14 December 2023
EMA/22098/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entyvio

International non-proprietary name: Vedolizumab

Procedure No. EMEA/H/C/002782/X/0075

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Act-1	Murine antihuman α4ß7 monoclonal antibody from which the complementarity determining regions of MLN0002 are derived
α4β7	Integrin involved in lymphocyte recruitment to normal gastrointestinal mucosa and gut-associated lymphoid tissue
ABC	AbbVie (previously Abbott Laboratories) Bioresearch Center – Worcester, MA
ABL	AbbVie (previously Abbott Laboratories) Biotechnology Ltd – Barceloneta, PR
ADCC	Antibody-Dependent Cellular Cytotoxicity
CD	Crohn's Disease
CHO	Chinese Hamster Ovary
Cmax	Maximum Concentration
CQA	Critical Quality Attribute
Da	Dalton
DNA	Deoxyribonucleic Acid
DP	Drug Product
DS	Drug Substance
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Host Cell Protein
HMW	High Molecular Weight
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin G1
IV	Intravenous
LMW	Low Molecular Weight
LPA	Leached Protein A
LRF	Log Reduction Factor
mAb	Monoclonal Antibody
MAdCAM-1	Mucosal Addressin Cell Adhesion Molecule-1
MCB	Master Cell Bank
mL	Millilitre
MLN0002	Company code for the vedolizumab drug substance
NOR	Normal Operating Range
Ph. Eur.	European Pharmacopoeia
PPCB	Post Production Cell Bank
PPQ	Process Performance Qualification
qPCR	Quantitative or Real Time Polymerase Chain Reaction
RCB	Research Cell Bank

SC	Subcutaneous
TEM	Transmission Electron Microscopy
UC	Ulcerative Colitis
VLP	Virus-Like Particles
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

Takeda Pharma A/S submitted on 28 November 2022 an extension of the marketing authorisation.

The MAH applied for the introduction of a new master cell bank (MCB) and working cell bank (WCB) and new process (process D) for the manufacturing of the active substance vedolizumab.

1.2. Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008 - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

Not applicable

1.5. Scientific advice

The Applicant received Scientific Advice on the development of VEDOLIZUMAB intended for the treatment of Ulcerative colitis, Crohn's disease from the CHMP on 22/04/2021 (EMA/SA/0000053520).

The Scientific Advice pertained to the following clinical, and quality aspects:

• MCB and WCB qualification and characterisation strategy, DS manufacturing process comparability, quality control strategy for DS produced with the new process, DS and DP release specifications, implementation strategy of new DS manufacturing process, shelf life of DS and DP produced with the new vs the old manufacturing process

• Multidisciplinary strategy to address observed quality differences between DS/DP produced with the new vs the old manufacturing process, adequacy of proposed phase 1 clinical study to demonstrate clinical comparability of DP produced with the new vs the old manufacturing process.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Paolo Gasparini

The application was received by the EMA on	28 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 April 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	10 August 2023
The CHMP Rapporteur circulated the CHMP Rapporteur's Assessment Report on the responses to the List of Questions to all CHMP members on	18 September 2023
The CHMP Rapporteur circulated the updated CHMP Rapporteur's Assessment Report on the responses to the List of Questions to all CHMP members on	07 October 2023
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	12 October 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	13 November 2023
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 December 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 Entyvio on	14 December 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ulcerative colitis

Entyvio 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 tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's disease

Entyvio 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 tumour necrosis factor-alpha (TNFα) antagonist.

Pouchitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy.

2.1.2. Epidemiology

No updates provided as part of this Line Extension (please refer to initial MAA EPAR).

2.1.3. Biologic features

No updates provided as part of this Line Extension (please refer to initial MAA EPAR).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

No updates provided as part of this Line Extension (please refer to initial MAA EPAR).

2.1.5. Management

No updates provided as part of this Line Extension (please refer to initial MAA EPAR). About the product

Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7.

Vedolizumab specifically inhibits the activity of the α4β7 integrin by selectively antagonizing binding and adhesion to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and to the extracellular matrix glycoprotein fibronectin but does not antagonize binding to vascular cell adhesion molecule-1. By antagonizing both the α4β7 MAdCAM-1 interaction and the associated migration of leukocytes into GI mucosa, vedolizumab reduces inflammation. Vedolizumab does not bind to, nor inhibit the function of, the α4β1 and αEβ7 integrins.

Entyvio is currently approved in the following dosages/forms:

300 mg powder for concentrate for solution for infusion

108 mg solution for injection in pre-filled syringe for subcutaneous use

108 mg solution for injection in pre-filled pen for subcutaneous use

2.2. Type of Application and aspects on development

Marketing authorization (MA) for vedolizumab, for the treatment of patients with moderately to severely active ulcerative colitis or Crohn's Disease, two closely related forms of inflammatory bowel disease, was granted in EU/EEA on 22 May 2014. Initially the MA was issued for Entyvio 300 mg powder for concentrate for solution for infusion (intravenous administration - IV), which later was complemented by the subcutaneous (SC) form intended for the maintenance treatment (following at least 2 intravenous infusions): Entyvio 108 mg solution for injection in pre-filled syringe / in pre-filled pen, granted via line-extension procedure in EU/EEA on 28 Apr 2020. Takeda filed for a new therapeutic indication in the treatment of moderately to severely active chronic pouchitis for Entyvio IV in 2021 which was approved on 31 Jan 2022.

The present line extension application aims to introduce a new manufacturing process (defined as Process D) for the vedolizumab drug substance (both IV and SC). The declared extension scope is given below:

Qualitative change in the declared active substance (vedolizumab), not defined as a new active substance:

Replacement of a biological substance of product of biotechnology - modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different.

The currently approved drug substance manufacturing process (Process C) is to be transitioned within to the new manufacturing process (Process D), for both drug products, Entyvio IV and SC.

An extended transition period was initially proposed by the MAH. Following the concerns raised by the Agency, the MAH has significantly reduced the duration of the intended transition period.

In addition to the quality dossier, the supporting package also includes non-clinical modules with data from an in-vitro (non-GLP) study (TKD-BCS-00379) to assess the relative immunogenicity risk of the Entyvio Process D drug products compared with the Entyvio Process C drug products, as well as clinical modules with data from a clinical Phase I study (vedolizumab-1019, an open label, randomized parallel group study to assess the pharmacokinetics of single intravenous and subcutaneous injections of vedolizumab administered to healthy human subjects) conducted to support the comparability between Process C and Process D.

2.3. Quality aspects

2.3.1. Introduction

The MAH has submitted an extension application to the existing MA for Entyvio 300 mg powder for concentrate for solution for infusion (intravenous formulation, IV) and 108 mg solution for injection in pre-filled syringe /in pre-filled pen (subcutaneous formulation, SC), aiming to introduce a new manufacturing process (defined as "Process D") for the vedolizumab active substance (IV and SC).

The new "Process D" utilizes a new master cell bank (MCB) and a new working cell bank (WCB) for the manufacturing of vedolizumab active substance (AS) derived from a different Chinese hamster ovary (CHO) host cell line.

Moreover, a new manufacturing and testing site for the new MCB/WCB has been introduced, as well as additional changes specific to the newly introduced "Process D" such as new cell culture media, updated process steps, adjustment of specification and analytical methods.

Two different finished product (FP) formulations are currently authorised for Vedolizumab (Entyvio): intravenous (IV) and subcutaneous (SC), containing vedolizumab as active substance (AS). Other ingredients for the IV formulation are: L-histidine; L-histidine monohydrochloride; L-arginine hydrochloride; Sucrose; Polysorbate 80. Other ingredients for the SC formulation are: citric acid monohydrate; sodium citrate dihydrate; L-histidine; L-histidine monohydrochloride; L-arginine hydrochloride; polysorbate 80 and water for injections.

Vedolizumab IV, 300 mg powder for concentrate for solution for infusion, is a lyophilized formulation in a vial intended for intravenous infusion, which has been granted marketing authorisation in the EU in 2014.

Moreover, a new pharmaceutical form (solution for injection), associated with a new strength (108 mg) and a new route of administration (subcutaneous use), which is a liquid formulation has been

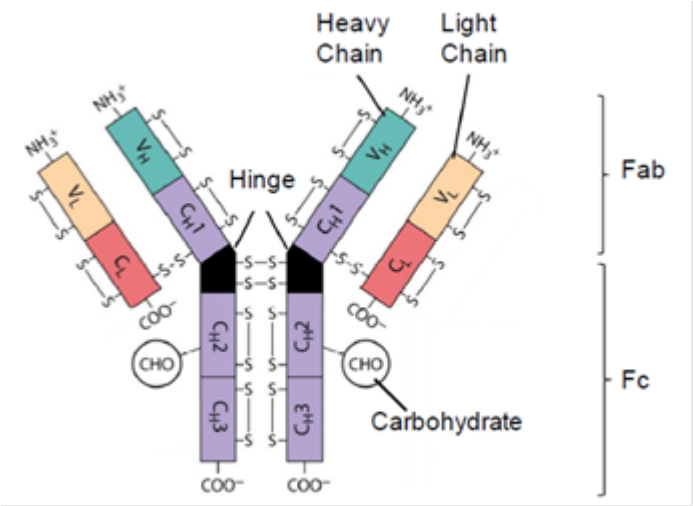
authorised in the EU in 2020. The vedolizumab SC is available for administration either via a single-use, prefilled syringe with needle safety device (PFS + NSD) or via a prefilled syringe in an autoinjector/pen (PFS + AI).

2.3.2. Active Substance

2.3.2.1. General information

Vedolizumab is a recombinant humanized IgG1 monoclonal antibody to the human α4β7 integrin. It is composed of two light chains of the kappa subclass and two heavy chains linked together by two disulfide bridges to form a Y-shaped molecule that is typical of IgG1 immunoglobulins as shown in the figure below. Each molecule contains twelve intra-chain and four inter-chain disulfide bonds and an asparagine-linked glycosylation site on each heavy chain at residue 301 (see Figure 1).

Figure 1: Structural Representation of Vedolizumab



The mechanism of action of Vedolizumab is to selectively block the adhesion of α4β7 + T cells and B cells to their natural ligand MAdCAM-1.

The isoelectric point is 7.6-8.3, the predicted mass for unmodified protein is 146,837 Da.

2.3.2.2. Manufacture, characterisation and process controls

Separate 3.2.S.2.1. Sections for "Process C" and "Process D", listing all the vedolizumab active substance manufacturing and control sites, will be maintained during the transition period. Therefore, new 3.2.S.2.1. Sections, for both the IV and the SC presentations, have been introduced for "Process D".

A new MCB and WCB manufacturer (GMP compliant) has been introduced as a manufacturer and testing site for the new MCB/WCB related to the new "Process D" AS manufacturing process for both the IV and the SC presentations.

Both Vedolizumab intravenous (IV) and Vedolizumab subcutaneous (SC) active substances are manufactured, according to "Process D", at AbbVie Bioresearch Center (ABC) - Worcester (USA), where the manufacture of active substance according to "Process C" is already authorised. All the proposed sites are GMP compliant.

The manufacturing process as well as the operating parameters for "Process D" active substance have been discussed and justified.

Moreover, monitoring of bioburden, endotoxin, and other in-process controls for each operation unit ensures appropriate control of the process stream and the quality of the AS manufactured according to the new "Process D".

In summary, some changes with respect to the currently authorised "Process C" have been introduced in "Process D" active substance manufacturing process to improve process efficiency.

- ✓ New MCB and WCB derived from a different CHO lineage host cell line
- ✓ New gene-expression vector
- ✓ New cell culture media
- ✓ New polishing chromatography
- ✓ Technology update
- ✓ Change in the container closure system for vedolizumab (IV) AS

Control of materials

As a consequence of the changes accompanying "Process D" introduction, new raw materials and starting materials have been introduced in the AS manufacturing process (IV and SC). It is noted that the raw materials used in the manufacture of "Process D" vedolizumab are identical between IV and SC active substance for all shared process steps.

In detail, all culture media used in Process D, including expansion, production and feed media, have been changed and have been described appropriately.

A qualitative description of the new culture media has been provided. Materials used in culture media are considered extremely low risk in terms of a potential TSE contamination.

A new CHO host cell line and, consequently, new cell banks have been introduced. Compared to cell banks currently authorised for "Process C", the new cell banks are derived from a different CHO host cell line.

A detailed description of host cell line origin and development has been provided. No materials of animal origin were used in the host cell line development process.

Moreover, a description of the vector has been also provided.

The vedolizumab "Process D" production cell line was created using the new host cell line adapted to culture.

Following defined selection steps, a clone was selected, expanded and frozen to create a research cell bank (RCB), shown to be stable, free of mycoplasma, bacteria, fungi, and adventitious virus, and used to establish the Master Cell Bank.

Two distinct approaches have been used to evaluate the clonal derivation of the production cell line.

The new "Process D" cell bank system (MCB/WCB/post production (PPCB)) has been prepared under cGMP conditions at the newly introduced manufacturer.

The newly manufactured "Process D" cell banks lots have been extensively characterised and tested. Phenotypic characterisation testing for MCB and WCB included viability at thaw, to determine if the banks were acceptable for use. Species identity testing was performed.

Moreover, sterility and mycoplasma testing, as well as viral detection assays, have been performed to ensure the absence of adventitious agents and inter-species contaminants in the new "Process D" cell banks system. *"In vivo"* tests for adventitious viruses on MCB were performed.

The genotypic characterisation of the MCB was performed.

Comparison of the vedolizumab gene copy number observed in the MCB and PPCB indicates that the PPCB and the MCB copy number did not have an effect on protein titer or product quality within generations assessed in the study.

The above described genotypic characterisation has been performed in conjunction with evaluation of the MCB genetic stability and establishment of the Limit of in Vitro Cell Age (LIVCA) for "Process D".

Overall, the results provided adequately support the conclusion that no detectable adventitious microbial agents or infectious endogenous retrovirus are present in the MCB, WCB or PPCB, and that the cells are of Chinese hamster origin. Being a CHO cell line, for which the endogenous production of defective retroviral virus-like particles (RVLPs) is well known and acknowledged in applicable regulatory guidance, detection of A-type and C-type retrovirus-like particles on MCB and PPCB levels is expected.

Overall, the activities performed to develop and characterize the new cell banks system for "Process D" result aligned with applicable guidelines ICH Q5A, ICH Q5D and ICH Q5B.

Process validation

The upstream and downstream manufacturing steps relative to "Process D" active substance (IV and SC) have been validated on several commercial-scale vedolizumab AS batches, for IV and for SC, manufactured at AbbVie Bioresearch Center, Inc. (ABC) in Worcester (US).

Overall, the process performance validation (PPQ) exercise has adequately demonstrated the capability of the new vedolizumab Process D (IV and SC) manufacturing process at ABC to consistently manufacture a AS having a quality profile suitable for further processing to finished product. In fact, all "Process D" active substance PPQ batches (IV/SC) manufactured within the process validation protocol fully met the final AS release specifications. Moreover, during the PPQ exercise almost all process parameters set for each unit operation remained within their normal operating ranges (NORs) and the few excursions registered are considered not critical and unlikely to have an impact on the "Process D" vedolizumab AS quality, process performance or validation of the affected unit operations.

With reference to impurities, clearance studies performed as part of the PPQ exercise, the orthogonal chromatography operations throughout the downstream process showed a suitable clearance capability of major impurities.

Hold times have been validated, both in terms of biochemical and microbiological stability.

Resins and membrane lifetime has been preliminary set and will be further confirmed through concurrent validation studies during routine production. Lifetime will be determined through concurrent validation during routine production. Adequate acceptance criteria have been included in the dossier for the continuous verification of membranes lifetime (IV and SC).

In the vedolizumab "Process D" AS (IV/SC) manufacturing process, filtration steps are supported by adequate studies and will be further validated through a concurrent validation performed according to a suitable protocol.

Manufacturing process development

Development of the vedolizumab AS manufacturing process to date has consisted of three process iterations, designated "A", "B," and "C" completed ahead of the initial Marketing Authorisation Application (please refer to respective EPAR).

The current submission describes the development of vedolizumab AS "Process D" (IV and SC) that, as previously anticipated, resulted in the introduction of several changes in the AS manufacturing process (IV/SC) with respect to the currently authorised Process C (IV/SC).

Based on risk assessments, the MAH has performed process characterisation and process performance qualification studies aiming to show that the introduced changes to the "Process D" manufacturing process do not have an impact to vedolizumab critical quality attributes (CQAs).

A comprehensive step by step comparison between the two AS manufacturing processes (Process C vs Process D) has been provided.

To support the introduction of the new "Process D" vedolizumab AS manufacturing process, characterisation experiments were performed for both upstream and downstream unit operations. Process characteristics, process parameters, raw materials, and the impact of process parameter and raw material variation on product quality attributes have been evaluated for each unit operation.

Overall, the adopted characterisation approach, including criticality assessment and design of experiment studies, was found suitably comprehensive to understand the influence of any potential process parameter or material attribute impact to a CQA. For both upstream and downstream unit operations, suitable process parameters and material attributes were evaluated for their impact. For upstream steps, the impact to vedolizumab titer, and other process performance outputs was also assessed. For downstream steps, the impact to step yield and other process performance outputs was also assessed.

Moreover, to support the introduction of "Process D" AS manufacturing process (IV and SC), comparability studies have been provided within the present submission.

Overall, the comparability exercises performed sufficiently support the conclusion that the processes are comparable at clinical and commercial scales.

It is noted that the variability between Process D and Process C is limited and overall remains consistent regardless of scale. No new impurities were identified in the Process D lots. Both processes exhibit highly similar trends and pathways of degradation.

The comparability assessment has also demonstrated that the AS from "Process D" commercial scale and clinical scale can be considered highly similar, as the observed differences are small and do not impact critical quality attributes. Therefore, the data from the single-dose PK study, performed using AS manufactured at the clinical scale, can be considered representative of the AS to be manufactured at the commercial scale.

In addition to the data package supporting Process C/Process D comparability referring to AS, the MAH has also provided the comparability evaluation with a comparison of FP release and stability data on finished product containing the AS manufactured either according to Process C and Process D, in line with the recommendation given in the Scientific Advice EMA/SA/0000053520. The data provided is sufficient and adequate.

Characterisation

As above described, "Process C" and "Process D" active substance lots resulted highly comparable, meeting the comparability acceptance criteria for almost all the quality attributes investigated with a couple of exceptions. Nonetheless, these have been assessed to be low impact quality attributes.

Based on the aforementioned similarities between the Process C and Process D vedolizumab AS, the structural characterisation studies already conducted for Process C vedolizumab IV and SC AS have been considered relevant also for Process D vedolizumab IV and SC AS. Moreover, no new impurities or post-translational modifications (PTMs) have been identified in the newly introduced "Process D" AS.

On these grounds, no additional characterisation work of Process D vedolizumab AS (IV and SC) has been performed, with a couple of exceptions due to the difference in such attributes observed during the comparability assessment.

Based on the results obtained from analysis and characterization studies performed for these exceptions, no differences have been reported between "Process D" and "Process C" concerning these exceptions.

To support the introduction of "Process D", elemental impurities and nitrosamine risk assessments have been provided. The potential presence of elemental impurities has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities has been provided. Based on the information presented it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Moreover, the MAH has adequately performed an evaluation on the changes made to the process from "C" to "D and their potential impact on new process related impurities.

Process C to Process D transition period

The MAH has initially requested a very extensive transition period to fully switch the vedolizumab AS manufacturing process from the current "Process C" to the new "Process D". This proposal lead the Agency to raise a number of questions since, as a consequence of the EU legal definition of 'biological medicinal product', alternative manufacturing processes are not allowed for biological products (ref. EMA/CHMP/BWP/187338/2014) and, therefore, it is expected that "Process D" material only will be used for the manufacture of all batches intended for the EU market within a justified time-period.

The potential quality and traceability concerns which could arise from the concurrent management of the two different manufacturing processes at the same facility, can be considered satisfactorily addressed. Moreover, despite slightly higher than the standard 6-months transition period, the agreed transition period can be considered acceptable, also considering the justifications provided by the MAH.

Two recommendations, REC 2 and 3 have been issued recommending the MAH to submit, at the end of the transition period, a variation procedure to remove from the Entyvio Marketing Authorisation all "Process C" CTD sections considered no longer relevant (REC 2). Moreover, on a regular basis until the end of the transition period, the MAH should submit to the Agency a full list of "Process D" finished product batches supplied to EU market and associated "Process D" active substance batches (REC 3).

2.3.2.3. Specification

The specifications for vedolizumab IV and SC active substance covers the appropriate tests to assure identity, purity, safety and potency.

The specifications, used either for IV or SC active substances release testing and monitoring of stability, appear to be adequate in line with ICH Q6B and Ph. Eur. 2031 monoclonal antibodies for human use. The proposed specifications are acceptable.

Analytical methods

The analytical procedures used for release and stability testing of either vedolizumab IV or SC active substances have been presented. Compendial methods are used for appearance, pH, bioburden, bacterial endotoxin.

Overall, the choice of analytical procedures to measure respective quality attributes of vedolizumab active substance (IV and SC) manufactured according to the new Process D is considered appropriate.

All methods are described in detail, correctly highlighting (where applicable) the main differences between the methods relative to "Process C" and those relative to the new proposed "Process D", also through an accurate side by side comparison. Noteworthy, such comparison study has demonstrated the equivalence of the methods used for Process C and Process D AS and, in some cases, has showed even the superiority of the updated methods that justify their implementation as analytical improvement.

A full analytical validation was performed for all vedolizumab intravenous (IV) and SC "Process D" AS non-compendial methods based on guidance provided in ICH Q2(R1) guideline. The complete results of the validation procedures are correctly provided for consultation and review.

No change to the vedolizumab reference standard has been introduced within the present procedure.

Batch analysis

Batch analysis data relative to all "Process D" AS PPQ batches manufactured at by AbbVie Bioresearch Center (Worcester, MA) have been provided. All data met the specification.

Container closure system

With the introduction of the new "Process D" AS manufacturing process for both the IV and SC, the MAH has taken the opportunity to introduce also a change in the container closure system for vedolizumab (IV) AS, thus, to align the container with that already adopted for vedolizumab SC AS (Process C).

The suitability of the newly proposed AS container closure has been previously assessed for the vedolizumab AS (Process C) for subcutaneous use.

The compatibility of the container closure system with "Process D" AS has been demonstrated through long-term stability studies confirming that the potency, purity, and other quality attributes of AS are maintained following long-term storage.

An extractable study was performed on the AS bottle and closure with results confirming the low leachable risk for the components. The data provided is sufficient and adequate.

2.3.2.4. Stability

Stability studies based on ICH guidelines have been conducted for vedolizumab active substance.

In addition, in the context of comparability exercise between "Process D" and "Process C" materials, comparative stability data have been presented for vedolizumab IV and SC active substance.

Overall, the stability studies presented appear to be compliant with the relevant guidelines, in terms of number of batches (commercial scale "Process D" AS PPQ batches) and test frequency, for both IV AS and SC AS.

The protocols and the selected tests are generally considered adequate to monitor possible changes in the quality of the product.

All data are within specifications for all Process D derived batches for both IV and SC active substance for the current observation period at long-term conditions as well as for the entire period under accelerated conditions.

In addition, the comparability exercise provided by the MAH correctly includes a comparative stability study between the batches of "Process D" and those of "Process C" at long term and stressed storage conditions. These studies are considered well designed and in compliance with the relevant guidelines as regards the number of involved lots.

Clear graphs illustrating the comparative trend of stability data between the relevant batches of process D and those of process C have been provided.

Also considering the recommended storage condition, collectively the provided data convincingly support the proposed shelf life for the active substance when stored in the indicated container closure for IV and SC AS material derived from process D.

2.3.3. Finished Medicinal Product

Process D is an active substance only change. The only change to the finished product is an update to specification, as described in the dossier section 3.2.P.5.6 -Process D - IV. Therefore, only the relevant finished product sections are included in this report.

2.3.3.1. Product specification

Adequate release and shelf life specifications have been defined for both IV and SC Vedolizumab finished product which covers appropriate tests to assure identity, purity, safety and potency.

Overall, the specifications are in line with ICH Q6B and Ph. Eur. 2031 "Monoclonal antibodies for human use" and are considered acceptable for routine control of the finished product both at release and shelf life.

Overall, acceptance criteria are aligned between processes C and D for IV and SC FP with some adjustments. Overall, the proposals for FP specifications adjustment are considered acceptable. Noteworthy, the MAH commits to review the release and stability specifications when more batches will be available (Recommendation 1).

In general, the methods proposed are appropriate for verifying the key attributes of the finished product and FP specific methods can be considered correctly described and validated also for Process D derived FP material.

2.3.3.2. Stability of the product

A shelf life of 36 months when stored at 2 °C-8 °C and 24 months when stored at 2 °C-8 °C is claimed for the IV and SC finished product respectively.

Stability studies based on ICH guidelines have been conducted for vedolizumab finished products. Furthermore, the applicant followed the recommendation given within the Scientific Advice EMA/SA/0000053520,

Overall, for both IV and SC FP, the stability studies are conducted in accordance with ICH Topic Q5C in terms of number of batches, test frequency and storage conditions, including accelerated and stress conditions. A detailed protocol for the assessment of the stability at the various conditions is provided.

Product characteristics chosen for monitoring finished product in its final container appear to be adequate; they also include container/closure integrity testing as well as sterility testing at a minimum initially and at the end of the proposed shelf-life, and functionality tests where appropriate (SC FP).

Stability data are within specifications for all Process D derived FP batches for both IV and SC presentations, for the observation periods available to date at long-term conditions.

Stability data remained within specifications during all the observation period in accelerated and stressed condition (complete) for all the IV FP lots, while data remained within specifications just for 1 month at accelerated storage condition for SC FP lots. As expected, degradation is observed at accelerated and stressed storage conditions.

In addition, the supportive clinical stability data available for FP cover the required shelf life of 36 and 24 months at the proposed storage conditions (refrigerator, i.e., 2 °C-8 °C), respectively. Stability studies at accelerated and stressed conditions are complete for these clinical lots.

Since there is no change in the methods used for finished product manufacture/release/stability, neither for the container closure system, as a result of Process D AS change, no critical issues are envisaged in this regard.

In summary, the overall data sufficiently support the proposed shelf life at the proposed storage conditions (refrigerator, i.e., 2 °C-8 °C), for the "Process D" IV and SC FP.

Overall, the stability data provided support the demonstration of comparability between FP Entyvio (IV and SC) derived from process D and from process C.

In conclusion based on the stability data provided the claimed shelf life is considered acceptable.

For the FP IV, in-use stability of the reconstituted solution in the vial has been demonstrated for 8 hours at 2°C-8°C. In-use stability of the diluted solution in sodium chloride 9 mg/mL (0.9%) solution for injection in infusion bag has been demonstrated for 12 hours at 20°C-25°C or 24 hours at 2°C-8°C. For the FP SC if needed, a single pre-filled syringe or pre-filled pen can be left out of the refrigerator protected from light at room temperature (up to 25 °C) for up to 7 days.

Post-approval stability protocol and stability commitments have been provided. Moreover, the MAH committed to inform the authorities of any confirmed out of specification test result observed during the stability studies and to provide data upon request.

2.3.3.3. Adventitious agents

The viral safety of the vedolizumab AS "Process D" with respect to adventitious agents is assured through the design and control of the manufacturing process and by routine testing for adventitious virus.

Viral clearance is achieved through multiple process steps. Suitable viral clearance studies, conducted in accordance with the ICH Q5A, have been performed to verify that potential adventitious agents will be removed or inactivated during "Process D" manufacturing process.

Moreover, a comparison of the Overall Log Reduction Factors (LRFs) relative to vedolizumab "Process C" and "Process D" has been performed and data show that the virus clearance capacity is very high for both processes.

The "Process D" vedolizumab AS manufacturing process is tested by in-process controls for potential viral contamination and all production bioreactor crude harvests undergo the following tests for viral contamination:

- ✓ *In vitro* assay for detection of adventitious virus using four cell lines.
- ✓ Detection and quantitation of MMV by quantitative polymerase chain reaction.

The overall strategy adopted to control the presence of adventitious agents in "Process D" vedolizumab AS is found to be adequate.

As the vedolizumab cell substrate is a CHO cell line, for which the endogenous production of defective retroviral virus-like particles is well known and acknowledged, some of the substrates tested showed the presence of intracytoplasmic A-type and C-type retrovirus-like particles. It is noted however that retrovirus infectivity assays, including endogenous retrovirus infectivity assay for the detection of xenotropic retroviruses or cocultivation with *Mus Dunni* cells for the detection of replication competent

retroviruses, gave negative/not detected results in the cell banks tested. The information provided concerning adventitious agents is appropriate.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The present line extension procedure refers to the introduction of a new active substance (IV/SC) manufacturing process (defined as Process D) based on a new cell bank system derived from a different CHO host cell line, a different vedolizumab expression vector, the introduction of a new manufacturing and testing site for the new MCB/WCB, as well as additional changes to the manufacturing process, including new cell culture media and updated purification steps.

To evaluate the potential impact of all changes introduced by the new "Process D" vedolizumab AS manufacturing process, with respect to the currently authorised "Process C", the MAH has performed three main comparability exercises supporting the conclusion that "Process D" active substance (IV and SC), at clinical and commercial scales, can be considered highly comparable to "Process C" commercial scale AS batches.

Only small differences emerge between processes. However, extended characterisation studies together with *in vitro* human cell-based studies support the conclusion that these differences do not impact on efficacy and safety. Nonetheless, the specification should be revised as more data become available (Recommendation).

Vedolizumab has been engineered to eliminate ADCC activity via the introduction of two point mutations within the CH2 domain, as evidenced by SPR binding and ADCC studies. In general, the present line extension application doesn't contain, from a quality point of view, major factors affecting the overall benefit/risk ratio of vedolizumab.

The extensive transition period initially requested by the MAH to fully switch from the current "Process C" to the new "Process D" has been significantly reduced. Moreover, suitable clarifications supporting the adequacy of the measures in place to prevent any potential drifts in quality attributes between the two different manufacturing processes and the lack of concurrent manufacturing of material obtained through the two manufacturing processes at the same manufacturing site have been provided. The MAH should also follow-up on the fulfilment of the transition period as agreed (Recommendations).

Additional data and further clarification requested during the assessment, including additional queries raised following the GMP inspection at the new site, have been provided and found acceptable.

2.3.5. 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 have been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The MAH is recommended to review the release and stability specifications for FP SC when additional batches are available.

2. At the end of the Process C/Process D transition period, the MAH should submit a variation procedure to duly update the Entyvio Marketing Authorization by removing "Process C" CTD sections that are considered no longer relevant.

3. On a regular basis from the EMEA/H/C002782/X/0075 line extension approval, the MAH is recommended to submit to the Agency a full list of "Process D" batches supplied to EU market until the end of the transition period.

2.4. Non-clinical aspects

2.4.1. Toxicology

A non-Good Laboratory Practice study utilizing in vitro human cell based assays has been conducted to assess the relative immunogenicity risk of vedolizumab Process D drug product compared with vedolizumab Process C drug product. Overall, this in vitro immunogenicity compatibility study suggests that the IV and SC formulated Process C and D drug products have similar immunogenic responses in both healthy and IBD patient donors.

2.4.2. Discussion on non-clinical aspects

A non-Good Laboratory Practice study utilizing in vitro human cell based assays has been conducted to assess the relative immunogenicity risk of vedolizumab Process D drug product compared with vedolizumab Process C drug product. This study suggests a similar immunogenicity risk between the old and new vedolizumab process materials and generally low immunogenicity potential for the tested Process D drug product.

The new expression system used with Process D drug product manufacturing, does not alter the previous environmental risk assessment on which basis vedolizumab is not expected to pose a risk to the environment due to its proteic nature (EMEA/CHMP/SWP/4447/00).

2.4.3. Conclusion on the non-clinical aspects

Data presented indicate that the new Process D material exhibit the same low immunogenicity potential as Process C material in humans, as the ex-vivo assessment demonstrated no meaningful differences in immunogenic potential between the test articles.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The MAH has provided a statement to the effect that the clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study No. No. of Sites-Country Study Start-End Dates	Study Design Primary Objective (Endpoint)	Population [a] and Type (Criteria) Sex and Race (n [%]) Mean Age (Min-Max)	Treatment Duration	Treatment (Randomized/Completed)
5.3.3.1 Healthy Subject PK and Initial Tolerability Studies				
Vedolizumab-1019 2 sites - United States 21 November 2019 – 19 August 2020	Open-label, randomized parallel group study to compare the PK of a single IV (Part A) or SC (Part B) dose of vedolizumab manufactured via Process D or Process C in healthy subjects	Part A 76 healthy subjects 40 (53%) Female 36 (47%) Male 2 (3%) Asian 15 (20%) Black or African American 56 (74%) White 3 (4%) Multiple 40.0 (20–64) years Part B 114 healthy subjects 64 (56%) Female 50 (44%) Male 1 (1%) American Indian or Alaska Native 13 (11%) Black or African American 93 (82%) White 7 (6%) Multiple 41.8 (19–63) years	Part A Single IV vedolizumab 300 mg dose infused over 30 minutes on Day 1 Part B Single SC vedolizumab 108 mg dose administered in the abdomen on Day 1	Part A Process C 38 (100%)/ 36 (95%) Process D 38 (100%)/ 38 (100%) Part B Process C 57 (100%)/ 55 (96%) Process D 57 (100%)/ 56 (98%)

IV: intravenous; PK: pharmacokinetics; SC: subcutaneous.
[a] Population = number of subjects who received at least 1 dose of study medication.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

To support the quality comparability exercise, the Applicant presented results from a phase 1, open-label, parallel group clinical study (vedolizumab-1019) investigating in healthy subjects the pharmacokinetics, immunogenicity, tolerability and safety of single IV (Part A) and SC (Part B) injections of vedolizumab manufactured by Process D and C, respectively.

Analytical methods

Vedolizumab serum concentrations were determined by using a validated sandwich ELISA, while the presence of anti-vedolizumab antibodies and their neutralizing activity were detected and tested through ECL assays

Bioequivalence (biosimilarity)

Vedolizumab-1019 was an open-label, randomized, parallel-group study to primarily compare the PK of a single intravenous (Part A) or subcutaneous (Part B) dose of vedolizumab manufactured via Process D or Process C in healthy subjects, whose design is resumed in the following table.

Part A (IV)

Screening		Treatment	Post-Treatment			
Days -28 to -2	Day -1 (Check-in)	Day 1	Day 2	Days 8±1, 15±1, 29±2, 57±2, 85±2, 113±2, 141±2	Final Visit/ Early Termination Day 169±3 (a)	Day 180±3 Follow-up Phone Call (b)
		Dosing, PK, and safety	PK and safety assessments			
	←----------Confinement ----------→					

(a) In case abnormal, clinically significant findings were observed upon discharge, subjects may have been brought back to the clinic for re-evaluation per investigator's discretion.
(b) Subjects were followed poststudy by telephone to administer a questionnaire, which included progressive multifocal leukoencephalopathy (PML) questions at Day 180 (±3 days).

Part B (SC)

Screening		Treatment	Post-Treatment			
Days -28 to -2	Day -1 (Check-in)	Day 1	Day 2	Days 4±1, 6±1, 8±1, 10±1, 15±1, 29±2, 43±2, 64±3, 85±3	Final Visit/ Early Termination Day 127±3 (a)	Day 180±3 Follow-up Phone Call (b)
		Dosing, PK, and safety	PK and safety assessments			
	←----------Confinement ----------→					

(a) In case abnormal, clinically significant findings were observed upon discharge, subjects may have been brought back to the clinic for re-evaluation per investigator's discretion.
(b) Subjects were followed poststudy by telephone to administer a questionnaire, which included PML questions at Day 180 (±3 days).

The primary endpoint concerned the measurement of vedolizumab Cmax, AUClast and AUC∞. In Part A, subjects received a single dose of 300 mg vedolizumab manufactured via Process D or Process C administered IV as a 30 minutes-infusion. In Part B, subjects received a single dose of 108 mg/0.68 mL vedolizumab manufactured via Process D or Process C in a prefilled syringe in needle safe device (PFS+NSD) administered SC in the abdomen. In Part A, 76 subjects entered the study and 74 completed it, while in Part B, 114 subjects entered the study and 111 completed it. In Part A, 8/38 subjects (21.1%) who received vedolizumab from Process C and 9/38 subjects (23.7%) from Process D had deviations leading to the non-collection or exclusion of vedolizumab samples. In Part B, 25/57 subjects (43.9%) who received Processes C and D had deviations leading to the non-collection or exclusion of vedolizumab samples. A post hoc analysis was performed to include all these samples with clotting deviations and statistical comparisons of both sets of analysis (primary analysis and post hoc additional analysis) confirmed that the clotting deviations did not appear to have an impact on the study PK analysis results.

Results Part A (intravenous)

A summary of respective serum vedolizumab PK parameters following a single 300 IV dose of vedolizumab 300 mg for Process D and Process C is shown below. The variability was similar for AUClast and AUC∞ between both treatments, but greater for Process D compared to Process C for Cmax, as shown in the following figures.

Summary of Serum Vedolizumab Pharmacokinetics Following a Single IV Dose of Vedolizumab 300 mg Process D and Process C Administered as a 30-minute Infusion in Healthy Subjects (Part A)

Pharmacokinetic Parameters	Process D	Process C
AUC_{last} (µg•day/mL)	2411 (24.6) [n=38]	2485 (21.2) [n=37]
AUC_{∞} (µg•day/mL)	2440 (24.4) [n=38]	2512 (21.1) [n=37]
C_{max} (µg/mL)	148.3 (24.8) [n=38]	147.0 (17.6) [n=38]
$t_{1/2}$ (day)	16.642 ± 4.3369 [n=38]	16.801 ± 3.8815 [n=37]
CL (L/day)	0.1267 ± 0.035628 [n=38]	0.1221 ± 0.026353 [n=37]
V_z (L)	2.920 ± 0.60537 [n=38]	2.888 ± 0.63080 [n=37]

Process D: Single 300 mg IV dose of vedolizumab administered as a 30-minute infusion (Test)
Process C: Single 300 mg IV dose of vedolizumab administered as a 30-minute infusion (Reference)
AUC_{last}, AUC_{∞}, and C_{max} are presented as geometric mean and geometric percent coefficient of variation.
Other parameters are presented as arithmetic mean ± standard deviation.

The statistical comparison of serum vedolizumab PK following a single IV dose of vedolizumab 300 mg Process D versus Process C (including both AVA-positive and AVA-negative subjects) shows that the ratios of geometric LSMs for AUClast, AUC∞ and Cmax were close to unity (100%) and the 90% CIs were included in the range 80.00% to 125.00%.

Results Part B (subcutaneous)

A summary of respective serum vedolizumab PK parameters following a single SC dose of vedolizumab 108 mg for Process D and Process C is shown below. The variability of individual AUC last, AUC∞ and Cmax values were higher following Process D compared to Process C.

Summary of Serum Vedolizumab Pharmacokinetics Following a Single SC Dose of Vedolizumab 108 mg Process D and Process C Administered with Pre-Filled Syringe in Needle Safe Device in Healthy Subjects (Part B)

Pharmacokinetic Parameters	Process D	Process C
AUC_{last} (µg•day/mL)	435.4 (48.6) [n=57]	437.3 (33.7) [n=55]
AUC_{∞} (µg•day/mL)	485.8 (41.5) [n=53]	468.9 (30.2) [n=52]
C_{max} (µg/mL)	14.14 (42.6) [n=57]	14.66 (30.3) [n=57]
t_{max} (day)	8.000 (0.33, 14.00) [n=57]	7.000 (1.00, 14.00) [n=57]
$t_{1/2}$ (day)	14.092 ± 3.7275 [n=53]	14.120 ± 3.9658 [n=52]
CL/F (L/day)	0.2418 ± 0.10991 [n=53]	0.2406 ± 0.074421 [n=52]
V_z/F (L)	4.694 ± 2.0903 [n=53]	4.674 ± 1.2667 [n=52]

Process D: Single 108 mg SC dose of vedolizumab administered in the abdomen with PFS+NSD (Test)
Process C: Single 108 mg SC dose of vedolizumab administered in the abdomen with PFS+NSD (Reference)
AUC_{last}, AUC_{∞}, and C_{max} are presented as geometric mean and geometric percent coefficient of variation.
t_{max} is presented as Median (Minimum, Maximum).
Other parameters are presented as arithmetic mean ± standard deviation.

The statistical comparison of serum vedolizumab PK following a single SC dose of vedolizumab 108 mg Process D versus Process C shows that the ratios of geometric LSMs for AUClast, AUC∞ and Cmax and the 90% CIs were within 80.00% to 125.00%.

2.5.2.2. Pharmacodynamics

The Immunogenicity profile of vedolizumab IV 800mg and SC 108 mg manufactured through either process C or D was investigated as part of study vedolizumab-1019 (please refer to 'Bioequivalence' section to see a description of the study).

In Part A of the study no anti-vedolizumab antibodies positive (AVA+) subjects were identified pre-dose. The number of AVA+ positive subjects increased at each time point throughout the study.

Overall, 32/76 (42%) subjects were AVA+ by the end of the study and most of them were persistently positive (26/32) and neutralizing (28/32). 17/38 (45%) subjects were AVA+ following Process C versus 15/38 (39%) subjects following Process D.

In Part B, prior to dosing, 3/57 (5%) subjects in the Process D cohort were AVA+, while none were in the Process C cohort. The number of AVA+ subjects increased at each time point throughout the study. Overall, 68/114 (60%) subjects were AVA+ by the end of the study and most of them were persistently positive (55/68) and neutralizing (62/68). 33/57 (58%) subjects following Process C were AVA positive versus 35/57 (61%) subjects following Process D.

2.5.3. Discussion on clinical pharmacology

From the clinical pharmacokinetics point of view, Phase 1 study CA28095 was well designed and conducted in line with both 'EMA Guideline on Comparability of Biotechnology-derived Medicinal Products after a Change in the Manufacturing Process' (EMEA/CHMP/BMWP/101695/2006) and 'Note for guidance on biotechnological/ biological products subject to changes in their manufacturing process' (CPMP/ICH/5721/03). Also, the study conception is aligned in terms of the clinical pharmacology investigation with the EMA scientific advice (EMA/SA/0000053520) released in 2021 to the Applicant. Drug exposures in terms of AUClast, AUC∞ and Cmax are comparable for vedolizumab manufactured either by process C or D, following i.v. or s.c. administration, thus bioequivalence can be considered fulfilled.

In terms of pharmacodynamics, PBMC, a broad and not reliable PD marker for vedolizumab were calculated as an exploratory endpoint and no investigation was conducted in terms of inhibition of other biomarkers, such as Act-1 and MAdCAM-1-Fc. However, measuring the PD markers in healthy subjects is not expected to reflect the performance of these markers in patients with active disease. Evaluation of comparability between processes through study vedolizumab-1019 by using pharmacodynamics was therefore hampered but do not change the overall conclusion on the comparability exercise.

The immunogenicity profile is similar between Process C and D; overall, the proportion of subjects that were AVA positive and neutralizing were comparable between subjects dosed with Processes C and D material in both IV and SC. As expected, the occurrence of AVA antibodies was higher in the SC groups.

2.5.4. Conclusions on clinical pharmacology

There are no clinical pharmacology concerns to the approval of this application.

2.5.5. Clinical efficacy

2.5.6. Discussion on clinical efficacy

Study Vedulizumab-1019 (A Phase 1, Open-Label, Randomized Parallel Group Study to Assess the Pharmacokinetics of Single Intravenous and Subcutaneous Injections of Vedolizumab Administered in Healthy Subjects) is described in the pharmacology part of this report and further below in the chapter on clinical safety. The study was designed to compare the PK of a single IV (Part A) or SC (Part B) dose of vedolizumab manufactured via Process D or Process C in healthy subjects; the target subject population (ie, patients with UC or CD) was not considered suitable for this study because of the potential for immunogenicity after single-dose administration. Similar PK has been observed in healthy subjects and patients with UC or CD following administration of vedolizumab. For these reasons, a clinical efficacy evaluation is not necessary to conduct.

2.5.7. Clinical safety

2.5.7.1. Patient exposure

The study was designed to assess and compare the PK, safety and tolerability, and immunogenicity after a single dose of vedolizumab manufactured by Process D versus vedolizumab manufactured by Process C, when administered by intravenous (IV) infusion (Part A) or by subcutaneous (SC) injection. The doses, devices, and modes of administration selected were the doses/devices/modes of administration approved or under regulatory review for approval.

The safety monitoring practices included physical examination findings, treatment-emergent adverse events (TEAEs), clinical laboratory test results, vital sign measurements, and 12-lead electrocardiograms (ECGs).

The study design is reported in the figure below for both part A (IV) and B (SC)

Schematic of Study Designs
Part A (IV)

<table>
<tr><th colspan="2">Screening</th><th>Treatment</th><th colspan="3">Post-Treatment</th></tr>
<tr><td rowspan="2">Days
-28 to -2</td><td rowspan="2">Day -1
(Check-in)</td><td>Day 1</td><td>Day 2</td><td>Days 8±1, 15±1, 29±2, 57±2, 85±2, 113±2, 141±2</td><td>Final Visit/ Early Termination Day 169±3 [a]</td><td>Day 180±3 Follow-up Phone Call [b]</td></tr>
<tr><td>Dosing, PK, and safety</td><td colspan="3">PK and safety assessments</td><td></td></tr>
<tr><td></td><td colspan="2">←----------Confinement ----------→</td><td colspan="3"></td></tr>
</table>

IV: intravenous; PK: pharmacokinetic; PML: progressive multifocal leukoencephalopathy.
[a] In case abnormal, clinically significant findings were observed upon discharge, subjects may have been brought back to the clinic for re-evaluation per investigator's discretion.
[b] Subjects were followed poststudy by telephone to administer a questionnaire, which included PML questions at Day 180 (±3 days).

Part B (SC)

<table>
<tr><th colspan="2">Screening</th><th>Treatment</th><th colspan="3">Post-Treatment</th></tr>
<tr><td rowspan="2">Days
-28 to -2</td><td rowspan="2">Day -1
(Check-in)</td><td>Day 1</td><td>Day 2</td><td>Days 4±1, 6±1, 8±1, 10±1, 15±1, 29±2, 43±2, 64±3, 85±3</td><td>Final Visit/ Early Termination Day 127±3 [a]</td><td>Day 180±3 Follow-up Phone Call [b]</td></tr>
<tr><td>Dosing, PK, and safety</td><td colspan="3">PK and safety assessments</td><td></td></tr>
<tr><td></td><td colspan="2">←----------Confinement ----------→</td><td colspan="3"></td></tr>
</table>

PK: pharmacokinetic; PML: progressive multifocal leukoencephalopathy; SC: subcutaneous.
a In case abnormal, clinically significant findings were observed upon discharge, subjects may have been brought back to the clinic for re-evaluation per investigator's discretion.
b Subjects were followed poststudy by telephone to administer a questionnaire, which included PML questions at Day 180 (±3 days).

2.5.7.2. Adverse events

A total of 45 TEAEs were reported by 26 (34%) subjects, including 13 (34%) subjects following each of Process D and Process C making the distribution of TEAEs between processes equal. Overall, 12 (16%) subjects reported 1 or more drug-related TEAE, including 8 (21%) subjects following Process D and 4 (11%) subjects following Process C. No TEAE was reported by >5% of subjects overall.

The most commonly reported TEAEs, overall, were diarrhoea and headache (4% subjects each), equally distributed between the two processes.

A difference could be seen in the incidence of these TEAEs falling in the following SOCs:

- Infections and infestations: 4 (11%) subjects in Process C versus 2 (5%) subjects in Process D, mostly driven by an higher incidence of Coronavirus infection in the Process C.

- Musculoskeletal and connective tissue disorders: 1 (3%) subject in Process C versus 4 (11%) subjects following Process D, with an higher incidence of pain in extremity in the process C.

- General disorders and administration site conditions: 3 (8%) subjects in process C versus 1 (3%) subject in process D.

All TEAEs were considered resolved at the end of the trial.

- Part B (SC)

A total of 162 TEAEs were reported by 65 (57%) subjects, including 28 (49%) subjects following Process D and 37 (65%) subjects following Process C. Fifty-eight (51%) subjects reported 1 or more drug-related TEAEs, including 26 (46%) subjects following Process D and 32 (56%) subjects following Process C.

The most commonly reported TEAEs following Process C and D, respectively, were weight increased (25% vs 16%), injection site erythema (9% vs 11%), and headache (12% vs 5%).

A difference was seen in the TEAEs incidence between the two processes in the following SOCs:

- Gastrointestinal disorders: 6 (11%) in Process C versus 3 (5%) in process D, without any clear increased incidence of one TEAE in one process in respect to the other;
- Musculoskeletal and Connective Tissue Disorders: 9 (16%) subjects in process C versus 3 (5%) subjects in process D, mostly driven by back pain, pain in extremity and myalgia in process C;
- Nervous System Disorders: 11 (19%) subjects in process C versus 4 (7%) subjects in process D, with an higher incidence of headache in process C;
- Infections and Infestations: 8 (14%) subjects in process D versus 5 (9%) subjects in process C, mostly driven by an higher incidence of viral infections in process D. The "upper respiratory tract infections" are equally distributed between the two processes and in line with what reports in the SmPC of the product;
- Eye disorders: 1 (2%) in process C versus 4 (7%) subjects in Process D.

Other TEAEs by SOCs with a frequency > 5% were "Investigations", mostly sustained by weight increase (25% subjects in process C and 16% in process D) and "Respiratory, thoracic and mediastinal disorders (12% subjects in process C and 7% in process D). In this latter case, the most common TEAE was represented by Oropharyngeal pain which was equally distributed between process C (4% subjects) and D (5% subjects).

Most of the TEAE reported were considered as resolved at the end of the study: regarding the "weight increase", they were noted at the final visit and generally ranged from +5 to 10% from baseline, with a maximum increase of 12.8%. All increased weight events were considered related to study drug by the investigator and 20 of the 23 AEs were considered not recovered/not resolved.

Analysis of TEAEs per Process

The table below summarized the incidence of TEAEs by SOC per Process

PART A		
TEAEs by SOC	**Process C**	**Process D**
Infections and Infestations	**11%**	5%

Musculoskeletal and connective tissue disorders	3%	**11%**
General disorders and administration site conditions	**8%**	3%
PART B		
Gastrointestinal disorders	**11%**	5%
Musculoskeletal and Connective Tissue Disorders	**16%**	5%
Nervous System Disorders	**19%**	7%
Infections and infestations	9%	**14%**
Eye Disorders	2%	**7%**

Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) evaluated in this study were injection site reaction (SC only), infusion related reactions (IV only), infections, hypersensitivity reactions, liver injury, and progressive multifocal leukoencephalopathy (PML).

- Part A

A total of 6 (8%) subjects experienced 6 adverse events of special interest (AESIs), including 2 (5%) subjects following Process D and 4 (11%) subjects following Process C. All AESIs fell under the infections and infestations System Organ Class (SOC), and there was a higher incidence following Process C than following Process D. The AESIs included coronavirus infection (2 subjects), urinary tract infection (2 subjects), and pharyngitis and upper respiratory tract infection (URTI) (1 subject each).

- Part B

A total of 24% subjects experienced 30 AESIs, including 23% subjects following Process D and 25% subjects following Process C. All AESIs were either injection site reactions, which had a higher incidence following Process C than Process D (16% subjects versus 11% subjects), or infections/infestations which had a higher incidence following Process D than Process C (14% subjects versus 9% subjects). The AESIs included injection site reactions (erythema [11 subjects]; pain [3 subjects]; and hemorrhage and induration [1 subject each]), URTI (5 subjects), viral infection (3 subjects), and abscess, asymptomatic bacteriuria, cellulitis, cystitis, oral herpes, and pharyngitis streptococcal (1 subject each).

Analysis per Process of AESIs

The most common AESI reported (Upper respiratory Tract Infection) was equally distributed between the two groups (2 subjects in process C and 3 in process D); regarding other infections, a specific association between incidence and production process could not be identified by comparing the two productive process in both parts of the protocol. Similarly, the incidence of injection site reaction (specific for part B) does not identify an association with a specific productive process.

No cases of other AESIs were reported; this is considered coherent with the reported incidence in the SmPC of other AESIs (infusion related reactions, hypersensitivity reactions, liver injury, PML) and the small number of subject enrolled in the protocol.

2.5.7.3. Serious adverse event/deaths/other significant events

The only one SAE recorded in this trial was the occurrence of psychiatric symptoms, which are not reported in the SmPC of Vedolizumab as a common site effect. Given the modality of occurrence and the previous history of the patient, it is reasonable to not consider this SAE as associated with Vedolizumab administration, according to the Investigator's evaluation.

2.5.7.4. Laboratory findings

No critical alterations of laboratory findings nor in ECG and vital signs were recorded in this trial. Most of the alterations in laboratory findings were recorded at the end of the follow up period and, consequently, far from the single dose administration of Vedolizumab. In some cases, like CPK elevation, subjects' personal behaviour has had an impact on the insurgence of these alterations. Overall, the laboratory finding deviations recorded in the protocol are not considered as related with drug administration.

2.5.7.5. Safety in special populations

There was 1 pregnancy reported in Part A, and no pregnancies reported in Part B.

A subject from Process C had a positive serum pregnancy test at the end of study visit (Day 169). The next day, the subject reported having a spontaneous miscarriage and stated she was seen by PCP to verify that. A quantitative choriogonadotropin beta level drawn 5 days later was 743.1 IU/L (reference range: 0 – 29 IU/L) suggesting that the subject was likely less than a week from expected menses. The event was recorded five days after the end of the follow up period (169+5 days) and was not considered related with study drug exposure considering that it happened in a time point after Vedolizumab exposition which is over the indicated maximum time limit for mandatory use of contraception (18 weeks, i.e. 126 days from last administration of Vedolizumab) requested in the SmPC of Vedolizumab. Considering the intended scope of this trial, the enrolled population was entirely represented by healthy young subjects; therefore, no data about elderly population are available.

2.5.7.6. Immunological events

Immunogenicity was an Additional Objective of the study; overall, in terms of safety, the immunogenicity profile is similar between Process C and D. The proportion of subjects that were AVA positive and neutralizing were comparable between subjects dosed with Processes C and D material in both IV and SC. As expected, the occurrence of AVA antibodies was higher in the SC groups, considering the higher immunogenicity reported with this administration route.

Table 12.i Summary of Overall Antivedolizumab Antibody Status (Part B)

AVA Status	Process C N=57	Process D N=57	Overall N=114
AVA Negative	24/57 (42)	22/57 (39)	46/114 (40)
AVA Positive	33/57 (58)	35/57 (61)	68/114 (60)
Transiently Positive	6/57 (11)	7/57 (12)	13/114 (11)
Persistently Positive	27/57 (47)	28/57 (49)	55/114 (48)
Neutralizing AVA Positive	32/57 (56)	30/57 (53)	62/114 (54)

Process C: Single 108 mg SC dose of vedolizumab administered in the abdomen with PFS+NSD
Process D: Single 108 mg SC dose of vedolizumab administered in the abdomen with PFS+NSD
AVA Negative: Subjects with no confirmed positive AVA result
AVA Positive: Subjects with a confirmed positive AVA result
Transiently Positive: Subjects with confirmed at least one positive AVA sample and no consecutive positive AVA samples.
Persistently Positive: Subjects with confirmed positive AVA results at 2 or more consecutive time points
Neutralizing AVA Positive: Subjects positive for neutralizing AVA
Denominator in proportion (X/XX) represents the number of subjects tested at least once in each treatment.
Percentage (XX) refers to the proportion expressed as a percentage.
Source: Table 15.3.1.2.16

Treatment emergent infusion reactions were considered AESIs and are extensively treated in the dedicated section: overall, no hypersensitivity reactions in this study were recorded. Reactions related to the infusions were recorded only in the SC way of administration, were mild in severity and coherent with the administration route (eritheema, hemorrage and pain).

2.5.8. Discussion on clinical safety

A single IV or SC dose of Vedolizumab in healthy subject appeared to be generally safe and well tolerated by the healthy adult subjects in this study. The safety profile was comparable following both Processes C and D for both SC and IV formulations; no specific safety alerts for the proposed D process have emerged in this trial.

The protocol structure and the follow up period were considered adequate for the rationale of the study. Cumulative dose and duration of treatment are not considered able to have impact on the safety of the enrolled patients considering that subjects were exposed to a single dose of Vedolizumab.

No differences were noted in terms of TEAEs between the two processes were noted; the most common reported TEAEs (headache, upper respiratory infections, diarrhoea, administration site reaction for subcutaneous use) were mild in severity, equally distributed in both part A and B, (regardless of the productive process) and considered in line with the published SmPC of the product. Some slightly differences were observed in AEs between Process C and Process D in both Part A and Part B (eg, AEs in musculoskeletal and connective tissue disorder SOCs were reported in a higher proportion in Process D in Part A versus Process C in Part B), in absence of clear trends of association with the mentioned productive processes. All TEAEs were considered resolved at the end of the observation period, except for increasing in weight, but the persistence of the weight gain at the end of the observation period is in line with the clinical behaviour of this side effect.

For the AESIs “infections” and “infusion site reactions” no differences have been identified between the two different productive processes.

One case of SAE is reported (anxiety, paranoia, and disruptive mood dysregulation disorder) in part B of the protocol but it is not considered as drug associated.

Similarly, the reported pregnancy and subsequent miscarriage is not considered related with study drug administration.

Regarding immunological events, the occurrence of neutralizing anti-vedolizumab antibodies after administration was not shown to be different for vedolizumab manufactured by process C and D: the occurrence of neutralizing anti-vedolizumab antibodies tended to be higher after administration of subcutaneous vedolizumab, but it is well known that subcutaneous administration route is associated with an higher risk of antibody development. In general, attention should be paid to the occurrence of neutralizing AVA (regardless of the productive process), considering the elevated percentage of development reported in this trial.

No other safety alerts were raised for laboratory findings deviations and for ECG or vital signs as well as new safety issues or signals.

Overall safety data from this trial should be interpreted with caution, considering that they came from a single-dose open-label Phase 1 study in healthy volunteers with limitations in the number of included subjects, and in the chosen study design. Long-term evaluation performed with standard pharmacovigilance activities in patients with IBD of the clinical safety of multiple administrations of vedolizumab manufactured by process D in multiple patients with IBD will provide more insight into the overall clinical safety of this active substance. Since no new safety issues were observed in conducted Phase 1 study, current safety monitoring may be appropriate for this.

2.5.9. Conclusions on the clinical safety

A single IV or SC dose of vedolizumab appeared to be generally safe and well tolerated by the healthy adult subjects in this study. No new safety issues were observed in the presented Phase 1 study Long-term evaluation of the clinical safety performed with standard pharmacovigilance activities in patients with IBD and treated with vedolizumab manufactured by process D in patients with IBD will provide more insight into the overall clinical safety profile of the active substance.

2.6. Risk Management Plan

The Risk Management Plan (RMP) has not been updated as a result of the new proposed process (Process D) for manufacture of vedolizumab drug substance (DS) because that the observed differences do not impact quality attributes with potential to impact safety, efficacy, pharmacokinetics and immunogenicity of vedolizumab. Therefore, no change to the existing RMP is required.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

No changes were submitted. The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. 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.

2.8. Product information

No changes to the product information were submitted and this is considered acceptable by the CHMP in light of the scope of the manufacturing changes introduced.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present line extension procedure refers to the introduction of a new active substance (IV/SC) manufacturing process (defined as Process D) based on a new cell bank system derived from a different CHO host cell line, a different vedolizumab expression vector, the introduction of a new manufacturing and testing site for the new MCB/WCB, as well as additional changes to the manufacturing process, including newcell culture media and updated purification steps.

Ulcerative colitis

Entyvio 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 tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's disease

Entyvio 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 tumour necrosis factor-alpha (TNFα) antagonist.

Pouchitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis and have had an inadequate response with or lost response to antibiotic therapy.

3.1.2. Available therapies and unmet medical need

The goal of therapy for both UC and CD is to induce and maintain clinical remission, with the optimal outcome of maintaining steroid free remission, induction and maintenance of mucosal healing, and reduction of complications and the need for hospitalizations and surgery. The standard approach to therapy for UC and CD is generally step wise and directed, based on disease activity and the extent and location of disease. Treatment of mild disease includes anti-inflammatory agents, progressing to more potent therapies for patients who have more severe disease.

Pharmacological treatments for UC and/or CD vary depending upon the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission. Conventional therapies that are used for IBD include oral 5 aminosalicylates (5 ASAs; eg, sulfasalazine, mesalamine), glucocorticoids (eg, prednisone, budesonide), and immunomodulators (eg, azathioprine [AZA], 6 mercaptopurine [6 MP], and methotrexate). Orally administered Janus kinase (JAK) inhibitor (e.g. tofacitinib, filgotinib) have been approved for the treatment of UC. Biologic treatments approved for IBD include TNF α antagonists (eg, infliximab, adalimumab, certolizumab), interleukin antagonists (eg, ustekinumab), and integrin antagonists (eg, natalizumab, vedolizumab).

Vedolizumab IV has demonstrated statistically significant and clinically relevant effectiveness in multiple clinical trials in subjects with moderately to severely active UC or CD with clinically important endpoints of durable clinical response, durable clinical remission, mucosal healing, and corticosteroid free remission, including subjects who have failed previous therapies such as corticosteroids, immunomodulators, or TNF α antagonists. Pharmacological treatments with SC routes of administration provide convenience for patients, Health Care Professionals, and caregivers by removing the time,

logistics, and burden to the health care system required for IV infusion and allows for patient preference. As a result, the sponsor has pursued development of vedolizumab SC to allow patients and Health Care Professionals the option to choose between IV infusion or SC injection for long term maintenance therapy for UC or CD.

3.1.3. Main clinical studies

In addition to the quality dossier, the supporting package also included non-clinical modules with data from an in-vitro (non-GLP) study (TKD-BCS-00379) to assess the relative immunogenicity risk of the Entyvio Process D drug products compared with the Entyvio Process C drug products, as well as clinical modules with data from a clinical Phase I study (vedolizumab-1019, an open label, randomized parallel group study to assess the pharmacokinetics of single intravenous and subcutaneous injections of vedolizumab administered to healthy human subjects) conducted to support the comparability between Process C and Process D.

3.2. Favourable effects

Efficacy assessment was out of scope of this procedure; no new data in patients was generated.

3.3. Uncertainties and limitations about favourable effects

Efficacy assessment was out of scope of this procedure; no new data in patients was generated.

3.4. Unfavourable effects

A single IV or SC dose of vedolizumab appeared to be generally safe and well tolerated by the healthy adult subjects in study vedolizumab-1019.

3.5. Uncertainties and limitations about unfavourable effects

Only data in healthy volunteers was presented within study vedolizumab-1019. There are no new safety concerns or uncertainties. Long-term evaluation of the clinical safety performed with standard pharmacovigilance activities in patients with IBD and treated with vedolizumab manufactured by process D in patients with IBD will provide more insight into the overall clinical safety of this active substance.

3.6. Benefit-risk assessment and discussion

The quality comparability of the active substance vedolizumab produced by the two manufacturing processes has been adequately demonstrated, the B/R of Entyvio in the treatment of Ulcerative colitis, Crohn’s disease, Pouchitis remains positive, considering the analysis of data provided for this extension application.

In particular, non-clinical and clinical data suggests a similar profile in terms of PK, immunogenicity and safety between the two manufacturing processes, for both the IV and SC formulations, with consequent absence of impact on the B/R profile.

Given that data from the submitted clinical trial have been obtained in healthy subjects, a long-term evaluation of the clinical safety performed with standard pharmacovigilance activities in patients with IBD will provide more insight into the overall clinical safety of this active substance in the intended target population.

3.7. Conclusions

The overall benefit/risk balance of Entyvio is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety, the CHMP considers by consensus that the benefit-risk balance of, Entyvio introducing a new manufacturing process (defined as Process D) for vedolizumab active substance (both IV and SC) is favourable in the following approved indication(s):

Ulcerative colitis

Entyvio 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 tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's disease

Entyvio 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 tumour necrosis factor-alpha (TNFα) antagonist.

Pouchitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy.

The CHMP therefore recommends the extension of the marketing authorisation for Entyvio 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).

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.