21 March 2024
EMA/146658/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Amgevita

International non-proprietary name: Adalimumab

Procedure No. EMEA/H/C/004212/X/0036/G

Note

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

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List of abbreviations

Abbreviation or Term	Definition
ADA	antidrug antibodies
ADR	adverse drug reaction
CPU	Clinical Pharmacology Unit
CSR	clinical study report
DLP	Data lock point
ECL	electrochemiluminescence
EMA	European Medicines Agency
EOI	Event of interest
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
IBD	International birth date
IFU	Instruction for use
G	gauge
GMR	Geometric mean ratio
HCF	high concentration formulation
HCP	Healthcare professional
LCF	low concentration formulation
PFP	prefilled pen
PFS	prefilled syringe
PK	pharmacokinetic(s)
PBRER/PSUR	Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report
Ps	plaque psoriasis
RA	rheumatoid arthritis
SC	subcutaneous
SmPC	Summary of Product Characteristics
STD	standard
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TNFRSF	tumor necrosis factor receptor superfamily
TPA	tripropylamine
UF/DF	ultrafiltration/diafiltration
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

Amgen Europe B.V. submitted on 26 May 2023 a group of variations consisting of an extension of the marketing authorisation and the following variations:

Variation(s) requested		**Type**
B.I.b.1.f	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	II
B.I.d.1.c	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	IB
B.II.d.1.e	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	II
B.II.f.1.e	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	IB
B.II.f.1.e	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	IB
B.II.f.1.b.5	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	IB
B.I.a.2.a	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	IB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin
B.II.a.5	B.II.a.5 - Change in concentration of a single-dose, total use parenteral product, where the amount of AS per unit dose (i.e. the strength) remains the same	II

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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 MAH 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 MAH received Scientific advice from the CHMP on 25 February 2021 (EMA/SA/0000050040). The Scientific advice pertained to the following aspects:

Quality

• analytical comparability, pharmacokinetic and device data requirements to support the approval of a higher concentration formulation and related devices.

Non-clinical

• the supportive non-clinical package.

Clinical

• pharmacokinetic comparability study design for the higher concentration formulation.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

The application was received by the EMA on	26 May 2023
The procedure started on	15 June 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 September 2023

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	12 October 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	18 January 2024
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 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 March 2024
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 Amgevita on	21 March 2024

2. Scientific discussion

2.1. Problem statement

The MAH has developed a new 100 mg/mL formulation and a new 80 mg strength. The new strength (80mg) and high concentration formulation (100mg/mL) will allow some patients to reduce the number of injections and decrease the volume of injection.

2.2. About the product

Amgevita (adalimumab, ABP 501) is an approved biosimilar product to Humira (adalimumab), with the same indications. ABP 501 is currently approved as a 50 mg/mL formulation (ABP 501 50 mg/mL) for subcutaneous (SC) administration. ABP 501 50 mg/mL is supplied as 9 presentations in different package sizes in the following strengths and container closure systems: a 40 mg single-dose SureClick prefilled pen (PFP), a 40 mg single-dose prefilled syringe (PFS), and a 20 mg single-dose PFS. In 2017, the European Medicines Agency (EMA) approved a new formulation and concentration (100 mg/mL) for Humira (adalimumab). The MAH has developed a new 100 mg/mL formulation (ABP 501 100 mg/mL) with the same concentration as the reference product: Humira (adalimumab) 100 mg/mL.

The product strength of ABP 501 100 mg/mL matches the strength of Humira (adalimumab) 100 mg/mL. ABP 501 100 mg/mL contains 100 mg/mL adalimumab formulated in 24 mM L-lactic acid, 8.4% (w/v) sucrose, 0.10% (w/v) polysorbate 80, at pH 5.2. The ABP 501 100 mg/mL formulation contains 2 of the same excipients (sucrose and polysorbate 80) as the ABP 501 50 mg/mL formulation but uses an L-lactate-based formulation compared to an acetate-based formulation used for ABP 501 50 mg/mL. ABP 501 100 mg/mL will be supplied as 13 presentations in different package sizes in the following strengths and

container closure systems: an 80 mg single-dose SureClick PFP, an 80 mg single-dose PFS, a 40 mg single-dose SureClick PFP, a 40 mg single-dose PFS, and a 20 mg single-dose PFS. This is summarized in Table 1 and Table 2.

Table 1: Strengths and presentations of Amgevita

Strength name	Concentration [mg/mL]	Formulation	Presentation	Regulatory status
20 mg	50	Old	PFS	Approved
20 mg/0.2 mL	**100**	**New**	**PFS**	**Applied for**
40 mg	50	Old	PFS	Approved
40 mg	50	Old	PFP	Approved
40 mg/0.4 mL	**100**	**New**	**PFS**	**Applied for**
40 mg/0.4 mL	**100**	**New**	**PFP**	**Applied for**
80 mg/0.8 mL	**100**	**New**	**PFS**	**Applied for**
80 mg/0.8 mL	**100**	**New**	**PFP**	**Applied for**

PFP = prefilled pen; PFS = prefilled syringe

Table 2: Device names and definitions

Device Name	Definition/Explanation
ABP 501 50 mg/mL PFS	A single-dose, 1-mL prefilled glass syringe providing a single, fixed dose of ABP 501 50 mg/mL. The PFS is assembled with a plunger rod and flange extender for ease of injection.
ABP 501 100 mg/mL PFS	A single-dose, 1-mL prefilled glass syringe providing a single, fixed dose of ABP 501 100 mg/mL. The PFS is assembled with a plunger rod and flange extender for ease of injection. The ABP 501 100 mg/mL PFS uses the same primary container (drug contacting component) as the approved ABP 501 50 mg/mL PFS.
ABP 501 50 mg/mL SureClick PFP	A single-dose SureClick PFP containing a 1-mL prefilled glass syringe providing a single, fixed dose of ABP 501 50 mg/mL.
ABP 501 100 mg/mL SureClick PFP	A single-dose SureClick PFP containing a 1-mL prefilled glass syringe providing a single, fixed dose of ABP 501 100 mg/mL. The SureClick PFP for use with ABP 501 100 mg/mL has an equivalent operating principle and functionality as that approved for ABP 501 50 mg/mL SureClick PFP.

PFP = prefilled pen; PFS = prefilled syringe

2.3. Type of application and aspects on development

2.4. Quality aspects

2.4.1. Introduction

Amgevita is Amgen's approved biosimilar product to Humira (adalimumab).

Amgevita is currently approved as a 50 mg/mL solution for subcutaneous injection (SC), supplied as 3 presentations (20 and 40 mg in prefilled syringe (PFS) and 40 mg in prefilled pen (PFP)) in different package sizes.

The purpose of this line extension/variation grouping is to introduce a new 80 mg strength and a new formulation with a 100 mg/ml concentration in line with Humira. The new formulation is introduced in the manufacturing of the already existing 20 mg and 40 mg strengths. The 100 mg/mL presentations contain two of the same excipients as the 50 mg/mL presentations (sucrose and polysorbate 80). L-lactic acid is used as buffer system instead of glacial acetic acid.

The finished product, subject of this line extension/variation grouping is Amgevita 100 mg/mL solution for SC injection containing 20 mg, 40 mg and 80 mg of adalimumab as active substance.

Other ingredients are: L-lactic acid, sucrose, polysorbate 80, sodium hydroxide and water for injections.

The following new additional presentations are proposed:

- A pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a stainless steel needle with a needle shield (thermoplastic elastomer) for the 20 mg, 40 mg, 80 mg solution for injection

And

- A pre-filled pen for patient use containing a pre-filled syringe (type I glass) for the 40 mg and 80 mg solution for injection. The pre-filled pen is also known as autoinjector (AI) and referred to as SureClick in the document.

In addition to the 100 mg/mL formulation change, variations related to the AS and FP specification limits specific to the 50 mg/mL authorised presentations have been submitted together with a variation for a shelf-life extension.

The shelf life for the 50 mg/mL finished product will be increased from 24 to 36 months, aligning with the proposed shelf life for the 100 mg/mL finished product.

2.4.2. Active Substance

2.4.2.1. General information

There are no updates to the general information on nomenclature, structure and general properties of the active substance adalimumab.

2.4.2.2. Manufacture, characterisation and process controls

No new manufacturing sites or contract laboratories have been introduced with this line extension application.

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described and is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted for the 50 mg/mL presentations. No changes have been introduced for the new 100 mg/mL presentations. Control of materials has been adapted to fit the new 100 mg/ml presentations. These changes have been found acceptable.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the adalimumab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Changes in IPC and hold times have been introduced.

Process validation

The active substance manufacturing process up to the viral filtration step for the new 100 mg/ml presentations is the same as the process validated for the current 50 mg/ml. Process validation for the 100 mg/ml active substance manufacturing process has not been repeated for the steps in common with the current 50 mg/ml manufacturing process, but it has been performed only for the updated steps

Process validation for the 100 mg/mL presentations has included the following process steps:

- UF/DF, polysorbate addition, active substance final filtration and fill
- In-process pool hold for UF/DF
- Protein A chromatography resin reuse (lifetime) extension
- UF/DF membrane cleaning and reuse

Consistency in production has been shown on four full scale commercial batches. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests were met demonstrating that the purification process consistently produces adalimumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria. The 100 mg/ mL adalimumab active substance manufacturing process has been validated adequately.

<u>Transportation Shipping Container Qualification</u>

Transportation Shipping Container Qualification has been provided for the 100 mg mL adalimumab active substance.

Characterisation

This section has not been subject to changes.

2.4.2.3. Specification

The proposed active substance specifications for the 100 mg/ml presentations are aligned with the approved commercial specifications the 50 mg/mL presentations, with the exception of the difference in protein concentration. The active substance specifications for the 100 mg/ml presentations include tests for: identity, purity, potency, adventitious agents, quantity, and general test methods.

Analytical methods

The analytical methods used are the same for the 50 mg/ml presentations and for the 100 mg/mL presentations.

Batch analysis

Batch analysis data of the 100 mg/ml active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

There are no updates to the reference materials section.

2.4.2.4. Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container. The proposed shelf-life for the 100 mg/mL presentations is 48 months when stored at -30°C ± 10°C, that is the same shelf-life as the 50 mg/ml presentations.

2.4.2.5. Comparability exercise for Active Substance

Comprehensive comparability studies have been performed to evaluate the impact of the formulation change and increased protein concentration on active substance quality.

Comparability was assessed on the 100 mg/mL active substance manufactured at both active substance manufacturing sites to the already approved 50 mg/mL active substance. Although the active substance will be commercially manufactured only at one site, the substance manufactured at the other site was included in the assessment to establish comparability for material used for clinical and stability studies to material for proposed commercial supply manufactured at the current site.

The 100 mg/mL active substance was also placed on stability at recommended and accelerated storage conditions, but these studies were not included in the formal comparability assessment.

Comparisons used to evaluate comparability was assessed to acceptable pre-determined comparability assessment criteria based on historical ranges for the 50 mg/mL active substance as well as side-by-side testing.

Comparability has been sufficiently demonstrated for the comparisons of the 100 mg/mL active substance to the already approved 50 mg/mL active substance, with a high degree of similarity and few minor differences noted for all the quality attributes studied. These differences have all been satisfactorily justified.

Comparability has also been sufficiently demonstrated for the 100 mg/mL active substance manufactured at the clinical site to the one manufactured at the commercial site.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Amgevita 100 mg/mL is supplied in the following strengths and container closure systems in different package sizes: 80 mg AI, 40 mg AI, 80 mg PFS, 40 mg PFS and 20 mg PFS. The primary packaging is a pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a stainless-steel needle with a needle shield (thermoplastic elastomer) for the 20 mg, 40 mg, 80 mg solution for injection and a pre-filled pen for patient use containing a pre-filled syringe (type I glass) for the 40 mg and 80 mg solution for injection. The pen is a single use, disposable, handheld, mechanical injection device. The needle cover of the pre-filled pen is made from synthetic rubber. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacturing process development

Manufacturing process development for the 100 mg/mL finished product has been sufficiently described. The higher concentration of the 100 mg/mL finished product is achieved at the level of the active substance.

The commercial manufacturing process for 100 mg/mL finished product includes the same conventional process steps as for the 50 mg/mL finished product. A comparison of the 100 mg/mL and 50 mg/mL commercial process has been provided and show few minor differences.

The 100 mg/mL commercial process has been characterised through process development studies at both development and commercial scale.

2.4.3.2. Manufacture of the product and process controls

Manufacture

The name, address, and responsibility for the sites of finished product manufacture, testing and release along with appropriate documents to support GMP compliance have been provided for each site. The manufacturers and testing sites are identical for the 100 mg/mL and 50 mg/mL finished product presentations.

The finished product has the same formulation and concentration as the active substance; therefore, no formulation buffer is required for finished product manufacture.

The manufacturing process for 100 mg/mL presentations includes the same steps as for the 50 mg/mL presentations. A comparison of the 100 mg/mL and 50 mg/mL commercial process has been provided and shows few and minor differences.

The in-process controls are mostly the same for the 100 mg/mL and the 50 mg/mL manufacturing process. There are few differences, which have been listed and properly justified. The in-process controls are adequate.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

All validation batches compiled with the established validation acceptance criteria for all process parameters as well as with the proposed finished product specifications and in-process controls. Moreover, filling homogeneity has been demonstrated for the filling step.

The aseptic filling process at the commercial manufacturing site has been validated by media fill validation, which has demonstrated that the aseptic conditions are maintained during the filling process of the 100 mg/mL finished product presentations.

A filter validation study has been performed to qualify the 0.22 µm-filter used for sterile filtration of the 100 mg/mL finished product. All study results met the pre-determined acceptance criteria and demonstrated that this 0.22 µm-filter is fit for the purpose and justifies the use in commercial manufacturing of the finished product.

Transport qualification studies of the 100 mg/mL finished product presentations have been performed and demonstrated that the 100 mg/mL finished product (PFS and AI) can be transported by air, ground, and ocean between manufacturing, packaging, and distribution sites without impact to product quality. Transport stresses of vibration, pressure, and shock events were evaluated, and the results confirmed that quality attributes are maintained when the finished product is transported within the temperature range 2 °C to 8 °C.

2.4.3.3. Product specification

Finished product specifications include tests and acceptance criteria typical for this type of product (monoclonal antibody for human use): appearance, identity, purity and impurities, potency, quantity, adventitious agents, and general test methods.

The majority of methods are used to control both the active substance and finished product.

SureClick prefilled pen/ Autoinjector (AI)

The 100 mg/mL SureClick autoinjector (AI) contains a prefilled syringe (PFS). The assembled AI specification includes functionality testing for both the 80 mg/0.8 mL and 40 mg/0.4 mL finished product presentations to ensure proper drug delivery.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed as requested considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No)

726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided 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.

Analytical methods

The analytical methods used have been adequately described and appropriately validated in accordance with ICH guidelines. Data have been provided and all results met the acceptance criteria demonstrating the methods appropriate for the new 100 mg/mL finished product.

Batch analysis

Batch analyses data have been provided for the 100 mg/mL finished product (PFS and AI) pilot scale batches used in clinical trials and stability, manufactured at the clinical site, and for batches at full commercial scale manufactured at the commercial site. In addition, a batch history of the 100 mg/mL finished product manufacturing (both PFS and AI) has been provided. All batch analysis data comply with the limits in the finished product release specifications in place at the time of manufacture and testing.

2.4.3.4. Stability of the product

Based on available stability data, the shelf-life of 36 months and storage condition of 2-8 °C as stated in the SmPC are acceptable. In addition, a storage period for 14 days at temperatures up to 25°C is acceptable for both the 100 mg/mL and 50 mg/mL PFS and AI as stated in the SmPC.

The batches of Amgevita are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are the same as for release.

Furthermore, comparability has been sufficiently demonstrated and concluded between the 100 mg/mL finished product and the 50 mg/mL finished product.

Based on the demonstrated analytical comparability and the accelerated storage condition data, a storage period for 14 days at temperatures up to 25°C is acceptable for both the 100 mg/mL and 50 mg/mL pre-filled syringe and the autoinjector.

Transportation has been evaluated and experimental stability studies demonstrated that the 100 mg/mL finished product remains stable under worst-case conditions that may be encountered during transport, storage, handling, and use.

The applicant has also taken the opportunity to update the shelf life of the 50 mg/mL finished product.

All data for finished product stored at 2-8°C comply with the proposed shelf-life specification. The proposal for the shelf-life extension from 24 months to 36 months at 2-8 °C for the 50 mg/mL finished product (both PFS and AI) is acceptable. Additionally, a storage period for 14 days at temperatures up to 25°C is also acceptable.

2.4.3.5. Comparability exercise for finished medicinal drug product

Comprehensive comparability studies have been performed to evaluate the impact of the formulation change on the finished product quality. Comparability was assessed on:

-100 mg/mL finished product manufactured at the commercial site to the current commercial 50 mg/mL finished product manufactured at the same commercial site.

-100 mg/mL commercial finished product lots manufactured at the commercial site to 100 mg/mL development and clinical finished product lots manufactured in the development site.

Finished product comparability was assessed according to ICH Q5E using biochemical, biological, and biophysical analytical methods including methods routinely used for batch analysis, as well as additional methods for orthogonal and supplemental product characterization. Side-by-side stressed stability data at 25 °C were provided for the active substance and these data were found sufficiently informative for judging finished product stability profiles since the active substance and finished product have the same formulation. Comparability has been sufficiently demonstrated with a high degree of similarity and few and minor differences noted for all the quality attributes studied. The few and minor differences noted have all been satisfactorily justified to have no effect on efficacy and safety.

satisfactory results have been provided on comparability assessment demonstrating that the assembly process for the 100 mg/mL autoinjector does not impact product quality.

2.4.3.6. Adventitious agents

Not applicable.

2.4.3.7. GMO

Not applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. No major objections in quality were raised during the procedure. The new strength (80 mg) and the new high concentration formulation (100 mg/mL) of Amgevita have been introduced in line with the currently approved presentations of the reference product, Humira. To achieve the final protein concentration (100 mg/ml), the active substance manufacturing process has been slightly modified with updates to the final UF/DF step.

The 100 mg/mL presentations contain two of the same excipients as the 50 mg/mL presentations (sucrose and polysorbate 80) with the exception of L-lactate which is used as buffer system instead of acetate. Comparability has been sufficiently demonstrated for the comparisons of the 100 mg/mL active substance to the already approved 50 mg/mL active substance, with a high degree of similarity and few minor differences noted for all the quality attributes studied.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

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.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

No new non-clinical data was submitted in this application. This is acceptable.

2.5.1. Ecotoxicity/environmental risk assessment

Amgevita (adalimumab) is a fully human recombinant monoclonal antibody (IgG1) with the same amino acid sequence as adalimumab, and it has a molecular weight of approximately 148 kilodaltons. Amgevita (adalimumab) is specific for human tumor necrosis factor alpha (TNFα), a cytokine involved in normal inflammatory and immune responses. By blocking the interaction of TNFα with the TNFRSF1A (p55) and TNFRSF1B (p75) cell surface receptors, adalimumab prevents the cascade of TNF signaling, production of additional proinflammatory cytokines, cellular responses, and tissue damage.

Amgevita (adalimumab) is expressed in a Chinese hamster ovary (CHO) cell culture line under defined and controlled conditions, harvested and purified by a series of proprietary processing steps, and formulated in a buffer before sterile filtration and dispensing.

As Amgevita (adalimumab) is a sequence of amino acids, it meets the criterion for compounds that are exempt from testing because of their chemical structure and constituents (here being amino acids and carbohydrate) that should degrade into its amino acid, sugar derivatives or constituent elements in the environment.

2.5.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data were submitted by the MAH which was considered acceptable by the CHMP.

According to the current CHMP guideline on environmental risk assessment (CHMP/SWP/4447/00 corr 2), for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment. As adalimumab is composed of naturally occurring amino acids, it falls within the scope of this provision. The MAH's ERA, providing a justification for not performing a detailed environmental risk assessment for adalimumab, is thereby considered acceptable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH 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**

Type of Study	Study Identifier Protocol No.	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	Number Subjects Randomized/ Analyzed for Safety	Diagnosis of Subjects and Key Entry Criteria	Duration of Study[a]	Study Status; Type of Report/Location
Study Reports of Healthy Subject PK and Initial Tolerability								
PK comparability study	20200286	Primary: PK comparability of ABP 501 100 mg/mL compared to ABP 501 50 mg/mL Secondary: Safety, tolerability, and immunogenicity of ABP 501 100 mg/mL compared with ABP 501 50 mg/mL	Randomized, single-blind, single-dose, 2-arm, parallel-group study	ABP 501 100 mg/mL (40 mg/0.4 mL) in a single-dose PFS, ABP 501 50 mg/mL (40 mg/0.8 mL) in a single-dose PFS; 40-mg SC injection on day 1	372/370	Healthy adult men and women aged 18 to 55 years, inclusive	63 days	Complete, full CSR/Module 5.3.3.1 (20200286)

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

This extension includes 13 presentations of ABP 501 100 mg/mL in different package sizes in the following strengths and container closure systems: an 80 mg single dose SureClick PFP, an 80 mg single dose PFS, a 40 mg single dose SureClick PFP, a 40 mg single dose PFS, and a 20 mg single dose PFS (see also Table 1). The extension is supported by one PK comparability study (20200286) in healthy adult subjects.

The same ligand binding assay as in the initial marketing authorisation application (MAA) was used to quantify ABP 501 in human serum.

For immunogenicity, a multitiered strategy was used consisting of screening, confirmation and neutralisation potential of antidrug antibodies (ADA). All methods were newly developed and validated for use in study 20200286. An electrochemiluminescence (ECL) bridging assay with acid pre-treatment and capture of soluble TNFα using etanercept was used for ADAs. Neutralising ADAs (nAb) were analysed in an ECL assay detecting the interruption of binding of ruthenylated drug to biotin TNFα by neutralizing ADA.

Study 20200286 was a randomized, single-blind, single-dose, 2-arm, parallel-group study in healthy adult male and female subjects with a body weight of ≥ 50 kg to ≤ 90 kg. Eligible subjects were randomized in a ratio of 1:1 stratified by gender prior to dosing on day 1 to receive either ABP 501 100 mg/mL PFS or ABP 501 50 mg/mL PFS as a single (40 mg) SC injection.

The primary objective was to determine the PK comparability between ABP 501 100 mg/mL (40 mg/0.4 mL) and ABP 501 50 mg/mL (40 mg/0.8 mL) following single dose SC injection, with AUCinf and Cmax as primary endpoints. Geometric least-squares (LS) mean, ratio of geometric LS means, and 90% confidence interval (CI) were estimated based on the analysis of covariance (ANCOVA) model with a fixed effect for treatment and adjusting for baseline weight since clearance of adalimumab has been observed to increase with increasing weight.

Overall, 370 randomized subjects were dosed with study drug (183 in the ABP 501 100 mg/mL treatment group and 187 in the ABP 501 50 mg/mL treatment group). All 370 were included in the PK concentration dataset. A total of 358 (96.2%) subjects completed the study, and 14 (3.8%) subjects discontinued the study prematurely (7 [3.8%] and 7 [3.7%] subjects, respectively). The most common reasons for discontinuation from the study included lost to follow-up (5 [1.3%] subjects), withdrawal by subject (4 [1.1%] subjects), and adverse events (2 [0.5%] subjects). Two subjects discontinued the study due to COVID-19-related reasons. There were no treatment-emergent serious adverse events.

Subjects ranged in age from 18 to 55 years, and the majority were white (72.4% of subjects overall). Demographic and baseline characteristics were generally comparable between the 2 treatment groups, with mean body weight of 72.8 and 72.0 kg in the ABP 501 100 mg/m and 50 mg/mL group, respectively.

A total of 364 subjects were included in the PK parameter analysis set (all subjects from the PK concentration analysis set with an evaluable ABP 501 100 mg/mL or ABP 501 50 mg/mL serum concentration-time profile); 180 (97.3%) subjects in the ABP 501 100 mg/mL treatment group and 184 (98.4%) subjects in the ABP 501 50 mg/mL treatment group. Three subjects per group were excluded as they did not have an evaluable concentration time profile.

The results of the study demonstrated PK comparability between ABP 501 100 mg/mL and ABP 501 50 mg/mL (Table 3). The point estimates and 90% CIs of the geometric mean ratios (GMRs) were fully contained within the prespecified equivalence margin of 0.8 to 1.25 for both the primary PK endpoints (AUC_{inf} and C_{max}) and the secondary PK endpoint of AUC_{last} for the comparison of ABP 501 100 mg/mL to ABP 501 50 mg/mL.

Table 3. Summary of Statistical Assessment of ABP 501 100 mg/mL and ABP 501 50 mg/mL PK Parameters (Study 20200286 PK Parameter Analysis Set)

Treatment and Comparison	AUC_{inf} (hr•ng/mL) LS Geometric Mean [n]	C_{max} (ng/mL) LS Geometric Mean [n]	AUC_{last} (hr•ng/mL) LS Geometric Mean [n]
ABP 501 100 mg/mL	2176667.1 [154]	3749.1 [180]	2058821.4 [177]
ABP 501 50 mg/mL	2086410.1 [153]	3521.5 [184]	2066337.7 [176]
Ratio of LS Geometric Means (90% CI)			
ABP 501 100 mg/mL vs ABP 501 50 mg/mL	1.0433 (0.9634, 1.1297)	1.0646 (0.9960, 1.1380)	0.9964 (0.9264, 1.0716)

ANCOVA = analysis of covariance; AUC = area under the serum concentration-time curve; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_{last} = AUC from time 0 to the last quantifiable concentration; C_{max} = maximum observed serum concentration; CSR = clinical study report; LS = least squares; PK = pharmacokinetic

Note: Geometric LS mean, ratio of geometric LS means and 90% CI were estimated based on the ANCOVA model with a fixed effect for treatment and adjusting for baseline weight.

Table 4 shows the secondary PK parameters for both formulations.

Table 4: Summary of PK parameters for ABP 501-HCF (100 mg/m and ABP 501-LCF (50 mg/mL)

A: ABP 501-HCF
(N=180)

Statistic	Cmax (ng/mL)	Tmax (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	T-HALF (h)	Vz/F (L)	CL/F (L/h)	MRT (h)	AUC%Extrap (%)
n	180	180	177	154	154	154	154	154	177
Mean	4090	-	2250000	2370000	245.558	6.16	0.0208	482	7.15
SD	1680	-	913000	982000	161.3392	3.37	0.0111	187	8.956
Min	272	24.00	508000	529000	34.65	1.19	0.00749	159	0.3
Q1	2860	-	1560000	1590000	116.333	3.52	0.0133	335	1.23
Median	4000	143.675	2210000	2330000	176.757	5.35	0.0171	445	2.88
Q3	5080	-	2870000	3010000	350.030	8.45	0.0252	572	11.06
Max	9980	507.07	5020000	5340000	632.31	20.0	0.0756	922	53.0
Geo Mean	3710	-	2040000	2150000	198.810	5.33	0.0186	448	3.24
GeoCV (%)	50.5	-	49.2	48.3	73.5	59.1	48.3	40.5	219.7

B: ABP 501-LCF
(N=184)

Statistic	Cmax (ng/mL)	Tmax (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	T-HALF (h)	Vz/F (L)	CL/F (L/h)	MRT (h)	AUC%Extrap (%)
n	184	184	176	153	153	153	153	153	176
Mean	3810	-	2260000	2330000	241.132	6.06	0.0212	495	6.74
SD	1380	-	867000	990000	146.8754	2.89	0.0115	178	7.845
Min	1020	8.00	454000	471000	32.11	1.71	0.00732	138	0.3
Q1	2850	-	1540000	1510000	125.228	4.13	0.0131	357	1.28
Median	3650	144.775	2250000	2220000	187.172	5.63	0.0180	475	2.92
Q3	4530	-	2880000	3050000	329.699	7.27	0.0265	625	10.50
Max	8060	626.62	4380000	5470000	618.42	17.1	0.0849	934	39.2
Geo Mean	3560	-	2080000	2110000	200.469	5.48	0.0190	462	3.44
GeoCV (%)	40.0	-	45.1	48.7	68.6	47.3	48.7	39.0	181.1

Immunogenicity results are summarised in Table 5. A subgroup analysis for neutralizing ADA negative subjects confirmed that the 90% CIs of the GMR for the parameters AUCinf, Cmax, and AUClast for the comparison of ABP 501 100 mg/mL to ABP 501 50 mg/mL were fully contained within the prespecified equivalence margin of 0.80 to 1.25.

ADAs were detected at baseline in 4% for both groups, nearly all were boosted by treatment with ABP 501. By the end of the study, 91% in the ABP 501 100 mg/mL treatment group tested positive for treatment emergent ADAs and 92% in the ABP 501 50 mg/mL treatment group. The majority of ADAs were persistent. The presence of neutralising antibodies was detected in 17.0% subjects in the ABP 501 100 mg/mL treatment group and 16% in the ABP 501 50 mg/mL treatment group.

Table 5: Antidrug Antibody Results (Study 20200286 Safety Analysis Set)

Variable	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Subjects with an on-study result[a]	183	187
Total antibody incidence, n (%)		
ADA positive anytime	172 (94.0)	179 (95.7)
Neutralizing antibody positive anytime	32 (17.5)	29 (15.5)
Subjects with a result at baseline	183	187
Pre-existing antibody incidence, n (%)		

ADA positive at or before baseline	7 (3.8)	8 (4.3)
Neutralizing antibody positive at or before baseline	1 (0.5)	0 (0.0)
Subjects with a postbaseline result through day 16	177	178
Treatment boosted antibody incidence, n (%)	2 (1.1)	2 (1.1)
Developing antibody incidence, n (%)		
ADA positive (treatment emergent) [b]	112 (63.3)	126 (70.8)
Neutralizing antibody positive (treatment emergent)	2 (1.1)	3 (1.7)
Subjects with a postbaseline result through day 29	181	182
Treatment boosted antibody incidence, n (%)	4 (2.2)	4 (2.2)
Developing antibody incidence, n (%)		
ADA positive (treatment emergent)	157 (86.7)	161 (88.5)
Neutralizing antibody positive (treatment emergent)	2 (1.1)	3 (1.6)
Subjects with a postbaseline result through end of study	182	185
Treatment boosted antibody incidence, n (%)	4 (2.2)	6 (3.2)
Developing antibody incidence, n (%)		
ADA positive (treatment emergent)	165 (90.7)	171 (92.4)
Transient[b]	4 (2.2)	3 (1.6)
Neutralizing antibody positive (treatment emergent)	31 (17.0)	29 (15.7)
Transient[b]	1 (0.5)	0 (0.0)

Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of study investigational product. Percentages were calculated using the corresponding category count as the denominator. Boosted: ≥ 4x increase in magnitude postbaseline.

[a] Subjects were considered on-study after signing informed consent.

[b] Negative result at the subject's last time point tested within the study period.

2.6.2.2. Pharmacodynamics

No new data has been provided.

2.6.3. Discussion on clinical pharmacology

The performance of the bioanalytical method for the quantification of ABP 501 was previously deemed acceptable. Within study validation showed adequate bioanalytical performance.

The ADA methods were adequately validated following current guidelines and white papers. The ADA method showed sufficient drug tolerance and no target interference at levels expected in healthy individuals.

The sensitivity of the nAb assay is 440 ng/mL, as compared with 4 ng/mL in the ADA assay, thus samples with low ADA levels are to be considered inconclusive rather than nAb negative. The performance of the nAb assay is generally acceptable, however drug tolerance is low, compared to the concentrations in the clinical study, thus only high concentrations of nAb are expected to be detected. However, since the assay is used to compare two products with the same assay, the issue is not pursued.

The study design follows what was proposed in the scientific advice in 2021 (EMA/SA/0000050040). A PK study with the PFS was considered to be acceptable, with no requirement to study the PFP as it is the same as already approved. The dose selection and study design are considered appropriate to assess the comparability between the two formulations. The selected PK endpoints and statistical analysis are adequate. The treatment groups were similar in age, bodyweight and BMI.

Both primary endpoints: AUCinf and Cmax and the secondary endpoint: AUClast were within the predefined margins demonstrating comparability in PK.

Immunogenicity as measured by ADAs and nAb was similar between treatments.

PK comparability between ABP 501 100 and 50 mg/mL is considered demonstrated based on the results of Study 20200286. It is thus acceptable that the same SmPC text is used for describing the PK of ABP 501.

2.6.4. Conclusions on clinical pharmacology

Comparability between ABP 501 100 mg/mL and ABP 501 50 mg/mL has been demonstrated in vivo. The extension to introduce a new strength 80 mg [0.8 ml (100 mg/ml)] is approvable from a PK perspective.

2.6.5. Clinical efficacy

No clinical studies were conducted to evaluate the efficacy of ABP 501 100 mg/mL. This is acceptable.

2.6.6. Clinical safety

The primary objective of Study 20200286 was to determine the PK comparability between ABP 501 100 mg/mL (40 mg/0.4 mL) and ABP 501 50 mg/mL (40 mg/0.8 mL) following a single SC injection, as assessed principally by AUC from time 0 extrapolated to infinity (AUCinf) and maximum observed serum concentration (Cmax) in healthy adult subjects. The secondary objective was to determine the safety, tolerability, and immunogenicity of ABP 501 100 mg/mL compared with ABP 501 50 mg/mL.

Eligible subjects were randomized in a ratio of 1:1 stratified by gender prior to dosing on day 1 to receive either ABP 501 100 mg/mL or ABP 501 50 mg/mL as a single (40 mg) SC injection. Study drug administration occurred on day 1 after predose baseline procedures were completed. Subjects remained resident in the Clinical Pharmacology Unit (CPU) until day 2 for safety evaluations and PK assessments. Subjects were discharged on day 2 after the 24-hour postdose study procedures were completed. Subjects returned to the CPU on days 3, 4, 5, 6, 7, 8, 9, 11, 14, 16, 22, 29, 36, 43, 50, 57, and 63 (end-of-study [EOS] visit) for safety evaluations and PK and immunogenicity assessments.

The safety endpoints analyzed were treatment-emergent adverse events, serious adverse events, and events of interest (EOIs). Changes in laboratory values and vital signs were not listed as safety endpoints for Study 20200286, but these were still analyzed. The immunogenicity endpoint was incidence of binding and neutralizing antidrug antibodies (ADA). All safety analyses, including immunogenicity, are presented descriptively.

The following EOIs were prespecified for this study: serious infections, malignancies, hypersensitivity, demyelinating diseases, hematological reactions, heart failure, lupus-like syndromes, liver enzyme elevations, and injection site reactions.

All safety data for the clinical studies are summarized by treatment group and overall.

2.6.6.1. Patient exposure

Table 6: Subject Disposition (Study 20200286 Randomized Analysis Set)

Variable	ABP 501 100 mg/mL (N = 185) n (%)	ABP 501 50 mg/mL (N = 187) n (%)	Total (N = 372) n (%)
Subjects randomized	185 (100.0)	187 (100.0)	372 (100.0)
Subjects dosed	183 (98.9)	187 (100.0)	370 (99.5)
Completed study	178 (96.2)	180 (96.3)	358 (96.2)
Discontinued study[a]	7 (3.8)	7 (3.7)	14 (3.8)
Adverse event	1 (0.5)	1 (0.5)	2 (0.5)
Lost to follow-up	3 (1.6)	2 (1.1)	5 (1.3)
Physician decision	1 (0.5)	0 (0.0)	1 (0.3)
Protocol violation	0 (0.0)	1 (0.5)	1 (0.3)
Withdrawal by subject	1 (0.5)	3 (1.6)	4 (1.1)
Other	1 (0.5)[b]	0 (0.0)	1 (0.3)
Discontinued study due to COVID-19-related reasons	1 (0.5)	1 (0.5)	2 (0.5)
COVID-19 infection	1 (0.5)	1 (0.5)	2 (0.5)

Table 7: Demographic and Baseline Characteristics by Treatment (Study 20200286 Safety Analysis Set)

Characteristic	ABP 501 100 mg/mL (N = 183)	ABP 501 50 mg/mL (N = 187)	Total (N = 370)
Sex [n (%)]			
Female	87 (47.5)	89 (47.6)	176 (47.6)
Male	96 (52.5)	98 (52.4)	194 (52.4)
Race [n (%)]			
White	135 (73.8)	133 (71.1)	268 (72.4)
Asian	11 (6.0)	22 (11.8)	33 (8.9)
Black or African American	24 (13.1)	23 (12.3)	47 (12.7)
Multiple	9 (4.9)	7 (3.7)	16 (4.3)
Black or African American/American Indian or Alaska Native/White	3 (1.6)	0 (0.0)	3 (0.8)
White/American Indian or Alaska Native	1 (0.5)	0 (0.0)	1 (0.3)
White/Asian	2 (1.1)	1 (0.5)	3 (0.8)
White/Black or African American	2 (1.1)	6 (3.2)	8 (2.2)

White/Native Hawaiian or Other Pacific Islander	1 (0.5)	0 (0.0)	1 (0.3)
American Indian or Alaska Native	2 (1.1)	2 (1.1)	4 (1.1)
Native Hawaiian or Other Pacific Islander	2 (1.1)	0 (0.0)	2 (0.5)
Ethnicity [n (%)]			
Hispanic or Latino	96 (52.5)	86 (46.0)	182 (49.2)
Not Hispanic or Latino	87 (47.5)	101 (54.0)	188 (50.8)
Age (years)			
Mean (SD)	34.6 (9.88)	35.0 (10.04)	34.8 (9.95)
Minimum, maximum	18, 55	18, 55	18, 55
Weight (kg)			
Mean (SD)	72.80 (10.043)	72.04 (11.179)	72.41 (10.625)
Minimum, maximum	50.6, 89.9	50.0, 89.9	50.0, 89.9
Height (cm)			
Mean (SD)	169.35 (8.515)	168.92 (9.088)	169.13 (8.800)
Minimum, maximum	152.0, 192.9	148.2, 194.1	148.2, 194.1
BMI (kg/m^2)			
Mean (SD)	25.353 (2.7829)	25.184 (2.9416)	25.268 (2.8616)
Minimum, maximum	18.61, 29.98	18.50, 30.04	18.50, 30.04

2.6.6.2. Adverse events

Table 8: Overall Summary of Adverse Events (Study 20200286 Safety Analysis Set)

	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Any adverse event	49 (26.8)	51 (27.3)
Any grade ≥ 3 adverse event	0 (0.0)	0 (0.0)
Any fatal adverse event	0 (0.0)	0 (0.0)
Any serious adverse event	0 (0.0)	0 (0.0)
Any adverse event leading to discontinuation of study	1 (0.5)	1 (0.5)
Any adverse event of interest	12 (6.6)	11 (5.9)

Table 9: Treatment-emergent Adverse Events Experienced by ≥ 2 Subjects in Any Treatment Group by Preferred Term (Study 20200286 Safety Analysis Set)

Preferred Term	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Any adverse event	49 (26.8)	51 (27.3)
Headache	8 (4.4)	9 (4.8)
COVID-19	5 (2.7)	3 (1.6)
Upper respiratory tract infection	4 (2.2)	1 (0.5)
Fatigue	3 (1.6)	2 (1.1)
Myalgia	3 (1.6)	0 (0.0)
Rash	3 (1.6)	1 (0.5)
Arthralgia	2 (1.1)	2 (1.1)
Blood creatine phosphokinase increased	2 (1.1)	2 (1.1)
Dermatitis contact	2 (1.1)	0 (0.0)
Diarrhoea	2 (1.1)	3 (1.6)
Injection site reaction	2 (1.1)	3 (1.6)
Cough	1 (0.5)	3 (1.6)
Injection site pain	1 (0.5)	3 (1.6)
Oropharyngeal pain	1 (0.5)	2 (1.1)
Dizziness	0 (0.0)	2 (1.1)
Presyncope	0 (0.0)	2 (1.1)

Table 10: Treatment-emergent Adverse Events Experienced by ≥ 2 Subjects in Any Treatment Group by System Organ Class - (Study 20200286 Safety Analysis Set)

System Organ Class	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Infections and infestations	13 (7.1)	8 (4.3)
Nervous system disorders	10 (5.5)	16 (8.6)
General disorders and administration site conditions	9 (4.9)	11 (5.9)
Musculoskeletal and connective tissue disorders	7 (3.8)	3 (1.6)
Skin and subcutaneous tissue disorders	7 (3.8)	2 (1.1)
Gastrointestinal disorders	4 (2.2)	4 (2.1)
Investigations	3 (1.6)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	3 (1.6)	8 (4.3)
Injury, poisoning and procedural complications	2 (1.1)	4 (2.1)
Psychiatric disorders	2 (1.1)	0 (0.0)
Immune system disorders	0 (0.0)	2 (1.1)

2.6.6.3. Serious adverse event/deaths/other significant events

Table 11: Overall Summary of Treatment-emergent Events of Interest (Study 20200286 Safety Analysis Set)

Event of Interest	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Any event of interest	12 (6.6)	11 (5.9)
Serious infections	0 (0.0)	0 (0.0)
Malignancies	0 (0.0)	0 (0.0)
Hypersensitivity reactions	5 (2.7)	4 (2.1)
Demyelinating disease	0 (0.0)	0 (0.0)
Hematological reactions	1 (0.5)	0 (0.0)
Heart failure	0 (0.0)	0 (0.0)
Lupus-like syndrome	0 (0.0)	0 (0.0)
Liver enzyme elevations	1 (0.5)	0 (0.0)
Injection site reactions	5 (2.7)	8 (4.3)

Table 12: Treatment-emergent Adverse Events of Special Interest by Preferred Term: Hypersensitivity (Safety Analysis Set)

Preferred Term	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Number of subjects reporting any hypersensitivity adverse event	5 (2.7)	4 (2.1)
Rash	3 (1.6)	1 (0.5)
Dermatitis contact	2 (1.1)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (0.5)
Injection site rash	0 (0.0)	1 (0.5)
Rhinitis allergic	0 (0.0)	1 (0.5)

Table 13: Treatment-emergent Adverse Events of Special Interest by Preferred Term: Injection Site Reactions (Safety Analysis Set)

Preferred Term	ABP 501 100 mg/mL (N = 183) n (%)	ABP 501 50 mg/mL (N = 187) n (%)
Number of subjects reporting any injection site reactions adverse event	5 (2.7)	8 (4.3)
Injection site reaction	2 (1.1)	3 (1.6)
Injection site erythema	1 (0.5)	1 (0.5)
Injection site haemorrhage	1 (0.5)	0 (0.0)
Injection site pain	1 (0.5)	3 (1.6)
Injection site pruritus	1 (0.5)	0 (0.0)
Injection site rash	0 (0.0)	1 (0.5)

2.6.6.4. Laboratory findings

A summary of haematology laboratory values (haematocrit, haemoglobin, red blood cell count, white blood cell count (with differential), and platelet count) and chemistry laboratory values (alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, calcium, chloride, creatine kinase, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, potassium, protein, sodium, and urea nitrogen) at baseline, day 2, day 8, day 16, day 36, and EOS was provided by the MAH.

According to the MAH, there were no clinically impactful differences in haematology or chemistry laboratory values between treatment groups or safety trends observed over time.

A summary of vital signs (temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate) at baseline, day 1 (1 hour postdose), day 2, day 8,day 16, day 29, day 43, and day 63 (EOS) was provided by the MAH.

According to the MAH, no clinically impactful differences between treatment groups were observed for vital signs over time.

2.6.6.5. Immunological events

For full assessment regarding ADAs, please see section 2.6.3 Discussion on clinical pharmacology.

A total of 7 (3.8%) subjects in the ABP 501 100 mg/mL treatment group and 8 (4.3%) subjects in the ABP 501 50 mg/mL treatment group were positive for pre-existing binding ADA at or before baseline; 1 (0.5%) subject in the ABP 501 100 mg/mL treatment group tested positive for pre-existing neutralizing ADA at or before baseline.

Over the course of the study, a total of 172 (94.0%) subjects in the ABP 501 100 mg/mL treatment group and 179 (95.7%) subjects in the ABP 501 50 mg/mL treatment group were positive for binding ADA, and 32 (17.5%) and 29 (15.5%) subjects, respectively, were positive for neutralizing ADA, at any time during the study.

Of the subjects with a postbaseline result through EOS, 165 (90.7%) subjects in the ABP 501 100 mg/mL treatment group and 171 (92.4%) subjects in the ABP 501 50 mg/mL treatment group tested positive for the development of binding ADAs, and 31 (17.0%) and 29 (15.7%) subjects, respectively, tested positive for the development of neutralizing ADAs. There was no observed correlation of binding or neutralizing ADA to adverse events.

2.6.6.6. Additional information regarding safe use of the product

The MAH has provided two device reports summarizing the human factors/usability engineering (HF/UE) activities conducted for the ABP 501 100mg/mL SureClick 1.5 Autoinjector (AI) and ABP 501 100mg/mL Prefilled syringe (PFS) product user interface design including the device design, packaging, instruction for use (IFU) and other labeling material(s) (see Table 14 and Table 15).

Regarding the PFS: 92 of 95 of participants completed a successful injection (delivered a full and correct dose of medication in an intended injection site). Paediatric patients (ages 6 to 10) and healthcare professionals (HCPs) were not included in this study.

• 32 of 32 adults administered a successful injection

• 29 of 32 caregivers administered a successful injection

• 31 of 31 adolescents administered a successful injection

Two caregivers selected the incorrect dose on Day 1 (first dose of new medication), which resulted in an underdose. The third caregiver prematurely extruded medication while removing the needle cap which resulted in an underdose.

Regarding the AI: 89 of 94 participants successfully operated the ABP 501 100mg/mL AI. Four participants experienced wet injections due to premature lift, and one participant refused to use the IFU and was unsuccessful with completing an injection as they did not remove the cap but believed that they had successfully injected.

Only 69 of 94 participants delivered a full, correct dose of medication in an intended injection site. 5 participants had failures attributable to low health literacy of adolescent participants (these participants noted in follow up that their parents would assist them for their first injection at home), and 7 participants had failures attributable to study artifact and/or habit/prior experience. The remaining 13 participants had failures that were attributable to the user interface.

Use-errors for the 25 participants that had a failure to deliver a full, correct dose of medication in an intended injection are summarized below.

- 2 Caregivers and 3 Adolescents made multiple errors that contributed to a failure such as selecting the incorrect dose and/or incorrect injection location.
- Select an appropriate injection site: 1 Adult, 4 Caregivers, and 4 Adolescents did not select an appropriate injection site. All participants with use errors were asked follow-up question on correct injection sites and answered correctly.
- Inject the correct dose of medicine: 1 Adult, 9 Caregivers and 5 Adolescents selected the incorrect dose for their next/first injection.

  • 1 Adult and 4 Caregivers administered a complete injection but thought they should only give one 80mg injection instead of two

  • 4 Caregivers and 4 Adolescents administered a complete injection but selected the 40mg AI instead of the 80mg AI

  • 1 Caregiver attempted injection with the 80mg AI instead of the 40mg AI

  • 1 Adolescent administered a complete injection but thought they should give three 80mg injections instead of two
- 1 Caregiver and 3 Adolescents failed to maintain safety guard compression throughout the injection. The 4 participants all knew they did not administer a complete injection.
- 1 Caregiver retracted early because they expected the device to inject quicker as there was not a lot of medicine in the injector.
- 1 Adolescent manipulated the device during injection to see the inspection window resulting in premature lift

- 1 Adolescent lifted early based experience watching a friend inject diabetes medication and expected the delivery to be quicker
- 1 Adolescent incorrectly chose the upper arm as an appropriate injection site and had difficulty maintaining compression as the injection pad shifted while attempting to give the injection.

Table 14: ABP 501 100mg/mL AI Simulated Use Summative Validation Data and Knowledge Comprehension (task 4.1)

Task 4.1 Select correct dose for next/first injection	15 use errors: 1 Adult, 9 Caregivers and 5 Adolescents selected the incorrect dose for their next/first injection. Dose selection errors can be categorized into the following: Participant gave a complete dose but thought they should only give one 80mg injection instead of two (1 Adult, 5 Caregivers). Participant gave a complete dose but selected 40mg dose instead of 80mg	No close calls No difficulties	Users were confused by the simulated pharmacy label stimuli or did not read closely. User thought they were supposed to simulate day 15 as well. Users grabbed the first device they saw and did not understand correct dosing regimen on the simulated pharmacy label stimuli .	Error attributable to study artifact and/or simulation limitation.	Carton text and colored flag communicates drug dose and concentration. IFU text communicates need to check that correct medicine and dose are selected. Carton colors are different for each dosage to enable differentiation. HF Validation analysis revealed no additional mitigations to further reduce or eliminate use errors. Note: Adolescents with use errors in dosing noted in
			User started with the lowest dose and described that the current medication they take started with the lowest and increases over time. User administered a single 80mg dose rather than 2 and assumed it was like an EpiPen which is just one pen per dose.	Habit/prior experience negatively impacted participants ability to select the correct dose.	
	(4 Caregivers, 4 Adolescents). Participant gave a complete dose but thought they should give three 80mg injections instead of two (1 Adolescent).		User selected the 40 mg dose when they should have administered an 80 mg dose. When selecting the dose they assumed the doses in the cartons provided were the same and that the bigger box (3x1ct 80 mg see Figure 9) just contained more of the same product.	Dose was not prominent to the user and/or participants did not understand the difference between a loading and a maintenance dose.	questioning that they would never use the device alone as they did in the simulated use, and instead would have their parent help during their first injection and to assist with correct dose selection.

Table 15: Preliminary Analyses and Evaluation Summary

Method Used	Reference to Report(s)	Objective(s)	Results/Findings	Post-study Recommendations/ Modifications
Formative Usability Study: • Simulated use and knowledge assessment • Iterative study, based on a single protocol with predefined objectives for each study iteration	ABP 501 100mg/mL SureClick® 1.5 Autoinjector Iterative Formative Study PTC-461026 [Ref. 17] APPX-455159 [Ref. 18] RPT-573816 [Ref. 19]	Iteration #1 (First study): The purpose of Iteration #1 was to investigate user perception of 100mg/mL (40mg/0.4mL) device. Patients using a 50mg/mL (40mg/0.8mL) device may transition to the ABP 501 100mg/mL concentration, which may appear to be partially filled to the user. Specific objectives: • Identify patient's ability to comprehend fill volume of 100mg/mL device. • Investigate opportunities for improved perception. • Evaluate opportunities for labeling changes to address partial fill volume.	18 representative users of the ABP 501 AI device (10 adults and 8 adolescents) took part in Iteration #1. The participants were asked to examine the AIs to elicit the participant's perception of the devices. All participants were able to identify the location of the medicine on the device. 3/18 participants did not understand what the word 'dosage' meant. This lack of understanding was further evident in comparing of device concentration, as only 2/18 participants understood that 40mg/0.4mL and 80mg/0.8mL had equal concentrations. 4/18 participants believed that the 40mg/0.4mL device was previously used because of the partial fill volume visible in window (Figure 2).	Modifications made post Iteration #1: • Needle guard terminology was updated to safety guard to help reduce stress and anxiety in needle averse patients. • "Important" boxes throughout the IFU were updated from grey background (which was missed by users) to a white background with a red border to increase prominence. • Arrows which were determined to be misleading to some patients were updated on cap removal step. • Addition of calendar graphic with "14 days" to help with storage at room temperature of up to 14 days.

2.6.6.7. Discontinuation due to adverse events

One subject each in the ABP 501 100 mg/mL and ABP 501 50 mg/mL treatment groups discontinued the study due to an adverse event of COVID-19 infection.

2.6.6.8. Post marketing experience

Cumulatively, since the International Birth Date (IBD) of 23 September 2016 to 31 December 2022 (data lock point [DLP] for Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report [PBRER/PSUR] #9), there was an estimated 415 022 patient-years of exposure to Amgevita (adalimumab) in the marketed setting.

As of 31 December 2022, Amgen received a total of 22 116 adverse drug reactions (ADRs) cumulatively from medically confirmed and unconfirmed spontaneous sources; 6900 of the 22 116 were serious ADRs and 15 216 were nonserious ADRs. Amgen has also received a total of 8037 serious adverse reactions cumulatively from noninterventional postmarketing sources and other solicited sources. Overall, according to the MAH the evaluation of postmarketing safety data did not result in the detection of any new risks for Amgevita.

2.6.7. Discussion on clinical safety

Safety was evaluated in healthy persons who were randomised in a ratio of 1:1 stratified by gender to receive either ABP 501 100 mg/mL (40 mg/0.4 mL) or 50 mg/mL (40 mg/0.8 mL) as a single (40 mg) SC injection in a prefilled pen. Subjects were evaluated for safety regularly up to two months (end of study at 63 days). All 370 subjects in the safety analysis set received a single injection of 40mg ABP 501 either 100 mg/mL (n=183) or 50 mg/mL (n=187). Seven patients in each group discontinued the study, the main reason being lost to follow up or withdrawal by subjects. One patient in each group discontinued because of AE (Covid-19 infection).

Numbers of AEs were similar in both groups, 26.8% in the 100mg/ml group and 27.3% in the 50mg/ml group. Most AEs were mild and there were no fatal or serious events. Most common AEs were headache, covid 19 infections and upper respiratory tract infections. There were no relevant differences between the two concentrations regarding AEs and the events were in line with the already known safety profile for adalimumab.

Numbers of subjects reporting events of special interest (serious infections, malignancies, hypersensitivity, demyelinating diseases, hematological reactions, heart failure, lupus-like syndromes, liver enzyme elevations, and injection site reactions) were also similar in both groups. No relevant differences were seen in events regarding injection site reactions or hypersensitivity reactions. There were no clinically important differences in haematology or chemistry laboratory values or vital signs between treatment groups or safety trends observed over time.

Although numbers of patients with ADA were high, there were no correlation to clinical event and the amount of ADA and neutralizing ADA were similar in the two concentrations.

To conclude no differences in safety findings were seen between the two concentrations and no new safety findings occurred in the PK-study in healthy subjects.

There were however some concerns regarding the presentation of the new strength and dose that needed additional comments. In the Human Factor/Usability Engineering study regarding AI, there were 15 patients/care givers that did not give the correct dose, and this seemed mainly because there were choosing the wrong strength or gave too few injections. This may indicate that the instruction regarding dosage (especially when 2 injections should be used at the same time) are insufficient or that there are problems to differentiate between different strengths when using the AI. This problem was not seen with the PFS. In addition, regarding the AI device the patients seems to struggle with understanding the concept of

different/similar concentrations (e.g., 2/18 patients did not understand that the 40mg/0.4mL and 80mg/0.8mL had the same concentration) and four patients also thought that the pen was already used since it contained only half the volume.

Upon request, the MAH has provided some information regarding the subjects who failed to select the appropriate induction dose, 6/24 patients and 11/24 caregivers. The errors were mainly (in 5 patients and 9 caregivers) because of issues with the simulated pharmacy label and these use errors were assessed by the MAH as result of artifacts of the simulated study environment and were not attributed to the proposed product user interface. All summative studies were conducted in the absence of any trained patient or caregiver arms to simulate the worst-case scenario. It is, as the MAH states, expected that the patients/caregivers receive instruction from the HCP when starting with the medication (and a bolus dose should be given) or when the dose is changed. There were no problems selecting the appropriate maintenance dose during the summative studies.

Since the observed dosing errors regarding the induction dose will not lead to any chronic over or underdosing and the fact that the appropriate doses were given during maintenance treatment by all participants this issue was not further pursued. It is anticipated that all patients will receive instruction from the HCP when initiating a new medication, or a new dose.

2.6.8. Conclusions on the clinical safety

No differences in safety findings were seen between the two concentrations and no new safety findings occurred in this study. The extension to introduce a new strength 80 mg [0.8 ml (100 mg/ml)] is approvable from a safety perspective.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	Serious infections
	Tuberculosis
	Malignancies
	Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)
	BCG disease following live BCG vaccination in infants with in utero exposure to Amgevita
Important potential risks	Progressive multifocal leukoencephalopathy
	Reversible posterior leukoencephalopathy syndrome
	Adenocarcinoma of colon in ulcerative colitis patients

Missing information	Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis Long-term safety data in the treatment of children with uveitis Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

BCG = Bacillus Calmette-Guérin

2.7.2. Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
(Amgevita) 20160264 A prospective observational study to evaluate long-term safety of Amgevita in patients with rheumatoid arthritis Ongoing	<u>Primary objectives:</u> • To estimate the incidence rates of serious infections (ie, infectious events which required IV antibiotics, hospitalization, or meet other criteria for a serious adverse event) <u>Secondary objective:</u> • Estimate the incidence rates of other serious adverse events (safety concerns) in patients with RA exposed to Amgevita • Estimate the incidence rates of the safety concerns from both the BSRBR-RA anti-TNF and nbDMARD comparison cohorts	• Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Protocol submission Interim reports Final report	2019 2Q (submitted) 1st annual report submitted: 2020 4Q Interim reports no longer an EMA requirement after the first report was submitted 2028 2Q

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious infections	Routine risk minimization measures: • SmPC Section 4.2 where dose interruption is discussed • SmPC Section 4.3 • SmPC Section 4.4 where close monitoring for infections and discontinuation of AMGEVITA is discussed • SmPC Section 4.8 • PL Section 2 where symptoms of infection, interruption of AMGEVITA, and advice not to take AMGEVITA with medicines containing anakinra or abatacept is discussed • PL Section 4 where symptoms of infection are discussed Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study
Tuberculosis	Routine risk minimization measures: • SmPC Section 4.2 where dose interruption is discussed • SmPC Section 4.3 • SmPC Section 4.4 where close monitoring for TB, treatment of latent TB before initiation of AMGEVITA, and discontinuation of AMGEVITA is discussed • SmPC Section 4.8 • PL Section 2 where symptoms of TB, interruption of AMGEVITA, and advice not to take AMGEVITA with medicines containing the active substances anakinra or abatacept is discussed • PL Section 4 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Malignancies	Routine risk minimization measures: • SmPC Section 4.4 where examination for the presence of NMSC prior to and during treatment with AMGEVITA is discussed • SmPC Section 4.8 • PL Section 2 where appearance of new skin lesions or change in the appearance of existing lesions during or after AMGEVITA therapy is discussed • PL Section 4 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study
Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)	Routine risk minimization measures: • SmPC Section 4.4 where neurologic evaluation in patients with non-infectious intermediate uveitis to assess for pre-existing or developing central demyelinating disorders is described • SmPC Section 4.8 • PL Sections 2 and 4 where symptoms of demyelinating disease are described Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • (AMGEVITA) 20160264 study
BCG disease following live BCG vaccination in infants with in utero exposure to AMGEVITA	Routine risk minimization measures: • SmPC Sections 4.4 and 4.6 where guidance that administration of live vaccines (eg, BCG vaccine) to infants exposed to AMGEVITA in utero is not recommended for 5 months following the mother's last AMGEVITA injection during pregnancy is provided • PL Section 2 Additional risk minimization measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Progressive multifocal leukoencephalopathy	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Reversible posterior leukoencephalopathy syndrome	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Adenocarcinoma of colon in ulcerative colitis patients	Routine risk minimization measures: • SmPC Section 4.4 where regular screening for the presence of colonic dysplasia prior to and during treatment with AMGEVITA is discussed Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Long-term safety information in the treatment of children, aged from 6 years to less than 18 years with Crohn's disease	Routine risk minimization measures: • SmPC Section 4.2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Long-term safety data in the treatment of children with uveitis	Routine risk minimization measures: • SmPC Section 4.2 where recommendation for yearly evaluation of benefit-risk is included Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information		
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	No risk minimization measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

BCG = Bacillus Calmette-Guérin; NMSC = non-melanoma skin cancer; PL = package leaflet; SmPC = summary of product characteristics; TB = tuberculosis

2.7.4. Conclusion

The CHMP considered that the risk management plan version 7.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the package leaflets are identical with the approved package leaflets (except a few product specific details) and the instructions for use are very similar.

3. Benefit risk assessment

3.1. Therapeutic context

Amgevita (adalimumab, ABP 501) is an approved biosimilar product to Humira. ABP 501 and Humira are both recombinant humanized immunoglobulin G type 1 monoclonal antibodies belonging to the pharmacologic class of human tumor necrosis factor (TNF) blockers. The approved indications for Amgevita are the same as for Humira; rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, Axial spondyloarthritis, psoriatic arthritis, Psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease (CD), paediatric CD, Ulcerative colitis (UC), paediatric UC, uveitis, paediatric uveitis.

Amgevita is currently approved as a 50 mg/mL formulation for subcutaneous (SC) administration and supplied as 9 presentations in different package sizes in the following strengths and container closure

systems: a 40 mg single-dose SureClick prefilled pen (PFP), a 40 mg single-dose prefilled syringe (PFS), and a 20 mg single-dose PFS.

The MAH has developed a new 100 mg/mL high concentration formulation (ABP 501 100 mg/mL) as the reference product Humira (adalimumab) 100 mg/mL. Amgevita 100 mg/mL will be supplied as 13 presentations in different package sizes in the following strengths and container closure systems: 80 mg single-dose SureClick PFP, 80 mg single-dose PFS, 40 mg single-dose SureClick PFP, 40 mg single-dose PFS and 20 mg single-dose PFS.

3.1.1. Main clinical study

Study 20200286 was a randomized, single-blind, single-dose, 2-arm, parallel-group study in healthy adult male and female subjects with a body weight of ≥ 50 kg to ≤ 90 kg. Eligible subjects were randomized in a ratio of 1:1 stratified by gender prior to dosing on day 1 to receive either ABP 501 100 mg/mL PFS or ABP 501 50 mg/mL PFS as a single (40 mg) SC injection.

3.2. Favourable effects

In the PK comparability study 20200286, both primary endpoints AUCinf and Cmax and the secondary endpoint AUClast were within the predefined margins demonstrating comparability in PK for the 50 and 100 mg/mL PFS. Immunogenicity as measured by ADAs and nAb was similar between treatments.

3.3. Uncertainties and limitations about favourable effects

No clinical studies were conducted to evaluate the efficacy of ABP 501 100 mg/mL, this is however acceptable.

3.4. Unfavourable effects

Healthy subjects in study 20200286 were evaluated for safety regularly up to two months. All 370 subjects in the safety analysis set received a single injection of 40mg ABP 501 either 100 mg/mL (n=183) or 50 mg/mL (n=187). Seven patients in each group discontinued the study, the main reason being lost to follow up or withdrawal by subjects. Numbers of AEs were similar in both groups, 26.8% in the 100mg/ml group and 27.3% in the 50mg/ml group. Most AEs were mild or moderate and there were no fatal or serious events. There were no relevant differences between the two concentrations regarding AEs and the events were in line with the already known safety profile for adalimumab.

Numbers of patients with ADA were high but there was no correlation to clinical event and the amount of ADA and neutralizing ADA were similar in the two concentrations.

3.5. Uncertainties and limitations about unfavourable effects

The Human Factor/Usability Engineering studies revealed some concerns regarding the presentation of the new strength/concentration/volume to the patients, especially with the AI device. There were several patients/care givers that did not give the correct dose, and this seemed mainly because there were choosing the wrong strength or gave to few injections. The MAH has provided information regarding the subjects who

failed to select the appropriate induction dose, 6/24 patients and 11/24 caregivers. According to the MAH this was mainly (in 5 patients and 9 caregivers) because of issues with the simulated pharmacy label and these use errors were assessed as result of artifacts of the simulated study environment and were not attributed to the proposed product user interface. All summative studies were conducted in the absence of any trained patient or caregiver arms to simulate the worst-case scenario. It is, as the MAH states, expected that the patients/caregivers receive instruction from the HCP when starting with the medication (and a bolus dose should be given) or when the dose is changed. There were no problems selecting the appropriate maintenance dose during the summative studies.

Since the observed dosing errors regarding the induction dose will not lead to any chronic over or underdosing and the fact that the appropriate doses were given during maintenance treatment by all participants this was not further pursued. It is anticipated that all patients will receive instruction from the HCP when initiating a new medication, or a new dose.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In the PK comparability study 20200286, comparability in PK is demonstrated between the new 100mg/ml presentations and the approved 50mg/ml presentations. A PK study with the PFS was considered to be sufficient, with no requirement to study the PFP as it is the same as already approved.

Immunogenicity as measured by ADAs and nAb was similar between treatments.

There were no relevant differences between the two concentrations regarding AEs and the events were in line with the already known safety profile for adalimumab.

The new strength (80mg) and concentration (100mg/mL) will make it possibly for some patients to reduce the numbers of injections needed to take and decreases the volume needed to be injected. The new strength and high concentration formulation are already approved for the reference product Humira.

3.6.2. Balance of benefits and risks

Comparability in PK is demonstrated between the new 100 mg/ml presentations and the already approved 50mg/ml presentations and immunogenicity as measured by ADAs and nAb was similar between treatments. No relevant differences between the two concentrations regarding AEs were seen and the adverse events were in line with the already known safety profile for adalimumab.

3.7. Conclusions

The overall benefit/risk balance of Amgevita is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Based on the CHMP review of data on quality, pharmacology and safety the CHMP considers by consensus that the benefit-risk balance of, Amgevita new strength 80 mg [0.8 ml (100, mg/ml)] solution for injection, is favourable in the following indications:

Rheumatoid arthritis

Amgevita in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Amgevita can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Amgevita reduces the rate of progression of joint damage as measured by x-ray and improves physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Amgevita in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. Amgevita can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Amgevita is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Amgevita is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Amgevita is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs.

Psoriatic arthritis

Amgevita is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Amgevita reduces the rate of progression of

peripheral joint damage as measured by x-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and improves physical function.

Psoriasis

Amgevita is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Amgevita is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Amgevita is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn’s disease

Amgevita is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Amgevita is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Amgevita is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6 -mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Amgevita is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Amgevita is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Amgevita is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The CHMP therefore recommends the extension of the marketing authorisation for Amgevita 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.
- **Additional risk minimisation measures**

The Patient Reminder Cards (adult and paediatric) contain the following key elements

- infections, including tuberculosis
- cancer
- nervous system problems
- vaccinations

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
B.I.a.2.a	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	Type IB	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.f.1.e	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	Type IB	None
B.II.a.5	B.II.a.5 - Change in concentration of a single-dose, total use parenteral product, where the amount of AS per unit dose (i.e. the strength) remains the same	Type II	I, IIIA, IIIB and A
B.II.f.1.b.5	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	Type IB	I
B.I.d.1.c	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	Type IB	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A
B.II.f.1.e	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	Type IB	None
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
B.II.d.1.e	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	Type II	None
B.I.b.1.f	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	Type II	None
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product -	Type	I, IIIA, IIIB

	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IAin	and A
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA, IIIB and A