9 November 2023
EMA/549260/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Uzpruvo

International non-proprietary name: ustekinumab

Procedure No. EMEA/H/C/006101/0000

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# Administrative information

| | |
|---|---|
| Name of the medicinal product: | Uzpruvo |
| Applicant: | STADA Arzneimittel AG<br>Stadastrasse 2-18<br>61118 Bad Vilbel<br>GERMANY |
| Active substance: | ustekinumab |
| International Non-proprietary Name/Common Name: | ustekinumab |
| Pharmaco-therapeutic group (ATC Code): | immunosuppressants, interleukin inhibitors (L04AC05) |
| Therapeutic indication(s): | Plaque psoriasis<br><br>Uzpruvo is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).<br><br>Paediatric plaque psoriasis<br><br>Uzpruvo is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).<br><br>Psoriatic arthritis (PsA)<br>Uzpruvo, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1). |

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| | Crohn’s Disease<br><br>Uzpruvo is indicated for the treatment of adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. |
| Pharmaceutical form(s): | Solution for injection |
| Strength(s): | 45 mg and 90 mg |
| Route(s) of administration: | Subcutaneous use |
| Packaging: | pre-filled syringe (glass) |
| Package size(s): | 1 pre-filled syringe |

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# List of abbreviations

| | |
|---|---|
| ADA | Antidrug antibody |
| ADCC | Antibody-dependent cellular cytotoxicity |
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| AUC | Area under the curve |
| AUC0-inf | Total AUC after extrapolation from time t to infinity, where t is the last time point with a concentration above LLOQ |
| AUC0-t | Area under the serum concentration time curve up to time t, where t is the last time point with concentrations above the lower limit of quantitation (LLOQ) |
| AUEC | Area under the effect curve |
| AVT04 | Alvotech proposed biosimilar to Stelara (ustekinumab) |
| AVT04-PFS | AVT04 prefilled syringe |
| BL | Baseline |
| BLA | Biologics License Application |
| BLQ | Below the lower limit of quantification |
| BLGF | break-loose and gliding force |
| BMI | Body mass index |
| BPD4 | Biosimilar Product Development Type 4 (meeting) |
| BSA | Body surface area |
| BSE | bovine spongiform encephalopathy |
| b.w. | Body weight |
| CAPA | Corrective and Preventive Action |
| CCS | container closure system |
| Cmax | Maximum drug concentration |
| Ctrough | Serum through drug concentrations (= lowest serum drug concentration before the next dose is administered) |
| CD | Crohn’s disease |
| CD4 + | Cluster of differentiation 4+ |
| CDC | Complement-dependent cytotoxicity assay |
| CE-SDS | capillary electrophoresis sodium dodecyl sulfate |
| CI | Confidence interval |
| cIEF | capillary isoelectric focusing |
| cLBA | Competitive ligand binding assay |
| CL/F | Apparent clearance |
| CPK | Creatinine phosphokinase |
| CPPs | critical process parameters |
| CQAs | critical quality attributes |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CV | Coefficient of variation |

| | |
|---|---|
| DDC | drug-device combination |
| DLQI | Dermatology Life Quality Index |
| DoE | Design of Experiment |
| DP | Drug product |
| DS | Drug substance |
| DSP | downstream manufacturing process |
| ECG | (12-lead) Electrocardiogram |
| ECL | Electrochemiluminescence |
| EFF | extended finger flange |
| EMA | European Medicine Agency |
| EoS | End of study |
| EoT | End of treatment |
| EPRs | essential performance requirements |
| ESI-Q-TOF-MS/MS | electrospray - time of flight mass spectrometry |
| EU-Stelara | EU-approved Stelara |
| Fab | Antigen binding fragment |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GM | Geometric means |
| GMP | Good Manufacturing Practice |
| h | Hour |
| HC | heavy chains |
| HCP | host cell protein |
| HMW | high molecular weight species |
| IFN-γ | Interferon gamma |
| i.v. | Intravenous |
| ICH | International Conference on Harmonization |
| IgG1κ | Immunoglobulin G, subclass 1, κ light chain |
| IL-12,-23 | Interleukin-12, -23 |
| INN | International nonproprietary name |
| IP | Investigational product |
| IPCs | in-process controls |
| ISR | Injection site reaction |
| ISS | Integrated Summary of Safety |
| ITT | Intention-to-treat |
| JP | Japan |
| JP-Stelara | Stelara sourced from Japan |
| Kel | Elimination rate constant |
| LC | light chains |
| LLOQ | Lower limit of quantitation |
| LOCF | Last observation carried forward |

| | |
|---|---|
| LS | Least square |
| MA(A) | Marketing authorization (application) |
| mAb | Monoclonal antibody |
| MCB | Master Cell Bank |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHLW | Ministry of Health, Labor and Welfare |
| MSD | Meso scale discovery |
| N, n | Number |
| nAb | Neutralizing antibody |
| NK cell | Natural killer cell |
| OOS | One out of specification |
| PASI | Psoriasis Area and Severity Index |
| PASI 50, 75, 90, 100 | A 50%, 75%, 90%, 100% reduction in PASI score |
| PCR | polymerase chain reaction |
| PDE | permitted daily exposure |
| PFS | Prefilled syringe |
| PK | Pharmacokinetic(s) |
| PP | Per protocol |
| PsA | Psoriatic arthritis |
| PPQ | process performance qualification |
| pPsO | Pediatric plaque psoriasis |
| pPsA | Pediatric psoriatic arthritis |
| PRV | pseudorabies |
| PsO | Plaque psoriasis |
| PT | Preferred term |
| SAP | Statistical Analysis Plan |
| s.c | Subcutaneous |
| SD | Standard deviation |
| SE | Standard error |
| SEC-HPLC | size exclusion-high-performance liquid chromatography |
| SOC | System organ class |
| sPGA | Static Physician Global Assessment |
| SUB | single use bags |
| t1/2 | Terminal elimination half-life |
| Tmax | Time to maximum serum concentration |
| TB | Tuberculosis |

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|---|---|
| TEAE | Treatment emergent adverse event |
| TEAESI | Treatment-emergent adverse events of special interest |
| TEM | Transmission electron microscopy |
| Th1/Th17 | T helper 1 cells / T helper 17 cells |
| TSE | transmissible spongiform encephalopathies |
| UC | Ulcerative colitis |
| US-Stelara | US-licensed Stelara |
| USP | upstream manufacturing process |
| WCB | working cell bank |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant STADA Arzneimittel AG submitted on 21 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Uzpruvo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications.

Plaque psoriasis

Uzpruvo is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

Uzpruvo is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Uzpruvo, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease

Uzpruvo is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis

STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

During the procedure the indication for the treatment of adult patients with moderately to severely active ulcerative colitis has been withdrawn, due to a pending patent for this indication.

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Union provisions in force

for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Stelara (Ustekinumab), 45 mg, 90 mg, Solution for injection in pre-filled syringe
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004

■ Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Stelara (Ustekinumab), 45 mg, 90 mg, Solution for injection in pre-filled syringe
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004

■ Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Stelara (Ustekinumab), 45 mg, 90 mg, Solution for injection in pre-filled syringe
- Marketing authorisation holder: Janssen-Cilag International NV
- Date of authorisation: 15-01-2009
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/494/003, EU/1/08/494/004

## *1.3. Information on paediatric requirements*

Not applicable

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *1.5. Scientific advice*

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 25 June 2020 | EMA/CHMP/SAWP/320580/2020; EMEA/H/SA/4502/1/2020/III | Carin Bergquist, Linda Trauffler |
| 14 October 2021 | EMA/CHMP/SAWP/592274/2021; EMA/SA/0000064154 | Anna Vikerfors, Dieter Deforce |

The applicant received scientific advice on the development of AVT04, a biosimilar to Stelara, from the CHMP on 25 June 2020 (EMEA/H/SA/4502/1/2020/III). The scientific advice pertained to the following quality and clinical aspects:

- The proposal of critical quality attributes (CQAs) and their corresponding analytical assays for the similarity assessment.
- The assessment of effector functions in AVT04.
- The approach to demonstrate analytical similarity between AVT04 and Stelara for different concentration and strengths.
- The determination and use of the experimentally determined absorption coefficient of ustekinumab.
- The assay design for the detection of anti-drug antibodies (ADA) and the competitive ligand binding assay design for the detection of neutralizing anti-drug antibodies (nAb) against AVT04 and Stelara.
- The design and objectives for the proposed clinical study to investigate PK, efficacy, safety, and immunogenicity similarity.
- The extrapolation of the study results to support similarity to all approved indications of Stelara.

The applicant received scientific advice on the development of AVT04, a biosimilar to Stelara, from the CHMP on 14 October 2021 (EMA/SA/0000064154). The scientific advice pertained to the following quality aspects:

- Testing and characterization of master cell bank, working cell bank, and post-production cells bank.
- Viral clearance strategy during the manufacturing process. Representativeness of the unprocessed bulk sample for testing for adventitious virus contamination in a perfusion process.
- Drug substance manufacturing process and controls. Drug product manufacturing process and controls and the definition of the in-process tests and controls. Tests and limits included in the overall drug substance and drug product release testing programs. Batch definition and exclusion of certain days of product either from perfusion or virus inactivated pool.
- Stability research programme.
- Comparability and similarity strategy between AVT04 and Stelara.

## *1.6. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner Co-Rapporteur: Frantisek Drafi

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| The application was received by the EMA on | 21 October 2022 |
| The procedure started on | 1 December 2022 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 20 February 2023 |
| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 6 March 2023 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 3 March 2023 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 30 March 2023 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 12 July 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 21 August 2023 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 31 August 2023 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on | 14 September 2023 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 09 October 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 25 October 2023 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Uzpruvo on | 9 November 2023 |

# 2. Scientific discussion

## *2.1. Problem statement*

Not applicable

## 2.2. About the product

AVT04 (ustekinumab) 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 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 natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signalling pathways.

AVT04 has been developed by Alvotech as a proposed biosimilar to the reference product Stelara (INN: ustekinumab), which was authorized via the Centralized Procedure in the European Union on 15.01.2009 (marketing authorization holder Janssen-Cilag).

## 2.3. Type of application and aspects on development

The applicant has developed AVT04 as a proposed biosimilar to the reference product Stelara. The company is applying for 45 mg and 90 mg PFS presentations.

The development program comprises 2 clinical studies:

• PK Study AVT04-GL-101

This comparative PK study was designed to demonstrate 3-way PK similarity between AVT04, and EU- and US-Stelara in healthy subjects. Safety, tolerability, and immunogenicity were also assessed in the study.

• Efficacy and Safety Study AVT04-GL-301

This comparative 52-week efficacy and safety study in patients with moderate-to -severe PsO was performed to establish therapeutic equivalence of AVT04 to EU-Stelara. Safety, immunogenicity and PK were also assessed in the study.

As mentioned above CHMP SA was sought for the quality aspects, overall design, study population, endpoints, and statistical approach of Studies AVT04-GL-101, and AVT04-GL-301; the assay design for the detection of antidrug antibodies (ADAs) and neutralizing antibodies (nAbs) against AVT04 and Stelara in serum samples from the clinical studies of AVT04.

## 2.4. Quality aspects

### 2.4.1. Introduction

The finished product is presented as a solution for injection for subcutaneous (s.c.) administration containing 90 mg/mL of the active substance ustekinumab.

The product is available in two presentations of 45 mg/0.5 mL and 90 mg/1.0 mL solution for injection in prefilled syringe (PFS). Pack sizes available: 1 pre-filled syringe.

The prefilled syringe is fitted with a plunger rod, extended finger flanges and a needle safety device (SD), forming the finished product, which is referred to as AVT04-PFS SD.

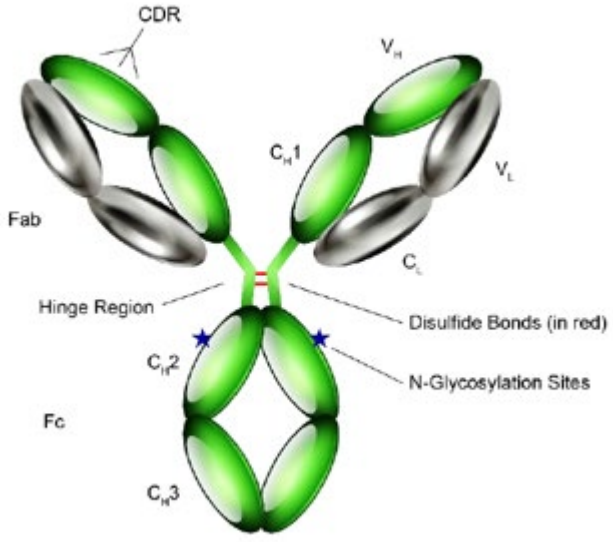
Other ingredients are: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection.

## 2.4.2. Active substance

### *2.4.2.1. General information*

The active substance (INN ustekinumab, company code AVT04) is a recombinant, fully human immunoglobulin G1 (IgG1) kappa monoclonal antibody consisting of two identical heavy chains (HC) of 449 amino acids residues paired with two identical light chains (LC) of 214 amino acids residues. The heavy and light chains are linked by covalent disulfide bonds (two heavy-heavy disulfide bonds and two heavy-light disulfide bonds) in addition to non-covalent heavy-heavy and heavy-light chain interactions. Twelve additional intrachain disulfide bonds are present in ustekinumab. The antibody bears one N-glycosylation site on each heavy chain within the constant region at asparagine (Asn) 299. The N-linked glycosylation structures in the CH2 region is essentially fully occupied with core-fucosylated, complex-type biantennary N-linked glycans with zero and one terminal galactose residues, abbreviated as FA2 and FA2G1, respectively.

*Figure 1. Schematic representation of a typical IgG molecule, such as ustekinumab, with locations of important structural components*




Ustekinumab binds to the p40 subunit of interleukin (IL)-12 and IL-23 and prevents human IL-12 and IL-23 from binding to the IL-12Rβ1 receptor chain of IL-12 (IL-12Rβ1/β2) and IL-23 (IL-12Rβ1/23R) receptor complexes on the surface of natural killer (NK) and T cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors.

### *2.4.2.2. Manufacture, process controls and characterisation*

The active substance is manufactured by Alvotech hf (Reykjavik, Iceland) in accordance with Good Manufacturing Practice (GMP).

#### *Description of manufacturing process and process controls*

The active substance is purified from a recombinant mouse SP2/0 cell line. The manufacturing of the active substance is divided into an upstream (USP) and a downstream (DSP) manufacturing process.

The process is typical for a monoclonal antibody, however more advanced due to the application of a continuous perfusion bioreactor and protein A capturing step.

The upstream manufacturing process consists of 8 process steps. In short, one working cell bank (WCB) vial is thawed, and the cells are expanded over several steps in shake flasks, and single use bags (SUB) used for inoculation of the SUB production bioreactor.

The downstream manufacturing process (DSP) includes protein A capturing, followed by viral inactivation, neutralisation, nanofiltration, ultrafiltration/diafiltration, formulation and finally bulk active substance filling and freezing.

Overall, the process controls defined in the flow-diagrams and tables including their criticality classification for the upstream and downstream process are sufficiently detailed.

One WCB vial is used to produce one single batch of active substance. The batch numbering system is deemed suitable to ensure traceability. The batch size range acceptable for further downstream processing is appropriately defined.

A summary of validated active substance process intermediate hold times is provided. Data on establishment of hold time stability for buffers and all process intermediates were appropriately presented in section 3.2.S.2.5 Process Validation.

The applicant states that there is no reprocessing during the manufacturing of the active substance.

To conclude, the description of the manufacturing process and controls is in line with the expectations.

***Control of materials***

*Reagents and Buffers*

A detailed list of compendial (Ph.Eur., USP) and non-compendial materials used in the upstream process for cell culture media and the downstream process for buffers and purification material was provided. For non-compendial materials, the certificates from the supplier are verified for conformity with the applicants specifications. Example certificate of analysis of the materials used in the upstream process were provided.

A transmissible spongiform encephalopathies (TSE)/ bovine spongiform encephalopathy (BSE) statement was provided in chapter 3.2.R confirming that all raw materials and excipients used in the production process other than the cell substrate are animal component-free. For some single use components, animal derived materials have been used (tallow-derivatives). However, appropriate statements of compliance and confirmation from the suppliers that these materials do not present a quantifiable BSE risk were attached to the dossier (3.2.R).

The purification materials and buffer compositions were appropriately listed. Overall, the section of reagents and buffers was well addressed.

*Generation of Cell Substrate and Cell line History*

The source of the cell substrate (mouse spleen, SP2/0) and analysis of the expression construct to develop the Master Cell Bank (MCB) is described in sufficient detail.

A common two-tiered cell banking system consisting of a MCB derived from the Research Working Cell Bank (RWCB01) and a WCB was established.

All applied characterization tests for the MCB, WCB and PPCB were appropriately described and are deemed state of the art.

To conclude, the establishment and characterization of the MCB, WCB and PPCB was described in detail and is deemed sufficient.

***Control of critical steps and intermediates***

The manufacturing process is controlled by in-process controls (IPCs) with an action limit for less critical steps. IPCs with acceptance criteria are used for critical process parameters (CPPs).

Tables describing the process controls, their criticality classification, action limit and acceptance criteria are appropriately presented in the dossier. In addition, the in-process analytical procedures are described in short.

Validation of hold time duration is presented and assessed in section 3.2.S.2.5 Process Validation.

Analytical methods used for in-process testing are adequately described.

The composition of cell culture media has been sufficiently clarified.

***Process validation***

Three consecutive process performance qualification (PPQ) batches were manufactured at full scale using the commercial process.

All process parameters presented in the dossier for all three PPQ batches were maintained near the set point/target and were consistently within the established acceptable ranges as presented in section 3.2.S.2.6. All IPC acceptance criteria were consistently met for the buffers, cell culture seed and growth media and the active substance upstream- and downstream manufacturing. Only very few minor deviations occurred that were appropriately followed up, or lead to the execution of the established control strategy. Release test results of all three active substance batches complied with the specification.

Impurities were consistently cleared to acceptable limits. Limits for respective impurities were appropriately established by evaluation of toxicological data as described in section 3.2.S.3.2 Impurities.

Overall, the manufacturing process validation is found acceptable.

***Manufacturing process development***

The applicant developed the active substance manufacturing in an iterative process from small scale to larger scale including characterisation in order to understand the operating range and define critical process parameters. Data from three manufacturing processes are presented. The process 1.0 is described as the first representative process, followed by minor process improvements for process 1.1 and 1.2. The manufacturing process 1.2 is the final manufacturing process as presented in section 3.2.S.2.2. Material from process 1.1 and 1.2 was used for clinical studies and process validation activities. The process development and the respective changes in the upstream- and downstream manufacturing steps are described in detail.

Process characterization is based on a qualified small-scale model applying uni- and multivariate Design of Experiment (DoE) studies. Based on the presented data, the small-scale models for the upstream- and downstream process can be regarded representative of the large-scale manufacturing process. Based on the process characterisation using the small-scale models the upstream and downstream critical process parameters / non critical process parameters including their proven acceptable range and characterisation range were defined and summarized. The process parameters that could impact quality attributes were chosen for the DoE studies based on a risk assessment. Critical material attributes were defined and characterized as well. The amount of characterized non critical and critical process parameters for which a characterization range and a proven acceptable

range is indicated is extensive and appears suitable and complete. The criticality assessment of quality attributes is presented and assessed in section 3.2.R.

Comparability between material derived from manufacturing process 1.0, 1.1 and 1.2 was confirmed by comparing in-process control results and release testing results. Extended characterisation was also performed, applying state-of-the-art assays to test for primary structure, higher order structure, post-translational modifications, functional activity, and physicochemical attributes. Multiple at-scale AVT04 batches including the technical, engineering, clinical, and performance qualification batches were included in the comparability exercise. Overall, it can be agreed that comparability was shown and that the batches derived from manufacturing process 1.0 and 1.1 can be regarded representative of the AVT04 commercial manufacturing process, which is represented by the manufacturing process 1.2.

The applicant assessed the consistency of manufacturing over multiple consecutive at-scale batches derived from process 1.0 and 1.1.

Compatibility of product contact material in the downstream process and the first finished product steps  was also assessed. The results indicate compatibility of the contact materials with active substance/finished product.

Extractable and Leachable Risk Assessment protocols for upstream-, downstream and finished product manufacturing were attached to the dossier. Medium- and high-risk items were further assessed regarding available extractable data. The strategy for extractables and leachables assessment is acceptable.

Overall, the manufacturing process development was appropriately presented.

***Characterisation***

In section 3.2.S.3.1 Elucidation of structure and other characteristics, the applicant presents a comprehensive list of characterization assays applied during comparative analytical similarity assessment. Because much of the characterization analysis was conducted as part of the comparative similarity assessment, results are presented and assessed in section 3.2.R.3.

Sufficient clearance of process related impurities was appropriately analysed over relevant processing steps during the process performance qualification.

Product related impurities were also characterized alongside the reference product using orthogonal methods and results are presented in section 3.2.R. The product related impurities of the proposed biosimilar in general are comparable to the reference product with slight differences, which are discussed in 3.2.R.

The toxicological assessment of impurities is based on literature research and ICHQ3C guidance. Where definitive toxicity data was not found, the no observed adverse effect levels (NOAEL), and permissible daily exposure (PDE) data from the FDA Inactive ingredient database were used to provide maximum limits. The assessment approach is regarded acceptable.

An appropriate risk assessment of Nitrosamines in the active substance and finished product was attached to this section.

### *2.4.2.3. Specification*

The following tests are included in the active substance specification: general tests (appearance, pH), identity (peptide mapping), purity (charge heterogeneity, size variants), process related impurities (Host Cell Protein, host cell DNA, residual Protein A), potency, protein content, and safety (bacterial endotoxins, bioburden).

Overall, the quality attributes listed in the active substance release specification complies with ICH Q6B, Ph. Eur. 2031 and EMA/CHMP/BWP/532517/2088 requirements and is acceptable.

Though the data set is currently limited, the proposed specification limits for the active substance can presently be regarded acceptable.

***Analytical methods***

Analytical procedures used for the routine control testing of the active substance are summarized in section S.4.2. The used analytical procedures have been sufficiently described, reference to compendial methods is made and considered acceptable. Validation of the analytical procedures has been conducted in accordance with ICH Q2(R1) and the results derived thereof demonstrate that the chosen procedures are suitable for its intended use. The applicant provided the requested validation reports for the host cell protein (HCP) assay. It can be concluded that the HCP assay is appropriately validated.

***Batch analysis***

Batch release data for multiple active substance batches manufactured at large scale using manufacturing process 1.0 and 1.1 as well as PPQ batches corresponding to manufacturing process 1.2 are presented. All batches met the current release specification, confirming that the active substance manufacturing process reliably delivers consistent product according to specifications.

***Reference materials***

The applicant intends to implement a two-tiered Reference Material System, consisting of a Primary Reference Material which is used for calibration of the Working Reference Material. The working Reference Material will be used to analyse product batches for Quality Control purposes.

The applicant´s strategy to establish a two-tiered Reference System (Primary in-house Reference Material and Working Reference Material) is endorsed.

The applicant provided appropriate test parameters and specifications to establish future reference standards.

***Container Closure System***

The container closure system used for the active substance is adequately described including a summary of product characteristics, specification, container closure components, a diagram of the container and an example certificate of release from the manufacturer.

Extractables and leachables were tested by the bag manufacturer. No leachables peaks were detected above the analytical evaluation threshold after long term storage.

#### *2.4.2.4. Stability*

The design of the stability study is in accordance with ICH Q5C.

To conclude, the applicant´s claim for the active substance shelf life is supported by real-time long-term stability data of three representative batches.-Therefore, the active substance stability claim of 24 months at -70°C ± 10°C is acceptable.

## 2.4.3. Finished medicinal product

#### *2.4.3.1. Description of the product and Pharmaceutical development*

The finished product is a sterile, preservative-free, practically free of visible particles, clear, colourless to slightly yellow solution for subcutaneous injection containing 45 mg or 90 mg of ustekinumab in 0.5

mL or 1 mL, respectively. The excipients are of compendial nature. There are no novel excipients, and no excipients of human or animal origin. No overage is required.

The composition of AVT04 45 mg and 90 mg includes ustekinumab, respectively, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection.

Characterization studies covering physicochemical and biological properties of ustekinumab were performed using AVT04 active substance as well as AVT04 finished product. The product is stabilized and suitable for injection.

The manufacturing process was established at Alvotech, Reykjavik, Iceland at the intended commercial manufacturing site and used to manufacture AVT04-finished product shelf-life assignment material and to generate clinical supply. A comparative analytical assessment, which include in-process testing, release and stability study and forced degradation studies, confirmed the comparability between 45 mg/0.5 mL and 90 mg/1.0 mL finished product batches.

The history of the release and shelf-life specifications has been provided. Characterization risk assessment and characterization studies have been performed to define ranges and criticality of each process parameter and define Key process/equipment features.

Additional development studies were conducted to support the intermediate storage of the formulated bulk.

The safety device selected is a marketed, off-the-shelf reliable and AVT04-DP PFS-compatible product. A routine industry standard assembly process is followed. Design, development and verification studies have been completed.

The AVT04-DP PFS container closure system (CCS) consists of a single-use, type I glass, pre-fillable 1 mL syringe with a fixed 29-gauge, 0.5-inch needle (container), and a plunger stopper with fluoropolymer barrier film (closure). Suitability of the device (including safety and biocompatibility studies, performance testing and design verification) and extractables and leachables analysis on the primary container closure components have been performed.

Currently, available stability study data do not indicate incompatibilities or interference with the glass or plunger stoppers throughout storage. Long-term leachable studies at real-time storage conditions have been completed, and results updated in dossier.

The final product is a single-use integral drug-device combination (DDC) product which consists of AVT04-DP prefilled syringe fitted to the non-product contact 1 mL staked safety device. The intended use is the subcutaneous delivery of ustekinumab. The safety device help handling by manually impaired patients, prevents users from accidental needle sticks, and allows visualization of the finished product inside the syringe. Suitability of the safety device, has been confirmed by biocompatibility testing including cytotoxicity, irritation, and sensitization, and a performance testing. The Notified Body Opinion Report was submitted, confirming the conformity of the device part of the AVT04 SD45/SD90 finished product (i.e. prefilled syringe with passive needle safety device) to the relevant GSPRs in Annex I of the Medical Devices Regulation.

Microbiological attributes

Microbiological quality is ensured by bioburden reduction filtration and sterile filtration of the formulated active substance, aseptic filling in sterile naked glass syringes (sterilized by ethylene oxide) and stoppering with sterile plunger stopper.

### *2.4.3.2. Manufacture of the product and process controls*

*Manufacture and Process controls*

The finished product is manufactured and batch released at Alvotech hf (Reykjavík, Iceland) in accordance with GMP. Assembly with safety device is done at AndersonBrecon (UK) Limited, United Kingdom. All sites have a GMP certificate.

The AVT04 active substance is fully formulated, and no further formulation steps are conducted during finished product manufacture. The two presentations of the AVT04-DP PFS are identical in all aspects except for the fill volume of the syringe.

AVT04-DP PFS is the active substance filled into syringes, each with a needle, needle-cap and plunger stopper. AVT04-DP PFS is manufactured by thawing and mixing the formulated active substance, followed by aseptic filling and stoppering. There are no reprocessing steps in the manufacture of AVT04-DP PFS.

Manufacturing of the finished product AVT04-PFS SD consists of the assembly of the prefilled syringe (AVT04-DP PFS) with a safety device (SD). There are no reprocessing steps in the manufacture of AVT04-PFS SD.

In-process controls (IPCs) for the manufacturing process of AVT04-DP PFS are listed for each manufacturing step, together with the method applied and the acceptance criteria. Hold times are presented. In-process analytical procedures are discussed. Acceptance criteria were based on data obtained during process development and further adapted following further manufacturing experience.

A nitrosamine risk assessment has been performed for active substance and finished product, and confirmed the absence of nitrosamine.

Process validation

Process performance validation (PPQ) of the AVT04 finished product prefilled syringe (AVT04-DP PFS) manufacturing process was performed on six consecutive batches at full scale using the intended commercial process.

All process parameters were consistently maintained within the manufacturing operating range. Furthermore, it is agreed that all IPC acceptance criteria were consistently met for all process steps. Release acceptance criteria for AVT04-DP PFS were also met. Minor deviations during manufacturing were appropriately followed up.

To conclude, the Process Performance Qualification study of the AVT04-DP PFS manufacturing process confirmed the ability to manufacture product of the specified quality. The exact numerical extractable volume results for the six AVT04-DP PFS PPQ batches is provided.

The AVT04-DP PFS is shipped from Alvotech hf, Iceland to UK for assembly with the safety device. The transport validation protocols provided are acceptable.

The (manual) assembly of AVT04-PFS with the safety device was validated with multiple consecutive batches covering the maximum commercial batch size.

### *2.4.3.3. Product specification*

*Specification of AVT04-DP PFS*

The specifications for the control of AVT04-DP PFS have been set in accordance with guideline "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" (ICH Q6B), Ph. Eur. 2031 and the "*Guideline on Development, Production, Characterization and Specifications for Monoclonal Antibodies and Related Products*" (EMEA/CHMP/BWP/157653/2007), and appear in most instances sufficiently justified.

AVT04-DP45 and AVT04-DP90 have the same release and shelf-life specifications, except for the extractable volume, which is NLT 0.50 ml and NLT 1.0 ml, respectively. Release and end of shelf-life specifications for AVT04-DP PFS have been established to ensure safety and consistency, based on available manufacturing, development, and stability experience from AVT04-DP PFS as well as data from the reference product, where applicable. The proposed acceptance criteria have been established based on results obtained with Stelara reference product, the specified target product profile as well as from AVT04-DP PFS manufacturing experience and product stability. Overall, the specifications are sufficiently justified.

*Specification AVT04-PFS SD*

Release and shelf-life specifications have been established for the finished product AVT04-DP PFS in safety device (AVT04-PFS SD), to ensure a safe and effective product for patients, by identifying essential performance requirements (EPRs).

***Analytical methods***

Methods have been properly validated and verified.

***Batch analysis***

Overall, batch analysis results provided confirm consistency and uniformity of the product, indicating that the process is under control.

***Justification of specifications***

Release and end of shelf-life specifications for AVT04-DP PFS have been established to ensure safety and consistency, based on available manufacturing, development, and stability experience from AVT04-DP PFS as well as data from the reference product, where applicable. The proposed acceptance criteria have been established based on results obtained with Stelara reference product, the specified target product profile as well as from AVT04-DP PFS manufacturing experience and product stability. Overall specifications appear sufficiently justified. Several issues have been appropriately addressed.

***Reference materials***

Refer to discussion in the active substance section.

***Container closure***

The primary container closure for AVT04-DP PFS is a single-use, glass pre-filled 1mL syringe (container) with a fixed needle and a rigid needle shield The secondary container closure for AVT04-PFS SD (AVT04 prefilled syringe safety device) is the passive safety system, which includes a plunger rod, a white extended finger flange (EFF) and a safety device. Intended use, composition, potential contact with the human body, and reference to quality standards and biocompatibility certificates, are provided for each component. There are no materials of animal origin.

Compatibility of the primary container closure components with the active substance formulation and suitability of the container closure system have been confirmed. Suitability of the container closure system is presented.

### *2.4.3.4. Stability of the product*

Stability of AVT04-DP PFS

Stability studies have been performed according to current guidance (ICH Q5C and ICH Q1A) to support the proposed shelf life of 24 months for the finished product stored at long-term storage conditions (5°C ±3°C) and storage out of fridge (up to 30°C ±2°C/65% ±5% Relative Humidity (RH)) for 30 days. The same analytical procedure described in 3.2.P.5.1 have been applied and the same testing strategy has been defined to study stability of all AVT04-DP PFS batches.

The proposed shelf-life of 24 months stability data at 5°C ±3°C has been demonstrated for three batches produced with the manufacture commercial process, therefore the proposed shelf-life can be accepted**.**

The proposed out of fridge stability at 30°C ±2°C, 65% ±5% RH for a maximum of 30 days as a single period within the 24-month shelf-life has been confirmed for three batches.

Stability of AVT04-PFS SD

Since the primary container closure system for AVT04-DP PFS is assembled with non-product-contact components of the safety device, the shelf-life assignment of AVT04-PFS SD will be based on the long-term stability data available on the AVT04-DP PFS, with a commitment to provide additional physicochemical and functional stability data on AVT04-PFS SD during the review. This is supported by data provided by the safety device manufacturer regarding stability of device function and design verification.

The claim that shelf life of AVT04-PFS SD can be supported by shelf-life study results on AVT04-PFS if comparability is confirmed, is acceptable. The proposed shelf-life of 24 months for AVT04-DP PFS is supported by the available data, and therefore applicable to AVT04-PFS SD.

As regard to post-approval stability, at least one commercial AVT04-PFS SD batch (if manufactured) per year will be placed into a long-term stability study at 5 °C ± 3 °C.

### *2.4.3.5. Adventitious agents*

MCB, WCB, and PPCB were tested for the absence of non-viral adventitious agents (bacterial/fungal contamination and mycoplasma) according to Ph. Eur. (2.6.1; 2.6.7) at appropriate steps of manufacture. No material of animal origin was used in MCB and WCB manufacture or in active substance or finished product production. Certificates of Origin/TSE statements have been provided for raw materials, consumables and contact materials (in Section 3.2.R.1). Based on the information provided, it is agreed that the risk with regard to TSE is minimal. The risk assessment is considered appropriate and in line with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents (EMA/410/01 rev.3).

Cell bank (MCB, WCB, PPCB) and unprocessed bulk testing for adventitious viruses and other agents is conducted in compliance with guidelines ICH Q5A(R1), ICH Q5B and ICH Q5D and is generally considered appropriate. The total process clearance determined by summation of orthogonal removal/inactivation methods indicates acceptable safety margins for viral particles are in line with ICH Q5A guidance (< 1 particle per million dose).

In conclusion, the two dedicated virus clearance steps in combination with the affinity and chromatography steps apparently provide for an effective and robust overall clearance capacity for enveloped and non-enveloped adventitious viruses. The risk of potential contamination and transmission of bacterial, viral, or TSE agents is considered to be acceptably low.

### *2.4.3.6. Biosimilarity*

A comprehensive similarity exercise has been performed using multiple AVT04-DP PFS batches of different age and manufactured from multiple independent active substance batches and eighteen EU-Stelara batches of different ages. Batches used in the clinical studies have been included in most, but not all, studies. US-Stelara batches in both dosage forms and with an age at testing ranging from 12 to 36 months (calculated based on 36 months shelf-life) were additionally included in the comparative Analytical Similarity Assessment Study.

The AVT04 critical quality attributes (CQAs) were identified by assessing potential CQAs based on general knowledge from literature and any project-specific knowledge available. Overall, the criticality assessment is well described and seems reasonable.

Comparative Analytical Similarity Head-to-Head (H2H) Testing

Results of the comparative analytical assessment are provided in tabular and graphical forms, allowing the comparison of individual batches and discussion on batches distribution, and as raw data. According to EMEA/H/SA/4502/1/2020/III, results for each strength have been presented separately. Results from the batches used in the clinical studies are highlighted in the assessment. Similarity between AVT04 and EU-Stelara could be confirmed for all quality attributes tested, and minor differences have been properly addressed and justified to have no impact on the biosimilarity claim or on safety and efficacy.

*Primary structure*

Identical amino acid sequence was confirmed by electrospray - time of flight mass spectrometry (ESI-Q-TOF-MS/MS) sequencing of endoproteinase-derived peptide fragments.

Similarity on the reduced molecular masses is shown: removal of N-glycans and C-terminal lysine variants by pre-treatment with PNGase F and CpB enzymes, confirmed the high similarity of the recorded reduced masses and shows that AVT04 has a higher average value of HC glycation, still within the quality range of both EU-Stelara and US-Stelara. HC glycation testing was done on the AVT04 clinical batch but not in Stelara clinical batches.

*Higher order structures*

Similarity of secondary and tertiary structures was demonstrated. Differences were detected only on the trisulfide linkages, i.e. presence of HC trisulfide in two AVT04 batches, including the clinical batch, and higher level of trisulfide at the LC and HC joining region in most of AVT04 batches, especially comparing the batches used in the clinical studies. Trisulfides are a common modification in IgG antibodies, converted to disulfides following systemic administration (as shown in rats), and shown to not affect the thermal stability, antigen binding, or potency of antibodies, but still considered as cQA because the tolerable percentage of trisulfide modification is not known. Similarity on the free thiol levels is shown.

*Post-translational modifications*

Similar sialylation levels are shown. Slightly lower levels of sialic acid (Neu5Gc) are found in AVT04 batches, but similar values are found on the batches used in the clinical studies were shown. High mannosylation is shown for AVT04 batches, but similar values between the batches used in the clinical studies. Similar levels of terminal galactose are shown, but much lower levels of alpha-1,3-galactose were detected in all AVT04 batches, especially when comparing batches used in the clinical studies. The low levels of alpha-1,3-galactose in comparison to Stelara are not considered to be of concern, since only higher amounts of this epitope could potentially result in increased immunogencity / hypersensitivity reaction. Lower levels of afucosylation with and without mannose were detected in all

AVT04 batches, especially comparing the batches used in the clinical studies. The four AVT04 batches with lowest afucosylation also have the highest mannosylation levels. Since ustekinumab is observed to not have effector functions as a MoA, afucosylation is not expected to impact efficacy of the molecule and this quality attribute has been rated as a non-CQA. Differences in afucosylation and mannosylation could have an effect on binding of ustekinumab to FcγRIIIa and with this have an impact on ADCC activity. However, the lack of afucosylation related ADCC effector functions was confirmed for AVT04 and Stelara, by an appropriate cell based ADCC assay. Overall, the differences in mannosylation and afucosylation were in principle well addressed.

Similar deamination levels are shown for the critical site HC Asn391, but higher oxidation of Met254HC, which is a critical site as it is most prone for oxidation due to solvent exposure and known to affect FcRn binding, is found in three ATV04 batches. Especially, differences are shown while comparing batches used in the clinical studies, but those differences are not considered to have an impact on FcRn binding. LC Trp32 di-oxidation was never detected.

Lower levels of Asp55 isomerization are shown for AVT04, but still within the EU-Stelara range and with similar values on the batches used in the clinical studies.

Similarity is shown for the low level of N-terminal HC pyroglutamate (≤ 1%). However, lower levels of intact C-terminus of HC (lower level C-terminal lysine: lower level of K1 and K2) were found in AVT04 compared to Stelara, especially comparing the batches used in the clinical studies. C-terminal lysine has been demonstrated to be cleaved off after administration of the finished product and to not have effect on the binding of human Fc to human FcRn and FcγRIIIa receptors; hence, to not affect the mAb on its FcRn based PK profiles and FcγRIIIa-driven cytotoxicity potencies, respectively. The applicant does not consider C-terminal lysine as a CQA, due to lack of impact on efficacy, PK/PD, immunogenicity, or safety, and differences observed are not expected to have a meaningful impact.

*Physicochemical analyses*

Wider distributions are shown for protein content in EU Stelara batches and differences are shown for the protein content of the batches used in the clinical, however, the protein content of KHS25MJ is still within the acceptance range of EU- Stelara. For the quantification, the experimentally determined absorption coefficient (ε) was used. The applicability of the same coefficient AVT04 and Stelara is justified.

Similarity was demonstrated for charge and size variants and differences were justified. Similarity of the levels of main peak and high molecular weight species (HMWs), molecular weight of the main peak, and relative amount of monomer, dimer and higher order aggregates is shown. Differences are shown for purity. The level of total fragments remains within the specification during stability studies. Absence of impact on potency is confirmed by additional statistical analyses on all available data.

Comparable subvisible particle sizes and % polydispersity was demonstrated.

*Functional activity*

The biological activity of AVT04 and Stelara batches was compared applying different assays. Similar results were obtained for potency (by IL-12 neutralization assay), binding of p40, IL-12, IL-23, FcRn, FcγRIa and C1q.

Lower FcγRIIIa (158F) and FcγRIIIa (158V) binding affinity of AVT04 correlates with to the lower afucosylation and higher mannosylation. Since afucosylated IgGs exhibit a significant increase in binding affinity to FcγRIIIa receptors, translating to increased ADCC activity, and "High mannose glycans are by default afucosylated", and since the absence of ADCC and CDC induction was confirmed in both AVT04 and Stelara batches in suitable in vitro assays, the observed differences in Fcγ binding have no functional consequence.

Reference Product Bridging

The clinical study on AVT04-GL-101 was performed to compare the pharmacokinetics (PK) of AVT04 versus EU- and US-Stelara, and the clinical study on AVT04-GL-301 to evaluate the therapeutic equivalence of AVT04 to EU-Stelara. Since the US reference product was not evaluated in the AVT04-GL-301 study, a three-way pairwise, analytical bridging assessment has been conducted. EU-Stelara batches have been compared to the US-Stelara quality ranges. Overall, the bridging analysis indicates that EU-Stelara is representative of US-Stelara with regard to physicochemical CQAs, and functional testing. Slight differences were justified.

Comparative forced degradation study

A Head-to-head comparative forced degradation study which included high temperature, photolytic stress, low and high pH, agitative- and oxidative stress condition was conducted with multiple AVT04 batches, EU-Stelara, and US-Stelara batches. Overall, the comparative forced degradation studies have been properly performed and no degradation products were detected in AVT04 that were not also found in Stelara.

**Table 1.** Summary of Comparative Analytical Similarity Assessment

| **Attribute** | | **Method** | **Similarity Conclusion** |
|---|---|---|---|
| Primary structure | Amino acid sequence | Primary sequence determination (multiple methods, including Edman's degradation and amino acid hydrolysis and peptide mapping by LC-MS & MS/MS using trypsin and other enzymes) | Identical amino acid sequence (100% sequence coverage) for AVT04 and Stelara. |
| | | Peptide mapping (LC-MS) | Identical amino acid sequence (>93% sequence coverage) for AVT04 and Stelara. |
| | Intact mass | LC-MS | Similar molecular mass and size demonstrated at the intact molecule level for AVT04 and Stelara, including glycoforms and partial lysine-clipping at the C-terminus of the heavy chain. |
| | Reduced mass | LC-MS | Similar molecular mass and size demonstrated at the reduced molecule level (heavy and light chain) for AVT04 and Stelara, including glycoforms and partial lysine-clipping at the C-terminus of the heavy chain. |
| | De-N-glycosylated and CpB treated reduced molecular mass and glycation | LC-MS | Similar molecular mass demonstrated at the reduced molecule level after de-glycosylation and CpB treatment for AVT04 and Stelara. Highly similar glycation levels were observed for AVT04 and Stelara. |
| Higher order structure | Secondary | Far-UV CD | Similar secondary structure for AVT04 and Stelara. |
| | | FT-IR | |
| | Tertiary, including disulfide and | DSC | Similar tertiary structure and identical disulfide bond connectivity demonstrated for AVT04 and Stelara. Overall low levels of |
| | | Near-UV CD | |

| Attribute | | Method | Similarity Conclusion |
|---|---|---|---|
| | trisulfide bonds | Intrinsic fluorescence | trisulfides (below 3.5% for all batches analyzed), albeit slightly higher levels of trisulfides observed for some batches of AVT04 compared to the quality ranges. |
| | | Non-reduced peptide mapping (LC-MS) | |
| | Free thiols | Ellman´s reagent | Similar free thiol content for AVT04 and Stelara. |

| Attribute | | Method | Similarity Conclusion |
|---|---|---|---|
| Post-translational modifications | Glycosylation | Rapifluor-UPLC-FLR | Similar N-linked glycan distribution profile, structure, composition, and glycosidic linkages for AVT04 and Stelara. Major glycan species are FA2G1 and FA2. |
| | Afucosylation | | Low levels of afucosylation were observed for both AVT04 and Stelara. Lower levels of afucosylation, and afucosylation without high mannose were observed for seven out of eight batches of AVT04 compared to the quality ranges of EU- and US-Stelara. The difference in afucosylation affects the binding to FcγRIIIa receptors, however as ustekinumab does not induce effector functions the difference observed do not affect the similarity evaluation. |
| | Terminal galactose | | Similar galactosylation levels for AVT04 and Stelara. |
| | Alpha-1,3-galactose | | Similar alpha-1,3-galactose content for AVT04 and Stelara. |
| | High mannose | | Very low levels of high mannose glycans in AVT04 and Stelara. One batch of AVT04 shows somewhat higher level of high mannose compared to EU- and US-Stelara ranges, while five additional AVT04 batches show marginally higher high mannose levels than the range for US-Stelara. High mannose glycans correlate with serum clearance and binding to FcγRIIIa and ADCC activity, but due to the lack of effector functions for ustekinumab and the overall low levels observed, the differences observed are not considered clinically meaningful. |
| | Sialylation | | Similar levels of sialylation for AVT04 and EU-Stelara were found. One batch of AVT04 fell below the US quality range (mean RP ±3 SD). |
| | N-glycolylneuraminic acid (Neu5Gc) | RP-HPLC with DMB labelling | Similar levels of N-glycolylneuraminic acid for AVT04 and Stelara. |
| | Deamidation | Peptide mapping (LC-MS) | Similar levels of deamidation observed for AVT04 and Stelara. |
| | Met oxidation | | Low levels of Met oxidation are present in AVT04 and Stelara analyzed. Three batches of AVT04 are marginally higher (0.1%-0.3%) than the EU-Stelara range for HC Met254 oxidation. Difference observed not expected to have a relevant impact. |

| Attribute | | Method | Similarity Conclusion |
|---|---|---|---|
| Post-translational modifications | Trp oxidation | | Very low levels (below limit of quantitation (LOQ)) of Trp oxidation found for AVT04 and Stelara. |
| | Aspartate isomerization | | Similar levels of aspartate isomerization for AVT04 and Stelara. |
| | N/C-terminal integrity | | No differences in N-terminal heterogeneity of L chain and H chain. No differences in C-terminal heterogeneity of L chain. Difference relating to HC C-terminal lysine content observed, as C-terminal lysine was present in roughly 10% in AVT04, but 30 – 40% in Stelara. C-terminal lysines are defined as non-CQA, as literature indicate that they have no impact on biological activity, PK, immunogenicity, or safety. This is also supported by in-house functional data. |
| Functional activity | Potency | IL-12 neutralization assay- inhibition of IFN-γ release from NK92 cells | Similar potency for AVT04 and Stelara. |
| | p40 binding | p40 binding SPR | Similar p40 binding for AVT04 and Stelara. |
| | IL-12 binding | IL-12 binding SPR | Similar IL-12 binding for AVT04 and Stelara. |
| | IL-23 binding | IL-23 binding SPR | Similar IL-23 binding for AVT04 and Stelara. |
| | FcRn binding | FcRn binding SPR | Similar FcRn binding for AVT04 and Stelara. |
| | C1q binding | C1q binding by ELISA | Similar C1q binding for AVT04 and Stelara. |
| | FcγRIa binding | FcγRIa binding SPR | Similar FcγRIa binding for AVT04 and Stelara. |
| | FcγRIIa (131H) binding | FcγRIIa (131H) binding SPR | Similar FcγRIIa binding for AVT04 and US-Stelara. Due to very tight clustering of EU-Stelara batches analyzed, one batch of AVT04 is higher than the EU range, while two AVT04 batches are below the range. The mean of EU- and US-Stelara is highly similar, which suggests that with additional EU-Stelara batches the distribution would likely increase, as is observed for the US-Stelara batches. |

| Attribute | | Method | Similarity Conclusion |
|---|---|---|---|
| Functional activity | FcγRIIIa (158F) binding | FcγRIIIa (158F) binding SPR | The binding to the FcγRIIIa receptor is highly influenced by fucosylated glycans on an antibody. Therefore, the differences observed in afucosylation between AVT04 and Stelara cause a considerable difference in the FcγRIIIa binding, where the binding of Stelara is roughly double that of AVT04. Differences observed in binding to the FcγRIIIa receptor correspond to effects on induction of ADCC activity. However ustekinumab does not induce any ADCC or CDC activity. Therefore, the differences observed for FcγRIIIa binding have no clinical impact of AVT04. |
| | FcγRIIIa (158V) binding | FcγRIIIa (158V) binding SPR | |
| | ADCC | ADCC Jurkat-FcγRIIIa (158V) NFAT Reporter Assay | No ADCC induction was observed for any AVT04 or Stelara batch analyzed. |
| | CDC | CDC reporter assay | No CDC induction was observed for any AVT04 or Stelara batch analyzed. |
| Physicochemical analyzes | Protein content | OD280 | Similar protein content for AVT04 and US-Stelara found. Four AVT04 batches were marginally higher in concentration (0.1 – 0.4 mg/mL) than quality range for US-Stelara. |
| | Charge variants | CEX | Higher levels of acidic and main peak variants for AVT04 than for Stelara. Concomitantly, lower levels of basic variants observed for AVT04 than for Stelara. The addition of CpB shows that the differences in charge variants are governed by C-terminal lysines, as highly similar levels of acidic, basic, and main peak variants observed for AVT04 and Stelara are present after CpB treatment. C-terminal lysines (higher levels in Stelara) are defined as non-CQA, as they have no impact on biological activity, PK profiles, immunogenicity, or safety. |
| | | CEX + CPB | |
| | | cIEF | |
| | | cIEF + CBP | |
| | Size variants | CE-SDS (non-reduced) | Overall high levels of monomer and low levels of fragments for AVT04 and Stelara, albeit slightly lower level of monomer is observed in AVT04. No clinical impact expected due to the differences observed. |
| | | CE-SDS (reduced) | Similar levels of HC+LC and other fragments for AVT04 and Stelara. Marginally higher DHC levels (0.1%) for AVT04 compared to US-Stelara, which are not expected to have any clinical impact. |
| | | SEC-HPLC | Similar high levels of main peak AVT04 and Stelara. Marginally higher HMW levels (0.1%) for AVT04 compared to EU-Stelara, which are not expected to have any clinical impact. |
| Physicochemical analyzes | Size variants | SEC-MALS | Similar molecular weights of monomer and aggregate (dimer) peaks observed for AVT04 and Stelara. |
| | | SV-AUC | Monomer, dimer, and higher-order aggregates of AVT04 and Stelara are highly similar when evaluated using interference detection in combination with SV-AUC. When using absorbance detection, one batch of |

| | | | |
|---|---|---|---|
| | | | AVT04 shows higher contribution of dimer than the quality range for US-Stelara. As this is not observed for the batch in question (DP220013) for the interference detection used in SV-AUC, this does not affect the overall conclusion that aggregate profiles are highly similar for AVT04 and Stelara. |
| Particle analyzes | Sub-visible particles | MFI | Similar, or lower, levels of subvisible particles observed for AVT04 compared to Stelara. |

## 2.4.4. Discussion on chemical, and pharmaceutical aspects

An extensive Module 3 of overall good quality about the proposed biosimilar Uzpruvo (AVT04) was provided by the applicant.

**Active Substance and Finished Product**

The AVT04 active substance and finished product manufacturing process was described in detail. AVT04 is already final formulated on active substance level. Finished product manufacturing consists only of active substance filling and assembly of the prefilled syringe with the safety device. Process controls are defined in the flow-diagrams and tables including their criticality classification. In-process controls for less critical steps are controlled with an action limit. Acceptance criteria are used for IPCs that control a critical process parameter. Tables describing the process controls, their criticality classification, action limit and acceptance criteria are appropriately presented in the dossier. A detailed lists of compendial (Ph.Eur., USP) and non-compendial materials used in the active substance and finished product manufacturing process was provided. An appropriate process performance qualification confirmed consistent manufacturing of AVT04-DS, AVT04-DP prefilled syringe and the finished product, referred to as AVT04-PFS SD, which is the PFS fitted with a plunger rod, extended finger flanges and a needle safety device. A suitable process development enabled the establishment of a consistent manufacturing process. The proposed shelf-life of active substance and finished product are supported by available real-time data.

The active substance process provides two dedicated virus clearance steps in combination with the affinity and chromatography steps. Overall, an effective and robust clearance capacity for enveloped and non-enveloped adventitious viruses was confirmed. The risk of potential contamination and transmission of bacterial, viral, or TSE agents appears acceptably low. The risk of nitrosamines contamination was determined to be low.

All other concerns in the active substance and finished product sections and one major objection concerning the provision of the Notified Body Opinion for the AVT04-PFS safety device have been appropriately addressed.

**Biosimilarity**

An extensive biosimilarity exercise has been performed on eight batches of AVT04 and multiple batches of EU-Stelara. The data confirm that AVT04 has an identical primary amino acid sequence to Stelara, highly similar higher order structure, potency and highly comparable physicochemical attributes. AVT04 showed slightly higher levels in the following quality attributes compared to Stelara: HC trisulfide, trisulfide at the LC and HC joining region, mannosylation, Met254HC oxidation and total fragments. Slightly lower levels were shown for alpha-1,3-galactose, afucosylation, lower C-terminal lysine and intact IgG. The quality differences have been generally well addressed and justified to have no impact

on the biosimilarity claim. In summary, it is agreed that AVT04 has a comparable quality profile to Stelara.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for AVT04 is approvable from the quality point of view.

### 2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

### 2.4.6. Recommendation(s) for future quality development

N/A

## *2.5. Non-clinical aspects*

### 2.5.1. Introduction

AVT04 is a fully human immunoglobulin G, subclass 1, κ light chain (IgG1κ) monoclonal antibody used as therapy for the treatment of plaque psoriasis, psoriatic arthritis (PsA) and Crohn's disease (CD). The primary mechanism of action is binding of the antigen binding fragment (Fab) domain of ustekinumab to the p40 protein subunit of both IL-12 and IL-23, thus preventing the cytokines from binding to IL-12 and IL-23 receptor complexes on the surface of natural killer cells or T cells, thereby initiating downstream immune-response signaling pathways.

### 2.5.2. Pharmacology

Analytical and functional similarity of AVT04 to EU- and US-Stelara was demonstrated in *in vitro* studies and is described in Module 3 and discussed above. No additional non-clinical pharmacodynamic studies, neither *in vitro* nor *in vivo*, were performed and included in Module 4 of this MAA.

### 2.5.3. Pharmacokinetics

A pharmacokinetics study (study number P20-S425-PK) was conducted to compare and evaluate the pharmacokinetic profiles of AVT04 and Stelara after a single subcutaneous injection to Cynomolgus monkeys. No separate absorption, distribution, metabolism and/or excretion studies were performed with AVT04.

AVT04 or CN-Stelara was administered as a single subcutaneous injection to male and female Cynomolgus monkeys at dose levels of 0.9 mg/kg (low dose groups) or 9 mg/kg (high dose groups), with 5 animals per sex per group. Blood samples for pharmacokinetic analysis were obtained pre-dose and several hours post-dose on day 1 until day 43. Additionally, blood samples were collected for anti-drug antibody (ADA) analysis. Meso Scale Discovery (MSD) electrochemiluminescent (ECL) methods for the quantification of Ustekinumab in serum samples (study number P20-207-MV), based on a sandwich ELISA, and for the analysis of antibodies against Ustekinumab in serum samples (study number P20-207-2MV), based on a bridging ligand binding assay (LBA), were validated in compliance with GLP. All projected validation parameters and acceptance criteria (e.g. accuracy, precision, freeze/thaw stability, long term stability, LLOQ determination) were met.

AVT04 and CN-Stelara concentrations in serum samples of Cynomolgus monkeys were comparable to each other at high (9mg/kg) and low (0,9mg/kg) doses, and a dose-response relationship was observed. No apparent gender differences were noticed.

Important PK parameters such as $t_{1/2}$, $C_{max}$ and $AUC_{0-336h}$ increased with dose and were comparable within the same dose groups between AVT04 and CN-Stelara. Mean $t_{1/2}$, $C_{max}$ and $AUC_{0-336h}$ values were determined to be 95.2h (SD 43.2), 10.3µg/ml (SD 3.91) and 2.25 h*mg/mL (SD 0.568) at 0.9mg/kg AVT04 and 175h (SD 61.6), 97.6µg/ml (SD 25.7) and 20.3 h*mg/mL (SD 3.27) at 9mg/kg AVT04. The time of maximum concentration ($T_{max}$) in the AVT04 low dose group ($T_{max}$ 54,8h, SD 36,9) was noticed to be almost half of the $T_{max}$ of the low dose group of CN-Stelara ($T_{max}$ 102h, SD 36.3), mainly due to differences in gender in AVT04 treated animals [$T_{max}$ 78.4h (SD 39.4) in males and $T_{max}$ 31.2h (SD 10.7) in females].

Furthermore, monkeys were monitored for clinical signs and local tolerance during the course of the study. No abnormalities were observed.

## 2.5.4. Toxicology

### *2.5.4.1. Single dose toxicity*

No dedicated single-dose toxicity study was conducted with AVT04.

### *2.5.4.2. Repeat dose toxicity*

To evaluate and compare the toxicological potential and toxicokinetic profile of AVT04 with its reference medicinal product Stelara, the Applicant conducted a four-week repeat-dose toxicity study in Cynomolgus monkeys, including a four-week recovery period after a once weekly subcutaneous injection regimen of excipient control and AVT04 at doses of 5, 15 or 45mg/kg or CN-Stelara at 45mg/kg. Furthermore, anti-drug antibody (ADA) formation against AVT04 and CN-Stelara was investigated in the course of the single dose pharmacokinetics study (study number P20-S425-PK) and the 4-week repeat-dose toxicity study in Cynomolgus monkeys (study number P20-207-RD), using a validated method (study number P20-207-2MV).

No findings and noteworthy differences were observed in the repeat-dose toxicity study between any of the five dose groups, in particular in regards to skin irritation, mortality, morbidity, clinical signs, body weight, body temperature, food consumption, electrocardiogram (ECG), respiratory parameters, blood pressure, blood oxygen saturation, ophthalmoscopy, clinical pathology (haematology, coagulation, clinical chemistry, and urinalysis), lymphocyte subset, cytokines in serum (TNF-α, IFN-γ, IL-2, IL-4, IL-5, and IL-6) and macroscopic and microscopic findings. The no observed adverse effect level (NOAEL) was determined to be 45 mg/kg AVT04 for subcutaneous administration. The $AUC_{last}$ and $C_{max}$ values obtained on day 22 were as follows: 143.48 h*mg/mL and 1072.62 µg/mL in males and 150.57 h*mg/mL and 1081.05 µg/mL in females, respectively. A dose-proportional increase in systemic exposure and increase with each additional subcutaneous administration were observed in all AVT04-treated animals, with no differences detected between males and females. Furthermore, a similar extent of drug accumulation occurred in AVT04 and CN-Stelara treated animals at 45mg/kg, reflected by an accumulation index (AI) of 2.24 and 2.14 for males, and 2.20 and 2.07 for females, respectively. Systemic exposure was comparable between AVT04 and Stelara treated males, whereas for Stelara slightly lower values for $C_{max}$ and $AUC_{last}$ were observed on day 1 and day 2 in female animals. After four weeks of 45mg/kg once weekly repeated subcutaneous injections to Cynomolgus monkeys, neither AVT04 nor CN-Stelara led to ADA formation and no ADAs were detected at any dose (5, 15 and 45mg/kg) of AVT04 at the end of the recovery period. Overall, the results of the repeat dose-toxicity

study in Cynomolgus monkeys indicate that AVT04 does not lead to any undesired treatment related effects and seems to have the same toxicological potential as its comparator CN-Stelara.

In the single-dose PK study, ADAs were detectable in all treatment groups with no noteworthy differences in gender observed, but with a higher incidence for low-dose treated animals. ADA development was comparable between AVT04 and CN-Stelara. Some animals showed to have ADAs pre-dose on Day 1, but with a low titer of <4, maybe due to non-specific background signals, as explained by the Applicant.

#### *2.5.4.3. Genotoxicity*

No dedicated Genotoxicity studies were conducted with AVT04.

#### *2.5.4.4. Carcinogenicity*

No dedicated Carcinogenicity studies were conducted with AVT04.

#### *2.5.4.5. Reproductive and developmental toxicity*

No dedicated Developmental and Reproductive studies were conducted with AVT04.

#### *2.5.4.6. Toxicokinetic data*

A comparative 4-week toxicity study was performed to evaluate and match potential toxicological findings and the toxicokinetic (TK) profile of AVT04 and Stelara (CN-Stelara, sourced from China) following subcutaneous injection in Cynomolgus monkeys. For further details please refer to section 2.5.4.2. Repeat dose toxicity.

#### *2.5.4.7. Local Tolerance*

No dedicated local tolerance studies were conducted with AVT04.

No skin irritations were observed in Cynomolgus monkeys after subcutaneous administration of AVT04, neither at doses of 5, 15 or 45mg/kg (concentration of 90mg/ml) in the four-week repeat dose toxicity study (study number P20-207-RD), nor at doses of 0.9 and 9mg/kg (concentration of 90mg/ml) in the single dose pharmacokinetic study.

#### *2.5.4.8. Other toxicity studies*

No dedicated other toxicity studies were conducted with AVT04.

### 2.5.5. Ecotoxicity/environmental risk assessment

In the case of products containing proteins as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) should be provided, whereby this ERA may consist of a justification for not submitting ERA studies, e.g. that due to the nature of particular pharmaceuticals they are unlikely to result in a significant risk to the environment (EMEA/CHMP/SWP/4447/00 corr 2 issued 01 June 2006).

The applicant provided a valid justification (see GL excerpt above) for the absence of ERA studies with Uzpruvo, which is deemed acceptable.

### 2.5.6. Discussion on non-clinical aspects

***Pharmacodynamics***

No *in vivo* pharmacodynamics animal studies investigating analytical, physiochemical and functional similarity between AVT04 and its referenced medicinal product (RMP) Stelara (sourced from EU) were conducted in addition to the analytical biosimilarity assessment. A cell-based IL-12 neutralization assay and state-of-the-art surface plasmon resonance (SPR) binding assays for all three ligands, p40, IL-12, and IL-23 (nonmembrane-bound targets); were used to assess the biological activity of the AVT04 and EU-Stelara batches. AVT04 inhibited IL-12-induced IFN-release from the NK cell line in a manner similar to EU-Stelara (within the range of the mean ±2.5 SD of EU-Stelara) and had similar bindings to p40, IL-12, and IL-23 (within the range of the mean ±2.5 SD, ±3 SD, and ±3 SD of EU-Stelara, respectively). This is accepted and in agreement with the EMA *Guideline on similar biological medicinal products* (CHMP/437/04 Rev 1; 2014) and the EMA *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/2005 Rev 1). *In vitro* assays may be considered paramount for the non-clinical biosimilar comparability exercise since they are generally more specific and sensitive in detecting differences between the biosimilar and the RMP.

For review of the biosimilar comparability exercise, please refer to the discussion and conclusion section of the quality part of the assessment report.

***Pharmacokinetics***

Although not necessary according to the *EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues* [EMA/ CHMP/ BMWP/ 403543/ 2010], the pharmacokinetics study after single subcutaneous injection of AVT04 and CN-Stelara in Cynomolgus monkeys was conducted to fulfil the expectations of non-European regulatory bodies.

In general, similarity between the originator and the biosimilar product should be proven in the frame of the in vitro quality biocomparability testing. In contrast to the respective *in vitro* methods, *in vivo* animal studies are frequently not sufficiently informative for similarity/comparability exercises. Due to potential intra-species variabilities at low group sizes, these models are frequently too insensitive. This conclusion concerns both pharmacokinetic comparisons and comparisons on the safety level. Thus, the presented in vivo studies, where PK parameters are monitored (non-GLP single dose study P20-S425-PK, GLP repeat dose study P20-207-RD), are, mainly due to their limitations, considered supportive.

***Toxicology***

The four-week repeat-dose toxicity study in Cynomolgus monkeys, including a four-week recovery period after a once weekly subcutaneous injection regimen of excipient control and AVT04 at doses of 5, 15 or 45mg/kg or CN-Stelara at 45mg/kg, was conducted to satisfy the requirements of the Chinese National Medical Products Administration (NMPA) for the development and evaluation of biosimilars in China.

The design of the four-week repeat-dose toxicity study is regarded as appropriate in terms of species selection (as the Cynomolgus monkey was already used in the toxicology assessment of the RMP Stelara), used dosages, frequency and route of administration (as subcutaneous injection is the anticipated clinical route of application). Again, the study P20-207-RD is of supportive character. Nevertheless, no treatment-related toxicity, irritation, mortality, morbidity, micro- or macro-scopic findings, and effects on the vital organ systems were observed in any cynomolgus monkeys given test article AVT04 at doses of 5, 15, and 45 mg/kg, or the 45 mg/kg comparator CN-Stelara. After dosing, some sporadic but statistically significant changes in haematology, clinical chemistry, lymphocyte subsets, or an increase in IL-6 were seen. However, because of their small magnitude, lack of dose-dependence, and gender consistency when compared to the concurrent excipient control group, these changes were not thought to be test article-related. The toxicokinetics of AVT04 was dose-proportional and TK parameters showed no obvious gender differences.

In general, because the predictability of animal studies for the immunogenic potential in humans is low, dedicated antigenicity studies, comparing ADA formation induced by the drug product and the RMP in animal models, are not recommended as part of the comparability exercise of the biosimilar. However, as the assessment of ADAs was incorporated in the single-dose PK and repeat-dose toxicity studies in Cynomolgus monkeys, which were conducted to satisfy the requirements of the Chinese National Medical Products Administration (NMPA), these data are considered supplementary to the overall biosimilarity exercise in the submitted dossier.

To emphasize, similarity between the originator Stelara (sourced from EU) and the biosimilar product AVT04 has to be proven in the first place with the quality testing and *in vitro* data. The data gathered in the toxicology and toxicokinetics evaluations in Cynomolgus monkeys only provide supportive information in addition to the *in vitro* biosimilar comparability exercise, as described in the quality assessment of this marketing authorization application. Again, though not requested, this *in vivo* study is considered supplementary to the overall biosimilarity exercise in the submitted dossier.

***Environmental Risk Assessment***

The active substance is a biological substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Uzpruvo is not expected to pose a risk to the environment.

Furthermore, Ustekinumab is already used in existing marketed products (Stelara) and no significant increase in environmental exposure is anticipated.

Therefore, Uzpruvo (AVT04 of STADA Arzneimittel AG) is not expected to pose a risk to the environment.

## 2.5.7. Conclusion on non-clinical aspects

From a non-clinical point of view, no concern was identified which would argue against marketing authorization. Please refer to the Quality part of the assessment report for discussion and conclusion on the biosimilar comparability exercise.

# *2.6. Clinical aspects*

## 2.6.1. Introduction

***GCP aspects***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

| **Study Number** | **AVT04 DP Batch Number** | **Main study objective** | **Study Design Study start/ completion** | **Test product Dosage, regimen Route of administration** | **Number of subjects treated** | **Healthy subjects or diagnosis of patients** | **Duration of Treatment** | **Primary and main secondary endpoints** |
|---|---|---|---|---|---|---|---|---|
| AVT04 -GL-101 completed | DP200011 | - PK similarity of AVT04 to EU-Stelara,<br>- PK similarity of AVT04 to US-Stelara,<br>- PK similarity of EU- to US-Stelara | Multicenter, randomized, double-blind, parallel, 3-arm | AVT04<br>EU-Stelara<br>US-Stelara<br>45 mg s.c. | Total: 294<br>AVT04: 98<br>EU-Stelara: 99<br>US-Stelara: 97 | Healthy subjects | Single dose | Primary endpoints: Cmax, AUC0-inf<br>Main Secondary PK endpoint: AUC0-t<br>Other secondary endpoints: General PK parameters |
| AVT04 -GL-301 Ongoing at the time of submisio n | DP200011 | Therapeutic equivalence of AVT04 to EU-Stelara | Multicenter, randomized, double-blind, parallel, 2-arm, 2 stage, active control | Stage 1<br>AVT04<br>EU-Stelara<br>45 mg s.c. (b.w.≤100 kg) or 90 mg s.c. (b.w.>100 kg) at Day 1 and after 4 weeks<br><br>Stage 2<br>AVT04/AVT04, EUStelara/AVT04, EU-Stelara/EU-Stelara<br>45 mg s.c. (b.w.≤100 kg) or 90 mg s.c. (b.w.>100 kg) at Weeks 16, 28, and 40 | Stage 1:<br>Total: 581<br>AVT04: 194<br>EU-Stelara: 387<br><br>Stage 2:<br>Total : 574<br>AVT04/AVT04:193<br>EU-Stelara/AVT04: 192<br>EU-Stelara/EU-Stelara: 189 | Patients with chronic moderate-to -severe PsO | Repeat dose<br><br>Stage 1<br>Day 1- Week 15*<br><br>Stage 2<br>Week 16-52 | PK: Ctrough values |

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

***Bioequivalence***

***Study AVT04-GL-101***

**Methods**

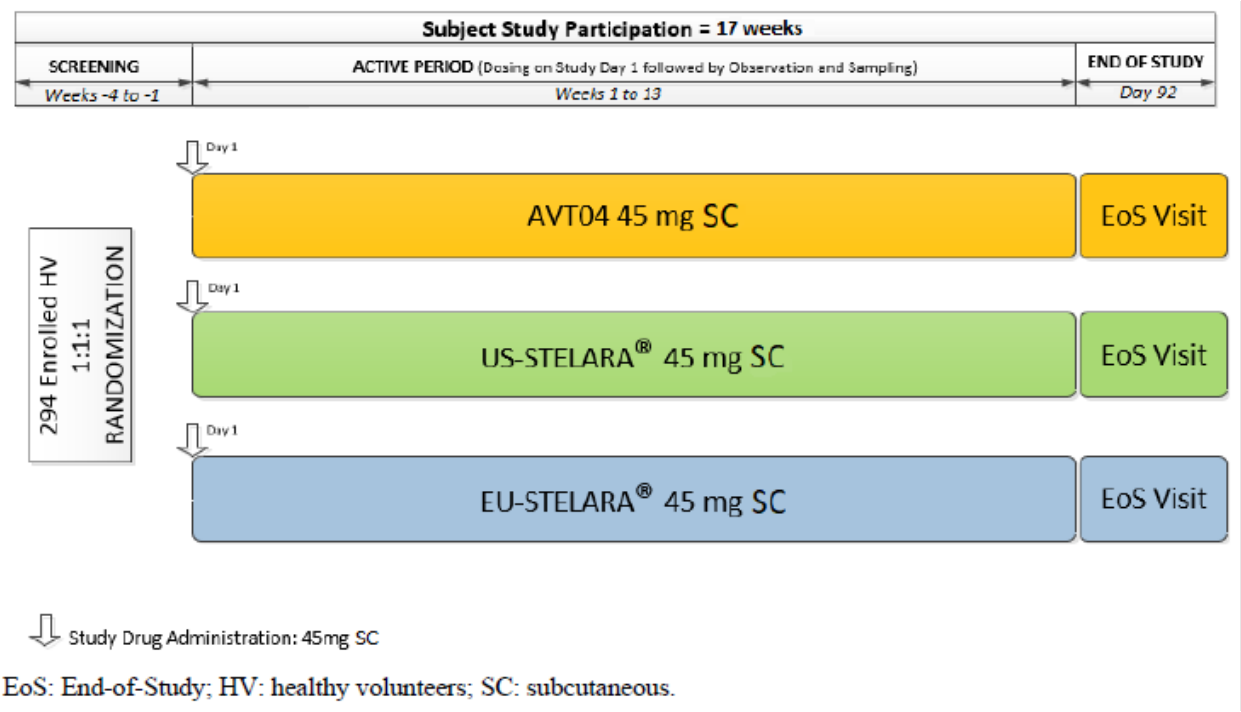
Study AVT04-GL-101 was a phase 1, first-in-Human (FIH), randomized, double-blind, single-dose, parallel group, 3-arm study comparing the pharmacokinetic, safety, tolerability and immunogenicity profiles of AVT04, EU-Stelara and US-Stelara in healthy adult subjects. This study was considered pivotal for investigation of PK similarity.

Subjects were randomized in a 1:1:1 ratio to receive either AVT04, EU-Stelara or US-Stelara.

Approximately 294 subjects (98 per group) were planned to be enrolled at multiple study sites in New Zealand and Australia.

The study duration per subject was approximately 17 weeks. The study consisted of a 4-week Screening period, a 13-week treatment and assessment period. The end of study (EoS) visit was on Day 92.

**Figure PH1: Schematic of Study Design**




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

**Key inclusion criteria**

Subjects were eligible to be included in the study only if all of the following criteria applied at any time starting from Screening up to Day 1 prior to IP administration:

1. Was capable of giving signed informed consent as described in Appendix 1 of the protocol, which included compliance with the requirements and restrictions listed in the ICF and in the protocol.

2. Male or female healthy subjects.

3. 18 to 55 years old (inclusive), at the time of signing the ICF.

4. Body weight of 50.0 to 90.0 kg (inclusive) and body mass index (BMI) of 17.0 to 30.0 kg/m2 (inclusive).

**Key exclusion criteria**

1. History of relevant drug and/or food allergies.

2. History of hypersensitivity to Stelara, AVT04, or their constituents.

3. Known history of previous exposure to IL-12 and/or IL-23 inhibitors.

4. Any past or concurrent medical conditions that could potentially increase the subject's risks or that would interfere with the study evaluation, procedures, or study completion. Examples of these included medical history with evidence of clinically relevant pathology (e.g., malignancies or demyelinating disorders).

**Treatments**

Subjects received a single dose of 45 mg/0.5 mL of either AVT04, EU-Stelara, or US-Stelara on Day 1 as a SC injection.

The SC route of administration was evaluated in this study, and the SC route represents the main route of administration for the Stelara reference products. The SC route was expected to be the most sensitive in detecting differences in immunogenicity, and SC administration (in contrast to the intravenous route) could provide insight into potential PK differences during the absorption phase, in addition to the distribution and elimination phases (i.e., it covers both absorption and elimination phases), which is supported.

The proposed dose for the study (45 mg/0.5 mL SC) was considered the most relevant dose level of AVT04 to be evaluated in this FIH study for the following reasons:

- It represents one of the approved doses for ustekinumab (Stelara).
- Both 45 mg/0.5 mL and 90 mg/mL SC doses fall within the linearity range. Previous Stelara Studies C0743T11 and CR016207 in healthy subjects showed an approximately linear PK of ustekinumab following the single SC injection at the dose levels studied (45 mg/0.5 mL and 90 mg/mL), with systemic exposure increasing in a dose-proportional manner. According to the body weight range allowed by the protocol for the current study (between 50 and 90 kg), a dose of 45 mg/0.5 mL would result in a weight-adjusted dose between 0.50 and 0.90 mg/kg, which would fall in the steep part of the exposure-response curve.
- Both 45 mg/0.5 mL and 90 mg/mL doses were well tolerated in healthy subjects. However, the 90 mg/mL dose was considered to be less immunogenic than 45 mg/0.5 mL; therefore, differences in PK parameters and in the immunogenic response (if any) are better detected by using the 45 mg/0.5 mL dose.

Details of the IPs and batch numbers are provided in the Table below. The protein concentrations for the IP batches used in this study were 91.0 mg/mL for AVT04, 82.3 mg/mL for EU-Stelara, and 88.3 mg/mL for US-Stelara based on the Sponsor's analysis using a validated analytical method (OD280 method).

**Table PH1** Investigational Product Details

| | Test Product | Reference Products | |
|---|---|---|---|
| **IP Name:** | AVT04 (ustekinumab) | EU-approved Stelara (ustekinumab) | US-licensed Stelara (ustekinumab) |
| **Dosage Formulation:** | 90 mg/mL ustekinumab<br>Formulated with: L-histidine, L-histidine monohydrochloride monohydrate, Sucrose, Polysorbate 80, Water for injection | | |
| **Unit Dose Strength:** | The IP was supplied as a prefilled syringe, which delivered 45 mg of AVT04 or Stelara; a dose volume of 0.5 mL was administered as a single dose. | | |
| **Packaging and Labeling:** | All clinical study material was packaged and labeled in compliance with GMP and local regulatory requirements. | | |
| **Manufacturer** | Alvotech Swiss AG | Janssen Biotech, Inc. | Janssen Biotech, Inc. |
| **Batch Numbers** | DP200011 | KHS25MJ | KCS11MN |

GMP: Good Manufacturing Practice; IP: investigational product.

**Objectives**

Primary objective:

- To compare the PK of AVT04 with EU- and US- Stelara and the PK of EU- Stelara with US-Stelara in terms of $C_{max}$ and $AUC_{0-inf}$ following a single 45 mg/0.5 mL SC injection in healthy subjects.

The PK similarity of AVT04 versus EU-Stelara, AVT04 versus US-Stelara, and US-Stelara versus EU-Stelara would be demonstrated if, for all pairwise comparisons, the 90% CIs of the GMRs for both $C_{max}$ and $AUC_{0-inf}$ were entirely contained within the equivalence margin of 0.8 to 1.25 (ie, 80% to 125% when the ratio was expressed as a percentage).

Secondary objectives:

- To further characterize the PK of AVT04 with EU- and US- Stelara following a single 45 mg/0.5 mL SC injection in healthy subjects.
- To compare the safety, tolerability, and immunogenicity of AVT04 with EU- and US- Stelara following a single 45 mg/0.5 mL SC injection in healthy subjects.

Tertiary/exploratory objectives (not reported in this CSR):

- To compare the ex-vivo inhibition of IFN-γ and IL-22 release of AVT04 with EU- and US-Stelara following a single 45 mg/0.5 mL SC injection in healthy subjects (Substudy).

**Outcomes/endpoints**

Primary endpoints

- maximum serum concentration ($C_{max}$) AND area under the serum concentration-time curve from time zero extrapolated to infinity ($AUC_{0-inf}$)

Secondary endpoints:

- The secondary PK parameters assessed were:
  - area under the concentration-time curve from time zero up to time t, where t is the last time point with quantifiable concentrations ($AUC_{0-t}$):

- time to maximum serum concentration ($T_{max}$):
- elimination rate constant ($K_{el}$)
- elimination half-life ($t_{1/2}$),
- volume of distribution during the terminal phase after SC administration ($V_{z/F}$)
- apparent clearance (CL/F).

- The safety parameters assessed included AEs, clinical laboratory assessments (haematology, clinical chemistry, coagulation, urinalysis, and urine microscopy), vital signs, ECG, physical examination findings, and injection site reactions.
- Immunogenicity assessments included antidrug antibodies (ADAs) and neutralising antibodies (Nabs).

Tertiary/Exploratory endpoints (Not reported in this CSR)

- The inflammatory cytokine biomarkers assessed included: IFN-γ, IL-22, IL-17, IL-5, IL-13, and IL-10.

Sampling time points

Blood samples for PK analyses were collected pre-dose, post-dose (Day1), then daily from Day 2 to Day 12, at Day 15 and then once weekly until Day 64 (Week 10), followed by once fortnightly through Day 92 (Week 14 i.e. EOS/ET).

Blood samples for immunogenicity were collected pre-dose, 12h post-dose, at Days 9, 15, 29, 57, 78 and 92 /EOS. Ex-vivo biomarker assessments were performed in a subset of 45 subjects (15 subjects per group).

**Sample size**

The co-primary PK endpoints for this Phase 1 study were $C_{max}$ and $AUC_{0\text{-}inf}$. Sample size calculations were performed using data from previous studies with Stelara. In these studies, the CV% for the 2 PK parameters following administration of Stelara 45 mg/0.5 mL SC was 33% and 34%, respectively. For each of the 3 pairwise treatment group comparisons, PK similarity would be established if the 90% CIs of the GMRs for each of these endpoints fell within the range 80% to 125%.

To achieve a power of at least 90% for all three pairwise comparisons of each coprimary endpoint, $C_{max}$ and $AUC_{0\text{-}inf}$, the individual pairwise comparisons had to be powered at least 96.6%. Assuming a true geometric ratio of 1.05 for both co-primary endpoints, 176 subjects (88 per treatment group) would have a power of 97.4% and 96.6% in each comparison of the co-primary endpoints $C_{max}$ and $AUC_{0\text{-}inf}$, respectively. This results in an overall power of at least 83.1% ($= 0.974^3 \times 0.966^3$) for the study (all pairwise comparisons and both PK parameters). Taking into consideration a non-evaluable/dropout rate of up to 10%, the required sample size was 294 subjects in total (98 per treatment group). Of the 294 subjects, at least 10% of subjects of Japanese origin were planned to be enrolled.

Based on the information provided and the assumptions made, sample size and power calculations can be followed. There are no methodological issues seen, which would require further elaboration.

**Randomisation**

Randomization to AVT04, EU-Stelara, or US-Stelara was performed in a 1:1:1 ratio. The randomization was stratified by 2 factors, ethnicity and body weight, but consisted of only 3 strata as follows: Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg.

After a randomization number was assigned, it was not to be reassigned, even if the subject was replaced.

**Blinding (masking)**

This was a double-blind study and therefore, apart from pre-specified unblinded individuals, the Investigator, site staff, Sponsor, Sponsor's delegates (if applicable) and all subjects were blinded to treatment. No individual subject information that could potentially unblind the Investigator or subject was reported until the end of the study. Dosing was performed separate from other blinded study site staff. The Investigator remained blinded unless knowledge of the subjects' treatment assignment was necessary for the clinical management or welfare of the subject.

**Statistical methods**

*Analysis populations*

*Enrolled Population*: All subjects who met all eligibility criteria, but not yet randomized. This population was used primarily for subject counting purposes.

*Randomized Population*: All subjects who were randomized into this study. Subjects were analyzed according to their randomized treatment, regardless of which treatment the subject actually received. This population was used for the summaries of all disposition, demographic data, protocol deviations, and baseline data. In addition, most listings were produced using the Randomized Population.

*Safety Population*: All randomized subjects who received any amount of the IP. Subjects were analyzed according to the treatment they actually received, if this differed from that to which the subject was randomized. This population was used for the summaries of all safety data.

*Pharmacokinetic Population*: All randomized subjects who received any amount of the IP and had at least 1 evaluable PK parameter. An evaluable profile allowed the determination of one or more PK parameters and was determined at the discretion of the pharmacokineticist. Subjects were analyzed according to the treatment they received, if this differed from that to which the subject was randomized. Subjects with dosing deviations that could potentially affect the PK profile were excluded from the PK Population, at the discretion of the blinded pharmacokineticist prior to analysis. This population was used for summaries of all PK data.

*Immunogenicity Population*: All randomized subjects who received any amount of the IP and had at least 1 evaluable postdose immunogenicity result (i.e., positive or negative for presence of ADAs). Subjects were analyzed according to the treatment they received, if this differed from that to which the subject was randomized. This population was used for the summaries of all ADA and nAb data.

*General aspects of statistical analysis*

In general, data were presented by treatment group. Data were summarized using descriptive statistics.

The primary objective of the study was to demonstrate PK similarity of AVT04 with EU- and US-Stelara and of EU-Stelara with US-Stelara in terms of $C_{max}$ and $AUC_{0\text{-}inf}$ following a single 45 mg/0.5 mL SC injection in healthy subjects.

For the pairwise comparisons of $AUC_{0\text{-}inf}$ and $C_{max,}$ the 90% CI for the ratio of the test and reference products were to be contained within the acceptance interval of 80% to 125% to demonstrate similarity.

*Statistical methods for the primary endpoints*

PK parameters were investigated with the PK population.

Three pairwise comparisons were performed for each maximum serum concentration ($C_{max}$) and area under the serum concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$) between AVT04 and EU-Stelara, AVT04 and US-Stelara, and US-Stelara vs. EU-Stelara. An ANCOVA was performed on the natural log-transformed values of $C_{max}$ and $AUC_{0\text{-}inf}$, respectively, which included fixed effects for treatment and body weight at baseline as covariates. The least squares means for treatment, their differences and 90% CIs for those differences were obtained.

PK similarity was to be concluded if the respective CIs for $C_{max}$ and $AUC_{0\text{-}inf}$ were completely included in the similarity margin of 0.80 to 1.25.

If differences were identified in the drug protein content between AVT04, US-Stelara, and EU-Stelara, a sensitivity analysis was planned to be performed using PK parameters adjusted by protein content administered. Protein adjusted PK parameters were then summarized using an ANCOVA model, which did not further include the actual dose as a covariate.

PK parameters were protein adjusted as follows: Adjusted PK Parameter = original PK Parameter x (45/(Actual Injected volume (mL) x protein concentration (mg/mL))), where actual injected volume (mL) x protein concentration (mg) is the actual protein content administered.

*Statistical analysis methods for secondary and other endpoints*

Serum ustekinumab concentrations by nominal (ie, protocol-specified) PK sampling time point and by treatment group were summarized using descriptive statistics. Individual and arithmetic mean per treatment concentration-time profiles on linear and logarithmic scales were displayed graphically.

Pharmacokinetic parameters of serum ustekinumab, including secondary PK endpoint $AUC_{0\text{-}t}$, $T_{max}$, Kel, $t_{1/2}$, Vz/F, and CL/F, were summarized by treatment group using descriptive statistics. Body weight-adjusted PK parameters (apparent total body clearance after SC administration [CL/F] and apparent volume of distribution during the terminal phase after SC administration [Vz/F]) using weight normalization were also summarized. Summaries were analogously presented by subgroups based on randomization strata and by immunogenicity subgroups.

Post-hoc PK similarity analyses for the secondary PK endpoint $AUC_{0\text{-}t}$ were performed using ANCOVA. Similar to the primary analysis, fixed effects for treatment and body weight at baseline were included. The analysis was repeated using protein content-normalized $AUC_{0\text{-}t}$ values, and also for subgroups based on randomization strata and immunogenicity subgroups.

All safety data were summarized for the Safety Population using descriptive statistics by treatment group, and included AEs, clinical laboratory assessments, vital signs, ECG, physical examination findings, and injection site reactions.

Immunogenicity data of ADAs and NAbs was analysed descriptively, and ADA titer values were also to be summarized if >20% of subjects within a single treatment group had positive results.

*Dropouts, Missing Data & LLOQ*

For subjects who were withdrawn from the study prior to their completion of the study for any reason, all data compiled up to the point of discontinuation were used for analysis. There was no imputation for

missing data. For the PK parameter data, all pre-dose BLQ values were substituted with zeros. Thereafter, BLQ values between evaluable concentrations and terminal BLQ were set to 0.5 × LLOQ.

**Results**

**Participant flow**

A total of 563 subjects provided informed consent and were screened in this study, of which 265 did not meet the eligibility criteria and failed screening. The most common reason for screening failure was 'inclusion criteria not met' (56.6%). In total, 298 subjects were enrolled into the study and were randomized to 1 of the 3 treatment groups: 98 to AVT04, 101 to EU-Stelara, and 99 to US-Stelara. Overall, the distribution of dosed subjects according to the predefined randomization strata was balanced across treatment groups.

Of the 298 randomized subjects, 294 (98.7%) were dosed. Four (4) randomized subjects (2 in the EU-Stelara group and 2 in the US-Stelara group) did not receive the IP and were withdrawn from the study [withdrawal due to fear of needles (n=1) and out-of-range BP values on Day 1 pre-dose (n=3)].

A total of 278 (93.3%) completed the study and the proportion of subjects who completed the study was similar in all three arms. Sixteen subjects (5.4%) discontinued the study; the primary reason for discontinuation being 'withdrawal of consent' (9 subjects), followed by 'lost to follow-up' (6 subjects). There was a small imbalance between the arms in the proportion of subjects who discontinued the study (6 subjects, 3 subjects and 7 subjects in AVT04, EU-Stelara and US-Stelara respectively), but due to overall small numbers, this should be interpreted with caution. The common reasons for discontinuation were withdrawal of consent and loss to follow-up. None of the subjects discontinued the study due to AEs.

**Recruitment**

This study was conducted at 4 study sites in 2 countries: New Zealand (2 sites) and Australia (2 sites). First subject was randomised on 09 June 2021. Last subject completed the study on 14 March 2022.

**Conduct of the study**

A total of 16 subjects (5.4% of randomized subjects) had at least 1 major protocol deviation, and the frequency of subjects with major deviations was similar across groups. The most common major deviations were related to the visit schedule criteria (9 of 16 subjects [56.3%]). All other major protocol deviations were reported in no more than 2 subjects in each group.

Five subjects had at least 1 major protocol deviation that was considered related to the COVID-19 pandemic during the study. These deviations were related to the visit schedule and study procedures. According to the applicant, these major deviations were considered to not have an impact on the data integrity for these subjects; none of these subjects were excluded from the final analyses.

One major site-level deviation related to laboratory assessments was reported for Site 201. It was identified that glucose levels were only tested as part of fasted Screening laboratory assessments for 23 subjects; no glucose testing was performed during visits from Day -1 onwards. This was due to the site's misinterpretation of the protocol. Corrective measures were taken including addition for glucose testing for future visits, as well as a PI review of out-of-range glucose results and associated AEs for the impacted subjects. This major deviation was considered to not have an impact on the data integrity for the impacted subjects; none of the impacted subjects from this site were excluded from the final analyses.

**Baseline data**

In the safety population, the demographic and baseline characteristics were generally balanced. The overall mean age of the subjects was 31.5 years (age range, 18 to 55 years).

The body weight and BMI of subjects were similar across treatment groups; which is important given the influence of body weight on ustekinumab exposure. The majority of subjects (74.5%) belonged to the non-Japanese ≤80 kg stratum at the time of randomization, with 18.7% in the non-Japanese >80 kg stratum and 6.8% in the Japanese stratum. No imbalances across groups are noted with respect to these strata. Overall, the majority of subjects were Caucasian/White (70.7%), and a small proportion were Asian (16.3%). The majority of subjects were female (60.9%).

In the pharmacokinetic population, the baseline characteristics were similarly distributed as in the safety population.

**Numbers analysed**

**Table 10-3 Analysis Populations (Randomized Population)**

| Status | Statistic | AVT04 (N=98) | EU-Stelara (N=101) | US-Stelara (N=99) | Overall (N=298) |
|---|---|---|---|---|---|
| Safety Population | n (%) | 98 (100.0) | 99 (98.0) | 97 (98.0) | 294 (98.7) |
| Pharmacokinetic Population | n (%) | 96 (98.0) | 97 (96.0) | 94 (94.9) | 287 (96.3) |
| Immunogenicity Population | n (%) | 98 (100.0) | 99 (98.0) | 97 (98.0) | 294 (98.7) |
| Pharmacokinetic Exclusion Reasons | | | | | |
| Removed due to Early Termination visit | n (%) | 0 | 0 | 1 (1.0) | 1 (0.3) |
| Too many samples missing | n (%) | 2 (2.0) | 2 (2.0) | 2 (2.0) | 6 (2.0) |

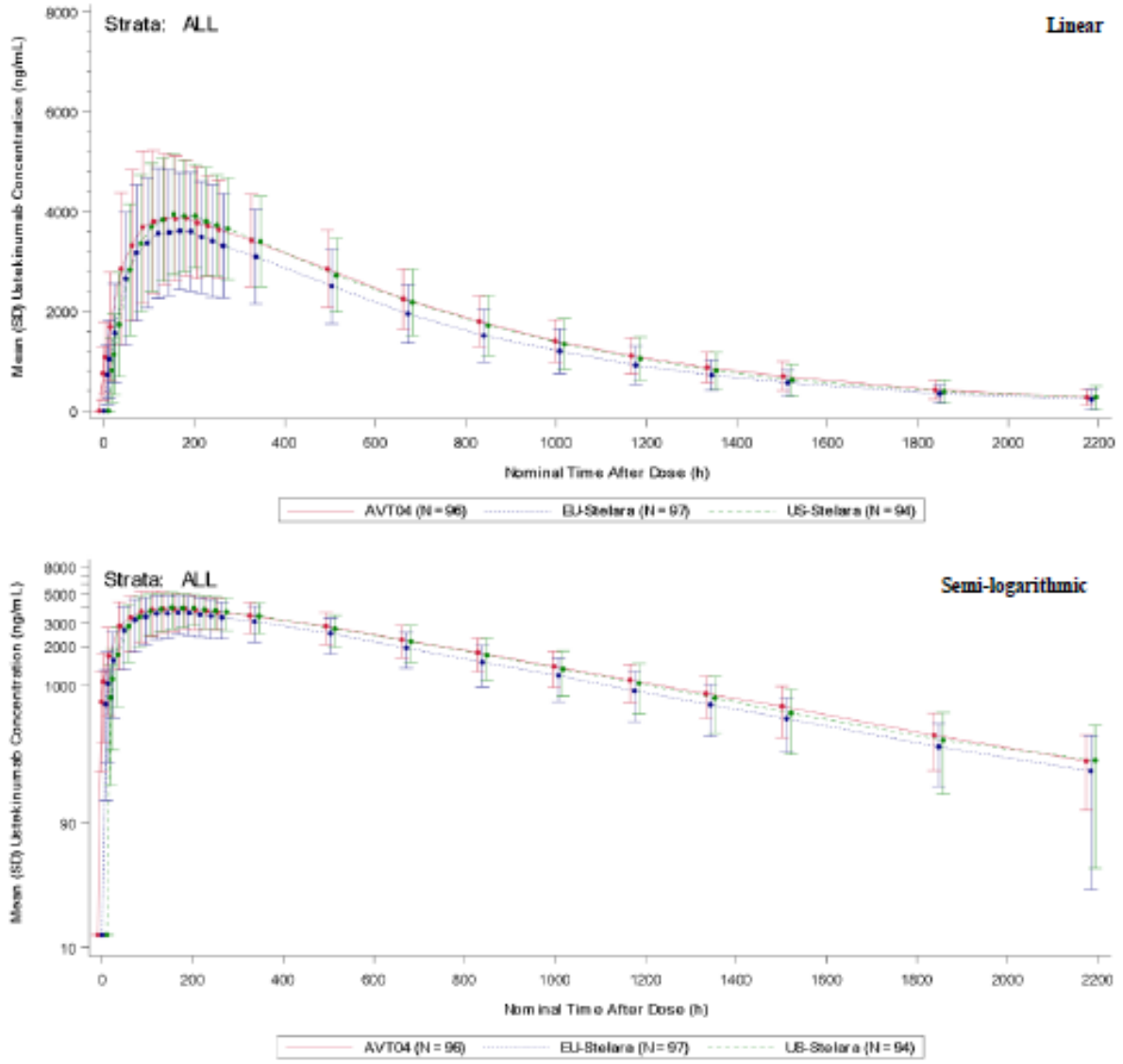
n: Number of subjects in each category; N: Total number of subjects randomized; %: Percentages are based on the number of subjects randomized. Reasons for exclusion for immunogenicity population are all "not treated". Not treated subjects are not included in the Safety Population.
Source: Table 14.1.1.

Of the 298 randomized subjects, excluding 4 subjects who were not dosed, a total of 294 subjects (98.7%) received the IP, and were included in the Safety and Immunogenicity Populations. Exclusion of subjects who were not dosed is considered acceptable. An additional 7 subjects were excluded from the PK Population; of these, 6 were excluded due to too many missing PK samples and 1 was excluded due to early termination (withdrawal of consent) on Day 7. Therefore, a total of 287 (96.3%) subjects were included in the PK Population. The number of subjects in this population was comparable across groups.

**Outcomes and estimation**

Ustekinumab serum concentrations

**Figure 11-1 Mean (±Standard Deviation) Serum Concentration-Time Profile of Ustekinumab by Treatment Group on Linear and Semilogarithmic Scales (Pharmacokinetic Population)**




BLQ: below limit of quantitation (25 ng/mL); LLOQ: lower limit of quantitation; SD: standard deviation.
All predose BLQ values were substituted by zeros. Thereafter, BLQ values between evaluable concentrations and terminal BLQ were set to 0.5 × LLOQ.
Sources: Figure 14.2.1.4 and Figure 14.2.1.5.

Serum ustekinumab pharmacokinetic parameters

**Table 11-1 Summary of Serum Ustekinumab Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)**

| Treatment | Median (Range) | Geometric Mean (Geometric CV%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $AUC_{0-inf}$ (h·ng/mL) | $K_{el}$ (1/h) | $t_{1/2}$ (h) | CL/F (L/h) | $V_z$/F (L) | CL/F/ BW (L/h/kg) | Vz/F/ BW (L/kg) |
| AVT04 (N = 96) | 168.0 (46.4–504.0) | 4019.2 (33%) | 32 86173 (32%) | 35 11612 (33%) | 0.0015 (24.9%) | 477.9 (24.9%) | 0.01 (33.1%) | 8.76 (31.6%) | 0.00018 (30.6%) | 0.12 (29.5%) |
| EU-Stelara (N = 97) | 167.7 (47.8–503.6) | 3681.7 (38%) | 28 72578 (38%) | 30 14505 (39%) | 0.0016 (27.8%) | 431.94 (27.8%) | 0.02 (39.2%) | 9.30 (36.6%) | 0.00021 (36.2%) | 0.13 (32.9%) |
| US-Stelara (N = 94) | 168.1 (48–339.5) | 4046.4 (31%) | 31 71230 (34%) | 33 44427 (36%) | 0.0016 (39.9%) | 438.17 (39.9%) | 0.01 (36.3%) | 8.46 (33.9%) | 0.00019 (33.3%) | 0.12 (33.6%) |

*Footnotes overleaf.*

$AUC_{0-inf}$: Area under the concentration-curve from time zero extrapolated to infinite time; $AUC_{0-t}$: Area under the concentration-curve from time zero to the last quantifiable concentration; BLQ: Below the lower limit of quantification (25 ng/mL); BW: body weight adjusted; CL/F: apparent clearance; $C_{max}$: maximum serum concentration; CV%: coefficient of variation; $K_{el}$: terminal elimination rate constant; LLOQ: lower limit of quantitation; $t_{1/2}$: apparent terminal elimination half-life; $T_{max}$: time of maximum serum concentration; Vz/F: apparent volume of distribution.

N: Total number of subjects in the relevant population.

Notes: All predose BLQ values were substituted by zeros. Thereafter BLQ values between evaluable concentrations and terminal BLQ were set to 0.5 × LLOQ.

It was noted that there were fewer evaluable subjects for determination of $AUC_{0-inf}$ than $AUC_{0-t}$ as not all subjects met the requirement for $AUC_{0-inf}$ (and associated parameters: CL/F, $t_{1/2}$, $V_z$/F). The PK parameters were determined by noncompartmental analysis methods using WinNonlin v8.3 or higher.

Source: Table 14.2.2.1.1.

The values for $K_{el}$ and CL/F presented in the table above are very small and difficult to interpret, thus the applicant was asked to present these parameters in different units (table below):

| PK Parameter (Unit) | Treatment group | Statistics | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n | Mean | Std. Dev | CV (%) | Median | Minimum | Maximum | Geo. Mean | Geo.CV (%) |
| $K_{el}$ (1/Day) | AVT04 (N= 96) | 96 | 0.0359 | 0.00941 | 26.233 | 0.0341 | 0.015 | 0.086 | 0.0348 | 24.903 |
| | US-Stelara (N= 94) | 94 | 0.0412 | 0.01945 | 47.199 | 0.0360 | 0.015 | 0.122 | 0.0380 | 39.907 |
| | EU-Stelara (N= 97) | 97 | 0.0401 | 0.01331 | 33.161 | 0.0366 | 0.019 | 0.115 | 0.0385 | 27.806 |
| CL/F (L/Day) | AVT04 (N= 96) | 93 | 0.3257 | 0.12926 | 39.689 | 0.3070 | 0.181 | 0.932 | 0.3076 | 33.059 |
| | US-Stelara (N= 94) | 93 | 0.3447 | 0.13752 | 39.899 | 0.3136 | 0.143 | 0.930 | 0.3229 | 36.269 |
| | EU-Stelara (N= 97) | 97 | 0.3894 | 0.20137 | 51.706 | 0.3379 | 0.203 | 1.668 | 0.3583 | 39.223 |

Kel: Terminal elimination rate constant; CL/F: Apparent Clearance; N: number of subjects randomized to the treatment group; n: number of subjects with evaluable data; Std. Dev: Standard Deviation; CV (%): Coefficient of variation; Geo.Mean: Geometric Mean. Geo.CV (%): Geometric CV%, calculated as Geo.CV(%) = SQRT(es2-1)*100.

Following a single SC dose of 45 mg/0.5 mL, the mean serum ustekinumab concentration-time profiles for AVT04, EU-Stelara, and US-Stelara were overall similar. However, ustekinumab concentrations with

AVT04 were higher compared to those with EU-Stelara across all measurements i.e. the concentration-time curve for AVT04 was consistently above the concentration-time curve for EU-Stelara. The same trend was observed when looking at the individual PK concentration-time profiles i.e. ustekinumab concentrations were generally higher with AVT04 compared to EU-Stelara.

The geometric mean $C_{max}$ value in the AVT04 group (4019.2 ng/mL) was higher than in the EU-Stelara group (3681.7 ng/mL) and similar to that in the US-Stelara group (4046.4 ng/mL). A similar trend was also seen for the geometric mean AUCs; both $AUC_{0-inf}$ and $AUC_{0-t}$ were higher in the AVT04 group ($AUC_{0-inf}$: 3 511 612 h·ng/mL; $AUC_{0-t}$: 3 286 173 h·ng/mL) compared to the EU- Stelara group ($AUC_{0-inf}$: 3 014 505 h·ng/mL; $AUC_{0-t}$ 2 872 578 h·ng/mL) and slightly higher compared to the US-Stelara group ($AUC_{0-inf}$: 3 344 427 h·ng/mL $AUC_{0-t}$: 3 171 230 h·ng/mL).

The median $T_{max}$ was 168 hours in all 3 treatment groups. The geometric CV% for tmax was moderate across groups (37.5% to 49.2%), with values ranging from 46.4 to 504.0 hours.

The geometric mean terminal half-life ($t_{1/2}$) in the AVT04 group (477.9 hours) was longer than that in the EU-Stelara (438.2 hours) and US-Stelara (431.9 hours) groups. The terminal elimination rate constants ($K_{el}$) of EU-Stelara and US-Stelara were very similar (geom. mean 0.0385/day and 0.0380/day, respectively), while the $K_{el}$ of AVT04 was slightly lower (0.0348/day). The apparent clearance (CL/F) of EU-Stelara and US-Stelara were similar (geom.mean 0.3583 L/day and 0.3229 L/day, respectively), whereas the CL/F for AVT04 was lower (0.3076 L/day).

Statistical Analysis of Pharmacokinetic Similarity

**Table 11-3 PK Similarity Assessment of Serum Ustekinumab Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)**

| Comparison (Test/Reference) | Parameter | Test n | Test Geometric LS Mean | Reference n | Reference Geometric LS Mean | Ratio of Geometric LS Means (%) Test/ Reference | 90% Confidence Interval for Ratio of Geometric LS Means [a] | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | $C_{max}$ (ng/mL) | 96 | 4010.4 | 97 | 3664.1 | 109.5 | **101.7** | **117.8** |
| | $AUC_{0-inf}$ (h·ng/mL) | 93 | 35 02232.8 | 97 | 29 96480.2 | 116.9 | 108.1 | 126.4 |
| | $AUC_{0-t}$ (h·ng/mL) | 96 | 32 78411.9 | 97 | 28 57759.1 | 114.7 | **106.5** | **123.6** |
| AVT04 / US-Stelara | $C_{max}$ (ng/mL) | 96 | 4010.4 | 94 | 4075.5 | 98.4 | **91.4** | **106.0** |
| | $AUC_{0-inf}$ (h·ng/mL) | 93 | 35 02232.8 | 93 | 33 74424.9 | 103.8 | **95.9** | **112.3** |
| | $AUC_{0-t}$ (h·ng/mL) | 96 | 32 78411.9 | 94 | 31 95908.9 | 102.6 | **95.2** | **110.6** |
| US-Stelara / EU-Stelara | $C_{max}$ (ng/mL) | 94 | 4075.5 | 97 | 3664.1 | 111.2 | **103.3** | **119.8** |
| | $AUC_{0-inf}$ (h·ng/mL) | 93 | 33 74424.9 | 97 | 29 96480.2 | 112.6 | **104.1** | **121.8** |
| | $AUC_{0-t}$ (h·ng/mL) | 94 | 31 95908.9 | 97 | 28 57759.1 | 111.8 | **103.8** | **120.5** |

$AUC_{0-inf}$: Area under the concentration-curve from time zero extrapolated to infinite time; $AUC_{0-t}$: Area under the concentration-curve from time zero to the last quantifiable concentration; CL: confidence limit; CL/F: apparent clearance; $C_{max}$: maximum serum concentration; GLM: general linear model; LS: Least-Squares; n: Number of subjects used in calculation; $t_{1/2}$: elimination half-life; Vz/F: apparent volume of distribution during the terminal phase after SC administration.

It is noted that there are fewer subjects in $AUC_{0-inf}$ than $AUC_{0-t}$ as not all subjects meet the requirement for $AUC_{0-inf}$ (and associated parameters: CL/F, $t_{1/2}$, $V_z$/F).

Treatment Comparison by analysis of covariance of log-transformed parameters using SAS proc GLM with model: <parameter> = Treatment + body weight at baseline as the covariate. 90% confidence interval for ratio of LS mean was constructed from the one-sided lower 5% CL and one-sided upper 5% CL.

a. Pharmacokinetic similarity was demonstrated if, for each pairwise comparison, the 90% confidence intervals for the ratios of geometric LS means were entirely contained with the equivalence margin 80% to 125%. Values in bold text indicate that the PK similarity criteria were met.

Source: Table 14.2.2.2.1 and Table 1.1.

**%$AUC_{extrap}$ (%):**

| | n | Mean | Std.dev | CV (%) | Median | Min. | Max. | Geo.mean | Geo.CV (%) |
|---|---|---|---|---|---|---|---|---|---|
| AVT04 | 96 | 7 | 8 | 120 | 5 | 0 | 52 | 5 | 95 |
| EU-Stelara | 97 | 5 | 4 | 80 | 4 | 0 | 30 | 3 | 121 |
| US-Stelara | 94 | 6 | 5 | 90 | 5 | 0 | 33 | 3 | 212 |

Biosimilarity of AVT04 compared to EU-Stelara could not be demonstrated for the co-primary endpoint $AUC_{0-inf}$, as the 90% CI for the geometric mean ratio for $AUC_{0-inf}$ fell outside the acceptance range of 80.00% to 125.00%. The GMR (AVT04 vs. EU-Stelara) for $AUC_{0-inf}$ was 116.9% (90% CI 108.1%, 126.4%).

For the co-primary endpoint $C_{max}$, the GMR (AVT04 vs. EU-Stelara) was 109.5% with the 90% CI entirely within the 80-125% acceptance criteria (101.7%, 117.8%).

For the secondary endpoint $AUC_{0-t}$, that was analysed post-hoc, the GMR (AVT04 vs. EU-Stelara) was within the 80-125% acceptance range, the point estimate was 114.7% (90% CI 106.5%, 123.6%), while the upper bound of the 90% CI was close to 125%, and the unity was not included suggesting higher exposure with AVT04 compared to EU-Stelara.

For the comparison *AVT04 vs. US-Stelara*, the 90% CIs were within pre-defined criteria for all three parameters ($C_{max}$, $AUC_{0-inf}$ and $AUC_{0-t}$) and 100% was included in the 90% CI, showing no substantial differences between treatments. Biosimilarity was demonstrated between *EU-Stelara and US-Stelara*, however CIs for all three parameters ($C_{max}$, $AUC_{0-inf}$ and $AUC_{0-t}$) were shifted above 100%. However, these comparisons are not considered relevant for the market authorization of AVT04 in the EU.

Extent of exposure

**Table 10-5 Summary of Exposure (Safety Population)**

| Parameters (unit) | Statistic | AVT04 (N=98) | EU-Stelara (N=99) | US-Stelara (N=97) |
|---|---|---|---|---|
| Predose weight of PFS (grams) | n | 98 | 99 | 97 |
| | Mean | 6.321 | 6.359 | 6.338 |
| | SD | 0.205 | 0.204 | 0.200 |
| Postdose weight of PFS (grams) | n | 98 | 99 | 97 |
| | Mean | 5.779 | 5.797 | 5.778 |
| | SD | 0.206 | 0.204 | 0.202 |
| Administered Injection Volume (mL) [a] | n | 98 | 99 | 97 |
| | Mean | 0.516 | 0.535 | 0.533 |
| | SD | 0.029 | 0.008 | 0.020 |
| Actual Protein Content Administered (mg) [b] | n | 98 | 99 | 97 |
| | Mean | 46.947 | 44.043 | 47.020 |
| | SD | 2.629 | 0.623 | 1.736 |
| Dosing Bias (%) [c] | n | 98 | 99 | 97 |
| | Mean | 104.327 | 97.873 | 104.489 |
| | SD | 5.841 | 1.385 | 3.857 |

*Footnotes overleaf.*
n: Number of subjects in each category; N: Total number of subjects in the relevant population; PFS: prefilled syringe; SD: standard deviation.

a. Administered Injection Volume (mL) = (Predose weight of PFS [grams] – Postdose weight of PFS [grams]/1.051, where 1.051 is the relative density of the formulation in g/mL.

b. Actual Protein Content Administered (mg) = Administered Injection Volume (mL) × (88.3, 82.3 or 91.0 mg/mL for US-Stelara, EU-Stelara and AVT04, respectively), with values provided by the analytical laboratory.

c. Dosing Bias (%) = (Actual Protein Content Administered [mg]) / 45(mg) × 100)

Source: Table 14.1.7.

In addition to differences in protein concentration, there were differences in the administered volumes between the products. In the Safety Population, the mean administered injection volume of IP was slightly lower in the AVT04 group (0.516 mL) compared with EU-Stelara (0.535 mL) and US-Stelara (0.533 mL) groups. The mean actual protein content administered in the IP doses was slightly higher in the AVT04 (46.95 mg) and US-Stelara (47.02 mg) groups compared with the EU-Stelara group (44.04 mg).

*Protein Content-Normalized* Serum Ustekinumab Pharmacokinetic Parameters

**Table 11-2 Summary of Serum Ustekinumab Protein Content-Normalized Exposure Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)**

| Treatment | Geometric Mean (Geometric CV%) $C_{max}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $AUC_{0-inf}$ (h·ng/mL) |
|---|---|---|---|
| AVT04 (N = 96) | 3857.5 (34%) | 31 53938 (32%) | 33 69848 (34%) |
| EU-Stelara (N = 97) | 3761.3 (38%) | 29 34704 (38%) | 30 79700 (39%) |
| US-Stelara (N = 94) | 3876.0 (32%) | 30 37712 (35%) | 32 04580 (37%) |

Analysis of Protein Content-Normalized Exposure Parameters

**Table 11-4 PK Similarity Assessment of Serum Ustekinumab Protein Content-Normalized Exposure Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)**

| Comparison (Test/Reference) | Protein Content-Normalized Parameter | Test n | Test LS Mean | Reference n | Reference LS Mean | Ratio of Geometric LS Means (%) Test/ Reference | 90% Confidence Interval for Ratio of Geometric LS Means* | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | $C_{max}$ (ng/mL) | 96 | 3848.8 | 97 | 3742.9 | 102.8 | **95.5** | **110.7** |
| | $AUC_{0-inf}$ (h·ng/mL) | 93 | 33 60604.3 | 97 | 30 60788.2 | 109.8 | **101.5** | **118.8** |
| | $AUC_{0-t}$ (h·ng/mL) | 96 | 31 46295.4 | 97 | 29 19171.0 | 107.8 | **100.0** | **116.2** |
| AVT04 / US-Stelara | $C_{max}$ (ng/mL) | 96 | 3848.8 | 94 | 3904.7 | 98.6 | **91.5** | **106.2** |
| | $AUC_{0-inf}$ (h·ng/mL) | 93 | 33 60604.3 | 93 | 32 34105.1 | 103.9 | **95.9** | **112.6** |
| | $AUC_{0-t}$ (h·ng/mL) | 96 | 31 46295.4 | 94 | 30 61970.0 | 102.8 | **95.3** | **110.8** |
| US-Stelara / EU-Stelara | $C_{max}$ (ng/mL) | 94 | 3904.7 | 97 | 3742.9 | 104.3 | **96.8** | **112.4** |
| | $AUC_{0-inf}$ (h·ng/mL) | 93 | 32 34105.1 | 97 | 30 60788.2 | 105.7 | **97.6** | **114.4** |
| | $AUC_{0-t}$ (h·ng/mL) | 94 | 30 61970.0 | 97 | 29 19171.0 | 104.9 | **97.3** | **113.1** |

For the calculation of protein-content normalized PK parameters, protein concentration as well as administered volume were taken into account. As the administered volume for VT04 was lower than for EU-Stelara, this resulted in about 6% difference in actual protein content administered.

After protein content normalization, the bioequivalence criterion 80-125% was met for both primary PK parameters $C_{max}$ and $AUC_{0-inf}$ as well as for the secondary PK parameter $AUC_{0-t}$ for all pairwise comparisons.

The point estimate of the protein-content normalized (PCN) geometric mean ratio (AVT04/EU-Stelara) for $C_{max}$ was 102.8% (90% CI 95.5%, 110.7%), with no significant difference between AVT04 and EU-Stelara; and the point estimate of the PNC GMR (AVT04/EU-Stelara) for $AUC_{0-inf}$ was 109.8% (90% CI 101.5%, 118.8%). For the secondary endpoint $AUC_{0-t}$, the point estimate of the PCN GMR was 107.8 (90% CI 100.0%, 116.2%).

After correction for protein content $C_{max}$, $AUC_{0-inf}$ and $AUC_{0-t}$ were entirely contained within the pre-specified margins (with 90% CIs including 100%) for the other 2 comparisons (AVT04/US-Stelara and EU-Stelara/US-Stelara).

**Table 2.** AVT04 and EU Stelara Partial AUC and Corresponding Ratio of Geometric LSM (90% CI)

| Partial Areas (h*ng/mL) | AVT04 | | EUS | | Ratio GLSM (90% CI) |
|---|---|---|---|---|---|
| | [N] | GLSM | [N] | GLSM | |
| AUC from 0H to 150H | 96 | 383782.9 | 97 | 376258.2 | 102.0 (91.8, 113.4) |
| AUC from 0H to 175H | 96 | 471803.2 | 97 | 462653.3 | 102.0 (92.2, 112.7) |
| AUC from 0H to 400H | 96 | 1216980.9 | 97 | 1174473 | 103.6 (95.9, 111.9) |
| AUC from 0H to 800H | 96 | 2152431.4 | 97 | 2024616 | 106.3 (99.2, 114.0) |
| AUC from 0H to 1000H | 96 | 2458052.9 | 97 | 2295904 | 107.1 (99.9, 114.8) |
| AUC from 0H to 1400H | 96 | 2854877.2 | 97 | 2640680 | 108.1 (100.7, 116.1) |
| AUC from 0H to 1800H | 96 | 3079641.4 | 97 | 2828039 | 108.9 (101.2, 117.2) |
| AUC from 400H to last | 96 | 1896158.9 | 97 | 1701722 | 111.4 (101.3, 122.5) |
| AUC from 800H to last | 94 | 986205.6 | 97 | 854671.4 | 115.4 (101.1, 131.7) |
| AUC from 1000H to last | 93 | 710545.1 | 97 | 583221 | 121.8 (105.2, 141.1) |
| AUC from 1400H to last | 93 | 319767.8 | 96 | 261797.9 | 122.1 (102.5, 145.6) |
| AUC from 1800H to last | 92 | 110687.4 | 96 | 86952.6 | 127.3 (104.2, 155.5) |
| AUC from 400H to inf | 93 | 2117631.4 | 97 | 1835674 | 115.4 (104.4, 127.4) |
| AUC from 800H to inf | 93 | 1180431.8 | 97 | 983895.7 | 120.0 (104.5, 137.8) |
| AUC from 1000H to inf | 93 | 874998.5 | 97 | 714613.8 | 122.4 (104.7, 143.2) |
| AUC from 1400H to inf | 93 | 480020.6 | 97 | 375428.5 | 127.9 (105.1, 155.5) |
| AUC from 1800H to inf | 93 | 260075.1 | 97 | 193486.6 | 134.4 (106.1, 170.3) |

**Ancillary analyses**

Subgroup analysis based on randomization strata

Systemic exposure to ustekinumab was body weight-dependent, with geometric mean $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ values being notably lower in the non-Japanese >80 kg subgroup compared with the non-Japanese ≤80 kg subgroup. This trend was consistently observed in all 3 treatment groups. Median $T_{max}$ did not appear to be impacted by body weight differences in the AVT04 and US- Stelara groups, whereas in the EU- Stelara group, median $T_{max}$ was shorter in the non-Japanese >80 kg subgroup.

Across treatment groups, the geometric mean $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ values in the Japanese subgroup were similar to those in the non-Japanese ≤80 kg subgroup and with the PK parameters of the overall PK Population. In the AVT04 and US- Stelara groups, the median $T_{max}$ was notably lower in the Japanese subgroup compared with the non-Japanese subgroups and of the overall PK Population, whereas no such difference was observed in the EU- Stelara group. Due to the very small sizes of the Japanese subgroup (20 enrolled subjects; n = 7 in the AVT04 group, 7 in the EU- Stelara group, and 6 in the US- Stelara group), these results should be interpreted with caution.

In non-Japanese subjects ≤80kg, for the comparison (AVT04/EU-Stelara), point estimates for GMRs for $C_{max}$, $AUC_{0-inf}$, and $AUC_{0-t}$ together with corresponding 90% CIs were contained within the pre-specified margins of 80% to 125%, although $AUC_{0-inf}$ and $AUC_{0-t}$ were slightly higher with AVT04. As this stratum contributed the most to the overall study population with respect to its size, the results are generally in line with those for the overall study population.

In non-Japanese subjects with BW>80 kg, the point estimates for GMRs for $AUC_{0-inf}$ and $AUC_{0-t}$ were above 100% (including CIs); i.e. for $AUC_{0-inf}$ the GMR was 135.8% (90% CI 111.1%, 161.3%) and for $AUC_{0-t}$ the GMR was 133.3% (90% CI 110.1%, 161.3%). After correction for protein content, the point estimate for GMR for $AUC_{0-inf}$ was 127.9% (90% CI 104.7%, 156. 2%) and point estimate for GMR for $AUC_{0-last}$ was 125.6% (90% CI 103.8%, 151.9%).

The size of the other Japanese strata was too small to draw robust conclusions.

**Table 11-5 Summary of Serum Ustekinumab Pharmacokinetic Parameters by Treatment – Subgroups based on Randomization Strata (Pharmacokinetic Population)**

| Randomization Strata | Median (Range) | Geometric Mean (Geometric CV%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (h·ng/mL) | $AUC_{0-inf}$ (h·ng/mL) | $K_{el}$ (1/h) | $t_{1/2}$ (h) | CL/F (L/h) | $V_z$/F (L) | CL/F/BW (L/h/kg) | Vz/F/BW (L/kg) |
| **AVT04 (N = 96)** | | | | | | | | | | |
| Non-Japanese ≤80 kg (N = 71) | 168.05 (46.42–504) | 4126.4 (32%) | 33 52914 (32%) | 36 00240 (33%) | 0.0015 (25.2%) | 475.99 (25.2%) | 0.01 (32.9%) | 8.48 (30.9%) | 0.00018 (29%) | 0.13 (28.5%) |
| Non-Japanese >80 kg (N = 18) | 167.18 (94.48–337.65) | 3573.7 (22%) | 30 18664 (16%) | 32 08256 (18%) | 0.0014 (28%) | 494.46 (28%) | 0.01 (18.4%) | 10.01 (22%) | 0.00017 (20.5%) | 0.12 (21.7%) |
| Japanese (N = 7) | 96.12 (72.27–264.1) | 4162.9 (63%) | 33 33853 (60%) | 34 77329 (61%) | 0.0015 (11.7%) | 456.03 (11.7%) | 0.01 (61%) | 8.51 (51.9%) | 0.0002 (61.1%) | 0.13 (55.1%) |
| **EU-Stelara (N = 97)** | | | | | | | | | | |
| Non-Japanese ≤80 kg (N = 71) | 167.98 (47.77–503.6) | 3858.8 (36%) | 30 41239 (34%) | 32 00642 (35%) | 0.0016 (24.8%) | 442.2 (24.8%) | 0.01 (34.8%) | 8.97 (32.7%) | 0.00021 (33.2%) | 0.13 (30.8%) |
| Non-Japanese >80 kg (N = 19) | 144.00 (72–338.87) | 2995.1 (36%) | 22 61644 (47%) | 23 57610 (49%) | 0.0017 (30%) | 414.64 (30%) | 0.02 (48.7%) | 11.42 (34.2%) | 0.00023 (48.5%) | 0.14 (34.3%) |
| Japanese (N = 7) | 168.00 (144.78–216.53) | 4003.3 (46%) | 30 81890 (30%) | 31 99048 (29%) | 0.0018 (47.5%) | 380.32 (47.5%) | 0.01 (29.3%) | 7.72 (59.7%) | 0.00023 (30.5%) | 0.12 (52.7%) |
| **US-Stelara (N = 94)** | | | | | | | | | | |
| Non-Japanese ≤80 kg (N = 71) | 168.15 (48–339.53) | 4173.4 (31%) | 33 26444 (32%) | 35 26103 (34%) | 0.0015 (38.2%) | 454.14 (38.2%) | 0.01 (34%) | 8.3 (33.5%) | 0.00019 (31.8%) | 0.12 (33.5%) |
| Non-Japanese >80 kg (N = 17) | 167.97 (73.22–264.78) | 3385.7 (27%) | 25 67824 (36%) | 26 76759 (39%) | 0.0018 (47.6%) | 389.34 (47.6%) | 0.02 (38.5%) | 9.44 (39.2%) | 0.0002 (39.5%) | 0.11 (38.7%) |
| Japanese (N = 6) | 130.53 (48–194.53) | 4651.7 (19%) | 32 76170 (33%) | 33 90933 (35%) | 0.0017 (33.9%) | 400.95 (33.9%) | 0.01 (34.9%) | 7.68 (12.6%) | 0.0002 (37.2%) | 0.11 (15.1%) |

$AUC_{0-inf}$: Area under the concentration-curve from time zero extrapolated to infinite time; $AUC_{0-t}$: Area under the concentration-curve from time zero to the last quantifiable concentration; BLQ: Below the lower limit of quantification (25 ng/mL); BW: body weight adjusted; CL/F: apparent clearance; $C_{max}$: maximum serum concentration; CV%: coefficient of variation; $K_{el}$: terminal elimination rate constant; LLOQ: lower limit of quantitation; $t_{1/2}$: apparent terminal elimination half-life; $T_{max}$: time of maximum serum concentration; Vz/F: apparent volume of distribution.

N: Total number of subjects in the relevant population.

Notes: All predose BLQ values were substituted by zeros. Thereafter BLQ values between evaluable concentrations and terminal BLQ were set to 0.5 × LLOQ.

It was noted that there were fewer evaluable subjects for determination of $AUC_{0-inf}$ than $AUC_{0-t}$ as not all subjects met the requirement for $AUC_{0-inf}$ (and associated parameters: CL/F, $t_{1/2}$, $V_z$/F). The PK parameters were determined using WinNonlin v8.3 or higher.

Source: Table 14.2.2.1.1.

**Table 11-6 PK Similarity Assessment of Serum Ustekinumab Pharmacokinetic Parameters by Treatment – Subgroups based on Randomization Strata (Pharmacokinetic Population)**

| Comparison (Test/Reference) | Parameter | Test | | Reference | | Ratio of Geometric LS Means (%) | 90% Confidence Interval for Ratio of Geometric LS Means [a] | |
|---|---|---|---|---|---|---|---|---|
| | | n | Geometric LS Mean | n | Geometric LS Mean | Test/ Reference | | |
| **Non-Japanese ≤80 kg** | | | | | | | | |
| AVT04 / EU-Stelara | $C_{max}$ (ng/mL) | 71 | 4119.2 | 71 | 3841.0 | 107.2 | 98.5 | 116.7 |
| | $AUC_{0-inf}$ (h·ng/mL) | 68 | 3587122.6 | 71 | 3182327.1 | 112.7 | 103.4 | 122.9 |
| | $AUC_{0-t}$ (h·ng/mL) | 71 | 3346060.9 | 71 | 3024904.8 | 110.6 | 101.9 | 120.1 |
| AVT04 / US-Stelara | $C_{max}$ (ng/mL) | 71 | 4119.2 | 71 | 4200.0 | 98.1 | 90.1 | 106.8 |
| | $AUC_{0-inf}$ (h·ng/mL) | 68 | 3587122.6 | 70 | 3559285.7 | 100.8 | 92.4 | 109.9 |
| | $AUC_{0-t}$ (h·ng/mL) | 71 | 3346060.9 | 71 | 3351256.4 | 99.8 | 92.0 | 108.4 |
| US-Stelara / EU-Stelara | $C_{max}$ (ng/mL) | 71 | 4200.0 | 71 | 3841.0 | 109.3 | 100.4 | 119.0 |
| | $AUC_{0-inf}$ (h·ng/mL) | 70 | 3559285.7 | 71 | 3182327.1 | 111.8 | 102.6 | 121.9 |
| | $AUC_{0-t}$ (h·ng/mL) | 71 | 3351256.4 | 71 | 3024904.8 | 110.8 | 102.1 | 120.2 |
| **Non-Japanese >80 kg** | | | | | | | | |
| AVT04 / EU-Stelara | $C_{max}$ (ng/mL) | 18 | 3574.4 | 19 | 2996.8 | 119.3 | 101.7 | 139.8 |
| | $AUC_{0-inf}$ (h·ng/mL) | 18 | 3213085.5 | 19 | 2366907.9 | 135.8 | 111.1 | 165.9 |
| | $AUC_{0-t}$ (h·ng/mL) | 18 | 3020937.9 | 19 | 2266104.9 | 133.3 | 110.1 | 161.3 |
| AVT04 / US-Stelara | $C_{max}$ (ng/mL) | 18 | 3574.4 | 17 | 3382.8 | 105.7 | 89.6 | 124.7 |
| | $AUC_{0-inf}$ (h·ng/mL) | 18 | 3213085.5 | 17 | 2660768.0 | 120.8 | 98.1 | 148.7 |
| | $AUC_{0-t}$ (h·ng/mL) | 18 | 3020937.9 | 17 | 2560131.9 | 118.0 | 96.8 | 143.9 |
| US-Stelara / EU-Stelara | $C_{max}$ (ng/mL) | 17 | 3382.8 | 19 | 2996.8 | 112.9 | 95.7 | 133.1 |
| | $AUC_{0-inf}$ (h·ng/mL) | 17 | 2660768.0 | 19 | 2366907.9 | 112.4 | 91.3 | 138.3 |
| | $AUC_{0-t}$ (h·ng/mL) | 17 | 2560131.9 | 19 | 2266104.9 | 113.0 | 92.7 | 137.7 |

**Table 11-6 PK Similarity Assessment of Serum Ustekinumab Pharmacokinetic Parameters by Treatment – Subgroups based on Randomization Strata (Pharmacokinetic Population) (contd.)**

| Comparison (Test/Reference) | Parameter | Test n | Test Geometric LS Mean | Reference n | Reference Geometric LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of Geometric LS Means [a] | |
|---|---|---|---|---|---|---|---|---|
| | | | Japanese | | | | | |
| AVT04 / EU-Stelara | $C_{max}$ (ng/mL) | 7 | 4152.4 | 7 | 3926.5 | 105.8 | 69.9 | 160.0 |
| | $AUC_{0-inf}$ (h·ng/mL) | 7 | 3471936.2 | 7 | 3161210.7 | 109.8 | 73.7 | 163.6 |
| | $AUC_{0-t}$ (h·ng/mL) | 7 | 3328437.2 | 7 | 3043712.8 | 109.4 | 73.9 | 161.7 |
| AVT04 / US-Stelara | $C_{max}$ (ng/mL) | 7 | 4152.4 | 6 | 4772.0 | 87.0 | 56.4 | 134.2 |
| | $AUC_{0-inf}$ (h·ng/mL) | 7 | 3471936.2 | 6 | 3444561.8 | 100.8 | 66.4 | 152.9 |
| | $AUC_{0-t}$ (h·ng/mL) | 7 | 3328437.2 | 6 | 3330472.7 | 99.9 | 66.4 | 150.5 |
| US-Stelara / EU-Stelara | $C_{max}$ (ng/mL) | 6 | 4772.0 | 7 | 3926.5 | 121.5 | 78.4 | 188.3 |
| | $AUC_{0-inf}$ (h·ng/mL) | 6 | 3444561.8 | 7 | 3161210.7 | 109.0 | 71.5 | 166.1 |
| | $AUC_{0-t}$ (h·ng/mL) | 6 | 3330472.7 | 7 | 3043712.8 | 109.4 | 72.3 | 165.5 |

$AUC_{0-inf}$: Area under the concentration-curve from time zero extrapolated to infinite time; $AUC_{0-t}$: area under the concentration-curve from time zero to the last quantifiable concentration; CL: confidence limit; $C_{max}$: maximum serum concentration; GLM: general linear model; LS: Least-Squares; n: Number of subjects used in calculation.
Treatment Comparison by analysis of covariance of log-transformed parameters using SAS proc GLM with model: <parameter> = Treatment + body weight at baseline as the covariate. 90% confidence interval for ratio of LS mean was constructed from the one-sided lower 5% CL and one-sided upper 5% CL.

a. Pharmacokinetic similarity was demonstrated if, for each pairwise comparison, the 90% confidence intervals for the ratios of geometric LS means were entirely contained with the equivalence margin 80% to 125%.

Source: Table 14.2.2.2.1 and Table 1.1.

Subgroup analysis based on immunogenicity

*Subgroup based on anti-drug antibodies*

Strata: ADA Positive

| Comparison (Test/Reference) | Parameter | Test n | Test Geometric LS Mean | Reference n | Reference Geometric LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax (ng/mL) | 36 | 3754.8 | 58 | 3486.5 | 107.7 | 96.6 | 120.1 |
| | AUC0-inf (h*ng/mL) | 34 | 3200007.8 | 58 | 2729897.6 | 117.2 | 103.8 | 132.4 |
| AVT04 / US-Stelara | Cmax (ng/mL) | 36 | 3754.8 | 52 | 3907.6 | 96.1 | 86.0 | 107.4 |
| | AUC0-inf (h*ng/mL) | 34 | 3200007.8 | 52 | 3040146.3 | 105.3 | 92.9 | 119.2 |
| US-Stelara / EU-Stelara | Cmax (ng/mL) | 52 | 3907.6 | 58 | 3486.5 | 112.1 | 101.6 | 123.6 |
| | AUC0-inf (h*ng/mL) | 52 | 3040146.3 | 58 | 2729897.6 | 111.4 | 100.0 | 124.0 |

Strata: ADA Negative

| Comparison (Test/Reference) | Parameter | Test n | Test Geometric LS Mean | Reference n | Reference Geometric LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax (ng/mL) | 60 | 4192.8 | 39 | 3927.9 | 106.7 | 96.2 | 118.5 |
| | AUC0-inf (h*ng/mL) | 59 | 3708071.7 | 39 | 3429101.3 | 108.1 | 98.0 | 119.3 |
| AVT04 / US-Stelara | Cmax (ng/mL) | 60 | 4192.8 | 42 | 4280.6 | 97.9 | 88.4 | 108.5 |
| | AUC0-inf (h*ng/mL) | 59 | 3708071.7 | 41 | 3837085.9 | 96.6 | 87.7 | 106.4 |
| US-Stelara / EU-Stelara | Cmax (ng/mL) | 42 | 4280.6 | 39 | 3927.9 | 109.0 | 97.3 | 122.0 |
| | AUC0-inf (h*ng/mL) | 41 | 3837085.9 | 39 | 3429101.3 | 111.9 | 100.6 | 124.5 |

Table 14.2.2.2.2
PK Similarity Assessment of Serum Ustekinumab of Dose Adjusted Pharmacokinetic Parameters by Treatment
Pharmacokinetic Population

Strata: ADA Positive

| Comparison (Test/Reference) | Parameter | Test n | Test LS Mean | Reference n | Reference LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of Geometric LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 36 | 3603.8 | 58 | 3570.2 | 100.9 | 90.6 | 112.5 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 34 | 3068304.9 | 58 | 2795392.3 | 109.8 | 97.2 | 124.0 |
| AVT04 / US-Stelara | Cmax Dose Adjusted (ng/mL) | 36 | 3603.8 | 52 | 3719.2 | 96.9 | 86.8 | 108.2 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 34 | 3068304.9 | 52 | 2893539.5 | 106.0 | 93.6 | 120.1 |
| US-Stelara / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 52 | 3719.2 | 58 | 3570.2 | 104.2 | 94.5 | 114.8 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 52 | 2893539.5 | 58 | 2795392.3 | 103.5 | 92.9 | 115.3 |

Table 14.2.2.2.2
PK Similarity Assessment of Serum Ustekinumab of Dose Adjusted Pharmacokinetic Parameters by Treatment
Pharmacokinetic Population

Strata: ADA Negative

| Comparison (Test/Reference) | Parameter | Test n | Test LS Mean | Reference n | Reference LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of Geometric LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 60 | 4023.6 | 39 | 3997.5 | 100.7 | 90.5 | 112.0 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 59 | 3559636.8 | 39 | 3489450.2 | 102.0 | 92.3 | 112.8 |
| AVT04 / US-Stelara | Cmax Dose Adjusted (ng/mL) | 60 | 4023.6 | 42 | 4135.0 | 97.3 | 87.7 | 108.0 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 59 | 3559636.8 | 41 | 3710506.3 | 95.9 | 86.9 | 105.9 |
| US-Stelara / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 42 | 4135.0 | 39 | 3997.5 | 103.4 | 92.2 | 116.1 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 41 | 3710506.3 | 39 | 3489450.2 | 106.3 | 95.4 | 118.6 |

*Subgroups based on neutralising antibodies*

Table 14.2.2.2.1
PK Similarity Assessment of Serum Ustekinumab Pharmacokinetic Parameters by Treatment
Pharmacokinetic Population

Strata: NAb Positive

| Comparison (Test/Reference) | Parameter | Test n | Test Geometric LS Mean | Reference n | Reference Geometric LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax (ng/mL) | 12 | 4341.4 | 25 | 3394.8 | 127.9 | 105.7 | 154.7 |
| | AUC0-inf (h*ng/mL) | 12 | 3577244.4 | 25 | 2453081.3 | 145.8 | 116.9 | 182.0 |
| AVT04 / US-Stelara | Cmax (ng/mL) | 12 | 4341.4 | 28 | 3858.7 | 112.5 | 93.3 | 135.7 |
| | AUC0-inf (h*ng/mL) | 12 | 3577244.4 | 28 | 2716404.3 | 131.7 | 105.9 | 163.8 |
| US-Stelara / EU-Stelara | Cmax (ng/mL) | 28 | 3858.7 | 25 | 3394.8 | 113.7 | 97.8 | 132.1 |
| | AUC0-inf (h*ng/mL) | 28 | 2716404.3 | 25 | 2453081.3 | 110.7 | 93.0 | 131.9 |

Table 14.2.2.2.1
PK Similarity Assessment of Serum Ustekinumab Pharmacokinetic Parameters by Treatment
Pharmacokinetic Population

Strata: NAb Negative

| Comparison (Test/Reference) | Parameter | Test n | Test Geometric LS Mean | Reference n | Reference Geometric LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax (ng/mL) | 24 | 3469.4 | 33 | 3551.3 | 97.7 | 85.6 | 111.5 |
| | AUC0-inf (h*ng/mL) | 22 | 2987238.0 | 33 | 2940570.8 | 101.6 | 89.9 | 114.9 |
| AVT04 / US-Stelara | Cmax (ng/mL) | 24 | 3469.4 | 24 | 4001.1 | 86.7 | 75.2 | 99.9 |
| | AUC0-inf (h*ng/mL) | 22 | 2987238.0 | 24 | 3524532.3 | 84.8 | 74.3 | 96.7 |
| US-Stelara / EU-Stelara | Cmax (ng/mL) | 24 | 4001.1 | 33 | 3551.3 | 112.7 | 98.7 | 128.6 |
| | AUC0-inf (h*ng/mL) | 24 | 3524532.3 | 33 | 2940570.8 | 119.9 | 106.3 | 135.1 |

Table 14.2.2.2.2
PK Similarity Assessment of Serum Ustekinumab of Dose Adjusted Pharmacokinetic Parameters by Treatment
Pharmacokinetic Population

Strata: NAb Positive

| Comparison (Test/Reference) | Parameter | Test n | Test LS Mean | Reference n | Reference LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of Geometric LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 12 | 4128.8 | 25 | 3478.0 | 118.7 | 98.3 | 143.3 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 12 | 3402123.6 | 25 | 2513246.5 | 135.4 | 108.5 | 168.8 |
| AVT04 / US-Stelara | Cmax Dose Adjusted (ng/mL) | 12 | 4128.8 | 28 | 3665.6 | 112.6 | 93.6 | 135.6 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 12 | 3402123.6 | 28 | 2580434.2 | 131.8 | 106.1 | 163.9 |
| US-Stelara / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 28 | 3665.6 | 25 | 3478.0 | 105.4 | 90.8 | 122.3 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 28 | 2580434.2 | 25 | 2513246.5 | 102.7 | 86.2 | 122.2 |

Table 14.2.2.2.2
PK Similarity Assessment of Serum Ustekinumab of Dose Adjusted Pharmacokinetic Parameters by Treatment
Pharmacokinetic Population

Strata: NAb Negative

| Comparison (Test/Reference) | Parameter | Test n | Test LS Mean | Reference n | Reference LS Mean | Ratio of Geometric LS Means (%) Test/Reference | 90% Confidence Interval for Ratio of Geometric LS Means | |
|---|---|---|---|---|---|---|---|---|
| AVT04 / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 24 | 3345.6 | 33 | 3635.5 | 92.0 | 80.7 | 105.0 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 22 | 2877495.5 | 33 | 3010299.5 | 95.6 | 84.5 | 108.1 |
| AVT04 / US-Stelara | Cmax Dose Adjusted (ng/mL) | 24 | 3345.6 | 24 | 3815.6 | 87.7 | 76.1 | 101.1 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 22 | 2877495.5 | 24 | 3361192.1 | 85.6 | 75.0 | 97.7 |
| US-Stelara / EU-Stelara | Cmax Dose Adjusted (ng/mL) | 24 | 3815.6 | 33 | 3635.5 | 105.0 | 92.0 | 119.8 |
| | AUC0-inf Dose Adjusted (h*ng/mL) | 24 | 3361192.1 | 33 | 3010299.5 | 111.7 | 99.0 | 125.9 |

More subjects developed ADAs in the EU-Stelara group than in the AVT04 group (36.8% versus 59.6%). In the ADA-positive subgroups (n=36 in the AVT04 group, n=58 in the EU-Stelara, and n=52 in the US-Stelara group), the geometric means of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were consistently lower compared with those in the ADA-negative subgroups (n=60 in the AVT04 group, n=39 in the EU-Stelara group, and n=42 in the US-Stelara group). The same trend was observed across treatment groups. The geometric mean $t_{1/2}$ was also shorter in the ADA-positive subgroup. In addition, larger differences between treatments were observed in ADA-positive subjects, compared to ADA-negative subjects.

In ADA negative subjects, similarity was observed for both Cmax and AUC0-inf, as the 90% CIs were within the 80% -125% similarity margin [i.e. the point estimate for Cmax was 106.7% (90%CI 96.2%, 118.5%); the point estimate for $AUC_{0-inf}$ was 108.1 (90% CI 98.0%, 119.3%)], whereas in ADA-positive subjects the upper bound of the 90% CI for $AUC_{0-inf}$ exceeded 125% [point estimate 117.2%

(90% CI 103.8%, 132.4%)]. After correction for protein content, the 90% CIs were within the similarity margin for both co-primary parameters in both ADA positive and ADA-negative subgroups.

In the nAb-positive subgroup for AVT04 (n=12), the geometric means of the systemic exposure PK parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were higher compared with those in the nAb-negative subgroup (n=24). This difference was due to 2 outlier subjects in the AVT04 nAb-positive subgroup with relatively higher $C_{max}$ and $AUC_{0-t}$ values compared with the rest of the subjects in the same subgroup. Similarity between AVT04 and EU-Stelara was observed in nAb-negative subjects for $C_{max}$ and $AUC_{0-inf}$. In nAb-positive subjects the point estimates for both $C_{max}$ and $AUC_{0-inf}$ were outside the similarity range, with very wide 90% CIs. In the nAb-positive subgroups for EU-Stelara (n=25) and US-Stelara (n=28), the geometric means of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were lower compared to that in nAb-negative subgroups (n=33 in the EU-Stelara group and n = 24 in the US- Stelara group). Across treatment groups, the geometric mean $t_{1/2}$ was shorter in the nAb-positive subgroup.

***Pharmacokinetics in target population***

Further support for PK similarity of AVT04 to Stelara was gained from Study AVT04-GL-301 in patients with moderate to severe Chronic Plaque-type Psoriasis (PsO).

Study AVT04-GL-301 was a randomized, double-blind, multicenter, active control clinical study to compare the efficacy, safety, and immunogenicity of AVT04 versus EU-Stelara in patients with moderate to severe chronic PsO.

Comparison of steady-state PK of AVT04 and EU-Stelara was one of the secondary objectives of the study. Serum trough concentrations ($C_{trough}$) of ustekinumab were determined in all patients at Week 1/Day 1 (pre-dose), and pre-dose at Weeks 4, 16, 28, 40, and 52 (EoS). Comparison was descriptive based on the safety analysis set.

**Table 11.30: Serum Trough Pharmacokinetic Concentrations over Time – Safety Analysis Set – Up to Week 16 (All Patients and Patients with Body Weight ≤100 kg)**

| | AVT04 Concentration (ng/mL) | | | | | | | EU-Stelara Concentration (ng/mL) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | n | Mean (SD) | Median | Min, Max | GEOM | Log_SD | CV% | n | Mean (SD) | Median | Min, Max | GEOM | Log_SD | CV% |
| **All patients** | | | | | | | | | | | | | | |
| Baseline | 194 | 0.30 (4.193) | 0.00 | 0.0, 58.4 | 58.40 | NA | 1392.8 | 387 | 0.63 (10.547) | 0.00 | 0.0, 204.0 | 88.51 | 1.181 | 1683.9 |
| Week 4 | 194 | 2136.96 (826.527) | 2080.00 | 229.0, 4860.0 | 1959.75 | 0.449 | 38.7 | 387 | 1947.67 (815.269) | 1940.00 | 12.5, 4360.0 | 1674.75 | 0.729 | 41.9 |
| Week 16 | 193 | 418.85 (293.366) | 396.00 | 12.5, 1350.0 | 273.88 | 1.175 | 70.0 | 381 | 356.91 (253.331) | 312.00 | 12.5, 1260.0 | 241.67 | 1.080 | 71.0 |
| **Patients with body weight ≤100 kg** | | | | | | | | | | | | | | |
| Baseline | 164 | 0.36 (4.560) | 0.0 | 0.0, 58.4 | 58.40 | NA | 1280.6 | 327 | 0.00 (0.000) | 0.00 | 0.0, 0.0 | NA | NA | NA |
| Week 4 | 164 | 2043.71 (718.613) | 2050.00 | 229.0, 3890.0 | 1892.60 | 0.430 | 35.2 | 327 | 1858.48 (760.599) | 1900.00 | 12.5, 4360.0 | 1590.43 | 0.757 | 40.9 |
| Week 16 | 163 | 413.09 (290.572) | 397.00 | 12.5, 1350.0 | 270.74 | 1.166 | 70.3 | 321 | 353.91 (256.036) | 307.00 | 12.5, 1260.0 | 237.52 | 1.089 | 72.3 |

Log_SD = SD of log-transformed data; CV% = (SD/Mean) × 100.
Concentrations below the lower limit of quantitation (<LLOQ) measurable concentration were assigned a value of 0 for Baseline values and a value of 0.5 × LLOQ, where LLOQ = 25 ng/mL, for post-Baseline values.
Abbreviations: EU = European Union; GEOM = geometric mean; Max = maximum; Min = minimum; NA = not available; SD = standard deviation.
Source: Table 14.3.5.2.1.

Overall, mean serum trough PK concentration increased from Baseline to Week 4 for AVT04 and EU-Stelara and then decreased at Week 16. At Week 4, geom. mean $C_{trough}$ was approximately 17% higher with AVT04 compared to EU-Stelara (1959.75 ng/mL vs. 1674.75 ng/mL) and at Week 16 geom. mean

$C_{trough}$ was approximately 13% higher with AVT04 compared to EU-Stelara (273.88 ng/mL vs. 241.67 ng/mL).

At Week 16, patients initially randomized to EU-Stelara arm were re-randomized in 1:1 ration to either continue treatment with EU-Stelara or switch to AVT04. Therefore, starting from Week 16, data is presented for 3 arms (AVT04/AVT04, EU-Stelara/AVT04, EU-Stelara/EU-Stelara). At Week 28, treatment was no longer administered to non-responders (details of study design are described in section 3.3). The applicant clarified that no patient was excluded from the presentation of PK data from Week 28 onwards due to being a non-responder.

**Table 11.31: Serum Trough Pharmacokinetic Concentrations over Time – Safety Analysis Set – Up to End of Study (All Patients and Patients with Body Weight ≤100 kg)**

| Visit | n | Mean (SD) | Median | Min, Max | GEOM | Log_SD | CV% |
|---|---|---|---|---|---|---|---|
| All patients | | | | | | | |
| AVT04/AVT04 Concentration (ng/mL) (n=191) | | | | | | | |
| Baseline | 191 | 0.31 (4.226) | 0.00 | 0.0, 58.4 | 58.40 | NA | 1382.0 |
| Week 16 | 191 | 418.03 (294.770) | 395.00 | 12.5, 1350.0 | 272.18 | 1.180 | 70.5 |
| Week 28 | 190 | 307.64 (260.365) | 252.50 | 12.5, 1270.0 | 193.24 | 1.143 | 84.6 |
| Week 40 | 191 | 403.49 (546.961) | 243.00 | 12.5, 3580.0 | 219.12 | 1.181 | 135.6 |
| Week 52 | 185 | 409.19 (486.917) | 276.00 | 12.5, 3570.0 | 253.88 | 1.042 | 119.0 |
| EU-Stelara/AVT04 Concentration (ng/mL) (n=184) | | | | | | | |
| Baseline | 184 | 1.32 (15.288) | 0.00 | 0.0, 204.0 | 88.51 | 1.181 | 1160.5 |
| Week 16 | 183 | 336.69 (271.559) | 277.00 | 12.5, 1260.0 | 219.09 | 1.103 | 80.7 |
| Week 28 | 182 | 265.08 (219.845) | 220.50 | 12.5, 1100.0 | 164.41 | 1.170 | 82.9 |
| Week 40 | 179 | 382.47 (592.403) | 215.00 | 12.5, 4060.0 | 193.31 | 1.248 | 154.9 |
| Week 52 | 178 | 409.67 (493.704) | 274.00 | 12.5, 3120.0 | 261.10 | 0.990 | 120.5 |
| EU-Stelara/EU-Stelara Concentration (ng/mL) (n=184) | | | | | | | |
| Baseline | 184 | 0.00 (0.000) | 0.00 | 0.0, 0.0 | NA | NA | NA |
| Week 16 | 184 | 381.41 (236.732) | 382.50 | 12.5, 945.0 | 270.63 | 1.037 | 62.1 |
| Week 28 | 184 | 298.42 (224.324) | 254.00 | 12.5, 957.0 | 188.82 | 1.170 | 75.2 |
| Week 40 | 181 | 391.18 (548.873) | 274.00 | 12.5, 3690.0 | 206.06 | 1.270 | 140.3 |
| Week 52 | 180 | 470.49 (569.148) | 309.00 | 12.5, 3600.0 | 280.23 | 1.109 | 121.0 |

In the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups, mean serum trough PK concentration increased from Baseline to Week 16 for all treatment groups, had then decreased at Week 28, and had increased again at Week 40 and at Week 52 (EoS), reaching values similar to those observed at Week 16. The PK profile was generally comparable in all 3 treatment groups. Similar results were observed for patients with body weight ≤100 kg. Higher $C_{trough}$ with AVT04 compared to EU-Stelara observed at Weeks 4 and 16 were no longer apparent at later stage of the study. At Week 52 $C_{trough}$ in the AVT04/AVT04 arm was slightly lower than in the EU-Stelara/EU-Stelara arm (253.88 ng/mL and 280.23 ng/mL, respectively).

Two different batches of EU-Stelara were used in AVT04-GL-301 (KHS25MJ and LBS1ZMC). The former batch was the same batch as used in the PK study, with approximately 10% lower protein concentration than AVT04 batch (82.3 mg/mL vs. 91.0 mg/mL, respectively), while the latter batch had similar protein conc. (90.0 mg/mL). For the presentation of $C_{trough}$ in AVT04-GL-301, data of both EU-Stelara batches were pooled together. The applicant clarified that all patients receiving EU-Stelara at Day 1 and Week 4 were administered batch KHS25MJ (82.3 mg/mL); the $C_{trough}$ values up to Week16 (including Week12, timing of the primary analysis) reflect the plasma concentrations obtained

from administration of batch KHS25MJ. The exclusive use of the same batches as in study AVT04-GL101 at the two first study drug administrations in study AVT04-GL-301 lead to similar slight differences in exposure as measured by the trough concentrations at Week 4 and Week 16.

Thereafter, all patients receiving EU-Stelara were administered batch LBS1ZMC (90.0 mg/m; the $C_{trough}$ values from Week 28 reflect the plasma concentrations obtained from administration of batch LBS1ZMC. Higher $C_{trough}$ with AVT04 compared to EU-Stelara observed at Weeks 4 and 16 were no longer apparent at later stage of the study, which can be explained by the use of different batches. The applicant also clarified that $C_{trough}$ values were not corrected for protein content.

At Week 4 and Week 16, AVT04 concentrations were higher than that of EU-Stelara for all patients and those stratified for body weight strata, as reflected in the mean, median and geometric mean. The variability in $C_{trough}$ concentration for AVT04 and EU-Stelara were comparable. After re-randomization, $C_{trough}$ concentration differences that were observed at Week 16 were no longer apparent by Week 52. This trend was observed in all patients and within each weight strata (≤80kg, 80-100kg, >100kg). The $C_{trough}$ concentration for treatment groups AVT04 / AVT04, EU-Stelara / AVT04, and EU-Stelara / EU Stelara up to Week 52 for all subjects followed a similar pattern as those for the weight strata where $C_{trough}$ was lower at Week 28 and then increased at Week 52 to near Week 16 values.

As regards immunogenicity, up to Week 16, 49 patients (25.4%) in the AVT04 group and 184 patients (48.2%) in the EU-Stelara group developed ADAs. Of these, 13 patients (26.5%) in the AVT04 group and 57 patients (31.0%) in the EU-Stelara group had nAbs. Up to Week 16 $C_{trough}$ values in ADA-negative patients were similar between treatments. In ADA-positive patients, $C_{trough}$ values were slightly higher in the AVT04 group.

The frequency of ADAs decreased over time, from 49 patients (25.7%) at Week 16 to 39 patients (21.2%) at Week 52 in the AVT04/AVT04 group; from 101 patients (54.9%) at Week 16 to 56 patients (31.5%) in the EU-Stelara/AVT04 group; and from 77 patients (41.8%) at Week 16 to 48 patients (26.7%) in the EU-Stelara/EU-Stelara group. The frequency of nAb slightly increased over time in the AVT04/AVT04 group (13 patients [26.5%] at Week 16 and 13 patients [33.3%] at Week 52), decreased over time in the EU-Stelara/AVT04 group (36 patients [35.6%] at Week 16 and 10 patients [17.9%] at Week 52; and remained stable in the EU-Stelara/EU-Stelara group (19 patients [24.7%] at Week 16 and 11 patients [22.9%] at Week 52).

In ADA negative patients, $C_{trough}$ values were overall comparable between AVT04/AVT04 and EU-Stelara/EU-Stelara groups from Week 16 to Week 52 as measured by mean $C_{trough}$, while median $C_{trough}$ values were slightly higher in the EU-Stelara/EU-Stelara group. Similar was observed in ADA-negative subjects.

**Table 14.3.5.3.3**
**Serum Trough PK Concentrations Over Time by Anti-drug Antibody (ADA)/Neutralizing Anti-drug Antibody (NAb) Status**
**Safety Analysis Set - Up to End of Study**

**Treatment: AVT04/AVT04/ All Patients**

| | ADA Negative* (N=117) | | | |
|---|---|---|---|---|
| Visit | n | Mean (SD) | Median | Min, Max |
| Baseline | 117 | 0.50 (5.399) | 0.00 | 0.0, 58.4 |
| Week 16 | 117 | 489.98 (278.532) | 458.00 | 12.5, 1350.0 |
| Week 28 | 117 | 334.40 (239.982) | 296.00 | 12.5, 1190.0 |
| Week 40 | 117 | 452.37 (535.736) | 292.00 | 12.5, 3580.0 |
| Week 52 | 114 | 451.96 (499.508) | 306.50 | 12.5, 3570.0 |

| | ADA Positive** (N=74) | | | |
|---|---|---|---|---|
| Visit | n | Mean (SD) | Median | Min, Max |
| Baseline | 74 | 0.00 (0.000) | 0.00 | 0.0, 0.0 |
| Week 16 | 74 | 304.27 (285.407) | 261.50 | 12.5, 1310.0 |
| Week 28 | 73 | 264.75 (286.590) | 166.00 | 12.5, 1270.0 |
| Week 40 | 74 | 326.20 (559.189) | 158.50 | 12.5, 3520.0 |
| Week 52 | 71 | 340.53 (461.157) | 207.00 | 12.5, 2750.0 |

Table 14.3.5.3.3
Serum Trough PK Concentrations Over Time by Anti-drug Antibody (ADA)/Neutralizing Anti-drug Antibody (NAb) Status
Safety Analysis Set - Up to End of Study

Treatment: EU-Stelara/EU-Stelara/ All Patients

| | ADA Negative* (N=77) | | | |
|---|---|---|---|---|
| Visit | n | Mean (SD) | Median | Min, Max |
| Baseline | 77 | 0.00 (0.000) | 0.00 | 0.0, 0.0 |
| Week 16 | 77 | 454.34 (218.854) | 467.00 | 12.5, 831.0 |
| Week 28 | 77 | 354.01 (213.971) | 356.00 | 12.5, 884.0 |
| Week 40 | 76 | 501.44 (696.122) | 332.50 | 12.5, 3690.0 |
| Week 52 | 75 | 448.38 (369.655) | 381.00 | 28.8, 2070.0 |

| | ADA Positive** (N=107) | | | |
|---|---|---|---|---|
| Visit | n | Mean (SD) | Median | Min, Max |
| Baseline | 107 | 0.00 (0.000) | 0.00 | 0.0, 0.0 |
| Week 16 | 107 | 328.93 (236.150) | 281.00 | 12.5, 945.0 |
| Week 28 | 107 | 258.41 (224.028) | 182.00 | 12.5, 957.0 |
| Week 40 | 105 | 311.38 (395.777) | 224.00 | 12.5, 2330.0 |
| Week 52 | 105 | 486.28 (678.012) | 285.00 | 12.5, 3600.0 |

**Special populations**

No PK data has been provided for subjects with impaired renal or hepatic function. No PK data are available for children.

*Gender:* Both female and male participants were included in clinical studies of AVT04. No subgroup analyses per gender were provided by the applicant. According to Stelara EPAR, small difference between male and female subjects was detected in terms of the effect on apparent clearance (CL/F) and apparent volume of distribution (V/F), which was considered unlikely to be significant.

*Race:* In study -101 the majority of subjects were Caucasian/White (70.7%), and a small proportion were Asian (16.3%). Ethnicity was a stratification factor in study -101. For results in Japanese subjects please refer to the main assessment. In study -301 all participants were White (100%).

*Weight:* Body weight is a major intrinsic factor affecting ustekinumab exposure. Weight was used as stratification factor in both clinical studies. For details, please refer to the main assessment.

*Elderly:* PK data for elderly subjects is limited. In study -101 the upper age limit was set to 55 years, therefore no elderly subjects were included in the study. In study -301 only 33 (5.7%) patients with PsO ≥65 years of age were included in the study. No separate analysis for elderly patients has been presented, and due to limited numbers, none is requested.

### *2.6.2.2. Pharmacodynamics*

In study AVT04-GL-101 a total of 45 subjects (15 per group) were planned to be included in the exploratory ex-vivo biomarker sub-study. The inflammatory cytokine biomarkers assessed included: IFN-γ, IL-22, IL-17, IL-5, IL-13, and IL-10.

The objective of this explorative study was to demonstrate that the binding of Ustekinumab to IL-12 or IL-23 inhibits IL-12- or IL-23 receptor mediated signalling and subsequent induction of inflammatory cytokines (biomarkers), released from T helper cells (Th1 and Th17) within 48h in healthy volunteers. For that purpose, the effector cytokines IFN-γ, IL-4, IL-10 and IL-22 were quantitated in human plasma samples after ex-vivo stimulation with a T cell specific agent. No significant differences were observed regarding target engagement and cytokine (biomarker) secretion between AVT04, EU-Stelara and US-Stelara treatment for most of the timepoints.

Mechanism of action

AVT04 has been developed by Alvotech as a proposed biosimilar to the reference product Stelara (approved in 2009 in the EU).

AVT04 is a recombinant, fully human immunoglobulin (Ig) G1 kappa monoclonal antibody (mAb) directed against interleukin (IL)-12 and IL-23, which are cytokines that are involved in immune and inflammatory responses.

Ustekinumab binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Binding of the antigen binding fragment (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 natural killer (NK) cells or T cells, thereby preventing initiation of downstream immune-response signalling pathways.

***Primary and Secondary pharmacology***

No data on PD has been provided. Since this is a biosimilar application, the secondary pharmacology does not have to be characterised anew.

## 2.6.3. Discussion on clinical pharmacology

Comparative PK data of AVT04 was generated in one PK study in healthy volunteers (AVT04-GL-101) following a single subcutaneous (SC) injection. Additionally, steady-state PK characteristics after repeat SC administration were evaluated in a phase 3 confirmatory study in adult patients with moderate to severe chronic plaque-type psoriasis (AVT04-GL-301).

**PK study AVT04-GL-101**

**Design and conduct of clinical study**

Phase I study AVT04-GL-101 is the pivotal study investigating PK similarity. This was a randomized, double-blind, 3-arm, parallel group, single dose, 3-arm study in healthy subjects to demonstrate similarity in PK, safety, tolerability and immunogenicity between AVT04, EU-sourced Stelara and US-sourced Stelara.

The total study duration was approximately 17 weeks (including the 4-week Screening period). Given the long elimination half-life of ustekinumab (approximately 3 weeks), a parallel design is acceptable. Subjects were randomized in a 1:1:1 ratio into 3 groups: AVT04, EU-Stelara or US-Stelara. The design of the study is overall in accordance with the "*Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues*" (EMA/CHMP/BMWP/403543/2010) and is generally in agreement with Scientific Advice received from EMA (EMEA/H/SA/4502/1/2020/III).

As body weight is a major intrinsic factor, a narrower BW range would have been preferred for a biosimilar study, as it would represent a more sensitive model to demonstrate, or exclude, differences between the treatment arms, if they exist. According to Stelara EPAR, small difference between male and female subjects was detected in terms of the effect on apparent clearance (CL/F) and apparent volume of distribution (V/F), which was considered unlikely to be significant. Further, according to Stelara EPAR, pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis and ulcerative colitis. Eligibility criteria were overall acceptable, although a more homogenous population would have been preferred for a biosimilarity setting.

Subjects received a single dose of 45 mg/0.5 mL of either AVT04, EU-Stelara, or US-Stelara as an SC injection. In cases where reference product can be administered both intravenously (IV) and subcutaneously (SC), the SC route is preferable regarding the objective of PK comparability, since it covers both absorption and elimination. The selected dose 45 mg/0.5 mL represents one of the approved doses for reference product Stelara, fall within the linearity range, was well tolerated in healthy subjects and is expected to induce a higher immunogenicity response compared to the 90 mg dose. Selected dose and route of administration are acceptable.

Study objectives and endpoints are overall adequate for the purpose of PK biosimilarity exercise. The primary endpoints were $C_{max}$ and $AUC_{0\text{-}inf}$, which is in line with EMA guidance for a single dose study with SC administration. The assessment of PK comparability was based on 90% confidence intervals (CIs) for the ratio of the geometric means (AVT04/EU-Stelara) for $C_{max}$ and $AUC_{0\text{-}inf}$ of the ustekinumab concentrations which had to be contained within the conventional bioequivalence limits of 80%-125%. The secondary PK endpoints comprised $AUC_{0\text{-}t}$, $t_{max}$, $K_{el}$, $t_{1/2}$, Vz/F and CL/F.

Blood samples for immunogenicity were collected pre-dose, 12h post-dose, at Days 9, 15, 29, 57, 78 and 92 /EOS. Sampling duration and frequency can be accepted, although it should be noted that taking into account the mean elimination half-life of about 21 days (Stelara SmPC), a sampling period over 92 days covers about 4.3 half-lives, instead of conventionally used 5 elimination half-lives (as initially planned). In general, this should be sufficient to obtain at least an $AUC_{0\text{-}t}$ of 80% of $AUC_{0\text{-}inf}$. However, this is based upon a mean elimination half-life, and it is noted that due to variability in elimination the sampling period may not be sufficient to adequately cover the AUC also in subjects with a slower elimination, which can lead to large extrapolations when estimating $AUC_{0\text{-}inf}$. Based on the observed results however (see later), no issues arise in this respect.

The planning of randomisation is considered reasonable. Randomization was stratified by 2 factors, ethnicity and body weight, but consisted of only 3 strata: Japanese, non-Japanese ≤80 kg, and non-Japanese >80 kg. The study was a subject-, investigator- and sponsor-blinded study. It is unclear how blinding of the patient was ensured given that syringes have different appearance. However, no additional concern on this is raised as the primary goal of the study is to assess relative bioavailability.

ANCOVA analysis methods applied for data analyses of primary endpoints are considered adequate. However, the ANCOVA model for PK parameters corrected for protein content, which was initially conducted as sensitivity analysis, was planned to include the actual dose as covariate. Such a double correction for actual dose would not have been acceptable. However, the Applicant explained that they presented a model that omitted the actual dose as covariate in the study report. This model is seen as the most appropriate one since PK should be linear over the dose range according to the SmPC of Stelara, and is endorsed. Other methodological aspects required further clarification, e.g. the timing of database lock in relation to release of the final version of SAP, as well as omission of the stratification variable *ethnicity* from the ANCOVA model. The applicant explained that the database lock and the SAP finalisation took place on the same date, but unblinding was requested eight days later. Therefore, it can be concluded that the biostatistician had no knowledge of the unblinded data at time of SAP finalisation. Regarding omission of the stratification variable ethnicity, a sensitivity analysis revealed almost the same point estimates and confidence intervals as the original analysis excluding the stratification factor ethnicity. Thus, the omission of ethnicity had hardly any impact on the study results.

Of the 298 randomized subjects, 294 (98.7%) were dosed and 278 (93.3%) completed the study. The proportion of subjects who completed the study was similar in all three arms. The conduct of the study was overall acceptable. Demographic and baseline characteristics were generally balanced between groups. The overall mean age of the subjects was 31.5 years, the mean weight was 70.93 kg and the mean BMI value was 24.52 kg/m2. The majority of subjects (74.5%) belonged to the non-Japanese

≤80 kg stratum at the time of randomization, with 18.7% in the non-Japanese >80 kg stratum and 6.8% in the Japanese stratum. The majority of subjects were female (60.9%) and Caucasian/White (70.7%).

**Pharmacokinetic results**

In the PK study in healthy volunteers, biosimilarity of AVT04 compared to EU-Stelara was shown for the co-primary endpoint $C_{max}$ (109.5% (90% CI 101.7%, 117.8%). In contrast, biosimilarity could not be demonstrated for the co-primary endpoint $AUC_{0\text{-}inf}$, as the 90% CI for the geometric mean ratio fell outside the acceptance range of 80.00% to 125.00% [116.9% (90% CI 108.1%, 126.4%)], suggesting higher exposure with AVT04 compared to EU-Stelara. For the co-primary endpoint $C_{max}$, the GMR (AVT04/EU-Stelara) was entirely within the 80-125% acceptance criteria i.e. the point estimate was 109.5% with a 90% CI 101.7%, 117.8%.

The applicant argues that the calculation of $AUC_{0\text{-}inf}$ includes extrapolation based on an average elimination constant which is not a true reflection of the elimination of Stelara that has an element of target-mediated-drug-disposition (TMDD), which can introduce variability and often over-estimation of the true exposure. It is agreed that in case of a non-linear clearance, the $AUC_{0\text{-}inf}$ can be slightly overestimated and the sampling should be sufficiently long and sufficiently frequent, particularly during the terminal elimination period.

The extrapolated part for $AUC_{0\text{-}inf}$ (%$AUC_{extrap}$) was generally small and similar between the treatments (5%, 3% and 3% for AVT04, EU-Stelara and US-Stelara, respectively). An extrapolated AUC of $\leqslant$20% is considered to be acceptable (see *EMA Clinical pharmacology and pharmacokinetics: Q&A, 7. Biosimilars*). In total 6 subjects had $AUC_{extrap}$ $\geqslant$20% (3 subjects in AVT04 group, 1 subject in EU-Stelara group and 2 subjects in US-Stelara arm). Since $AUC_{0\text{-}t}$ $\leqslant$80% of $AUC_{0\text{-}inf}$ in less than 20% of the observations, $AUC_{0\text{-}inf}$ can be considered a reliable parameter (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Therefore, the Applicant's explanation does not appear to be supported by data.

According to the applicant, the major factor why comparability of exposure (as measured by $AUC_{0\text{-}inf}$) was not demonstrated were differences in protein concentrations between EU-Stelara and AVT04 batches used in the PK study. The claimed protein concentration for Stelara is 90 mg/mL. The EU-Stelara batch (# KHS25MJ) had approximately 9% lower protein concentration (82.3 mg/mL) than the AVT04 batch (91.0 mg/mL). There was also a difference in protein concentration of about 6% between the US-Stelara batch (# KCS11MN, 88.3 mg/mL) and EU-Stelara batch. In order to account for different protein concentrations, the Applicant performed an analysis using adjusted PK parameters.

In addition to differences in protein concentration, there were differences in the administered volumes between the products i.e. the mean administered injection volume of IP was slightly lower in the AVT04 group (0.516 mL) compared with EU-Stelara (0.535 mL). Therefore, for the calculation of protein-content normalized PK parameters, protein concentration as well as administered volume were taken into account. The observed difference between the reference and biosimilar batch was approximately 9%. Taking into account the somewhat differing delivered volumes, the difference in the *administered protein content* between the reference product and biosimilar was 6.6%. After protein content normalization, the bioequivalence criterion 80-125% was met for both primary PK parameters $C_{max}$ and $AUC_{0\text{-}inf}$. Therefore, differences in protein content seem to account at least partly for the observed differences in PK. However, the sequence of events around the decision to perform these analyses is still unclear and the vague preconsideration is not optimal.

In the statistical analysis plan it was noted that "if differences are identified in the drug protein content between AVT04, US-Stelara, and EU-Stelara, a sensitivity analysis will be performed using PK parameters adjusted by protein content. Protein adjusted PK parameters will be summarized and the model for PK similarity will be additionally presented with the inclusion of actual dose as a covariate."

This sentence appears overly generic, as no specific condition, i.e. cut-off criterion for difference in protein concentration/content that would trigger such a correction was pre-defined. Of note, the absolute difference in actual protein content between AVT04 and EU-Stelara was 46.95 mg vs. 44.04 mg (6.6%).

Lack of a pre-specified criterion gave the impression that protein correction was driven by the negative results in the primary PK parameter $AUC_{0\text{-inf.}}$

In the responses to an initially raised major objection the Applicant referred to the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr *) which allows the adjustment of PK parameters for differences in assayed content of the test and reference batch in exceptional cases where a reference batch with an assay content differing less than 5% from test product cannot be found. The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/2005 Rev1) explicitly mentions that, if content correction is to be used, this should be pre-specified in the protocol. It should be mentioned that the scope of the afore-mentioned bioequivalence guideline pertains to chemical entities and does not necessarily apply in its entirety to biologicals. Therefore, the Applicant's extrapolation of the arguments from chemical entities to biologicals, i.e. that a protein-adjusted analysis is justified based on the threshold of 5% as stated in the bioequivalence guideline is debatable.

For therapeutic proteins, there is no concrete guidance on protein content correction. This topic is addressed by EMA guideline (EMEA/CHMP/BMWP/42832/2005 Rev1) reporting: "Correction for protein content may be acceptable on a case-by-case basis if pre-specified and adequately justified, with the results from the assay of the test and reference products being included in the protocol". Therefore, while the option to correct for protein content is given in the above-mentioned EMA guidance applicable to biosimilars, no specific details are provided in the guidance as to when it should be considered acceptable.

The applicant argued that the availability of EU-Stelara batches fulfilling all requirements (in terms of delivery lead time, expiry date, quantity) was very limited, leading to procurement of EU-Stelara batch KHS25MJ which turned out to have lower than nominal protein content. The applicant provided a detailed description of the batch selection process, which can be followed.

However, the Applicant confirmed that the differences in protein concentration between the batches were already known prior to the protocol/SAP finalization. The actual protein concentrations of the AVT04, EU-Stelara and US-Stelara batches tested in study AVT04-GL-101 have also been stated in the SAP (version 2.0, 21-April-2022). Nonetheless, the protein-corrected analysis was not pre-specified as the primary analysis. The applicant's argument regarding the absence of concrete guidance on protein content correction for therapeutic proteins is acknowledged. Also, it is agreed that the guideline does not specify whether an analysis corrected for protein content should be the primary or the sensitivity analysis. However, this means that no rule is yet prescribed and thereby the decision is left at the discretion of the Applicant but should be determined prior to the start of the PK study taking into consideration any differences between the biosimilar and the reference product batches identified at the quality level. Arguing with the existence of differences between the products (i.e. "if differences are identified"), without specifying the extent thereof that would trigger a protein-corrected analysis can result in ambiguity regarding whether (or not) to conduct such an analysis based on observed data. In conclusion, it is not agreed with the Applicant that the protein-corrected analysis was prespecified in an adequate way.

The applicant argued that study AVT04-GL-101 is performed within the steep part of the dose-concentration curve, wherein comparison is made using a dose within the linear portion of the dose-exposure curve. Stelara is known to be approximately dose proportional for both $AUC_{0\text{-inf}}$ and $C_{max}$ after

single and multiple doses at the dose level used in the AVT04-GL-101. Consequently, assessing PK comparability in presence of a difference in the dose administered introduces a bias that is not a true reflection of the PK comparability, as per Applicant. These points are agreed with the applicant.

The applicant further argued that the protein concentration of the EU-Stelara batch KHS25MJ used in the PK trial was lower than expected. The protein concentration is considered one of the very highly critical quality attributes (obligatory CQA) in the overall analytical similarity assessment. However, all quality attributes (structural, functional, and post-translational modification) of the EU-Stelara batch KHS25MJ analysed as part of the analytical similarity assessment, were within the pre-specified acceptance criteria of other commercially available EU-Stelara batches tested, except the protein concentration. According to the Applicant, the protein content-corrected analysis was intended to address this deviation in protein concentration.

EMA Q & A on Biosimilars state that "*Representative batches of the biosimilar and innovator product should be used in the comparative PK study and it should be documented how the used batches have been selected. When pre-filled syringes, injection pens, etc. are being used, protein content of the batch, as well as delivered volume, should be considered in selection of the batches. The protein content of the selected biosimilar and reference product batches should be determined beforehand and analysed using the same analytical method.*" The same EMA document also states that that "*Alternative methods to ensure delivery of the same protein dose could be considered. For example, the same content of the biosimilar and reference product in prefilled syringes could be transferred into identical syringes, thus avoiding any dose correction due to the device or protein content. Such a solution requires further discussion on potential effects of the devices on the delivered doses, where needed, supported with additional data, e.g. looking for systematic differences in delivered volume, effects of needle size etc., to support that there is no difference in local delivery of the product.*"

Although there is not specific guidance on content correction for therapeutic proteins the above-mentioned 'EMA Clinical pharmacology and pharmacokinetics: Q&A, Biosimilars' emphasizes the importance of delivering the same protein content/dose with the RMP and the biosimilar candidate.

Given two critical factors: 1) the 6.6% difference in actual delivered protein content between EU-Stelara and AVT04, and 2) the understanding that within the steep segment of the linear dose-concentration curve, differences in the administered protein content directly influence plasma protein concentration, subsequently impacting PK parameters; it becomes pharmacologically plausible that the failure to meet the similarity acceptance criteria for $AUC_{0\text{-}inf}$ in the protein-unadjusted analysis was impacted by the difference in protein content.

In conclusion, the CHMP consider the protein-corrected analysis to be a relevant analysis for this application, given the differences in the delivered protein dose between the reference product and the biosimilar candidate applied in this clinical study. In this case, the adequacy of the analysis unadjusted for the protein content, which was prespecified as the primary analysis by the Applicant, is arguable due to the differences in protein content. In consequence, the validity of demonstrating PK equivalence when the conclusion relies on significantly different content administration to determine equivalent PK is likewise arguable.

Furthermore, and of importance for the consideration of the analysis corrected for protein content is, that additional data presented by the Applicant confirmed that the difference in protein concentration between AVT04 batch DP200011 and EU-Stelara batch KHS25MJ does not reflect a systematic difference between AVT04 and EU-Stelara.

The point estimate of the protein-content normalized (PCN) geometric mean ratio (AVT04/EU-Stelara) for $C_{max}$ was 102.8% (90% CI 95.5%, 110.7%), with no significant difference between AVT04 and EU-Stelara; and the point estimate of the PNC GMR (AVT04/EU-Stelara) for $AUC_{0\text{-}inf}$ was 109.8% (90% CI

101.5%, 118.8%). The $AUC_{0\text{-}inf}$ was still about 10% greater with AVT04 compared to EU-Stelara, even after the adjustment for protein content. It is questionable whether protein content is the (sole) factor contributing to the initially observed difference, or whether other factors may have contributed to the higher $AUC_{0\text{-}inf}$ observed with AVT04. Accordingly, a root-cause analysis was requested. The applicant performed a root-cause analysis on data already corrected for protein content and subject weight. Therefore, the root-cause analysis addresses only the residual higher $AUC_{0\text{-}inf}$ after the correction for protein content. The root-cause analysis included investigation of the impact of weight category and ADA/nAB status and titre on exposure ($AUC_{0\text{-}inf}$), concentration profiles and clearance.

The applicant's conclusions based on the conducted root-cause analysis are summarized as follows: A higher residual exposure of AVT04 compared to EU-Stelara (after correction for protein content) can be attributed to the impact of the presence of nAb in EU-Stelara administered patients >80kg, leading to significantly higher clearance resulting in lower exposure. Limited sample size and variability prevent further conclusions. AVT04 and EU-Stelara sample size in nAb positive patients >80kg is 3 and 5, respectively. In addition, the variability for EU-Stelara is notably higher. Comparison of individual PK profiles for these strata (nAb positive, >80kg) showed three patients with significantly lower concentrations in the EU-Stelara group. In addition to the (imbalanced) number of subjects impacting the overall comparison of exposure of AVT04 to EU-Stelara, various factors including subject characteristics and immunogenicity development hinder conclusive explanations. Thus, the Applicant therefore believes that differences in exposure stem from a small number of subjects and won't impact the overall PK similarity of AVT04 to EU-Stelara.

The applicant's conclusions on the patients >80kg is not followed. Since the number of nAb-positive subjects >80kg was very low (3 and 5 in the AVT04 and EU-Stelara group, respectively), results should be interpreted with caution and not be overinterpreted. Instead, their impact on the primary ANCOVA models is considered minor. The provided analyses (box plots) do not take into consideration the imbalances in the proportion of ADA-positive and nAb-positive subjects between AVT04 and EU-Stelara, which is considered a more plausible root-cause and explanation for the difference of the point estimates between AVT04 and EU-Stelara. Also, ADA/nAb-positivity can explain an increase in variability, thereby making confidence intervals wider. For the comparison of groups with unequal sizes, boxplots may give a misleading visual impression of the data distribution. The incidence of ADAs in the AVT04 group was lower compared to the EU-Stelara group (36.7% vs 59.6%). Within ADA-positive subjects, the proportion of subjects with nAbs was lower in the AVT04 group than in the EU-Stelara group (33.3% vs 42.4%).

ANCOVA analyses for the ADA positive/negative and nAb positive/negative subgroups showed the following: in ADA-negative and nAb-negative subjects, for both $C_{max}$ and $AUC_{0\text{-}inf}$ the 90% CI were clearly within the 80% -125% similarity margin, with and without correction for the protein content. In ADA-negative subjects, $C_{max}$ was 106.7% (90% CI 96.2%, 118.5%) and $AUC_{0\text{-}inf}$ was 108.1% (90% CI 98.0%, 119.3%) in the protein-unadjusted analysis; and $C_{max}$ was 100.7% (90% CI 90.5%, 112.0%) and $AUC_{0\text{-}inf}$ was 102.0 (90% CI 92.3%, 112.8%) in the protein-adjusted analysis. In ADA-positive subjects the upper bound of the 90% CI for $AUC_{0\text{-}inf}$ exceeded the biosimilarity range [117.2% (90% CI 103.8%, 132.4%)] in the analysis uncorrected for the protein content whereas in the analysis corrected for the protein content the 90% CI for $AUC_{0\text{-}inf}$ were contained within the biosimilarity margins (109.8% (90% CI 97.2%, 124%). In nAb-negative subjects, $C_{max}$ was 97.7% (90% CI 85.6%, 111.5%) and $AUC_{0\text{-}inf}$ was 101.6% (90% CI 89.9%, 114.9%) in the protein-unadjusted analysis; and $C_{max}$ was 92% (90% CI 80.7%, 105.0%) and $AUC_{0\text{-}inf}$ was 95.6% (90% CI 84.5%, 108.1%) in the protein-adjusted analysis. In the nAb positive subjects both the point estimates for $AUC_{0\text{-}inf}$ and their corresponding upper bounds of 90% CI were considerably outside the 80-125% margin for protein-unadjusted analysis (PE 145.8%) as well as protein-adjusted analysis (PE 135.4%).

If we consider that ADAs/nAbs introduce interference/noise, hampering similarity assessment, ADA-negative subjects may be viewed as a more sensitive population to detect PK differences between products that represent differences between the protein, and are not impaired by intercurring ADA events. However, 'ADA-negative subjects' is not a group of subjects that can be determined at baseline. Anti-drug antibodies formation depends on the interplay between several factors, which can be subject-related (e.g. genetic background or co-treatment) or drug-related (e.g. mAb target, antibody origin, post-translational modifications) or impurities etc. Pertaining to the latter, no relevant differences between proteins were observed at the quality level. As regards the subject-related factor, a possible imbalance in the likelihood of developing ADAs at baseline cannot be assessed.

This said, imbalances in the number of ADA/nAb positive/negative subjects, as well as the higher clearance of EU-Stelara promoted by the increased formation of ADAs/nAbs and, consequently, lower exposure with EU-Stelara are considered to have contributed to differences observed between products in the PK. In ADA negative subjects however, equivalent PK is observed, and this analysis is considered of interest.

As in the protein-corrected analysis also the analysis of ADA-negative subgroups is post-hoc and these analyses are subject to a multiple testing issue and increased type-I error.

Longer half-life was observed with AVT04 compared to EU-Stelara (geometric mean $t_{1/2}$ were 477.9h and 438.2h in the AVT04 and EU-Stelara group, respectively). The terminal elimination rate constant ($K_{el}$) was higher with EU-Stelara (0.0385/day) compared to AVT04 (0.0348/day). Also the apparent clearance (CL/F) was higher with EU-Stelara (0.3583 L/day) compared to AVT04 (0.3076 L/day). Lower terminal elimination rate constant, lower clearance and longer terminal half-life observed with AVT04 suggest differences in the elimination between AVT04 and EU-Stelara. This is corroborated by several partial AUCs that indicated differences in elimination, while there was good alignment in absorption.

The applicant was asked to provide partial AUC analyses with several varying time points. This is also relevant for the extrapolation of results with subcutaneous administration to intravenous administration, which is planned to be applied for as a line extension.

As mentioned before, $AUC_{0\text{-}inf}$ was higher with AVT04 compared to EU-Stelara both in the protein-unadjusted analysis [116.9% (90% CI 108.1%, 126.4%) and in the protein-adjusted analysis [109.8% (90% CI 101.5%, 118.8%)]. The applicant was requested to discuss an observed higher exposure (in terms of $AUC_{0\text{-}inf}$) with respect to the clinical relevance thereof.

The applicant argued that the available efficacy data, including newly submitted data until the end of the study, did not show any significant difference when the test product was compared with the reference product. For example, results of the primary analysis were well within a rather small range (point estimate 0.4%, 95%CI -2.63%, 3.50% (PP); point estimate 0.4%, 95% CI -2.66%, 3.34% (ITT)] that is considered to exclude a clinically relevant difference. This is reassuring as differences in AUC would be expected to translate primarily into efficacy. Overall, the available evidence consistently shows that there is a plateau in the relationship between the ustekinumab serum concentration and efficacy across a broad range of concentrations. Therefore, it is not expected that about 17% higher exposure to ustekinumab would result in a clinically relevant impact on the efficacy of ustekinumab.

The applicant also showed that available safety data, now from more than 360 subjects exposed to the test product, did not indicate any differences between the test and the reference product. The applicant supported this statement by other references where different ustekinumab products were tested, showing that serum concentrations of ustekinumab were not associated with infections, serious infections, or serious adverse events. This can be reassuring, as data seem to be consistent in this regard. Further to this note, $C_{max}$ was well within the equivalence range which can further alleviate the

concern, as $C_{max}$ is usually connected with safety issues. It must be however said that these safety datasets have their limitations and cannot provide conclusive data for adverse events of uncommon, rare or very rare frequencies. This is on one side acknowledged as registrational trials by design are almost never capable to characterize rare events, but on the other side, it leaves some space for uncertainty.

To conclude, available data do not indicate any clinically significant differences, taking into account their inherent limitations with regards to safety.

*Subgroup analyses*

Systemic exposure to ustekinumab was body weight dependent, with geometric mean Cmax, AUC0-t, and AUC0-inf values being notably lower in the non-Japanese >80 kg subgroup compared with the non-Japanese ≤80 kg subgroup. This trend was consistently observed in all 3 treatment groups and is known from previous studies with Stelara.

In non-Japanese subjects ≤80kg, for the comparison (AVT04/EU-Stelara), point estimates for GMRs for $C_{max}$, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ together with corresponding 90% CIs were contained within the pre-specified margins of 80% to 125%, although $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were slightly higher with AVT04, which is in accordance with results observed for the overall study population.

Contrary to that, in non-Japanese subjects with BW >80 kg, the point estimates for GMRs for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were outside the pre-specified margins; i.e. for $AUC_{0\text{-}inf}$ the GMR was 135.8% (90% CI 111.1%, 161.3%) and for $AUC_{0\text{-}t}$ the GMR was 133.3% (90% CI 110.1%, 161.3%). After correction for protein content, the point estimate for GMR for AUC0-inf was 127.9% (90% CI 104.7%, 156. 2%) and point estimate for GMR for AUC0-last was 125.6% (90% CI 103.8%, 151.9%). It should be noted that the number of subjects in each arm was too small (18, 19 and 17 in the AVT04, EU-Stelara and US-Stelara arm, respectively) to draw robust conclusions and a chance finding cannot be excluded, however a trend toward substantially higher exposure with AVT04 in these subjects was apparent. The applicant ascribed the observed difference between treatments to an impact of the presence of nAb on EU Stelara, increasing the clearance and resulting in lower exposure values. The root-cause analysis based on which these conclusions were made did not take into consideration the imbalances in the proportion of ADA-positive and nAb-positive subjects between AVT04 and EU-Stelara. The substantially higher exposure with AVT04 compared to EU-Stelara in subjects with BW >80 kg was most likely dominated by an effect of ADA+/nAb+, and the small size of this subgroup and should not be overinterpreted.

More subjects developed ADAs in the EU-Stelara group than in the AVT04 group (59.6% versus 36.8%). In ADA-positive subjects, the geometric means of the systemic exposure PK parameters $C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were consistently lower compared with those in ADA-negative subgroup, and consistent with the lower exposure was the shorter half-life.

**PK in target population (Study AVT04-GL-301)**

*(Details on study design and conduct are described in discussion on clinical efficacy)*

**Pharmacokinetic results**

One of the secondary objectives in patients with Plaque-type Psoriasis (PsO) was comparison of steady-state pharmacokinetics between AVT04 and EU-Stelara. For this purpose, $C_{trough}$ levels were measured at baseline, Week 4, Weeks 16, 28, 40 and 52. For PK assessment in PsO patients, no equivalence range has been pre-defined, and results are summarized descriptively.

Overall, mean serum trough PK concentration increased from Baseline to Week 4 and then decreased at Week 16 for both treatment groups. At Week 4, geom. mean $C_{trough}$ was approximately 17% higher

with AVT04 compared to EU-Stelara and at Week 16 geom. mean $C_{trough}$ was approximately 13% higher with AVT04 compared to EU-Stelara.

At Week 16, patients initially randomized to EU-Stelara arm were re-randomized in 1:1 ratio to either continue treatment with EU-Stelara or switch to AVT04. Therefore, starting from Week 16, data is presented for 3 arms (AVT04/AVT04, EU-Stelara/AVT04, EU-Stelara/EU-Stelara). At Week 28, treatment was no longer administered to non-responders (details of study design are described in section 2.6.5). The applicant clarified that no patient was excluded from the presentation of PK data from Week 28 onwards due to being a non-responder.

In the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups, mean serum trough PK concentration increased from Baseline to Week 16 for all treatment groups, had then decreased at Week 28, and had increased again at Week 40 and at Week 52 (EoS), reaching values similar to those observed at Week 16. The PK profile was generally comparable in all 3 treatment groups. Similar results were observed for patients with body weight ≤100 kg. Higher $C_{trough}$ with AVT04 compared to EU-Stelara observed at Weeks 4 and 16 were no longer apparent at later stage of the study. At Week 52 $C_{trough}$ in the AVT04/AVT04 arm was slightly lower than in the EU-Stelara/EU-Stelara arm (253.88 ng/mL and 280.23 ng/mL, respectively).

Two different batches of EU-Stelara were used in AVT04-GL-301 (KHS25MJ and LBS1ZMC). The former batch was the same batch as used in the PK study, with approximately 10% lower protein concentration than AVT04 batch (82.3 mg/mL vs. 91.0 mg/mL, respectively). The other EU-Stelara batch (LBS1ZMC) had a protein concentration of 90.0 mg/mL. For the presentation of $C_{trough}$ in AVT04-GL-301, data of both EU-Stelara batches were pooled together. The applicant clarified that all patients receiving EU-Stelara at Day 1 and Week 4 were administered batch KHS25MJ (82.3 mg/mL); the $C_{trough}$ values up to Week 16 (including Week12, timing of the primary analysis) reflect the plasma concentrations obtained from administration of batch KHS25MJ. The exclusive use of the same batches as in study AVT04-GL101 at the two first study drug administrations in study AVT04-GL-301 lead to similar slight differences in exposure as measured by the $C_{trough}$ concentrations at Week 4 and Week 16. Thereafter, all patients receiving EU-Stelara were administered batch LBS1ZMC (90.0 mg/m); the $C_{trough}$ values from Week 28 reflect the plasma concentrations obtained from administration of batch LBS1ZMC. Higher $C_{trough}$ with AVT04 compared to EU-Stelara observed at Weeks 4 and 16 were no longer apparent at later stage of the study, which can be explained by the use of different batches. The applicant also clarified that $C_{trough}$ values were not corrected for protein content. No additional PK parameters (e.g. $C_{max}$, $T_{max}$, volume of distribution, $t_{1/2}$ or partial AUCs) were defined that could support the claim of similar pharmacokinetics compared with the reference product also in the multiple dosing setting in patients, although this was recommended by the CHMP in a scientific advice.

As regards immunogenicity, up to Week 16, 49 patients (25.4%) in the AVT04 group and 184 patients (48.2%) in the EU-Stelara group developed ADAs. Of these, 13 patients (26.5%) in the AVT04 group and 57 patients (31.0%) in the EU-Stelara group had nAbs. Up to Week 16, $C_{trough}$ levels in ADA negative patients were similar between treatments. In ADA positive patients $C_{trough}$ values were slightly higher in the AVT04 group.

The frequency of ADAs decreased over time, from 49 patients (25.7%) at Week 16 to 39 patients (21.2%) at Week 52 in the AVT04/AVT04 group; from 101 patients (54.9%) at Week 16 to 56 patients (31.5%) in the EU-Stelara/AVT04 group; and from 77 patients (41.8%) at Week 16 to 48 patients (26.7%) in the EU-Stelara/EU-Stelara group. The frequency of nAb slightly increased over time in the AVT04/AVT04 group (13 patients [26.5%] at Week 16 and 13 patients [33.3%] at Week 52), decreased over time in the EU-Stelara/AVT04 group (36 patients [35.6%] at Week 16 and 10 patients [17.9%] at Week 52; and remained stable in the EU-Stelara/EU-Stelara group (19 patients [24.7%] at Week 16 and 11 patients [22.9%] at Week 52). In ADA negative patients, $C_{trough}$ values were overall

comparable between AVT04/AVT04 and EU-Stelara/EU-Stelara groups from Week 16 to Week 52 as measured by mean $C_{trough}$, while median $C_{trough}$ values were slightly higher in the EU-Stelara/EU-Stelara group. Similar was observed in ADA-negative subjects.

## 2.6.4. Conclusions on clinical pharmacology

The PK study did not show comparability between AVT04 and EU-Stelara in the analysis uncorrected for protein content, that was the predefined primary analysis, as the 90% CI for the geometric mean ratio for the co-primary endpoint $AUC_{0\text{-}inf}$ exceeded the upper limit of the biosimilarity acceptance range. Due to differences between EU-Stelara and AVT04 in delivered protein content, the applicant performed an analysis using PK parameters adjusted for the protein content. After protein content normalization, biosimilarity criteria were met for both co-primary endpoints ($C_{max}$ and $AUC_{0\text{-}inf}$).

While correction for protein content is considered meaningful due to differences in the delivered protein dose, this analysis was pre-specified in a general manner and was foreseen as a sensitivity analysis only. Nonetheless, the adequacy of the analysis unadjusted for the protein content, which was prespecified as the primary analysis by the Applicant, is also arguable due to the differences in protein content delivered in the two study arms. The validity of demonstrating PK equivalence when the conclusion relies on notable different content administration to determine equivalent PK is also arguable. Therefore, while PK similarity has not been demonstrated in this analysis, the different protein content is considered a relevant aspect to consider.

Importantly with this respect is that additional data presented by the Applicant confirmed that the difference in protein concentration between AVT04 batch DP200011 and EU-Stelara batch KHS25MJ does not reflect a systematic difference between AVT04 and EU-Stelara, which is reassuring.

After the adjustment for protein content, the $AUC_{0\text{-}inf}$ of AVT04 was still about 10% larger compared to EU-Stelara, while meeting the 80-125% criterion. This residual higher exposure appears likely caused by the lower immunogenicity of AVT04 compared to EU-Stelara, which also impacts the drug clearance. This is corroborated by lower terminal elimination rate constant, lower clearance and longer terminal half-life observed with AVT04. In principle, it is acceptable for the biosimilar candidate to be less immunogenic than the reference product, provided that this did not modify the efficacy of the product or increase the incidence or severity of adverse reactions, which has been demonstrated for AVT04 (see Clinical efficacy and safety sections).The ADA/nAb negative populations are of interest to investigate similarity of the proteins, when unimpacted by intercurrent ADA/nAb events. In these analyses equivalent exposure of AVT-04 and EU-Stelara is observed. While the protein-corrected analysis as well as the analysis of ADA-negative subgroups are prone to multiple testing, both analyses are considered relevant, and both separately show similarity in PK. When combined, the protein corrected analysis in ADA negative subjects clearly show equivalent exposure, despite the reduced sample size.

## 2.6.5. Clinical efficacy

The clinical development programme to compare clinical efficacy, safety and immunogenicity between AVT04 and EU-Stelara comprised a single randomized, double-blind, phase III study (AVT04-GL-301). The study was designed to assess equivalence of AVT04 to Stelara in patients with moderate to severe plaque-type psoriasis (PsO).

**Table 3.** Description of the Study AVT04-GL- 301

| Study Number | AVT04 DP Batch Number | Main study objective | Study Design Study start/ | Test product Dosage, regimen Route of | Number of subjects treated | Healthy subjects or diagnosis | Duration of Treatment | Primary and main secondary endpoints |
|---|---|---|---|---|---|---|---|---|
| AVT04-GL- 301 | DP200011 | Therapeutic equivalence of AVT04 to EU-Stelara | Multicenter, randomized, double-blind, parallel, 2-arm, 2 stage, active control | <u>Stage 1</u><br>AVT04<br>EU-Stelara<br>45 mg s.c. (b.w.≤100 kg) or 90 mg s.c. (b.w.>100 kg) at Day 1 and after 4 weeks<br><br><u>Stage 2</u><br>AVT04/AVT04,<br>EU-Stelara/ AVT04,<br>EU- Stelara/ EU- Stelara<br>45 mg s.c. (b.w.≤100 kg) or 90 mg s.c. (b.w.>100 kg) at Weeks 16, 28, and 40 | <u>Stage 1:</u><br>Total: 581<br>AVT04: 194<br>EU-Stelara: 387<br><br><u>Stage 2:</u><br>Total : 574<br>AVT04/ AVT04: 193<br>EU-Stelara/ AVT04: 192<br>EU-Stelara/ EU-Stelara: 189 | Patients with chronic moderate-to-severe PsO | <u>Repeat dose</u><br><br><u>Stage 1</u><br>Day 1-Week 15*<br><br><u>Stage 2</u><br>Week 16-52 | <u>Primary efficacy endpoint</u>:<br>% improvement in PASI from BL to Week 12<br><br><u>Secondary endpoints</u><br>Efficacy:<br>• Percent improvement in PASI from BL to Week 4, 8, 16, 28, 40 (EoT), and 52 (EoS).<br>• N (%) of patients achieving response rates of PASI 50, 75, 90, and 100 at Weeks 4, 8, 12, 16, 28, 40, and 52 were presented by treatment<br>• Area under the effect curve (AUEC) for PASI from Baseline through Week 12<br>• N (%) of patients |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | achieving sPGA responses of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16, 28, 40, and 52<br>• Change in DLQI at Weeks 12, 28, 40, and 52<br>• Change in %BSA affected by chronic PsO at Weeks 4, 8, 12, 16, 28, 40, and 52<br>• General safety assessments,<br>• immunogenicity (ADA, nAb)<br>• PK: Ctrough values |

### *2.6.5.1.* Dose-response studies

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

### *2.6.5.2.* Main study(ies)

***Study AVT04-GL-301***

***Methods***

Study AVT04-GL-301 was a randomized, double-blind, multicentre, active control clinical study to compare the efficacy, safety, and immunogenicity of AVT04 versus EU-Stelara in patients with moderate to severe chronic plaque-type psoriasis (PsO).

The active period of Study AVT04-GL-301 comprised 2 stages:

- Stage 1: Primary Efficacy Assessment (Day 1 to Week 15)
- Stage 2: Long-Term Efficacy and Safety Assessment (Week 16 to 52)

**Stage 1**

On Day 1, eligible patients were randomly assigned into Groups 1 and 2, in a 1:2 ratio (AVT04:EU-Stelara). Patient randomization was stratified by presence or absence of previous biologic treatment for PsO and body weight category (≤80kg, >80 kg to ≤100 kg, >100 kg).

- Group 1: Patients received an initial dose of AVT04 45 mg (≤100 kg) or 90 mg (>100 kg) administered SC, followed by 45 mg or 90 mg 4 weeks later.
- Group 2: Patients received an initial loading dose of EU-Stelara 45 (≤100kg) or 90 mg (>100 kg) administered SC, followed by 45 mg or 90 mg 4 weeks later.

**Stage 2**

At Week 16:

Patients who were initially randomized in Group 1 (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 in Group 2 (EU-Stelara) were re-randomized into Groups 2A and 2B, in a 1:1 ratio:

- Group 2A: Patients started receiving AVT04 45 mg or 90 mg SC every 12 weeks, at Weeks 16, 28, and 40 (unless withdrawn from the study).
- Group 2B: Patients continued to receive EU-Stelara 45 mg or 90 mg SC every 12 weeks, at Weeks 16, 28, and 40 (unless withdrawn from the study).

At Week 28:

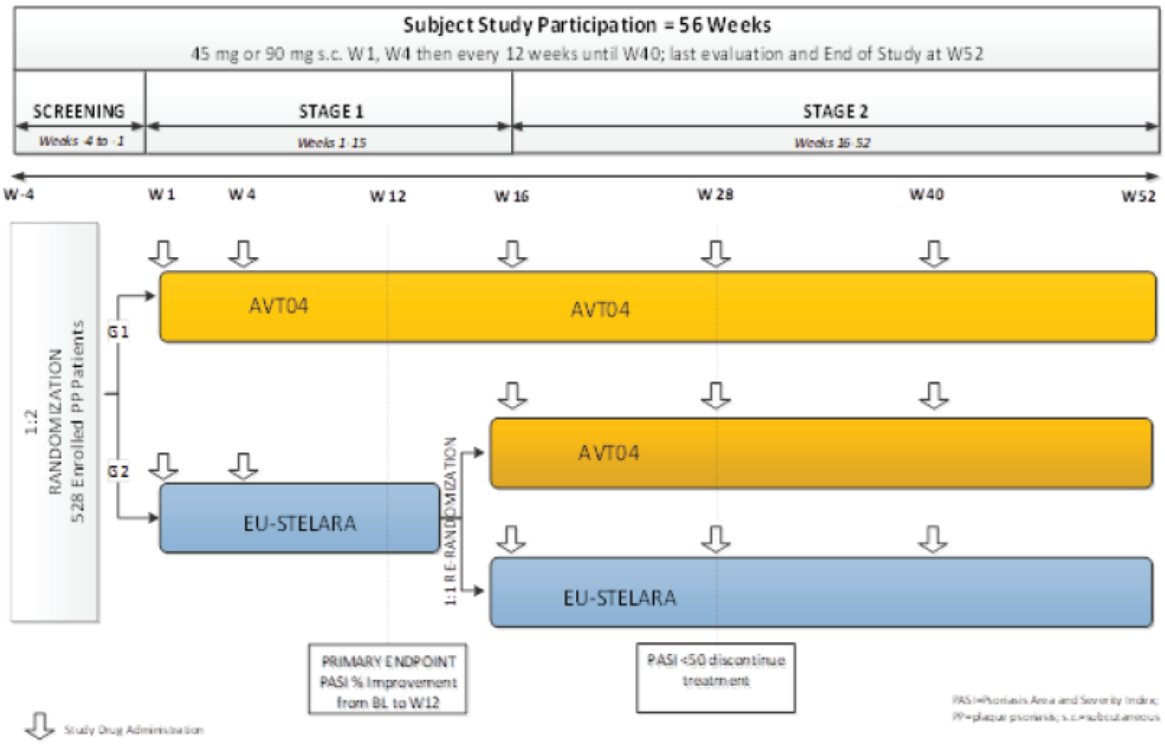
- **Nonresponsive patients** (PASI improvement <50% compared to Baseline) were not administered treatment at Week 28. For these patients, the end-of-treatment (EoT) electronic case report forms (eCRFs) were completed. These patients could decide to withdraw from the study and complete the end-of-study (EoS) assessments; however, they were encouraged to continue the study for safety and immunogenicity (anti-drug antibodies [ADAs]) assessments through Week 52, per the Schedule of Assessments (SoA)
- Responsive patients (PASI improvement ≥50% compared to Baseline) continued in the study.

At Week 40 (EoT): All patients who are on treatment at Week 40 will receive the final study drug administration.

At Week 52 (EoS): All responders still on study at Week 52 will undergo final efficacy and safety assessments. All non-responders still on study will undergo safety and immunogenicity (formation of ADAs) assessments.

This primary clinical study report (CSR1) includes data through Week. A final CSR (CSR2) will include data collected through Week 52.

**Figure 9.1: Study Schematic**




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.

***Study Participants***

**Main inclusion criteria**

1. Patient signed the ICF, and documentation as required by relevant competent authorities and was able to understand and adhere to the visit schedule and study requirements.

2. Patient was male or female, aged 18 to 75 years old, inclusive, at time of Screening.

3. Patient had moderate to severe chronic PsO for at least 6 months.

4. Patient had involved BSA ≥10%, PASI ≥12, and static Physician's Global Assessment (sPGA)≥3 (moderate) at screening and at Baseline.

5. Patient had stable psoriatic disease for at least 2 months (ie, without significant changes as defined by the investigator or designee) prior to Screening.

6. Patient was a candidate for systemic therapy because the patient had 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).

8. Patient was naïve to ustekinumab therapy, approved or investigational.

**Main exclusion criteria**

1. Patient diagnosed with psoriatic arthritis, erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, other skin conditions (eg, eczema), or other systemic autoimmune disorder inflammatory disease at the time of the Screening Visit that would have interfered with evaluations of the effect of the study drug on psoriasis.

2. Patient had prior use of any of the following medications within specified time periods or would have required use during the study:

a. Topical medications within 2 weeks of Baseline Visit (except low- to mid-potency topical corticosteroids on face, eyes, scalp, palms, soles, and genital area only).

b. PUVA phototherapy and/or UVB phototherapy within 4 weeks prior to the Baseline Visit.

c. Nonbiologic psoriasis systemic therapies (eg, cyclosporine, methotrexate, and acitretin) within 4 weeks prior to the Baseline Visit.

d. Any systemic steroid in the 4 weeks prior to the Baseline Visit.

e. Investigational agent(s) within 90 days or 5 half-lives (whichever was longer) before BL Visit.

f. Other systemic biologics within 90 days or 5 half-lives (whichever was longer) before BL Visit.

g. Any therapeutic agent targeting IL-12, IL-17, or IL-23 at any time (eg, secukinumab, briakinumab, guselkumab, ixekizumab, and brodalumab).

Specified washout periods for approved/marketed products were as follows:

| Medication or Therapy | Washout before Baseline |
|---|---|
| Biologic therapies, including but limited to:<br>Adalimumab<br>Etanercept<br>Infliximab<br>Certolizumab pegol<br>Alefacept | <br>12 weeks<br>8 weeks<br>12 weeks<br>24 weeks<br>24 weeks |
| Any kinase inhibitor for any reason (eg, tofacitinib citrate) | 1 day |
| Any phosphodiesterase type 4 inhibitor (eg, apremilast [Otezla]) | 4 weeks |
| Cyclosporine | 4 weeks |
| Methotrexate | 4 weeks |
| PUVA-UVA/UVB phototherapy and laser therapy | 4 weeks |
| Topical psoriasis treatments (examples include vitamin D analogs, topical steroids, polifenols, etc) (except low- to mid-potency topical corticosteroids on face, eyes, scalp, palms, soles, and genital area only) | 2 weeks |
| Oral retinoids | 4 weeks |
| Corticosteroids IM – IV – oral – intra-articular | 4 weeks |
| Drugs that may cause new onset or exacerbation of psoriasis (including, but not limited to, beta blockers, lithium, and antimalarials) | 6 months[1] |

Abbreviations: IM = intramuscular; IV = intravenous; PUVA = psoralen plus ultraviolet light A; UVA = ultraviolet light A; UVB = ultraviolet light B.
[1] Unless the patient has been on a stable dose for at least 6 months prior to Baseline Visit without exacerbation of psoriasis.

3. Patient had received live or attenuated vaccines during the 4 weeks prior to Baseline Visit or had the intention of receiving a live or attenuated vaccine at any time during the study.

Note: Inactivated (non-live and non-attenuated) vaccines were allowed.

4. Patient had an active infection or history of infections, including SARS-CoV-2 (details are provided in the CSR).

5. Patient had a history of hypersensitivity to the active substance or to any of the excipients of EU-Stelara or AVT04.

There were no restrictions regarding upper and lower BW in the eligibility criteria.

***Treatments***

Patients with body weight ≤100 kg received a dose of 45mg ustekinumab SC (AVT04 or Stelara), while patients with body weight > 100 kg received a dose of 90 mg (2x45mg) ustekinumab SC (AVT04 or Stelara) based on the weight measured at baseline. Initial loading doses were administered at Weeks 1 and 4, followed by same dose once every 12 weeks (Weeks 16, 28 and 40).

The SC injection was administered in the abdomen (preferred site) or thigh (secondary site). Patients who required 2 injections of 45 mg, each of which were to be given to different body areas. Route of administration, dosing and schedule are in line with the posology of Stelara for the treatment of PsO in subjects with BW≥60 kg (see Stelara SmPC).

Allowed and prohibited medications

The following concomitant medications were permitted:

- Low- to mid-potency (American Dermatology Association class 6 to 7) topical corticosteroids on face, eyes, scalp, palms, soles, and genitalia except within 24 hours prior to PASI assessment at Screening and study visits.
- Mild/bland moisturizers/lubricants at any time except within 24 hours prior to PASI assessment at Screening and study visits.
- Single type of nonsteroidal anti-inflammatory drug (NSAID) use was permitted in this study; however, the dose should not have exceeded the maximum dose recommended for that NSAID. Other painkillers were permitted.
- Insulin and hormone replacement therapy.
- Topical antibiotics for facial acne.
- All medications required to adequately treat AEs or concomitant medical conditions were at the discretion of the investigator, unless on the prohibited medication list.

The following concomitant medications were prohibited during the study:

- All biologics either for PsO or indications other than PsO (including, but not limited to, adalimumab, etanercept, secukinumab, infliximab, certolizumab pegol, alefacept, briakinumab, guselkumab, ixekizumab, and brodalumab).
- Any kinase inhibitor for any reason (eg, tofacitinib citrate).
- Any phosphodiesterase type 4 inhibitor (eg, apremilast [Otezla]).
- Systemic psoriasis treatments such as oral retinoids, methotrexate, cyclosporine, vitamin A or D analog preparations, dithranol, PUVA-UVA, UVB phototherapy, and laser therapy.
- Systemic corticosteroids.
- American Dermatology Association class 1 to 5 topical corticosteroids.
- Drugs that could cause new onset or exacerbation of psoriasis (including, but not limited to, beta blockers, lithium, and antimalarials) during the study unless the patient was on a stable dose for at least 6 months prior to Baseline Visit without exacerbation of psoriasis.
- Live or attenuated vaccines during the study and for 3 months after the final dose of study drug.

***Objectives***

Primary Study Objective

The primary objective of this study was to evaluate the therapeutic equivalence of AVT04 compared to EU- Stelara (EU-Stelara) in the treatment of moderate to severe chronic PsO.

If the 95% CI for the adjusted mean difference in percentage PASI improvement between test and reference groups is contained within the range [-15%, 15%] then clinical similarity will be established.

Secondary Study Objectives

- To compare the safety, tolerability, and immunogenicity of AVT04 and EU-Stelara in the treatment of moderate to severe chronic PsO
- To compare steady-state PK of AVT04 and EU-Stelara
- To compare efficacy of AVT04 and EU-Stelara in patients with moderate to severe chronic PsO

For hypotheses testing, please refer to the Statistical methods section.

***Outcomes/endpoints***

**Primary efficacy endpoint:**

- Percent improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12

The PASI were assessed by the scoring of PsO lesions on a scale of 0 to 4 for 3 characteristics: erythema, infiltration, and desquamation, weighted by the area of involvement. The lesions were scored within 4 anatomical regions: head, upper extremities, trunk, and lower extremities including buttocks. Within each of these regions, the area of involvement was scored on a scale of 0 to 6.

**Secondary efficacy endpoints**

- 50% improvement in PASI (PASI50), 75% improvement in PASI (PASI75), 90% improvement in PASI (PASI90), and 100% improvement in PASI (PASI100) response rates at Weeks 4, 8, 12, 16, 28, 40 (EoT), and 52 (EoS)
- Percent improvement in PASI from Baseline to Week 4, 8, 16, 28, 40 (EoT), and 52 (EoS)
- Area under the effect curve for PASI from BL through Week 12.
- Proportion of patients achieving static Physician's Global Assessment (sPGA) responses of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16, 28, 40 (EoT), and 52 (EoS).
- Change in Dermatology Life Quality Index (DLQI) scores from BL to Weeks 12, 28, 40 (EoT), and 52 (EoS).
- Change in percentage body surface area (%BSA) affected by chronic PsO from BL to Weeks 4, 8, 12, 16, 28, 40 (EoT), and 52 (EoS)

Static Physician's Global Assessment

The sPGA of PsO was assessed on a scale of 0 to 5, with 0 indicating no psoriasis (clear of disease), 1 (almost clear), and 2 or higher scores indicating more severe disease.

Dermatology Life Quality Index

The DLQI is a 10-question validated questionnaire. It was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Body Surface Area Affected by Psoriasis

The %BSA affected by chronic PsO was estimated by assuming that the patient's hand, including the palm, fingers, and thumb, represented roughly 1% of the body's surface. The total %BSA was estimated as the number of hands necessary to cover the total affected area. Because of interobserver variability in estimated BSA, whenever possible, all assessments for a given patient were made by the same observer.

Secondary endpoints are considered relevant for the overall assessment of comparability in efficacy.

**PK assessments**

- Serum trough concentrations at steady-state

Blood samples for the PK assessment were collected at baseline, Week 4, Weeks 16, 28, 40 and 52.

For the PK assessments please refer to the section 2.6.2, subsection Pharmacokinetics in target population.

**Immunogenicity Assessments**

- Proportion of patients with anti-ustekinumab antibody and neutralizing anti-body

Blood samples for immunogenicity assessment were taken at baseline, Week 4, Weeks 12, 16, 28, 40 and 52.

**Safety assessments**

- Frequency, type, and severity of treatment-emergent adverse events (TEAEs) including adverse drug reactions (ADRs)
- Frequency and severity of ISRs
- Routine safety parameters, including laboratory safety, vital sign measurements, 12-lead electrocardiogram (ECG) results, chest X-ray, and physical examination findings

***Sample size***

A meta-analysis of the PHOENIX 1 and PHOENIX 2 studies revealed a difference in mean PASI percent improvement from Baseline to Week 12 with ustekinumab (EU-Stelara) (45 mg) versus placebo of 70.7% (SE = 0.82%) with a 95% CI of 69.1% to 72.3%. Using the lower bound of the CI as a conservative estimate of the treatment effect, a 10% margin for equivalence retains 85.5% of the original ustekinumab effect, while a 15% margin is expected to retain 78.3% of the original ustekinumab effect.

Assuming a true difference in mean percent PASI improvement with test versus reference treatment of 2.5%, a conservative estimate of standard deviation (SD; 27.04% observed in PHOENIX 1) and an expectation of 5% operational withdrawal rate through to Week 12, a sample size of 528 (including approximately 66 patients with body weight >100 kg) in a 1:2 randomization would give 89.9% power in an one-sided 5% level test with equivalence margins at ±10% (for application at the FDA). The number of patients with body weight >100 kg (ie, approximately 66 patients) was based on statistical simulation following a consistency check approach. Under the same conditions, a sample size of 462 patients (excluding approximately 66 patients with weight >100 kg) in a 1:2 randomization would give 99.5% power in a one-sided 2.5% level test with equivalence margins at ±15% (for an MAA at EMA).

***Randomisation and blinding (masking)***

Eligible patients were assigned to study drug in accordance with the randomization schedule generated using permuted block randomization by an independent statistician.

Patients were randomly assigned in a 1:2 ratio to receive 1 of the following treatments during Stage 1:

- Group 1: patients were assigned to receive AVT04 45 mg or 90 mg on Day 1 and at Week 4.
- Group 2: patients were assigned to receive EU-Stelara 45 mg or 90 mg on Day 1 and at Week 4.

On Day 1, patient randomization was stratified by presence or absence of previous biologic treatment for PsO, and by body weight category (≤80 kg, >80 kg to ≤100 kg, >100 kg).

In Stage 2, patients who were taking EU-Stelara in Stage 1 (Group 2) were re-randomized to switch to either AVT04 at Week 16 (Group 2A) or continued taking EU-Stelara at Week 16 and following visits (Group 2B).

Blinding of the double-blind study was achieved by the following measures:

- EU-Stelara and AVT04 prefilled syringes were masked using a yellow semi-opaque blinding label applied to the syringe barrel, which concealed the syringe content and plunger stoppers during the storage, handling, and drug administration.

- Patients and investigators remained unaware of the treatment allocation until study completion.
- A patient's treatment assignment was only unblinded when knowledge of the treatment was essential for the further management of the patient in this study.
- Any intentional or unintentional breaking of the blind was reported immediately to the Sponsor.

The descriptions regarding planning and conduct of randomisation were considered reasonable. An additional body weight (>100kg) category was introduced in the stratification factor "weight" in protocol 3.0 after study initiation.

Dedicated blinded and unblinded teams were implemented within the Sponsor and CRO before the Week 28 Data Unblinding. An independent unblinded team was assigned for the primary statistical analysis. After the Week 28 Data Unblinding, only this team was planned to become aware of the patient treatment allocation. Further details, including details of the assigned Sponsor and CRO blinded and unblinded teams, were planned to be provided in the study's Blinded-Unblinded Plan.

**Statistical methods**

Analysis sets

A subset with patients whose body weight is ≤100 kg was used in the analyses for submission to EMA. This applied for all analysis of efficacy, safety, and immunogenicity.

*Enrolled Set:* The Enrolled Set includes all patients who have given informed consent to participate in the study.

*Randomized Set:* The Randomized Set includes all patients who were allocated a randomization number.

*Intention-to-Treat Set:* The Intention-to-Treat (ITT) Set, consistent with intention-to-treat principles, is defined as all randomized patients who received at least one dose of randomly allocated treatment.

*Per Protocol Set:* The Per Protocol (PP) Analysis Set is a subset of the ITT Set, which includes patients who have completed the study period up to Week 12 without protocol deviations that impact the efficacy assessment. Protocol deviations considered to have a serious impact on the efficacy and/or safety results will lead to the relevant patients(s) being excluded from the PP Set. Protocol deviations leading to exclusion from an analysis set will be decided at a blinded data review prior to database freeze upon completion of Week 28 visit by the last patient and database lock at the EoS.

*Safety Analysis Set:* The Safety Analysis Set (SAS) includes all randomized patients who received at least 1 dose of randomly allocated treatment, with treatment assignment based on actual treatment received.

*Definition of Study Period Based Analysis Set*: Different analysis sets were defined and documented for each specific analysis period.

For ITT Set, the following analysis sets were defined:

- Up to Week 16 (including all randomized patients who received at least 1 dose of study treatment)
- Up to Week 28 (including all re-randomized patients who received a dose at Week 16)
- Up to End of Study (including all responders who received a dose at Week 28)

For Safety Analysis Set, the following analysis sets were defined:

- Up to Week 16 (including all randomized patients who received at least 1 dose of study treatment)
- Up to Week 28 (including all re-randomized patients who received a dose at Week 16)
- Up to End of Study (including all responders who received a dose at Week 28)

Primary efficacy analysis

The primary analysis was to be based on the PP population. The primary endpoint was the percent improvement in PASI from Baseline to Week 12.

Similarity was to be assessed based on the following set of hypothesis:

$H01$: $\bar{x}AVT04 - \bar{x}EU{-}Stelara \leq -15\%$ or $H02$: $\bar{x}AVT04 - \bar{x}EU{-}Stelara \geq 15\%$ vs.

$H11$: $\bar{x}AVT04 - \bar{x}EU{-}Stelara > -15\%$ and $H12$: $\bar{x}AVT04 - \bar{x}EU{-}Stelara < 15\%$

where $\bar{x}$ is the sample mean and $\bar{x}AVT04$ and $\bar{x}EU{-}Stelara$ represent the mean percent improvement in PASI from baseline to Week 12 in AVT04 and EU-Stelara groups, respectively.

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model. The ANCOVA model included percent improvement in PASI as the response variable, randomized treatment group, and baseline stratification variables of previous biologic treatment for PsO (yes/no) as factors. Baseline PASI score and body weight were also included as continuous covariates. Estimates for the adjusted mean difference between treatment arms at Week 12 were obtained from the model and the 2-sided 95% CI for the adjusted mean difference was provided to address equivalence.

To test the robustness of the primary analysis, the equivalence tests on the primary endpoint was also performed using the ITT Set – Up to Week 16 as sensitivity analysis. The impact of missing data on the primary endpoint was to be explored where appropriate.

Subgroup analysis for primary efficacy comparison

The homogeneity of treatment effect across stratification factors (body weight [≤80 kg, >80 kg to ≤100 kg, >100 kg, (as well as body weight ≤100 kg and overall)] and previous biologic treatment for PsO [yes/no]) was to be investigated. The 95% CIs for the treatment difference in PASI percent change from baseline to Week 12 was to be calculated overall and separately for the defined subgroups using an ANCOVA model adjusted only for baseline PASI score. Data will be presented in a forest plot to provide visual evidence for homogeneity.

In addition, the following subgroups will also be presented:

- Age Group (< 65 years, ≥ 65 years)
- Gender (Male, Female)
- ADA status up to Week 12 (Positive, Negative)
- nAb status up to Week 12 (Positive, Negative)

Secondary efficacy analysis

All secondary efficacy analyses were performed to evaluate the clinical similarity of AVT04 compared with EU-Stelara in the ITT Set.

The number and percentage of patients achieving response rates of PASI50, PASI75, PASI90, and PASI100 at Weeks 4, 8, 12, 16, 28, 40, and 52 were presented by treatment and study period and the difference of proportion between treatment group and associated 95% CI was provided. Similarly, the number and percentage of patients achieving sPGA responses of clear (0) or almost clear (1) were summarized similarly at Weeks 4, 8, 12, 16, 28, 40, and 52.

The ANCOVA model used in the primary analysis was also applied to assess the percent improvement in PASI at Weeks 4, 8, 16, 28, 40, and 52; to assess the change in DLQI at Weeks 12, 28, 40, and 52;

and to compare the area under the effect curve for PASI score through Week 12. Treatment comparisons obtained from the model were provided purely for descriptive purposes.

Descriptive statistics of %BSA affected by chronic PsO were presented by treatment and visit.

Pharmacokinetic analysis

Descriptive statistics for serum trough concentrations of AVT04 and EU-Stelara were summarised over time by visit and study period based on the Safety Analysis Set (SAS).

Immunogenicity analysis

Presence of ADAs and nAbs was tabulated by treatment group and study visit. Confirmed positive antibody incidence was also tabulated by study period. The denominator of the Nab summary was the number of ADA patients at that visit. Titers for positive ADA results were also summarised.

Safety analysis

The safety endpoints (TEAEs including ADRs, injection site reactions, and routine safety parameters including laboratory safety, vital sign measurements, 12-lead ECG results, chest X-ray, and physical examination findings) were summarised by treatment received.

Details on the statistical analysis and preparation of the listings and summary tables and figures can be found in the SAP of the study, which was finalised on 11 May 2022. Clinical database freeze took place on 12-May-2022. Unblinding of the study took place on 13-May-2022.

***Results***

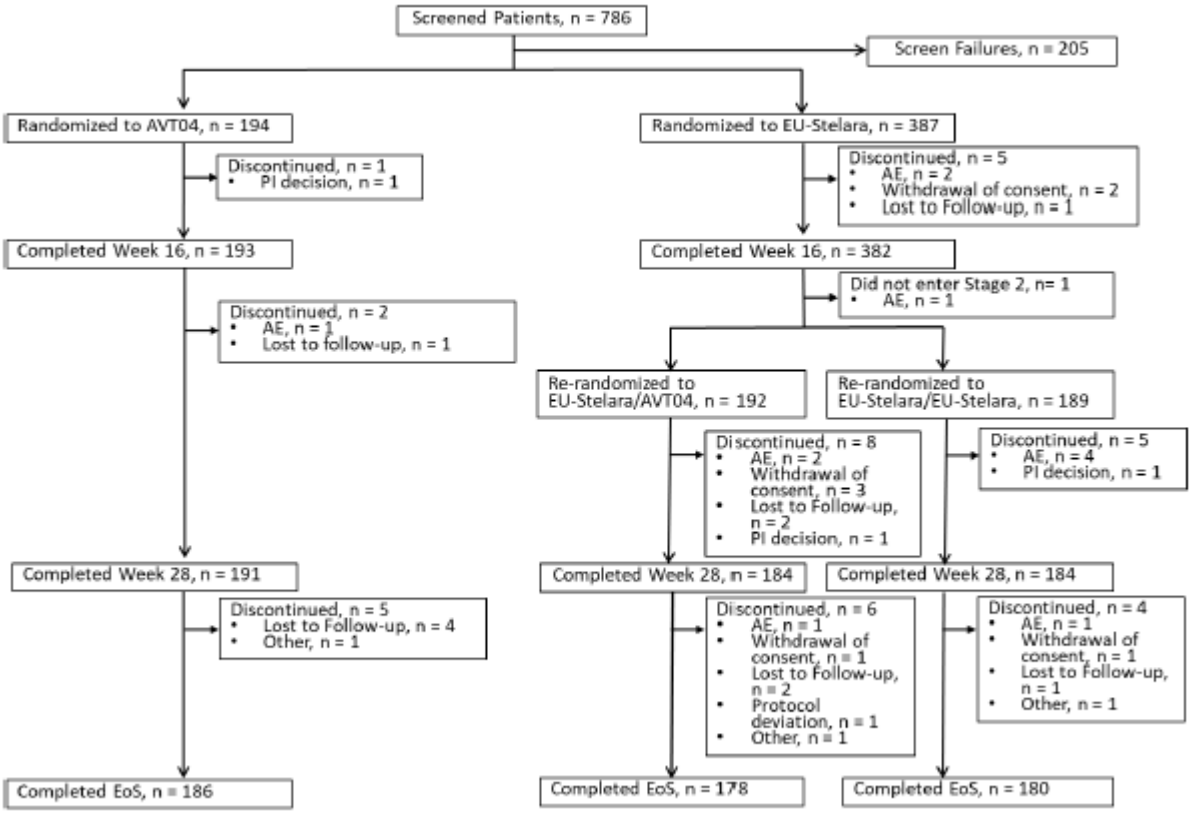
***Participant flow***

There were 581 patients who entered the study, comprising 194 patients who received AVT04, and 387 patients who received EU-Stelara up to Week 16 (Stage 1). The percentage of patients who completed Stage 1 (before re-randomization) at Week 16 was high and comparable between both treatment arms (99.5% and 98.7% in AVT04 and EU-Stelara arm, respectively). The proportion of patients who discontinued the study during Stage 1 was low and comparable between treatments.

At Week 16, patients initially randomized to EU-Stelara were re-randomized in a 1:1 ratio to enter Stage 2 and either continue treatment with EU-Stelara or to switch to AVT04. All patients (100%) entered Stage 2 and 559 patients (97.4%) completed Week 28. The percentage of patients who completed Week 28 was high and comparable between treatment arms (99%, 95.8% and 97.4% in the AVT04/AVT04, EU-Stelara/AVT04 and EU-Stelara/Eu-Stelara arm, respectively).

Overall, 544 patients (97.3% of the patients who completed Week 28) completed Stage 2 up to Week 52 (EoS). Fifteen patients (2.7%) discontinued the study after Week 28. Primary reasons for early study drug discontinuation included lost to follow-up (7 patients), AEs (2 patients), withdrawal of consent (2 patients), protocol deviations (1 patient), and other reasons (3 patients). No patient discontinued the treatment at Week 28 due to being a non-responder.

**Figure 10.1: Disposition of Study Patients (All Patients)**




Abbreviations: AE = Adverse Event; EoS = End of Study; EU = European Union; PI = principal investigator.
Source: Table 14.1.1.1a, Table 14.1.1.1b, Table 14.1.1.1c, Table 14.1.1.2, and Table 14.1.2.3.

***Recruitment***

First patient had their first visit on 03 Jun 2021. Last patient had their last visit on 03 May 2022 (with respect to data included in CSR1).

***Conduct of the study***

The original protocol was amended twice: to clarify the error identified in protocol and update the requirement for COVID-19 testing; to revise the inclusion criteria related to body weight for subjects as to better reflect the average demographic for Japanese subjects.

Overall, 466 patients (80.2%) had at least 1 protocol deviation, of which 111 patients (19.1%) had major and 455 patients (78.3%) had minor protocol deviations. The most common major protocol deviations were related to patient visits-UKR crisis (46 patients [7.9%]), study procedures-out of window-UKR crisis (20 patients [3.4%]), and study procedures-lab issues (14 patients [2.4%]). The most common minor protocol deviations were related to study procedures-out of window (198 patients [34.1%]), study procedures-lab issues-UKR crisis (178 patients [30.6%]), and study procedures-lab issues (121 patients [20.8%]). The number of patients with major PD increased markedly since the last submitted data, when only 9 patients (1.5%) had major PD. The proportion of patients affected by the protocol deviations was comparable between arms. One patient with a major PD was excluded from the PP analysis set due to receiving a wrong dose (BW >100 kg but received 45 mg instead of 90 mg at Baseline and Weeks 4 and 16). One patient with a major PD terminated the study earlier due to receiving a prohibited medication. These PDs occurred after the primary efficacy analysis, and therefore do not impact the results of the primary analysis.

In addition to the patient-level protocol deviations, site or study-level minor protocol deviations were recorded, all of which were related to registration of IP shipments to the IRT system. These PDs are not considered to have a relevant effect on the study integrity.

As regards study AVT04-GL-101 several audits were performed by the Sponsor that were relevant to the study. No critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

***Baseline data***

**Table 11.4: Demographics and Baseline Characteristics – Intention-to-Treat Set – Up to Week 16**

| | AVT04 (N=194) n (%) | EU-Stelara (N=387) n (%) | Overall (N=581) n (%) |
|---|---|---|---|
| All patients | | | |
| Age (years) at informed consent | | | |
| n | 194 | 387 | 581 |
| 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 |
| Age group, n (%) | | | |
| <65 years | 183 (94.3) | 365 (94.3) | 548 (94.3) |
| ≥65 years | 11 (5.7) | 22 (5.7) | 33 (5.7) |
| Gender, n (%) | | | |
| Female | 87 (44.8) | 130 (33.6) | 217 (37.3) |
| Male | 107 (55.2) | 257 (66.4) | 364 (62.7) |
| Ethnicity, n (%) | | | |

| | | | |
|---|---|---|---|
| Hispanic or Latino | 1 (0.5) | 3 (0.8) | 4 (0.7) |
| Not Hispanic or Latino | 193 (99.5) | 384 (99.2) | 577 (99.3) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 194 (100.0) | 387 (100.0) | 581 (100.0) |
| Other | 0 | 0 | 0 |
| Not reported | 0 | 0 | 0 |
| Height (cm) at Screening | | | |
| N | 194 | 387 | 581 |
| Mean (SD) | 172.11 (9.519) | 173.90 (8.996) | 173.30 (9.204) |
| Median | 172.00 | 175.00 | 174.00 |
| Min, max | 152.0, 196.0 | 149.0, 198.0 | 149.0, 198.0 |
| Weight (kg) at Screening | | | |
| N | 194 | 387 | 581 |
| Mean (SD) | 83.48 (18.368) | 84.19 (18.538) | 83.96 (18.468) |
| Median | 84.05 | 83.50 | 84.00 |
| Min, max | 45.0, 146.0 | 40.7, 150.2 | 40.7, 150.2 |
| Body weight category | | | |
| ≤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) |
| >100 kg | 30 (15.5) | 60 (15.5) | 90 (15.5) |
| BMI (kg/m²) at Screening | | | |
| N | 194 | 387 | 581 |
| Mean (SD) | 28.08 (5.334) | 27.76 (5.474) | 27.87 (5.425) |
| Median | 27.96 | 27.55 | 27.73 |
| Min, max | 16.9, 42.2 | 16.1, 46.2 | 16.1, 46.2 |
| Prior biologic therapy for PsO | | | |
| Yes | 15 (7.7) | 29 (7.5) | 44 (7.6) |
| No | 179 (92.3) | 358 (92.5) | 537 (92.4) |

| | | | |
|---|---|---|---|
| Psoriasis Area and Severity Index (PASI) | | | |
| N | 194 | 387 | 581 |
| Mean (SD) | 22.05 (8.133) | 22.22 (7.549) | 22.17 (7.742) |
| Median | 20.20 | 20.00 | 20.00 |
| Min, max | 12.2, 55.2 | 12.2, 64.8 | 12.2, 64.8 |
| Static Physician's Global Assessment (sPGA), n (%) | | | |
| Minimal | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 |
| 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) |
| Percentage of body surface area (%BSA) affected (%) | | | |
| N | 194 | 387 | 581 |
| Mean (SD) | 26.02 (13.231) | 26.41 (12.256) | 26.28 (12.579) |
| Median | 23.00 | 23.00 | 23.00 |
| Min, max | 10.0, 75.0 | 10.0, 84.0 | 10.0, 84.0 |
| Months from diagnosis of chronic plaque psoriasis to informed consent | | | |
| N | 194 | 387 | 581 |
| Mean (SD) | 193.4 (139.86) | 201.0 (136.46) | 198.5 (137.53) |
| Median | 156.5 | 186.0 | 176.0 |
| Min, max | 7, 703 | 6, 691 | 6, 703 |
| Country | | | |
| Estonia | 3 (1.5) | 7 (1.8) | 10 (1.7) |
| Georgia | 25 (12.9) | 37 (9.6) | 62 (10.7) |
| Poland | 107 (55.2) | 214 (55.3) | 321 (55.2) |
| Ukraine | 59 (30.4) | 129 (33.3) | 188 (32.4) |
| | **AVT04 (N=164) n (%)** | **EU-Stelara (N=327) n (%)** | **Overall (N=491) n (%)** |

***Numbers analysed***

The per-protocol analysis set was used for the analysis of the primary endpoint. An ITT analysis was defined as sensitivity analysis by the Applicant.

***Outcomes and estimation***

**Primary endpoint**

Percent Improvement from Baseline to Week 12 in Psoriasis Area and Severity Index (PP analysis)

**Table 11.8: Analysis of Covariance of Percent Improvement in Psoriasis Area and Severity Index from Baseline to Week 12 – Per Protocol Set**

| Time Point | AVT04 (N=194) | EU-Stelara (N=383) |
|---|---|---|
| **All patients** | | |
| Week 12 | | |
| n | 194 | 383 |
| LS mean (SE) (%) | 87.3 (1.73) | 86.8 (1.49) |
| LS mean difference (SE) (AVT04 vs EU-Stelara) | 0.4 (1.56) | |
| 90% confidence interval | -2.14, 3.01 | |
| 95% confidence interval | -2.63, 3.50 | |
| **Time Point** | **AVT04 (N=164)** | **EU-Stelara (N=324)** |
| **Patients with body weight ≤100 kg** | | |
| Week 12 | | |
| n | 164 | 324 |
| LS mean (SE) (%) | 86.9 (1.91) | 86.8 (1.64) |
| LS mean difference (SE) (AVT04 vs EU-Stelara) | 0.1 (1.70) | |
| 90% confidence interval | -2.71, 2.89 | |
| 95% confidence interval | -3.25, 3.43 | |

Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the patient received the first dose of study drug (Day 1).
Two-sided 90% and 95% CIs for the difference in LS means between AVT04 and EU-Stelara groups were obtained from an ANCOVA model including percent PASI improvement as response variable, randomized treatment, and stratification factor (prior biologic therapy) as factors, and with Baseline PASI score and Baseline body weight as continuous covariates.
Clinical similarity of AVT04 was established if the CI for adjusted mean difference was contained within the range [-10%, 10%] for the 90% CI and range [-15%, 15%] for the 95% CI.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EU = European Union; LS = least squares; PASI = Psoriasis Area and Severity Index; SE = standard error.
Source: Table 14.2.1.1

As shown in the table above, both 90% CI and 95% CI were reported, the former in accordance with FDA requirements and the latter in line with EMA requirements (EMEA/CPMP/EWP/2158/99).

The least squares (LS) mean for percent improvement in PASI from baseline to Week 12 was comparable between AVT04 group (87.3%) and the EU-Stelara group (86.8%) in the PP analysis set. The LS mean difference (AVT04 vs EU-Stelara) was 0.4% with 95% confidence interval from -2.63% to 3.50%. The pre-specified acceptance range [-15%, 15%] had not been clinically justified and appears large. However, as the 95% CI demonstrated equivalent efficacy of the two treatments within a narrow range, and clinical comparability. The results were similar in patients with body weight ≤100kg compared to the overall study population. In patients wit BW≤100kg the LS mean for percent improvement in PASI from baseline to Week 12 was comparable between AVT04 group (86.9% improvement) and the EU-Stelara group (86.8% improvement). The LS mean difference (AVT04 vs EU-Stelara) was 0.1% with 95% confidence interval from -3.25% to 3.43%. Clinical comparability can be concluded in patients with BW ≤100kg as well.

Percent Improvement from Baseline to Week 16 in PASI (ITT analysis)

**Table 11.9: Sensitivity Analysis (1): Analysis of Covariance of Percent Improvement in Psoriasis Area and Severity Index from Baseline to Week 12 Using Observed Data – Intention-to-Treat Set – Up to Week 16**

| Time Point | AVT04 (N=194) | EU-Stelara (N=387) |
|---|---|---|
| **All patients** | | |
| Week 12 | | |
| n | 194 | 384 |
| LS mean (SE) | 87.2 (1.73) | 86.8 (1.49) |
| LS mean difference (SE) (AVT04 vs EU-Stelara) | 0.4 (1.56) | |
| 90% confidence interval | -2.16, 2.98 | |
| 95% confidence interval | -2.66, 3.47 | |
| **Time Point** | **AVT04 (N=164)** | **EU-Stelara (N=327)** |
| **Patients with body weight ≤100 kg** | | |
| Week 12 | | |
| n | 164 | 324 |
| LS mean (SE) | 86.9 (1.91) | 86.8 (1.64) |
| LS mean difference (SE) (AVT04 vs EU-Stelara) | 0.1 (1.70) | |
| 90% confidence interval | -2.71, 2.89 | |
| 95% confidence interval | -3.25, 3.43 | |

Baseline was defined as the last nonmissing value (either scheduled, unscheduled, or repeat) before the patient received the first dose of study drug (Day 1).
Two-sided 90% and 95% CIs for the difference in LS means between AVT04 and EU-Stelara groups were obtained from an ANCOVA model including percent PASI improvement as response variable, randomized treatment, and stratification factor (prior biologic therapy) as factors, and with Baseline PASI score and Baseline body weight as continuous covariates.
Missing percent improvement in PASI was not imputed.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EU = European Union; LS = least squares; PASI = Psoriasis Area and Severity Index; SE = standard error.
Source: Table 14.2.1.2

The analysis based on the ITT set showed similar results. The least squares (LS) mean for percent improvement in PASI from baseline to Week 12 was comparable between AVT04 group (87.2%) and the EU-Stelara group (86.8%) in the ITT analysis. The LS mean difference (AVT04 vs EU-Stelara) was 0.4% with 95% confidence interval from -2.66% to 3.34%. Results were similar in patients with BW≤100kg. All secondary parameters are reported for ITT set.

**Secondary endpoints**

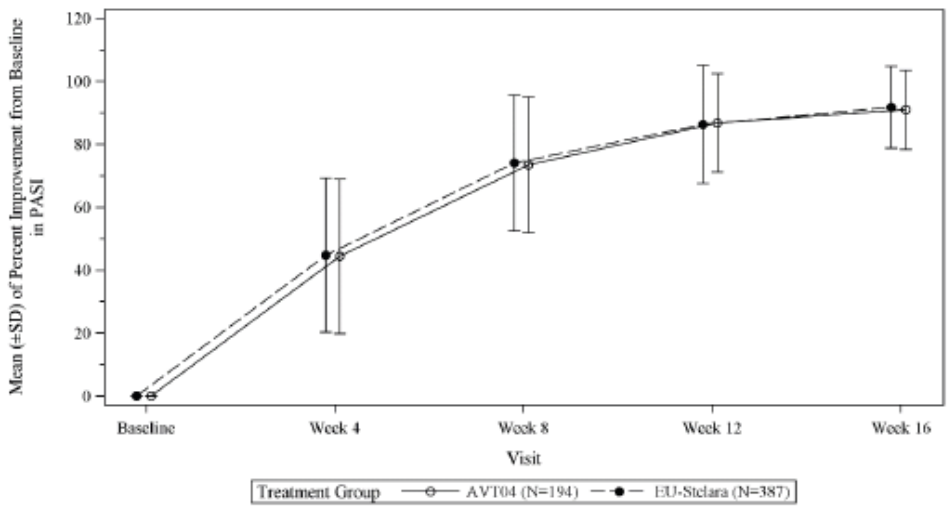
Percent Improvement in Psoriasis Area and Severity Index from Baseline to Week 4, 8, 12 and 16 (ITT set)

**Table 11.12: Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit – Analysis of Covariance – Intention-to-Treat Set – Up to Week 16**

| | Actual Value | | | | Percent Improvement from Baseline | | | | LS Mean | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean (SD) | Median | Min, Max | n | Mean (SD) | Median | Min, Max | LS Mean | LS Mean Difference (SE) (AVT04 vs EU-Stelara) and 95% CI |
| **All patients** | | | | | | | | | | |
| AVT04 (N = 194) | | | | | | | | | | |
| Baseline | 194 | 22.05 (8.133) | 20.20 | 12.2, 55.2 | | | | | | |
| Week 4 | 194 | 12.21 (7.100) | 11.00 | 0.0, 38.1 | 194 | 44.41 (24.499) | 41.79 | 0.0, 100.0 | 45.1 (2.381) | -0.4 (2.14)<br>-4.60, 3.81 |
| Week 8 | 193 | 5.91 (5.506) | 4.60 | 0.0, 30.6 | 193 | 73.48 (21.594) | 77.01 | 4.2, 100.0 | 75.2 (2.098) | -0.7 (1.89)<br>-4.44, 2.99 |
| Week 12 | 194 | 3.08 (4.114) | 1.60 | 0.0, 21.6 | 194 | 86.81 (15.646) | 91.12 | 13.0, 100.0 | 87.2 (1.732) | 0.4 (1.56)<br>-2.66, 3.47 |
| Week 16 | 193 | 2.08 (3.216) | 0.90 | 0.0, 21.0 | 193 | 90.96 (12.616) | 95.74 | 19.5, 100.0 | 89.8 (1.248) | -0.8 (1.13)<br>-3.04, 1.38 |
| EU-Stelara (N = 387) | | | | | | | | | | |
| Baseline | 387 | 22.22 (7.549) | 20.00 | 12.2, 64.8 | | | | | | |
| Week 4 | 387 | 12.19 (6.842) | 11.30 | 0.0, 40.3 | 387 | 44.72 (24.493) | 44.72 | -22.1, 100.0 | 45.5 (2.047) | |
| Week 8 | 384 | 5.72 (5.196) | 4.45 | 0.0, 27.9 | 384 | 74.06 (21.645) | 78.63 | -4.5,100.0 | 76.0 (1.803) | |
| Week 12 | 384 | 2.90 (3.918) | 1.50 | 0.0, 22.2 | 384 | 86.33 (18.805) | 92.84 | -29.8, 100.0 | 86.8 (1.490) | |
| Week 16 | 382 | 1.73 (2.665) | 0.80 | 0.0, 17.8 | 382 | 91.73 (12.972) | 96.12 | 0.0, 100.0 | 90.6 (1.073) | |
| **Patients with body weight ≤100 kg** | | | | | | | | | | |
| AVT04 (N = 164) | | | | | | | | | | |
| Baseline | 164 | 21.55 (7.965) | 19.80 | 12.2, 51.6 | | | | | | |
| Week 4 | 164 | 11.70 (6.589) | 10.80 | 0.0, 38.1 | 164 | 44.98 (24.267) | 43.09 | 0.0, 100.0 | 46.1 (2.657) | -0.4 (2.36)<br>-5.08, 4.21 |
| Week 8 | 163 | 5.66 (5.185) | 4.40 | 0.0, 30.6 | 163 | 73.78 (21.456) | 77.53 | 4.2, 100.0 | 75.2 (2.279) | -1.3 (2.03)<br>-5.31, 2.67 |
| Week 12 | 164 | 2.98 (3.811) | 1.70 | 0.0, 17.4 | 164 | 86.74 (15.536) | 90.85 | 13.0, 100.0 | 86.9 (1.907) | 0.1 (1.70)<br>-3.25, 3.43 |
| Week 16 | 163 | 1.97 (2.915) | 0.90 | 0.0, 13.8 | 163 | 90.97 (12.764) | 95.24 | 19.5, 100.0 | 89.6 (1.382) | -0.9 (1.23)<br>-3.33, 1.51 |
| EU-Stelara (N = 327) | | | | | | | | | | |
| Baseline | 327 | 21.92 (7.671) | 19.40 | 12.2, 64.8 | | | | | | |
| Week 4 | 327 | 11.82 (6.801) | 10.80 | 0.0, 40.3 | 327 | 45.39 (25.160) | 44.93 | -22.1, 100.0 | 46.6 (2.286) | |
| Week 8 | 324 | 5.45 (5.013) | 4.20 | 0.0, 27.9 | 324 | 74.95 (21.287) | 79.85 | -4.5, 100.0 | 76.5 (1.960) | |
| Week 12 | 324 | 2.75 (3.744) | 1.40 | 0.0, 22.2 | 324 | 86.61 (18.983) | 93.06 | -29.8, 100.0 | 86.8 (1.642) | |
| Week 16 | 322 | 1.66 (2.563) | 0.80 | 0.0, 17.8 | 322 | 91.82 (13.165) | 96.12 | 0.0, 100.0 | 90.5 (1.189) | |

Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the patient received the first dose of study drug (Day 1).
Two-sided 95% CI for the difference in least squares means between AVT04 and EU-Stelara groups was obtained from an ANCOVA model including percent PASI improvement as response variable, randomized treatment and stratification factor (prior biologic therapy) as factors, and with baseline PASI score and baseline body weight as continuous covariates. Missing percent improvement in PASI was not imputed.
Abbreviations: CI = confidence interval; EU = European Union; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error.
Source: Table 14.2.2.2.1

**Figure 11.1: Mean (±Standard Deviation) of Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit – Observed Data – Intention-to-Treat Set – Up to Week 16**




Missing percent improvement in PASI was not imputed.
Abbreviations: PASI = Psoriasis Area and Severity Index; SD = standard deviation.
Source: Figure 14.2.1.1.2

At Week 4 and 8, the LS mean differences (AVT04 vs EU-Stelara) were -0.4% (95% CI -4.60%, 3.81%) and -0.7% (95%CI -4.4%, 2.99%), respectively for the ITT analysis. These differences were slightly higher than the difference at Week 12. Percent improvement in PASI from baseline to Week 16 was also considered similar between the AVT04 and EU-Stelara group. In summary, the percentage change in PASI from baseline through Week 16 was comparable between AVT04 and EU-Stelara. The results for patients with body weight ≤100kg were similar to that of all patients. For the PP analyses at Week 4 and 8, the LS mean differences (AVT04 vs EU-Stelara) were -0.6% (95% CI -4.77%, 3.66%) and -0.8% (95%CI -4.56%, 2.87%), respectively.

Percent Improvement in Psoriasis Area and Severity Index from Baseline up to Week 52

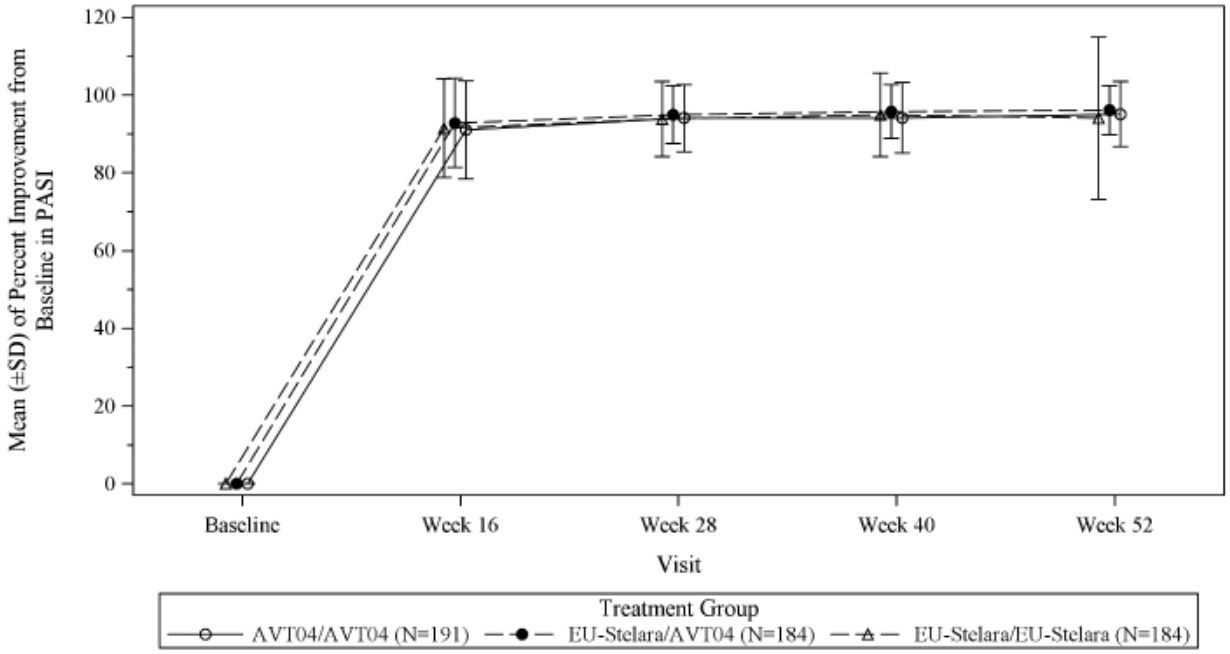
**Table 4.** Table 16. Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit – Analysis of Covariance –Intention-to-Treat Set – Up to End of Study (All Patients)

| | Actual Value | | | | Percent Improvement from Baseline | | | | LS Mean | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean (SD) | Median | Min, Max | n | Mean (SD) | Median | Min, Max | LS Mean | LS Means Difference (SE) and 95% CI |
| **All patients** | | | | | | | | | | |
| **AVT04/AVT04 [1] (n = 191)** | | | | | | | | | | |
| Baseline | 191 | 22.14 (8.159) | 20.20 | 12.2, 55.2 | - | - | - | - | - | [1] vs [3] |
| Week 16 | 191 | 2.07 (3.216) | 0.90 | 0.0, 21.0 | 191 | 91.02 (12.571) | 95.74 | 19.5, 100.0 | 89.8 (1.196) | -0.6 (1.25)<br>-3.02, 1.90 |
| Week 28 | 191 | 1.34 (2.395) | 0.40 | 0.0, 21.0 | 191 | 94.10 (8.664) | 98.01 | 56.5, 100.0 | 93.6 (0.836) | 0.2 (0.88)<br>-1.55, 1.89 |
| Week 40 | 191 | 1.32 (2.222) | 0.40 | 0.0, 12.9 | 191 | 94.17 (9.007) | 98.10 | 45.5, 100.0 | 93.3 (0.889) | -0.8 (0.93)<br>-2.63, 1.01 |
| Week 52 | 186 | 1.08 (1.829) | 0.00 | 0.0, 10.1 | 186 | 95.09 (8.400) | 100.00 | 34.4, 100.0 | 93.5 (1.355) | 1.0 (1.40)<br>-1.73, 3.76 |
| **EU-Stelara/AVT04 [2] (n= 184)** | | | | | | | | | | |
| Baseline | 184 | 22.00 (7.723) | 19.30 | 12.9, 64.8 | - | - | - | - | - | [1] vs [2] |
| Week 16 | 184 | 1.52 (2.460) | 0.80 | 0.0, 14.7 | 184 | 92.83 (11.464) | 96.34 | 10.8, 100.0 | 91.6 (1.211) | -1.9 (1.25)<br>-4.31, 0.61 |
| Week 28 | 184 | 1.06 (1.774) | 0.50 | 0.0, 16.0 | 184 | 94.99 (7.385) | 97.26 | 56.7, 100.0 | 94.5 (0.847) | -0.9 (0.88)<br>-2.65, 0.79 |
| Week 40 | 180 | 0.91 (1.683) | 0.00 | 0.0, 14.7 | 180 | 95.77 (6.923) | 100.00 | 56.7, 100.0 | 94.9 (0.904) | -1.6 (0.93)<br>-3.47, 0.17 |
| Week 52 | 178 | 0.82 (1.535) | 0.00 | 0.0, 12.7 | 178 | 96.20 (6.306) | 100.00 | 65.0, 100.0 | 94.6 (1.365) | -1.1 (1.40)<br>-3.88, 1.63 |
| **EU-Stelara/EU-Stelara [3] (n = 184)** | | | | | | | | | | |
| Baseline | 184 | 22.50 (7.099) | 20.95 | 12.2, 53.8 | - | - | - | - | - | [2] vs [3] |
| Week 16 | 184 | 1.77 (2.580) | 0.80 | 0.0, 14.8 | 184 | 91.51 (12.616) | 96.09 | 13.9, 100.0 | 90.3 (1.213) | 1.3 (1.26)<br>-1.19, 3.78 |
| Week 28 | 184 | 1.30 (2.062) | 0.40 | 0.0, 14.8 | 184 | 93.85 (9.648) | 97.55 | 52.4, 100.0 | 93.4 (0.848) | 1.1 (0.88)<br>-0.63, 2.84 |
| Week 40 | 181 | 1.04 (1.787) | 0.20 | 0.0, 13.8 | 181 | 94.94 (10.707) | 99.01 | -13.1, 100.0 | 94.1 (0.916) | 0.8 (0.94)<br>-1.01, 2.69 |
| Week 52 | 180 | 1.26 (5.027) | 0.00 | 0.0, 64.2 | 180 | 94.07 (20.812) | 100.00 | -157.8, 100.0 | 92.5 (1.383) | 2.1 (1.42)<br>-0.64, 4.92 |

Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the patient received the first dose of study drug (Day 1). Two-sided 95% CI for the difference in least squares means between AVT04 and EU-Stelara groups was obtained from an ANCOVA model including percent PASI improvement as response variable, randomized treatment and stratification factor (prior biologic therapy) as factors, and with Baseline PASI score and Baseline body weight as continuous covariates. Missing percent improvement in PASI was not imputed. Abbreviations: CI = confidence interval; EU = European Union; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error.

Source: Table 14.2.2.2.3

**Figure 11.4: Mean (±Standard Deviation) of Percent Improvement from Baseline in Psoriasis Area and Severity Index by Visit – Intention-to-Treat Set – Up to End of Study (All Patients)**




Missing percent improvement in PASI was not imputed.
Abbreviations: PASI = Psoriasis Area and Severity Index; SD = standard deviation.
Source: Figure 14.2.1.1.5

The percentage change in PASI from baseline up to week 52 was comparable between AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups.

Psoriasis Area and Severity Index 50, 75, 90, and 100 Response Rates at Weeks 4, 8, 12, 16

**Table 11.10: Percentage of Patients Achieving PASI50, PASI75, PASI90, and PASI100 Over Time – Intention-to-Treat – Up to Week 16**

| Visit<br>Treatment<br>Parameter | m | n | p | Difference in Proportions (AVT04 vs EU-Stelara) | 95% CI |
|---|---|---|---|---|---|
| **All patients** | | | | | |
| Week 4 | | | | | |
| AVT04 N=194 | | | | | |
| PASI50 | 194 | 79 | 40.7 | -0.9 | -9.36, 7.60 |
| PASI75 | 194 | 22 | 11.3 | -0.5 | -6.05, 4.96 |
| PASI90 | 194 | 6 | 3.1 | -1.0 | -4.18, 2.10 |
| PASI100 | 194 | 3 | 1.5 | 0.5 | -1.49, 2.52 |
| EU-Stelara N=387 | | | | | |
| PASI50 | 387 | 161 | 41.6 | | |
| PASI75 | 387 | 46 | 11.9 | | |
| PASI90 | 387 | 16 | 4.1 | | |
| PASI100 | 387 | 4 | 1.0 | | |
| Week 8 | | | | | |
| AVT04 N=193 | | | | | |
| PASI50 | 193 | 163 | 84.5 | -2.0 | -8.15, 4.15 |
| PASI75 | 193 | 101 | 52.3 | -3.1 | -11.76, 5.49 |
| PASI90 | 193 | 46 | 23.8 | -3.5 | -10.99, 3.97 |
| PASI100 | 193 | 27 | 14.0 | -0.1 | -6.08, 5.93 |
| EU-Stelara N=384 | | | | | |
| PASI50 | 384 | 332 | 86.5 | | |
| PASI75 | 384 | 213 | 55.5 | | |
| PASI90 | 384 | 105 | 27.3 | | |
| PASI100 | 384 | 54 | 14.1 | | |
| Week 12 | | | | | |
| AVT04 N=194 | | | | | |
| PASI50 | 194 | 184 | 94.8 | 0.1 | -3.77, 3.88 |
| PASI75 | 194 | 157 | 80.9 | -1.1 | -7.83, 5.63 |
| PASI90 | 194 | 106 | 54.6 | -2.9 | -11.49, 5.66 |

| Visit<br>Treatment<br>Parameter | m | n | p | Difference in Proportions (AVT04 vs EU-Stelara) | 95% CI |
|---|---|---|---|---|---|
| PASI100 | 194 | 58 | 29.9 | -0.1 | -7.96, 7.85 |
| EU-Stelara N=384 | | | | | |
| PASI50 | 384 | 364 | 94.8 | | |
| PASI75 | 384 | 315 | 82.0 | | |
| PASI90 | 384 | 221 | 57.6 | | |
| PASI100 | 384 | 115 | 29.9 | | |
| Week 16 | | | | | |
| AVT04 N=193 | | | | | |
| PASI50 | 193 | 191 | 99.0 | 0.3 | -1.55, 2.10 |
| PASI75 | 193 | 166 | 86.0 | -4.3 | -10.03, 1.42 |
| PASI90 | 193 | 133 | 68.9 | -5.4 | -13.30, 2.43 |
| PASI100 | 193 | 70 | 36.3 | -0.4 | -8.71, 7.95 |
| EU-Stelara N=382 | | | | | |
| PASI50 | 382 | 377 | 98.7 | | |
| PASI75 | 382 | 345 | 90.3 | | |
| PASI90 | 382 | 284 | 74.3 | | |
| PASI100 | 382 | 140 | 36.6 | | |

Psoriasis Area and Severity Index 50, 75, 90, and 100 Response Rates up to Week 52

**Table 11.17: Percentage of Patients Achieving PASI50, PASI75, PASI90, and PASI100 Over Time – Intention-to-Treat – Up to End of Study (All Patients)**

| Visit<br>Treatment<br>Parameter | m | n | p | Difference in Proportions (Comparison) | 95% CI |
|---|---|---|---|---|---|
| **Week 16** | | | | | |
| **AVT04/AVT04 n=191 [1]** | - | - | - | [1] vs [3] | - |
| PASI50 | 191 | 189 | 99.0 | 0.6 | -1.75, 2.91 |
| PASI75 | 191 | 165 | 86.4 | -2.2 | -8.89, 4.49 |
| PASI90 | 191 | 132 | 69.1 | -5.3 | -14.44, 3.74 |
| PASI100 | 191 | 69 | 36.1 | 1.3 | -8.34, 11.03 |
| **EU-Stelara/AVT04 n=184 [2]** | - | - | - | [1] vs [2] | - |
| PASI50 | 184 | 183 | 99.5 | -0.5 | -2.30, 1.29 |
| PASI75 | 184 | 172 | 93.5 | -7.1 | -13.12, -1.06 |
| PASI90 | 184 | 141 | 76.6 | -7.5 | -16.48, 1.44 |
| PASI100 | 184 | 72 | 39.1 | -3.0 | -12.81, 6.80 |

| Visit<br>Treatment<br>Parameter | m | n | p | Difference in Proportions (Comparison) | 95% CI |
|---|---|---|---|---|---|
| **EU-Stelara/EU-Stelara n=184 [3]** | - | - | - | [2] vs [3] | - |
| PASI50 | 184 | 181 | 98.4 | 1.1 | -1.03, 3.20 |
| PASI75 | 184 | 163 | 88.6 | 4.9 | -0.93, 10.71 |
| PASI90 | 184 | 137 | 74.5 | 2.2 | -6.61, 10.95 |
| PASI100 | 184 | 64 | 34.8 | 4.3 | -5.51, 14.20 |
| **Week 28** | | | | | |
| **AVT04/AVT04 n=191[1]** | - | - | - | [1] vs [3] | - |
| PASI50 | 191 | 191 | 100.0 | 0 | NA |
| PASI75 | 191 | 180 | 94.2 | 0.2 | -4.54, 4.98 |
| PASI90 | 191 | 153 | 80.1 | 0.2 | -7.89, 8.31 |
| PASI100 | 191 | 83 | 43.5 | 2.2 | -7.85, 12.15 |
| **EU-Stelara/AVT04 n=184 [2]** | - | - | - | [1] vs [2] | - |
| PASI50 | 184 | 184 | 100.0 | 0 | NA |
| PASI75 | 184 | 180 | 97.8 | -3.6 | -7.50, 0.33 |
| PASI90 | 184 | 151 | 82.1 | -2.0 | -9.88, 5.96 |
| PASI100 | 184 | 73 | 39.7 | 3.8 | -6.19, 13.75 |
| **EU-Stelara/EU-Stelara n=184[3]** | - | - | - | [2] vs [3] | - |
| PASI50 | 184 | 184 | 100.0 | 0 | NA |
| PASI75 | 184 | 173 | 94.0 | 3.8 | -0.22, 7.83 |
| PASI90 | 184 | 147 | 79.9 | 2.2 | -5.84, 10.19 |
| PASI100 | 184 | 76 | 41.3 | -1.6 | -11.66, 8.40 |
| **Week 40** | | | | | |
| **AVT04/AVT04 n=193 [1]** | - | - | - | [1] vs [3] | - |
| PASI50 | 191 | 190 | 99.5 | 0.0 | -1.46, 1.52 |
| PASI75 | 191 | 184 | 96.3 | -0.9 | -4.48, 2.68 |
| PASI90 | 191 | 150 | 78.5 | -7.7 | -15.35, 0.04 |
| PASI100 | 191 | 84 | 44.0 | -4.1 | -14.21, 6.04 |
| **EU-Stelara/AVT04 n=180 [2]** | - | - | - | [1] vs [2] | - |
| PASI50 | 180 | 180 | 100.0 | -0.5 | -1.55, 0.50 |
| PASI75 | 180 | 177 | 98.3 | -2.0 | -5.25, 1.26 |
| PASI90 | 180 | 155 | 86.1 | -7.6 | -15.29, 0.13 |
| PASI100 | 180 | 93 | 51.7 | -7.7 | -17.83, 2.45 |

| | | | | | |
|---|---|---|---|---|---|
| **EU-Stelara/EU-Stelara n=181 [3]** | - | - | - | [2] vs [3] | - |
| PASI50 | 181 | 180 | 99.4 | 0.6 | -0.53, 1.63 |
| PASI75 | 181 | 176 | 97.2 | 1.1 | -1.94, 4.13 |
| PASI90 | 181 | 156 | 86.2 | -0.1 | -7.20, 7.05 |
| PASI100 | 181 | 87 | 48.1 | 3.6 | -6.71, 13.91 |
| **Week 52** | | | | | |
| **AVT04/AVT04 n=186 [1]** | - | - | - | [1] vs [3] | - |
| PASI50 | 186 | 185 | 99.5 | 1.1 | -1.02, 3.27 |
| PASI75 | 186 | 180 | 96.8 | 0.1 | -3.54, 3.76 |
| PASI90 | 186 | 151 | 81.2 | -4.4 | -11.98, 3.24 |
| PASI100 | 186 | 99 | 53.2 | 0.4 | -9.78, 10.68 |
| **EU-Stelara/AVT04 n=178 [2]** | - | - | - | [1] vs [2] | - |
| PASI50 | 178 | 178 | 100.0 | -0.5 | -1.59, 0.51 |
| PASI75 | 178 | 175 | 98.3 | -1.5 | -4.71, 1.63 |
| PASI90 | 178 | 155 | 87.1 | -5.9 | -13.37, 1.58 |
| PASI100 | 178 | 102 | 57.3 | -4.1 | -14.29, 6.13 |
| **EU-Stelara/EU-Stelara n=180 [3]** | - | - | - | [2] vs [3] | - |
| PASI50 | 180 | 177 | 98.3 | 1.7 | -0.20, 3.54 |
| PASI75 | 180 | 174 | 96.7 | 1.6 | -1.59, 4.88 |
| PASI90 | 180 | 154 | 85.6 | 1.5 | -5.59, 8.64 |
| PASI100 | 180 | 95 | 52.8 | 4.5 | -5.77, 14.82 |

Abbreviations: CI = confidence interval; EU = European Union; m = number of patients in treatment group with assessment at both Baseline and the specified time point and was used as the denominator for percentage calculations; n = number of patients achieving PASI50, PASI75, PASI90, or PASI100 at time point; p = percentage of patients achieving PASI50, PASI75, PASI90, or PASI100; PASI = Psoriasis Area and Severity Index.
Source: Table 14.2.2.1.3

The proportion of patients achieving PASI50, PASI75, PASI90, and PASI100 broadly increased over time, and was similar between the AVT04 and EU-Stelara groups at time points up to Week 12, and, after re-randomization at Week 16, was similar between the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups at time points up to Week 52 (EoS). Similar results were observed for patients with body weight ≤100 kg.

Area Under the Effect Curve for Psoriasis Area and Severity Index from Baseline Through Week 12

**Table 11.13: Area Under the Effect Curve of Percent Improvement in Psoriasis Area and Severity Index Through Week 12 – Analysis of Covariance – Intention-to-Treat Set – Up to Week 16**

| Time Point | AVT04 (N=194) | EU-Stelara (N=387) |
|---|---|---|
| **All patients** | | |
| Week 12 | | |
| n | 194 | 384 |
| Mean (SD) | 620.26 (202.956) | 633.19 (199.910) |

| | | |
|---|---|---|
| Median | 644.87 | 665.82 |
| Minimum, maximum | 109.1, 1000.0 | -45.5, 1000.0 |
| LS Mean (SE) | 632.85 (19.420) | 647.10 (16.694) |
| LS mean difference (SE) (AVT04 vs EU-Stelara) | -14.25 (17.494) | |
| 90% confidence interval | -43.070, 14.573 | |
| 95% confidence interval | -48.608, 20.111 | |
| **Time Point** | **AVT04 (N=164)** | **EU-Stelara (N=327)** |
| **Patients with body weight ≤100 kg** | | |
| Week 12 | | |
| n | 164 | 324 |
| Mean (SD) | 621.94 (204.855) | 639.86 (201.433) |
| Median | 648.16 | 675.00 |
| Minimum, maximum | 109.1, 1000.0 | -45.5, 1000.0 |
| LS mean (SE) | 636.60 (21.482) | 655.94 (18.473) |
| LS mean difference (SE) (AVT04 vs EU-Stelara) | -19.34 (19.136) | |
| 90% confidence interval | -50.874, 12.199 | |
| 95% confidence interval | -56.938, 18.263 | |

Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the patient received the first dose of study drug (Day 1).
Two-sided 90% and 95% CIs for the difference in LS means between AVT04 and EU-Stelara groups were obtained from an ANCOVA model including AUEC of percent PASI improvement as response variable, randomized treatment, and stratification factor (prior biologic therapy) as factors, and with baseline PASI score and baseline body weight as continuous covariates.
Missing percent improvement in PASI was not imputed.
Abbreviations: ANCOVA = analysis of covariance; AUEC = area under the effect curve; CI = confidence interval; LS = least squares; PASI = Psoriasis Area and Severity Index; SD = standard deviation; SE = standard error.
Source: Table 14.2.2.3.1

The LS mean for *area under the effect Curve for PASI from Baseline Through Week* 12 was slightly lower for AVT04 group (632.85 in AVT04 group vs. 647.10 in EU-Stelara group), though not significantly. LS mean difference (AVT04 vs EU-Stelara) was -14.25 (95% CI -48.608, 20.111). Results were similar in patients with BW ≤100kg, with difference being slightly bigger compared to the overall study population, however not significantly. The LS mean difference (AVT04 vs EU-Stelara) was -19.34 (95% CI -56.938, 18.263).

Proportion of Patients Achieving Static Physician's Global Assessment Responses of Clear (0) or Almost Clear (1) at Weeks 4, 8, 12, 16

**Table 5.** Percentage of Patients Achieving Static Physician's Global Assessment Responses of Clear (0) or Almost Clear (1) Over Time – Intention-to-Treat Set – Up to Week 16 (All Patients)

| Parameter<br>Treatment<br>Visit | m | n | p | Difference in Proportions (AVT04 vs EU-Stelara) | 95% Confidence Interval |
|---|---|---|---|---|---|
| **All patients** | | | | | |
| **sPGA response is clear (0) or almost clear (1)** | | | | | |
| **AVT04 n=194** | | | | | |
| Week 4 | 194 | 40 | 20.6 | 0.2 | -6.76, 7.17 |
| Week 8 | 193 | 121 | 62.7 | -1.1 | -9.45, 7.24 |
| Week 12 | 194 | 152 | 78.4 | -2.1 | -9.14, 4.90 |
| Week 16 | 193 | 165 | 85.5 | -3.0 | -8.90, 2.92 |
| **EU-Stelara n=387** | | | | | |
| Week 4 | 387 | 79 | 20.4 | - | - |
| Week 8 | 384 | 245 | 63.8 | - | - |
| Week 12 | 384 | 309 | 80.5 | - | - |
| Week 16 | 382 | 338 | 88.5 | - | - |

From Baseline to Week 16, the proportion of patients achieving sPGA responses of clear (0) or almost clear (1) increased from 20.6% to 85.5% in AVT04 group and from 20.4% to 88.5% in EU-Stelara group. The difference in proportions (AVT04 vs EU-Stelara) between treatments at various time points through Week 16 ranged from 0.2 (95% CI -6.76, 7.17) at Week 4 to -3.0 (95% CI -8.90, 2.92) at Week 16. Results were similar in patients with BW ≤100kg.

Proportion of Patients Achieving Static Physician's Global Assessment Responses of Clear (0) or Almost Clear (1) up to Week 52

**Table 6.** Percentage of Patients Achieving Static Physician's Global Assessment Responses of Clear (0) or Almost Clear (1) Over Time – Intention-to-Treat Set – Up to End of Study (All Patients)

| Parameter<br>Treatment<br>Visit | m | n | p | Difference in Proportions | 95% Confidence Interval |
|---|---|---|---|---|---|
| **All patients** | | | | | |
| **sPGA response is clear (0) or almost clear (1)** | | | | | |
| **AVT04/AVT04 n=191 [1]** | - | - | - | [1] vs [3] | - |
| Week 16 | 191 | 163 | 85.3 | -0.5 | -7.64, 6.58 |
| Week 28 | 191 | 169 | 88.5 | -0.6 | -7.03, 5.73 |
| Week 40 | 191 | 165 | 86.4 | -0.4 | -7.29, 6.58 |
| Week 52 | 186 | 162 | 87.1 | -0.7 | -7.47, 6.11 |
| **EU-Stelara/AVT04 n=184 [2]** | - | - | - | [1] vs [2] | - |
| Week 16 | 184 | 167 | 90.8 | -5.4 | -11.95, 1.11 |
| Week 28 | 184 | 164 | 89.1 | -0.6 | -7.03, 5.73 |
| Week 40 | 180 | 164 | 91.1 | -4.7 | -11.12, 1.67 |
| Week 52 | 178 | 162 | 91.0 | -3.9 | -10.31, 2.48 |
| **EU-Stelara/EU-Stelara n=184 [3]** | - | - | - | [2] vs [3] | - |
| Week 16 | 184 | 158 | 85.9 | 4.9 | -1.65, 11.44 |
| Week 28 | 184 | 164 | 89.1 | 0.0 | -6.36, 6.36 |
| Week 40 | 181 | 157 | 86.7 | 4.4 | -2.09, 10.83 |
| Week 52 | 180 | 158 | 87.8 | 3.2 | -3.13, 9.60 |

From Baseline to the EOS, the proportion of patients achieving sPGA responses of clear (0) or almost clear (1) were similar in the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups, respectively.

Change in Dermatology Life Quality Index Scores from Baseline to Week 12

**Table 7.** Change from BL in Dermatology Life Quality Index–ITT Set–Up to Week 16 (All Patients)

| - | AVT04 | | | EU-Stelara | | |
|---|---|---|---|---|---|---|
| | N | Actual Value Mean (SD) | Change from Baseline Mean (SD) | n | Actual Value Mean (SD) | Change from Baseline Mean (SD) |
| **All patients** | | | | | | |
| Baseline | 194 | 15.47 (7.097) | - | 387 | 14.15 (7.278) | - |
| Week 12 | 194 | 2.99 (4.080) | -12.48 (7.141) | 384 | 2.69 (3.836) | -11.41 (7.928) |
| LS mean (SE) | - | - | -11.4 (0.379) | - | - | -11.5 (0.325) |
| LS means difference (SE) (AVT04 vs EU-Stelara) | - | - | 0.2 (0.34) | - | - | - |
| 95% confidence interval | - | - | -0.50, 0.84 | - | - | - |

From Baseline to Week 12, the mean Dermatology Life Quality Index (DLQI) score in the AVT04 group improved from 15.47 to 2.99, with a mean change of -12.48. During the same time period, the mean DLQI score in the EU-Stelara group improved from 14.10 to 2.65, with a mean change of -11.40. The LS mean difference (AVT04 vs EU-Stelara) was 0.2 (95% CI: -0.46, 0.87). Results were similar in patients with BW ≤100kg.

Change in Dermatology Life Quality Index Scores from Baseline to Week 52

**Table 11.25: Change from Baseline in Dermatology Life Quality Index – Intention-to-Treat Set – Up to End of Study (All Patients)**

| Time Point<br>Statistic | AVT04/AVT04 [1] (n=191) | | EU-Stelara/AVT04 [2] (n=184) | | EU-Stelara/EU-Stelara [3] (n=184) | |
|---|---|---|---|---|---|---|
| **Baseline** | **Actual Value** | **Change from Baseline** | **Actual Value** | **Change from Baseline** | **Actual Value** | **Change from Baseline** |
| N | 191 | - | 184 | - | 184 | - |
| Mean (SD) | 15.48 (7.149) | - | 14.77 (7.314) | - | 13.87 (7.258) | - |
| Median | 15.00 | - | 14.00 | - | 14.00 | - |
| Min, max | 1.0, 29.0 | - | 0.0, 30.0 | - | 0.0, 30.0 | - |
| **Week 28** | - | - | - | - | - | - |
| N | 191 | 191 | 184 | 184 | 183 | 183 |
| Mean (SD) | 2.06 (3.758) | -13.41 (6.933) | 1.82 (3.116) | -12.95 (7.705) | 2.31 (4.342) | -11.60 (7.827) |
| Median | 1.00 | -14.00 | 1.00 | -13.00 | 1.00 | -11.00 |
| Min, max | 0.0, 22.0 | -29.0, 0.0 | 0.0, 17.0 | -30.0, 2.0 | 0.0, 30.0 | -30.0, 6.0 |
| LS mean (SE) | - | -12.6 (0.366) | - | -12.7 (0.370) | - | -12.2 (0.371) |
| Comparison | - | [1] vs [3] | - | [1] vs [2] | - | [2] vs [3] |
| LS means difference (SE) | - | -0.4 (0.38) | - | 0.2 (0.38) | - | -0.6 (0.39) |
| 95% confidence interval | - | -1.15, 0.36 | - | -0.58, 0.93 | - | -1.33, 0.19 |
| **Week 40** | - | - | - | - | - | - |
| n | 190 | 190 | 179 | 179 | 181 | 181 |
| Mean (SD) | 2.21 (3.989) | -13.26 (7.177) | 1.83 (3.277) | -12.75 (7.434) | 2.30 (4.421) | -11.56 (8.105) |
| Median | 1.00 | -13.00 | 0.00 | -12.00 | 1.00 | -11.00 |
| Min, max | 0.0, 25.0 | -29.0, 6.0 | 0.0, 18.0 | -29.0, 3.0 | 0.0, 30.0 | -30.0, 19.0 |
| LS mean (SE) | - | -12.5 (0.388) | - | -12.8 (0.396) | - | -12.3 (0.399) |
| Comparison | - | [1] vs [3] | - | [1] vs [2] | - | [2] vs [3] |
| LS means difference (SE) | - | -0.2 (0.40) | - | 0.3 (0.40) | - | -0.5 (0.41) |
| 95% confidence interval | - | -1.03, 0.55 | - | -0.51, 1.08 | - | -1.33, 0.28 |

| Time Point<br>Statistic | AVT04/AVT04 [1] (n=191) | | EU-Stelara/AVT04 [2] (n=184) | | EU-Stelara/EU-Stelara [3] (n=184) | |
|---|---|---|---|---|---|---|
| Baseline | Actual Value | Change from Baseline | Actual Value | Change from Baseline | Actual Value | Change from Baseline |
| Week 52 | - | - | - | - | - | - |
| n | 185 | 185 | 178 | 178 | 180 | 180 |
| Mean (SD) | 1.77 (3.472) | -13.78 (7.083) | 1.42 (2.850) | -13.20 (7.302) | 1.75 (3.862) | -12.09 (7.810) |
| Median | 0.00 | -14.00 | 0.00 | -13.00 | 0.00 | -12.00 |
| Min, max | 0.0, 22.0 | -29.0, 0.0 | 0.0, 14.0 | -30.0, 2.0 | 0.0, 24.0 | -30.0, 8.0 |
| LS mean (SE) | - | -12.8 (0.342) | - | -13.1 (0.344) | - | -12.7 (0.348) |
| Comparison | - | [1] vs [3] | - | [1] vs [2] | - | [2] vs [3] |
| LS means difference (SE) | - | -0.1 (0.35) | - | 0.3 (0.35) | - | -0.4 (0.36) |
| 95% confidence interval | - | -0.83, 0.56 | - | -0.43, 0.96 | - | -1.10, 0.30 |

Baseline was defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient received the first dose of study drug (Day 1).
Two-sided 95% CIs for the difference in least squares means between AVT04 and EU-Stelara groups were obtained from an ANCOVA model including change from Baseline in Dermatology Life Quality Index as response variable, randomized treatment and stratification factor (prior biologic therapy)
as factors, and with Baseline PASI score and Baseline body weight as continuous covariates.
Missing DLQI was not imputed.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; DLQI = Dermatology Life Quality Index; EU = European Union; LS = least squares; PASI = Psoriasis Area and Severity Index; SD = standard deviation; SE = standard error.
Source: Table 14.2.2.5.3

The improvement in DLQI scores from Baseline broadly increased over time, was similar between the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups at time points up to Week 52 (EoS). Similar results were observed for patients with body weight ≤100 kg.

Change in Percentage Body Surface Area Affected by Chronic Plaque Psoriasis from Baseline to Weeks 4, 8, 12, 16

**Table 8.** Change from Baseline in Percentage of Body Surface Area Affected by Psoriasis Evaluation – Intention-to-Treat Set – Up to Week 16 (All Patients)

| | Actual Value | | | | Change from Baseline | | | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean (SD) | Median | Min, Max | n | Mean (SD) | Median | Min, Max |
| All patients | | | | | | | | |
| AVT04 (n=194) | | | | | | | | |
| Baseline | 194 | 26.02 (13.231) | 23.00 | 10.0, 75.0 | - | - | - | - |
| Week 4 | 194 | 19.94 (12.570) | 17.00 | 0.0, 73.0 | 194 | -6.08 (8.853) | -2.00 | -58.4, 3.0 |
| Week 8 | 193 | 12.23 (11.192) | 10.00 | 0.0, 52.5 | 193 | -13.80 (12.274) | -11.00 | -67.0, 7.0 |
| Week 12 | 194 | 6.75 (8.830) | 4.00 | 0.0, 52.5 | 194 | -19.27 (12.377) | -17.75 | -70.0, 1.0 |
| Week 16 | 193 | 4.81 (7.623) | 2.00 | 0.0, 52.5 | 193 | -21.27 (12.485) | -19.00 | -70.0, 1.0 |
| EU-Stelara (n=387) | | | | | | | | |
| Baseline | 387 | 26.41 (12.256) | 23.00 | 10.0, 84.0 | - | - | - | - |
| Week 4 | 387 | 20.45 (12.170) | 18.00 | 0.0, 76.0 | 387 | -5.96 (9.788) | -3.00 | -72.8, 33.2 |
| Week 8 | 384 | 11.89 (11.100) | 10.00 | 0.0, 73.0 | 384 | -14.49 (12.361) | -12.75 | -79.8, 6.0 |
| Week 12 | 384 | 6.35 (7.827) | 4.00 | 0.0, 50.0 | 384 | -20.11 (13.436) | -18.00 | -81.0, 20.0 |
| Week 16 | 382 | 4.08 (6.210) | 2.00 | 0.0, 38.0 | 382 | -22.44 (13.156) | -20.00 | -83.0, 4.0 |

From Baseline to Week 16, mean (SD) %BSA in the AVT04 group improved from 26.02 to 4.81, with a mean change of -21.27 at Week 16. During the same time period, the mean (SD) %BSA in the EU-Stelara group improved from 26.41 to 4.08, with a mean change of -22.44 at Week 16.

**Table 9.** Change from Baseline in Percentage of Body Surface Area Affected by Psoriasis Evaluation – Intention-to-Treat Set – Up to End of Study (All Patients)

| | Actual Value | | | | Change from Baseline | | | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean (SD) | Median | Min, Max | n | Mean (SD) | Median | Min, Max |
| **All patients** | | | | | | | | |
| **AVT04/AVT04 (n=191)** | | | | | | | | |
| Baseline | 191 | 26.14 (13.292) | 23.00 | 10.0, 75.0 | | | | |
| Week 16 | 191 | 4.78 (7.612) | 2.00 | 0.0, 52.5 | 191 | -21.36 (12.508) | -19.00 | -70.0, 1.0 |
| Week 28 | 191 | 2.58 (5.206) | 1.00 | 0.0, 52.5 | 191 | -23.56 (12.899) | -21.00 | -73.5, -3.0 |
| Week 40 | 191 | 2.22 (4.409) | 0.50 | 0.0, 39.5 | 191 | -23.92 (12.902) | -22.00 | -73.5, -3.0 |
| Week 52 | 186 | 1.77 (3.857) | 0.00 | 0.0, 36.2 | 186 | -24.50 (12.989) | -21.75 | -75.0, -2.0 |
| **EU-Stelara/AVT04 (n=184)** | | | | | | | | |
| Baseline | 184 | 26.83 (12.711) | 24.00 | 10.0, 84.0 | - | - | - | - |
| Week 16 | 184 | 3.53 (5.757) | 1.65 | 0.0, 34.0 | 184 | -23.31 (13.516) | -20.50 | -83.0, 0.0 |
| Week 28 | 184 | 2.12 (3.688) | 1.00 | 0.0, 33.5 | 184 | -24.71 (12.919) | -22.00 | -83.0, -5.6 |
| Week 40 | 180 | 1.44 (3.101) | 0.00 | 0.0, 32.0 | 180 | -25.09 (12.805) | -22.00 | -84.0, -5.6 |
| Week 52 | 178 | 1.32 (3.035) | 0.00 | 0.0, 29.6 | 178 | -25.32 (12.558) | -22.00 | -84.0, -7.2 |

| | Actual Value | | | | Change from Baseline | | | |
|---|---|---|---|---|---|---|---|---|
| Time Point | n | Mean (SD) | Median | Min, Max | n | Mean (SD) | Median | Min, Max |
| **EU-Stelara/EU-Stelara (n=184)** | | | | | | | | |
| Baseline | 184 | 26.11 (11.471) | 23.00 | 10.0, 73.0 | - | - | - | - |
| Week 16 | 184 | 4.22 (6.214) | 2.00 | 0.0, 38.0 | 184 | -21.89 (12.041) | -20.00 | -59.0, 0.0 |
| Week 28 | 184 | 2.63 (4.154) | 1.00 | 0.0, 29.0 | 184 | -23.48 (11.539) | -21.25 | -73.0, 0.0 |
| Week 40 | 181 | 1.71 (2.778) | 0.40 | 0.0, 23.0 | 181 | -24.37 (11.437) | -22.00 | -73.0, 1.0 |
| Week 52 | 180 | 1.83 (6.301) | 0.00 | 0.0, 79.0 | 180 | -24.25 (12.542) | -22.00 | -73.0, 42.0 |

From Baseline to EoS, the improvement in %BSA affected by chronic PsO was similar for the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups.

Similar results were observed for patients with body weight ≤100kg.

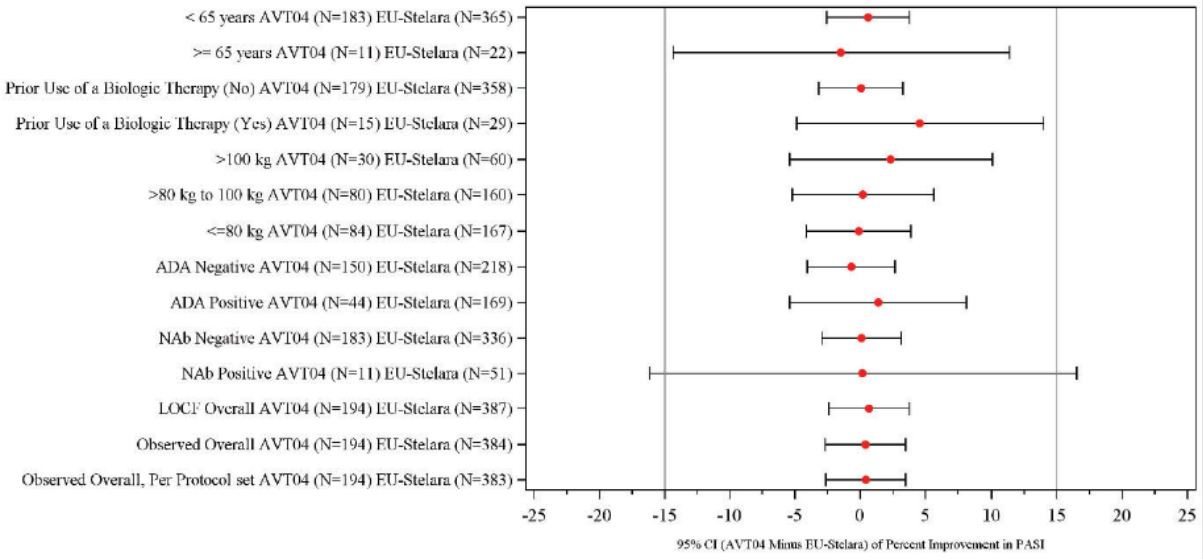
***Ancillary analyses***

The homogeneity of treatment effect across stratification factors (body weight [≤80 kg, >80 kg to ≤100 kg, >100 kg, (as well as body weight ≤100 kg and overall)] and previous biologic treatment for PsO [yes/no]) was investigated.

In addition, the following subgroup analyses were presented:

- Age Group (< 65 years, ≥ 65 years)
- Gender (Male, Female)
- ADA status up to Week 12 (Positive, Negative)
- nAb status up to Week 12 (Positive, Negative)

**Figure 11.4: Forest Plot of 95% Confidence Interval of Percent Improvement from Baseline in Psoriasis Area and Severity Index at Week 12 – Intention-to-Treat Set – Up to Week 16**




The subgroup analysis results of percent improvement from Baseline up to Week 16 in the subset of patients by body weight, prior biologic therapy for psoriasis, age, gender, ADA status, and nAb status did not reveal any major differences between the treatment groups.

Impact of Covid-19

Protocol deviations related to COVID-19 were to be captured and presented in tables and listings according to country-specific COVID-19 guidelines.

### *2.6.5.3. Summary of main efficacy results*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 10.** Summary of efficacy for trial AVT04-GL-301

| **Title: Randomized, Double-blind, Multicenter Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Ustekinumab (AVT04) and Stelara® in Patients with Moderate to Severe Chronic Plaque-type Psoriasis** | | |
|---|---|---|
| Study identifier | EudraCT-Number 2020-004493-22 | |
| Design | randomized, double-blind, parallel, 2-arm, 2 stage, active control, multicenter | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | 03 Jun 2021 – ongoing<br>not applicable<br>not applicable |
| Hypothesis | Equivalence | |

| **Title: Randomized, Double-blind, Multicenter Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Ustekinumab (AVT04) and Stelara® in Patients with Moderate to Severe Chronic Plaque-type Psoriasis** | | | | |
|---|---|---|---|---|
| Study identifier | EudraCT-Number 2020-004493-22 | | | |
| Treatments groups | Group 1 (Day 1 – Week 52) | | Patients received two doses of AVT04 45 mg (≤100 kg) or 90 mg (>100 kg) administered SC, with 4 weeks interval, followed by the same dose once every 12 weeks up to Week 40 (EoT); last assessments to be performed at Week 52 (EoS)<br>194 patients randomized to AVT04 | |
| | Group 2 (Day 1-Week 15) | | Patients received an initial dose of EU-Stelara 45 mg (≤100 kg) or 90 mg (>100 kg) administered SC, followed by 45 mg or 90 mg 4 weeks later.<br>387 patients randomized to EU-Stelara | |
| | Week 16- Week 52:<br>At Week 16 patients from Group 2 were re-randomized in a 1:1 ratio into Group 2A and Group 2B | | Group 2A (EU-Stelara/AVT04): Patients started receiving AVT04 45 mg or 90 mg SC every 12 weeks, at Weeks 16, 28, and 40 (unless withdrawn from the study).<br>192 patients re-randomized to AVT04 | Group 2B (EU-Stelara/EU-Stelara): Patients continued to receive EU-Stelara 45 mg or 90 mg SC every 12 weeks, at Weeks 16, 28, and 40 (unless withdrawn from the study).<br>189 patients re-randomized to EU-Stelara |
| | | | | |
| Endpoints and definitions | Primary endpoint | Percent improvement in PASI from BL to W12. | Percent improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12. Clinical similarity is demonstrated if the 95% CI for the adjusted mean difference in percentage PASI improvement between test and reference groups is contained within the range [-15%, 15%] | |
| | Secondary endpoint | PASI50, PASI75, PASI90, and PASI100 | PASI50, PASI75, PASI90, and PASI100 response rates at Weeks 4, 8, 12, 16, 28, 40 (EoT), and 52 (EoS). | |
| | Secondary endpoint | Percent improvement in PASI | Percent improvement in PASI from Baseline to Weeks 4, 8, 16, 28, 40 (EoT), and 52 (EoS). | |
| | Secondary endpoint | AUEC | Area under the effect curve for PASI from Baseline through Week 12. | |
| | Secondary endpoint | sPGA responses of clear (0) or almost clear (1) | Proportion of patients achieving static Physician's Global Assessment (sPGA) responses of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16, 28, 40 (EoT), and 52 (EoS). | |
| | Secondary endpoint | Change in DLQI scores | Change in Dermatology Life Quality Index (DLQI) scores from Baseline to Weeks 12, 28, 40 (EoT), and 52 (EoS). | |
| | Secondary endpoint | Change in %BSA affected by PsO | Change in % body surface area (%BSA) affected by chronic PsO from Baseline to Weeks 4, 8, 12, 16, 28, 40 (EoT), and 52 (EoS). | |
| Database lock | Study is ongoing | | | |

| | | | |
|---|---|---|---|
| **Title: Randomized, Double-blind, Multicenter Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Ustekinumab (AVT04) and Stelara® in Patients with Moderate to Severe Chronic Plaque-type Psoriasis** | | | |
| Study identifier | EudraCT-Number 2020-004493-22 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis: Percent improvement in PASI from Baseline to Week 12** | | |
| Analysis population and time point description | Per protocol set – a subset of the ITT Set, which includes patients who have completed the study period up to Week 12 without protocol deviations that impact the efficacy assessment.<br>Primary analysis was conducted at Week 12 | | |
| Descriptive statistics and estimate variability | Treatment group | AVT04 (Group 1) | EU-Stelara (Group 2) |
| | Number of subject | 194 | 383 |
| | LS mean in percent improvement in PASI from BL to Week12 | 87.3% | 86.8% |
| | Standard error | 1.73% | 1.49% |
| Effect estimate per comparison | PEP: Percent improvement in PASI from Baseline to Week 12 | Comparison groups | AVT04 (Group1) vs. EU-Stelara (Group 2) |
| | | LS mean difference (SE) | 0.4 (1.56) |
| | | 95% confidence interval for difference | [-2.63, 3.50] |
| Notes | Clinical similarity is planned to be demonstrated if the 95% CI for the adjusted mean difference in percentage PASI improvement between test and reference groups is contained within the range [-15%, 15%]. However, no clinical justification for this wide range has been provided. Therefore, this range is not further used in the assessment. | | |
| **Analysis description** | **Primary Analysis: Percent improvement in PASI from Baseline to Week 12** | | |
| Analysis population and time point description | ITT set – all randomized patients who received at least one dose of randomly allocated treatment.<br>Primary analysis was conducted at Week 12 | | |
| Descriptive statistics and estimate variability | Treatment group | AVT04 (Group 1) | EU-Stelara (Group 2) |
| | Number of subject | 194 | 384* |
| | LS mean in percent improvement in PASI from BL to Week12 | 87.2% | 86.8% |
| | Standard error | 1.73% | 1.49% |
| Effect estimate per comparison | PEP: Percent improvement in PASI from Baseline to Week 12 | Comparison groups | AVT04 (Group1) vs. EU-Stelara (Group 2) |
| | | LS mean difference (SE) | 0.4 (1.56) |

| **Title: Randomized, Double-blind, Multicenter Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Ustekinumab (AVT04) and Stelara® in Patients with Moderate to Severe Chronic Plaque-type Psoriasis** | | | |
|---|---|---|---|
| Study identifier | EudraCT-Number 2020-004493-22 | | |
| | | 95% confidence interval for difference | [-2.66, 3.47] |
| **Analysis description** | **Secondary endpoint: Percent Improvement in PASI from Baseline to Week 4, 8, and 16** | | |
| **Analysis population and time point description** | ITT set: all randomized patients who received at least one dose of randomly allocated treatment.<br>Analyses were conducted at Weeks 4, 8 and 16 | | |
| Descriptive statistics and estimate variability | Treatment group | AVT04 (Group 1) | EU-Stelara (Group 2) |
| | Number of subject | 194 (Week 4)<br>193 (Week 8)<br>193 (Week 16) | 387 (Week 4)<br>384 (Week 8)<br>382 (Week 16) |
| | LS mean in percent improvement in PASI from BL to Week12 | 45.1% (Week 4)<br>75.2% (Week 8)<br>89.8% (Week 16) | 45.5% (Week 4)<br>76.0% (Week 8)<br>90.6% (Week 16) |
| | Standard error | 2.381% (Week 4)<br>2.098% (Week 8)<br>1.248% (Week 16) | 2.047% (Week 4)<br>1.803% (Week 8)<br>1.073% (Week 16) |
| Effect estimate per comparison | SEP: Percent improvement in PASI from Baseline to Week 4, 8 and 16 | Comparison groups | AVT04 (Group1) vs. EU-Stelara (Group 2) |
| | | LS mean difference (SE) | -0.4% (2.14) (Week 4)<br>-0.7% (1.89) (Week 8)<br>-0.8% (1.13) (Week 16) |
| | | 95% confidence interval for difference | [-4.60, 3.81] (Week 4)<br>[-4.44, 2.99] (Week 8)<br>[-3.04, 1.38] (Week 16) |

*3 patients were not included in the ITT analysis because of missing values in the endpoint.

In the context of a biosimilar application, only the most important efficacy results are presented above. The applicant has provided a table with all efficacy results included (data not presented).

### *2.6.5.4. Clinical studies in special populations*

Not applicable for biosimilars.

### *2.6.5.5. In vitro biomarker test for patient selection for efficacy*

Not applicable.

### *2.6.5.6. Analysis performed across trials (pooled analyses AND meta-analysis)*

Not applicable.

#### *2.6.5.7. Supportive study(ies)*

Not applicable.

## 2.6.6. Discussion on clinical efficacy

***Design and conduct of clinical studies***

The clinical development programme to compare clinical efficacy, safety and immunogenicity between AVT04 and EU-Stelara comprised a single randomized, double-blind, active-controlled phase III study (AVT04-GL-301). The study was designed to assess equivalence of AVT04 to Stelara in patients with moderate to severe plaque-type psoriasis (PsO).

The study comprised two stages: Stage 1 (Week 1 to 15) for assessment of primary efficacy; and Stage 2 (Week 16 to 52) for assessment of long-term efficacy and safety. On Day 1, eligible patients were randomized in a 1:2 ratio to AVT04 or EU-Stelara group. Patients with body weight ≤100 kg received a dose of 45mg ustekinumab subcutaneously (AVT04 or Stelara), while patients with body weight >100 kg received a dose of 90 mg (2x45mg) ustekinumab SC (AVT04 or Stelara) based on the weight measured at baseline. Initial loading doses were administered at Weeks 1 and 4, followed by same dose once every 12 weeks (Weeks 16, 28 and 40). At Week 16, patients initially randomized to AVT04 group continued to receive AVT04, while patients initially randomized to EU-Stelara were re-randomized in a 1:1 ratio either to switch to AVT04 or continue treatment with EU-Stelara. For an EU MA, the most relevant comparison is between patients continuously treated with AVT04 and patients who remained in EU-Stelara group after Week 16 (i.e. AVT04/AVT04 vs. EU-Stelara/EU-Stelara). Therefore, an early re-randomization after only two doses were administered is not ideal, as it reduces the number of patients who remain on EU-Stelara for the comparison of secondary endpoints, and a later time point for the transition would have been preferred. From Week 28, nonresponsive patients no longer received treatment, but were encouraged to stay in the study for safety and immunogenicity follow up. At Week 40 (EoT), all patients still on treatment received the final study drug administration. At Week 52 (EoS) all patients still on study underwent final efficacy and/or safety and immunogenicity assessments. The overall study design is acceptable, although a re-randomization at a later time point would have been preferred.

The study was conducted in patients with moderate-to-severe plaque-type psoriasis (PsO). Of all indications approved for Stelara (PsO, PsA, CD, UC), plaque-type psoriasis represents the most sensitive setting to demonstrate biosimilarity. Patients were required to have PsO for at least 6 months (with stable disease for at least 2 months), involved BSA ≥10%, PASI ≥12, and static Physicians Global Assessments sPGA ≥3 (moderate) at screening and at baseline and be candidates for systemic therapy with previous failure, inadequate response, intolerance, or contraindication to at least 1 systemic antipsoriatic therapy. Only one dose, 45 mg was initially planned to be used in the study, which is an adequate dose for patients with body weight ≤100kg. This was also endorsed during a scientific advice procedure, since BW is a major intrinsic factor affecting ustekinumab exposure and response. Nonetheless, the inclusion criterion regarding body weight was changed in one of the protocol amendments; and consequently, a dose of 90mg was added for patients with BW >100kg. This is considered suboptimal, as it introduces more variability and could reduce sensitivity. Generally, a narrower BW range at inclusion would ensure a more homogenous study population and investigation of only one dose would have been preferred. Apart from these issues, eligibility criteria were overall acceptable.

Study objectives are considered appropriate to compare the clinical efficacy, safety and tolerability, PK and immunogenicity of proposed biosimilar AVT04 and EU-Stelara. The primary efficacy endpoint was percent improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12. PASI is a

continuous endpoint that is considered sufficiently sensitive to detect potential differences between both treatments. Regarding the timing of the primary analysis, Week 12 is not considered the most sensitive time point to detect differences between treatments as the time/response curve already reaches the plateau by then, as pointed out by the CHMP during the scientific advice procedure. The CHMP recommended an earlier time point within the ascending part of the time/response curve (e.g. Week 8). Although the CHMP's recommendation was not followed, data on earlier timepoints is available and more weight was put on these analyses. Secondary efficacy endpoints including PASI50, PASI75, PASI90 PASI100, percent improvement in PASI from baseline over time, area under the effect curve for PASI from BL through Week 12, proportion of patients achieving static Physician''s Global Assessment (sPGA) responses of clear (0) or almost clear (1) at all visits up to Week 52, change in Dermatology Life Quality Index (DLQI) scores from BL at different time points and change in percentage body surface area (%BSA) affected by chronic PsO from BL to different time points up to Week 52 are considered relevant for the overall assessment of comparability in efficacy.

The non-inferiority margin of 15% was derived from the meta-analysis of the originator's registration studies (PHOENIX 1 and 2), which showed a treatment difference in mean PASI percent improvement from baseline to Week 12 of 70.7% (95% CI 69.1%, 72.3%). A 15% margin was expected to retain 78.3% of the original ustekinumab effect, which ensures that the biosimilar would be superior to putative placebo. While the statistical justification of the margin is acceptable, no clinical justification of the 15% non-inferiority margin has been provided. Nonetheless, as results of the primary analysis were within a rather small range (point estimate 0.4%, 95%CI -2.63%, 3.50% (PP); point estimate 0.4%, 95% CI -2.66%, 3.34% (ITT)] that is considered to exclude a clinically relevant difference, no issues are raised. Patient randomization was stratified by presence or absence of previous biologic treatment for PsO and body weight category (≤80kg, >80 kg to ≤100 kg, >100 kg).

Based on the information provided and the assumptions made, sample size and power calculations can be followed. Blinding procedures appear reasonable as regards planning and study conduct.

Of 581 patients who were randomized, 575 patients (99.0%) completed Stage 1 (Week 16) and 559 patients (97.4%) completed Week 28. Overall, 544 patients (97.3% of the patients who completed Week 28) completed Stage 2 up to Week 52 (EoS). No patient discontinued the treatment at Week 28 due to being a non-responder.

Overall, 466 patients (80.2%) had at least 1 protocol deviation, of which 111 patients (19.1%) had major and 455 patients (78.3%) had minor protocol deviations. The most common major protocol deviations were related to patient visits-UKR crisis (46 patients [7.9%]), study procedures-out of window-UKR crisis (20 patients [3.4%]), and study procedures-lab issues (14 patients [2.4%]). The number of patients with major PD increased markedly since the last submitted data, when only 9 patients (1.5%) had major PD. The proportion of patients affected by the protocol deviations was comparable between arms. These PDs occurred after the primary efficacy analysis, and therefore do not impact the results of the primary analysis. In addition to the patient-level protocol deviations, site or study-level minor protocol deviations were recorded, all of which were related to registration of IP shipments to the IRT system. These PDs are not considered to have a relevant effect on the study integrity.

Overall, the study population is considered representative of the target population in plaque-type psoriasis; baseline characteristics were comparable between study arms.

Several audits were performed by the Sponsor for study AVT04-GL-101 that were relevant to the study and no critical audit findings were observed.

***Efficacy data and additional analyses***

The per-protocol analysis set was used for the analysis of the primary endpoint. An ITT analysis was defined as sensitivity analysis by the Applicant. However, in an equivalence setting, both ITT and PP analyses set are considered equally relevant and therefore considered primary.

The definition of the analysis sets, except for the PP set, was consistent across protocol versions, SAP and CSR. Whereas in the latest protocol, the PP set was defined at week 12, 16, 28 and end of study, it was only defined at week 12 in the SAP. This is probably due to the fact, that the secondary efficacy endpoint evaluation was reduced to be done in the ITT set only but not in the PP set. This does not trigger further concern.

Of note, the Applicant included all randomised patients receiving at least one dose in the ITT set. As the ITT set usually comprises all patients who were randomised without considering the receipt of treatment, the chosen approach corresponds to a "modified ITT" principle. However, no concern is raised since the number of participants in the randomized set is equal to the number in the ITT set up to week 16.

Some discrepancies were found in the ITT analysis of the PEP. These pertain to the number of subjects in the EU-Stelara group (387 vs 384 in all patients; 327 vs 324). These numbers correspond to the number is the PP set. The applicant explained that 3 patients were not included in the ITT analysis because of missing values in the endpoint. For an ITT analysis, all randomised patients should be included. The mentioned analysis using LOCF as imputation method would only be appropriate if it can be assumed that the PASI stays constant, and the missing at random (MAR) assumption is valid. Since patients discontinued or had adverse events, this assumption might not be reasonable. However, from an assessment perspective, it is very unlikely that the impact would be of a magnitude which would alter the general study conclusions. Results for secondary endpoints are provided for ITT set only, which can be accepted, as differences in number of patients between ITT and PP sets are negligible.

In general, the statistical methods chosen for descriptive as well as inferential analyses are considered suitable. The use of an ANCOVA for the primary efficacy evaluation of percent improvement in PASI from baseline up to week 12 is endorsed. Although the primary efficacy endpoint was evaluated in the PP up to week 12, the corresponding sensitivity analysis was conducted in the ITT set up to week 16. However, the analysis in the ITT set at week 16 as well as the analysis in the PP set at week 12 are considered both primary in our CHMP's assessment.

In the protocol, safety analyses were to be conducted per treatment group and overall. However, in the CSR the numbers are given only per treatment group. The assessment is not hampered by this.

The applicant has presented demographic and baseline characteristics for the ITT Set up to Week 16 and Week 28 (following re-randomization at Week 16). Up to Week 16, treatment arms (AVT04 and EU Stelara) were comparable with regard to age, weight (including percentage of patients in each BW category) and BMI, prior biologic therapy for PsO and baseline disease severity (measured by PASI, sPGA, %BSA affected). The majority of patients was naïve to biologic therapy for psoriasis (92.4%). In patients with BW ≤100kg the results were similar to those as described for overall patients. Up to Week 16, the treatment group contained all White patients (100.0%) and was predominantly male (62.7%), with few patients over the age of 65 years (5.7%). Most of the patients were not Hispanic or Latino (99.3%). The mean (SD) height, weight, and body mass index (BMI) were 173.30 (9.204) cm, 83.96 (18.468) kg, and 27.87 (5.425) kg/m2 at Screening. Only 7.6% of patients had prior biologic therapy for psoriasis. The mean (SD) PASI, %BSA, and duration of chronic PsO from informed consent were 22.17 (7.742), 26.28 (12.579), and 198.5 (137.53) months, respectively. Most of the patients (64.2%) had moderate sPGA. A lower percentage of patients had severe (28.6%) and very severe (7.2%) sPGA. In patients with BW ≤100kg the results were similar to those as described for overall patients. In the ITT Set, for up to Week 28, demographic and other baseline characteristics were

similar between the treatment groups (AVT04/AVT04, EU-Stelara/AVT04 and EU Stelara/EU-Stelara). The study population is considered representative of the target population in plaque-type psoriasis.

The least squares (LS) mean for percent improvement in PASI from baseline to Week 12 was comparable between AVT04 group (87.3%) and the EU-Stelara group (86.8%) in the PP analysis set. The results were also similar for the ITT set (87.2% versus 86.8% in the AVT04 and EU-Stelara group, respectively. The LS mean difference (AVT04 vs EU-Stelara) was 0.4% (95% CI -2.63%, 3.50%) for PP analysis; and 0.4% (95% CI -2.66%, 3.34%) for ITT analysis. The pre-specified acceptance range [-15%, 15%] had not been clinically justified and appears large. However, as the 95% CI for both the ITT and the PP analysis clearly demonstrated equivalent efficacy of the two treatments within a narrow range, clinical comparability can be concluded. Similar results were also reported in the subset of patients with BW≤100kg.

However, as mentioned previously, as Week 12 is not considered the most sensitive time point to detect differences between treatments, more weight was put on analyses at earlier time points within the ascending part of the time/response curve. At Week 4 and 8, the LS mean differences (AVT04 vs EU-Stelara) were -0.4% (95% CI -4.60%, 3.81%) and -0.7% (95%CI -4.4%, 2.99%), respectively for the ITT analysis. For the PP analyses at Week 4 and 8, the LS mean differences (AVT04 vs EU-Stelara) were -0.6% (95% CI -4.77%, 3.66%) and -0.8% (95%CI -4.56%, 2.87%), respectively.

While in principle the equivalence margin would have had to be revised in order to be aligned with the endpoint at Week 4 or Week 8, observed differences can be considered sufficiently small (as assessed by the 95% CIs) and acceptable. The percent improvement in PASI was similar between the AVT04 and EU-Stelara group from baseline to Week 16, and similar between AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups up to Week 52 (EoS). The results for patients with body weight ≤100kg were similar to that of all patients.

With regard to the results for Percentage of Patients Achieving PASI50, PASI75, PASI90, and PASI100 Up to Week 16, the proportion of responders for the majority of PASI response rates was slightly lower with AVT04 compared to EU-Stelara. The results for patients with body weight ≤100kg were similar to that of all patients. The proportion of patients achieving PASI50, PASI75, PASI90, and PASI100 broadly increased over time, was similar between the AVT04 and EU-Stelara groups at time points up to Week 12, and, after rerandomization at Week 16, was similar between the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara groups at time points up to Week 52 (EoS). Similar results were observed for patients with body weight ≤100 kg.

The LS mean for area under the effect Curve for PASI from Baseline Through Week 12 was slightly lower for AVT04 group (632.85 in AVT04 group vs. 647.10 in EU-Stelara group), though not significantly. LS mean difference (AVT04 vs EU-Stelara) was -14.25 (95% CI -48.608, 20.111) (ITT set).

Similar results between treatments were observed with respect to (1) Proportion of Patients Achieving sPGA Responses of Clear (score 0) or Almost Clear (score 1) at various time points from BL through Week 52; (2) Change in DLQI Scores from Baseline to Week 12 and; (3) Change in %BSA affected by PsO at various time points from BL through Week 52.

The subgroup analysis results of percent improvement from Baseline up to Week 16 in the subset of patients by body weight, prior biologic therapy for psoriasis, age, gender, ADA status, and nAb status did not reveal any major differences between the treatment groups.

## 2.6.7. Conclusions on clinical efficacy

Primary efficacy endpoint analysis at Week 12 showed clinical similarity between the AVT04 group and the EU-Stelara group. Secondary efficacy endpoint analyses support the clinical similarity between the two products. No clinically relevant differences between the two treatments were observed in the later stage of the study i.e. up to Week 52.

## 2.6.8. Clinical safety

Safety data on AVT04 is available from two clinical studies (Study AVT04-GL-101 and Study AVT04-GL-301), where safety was assessed as part of the secondary study objectives.

Study AVT04-GL-101 was conducted in healthy subjects following single dose administration and Study AVT04-GL-301 was conducted in patients with PsO following multiple dose administration. Thus, a single pooled safety analysis of both studies was not considered meaningful and safety results are discussed below per individual study.

In all individual clinical studies, safety analyses were carried out using the safety population, which was defined as all randomized subjects who received at least one dose of the IP or comparator, with treatment assignment based on the actual treatment received.

In the PK study AVT04-GL-101, efforts were made to include at least 10% of subjects (30 subjects, i.e., 10 per group) who are of Japanese origin or ethnicity to meet Japan's PMDA’ s requirements. In addition, randomization was stratified by two factors (categories), b.w. and ethnicity: non-Japanese subjects ≤80 kg, non-Japanese subjects >80 kg and Japanese subjects. As the PK of ustekinumab is known to be b.w. dependent, but not affected by age, gender, ethnicity or race, and as the sample size of Japanese subjects is considered too small to detect differences in safety aspects, the present safety assessment does not specifically discuss adverse events according to ethnicity.

### *2.6.8.1. Patient exposure*

In the clinical studies included in this application, the safety of AVT04 was investigated in 98 adult healthy male and female healthy subjects (Study AVT04-GL-101: single s.c. dose) and in 386 adult patients with chronic plaque psoriasis (PsO, Study AVT04-GL-301 multiple s.c. doses).

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

**Study AVT04-GL-101**

A total of 98 healthy adult subjects received a single 45 mg/0.5 mL s.c. dose of AVT04 on Day 1, 99 subjects received EU-Stelara and 97 subjects received US-Stelara (Safety population). The IP was administered according to the protocol in all subjects.

**Study AVT04-GL-301**

In Stage 1 (Day 1), eligible patients were randomly assigned in a 1:2 ratio to an initial dose of 45 or 2 x 45 mg/0.5 mL s.c. ustekinumab as AVT04 or EU approved Stelara followed by 45 mg or 2 x 45 mg/0.5 mL mg 4 weeks later, with the 2 x 45 mg/0.5mL recommended for patients with >100 kg body weight. At Stage 2 (Week 16) Group 1 receiving AVT04 continued with 45 mg or 2 x 45 mg/0.5 mL AVT04 at Week 16, 28 and 40 and Group 2 receiving EU-Stelara was randomly assigned to 45 or 2 x 45 mg/0.5 mL AVT04 at Week 16, 28 and 40 or continued receiving 45 or 2 x 45 mg/0.5 mL) mg EU-Stelara at Week 16, 28 and 40.

During Stage 1 up to Week 16, i.e. at baseline and at Week 4, all patients received the correct dose, except one patient with b.w. >100 kg in the EU-Stelara cohort who was then randomized to EU-Stelara/AVT04 group at Week 16. This patient received 45 mg dose (1 injection) instead of 90 mg dose (2 injections) of investigational product at Baseline and at Week 4 despite the fact that his/her weight at the Baseline Visit was over 100 kg. This was recorded as a major protocol deviation.

During Stage 2 from Week 16 to EOS, i.e. at Week 16, Week 28, and Week 40, all patients in the AVT04/AVT04, EU-Stelara/AVT04, and EU-Stelara/EU-Stelara cohorts who received study drug, received the correct dose, except one patient with b.w. >100 kg in the EU-Stelara/AVT04 cohort. This patient received 45 mg dose (1 injection) instead of 90 mg dose (2 injections) of investigational product at Week 16 despite the fact that his/her weight at the Baseline Visit was over 100 kg. As noted above, this was recorded as a major protocol deviation.

### *2.6.8.2. Adverse events*

**Study AVT04-GL-101: TEAEs in Healthy Subjects**

An overview of treatment emergent adverse events (TEAEs) is presented in the following table.

**Table 11.** Overview of TEAEs in Healthy Subjects (Study AVT04-GL-101, Safety Population)

| Category | Statistic | AVT04 | EU-Stelara | US-Stelara | Overall |
|---|---|---|---|---|---|
| **Healthy Subjects** | | | | | |
| | **N** | **98** | **99** | **97** | **294** |
| At least one TEAE | n (%) E | 67 (68.4) 151 | 67 (67.7) 155 | 69 (71.1) 190 | 203 (69.0) 496 |
| At least one related[1] TEAE | n (%) E | 34 (34.7) 46 | 34 (34.3) 59 | 43 (44.3) 61 | 111 (37.8) 166 |
| At least one TEAE of special interest[3] | n (%) E | 10 (10.2) 11 | 9 (9.1) 9 | 12 (12.4) 13 | 31 (10.5) 33 |
| At least one related[1] TEAE of special interest[3] | n (%) E | 9 (9.2) 9 | 8 (8.1) 8 | 11 (11.3) 12 | 28 (9.5) 29 |
| At least one TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | 3 (3.1) 3 | 5 (5.1) 5 | 2 (2.1) 2 | 10 (3.4) 10 |
| At least one related[1] TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | - | 1 (1.0) 1 | - | 1 (0.3) 1 |
| At least one serious TEAE[2] | n (%) E | 1 (1.0) 1 | 1 (1.0) 1 | 1 (1.0) 1 | 3 (1.0) 3 |
| At least one serious related TEAE[1,2] | n (%) E | - | - | - | - |
| Any TEAE leading to death | n (%) | - | - | - | - |
| Any TEAE leading to discontinuation from the study | n (%) | - | - | - | - |
| At least one TEAE by severity | | | | | |
| Mild | n (%) | 67 (68.4) | 65 (65.7) | 66 (68.0) | 198 (67.3) |
| Moderate | n (%) | 3 (3.1) | 8 (8.1) | 7 (7.2) | 18 (6.1) |
| Severe[4] | n (%) | 2 (2.0) | 3 (3.0) | 1 (1.0) | 6 (2.0) |
| At least one related[1] TEAE by severity | | | | | |
| Mild | n (%) | 33 (33.7) | 33 (33.3) | 41 (42.3) | 107 (36.4) |
| Moderate | n (%) | 1 (1.0) | 3 (3.0) | 3 (3.1) | 7 (2.4) |
| Severe[4] | n (%) | - | 1 (1.0) | - | 1 (0.3) |

| | | | | | |
|---|---|---|---|---|---|
| At least one TEAE of special interest by severity | | | | | |
| Mild | n (%) | 10 (10.2) | 8 (8.1) | 12 (12.4) | 30 (10.2) |
| Moderate | n (%) | - | 1 (1.0) | - | 1 (0.3) |
| Severe[4] | n (%) | - | - | - | - |
| At least one related[1] TEAE of special interest by severity | | | | | |
| Mild | n (%) | 9 (9.2) | 7 (7.1) | 11 (11.3) | 27 (9.2) |
| Moderate | n (%) | - | 1 (1.0) | - | 1 (0.3) |
| Severe[4] | n (%) | - | - | - | - |
| **Non-Japanese, ≤80 kg** | | | | | |
| | **N** | **98** | **99** | **97** | **294** |
| At least one TEAE | n (%) E | 52 (71.2) 115 | 52 (71.2) 127 | 50 (68.5) 150 | 154 (70.3) 392 |
| At least one related[1] TEAE | n (%) E | 26 (35.6) 36 | 28 (38.4) 50 | 33 (45.2) 50 | 87 (39.7) 136 |
| At least one TEAE of special interest[3] | n (%) E | 8 (11.0) 8 | 7 (9.6) 7 | 9 (12.3) 10 | 24 (11.0) 25 |
| At least one related[1] TEAE of special interest[3] | n (%) E | 7 (9.6) 7 | 6 (8.2) 6 | 8 (11.0) 9 | 21 (9.6) 22 |
| At least one TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | 2 (2.7) 2 | 3 (4.1) 3 | - | 5 (2.3) 5 |
| At least one related[1] TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | - | 1 (1.4) 1 | - | 1 (0.5) 1 |
| At least one serious TEAE[2] | n (%) E | 1 (1.4) 1 | 1 (1.4) 1 | - | 2 (0.9) 2 |
| At least one serious related TEAE[1,2] | n (%) E | - | - | - | - |
| Any TEAE leading to death | n (%) | - | - | - | - |
| Any TEAE leading to discontinuation from the study | n (%) | - | - | - | - |
| At least one TEAE by severity | | | | | |
| Mild | n (%) | 52 (71.2) | 51 (69.9) | 49 (67.1) | 152 (69.4) |
| Moderate | n (%) | 3 (4.1) | 5 (6.8) | 5 (6.8) | 13 (5.9) |
| Severe[4] | n (%) | 1 (1.4) | 2 (2.7) | - | 3 (1.4) |
| At least one related[1] TEAE by severity | | | | | |
| Mild | n (%) | 25 (34.2) | 27 (37.0) | 31 (42.5) | 83 (37.9) |
| Moderate | n (%) | 1 (1.4) | 3 (4.1) | 3 (4.1) | 7 (3.2) |
| Severe[4] | n (%) | - | 1 (1.4) | - | 1 (0.5) |
| At least one TEAE of special interest by severity[3] | | | | | |
| Mild | n (%) | 8 (11.0) | 6 (8.2) | 9 (12.3) | 23 (10.5) |
| Moderate | n (%) | - | 1 (1.4) | - | 1 (0.5) |
| Severe[4] | n (%) | - | - | - | - |
| At least one related[1] TEAE of special interest by severity[3] | | | | | |
| Mild | n (%) | 7 (9.6) | 5 (6.8) | 8 (11.0) | 20 (9.1) |
| Moderate | n (%) | - | 1 (1.4) | - | 1 (0.5) |
| Severe[4] | n (%) | - | - | - | - |

| Non-Japanese, >80 kg | | | | | |
|---|---|---|---|---|---|
| | **N** | **18** | **19** | **18** | **55** |
| At least one TEAE | n (%) E | 11 (61.1) 26 | 11 (57.9) 18 | 15 (83.3) 28 | 37 (67.3) 72 |
| At least one related[1] TEAE | n (%) E | 6 (33.3) 8 | 3 (15.8) 4 | 7 (38.9) 8 | 16 (29.1) 20 |
| At least one TEAE of special interest[3] | n (%) E | - | - | 2 (11.1) 2 | 2 (3.6) 2 |
| At least one related[1] TEAE of special interest[3] | n (%) E | - | - | 2 (11.1) 2 | 2 (3.6) 2 |
| At least one TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | 1 (5.6) 1 | 2 (10.5) 2 | 2 (11.1) 2 | 5 (9.1) 5 |
| At least one related[1] TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | - | - | - | - |
| At least one local administration site reaction[4] | n (%) E | - | - | 2 (11.1) 2 | 2 (3.6) 2 |
| At least one serious TEAE[2] | n (%) E | - | - | 1 (5.6) 1 | 1 (1.8) 1 |
| At least one serious related TEAE[1,2] | n (%) E | - | - | - | - |
| Any TEAE leading to death | n (%) | - | - | - | - |
| Any TEAE leading to discontinuation from the study | n (%) | - | - | - | - |
| At least one TEAE by severity | | | | | |
| Mild | n (%) | 11 (61.1) | 10 (52.6) | 14 (77.8) | 35 (63.6) |
| Moderate | n (%) | - | 3 (15.8) | 1 (5.6) | 4 (7.3) |
| Severe[4] | n (%) | 1 (5.6) | - | 1 (5.6) | 2 (3.6) |
| At least one related[1] TEAE by severity | | | | | |
| Mild | n (%) | 6 (33.3) | 3 (15.8) | 7 (38.9) | 16 (29.1) |
| Moderate | n (%) | - | - | - | - |
| Severe[4] | n (%) | - | - | - | - |
| At least one TEAE of special interest by severity | | | | | |
| Mild | n (%) | - | - | 2 (11.1) | 2 (3.6) |
| Moderate | n (%) | - | - | - | - |
| Severe[4] | n (%) | - | - | - | - |
| At least one related[1] TEAE of special interest by severity | | | | | |
| Mild | n (%) | - | - | 2 (11.1) | 2 (3.6) |
| Moderate | n (%) | - | - | - | - |
| Severe[4] | n (%) | - | - | - | - |
| **Japanese** | | | | | |
| | **N** | **7** | **7** | **6** | **20** |
| At least one TEAE | n (%) E | 4 (57.1) 10 | 4 (57.1) 10 | 4 (66.7) 12 | 12 (60.0) 32 |
| At least one related[1] TEAE | n (%) E | 2 (28.6) 2 | 3 (42.9) 5 | 3 (50.0) 3 | 8 (40.0) 10 |
| At least one TEAE of special interest[3] | n (%) E | 2 (28.6) 3 | 2 (28.6) 2 | 1 (16.7) 1 | 5 (25.0) 6 |
| At least one related[1] TEAE of special interest[3] | n (%) E | 2 (28.6) 2 | 2 (28.6) 2 | 1 (16.7) 1 | 5 (25.0) 5 |

| | | | | | |
|---|---|---|---|---|---|
| At least one TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | - | - | - | - |
| At least one related[1] TEAE of laboratory abnormality of at least CTCAE Grade 3 | n (%) E | - | - | - | - |
| At least one serious TEAE[2] | n (%) E | - | - | - | - |
| At least one serious related[1] TEAE[2] | n (%) E | - | - | - | - |
| Any TEAE leading to death | n (%) | - | - | - | - |
| Any TEAE leading to discontinuation from the study | n (%) | - | - | - | - |
| At least one TEAE by severity | | | | | |
| Mild | n (%) | 4 (57.1) | 4 (57.1) | 3 (50.0) | 11 (55.0) |
| Moderate | n (%) | - | - | 1 (16.7) | 1 (5.0) |
| Severe[4] | n (%) | - | 1 (14.3) | - | 1 (5.0) |
| At least one related[1] TEAE by severity | | | | | |
| Mild | n (%) | 2 (28.6) | 3 (42.9) | 3 (50.0) | 8 (40.0) |
| Moderate | n (%) | - | - | - | - |
| Severe[4] | n (%) | - | - | - | - |
| At least one TEAE of special interest by severity[3] | | | | | |
| Mild | n (%) | 2 (28.6) | 2 (28.6) | 1 (16.7) | 5 (25.0) |
| Moderate | n (%) | - | - | - | - |
| Severe[4] | n (%) | - | - | - | - |
| At least one related[1] TEAE of special interest by severity[3] | | | | | |
| Mild | n (%) | 2 (28.6) | 2 (28.6) | 1 (16.7) | 5 (25.0) |
| Moderate | n (%) | - | - | - | - |
| Severe[4] | n (%) | - | - | - | - |

Adverse Events were coded according to MedDRA Version 24.0

[1] Related TEAE: any TEAE reported as having a possible, probable or highly probable relationship to IP including events with a missing relationship. AES with missing relationship to IP were classified as 'Related'.

[2] Serious TEAE: any TEAE for which 'Serious event' is indicated as 'Yes'.

[3] TEAE of special interest: any AE considered to be of special interest per protocol.

[4] AES with missing severity were classified as 'severe'.

AE=adverse event; CTCAE= Common Terminology Criteria for AE; MedDRA=Medical Dictionary for Regulatory Activities; E=Number of TEAEs in each category; N=number of subjects; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent AE defined as any AE which commenced or worsened in severity on or after the start of IP administration;
%=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

Overall, 69% of subjects reported at least 1 TEAE during the study. A total of 67 subjects (68.4%) reported 151 TEAEs in the AVT04 cohort, 67 (67.7%) reported 155 TEAEs in the EU-Stelara cohort and 69 subjects (71.1%) reported 190 TEAEs in the US-Stelara cohort. Most TEAEs were mild in the AVT04 cohort (67 subjects [68.4%]), in the EU-Stelara cohort (65 subjects [65.7%]), and in the US-Stelara cohort (66 subjects [68.0%]). Two subjects (2.0%) in the AVT04 cohort reported severe TEAEs, 3 subjects (3.0%) in the EU-Stelara cohort, and 1 patient (1.0%) in the US-Stelara cohort reported severe TEAEs. A total of 34 subjects (34.7%) reported 46 **treatment-related TEAEs** in the AVT04 cohort, 34 subjects (34.3%) reported 59 treatment-related TEAEs in the EU-Stelara cohort, and 43

subjects (44.3%) reported 61 treatment-related TEAEs in the US-Stelara cohort. In the subgroup "non-Japanese >80 kg" more subjects reported treatment-related TEAEs in the AVT04 cohort compared to the EU-Stelara cohort (AVT04: 6 subjects (33.3%) reported 8 events; EU-Stelara: 3 subjects (15.8%) reported 4 events).

One patient (1.0%) in the AVT04 cohort had 1 **serious** TEAE (which was assessed as unrelated to treatment), 1 patient (1.0%) in the EU-Stelara cohort had 1 serious TEAE (unrelated), and 1 patient (1.0%) in the US-Stelara cohort had 1 serious TEAE (unrelated). No patient in the AVT04 cohort had TEAEs that led to IP discontinuation. A total of 11 TEAEs of special interest were reported in 10 subjects (10.2%) in the AVT04 cohort, 9 **TEAEs of special interest** were reported in 9 subjects (9.1%) in the EU-Stelara cohort, and 13 TEAEs of special interest were reported in 12 subjects (12.4%) in the US-Stelara cohort; most TEAESIs were mild and none were severe. Frequencies of ISRs were also balanced and were all assessed as mild. The frequency of Grade 3 laboratory abnormalities was low (3.4% of subjects overall), and similar across cohorts. One subject in the EU approved Stelara cohort had a Grade 3 laboratory abnormality of neutropenia that was IP-related. No patient died in the study. No TEAEs leading to study discontinuation occurred during the study.

By **SOC**, the most frequently reported **TEAEs** were (in % healthy subjects; AVT04, EU-Stelara, and US-Stelara cohorts, respectively): nervous system disorders (25.5%, 19.2%, and 28.9%); general disorders and administration site conditions (20.4%, 17.2%, and 27.8%); infections and infestations (24.5%, 26.3%, and 26.8%); musculoskeletal and connective tissue disorders (12.2%, 13.1%, and 12.4%); injury, poisoning and procedural complications (15.3%, 8.1%, 13.4%), gastrointestinal disorders (7.1%, 15.2%, and 13.4%).

By **PT**, the most frequently-reported TEAEs were (in % healthy subjects; AVT04, EU-Stelara, and US-Stelara cohorts, respectively): headache (19.4%, 14.1%, and 19.6%), upper respiratory tract infection (11.2%, 19.2%, and 17.5%), injection site erythema (4.1%, 4.0%, and 5.2%), back pain (4.1%, 5.1%, and 2.1) and fatigue (2.0%, 2.0%, and 6.2%).

Overall, AVT04 and EU-Stelara had similar results on the distributions of TEAEs (by SOC and PT) in cohorts in healthy subjects except for headache, which was more frequently observed in the AVT04 cohort (19.4%) than in the EU-Stelara cohort (14.1%); nausea, which was only observed in the EU-Stelara cohort (6.1%) but not with AVT04 (0%); and upper respiratory tract infection, which was more frequently observed in the EU-Stelara cohort (19.2%) than in the AVT04 cohort (11.2%).

By **SOC**, the most frequently-reported **treatment related TEAEs** were (in % healthy subjects; AVT04, EU-Stelara, and US-Stelara cohorts, respectively): nervous system disorders (14.3%, 10.1%, 11.3%), general disorders and administration site conditions (10.2%, 10.1%, and 14.4%), infections and infestations (9.2%, 8.1%, and 9.3%), gastrointestinal disorders (3.1%, 7.1%, and 9.3%), skin and subcutaneous tissue disorders (1.0%, 3.0%, and 6.2%), and respiratory, thoracic and mediastinal disorders (0%, 3.0%, 2.1%).

By **PT**, the most frequently-reported **treatment-related TEAEs** were (in % healthy subjects; AVT04, EU-Stelara, and US-Stelara cohorts, respectively): headache 12.2%, 7.1%, and 9.3%), injection site erythema (4.1%, 4.0%, 5.2%), upper respiratory tract infection (3.1%, 4.0%, and 4.1%), nausea (0%, 6.1%, 3.1%), fatigue (1.0%, 2.0%, 3.1%), dizziness (1.0%, 3.0%, 1.0%), vomiting (0%, 3.0%, 2.1%), and rash (0%, 1.0%, 3.1%). The number of most treatment-related TEAEs by SOC and PT was similar for AVT04, EU-Stelara and US-Stelara.

In summary, the number of treatment-related TEAEs by SOC and PT was higher for EU-Stelara (and US-Stelara) for gastrointestinal disorders (especially nausea and vomiting), Respiratory, thoracic and mediastinal disorders and rash. In contrast to this, there was an increased number for PT headache in

the AVT04 cohort compared to EU-Stelara (and US-Stelara). More treatment-related TEAEs were observed with AVT04 compared to EU-Stelara in the non-Japanese >80 kg subgroup.

The only severe treatment-related TEAE was a case of neutropenia in the EU-Stelara cohort. Related TEAEs of moderate severity were: one case of pneumonia in the AVT04 cohort; one case each of vomiting, lower abdominal pain and hypersensitivity in the EU Stelara cohort; one case each of otitis media, skin infection and decreased vitamin D in the US-Stelara cohort. All other related TEAEs were of mild severity.

Additional information regarding the incidence of TEAEs by maximum relationship to the IP is provided in the following table.

**Table 12.** Incidence of TEAEs (≥3% of Subjects in any Cohort) by Maximum Relationship to IP in Healthy Subjects (Study AVT04-GL-101, Safety Population)

| **System Organ Class Preferred Term** | | **Statistic** | **AVT04** | **EU-Stelara** | **US-Stelara** | **Overall** |
|---|---|---|---|---|---|---|
| | | **N** | **98** | **99** | **97** | **294** |
| At least one TEAE | Not related | n (%) | 33 (33.7) | 33 (33.3) | 26 (26.8) | 92 (31.3) |
| | Related | n (%) | 34 (34.7) | 34 (34.3) | 43 (44.3) | 111 (37.8) |
| Infections and infestations | Not related | n (%) | 15 (15.3) | 18 (18.2) | 17 (17.5) | 50 (17.0) |
| | Related | n (%) | 9 (9.2) | 8 (8.1) | 9 (9.3) | 26 (8.8) |
| Upper respiratory tract infection | Not related | n (%) | 8 (8.2) | 15 (15.2) | 13 (13.4) | 36 (12.2) |
| | Related | n (%) | 3 (3.1) | 4 (4.0) | 4 (4.1) | 11 (3.7) |
| Gastroenteritis | Not related | n (%) | 3 (3.1) | 1 (1.0) | 5 (5.2) | 9 (3.1) |
| | Related | n (%) | - | - | - | - |
| Nervous system disorders | Not related | n (%) | 11 (11.2) | 9 (9.1) | 17 (17.5) | 37 (12.6) |
| | Related | n (%) | 14 (14.3) | 10 (10.1) | 11 (11.3) | 35 (11.9) |
| Headache | Not related | n (%) | 7 (7.1) | 7 (7.1) | 10 (10.3) | 24 (8.2) |
| | Related | n (%) | 12 (12.2) | 7 (7.1) | 9 (9.3) | 28 (9.5) |
| Dizziness | Not related | n (%) | 1 (1.0) | 1 (1.0) | 2 (2.1) | 4 (1.4) |
| | Related | n (%) | 1 (1.0) | 3 (3.0) | 1 (1.0) | 5 (1.7) |
| General disorders and administration site conditions | Not related | n (%) | 10 (10.2) | 7 (7.1) | 13 (13.4) | 30 (10.2) |
| | Related | n (%) | 10 (10.2) | 10 (10.1) | 14 (14.4) | 34 (11.6) |
| Injection site erythema | Not related | n (%) | - | - | - | - |
| | Related | n (%) | 4 (4.1) | 4 (4.0) | 5 (5.2) | 13 (4.4) |
| Fatigue | Not related | n (%) | 1 (1.0) | - | 3 (3.1) | 4 (1.4) |
| | Related | n (%) | 1 (1.0) | 2 (2.0) | 3 (3.1) | 6 (2.0) |
| Vessel puncture site bruise | Not related | n (%) | 1 (1.0) | 3 (3.0) | 4 (4.1) | 8 (2.7) |
| **System Organ Class Preferred Term** | | **Statistic** | **AVT04** | **EU-Stelara** | **US-Stelara** | **Overall** |
| | Related | n (%) | - | - | - | - |
| Muscolosceletal and connective tissue disorders | Not related | n (%) | 9 (9.2) | 7 (7.1) | 11 (11.3) | 27 (9.2) |
| | Related | n (%) | 3 (3.1) | 6 (6.1) | 1 (1.0) | 10 (3.4) |
| Back pain | Not related | n (%) | 4 (4.1) | 3 (3.0) | 2 (2.1) | 9 (3.1) |
| | Related | n (%) | - | 2 (2.0) | - | 2 (0.7) |
| Arthralgia | Not Related | n (%) | 2 (2.0) | 3 (3.0) | 2 (2.1) | 7 (2.4) |
| | Related | n (%) | - | - | - | - |
| Injury, poisoning and procedural complications | Not Related | n (%) | 15 (15.3) | 8 (8.1) | 12 (12.4) | 35 (11.9) |
| | Related | n (%) | - | - | 1 (1.0) | 1 (0.3) |
| Vaccination complications | Not Related | n (%) | 6 (6.1) | 1 (1.0) | 2 (2.1) | 9 (3.1) |
| | Related | n (%) | - | - | - | - |
| Arthropod bite | Not Related | n (%) | 1 (1.0) | - | 3 (3.1) | 4 (1.4) |
| | Related | n (%) | - | - | - | - |
| Gastrointestinal disorders | Not related | n (%) | 4 (4.1) | 8 (8.1) | 4 (4.1) | 16 (5.4) |
| | Related | n (%) | 3 (3.1) | 7 (7.1) | 9 (9.3) | 19 (6.5) |
| Nausea | Not related | n (%) | - | - | - | - |
| | Related | n (%) | - | 6 (6.1) | 3 (3.1) | 9 (3.1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Abdominal pain | Not related<br>Related | n (%)<br>n (%) | 1 (1.0)<br>2 (2.0) | 3 (3.0)<br>- | 1 (1.0)<br>- | 5 (1.7)<br>2 (0.7) |
| Vomiting | Not related<br>Related | n (%)<br>n (%) | 1 (1.0)<br>- | -<br>3 (3.0) | -<br>2 (2.1) | 1 (0.3)<br>5 (1.7) |
| Skin and subcutaneous tissue disorders | Not related<br>Related | n (%)<br>n (%) | 5 (5.1)<br>1 (1.0) | 2 (2.0)<br>3 (3.0) | 6 (6.2)<br>6 (6.2) | 13 (4.4)<br>10 (3.4) |
| Rash | Not related<br>Related | n (%)<br>n (%) | 2 (2.0)<br>- | 1 (1.0)<br>1 (1.0) | -<br>3 (3.1) | 3 (1.0)<br>4 (1.4) |
| Respiratory, thoracic and mediastinal disorders | Not related<br>Related | n (%)<br>n (%) | 5 (5.1)<br>- | 6 (6.1)<br>3 (3.0) | 3 (3.1)<br>2 (2.1) | 14 (4.8)<br>5 (1.7) |
| Investigations | Not related<br>Related | n (%)<br>n (%) | 3 (3.1)<br>1 (1.0) | 5 (5.1)<br>- | 5 (5.2)<br>1 (1.0) | 13 (4.4)<br>2 (0.7) |
| Blood creatine phosphokinase increased | Not related<br>Related | n (%)<br>n (%) | 3 (3.1)<br>- | 3 (3.0)<br>- | 2 (2.1)<br>- | 8 (2.7)<br>- |
| Eye disorders | Not related<br>Related | n (%)<br>n (%) | 4 (4.1)<br>- | -<br>- | 2 (2.1)<br>- | 6 (2.0)<br>- |
| Psychiatric disorders | Not related<br>Related | n (%)<br>n (%) | -<br>- | 3 (3.0)<br>- | 2 (2.1)<br>- | 5 (1.7)<br>- |

Adverse Events were coded according to MedDRA Version 24.0
A TEAE is defined as any AE which commence or worsened in severity on or after the start of IP administration.
A related TEAE is defined as any TEAE reported as having a possible, probable or highly probable relationship to IP and includes events with a missing relationship.
Maximum relationship to IP is defined as the strongest relationship occurrence within each subject, system organ class and preferred term.
IP=investigational product; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N=Total number of subjects in the relevant population for each Strata (where relevant); TEAE= treatment-emergent AE; %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

**Study AVT04-GL-301: TEAEs in Patients**

*From Baseline to Week 16*

An overview of **TEAEs up to Week 16** for all patients is presented in the following table. A total of 67 patients (34.5%) reported 104 **TEAEs** in the AVT04 cohort and 129 patients (33.3%) reported 223 TEAEs in the EU-Stelara cohort. Most TEAEs were mild in the AVT04 cohort (64 TEAEs in 40 patients [20.6%]) and the EU-Stelara cohort (115 TEAEs in 65 patients [16.8%]). Two patients (1.0%) in the AVT04 cohort reported 3 severe TEAEs and 6 patients (1.6%) in the EU-Stelara cohort reported 9 severe TEAEs. A total of 10 patients (5.2%) reported 13 **treatment-related TEAEs** in the AVT04 cohort and 36 patients (9.3%) reported 38 treatment-related TEAEs in the EU-Stelara cohort. Seven patients (1.8%) in the EU-Stelara cohort had 10 serious TEAEs, which were not considered related to study treatment; no serious TEAEs were reported in the AVT04 cohort. Three patients (0.8%) reported 3 TEAEs that led to early termination (ET) in the EU-Stelara cohort; all these TEAEs also led to IP discontinuation. Two patients (0.5%) reported 2 **serious TEAEs** that led to ET in the EU-Stelara cohort. No patient in the AVT04 cohort had TEAEs that led to ET or IP discontinuation. A total of 4 **TEAEs of special interest** were reported in 3 patients (1.5%) in the AVT04 cohort and 15 TEAEs of special interest were reported in 14 patients (3.6%) in the EU-Stelara cohort. No patient died up to Week 16.

In general, there were no remarkable imbalances between the cohorts for the 'all patients cohort' or the 'patients with body weight ≤100 kg'.

**Table 13.** Overview of TEAEs in Patients – From Baseline to Week 16 (Study AVT04-GL- 301, Safety Analysis Set)

| **All Patients** |
|---|

| | AVT04 (N=194) | | EU-Stelara (N=387) | |
|---|---|---|---|---|
| | **Subjects n (%)** | **Events n** | **Subjects n (%)** | **Events n** |
| Any TEAE | 67 (34.5) | 104 | 130 (33.6) | 223 |
| Maximum Severity of TEAEs[1] | | | | |
| Mild | 40 (20.6) | 64 | 66 (17.1) | 115 |
| Moderate | 25 (12.9) | 37 | 58 (15.0) | 99 |
| Severe | 2 (1.0) | 3 | 6 (1.6) | 9 |
| Treatment-Related TEAEs | 10 (5.2) | 13 | 37 (9.6) | 39 |
| Serious TEAEs[3] | 0 | 0 | 7 (1.8) | 10 |
| Treatment-Related Serious TEAEs [2] | 0 | 0 | 0 | 0 |
| TEAE Leading to Discontinuation from Study Treatment Phase | 0 | 0 | 3 (0.8) | 3 |
| Treatment-Related TEAE Leading to Discontinuation from Study Treatment Phase [2] | 0 | 0 | 0 | 0 |
| TEAE Leading to Early Termination from Study | 0 | 0 | 3 (0.8) | 3 |
| Treatment-Related TEAE Leading to Early Termination from Study[2] | 0 | 0 | 0 | 0 |
| Serious TEAE Leading to Early Termination from Study | 0 | 0 | 2 (0.5) | 2 |
| Treatment-Related Serious TEAE Leading to Early Termination from Study[2,3] | 0 | 0 | 0 | 0 |
| TEAEs of Special Interest[3] | 3 (1.5) | 4 | 16 (3.1) | 17 |
| Death | 0 | 0 | 0 | 0 |
| **Patients with Body Weight ≤100 kg** | | | | |
| | **AVT04 (N=164)** | | **EU-Stelara (N=327)** | |
| | **Subjects n (%)** | **Events n** | **Subjects n (%)** | **Events n** |
| Any TEAE | 58 (35.4) | 94 | 121 (37.0) | 211 |
| Maximum Severity of TEAEs[1] | | | | |
| Mild | 37 (22.6) | 60 | 62 (19.0) | 110 |
| Moderate | 20 (12.2) | 32 | 53 (16.2) | 92 |
| Severe | 1 (0.6) | 2 | 6 (1.8) | 9 |
| Treatment-Related TEAEs[2] | 10 (6.1) | 13 | 37 (11.3) | 39 |
| Serious TEAEs[3] | 0 | 0 | 7 (2.1) | 10 |
| TEAE Leading to Discontinuation from Study Treatment Phase | 0 | 0 | 3 (0.9) | 3 |
| Treatment-Related TEAE Leading to Discontinuation from Study Treatment Phase[2] | 0 | 0 | 0 | 0 |
| TEAE Leading to Early Termination from Study | 0 | 0 | 3 (0.9) | 3 |
| Treatment-Related TEAE Leading to Early Termination from Study[2] | 0 | 0 | 0 | 0 |
| Serious TEAE Leading to Early Termination from Study | 0 | 0 | 2 (0.6) | 2 |
| Treatment-Related Serious TEAE Leading to Early Termination from Study[2,3] | 0 | 0 | 0 | 0 |
| TEAEs of Special Interest[4] | 3 (1.8) | 4 | 16 (4.9) | 17 |
| Death | 0 | 0 | 0 | 0 |

Adverse Events were coded according to MedDRA Version 24.1

[1] AEs with missing severity were classified as 'severe'.

[2] Related TEAE: any TEAE reported as having a possible, probable or highly probable relationship to IP including events with a missing relationship. AEs with missing relationship to IP were classified as 'Related'.

[3] Serious TEAE: any TEAE for which 'Serious event' is indicated as 'Yes'.

[4] TEAE of special interest: any AE considered to be of special interest per protocol.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); TEAE=treatment- emergent AE defined as any AE which commenced or worsened in

severity on or after the start of IP administration; %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

*From Week 16 to Week 28*

A total of 21 patients (10.9%) reported 26 **TEAEs** in the AVT04/AVT04 cohort, 30 patients (15.6%) reported 35 TEAEs in the EU-Stelara/AVT04 cohort, and 29 patients (15.3%) reported 36 TEAEs in the EU- Stelara/EU-Stelara cohort. Most TEAEs were mild in the AVT04/AVT04 cohort (14 TEAEs in 10 patients [5.2%]), the EU-Stelara/AVT04 cohort (21 TEAEs in 18 patients [9.4%]), and the EU-Stelara/EU-Stelara cohort (26 TEAEs in 20 patients [10.6%]). One patient (0.5%) reported 1 severe TEAE each in the AVT04/AVT04 cohort and the EU-Stelara/EU-Stelara cohort. A total of 5 patients (2.6%) reported 5 **treatment-related TEAEs** in the EU-Stelara/AVT04 cohort and 2 patients (1.1%) reported 2 treatment-related TEAEs in the EU-Stelara/EU-Stelara cohort. One patient (0.5%) in the EU-Stelara/EU-Stelara cohort had 1 serious TEAE, which was not considered related to study treatment; no serious TEAEs were reported in the other 2 cohorts. One patient (0.5%) reported 1 TEAE that led to ET in the AVT04/AVT04 cohort, 3 patients (1.6%) reported 3 TEAEs that led to ET in the EU-Stelara/AVT04 cohort, and 4 patients (2.1%) reported 4 TEAEs that led to ET in the EU- Stelara/EU-Stelara cohort; all these TEAEs also led to IP discontinuation, and none was serious. Two patients (1.0%) reported 2 **TEAEs of special interest** each in the EU-Stelara/AVT04 cohort and one (0.5%) patient reported 1 TEAE of special interest in the EU-Stelara/EU-Stelara cohort. No patient died from Week 16 to Week 28.

**From Baseline to Week 16**, the most frequently reported TEAEs, i.e., in at least 5% of patients by **SOC**, were infections and infestations (17.0% in the AVT04 cohort, 14.5% in the EU-Stelara cohort) and investigations (8.2% in the AVT04 cohort, 8.5% in the EU-Stelara cohort). No TEAE by **PT** was reported in 5% or more patients.

Among patients with body weight ≤100 kg, the most frequently reported TEAEs, i.e., in at least 5% of patients by **SOC** were infections and infestations (17.7% in the AVT04 cohort, 16.8% in the EU-Stelara cohort) and investigations (6.7% in the AVT04 cohort, 8.3% in the EU-Stelara cohort) and by **PT** were nasopharyngitis (4.3% in the AVT04 cohort, 5.2% in the EU-Stelara cohort) and upper respiratory tract infection (5.5% in the AVT04 cohort, 4.0% in the EU-Stelara cohort).

**From Week 16 to Week 28**, the most frequently reported TEAEs, i.e., in at least 5% of patients by **SOC** were infections and infestations (4.7% in the AVT04/AVT04 cohort, 7.8% in the EU-Stelara/AVT04 cohort, and 9.5% in the EU-Stelara/EU-Stelara cohort) and by **PT** was COVID-19 (1.0% in the AVT04/AVT04 cohort, 3.6% in the EU-Stelara/AVT04 cohort, and 5.3% in the EU- Stelara/EU-Stelara cohort).

Among patients with body weight ≤100 kg, the most frequently reported TEAEs, i.e., in at least 5% of patients by **SOC** were infections and infestations (4.9% in the AVT04/AVT04 cohort, 9.3% in the EU-Stelara/AVT04 cohort, and 10.0% in the EU-Stelara/EU-Stelara cohort) and by **PT** was COVID-19 (1.2% in the AVT04/AVT04 cohort, 4.3% in the EU-Stelara/AVT04 cohort, and 5.0% in the EU-Stelara/EU-Stelara cohort).

*From Week 28 to EOS*

A total of 32 patients (16.6%) reported 49 **TEAEs** in the AVT04/AVT04 cohort, 42 patients (21.9%) reported 66 TEAEs in the EU-Stelara/AVT04 cohort, and 39 patients (20.6%) reported 49 TEAEs in the EU- Stelara/EU-Stelara cohort. These differences in number of TEAEs reported among the groups were minor and not clinically significant. Most TEAEs were mild in the AVT04/AVT04 cohort (26 TEAEs in 15 patients [7.8%]), the EU-Stelara/AVT04 cohort (41 TEAEs in 21 patients [10.9%]), and the EU-Stelara/EU-Stelara cohort (23 TEAEs in 19 patients [10.1%]). Three patients (1.6%) reported 4 severe

TEAEs in the AVT04/AVT04 group and 2 patients (1.0%) reported 2 severe TEAEs in the EU-Stelara/AVT04 group; there were no severe TEAEs reported in the EU-Stelara/EU-Stelara group. A total of 3 patients (1.6%) reported 4 **treatment-related TEAEs** in the EU-Stelara/AVT04 cohort and 6 patients (3.2%) reported 8 treatment-related TEAEs in the EU-Stelara/EU-Stelara cohort; there were no treatment-related TEAEs in the AVT04/AVT04 cohort. One patient each (0.5%) in the AVT04/AVT04, EU-Stelara/AVT04, EU-Stelara/EU-Stelara cohort had 1 serious TEAE each, which were not considered related to study treatment. One patient (0.5%) reported 2 TEAEs that led to ET in the EU-Stelara/EU-Stelara cohort, which also led to IP discontinuation; none were serious. Three patients (1.6%) reported 4 **TEAEs of special interest** in the EU-Stelara/AVT04 cohort and two (1.1%) patient reported 2 TEAEs of special interest in the EU- Stelara/EU-Stelara cohort. No patient died from Week 28 to EOS.

The numbers of treatment-related TEAEs up to Week 16 are listed in the following table.

**Table 14.** Treatment-related TEAEs (≥1% of Patients in any Cohort) in Patients by SOC, PT and Maximum Severity – From Baseline to Week 16 (Study AVT04-GL-301, Safety Analysis Set)

| | AVT04 (N=194) | | EU-Stelara (N=387) | |
|---|---|---|---|---|
| **System Organ Class** | **Subjects** | **Events** | **Subjects** | **Events** |
| **Preferred Term** | **n (%)** | **n** | **n (%)** | **n** |
| **All Patients** | | | | |
| Any Reported | 10 (5.2) | 13 | 36 (9.3) | 38 |
| Maximum Severity of TEAEs | | | | |
| Mild | 5 (2.6) | 8 | 29 (7.5) | 31 |
| Moderate | 5 (2.6) | 5 | 7 (1.8) | 7 |
| Severe | 0 | 0 | 0 | 0 |
| INFECTIONS AND INFESTATIONS | 6 (3.1) | 6 | 14 (3.6) | 14 |
| Mild | 4 (2.1) | 4 | 10 (2.6) | 10 |
| Moderate | 2 (1.0) | 2 | 4 (1.0) | 4 |
| Severe | 0 | 0 | 0 | 0 |
| Upper respiratory tract infections | 3 (1.5) | 3 | 7 (1.8) | 7 |
| Mild | 2 (1.0) | 2 | 5 (1.3) | 5 |
| Moderate | 1 (0.5) | 1 | 2 (0.5) | 2 |
| Severe | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 2 (1.0) | 2 | 3 (0.8) | 3 |
| Mild | 1 (0.5) | 1 | 3 (0.8) | 3 |
| Moderate | 1 (0.5) | 1 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 (1.0) | 3 | 11 (2.8) | 12 |
| Mild | 2 (1.0) | 3 | 10 (2.6) | 11 |
| Moderate | 0 | 0 | 1 (0.3) | 1 |
| Severe | 0 | 0 | 0 | 0 |
| Injection site reaction | 1 (0.5) | 1 | 7 (1.8) | 7 |
| Mild | 1 (0.5) | 1 | 7 (1.8) | 7 |
| Moderate | 0 | 0 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 0 | 0 | 6 (1.6) | 6 |
| Mild | 0 | 0 | 4 (1.0) | 4 |
| Moderate | 0 | 0 | 2 ( 0.5) | 2 |
| Severe | 0 | 0 | 0 | 0 |
| | | | | |
| **Patients with Body Weight ≤100kg** | | | | |
| Any Reported | 10 (6.1) | 13 | 36 (11.0) | 38 |
| Maximum Severity of TEAEs | | | | |
| Mild | 5 (3.0) | 8 | 29 (8.9) | 31 |

| | | | | |
|---|---|---|---|---|
| Moderate | 5 (3.0) | 5 | 7 (2.1) | 7 |
| Severe | 0 | 0 | 0 | 0 |
| INFECTIONS AND INFESTATIONS | 6 (3.7) | 6 | 14 (4.3) | 14 |
| Mild | 4 (2.4) | 4 | 10 (3.1) | 10 |
| Moderate | 2 (1.2) | 2 | 4 (1.2) | 4 |
| Severe | 0 | 0 | 0 | 0 |
| Upper respiratory tract infection | 3 (1.8) | 3 | 7 (2.1) | 7 |
| Mild | 2 (1.2) | 2 | 5 (1.5) | 5 |
| Moderate | 1 (0.6) | 1 | 2 (0.6) | 2 |
| Severe | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 2 (1.2) | 2 | 3 (0.9) | 3 |
| Mild | 1 (0.6) | 1 | 3 (0.9) | 3 |
| Moderate | 1 (0.6) | 1 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 (1.2) | 3 | 11 (3.4) | 12 |
| Mild | 2 (1.2) | 3 | 10 (3.1) | 11 |
| Moderate | 0 | 0 | 1 (0.3) | 1 |
| Severe | 0 | 0 | 0 | 0 |
| Injection site reaction | 1 (0.6) | 1 | 7 (2.1) | 7 |
| Mild | 1 (0.6) | 1 | 7 (2.1) | 7 |
| Moderate | 0 | 0 | 0 | 0 |
| Severe | 0 | 0 | 0 | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 0 | 0 | 6 (1.8) | 6 |
| Mild | 0 | 0 | 4 (1.2) | 4 |
| Moderate | 0 | 0 | 2 (0.6) | 2 |
| Severe | 0 | 0 | 0 | 0 |

Adverse Events were coded according to MedDRA Version 24.1
AE=adverse event; TEAE= treatment-emergent AE; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N=Total number of subjects in the relevant population for each Strata (where relevant); %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

The incidences of treatment-related TEAEs from Week 16 to Week 28 were as follows: none in the AVT04/AVT04 group, 2.6% in the EU-Stelara/AVT04 group and 1.1% in the EU-Stelara/ EU-Stelara group.

The incidences of treatment-related TEAEs from Week 28 to EOS were as follows: none in the AVT04/AVT04 group, 1.6% in the EU-Stelara/AVT04 group and 3.3% in the EU-Stelara/ EU-Stelara group.

### *2.6.8.3. Serious adverse events, deaths, other significant events*

No deaths were reported in the clinical studies.

***Serious TEAEs***

**Study AVT04-GL-101: Serious TEAEs in Healthy Subjects**

There were 3 serious TEAEs reported in Study AVT04-GL-101 including one in each cohort (AVT04: PT Anaphylactic reaction, EU-Stelara: PT Abdominal pain, US Stelara: PT Cerebrovascular accident). No serious TEAEs related to IP were reported.

**Study AVT04-GL-301: Serious TEAEs Primary SOC and PT in Patients**

*From Baseline to Week 16*

**Table 15.** Serious TEAEs in Patients by Primary SOC, PT – From Baseline to Week 16 (Study AVT04-GL-301, Safety Analysis Set)

| **All Patients** | | | | |
|---|---|---|---|---|
| | **AVT04 (N=194)** | | **EU-Stelara (N=387)** | |
| **System Organ Class** | **Subjects** | **Events** | **Subjects** | **Events** |
| **Preferred Term** | **n (%)** | **n** | **n (%)** | **n** |
| Any Reported | 0 | 0 | 7 (1.8) | 10 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 0 | 0 | 3 (0.8) | 3 |
| Compression fracture | 0 | 0 | 1 (0.3) | 1 |
| Limb fracture | 0 | 0 | 1 (0.3) | 1 |
| Lower limb fracture | 0 | 0 | 1 (0.3) | 1 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 0 | 0 | 2 (0.5) | 2 |
| Pancreatic carcinoma metastatic | 0 | 0 | 1 (0.3) | 1 |
| Salivary gland neoplasm | 0 | 0 | 1 (0.3) | 1 |
| CARDIAC DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Atrial fibrillation | 0 | 0 | 1 (0.3) | 1 |
| GASTROINTESTINAL DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Intestinal obstruction | 0 | 0 | 1 (0.3) | 1 |
| HEPATOBILIARY DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Gallbladder rupture | 0 | 0 | 1 (0.3) | 1 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Intervertebral disc disorder | 0 | 0 | 1 (0.3) | 1 |
| VASCULAR DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Arteriosclerosis | 0 | 0 | 1 (0.3) | 1 |

Adverse Events were coded according to MedDRA Version 24.1
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects; n=number of subjects in the sample; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent AE.; %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

No serious TEAEs were reported for AVT04. Serious TEAEs that have been reported for EU-Stelara were of moderate (n=4, 1.0%) or severe (n=3, 0.8%) severity. All occurred in patients with a body weight of ≤100kg and were not considered related to study treatment. Severe TEAEs reported for EU-Stelara were compression fracture, limb fracture, pancreatic carcinoma metastatic, intestinal obstruction, and gallbladder rupture (each n=1, 0.3%). Moderate TEAEs reported for EU-Stelara were lower limb fracture, salivary gland neoplasm, atrial fibrillation, intravertebral disc disorder, and arteriosclerosis (each n=1, 0.3%).

*From Week 16 to Week 28*

During the timeframe from Week 16 to Week 28 only one patient (≤100 kg) experienced a serious TEAE after treatment with EU-Stelara that was not considered related to study treatment. This patient experienced severe vitamin B12 deficiency anaemia. No serious TEAEs were reported after treatment with AVT04.

*From Week 28 to EOS*

During the timeframe from Week 28 to EOS, one patient in each treatment group (all ≤100 kg) experienced a serious TEAE after treatment with AVT04/AVT04 (intervertebral disc protrusion), EU-Stelara/AVT04 (lower respiratory tract infection), or EU-Stelara/EU-Stelara (otosclerosis); none were considered related to study treatment.

***TEAEs of Special Interest***

Treatment-emergent AEs of special interest (TEAESIs), encompassing all relevant warnings and precautions from the EU-Stelara label, were defined for the safety analysis. All TEAESIs were reported and assessed in the same manner as standard TEAEs including determination of seriousness criteria and causal relationship to the IP.

**Study AVT04-GL-101: TEAESIs in Healthy Subjects**

**Table 16.** Incidence of TEAEs of Special Interest by Maximum Severity in Healthy Subjects (Study AVT04-GL-101, Safety Population)

| System Organ Class<br>Preferred Term | | Statistic | AVT04 | EU-Stelara | US-Stelara | Overall |
|---|---|---|---|---|---|---|
| | | **N** | **98** | **99** | **97** | **294** |
| At least one TEAE of Special Interest | Mild | n (%) | 10 (10.2) | 8 (8.1) | 12 (12.4) | 30 (10.2) |
| | Moderate | n (%) | - | 1 (1.0) | - | 1 (0.3) |
| | Severe | n (%) | - | - | - | - |
| General disorders and administration site conditions | Mild | n (%) | 10 (10.2) | 8 (8.1) | 11 (11.3) | 29 (9.9) |
| Injection site erythema | Mild | n (%) | 4 (4.1) | 4 (4.0) | 5 (5.2) | 13 (4.4) |
| Injection site pain | Mild | n (%) | 3 (3.1) | 1 (1.0) | 3 (3.1) | 7 (2.4) |
| Injection site bruising | Mild | n (%) | 2 (2.0) | - | 1 (1.0) | 3 (1.0) |
| Injection site pruritus | Mild | n (%) | - | 1 (1.0) | 1 (1.0) | 2 (0.7) |
| Injection site reaction | Mild | n (%) | - | 2 (2.0) | - | 2 (0.7) |
| Injection site swelling | Mild | n (%) | 1 (1.0) | - | - | 1 (0.3) |
| Injection site urticaria | Mild | n (%) | - | - | 1 (1.0) | 1 (0.3) |
| Skin and subcutaneous tissue disorders | Mild | n (%) | 1 (1.0) | - | 1 (1.0) | 2 (0.7) |
| Rash | Mild | n (%) | 1 (1.0) | - | 1 (1.0) | 2 (0.7) |
| Immune system disorders | Moderate | n (%) | - | 1 (1.0) | - | 1 (0.3) |
| Hypersensitivity | Moderate | n (%) | - | 1 (1.0) | - | 1 (0.3) |

Adverse Events were coded according to MedDRA Version 24.0
A TEAE is defined as any AE which commence or worsened in severity on or after the start of IP administration. A TEAE of special interest is defined as any AE considered to be of special interest per protocol.
TEAE= treatment-emergent AE; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N=Total number of subjects in the relevant population for each Strata (where relevant).

Overall, 31 subjects (10.5% of the safety population) reported at least one TEAESI. The number of subjects who reported any TEAESI was comparable between groups (10 (10.2%), 9 (9.1%) and 12 (12.4%) in the AVT04, EU-Stelara and US-Stelara cohort, respectively). Almost all of the events pertained to SOC General disorders and administration site conditions. Additionally, one subject each had TEAESI of rash, hypersensitivity and rash in the AVT04, EU-Stelara and US-Stelara cohort, respectively.

**Study AVT04-GL-301: TEAESIs in Patients**

*From Baseline to Week 16*

A complete presentation of all TEAEs of special interest by SOC and PT up to Week 16 is found below for all patients and for patients with body weight ≤100 kg.

Among all patients, the only TEAE of special interest reported in at least 1% of patients in any cohort was ISR (1 patient [0.5%] in the AVT04 cohort and 7 patients [1.8%] in the EU-Stelara cohort).

Among patients with body weight ≤100 kg, the only TEAE of special interest reported in at least 1% of patients in any cohort was ISR (1 patient [0.6%] in the AVT04 cohort and 7 patients [2.1%] in the EU-Stelara cohort).

**Table 17.** Incidence of TEAEs of Special Interest by Primary SOC and PT in Patients – From Baseline to Week 16 (Study AVT04-GL-301, Safety Analysis Set)

| **All Patients** | | | | |
|---|---|---|---|---|
| | **AVT04** | | **EU-Stelara** | |
| | **(N=194)** | | **(N=387)** | |
| **System Organ Class** | **Subjects** | **Events** | **Subjects** | **Events** |
| **Preferred Term** | **n (%)** | **n** | **n (%)** | **n** |
| Any Reported | 3 (1.5) | 4 | 14 (3.6) | 15 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 (1.0) | 3 | 10 (2.6) | 11 |
| Injection site reaction | 1 (0.5) | 1 | 7 (1.8) | 7 |
| Injection site erythema | 1 (0.5) | 2 | 0 | 0 |
| Injection site pain | 0 | 0 | 1 (0.3) | 2 |
| Injection site haematoma | 0 | 0 | 1 (0.3) | 1 |
| Injection site pruritus | 0 | 0 | 1 (0.3) | 1 |
| VASCULAR DISORDERS | 1 (0.5) | 1 | 2 (0.5) | 2 |
| Haematoma | 1 (0.5) | 1 | 2 (0.5) | 2 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 0 | 0 | 1 (0.3) | 1 |
| Pancreatic carcinoma metastatic | 0 | 0 | 1 (0.3) | 1 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Pruritus | 0 | 0 | 1 (0.3) | 1 |
| **Patients with Body Weight ≤100kg** | | | | |
| | **AVT04** | | **EU-Stelara** | |
| | **(N=164)** | | **(N=327)** | |
| **System Organ Class** | **Subjects** | **Events** | **Subjects** | **Events** |
| **Preferred Term** | **n (%)** | **n** | **n (%)** | **n** |
| Any Reported | 3 (1.8) | 4 | 14 (4.3) | 15 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 (1.2) | 3 | 10 (3.1) | 11 |
| Injection site reaction | 1 (0.6) | 1 | 7 (2.1) | 7 |
| Injection site erythema | 1 (0.6) | 2 | 0 | 0 |
| Injection site pain | 0 | 0 | 1 (0.3) | 2 |
| Injection site haematoma | 0 | 0 | 1 (0.3) | 1 |
| Injection site pruritus | 0 | 0 | 1 (0.3) | 1 |
| VASCULAR DISORDERS | 1 (0.6) | 1 | 2 (0.6) | 2 |
| Haematoma | 1 (0.6) | 1 | 2 (0.6) | 2 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 0 | 0 | 1 (0.3) | 1 |
| Pancreatic carcinoma metastatic | 0 | 0 | 1 (0.3) | 1 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 0 | 0 | 1 (0.3) | 1 |
| Pruritus | 0 | 0 | 1 (0.3) | 1 |

Adverse Events were coded according to MedDRA Version 24.1
AE=adverse event; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N=Total number of subjects in the relevant population

for each Strata (where relevant); TEAE= treatment-emergent AE; %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

*From Week 16 to Week 28*

Among all patients, the TEAEs of special interest reported were injection site hematoma (1 patient [0.5%] in the EU-Stelara/AVT04 cohort) and ISR (1 patient [0.5%] in the EU-Stelara/EU-Stelara cohort). Among patients with body weight ≤100 kg, the TEAEs of special interest reported were identical to those reported in all patients.

*From Week 28 to EOS*

Among all patients, the TEAEs of special interest reported were injection site pain (1 patient [0.5%] in the EU-Stelara/AVT04 cohort), ISR (1 patient [0.5%] in the EU-Stelara/AVT04 cohort; 2 patient [1.1%] in the EU-Stelara/EU-Stelara cohort), and lower respiratory tract infection (1 patient [0.5%] in the EU-Stelara/AVT04 cohort).

Among patients with body weight ≤100 kg, the TEAEs of special interest reported (predominantly injection site reactions) were identical to those reported in all patients.

### *2.6.8.4. Laboratory findings*

**Study AVT04-GL-101: Chemistry, Coagulation, Haematology and Urinalysis in Healthy Subjects**

Shifts in haematology, coagulation, or clinical chemistry parameters from normal at baseline to either low or high at the Day 92 EOS visit were generally infrequent. The most frequent shifts (≥10% of subjects in any group) were observed in the following parameters:

- Haemoglobin (normal to low): 2.0% in the AVT04 group, 2.0% in the EU- Stelara, and 10.3% in the US- Stelara group.
- Leukocytes (normal to low): 8.2% in the AVT04 group, 10.1% in the EU- Stelara group, and 5.2% in the US- Stelara group.
- Protein (normal to low): 12.2% in the AVT04 group, 15.2% in the EU- Stelara group, and 11.3% in the US- Stelara group.
- Triglycerides (normal to high): 5.1% in the AVT04 group, 10.1% in the EU- Stelara group, and 2.1% in the US- Stelara group.
- Creatine kinase (normal to high): 5.1% in the AVT04 group, 9.1% in the EU- Stelara group, and 15.5% in the US- Stelara group.

These shifts were not considered to be clinically meaningful.

There were no abnormal not clinically significant or clinically significant findings in urinalysis parameters at any visit based on the Investigator's assessment.

Twelve subjects had TEAEs of laboratory abnormalities during the study. Ten subjects (3.4%) had TEAEs of Grade ≥3 laboratory abnormalities: 3 in the AVT04 cohort, 5 in the EU-Stelara cohort, and 2 in the US-Stelara cohort. The most frequently reported Grade ≥3 laboratory abnormality was blood creatinine phosphokinase increased (7 subjects). The other Grade ≥3 events were blood triglycerides increased (2 subjects) and neutropenia (1 subject). Although graded as Grade ≥3, the majority of these events were mild. The event of neutropenia (EU-Stelara cohort) was severe and also considered

related to the IP. Except for 2 events (blood creatine phosphokinase increased in the AVT04 and US-Stelara cohorts) with an unknown outcome, all Grade ≥3 events had resolved by the end of the study.

**Study AVT04-GL-301: Chemistry and Hematology in Patients**

No clinically significant changes from Baseline over time (up to Week 16, Week 16 to 28, and Week 28 to EOS) were observed across the cohorts in any hematology, chemistry and urinalysis values during the study.

No clinically relevant differences were observed in shifts from normal to low or high across the cohorts in any hematology results for up to Week 16, Week 28 and Week 52, chemistry, and urinalysis values during the study.

*Individual Clinically Significant Abnormalities*

Up to Week 16 for all patients, 1 patient (0.5%) each had ALT or AST >8 × upper limit of normal (ULN) and >10 × ULN in the AVT04 cohort, 1 patient (0.5%) each had bilirubin 3 × ULN in the AVT04 and EU-Stelara cohorts, 4 patients (2.1%) in the AVT04 cohort and 21 patients (5.4%) in the EU-Stelara cohort had Creatine phosphokinase (CPK) 2.5 × ULN.

Two patients (0.5%) in the EU-Stelara cohort with post-Baseline ALT or AST and bilirubin had ALT >3 × ULN or AST >3 × ULN and bilirubin >1.5 × ULN and ALP <2 x ULN.

Up to Week 28 for all patients, 1 patient (0.6%) had ALT or AST >8 × ULN in the EU-Stelara/EU-Stelara cohort, 3 patients (1.8%) in the AVT04/AVT04 cohort, 5 patients (3.2%) in the EU-Stelara/AVT04 cohort, and 8 patients (4.9%) in the EU-Stelara/EU-Stelara cohort had CPK 2.5 × ULN. One patient (0.6%) in the EU-Stelara/AVT04 cohort with post-Baseline ALT or AST and bilirubin had ALT >3 × ULN or AST >3 × ULN and bilirubin >1.5 × ULN and ALP<2 x ULN.

From Week 28 through EOS for all patients, 1 patient (0.5%) had ALT or AST >10 × ULN in the EU-Stelara/AVT04 cohort; 1 patient (0.5%) in the AVT04/AVT04 cohort had bilirubin >3 × ULN; and 9 patients (5.7%) in the AVT04/AVT04 cohort, 13 patients (8.8%) in the EU-Stelara/AVT04 cohort, and 4 patients (2.7%) in the EU-Stelara/EU-Stelara cohort had CPK >2.5 × ULN. Two patients (1.1%) in the EU Stelara/AVT04 cohort and 1 patient (0.6%) in the EU Stelara/EU Stelara cohort with post Baseline ALT or AST and bilirubin results had ALT or AST >3 × ULN, bilirubin >1.5 × ULN, and ALP <2 × ULN.

**Vital Signs, Physical Examinations, 12-Lead ECG, and Other Safety Related Findings**

In Study AVT04-GL-101, there were no clinically meaningful changes in mean values for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and ECG parameters over the course of the study and no meaningful differences across treatment groups. There were two abnormal physical examination findings in patients treated with AVT04, which were judged as not related to the drug by the investigator.

In Study AVT04-GL-301 (PsO patients), no significant changes in vital signs and ECG parameters over time were observed across the treatment groups and no meaningful differences across treatment groups were observed. There were also no notable differences between treatment cohorts in physical examinations over the entire study period.

### *2.6.8.5. In vitro biomarker test for patient selection for safety*

Not available

### *2.6.8.6. Safety in special populations*

Not applicable

### *2.6.8.7. Immunological events*

The applicant has adopted an electrochemiluminescence immunoassay (ECLIA) bridging assay to screen, confirm and quantify ustekinumab specific antibodies in human serum matrix. The adopted three-tiered approach for determination of ADAs was well described and developed and is considered state of the art. The method is considered valid for its intended use.

Further, the Applicant presented a qualitative assay for the detection of neutralising ADA's in human serum. The presented assay was well described and established.

The applicant was requested to discuss false positive rate of methods for ADA and nAb determination as false positive rate was higher than recommended in the available guidelines. The applicant justified that the impact of high screening assay false positive rate was sufficiently reduced by confirmatory assay false positive rate (equal to 2.4%) and this was supported.

**ADA and nAb formation in healthy subjects**

Following single s.c. administration, in the 3 treatment groups AVT04, EU-Stelara and US-Stelara, ADAs and nAbs progressively increased during the study with a similar time of onset of ADA and nAb development across treatments. There was a tendency that the incidence of ADA positive and nAb positive patients was lower in the AVT04 group as compared to US-Stelara and EU-Stelara.

**Table 18.** Frequency Count (%) of ADAs and nAbs to Ustekinumab Over Time (Study AVT04-GL-101, Immunogenicity Population)

| | AVT04 (N=98) | EU-Stelara (N=99) | US-Stelara (N=97) |
|---|---|---|---|
| **ADA positive*** | | | |
| Day 1, predose | 1 (1.0) | 3 (3.0) | 1 (1.0) |
| Day 1, 12 hours | 0 | 1 (1.0) | 2 (2.1) |
| Day 9 | 11 (11.2) | 30 (30.3) | 19 (19.6) |
| Day 15 | 14 (14.3) | 19 (19.2) | 15 (15.5) |
| Day 29 | 9 (9.2) | 14 (14.1) | 14 (14.4) |
| Day 57 | 13 (13.3) | 30 (30.3) | 33 (34.0) |
| Day78 | 21 (21.4) | 43 (43.4) | 37 (38.1) |
| Day 92/EoS | 27 (27.6) | 48 (48.5) | 44 (45.4) |
| Any Positive | 36 (36.7) | 59 (59.6) | 52 (53.6) |
| **ADA negative*** | | | |
| Day 1, predose | 97 (99.0) | 96 (97.0) | 96 (99.0) |
| Day 1, 12 hours | 98 (100) | 98 (99.0) | 95 (97.9) |
| Day 9 | 84 (85.7) | 64 (64.6) | 73 (75.3) |
| Day 15 | 81 (82.7) | 76 (76.8) | 78 (80.4) |
| Day 29 | 84 (85.7) | 80 (80.8) | 74 (76.3) |
| Day 57 | 74 (75.5) | 56 (56.6) | 55 (56.7) |
| Day78 | 69 (70.4) | 48 (48.5) | 49 (50.5) |

| | | | |
|---|---|---|---|
| Day 92/EoS | 65 (66.3) | 49 (49.5) | 49 (50.5) |
| | **AVT04 (N=98)** | **EU-Stelara (N=99)** | **US-Stelara (N=97)** |
| All negative | 62 (63.3) | 40 (40.4) | 45 (46.4) |
| **nAb positive[#]** | | | |
| Day 1, predose | 0 | 0 | 0 |
| Day 1, 12 hours | 0 | 0 | 0 |
| Day 9 | 0 | 5 (8.5) | 2 (3.8) |
| Day 15 | 1 (2.8) | 3 (5.1) | 2 (3.8) |
| Day 29 | 0 | 1 (1.7) | 4 (7.7) |
| Day 57 | 2 (5.6) | 10 (16.9) | 20 (38.5) |
| Day78 | 7 (19.4) | 14 (23.7) | 19 (36.5) |
| Day 92/EoS | 11 (30.6) | 20 (33.9) | 22 (42.3) |
| Any positive | 12 (33.3) | 25 (42.4) | 28 (53.8) |
| **nAb negative[#]** | | | |
| Day 1, predose | 1 (2.8) | 3 (5.1) | 1 (1.9) |
| Day 1, 12 hours | 0 | 1 (1.7) | 2 (3.8) |
| Day 9 | 11 (30.6) | 25 (42.4) | 17 (23.7) |
| Day 15 | 13 (36.1) | 16 (27.1) | 13 (25.0) |
| Day 29 | 9 (25.0) | 13 (22.0) | 10 (19.2) |
| Day 57 | 11 (30.6) | 20 (33.9) | 13 (25.0) |
| Day78 | 14 (38.9) | 29 (49.2) | 18 (34.6) |
| Day 92/EoS | 16 (44.4) | 28 (47.5) | 22 (42.3) |
| All negative | 24 (66.7) | 34 (57.6) | 24 (46.2) |

[*] Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.
[#] Percentage of subjects at each timepoint who are positive to nAbs divided by total number of subjects with any ADA positive result.
ADA=antidrug antibody; EoS=end of study; N=number of treated patients; nAb=neutralizing antibodies

At the end of the study (Day 92), the frequency of ADA positive subjects was 27.6% in the AVT04 group, 48.5% in the EU-Stelara group and 45.4% in the US-Stelara group. Of the ADA positive subjects, 33.3% in the AVT04 group, 42.4% in the EU-Stelara group and 53.8% in the US-Stelara group were nAb positive. As expected, there appeared to be a lag time between positive detection of ADAs and formation of nAbs in all 3 treatment groups.

ADA titers are summarized in Module 5. The ADA titers were generally very low but highly variable in all treatment groups.

A summary of PK parameters by ADA and nAb positive/negative subgroups is presented in Section 2.6.2 of this report. Of note, in line with the overall population, also in the ADA positive and nAb positive subgroups systemic exposure in the EU-Stelara group was lower as compared to US-Stelara and AVT04, and there were differences in exposure within the respective subgroups (ADA positive, ADA negative, nAb positive and nAb negative) in that the PK parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$

were consistently lower in the ADA positive subgroups as compared to the ADA negative subgroups for all treatments. Also $t_{1/2}$ was shorter in the ADA positive subgroups.

The frequency of at least one (any) TEAE was comparable in the AVT04 versus the EU-Stelara and US-Stelara ADA positive groups (63.9%, 67.8%, and 69.2%, respectively). Similarly, the frequency of at least one (related) TEAE was comparable in the AVT04 versus the EU-Stelara ADA positive group (30.6% and 33.9%, respectively).

The number of subjects who developed nAbs was quite low (AVT04: n=12; EU-Stelara: n=25; US-Stelara: n=28), making robust comparisons between cohorts in the nAb positive subgroups difficult. However, the frequency of at least one (any) TEAE was highest in the AVT04 versus the EU-Stelara and US-Stelara ADA positive groups (75.0%, 68.0%, 67.9%, respectively). In contrast, the frequency of at least one (related) TEAE was lowest in the AVT04 versus the EU-Stelara and US-Stelara nAb positive groups (33.3%, 44.0%, and 39.3%, respectively), suggesting that some of these minor imbalances are due to chance.

**ADA and nAb formation in PsO patients**

Differences in ADA and nAb development between AVT04 and EU-Stelara were also observed in Study AVT04-GL-301.

Up to Week 16, the total binding ADA incidence (positive result at any visit up to Week 16) was 28.4% in the AVT04 group and 54.5% in the EU-Stelara group and the total nAb incidence was 27.3% in the AVT04 group and 32.2% in the EU-Stelara group. The treatment-emergent ADA incidence up to Week 16 was 24.9% in the AVT04 group and 53.9% in the EU-Stelara group.

**Table 19.** Frequency Count (%) of ADAs and nAbs to Ustekinumab Over Time from Baseline to Week 16 (Study AVT04-GL-301, Safety Analysis Set)

| | **AVT04 (N=194) n (%)** | **EU-Stelara (N=387) n (%)** |
|---|---|---|
| **Total antibody incidence[1]** | **m=194** | **m=387** |
| Binding (ADA)[A] | 55 (28.4) | 211 (54.5) |
| Neutralizing Antibodies[B] | 15 (27.3) | 68 (32.2) |
| **Baseline (Pre-existing Antibody Incidence)[2]** | **m=194** | **m=387** |
| Binding (ADA)[A] | 9 (4.6) | 5 (1.3) |
| Neutralizing Antibodies[B] | 0 | 0 |
| **Treatment-emergent ADA incidence up to Week 16[3]** | **m1=185** | **m1=382** |
| Binding (ADA)[C] | 46 (24.9) | 206 (53.9) |
| **Treatment-emergent nAb incidence up to Week 16[3]** | **m2=46** | **m2=206** |
| Neutralizing Antibodies[D] | 14 (30.4) | 67 (32.5) |
| | | |
| **Week 4** | **m=194** | **m=387** |
| Binding (ADA)[A] | 19 (9.8) | 83 (21.4) |
| Neutralizing Antibodies[B] | 1 (5.3) | 7 (8.4) |
| **Week 12** | **m=194** | **m=384** |
| Binding (ADA)[A] | 35 (18.0) | 155 (40.4) |
| Neutralizing Antibodies[B] | 11 (31.4) | 50 (32.3) |
| **Week 16** | **m=193** | **m=382** |

| | | |
|---|---|---|
| Binding (ADA)[A] | 49 (25.4) | 184 (48.2) |
| Neutralizing Antibodies[B] | 13 (26.5) | 57 (31.0) |

[1] Positive result at any visit before Week 16 dose
[2] Baseline was defined as the last nonmissing assessment prior to the first dose (Day 1)
[3] Negative result or no result at baseline and positive result post-dose but before Week 16 dose.
[A] %=n/m, where m is the total number of patients with ADA assessed at the specified time period.
[B] %=n/ADA+, where ADA+ is the total number of patients with positive ADA status in the specified time period.
[C] %=n/m1, where m1 is the number of patients with ADA assessed post-dose up to Week 16 dose. Patients with ADA positive at baseline are not included in m1.
[D] %=n/m2, where m2 is the number of patients with treatment-emergent ADA incidence up to Week 16 dose. Patients with ADA/nAb positive at baseline are not included in m2.
ADA=antidrug antibody; ET=early termination; nAb=neutralizing antibody; PsO=plaque psoriasis; SAS=safety analysis set

In Stage 2, the total antibody incidence (positive result at any visit up to Week 52) was lower in the AVT04/AVT04 group (38.7%) compared to the EU-Stelara/AVT04 group (64.1%) and the EU-Stelara/EU-Stelara group (58.2%). The overall frequency of neutralizing antibodies was 32.4%, 36.4% and 28.0%, respectively. Only one patient each in the AVT04/AVT04 group and EU-Stelara/EU-Stelara group had detectable treatment-emergent nAbs during Stage 2.

**Table 20.** Frequency Count (%) of ADAs and nAbs to Ustekinumab Over Time from Week 16 to Week 52 (Study AVT04-GL-301, Safety Analysis Set)

| | **AVT04/AVT04 (N=191) n (%)** | **EU-Stelara/AVT04 (N=184) n (%)** | **EU-Stelara/EU-Stelara (N=184) n (%)** |
|---|---|---|---|
| **Total antibody incidence[1]** | **m=191** | **m=184** | **m=184** |
| Binding (ADA)[A] | 74 (38.7) | 118 (64.1) | 107 (58.2) |
| Neutralizing Antibodies[B] | 24 (32.4) | 43 (36.4) | 30 (28.0) |
| | | | |
| **Week 16** | **m=191** | **m=184** | **m=184** |
| Binding (ADA)[A] | 49 (25.7) | 101 (54.9) | 77 (41.8) |
| Neutralizing Antibodies[B] | 13 (26.5) | 36 (35.6) | 19 (24.7) |
| **Week 28** | **m=190** | **m=182** | **m=184** |
| Binding (ADA)[A] | 42 (22.1) | 69 (37.9) | 68 (37.0) |
| Neutralizing Antibodies[B] | 14 (33.3) | 17 (24.6) | 16 (23.5) |
| **Week 40** | **m=191** | **m=179** | **m=181** |
| Binding (ADA)[A] | 44 (23.0) | 64 (35.8) | 56 (30.9) |
| Neutralizing Antibodies[B] | 15 (34.1) | 10 (15.6) | 8 (14.3) |
| **Week 52** | **m=184** | **m=178** | **m=180** |
| Binding (ADA)[A] | 39 (21.2) | 56 (31.5) | 48 (26.7) |
| Neutralizing Antibodies[B] | 13 (33.3) | 10 (17.9) | 11 (22.9) |

[1] Positive result at any visit up to End of Study (Week 52)
[A] %=n/m, where m is the total number of patients with ADA assessed at the specified time period.
[B] %=n/ADA+, where ADA+ is the total number of patients with positive ADA status in the specified time period.
ADA=antidrug antibody; ET=early termination; m=total number of subjects with ADA assessed at specified time point; nAb=neutralizing antibody

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. Median ADA titers reached a plateau at Week 16 and were comparable between Week 16 and Week 52 in all treatment groups.

Similar results were observed for the subgroup of patients with body weight ≤100 kg.

For both Stage 1 and Stage 2, ustekinumab $C_{trough}$ values were higher in ADA negative patients and lower in ADA positive compared to the overall population. Patients who were nAb positive had lower serum concentrations of study drug compared to the overall population.

There was no considerable difference between AVT04 or EU-Stelara (Stage 1) or between AVT04/AVT04, or EU-Stelara/AVT04 or EU-Stelara/EU-Stelara (Stage 2) in $C_{trough}$ values when comparing ADA positive, ADA negative, nAb positive, or nAb negative subgroups.

In the ADA positive subgroups, the frequency of (any) TEAE was higher in AVT04 versus EU-Stelara (47.3% versus 35.5%, respectively). The frequency of related TEAEs in ADA positive subgroups was comparable in the AVT04 versus the EU-Stelara cohort (7.3% versus 9.5%).

From Week 16 to Week 28, 61/193 (31.6%) patients on AVT04/AVT04, 118/192 (61.5%) patients on EU-Stelara/AVT04, and 98/189 (51.9%) patients on EU-Stelara/EU-Stelara patients were ADA positive. In this subgroup, the frequency of (any) TEAE was lower in AVT04/AVT04 versus the EU-Stelara/AVT04 and EU-Stelara/EU-Stelara cohorts (11.5%, 12.7%, and 16.3%, respectively). Similarly, the frequency of related TEAEs was lower in AVT04/AVT04 versus the EU-Stelara/AVT04 and EU-Stelara/EU-Stelara cohorts (0%, 3.4%, and 1.0%, respectively).

From Week 28 to EOS, it was confirmed that the AVT04 safety for TEAEs by ADA status was overall similar to EU-Stelara for all patients as well as for patients with ≤100 kg body weight.

From Week 28 to Week 52 the frequency of "any TEAE" in the ADA positive AVT04/AVT04 cohort was between that of the corresponding EU-Stelara/EU-Stelara and EU-Stelara/AVT04 cohorts, and similar to that of the other cohorts. Among the ADA negative patients, TEAE frequencies were lowest in the AVT04/AVT04 cohort, suggesting no robust trends between the cohorts. The frequencies of related TEAEs were balanced among the cohorts (<5% differences).

For nAbs, only 14/194 (25.5%) patients on AVT04 and 68/387 (32.2%) patients on EU-Stelara tested nAb positive from BL to Week 16. In the nAb positive subgroups, the frequency of (any) TEAE was lower in AVT04 versus EU-Stelara (28.6% versus 36.8%, respectively). Similarly, in the nAb positive subgroups, the frequency of related TEAEs was lower in AVT04 versus EU-Stelara (7.1% versus 11.8%, respectively).

From Week 16 to Week 28, only 19/193 (31.1%) patients on AVT04/AVT04, 43/192 (36.4%) patients on EU-Stelara/AVT04, and 29/189 (29.6%) patients on EU-Stelara/EU-Stelara were tested nAb positive. In this subgroup, the frequency of (any) TEAE was lower in AVT04/AVT04 versus the EU-Stelara/AVT04 and EU-Stelara/EU-Stelara cohorts (5.3%, 16.3%, and 24.1%, respectively). Similarly, the frequency of related TEAEs was lower in AVT04/AVT04 versus the EU-Stelara/AVT04 and EU-Stelara/EU-Stelara cohorts (0%, 4.7%, and 3.4%, respectively).

From Week 28 to EOS the frequency of "any TEAE" was lowest in the nAb positive AVT04/AVT04 cohort, but this was also the cohort that contained the smallest sample size (N=24 compared to nAb positive EU-Stelara/AVT04 patients: N=43 and nAb positive EU-Stelara/EU- Stelara patients: N=30). The frequencies of related TEAEs were balanced among the cohorts (<5% differences).

Subgroup Analysis: TEAEs by Anti-drug Antibody (ADA) Status

*From Baseline to Week 16*

**Table 21.** TEAEs by Primary SOC and PT by ADA Status in Patients (≥5% of Patients in any Cohort) – From Baseline to Week 16 (Study AVT04-GL-301, Safety Analysis Set)

| **All Patients** |
|---|

| | AVT04 | | EU-Stelara | |
|---|---|---|---|---|
| **System Organ Class** | **ADA Positive** | **ADA Negative** | **ADA Positive** | **ADA Negative** |
| **Preferred Term** | **(N=55)** | **(N=139)** | **(N=211)** | **(N=176)** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Any TEAEs | 26 (47.3) | 41 (29.5) | 76 (36.0) | 54 (30.7) |
| General disorders and administration site conditions | 3 (5.5) | 1 (0.7) | 8 (3.8) | 5 (2.8) |
| Infections and infestations | 11 (20.0) | 22 (15.8) | 32 (15.2) | 24 (13.6) |
| COVID-19 | 3 (5.5) | 4 (2.9) | 5 (2.4) | 4 (2.3) |
| Nasopharyngitis | 1 (1.8) | 7 (5.0) | 10 (4.7) | 7 (4.0) |
| Upper respiratory tract infection | 3 (5.5) | 6 (4.3) | 9 (4.3) | 5 (2.8) |
| Investigations | 6 (10.9) | 10 (7.2) | 17 (8.1) | 16 (9.1) |
| Alanine aminotransferase increased | 4 (7.3) | 1 (0.7) | 5 (2.4) | 3 (1.7) |
| Metabolism and nutrition disorders | 3 (5.5) | 4 (2.9) | 7 (3.3) | 1 (0.6) |
| Nervous system disorders | 3 (5.5) | 1 (0.7) | 5 (2.4) | 3 (1.7) |
| **Patients with Body Weight ≤100 kg** | | | | |
| | **AVT04** | | **EU-Stelara** | |
| **System Organ Class** | **ADA Positive** | **ADA Negative** | **ADA Positive** | **ADA Negative** |
| **Preferred Term** | **(N=48)** | **(N=116)** | **(N=181)** | **(N=146)** |
| | n (%) | n (%) | n (%) | n (%) |
| Any TEAEs | 21 (43.8) | 37 (31.9) | 70 (38.7) | 51 (34.9) |
| General disorders and administration site conditions | 3 (6.3) | 1 (0.9) | 8 (4.4) | 5 (3.4) |
| Infections and infestations | 8 (16.7) | 21 (18.1) | 31 (17.1) | 24 (16.4) |
| Nasopharyngitis | 0 | 7 (6.0) | 10 (5.5) | 7 (4.8) |
| Upper respiratory tract infection | 3 (6.3) | 6 (5.2) | 8 (4.4) | 5 (3.4) |
| Investigations | 4 (8.3) | 7 (6.0) | 14 (7.7) | 13 (8.9) |
| Metabolism and nutrition disorders | 3 (6.3) | 4 (3.4) | 6 (3.4) | 1 (0.7) |
| Nervous system disorders | 3 (6.3) | 1 (0.9) | 5 (2.8) | 3 (2.0) |

Adverse Events were coded according to MedDRA Version 24.1
ADA=Anti-drug antibody; n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N=Total number of subjects in the relevant population for each Strata (where relevant); PT=Preferred Term; SOC= System Organ Class; TEAE=Treatment-emergent Adverse Event; %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

The number of ADA positive patients who reported at least 1 TEAE during the study was higher in the AVT04 cohort (47.3%, N=26 of 55), than in the EU-Stelara cohort (36.0%, N=76 of 211).

The number of ADA negative patients who reported at least 1 TEAE during the study was similar in the AVT04 cohort (29.5%, N=41 of 139) and in the EU-Stelara group (30.7%, N=54 of 176).

*From Week 16 to Week 28*

From Week 16 to Week 28, the number of ADA positive patients who reported at least 1 TEAE during the study was similar between cohorts (10.9% in the AVT04 cohort, 13.3% in the EU-Stelara/AVT04 cohort, 16.0% in the EU-Stelara/EU-Stelara cohort).

From Week 16 to Week 28, the number of ADA negative patients who reported at least 1 TEAE during the study was lower in the AVT04 cohort (10.6% in the AVT04 cohort) than the EU-Stelara/AVT04 (18.9%) and EU-Stelara/EU-Stelara cohorts (14.3%).

From Week 28 to EOS the number of ADA positive patients who reported at least 1 TEAE during the study was similar between cohorts (23.0% in the AVT04 cohort, 26.3% in the EU- Stelara/AVT04 cohort, 20.6% in the EU-Stelara/EU-Stelara cohort). The number of ADA negative patients who reported at least 1 TEAE during the study was lower in the AVT04 cohort (12.8%) than in the EU-Stelara/AVT04 (16.7%) and EU-Stelara/EU-Stelara cohorts (22.1%).

Subgroup Analysis: TEAEs by Neutralizing Anti-drug Antibody (nAb) Status

*From Baseline to Week 16*

**Table 22.** TEAEs by Primary SOC and PT by nAb Status in Patients (≥5% of Patients in any Cohort) - From Baseline to Week 16 (Study AVT04-GL-301, Safety Analysis Set)

| **All Patients** | | | | |
|---|---|---|---|---|
| System Organ Class<br>Preferred Term | **AVT04 (N=194)**<br>**nAb Positive (N=15)**<br>**n (%)** | <br>**nAb Negative (N=179)**<br>**n (%)** | **EU-Stelara (N=164)**<br>**nAb Positive (N=68)**<br>**n (%)** | <br>**nAb Negative (N=319)**<br>**n (%)** |
| Any TEAEs | 5 (33.3) | 62 (34.6) | 26 (38.2) | 104 (32.6) |
| General disorders and administration site conditions | 1 (6.7) | 3 (1.7) | 6 (8.8) | 7 (2.2) |
| Injection site reaction | 1 (6.7) | 1 (0.6) | 4 (5.9) | 5 (1.6) |
| Infections and infestations | 1 (6.7) | 32 (17.9) | 12 (17.6) | 44 (13.8) |
| Pharyngitis | 1 (6.7) | 1 (0.6) | 0 | 4 (1.3) |
| Upper respiratory tract infection | 0 | 9 (5.0) | 3 (4.4) | 11 (3.4) |
| Investigations | 0 | 16 (8.9) | 6 (8.8) | 27 (8.5) |
| Metabolism and nutrition disorders | 1 (6.7) | 6 (3.4) | 2 (2.9) | 6 (1.9) |
| Dyslipidaemia | 1 (6.7) | 0 | 1 (1.5) | 1 (0.3) |
| Hypertriglyceridaemia | 1 (6.7) | 2 (1.1) | 1 (1.5) | 2 (0.6) |
| Musculoskeletal and connective tissue disorders | 1 (6.7) | 4 (2.2) | 2 (2.9) | 6 (1.9) |
| Pain in extremity | 1 (6.7) | 0 | 0 | 0 |
| Nervous system disorders | 1 (6.7) | 3 (1.7) | 2 (2.9) | 6 (1.9) |
| Headache | 1 (6.7) | 2 (1.1) | 1 (1.5) | 4 (1.3) |
| Vascular disorders | 1 (6.7) | 1 (0.6) | 0 | 10 (3.1) |
| Hypertension | 1 (6.7) | 0 | 0 | 6 (1.9) |
| **Patients with Body Weight ≤100 kg** | | | | |
| System Organ Class<br>Preferred Term | **AVT04 (N=164)**<br>**nAb Positive (N=15)**<br>**n (%)** | <br>**nAb Negative (N=149)**<br>**n (%)** | **EU-Stelara (N=327)**<br>**nAb Positive (N=59)**<br>**n (%)** | <br>**nAb Negative (N=268)**<br>**n (%)** |
| Any TEAEs | 5 (33.3) | 53 (35.6) | 24 (40.7) | 97 (36.2) |
| General disorders and administration site conditions | 1 (6.7) | 3 (2.0) | 6 (10.2) | 7 (2.6) |
| Injection site reaction | 1 (6.7) | 1 (0.7) | 4 (6.8) | 5 (1.9) |
| Infections and infestations | 1 (6.7) | 28 (18.8) | 11 (18.6) | 44 (16.4) |
| Nasopharyngitis | 0 | 7 (4.7) | 2 (3.4) | 15 (5.6) |
| Pharyngitis | 1 (6.7) | 1 (0.7) | 0 | 4 (1.5) |
| Upper respiratory tract infection | 0 | 9 (6.0) | 2 (3.4) | 11 (4.1) |
| Investigations | 0 | 11 (7.4) | 6 (10.2) | 21 (7.8) |
| Metabolism and nutrition disorders | 1 (6.7) | 6 (4.0) | 1 (1.7) | 6 (2.2) |
| Dyslipidaemia | 1 (6.7) | 0 | 1 (1.7) | 1 (0.4) |
| Hypertriglyceridaemia | 1 (6.7) | 2 (1.3) | 0 | 2 (0.7) |

| | | | | |
|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | 1 (6.7) | 4 (2.7) | 2 (3.4) | 6 (2.2) |
| Pain in extremity | 1 (6.7) | 0 | 0 | 0 |
| Nervous system disorders | 1 (6.7) | 3 (2.0) | 2 (3.4) | 6 (2.2) |
| Headache | 1 (6.7) | 2 (1.3) | 1 (1.7) | 4 (1.5) |
| Vascular disorders | 1 (6.7) | 1 (0.7) | 0 | 10 (3.7) |
| Hypertension | 1 (6.7) | 0 | 0 | 6 (2.2) |

Adverse Events were coded according to MedDRA Version 24.1
n=Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N=Total number of subjects in the relevant population for each Strata (where relevant); nAB=neutralizing antobody; PT=Preferred Term; SOC= System Organ Class; TEAE=Treatment-emergent Adverse Event; %=Percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.

From Baseline to Week 16, attempts to identify trends in nAb positive patients was limited by low sample sizes in the nAb positive AVT04 (N=15) and EU-Stelara (N=68) subgroups. The number of nAb positive patients who reported at least 1 TEAE during the study was lower in the AVT04 cohort (33.3%) than in the EU-Stelara cohort (38.2%).

Potential trends were easier to evaluate in nAb negative patients, due to the larger sample sizes in the nAb negative AVT04 (N=179) and EU-Stelara (N=319) subgroups. The number of nAb negative patients who reported at least 1 TEAE during the study was slightly higher in the AVT04 cohort (34.6%) than in the EU-Stelara cohort (32.6%). The number of reported TEAEs was similar between cohorts for most SOCs.

From Week 16 to Week 28 as well as from Week 28 to EOS, attempts to identify trends in nAb positive patients was limited by low sample sizes.

#### *2.6.8.8. Safety related to drug-drug interactions and other interactions*

Not applicable

#### *2.6.8.9. Discontinuation due to adverse events*

There were no Early Terminations or Discontinuations in Study AVT04-GL-101.

From baseline to Week 16 of Study AVT04-GL-301, 3 patients (0.8%) in the EU-Stelara group experienced TEAEs leading to discontinuation from study treatment and early termination from study. The TEAEs were judged as non-treatment related. There were no discontinuations or early terminations in the AVT04 group. From Week 16 to Week 28, 1 (0.5%), 3 (1.6%) and 4 (2.1%) patients in the AVT04/AVT04, EU-Stelara/AVT04 and EU-Stelara/EU-Stelara group experienced TEAEs leading to discontinuation and early termination; all were judged not treatment-related. From Week 28 to Week 52, no TEAEs leading to discontinuation and early termination were recorded for the AVT04/AVT04 and the EU-Stelara/AVT04 treatment groups, whereas in the EU-Stelara/EU-Stelara group, there was 1 (0.5%) patient reported with a TEAE judged as not treatment-related leading to discontinuation and early termination.

#### *2.6.8.10. Post marketing experience*

Not available

## 2.6.9. Discussion on clinical safety

Safety data on AVT04 is available from two clinical studies (Study AVT04-GL-101 and Study AVT04-GL-301), where safety was assessed as part of the secondary study objectives.

Study AVT04-GL-101 was conducted in healthy subjects following single dose administration and Study AVT04-GL-301 was conducted in patients with PsO following multiple dose administration.

In all individual clinical studies, safety analyses were carried out using the safety population, which was defined as all randomized subjects who received at least one dose of the IP or comparator, with treatment assignment based on the actual treatment received.

Demographic and baseline characteristics

In the safety population of Study AVT04-GL-101, the demographic and baseline characteristics were generally balanced. Small differences between the groups are noted with respect to the medical history and concurrent disease, though not considered important. The most frequently received concomitant medications were paracetamol (31.3%), tozinameran (26.2%), ibuprofen (18.7%).

In Study AVT04-GL-301, patients initially randomized to EU-Stelara were re-randomized in a 1:1 ratio at Week 16, to enter Stage 2 and either continue treatment with EU-Stelara or to switch to AVT04. Overall, demographic and other baseline characteristics were similar between the treatment groups.

According to the provided information on patient exposure, all patients received two doses of the IP as per protocol, i.e. one at baseline and one at Week 4. The majority of these patients had a b.w. of ≤100 kg, i.e. 164 of 194 patients in the AVT04 cohort and 328/387 in the EU-Stelara cohort. The remaining patients (30/194 in the AVT04 and 59/387 in the EU-Stelara cohort) had >100 kg b.w. The safety data from the latter subset of patients is considered too small to draw firm conclusions on potential safety issues. Therefore, the safety data have been assessed for 'all patients' and 'patients with body weight ≤100'.

Almost 90% of all patients in Study AVT04-GL-301 had a history of prior medications. Differences observed in individual medications between cohorts are not considered to affect the safety evaluation. For the all patients group, the most frequently reported concomitant medications in patients by ATC Level 2 were: progestogens and estrogens, fixed combinations; HMG CoA reductase inhibitors; ACE inhibitors, plain; anilides; beta blocking agents; selective, and other viral vaccines.

Adverse events

In the Phase 1 PK study in healthy volunteers (AVT04-GL-101), 69% of subjects reported at least 1 TEAE during the study and the proportion of subjects with TEAE was comparable between groups (68.4%, 67.7%, and 71.1% in the AVT04, EU-Stelara and US-Stelara cohort, respectively). Also, the proportion of subjects with treatment-related TEAEs was comparable between the AVT04 and EU-Stelara group, whereas around 10% more subjects reported treatment-related TEAEs in the US-Stelara group (34.7%, 34.3% and 44.3% in the AVT04, EU-Stelara and US-Stelara cohort, respectively). The total number of treatment-related TEAEs was lower in the AVT04 cohort compared to the EU-Stelara and US-Stelara cohorts (46, 59 and 61, respectively). Overall, most TEAEs were mild in this study. Two subjects (2.0%) in the AVT04 cohort, 3 subjects (3.0%) in the EU-Stelara cohort, and 1 patient (1.0%) in the US-Stelara cohort reported severe TEAEs. The frequency of Grade 3 laboratory abnormalities was low (3.4% of subjects overall), and similar across cohorts. One subject in the EU approved Stelara cohort had a Grade 3 laboratory abnormality of neutropenia that was IP-related. No patient died in the study. No TEAEs leading to study discontinuation occurred during the study.

The number of treatment-related TEAEs by SOC and PT was higher for EU-Stelara (and US-Stelara) for gastrointestinal disorders (especially nausea and vomiting), Respiratory, thoracic and mediastinal disorders and rash. In contrast, there was an increased number for PT headache in the AVT04 cohort compared to EU-Stelara (and US-Stelara).

The number of treatment-related TEAEs in the subgroup "non-Japanese >80 kg" was twice as high in the AVT04 cohort compared to the EU-Stelara cohort (AVT04: 6 subjects (33.3%) reported 8 events; EU-Stelara: 3 subjects (15.8%) reported 4 events). These differences might be due to the small sample size in this subgroup (18 and 19 subjects, respectively). The observed treatment-related events in the AVT04 arm were graded as mild, none were considered serious or events of special interest, nor did any lead to treatment discontinuation. Of note, the frequency of treatment-related TEAEs in the US-Stelara arm was also higher than in the EU-Stelara arm and comparable to the AVT04 arm.

The applicant was requested to discuss increases in hepatic liver enzymes. On multiple occasions, increases in different liver enzymes were reported under both test and reference product and number of them was considered to be clinically significant. Such adverse events are not reported in the SmPC of Stelara and their causality was requested to be discussed in more detail. The potential for more severe manifestation in terms of liver injury was requested to be discussed as well. The applicant discussed the requested issue. It was agreed that abnormal liver function tests seemed to be comparable between different arms and so this issue is not unique to the test product. The applicant further clarified that out of 91 reported cases, only 3 were considered to be treatment-related and all these cases were treated with EU-Stelara. The applicant also confirmed that there were no persistent liver injuries.

The frequency of TEAE of special interest (TEAESI) was well balanced between treatment groups. Most were mild and none were severe. All but two TEAESIs were administration site related disorders. All local ISRs were of mild severity and occurred at comparable frequencies in the three treatment groups (AVT04: 10.2% of subjects, EU-Stelara: 8.1%; US-Stelara: 11.3%).

Overall, none of the treatment-related TEAEs was unexpected and the reported safety findings after a single dose in the PK study in healthy subjects reflects the known safety profile of the originator as per Stelara SmPC.

Initially, the Applicant only provided safety and immunogenicity data through Week 28 for the pivotal efficacy and safety study AVT04-GL-301. The remaining data through week 52 were provided with the answers to the Day 120 List of Questions.

During Stage 1 (i.e., from Day 0 through Week 16), a total of 67 patients (34.5%) reported 104 TEAEs in the AVT04 cohort and 130 patients (33.6%) reported 223 TEAEs in the EU-Stelara cohort. In both cohorts, most TEAEs were mild and no treatment-related severe TEAEs have been reported. Seven patients (1.8%) in the EU-Stelara cohort had 10 serious TEAEs, which were not considered related to study treatment; no serious TEAEs were reported in the AVT04 cohort. Three patients (0.8%) reported 3 TEAEs that led to early termination in the EU-Stelara cohort; all these TEAEs also led to IP discontinuation. Two patients (0.5%) reported 2 serious TEAEs that led to ET in the EU-Stelara cohort. No patient in the AVT04 cohort had TEAEs that led to early termination or IP discontinuation. A total of 4 TEAEs of special interest were reported in 3 patients (1.5%) in the AVT04 cohort and 15 TEAEs of special interest were reported in 14 patients (3.6%) in the EU-Stelara cohort. No patient died up to Week 16.

Among the patients evaluated through Week 16, fewer treatment-related TEAEs were reported in the AVT04 group as compared to the EU-Stelara group (AVT04: 10 patients (5.2%) reporting 13 events; EU-Stelara: 37 patients (9.6%) reporting 39 events). According to SOC, the frequency of treatment-related TEAE was higher in the EU-Stelara group as compared to the AVT04 group in all of the following: infections and infestations, general disorders and administration site conditions skin and subcutaneous tissue disorders. In both cohorts, all treatment-related TEAEs were mild or moderate and no severe events have been reported.

Only few TEAESIs were reported in study AVT04-GL-301 with 1.5% of patients on AVT04 reporting 4 events and 3.1% of patients on EU-Stelara reporting 17 events up to Week 16. The majority of events were general disorders and administration site related disorders. All ISRs in both stages of the study were of mild severity with a tendency of more frequent ISRs in the EU-Stelara group.

From Week 16 to Week 28, 10.9% of patients reported TEAEs in the AVT04/AVT04 cohort compared to 15.6% in the EU-Stelara/AVT04 cohort, and 15.3% in the EU- Stelara/EU-Stelara cohort. Most TEAEs were mild in severity. One patient (0.5%) reported 1 severe TEAE each in the AVT04/AVT04 cohort and the EU-Stelara/EU-Stelara cohort. 2.6% of patients reported treatment-related TEAEs in the EU-Stelara/AVT04 cohort compared to 1.1% of patients in the EU-Stelara/EU-Stelara cohort, whereas no treatment related TEAEs were reported in the AVT04/AVT04 cohort. One patient (0.5%) in the EU-Stelara/EU-Stelara cohort had 1 serious TEAE, which was not considered related to study treatment; no serious TEAEs were reported in the other 2 cohorts. One patient (0.5%) reported 1 TEAE that led to ET in the AVT04/AVT04 cohort, 3 patients (1.6%) reported 3 TEAEs that led to ET in the EU-Stelara/AVT04 cohort, and 4 patients (2.1%) reported 4 TEAEs that led to ET in the EU- Stelara/EU-Stelara cohort; all these TEAEs also led to IP discontinuation, and none was serious. Two patients (1.0%) reported 2 TEAEs of special interest each in the EU-Stelara/AVT04 cohort and one (0.5%) patient reported 1 TEAE of special interest in the EU-Stelara/EU-Stelara cohort. No patient died from Week 16 to Week 28.

A similar pattern was observed from Week 28 to the end of study. Overall, comparable results were observed in laboratory parameters between cohorts throughout the entire phase 3 study. Individual shifts in certain parameters were not considered to be clinically relevant.

Concluding on the safety data in PsO patients, AVT04 appears to have a comparable safety profile to the reference product. Minor differences in certain TEAEs observed between cohorts were mostly lower in the AVT04 group compared to the EU-Stelara group.

Immunogenicity

Immunogenicity was a secondary objective in both studies AVT04-GL-101 and AVT04-GL-301 and was assessed by means of monitoring development of ADAs and nAbs during the studies.

Both clinical studies of AVT04 supported a consistent immunogenicity profile of Stelara and AVT04 in healthy subjects and in patients with PsO. The incidence of ADAs directed against Stelara (both US- and EU-Stelara) was found to be higher than for AVT04 in both settings in healthy subjects following single administration (AVT04: 36.7%; EU-Stelara: 59.6%; US-Stelara: 53.6%) as well as in patients with PsO following repeat administration up to Week 16 (AVT04: 28.4%; EU-Stelara: 54.5%). After re-randomization at Week 16, the treatment-emergent ADA incidence was comparable in the AVT04/AVT04 group, in the EU-Stelara/AVT04 group, and in the EU-Stelara/EU-Stelara group (4.8% vs. 4.5% vs. 6.7%, respectively), with no detectable treatment-emergent nAbs in any treatment group. The observed differences in ADA incidences between HV and PsO patients are probably caused by differences in study design and population taking into account, amongst others, that PsO patients may be immune compromised and thus develop less ADA overall than healthy volunteers.

Overall, systemic ustekinumab exposure was similar across all treatment groups within the ADA positive, ADA negative, nAb positive and nAb negative subgroups. As expected, ustekinumab exposure was in general lower in ADA positive and nAb positive subgroups than in the overall population. Also $t_{1/2}$ was shorter in the ADA positive subgroups.

## 2.6.10. Conclusions on clinical safety

Overall, the AVT04 clinical development programme and design of the studies is considered adequate to evaluate the comparability of AVT04 and its reference product EU-Stelara in terms of safety and immunogenicity. Considering the provided safety data from the clinical development programme, AVT04 and Stelara can be concluded to be biosimilar in terms of safety.

In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with AVT04 had lower ADA and nAb frequencies than subjects treated with Stelara. Whereas presence of ADA led to lower exposure, no immunogenicity related difference was observed in the safety profile of the two products.

## *2.7. Risk management plan*

### 2.7.1. Safety concerns

**Table 23.** Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | Serious systemic hypersensitivity reactions |
| **Important potential risks** | Serious infections (including mycobacterial and salmonella infections)<br>Malignancy<br>Cardiovascular (CV) events<br>Serious depression including suicidality<br>Venous thromboembolism (VTE)<br>Exposure during pregnancy |
| **Missing information** | Long-term safety in paediatric psoriasis patients 6 years and older<br>Long-term impact on growth and development in paediatric psoriasis patients 6 years and older<br>Long-term safety in adult patients with moderately to severely active Crohn's disease |

### 2.7.2. Pharmacovigilance Plan

**Table 24.** On-going and planned additional pharmacovigilance activities

| **Study**<br><br>**Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| N/A | | | | |

## 2.7.3. Risk minimisation measures

**Table 25.** Description of routine risk minimisation measures by safety concern

| Safety concern | Routine risk minimisation activities |
|---|---|
| Serious systemic hypersensitivity reactions | Routine risk communication:<br><br>SmPC sections 4.3, 4.4 and 4.8.<br><br>In order to inform patients of this risk, corresponding text is also present in the Patient Information Leaflet (PIL) sections 2 and 4.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>Section 4.3 of the SmPC states that ustekinumab is contraindicated in case of hypersensitivity to the active substance or to any of the excipients. In addition, according to section 4.4 of the SmPC, if an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Serious infections (including mycobacterial and salmonella infections) | Routine risk communication:<br><br>SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Section 4.3 of the SmPC states that ustekinumab is contraindicated in case of clinically important, active infection. In addition, according to section 4.4 of the SmPC, caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Prior to initiating treatment with ustekinumab, patients should be evaluated for TB infection. Ustekinumab must not be given to patients with active TB. Treatment of latent TB infection should be initiated prior to administering ustekinumab. Anti-TB therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active TB during and after treatment. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves. |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | Section 4.4 of the SmPC also states that because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.<br><br>Section 4.6 of the SmPC states that ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Malignancy | Routine risk communication:<br><br>SmPC sections 4.4 and 4.8.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL section 2.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Section 4.4 of the SmPC states that all patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL section 2.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Cardiovascular (CV) events | Routine risk communication:<br><br>None.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>None.<br><br>Other routine risk minimisation measures beyond the Product Information: |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | Legal status: Restricted medical prescription. |
| Serious depression including suicidality | Routine risk communication:<br><br>SmPC section 4.8.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL section 4.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None.<br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Venous thromboembolism (VTE) | Routine risk communication:<br><br>None.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None.<br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Exposure during pregnancy | Routine risk communication:<br><br>SmPC section 4.6.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL section 2.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>According to section 4.6 of the SmPC, women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment. There are no adequate data from the use of ustekinumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.<br><br>In order to inform patients of this risk, corresponding text is also present in the PIL section 2.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Long-term safety in paediatric psoriasis | Routine risk communication: |

| Safety concern | Routine risk minimisation activities |
|---|---|
| patients 6 years and older | SmPC section 4.2.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>None.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Long-term impact on growth and development in paediatric psoriasis patients 6 years and older | Routine risk communication:<br><br>SmPC section 4.2.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>None.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |
| Long-term safety in adult patients with moderately to severely active Crohn's disease | Routine risk communication:<br><br>None.<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br><br>None.<br><br>Other routine risk minimisation measures beyond the Product Information:<br><br>Legal status: Restricted medical prescription. |

### 2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.9. Product information*

### 2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Stelara (ustekinumab) 45 mg and 90 mg solution for injection in pre-filled syringe. The bridging report submitted by the applicant has been found acceptable.

### 2.9.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing statutory and additional information (see below) has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: SmPC, package leaflet and instructional video.

### 2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Uzpruvo (ustekinumab) is included in the additional monitoring list as.

- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Biosimilarity assessment

## *3.1. Comparability exercise and indications claimed*

The applicant has developed Uzpruvo (AVT04, ustekinumab) as a proposed biosimilar product to Stelara (ustekinumab), which was authorized via the Centralized Procedure in the European Union on 15.01.2009 (marketing authorization holder Janssen-Cilag). Ustekinumab 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, thereby preventing initiation of immune-response signalling pathways.

In the present MAA, only the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringe (PFS) presentations are applied for.

The applicant is seeking approval for AVT04 for the following indications approved for the reference medicinal product Stelara.

- Plaque psoriasis (PsO)
- Paediatric plaque psoriasis (pPsO) in children and adolescents ≥ 6 to < 17 years of age
- Psoriatic arthritis (PsA)

- Crohn's disease (CD)

AVT04 Prefilled syringe PFS-SD 45 mg/0.5 mL and 90 mg/1 mL are indicated for maintenance dosing in the treatment of Crohn's disease. The 130 mg/26 mL vial presentation for treatment initiation of CD by intravenous administration is not included in the initial MAA. The 45 mg/0.5 mL vial presentation of the AVT04 drug product, required for body weight (b.w.) based dosing of patients with pPsO and a b.w. <60 kg, is also not part of the initial MAA submission.

The currently applied for PFS presentations are suitable for the maintenance therapy of CD as well as treatment of paediatric PsO in subjects with BW >60kg.

The applicant has included amendments to the SmPC, to reflect the unavailability of vial presentations and refer to other products available on the market.

**Quality aspects**

The applicant performed a comprehensive analytical Biosimilarity exercise comparing AVT04 with the reference medicinal product EU-Stelara, and US-Stelara that were used in the clinical studies AVT04-GL-101 and AVT04-GL-301. The number of AVT04 and Stelara batches included in the analytical Biosimilarity exercise can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product.

Relevant quality attributes of the ustekinumab molecule were assessed using a broad panel of orthogonal standard and state of the art techniques. Analyses covered primary sequence, higher order structure, size and charge variants, glycosylation and other post-translational modifications, as well as protein concentration. Functional activity was compared by a large panel of binding assays, and cell-based biological assays confirmed the absence of Fc-related effector functions. Based on the provided information it is concluded that the analytical methods are suitable and sensitive to detect minor differences.

The quality attributes were either evaluated against a quality range or assessed qualitatively. Analytical results including chromatograms, spectra, response curves etc. for the individual lots have been provided and enabled an independent assessment.

**Clinical aspects**

The clinical development programme comprises two comparative studies with the aim of establishing PK equivalence to the reference product Stelara: one comparative PK study (Study AVT04-GL-101) in healthy subjects and one comparative efficacy, safety, immunogenicity, and PK study (Study AVT04-GL-301) in patients with moderate to severe PsO were conducted.

Study AVT04-GL-101 is a phase 1, first-in-Human (FIH), randomized, double-blind, single-dose, parallel group, 3-arm study comparing the pharmacokinetic, safety, tolerability and immunogenicity profiles of AVT04, EU-Stelara and US-Stelara in healthy adult subjects.

Study AVT04-GL-301 is a randomized, double-blind, multicenter, active control clinical study to compare the efficacy, safety, and immunogenicity of AVT04 versus EU-Stelara in patients with moderate to severe chronic plaque-type psoriasis (PsO).

In the study AVT04-GL-101, the primary objective was to demonstrate PK similarity of AVT04 to both EU-Stelara and US-Stelara; as well as to demonstrate similarity between EU-Stelara and US-Stelara, in terms of both $C_{max}$ and $AUC_{0\text{-}inf}$ (co-primary endpoints). The selected endpoints are in line with relevant EMA guideline (EMA/CHMP/BMWP/403543/2010) for a single dose study with subcutaneous administration. The assessment of biosimilarity was based on 90% confidence intervals (CIs) for the ratio of the geometric means (AVT04/EU-Stelara) for $C_{max}$ and $AUC_{0\text{-}inf}$ of the ustekinumab concentrations, which had to be contained within the acceptance limits of 80-125%. The equivalence

margins used in the study are in line with conventionally used margins for biosimilar products. Secondary objectives comprised additional PK parameters to support similarity comparability ($AUC_{0\text{-last}}$, $t_{max}$, $K_{el}$, $t_{1/2}$, Vz/F, CL/F), comparison of safety, tolerability and immunogenicity between AVT04 and reference products.

In the study AVT04-GL-301, the primary objective was to evaluate the therapeutic equivalence of AVT04 compared to EU-Stelara in the treatment of moderate to severe chronic PsO. The primary efficacy endpoint was percent improvement in Psoriasis Area and Severity Index (PASI) from Baseline to Week 12. The CHMP's advice to revise the timing of the primary analysis was not followed, however the Applicant provided data for earlier time points as secondary endpoints. Secondary Objectives were to compare the safety, tolerability, and immunogenicity of AVT04 and EU-Stelara, to compare steady-state PK of AVT04 and EU-Stelara by measuring $C_{trough}$ values and to compare efficacy of AVT04 and EU-Stelara by measuring additional efficacy endpoints commonly used in patients with PsO.

## *3.2. Results supporting biosimilarity*

**Quality aspects**

Overall, from a quality perspective similarity between AVT04 and EU-Stelara could be confirmed for most of the quality attributes tested and only slight differences were detected. These differences have been generally well addressed and justified to have no impact on the Biosimilarity claim or on safety and efficacy.

Analytical comparability of EU-Stelara and US-Stelara was satisfactorily demonstrated.

**Clinical aspects**

In the phase 1 PK study, primary endpoints were $AUC_{0\text{-inf}}$ and $C_{max}$. PK comparability criteria were met for one of the two co-primary endpoints, $C_{max}$ [109.5% (90% CI 101.7%, 117.8%)]. The 90% CI for the secondary endpoint, $AUC_{0\text{-last}}$ was also contained within the pre-specified acceptance limits [114.7% (90% CI 106.5%, 123.6%)].

Additionally, the analyses in the ADA negative and nAb-negative subgroups showed that the 90% CI for both co-primary parameters were within the similarity margin [$C_{max}$: 106.7% (90% CI 96.2%, 118.5%), $AUC_{0\text{-inf}}$: 108.1% (90% CI 98.0%, 119.3%) in ADA-negative subgroup and; $C_{max}$: 97.7% (90% CI 85.6%, 111.5%), AUCinf 101.6% (90% CI 89.9%, 114.9%) in nAb-negative group]. In ADA-positive subgroup $C_{max}$ was also within the similarity margin [107.7% (90% CI 96.6%, 120.1%)].

Due to differences in protein concentration between the AVT04 batch and EU-Stelara batch, the applicant presented an analysis using PK parameters adjusted for protein content that was pre-planned as sensitivity analysis. After protein content correction, the bioequivalence criteria for both primary PK parameters $C_{max}$ [102.8% (90% CI 95.5%, 110.7%)] and $AUC_{0\text{-inf}}$ [109.8% (90% CI 101.5%, 118.8%)] as well as for the secondary PK parameter $AUC_{0\text{-t}}$ [107.8 (90% CI 100.0%, 116.2%)] were met.

The protein-adjusted analyses in the ADA negative and nAb-negative subgroups showed that the 90% CI for both co-primary parameters were within the similarity margin [protein-adjusted $C_{max}$: 100.7% (90% CI 90.5%, 112.0%), protein-adjusted $AUC_{0\text{-inf}}$: 102.0 (90% CI 92.3%, 112.8%) in ADA-negative subgroup and; protein-adjusted $C_{max}$: 92% (90% CI 80.7%, 105.0%), protein-adjusted $AUC_{0\text{-inf}}$: 95.6% (90% CI 84.5%, 108.1%) in nAb-negative subjects]. Also, in ADA-positive subgroup both co-primary parameters were within the similarity margin after protein-correction [$C_{max}$: 100.9% (90% CI 90.6%, 112.5%), $AUC_{0\text{-inf}}$: 109.8% (90% CI 97.2%, 124.0%)].

In the efficacy and safety study, AVT04 demonstrated similar efficacy as EU-Stelara in primary and secondary efficacy endpoints through Week 52. The primary efficacy endpoint, percentage improvement in PASI from baseline to Week 12 was met. The LS mean difference (AVT04 vs EU-Stelara) was 0.4 (95% CI -2.63, 3.50) for PP set and 0.4% (95% CI -2.66%, 3.34%) for the ITT set. The 95% CI for both the ITT and the PP analysis were within a narrow range; therefore, clinical comparability can be concluded. Similar results were observed for secondary endpoints percentage improvement in PASI from baseline over time, percentage of patients achieving PASI50/PASI75/ PASI90/PASI100 up to Week 52, AUEC for PASI from baseline through Week 12, proportion of patients achieving sPGA responses of clear (score 0) or almost clear (score 1) at various time points from BL through Week 52; change in DLGI scores from baseline to week 52 and; change in %BSA affected by PsO at various time points from baseline through week 52. No patient is either group discontinued the treatment due to being a non-responder (PASI improvement <50% compared to Baseline).

Trough concentrations measured in patients with PsO during a later phase of the study, when the test and reference products had comparable protein concentrations, showed no significant difference between the group that exclusively received AVT04 and the group that exclusively received EU-Stelara over the duration of the study (see Clinical pharmacology and Efficacy sections).

In the Phase 1 PK study in healthy volunteers, the proportion of subjects with TEAE as well as the proportion of subjects with treatment-related TEAEs were comparable between groups. The total number of treatment-related TEAEs was lower in the AVT04 cohort compared to the EU-Stelara and US-Stelara cohorts. Overall, most TEAEs were mild in this study. The frequency of TEAE of special interest was well balanced between treatment groups. Most were mild and none were severe. No patient died in the study. No TEAEs leading to study discontinuation occurred during the study (refer to Clinical safety section).

The pivotal safety data of the phase 3 study showed a comparable frequency of TEAEs for both products (refer to Clinical safety section). In both cohorts, most TEAEs were mild and no treatment-related severe or serious TEAEs have been reported. Fewer treatment-related TEAEs and fewer TEAEs of special interest were reported in the AVT04 group as compared to the Stelara group. No patient died during the study (refer to Clinical safety section).

Both studies supported a consistent immunogenicity profile of Stelara and AVT04 in healthy subjects following single administration and in patients with PsO following repeat administration. The incidence of ADAs directed against AVT04 was found to be lower than for Stelara in both settings. In ADA-negative healthy subjects, similarity was observed for both $C_{max}$ and $AUC_{0\text{-}inf}$, which is supportive of comparability, as the comparison of pharmacokinetics in ADA-negative subjects is of interest, since it allows direct evaluation of elimination of the substances without interference of ADAs (refer to discussions above).

In patients with PsO, efficacy results as measured by percent improvement from baseline in PASI at Week 12 did not reveal notable differences between products neither in ADA negative nor in ADA positive patients. In the ADA positive subgroups, the frequency of (any) TEAE was higher in AVT04 compared to EU-Stelara (47.3% versus 35.5%, respectively). However, the frequency of related TEAEs in ADA positive subgroups was comparable between the treatments (7.3% versus 9.5% in AVT04 and EU-Stelara group, respectively).

## *3.3. Uncertainties and limitations about biosimilarity*

**Clinical aspects**

In the phase 1 PK study, biosimilarity of AVT04 compared to EU-Stelara could not be demonstrated for the co-primary endpoint $AUC_{0\text{-}inf}$, in the analysis uncorrected for protein-content as the 90% CI for the geometric mean ratio fell outside the acceptance range of 80.00% to 125.00% [116.9% (90% CI 108.1%, 126.4%)], failing to demonstrate equivalent drug exposure, suggesting higher $AUC_{0\text{-}inf}$ with AVT04 compared to EU-Stelara. The protein-corrected analysis was originally not labelled to substitute the primary analysis but was specified as sensitivity analysis only. In addition, the conditions under which this analysis were to be conducted were not adequately prespecified.

Frequency of ADA development was higher with EU-Stelara. In ADA-positive subgroup (protein-unadjusted) the 90% CI for $AUC_{0\text{-}inf}$ exceeded the upper biosimilarity margin [117.2% (90% CI 103.8%, 132.4%)]. In nAb positive subgroups (protein-unadjusted and protein-adjusted) both co-primary parameters fell outside the biosimilarity margin (Cmax: 127.9% (90% CI 105.7%, 154.7%), AUCinf: 145.8% (90% CI 116.9%, 182.0%) in the protein-unadjusted analysis and; $C_{max}$: 118.7% (90% CI 98.3%, 143.3%), $AUC_{0\text{-}inf}$: 135.4% (90% CI 108.5%, 168.8%) in the protein-adjusted analysis]. Due to small size of this subgroup (12 vs 25 nAb-positive subjects in AVT04 and Eu-Stelara group, respectively) as well as higher variability with EU-Stelara, these results should be interpreted with caution and not be overinterpreted.

In healthy volunteers >80 kg, the point estimates for GMRs for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ fell far above 100% (including CIs); i.e. for $AUC_{0\text{-}inf}$ the GMR was 135.8% (90% CI 111.1%, 161.3%) and for $AUC_{0\text{-}t}$ the GMR was 133.3% (90% CI 110.1%, 161.3%). It should be noted that the number of participants in this BW category was too low to draw robust conclusions and a chance finding cannot be excluded; however a trend toward higher exposure with AVT04 in these subjects is apparent. The substantially higher exposure with AVT04 compared to EU-Stelara in subjects with BW >80 kg was most likely dominated by an effect of ADA+/Nab+, and the small size of this subgroup and should not be overinterpreted.

In Study AVT04-GL-101, the number of treatment-related TEAEs in the subgroup "non-Japanese >80 kg" was twice as high in the AVT04 cohort compared to the EU-Stelara cohort. However, those events were comparable between AVT04 and US-Stelara in this subgroup indicating that the observed difference may be a chance finding that is due to the small sample size in the respective subgroup.

## *3.4. Discussion on biosimilarity*

Overall, from a quality perspective similarity between AVT04 and EU-Stelara could be confirmed for most of the quality attributes tested and only slight differences were detected. These differences have been generally well addressed and justified to have no impact on the Biosimilarity claim or on safety and efficacy. Analytical comparability of EU-Stelara and US-Stelara was satisfactorily demonstrated.

In the PK study in healthy volunteers, biosimilarity of AVT04 compared to EU-Stelara was demonstrated for the co-primary endpoint $C_{max}$ (109.5% (90% CI 101.7%, 117.8%). In contrast, biosimilarity could not be demonstrated for the other co-primary endpoint $AUC_{0\text{-}inf}$, as the 90% CI for the geometric mean ratio fell outside the acceptance range of 80.00% to 125.00% (116.9% (90% CI 108.1%, 126.4%), suggesting higher exposure with AVT04. These results were obtained in the predefined initial analysis that did not account for protein content.

Differences in protein content between EU-Stelara and AVT04 batch (about 6.6%) were suggested as the main reason for missing the equivalence criteria for AUCinf. In order to account for these differences, an analysis adjusted for protein content was performed. After protein content normalization, the equivalence criteria for both primary PK parameters were met [Cmax: 102.8% (90% CI 95.5%, 110.7%); AUC0-inf: 109.8% (90% CI 101.5%, 118.8%).

While correction for protein content is considered meaningful due to differences in the delivered protein dose, this analysis was pre-specified in a general manner and was foreseen as a sensitivity analysis only. Nonetheless, the adequacy of the analysis unadjusted for the protein content, which was pre-specified as the primary analysis by the Applicant, is arguable due to the differences in protein content. Thereby, the validity of demonstrating PK equivalence when the conclusion relies on relevantly different content administration to determine equivalent PK, is also arguable. Therefore, PK similarity has not been unequivocally demonstrated. Of importance is, that additional data presented by the Applicant confirmed that the difference in protein concentration between AVT04 batch DP200011 and EU-Stelara batch KHS25MJ does not reflect a systematic difference between AVT04 and EU-Stelara, which is reassuring.

The residual higher exposure is likely caused by a lower immunogenicity of AVT04 compared to EU-Stelara which also impacts the drug clearance. This is corroborated by lower terminal elimination rate constant, lower clearance and longer terminal half-life observed with AVT04. In principle, it is acceptable for the biosimilar candidate to be less immunogenic than the reference product, provided that this does not modify the efficacy of the product or increase the incidence or severity of adverse reactions, which has been demonstrated for AVT04 (see discussions on PK, efficacy and safety).

Anti-drug antibodies formation depends on the interplay between several factors, which can be subject-related (e.g. genetic background or co-treatment) or drug-related (e.g. mAb target, antibody origin, post-translational modifications) or impurities etc. Pertaining to the latter, no relevant differences between proteins were observed at the quality level. As regards the subject-related factor, a possible imbalance in the likelihood of developing ADAs at baseline cannot be assessed.

The ADA/Nab negative populations are of interest to investigate similarity of the proteins, when unimpacted by intercurrent ADA/Nab events. In these analyses equivalent exposure of AVT-04 and EU-Stelara is observed. While the protein-corrected analysis as well as the analysis of ADA-negative subgroups are prone to multiple testing, both analyses are considered relevant, and both separately show similarity in PK. When combined, the protein corrected analysis in ADA negative subjects clearly show equivalent exposure, despite the reduced sample size (see section 5.2).

Primary efficacy endpoint analysis at Week 12 showed clinical similarity between the AVT04 group and the EU-Stelara group. Secondary efficacy endpoint analyses support the clinical similarity between the two products. No clinically relevant differences between the two treatments were observed in the later stage of the study i.e. up to Week 52.

As regards the safety profile of AVT04 no relevant differences in safety have been detected based on the available data. In terms of immunogenicity, subjects (both healthy volunteers and patients) treated with AVT04 had lower ADA and nAb frequencies than subjects treated with Stelara. Whereas presence of ADA led to lower exposure, no immunogenicity-related difference was observed in the safety profile of the two products. No immunogenicity-related differences were observed between the products for the percent improvement in PASI at Week 12 up to Week 16.

In conclusion, while PK equivalence has not been demonstrated in the analysis uncorrected for protein content in the presence of a difference of 6.6% in delivered protein content, the respective protein-adjusted analysis did. Currently no guideline exists under which conditions protein-adjusted analysis should be considered, and taking into consideration that 1) the results of the protein-unadjusted analysis were just slightly outside the 80-125% acceptance range for one of the two co-primary endpoints ($AUC_{0\text{-}inf}$), while $C_{max}$ was within the acceptance range; 2) both co-primary endpoints were within the acceptance range in the protein-adjusted analysis, and are further supported by analyses by ADA status; and 3) the efficacy and safety study in patients demonstrated that AVT04 had similar efficacy and safety as the reference product, despite the slightly higher exposure with AVT04, AVT04 can be considered biosimilar to EU-Stelara.

## *3.5. Extrapolation of safety and efficacy*

The mechanism of action for ustekinumab – inhibition of IL-12- and IL-23-mediated signalling by binding the shared p40 subunit of IL-12 and IL-23, thereby interrupting the Th1 and Th17 cytokine pathways – is the common MoA in each of the originator indications (PsO, paediatric PsO, PsA, CD, UC).

Analytical and functional similarity of AVT04 to EU- and US-Stelara was demonstrated in *in vitro* studies and is described and discussed in the Module 3. No additional non-clinical pharmacodynamics studies, neither *in vitro* nor *in vivo*, were performed and included in Module 4 of this MAA. Similar physicochemical analytical quality results and the similar biological activity results for the biological properties involved in the MoA of ustekinumab support extrapolation from the results obtained in the comparative clinical efficacy and safety Study AVT04-GL-301 in patients with PsO to all other approved indications of Stelara not studied in the clinical program of AVT04.

The applicant is seeking approval for AVT04 for the same indications approved for the reference medicinal product Stelara, except for UC. The applicant intends to make AVT04 available in the same dosage forms, strengths and presentations as approved for Stelara in the EU (see section 2.4). In the present MAA, only the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringe (PFS) presentations are applied for.

AVT04 prefilled syringes PFS-SD 45 mg/0.5 mL and 90 mg/1 mL are intended for the treatment of plaque psoriasis (PsO) in patients with BW≥60 kg, psoriatic arthritis and maintenance dosing in the treatment of Crohn's disease. The 130 mg/26 mL vial presentation as well as the 45 mg/0.5 mL vial presentation intended for treatment initiation of CD by intravenous administration and for the treatment of paediatric plaque psoriasis in children with BW< 60 kg, respectively, are not included in the initial MAA.

To reflect the unavailability of vial presentations and refer to other products available on the market that should be used for initiation of treatment of CD as well as for treatment of paediatric PsO in patients with BW <60 kg, as presented in the table below.

| | Stelara SmPC | AVT04 proposed SmpC |
|---|---|---|
| Section 4.2 | *Table 1 Recommended dose of STELARA for paediatric psoriasis*<br>**Body weight at the time of dosing** / **Recommended Dose**<br>< 60 kg / 0.75 mg/kg<br>≥ 60-≤ 100 kg / 45 mg<br>> 100 kg / 90 mg<br>To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: body weight (kg) x 0.0083 (mL/kg) or see Table 2. The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for paediatric patients who need to receive less than the full 45 mg dose.<br>*Table 2 Injection volumes of STELARA for paediatric psoriasis patients < 60 kg*<br>**Body weight at time of dosing (kg)** / **Dose (mg)** / **Volume of injection (mL)**<br>15 / 11.3 / 0.12<br>16 / 12.0 / 0.13<br>17 / 12.8 / 0.14<br>18 / 13.5 / 0.15<br>19 / 14.3 / 0.16<br>20 / 15.0 / 0.17<br>21 / 15.8 / 0.17<br>22 / 16.5 / 0.18<br>23 / 17.3 / 0.19<br>24 / 18.0 / 0.20<br>25 / 18.8 / 0.21<br>26 / 19.5 / 0.22<br>27 / 20.3 / 0.22<br>28 / 21.0 / 0.23<br>29 / 21.8 / 0.24<br>30 / 22.5 / 0.25<br>31 / 23.3 / 0.26<br>32 / 24.0 / 0.27<br>33 / 24.8 / 0.27<br>34 / 25.5 / 0.28<br>35 / 26.3 / 0.29<br>36 / 27.0 / 0.30<br>37 / 27.8 / 0.31<br>38 / 28.5 / 0.32<br>39 / 29.3 / 0.32<br>40 / 30.0 / 0.33 | *Table 1 Recommended dose of Uzpruvo for paediatric psoriasis*<br>**Body weight at the time of dosing** / **Recommended dose**<br>< 60 kg / -<br>≥ 60 kg to ≤ 100 kg / 45 mg<br>> 100 kg / 90 mg<br>**There is no dosage form for Uzpruvo that allows weight-based dosing for paediatric patients below 60 kg.** |

| | | |
|---|---|---|
| | | |
| | Crohn's Disease<br>In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.<br><br>The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended. | Crohn's disease<br>**Uzpruvo is not available for the first dose by intravenous administration and another ustekinumab product 130 mg concentrate for solution for infusion must be used as first intravenous dose**.<br>The first subcutaneous administration of 90 mg Uzpruvo should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended |

| | | |
|---|---|---|
| 41 | 30.8 | 0.34 |
| 42 | 31.5 | 0.35 |
| 43 | 32.3 | 0.36 |
| 44 | 33.0 | 0.37 |
| 45 | 33.8 | 0.37 |
| 46 | 34.5 | 0.38 |
| 47 | 35.3 | 0.39 |
| 48 | 36.0 | 0.40 |
| 49 | 36.8 | 0.41 |
| 50 | 37.5 | 0.42 |
| 51 | 38.3 | 0.42 |
| 52 | 39.0 | 0.43 |
| 53 | 39.8 | 0.44 |
| 54 | 40.5 | 0.45 |
| 55 | 41.3 | 0.46 |
| 56 | 42.0 | 0.46 |
| 57 | 42.8 | 0.47 |
| 58 | 43.5 | 0.48 |
| 59 | 44.3 | 0.49 |

## *3.6. Additional considerations*

Not applicable.

## *3.7. Conclusions on biosimilarity and benefit risk balance*

Based on the review of the submitted data, Uzpruvo is considered biosimilar to Stelara. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Uzpruvo is favourable in the following indication(s):

Plaque psoriasis

Uzpruvo is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

Uzpruvo is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

Uzpruvo, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's Disease

Uzpruvo is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Not applicable.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States***

Not applicable.