approved for US-Stelara using the 45 mg/0.5 mL and 90 mg/1.0 mL single-dose prefilled syringe (PFS) presentations. (b) (4)

Although the Division of Dermatology and Dentistry (DDD) is the lead division for this application and provided the written clinical review, clinical input pertaining to the indication of psoriatic arthritis was obtained from the Division of Rheumatology and Transplant Medicine (DRTM) during the course of the review.

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

Not applicable.

Reference ID: 5258586

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

AVT04 is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of the human cytokines IL-12 and IL-23. Binding of the Fab domain of ustekinumab to the p40 protein subunit of both IL-12 and IL-23 inhibits the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of NK cells or T cells, thereby preventing initiation of downstream immune-response signaling pathways. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines are involved in inflammatory and immune responses. Among other biological activities, IL-12 activates NK cells to produce and release the interferon gamma (IFN-γ) cytokine and drives CD4+ T cell differentiation toward the T helper 1 (Th1) phenotype; IL-23 induces the T helper 17 (Th17) pathway which are both central to the pathology of certain immune mediated diseases.

AVT04 product is a sterile liquid solution for subcutaneous (SC) injection available in a PFS.

The route of administration, dosage form, and strength of AVT04 are the same as those approved for US-Stelara 45 mg/0.5 mL and 90 mg/mL . . The 45 mg/0.5 mL and 90 mg/1.0 mL PFS concentrations of AVT04 support the dosing regimens for the proposed indications of adults with PsO and PsA, and for the pediatric indications of children 6 years and older with PsO and PsA (b) (4)

Inspection of Manufacturing Facilities

Alvotech hf (FEI 3013702557) is responsible for manufacturing PFS, release and stability testing, and AI release testing. A pre-licensing inspection (PLI) was conducted by OPQ and the Office of Regulatory Affairs (ORA). The inspection covered the firm's Quality, Facilities and Equipment Production, Material, and Laboratory Systems used in the manufacturing and testing of AVT04 drug substance (DS) and drug product (DP) on March 6 – March 17, 2023. The Agency conveyed deficiencies to the representative of the facility; satisfactory resolution of these deficiencies is required before this application may be approved. See the OPQ Executive Summary assessment memo dated July 17, 2023, and addendum dated August 17, 2023, for the complete review.

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

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the comparative clinical study AVT04-GL-301, which used EU-Stelara as the comparator, for the assessment of biosimilarity:

- OPQ has determined, that based on the data provided by the Applicant, the analytical component of the scientific bridge between AVT04, US-Stelara, and EU-Stelara was established.
- The Office of Clinical Pharmacology (OCP) has determined, that based on the data provided by the Applicant, the PK data established the PK component of the scientific bridge.

Reference ID: 5258586

1.5. Biosimilarity Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies[2]	
Summary of Evidence	• AVT04 is highly similar to US-Stelara notwithstanding minor differences in clinically inactive components. • AVT04 45 mg/0.5 mL and 90 mg/mL PFS have the same strength as those of US-Stelara 45 mg/0.5 mL and 90 mg/mL, respectively. • The dosage form and route of administration are also the same as those of US-Stelara. • The analytical component of the scientific bridge between AVT04, US-Stelara, and EU-Stelara was established to support the relevance of the data generated from studies using EU-Stelara as the comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment.
Clinical Studies	
Clinical Pharmacology Studies	

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Reference ID: 5258586

Summary of Evidence	• PK similarity between AVT04, US-Stelara, and EU-Stelara was evaluated in a multicenter, randomized, double-blind, 3-arm, parallel-group PK similarity study in healthy adult subjects (Study AVT04-GL-101). • PK similarity between AVT04 and US-Stelara was established and supports a demonstration of no clinically meaningful differences between AVT04 and US-Stelara. • PK similarity between AVT04, EU-Stelara, and US-Stelara provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Stelara to the assessment of biosimilarity. • In Study AVT04-GL-101 in healthy subjects, the overall frequency of ADAs and NAbs was slightly higher in the US-Stelara and EU-Stelara groups as compared to the AVT04 group. These differences were not considered to be clinically significant. • In Study AVT04-GL-301 in patients with PsO, the overall frequency of ADAs was slightly higher in the EU-Stelara group compared to the AVT04 group. The slight differences in ADA were not considered to be clinically significant. The overall frequency of NAbs were generally comparable between the two treatment arms, and the single transition from EU-Stelara to AVT04 did not result in a change in immunogenicity. • Given the scientific bridge was established (based on the analytical similarity and PK similarity) between AVT04, US-Stelara and EU-Stelara to justify the relevance of data generated with EU-Stelara as the comparator, these collective immunogenicity results support the assessment of no clinically meaningful differences between AVT04 and US-Stelara. • .
Assessment of Residual Uncertainties	• There are no clinical pharmacology residual uncertainties from a clinical pharmacology perspective.
Additional Clinical Studies	

Reference ID: 5258586

Summary of Evidence	• In Study AVT04-GL-301, there were no meaningful differences in terms of efficacy between AVT04 and EU-Stelara. The frequency of treatment emergent adverse events, serious events, and events leading to discontinuation of study drug demonstrated no meaningful differences between the treatment arms. • Given that the scientific bridge was established (based on the analytical and PK comparisons) between AVT04, US-Stelara, and EU-Stelara to justify the relevance of the data generated with EU-Stelara as the comparator, the collective evidence from submitted clinical studies, including the comparative clinical studyAVT04-GL-301, supports a demonstration of no clinically meaningful differences between AVT04 and US-Stelara in the studied indication (PsO).
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or statistical perspective regarding the demonstration of no clinically meaningful differences between AVT04 and US-Stelara.
Extrapolation	
Summary of Evidence	• DRTM has determined that the Applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (PsO), to support licensure of AVT04 as a biosimilar, under section 351(k) of the PHS Act, for the following indications for which US- Stelara has been previously approved: Active Psoriatic Arthritis in adults and pediatric patients 6 years or older
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of AVT04 as a biosimilar to US-Stelara for the above indications.

1.6. Conclusions on Approvability

The Applicant is seeking licensure of AVT04 for the following indications: treatment of patients 6 years or older with PsO and treatment of patients 6 years or older with PsA, . The totality of the evidence submitted by the Applicant supports our conclusion that AVT04 is highly similar to U.S.-Stelara, notwithstanding minor differences in clinically inactive components, and that

Reference ID: 5258586

there are no clinically meaningful differences between AVT04 and U.S.-Stelara in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of AVT04 for patients 6 years or older with PsO and patients 6 years or older with PsA. The Applicant has sufficiently demonstrated that AVT04 is biosimilar to U.S.-Stelara for each of the requested indications for which U.S.-Stelara is currently licensed.

However, data submitted in this application is not sufficient to support a conclusion that the manufacture of AVT04 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:
Snezana Trajkovic, MD
Cross-Discipline Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Division of Dermatology and Dentistry (DDD) had several interactions with the Applicant during the development of AVT04. Key discussions are detailed below:

A Biosimilar Biological Product Development (BPD) Type 2 meeting was held on July 8, 2020, to discuss the proposed development program for AVT04, as a biosimilar to US-licensed Stelara.

A BPD Type 2 meeting was held on September 13, 2021, to seek advice and agreement on the Applicant's Chemistry, Manufacturing, and Controls (CMC) strategy to support licensure of AVT04 as a biosimilar to US-Stelara.

A BPD Type 2 meeting was held on March 7, 2022, to discuss the development plan for AVT04 specific to CMC questions.

The pre-BLA (BPD Type 4) meeting took place on August 15, 2022. The content and format of a complete application to support a 351(k) BLA submission demonstrating biosimilarity of AVT04 with U.S.-licensed Stelara were discussed including an amendment or appendix to the initial Pediatric Study Plan (iPSP). The most current version of the iPSP is dated March 2022 with an appendix.

Reference ID: 5258586

2.2. Studies Submitted by the Applicant

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

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Table 2: Listing All Relevant Submitted Clinical Studies

StudyIdentity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment G
	PK Similarity Study				
AVT04-GL-101	NCT04744363	Pharmacokinetic similarity and safety of AVT04, US-Stelara, and EU-Stelara	Double-blind, randomized, parallel-group, active-controlled, single-dose, 3-arm	Healthy adults	AVT04: 98 US-Stelara: 9 EU-Stelara: 9 45 mg SC
	Comparative Clinical Study				
AVT04-GL-301	NCT04930042	Comparative efficacy, safety, and immunogenicity of AVT04 vs EU-Stelara	Double-blind, randomized, parallel-group, active-controlled	Chronic moderate to severe PsO	Stage 1: AVT04: 194 EU-Stelara: 3 45 mg SC or SC at Day 1 a Week 4 Stage 2: AVT04/AVT0 EU-Stelara/A 192 EU-Stelara/E Stelara: 189 45 mg SC or SC at Weeks and 40

Source: Clinical Reviewer
PK = Pharmacokinetics; PsO = Plaque Psoriasis; SC= subcutaneously; US = United States; EU=European Union

Authors:

Authors:
Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

3. Summary of Conclusions of Other Review Disciplines

Reference ID: 5258586

3.1. Office of Pharmaceutical Quality (OPQ)

The overall control strategy for AVT04 manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls and release and stability testing ensures process consistency, and drug substance and drug product that have appropriate quality and are free of adventitious agents.

AVT04 drug product is manufactured to have the same strength, dosage form and route of administration as 45 mg/0.5 mL and 90 mg/1.0 mL of US-licensed Stelara in single-dose prefilled syringes (PFS)s. Alvotech USA, Inc. performed a three-way pairwise comparative analytical assessment (CAA) of AVT04, US-licensed Stelara and EU-approved Stelara to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU-approved Stelara as a comparator. The CAA results support the demonstration that AVT04 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components, and the establishment of the analytical component of the scientific bridge. The proposed AVT04 single-use PFSs (i.e., 45 mg/0.5 mL or 90 mg/1.0 mL) have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Stelara (45 mg/0.5 mL and 90 mg/1.0 mL). The strength of the AVT04 is the same as that of US-licensed Stelara.

OPQ has completed review of BLA 761343 for AVT04 manufactured by Alvotech USA, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of AVT04 is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. OPQ is recommending that a Complete Response letter be issued to Alvotech USA, Inc., to outline the deficiencies and the information and data that will be required to support approval. During a recent inspection of the Alvotech hf. Reykjavik, Iceland manufacturing facility for this application, our field inspector conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

The CDTL and Division Signatory agree with this assessment and the recommendation for a Complete Response.

3.2. Devices

AVT04 drug product (AVT04-DP) is a sterile, preservative-free, practically free of visible particles, clear, colorless to slightly yellow solution for subcutaneous injection containing 45 mg (AVT04-DP45) or 90 mg (AVT04-DP90) of AVT04 in 0.5 mL or 1 mL, respectively.

AVT04-DP45 and AVT04-DP90 are supplied as a sterile solution in a single-use, 1 mL long, pre-filled syringe (PFS), stoppered with a rubber stopper. The PFS is fitted with a plunger rod, extended finger flanges and a needle safety device (SD), forming the finished product, which

Reference ID: 5258586

is referred to as AVT04-PFS SD.

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH was consulted to provide an assessment of the needle safety device constituent part of the prefilled syringe product. On assessment of device constituent parts of the combination product, CDRH recommends approval stating, “Device constituent parts of the combination product are approvable.” Refer to the full CDRH OPEQ review dated May 8th, 2023.

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

The safety evaluator Dr. Murewa Oguntimein, PhD, MHS, CPH, MCHES from DMEPA concluded:

“We maintain that Alvotech does not need to submit human factors validation study results with their biologics license application (BLA) under BLA 761343 for Selarsdi injection, 45 mg/0.5 mL and 90 mg/m; a proposed biosimilar to US-licensed Stelara. We have no HF recommendations for this marketing application.”

Refer to DMEPA review dated May 18th, 2023.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS audit for the PK similarity Study and bioanalytical facilities are going to be deferred until the next review cycle.

3.4. Office of Scientific Investigations (OSI)

OSI audit was requested and clinical inspections of two clinical investigators (Drs. Wilkowska-Trojniel and Pulka) were conducted. These investigators were inspected as a routine BsUFA inspection for Study AVT04-GL-301.The sponsor of the study, Alvotech Swiss AG, was also inspected in support of this BLA. Per the OSI review, the inspections did not find significant concerns regarding the management and oversight of the clinical trial or GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected clinical investigators and submitted by the sponsor appear acceptable in support of the proposed indication. Refer to the full OSI review dated July 19th, 2023.

Author:
Snezana Trajkovic,
Cross-Discipline Team Leader

Reference ID: 5258586

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The results of the in vitro studies are adequate to support a demonstration of biosimilarity between AVT04 and US-Stelara. Refer to the OBP/CMC section for detailed documentation (Section 3.1). In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo animal studies are not expected to provide additional meaningful information to inform the evaluation of toxicity.

However, the applicant conducted two animal studies (a PK study and a 4-week repeat-dose toxicity study in monkeys) using AVT04 and Stelara sourced from China (CN-Stelara) to meet the requirement of other international regulatory authorities and submitted the study reports to the BLA. These studies are reviewed in Section 14 for completeness. The study results showed that the PK/toxicokinetic (TK) and toxicity profiles of AVT04 and CN-Stelara are similar. These studies are not relevant to this application because there is no adequate scientific bridge to support the acceptability of CN-Stelara as the comparator.

This BLA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical PMC/PMR for this BLA.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The composition of the AVT04 DP (with comparison to US-Stelara) is shown in the table below.

Reference ID: 5258586

Formulation component	Category	Concentration/value	
		AVT04-DS/DP PFS formulation (90 mg/mL)	Reference product 90 mg/mL formulation
Ustekinumab	Active substance	90 mg/mL	90 mg/mL
L-histidine	(b) (4)	0.243 mg/mL (1.6 mM)	1 mg/mL (6.4 mM)
L-histidine monohydrochloride monohydrate		1.013 mg/mL (4.8 mM)	
Sucrose		76 mg/mL (222 mM)	76 mg/mL
Polysorbate 80		0.04 mg/mL (0.004% (w/v))	0.04 mg/mL
pH		6.0	5.7-6.3
Water for injection (WFI)		q.s.	q.s.

(b) (4)

Comments on Excipients

The excipients in AVT04 are the same and present in the same levels as the excipients in US-Stelara.

Comments on Impurities of Concern

There are no concerns for potential impurities contained in the biosimilar product.

Authors:

Jianyong Wang
Master Toxicologist

Barbara Hill
Supervisory Pharmacologist

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Alvotech USA Inc. is seeking licensure for AVT04, a recombinant, fully human IgG1κ mAb directed against IL-12 and IL-23 that has been developed as a proposed biosimilar to US-Stelara, which was previously approved under BLA 125261.

In the current submission, the Applicant is seeking approval for AVT04 45 mg/0.5 mL and 90 mg/1.0 mL injection in a PFS to support the following approved indications for US-Stelara:

Reference ID: 5258586

patients 6 years and older with PsO, and patients 6 years and older with PsA [redacted] (b) (4)

Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• A PK similarity study (Study AVT04-GL-101) evaluated PK similarity between AVT04, EU-Stelara and US-licensed Stelara in healthy subjects. • PK similarity has been demonstrated between AVT04 and US-licensed Stelara, and supports a demonstration of no clinically meaningful differences between AVT04 and US-licensed Stelara. • PK similarity between EU-Stelara and US-licensed Stelara supports the PK component of the scientific bridge to support the relevance of comparative clinical similarity data generated using EU-Stelara to the assessment of biosimilarity. • When comparing AVT04 and EU-Stelara, the 90% CI of the AUCinf exceeded the prespecified margin of 80% to 125% (upper limit was 126.4%). However, this small excursion was deemed not impactful on the validity of the PK component of the scientific bridge, based on the totality of evidence (i.e., analytical similarity along with the results from the comparative clinical study).
Pharmacodynamics	• Not applicable
Immunogenicity	• In Study AVT04-GL-101 in healthy subjects, the overall frequency of ADAs and NAbs was slightly higher in the US-Stelara and EU-Stelara groups as compared to the AVT04 group. These differences were not considered to be clinically significant. • In Study AVT04-GL-301 in patients with PsO, the overall frequency of ADAs was slightly higher in the EU-Stelara group compared to the AVT04 group. The slight differences in ADA were not considered to be clinically significant.The overall frequency of NAbs were

Reference ID: 5258586

	generally comparable between the two treatment arms, and the single transition from EU-Stelara to AVT04 did not result in a change in immunogenicity. • • Given the scientific bridge was established (based on the analytical similarity and PK similarity) between AVT04, US-Stelara and EU-Stelara to justify the relevance of data generated with EU-Stelara as the comparator, these collective immunogenicity results support the assessment of no clinically meaningful differences between AVT04 and US-Stelara.

The clinical development program comprised of two studies (AVT04-GL-101 and AVT04-GL-301).

• AVT04-GL-101 was a multicenter, randomized, double-blind, 3-arm parallel-group, single-dose (45 mg/0.5 mL SC) PK similarity study comparing AVT04, US-Stelara, and EU-Stelara.
• AVT04-GL-301 was a randomized, double-blind, parallel-group, comparative clinical study in adults with moderate to severe chronic plaque psoriasis (PsO) to establish therapeutic equivalence between AVT04 and EU-Stelara.

PK similarity was established in the PK similarity study (Study AVT04-GL-101) between AVT04 and US-Stelara (Table 3). PK similarity was also established between AVT04, EU-Stelara and US-licensed Stelara which provides the PK component of the scientific bridge to support the relevance of comparative clinical data generated using EU-Stelara from Study AVT04-GL-301 to the assessment of biosimilarity.

PK similarity was assessed using a prespecified criteria of 80 to 125% for the 90% CI of the least square (LS) geometric means ratios (LS GMRs) for area under the serum drug concentration-time curve (AUC) from time zero to infinity (AUC0-inf), AUC from time zero to the last quantifiable concentration (AUC0-last), and maximum observed drug concentration (Cmax).

Table 3. Summary of statistical analyses for assessment of PK similarity (Study AVT04-GL-101)

Parameter	Geometric Mean (%CV)			Geometric Mean Ratio* (90% CI)		
	AVT04 (n=96)	US-Stelara (n=94)	EU-Stelara (n=97)	AVT04 / US-Stelara	AVT04 / EU-Stelara	EU-Stelara / US-Stelara
Primary						
$AUC_{0\text{-inf}}$ (h·ng/mL)	3,511,612 (33)	3,344,427 (36)	3,014,505 (39)	103.8 (95.9-112.3)	116.9 (108.1-126.4)	89 (82.3- 96.2)

Reference ID: 5258586

C_{max} (ng/mL)	4,019.2 (33)	4,046.4 (31)	3,681.7 (38)	98.4 (91.4-106.0)	109.5 (101.7-117.8)	90.1 (83.6 - 97.0)
Secondary						
AUC_{last} (h·ng/mL)	3,286,173 (32)	3,171,230 (34)	2,872,578 (38)	102.6 (95.2-110.6)	114.7 (106.5-123.6)	89.6 (83.1 - 96.6)

*Presented as percent. Source: Reviewers analysis of Applicant's data

In Study AVT04-GL-101, the ADA incidence and nAb incidence in the AVT04 treatment group was slightly lower as compared to EU-Stelara and US-Stelara. The incidence of ADA formation at the end of the study (Day 92) in healthy subjects was 27.6% in the AVT04 group compared to the EU-approved Stelara (48.5%) and US-licensed Stelara groups (45.4%). The frequency of subjects with at least 1 positive ADA result at any post-baseline time point was lower in the AVT04 group (36.7%) compared with the EU-Stelara (59.6%) and US-Stelara groups (53.6%). There was no apparent impact of immunogenicity on the PK of the study drugs. Overall, we conclude that these differences are not considered to be clinically significant, and the results support a conclusion of no clinically meaningful differences between AVT04 and US-Stelara.

After multiple SC doses, the overall frequency of ADAs was higher in the EU-Stelara group compared to the AVT04 group (54.5% vs. 28.4%, respectively) in patients with PsO (Study AVT04-GL-301). The overall frequency of NAbs were generally comparable between the EU-Stelara group (32.2%) and the AVT04 group (25.5%).The single transition from EU-Stelara to AVT04 did not result in a change in immunogenicity; the treatment-emergent ADA incidence was comparable across the AVT04/AVT04, EU-Stelara/AVT04 and the EU-Stelara/EU-Stelara groups (4.8% vs. 4.5% vs. 6.7%, respectively), with no detectable treatment-emergent NAbs in any treatment group. There was no apparent impact of immunogenicity on the PK of the study drugs before or following the single transition. The totality of immunogenicity data from the study, including following the single transition, support the conclusion that there are no clinically significant differences in immunogenicity between AVT04 and EU-Stelara, and do not preclude a conclusion of no clinically meaningful differences between AVT04 and US-Stelara. Overall, this submission is approvable from a clinical pharmacology perspective pending OSIS inspection.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was assessed through the three pair-wise comparisons between AVT04, EU-Stelara and US-Stelara in healthy subjects in Study AVT04-GL-101 (Table 3).

PK similarity was demonstrated between AVT04 and US-Stelara, and this supports a demonstration of no clinically meaningful differences between AVT04 and US-Stelara. PK similarity between EU-Stelara and US-Stelara was established which supports the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Stelara in the comparative clinical study to the assessment of biosimilarity.

However, PK similarity assessment did not meet the pre-specified margin when comparing AVT04 and EU-Stelara, as the 90% CI of the AUCinf exceeded the 80% to 125% margin (upper limit was 126.4%). The Applicant postulated that this is related to the relatively lower protein concentration of the EU-Stelara lot (KHS25MJ) used in the PK similarity study. The

Reference ID: 5258586

Applicant conducted post-hoc analysis using protein content as a covariate and concluded that the PK similarity criterion was met for all three comparisons. Use of post-hoc analysis is not considered an acceptable approach for establishing PK similarity and, therefore, the results of the post-hoc analysis are not included in this review.

The review team concluded that the deviation from the upper limit of PK similarity for the AVT04/EU-Stelara comparison (126.4%) does not impact the validity of establishing the PK component of the scientific bridge, based on the totality of evidence. This conclusion was based on the following considerations:

- The extent of deviation from the prespecified criterion of the 125% upper bound of the 90% CI for AUCinf is small (1.4% difference (126.4%)).
- The GMR for AUClast and Cmax were entirely contained within the prespecified margins of 80% and 125% for each of the 3 pairwise comparisons (ie, AVT04 vs. EU-Stelara, AVT04 vs. US-Stelara, and US-Stelara vs. EU-Stelara).
- Comparison of the protein concentrations of AVT04, US-Stelara and EU-Stelara over multiple lots suggest that the EU-Stelara lot (KHS25MJ) used in the PK similarity study was a outlier with a lower protein concentration compared to the other batches evaluated.

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

Study AVT04-GL-101 adequately demonstrated PK similarity between AVT04 and US-Stelara, and between EU-Stelara and US-Stelara, thus establishing the PK component of the scientific bridge. This data supported the use of EU-Stelara in the comparative clinical study.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

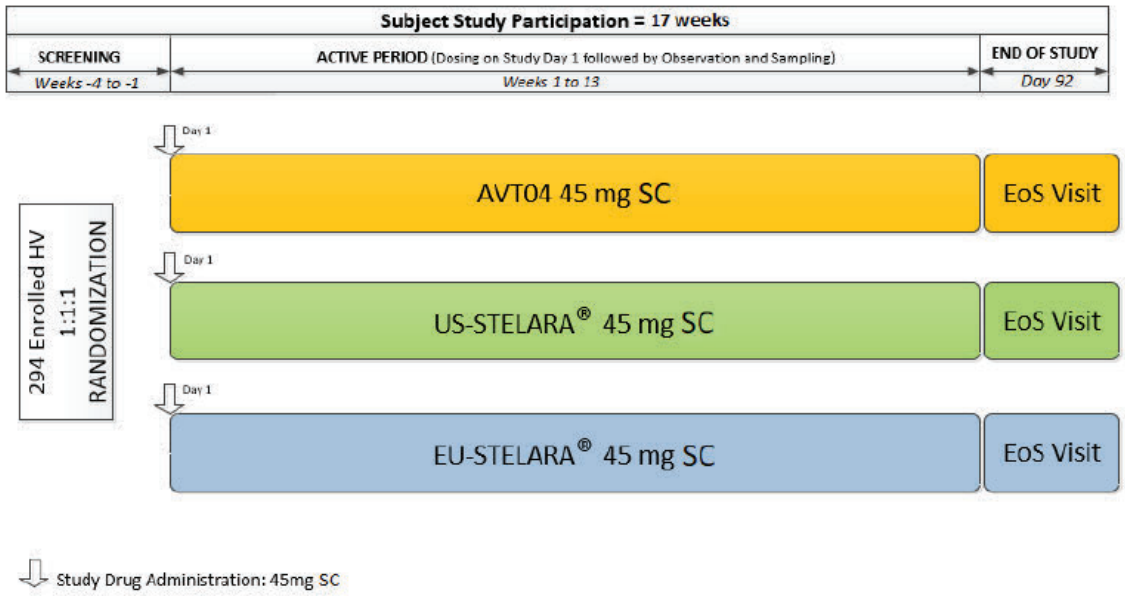
5.3.1. Study AVT04-GL-101

Clinical Pharmacology Study Design Features

The PK similarity study comparing AVT04, EU-Stelara and US-Stelara was conducted in healthy subjects (Study AVT04-GL-101). This was a multiple-center study conducted in 2 countries: New Zealand (2 sites) and Australia (2 sites). Approximately 294 subjects (98 per group) were planned to be enrolled. A schematic representation of the study design is shown below in Figure 1.

Figure 1: Schematic of study design for Study AVT04-GL-101

Reference ID: 5258586



EoS: End-of-Study; HV: healthy volunteers; SC: subcutaneous.

Clinical Pharmacology Study Endpoints

In Study AVT04-GL-101, the following primary endpoints were selected for establishing PK similarity: maximum serum concentration (Cmax) and total area under the serum concentration-time curve (AUC) from time zero (predose) extrapolated to infinity based on the last quantifiable concentration ($AUC_{0\text{-}inf}$).

The secondary PK parameters to be determined or calculated from the serum concentration-time data were the area under the serum concentration-time curve up to time t ($AUC_{0\text{-}t}$), where t is the last time point with concentrations above the lower limit of quantitation (LLOQ), time to maximum serum concentration (Tmax), elimination rate constant (Kel), elimination half-life (t1/2), volume of distribution (Vz/F) and apparent clearance (CL/F). Other secondary endpoints included safety, tolerability, and immunogenicity.

Bioanalytical Method and Performance for PK samples

The quantitation of study drug in human serum was performed with a sandwich assay on 96-well microtiter plates using Meso Scale Discovery (MSD) electrochemiluminescence (ECL) technology. The assay was validated for the quantitation of study drugin serum of healthy subjects as well as in serum of PsO patients (validation reports Reports N-A-IMM-18-167 and N-A-IMM-19-126, respectively). During the method validation, AVT04, EU-Stelara, and US-Stelara were used as QC samples to assess the suitability of the assay. See detailed information about the assay validation in Appendix 13.2.1.

Bioanalytical Method and Performance for Immunogenicity samples

See review by Office of Biotechnology Products (OBP) for details.

Reference ID: 5258586

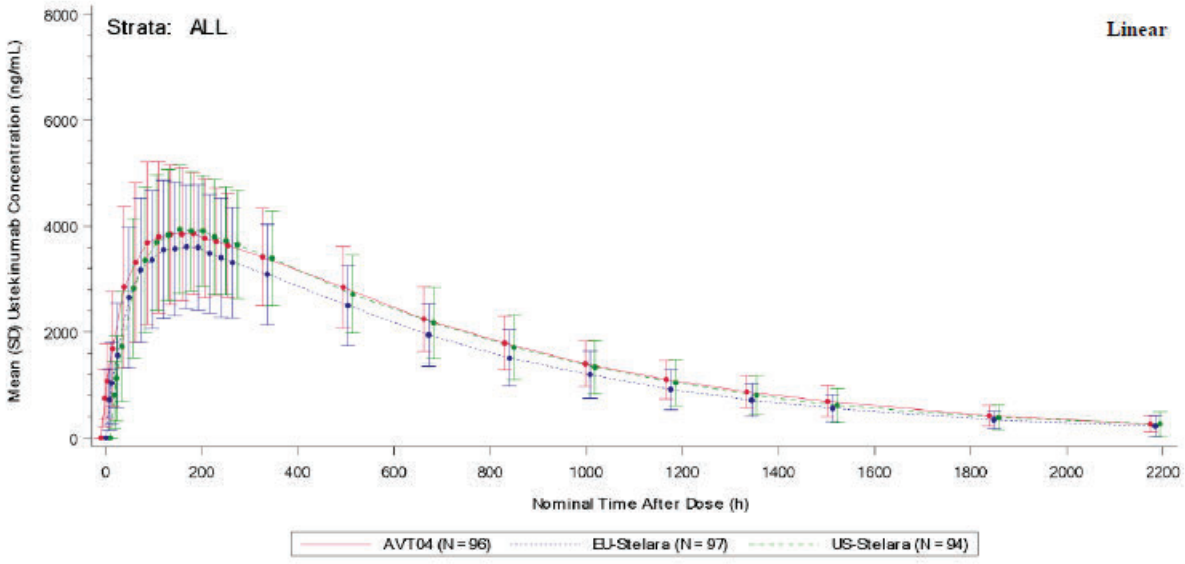
PK Similarity Assessment

Mean serum concentration-time profiles were similar following a single 45 mg/0.5 mL SC injection of either AVT04, EU-Stelara or US-Stelara, with mean EU-Stelara concentrations being slightly lower than those observed for AVT04 and US-Stelara (Figure 2).

PK similarity was demonstrated between AVT04 and US-Stelara and between EU-Stelara and US-Stelara. The 90% CIs for the least squares (LS) GMRs of Cmax, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ for these pairwise comparisions were all within the pre-defined criteria of 80% –125%. The statistical analysis results of GMR and 90% CI of the primary PK endpoints are listed in (Table 3 in section 5.1).

PK similarity assessment did not meet the pre-specified margin when comparing AVT04 and EU-Stelara as the 90% CI of the AUC_{inf} exceeded 80% to 125% margin (upper limit was 126.4%). The review team concluded that the deviation from the upper limit of PK similarity for the AVT04/EU-Stelara comparison (126.4%) does not impact the validity of establishing the PK component of the scientific bridge, based on the totality of evidence. See section 5.1.1 for additional details.

Figure 2: Serum concentration time profile (mean ± SD) of study drug by treatment group



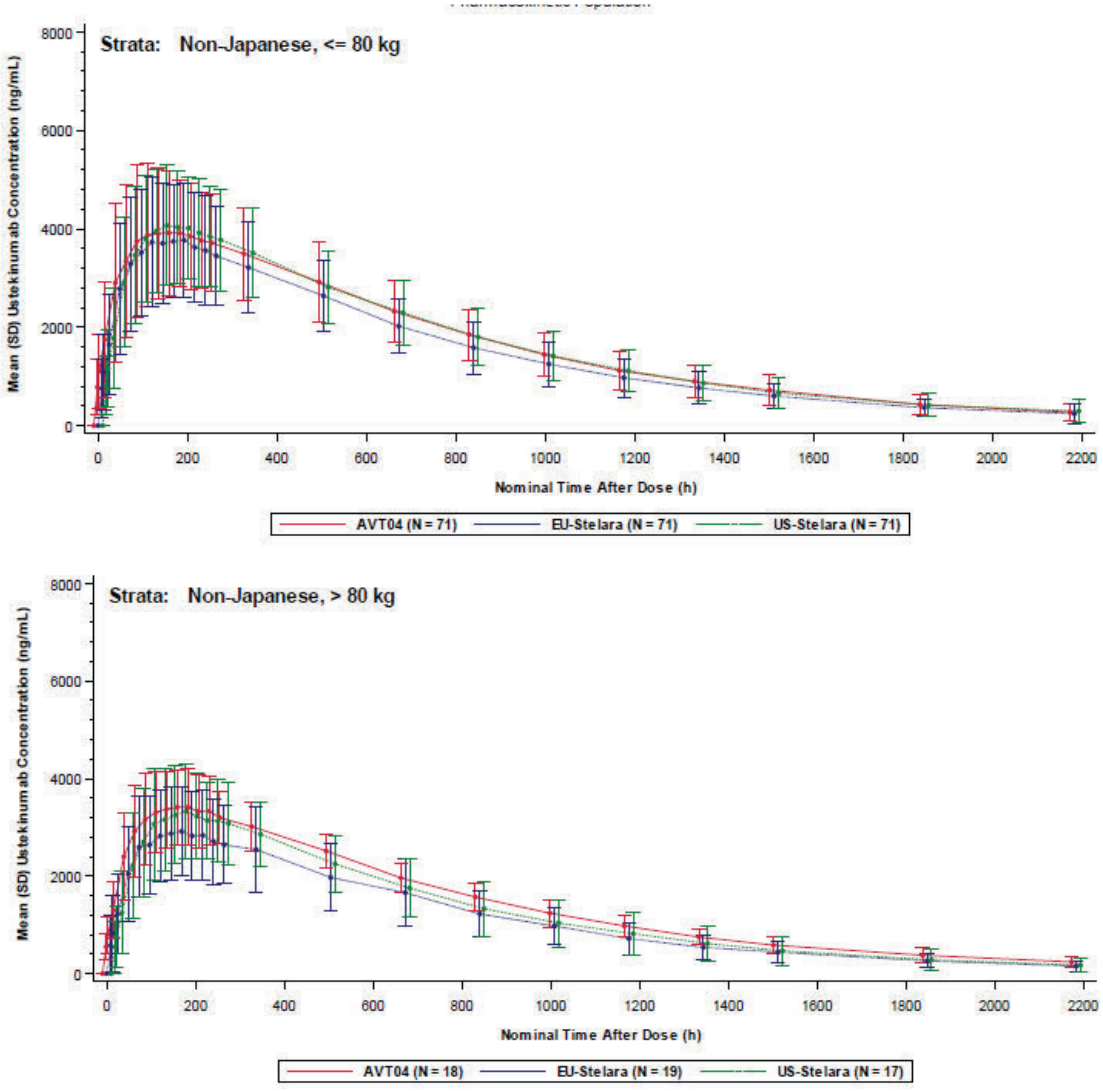
Source: Applicant CSR AVT04-GL-101, Table Figure 14.2.1.4

Systemic exposure to study drug is expected to be body weight dependent. As a result the effect of body weight on PK was evaluated in subjects with body weight ≤ 80 kg and > 80 kg.

Reference ID: 5258586

Systemic exposure to study drug was body weight dependent, with lower exposures in the non-Japanese >80 kg subgroup compared with the non-Japanese ≤80 kg subgroup across all three treatment groups (Figure 3). Mean concentration time profiles were generally comparable between AVT04 versus US-Stelara for both ≤ 80 kg and >80 kg subgroups. A trend towards lower exposures for EU-Stelara relative to AVT04 and US-Stelara was seen in both ≤ 80 kg and >80 kg subgroups. However, this does not impact the overall interpretation of the results as the distribution of subjects are comparable in both body weight tiers across all the treatment groups.

Figure 3: Serum concentration time profile (mean ± SD) of study drug in subjects ≤ 80 kg and subjects > 80 kg.



Source: Applicant CSR AVT04-GL-101, Figure 14.2.1.5

Reference ID: 5258586

OSIS Inspection results:

OSIS inspections for the clinical and bioanalytical sites are going to be deferred until the next review cycle.

Reference ID: 5258586

5.3.2. Study AVT04-GL-301

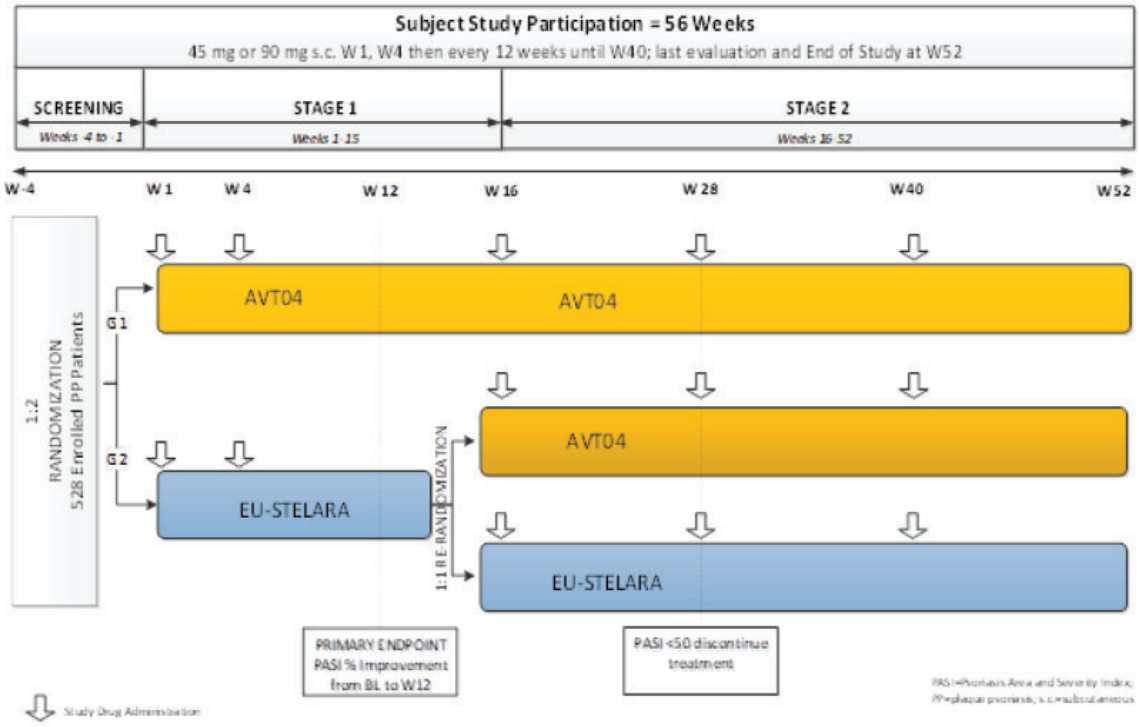
Clinical Pharmacology Study Design Features

Study AVT04-GL-301 was a multicenter, double-blind, randomized, active-control clinical study to compare the efficacy, safety, PK and immunogenicity of AVT04 versus EU-Stelara in patients with moderate to severe chronic PsO. Patient randomization was stratified by presence or absence of previous biologic treatment and by body weight category. Figure 4 describes the study scheme.

Patients received an initial dose of AVT04 or EU-Stelara at a dose of 45 mg SC for patients ≤ 100 kg or 90 mg SC for patients >100 kg followed by 45 mg SC or 90 mg SC 4 weeks later. At Week 16, patients who were initially randomized to receive AVT04 continued to receive AVT04 45 mg or 90 mg SC every 12 weeks at Weeks 16, 28, and 40 (unless withdrawn from the study). Patients who were initially randomized to EU-Stelara were re-randomized at Week 16 to receive AVT04 or continue to receive EU-Stelara in a 1:1 ratio. Serum trough concentrations (Ctrough) of AVT04 and EU-Stelara at steady state were evaluated in all patients with PK sampling at Week 1/Day 1 (pre-dose), and pre-dose at Weeks 4, 16, 28, 40, and at the EoS visit at Week 52. Serum samples for immunogenicity assessment (ADA and NAb) were collected pre-dose, Week 1/Day 1, 4, 12, 16, 28, 40 (end of treatment (EoT)), and 52 (EoS). A schematic representation of the study design is shown in Figure 4 below.

Reference ID: 5258586

Figure 4: Schematic of study design for Study AVT04-GL-301



Abbreviations: BL = Baseline; EoS = End-of-Study; EU = European Union; G = group; PASI <50 = less than 50% improvement in Psoriasis Area and Severity Index; PP = plaque psoriasis; s.c. = subcutaneous; W = week.

A comparison of trough concentration (Ctrough) between AVT04 and EU-Stelara is provided in Table 4 below. Ctrough were comparable across AVT04 and EU-Stelara treated groups at Week 16. Ctrough in patients who were switched to AVT04 (EU-Stelara/AVT04) at Week 28 remained comparable to patients who remained on EU-Stelara for the same period (EU-Stelara/EU-Stelara).

Reference ID: 5258586

Table 4: Serum Trough Study Drug Concentrations (ng/mL) from Baseline to Week 28 (Study AVT04-GL-301)

Visit	n	Mean (SD)
AVT04/AVT04 (N=193)		
Baseline	193	0.28 (3.966)
Week 16	192	420.82 (292.844)
Week 28	173	319.10 (259.228)
EU-Stelara/AVT04 (N=192)		
Baseline	192	1.29 (15.449)
Week 16	188	334.78 (265.512)
Week 28	162	283.00 (219.661)
EU-Stelara/EU-Stelara (N=189)		
Baseline	188	NA
Week 16	188	381.15 (235.408)
Week 28	167	310.74 (220.893)

Source: Applicant CSR AVT04-GL-301, Table 14.3.5.2.2

5.4. Clinical Immunogenicity Studies

5.4.1. Study AVT04-GL-301

Immunogenicity upon repeated dosing was evaluated in Study AVT04-GL-301 in subjects with PsO.

Immunogenicity endpoints

Anti-drug antibodies (ADA) and neutralizing antibodies (nAb) were selected as the immunogenicity endpoints. Further, the impact of immunogenicity on PK was compared across both treatment arms and also following a single transition from EU-Stelara to AVT04.

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 in the study samples

The ADA response to study drug was detected using a validated bridging assay based on MSDelectrochemiluminescent method (ECL) (validation report N-A-IMM-19-127). The NAb against study drug were detected using a validated MSD-ECL method (validation report N-A-IMM-19-128). Both assays appear to have exhibited adequate drug tolerance considering the systemic levels of study drug in the study. Clinical pharmacology defers to the Office of Biotechnology Products (OBP) for the acceptability of ADA and NAb bioassay methods. Refer to the OBP Immunogenicity review for further details.

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

Reference ID: 5258586

Serum samples for ADA and NAb assay were collected in Study AVT04-GL-301 from Week 0 to Week 52 at Day 1, and Weeks 4, 12, 16, 28, 40 (EoT), and 52 (EoS) along with serum PK samples at each timepoint. The last dose, either AVT04 or EU- Stelara, was administered at Week 40. The last ADA and NAb samples were collected 12 weeks after the last dose. The sampling time points for ADA and NAb were adequate to capture the early onset of immunogenicity as well as assess the impact of immunogenicity on PK.

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

The incidence of ADA- and NAb-positive patients from Baseline up to Week 16 are summarized in Table 5 and from Baseline up to Week 28 in Table 6.

Table 5: Immunogenicity results for binding ADA and NAb in Study AVT04-GL-301 up to week 16

	N	Anti-Drug antibody		NAb
		Baseline	Treatment-Induced	
AVT04	194	9/194 (4.6%)	46/185 (24.9%)	14/194 (7.2%)
EU-Stelara	387	5/386 (1.3%)	206/382 (53.9%)	68/387 (17.6%)

Source: Applicant analysis (CSR Study AVT04-GL-301 Table 11.23)

Table 6: Immunogenicity results for binding ADA and NAb in Study AVT04-GL-301 at Week 16 and Week 28 following single switch at Week 16.

	AVT04/AVT04 n (%)	EU-Stelara /AVT04 n (%)	EU-Stelara/EU-Stelara n (%)
Week 16	m=192#	m=189#	m=188#
Binding (ADA)	48 (25.0)	103 (54.5)	79 (42.0)
Neutralizing Antibodies	12 (25.0*)	36 (35.0*)	20 (25.3*)
Week 28	m=173#	m=162#	m=168#
Binding (ADA)	37 (21.4)	62 (38.3)	61 (36.3)
Neutralizing Antibodies	14 (37.8*)	16 (25.8*)	15 (24.6*)

m=number of patients assessed for ADA post-dose up to Week 16 dose. Patients with ADA positive at baseline are not included in m.
* Value represents the percentage of ADA positive patients who developed neutralizing antibodies.
Source: Applicant analysis (CSR Study AVT04-GL-301 Table 11.24)

The ADA positive rate in patients receiving AVT04 was numerically lower than patients receiving EU-Stelara. Up to Week 16, the frequency of treatment-emergent ADAs was 53.9% in the EU-Stelara group compared to 24.9% in the AVT04 group. The overall frequency of

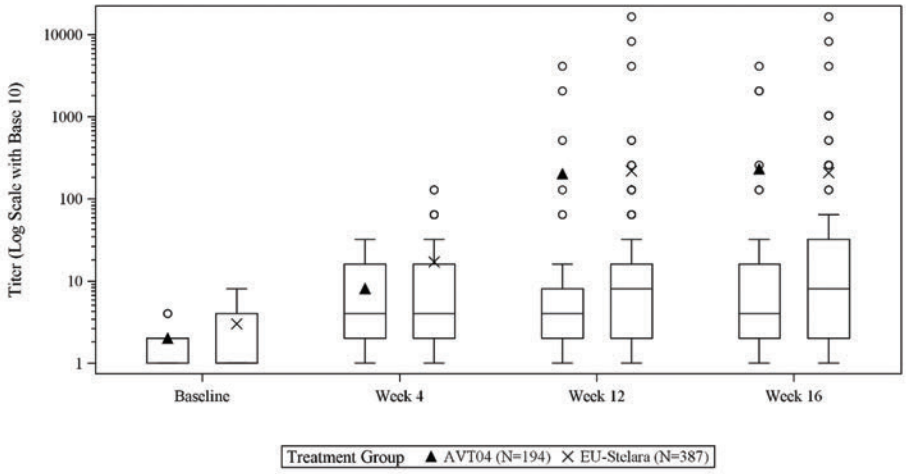
Reference ID: 5258586

NAbs was lower in the AVT04 group compared to EU-Stelara group.

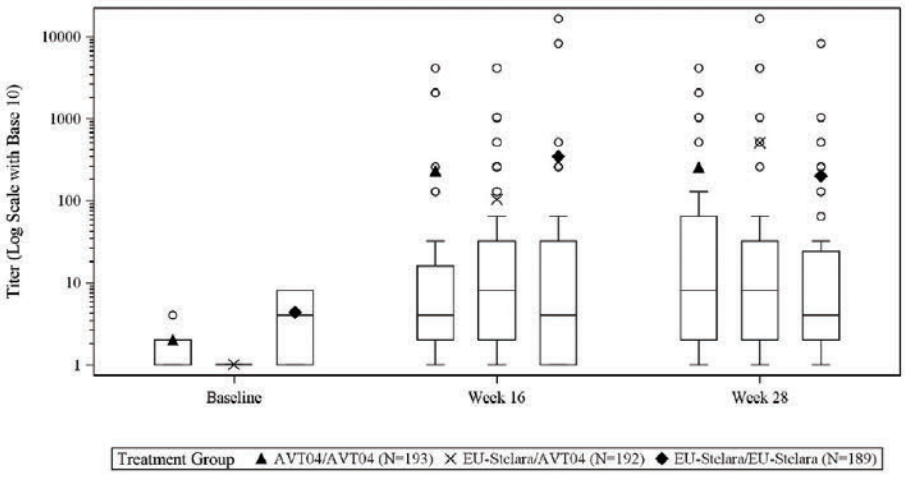
In patients switched from EU-Stelara to AVT04 at Week 16, the ADA incidence through Week 28 was generally comparable to patients who remained on EU-Stelara. Treatment-emergent ADA incidence was 4.8%, 4.5%, and 6.7% in AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups, respectively, through Week 28. Of patients with treatment-emergent ADAs, no patient was positive for NAbs through Week 28.
Median ADA titers increased up to Week 12 in all treatment groups and were similar at Week 12 and Week 16 between the treatment groups (Figure 5 Panel A). Similar trends were observed at Week 28 following a single switch at Week 16 (Figure 5 Panel B).

Figure 5: Box Plot of ADA titers from across treatment groups in Study AVT04-GL-301

Panel A: ADA titer through Week 16 across the treatment groups



Panel B: ADA titer through Week 28 following a single switch at Week 16



Source: CSR Study AVT04-GL-301 Figure 11.5 and Figure 11.6

Reference ID: 5258586

Analysis of the immunogenicity incidence including following the single transition, support the conclusion that there are no clinically significant differences in immunogenicity incidence between AVT04 and EU-Stelara.

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

ADA had similar effects on pharmacokinetics of AVT04 and EU-Stelara (Table 7, Table 9). Mean study drug serum trough levels of both AVT04 and EU-Stelara treatment groups were lower in patients who were ADA positive compared to patients who were ADA negative. Similarly, mean study drug serum trough levels in NAb-positive patients were lower compared to the overall population in both AVT04 and EU-Stelara treatment groups (,). Overall, Ctrough concentrations were generally comparable between AVT04 and EU-Stelara arms in the ADA-positive and NAb-positive subjects.

At week 28, mean study drug serum trough levels of all treatment groups (AVT04/AVT04, EU-Stelara/AVT04 and EU-Stelara/EU-Stelara) were higher in those patients who were ADA negative and lower in those patients who were ADA positive compared to the overall population ().

Table 7: Effect of ADA status on Serum Trough Levels (ng/mL) up to Week 16

		AVT04		EU-Stelara
	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
ADA positive		N=55		N=211
Week 4	55	1,864.93 (831.145)	211	1,734.61 (803.945)
Week 16	54	278.79 (269.734)	204	266.66 (218.099)
ADA negative		N=139		N=176
Week 4	139	2,244.60 (802.458)	176	2,203.10 (755.058)
Week 16	138	476.40 (283.461)	173	465.26 (245.940)

Source: Created by Reviewer based on data from CSR Study AVT04-GL-301 Table 14.3.5.3.1

Table 8: Effect of NAb status on Serum Trough Levels (ng/mL) up to Week 16

		AVT04		EU-Stelara
NAb positive		N=14		N=68
Week 4	14	1,628.43	68	1,628.53

Reference ID: 5258586

		(814.637)		(844.118)
Week 16	14	121.78 (184.653)	65	165.12 (184.679)
NAb negative		N=180		N=319
Week 4	180	2,176.51 (816.445)	319	2,015.70 (793.881)
Week 16	178	444.34 (287.065)	312	397.94 (244.907)

Source: Created by Reviewer based on data from CSR Study AVT04-GL-301 Table 14.3.5.3.1

Table 9: Effect of ADA status on Serum Trough Levels (ng/mL) up to Week 28 following single switch at Week 16

	AVT04/AVT04		EU-Stelara/ AVT04		EU-Stelara/EU-Stelara	
	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
ADA positive		N=61		N=118		N=98
Week 16	60	269.94 (261.277)	115	237.97 (209.780)	98	312.36 (232.485)
Week 28	56	238.25 (268.176)	99	212.59 (174.286)	87	256.02 (217.926)
ADA negative		N=132		N=74		N=91
Week 16	132	489.41 (281.289)	73	487.28 (273.624)	90	456.06 (215.977)
Week 28	117	357.79 (246.730)	63	393.65 (238.594)	80	370.26 (209.627)

Source: Created by Reviewer based on data from CSR Study AVT04-GL-301 Table 14.3.5.3.2

Table 10: Effect of NAb status on Serum Trough Levels (ng/mL) following single switch at Week 16

	AVT04/AVT04		EU-Stelara/ AVT04		EU-Stelara/EU-Stelara	
	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)	n	Mean (SD) (ng/mL)
NAb positive		N=19		N=43		N=29
Week 16	19	180.74 (245.343)	42	170.77 (187.049)	29	180.97 (183.057)
Week 28	16	165.74 (200.887)	35	153.87 (153.396)	26	120.87 (99.326)

Reference ID: 5258586

NAb negative		N=147		N=149		N=160
Week 16	173	447.19 (286.121)	146	381.96 (266.441)	159	417.66 (225.728)
Week 28	157	334.73 (259.910)	127	318.59 (222.252)	141	345.75 (219.463)

Source: Created by Reviewer based on data from CSR Study AVT04-GL-301 Table 14.3.5.3.2

ADA status did not appear to have a significant effect on clinical efficacy (Table 11). Similar changes in the Psoriasis Area and Severity Index (PASI) score was observed for both AVT04 and EU-Stelara in both ADA-positive and ADA-negative patients (Table 11). Similar trends were observed when comparing NAb positive and NAb negative patients in both AVT04 and EU-Stelara groups (Table 12).

Reference ID: 5258586

Table 11: Effect of ADA status on percent improvement from baseline in Psoriasis Area and Severity Index (PASI) at Week 12

% change from baseline	AVT04	EU-Stelara
	LS Mean (SE)	LS Mean (SE)
ADA positive	N=44	N=168
Week 12	86.0 (3.053)	84.3 (1.562)
ADA negative	N=150	N=216
Week 12	87.0 (1.322)	87.9 (1.102)

Source: Created by Reviewer based on data from CSR Study AVT04-GL-301 Table 14.2.4.5

Table 12: Effect of NAb status on percent improvement from baseline in Psoriasis Area and Severity Index (PASI) at Week 12

% change from baseline	AVT04	EU-Stelara
	LS Mean (SE)	LS Mean (SE)
NAb positive	N=11	N=51
Week 12	83.2 (7.137)	83.2 (3.308)
NAb negative	N=183	N=333
Week 12	87.0 (1.255)	86.8 (0.930)

Source: Created by Reviewer based on data from CSR Study AVT04-GL-301 Table 14.2.4.6

Overall, evaluations of immunogenicity incidence and its impact on pharmacokinetic, and efficacy responses support the conclusion of similar immunogenicity response between AVT04 and EU-Stelara.

5.4.2. Study AVT04-GL-101

In the PK similarity study, Study AVT04-GL-101, immunogenicity of AVT04 was compared to US-Stelara and EU-Stelera after a single dose in healthy subjects (). ADA Incidence and nAb incidence in the AVT04 treatment group were slightly lower compared to EU-Stelara and US-Stelara in the PK similarity study. The incidence of anti-drug antibody (ADA) formation at the end of the study (Day 92) in healthy subjects was 27.6 % in the AVT04 group compared to 48.5% in the EU-approved Stelara and 45.4% in the US-licensed Stelara groups. There was no apparent impact of immunogenicity on the PK of the study drugs. Overall, we conclude that the these differences are not considered to be clinically significant and the results support a conclusion of no clinically meaningful differences between AVT04 and US-Stelara.

Reference ID: 5258586

Table 13: Summary of ADA and NAb incidence in Study AVT04-GL-101

Treatment Group		Day 1 Pre-dose	Day 1 12 h Postdose	Day 9	Day 15	Day 29	Day 57	Day 78	Day92 /EOS	Any Positive
Antidrug Antibody Positivity										
AVT04 (N = 98)	n (%)	1 (1.0)	0	11 (11.2)	14 (14.3)	9 (9.2)	13 (13.3)	21 (21.4)	27 (27.6)	36 (36.7)
EU-Stelara (N = 99)	n (%)	3 (3.0)	1 (1.0)	30 (30.3)	19 (19.2)	14 (14.1)	30 (30.3)	43 (43.4)	48 (48.5)	59 (59.6)
US-Stelara (N = 97)	n (%)	1 (1.0)	2 (2.1)	19 (19.6)	15 (15.5)	14 (14.4)	33 (34.0)	37 (38.1)	44 (45.4)	52 (53.6)
Neutralizing Antibody Positivity										
AVT04 (N = 98)	n (%)	0	0	0	1 (2.8)	0	2 (5.6)	7 (19.4)	11 (30.6)	12 (33.3)
EU-Stelara (N = 99)	n (%)	0	0	5 (8.5)	3 (5.1)	1 (1.7)	10 (16.9)	14 (23.7)	20 (33.9)	25 (42.4)
US-Stelara (N = 97)	n (%)	0	0	2 (3.8)	2 (3.8)	4 (7.7)	20 (38.5)	19 (36.5)	22 (42.3)	28 (53.8)

Authors:
Anand Balakrishnan
Clinical Pharmacology Reviewer

Chinmay Shukla
Clinical Pharmacology team leader

6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

Comparative Efficacy: The comparative efficacy of AVT04 and EU-Stelara was evaluated in Study AVT04-GL-301 for the FDA's recommended primary endpoint of the percent improvement in PASI at Week 12. The 90% CI for the treatment difference for both the Per Protocol Set (PPS) and the Intent-to-Treat (ITT) set fell within the prespecified margins of ±10 [PPS CI: (-2.36, 3.50); ITT set CI: (-2.40, 3.78)]. Thus, the study demonstrated no meaningful differences between AVT04 and EU-Stelara regarding the primary efficacy endpoint.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual clinical or statistical uncertainties that impact a demonstration of no meaningful differences between AVT04 and EU-Stelara.

Authors:
Carin Kim
Clinical Statistics Reviewer

Somesh Chattopadhyay
Clinical Statistics Team Leader

Reference ID: 5258586

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. Study AVT04-GL-301

Study AVT04-GL-301, a comparative clinical study in subjects with chronic moderate to severe PsO, was evaluated to assess whether there were any meaningful differences between AVT04 and EU-Stelara.

Data and Analysis Quality

There are no concerns regarding data quality and integrity.

Study Design and Endpoints

Study AVT04-GL-301 was a multicenter, double-blind, randomized, active-control comparative clinical study comparing the efficacy, safety, and immunogenicity of AVT04 and EU-Stelara in subjects with moderate to severe chronic PsO. The study included two stages. In Stage 1, subjects were randomized to either AVT04 or EU-Stelara in a 1:2 ratio to the following treatment arms:

- AVT04: Initial loading dose of AVT04 45 mg ≤100kg) or 90 mg (>100 kg) administered SC, followed by 45 mg or 90 mg 4 weeks later.
- EU-Stelara: Initial loading dose of EU-Stelara 45 mg ≤100kg) or 90 mg (>100 kg) administered SC, followed by 45 mg or 90 mg 4 weeks later.

At Week 16, subjects initially randomized to AVT04 continued to receive AVT04 45 mg or 90 mg every 12 weeks at Weeks 16, 28, and 40. Subjects initially randomized to EU-Stelara were re-randomized to the following treatment groups in a 1:1 ratio:

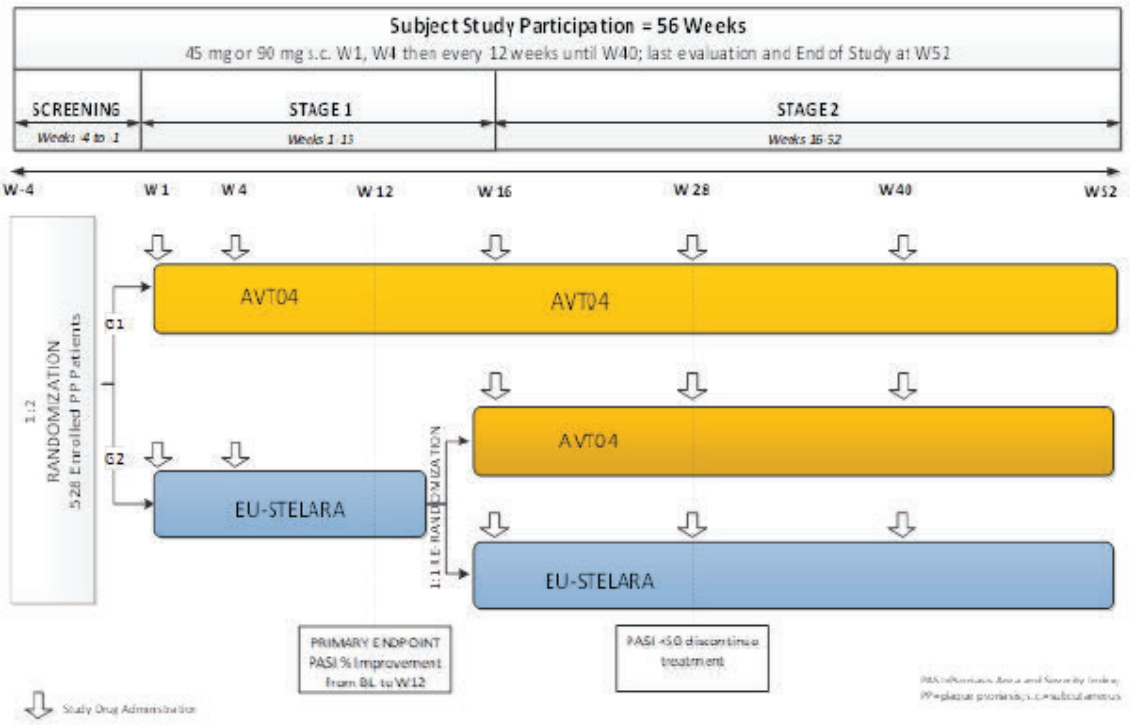
- AVT04 45 mg or 90 mg every 12 weeks, at Weeks 16, 28, 40
- EU-Stelara 45 mg or 90 mg every 12 weeks at Weeks 16, 28, 40

At Week 28, non-responders (PASI improvement <50% compared to baseline) were not administered treatment at Week 28. Subjects achieving at least PASI 50 continued in the study.

In Stage 2, subjects originally randomized to AVT04 in Stage 1 continued to receive AVT04. At Week 16, subjects with less than 50% improvement in PASIscore were withdrawn from the study, while subjects with at least 50% improvement in PASI entered Stage 2. Subjects originally randomized to EU-Stelara were randomized to receive AVT04 or EU-Stelara in a 1:1 ratio. Subjects received their last dose of study treatment at Week 40 and were followed for efficacy through Week 52. See Figure 6. Note that the Applicant's primary clinical study report (CSR1) included data through Week 28 database freeze.

Figure 6: Study Design (AVT04-GL-301)

Reference ID: 5258586



Abbreviations: BL = Baseline; EoS = End-of-Study; EU = European Union; G = group; PASI <50 = less than 50% improvement in Psoriasis Area and Severity Index; PP = plaque psoriasis; s.c. = subcutaneous; W = week.

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Source: Applicant's Study Report (page 29 of 198)

The study enrolled subjects ages 18 to 75 years of age with stable moderate to severe PsO who had involved body surface area BSA) ≥ 10%, PASI ≥ 12, and static Physician's Global Assessment sPGA) ≥ 3, with stable disease for at least 2 months.

The sPGA was calculated by averaging the induration, erythema, and scaling scores that was then rounded to the nearest whole number. The subscales and the sPGA are shown below.

Static Physician's Global Assessment (sPGA)
Induration (I) (averaged over all lesions):
0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = severe plaque elevation, = 1 mm
5 = very severe plaque elevation, = 1.25 mm or more
Erythema (E) (averaged over all lesions):
0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration
5 = dusky to deep red coloration

Reference ID: 5258586

Scaling (S) (averaged over all lesions):
0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion
2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = severe; thick, non-tenacious scale dominates
5 = very severe; very thick tenacious scale predominates
Total Average=(I+E+S)/ 3
Physician's Static Global Assessment based upon the Total Average
0 = Clear, except for residual discoloration
1 = Minimal-majority of lesions have individual scores for I+E+S / 3 that averages 1
2 = Mild-majority of lesions have individual scores for I+E+S / 3 that averages 2
3 = Moderate-majority of lesions have individual scores for I+E+S / 3 that averages 3
4 = Severe-majority of lesions have individual scores for I+E+S / 3 that averages 4
5 = Very severe-majority of lesions have individual scores for I+E+S / 3 that averages 5
Note: Scores should be rounded to the nearest whole number.
Source: Applicant's annotated ePRO form (pages 9-10 of 13)

Statistical Methodologies

- The primary endpoint of the percent improvement in PASI at Week 12 was analyzed with analysis of covariance (ANCOVA) including terms for treatment and the stratification variables (prior use of biologic therapy), and the baseline PASI score and baseline body weight as a covariate. Two-sided 90% CIs for the treatment difference were calculated using least squares means (LS means) and compared to margins of ±10.
-
- The primary analysis population was the PPS and the ITT set was used for sensitivity analyses. The PPS was defined as all subjects who had completed the treatment period without protocol deviations that impacted the efficacy assessment. The PPS excluded 3 subjects due to protocol deviations, and 1 subject due to ending treatment in Stage 1. The PPS analysis was supportive. The primary method of handling missing data was the last observation carried forward (LOCF).
-
- The secondary efficacy endpoints were analyzed with descriptive statistics and were not adjusted for multiplicity.

- Subgroup analyses for the primary endpoint were calculated by weight (≤80 kg, >80Kg), regions (Europe vs. China), previous biologic treatment (yes/no), and the analyses were based on the ITT set.

Subject Disposition

Study AVT04-GL-301 randomized a total of 581 subjects: 194 to AVT04 and 387 to EU-Stelara. Of the 581 subjects, 575 (99%) completed Stage 1 (Week 16), and 6 subjects (1%) discontinued Stage 1 (1 in AVT04, 5 in EU-Stelara). Reasons for discontinuation include

Reference ID: 5258586

adverse events (2 in EU-Stelara), withdrawal of consent (2 in EU-Stelara), lost to follow-up (1 in EU-Stelara), and principal investigator (PI) decision (1 in AVT04). See Table 14.

Table 14: Subject Disposition – Stage 1

	AVT04 N=194	EU-Stelara N=387	Total N=581
Randomized (ITT)	194	387	581
Discontinued Stage 1 (Week 16)	1 (0.5%)	5 (1.3%)	6 (1.0%)
Primary reason for early study drug discontinuation			
Adverse event	0	2	2
Death	0	0	0
Withdrawal of consent	0	2	2
Lost to follow-up	0	1	1
Protocol deviation	0	0	0
PI decision	1	0	1
Other	0	0	0
Primary reason for early termination from study			
Adverse event	0	2	2
Death	0	0	0
Withdrawal of consent	0	2	2
Lost to follow-up	0	1	1
Protocol deviation	0	0	0
PI decision	1	0	1
Other	0	0	0
Completed Stage 1 (Week 16)	193 (99.5%)	382 (98.7%)	585 (99.0%)
Completed Stage 1 but did not enter Stage 2	0	1	1
Adverse event	-	1	1

Source: Applicant's Study Report (page 67 of 198)

At Week 16, subjects randomized to AVT04 in Stage 1 continued treatment with AVT04, and subjects randomized to EU-Stelara in Stage 1 were randomized in a 1:1 ratio to continue EU-Stelara or switch to AVT04. The most common reason for study discontinuation in Stage 2 was adverse events. See Table 15.

Table 15: Subject Disposition – Stage 2

	AVT04 N=193	EU-Stelara/ AVT04 N=192	EU-Stelara/ EU-Stelara N=189	EU-Stelara N=381	Total N=574
Entered Stage 2	193	192	189	381	574
Completed Week 28	189 (97.9%)	180 (93.8%)	184 (97.4%)	364 (95.5%)	553 (96.3%)

Reference ID: 5258586

Discontinued in Stage 2 through 28	1 (0.5%)	5 (2.6%)	5 (2.6%)	10 (2.6%)	11 (1.9%)
Primary reason for early study discontinuation					
Adverse event	1	2	4	6	7
Death	0	0	0	0	0
Withdrawal of consent	0	2	0	2	2
Lost to follow-up	0	0	0	0	0
Protocol deviation	0	0	0	0	0
PI decision	0	1	1	2	2
Other	0	0	0	0	0
Primary reason for early termination from study					
Adverse event	1	2	4	6	7
Death	0	0	0	0	0
Withdrawal of consent	0	2	0	2	2
Lost to follow-up	0	0	0	0	0
Protocol deviation	0	0	0	0	0
PI decision	0	1	1	2	2
Other	0	0	0	0	0

Source: Applicant's Study Report (page 70 of 198)

Table 16 shows the number and reason of exclusion from the PPS. Note that Subject (b) (6) in the EU-Stelara arm weighed 100.5 kg and was supposed to receive 90 mg, but received 45 mg, and was excluded from the PPS. However, this subject was 100% clear on PASI by Week 8.

Table 16: Reasons for exclusion from the PPS

	AVT04 N=194	**EU-Stelara N=387**	**Total N=581**
Randomized (ITT)	194	387	581
PPS	194 (100%)	383 (99%)	577 (99%)
Early Termination before Week 12	0	1	1
Protocol deviations that impact the primary endpoint assessment (during blinded review)	0	3	3
Wrong treatment/dose (subject>100 kg received 45 mg instead of 90 mg) [(1)] ***(1)***	0	1	1
Week 12 visit not performed due to SAE [(2)]	0	1	1

Reference ID: 5258586

Week 12 visit not performed due to AE [3]	0	1	1

Source: Applicant's Table 11.2 (study report page 79 of 198); (1) subject ID [redacted] SAE caused immobility, Week 12 visit not performed; (3 [redacted] (elevated liver enzymes – violation of inclusion criterion)

Four subjects excluded from the PPS were from 3 sites (4801, 4802, and 4808) in Poland. See Table17 regarding the list of subjects that were excluded from the PPS.

Table 17: List of subjects excluded from PPS

Subject ID	Treatment	Reasons for exclusion
[redacted]	EU-Stelara 45 mg	Wrong treatment/dose (subject>100 kg received 45 mg instead of 90 mg)
	EU-Stelara 45 mg	Early Termination before Week 12
	EU-Stelara 45 mg	Week 12 visit not performed due to SAE [2
	EU-Stelara 45 mg	Week 12 visit not performed due to AE [3]

Source: Reviewer table

Demographics and Baseline Characteristics

The demographic characteristics were generally balanced across treatment groups. The mean age was about 42 years and 6% of subjects were of age 65 years and older. The majority of subjects were male (63%), and all subjects were white. Eight percent of the subjects had prior use of biologics. Approximately 16% of the subjects weighed 100 kg at baseline.

Subjects were to have PASI ≥ 12, sPGA ≥ 3 and BSA ≥ 10% at baseline. Subjects had a mean PASI score of approximately 22 and 26% BSA. Approximately 56% of subjects had a sPGA score of 3 (moderate). The baseline disease characteristics were balanced across treatment arms. See Table 18.

Table 18: Demographics – Stage 1

	AVT04 N=194	EU-Stelara N=387	Total N=581
Age			
Mean (SD)	42.3 (12.96)	41.9 (12.77)	42.0 (12.83)
Median	41.0	40.0	40.0
Min, Max	18, 74	18, 73	18, 74
<65 years	183 (94.3%)	365 (94.3%)	548 (94.3%)
≥65 years	11 (5.7%)	22 (5.7%)	33 (5.7%)
Gender			
Female	87 (44.8%)	130 (33.6%)	217 (37.3%)
Male	107 (55.2%)	257 (66.4%)	364 (62.7%)
Race			
White	194 (100%)	387 (100%)	581 (100%)
Weight			

Reference ID: 5258586

Mean (SD)	83.48 (18.37)	84.19 (18.54)	83.96 (18.5)
Median	84.05	83.05	84.00
Min, Max	45.0, 146.0	40.7, 150.2	40.7, 150.2
≤80 kg	84 (43.3%)	167 (43.2%)	251 (43.2%)
>80 kg to ≤100 kg	80 (41.2%)	160 (41.3%)	240 (41.3%)
>100kg	30 (15.5%)	60 (15.5%)	90 (15.5%)
Prior biologic for psoriasis			
Yes	15 (7.7%)	29 (7.5%)	44 (7.6%)
No	179 (92.3%)	358 (92.5%)	537 (92.4%)
PASI			
Mean (SD)	22.05 (8.13)	22.22 (7.55)	22.17 (7.74)
Median	20.20	20.00	20.00
Min, Max	12.2, 55.2	12.2, 64.8	12.2, 64.8
sPGA			
Moderate	132 (68.0%)	241 (62.3%)	373 (64.2%)
Severe	49 (25.3%)	117 (30.2%)	166 (28.6%)
Very severe	13 (6.7%)	29 (7.5%)	42 (7.2%)
%BSA			
Mean (SD)	26.02 (13.23)	26.41 (12.26)	26.28 (12.58)
Median	23.00	23.00	23.00
Min, Max	10.0, 75.0	10.0, 84.0	10.0, 84.0

Source: Reviewer Analysis

As Stelara is a weight-based treatment, we evaluated the baseline disease characteristics by baseline weight group. See Table19. While the number of subjects is small for those that weigh > 100 kg, especially for those in the AVT04 arm (30 subjects) compared to those in the EU-Stelara arm (60 subjects), for subjects >100 kg, it appears that there were more sPGA of Severe subjects in the EU-Stelara arm (33%) compared to that in the AVT04 (20%) arm.

Table 19: Baseline Disease Characteristics by Baseline Body Weight

	≤100 kg		**>100 kg**	
	AVT04 45 mg N=164	**EU-Stelara 45 mg N=327**	**AVT04 90 mg N=30**	**EU-Stelara 90 mg N=60**
PASI				
Mean (SD)	21.55 (7.97)	21.92 (7.67)	24.80 (8.62)	23.88 (6.66)
Median	19.8	19.4	22.05	22.25
Min, Max	12.2, 51.6	12.2, 64.8	14.2, 55.2	14.2, 45.0
sPGA				
Moderate	112 (68%)	209 (64%)	20 (67%)	32 (53%)
Severe	43 (26%)	97 (30%)	6 (20%)	20 (33%)
Very severe	9 (6%)	21 (6%)	4 (13%)	8 (13%)
%BSA				
Mean (SD)	25.31 (12.66)	26.41 (12.46)	29.93 (15.69)	26.37 (11.18)
Median	23.0	23.0	25.0	22.5

Reference ID: 5258586

Min, Max	10.0, 75.0	10.0, 84.0	13.0, 84.0	12.0, 56.0

Source: Reviewer Analysis

Analysis of Primary Clinical Endpoint(s)

The primary efficacy endpoint was the percent improvement in PASI from baseline to Week 12 in the PPS with the analysis in the ITT set as supportive. The treatment difference was estimated using ANCOVA including terms for treatment and the stratification variable of prior use of biologic therapy, and weight and baseline PASI score as covariates. Two-sided 90% CIs for the treatment difference are calculated using LS means and compared to margins of ±10.

The 90% CIs for the difference in the percent improvement in PASI at Week 12 for both the ITT set and PPS fell within the margins of ±10, indicating no meaningful differences between AVT04 and EU-Stelara. See Table 20**.**

Table 20: Percent Improvement in PASI from Baseline to Week 12

Percent Improvement in PASI from Baseline to Week 12			
	AVT04	**EU-Stelara**	**Difference (SE) 90% CI**
Applicant's PPS LS Mean (SE)	N=194 87.3 (1.73)	N=383 86.8 (1.49)	0.4 (1.56) (-2.14, 3.01)
Applicant's ITT set (Observed) LS Mean (SE)	N=194 87.2 (1.73)	N=384 86.8 (1.49)	0.4 (1.56) (-2.16, 2.98)
Reviewer's PPS LS Mean (SE)	N=194 87.25 (1.73)	N=383 86.82 (1.49)	0.43 (1.56) (-2.63, 3.50)
Reviewer's ITT set LS Mean (SE)	N=194 87.31 (1.77)	N=387 86.62 (1.50)	0.69 (1.57) (-2.40, 3.78)

Source: Applicant's study report (Table 11.9) and Reviewer Analysis; LS Mean = Least squares mean, SE = standard error. The primary anlaysis method for the primary endpoint was the analysis of covariance (ANCOVA) including percent improvement in PASI as the response variable, randomized treatment group, baseline stratification variables of previous biologic treatment for psoriasis as factors, and with Baseline PASI score and Baseline body weight as continuous covariates.

For both the ITT set and PPS, subgroup analysis results of the percent improvement in PASI from baseline to Week 12 by baseline weight group are presented in Table 21. The treatment difference was estimated using ANCOVA including terms for treatment and the stratification variable of prior use of biologic therapy, and weight and baseline PASI score as covariates. For both the ITT set and PPS, the LS means were similar across the treatment arms. Two-sided 90% CIs for the treatment difference are provided for completion; however, as the number of subjects for the subgroup of bodyweight >100 kg at baseline is small, these subgroup analyses are considered exploratory and descriptive in nature.

Table 21: Percent Improvement in PASI from Baseline to Week 12 by Weight Group

Percent Improvement in PASI from Baseline to Week 12

Reference ID: 5258586

	AVT04	EU-Stelara	Difference (SE) 90% CI
≤ 100 kg			
Reviewer's PPS **LS Mean (SE)**	N=164 86.93 (1.91)	N=324 86.84 (1.64)	0.09 (1.70) (-3.25, 3.43)
Reviewer's ITT set **LS Mean (SE)**	N=164 87.01 (1.92)	N=327 86.59 (1.66)	0.42 (1.71) (-2.94, 3.78)
>100 kg			
Reviewer's PPS **LS Mean (SE)**	N=30 89.74 (4.12)	N=59 87.14 (3.54)	2.60 (3.91) (-5.18, 10.38)
Reviewer's ITT set **LS Mean (SE)**	N=30 89.63 (4.10)	N=60 87.29 (3.52)	2.35 (3.89) (-5.38, 10.07)

Source: Reviewer Analysis; LS Mean = Least squares mean, SE = standard error. The primary anlaysis method for the primary endpoint was the analysis of covariance (ANCOVA) including percent improvement in PASI as the response variable, randomized treatment group, baseline stratification variables of previous biologic treatment for psoriasis as factors, and with Baseline PASI score and Baseline body weight as continuous covariates.

Potential Effects of Missing Data

The proportion of subjects who discontinued the study was small with 4 subjects that were excluded from the PPS. To assess whether the conclusions could be impacted by even more extreme outcomes from subjects who did not have a Week 12 visit, instead of using LOCF, we considered two other approaches: 1) Baseline Carried Forward (BOCF) for the two subjects that were excluded from the per protocol (PP) analysis (i.e., 0% improvement), and 2) imputing 100% improvement in PASI for the two subjects that were excluded from the PP analysis for not having the Week 12 visit. Table 22 shows that, from the estimated treatment difference of 0.69 for the ITT analysis, this estimated treatment difference increases to 0.97 and 1.49 if you consider 0% improvement in PASI by using BOCF or 100% improvement in PASI, respectively. However, the CIs remain inside the margins of ±10. Therefore, the conclusion of no meaningful differences remains unchanged under both extreme scenarios. See Table 22.

Table 22: Reviewer's Results for the Primary Endpoint (BOCF, and 100% PASI)

Percent Improvement in PASI from Baseline to Week 12			
	AVT04	**EU-Stelara**	**Difference (SE) 90% CI**
Reviewer's ITT set **LS Mean (SE)**	N=194 87.31 (1.77)	N=387 86.62 (1.50)	0.69 (1.57) (-2.40, 3.78)
Reviewer's ITT set (BOCF) **LS Mean (SE)**	N=194 87.37 (1.73)	N=387 86.40 (1.49)	0.97 (1.56) (-2.22, 4.16)
Reviewer's ITT set (PASI100) **LS Mean (SE)**	N=194 87.50 (1.77)	N=387 86.01 (1.50)	1.49 (1.57) (-2.15, 5.09)

Source: Applicant's study report (Table 11.9) and Reviewer Analysis; LS Mean = Least squares mean, SE = standard error. The primary anlaysis method for the primary endpoint was the analysis of covariance (ANCOVA) including percent improvement in PASI as the response

Reference ID: 5258586

variable, randomized treatment group, baseline stratification variables of previous biologic treatment for psoriasis as factors, and with Baseline PASI score and Baseline body weight as continuous covariates.

Analysis of Secondary Clinical Endpoint(s)

The additional secondary efficacy endpoints were PASI response endpoints (PASI 50, PASI 75, PASI 90, PASI 100), success on the sPGA (0 or 1), change from baseline on the Dermatology Life Quality Index (DLQI), and change from baseline in %BSA. The endpoints were evaluated at a variety of timepoints. The response rates for the PASI response endpoints and sPGA at Week 12 for the ITT set and PPS are presented in Table 23. For both the ITT set and PPS, the response rates were generally similar across the treatment arms.

Table 23: Selected Secondary Endpoint Response Rates at Week 12

	ITT set		PPS	
Week 12	AVT04 N=194	EU-Stelara N=387	AVT04 N=194	EU-Stelara N=383
PASI50	156 (95%)	308 (94%)	184 (95%)	363 (95%)
PASI75	157 (81%)	315 (81%)	157 (81%)	314 (82%)
PASI90	106 (55%)	221 (57%)	106 (55%)	220 (57%)
PASI100	58 (30%)	115 (30%)	58 (30%)	115 (30%)
sPGA 0 or 1	152 (78%)	309 (80%)	152 (78%)	309 (80%)

Source: Reviewer analysis

Table 24 below shows the selected secondary endpoint response rates at Week 12 by weight group (≤100 kg, >100 kg). For subjects ≤ 100 kg, the response rates were generally slightly higher in the EU-Stelara arm compared to those in the AVT04 arm. For the subjects > 100 kg, the response rates at Week 12 for PASI75, PASI90, PASI100, sPGA 0 or 1 were numerically higher in the AVT04 arm compared to those in the EU-Stelara arm, and such findings might be due to having more sPGA of Severe subjects that weigh >100 kg in the EU-Stelara arm (33%) compared to the AVT04 (20%) arm at baseline. [Refer to Table19.] Given the small number of subjects in the subgroup of subjects with bodyweight > 100 kg at baseline, it would be difficult to draw a meaningful conclusion based on these findings.

Table 24: Selected Secondary Endpoint Response Rates at Week 12 by Weight Group

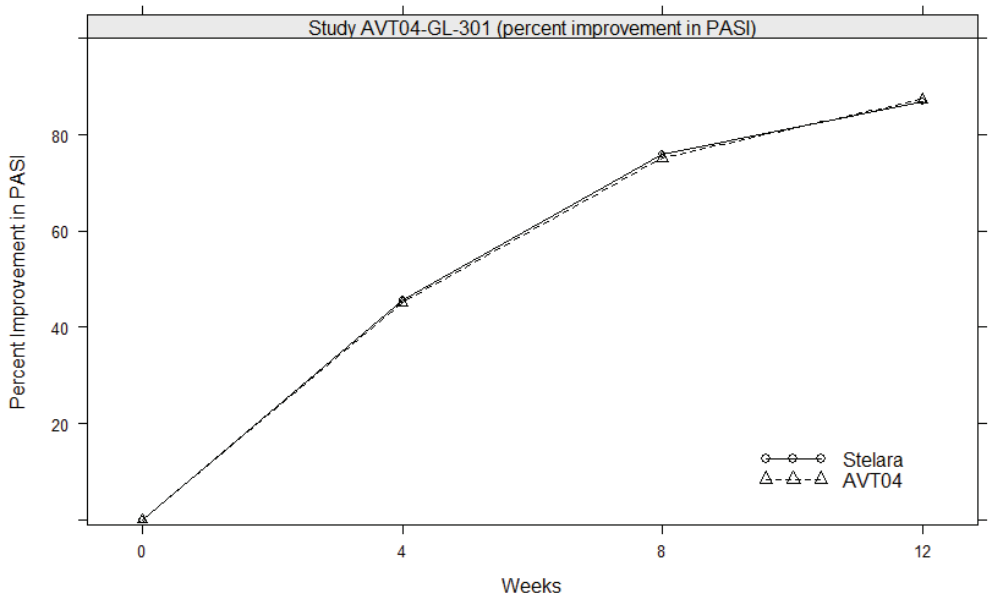
	ITT set ≤100 kg)		ITT set >100kg)	
Week 12	AVT04 45 mg N=164	EU-Stelara 45 mg N=327	AVT04 90 mg N=30	EU-Stelara 90 mg N=60
PASI50	156 (95%)	308 (94%)	28 (93%)	56 (93%)
PASI75	134 (82%)	271 (83%)	23 (77%)	44 (73%)
PASI90	88 (54%)	189 (58%)	18 (60%)	32 (53%)
PASI100	45 (27%)	96 (29%)	13 (43%)	19 (32%)
sPGA 0 or 1	128 (78%)	266 (82%)	24 (80%)	43 (72%)

Source: Reviewer Analysis

The percent changes in PASI for AVT04 and EU-Stelara were similar at each visit through Week 12. See Figure 7.

Reference ID: 5258586

Figure 7: Percent Improvement in PASI by Visit (PPS)



Source: Reviewer figure

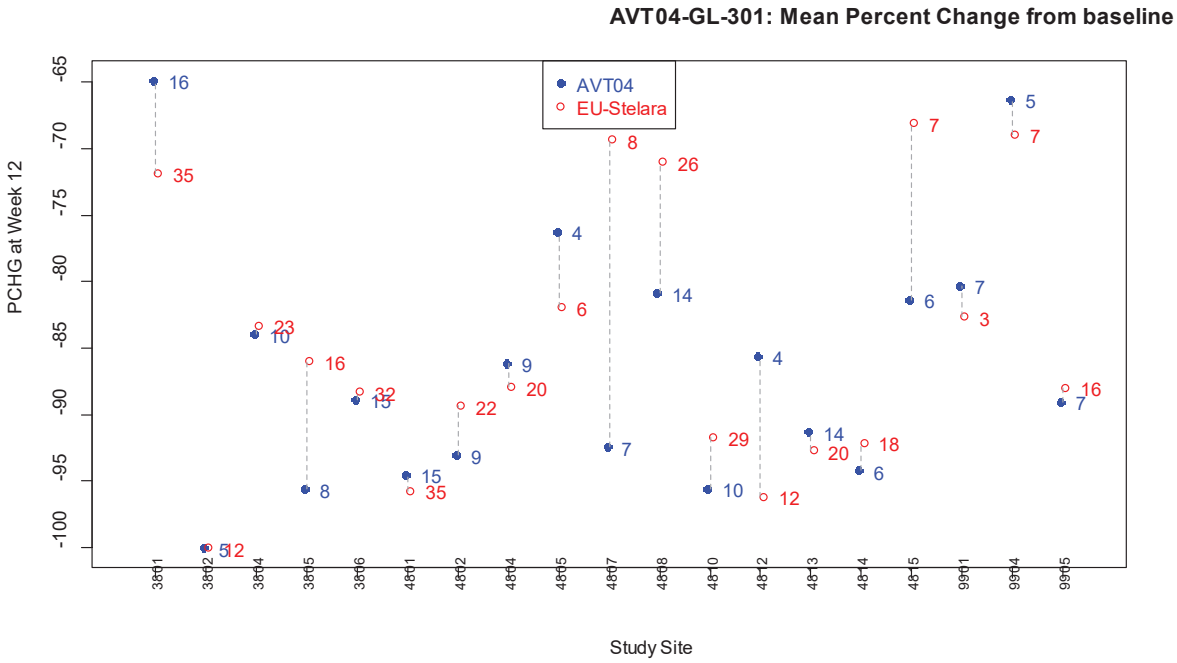
Additional Analyses

Subgroup Analyses

Subgroup analyses for the primary endpoint by site is presented in Figure 8. As there were many small sites, only those sites with a minimum of 10 subjects were included.

Figure 8: Percent Improvement in PASI by Site

Reference ID: 5258586



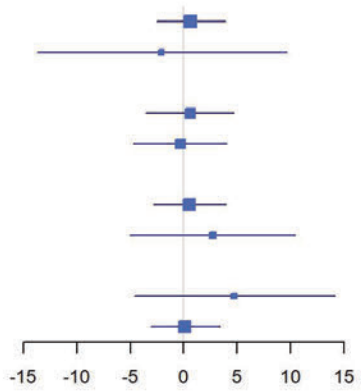
Source: Reviewer Figure

Figure 9presents subgroup analysis by age group, and sex along with 95% CIs for the difference in LS means. The number of subjects ≥ 65 years of age, the number of subjects with prior biologics, and the number of subjects with baseline weight >100 kg in AVT04 were small, so it is difficult to make meaningful comparisons across age, prior biologic use, and baseline bodyweight classifications. For the subgroup by sex, results for male and female subjects were similar. All subjects in the study were white, so subgroup analyses by race were not possible.

Table25: Percent Improvement in PASI by Age, Gender, Weight, Prior Biologic for Psoriasis Groups

Reference ID: 5258586

Subgroups (n[B], n[A])	AVT04 (N=194)	EU-Stelara (N=387)	LSM diff
Age			
<65 years (183, 365)	86.8	86.2	0.6
>=65 years (11, 22)	86.7	88.7	-2.1
Sex			
Male (107, 257)	89.0	88.4	0.6
Female (87, 130)	85.0	85.3	-0.3
Weight			
<=100 kg (164, 327)	86.8	86.3	0.5
>100 kg (30, 60)	87.4	84.7	2.7
Prior Biologic for Ps			
Yes (15, 29)	90.2	85.5	4.7
No (179, 358)	86.5	86.4	0.1



Source: Reviewer Figure; Two-sided 95% CI for the difference in LS Means plotted above. ANCOVA model included percent PASI improvement as response variable, randomized treatment as a factor, and baseline PASI score as a continuous covariate.

Assay Sensitivity and Constancy

Study AVT04-GL-301 was a comparative clinical study of AVT04 and EU-Stelara; it did not include a placebo arm. The following published placebo-controlled trials of Stelara in subjects with moderate to severe PsO included the percent improvement in PASI at Week 12 as a secondary endpoint. The key design criteria and results for these published Stelara trials are presented in Table 26.

All trials below had similar inclusion criteria (BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ Moderate or Marked). The percent improvement in PASI on the EU-Stelara arm in Study AVT04-GL-301 was generally consistent with the results from the published Stelara studies at Week 12. Study AVT04-GL-301 results were slightly higher than those of the published studies. Given the low placebo response rates in the previous studies, and the consistent response rates of Stelara across the published studies, the assumption of assay sensitivity may be reasonable for Study AVT04-GL-301.

Table 26: Study Characteristics and Results of Published Stelara Studies

	Leonardi (2008)	Papp (2008)	Tsai (2011)	Study AVT04-GL-301
Selected inclusion criteria	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Marked (3)	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Moderate (3)	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Moderate (3)	BSA ≥ 10% PASI ≥ 12 sPGA ≥ Moderate (3)
Region/Country	USA, Canada, Belgium	Austria, Canada, France, Germany,	Korea, Taiwan	Estonia, Georgia, Ukraine, Poland

Reference ID: 5258586

		Switzerland, UK, USA		
Baseline PASI Mean Stelara 45 mg Stelara 90 mg	 20.5 19.7	 19.4 20.1	 25.2 -	 21.9 23.9
% Imp. In PASI Stelara 45 mg Stelara 90 mg Placebo	 75.6 77.2 7.0	 77.0 82.1 4.9	 78.5 - 3.1	 86.6 87.3 -

Source: Reviewer Table

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The Applicant collected safety data from two clinical studies, as listed in Section 2.3 and summarized below. In two studies, subjects received at least one dose of either AVT04, US-Stelara or EU-Stelara SC. The primary safety data was derived from the conduct of Study AVT04-GL-301.

Study AVT04-GL-101 was a multicenter, randomized, double-blind, single-dose, three-arm parallel group study in healthy subjects designed to compare the PK of ATV04, US-Stelara, and EU-Stelara administered as a single-dose 45mg/0.5 mL SC injection. There were 294 subjects (97 subjects (US-Stelara), 98 subjects (AVT04), and99 subjects (EU-Stelara) who received the study drug. Randomization was stratified by body weight and ethnicity.

The primary safety database consists of data from the comparative clinical study, AVT04-GL-301, which was a randomized, double-blind, parallel group, active-controlled study in subjects withmoderate to severe chronic PsO. The safety population included 581 subjects, 194 initially randomized to AVT04 and 387 initially randomized to EU-Stelara. Randomization was stratified by the presence or absence of previous biologic treatment for PsO, and by b.w. category (≤80 kg; >80 kg to ≤100 kg; >100 kg). At Week 16, subjects who were initially randomized to Group 1 (AVT04) continued to receive AVT04 (AVT04/AVT04; N = 193). Subjects who were initially randomized to Group 2 (EU-Stelara) were re-randomized in a 1:1 ratio to Group 2A receiving AVT04 starting from Week 16 (EU-Stelara/AVT04, N = 192) to allow investigating whether there was an effect of switching from EU-Stelara to AVT04 in terms of long-term efficacy and safety endpoints, and Group 2B: continuing on EU-Stelara (Group 2B = EU-Stelara/EU-Stelara, N = 189). The transition was used to assess potential risks in safety and immunogenicity as a result of transitioning from EU-Stelara to AVT04. Additional details of the studydesign are described in Section 6.2 above.

Extent of exposure: The safety of AVT04 was investigated in 98 healthy adult male and female healthy subjects (Study AVT04-GL-101: single SC dose) and in 386 adult patients with chronic PsO (StudyAVT04-GL-301 multiple SC doses).

Reference ID: 5258586

For Study AVT04-GL-301, the exposure data set (386 patients) comprised 194 subjects on AVT04 in Stage 1 plus 192 subjects switching from EU-Stelara to AVT04 in Stage 2.

The safety database included a total of 875 subjects who received at least one dose of study drug. The number of subjects allocated to AVT04 or the comparator arms (EU-Stelara or US-Stelara) and duration of treatment are adequate to support a comparative safety assessment.

- Healthy subjects (N=294) received a single 45 mg/0.5 mL SC dose of study drug with 8-10 weeks of post-dosing safety follow-up
  - AVT04: N=98
  - US-Stelara: N=97
  - EU-Stelara: N=99

- Subjects with PsO (N=581) received a loading dose SC injection followed by a dose 4 weeks later, and then every 12 weeks thereafter:
  - AVT04: N=194 for 16 weeks; 193 continued for up to 52 weeks
  - EU-Stelara/EU-Stelara: N= 387 for 16 weeks; 189 continued for up to 52 weeks
  - EU-Stelara switched to AVT04 at Week 16; 192 continued for up to 52 weeks

Table 27: Extent of Exposure for Study AVT04-GL-301 up to Week 16 (Stage 1)

Cumulative duration of treatment	AVT04 (N=194) n (%)		EU-Stelara N=387) n (%)	
>0 weeks	194	(100)	387	(100)
>4 weeks	194	(100)	387	(100)

Source: Clinical Information Amendment Module 1.11.3

Table 28: Extent of Exposure for Study AVT04-GL-301 through Week 40

Cumulative duration of treatment	AVT04/AVT04 (N=193) n (%)		EU-Stelara/AVT04 (N=192) n (%)		EU-Stelara/ EU-Stelara N=189) n (%)	
>0 weeks	193	(100)	192	(100)	189	(100)
>4 weeks	193	(100)	192	(100)	189	(100)
>16 weeks	193	(100)	192	(100)	189	(100)
>28 weeks	191	(99.0)	184	(95.8)	184	(97.4)
>40 weeks	191	(99.0)	180	(93.8)	181	(95.8)

Source: Clinical Information Amendment Module 1.11.3

Population Demographics

The PK similarity study enrolled healthy subjects. The demographics of subjects in the PK similarity studyare presented in the table below. There were no differences across treatment

Reference ID: 5258586

groups between age, race, ethnicity, country, weight or body mass index (BMI) at screening. In the EU-Stelara treatment arm, there were more females (65.7%) than in the AVT04 (58.2%) or US-Stelara (58.8%) treatment arms.

Table 29: Baseline Demographics and Clinical Characteristics of Subjects in Study AVT04-GL-101

	AVT04 PFS (N=98)	EU-Stelara (N=99)	US-Stelara (N=97)
SEX			
F	57 (58.2)	65 (65.7)	57 (58.8)
M	41 (41.8)	34 (34.3)	40 (41.2)
AGE			
Mean (SD)	32.0 (10.09)	30.5 (9.65)	32.0 (9.96)
Median (Min, Max)	29.0 (18, 55)	28.0 (18, 55)	31.0 (18, 55)
RACE			
WHITE	71 (72.4)	73 (73.7)	64 (66.0)
ASIAN	13 (13.3)	12 (12.1)	23 (23.7)
MULTIPLE	5 (5.1)	4 (4.0)	2 (2.1)
OTHER	5 (5.1)	4 (4.0)	2 (2.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (1.0)	4 (4.0)	3 (3.1)
AMERICAN INDIAN OR ALASKA NATIVE	2 (2.0)	1 (1.0)	3 (3.1)
BLACK OR AFRICAN AMERICAN	1 (1.0)	1 (1.0)	0
ETHNICITY			
Non-Japanese	91 (92.9)	92 (92.9)	91 (93.8)
Japanese	7 (7.1)	7 (7.1)	6 (6.2)
COUNTRY			
Australia	52 (53.1)	51 (51.5)	50 (51.5)
New Zealand	46 (46.9)	48 (48.5)	47 (48.5)
BMI			
Mean (SD)	24.3 (2.94)	24.4 (2.68)	24.8 (2.80)
Median (Min, Max)	24.1 (17.9, 29.9)	24.5 (18.3, 30)	25.1 (19, 30)
WEIGHT			
≤ 80 kg	73 (74.5)	73 (73.7)	73 (75.3)
> 80 kg	18 (18.4)	19 (19.2)	18 (18.6)
Not reported	7 (7.1)	7 (7.1)	6 (6.2)

Source: Reviewer's analysis

The baseline demographics and clinical characteristics of patients in Study AVT04-GL-301 are summarized in the table below. In general, the baseline characteristics of the patients in Study AVT04-GL-301 are representative of a PsO population with moderate to severely active disease with the exception of race. The study was conducted entirely in the white race category. The baseline characteristics were similar between the AVT04 and EU-Stelara treatment arms.

Table 30: Baseline Demographics and Clinical Characteristics of Subjects in StudyAVT04-GL-301

Reference ID: 5258586

	AVT04 (N=194)	EU-Stelara (N=387)
SEX		
M	107 (55.2)	257 (66.4)
F	87 (44.8)	130 (33.6)
AGE		
Mean (SD)	42.3 (12.96)	41.9 (12.77)
Median (Min, Max)	41.0 (18, 74)	40.0 (18, 73)
< 65 years	183 (94.3)	365 (94.3)
≥65 years	11 (5.7)	22 (5.7)
RACE		
WHITE	194 (100.0)	387 (100.0)
ETHNICITY		
NOT HISPANIC OR LATINO	193 (99.5)	384 (99.2)
HISPANIC OR LATINO	1 (0.5)	3 (0.8)
COUNTRY		
POL	107 (55.2)	214 (55.3)
UKR	59 (30.4)	129 (33.3)
GEO	25 (12.9)	37 (9.6)
EST	3 (1.5)	7 (1.8)
WEIGHT (kg)		
Mean (SD)	83.5 (18.40)	84.2 (18.54)
Median (Min, Max)	84.1 (45.3, 150)	83.2 (41, 150.7)
≤80 kg	84 (43.3)	167 (43.2)
>80 kg to 100 kg	80 (41.2)	160 (41.3)
>100 kg	30 (15.5)	60 (15.5)

Source: Reviewer's analysis

Categorization of Adverse Events

Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by primary System Organ Class (SOC) and Preferred Term (PT). Prior and concomitant medications were coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

- StudyAVT04-GL-101 coded by MedDRA 24.1 and WHO-DDE Global, Version MAR 2021
- Study AVT04-GL-301 coded by MedDRA 24.1 and WHO-Drug Dictionary, Version SEP 2021

A Serious Adverse Event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (e.g., intensive treatment in an emergency room or at

Reference ID: 5258586

homefor 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])

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

A treatment-emergent adverse event (TEAE) was defined as any adverse event (AE) that occurred after the beginning of the study treatment or any pre-existing AE that worsened after the beginning of the study drug treatment during the study (until the last visit).

Adverse events of specific interest (AESIs) were defined based on the known risks associated with treatment with US-Stelara and other IL-12 and -23 antagonists including serious infections, tuberculosis, malignancy, hypersensitivity reactions, injection site reactions and posterior reversible encephalopathy syndrome (PRES).

The severity of AEs was assessed according to the following categories:

- Mild – Not interfering in a significant manner with the subject’s normal level of functioning
- Moderate – Producing some impairment of functioning but is not hazardous to the patient’s health
- Severe – Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject’s health
- Causality of TEAEs were initially assessed by the investigator, and were subsequently assessed by the sponsor.

Safety Analyses

All subjects randomized and treated with at least 1 dose of study drug defined the safety population and were included in the safety analyses. The Applicant did not plan and perform any integrated (pooling) analysis of the AE data across the two clinical studies due to inherentdifferences in the study design.

AEs, TEAEs, and SAEs were summarized by SOC and PT according to MedDRA terminology with descriptive comparisons between AVT04 and EU-Stelara and, where applicable, US-Stelara.

For the comparative clinical study AVT04-GL-301, the Applicant pre-specified the following safety endpoints and analyses:

- Frequency, type, and severity of AEs including adverse drug reactions (ADRs)
- Frequency and severity of injection site reactions (ISRs)
- Routine safety parameters, including laboratory safety, vital sign measurements, 12-lead ECG results, chest x-ray, and physical examination findings

Reference ID: 5258586

6.3.2. Major Safety Results

A summary of AEs observed in the single-dose PK similarity study in healthy subjects (Study AVT04-GL-101) is presented below. No new safety signals were identified in the AVT04 treatment arm compared with the known AE profiles of US-Stelara and EU-Stelara.

Table 31: Safety Summary for Study AVT04-GL-101

	AVT04 (N=98) n (%)	EU-Stelara (N=99) n (%)	US-Stelara (N=97) n (%)
Number of Deaths	0	0	0
Number of subjects with any TEAEs	67 (68.4)	56 (56.6)	69 (71.1)
Mild	62 (63.3)	21 (10.9)	61 (62.9)
Moderate	3 (3.1)	8 (8.1)	7 (7.2)
Severe	2 (2.0)	3 (3.0)	1 (1.0)
Number of subjects with SAEs	1 (0.5)	1 (0.5)	1 (0.5)
Discontinuations due to an AE	0	0	0
Number of subjects with AESIs	10 (10.2)	9 (9.1)	12 (12.4)

Source: Reviewer's analysis
TEAE: treatment emergent adverse event; SAE: serious adverse event; AE: adverse event; AESI: adverse events of special interest

A summary of AEs observed in Study AVT04-GL-301 is presented below. No new safety signals wereidentified in the AVT04/AVT04 treatment arm compared with the known AE profile of US-Stelara. The overall all-causality AE profile in this study was similar for AVT04 when compared with EU-Stelara during the first 16 weeks of double-blind treatment (Stage 1) and between AVT04, EU-Stelara and in patients who transitioned from EU-Stelara to AVT04 (EU-Stelara/AVT04) during the second 12 weeks of double-blind treatment (Stage 2). However, taking into consideration that most of the reported AEs were not considered drug related, this reviewer finds that there were no meaningful differences in safety between AVT04 and EU-Stelara.

Table 32: Safety Summary for Study AVT04-GL-301, Stage 1 (Up to 16 weeks)

	AVT04 (N=194) n(%)	EU-Stelara (N=387) n(%)
Number of Deaths	0	0
Number of subjects with any TEAEs	93 (47.9)	213 (55.0)
Mild	57 (29.4)	107 (27.6)
Moderate	33 (17.0)	97 (25.1)
Severe	3 (1.5)	9 (2.3)

Reference ID: 5258586

Number of subjects with SAEs	0	10 (2.6)
Discontinuations due to an AE	0	3 (0.8)
Number of subjects with AESIs	3 (1.5)	14 (3.6)

Source: Reviewer's analysis
TEAE: treatment emergent adverse event; SAE: serious adverse event; AESI: adverse events of special interest

Table 33: Safety Summary for Study AVT04-GL-301, Stage 2 (16-28 weeks)

	AVT04/AVT04 (N=193) n (%)	EU-Stelara/AVT04 (N=192) n (%)	EU-Stelara/EU-Stelara (N=189) n (%)
Number of Deaths	0	0	0
Number of subjects with any TEAEs	25 (13.0)	35 (18.2)	36 (19.0)
Mild	13 (6.7)	21 (10.9)	26 (13.8)
Moderate	11 (5.7)	14 (7.3)	9 (4.8)
Severe	1 (0.5)	0	1 (0.5)
Number of subjects with SAEs	0	0	1 (0.5)
Discontinuations due to an AE	1 (0.5)	2 (1.0)	4 (2.1)
Number of subjects with AESIs	0	1 (0.5)	1 (0.5)

Source: Reviewer's analysis
TEAE: treatment emergent adverse event; SAE: serious adverse event; AE: adverse event; AESI: adverse events of special interest

Relevant Characteristics of the Population Evaluated for Safety

The safety database submitted for assessment of comparative safety between AVT04, US-Stelara and EU-Stelara included two clinical studies (one single-dose PK similarity study and one comparative clinical study) as summarized above. Due to differences in clinical study design and studypopulation, no pooled analyses by demographic subgroups wereperformed. The comparative clinical study, Study AVT04-GL-301, was conducted in subjects with moderate to severe PsO, who had BSA involvement of ≥10%, PASI score of ≥12, and sPGA score of ≥3 (moderate) at screening and baseline. Subjects had stable PsO for ≥2 months and were candidates for systemic therapy with a previous failure, inadequate response, intolerance, or contraindication to at least 1 systemic anti-psoriatic therapy including, but not limited to, methotrexate, cyclosporine, psoralen plus ultraviolet light A (PUVA), and ultraviolet light B (UVB). The study design was not powered for any subgroup analyses of safety. Refer to Section 6.2 regarding population demographics.

Other Product-Specific Safety Concerns

Deaths

There were no deaths reported in the clinical program for AVT04.

Reference ID: 5258586

Treatment Emergent Adverse Events

In the two AVT04 clinical studies, there was 1 subject who reported an SAE in the AVT04 treatment arm. The SAE of anaphylactic reaction is described below.

Study AVT04-GL-101

Table 34: Summary of SAEs in Study AVT04-GL-101

Preferred Term	AVT04 N=98) n (%)	EU-Stelara (N=99) n (%)	US-Stelara (N=97) n (%)
Anaphylactic reaction	1 (1.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (1.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (1.0)

Source: Reviewer's analysis

Narrative of SAEs in Study AVT-GL-101 in the AVT04 treatment arm:

- Anaphylactic reaction: 26-year-old healthy female received AVT04 on Day 56 and developed an SAE of anaphylactic reaction. One day later, on Day 57, the event was resolved and the subject was discharged from the hospital. The subject was then lost to follow up. The event of anaphylactic reaction was assessed as severe, serious, and unrelated to the study drug by the Investigator.

Study AVT04-GL-301

There were no SAEs reported in the AVT04 arm through week 28. Seven subjects (7/387; 2.1%) reported SAEs in the EU-Stelara arm through week 16 and 1 subject (1/189; 0.5%) reported an SAE in the EU-Stelara/EU-Stelara arm from weeks 16-28. None of these SAEs were considered treatment-related by the Applicant. This reviewer agrees with the assessment by the Applicant that none of these SAEs were treatment related.

Table 35: Summary of SAEs in Study AVT04-GL-301 Through Week 16 (Stage 1)

Preferred Term	AVT04 (N=194) n (%)	EU-Stelara N=387) n (%)
Arteriosclerosis	0 (0.0)	1 (0.3)
Atrial fibrillation	0 (0.0)	1 (0.3)
Compression fracture	0 (0.0)	1 (0.3)
Gallbladder rupture	0 (0.0)	1 (0.3)
Intervertebral disc disorder	0 (0.0)	1 (0.3)
Intestinal obstruction	0 (0.0)	1 (0.3)
Limb fracture	0 (0.0)	1 (0.3)
Lower limb fracture	0 (0.0)	1 (0.3)
Pancreatic carcinoma metastatic	0 (0.0)	1 (0.3)
Salivary gland neoplasm	0 (0.0)	1 (0.3)

Source: Reviewer's analysis

Reference ID: 5258586

Table 36: Summary of Serious TEAEs in StudyAVT04-GL-301 from week 16 to 28 (Stage 2)

Preferred Term	AVT04/AVT04 (N=193) n (%)	EU-Stelara/ AVT04 (N=192) n (%)	EU-Stelara/EU-Stelara (N=189) n (%)
Anaemia vitamin b12 deficiency	0 (0.0)	0 (0.0)	1 (0.5)

Source: Reviewer's analysis

Dropouts and/or Discontinuations

Study AVT04-GL-101

Of the 298 randomized subjects, 278 subjects (278/298; 93.3%) completed the study. Twenty subjects (20/298; 6.7%) discontinued due to withdrawal of consent or loss to follow-up. No subjects discontinued the study due to an AE.

Study AVT04-GL-301

Through week 16 (Stage 1):
Of the 581 randomized subjects, 574 subjects (574/581; 99.0%) completed to week 16. There were no discontinuations in the AVT04 cohort due to AEs.

Table 37: Summary of Discontinuations in the Safety Population in Study AVT04-GL-301 up to week 16 (Stage 1)

Reason For Discontinuation	AVT04 (N=194) n(%)	EU-Stelara (N=387) n(%)
Lost to Follow-Up	0	1 (0.3)
PI Decision	1 (0.5)	0
Withdrawal of Consent	0	2 (0.5)
Adverse Event	0	3 (0.8)
Hepatic enzyme increased	0	1 (0.3)
Pancreatic carcinoma metastatic	0	1 (0.3)
Salivary gland neoplasm	0	1 (0.3)

Source: Reviewer's analysis

Week 16 to 28 (Stage 2):
Of the 574 subjects in Stage 2, 553 subjects (574/553; 96.3%) completed Week 28 (AVT04/AVT04: 189; EU-Stelara/AVT04: 180; EU-Stelara/EU-Stelara: 184). Ten subjects (AVT04/AVT04: 3/193; 1.6%; EU-Stelara/AVT04: 7/192; 3.6%) did not complete the Week 28 visit due to war in Ukraine prior to the data cut-off date; however, they were not considered to be early terminations by the Investigator.

Reference ID: 5258586

Table 38: Summary of Discontinuations in the Safety Population in StudyAVT04-GL-301 week 16-28 (Stage 2)

Reason For Discontinuation	AVT04/AVT04 (N=193) n(%)	EU-Stelara/AVT04 (N=192) n(%)	EU-Stelara/ EU-Stelara (N=189) n(%)
Lost to Follow Up Due to War	3 (1.6)	7 (3.6)	0
PI Decision	0	1 (0.5)	1 (0.5)
Withdrawal of Consent	0	2 (1.0)	0
Adverse Event	1 (0.5)	2 (1.0)	4 (2.1)
Tuberculosis	1(0.5)	0	4(2.1)
Indeterminate tuberculosis test	0	1(0.5)	0
Mycobacterium tuberculosis complex test positive	0	1 (0.5)	0

Source: Reviewer's analysis

Common TEAEs

In general, with respect to safety, AVT04 had a similar safety profile when compared to EU-Stelara in Study AVT04-GL-301 as shown in the tables below. In Stage 1 there was a higher incidence in TEAEs of COVID-19, elevated transaminases, bronchitis, influenza and oropharyngeal pain occurring with AVT04. In Stage 2 there was a higher incidence in TEAEs of hypertriglyceridemia, pain in extremity and sciatica in subjects who continued AVT04 and upper respiratory infection in subjects who were switched to AVT04 from EU-Stelara. However, with the limitations of AVT04-GL-301, a single study with a relatively small number of subjects and with a switch in treatment, it is difficult to interpret these findings and come to a definitive conclusion that these are meaningful differences between AVT04 and EU-Stelara.

Study AVT04-GL-301

To week 16 (Stage 1):

Table 39: Summary of Common TEAEs by ≥1% of Subjects in Study AVT04-GL-301 through week 16 (Stage 1)

Preferred Term	AVT04 (N=194) n (%)	EU-Stelara (N=387) n (%)
Upper respiratory tract infection [a]	19 (9.8)	37 (9.6)
Transaminases increased [b]	9 (6.2)	18 (4.7)
COVID-19	7 (3.6)	9 (2.3)
Dyslipidemia [c]	4 (2.1)	12 (3.1)
Blood creatine phosphokinase increased	3 (1.5)	8 (2.1)

Preferred Term	AVT04 (N=194) n (%)	EU-Stelara N=387) n (%)
Gamma-glutamyl transferase increased	3 (1.5)	6 (1.6)
Headache	3 (1.5)	5 (1.3)
Bronchitis	3 (1.5)	1 (0.3)
Influenza	3 (1.5)	0 (0.0)
Oropharyngeal pain	2 (1.0)	0 (0.0)
Injection site reaction [d]	2 (1.0)	10 (2.6)
Hypertension	1 (0.5)	15 (3.9)
Sinusitis	1 (0.5)	4 (1.0)
Rhinitis [e]	0 (0.0)	5 (1.3)
Gastroenteritis [f]	0 (0.0)	4 (1.0)
Pruritus	0 (0.0)	4 (1.0)

Source: Reviewer's analysis
a: Upper respiratory tract infection includes nasopharyngitis, pharyngitis and laryngitis
b: Transaminases increased includes alanine aminotransferase increased, hepatic enzyme increased, liver function test increased, aspartate aminotransferase increased, hypertransaminaseaemia
c: Dyslipidemia includes hypertriglycerideaemia, blood triglycerides increased, and hypercholesterolaemia
d: injection site reaction includes haematoma, injection site erythema, injection site haematoma, injection site pain, injection site pruritus
e: rhinitis includes rhinorrhea
f: gastroenteritis includes diarrhoea

Week 16-28 (Stage 2):

Table 40: Summary of Common TEAEs by ≥1% of Subjects in Study AVT04-GL-301 from Week 16-28 (Stage 2)

Preferred Term	AVT04/AVT04 (N=193) n (%)	EU-Stelara/AVT04 (N=192) n (%)	EU-Stelara/ EU-Stelara N=189) n (%)
Upper respiratory tract infection [a]	4 (2.1)	7 (3.6)	4 (2.1)
Transaminases increased [b]	2 (1.0)	3 (1.6)	2 (1.1)
COVID-19	2 (1.0)	7 (3.6)	10 (5.3)
Hypertriglyceridemia	3 (1.6)	0 (0.0)	0 (0.0)
Pain in extremity	2 (1.0)	0 (0.0)	0 (0.0)
Sciatica	4 (2.1)	0 (0.0)	0 (0.0)
Tuberculosis	1 (0.5)	0 (0.0)	4 (2.1)
Hypertension	0 (0.0)	2 (1.0)	2 (1.1)
Injection site reaction [c]	0 (0.0)	2 (1.0)	2 (1.1)

Source: Reviewer's analysis
a: Upper respiratory tract infection includes nasopharyngitis, pharyngitis and laryngitis
b: Transaminases increased includes alanine aminotransferase increased, hepatic enzyme increased, hypertransaminaseaemia
c: injection site reaction includes injection site erythema, injection site haematoma, injection site pain, injection site pruritus

Reference ID: 5258586

AESIs

The AESIs for this study encompass all relevant warnings and precautions from the US-Stelara label and include:

- Serious infections (bacterial, mycobacterial, fungal or viral)
- Malignancies especially non-melanoma skin cancers
- Hypersensitivity reactions including anaphylaxis and angioedema
- PRES
- Non-infectious pneumonia such as interstitial, eosinophilic or cryptogenic organizing pneumonia
- ISRs(pain/tenderness, erythema/redness, swelling/induration, pruritus/itching, hematoma/ecchymosis/bruising)

Overall, there was a small number of AESIs in Study AVT04-GL-301. Of note, there was a higher incidence of ISRs in stage 1 and tuberculosis in stage 2 in subjects who received EU-Stelara compared to subjects who received AVT04. With a relatively small number of subjects and with a switch in treatment, it is difficult to interpret these findings and come to a definitive conclusion that these are meaningful differences between AVT04 and EU-Stelara.

Table 41: Summary of AESIs in StudyAVT04-GL-301 Up to Week 16 (Stage 1)

Preferred Term	AVT04 (N=194) n (%)	EU-Stelara N=387) n (%)
Malignancy		
Pancreatic carcinoma metastatic	0 (0.0)	1 (0.3)
Salivary gland neoplasm	0 (0.0)	1 (0.3)
Pruritus	0 (0.0)	1 (0.3)
Injection site reactions [a]	2 (1.0)	10 (2.6)
Serious Infection		
Herpes infections [b]	0 (0.0)	4 (1.0)

Source: Reviewer's analysis
a: Injection site reactions include haematoma, injection site erythema, injection site pain, injection site pruritus, injection site haematoma
b: Herpes infections include herpes simplex, herpes zoster and oral herpes

Table 42: Summary of AESIs in Study AVT04-GL-301 Weeks 16-28 (Stage 2)

Preferred Term	AVT04/AVT04 (N=193) n (%)	EU-Stelara/AVT04 (N=192) n (%)	EU-Stelara/ EU-Stelara N=189) n (%)
Injection site reaction [a]	0	2 (1.0)	3 (1.6)
Tuberculosis	1 (0.5)	0	4 (2.1)
Mycobacterium tuberculosis complex test positive	0	1 (0.5)	0
Indeterminate tuberculosis test	0	1 (0.5)	0

Source: Reviewer's analysis
a: injection site reaction includes injection site haematoma, and vaccination site pain

Reference ID: 5258586

Narratives regarding tuberculosis in subjects who received AVT04:

- A 35–40-year-old male subject in the AVT04/AVT04 arm (Subject (b) (6)) with a history of chronic plaque psoriasis received the third dose of AVT04 45 mg SC on Day 112 (Week 16) and developed a positive QuantiFERON-TB Gold test. The TEAE was reported as tuberculosis and was deemed as mild. The subject was asymptomatic and received no treatment for the event. Tuberculosis was excluded by pulmonologist. Study drug dosing was discontinued. The event was recorded as ongoing at the time of data cutoff. The subject discontinued from the study on Day 155 (Week 23).
- A 25–30-year-old male in the EU-Stelara/AVT04 arm (Subject (b) (6) received AVT04 45 mg SC, on Day 111- (Week 16). On the same day of administration of AVT04 45 mg, the subject developed a moderate TEAE of Mycobacterium tuberculosis complex test positive. The patient received no treatment for the TEAE of Mycobacterium tuberculosis complex test positive (positive QuantiFERON) and study drug dosing was discontinued. The TEAE of the Mycobacterium tuberculosis complex test positive was recorded as resolving (recovering) at the time of data cutoff (Week 28 Visit). The patient discontinued from the trial on Day 202 (Week 29). The TEAE of Mycobacterium tuberculosis complex test positive leading to study discontinuation was assessed as not related to the study drug.
- A 60–65-year-old male in the EU-Stelara/AVT04 arm (Subject (b) (6)) received AVT04 45 mg SC on Day 110 (Week 16). On Day 124 (Week 18), 14 days after receiving the dose of AVT04 45 mg, the subject had a TEAE of indeterminate tuberculosis test (QuantiFERON–TB Gold test at Week 16 assessment). The patient received no treatment for the TEAE of indeterminate tuberculosis test and study drug dosing was discontinued. The TEAE of indeterminate tuberculosis test was recorded as not resolved at the time of data cutoff (Week 28 Visit). The patient discontinued from the study on Day 181 (Week 26). The TEAE of indeterminate tuberculosis test was assessed by the Investigator as not related to the study drug.

Reviewer's comment: *As Tuberculosis is included in the "Warnings and Precautions" section of the US-Stelara label, this reviewer considers the TEAEs of tuberculosis, Mycobacterium tuberculosis complex test positive and indeterminate tuberculosis test as related to study drug.*

Subgroup Analyses in Study AVT04-GL-301

Subgroup analyses were performed based on sex, age, weight, and NAb status. Subgroup analysis could not be performed based on race as Study AVT04-GL-301 was conducted entirely in White subjects.

TEAEs by Sex

Overall, there was a higher percentage of TEAEs in the female subjects than in the male subjects in Stage 1 (Week 0-16) of the study which was not seen in Stage 2 (Week 16-28) as shown in the tables below. During stage 1, there was a higher incidence of hypertension and ISRs in males who received EU-Stelara than males who received AVT04. However, given the

Reference ID: 5258586

small number of subjects in each arm, there were no meaningful differences between the treatment arms.

Table 43: Summary of TEAEs by Sex in ≥ 2 Subjects in Study AVT04-GL-301 from Week 0-16 (Stage 1)

	AVT04		EU-Stelara	
	Female (N=87) n (%)	Male (N=107) n (%)	Female (N=130) n (%)	Male (N=257) n (%)
Number of subjects with any TEAEs	52 (59.8)	41 (38.3)	83 (63.8)	130 (50.6)
Upper respiratory tract infection [a]	7 (8.0)	12 (11.2)	16 (12.3)	21 (8.2)
Hepatic enzyme increased [b]	5 (5.7)	4 (3.7)	4 (3.1)	14 (5.4)
COVID-19	5 (5.7)	2 (1.9)	5 (3.8)	4 (1.6)
Dyslipidaemia[c]	2 (2.3)	4 (3.7)	5 (3.8)	4 (1.6)
Blood creatine phosphokinase increased	0	3 (2.8)	0	8 (3.1)
Hyperglycaemia	0	3 (2.8)	1 (0.8)	2 (0.8)
Gamma-glutamyltransferase increased	1 (1.1)	2 (1.9)	2 (1.5)	4 (1.6)
Headache	2 (2.3)	1 (0.9)	4 (3.1)	1 (0.4)
Injection site reaction [d]	2 (2.3)	0	5 (3.8)	5 (1.9)
Abdominal pain upper	1 (1.1)	0	3 (2.3)	0
Arthralgia	1 (1.1)	0	0	3 (1.2)
Vaginal infection [e]	2 (2.3)	0	0	0
Hypertension	1 (1.1)	0	0	6 (2.3)
Influenza	2 (2.3)	1 (0.9)	0	0
Oropharyngeal pain	2 (2.3)	0	0	0
Pruritus	0	0	2 (1.5)	2 (0.8)
Rhinitis [f]	0	0	2 (1.5)	3 (1.2)
Tonsillitis	0	0	2 (1.5)	1 (0.4)
Hyperbilirubinaemia [g]	0	0	0	2 (0.8)
Musculoskeletal pain	0	0	2 (1.5)	0
Acne	0	0	2 (1.5)	0

Source: Reviewer's analysis
a: upper respiratory infection includes nasopharyngitis, laryngitis and pharyngitis
b: hepatic enzymes increased includes alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test increased
c: hyperlipidaemia includes blood triglycerides increased, dyslipidaemia, hypercholesterolaemia and hypertriglyceridaemia
d: injection site reaction includes injection site erythema, injection site haematoma, injection site pain, injection site pruritus
e: vaginal infection includes vulvovaginal mycotic infection
f: rhinitis includes rhinorrhea
g: hyperbilirubinaemia includes blood bilirubin increased

Table 44: Summary of TEAEs by Sex in ≥ 2 Subjects in Study AVT04-GL-301 from Week 16-28 (Stage 2)

Reference ID: 5258586

	AVT04/AVT04		EU-Stelara/AVT04		EU-Stelara/ EU-Stelara	
	Female N= 87 n (%)	Male N= 106 n (%)	Female N= 60 n (%)	Male N= 132 n (%)	Female N= 67 n (%)	Male N= 122 n (%)
Number of subjects with any TEAEs	8 (9.2)	17 (16.0)	13 (21.7)	22 (16.7)	7 (10.4)	29 (23.8)
COVID-19	0	2 (1.9)	2 (3.3)	5 (3.8)	4 (6.0)	6 (4.9)
Upper respiratory tract infection [a]	1 (1.1)	3 (2.8)	5 (8.3)	2 (1.5)	0	4 (3.3)
Blood pressure increased [b]	0	0	2 (3.3)	1 (0.8)	1 (1.5)	2 (1.6)
Hepatic enzyme increased[c]	0	2 (1.9)	1 (1.7)	2 (1.5)	0	2 (1.6)
Hypertriglyceridaemia	1 (1.1)	2 (1.9)	0	0	0	0
Injection site reaction [d]	0	0	1 (1.7)	1 (0.8)	1 (1.5)	2 (1.6)
Back pain [e]	2 (2.3)	2 (1.9)	0	1 (0.8)	0	0
Tuberculosis	0	1 (0.9)	0	0	0	4 (3.3)

Source: Reviewer's analysis
a: upper respiratory tract infection includes nasopharyngitis, laryngitis
b: blood pressure increased includes hypertension and hypertensive crisis
c: hepatic enzyme increased includes alanine aminotransferase increased, hypertransaminasaemia, and transaminases increased
d: injection site reaction includes injection site haematoma and vaccination site pain
e: back pain includes sciatica

TEAEs by Age

For the majority of TEAEs, there were no differences due to age. While there were higher incidences of TEAEs of hepatic enzyme increased, headache and ISR in subjects <65 years of age receiving EU-Stelara than in subjects <65 years of age receiving AVT04, due to the small number of subjects in each treatment arm, it is difficult to make any meaningful conclusions. The number of subjects in the age ≥ 65 years treatment arms wastoo small to make any meaningful conclusions in both stage 1 and stage 2 of the study as shown in the tables below.

Table 45: Summary of TEAEs by Age in ≥ 2 Subjects in Study AVT04-GL-301 from Week 0-16 (Stage 1)

	AVT04		EU-Stelara	
	<65 years (N=183) n (%)	≥ 65 years (N=11) n (%)	<65 years (N=365) n (%)	≥ 65 years (N=22) n (%)
Number of subjects with any TEAEs	65 (35.6)	2 (18.2)	119 (32.6)	10 (45.5)
Number of TEAEs	84	9	190	23
Upper respiratory tract infection [a]	19 (10.4)	0	37 (10.1)	0
Hepatic enzyme increased [b]	9 (4.9)	0	16 (8.7)	2 (1.1)
COVID-19	6 (3.3)	1 (.1)	9 (4.6)	0
Dyslipidaemia[c]	5 (2.7)	0	3 (1.6)	3 (1.6)
Blood creatine phosphokinase increased	3 (1.6)	0	8 (4.4)	0

Reference ID: 5258586

Hyperglycaemia	3 (1.6)	0	2 (1.1)	1 (0.5)
Gamma-glutamyltransferase increased	3 (1.6)	0	6 (3.3)	0
Headache [d]	3 (1.6)	0	6 (3.3)	0
Injection site reaction [e]	2 (1.1)	0	9 (4.6)	1 (0.5)
Hypertension	1 (0.5)	0	7 (3.8)	0
Tonsillitis	0	0	3 (1.6)	0
Diarrhoea	0	0	3 (1.6)	0
Influenza	3 (1.6)	0	0	0
Musculoskeletal pain	0	0	2 (1.1)	0
Herpes infection[f]	0	0	3 (1.6)	0
Oropharyngeal pain	2 (1.1)	0	0	0
Pruritus	0	0	4 (2.2)	0
Rhinitis [g]	0	0	5 (2.7)	0
Abdominal pain upper	1 (0.5)	0	3 (1.6)	0
Arthralgia	1 (0.5)	0	3 (1.6)	0
Bronchitis	3 (1.6)	0	1 (0.5)	0
Haematoma	1	0	3 (1.6)	0
Acne	0	0	2 (1.1)	0

Source: Reviewer's analysis; TEAE = treatment emergent adverse event
a: upper respiratory infection includes nasopharyngitis, laryngitis and pharyngitis
b: hepatic enzymes increased includes alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test increased
c: hyperlipidaemia includes blood triglycerides increased, dyslipidaemia, hypercholesterolaemia and hypertriglyceridaemia
d: headache includes migraine
e: injection site reaction includes injection site erythema, injection site haematoma, injection site pain, injection site pruritus
f: herpes infection includes herpes simplex and oral herpes

Table 46: Summary of TEAEs by Age in ≥ 2 Subjects in Study AVT04-GL-301 from Week 16-28 (Stage 2)

	AVT04/AVT04		EU-Stelara/AVT04		EU-Stelara/ EU-Stelara	
	<65 years N= 182 n (%)	≥ 65 years N= 11 n (%)	<65 years N= 179 n (%)	≥ 65 years N= 13 n (%)	<65 years N= 181 n (%)	≥ 65 years N= 8 n (%)
Number of subjects with any TEAEs	23 (12.6)	2 (18.2)	35 (19.6)	0	34 (18.8)	2 (25.0)
COVID-19	2 (1.1)	0	7 (3.8)	0	9 (4.9)	0
Upper respiratory tract infection [a]	4 (2.2)	0	7 (3.8)	0	4 (2.2)	0
Blood pressure increased [b]	0	0	3 (1.6)	0	2 (1.1)	0
Hepatic enzyme increased[c]	2 (1.1)	0	3 (1.6)	0	2 (1.1)	0
Hypertriglyceridaemia	3 (1.6)	0	0	0	0	0
Injection site reaction [d]	0	0	2 (1.1)	0	2 (1.1)	1 (12.5)
Back pain [e]	3 (1.6)	1 (9.1)	1 (0.5)	0	0	0
Tuberculosis	1 (0.5)	0	0	0	4 (2.2)	0

Source: Reviewer's analysis
a: upper respiratory tract infection includes nasopharyngitis, laryngitis
b: blood pressure increased includes hypertension and hypertensive crisis
c: hepatic enzyme increased includes alanine aminotransferase increased, hypertransaminasaemia, and transaminases increased
d: injection site reaction includes injection site haematoma and vaccination site pain
e: back pain includes sciatica

Reference ID: 5258586

TEAEs by Weight

In Stage 1, there was a higher incidence of TEAEs of upper respiratory infection, hepatic enzyme increased, blood creatinine phosphokinase increased, and rhinitis in subjects <100 kg in the EU-Stelara treatment arm compared to the AVT04 treatment arm. In subjects >100 kg, there was a higher incidence of dyslipidemia and ISRs in the EU-Stelara treatment arm compared to the AVT04 treatment arm. However, as the number of subjects in each treatment arm was too small to make any meaningful conclusions in both stage 1 and stage 2, there were no meaningful differences between the subject groups. TEAEs by weight are shown in the table below.

Table 47: Summary of TEAEs by Weight in ≥ 2 Subjects in Study AVT04-GL-301 from Week 0-16 (Stage 1)

Preferred Term	AVT04			EU-Stelara		
	≤ 80 kg (N=84) n (%)	>80 to <100 kg (N=80) n (%)	>100 kg (N=30) n (%)	≤ 80 kg (N=167) n (%)	>80 to <100 kg (N=160) n (%)	>100 kg (N=60) n (%)
Number of subjects with any TEAEs	26 (31.0)	32 (40.0)	9 (30.0)	63 (37.7)	57 (35.6)	9 (15.0)
Number of TEAEs	43	41	9	120	81	12
Upper respiratory tract infection [a]	7 (8.3)	11 (13.1)	1 (1.2)	22 (26.2)	14 (16.7)	1 (1.2)
Hepatic enzyme increased [b]	2 (2.4)	4 (4.8)	3 (3.6)	7 (8.3)	9 (10.7)	2 (2.4)
COVID-19	2 (2.4)	2 (2.4)	3 (3.6)	4 (4.8)	5 (6.0)	0
Dyslipidaemia[c]	2 (2.4)	0	0	2 (2.4)	6 (7.1)	2 (2.4)
Blood creatine phosphokinase increased	1 (1.2)	1 (1.2)	1 (1.2)	4 (4.8)	3 (3.6)	1 (1.2)
Hyperglycaemia	1 (1.2)	2 (2.4)	0	1 (1.2)	1 (1.2)	1 (1.2)
Gamma-glutamyltransferase increased	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.4)	3 (3.6)	1 (1.2)
Headache [d]	2 (2.4)	1 (1.2)	0	5 (6.0)	1 (1.2)	0
Injection site reaction [e]	0	2 (2.4)	0	0	5 (6.0)	5 (6.0)
Hypertension	1 (1.2)	0	0	3 (3.6)	4 (4.8)	0
Tonsillitis	0	0	0	2 (2.4)	1 (1.2)	0
Diarrhoea	0	0	0	2 (2.4)	1 (1.2)	0
Influenza	1 (1.2)	2 (2.4)	0	0	0	0
Herpes infection[f]	0	0	0	1 (1.2)	2 (2.4)	0
Pruritus	0	0	0	2 (2.4)	2 (2.4)	0
Rhinitis [g]	0	0	0	5 (6.0)	5 (6.0)	0
Sinusitis	1 (1.2)	0	0	1 (1.2)	3 (3.6)	0
Abdominal pain upper	1 (1.2)	0	0	2 (2.4)	1 (1.2)	0
Arthralgia	1 (1.2)	0	0	2 (2.4)	1 (1.2)	0
Bronchitis	1 (1.2)	2 (2.4)	0	1 (1.2)	0	0
Haematoma	0	1 (1.2)	0	2 (2.4)	1 (1.2)	0

Source: Reviewer's analysis; TEAE = treatment emergent adverse event

a: upper respiratory infection includes nasopharyngitis, laryngitis and pharyngitis
b: hepatic enzymes increased includes alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test increased
c: hyperlipidaemia includes blood triglycerides increased, dyslipidaemia, hypercholesterolaemia and hypertriglyceridaemia
d: headache includes migraine
e: injection site reaction includes injection site erythema, injection site haematoma, injection site pain, injection site pruritus
f: herpes infection includes herpes simplex and oral herpes

Table 48: Summary of TEAEs by Weight in ≥ 2 Subjects in Study AVT04-GL-301 from Week 16-28 (Stage 2)

	AVT04/AVT04			EU-Stelara/AVT04			EU-Stelara/ EU-Stelara		
	≤ 80 kg N= 84 n (%)	>80 to <100 kg N= 79 n (%)	>100 kg N= 30 n (%)	≤ 80 kg N= 81 n (%)	>80 to <100 kg N= 80 n (%)	>100 kg N= 31 n (%)	≤ 80 kg N= 81 n (%)	>80 to <100 kg N= 79 n (%)	>100 kg N= 21 n (%)
Number of subjects with any TEAEs	7 (8.3)	10 (12.7)	4 (13.3)	18 (22.2)	8 (10.0)	3 (9.7)	8 (9.9)	2 (2.5)	13 (61.9)
COVID-19	0	2 (2.5)	0	0	4 (5.0)	0	5 (6.3)	3 (3.8)	2 (9.5)
Upper respiratory tract infection [a]	1 (1.2)	2 (2.5)	1 (3.3)	7 (8.6)	0	0	2 (2.5)	2 (2.5)	0
Blood pressure increased [b]	0	0	0	2 (2.5)	1 (1.3)	0	3 (3.8)	0	0
Hepatic enzyme increased[c]	1 (1.2)	0	2 (6.7)	1 (1.2)	2 (2.5)	0	0	2 (2.5)	0
Hypertriglyceridaemia	1 (1.2)	0	0	0	0	0	0	0	0
Injection site reaction [d]	0	0	0	1 (1.2)	1 (1.3)	0	2 (2.5)	1 (1.3)	0
Pain in extremity	0	2 (2.5)	0	0	0	0	0	0	0
Back pain [e]	2 (2.4)	1 (1.3)	1 (3.3)	1 (1.2)	0	0	0	0	0
Tuberculosis	0	1 (1.3)	0	0	0	0	2 (2.5)	2 (2.5)	0

Source: Reviewer's analysis
a: upper respiratory tract infection includes nasopharyngitis, laryngitis
b: blood pressure increased includes hypertension and hypertensive crisis
c: hepatic enzyme increased includes alanine aminotransferase increased, hypertransaminasaemia, and transaminases increased
d: injection site reaction includes injection site haematoma and vaccination site pain
e: back pain includes sciatica

TEAEs by NAb Status

Overall, there were no meaningful differences between the frequency of TEAEs in subjects based on NAb status who received AVT04 and those who received EU-Stelara in any stage and treatment group in the study as shown in the tables below. In Stage 1, it appears that AVT04 was less immunogenic than EU-Stelara. There were 5 TEAEs in subjects who were Nab positive (5/14; 35.7%) in the AVT04 treatment arm in Stage 1: headache, ISR, hypertension, pain in extremity and pharyngitis while there were 45 subjects (45/68; 66.2%) in the EU-Stelara arm with TEAEs.

Table 49: Summary of TEAEs by NAb Status in ≥ 2 Subjects in Study AVT04-GL-301 from Week 0-16 (Stage 1)

Preferred Term	AVT04		EU-Stelara	
	NAb Negative (N=180) n (%)	NAb Positive (N=14) n (%)	NAb Negative (N=319) n (%)	NAb Positive (N=68) n (%)

Reference ID: 5258586

Number of subjects with any TEAEs	88 (48.9)	5 (35.7)	168 (52.7)	45 (66.2)
Upper respiratory tract infection [a]	18 (10)	1(7.1)	31 (9.7)	6 (8.8)
Hepatic enzyme increased [b]	9(5.0)	0	13 (4.1)	5 (7.4)
COVID-19	7 (3.9)	0	8 (2.5)	1 (1.5)
Dyslipidaemia[c]	5 (2.8)	0	4 (1.3)	2 (2.9)
Blood creatine phosphokinase increased	3 (1.7)	0	6 (1.9)	2 (2.9)
Hyperglycaemia	3 (1.7)	0	2 (0.6)	1 (1.5)
Gamma-glutamyltransferase increased	3 (1.7)	0	5 (1.6)	1 (1.5)
Headache	2 (1.1)	1 (7.1)	5 (1.6)	1 (1.5)
Injection site reaction [d]	1 (0.6)	1 (7.1)	6 (1.9)	4 (5.9)
Hypertension	0	1 (7.1)	6 (1.9)	0
Tonsillitis	0	0	2 (0.6)	1 (1.5)
Diarrhoea	0	0	2 (0.6)	1 (1.5)

Source: Reviewer's analysis; NAb = neutralizing antibody
a: upper respiratory infection includes nasopharyngitis, laryngitis and pharyngitis
b: hepatic enzymes increased includes alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test increased
c: hyperlipidaemia includes blood triglycerides increased, dyslipidaemia, hypercholesterolaemia and hypertriglyceridaemia
d: injection site reaction includes injection site erythema, injection site haematoma, injection site pain, injection site pruritus

Table 50: Summary of TEAEs by NAb Status in ≥ 2 Subjects in Study AVT04-GL-301 from Week 16-28 (Stage 2)

	AVT04/AVT04		EU-Stelara/AVT04		EU-Stelara/ EU-Stelara	
	NAb Negative N= 179 n (%)	NAb Positive N= 14 n (%)	NAb Negative N= 151 n (%)	NAb Positive N= 41 n (%)	NAb Negative N= 164 n (%)	NAb Positive N= 25 n (%)
Number of subjects with any TEAEs	24 (13.4)	1 (7.1)	26 (17.2)	9 (22.0)	31 (18.9)	5 (20.0)
COVID-19	1 (0.6)	1 (7.1)	3 (2.0)	4 (9.8)	10 (6.1)	0
Upper respiratory tract infection [a]	4 (2.2)	0	5 (3.3)	2 (4.9)	2 (1.2)	2 (8.0)
Blood pressure increased [b]	0	0	3 (2.0)	0	2 (1.2)	1(4.0)
Hepatic enzyme increased[c]	2 (1.1)	0	3 (2.0)	0	2 (1.2)	0
Hypertriglyceridaemia	3 (1.7)	0	0	0	0	0
Injection site reaction [d]	0	0	2 (1.3)	0	2 (1.2)	1 (4.0)
Back pain [e]	4 (2.2)	0	1 (0.7)	0	0	0
Tuberculosis	1 (0.6)	0	0	0	4 (2.4)	0

Source: Reviewer's analysis
a: upper respiratory tract infection includes nasopharyngitis, laryngitis
b: blood pressure increased includes hypertension and hypertensive crisis
c: hepatic enzyme increased includes alanine aminotransferase increased, hypertransaminasaemia, and transaminases increased
d: injection site reaction includes injection site haematoma and vaccination site pain
e: back pain includes sciatica

Reference ID: 5258586

6.3.3. Additional Safety Evaluations

Laboratory evaluations

Chemistry and hematology evaluations were performed as follows:

- AVT04-GL-101 – Baseline to Day 92
- AVT04-GL-301 (Stages 1 and 2) - Baseline through Week 28

There were no meaningful differences between the subject groups within each study.

Vital signs**:** There were no meaningful differences between the healthy subjects in AVT04-GL-101 and AVT04 and EU-Stelara subjects in AVT04-GL-301.

ECGs**:** There were no meaningful differences between the healthy subjects in AVT04-GL-101 and AVT04 and EU-Stelara subjects in AVT04-GL-301.

6.4. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from a single-dose PK similarity study) and in subjects with PsO (multiple doses up to 52 weeks in a comparative clinical study), and an assessment of the impact of ADA on PK, efficacy, and safety. In particular, there were no meaningful differences between the frequency of treatment-emergent AEs in the AVT04/AVT04 group versus the other treatment arms (EU-Stelara/AVT04 and EU-Stelara/EU-Stelara) respectively, in ADA positive and ADA negative subjects. This reviewer concludes that there were no clinically significant differences between AVT04 and EU-Stelara in the production of ADA/NAb and their impact on PK, efficacy and safety. Refer to Section 5.4 *Clinical Immunogenicity Studies* for results of the immunogenicity assessments.

Authors:

Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

6.5. Extrapolation

\The Applicant submitted data and information in support of a demonstration that AVT04 is highly similar to U.S.-Stelara notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between AVT04 and U.S.-Stelara in terms of safety, purity and potency.

Reference ID: 5258586

The Applicant is seeking licensure of AVT04 for the following indication(s) for which U.S.-Stelara has been previously licensed and for which AVT04 has not been directly studied:

- Pediatric patients 6-17years with PsO
- Patients 6 years and older with PsA

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of AVT04 as a biosimilar for each such indication for which licensure is sought and for which U.S.-Stelara has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below.

Therefore, the totality of the evidence provided by the Applicant supports licensure of AVT04 for each of the following indication(s) for which Alvotech is seeking licensure of AVT04:

- Pediatric patients 6-17 years with PsO
- Patients 6 years and older with PsA

Author:
Snezana Trajkovic, MD
CDTL

6.5.1. Division of Rheumatology and Transplant Medicine

In addition to the PsO indication, the Applicant is seeking licensure of AVT04 for the following indication under the purview of DRTM:

- PsA in adults and pediatric patients 6 years or older

In their application, the Applicant has provided justification for extrapolation of data and relevant supportive information for licensure of AVT04 as a biosimilar for the above indication for which licensure is sought and for which US-Stelara has been previously licensed and AVT04 has not been directly studied.

First, as summarized above, the Applicant submitted data and information to demonstrate that AVT04 is highly similar to US-Stelara and that there are no clinically meaningful differences between AVT04 and US-Stelara in terms of safety, purity, and potency based on similar clinical PK (Study AVT04-GL-101), and similar efficacy, safety, and immunogenicity in patients with PsO (Study AVT04-GL-301).

Further, the additional points considered in the scientific justification for extrapolation of data and information to support licensure of AVT04 for the treatment of PsA are described below.

Mechanism of Action (MOA)
In a number of functional cell-based and ligand-binding assays, AVT04 has been shown to be functionally similar to ustekinumab. These data demonstrate that the biologic activity and

Reference ID: 5258586

potency of AVT04 have a high degree of similarity to ustekinumab and provide additional evidence that the MOA of the two products is the same, both in neutralization of IL-12 and in Fab-related critical attributes.

The Applicant adequately addressed each of the known and potential mechanisms of action of US-Stelara and submitted data to support the conclusion that AVT04 and US-Stelara have the same mechanisms for the sought indication of PsA to the extent that the mechanisms of action are known or can reasonably be determined.

PK

Similar PK was demonstrated between AVT04 and US-Stelara in Study AVT04-GL-101, a randomized, double-blind, single-dose, 3-arm, parallel group PK similarity study in healthy adult subjects, as reviewed in the section on Clinical Pharmacology. Importantly, AVT04 was also demonstrated to be highly similar to US-Stelara, as discussed in the section on CMC/Product Quality; therefore, there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between AVT04 and US-Stelara in the PsA indication. Thus, a similar PK profile would be expected between AVT04 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar PK profile is expected between AVT04 and US-Stelara for PsA.

Immunogenicity

Immunogenicity of AVT04 was examined in the PK similarity study (AVT04-GL-101, healthy subjects) and comparative clinical study (AVT04-GL-301, subjects with PsO), and development of binding and neutralizing ADAs was numerically lower or similar for the AVT04 treatment groups compared with US-Stelara and EU-Stelara. As reviewed elsewhere in this document, the clinical PK and safety data support that the observed differences between AVT04 and US-Stelara are not clinically meaningful. The Agency has concluded that there are sufficient data to support similar immunogenicity between AVT04 and US-Stelara after a single dose in healthy subjects and with repeat dosing in patients with PsO. Accordingly, similar immunogenicity would be expected between AVT04 and US-Stelara in patients with PsA. DRTM notes that similar rates of antibodies to US-Stelara were seen in clinical studies of patients with PsO and PsA.[3]

The Applicant provided adequate justification that similar immunogenicity is expected between AVT04 and US-Stelara for PsA.

Toxicity

The Applicant demonstrated that there are no meaningful differences in safety between AVT04 and EU-Stelara in patients with PsO and between AVT04, EU-Stelara, and US-Stelara following single doses in healthy subjects. Additionally, in controlled clinical studies of US-Stelara submitted to support its approval, as described in the approved labeling,[4] the types of AEs and their rates were similar across indications. Together with the demonstration of analytical and PK similarity between AVT04, US-Stelara, and EU-Stelara, a similar safety

[3] Stelara USPI approved 03/06/2023, available on Drugs@fda

[4] Ibid.

Reference ID: 5258586

profile would be expected between AVT04 and US-Stelara in patients with PsA.

The Applicant provided adequate justification that a similar safety profile would be expected between AVT04 and US-Stelara for PsA.

Additional factors considered (if applicable)
None

Conclusions
Based on the above considerations, DRTM concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity, and toxicity profile) for extrapolation of the data and information to support licensure of AVT04 for the rheumatologic indication of psoriatic arthritis (6 years or older) for which US-Stelara has been previously licensed and for which the Applicant is seeking licensure.

Authors:

Suzette Peng, MD	Raj Nair, MD
Clinical Reviewer, DRTM	Acting Deputy Division Director, DRTM

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, ustekinumab-aekn, was found to be conditionally accepted by the Agency.

7.2. Proprietary Name

The proposed proprietary name for AVT04 is conditionally approved as Selarsdi. This name has been reviewed by DMEPA, who concluded the name was acceptable.

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:

Sangeeta Jain, MD	Snezana Trajkovic, MD
Clinical Reviewer	Clinical Team Leader

Reference ID: 5258586

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

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.2 and verifies that no compensation is linked to study outcome. The PIs did not disclose any proprietary interest to the Applicant.

Authors:

Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

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

Author:
Snezana Trajkovic, MD
CDTL

10. Pediatrics

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on November 10, 2021. After receiving comments from the Agency, the Applicant submitted an iPSP with an appendix on March 23, 2022. The iPSP was presented to the Pediatric Review Committee (PeRC) on April 26, 2022, at which the PeRC agreed with the Applicant's plan as proposed. An agreed iPSP was submitted on July 18, 2022.

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

Authors:

Reference ID: 5258586

Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

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

In view of the recommendation for a Complete Response, any recommendations for post-marketing requirements and commitments were deferred until the next review cycle.

Authors:
Sangeeta Jain, MD
Clinical Reviewer

Snezana Trajkovic, MD
Clinical Team Leader

12. Comments to Applicant

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

Following inspection of Alvotech 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.

13. Division Director Comments

13.1. Division Director (OND – Clinical) Comments

[Insert text here.]

Author:
[Insert author name here]
[Insert title here]

Reference ID: 5258586

14. Appendices

14.1. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

Covered Clinical Study: AVT04-GL-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 54		
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)): 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 in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	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 ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: AVT04-GL-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Reference ID: 5258586

Total number of investigators identified: 143		
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)): 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 in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	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 ☐	No ☐ (Request explanation from Applicant)

14.2. Nonclinical Appendices

14.2.1. Nonclinical Pharmacology

No data provided.

14.2.2. Nonclinical Pharmacokinetics

The PK profile of AVT04 was evaluated in Cynomolgus monkeys and compared to CN-Stelara (Study# P20-S425-PK). Single subcutaneous doses of 0.9 and 9 mg/kg AVT04or CN-Stelara were administered to Cynomolgus monkeys (5/sex/group). The PK parameters and the development of ADAs were evaluated.

The serum PK parameters are shown in the table below. ADAs were detected in most AVT04and CN-Stelara dosed animals with similar incidences between the two products. The PK profiles of the two products were similar.

Reference ID: 5258586

Table 51: PK parameters of AVT04and CN-Stelara in Cynomolgus monkeys

Analyte	Group Dosage	Gender		$t_{1/2}$ hr	T_{max} hr	C_{max} ng/mL	AUC_{0-336h} hr·mg/mL	Vd mL/kg	Cl mL/hr/kg	MRT hr
AVT04	Low dose 0.9 mg/kg	Male n=5	Mean	85.7	78.4	11.1	2.41	38.6	0.311	204
			SD	41.9	39.4	5.24	0.672	22.0	0.0793	55.2
		Female n=5	Mean	105	31.2	9.49	2.09	54.9	0.372	179
			SD	47.1	10.7	2.30	0.460	24.1	0.0898	20.7
		Male&Female n=10	Mean	95.2	54.8	10.3	2.25	46.8	0.342	191
			SD	43.2	36.9	3.91	0.568	23.4	0.0859	41.5
	High dose 9 mg/kg	Male n=5	Mean	199	31.2	96.2	20.8	79.1	0.294	274
			SD	62.4	10.7	35.0	4.65	12.5	0.0828	47.4
		Female n=5	Mean	150	28.0	98.9	19.8	74.2	0.348	216
			SD	56.2	17.2	16.1	1.34	26.8	0.0363	44.1
		Male&Female n=10	Mean	175	29.6	97.6	20.3	76.7	0.321	245
			SD	61.6	13.6	25.7	3.27	19.9	0.0666	52.8
Stelara	Low dose 0.9 mg/kg	Male n=5	Mean	109	106	9.60	2.34	49.0	0.352	206
			SD	53.8	36.4	3.71	0.977	24.0	0.155	50.7
		Female n=5	Mean	96.0	98.4	7.47	1.81	57.6	0.440	192
			SD	49.3	40.2	0.685	0.391	24.2	0.162	49.8
		Male&Female n=10	Mean	103	102	8.53	2.07	53.3	0.396	199
			SD	49.2	36.3	2.75	0.756	23.2	0.156	47.9
	High dose 9 mg/kg	Male n=5	Mean	173	25.6	94.5	19.1	83.4	0.345	243
			SD	48.1	14.3	13.5	2.59	17.1	0.0738	30.5
		Female n=5	Mean	115	20.8	104	20.2	60.1	0.374	197
			SD	55.6	14.0	9.75	2.90	30.6	0.0842	40.2
		Male&Female n=10	Mean	144	23.2	99.3	19.7	71.8	0.359	220
			SD	57.5	13.6	12.2	2.65	26.4	0.0762	41.4

Notes: n means the number of animals, the serum concentration dropped sharply in some animals at 336 h post dose maybe due to the influence of the anti-drug antibody, the AUC_{0-336h} is calculated in order to make the exposure of different animals in four groups could be comparable.

14.2.3. General Toxicology

A 4-week repeat-dose toxicity study was conducted in Cynomolgus monkeys with AVT04and CN-Stelara (Study# P20-207-RD, GLP). Subcutaneous doses of 0 (vehicle: formulation buffer containing 222 mM sucrose, 6.4 mM histidine, and 0.004% polysorbate 80), 5, 15, and 45 mg/kg AVT04and 45 mg/kg CN-Stelara were administered to Cynomolgus monkeys (3/sex/group) once weekly for 4 weeks (5 doses in total), followed by a 4-week recovery period (2/sex/group).

Study endpoints included clinical signs, body weights, food consumption, body temperature, ECG, respiratory parameters, blood pressure, blood oxygen saturation, ophthalmology, clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), lymphocyte subsets, and serum cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-6), and pathology examinations (organ weight, gross and histopathological examinations in all animals). TK parameters and ADAs were also evaluated.

Reference ID: 5258586

There were no significant treatment-related findings. The toxicity profiles of the two products were similar. The TK parameters were evaluated for Days 1 and 22. The TK profiles of the two products at the 45 mg/kg dose were similar as well.

Table 52: TK parameters of AVT04 and CN-Stelara in Cynomolgus monkeys

Group	Time	Sex	$t_{1/2}$ h	T_{max} h	C_{max} μg/mL	AUC_{last} h*mg/mL	AUC_{INF} h*mg/mL	MRT h	C_{max} Ratio	AUC_{last} Ratio	AI
AVT04 5 mg/kg group	Day1	♂	173.69	52.80	53.86	7.46	15.97	80.43	1.00	1.00	—
		♀	167.12	62.40	50.73	6.89	14.34	80.54	1.00	1.00	—
	Day22	♂	285.01	30.40	116.53	16.09	47.70	79.63	1.00	1.00	2.16
		♀	232.45	32.00	111.30	14.85	39.25	77.74	1.00	1.00	2.16
AVT04 15 mg/kg group	Day1	♂	203.87	33.60	160.93	21.84	52.70	80.89	2.99	2.93	—
		♀	207.63	38.40	177.38	23.87	58.67	81.01	3.50	3.47	—
	Day22	♂	156.97	30.40	315.99	45.81	95.19	79.26	2.71	2.85	2.10
		♀	151.33	17.60	308.96	40.91	79.67	76.04	2.78	2.76	1.71
AVT04 45 mg/kg group	Day1	♂	213.06	24.00	492.52	63.96	159.50	81.78	9.14	8.57	—
		♀	218.72	24.00	538.43	68.38	174.46	80.48	10.61	9.93	—
	Day22	♂	132.30	48.00	1072.62	143.48	258.45	76.36	9.20	8.92	2.24
		♀	186.88	30.40	1081.05	150.57	341.82	78.31	9.71	10.14	2.20
Stelara 45 mg/kg group	Day1	♂	215.58	28.80	458.48	61.57	153.93	81.24	—	—	—
		♀	183.98	28.80	443.03	56.66	124.84	79.85	—	—	—
	Day22	♂	144.67	25.60	974.08	131.85	248.61	76.96	—	—	2.14
		♀	144.81	24.00	887.69	117.38	224.87	76.54	—	—	2.07

Note: C_{max} Ratio=AVT04 C_{max}/C_{max} 5 mg/kg group; AUC_{last} Ratio=AVT04 AUC_{last}/AUC_{last} 5 mg/kg group; AI=Day22 AUC_{last}/Day1 AUC_{last}.

14.2.4. Nonclinical Labeling Review

The applicant proposed to use the same labeling for nonclinical potions of the drug label as the approved US-Stelara label, except the revised labeling for Section 12.1 as shown below (the ~~strikethrough~~ wording is deleted from the US-Stelara label):

12.1 Mechanism of Action

Ustekinumab-xxxx is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In in vitro models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-

Reference ID: 5258586

12Rβ1. ~~The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's Disease. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.~~

The applicant proposed nonclinical labeling is acceptable. However, please refer to Section 7.3, indicating that in view of the recommendation for a Complete Response for this application, the labeling review will be deferred until the next review cycle.

14.3. Clinical Pharmacology Appendices

14.3.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

The quantitation of study drug in human serum was performed with a sandwich assay on 96-well microtiter plates using Meso Scale Discovery (MSD) electrochemiluminescence (ECL) technology. The assay was validated for the quantitation of study drug in serum of healthy subjects as well as in serum of PsO patients (validation reports Reports N-A-IMM-18-167 and N-A-IMM-19-126, respectively). During the method validation, AVT04, EU-Stelara, and US-Stelara were used as QC samples to assess the suitability of the assay. Table 53 and Table 54 below show the summary of RKAJ8 method performance in quantification of AVT04, US-Stelara, and EU-Stelara in serum samples from healthy subjects and in serum samples from PsO patients.
.

Table 53. Summary of the bioanalytical method validation and in-study performance for measurement of AVT04, US-Stelara, and EU-Stelara in PK similarity study (AVT04-GL-101)

Bioanalytical method validation report name, amendments, and hyperlinks	Report N-A-IMM-18-167 Report Amendment 01 of N-A-IMM-18-167
Method description	A validated sandwich format on 96 well plates using commercial anti-ustekinumab Fab fragment as capture and anti-ustekinumab IgG coupled to ECL-Sulfo-Tag as detection.
Materials used for standard calibration curve and concentration	AVT04, lot# R20035, 90 mg/mL, expiration date 21 Apr 2022
Validated assay range	25 – 6400 ng/mL (at MRD: 0.5 - 128 ng/mL)
Material used for quality controls (QCs) and concentration	AVT04, lot# R20035, 90 mg/mL, expiration date 21 Apr 2022 EU-Stelara, lot# JFS1VMX, 91 mg/mL, expiration date 30 May 2022 US-Stelara, lot# JCS11ME, 90 mg/mL, expiration date Feb 2022

Reference ID: 5258586

Minimum required dilutions (MRDs)	1:50 (2% 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	7	Table 8 of report N-A-IMM-18-167
	Cumulative accuracy (%bias) from LLOQ to ULOQ (AVT04)	-1.5 to 4.1%	Table 44 of report N-A-IMM-18-167
	Cumulative precision (%CV) from LLOQ to ULOQ (AVT04)	≤ 4.9%	Table 44 of report N-A-IMM-18-167
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs**		Table 1 of report N-A-IMM-18-167
	QCs for product AVT04 (6400, 5000, 500, 75.0, 25.0 ng/mL)	1.6 to 4.8%	
	QCs for product EU-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	-13.2 to -7.5%	
	QCs for product US-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	-6.9 to 1.3%	
	Inter-batch %CV		Table 1 of report N-A-IMM-18-167
	QCs for product AVT04 (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 8.4%	
	QCs for product EU-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 9.1%	
	QCs for product US-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 7.8%	
	Total Error (TE)		Table 1 of report N-A-IMM-18-167
	QCs for product AVT04 (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 12.6%	

Reference ID: 5258586

	QCs for product EU-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 20.9%	
	QCs for product US-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 13.0%	
Selectivity & matrix effect	For AVT04: 10 lots tested, 100% of analyzed samples were acceptable For EU-Stelara: 10 lots tested, 100% of analyzed samples were acceptable For US-Stelara: 10 lots tested, 90% of analyzed samples were acceptable		Table 1 of report N-A-IMM-18-167
Interference & specificity	No interference tested since no co-medication was performed in the clinical studies.		NA
Hemolysis effect	For AVT04: 2 lots tested, both samples passed For EU-Stelara: 2 lots tested, both samples passed For US-Stelara: 2 lots tested, both samples passed		Table 1 of report N-A-IMM-18-167
Lipemic effect	For AVT04: 2 lots tested, both samples passed For EU-Stelara: 2 lots tested, both samples passed For US-Stelara: 2 lots tested, both samples passed		Table 1 of report N-A-IMM-18-167
Dilution linearity & hook effect	Start concentration: 100000 ng/mL; 4 dilutions tested (1:50, 1:1000, 1:10000; 1:50000); 5 sets measured per dilution For AVT04: Bias between -11.4% and 3.0% and mean precision (DF1000 - DF50000) at 4.5% For EU-Stelara: Bias between -16.8% and 1.3% and mean precision (DF1000 - DF50000) at 6.2% For US-Stelara: Bias between -9.3% and 10.8% and mean precision (DF1000 - DF50000) at 6.7% No hook effect observed (signal at 100000 ng/mL above ULOQ)		Table 1 of report N-A-IMM-18-167
Bench-top/process stability	For AVT04: Demonstrated for 24 hours at ambient temperature for samples previously stored at -20°C±5°C or at -75°C±15°C For EU-Stelara: Demonstrated for 24 hours at ambient temperature for samples previously stored at -20°C±5°C and demonstrated for 16 hours if samples were stored at -75°C±15°C For US-Stelara: Demonstrated for 24 hours at ambient temperature for samples previously stored at -20°C±5°C or at -75°C±15°C Working Stock Solution Stability: AVT04: Demonstrated for 30 days at -75°C±15°C EU-Stelara: Demonstrated for 30 days at -75°C±15°C US-Stelara: Demonstrated for 30 days at -75°C±15°C		Table 1 of report N-A-IMM-18-167
Freeze-Thaw stability	For AVT04: Demonstrated for 5 cycles at -20°C±5°C and at -75°C±15°C For EU-Stelara: Demonstrated for 5 cycles at -20°C±5°C and at -75°C±15°C For US-Stelara: Demonstrated for 5 cycles at -20°C±5°C and at -75°C±15°C		Table 1 of report N-A-IMM-18-167
Long-term storage	For AVT04: Demonstrated for 18 months (562 days) at -20°C±5°C and for 18 months (562 days) at -75°C±15°C		Table 1 of report N-A-IMM-18-167

Reference ID: 5258586

	For EU-Stelara: Demonstrated for 18 months (566 days) at -20°C±5°C and for 18 months (566 days) at -75°C±15°C For US-Stelara: Demonstrated for 18 months (566 days) at -20°C±5°C and for 18 months (566 days) at -75°C±15°C	Table 1 of report amendment 01 N-A-IMM-18-167
Parallelism	Performed in clinical Study AVT04-GL-101; 2 samples analyzed; mean CV% 3.0 and 1.3; parallelism passed	Table 18 of report N-A-IMM-18-168
Carry over	NA	NA
Method performance in Study AVT04-GL-101 (Report N-A-IMM-18-168)		
Assay passing rate	262 runs were analyzed for final data evaluation with 27 failing runs due to inacceptable Cal and QC performance. 235 runs met all applicable acceptance criteria. Within the qualifying runs 4 out of 11 did not fulfill acceptance criteria due to inacceptable QC performance. One run was excluded due to technical error (Run096). 89.7% of the assays passed.	Chapter 3.1 and Table 1 of report N-A-IMM-18-168
Standard curve performance	Cumulative bias range: -2.0 to 3.1% Cumulative precision: ≤ 2.7% CV	Table 20 of report N-A-IMM-18-168
QC performance	Cumulative bias range: -2.9 to -2.2% Cumulative precision: ≤ 11.0% CV TE: ≤ 13.6%	Table 21 of report N-A-IMM-18-168
Method reproducibility	A total of 398 samples were selected for ISR and reanalyzed. 391 (98.2%) of the 398 selected samples were within ± 30.0% deviation.	Table 17 of report N-A-IMM-18-168
Study sample analysis/ stability	All samples were stored at -75°C±15°C upon arrival and analyzed within 308 days after sample collection. The documented stability data for AVT04 is 562 days, for EU-Stelara and US-Stelara 566 days at -75°C±15°C. Long term stability was reported in validation report N-A-IMM-18-167 and N-A-IMM-18-167 Amendment 01.	Executive summary of report N-A-IMM-18-168

Source:Report N-A-IMM-18-167, Report Amendment 01 of N-A-IMM-18-167, and Report N-A-IMM-18-168
ab=antibody; CV=coefficient of variation; ECL=electrochemiluminescence; Fab=antigen binding fragment; IgG=immunoglobulin G; ISR=incurred sample re-analysis; LLOQ=lower limit of quantitation; LTS=long-term storage; MRD=minimum required dilution; NA=not applicable; PK=pharmacokinetics; PsO=plaque psoriasis; QC=quality control; TE=total error; ULOQ=upper limit of quantitation

Table 54. Summary of the bioanalytical method validation and in-study performance for measurement of AVT04 and EU-Stelara in comparative clinical study (AVT04-GL-301)

Bioanalytical method validation report name, amendments, and hyperlinks	Report N-A-IMM-19-126
Method description	A validated sandwich format on 96 well plates using commercial anti-ustekinumab Fab fragment as capture and anti-ustekinumab IgG coupled to ECL-Sulfo-Tag as detection.
Materials used for standard calibration curve and concentration	AVT04, lot# R20035, 90 mg/mL, expiration date 21 Apr 2022
Validated assay range	25 – 6400 ng/mL (at MRD: 0.5 - 128 ng/mL)

Reference ID: 5258586

Material used for quality controls (QCs) and concentration	AVT04, lot# R20035, 90 mg/mL, expiration date 21 Apr 2022 EU-Stelara, lot# JFS1VMX, 91 mg/mL, expiration date 30 May 2022 US-Stelara, lot# JCS11ME, 90 mg/mL, expiration date Feb 2022		
Minimum required dilutions (MRDs)	1:50 (2% 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	7	Table 9 of report N-A-IMM-19-126
	Cumulative accuracy (%bias) from LLOQ to ULOQ (AVT04)	-2.6 to 5.0%	Table 33 of report N-A-IMM-19-126
	Cumulative precision (%CV) from LLOQ to ULOQ (AVT04)	≤ 4.0%	Table 33 of report N-A-IMM-19-126
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs**		Table 1 of report N-A-IMM-19-126
	QCs for product AVT04 (6400, 5000, 500, 75.0, 25.0 ng/mL)	-8.4 to 2.3%	
	QCs for product EU-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	-13.9 to 7.0%	
	QCs for product US-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	-14.1 to 5.9%	
	Inter-batch %CV		Table 1 of report N-A-IMM-19-126
	QCs for product AVT04 (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 11.5%	
	QCs for product EU-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 10.3%	
	QCs for product US-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 8.9%	
	Total Error (TE)		Table 1 of report N-A-IMM-19-126
	QCs for product AVT04 (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 19.9%	

Reference ID: 5258586

	QCs for product EU-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 20.7%	
	QCs for product US-Stelara (6400, 5000, 500, 75.0, 25.0 ng/mL)	≤ 20.4%	
Selectivity & matrix effect	For AVT04: 10 lots tested, 80% of analyzed samples were acceptable For EU-Stelara: 10 lots tested, 90% of analyzed samples were acceptable For US-Stelara: 10 lots tested, 90% of analyzed samples were acceptable		Table 1 of report N-A-IMM-19-126
nterference & specificity	No interference tested since no co-medication was performed in the clinical studies.		NA
Hemolysis effect	For AVT04: 2 lots tested, both samples passed For EU-Stelara: 2 lots tested, both samples passed For US-Stelara: 2 lots tested, 1 sample passed, 1 sample with accuracy > 20%		Table 1 of report N-A-IMM-19-126
Lipemic effect	For AVT04: 2 lots tested, both samples passed For EU-Stelara: 2 lots tested, both samples passed For US-Stelara: 2 lots tested, both samples passed		Table 1 of report N-A-IMM-19-126
Dilution linearity & hook effect	Start concentration: 100000 ng/mL; 4 dilutions tested (1:50, 1:1000, 1:10000; 1:50000); 5 sets measured per dilution For AVT04: Bias between -9.3% and 6.8% and mean precision (DF1000 – DF50000) at 5.6% For EU-Stelara: Bias between -18.0% and -13.7% (4 of 5 sets at DF1000 failed but DF10000 and DF50000 passed) and mean precision (DF1000 – DF50000) at 5.5% For US-Stelara: Bias between -19.9% and -10.0% (-21.7% at 1 of 5 sets at DF1000) and mean precision (DF1000 – DF50000) at 4.2% No hook effect demonstrated in the validation of Nuvisan project N-A-IMM-18-167.		Table 1 of report N-A-IMM-19-126
Bench-top/process stability	Not validated in this partial validation; stability already validated in N-A-IMM-18-167.		NA
Freeze-Thaw stability	Not validated in this partial validation; stability already validated in N-A-IMM-18-167.		NA
Long-term storage	Not validated in this partial validation; stability already validated in N-A-IMM-18-167.		NA
Parallelism	Performed in clinical Study AVT04-GL-301; 2 samples analyzed; mean CV% 2.5 and 3.6; parallelism passed		Table 18 of report N-A-IMM-18-169
Carry over	NA		NA
Method performance in Study AVT04-GL-301 (Interim Report N-A-IMM-18-169)			
Assay passing rate	A total of 78 runs and 4 pre-study qualifying runs were analyzed for interim data evaluation. All 78 analytical runs met the applicable acceptance criteria. Within the qualifying runs 2 out		Chapter 3.1 and table 1 of interim report N-A-IMM-18-169

Reference ID: 5258586

	of 4 did not fulfill acceptance criteria due to inacceptable QC performance. 100% of the assays for sample analysis passed.	
Standard curve performance	Cumulative bias range: -3.0 to 3.3% Cumulative precision: ≤ 3.4% CV	Table 20 of interim report N-A-IMM-18-169
QC performance	Cumulative bias range: -4.8 to -1.4% Cumulative precision: ≤ 7.6% CV TE: ≤ 10.4%	Table 21 of interim report N-A-IMM-18-169
Method reproducibility	A total of 126 samples were selected for ISR and reanalyzed. 126 (100%) of the 126 selected samples were within ± 30.0% deviation.	Table 17 of interim report N-A-IMM-18-169
Study sample analysis/ stability	All samples were stored at -75°C±15°C upon arrival and analyzed within 316 days after sample collection. The documented stability data for AVT04 is 562 days, for EU-Stelara and US-Stelara 566 days at -75°C±15°C. Long term stability was reported in validation report N-A-IMM-18-167 and N-A-IMM-18-167 Amendment 01.	Executive summary of interim report N-A-IMM-18-169

Source: Report N-A-IMM-19-126, and Interim Report N-A-IMM-18-169

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

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/s/

SNEZANA TRAJKOVIC
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